Dear Friends and Colleagues,

It is our great pleasure to welcome you to the XIII International Symposium on Inorganic Chemistry. The first International Symposium on Inorganic Biochemistry took place in Karpacz in 1985, and has been followed by eleven others in the series. All of them have been organised by Professor Henryk Kozłowski, and have been a great success, bringing together top researchers from around the world. As the subtitles of previous symposia say: “Where to go?”, “Challenge for New Generation”, “Challenge for all Generations”, “Collaboration and Beyond”, Henryk has been not only a source of inspiration for several generations of bioinorganic chemists but also their friend.

Three decades later, we are delighted to present the XIII International Symposium on Inorganic Biochemistry as the tribute to Henryk for his friendship, his role as a teacher and mentor, his far-reaching vision, and his important and extensive contributions to bioinorganic chemistry. This Symposium is a token of our appreciation of a truly outstanding chemist - Professor Henryk Kozłowski.

Happy 70th birthday Henryk!

On behalf of the Organizers

Elżbieta Gumienna-Kontecka
Magdalena Rowińska-Żyrek
Marek Łuczkowski
XIII International Symposium on Inorganic Biochemistry
Happy Anniversary
1-6 September 2015 Karpacz, Poland

ORGANIZING COMMITTEE:
Elżbieta Gumienna-Kontecka – University of Wrocław, Poland
Magdalena Rowińska-Żyrek – University of Wrocław, Poland
Marek Łuczkowski – University of Wrocław, Poland
Paulina Kołkowska – University of Wrocław, Poland
Aleksandra Hecel – University of Wrocław, Poland
Karolina Zdyb – University of Wrocław, Poland

Conference organized under the auspices of the Rector of the University of Wrocław and Mayor of Wrocław

Sponsored by:

[Logos of赞助商]
**Tuesday, 01.09.2015**

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<tr>
<td>14:00-17:30</td>
<td>Check-in and Registration</td>
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<tr>
<td>17:30-18:00</td>
<td>Opening Ceremony</td>
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<tr>
<td></td>
<td><strong>chairperson:</strong> Andrea Scozzafava</td>
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<tr>
<td>18:00-18:30</td>
<td><strong>IL-1</strong> Astrid Sigel, Basel, Switzerland</td>
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<tr>
<td></td>
<td>&quot;A Tribute to Henryk Kozlowski&quot;</td>
</tr>
<tr>
<td>18:30-19:00</td>
<td><strong>IL-2</strong> Helmut Sigel, Basel, Switzerland</td>
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<td>&quot;Henryk Kozlowski and His love for bioinorganic chemistry. A very personal view focusing on the metal ion-binding properties of thio-pyrimidine derivatives&quot;</td>
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<tr>
<td>19:00</td>
<td>Welcome reception</td>
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**Wednesday, 02.09.2015**

**chairperson:** Vincent Pecoraro

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<tr>
<th>Time</th>
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<tr>
<td>9:00-9:30</td>
<td><strong>IL-3</strong> Elżbieta Gumienna-Kontecka, Wrocław, Poland</td>
</tr>
<tr>
<td></td>
<td>&quot;Hydroxamates in bioinorganic modeling and applications. How Henryk introduced me into science&quot;</td>
</tr>
<tr>
<td>9:30-10:00</td>
<td><strong>IL-4</strong> Magdalena Rowińska-Żyrek, Wrocław, Poland</td>
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<td>&quot;Impact of Henryk on my metal ion – protein interactions&quot;</td>
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<tr>
<td>10:00-10:30</td>
<td><strong>IL-5</strong> Daniela Valensin, Siena, Italy</td>
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<td>&quot;Cu(I) bioinorganic chemistry of amyloidogenic proteins&quot;</td>
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<tr>
<td>10:30-11:00</td>
<td><strong>IL-6</strong> Andrea Scozzafava, Florence, Italy</td>
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<td>&quot;From inorganic to bioinorganic chemistry for health and environment protection: a common forty years pathway of the Wrocław and Florence groups&quot;</td>
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<tr>
<td>11:00-11:30</td>
<td>Coffee break</td>
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**chairperson:** Paola Turano

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<th>Time</th>
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<tr>
<td>11:30-12:00</td>
<td><strong>IL-7</strong> Wolfgang Maret, London, United Kingdom</td>
</tr>
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<td>&quot;Coordination dynamics in the biometallome: metal ions on the move&quot;</td>
</tr>
<tr>
<td>12:00-12:30</td>
<td><strong>IL-8</strong> Eva Freisinger, Zurich, Switzerland</td>
</tr>
<tr>
<td></td>
<td>&quot;Like the HK-variant, the structure and metal ion binding abilities of the γ-E-1domain from a wheat MT remain unperturbed in view of a multitude of manipulations&quot;</td>
</tr>
<tr>
<td>12:30-13:00</td>
<td><strong>IL-9</strong> Milan Vasak, Zurich, Switzerland</td>
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<tr>
<td></td>
<td>&quot;Zinc, metallothionein-3 and the ageing human brain&quot;</td>
</tr>
<tr>
<td>13:00-15:00</td>
<td>Lunch</td>
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**chairperson:** Marek Łuczkowski

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<th>Time</th>
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<tbody>
<tr>
<td>15:00-15:30</td>
<td><strong>IL-10</strong> Yifat Miller, Beer-Sheva, Israel</td>
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<td>&quot;Self-assembly of metal binding β-hairpin peptide: De novo design and structural characterization&quot;</td>
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### XIII International Symposium on Inorganic Biochemistry

**Happy Anniversary**

1-6 September 2015 Karpacz, Poland

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<tr>
<th>Time</th>
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<tbody>
<tr>
<td>15:30-16:00</td>
<td>IL-11</td>
<td>Gianni Valensin, Siena, Italy</td>
<td>“Copper (II) binding to α-synuclein, the main protein involved in Parkinson's disease”</td>
</tr>
<tr>
<td>16:00-16:30</td>
<td>IL-12</td>
<td>Imre Sóvágó, Debrecen, Hungary</td>
<td>“Metal binding properties of peptides of histidine: complex formation by prion protein and amyloid-β”</td>
</tr>
<tr>
<td>16:30-17:00</td>
<td>IL-13</td>
<td>Wojciech Bal, Warszawa, Poland</td>
<td>“Metal assisted peptide bond hydrolysis and its consequences in biology”</td>
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<tr>
<td>17:00-17:30</td>
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<td>Coffee break</td>
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<tr>
<td>17:30-19:00</td>
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<td>Poster Session</td>
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<td>20:00</td>
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<td>Dinner</td>
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**Thursday, 3.09.2015**

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<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker</th>
<th>Title</th>
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<tbody>
<tr>
<td>9:00-9:30</td>
<td>IL-14</td>
<td>Maurizio Remelli, Ferrara, Italy</td>
<td>“Metal-histidine interactions: a “fil-rouge“ connecting Ferrara and Wrocław Universities”</td>
</tr>
<tr>
<td>9:30-10:00</td>
<td>IL-15</td>
<td>Julia Jezierska, Wrocław, Poland</td>
<td>“From strong to weak exchange between metal partners. Magnetic, EPR and DFT studies”</td>
</tr>
<tr>
<td>10:00-10:30</td>
<td>IL-16</td>
<td>Franc Meyer, Goettingen, Germany</td>
<td>“Proton-coupled electron transfer with [2Fe-2S] clusters”</td>
</tr>
<tr>
<td>10:30-11:00</td>
<td>IL-17</td>
<td>Grażyna Stochel, Kraków, Poland</td>
<td>“Bioinorganic photochemistry perspectives”</td>
</tr>
<tr>
<td>11:00-11:30</td>
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<td></td>
<td>Coffee break</td>
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**chairperson:** Bernhard Lippert

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<tr>
<th>Time</th>
<th>Session</th>
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<tbody>
<tr>
<td>11:30-12:00</td>
<td>IL-18</td>
<td>Peggy Carver, Ann Arbor, USA</td>
<td>“Infections associated with intravenous iron administration in hospitalized patients with acute heart failure”</td>
</tr>
<tr>
<td>12:00-12:30</td>
<td>IL-19</td>
<td>Abraham Shanzer, Rehovot, Israel</td>
<td>“Inducing broad-range activity to ferrichrome mimics: new hopes for siderophore based therapeutics”</td>
</tr>
<tr>
<td>12:30-13:00</td>
<td>IL-20</td>
<td>Bogusław Buszewski, Toruń, Poland</td>
<td>“Immobilization of silver onto lactoferrin in light of new antimicrobial application”</td>
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<tr>
<td>13:00-15:00</td>
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<td>Lunch</td>
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**chairperson:** Claudio Luchinat

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<tbody>
<tr>
<td>15:00-15:30</td>
<td>IL-21</td>
<td>Bernhard Lippert, Dortmund, Germany</td>
<td>“Serendipity and pseudoserendipity in science – cases of important discoveries”</td>
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<tr>
<td>Time</td>
<td>Session</td>
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<td>Title</td>
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<tr>
<td>15:30-16:00</td>
<td>IL-22</td>
<td>Roland Sigel, Zurich, Switzerland</td>
<td>&quot;How H⁺ and Mg²⁺ shape and form complex RNA structures&quot;</td>
</tr>
<tr>
<td>16:00-16:30</td>
<td>IL-23</td>
<td>Elene C. Pereira Maia, Belo Horizonte, Brasil</td>
<td>&quot;Novel complexes of Ru(II) as fotocytotoxic agents&quot;</td>
</tr>
<tr>
<td>16:30-16:50</td>
<td>OC-1</td>
<td>Iwona Łakomska, Toruń, Polska</td>
<td>&quot;Interaction of cytotoxic ruthenium complexes with DNA and proteins&quot;</td>
</tr>
<tr>
<td>16:50-17:30</td>
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<td>Coffee break</td>
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</tr>
<tr>
<td>17:30-17:50</td>
<td>OC-2</td>
<td>Mauro Carraro, Padova, Italy</td>
<td>&quot;Polyoxometalate-based systems as artificial antioxidant enzymes&quot;</td>
</tr>
<tr>
<td>17:50-18:10</td>
<td>OC-3</td>
<td>Ester Vilchez-Rodríguez, Granada, Spain</td>
<td>&quot;A novel copper(II) compound with μ3-bridging, O',O''-chelating and tetratdentate acyclovir&quot;</td>
</tr>
<tr>
<td>18:10-18:30</td>
<td>OC-4</td>
<td>Aleksandra Hecel, Wrocław, Poland</td>
<td>&quot;Specific interaction of Cu²⁺ and Cu⁺ ions with the amyloidogenic human prion protein* fragments in presence of SDS surfactant&quot;</td>
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<tr>
<td>19:00-19:30</td>
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<td>Barbeque</td>
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**Friday, 4.09.2015**

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<tr>
<th>Time</th>
<th>Session</th>
<th>Name</th>
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<tbody>
<tr>
<td>9:00-9:30</td>
<td>IL-24</td>
<td>Matteo Tegoni, Parma, Italy</td>
<td>&quot;'Forever young': the nice story of Metallacrowns from the perspective of a solution chemist&quot;</td>
</tr>
<tr>
<td>9:30-10:00</td>
<td>IL-25</td>
<td>Vincent Pecoraro, Ann Arbor, USA</td>
<td>&quot;Metallacrowns developed for smm, near ir and molecular recognition applications&quot;</td>
</tr>
<tr>
<td>10:00-10:30</td>
<td>IL-26</td>
<td>Stephane Petoud, Orleans, France</td>
<td>&quot;Near-infrared emitting lanthanine-containing metallacrowns as novel imaging agents for cellular biological imaging&quot;</td>
</tr>
<tr>
<td>10:30-11:00</td>
<td>IL-27</td>
<td>Talal Mallah, Paris, France</td>
<td>&quot;Highly symmetrical LnZn_{16} metallacrown complexes: experiment, theory and single molecule magnet behavior&quot;</td>
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<tr>
<td>11:00-11:30</td>
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<td>Coffee break</td>
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<tr>
<td>11:30-11:50</td>
<td>OC-5</td>
<td>Małgorzata Ostrowska, Wrocław, Poland</td>
<td>&quot;Since 1991 until today – Bioinorganic and Biomedical Chemistry Group adventures of metallacrowns&quot;</td>
</tr>
<tr>
<td>11:50-12:10</td>
<td>OC-6</td>
<td>Svetlana Eliseeva, Orleans, France</td>
<td>&quot;Visible and near-infrared emitting Ga³⁺/Ln³⁺ metallacrown complexes&quot;</td>
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XIII International Symposium on Inorganic Biochemistry  
*Happy Anniversary*  
1-6 September 2015 Karpacz, Poland

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<tr>
<td>12:10-12:30</td>
<td>OC-7</td>
<td>Corrado Atzeri, Parma, Italy</td>
<td>„Linking metallacrowns: from porous solids to magnetic materials“</td>
</tr>
<tr>
<td>12:30-13:00</td>
<td>IL-28</td>
<td>Igor Fritsky, Kiev, Ukraine</td>
<td>„Co-ordination polymers and metal-organic frameworks based on hydroxamates“</td>
</tr>
<tr>
<td>13:00-14:00</td>
<td></td>
<td>Lunch</td>
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<tr>
<td>14:30-18:30</td>
<td></td>
<td>Tour to Vang Church and Czocha Castle</td>
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<tr>
<td>19:00</td>
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<td>Dinner at Czocha Castle</td>
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**Saturday, 5.09.2015**

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<th>Time</th>
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<tr>
<td>9:00-9:30</td>
<td>IL-29</td>
<td>Claudio Luchinat, Florence, Italy</td>
<td>„Paramagnetic metal ions are a versatile tool for the investigation of biomolecules“</td>
</tr>
<tr>
<td>9:30-10:00</td>
<td>IL-30</td>
<td>Tamas Kiss, Szeged, Hungary</td>
<td>„Parallel interactions of dendrimers and metal ion chelators on the oligomerisation of β-amyliods – a potential use in the therapy of Alzheimer’s disease“</td>
</tr>
<tr>
<td>10:00-11:00</td>
<td>IL-31</td>
<td>Elżbieta Łodyga-Chruścińska, Łódź, Poland</td>
<td>„Copper coordination compounds with modified small biomolecules“</td>
</tr>
<tr>
<td>10:30-11:00</td>
<td>IL-32</td>
<td>Guido Crisponi, Gagliari, Italy</td>
<td>„A speciation study on the perturbing effects of iron chelators on the homeostasis of essential metal ions“</td>
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<tr>
<td>11:00-11:30</td>
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<td>Coffee break</td>
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**chairperson:** Daniela Valensin

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<th>Time</th>
<th>Session</th>
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<tr>
<td>11:30-11:50</td>
<td>OC-8</td>
<td>Amelia Santos, Lisboa, Portugal</td>
<td>„Metal-targeting in multifunctional drugs against Alzheimer’s disease“</td>
</tr>
<tr>
<td>11:50-12:10</td>
<td>OC-9</td>
<td>Piotr Mlynarz, Wroclaw, Poland</td>
<td>„Electrochemical and spectroscopic investigations of selected aminomethylenebisphosphonic acids towards Pb(II) ions“</td>
</tr>
<tr>
<td>12:10-12:30</td>
<td>OC-10</td>
<td>Yan Voloshin, Moscow, Russia</td>
<td>„Transition metal ion strikes back: large magnetic susceptibility anisotropy in cobalt (II) pseudo- and clathrochelates and those as prospective paramagnetic probes for biochemistry and molecular biology“</td>
</tr>
<tr>
<td>12:30-13:00</td>
<td>IL-33</td>
<td>Sylwia Rodziewicz-Motowidło, Gdańsk, Poland</td>
<td>„Is this love to Gdańsk peptides?“</td>
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<tr>
<td>13:00-15:00</td>
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<td>Lunch</td>
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<tr>
<td>Time</td>
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<tr>
<td>15:00-15:30</td>
<td>IL-34</td>
<td>Milena Salerno, Paris, France</td>
<td>&quot;Studies of cellular transport of inorganic complexes&quot;</td>
</tr>
<tr>
<td>15:30-16:00</td>
<td>IL-35</td>
<td>Paola Turano, Florence, Italy</td>
<td>&quot;Solution and solid state approaches to detect transient iron coordination sites in proteins&quot;</td>
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<tr>
<td>16:00-16:30</td>
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<td>Symposium Closing</td>
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<td>16:30-17:00</td>
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<td>Coffee break</td>
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<tr>
<td>20:00</td>
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<td>Banquet</td>
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INVITED LECTURES
When I saw Henryk in Zürich last year at EuroBIC-12 announcing the XIII International Symposium on Inorganic Biochemistry, I did not think that I would have the honor and privilege to present at this Symposium some personal impressions and reflections about Henryk and the series of his Symposia. I did not participate at the first of these meetings in June 1985; also in Karpacz -- only Helmut was there. However, I had the pleasure to be present at about half of these meetings, including no. XII, which took place in Wrocław at the end of August in 2013. All of these events were very enjoyable due to the hospitality and friendship provided by Henryk and his organizing crews.

Let us hope that there will be many more of these ISIBs forthcoming in the future and that we all are able to participate in them.
Acknowledgment: Supported by the Department of Chemistry of the University of Basel, Switzerland.
IL-2
Henryk Kozłowski and His Love for Bioinorganic Chemistry.
A Very Personal View Focusing on the Metal Ion-Binding Properties of Thio-Pyrimidine Derivatives

Helmut Sigel

Department of Chemistry, Inorganic Chemistry, University of Basel, Spitalstrasse 51, CH-4056 Basel, Switzerland (email: helmut.sigel@unibas.ch)

This lecture is devoted to Henryk with best wishes for all his future endeavors

When I was invited to lecture about Henryk's scientific achievements, I quickly discovered that I was facing an "impossible" task. Henryk is one of today's giants in Bioinorganic Chemistry: He published more than 500 research papers, contributed more than 15 chapters to books, and presented over 350 invited lectures -- his work is cited in the literature nearly 10'000 times [1].

One of Henryk's prominent topics is "Metals in Brain Diseases", about which he also lectured at a symposium held in honor of Osamu Yamauchi's 70th birthday in October 2006 (see pictures). On the same topic he contributed together with colleagues a
Chapter entitled "Metal Ion Binding Properties of Proteins Related to Neurodegeneration" to our series Metal Ions in Life Sciences [2]. However, the chapter entitled "Nickel Ion Complexes of Amino Acids and Peptides", which appeared in the same series [3], demonstrates that he also has a keen interest in the coordination chemistry of smaller bio-molecules. With this in mind I decided to focus in this lecture on two papers which are joint endeavors between the groups in Wroclaw and in Basel [4,5], and which were cited more than 20 times.

The first of these two papers [4] was drafted together with Henryk and Akira Odani (at that time at Nagoya University), during the mentioned Yamauchi Symposium. The two pictures shown above were taken during this Symposium and they are reproduced by courtesy of Osamu Yamauchi. Among the more than 50 participants of the Kansai Symposium, you will discover several faces of colleagues who are now also present at this Karpacz Symposium held in honor of Henryk at the occasion of his 70th birthday – time is fleeting ... there are nearly 10 years between the two Birthday Symposia.

Thio-pyrimidine derivatives occur in Nature (e.g., [6]) and the presence of a sulfur atom alters, e.g., the metal ion-binding properties of DNA [7]. Plots of \( \log K_{M(U)}^{M} \) versus \( pK_{U}^{M} \) for \( M^{2+} \) complexes of uridinate derivatives (U) allowed a quantitative evaluation of the effects that the exchange of a (C)O by a (C)S group has on the stability of the corresponding complexes [4]. For example, the stability of the Ni\(^{2+}\), Cu\(^{2+}\), and Cd\(^{2+}\) complexes of 2-thiouridinate (U2S) increases by about 1.6, 2.3, and 1.3 log units, respectively, by the indicated exchange of groups. Note, this
increase in complex stability occurs despite the decreasing basicity of the (N3)− site: $pK_{\text{Urd}}^H = 9.18$ and $pK_{\text{U2S}}^H = 8.05$ [4]. Similar results were obtained for other thiouridinates, including 4-thiouridinate [4].

Replacement of the (C2)O unit in cytidine (Cyd) by (C2)S facilitates the release of the proton from (N3)H+ in monoprotonated 2-thiocytidine (C2S) ($pK_a = 3.44$) somewhat, if compared with H(Cyd)+ ($pK_a = 4.24$) [5]. This moderate effect of about 0.8 pK units contrasts with the strong acidification of about 4 pK units of the (C4)NH2 group in C2S ($pK_a = 12.65$) compared with Cyd ($pK_a \approx 16.7$); the reason for this result is that the amino-thione tautomer, which dominates for the neutral C2S molecule, is transformed upon deprotonation into the imino-thioate form with the negative charge largely located on the sulfur. Upon metal ion binding, the deprotonation of the (C4)NH2 group in C2S ($pK_a = 12.65$) is dramatically acidified ($pK_a \approx 3$), confirming the very high stability of the monodeprotonated M(C2S−H)+ complexes [5]. To conclude, the hydrogen-bonding and metal ion-complex forming capabilities of C2S differ strongly from those of its parent Cd.

Acknowledgement: Supported by the Department of Chemistry of the University of Basel, Switzerland.

References:
Hydroxamates in bioinorganic modeling and applications: How Henryk introduced me into science

E. Gumienna-Kontecka

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When I have joined Henryk for my PhD studies I was given a very new topic in the group: studies of interactions of aluminium with low molecular weight compounds, i.e. hydroxamates and bisphosphonates. After many unsuccessful hours (days 😞) in the lab, following the advices of people not at all experienced with this metal ion, Henryk decided to facilitate my life and show that experiments can (sometimes) go smoothly. First, I have started to work on Cu(II) complexes, and later on (not to give up aluminium) was sent for a short scientific mission to the lab of Prof. Guy Berthon in Toulouse ... And here I am – enjoying science!

During the lecture I will show where we are now with hydroxamates, which biological activity stems from complexing capacity towards various metal ions. Diversity of coordination modes of these functions with metals makes them very promising ligands in coordination and bioinorganic chemistry.

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

• studies of biomimetic analogues of siderophores as structural probes for microbial iron uptake processes - the research especially important at the time of increasing number of severe and often lethal infections caused by multiresistant bacterial and fungal strains [1];
• use of hydroxamate ligands for preparation of high nuclearity discrete coordination compounds, coordination polymers and metallacrowns [2-3].

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References:
Summer Inorganic Medicinal Chemistry School, Cagliari, Italy, September 2013.

Henryk – thank you for being not only “the super boss”
but, first of all, the friend of my family!
Happy Birthday!
I will never forget my first conversation with Henryk. I knocked on the door of his office, introduced myself and told him all about my life plans in one sentence, without taking a breath in between: ‘I would like to do my master thesis with you, and then my PhD thesis, and then I would like to do a postdoc somewhere in Europe and then come back and become a permanent member of your group. Can I do that, please?’ Right now, I wish the very young me had taken a picture of his facial expression. Back then, the very young me wished she could disappear 😊.

He agreed that I can start with my thesis. And I did. It felt like an uphill climb… How I wished someone knew what was wrong with my bismuth-peptide complexes! Henryk did not know either, but he knew exactly, in which direction to push me, so that I can find out. Beyond any doubt, that kind of ‘push’ is the best thing you can get from a scientific supervisor.

In this talk, I will show how far we went from that day in understanding metal homeostasis and transport in pathogens, basing on the coordination chemistry of their proteins. We explained why bismuth(III) is able to inhibit nickel accessory proteins from *Helicobacter pylori*, a human pathogen responsible for most stomach ulcers [1]. Those nickel homeostasis proteins deliver this element to urease and hydrogenase, which are crucial for the survival of the bacteria at low pH of the stomach. We provided insight into the basic bioinorganic chemistry of Bi(III)-peptide complexes and showed how unexpectedly stable Bi(III)-Cys-rich peptide complexes can be (several orders of magnitude more stable than the nickel ones).

We showed that polyHis sequences from such proteins are in fact not the ones that have most affinity towards metal ions [2] and we discovered the impact of glutamine residues on the stability of metal complexes and showed how much the hydrogen bonds which they form increase the stability of the species [3].

Right now, we are trying to explain the bioinorganic chemistry behind zincophores – polypeptides that scavenge Zn(II) from the host and deliver it to *C. albicans*, a common human fungal pathogen [4].

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**References:**


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Henryk, knocking on your door that day was one of the best decisions I took in life. It gave me an excellent supervisor, boss and a true friend. Happy birthday!
Cu(I) Bioinorganic chemistry of amyloidogenic proteins

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Amyloid $\beta$ (A$\beta$), alfa synuclein ($\alpha$S) and prion proteins (PrP) share the ability to selectively bind Cu$^{2+}$. During the last decade large efforts have been directed to fully characterize the copper(II) binding domains in A$\beta$, $\alpha$S and human PrP [1-5 and reference therein]. On the other hand, the corresponding Cu(I) sites have been less considered [2, 4-6 and reference therein]. Interestingly $\alpha$S and PrP contain [M(X)nM] motifs which are well known to act as Cu(I) binding sites [6, 7]. In this study the structural features of Cu(I) complexes with A$\beta$, $\alpha$S and human PrP are discussed.

\begin{center}
\includegraphics[width=0.5\textwidth]{amyloid_cu.png}
\end{center}

Acknowledgement: This study is supported by Programmi di Ricerca di Rilevante Interesse Nazionale (PRIN) (2010M2JARI_004).

References:
I was a young assistant when I met for the first time a young Henryk in the 70's.

Wroclaw, under the strong personality of Madame Jezowska-Trzebiatowska was an international renown centre for Inorganic Chemistry. In particular Conferences were frequently organized there, and Luigi Sacconi, who was a great friend of Madame, participated to them surrounded by his assistants and coworkers. I remember that I met Henryk for the first time in Karpacz, probably around 1975. From then Henryk has been for me a friend and a constant point of reference, in consideration also of the common interest toward Bioinorganic Chemistry which at that times was a really innovative branch of Inorganic Chemistry.

I have 3 papers in common with Henryk in the period 1979-1990, on Copper Thermolysin, Copper transferrin and Carboxypeptidase A.

Henryk was often in Florence and I too often visited him in Wroclaw. Some of my visits occurred during the 80's when Poland and its inhabitants had to suffer hard conditions and I still have vivid in my memory the long lines of people in front of empty shops. I want to underline this, because in spite of the everyday difficulties, Henryk was able to continue his scientific activity.

Those times fortunately belong to the past and now we are here, happy to give our tribute of friendship to him, which beside his valuable scientific contributions has to be strongly acknowledged for his constant action in organizing Workshops and Schools which helped to consolidate the Bioinorganic Community during these years.

Having Henryk mostly characterized the interaction of copper ions with polypeptides and proteins I also will report some results we obtained using laccases, well known multicopper proteins, for degrading xenobiotics.
Coordination Dynamics in the Biometallome:
Metal Ions on the Move

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This lecture is dedicated to Professor Henryk Kozlowski who had the patience to share his vast knowledge of bioinorganic chemistry with me[1,2], and, with his infective enthusiasm, influenced my choice of a most rewarding area of chemistry for future research.

In contrast to metallomes in the inanimate world (air, water, soil), the biometallome describes the speciation of metals in living systems. Metallomes gain functional significance in the biological context, and make it possible to develop a true understanding of the coordination environments of biometals. In contrast to bioinorganic chemistry, which focuses primarily on isolated molecules, a metallomics approach considers the boundary conditions imposed by all the essential and non-essential metals present simultaneously in a biological system. The control, transport, sensing, storage and re-distribution of metal ions requires coordination environments with dynamic properties for metal binding and release [3]. Among all the biometals, zinc is taking center stage in terms of its importance for cell function. The human zinc metalloproteome is estimated to contain about 3000 zinc proteins. At least 24 human membrane transporters and dozens of additional proteins control cellular zinc metabolism. Induced zinc(II) ion fluctuations target proteins that hitherto were not considered to interact with metal ions. The coordination chemistry of transporters, signalling zinc(II) ions and client proteins of zinc are beginning to define a new chapter in the book of bioinorganic chemistry.

Acknowledgement: I thank the Biotechnology and Biological Sciences Research Council UK (grant BB/K001442/1) for supporting our work.

References:
IL-8

Like the HK-variant, the structure and metal ion binding abilities of the $\gamma$-E$_c$-1 domain from a wheat MT remain unperturbed in view of a multitude of manipulations

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The metallothionein (MT) E$_c$-1 from common bread wheat was the first and is still the only plant MT with a known three-dimensional structure.[1,2] The smaller N-terminal domain of the two-domain protein was denoted $\gamma$-domain in continuation of the cluster nomenclature used for the mammalian MTs and hosts a Zn$_2$Cys$_6$ cluster in its native form (see figure). Accordingly, it represents the smallest metal-thiolate cluster feasible with divalent metal ions. Using this cluster as a model system we investigated the influence of structural manipulations on the metal ion binding abilities of this domain and also attempted to produce stable cluster forms with metal ions preferring a different coordination geometry than Zn(II).

Manipulations of the peptide ligand include

(i) head-to-tail backbone cyclization to increase/influence metal ion binding stability and selectivity by restricting the size and flexibility of binding sites,[3]

(ii) Cys-to-His mutations to increase selectivity for Zn(II) ions in a mixture with Cd(II) due to the higher thiophilicity of the latter, as well as

(iii) (partial) oxidation of Cys residues to investigate possible pathways and the fate of oxidized MTs that have been found to exist also in vivo.

Additionally, the coordination of a non-native metal ion was studied. For this Cu(I) was chosen as it is an essential, thiophilic metal ion found in certain MTs in vivo but prefers, in contrast to tetrahedral coordinated Zn(II) ions, trigonal-planar or linear coordination spheres.

Acknowledgement: Financial support by the Swiss National Science Foundation (EF) and the Department of Chemistry is gratefully acknowledged.

References:
Zinc is essential for normal brain function. Zinc is now accepted as a potent neuromodulator, affecting a variety of signalling pathways at the synapse that are critical to normal cognition. Recently, zinc deficiency, as occurring in ageing, has emerged as a potential mechanism underlying the cognitive changes that occur in both ageing and late-life neurodegenerative disorders [1]. Metallothionein-3 (Zn₇MT-3), a small intra- and extracellularly occurring metalloprotein, plays a crucial role in homeostasis of zinc and copper in the brain. While intracellular Zn₇MT-3 actively participates in zinc-dependent synaptic activity, extracellular Zn₇MT-3 plays a protective role in metal-linked neurodegenerative diseases [2]. Aberrant interactions of Cu(II) with amyloid-β (Aβ) in Alzheimer's disease (AD), prion protein (PrP) in Creutzfeldt-Jakob disease and α-synuclein (α-Syn) in Parkinson's disease (PD) potentiate their progression by participating in the aggregation process and the production of reactive oxygen species (ROS) [3]. In AD, Cu(II) and Zn(II) are involved in the disease progression. Whereas the copper-induced Aβ aggregation is related to the ROS production and neurotoxicity, the zinc-induced Aβ aggregation is considered to be neuroprotective. We found that the protective effect of extracellular Zn₇MT-3 from Aβ toxicity originate from a metal swap between Zn₇MT-3 and soluble and aggregated Aβ-Cu(II)[4]. In this process, Cu(II) is reduced by the protein thiolates forming Cu(I)₄Zn₄MT-3, in which an air stable Cu(I)₄-thiolate cluster and two disulfide bonds are present. To examine a potential protective effect of the protein in other metal-linked neurodegenerative pathologies, similar studies using α-Syn and the prion protein/peptides in complex with Cu(II) were conducted. The finding that Zn₇MT-3 in a similar reaction also removes Cu(II) from the binding sites in α-Syn and PrP [2] signifies a general protective role of the protein from Cu(II) toxicity in the brain.

References:
Hydrogels are proving to be an excellent class of materials for biomedical applications. The molecular self-assembly of designed β-hairpin peptides into fibrillar networks has emerged as a novel route to form responsive hydrogels. Herein, computational modeling techniques are used to investigate the relative arrangements of individual hairpins within the fibrils that constitute the gel. The talk will discuss the self-assembly of designed novel zinc-binding β-hairpin peptides. Zinc is an essential cofactor in many cell processes, promotes wound repair and has an anti-bacterial effect. Therefore, formation of zinc-binding peptides could be highly beneficial for tissue engineering and other biomedical applications. Our goal is to design novel zinc-binding peptides that form stable self-assembly fibrilar structures for the formation of new hydrogel materials. MAX1 is an amphiphilic β-hairpin peptide that undergoes triggered self-assembly to form a rigid hydrogel. To form self-assembled zinc-binding peptides, we mutated His and Cys residues along the MAX1 peptide in order to bind zinc. MD simulations have shown that mutations of His lead to stable structures, while Cys does not lead to stable structures. Our designed novel peptides may pave the way to the development of new hydrogels for tissue engineering, drug delivery, and other biomedical and biotechnological applications.

Acknowledgement: All simulations had been performed using the high-performance computational facilities of the Miller lab in the BGU HPC computational center. The support of the BGU HPC computational center staff is greatly acknowledged. This project has been funded by the Israel Binational Science Foundation Grant No. 2011128.

References:
COPPER (II) BINDING TO \( \alpha \)-SYNUCLEIN, THE MAIN PROTEIN INVOLVED IN PARKINSON’S DISEASE

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\( \alpha \)-Synuclein is implicated in the pathogenesis of severe neurodegenerative disorders known as synucleinopathies, including Parkinson’s disease and dementia with Lewy’s bodies. Together with \( \beta \)- and \( \gamma \)-synuclein, belongs to the synuclein protein family. Although \( \gamma \)S does not seem to be involved in neurodegenerative disorders, \( \beta \)S is considered as the \( \alpha \)S aggregation antagonist and it might play a preventing key role in the neurodegenerative cascade. Both \( \beta \)S and \( \alpha \)S are co-localized in the presynaptic nerve terminals and are considered as intrinsically disordered proteins in solution. The main difference between the two proteins is the presence in \( \alpha \)S of the NAC (non-amyloid component) region, which is responsible for aggregation, leading to the formation of parallel \( \beta \)-sheet-rich fibril structures. Metal ions, mainly copper, may contribute either to self-oligomerization of aS, as well as to the production of highly reactive oxygen species (ROS). Copper increases the aggregation ability and enhances the toxicity of \( \alpha \)S \textit{in vivo} and \textit{in vitro}, by favoring the formation of the toxic oligomeric forms. Most investigators agree with Cu\( ^{II} \) anchoring to the N-terminal region of \( \alpha \)S, but the acquired evidence of post-translational acetylation of the protein has raised renewed interest on the Cu\( ^{II} \) site localized around His50. In the work presented here we summarize all the data on this topics.

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Metal binding properties of peptides of histidine: complex formation by prion protein and amyloid-β.

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Imidazole-N donors of histidyl residues are the most common metal binding sites of peptides and proteins involved in various forms of neurodegenerative disorders. The coordination chemistry of peptides of histidine has already been satisfactorily clarified and the results reveal a high versatility depending on the nature of the metal ions and the number of histidyl residues [1]. Peptide fragments of human prion protein and amyloid-β are rich in histidyl residues and serve as appropriate models to demonstrate the similarities and differences in the complex formation processes of multihistidinepeptides [2,3].

In the case of prion protein, histidyl side chains and neighboring amide nitrogens are the primary metal binding sites and the peptide fragments have an outstanding affinity for the complex formation with copper(II) ions. The copper(II)-prion interaction is very much pH-dependent but the imidazole-N donors are almost exclusive metal binding sites in the physiological pH range providing a chance for the existence of a series of coordination isomers.

For amyloid-β the presence of terminal amino group and high number of polar side chains (Asp, Glu and Ser residues) results in a much higher versatility in complex formation as it was reported for prions. Binding of copper(II) is preferred in this case, too but the corresponding zinc(II) complexes also have an outstanding thermodynamic stability. Moreover, it was also demonstrated that the presence of copper(II) or zinc(II) ions can promote the oligomerization of amyloid peptides.

References:
In contrast to most proteins, peptides can bind some metal ions, including Cu(II), Ni(II) and Pd(II) via amide nitrogen donors. We discovered that these metal ions can hydrolyze peptide bonds in the middle of the peptide/protein chain, two residues upstream of a His or a Cys residue, if this position is occupied by a Ser or Thr. In contrast to all other metal-dependent peptide bond hydrolysis reactions, the novel mechanism of our reaction does not depend on Lewis acid properties of the metal ion. Instead, the metal ion acts primarily structurally, by enforcing the complex geometry that enables the N-O acyl-shift of the peptide carbonyl to the side chain hydroxyl group[1].

We used this reaction for affinity tag removal in a novel protocol of purification of recombinant proteins, yielding particularly pure products [2]. We also indicated a range of human proteins which can be targeted by this reaction, including zinc fingers, annexins, filaggrin, antitrypsin and many others [3].

In our current studies we exploit the three-dimensional pathway of the hydrolysis reaction and apply it to semisynthetic reaction systems in a peptidomimetic context. We also study properties of products of this reaction and their naturally occurring analogues with respect to human physiology and disease [4].

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References:


With my best wishes and dedication to Henryk who brought me to the field and equipped me with the right approach to research and study management, the way I try to keep going.

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Metal-histidine interactions: a “fil-rouge” connecting Ferrara and Wrocław Universities

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The imidazole ring of histidine (His) is one of the most important metal-binding sites of peptides and proteins. Due to its intermediate pKₐ value (≈ 6.5) the imidazole nitrogen is only partially deprotonated at physiological pH and thus it is readily available to bind metal ions. In addition, the tautomeric protonation equilibrium between the two nitrogen atoms of imidazole aromatic ring gives His an additional degree of flexibility towards metal-complex geometry and increases its capability of behaving as the first anchoring-site for metal complexation. In short peptides, this anchoring capability is in competition with the terminal amine group, if not protected.

The position of His in a peptide strongly affects the complex stability and geometry. For instance, when His is the third residue of a non-protected peptide (or protein), the so-called ATCUN (Amino Terminal Cu(II) and Ni(II)) binding motif is realized, constituting a very strong metal-binding sequence which is typical of serum albumin and many natural peptides. Moreover, depending on both the His position and the nature of the neighboring residues, after the metal anchoring at His, some other groups normally take part to complexation which can progress towards either the N- or C-terminus, depending on the strength of the new interactions. In particular, Cu(II) and Ni(II) ions can displace one or more protons from the amide nitrogens of the peptidic backbone thus forming new five- or six-membered chelate rings which highly stabilize the complex.

Finally, it is worth to notice that in many proteins multiple His domains are present and highly conserved. The biological reason of this is not fully clear yet, but certainly these His domains impart to the protein extraordinary metal-binding capabilities, which are also exploited for protein purification by means of the Immobilized-Metal Affinity Chromatography (IMAC) technique.

The investigation on thermodynamic metal-binding properties of His-containing peptides has been the main topic of a very fruitful collaboration between our group at the University of Ferrara and the Bioinorganic and Biomedical Chemistry group, headed by Prof. Henryk Kozłowski at the University of Wrocław. The main achievements of this almost 20 year of cooperation will be described.
From strong to weak exchange between metal partners.
Magnetic, EPR and DFT studies

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1. Introduction on the occasion of Happy Anniversary
2. Isotropic and anisotropic magnetic exchange--theoretical and experimental basis.
3. An overview of the magnetic and EPR properties of different binuclear metal complexes based on our recent studies:
   3.1. It was shown that two metal M ions are held in close proximity by single M-X-M bridges in the binuclear metallocycles with ligands L composed of two bis(3,5-R-pyrazolyl)methane units linked by a m-substituted aren spacer, with R=H or CH$_3$ for L=L$_m$ or L$_m^*$, respectively. A very strong antiferromagnetic exchange between M ions increased along two series (a) with different linear bridges X=F$^-$<Cl$^-$<Br$^-$ when M=Cu$^{II}$, L=L$_m^*$ (although anisotropic magnetic coupling increased moderately);
      (b) with different metals: M=Mn$^{II}$<Fe$^{II}$<Co$^{II}$<Ni$^{II}$<Cu$^{II}$ when X=F$^-$, L=L$_m^*$.
In contrast, the antiferromagnetic exchange decreased due to the bending of Cu-X-Cu bridge when L$_m^*$ was replaced by L$_m$ for X=OH and also, regardless on the ligand L, for X=CN$^-$ as diatomic bridge[1-4].
   3.2. Both, isotropic (antiferromagnetic) and anisotropic (Zero Field Splitting) interactions appeared to be significantly reduced owing to the change of COO$^-$ group bridging mode, from bidentate to monodentate, for binuclear Cu$^{II}$ complexes with the ligands containing the COO$^-$ groups differently linked to 1,8-naphthylimide[5].
   3.3. The characteristic transition of spin-spin coupling from antiferromagnetic to ferromagnetic was induced by decrease of Cu-OR-Cu bridge angle and deviation of the bridge from xy plane in µ-dialkoxodicopper(II) compounds with triethanolamine and monodentate benzoate derivatives [6].
   3.4. Examples where the EPR has proved to be the only method of providing unequivocal evidence for the formation of binuclear complexes will be presented.

References
Proton-Coupled Electron Transfer with [2Fe-2S] Clusters

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Protein-bound [2Fe–2S] sites are fundamental biological cofactors. Their dominant function is electron transfer, where the Fe/S core shuttles between the [Fe₂S₂]²⁺ and [Fe₂S₂]⁺ states. While common ferredoxin-type Fe/S clusters are ligated by four cysteines, a subset of [2Fe–2S] cofactors contain alternative protein-bound ligands. Except for the Rieske center featuring heteroleptic {His₂Cys₂} ligation, the functions of these cofactors such as the {HisCys₃}-ligated mitoNEET cluster remain poorly understood. Non-cystein ligands are assumed to play a role in controlling the redox properties of the Fe/S clusters, and to couple proton and electron transfer [1].

Building upon the first structural Rieske model [2], we now present functional model systems that also emulate the pH-dependent redox potentials and the proton-coupled electron transfer (PCET) as it has been proposed for some Rieske proteins [3]. Furthermore, the first high fidelity model for the mitoNEET cofactor will be reported [4]. Thermodynamic and kinetic information for the PCET events has been obtained, and structures of the [2Fe–2S] clusters in different oxidation and protonation states have been elucidated by X-ray diffraction.

Acknowledgement: This work has been performed in the framework of the International Research Training Group 1422 (see www.biometals.eu) funded by the DFG.

References:

Dedicated to, and with best personal wishes to, a great scientist in bioinorganic chemistry and a great friend: Henryk Kozlowski.
Bioinorganic photochemistry perspectives

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Bioinorganic photochemistry is a rapidly growing and evolving new interdisciplinary research area integrating inorganic photochemistry with biological, medical and environmental sciences (Fig.1)[1].

The role of light and inorganic species in natural systems and the possibility of their applications in artificial systems of biomedical, medical or environmental importance are in the center of bioinorganic photochemistry [1-3]. In the presentation future perspectives of bioinorganic photochemistry will be discussed and illustrated on selected examples [4-7].

References

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Background: Intravenous iron (IV-Fe) is commonly administered in patients with acute decompensated heart failure. [1,2] IV-Fe may decrease chemotaxis, phagocytosis, and intracellular killing ability of polymorphonuclear cells limiting the ability to control infection. One meta-analysis [1] reported an increased rate of infections with IV-Fe.

Methods: We conducted a retrospective, single-center study in adult (≥18 years old) patients with a primary diagnosis of acute decompensated heart failure, admitted from 1/2010 - 8/31/14, who had a low hemoglobin (Hgb) and iron deficiency (TSAT < 20%). All patients who received therapy with IV-Fe patients identified from all IV-Fe medication orders. Control patients identified from all heart failure admissions. We used a mixed-models analysis controlling for baseline Hgb to assess change in Hgb over time in patients receiving IV iron compared to those not receiving iron therapy, and a Cox proportional hazard model to assess time to assess rates of infection.

Results: Although patients who received IV-Fe were similar in age, race, gender, and co-morbidities, they experienced significantly increased hospital lengths of stay. There were no differences in rates of hospital readmission.

References
Inducing Broad–Range Activity to Ferrichrome Mimics: New Hopes for Siderophore Based Therapeutics

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Ferrichrome is a prototype of cyclic hydroxamate siderophores. Like most siderophores, ferrichrome exhibits broad-range activity and can be recognized by various microorganism. Synthetic mimics to ferrichrome show high specificity toward \textit{P. putida} but no activity toward \textit{E. coli}.

While species-specific siderophore offer the potential to develop selective diagnostic tools, siderophore mimics possessing broad-range activity may have therapeutic advantages, as siderophores have no mammalian targets. However, the limited number of species-specific mimics in general, the lack of mimics to \textit{E. coli} in particular, and the lack of mimics exhibiting broad-range activity remained major challenges.

To overcome these challenges, we decided to capitalize on the extensive H-bonding networks observed in the detailed x-ray structure of FhuA transporter (of \textit{E. coli}) with ferrichrome. The strategy relays on preserving or enhancing the H-bonding network observed. Analogs possessing broad-range activity were obtained by a ‘reductive’ process carried out at the refining stage. The methodology includes: (i) side chain removal (ii) templates are replaced by complementary templates and (iii) spacers between ‘essential’ building-blocks are systematically shortened. The newly obtained ‘optimized’ mimics will be described and discussed.

The most successful analogs equipped with fluorescent probe, at the carbon apical site, allowed visual tracing of iron-free siderophore (fluorescent) accumulation in the periplasmic space in both \textit{P. putida} and \textit{E. coli}. Thus, reviling possible new bacterial targets for siderophore-drug conjugates. In contrast, uptake by the fungus \textit{Ustilago maydis} by the ferrichrome mimic, show siderophore internalization in the cytosol.
IMMOBILIZATION OF SILVER ONTO LACTOFERRIN IN LIGHT OF NEW ANTIMICROBIAL APPLICATION

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Lactoferrin (lactotransferrin, LTF) is the protein of whey and the most useful building block for the synthesis of hemoglobin, plasma proteins and stimulate the proliferation lymphocytes, phagocytic activities of macrophages. Lactoferrin biocolloids have naturally tendency of metal binding, to form.

Silver cations are involved in many centers of active enzymes localized e.g. in nucleolus. Therefore, they are used in many staining methods. However, the major problem is toxicity of free silver cations. They may cause degradation of neurons, glia and all cells. On the other hand, silver nanocomplex are widely used as antimicrobial, antiviral agents. Therefore, there is a need to binding the silver cations with bioactive ligands, to eliminate its toxic properties for human cells and increased antimicrobial properties.

Methods
Spectrometric measurements of lactoferrin, its isoelectric point and electrophoretic analysis was applied for protein characterization. Nanocomplex was obtained by binding of silver cations to lactoferrin. The infrared spectroscopic, chromatographic study combined with spectrometric analysis were confirmed sorption process. Physicochemical description of immobilization silver to lactoferrin and was carried out such as a crucial point in its comprehension and potential applications in the field of medicine. The application studies were carried out using flow cytometry and antibiograms tests against clinical bacteria.

Results and Discussion
The isoelectric point (pI) and mass of lactoferrin amounts 6 ± 0,5 and 80 000 ± 10 Da, respectively. Concentration of silver in supernatant decreased with increasing incubation time. The kinetic curve was expressed by two different stages: the first one - initially rapid stage of silver adsorption, and the second stage with much slower silver immobilization approaching to equilibrium. The differences in retention time between LTF and Ag-LTF complex and differences in PMF spectra are proof of immobilization process. Moreover, the change in infrared spectra between LTF and Ag-LTF determine contribution of amino, carboxyl and imidazole group of aminoaced in binding process. The results obtained from flow cytometry showed the antimicrobial properties against MRSA, MSSA and S.aureus. Ag-LTF complex exhibited bacteriostatic and bactericide mechanisms with amoxicillin and metronidazole.
Novel Aspect
Ag-LTF can be used in the field of medicine and food industry as new alternative/additives to commercial available antibiotics.

Keywords
Lactoferrin, metallocomplex, nanoparticles, silver nanocomplex

Acknowledgement
This work was supported by the National Science Centre (NCN, Poland) Grant No. 2013/08/W/NZ8/00701 (Symfonia-1) and No. UMO-2013/11/N/ST4/01835 (Preludium) as well as from grant “Step in the future” (KWP V)
Representatives of the Natural Sciences tend to claim that all or at least most of their approaches to scientific questions are rational and planned, unlike in other fields of science. However, as a view into the history proves, a large number of important scientific discoveries in the Natural Sciences were the consequences of sheer luck, of faulty concepts, of wrongly carried out experiments, etc. In general, it was the careful observation of an unexpected finding and the subsequent correct interpretation that led to important advances and novel concepts.

The lecture will start with a short introduction in the topic and will summarize a number of selected, by now classical cases of scientific discoveries based solely on serendipity [1, 2]. In the second part the history of the serendipitous discovery of the antitumor agent Cisplatin [3] will be reviewed, and a brief update of the present state of the art will be provided. Without the accidental discovery of the biological effects of Cisplatin the speaker would probably never have become attracted to Bioinorganic Chemistry…

References:
IL-22

How H\(^+\) and Mg\(^{2+}\) shape and form complex RNA structures

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Large functional RNAs adopt complex three-dimensional shapes. While standard Watson-Crick base pairing accounts for most of the secondary and tertiary interactions, numerous other factors are equally decisive. For example, local non-canonical structures are only formed upon binding of M\(^{2+}\) ions, majorly Mg\(^{2+}\). Mg\(^{2+}\) ions are also crucially involved in catalysis of RNA, i.e. in ribozymes [1]. Thereby, often acid-base catalysis is observed, although the origin of the de/protonation is unknown: a basic problem is that the intrinsic pK\(_a\) values of all four nucleotides are far off from physiological pH.

Here we present several examples of larger RNAs that on the one hand are stabilized by Mg\(^{2+}\) [2-5], as well as two protonation events with pK\(_a\) values close to physiological pH within a RNA hairpin comprising the catalytic core of a larger self-splicing group II intron ribozyme [5]. H\(^+\) addition at adenine N1 leads to a stabilization of local structure by the formation of a protonated G(syn)-AH\(^{+}\)(anti) base pair. This base pair is located within the catalytic core of the ribozyme, presumably controlling the conformational change between two splicing steps of the whole ribozyme.

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References:
IL–23

Novel complexes of Ru(II) as fotocytotoxic agents

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We have been exploring the antitumoral potential and the DNA cleavage activity mediated by metal compounds. Copper(II) complexes containing an antibiotic molecule and a heterocyclic nitrogen compound as ligands cleave DNA molecule in mild conditions. It is worth notifying that a correlation between cytotoxic activity, DNA binding and cleavage was found. \cite{1-3}. \textbf{In this work, we describe nine novel complexes with Ru(II) of type \([\text{RuLL’}])\text{PF}_6\), in which \(L = \text{sulfamethizole (smz), sulfamethoxazole (smx), sulfasalazine (ssz), sulfamethoxypyridazine (smp) or 2-thiophenecarboxylic acid hydrazide (shyd)}\) and \(L’ = 2,2’\text{-bipyridine (bpy) or 1,10-phenanthroline (phen). Single-crystal X-ray analysis reveals that the compounds exhibit a distorted tetragonal geometry around \text{Ru(II), which is coordinated to smz, smx and smp via the sulfonamidic and the heterocyclic ring nitrogens; to ssz via the phenolic and carboxylic oxygens; and to shyd via the terminal nitrogen and the carbonyl oxygen. Two heterocyclic nitrogens of the \(\alpha\alpha\)-diimines complete the coordination sphere. The presence of the compounds in solution was confirmed by \textsuperscript{1}H NMR, ESI-MS and UV-Vis studies. All complexes are able to inhibit the growth of chronic myelogenous leukemia cells in a concentration-dependent manner, with an activity higher than that of free ligands. UV-light exposure for 5 min increases the cytotoxic activities by around 10 times, which make the compounds good candidates for photodynamic therapy. When excited at the MLCT band, the complexes emit a fluorescence signal nearly 600 nm, which is used to study their intracellular location.}

\textbf{Acknowledgements:} CNPq, FAPEMIG, CAPES, and INCT-catálise.

\textbf{References:}

Thank you Henryk for your support and for participating in my thesis defense committee. Paris 1994.
IL-24

“Forever young”: the nice story of Metallacrowns from the perspective of a solution chemist

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Metallacrowns (MCs) are the inorganic analogs of organic crown ethers, and their development, since their discovery back in the late 80s, is a story of success. By virtue of the confinement of a large number of metal ions in a limited molecular constructs, MCs show peculiar properties including recognition of anions and cations, excellent luminescence in the near infra-red and single-molecule magnets behavior.

Back in 2000 we started a deep investigation of the thermodynamics of self-assembly of MCs in solution.\cite{1} Inspired by the pioneering work of Kozlowski and coworkers, we have been able to clarify the relationship between the behavior of MCs in solution and in the solid state. With these results in our hands we have now sound structural and thermodynamics foundations for the design of new functional MC-based materials. Recently, our research group also focused on the preparation of porous materials and MOF-like large assemblies with MCs as the nodes.

This contribution will present the most recent advances in the development of MCs carried out in our laboratories. Many of the studies on MCs are now performed within the framework of the European Marie Curie project “Metallacrowns”.\cite{2}

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

References:
\cite{2} Metallacrowns project website: https://sites.google.com/site/metallacrowns/project
Metallacrowns were among the first metallamacrocyclic complexes. Complexes ranging from 9-MC-3 to much larger and more complex are now known. This presentation will focus on synthetic methodologies to prepare a variety of metallacrown structures that can be used to understand molecular magnetism, molecular recognition and optical imaging of biological materials. Emphasis will be placed on metallacrowns containing Zn(II) and Ga(III) as the ring metal and Ln(III) ions as the encapsulated structure. One example of such a compound is that shown in the Figure, which is a combination of two Zn12MC4 and one Zn24MC8 motifs. Clearly, this structure is sufficiently large so as to encapsulate the trans actinide element Kz(70+), better known as the Kozlowskium +70 cation.

Acknowledgement: “The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007–2013) under grant agreement number 611488. NSF division of chemistry.
Near-Infrared Emitting Lanthanine-Containing Metallacrowns as Novel Imaging Agents for Cellular Biological Imaging


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A large number of advanced detection techniques and methodologies require the unique spectroscopic properties of lanthanide(III) ions. In particular, their ability to generate characteristic sharp emission bands in the near-infrared (NIR) range has a growing interest in view of the exponentially increasing number of applications in bioanalysis and optical imaging.[1] Near-Infrared (NIR) optical imaging has great research and clinical potentials to significantly improve diagnosis in real time imaging experiments.[2] NIR photons can cross deeply tissues for non-invasive investigations and allow for improved detection sensitivity due to the absence of native NIR luminescence from tissues and cells. The main requirement to generate lanthanide(III) emission is to sensitize them with a chromophore. As of today, the main limitation lies in the low number of photons emitted by the existing lanthanide(III) complexes and nanomaterials. We have recently demonstrated that Zn$_{16}$Ln metallacrowns (MCs) obtained by the self-assembly of Ln(III), Zn(II) ions and the chromophoric quinaldichydroxamic acid (quinHA) ligand, is an innovative approach allowing the precise localization of lanthanides at a predetermined and shielded position to achieve high quantum yields and long luminescence lifetimes.[3] In addition, such MCs possess very good photostability. Here, we expand this strategy to Zn$_{16}$Ln MCs assembled from derivatives of pyrazinehydroxamic acid with the goal to improve biocompatibility and further shift excitation wavelength towards the visible/NIR range. Examples of applications of these MCs in optical microscopy experiments in cells will also be presented.

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References:
Highly symmetrical LnZn$_{16}$ metallacrown complexes: experiment, theory and single molecule magnet behavior

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The LnZn16 complexes are highly symmetric species that are formed by the assembly of two 12-MC$_2$Zn$_2$N(pic)$_4$ metallacrown units (pic = picolyhydroximate$^2^-$) around a central Ln$^{III}$ ion in an eclipsed manner. A second 24-MC$_2$Zn$_2$N(pic)$_8$ metallacrown assembles between these two 12-MC-4 units leading to a highly symmetrical complex with a quasi $D_{4d}$ local symmetry as depicted in Figure 1.[1]

Figure 1. View along the C$_4$ axis of the LnZn$_{16}$ complex, part of pic is removed for clarity (left) and magnetization hysteresis at $T = 0.03$ K for different magnetic field sweep rates.

The magnetic studies show that the Er$^{III}$ complex behaves as a single molecule magnet with a hysteresis opening at zero field at low temperature (Fig. 1), while the Dy$^{III}$ derivative is a simple paramagnet down to 30 mK. ab initio calculations show that the $M_J$ ground levels are equal to $\pm 13/2$ and $\pm 1/2$ corresponding to the presence of an easy and hard axis of the magnetization for the Er$^{III}$ and the Dy$^{III}$ complexes, respectively. This is consistent with the magnetic behavior correlated to the compressed antiprismatic geometry around the Ln$^{III}$ ions as expected from the quadruple approximation within the framework of the crystal field theory.[2] The crystal field parameters $B_2^0$ and $B_4^0$ extracted from the calculations can be transferred along the series from Gd to Er. This simple, highly symmetric system provides general insight for designing single molecule magnets that exploit the optimal geometric orientation of ligands around Ln$^{III}$ ions.

References:
IL-28

Co-ordination Polymers and Metal-organic Frameworks
Based on Hydroxamates

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Hydroxamic acids attract considerable attention in the field of bioinorganic chemistry, molecular magnetochemistry and supramolecular chemistry. Despite the fact that hydroxamic acids have been extensively studied their potential as bridging and polynucleative ligands started to be utilized only within past 15-20 years. A series of principally novel structures of hydroxamate complexes have been reported during the past decades which demonstrated marked tendency of hydroxamates to bridging of two, three or even four metal ions. This can result in formation of discrete high nuclearity complexes (e.g., metallacrowns) or coordination polymers. The latter can possess original magnetic, catalytic properties, in the case of porous structures – selective sorption of different substrates, etc., as well as combination of several useful properties. Building block approach is one of the most used methods for obtaining such assemblies. Metallacrowns appear to be promising building blocks for construction of co-ordination polymers and MOFs, and a series of such assemblies has been reported recently.

Here we present a series of coordination polymers of different dimensionality based on various functionalized hydroxamic acids: isomeric (\(o\)-, \(m\)- and \(p\)-) picolinehydroxamic acids \cite{1}, malonodi- and mono-hydroxamic acid, and amino hydroxamic acids. We have succeeded to isolate and structurally characterize compounds of various molecular topology, including networks incorporating 12-metallacrown-4 and 15-metallacrown-5 units as building blocks \cite{2}, 2D-coordination polymers formed by \(m\)- and \(p\)-picolinehydroxamic acids \cite{1}, as well as a series of linear coordination polymers in which hydroxamic acids act in a chelating-and-bridging mode. The obtained compounds were characterized by elemental analysis, X-ray single crystal analysis, IR, UV-Vis, ESI-MS. Synthetic and structural aspects as well as magnetic and sorption properties of the reported compounds will be discussed.

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

References:
Besides being essential for life, many metal ions have also physico-chemical properties that make them useful, both as natural or artificial probes, for a variety of NMR-based investigation tools.

I will summarize the use of paramagnetic metal ions as:

- structural probes, from the early applications to the most recent developments;
- powerful refinement tools for X-ray-derived three-dimensional structures;
- unique probes to assess dynamics and conformational freedom of biomolecules in solution;
- contrast agents to be embedded in new-generation nanoparticles;
- bioNMR sensitivity enhancers through dynamic nuclear polarization.
Parallel interactions of dendrimers and metal ion chelators on the oligomerisation of β-amyliods – a potential use in the therapy of Alzheimer’s disease

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According to the amyloid cascade hypothesis, amyloid peptide aggregation is related to the onset and development of Alzheimer’s disease (AD). The first steps of β-amyloid oligomerisation is assumed to be promoted by metal ions such as Cu(II), Fe3+, and Zn2+. Various chelator molecules which can bind these metal ions stronger than amyloids will hinder amyloidogenesis and thus prevent development of AD. Similarly, various organic molecules among others glycodendrimers can also behave as anti-amyloidogenic agents.

In this work we studied the parallel effects of two different maltose (Mal) modified poly(propyleneimine)(PPI) type dendrimers [1] and various efficient metal ion chelators [2,3] on the oligomerisation of β-amyloids.

The dendrimers efficiently blocked amyloid fibril formation alone and both in the absence and the presence of pyridyl-type-chelators [2] if Cu(II) ion was added to the system in equimolar amount of the chelator. The larger generation (PPI-G5-Mal) dendrimer was more efficient than the lower generation (PPI-G4-Mal) dendrimer. It was interesting to observe that the chelator and the dendrimer together seemed to show more efficient anti-amyloidogenic effect than added separately. The observed effect is probably due to some quaternary interactions between the metal ion, the chelator, the dendrimer and the amyloid. Deeper EPR and fluorimetric studies, however, did not prove any synergism between the individual components.

Acknowledgement: Financial support by the TAMOP 4.2.2.4 A “Dementia, neurodegenerative diseases: early recognition, new therapies” EU project and the OTKA 77833 is gratefully acknowledged.

References
Copper coordination compounds with modified small biomolecules

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Many metal ions due to their specific binding with biologically important molecules have a direct impact on the normal or abnormal functioning of living organisms. The unique properties of metal complexes, such as spectroscopic, electrophilic, redox activity, acidity, formation of different chemical forms from the cationic to radical, offer interesting possibilities for the future development of metallopharmaceuticals. Therefore, it is reasonable to conduct research to clarify the coordination of metal ions with selected molecules. It is worth noting that even a small modification in the structure of the molecule can cause a drastic change in its physicochemical and biological properties, including the manner and effectiveness of its coordination with metal ions.

Group of compounds, arousing the interest of scientists are synthetic analogs of natural flavonoids. The object of intensive research in recent years become Schiff bases of some flavones \cite{1-3}. The objects of this study have been synthetic derivative of hesperetin (HHSB) (hydrazone hesperetin Schiff base N-[(±)-5,7-dihydroxy-2-(3-hydroxy-4-methoxy-phenyl)chroman-4-ylidene] amino]benzamide) and its copper(II) chelate. Stoichiometric characterization of the complexes formed, the pH extent of their occurrence and the coordination donor atoms set around Cu(II) ions have been obtained by using various methods: potentiometric titration, UV-Vis, EPR, NMR, ESI-MS and CD spectroscopy. An attempt to elucidate the mechanism of interaction of these compounds with CT-DNA and plasmid DNA has been made. The promising results for HHSB and its copper complex CuHHSB have prompted us to examine the cytotoxic properties of these systems to selected cancer cell lines (HeLa and K562) and HUVEC (human umbilical vein endothelial cells) as classical model system. Furthermore, antibacterial activities of HHSB and CuHHSB have been specified against three strains of Gram-negative bacteria of the family \textit{Enteriobacteriaceae}: \textit{Salmonella enteritidis} ATCC 13076, \textit{Salmonella typhimurium} ATCC 14028, \textit{E. coli} ATCC 8739 and two strains of Gram-positive \textit{S. aureus} ATCC 25923, \textit{L. monocytogenes} ATCC 19111.

References:

Photographs of Henryk
A Speciation Study on the Perturbing Effects of Iron Chelators on the Homeostasis of Essential Metal Ions

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A number of reports have appeared in literature calling attention to the depletion of essential metal ions during iron chelation therapy on $\beta$-thalassaemia patients.

We will present a speciation study to determine how the iron chelators used in therapy \cite{1} interfere with the homeostatic equilibria of essential metal ions. Our work will include a thorough analysis of the pharmacokinetic properties of the chelating agents currently in clinical use, of the amounts of iron, copper and zinc available in plasma for chelation, and of all the implied complex formation constants.

The results of our study show that a significant amount of essential metal ions is complexed whenever the chelating agent concentration exceeds the amount necessary to coordinate all disposable iron— a frequently occurring situation during chelation therapy. On the contrary, copper and zinc do not interfere with iron chelation, except for a possible influence of copper on iron speciation during deferiprone treatment \cite{2}.

\textbf{Acknowledgement:} GC was supported by the Regione Sardegna for the project "Integrated approach in the design of metal chelators for human diseases", and VMN and MAZ for the project “CRP-26712”

\textbf{References:}
\begin{itemize}
\item [{\textsuperscript{1}}] G. Crisponi G, V.M. Nurchi, M.A. Zoroddu, Thalassaemia Rep., 4(s1), 13–18, (2014)
\end{itemize}
A very important theme in the career of Professor Kozłowski is his collaboration with scientists from the Faculty of Chemistry at the University of Gdańsk, dealing with the chemistry of peptides.

The cooperation is dated back to the 70s - the last century, when he inspired a group of professor Kupryszewski to start joint research on complexing ability ions Cu (II) by thyrotropin-releasing hormone. As the result two joint work were published in the highly prestigious world magazines: Inorganic and Nuclear Chemistry Letters and Inorganica Chimica Acta.

In subsequent years, a group of peptide Gdańsk Chemists together with the team of Professor Kozłowski examined the impact of Cu (II) and Ni (II) with melanocyte-inhibiting factor, opioid peptides: β-casomorphin, enkephalins and their derivatives, vasopressin analogues and model peptides.

For series of works in this field Gdańsk and Wrocław Chemists were honored with Award of the Minister of Education in 1988. In the last decade the subject of joint research by Professor Kozlowski with the Department of Medical Chemistry (headed by Prof. Z. Grzonka and since 2012 by Dr. S. Rodziewicz - Motowidło) and the Department of Bioorganic Chemistry (headed by Prof. K. Rolka) were fragments of human prion protein HPrP, responsible for the formation of Creutzfeldt-Jakob disease.

Their aim was to determine the role of copper ions in the formation of amyloid plaques. This work also focused on the determination of binding characteristics of these ions by beta-amylloid precursor protein.

Research led by Professor Kozłowski with the use of peptides received from Gdańsk Chemist group have led to a better understanding of the impact of metal ions on the properties and structure of proteins involved in neurodegenerative processes. This fruitful cooperation established a total of 45 joint original works published in international scientific journals of the JCR list. In 2015 Professor Kozłowski was titled by the University of Gdańsk as a doctor honoris causa.
Studies of cellular transport of inorganic complexes

Milena Salerno

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The development of new drugs or diagnosis molecules using inorganic complexes grows everyday (ex. Platinum complexes etc). A lot of them are devoted to reach intracellular targets or cross cells in order to reach their targets. However, most of these developments leave out the question of how these molecules reach their target inside the cell or how they cross them. In this talk I will present different cellular transport mechanisms and explain why the studies of these cellular transport parameters are important in the development of new drugs. Some examples will be cited.

References:
Solution and solid state approaches to detect transient iron coordination sites in proteins

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Iron is an essential element: virtually all living organisms require a minimum effective iron concentration of 10^{-8} M. The high toxicity of iron(II) associated to its redox activity and the extremely low solubility of iron(III) species present under aerobic conditions require that iron ions in living systems are sequestered in high affinity binding proteins. Extracellular iron is bonded to lactoferrin and transferrin, while intracellular iron (when not in functional iron sites) is stored in the nanocavity of ferritin as an iron-oxo biomineral. Studying proteins involved in iron uptake and storage requires the definition of the coordination properties that make them able to bind the metal ion with high affinity albeit allowing its release to downstream partners, in response to specific signals. Examples are provided of the use of combined solution and solid state NMR approaches and complementary x-ray crystallography to learn about heme acquisition systems and and iron storage ferritins. Each of them has required the development of ad hoc methodological approaches that take into account the dynamics and the size of the systems under investigation [1,2].

References:
The transition metal complexes with peptides having antimicrobial activity

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Peptide antibiotics are produced by bacterial, plant, insect or mammalian organism in defense against invasive microbial pathogens. Therefore, they are gaining importance as anti-infective agents. There is a number of antibiotics that require metal ions to function properly. Metal ions play a key role in their action and are involved in specific interactions of these antibiotics with proteins, nucleic acids and other biomolecules. On the other hand, it is well known that some peptide antibiotics possess functional groups that enable them to interact with metal ions present in physiological fluids. Some findings support hypothesis that they may alter serum metal ions concentration in human.

Complexes usually have a higher positive charge than uncomplexed compounds. This means that they might interact more tightly with polyanionic DNA and RNA molecules. It has been shown that several metal ion complexes with antibiotics promote degradation of DNA [1]. Some of them, such as bleomycin, form stable complexes with redox metal ions and split the RNA chain via the free radicals mechanism [2]. However, this is not a rule. For example, in contrast to the above complexes, blasticidin does not cause DNA damage. It indicates that this antibiotic can be considered as a ligand that effectively lowers the oxidative activity of Cu^{2+} ion [3].

Acknowledgment: The research was supported by Wroclaw Research Center EIT+ under the project “Biotechnologies and advanced medical technologies – BioMed” (POIG 01.01.02-02-003/08-00) financed from the European Regional Development Fund (Operational Programme Innovative Economy, 1.1.2).

References:
I met Henryk on the beginning of my "chemical life". He has always had a remarkable gift of persuasion.

It was Henryk who convinced me that working in the research area of bioinorganic chemistry can be exciting and compelling.

It was he who introduced me into this world.

Henryk, I wish you Happy Anniversary and many success in the future. Thank you for many years of fruitful cooperation.

Małgorzata
Interaction of cytotoxic ruthenium complexes with DNA and proteins

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Although cisplatin is currently holding its well-established position in the list of drugs used in cancer therapy the clinical use of cisplatin is severely limited by toxic side-effects. In the search for novel non-platinum metal anticancer drugs with improved properties, ruthenium compounds show extraordinary promise, especially because two Ru(III) coordination compounds, NAMI-A [HIm\textsuperscript{trans}[RuCl\textsubscript{4}(dmso)(Im)], Im = imidazole and KP1019 [HInd\textsuperscript{trans}[RuCl\textsubscript{4}(Ind)\textsubscript{2}], Ind = indazole, entered clinical trials. These two complexes display activities that are markedly different from that of cisplatin and the other previously established platinum anticancer chemotherapeutics.

The aim of this communication is to present knowledge on the structural properties of novel ruthenium coordination compounds with different triazolopyrimidines. Special attention is paid to correlation of structural parameters with \textit{in vitro} cytotoxicity and lipophilicity.

On the other hand, a full understanding of the mode of action of the metal-based antitumor drug requires the study of their interaction with possible biological targets, including DNA and proteins. Albumin is the most abundant plasma protein and it is reasonable to expect that any injected metal drug will present some kind interaction with this macromolecule, which could crucially determine its bioavailability. However, relatively few detailed mechanistic studies have been performed on such interaction, in comparison to studies with DNA. Therefore binding of our ruthenium complexes with DNA and proteins (albumin and apotransferrin) were studied by CD. Proteins are good binding partners for new ruthenium complexes with triazolopyrimidines, which can lead to the action of the anticancer effect.

Acknowledgements

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\textit{Special dedication to Professor Henryk Kozłowski with the best wishes of the authors for all his future endeavors and with a deep appreciation for his friendship shown over many years to I.L.}
Polyoxometalate-based systems as artificial antioxidant enzymes

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The tetraruthenium substituted polyoxometalate \([\text{Ru}_4\text{O}_4(\text{OH})_2(\text{H}_2\text{O})_4(\gamma-\text{SiW}_{10}\text{O}_{36})_2]^{10-}\) (RuPOM) is an inorganic and robust oxygenic synzyme.\(^1\) We have investigated its catalase (CAT) and superoxide dismutase (SOD) biomimetic activity in physiological environment, demonstrating the potential for Reactive Oxygen Species (ROS) scavenging and for reducing metal-induced oxidative stress, with high turnover number. Tests \textit{in vitro} have also been performed to assess its detoxifying activity as well as the reduced cytotoxicity. In addition, the RuPOM has been supported onto two different templates (core-shell polyelectrolyte multilayer microcapsules, PEMCs\(^2\) and tobacco mosaic virus, TMV\(^3\)), by using Layer-by-Layer (LbL) self-assembly procedures. Retention of CAT activity has been assessed for both systems, for which \(\text{H}_2\text{O}_2\) has also been used to trigger the autonomous movement of the scaffolds.

![Figure 1](image)

\textbf{Figure 1:} left: RuPOM structure and CAT/SOD–like activities; right: schematic representations of PEMC (with a dextran core and the RuPOM embedded into the shell layers), and of TMV as biogenic scaffold for RuPOM.

\textbf{References}

A novel copper(II) compound with $\mu_3$-bridging, O’,O’’-chelating and tetradsentate acyclovir

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Henryk, always remember how much you are appreciated by all of us!

Equimolar amounts (0.5 mmol) of CuSO$_4$·5H$_2$O, acyclovir (acv) and diethanolamine (dienol) in MeOH:DMF (40:15) yield a green solution. Solvent evaporation yields green crystals of $[[\text{Cu}_2(\text{acv})(\mu_3-\text{acv})(\text{SO}_4)(\mu_2-\text{SO}_4)(\text{H}_2\text{O})_4] \cdot \text{H}_2\text{O} \cdot \text{MeOH}]_n$, hence a dienol-free polymer which has been studied by single-crystal X-ray crystallography (100 K, final $R_1$ 0.046- see figure). At this moment the role of dienol in the construction of this 1D-coordination polymer (see figure) remain still unclear.

There are two non-equivalent Cu$^{II}$ centers (Cu1 and Cu2) with ~4+2 coordination. Cu1 center builds a trans-CuN$_2$O$_4$ chromophore whereas Cu2 atom falls in a CuO$_6$ chromophore. Also there are two non-equivalent acv and sulfate ligands. The monodentate acv-1 builds the Cu1-N27 bond (2.029 Å) that cooperates with an (aqua)O-H···O6(acv-1) intra-molecular interaction. The bridging acv-2 acts in a $\mu_3$-mode, which implies (a) a novel bridging-acv role between three metallic centers (one Cu1 and two Cu2) and (b) an unprecedented tetradsentate role for this acyclic nucleoside-analog! [1].
This highest tetradentate denticity for \( \mu_3\text{-acv} \) is fulfilled:

1. by the Cu1-N7 bond plus the (aqua)O1-H1B···O6 interligand interaction.
2. by the longest Cu2-O6#1 bond (2.362(5) Å, \#1 = x,y,z-1)
3. and the O,O’-bidentate chelation of the N9-side chain (Cu2-O11(ether) 2.489(6) Å and Cu2-O14(ol) 1.983(5) Å).

Polymeric chains run parallel to the \( c \) axis of the crystal and its stability is markedly reinforced by the \( \mu_2\text{-sulfate} \) with additional contributions of intra-chain (aqua)O-H···O(unidentate or bridging sulfate) interactions. The crystal has may other H-bonds and also a multi-\( \pi \pi \)-staking between the six-membered rings of guanine moieties of alternating acv-1 and -2. Also an anion/\( \pi \) interaction is observed.

In conclusion, this work opens a window towards the possibility to expand the coordination chemistry with rather stable synthetic purine-nucleosides, including BioMOFs analogues.

In occasion of the Alicia Domínguez-Martín Ph.D. Thesis (Granada, December 20\textsuperscript{th}, 2012), Henryk Kozlowski and Helmut Sigel, as foreign members of the Evaluation Committee, that was led by Alfonso Castiñeiras.

Acknowledgement: Financial support from UGR-FQM-283, USC, IACT (LEC) CSIC-UGR. ADM thanks for a Ramón Areces Foundation Posdoc position.

Reference:
Specific interaction of Cu\(^{2+}\) and Cu\(^{+}\) ions with the amyloidogenic human prion protein* fragments in presence of SDS surfactant

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Prion diseases are neurodegenerative disorders associated with a conformational change in the normal cellular isoform of the Prion Protein (PrP\(^C\)) to an abnormal scrapie isoform (PrP\(^Sc\)) [1]. The human prion protein (hPrP) is a membrane-anchored glycoprotein of unknown function [2], which consists of two distinct domains: unstructured N-terminus and the globular, mostly α-helical C-terminal domain [3]. hPrP is able to bind up to six Cu\(^{2+}\) ions. Four of them are allocated in the octarepeat domain containing four tandem-repetitions of the sequence PHGGGWGQ [4]. Immediately outside the octarepeat domain, in so called PrP amyloidogenic region, two additional and independent Cu\(^{2+}\) binding sites, encompassing His96 and His111 residues, respectively, are present [5].

Unstructured hydrophobic region of PrP may be critical for PrP\(^C\) misfolding mainly due to the role played by fragment comprising 106-126 residues in prion propagation. Interaction of Cu\(^{2+}\) with human prion protein (hPrP) fragments within the amyloidogenic domain has been thoroughly investigated: Cu\(^{2+}\) binds to two independent binding sites, anchored at His96 and His111, with preference to the latter one [6]. Potential involvement of PrP in cellular redox homeostasis rationalize the sophisticated characterization of Cu\(^{+}\) interaction with this amyloidogenic fragment. Interestingly this fragment contains a –M(X)\(_n\)M– motif, known to act as Cu\(^{+}\) binding site in different proteins [7]. In order to shed more light on this issue, Cu\(^{+}\) and Ag\(^{+}\) (used as Cu\(^{+}\) probe) interactions with model peptides derived from that region were analyzed.

Anionic surfactants are known of their high affinity to hydrophobic surfaces of proteins. Metal binding was also investigated in presence of negatively charged micelles formed by the anionic surfactant sodium dodecyl sulfate (SDS). Our results strongly support that metal binding mode strongly depends on the protein backbone structure. In particular we show that α-helix structuring of the amyloid PrP domain influences either the metal coordination sphere and the binding affinity [8].

Acknowledgement: This work was supported by the Italian MIUR, through the PRIN (Programmi di Ricerca di Rilevante Interesse Nazionale) project 2010M2JARJ_004 and by MNiSW (Ministerstwo Nauki i Szkolnictwa Wyższego) project 2429/M/WCH/14. The CIRMMP and CIRCMSB are also gratefully acknowledged.
References:

*What does hPrP stand for? We all believe that the hPrP abbreviation means Human Prion Protein but Stanley Prusiner was wrong! It is Henryk Prion Protein! And the best candidate to interaction with this molecule is discovered by Professor Pecoraro new metal ion named Kozlowskium (Kz^{70+}).

HAPPY BIRTHDAY PROFESSOR!
Metallacrowns (MCs) are a class of metallamacrocycles that are analogous to crown ethers in both structure and function. Since the first MC were reported in 1989 by Pecoraro and Lah, this class of macrocyclic compounds have been extensively studied [1]. The history of MCs in Professor Kozlowski’s group have been started at 1991 when for the first time β-alaninehydroxamate Cu(II) MC complex has been crystallized and evidenced in solution. Since this paper other hydroxamate ligands have been studied successfully by our group [2].

Our recent studies are inspired by pyridinehydroxamic acid forming the most stable Cu(II) 12-MC-4 [3] and are devoted to the stability of its analogues.

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

References:
Happy Birthday Professor!

13.06.2015, 13th International Symposium on Applied Bioinorganic Chemistry, Galway, Ireland.
Visible and Near-Infrared Emitting Ga$^{3+}$/Ln$^{3+}$ Metallacrown Complexes

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Luminescent lanthanide(III)-based molecular scaffolds hold great promises for bioanalytical applications and biological imaging as their fascinating photophysical properties enable spectral and time discrimination of emission bands ranging from visible to near-infrared (NIR) regions in addition to the strong resistance to photobleaching. [1] A major synthetic challenge to design lanthanide(III) luminescent compounds is to find a combination of a protective structure minimizing nonradiative deactivations and a universal chromophore with large absorbances able to sensitize the whole series of lanthanide(III) ions with high quantum efficiencies.

Herein, two series of mixed Ga$^{3+}$/Ln$^{3+}$ metallacrown complexes, [LnGa$_4$(shi$^3$)$_4$(H$_2$shi$^-$)$_2$(C$_6$H$_5$N)$_4$(NO$_3$)$_2$] (Ln-1) and [LnGa$_4$(shi$^3$)$_4$(C$_6$H$_5$CO$_2$)$_4$(C$_5$H$_5$N)(CH$_3$OH)]$_2$ (Ln-2) where H$_2$shi is the salicylhydroxamic acid, are reported. The organic scaffold is able to efficiently sensitize characteristic sharp transitions of visible- and NIR-emitting lanthanide(III) ions, Sm$^{3+}$, Eu$^{3+}$, Tb$^{3+}$, Dy$^{3+}$, Ho$^{3+}$, Er$^{3+}$, Tm$^{3+}$, and Yb$^{3+}$. A detailed comparison of photophysical properties of the two series of MCs revealed improved performances of Ln-2 with the highest reported quantum yields for Yb-2 and Er-2 in the solid state among complexes formed from the ligands containing C-H bonds. This work represents a major step forward to prepare highly luminescent Ga$^{3+}$/Ln$^{3+}$ complexes that are promising candidates for biological imaging and material science applications.

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References:

Linking metallacrowns: from porous solids to magnetic materials

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Metallacrowns (MCs) are a class of metallamacrocycles that possess an oxygen-rich coordinating framework analogous to that of crown ethers, able of including metal guests, from alkali metals to lanthanides.\textsuperscript{[1]} In the last decade a significant number of MCs has been shown to be endowed with luminescence or single molecule magnetism. Herein, we report novel coordination polymers established by linked MCs and we present a new magnetic metallacryptate composed of merged MCs. Properties such as porosity and magnetism are analyzed. Furthermore, we present \textsuperscript{1}H-NMR studies on a class of single molecule magnets MCs, apt to describing the paramagnetic behavior of the Ln(III) ion hosted within their cavity. In the future, we aim at linking magnetic MC units into coordination polymers, which could lead to the obtainment of porous magnetic materials.

Figure: Schematic representation of a porous coordination MC polymer and its isothermal N\textsubscript{2} absorption curve at 77.4 K.

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References:
Alzheimer’s disease (AD) is the most common cause of age-related senile dementia, with no cure so far, and so a major health concern to societies worldwide. AD is clinically characterized by severe memory impairment due to progressive degradation of the cholinergic system. The etiology of AD is not completely known but there are diverse factors, such as amyloid-β (Aβ) deposits, oxidative stress and decreased levels of acetylcholine, which play significant roles in the pathophysiology of the disease. The current approved drugs only treat disease symptoms, namely enhancing the cholinergic neurotransmission, as acetylcholinesterase (AChE) inhibitors. Due to the complex pathophysiology of AD, there has been a growing interest on multitarget drug developing strategies to include some of these targets in one molecule.[1]

Thus, new drugs have been recently developed by different groups, including ours, conjugating the AChE inhibition with Aβ antiaggregation and neuroprotection activity against ROS species. Since cerebral biometal (Fe, Cu, Zn) dyshomeostasis and oxidative stress are associated with protein misaggregation, metal chelation can also attenuate a broad spectrum of oxidative stress as well as Aβ production/aggregation.[2-3]

In this communication we report a few recent developments of our group on a family of multitarget compounds, based on conjugating a tacrine moiety, as AChE inhibitor, with other functional molecular moieties with important biological activity, such as antioxidant, metal chelator and Aβ antiaggregation. For design of the compounds, besides the selection of the main bioactive moieties, the size and type of the linker is also determinant to enable the coadjuvatin/enhancement of the functional group activities. Herein, a major focus will be made on the results of solution studies (metal complexation and anti-oxidant activity), although interaction with proteins (AChE inhibition and Aβ antiaggregation) and cells (neuroprotection/rescuing of stressed neuroblastome cells) will be also discussed, aimed at structure-activity relationships.

References:
Electrochemical and spectroscopic investigations of selected aminomethylenebisphosphonic acids towards Pb(II) ions

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Aminomethylenebisphosphonates are the class of compounds that can easily bind many metal ions. There are many papers presented their coordinating abilities towards Ca(II), Mg(II), Zn(II) or Cu(II) ions. The aim of this work was to examine some aminomethylenebisphosphonates with N-substituted heteroalkyl moieties (L\textsubscript{1-3}) and their N-pyridyl (L\textsubscript{4}) and piperazine derivatives (L\textsubscript{5}) according to their abilities to bind Pb(II) ions. Aminomethylenebisphosphonates can bind Pb(II) ions over the broad range of pH and its the reason why they can be the good candidates for heavy metal detoxificants.

Four analytical methods (potentiometry, pulse polarography (DPP), NMR and ESI-MS) were used to determine the stability constants and coordination mode of the selected compounds. These studies showed that L\textsubscript{1}, L\textsubscript{2} and L\textsubscript{3} have the similar coordinating abilities towards Pb(II) ions. They start to bind metal ions at pH below 2 with the strong tendency to form polynuclear species till pH about 6.5. Over pH 7 only equimolar species are present in the solution. L\textsubscript{4} behaves in the different way. It doesn’t form any polynuclear species in the whole range of pH. Only equimolar and bis-complexes are present. L\textsubscript{5} forms polynuclear species in pH about 3. In the pH range between 5-11 only equimolar complexes can be found.

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Transition metal complexes are rarely considered as paramagnetic probes for spectroscopy due to them generally having relatively low magnetic anisotropy. We synthesized cobalt(II) pseudo- and clathrochelates (Scheme) with the largest (among the transition metal complexes) axial anisotropy of magnetic susceptibility [1–3]. This remarkable anisotropy, which results from an unusual trigonal prismatic geometry of the complexes and translates into large negative value of the zero-field splitting energy, is high enough to promote reliable paramagnetic pseudocontact shifts at the distance beyond 2 nm. Our finding paves the way towards the applications of such complex as future paramagnetic probes.

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References:
POSTERS
In honor of Professor Henryk Kozłowski on the occasion of his birthday with best wishes

Extensive structural studies on the lead(II) coordination chemistry give some evidence why Pb(II) as a central ion in complexes displays many different geometries. The obtained data mainly pointed on: (i) the effect of inert electron-pair, (ii) the broad range of coordination number (CN from 2 to 12), (iii) the kind of donating ligands and their flexibility. In view of the aforementioned, we have successfully synthesized Pb(II) coordination dimmer, \([\text{Pb}_2\text{L}_6(\text{NO}_3)_2]\) (\(\text{NO}_3\)) \(_2\) (1) and two polymers: \([\text{Pb(L}^1)_2(\text{H}_2\text{O})]_n\) (2); \([\text{Pb(L}^2)_2]_n\) (where \(L=4(5)\)-carbaldehyde-4(5)methylimidazole; \(L^1=\text{pyrazine-2-carboxylicacid}, L^2=\text{tiophene-2-carboxylicacid}\)).

All complexes have been characterized by X-ray single crystal structure analysis, FTIR, TG, DTG and PL. Reported complexes exhibit the photoluminescence properties at room temperature in solid state (metal-to-ligand charge transfer transition). Additionally, a possible stereochemical activity of the lone pair in the complexes has been discussed. The DFT calculations and the X-ray data point on rather hemidirected type of coordination around Pb(II) ions.

Fig.1. The coordination polyhedra around Pb\(^{2+}\) ion in the obtained complexes.
New arene-ruthenium(II) complexes as potential cytotoxic agents

A. Pastuszko, B. Kupcewicz, K. Majchrzak, M. Czyż, E. Budzisz

A new family of half-sandwich arene ruthenium(II) complexes with the general formula [(n⁶-arene)RuLX₂] were synthesized and carefully investigated. The lipophilicity and cytotoxic activity against melanoma cell lines has been analyzed. The aim of this work was to examine the influence of structural modifications on the cytotoxic activity of complexes. We used five neutral ligands (L): aminoflavone (1 and 2), aminochromone (3 and 4) or aminobenzofuranone (5) derivatives and four arene ruthenium(II) dimers with different aromatic substituents p-cymene (series a and b), benzene (c), hexamethylbenzene (d) or mesitylene (e); (X=Cl or I).

The complexes were fully characterized by elemental analysis, UV-Vis, IR, NMR and mass spectrometry. In addition, the lipophilicity of complexes was assessed by shake-flask method. The comparison of logP values in the five groups of complexes determined by arene-ruthenium(II) type gave two different lipophilicity patterns, one in the set of complexes with p-cymene and mesitylene while another in the series with benzene and hexamethylbenzene. The most lipophilic complexes in each series are those with flavanone derivatives as ligands. However logP values of all complexes are in the relatively narrow range 0.81-1.45.

The cytotoxicity of arene ruthenium(II) complexes has been evaluated in vitro on patient-derived melanoma populations. Two lines of advanced melanoma, namely nodular melanoma (NM), the most aggressive form of this cancer, and superficial spreading melanoma (SSM), the most common one, were used in the study. The highest cytotoxic activity against cancer cells derived from surgical specimens was obtained for ruthenium(II) complexes 1b and 2b-e containing 6-aminoflavonone and 7-aminoflavone, respectively. The IC₅₀ values are in the range of 1.13 – 19.15 μM. The results for all complexes demonstrate a general trend of increase in cytotoxicity with increasing of logP value. The NM population seems to be more sensitive to the novel complexes than SSM population, but further studies are necessary to reveal potential mechanisms of their action.

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Cytotoxic properties of copper(I) and copper(II) complexes with phosphine derivatives of fluoroquinolones.

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The discovery of the anticancer properties of cisplatin in mid-twentieth century resulted in an intensive development of medicinal and bioinorganic chemistry. Metal complexes as potential therapeutics are very interesting compounds due to (i) accessible redox states of metal ions, (ii) wide range of coordination numbers, (iii) interesting kinetic and thermodynamic properties [1-3]. Recently much research attention has been paid to complexes with biological active molecules for example drugs, which are donor-rich compounds efficiently bind metal ions. Numerous literature reports state that coordination compounds often have better biological properties than uncoordinated drugs. Formation of a complex frequently changes the solubility, bioavailability and the mechanism of action of the parent molecule. The consequence of these changes can be better biological properties of the complex or its broader spectrum of activity in comparison to the free drug.

We present herein cytotoxic properties of copper(I) and (II) complexes with phosphine derivatives of ciprofloxacin or norfloxacin [4,5] and diimine as an auxiliary ligand. Complexes were tested in vitro as anticancer agents towards two cell lines: mouse colon carcinoma (CT26) and human lung adenocarcinoma (A549). Cytotoxicity studies revealed that complexes are able to inhibit the proliferation of the cells at relatively low concentrations. Moreover, they are more active against tested cell lines than cisplatin – the main representative of antitumor drugs. Flow cytometry studies showed that treatment of the cells with the investigated complexes resulted in appearance the population of apoptotic cells, while necrotic cells constitute only a small percentage.

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References:
The anchoring ability of specific non-coordinating side chains in fragments of the rat and the human amylin

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

Copper(II) and nickel(II) complexes of peptides modelling the sequence of the 17-22 residues of rat amylin have been studied by potentiometric, UV-Vis, CD and ESR spectroscopic methods. The peptides were synthesized in N-terminally free forms, NH\(_2\)-VRSSNN-NH\(_2\), NH\(_2\)-VRSSAA-NH\(_2\), NH\(_2\)-VRAANN-NH\(_2\), NH\(_2\)-VRSS-NH\(_2\), NH\(_2\)-SSNN-NH\(_2\), NH\(_2\)-SSNA-NH\(_2\) and NH\(_2\)-AANN-NH\(_2\), providing a possibility for the comparison of the metal binding abilities of the amino terminus and the –SSNN– domain. The amino terminus was the primary ligating site in all cases and the formation of only mononuclear complexes was obtained for the tetrapeptides. The thermodynamic stability of the (NH\(_2\),N–,N–) coordinated complexes was, however, enhanced by the asparaginyl moiety in the case of NH\(_2\)-SSNN-NH\(_2\), NH\(_2\)-SSNA-NH\(_2\) and NH\(_2\)-AANN-NH\(_2\). Among the hexapeptides the formation of dinuclear complexes was characteristic for NH\(_2\)-VRSSNN-NH\(_2\) demonstrating the anchoring ability of the –SSNN– (SerSerAsnAsn) domain. The complexes of the heptapeptide NH\(_2\)-GGHSSNN-NH\(_2\) were also studied and the data supported the above mentioned anchoring ability of the –SSNN– site.

\textbf{Acknowledgement:} The authors thank the project TÁMOP-4.2.2.B-15/1/KONV-2015-0001 for financial support.

\textbf{References:}
Restricted metal binding pattern of acyclovir in a Cu(II) chelate with tripodal tetradentate-NO$_2$S(thioether) ligand

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To our friend Henryk Kozlowski in occasion of his very special anniversary

The reaction between Cu$_2$CO$_3$(OH)$_2$ (0.5 mmol), N,N-bis(carboxymethyl)-S-benzylcysteamine (H$_2$BCBC, 1 mmol) and acyclovir (acv, 1 mmol) in MeOH (100 ml) yields the compound [Cu(BCBC)(acv)]$_2$·5MeOH·H$_2$O (1), which has been studied by single-crystal X-ray crystallography (monoclinic, P2$_1$/c, 100 K, final R$_1$ 0.032). The crystal consists of two non-equivalent but close similar [Cu(BCBC)(acv)] complex molecules (1 and 2, see figure) and the corresponding solvent molecules. The metal exhibits a square base pyramidal coordination, type 4+1, with the tripodal-tetradentate BCBC$^{2-}$ chelator in a mer-NO$_2$S(distal) conformation [1] and the acv acting as N7-unidentate ligand. The four shortest donor atoms of each Cu(II) center are supplied by the mer-NO$_2$ tridentate iminodiacetate moiety of the BCBC chelator and the N7-acv (Cu1-N27 1.971(2) Å, Cu2-N67 1.963(2) Å). Because the O-carboxylate atoms cannot act as H-donors, the metal binding patterns of acv in the novel compound is restricted to the formation of the Cu-N7(acv) bond.

H-bonding interactions connect pairs of the two non-equivalent complex molecules. H-atoms omitted for clarity.
Differences between complex molecules 1 and 2 are mainly related to (a) the Cu-S(thioether) bond length (Cu1-S12 2.643(1) Å, Cu2-S52 2.580(1) Å), (b) The Reedijk-Addison parameter \( \tau = (\theta - \varphi)/60 \) (\( \theta \) and \( \varphi \) being the trans-basal coordination angles; \( \tau_1 \) 0.001!, \( \tau_2 \) 0.12), (c) torsion angles related to the B-benzyl arm (i.e. the Cu-S-C-C(\( \varphi \)) is +137.56° or -154.87° for molecules 1 and 2, respectively) and (d) the conformation torsion angles defining of the N9-side chain of acv ligands.

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**Reference:**
Transition metal complexes of peptides containing thiolate functions

Á. Grenács, N. Lihi, S. Timári, I. Turi, K. Várnagy, I. Sóvágó

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Blue copper and zinc finger proteins, metallothionenins are a few examples for the metal ion interaction with thiolate groups of cysteine.[1] This function group is, however, rather selective to metal ions with different characters, the typically soft ones being the most effective ions in complex formation. [2] In the case of hard metal ions the interactions are weak or missing, which gives the possibility for synthesis of metal ion selective complexing agent by using of peptides containing more cysteine residues.

Three peptides containing two thiolate functions were synthesized two of them containing two cysteine residues with the sequences AlaCysSerSerAlaCysSer-NH$_2$, CysSerSerAlaCysSer-NH$_2$. In the case of nickel(II) – CysSerSerAlaCysSer-NH$_2$ system the formation of insoluble polynuclear species hindered the potentiometric and spectroscopic studies. Therefore an analogue of this peptide containing D-penicillamine in N-terminal position, PenSerSerAlaCysSer-NH$_2$, has also been synthesized and its complexes were studied by the combined application of potentiometric and spectroscopic techniques. All the peptides were studied in the presence of zinc(II) and cadmium(II) ions and their complexes were investigated by pH-potentiometric, NMR and ESI-MS techniques. One of the most important findings is the cadmium(II) ion induced deprotonation of the amide function on the amino terminal part of the heptapeptide.

**Acknowledgement:**  
Financial supports from the TÁMOP-4.2.2.B-15/1/KONV-2015-0001 are acknowledged.

**References:**  
CAGEDRUGS: Design and elaboration of novel topological drugs based on cage compounds

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The CAGEDRUGS project (2011-2015), supported by the Marie Curie IRSES Scheme of the 7th EU Framework Program (FP7-PEOPLE-2011-IRSES, grant 295160), has brought together five research centres (see above) devoted to the development of new nanomaterials for biomedical use based on macrobicyclic cage metal complexes (clathrochelates) [1].

During the course of the project a series of new clathrochelate compounds based on tris-dioximate and tris-oxalodihydrazide structures has been elaborated. Their design, synthesis and physico-chemical characteristics, as well as biological activities were performed in five work packages (WP1: Design and template synthesis, WP2: Identification and structure studies, WP3: Spectral and physico-chemical characterisation, WP4: Reactivity and functionalisation, WP5: Biomedical applications of cage compounds).

Scheme 1. Supramolecular binding of bis-clathrochelate Fe(II) as effective inhibitor of T7 RNA polymerase (IC50=500nM) to replicative fork by data of molecular docking.

The ability of clathrochelates to interact with proteins, their activity as transcription inhibitors of DNA and RNA polymerases (Scheme 1), as well as anti-fibrillogenic activity has been reported and summarized during the CAGEDRUGS Closing Workshop which took place in Wroclaw, Poland, 24 June 2015.
The joint research carried out in the frame of CAGEDRUGS project was due to an efficient collaboration and mobility of researchers from five research teams, sharing their expertise, knowledge and best practice. The laboratory activities with learning by doing, planning of scientific activities, participation to scientific lectures/group discussions/workshops and networking activities were main elements of training of Early Stage Researchers and transfer of knowledge.

References:

We devote this presentation to Prof. Henryk Kozłowski – the Scientist of the CAGEDRUGS Project, with the best wishes for his future activity in the European Framework Programmes!

CAGEDRUGS Closing Workshop, Wrocław, Poland, 24 June 2015.
Peptides as potential receptors for sensing metal ions

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Toxic metal ions appear in the environment from natural or anthropogenic sources and present a hazard to living organisms. These contaminants may execute adverse effects in organisms at various levels of the food chain. Methodologies that allow the fast and sensitive (on-site) detection of toxic metal ions could be real alternatives of the robust, efficient but expensive laboratory-based instrumental techniques. The development of such novel methods is in the focus of environmental / analytical chemistry research.

Our recent project aims at the design and investigation of oligopeptides that are able to efficiently bind toxic metal ions and as such may potentially function as receptors in optochemical metal ions sensors.

The sequences of the studied ligands were inspired by the metal binding domains of various metalloproteins (chaperons, transport or regulatory proteins) [1,2,3]. Fluorophore units were also introduced into these oligopeptides allowing the optical detection of metal ion binding. One of these candidates was equipped with fluorophore residues at both termini (Trp and dansyl). The idea behind this construct was to observe fluorescence resonance energy transfer (FRET) if metal ion coordination resulted in a structural rearrangement bringing the fluorophores into close proximity. Some of the ligands have also been synthesized onto various solid supports (e.g. resin, silica – see scheme below).

We present here our recent results on the toxic metal ion (Cd$^{2+}$, Hg$^{2+}$) binding of the synthesized peptides and the metal ion capturing ability of the immobilized systems.

References:

Coordination properties of the C-terminal fragment of human serum amyloid A with Cu(II) ions.

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Chronic acute inflammation may lead to severe secondary amyloidosis. The N-terminal part of human serum amyloid A (SAA) is a major constituent of amyloids appearing in these diseases. A recent crystallographic structure of SAA revealed that the protein is stabilized by its C-terminal part, which forms multiple specific interactions with three out of four core α-helices of SAA [1]. Here we present the thermodynamic parameters of the interaction of copper (II) ions with the C-terminal fragment of SAA consisting of residues 86 to 104. Coordination of Cu(II) by the wild type peptide and its mutants were characterized with potentiometric and spectroscopic methods.

Dear Professor,
My dream is now coming true due to Your invaluable help. Thank you so much for Your kindness, Your help, Your heart and Your inspiration. I wish You that all Your dreams come true, too. I wish you good health, inexhaustible energy, and all the happiness!

References:
Much of the recent impetus for the studies of vanadium(V) chemistry derives from the fact that there is marked diversity in biochemical activity associated with this oxidation states. Vanadium(V) occurs naturally in vanadium-dependent haloperoxidases, but beyond this, various complexes of V(V) have powerful influences, inhibiting the function of a large of enzymes and promoting the function of others[1]. The key to our understanding all such functionality relies on understanding the basic chemistry of vanadium in various donor atoms environmental and oxidation states. In this context we synthesized new tetradentate O,N,N,O-type ligand precursors via the Mannich condensation of ethylenediamine, paraformaldehyde and appropriate phenol derivatives as well as their vanadate complexes (Scheme).

**Scheme.** Synthetic strategy of [VO(L\(^1\)-\(\kappa^4\)-O,N,N,O)(OMe)] (1) and [VO(L\(^2\)-\(\kappa^4\)-O,N,N,O)(OMe)] (2).

**Acknowledgement:** The authors would like to thank the National Science Centre (Poland) (Grant Nr 2012/05/N/ST5/00697) for the financial support.

**References:**
The influence of HypA loop sequence on binding ability towards metal ions

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Bacteria *Helicobacter pylori* colonize human stomach and is a causative agent of peptic ulcers and stomach cancer. The presence of urease and [NiFe] hydrogenase provide surviving of these bacteria in acidic environment of human stomach. HypA is a metallochaperone protein required for maturation of these enzymes. HypA protein consists of two metal ion binding sites: nickel binding domain and zinc binding loop domain. The zinc binding loop contains conserved cysteine residues in two CXXC motifs, each accompanied by a histidine residue. The zinc binding mode changes from $\text{Zn(His)}_3\text{(Cys)}_2$ at an acidic pH to $\text{Zn(Cys)}_4$ at a neutral pH. This pH-dependent alterations in the zinc coordination influence the nickel binding domain, which indicates a communication between the zinc and the nickel site. The zinc loop domain may act as a pH sensor, which provides a mechanism for correct delivery of $\text{Ni}^{2+}$ to a target protein [1].

Studies on Ac-ELECKDCSHVFKPNALDYGVCEKCHS-NH$_2$ – the HypA loop fragment – have shown the same pH-dependent changes in the $\text{Zn}^{2+}$ binding mode [2]. In our studies, the HypA loop fragment was modified by substitution of Pro, which is between the motifs, by Ala, resulting in increasing of the binding ability of the loop towards $\text{Zn}^{2+}$ and $\text{Cd}^{2+}$. Another modification – a deletion of some hydrophobic residues and decreasing the distance between the motifs – also improves the binding efficacy of the loop. Studies carried out with peptides containing only one of the CXXC motifs have revealed some differences between the binding ability of these two motifs [3].

References:
Happy Birthday to Professor Henryk Kozłowski – probably the best supervisor in the world!
Copper(I) complexes with phosphine derived from sparfloxacin: a first insight into the cytotoxic action mode.

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We present a first insight into the cytotoxic action mode of copper(I) iodide or copper(I) thiocyanate complexes with phosphine derivative of sparfloxacin (a 3\textsuperscript{rd} generation fluoroquinolone antibiotic agent) and 2,9-dimethyl-1,10-phenanthroline or 2,2'-biquinoline as auxiliary ligands. Cytotoxic activity \textit{in vitro} of new complexes was tested against two cancer cell lines (CT26 – mouse colon carcinoma and A549 – human lung adenocarcinoma). ICP-MS study revealed a marked time-dependent intracellular copper accumulation of the tested compounds. As well, confocal microscopic analysis showed accumulation of complexes inside whole cells and their emission of blue light. The resulting complexes generate reactive oxygen species in the cells, examined by using two different fluorescent probes. Moreover, (i) DNA intercalations studied by luminescence spectroscopy, circular dichroism and molecular docking, and (ii) plasmid DNA damage also, demonstrate significant cytotoxicity. All these observed biological effects contribute in induction of apoptosis, observed at a great advantage.

Acknowledgement: The authors are grateful to Bernadeta Nowak, PhD. Jagiellonian University in Kraków for flow cytometry measurements and Mariusz Kępczyński PhD. Jagiellonian University in Kraków for confocal imagining.

References:

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Probing Cu\(^+\) Binding Properties of Cysteine-Rich Fragment of BRI2 the natural inhibitor of A\(\beta\) aggregation

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The amyloid-\(\beta\) peptide (A\(\beta\)) and its precursor protein (APP) are known to interact with number of protein partners located within or in close proximity to cellular membrane. The evolution of amyloid is related to the activity of secretases.[1] They are involved in posttranslational processing of the 1st type of membrane proteins (e.g. APP). Their activity can be modulated by multiple agents such as BRI2 protein which interacts with the APP, thus shielding the site of proteolytic cleavage.[2] BRI2 is a subject of post-translational proteolytic treatment that yields peptidic fragments of BRI2 both inside and outside the cell.[3] Two of them are particularly interesting; 10kDa domain ICD containing cysteine-rich segment of BRI2 acting as a secondary messenger of cellular signals,[2] and a peptide called BRI2-23 which has a capacity of braking aggregation of A\(\beta\) in vivo and in vitro.[4] APP and A\(\beta\) are involved in the copper ions homeostasis. Since this might be influenced by protein interactome, the evaluation of metal binding properties of cysteine-rich domains of BRI2 and C-terminal furin cleaved peptide (BRI2-23) [5] towards Cu(I) ions or its metallic molecular probes like Hg(II) and Ag(I) is of particular importance. In this work we have used Hg(II) and Ag(I) to probe the interactions of Cu(I) with peptidic model of cysteine-rich domain of BRI2.

References:

Right before the opening of ISMEC 2015 Conference in Wroclaw

Thank you for these few years. Happy Birthday Henryk!
Coordination abilities of biologically relevant imidazole-based bicycles functionalized by an acetate group

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Synthetic bicyclic heterocycles constitute a vast family of compounds gaining substantial interest in the field of medicinal chemistry. Their pharmacological potential lies in structural similarity to naturally occurring compounds, which makes them capable of binding to multiple biological targets with high affinity and providing pharmaceutical activities in essential cellular processes. Among bicyclic systems containing fused imidazole ring, imidazo[1,2-a]pyridine (IP) is the most widely studied and most frequently represented in marketed drug formulations. A highly promising scaffold for new drugs development are also imidazo[1,2-a]pyrimidine (IPm) and imidazo[2,1-b]thiazole (ITz).

Recently, we have demonstrated that suitable position of flexible carboxylic group allows imidazo[1,2-a]pyridin-2-ylacetatic acid (HIP-2-ac) to react with divalent metal ions through N,O donor set, resulting mostly in the formation of discrete mononuclear complexes \cite{1, 2}. Moreover, it has been revealed that zinc(II) complex based on the IP-2-acanion displays interesting antibacterial activity \cite{2}.

Herein we present structural characterization and properties of a series of imidazo[2,1-b]thiazol-2-yl-, imidazo[1,2-a]pyrimidin-2-yl- and imidazo[1,2-a]pyridin-3-yl-acetate derived complexes with biologically significant Zn(II), Co(II) and Mn(II) ions. Notably, the 3-position of carboxylate group on a heterocyclic ring afforded the formation of 1-D polymeric complexes of Co(II) and Mn(II).

References:

Transition metal complexes of TREN-based tripodal ligands

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It’s an important step towards understanding and mimicking metalloenzymes to model the active site with small molar mass complexes. In many enzymes the metal ion is coordinated by three or four nitrogen donor atom (usually through imidazole sidechains), while the remaining one or two coordination site is occupied by either water or substrate. Tripodal ligands can be utilized quite effectively to model these sites, since the structure of the ligands creates a preorganized binding site for the metal ion. One of the most studied tripodal ligand is the TREN (tris-2-aminomethylamine). In our opinion the N-substituted TREN derivatives can be used to build further functions to the ligand, eg. more metal binding sites, because the cooperation of those metal ions can induce a better enzyme mimicking function. For this purpose, we synthesised methylpirazol-substituted TREN derivatives (fig 1) to provide 6 more donor atoms to bind metal ions. Both of these ligands forms high stability trigonal bipyramidal monocomplexes with \textsuperscript{Mn(II)}, \textsuperscript{Fe(II)}, \textsuperscript{Co(II)}, \textsuperscript{Cu(II)} and \textsuperscript{Zn(II)}, while two tris[N-(5-pyrazolilmethyl)-2-aminoethyl]amine can bind three copper ion forming \textsuperscript{Cu}_3\textsubscript{H}_x\textsubscript{L}_2 (x=2-4) extra deprotonated pyrazolate-bridged complexes. Exceptional catecholase-activity could be detected for the \textsuperscript{Cu}_3\textsubscript{H}_3\textsubscript{L}_2 with unusually low pH-optimum (pH≈7.2).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Schematic structure tris[N-(4-pyrazolilmethyl)-2-aminoethyl]amine and tris[N-(5-pyrazolilmethyl)-2-aminoethyl]amine}
\end{figure}
Although the interactions of ruthenium polypyridyl complexes with biological molecules (mainly DNA) have been of a long-standing interest, surprisingly, the use of luminescent ruthenium complexes as cellular probes and bioimaging reagents has not been focused upon until recently.

The present study has been dedicated to understanding the interplay between emission properties, lipophilicity and the interaction with biomacromolecules on the cellular uptake, localization and cytotoxic properties of the family of Ru polypyridyl complexes, containing two 4,7-diphenyl-1,10-phenanthroline (dip) ligands and modified 2,2'-bipyridine (bpy) ligands [1].

Cytotoxicity of all the studied Ru complexes is superior to clinically used cisplatin and correlates well with the amount of ruthenium accumulated in cells. Luminescence intensity of the studied Ru complexes exhibited in vitro depends not solely on the luminescence parameters (ϕ and τ) expressed by the complexes in solution, but mainly on the efficiency of their cellular accumulation and the influence of the proteins on the Ru complexes excited states.

Acknowledgement: Financial support from the National Science Center (grant by the decision DEC-2013/11/N/ST5/01606) 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).

References:
Metal-binding pattern of adeninium(1+) ion in the crystal of 
\([\text{Co}^{\text{II}}(\text{nitrilotriacetate})(\text{H}_2\text{ade})(\text{H}_2\text{O})]\cdot3\text{H}_2\text{O}\)

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To our friend Henryk Kozłowski in occasion of his very special anniversary

Previous works: Acidic metal(II) chelates \([\text{M}^{\text{III}}(\text{Hnta})(\text{H}_2\text{O})_3]\cdot\text{H}_2\text{O} \ (\text{M} = \text{Co}, \text{Ni}, \text{Zn})\) crystallizes in the orthorhombic system, \(\text{Pbca}\) group. In these complex molecules the Hnta\textsuperscript{2-} anion of nitrilotriacetic acid only acts as a N-(carboxymethyl)iminoacetate(2-) tridentate chelator, in \(\text{fac-NO}_2\) conformation, hence having a free N-acetic arm. Aoki et al. has proved that the \([\text{Ni}^{\text{II}}(\text{Hnta})(\text{H}_2\text{ade})(\text{H}_2\text{O})]\cdot2\text{H}_2\text{O}\) (Hade being adenine) \([1]\). The corresponding proton-transfer process represents (a) the role of the nta\textsuperscript{3-} ions as tripodal-tetradentate chelator, and (b) the coordination of the H\(_2\text{ade}^+\) cation to the Ni\textsuperscript{II} center. There are two non-equivalent \([\text{Ni}^{\text{II}}(\text{Hnta})(\text{H}_2\text{ade})(\text{H}_2\text{O})]\) developing a metal binding pattern (MBP) that essentially consist of the formation of the Ni-N7 bond assisted by an intra-molecular interligand N6-H···O(coordinated, nta) interaction.

Aims: The aim of this work is (1) to propose a synthesis for pure (and crystallized) samples of \([\text{M}^{\text{III}}(\text{Hnta})(\text{H}_2\text{O})_3]\cdot\text{H}_2\text{O} \ (\text{M} = \text{Co}, \text{Ni}, \text{Zn})\) and (2) their use to the novel compounds having a protonaded(1+) cation of Hade as well as various deaza- oraza-adenines as potential ligands of neutral (molecular) complexes. Their structures can afford additional insights on the MBP of such cationic forms for such purine analogue N-ligands.

Results: By this way the obtained \([\text{Co}^{\text{II}}(\text{Hnta})(\text{H}_2\text{O})_3]\cdot\text{H}_2\text{O}\) compound have been crystallized and identified as that previously reported by Polynova et al. \([2]\). Its reaction with Hade pale-brown crystals of the title compound (100 K, triclinic, \(\text{P-1}\) space group, final \(R_1\), see figure). The Co\textsuperscript{II} atom exhibits an octahedral coordination fulfilled by the tripodal-tetratentatentachelor, the monodentate H\(_2\text{ade}^+\) cation and one aqua ligand. In this crystal there is only a kind on complex molecules. The MBP of the H\(_2\text{ade}^+\) ligand...
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consists of the Co\(^{II}\)-N7(H\(_2\)ade\(^+\)) bond (2.125(1) Å) and the rather-linear intra-molecular interligand (H\(_2\)ade\(^+\))N6-H⋯O(nta) interaction (2.731(2) Å, 176.5º).

Discussion: In the novel compound, crystal packing influences does not produce non-equivalent complex molecules, as is the case of the Ni\(^{III}\) analogue reported by Aoki [1]. Hence, the cooperation of the Co-N7(H\(_2\)ade\(^+\)) bond and the interligand N6-H⋯O(nta) interaction is clearly observed as the MBP to the molecular recognition between the H\(_2\)-N1,N9-adeninium(1+) ion and the Co\(^{II}\)(nta) chelate.

Acknowledgement: Financial support from UGR-FQM-283 Research Group, USC and IACT (LEC) CSIC-UGR. ADM thanks for a Ramón Areces Foundation Posdoc position. MEGR also thanks for a Torres Quevedo Posdoc position.

References:

Two enthusiastic friends sharing Inorganic Biochemistry
(Eurobic 12, Zürich, 2014)
Complex-Formation Ability of Thiosemicarbazones towards Cu (II) Ions

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Thiosemicarbazones (TSCs) are a class of compounds with a very wide range of applications, e.g., spectrophotometric and spectrofluorimetric detection of various metal ions. The ability of TSCs to form stable complexes with important biological metal ions makes them also versatile pharmacophores. They possess a broad range of pharmaceutical properties such as antimalarial, antimicrobial and antitumor activity [1, 2].

Taking into account the fact that cancer is one of the main health concerns confronting humanity and one of the primary targets in therapeutic chemistry, studies of new compounds which may possess antitumor properties are very important [3]. Triapine (Figure 1) is the best known example of TSCs family and has been extensively studied as a single agent and in combination with established drugs in phase I and phase II clinical trials with mixed results [4].

Figures 1: Structure of Triapine.

In connection with the anticancer applications of TSCs there have been proposed several mechanisms of action, but many questions still remain unanswered. Information on the speciation of metal complexes, particularly at physiological pH, can be the first step towards elucidation of the cytotoxic mechanism of TSCs. In this work, we characterize novel thiosemicarbazone ligands, in terms of complex formation with Cu(II) ions and their stability constants.

References:
Antibiotics are a vital part of modern medicine. However, the available arsenal of antibiotics becomes less effective as microorganisms develop "resistance" against them. The resulting crisis in medicine necessitates development of new drugs. Natural products inspired compounds are a potential solution to this challenge. For example, gladiolin biosynthesized by a mulitenzyme polyketide synthase (PKS) was shown to be active against *Mycobacterium tuberculosis*, a multidrug resistant bacterium that one third of world’s population is infected with [1]. The PKS producing gladiolinum is a good example of multienzymatic assembly lines that due to their modular nature are ideal for genetic manipulation paving the way for synthetic biology approach to produce new drugs (that are difficult to synthesize using chemical methods). However, for such approach to be successful it is crucial to understand molecular level structural and dynamical factors responsible for controlling directionality and specificity of biosynthesis. Neglecting such factors, when modifying PKSs often results in assembly lines that are inactive or dysfunctional [2, 3]. Here we propose to use a novel approach combining state-of-the-art solution and solid-state NMR methods to investigate structure, dynamics and interactions of proteins from module 12 of gladiolin PKS, particularly acyl carrier proteins (ACP12a and ACP12b) and special adapter ketosynthase (KS12), all of them highly required in industrial biosynthesis toolbox. We will use solution NMR to characterize isolated ACPs and solid-state NMR to study ACPs-KS12 complexes (direct structural information is difficult to obtain by solution NMR due to the large complex size). Combining solution and solid-state NMR relaxation methods will allow us to probe protein motions over 6 orders of magnitude [4] providing a comprehensive picture of relevant dynamic changes in ACPs-KS12 complexes.

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Bio-inspired fixation of CO$_2$ on organozinc hydroxides: efficient routes to novel nanomaterials based on zinc carbonates

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Carbon dioxide (CO$_2$) is the most abundant C-1 building block in Nature that is widely used to synthesize complex organic molecules in living organisms. The particularly intriguing examples of CO$_2$ fixation concern reaction systems patterned on active center of carbonic anhydrase (CA) that contains Zn-OH group. Surprisingly, while a number of zinc complexes supported by multidentate ligands and terminal or bridging hydroxide ligation have been widely investigated experimentally as synthetic analogues of CA, the related organozinc hydroxide compounds have not been explored in this context.[1]

In the first part we report on the fixation of CO$_2$ by the well-defined alkylzinc hydroxide (tBuZnOH)$_6$.[2] The slight modifications in reaction systems enable control of the reaction products with high selectivity leading to the isolation of the mesoporous solid based on ZnCO$_3$ nanoparticles or unprecedented discrete alkylzinc carbonate [(tBuZn)$_2$(µ$_5$-CO$_3$)]$_6$ cluster with the Zn-C bond intact, respectively. The Density Functional Theory calculations indicate that this process is a multistep reaction, where the insertion of CO$_2$ into RZnOH species seems to be the rate determining step.[3] Moreover, the introduction of an additional supporting ligand to an alkylzinc hydroxide system allowed us the construction of new materials of desired functionality. The successful utilization of the tetranuclear hydroxo cluster [Zn(q)$_2$][tBuZn(OH)]$_2$ (where q = 8-hydroxyquinolinate)[4] as a predesigned organozinc precursor led to the unique and permanently porous fluorescent non-covalent porous material (NPM) WUT-1 based on discrete molecules of heteroleptic zinc carbonate-hydroxyquinolinate clusters.[5]

References:


Tuberculosis is a serious global health problem caused by the bacillus *M. tuberculosis* [1], associated with the human population since antiquity [2]. Viomycin, capreomycin and ethambutol are members of anti-tuberculosis agents family. It has been evidenced that serum copper(II) pool is elevated during tuberculosis around 21% [3]. Even more interesting is the fact that this pool may be decreased during the treatment and returns to normal levels. One of the possible explanation is that anti-tuberculosis agents can chelate Cu$^{2+}$ ions and influence their homeostasis [4]. Therefore, it was decided to compare the strength of copper(II) binding by three mentioned above anti-tuberculous drug. What is apparent in the distribution curves copper(II) ions are most effectively bound by viomycin. At physiological pH up to 70% of Cu$^{2+}$ pool is bound by the antibiotic, and the remaining 30% by capreomycin. In contrast, ethambutol considered as an effective chelator of these ions which affect its homeostasis in the human body [4], is in this system with no chance (binding less than 1 ‰ of Cu$^{2+}$ ions). It can be assumed that treatment with capreomycin, and in particular with viomycin, may cause faster return to physiological level of Cu$^{2+}$ ions concentration, than in the case of ethambutol. It can entail not only the desired effects, but also disturb copper homeostasis.

**Acknowledgement:** The research was supported by Wroclaw Research Center EIT+ under the project „Biotechnologies and advanced medical technologies – BioMed” (POIG 01.01.02-02-003/08-00) financed from the European Regional Development Fund (Operational Programme Innovative Economy, 1.1.2).

**References:**

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

The project involves six research groups from five countries (Italy-Coordinator, Poland, France, Ukraine and USA) with complementary expertises and the common aim to devise new metallacrown complexes with novel magnetic, photophysical and structural properties be used as tools in bio- or nanotechnological devices.

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

References:
pH-Dependent copper (II) binding on branched peptides: one construct, two stoichiometries

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Branched peptides can be obtained from a central scaffold (core) to which a variable number of peptide sequences are linked. We describe the study of two Cu(II)-binding oligopeptides, and of their tetrameric branched forms. The peptide sequences AAHAWGNH\textsubscript{2} (P\textsubscript{1}) and HAWGNH\textsubscript{2} (P\textsubscript{2}) were synthesized using solid phase synthesis. Their tetrameric forms were obtained using one amino acid longer sequences (AAHAWG\textsubscript{C}NH\textsubscript{2} and HAWG\textsubscript{C}NH\textsubscript{2}). The cysteine SH group allowed to bind the peptides to a maleimide-functionalized cyclam platform via a thiol/Michael reaction [1].

\[
P^1 = \text{Ala-Ala-His-Ala-Trp-Gly(NH}_2)\textsuperscript{\textsuperscript{}p1.2}
\]

\[
P^2 = \text{His-Ala-Trp-Gly(NH}_2)\textsuperscript{\textsuperscript{}p1.2}
\]

Peptide P\textsuperscript{1} bears a XXH ATCUN motif. Potentiometric studies showed that [Cu(P\textsuperscript{1}H\textsubscript{2})\textsuperscript{2+}] is the major species in the 4-9 pH range. Spectroscopic data are fully consistent with a 1:1 ATCUN Cu:peptide binding stoichiometry. Data on the tetrameric (P\textsuperscript{1})\textsubscript{4}cyclam construct show that the construct has the capacity to bind 4 eq. of Cu(II).

On the other hand, peptide P\textsuperscript{2} forms [Cu(P\textsuperscript{2}H\textsubscript{3})\textsuperscript{2+}] as the major species at pH 7. However, by increasing the pH to 9, a [Cu(P\textsuperscript{2}H\textsubscript{3})\textsuperscript{2+}] complex is obtained as the major species where three deprotonated peptide nitrogen atoms are involved in the binding of Cu(II). We aim now to use these scaffolds to prepare novel functional \textit{de novo} designed copper peptides [2].

References:
Zincophores - zinc acquisition strategy of *Candida albicans*, a human fungal pathogen

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*Candida albicans* is one of the few fungal species of the normal human microbiome. Simultaneously this commensal is also an extremely frequent cause of candidasis and potentially lifethreatening candidemia [1].

Assimilation of essential nutrients by pathogenic microorganisms from their host is one of the fundamental aspects of infection. Certain trace minerals, such as iron and zinc, are actively withheld from pathogens in a process called nutritional immunity. Therefore pathogenic fungi evolved specialized uptake systems in order to proliferate in their host and cause disease [1,2].

*Candida albicans* scavenge zinc via specific and selective chelators called “zincophores” or Pra1. Pra1 is a small, 299 amino acid, zinc binding protein, which can uptake metal from host cells and tissues and subsequently re-associate with the fungus via a co-expressed membrane transporter, Zrt1 [2].

**Scheme 1.** Schematic model of *C. albicans* zinc scavenging from host cells. After invasion of the host cell, Pra1 is expressed and secreted. It binds zinc either in the form of free Zn$^{2+}$ or from zinc-binding proteins of the host. Reassociation with *C. albicans* cell surface and Zn$^{2+}$ transport into the cell occurs via a Pra1-Zrt1 interaction.

The main aim of our project is to understand, from the viewpoint of bioinorganic chemistry, the interactions of Zn$^{2+}$ with zincophore Pra1 and zinc transporter Zrt1. In this work, we focus on two specific Zn$^{2+}$ binding sites in Pra1 and discusse the binding mode and thermodynamic properties of complexes of those two regions with Zn$^{2+}$ and Co$^{2+}$, an extremely useful spectroscopic probe for Zn$^{2+}$. 
Mass spectrometry confirmed the stochiometry of the Zn$^{2+}$ and Co$^{2+}$ complexes with Pra1 fragments. Potentiometric studies allowed us to determine the thermodynamic parameters for our systems and gave us partial and overall stability constants for all formed zinc and cobalt complexes. Profound analysis of these results indicated which protein fragments bind Zn$^{2+}$ and Co$^{2+}$ with the highest affinity and gave us an indication which part of Pra1 might be responsible for zinc acquisition. In order to precisely identify the binding sites, donor atoms and coordination geometry of complex species formed in solution at given pH values, spectroscopic techniques such as NMR, UV-Vis and CD were used.

The results are not only the first step towards understanding the inorganic biochemistry of zincophores, biologically relevant molecules, but they might at some point be a stepping stone towards finding new, fungus-specific treatments based on parts of zincophores coupled with an imidazole- or triazole- based antifungal drugs.

**Acknowledgement:** Financial support by Polish National Science Centre (UMO-2014/13/D/STS/02868: „Understanding the interactions of zinc with zincophores and zinc transporters in fungal pathogens”) is gratefully acknowledged.

**References:**

Most professors are experts in subjects that they teach their students. But You are also an expert in two more subjects called Motivation and Inspiration, which You give us every day. 

Happy Birthday!
The Impact of the Cu(II) Coordination on the Structural and Thermodynamic Properties of Poly-His Peptides.

J. Wątły a, H. Kozłowski a, Y. Miller b,c, M. Remelli d, R. Wieczorek a, Sylwia Rodziewicz-Motowidło e, E. Simonovsky b,c, N. Barbosa a, Marta Spodzieja e

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A huge number of polyhistidine proteins have been discovered in the last decades both in eukaryote and prokaryote organisms, playing a critical role in metal regulation and homeostasis [1,2]. The multi-histidine sequences are also the basis of one of the most effective methods of protein purification - Immobilized Metal Ion Affinity Chromatography [3].

We have recently studied the coordination of Cu(II) with (His)6-tag peptide used in IMAC chromatography and peptides, found in African snake venoms: EDD(His)9G (pHG), DHDHD(His)6PGSSV (D3pH) using experimental and computational tools.

The results showed that all studied peptides have a high affinity towards Cu(II) ions. It was proposed that increasing the length of the His-rich chain increases the efficiency of metal ion binding. CD spectroscopy and computational studies showed that the metal–pHG complex has an α-helical structure of a 310 helix stabilized by a hydrogen-bonding network [4]. Multiple His residues along His6-tag, pHG and D3pH peptides, can bind metal ions with various imidazole sets along the sequence and therefore form polymorphic states [4,5]. The pHG peptide is able to exist in more polymorphic states. Furthermore, while the His6 tag showed a slight preference for an α-helix-like structure, the pHG is a regular α-helix. There is a pronounced correlation between the well defined secondary structure of the predicted complexes and their thermodynamic stability. The capping of the peptide termini promotes α-helical conformations that are induced by the metal binding sites [6].

Acknowledgement:
Financial from the project “Academy of Development as the Key To Strengthen Human Resources of the Polish Economy” cofinanced by the European Union under the European Social Fund.

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The role of the hydrogen bond in peptides.

Robert Wieczorek and Akmaral Kussayeva

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Peptides as the most completed chemical systems are important for the life we know. Peptides deliver fringe of use as antibiotics, neurotoxines and as base timber of many tissues. The secondary structure is one of the most important structural factor that influences on properties of the peptides.

One can distinguish regular and unregular secondary structures and meet both types of them in one peptide. Hydrogen bond is the most universal brick that builds secondary structure – apart from complex side chains that can form complicated interactions the backbone itself consist of formamide-like fragments that are able to form many regular secondary structures. The helix commonly named after number of aminoacids and atoms necessary to close hydrogen bond ring, is common regular fragment of peptides, builds very effectively additional stability. This is important however not only effect that hydrogen bonds bring to peptides. Typical formamide-like hydrogen bond chain in secondary structure play a role as „communication” medium that allows effectively couple carbonyl stretching modes what can be observed in Amide-I vibration [1] – coupling through space gives weak band against strong through hydrogen bond chain. In effect the most typical vibration of peptides is: in phase coupled C=O stretching mode of carbonyls that lie in one hydrogen bonds chain. The hydrogen bond often seen as weak interaction if considered in peptides often shows its unique property – nonadditivity. The quantum chemistry allows to expect one hydrogen bond enthalpy close to 4,5 kcal/mol – not enough to overcome strain energy upon two, three or four residues and effectively lock short helix. The chain structure allows to turn on cooperativity of hydrogen bonds that can build enthalpy of average hydrogen bond in chain up to ~300% (~13 kcal/mol for chain of 14 bonds) [2]. The cooperativity – strain energy balance is the reason why meet 3-10 helices more often in short peptides and alpha helical fragments in longer ones.

The protonation of the peptides that results in change of the secondary structure can be also driven by hydrogen bond system – even in absence of sensitive to pH side chains the proton affinity shows that peptides are protonated at C-terminus and one can expect the most dramatically changes in this area [3]. The interaction between metal cations and peptides focuses attention number of the researchers. Strong metal – charged peptide interaction usually well defines the structure of interaction area neighborhood, however access to the docking areas is guaranteed by delicate balance of many factors as aminoacid sequence, hydrogen bonds, hydrogen bond arrangement and cooperativity[4]...

References:
Oxime-containing Schiff base ligand and its coordination properties towards nickel(II), zinc(II) and copper(II) ions

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Coordination polymers and grid complexes are structures created as a result of self-assembly of polynuclear complexes. The design of such systems requires the use of algorithms covering most advantageous coordination geometry of the metal ion coordination and ligand binding sites [1-2].

Coordination polymers are defined as infinite systems composed of two basic elements, which are organic ligands and metal ions linked with coordination bond and other weaker interactions. These compounds impress not only the diversity of structures that are created, but most of all they are a group of materials with various properties. Research on the potential application consists primarily of magnetic and optical properties [2].

Grid complexes are complex systems containing metal ions maintained in a scaffold formed by organic ligands arranged perpendicularly. They are very popular because of their interesting magnetic, electronic and photophysical properties [3]. They are considered as potential molecular storage media in the age of miniaturization of electronic devices. The redox and magnetic properties of such systems are fairly well understood [4].

The study of grid complexes in solution is not easy, therefore there are limited data about this in the literature. However, they are a necessary complement to crystallographic data and magnetic measurements. The subject of the study was new polynucleative ligand with the ability to self-assembly. The study included the characterization of the coordination properties of 2-[1-(3,5-dimethyl)pyrazolyl]-2-hydroxyimino-N'-[1-(2-pyridyl)ethylidene]aceto-hydrazide (Hpoap) (Scheme 1) containing several donor functions of different nature towards nickel(II), zinc(II) and copper(II) ions and its ability to aggregate.

Scheme 1. Hpoap - 2-[1-(3,5-dimethyl)pyrazolyl]-2-hydroxyimino-N'-[1-(2-pyridyl)ethylidene]aceto-hydrazide
Protonation constants of ligands, the stoichiometry and the stability constants of complexes of ligand with metal ions were determined by potentiometric titration, mass spectrometry and EPR and UV-Vis spectroscopy.

References:

Happy Anniversary Professor! 😊
Impact of the BOSS ion on the structure, specificity and cooperativity of the Bioinorganic and Biomedical Chemistry Group.


\[ a \] Department of Chemistry, University of Wrocław, F. Joliot-Curie 14, Wrocław, 50-383, Poland.

The whole group loves our boss
Though when our labwork fails, he is rather cross
Chemical problems should quickly be explained
Or you, poor student, yes, you will be blamed.
Work hard, young scientist, and do not be stressed,
Because with an awesome supervisor you have been blessed.

Do not worry, everything will be fine,
You only have to work from dawn till nine!
When he retires, you will miss him a lot,
No one else will help you with that stupid plot.
His is 70? In his heart he’s 32!
He feels so young, the time just flew!
His affection for metal ions still remains unchanged
And explaining unknown phenomena can quickly be arranged.

Although chemistry is his major aim
He really does fancy a little tennis game
He also likes a glass of good wine
And a cozy place where he can dine
If you join him, please do not be late
Or else I do not envy you your fate
But here today, you’re well on time,
So sit back, relax and wish Henryk happy birthday –
You can use a rhyme!
Figure 1. The structure of the HENRYK peptide complex with the Bioinorganic and Biomedical Chemistry Group (without the BOSS ion the complex is completely unstructured).
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XIII International Symposium on Inorganic Biochemistry
Happy Anniversary
1-6 September 2015 Karpacz, Poland

Notebook