6th International Symposium on Bioorganometallic Chemistry

JULY 8-12, 2012, University of Toronto Scarborough, Canada

Book of Abstracts

UNIVERSITY OF TORONTO SCARBOROUGH
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Foreword

We are pleased to invite you to the 6th International Symposium on Bioorganometallic Chemistry (ISBOMC’12) at the University of Toronto Scarborough (UTSC) in Toronto, Canada. UTSC is one of the three sister campuses making up the University of Toronto (St. George, Scarborough and Mississauga).

Bioorganometallic chemistry has become a topic of great interest to both chemists and biologists and a number of promising organometallic drug candidates have now been identified and are in various stages of clinical trials. This meeting serves as a platform to bring together scientists from around the world to discuss exciting new developments in drug discovery and therapeutics, diagnostics, and supramolecular materials. We hope that this meeting will provide a stimulating environment that fosters exchange of scientific information and ideas. All participants are encouraged to explore their favourite bioorganometallic topic and explore the city of Toronto, Canada's largest city and capital of the Province of Ontario.

The city has a number of noticeable architectural landmarks including the Royal Ontario Museum, the CN Tower, and Fort York to name a few. As part of the symposium and to welcome you to Toronto, we will provide a time slot for a guided tour of the city that you might want to explore further after the meeting. The city has a vibrant cultural scene, including a large number of performing art venues and theatres and a range of music genres to suit any taste. Toronto offers a multicultural experience which is best explored by visiting its many neighborhoods and sampling the authentic cuisines. To offer you a snapshot of what Canada has to offer, there will be optional visits to Niagara wine country and Niagara Falls.

I hope you will enjoy this ISBOMC meeting. We have done our best to facilitate that you have time to enjoy other Canadian landmarks and participate in scientific discussions in a less formal environment. The organizers are confident that the tour of Toronto, the wineries of the Niagara region, and a ride on the Maid of the Mist will expose you to some of the Canadian landmarks that will make this meeting memorable. I want to take this opportunity to thank all the volunteers who worked tirelessly to make this meeting happen. It would not have been possible without your dedication and help.

Toronto, July 2012

Bernie Kraatz
Sponsors
Venue and travel directions

The 6th International Symposium on Bioorganometallic Chemistry (ISBOMC’12) will be held at the Humanities Wing (HW) of University of Toronto Scarborough. The lectures will take place in the conference room (HW 216, #2-map) and the poster session will be located in front of the conference room. The conference registration on Sunday, July 9th, will be located just in front of the Ralph Campbell Lounge (#1-map) where the opening mixer will be taking place. On other conference days, the registration desk will be located just outside the conference room.

For transport from the Toronto International Airport (Lester B. Pearson International Airport):

1) Airport Express shuttle bus from Terminal 1 and 3 to downtown Toronto (9 stops including the major hotels and the main Bus station). This route gives you access to the Toronto metro/bus system and GO Transit. Buses leave every 30 minutes. Please use the link below to purchase your ticket online in advance:

http://www.torontoairportexpress.com/

2) Go to Terminal 1, board GO Transit bus, Pearson Airport Express bus, towards 40- Richmond Hill. At Yonge Street at Highway 407 bus stop board the Pickering/York University bus towards 51-Pickering GO station. Get off the bus at the University of Toronto Scarborough.

For access to the Toronto metro/bus system and GO Transit, from UTSC campus, please check the UTSC map on the next page.

Conference Venue (map of UTSC campus) see next page

The map of UTSC campus includes the key places such as the registration and the welcome mixer location as well as the conference hall and poster hall. In addition, a list of suggested restaurants is provided for your convenience. For access to the Toronto metro/bus system and GO Transit please check the bus routes.
1. Ralph Campbell Lounge
   - Registration
   - Welcome Mixer
2. Conference Room HW 216
   - Conference Room
   - Poster Session
   - Late Registration
3. Italian Food, Bakery, Three Amigo's Pub
4. Fossil & Haggis Pub, Pizzeria, Popeye's Chicken, Convenience Store
5. Tim Horton's, Wendy's, A&W, Grocery Store
6. Tim Horton's
7. Subway, Asian Gourmet, Treats, Rex's Den, Convenience Store
8. Market Place
   - Pizza Pizza, Spring Rolls, Pasta Bar
9/10 Transportation
General information

Bus transfers

The buses for the excursions will be 5 min walk from the conference venue. We will offer a guided tour to the buses. Our volunteers will be wearing clothing with the ISBOMC’12 logos. Departure for the guided walk to the bus stop is at 16:15 on Monday, July 9th. The drop off downtown Toronto location is at the Raddison Plaza Hotel (249 Queens Quay West, East of Rees Street, Toronto) where you can board the touring bus at 18:30 (CitySightseeing Toronto) and enjoy an organized 2-hours long Toronto City Tour. After the tour, you will be dropped off at the Nathan Philip Square (corner of Bay Street/Queen Street). To go back to the UTSC, the return busses (marked with the “Magic Bus Company” and ISBOMC12 panel in the front window) will be leaving at 22:30 and 23:00 from the at Nathan Philip Square.

On Wednesday July 11th, the departure bus from the conference venue for the Niagara Falls and winery excursion will be at 13:00. The bus from the conference dinner location will leave for the UTSC by 23:00 pm. Departure times and other pertinent information will be announced.

Poster session

The poster session will take place in the Hall in front of the conference room (HW 216, #2-map) on Tuesday, July 10th. Please hang you posters immediately after arrival to the conference, latest till Tuesday before the morning session and remove them on Thursday, before the conference dinner. The material for poster hanging will be provided in the poster room.

Please vote for your favorite poster!!!! You will find the voting ballot with you badge.

Poster Prizes

There will be 5 poster prizes to be given to outstanding poster presentations. Poster prizes are sponsored by Elsevier, the Royal Society of Chemistry, and the University of Toronto Scarborough.

Refreshments, Lunch and Dinner

Welcome reception will be on Sunday, July 8th in the Ralph Campbell Lounge (#1-map). Cold and warm refreshments will be served every day during coffee breaks and will be located in the hallway in front of the conference room (#2-map). The lunch will be catered daily. Alternative food venues are depicted on the map on the previous page. On Tuesday, July 10th, a BBQ dinner will be provided and will take place on campus. On Wednesday, July 11th, the packed lunch will be provided before boarding the tour bus.

Internet connection

All participants will have access to the wireless internet at UTSC by using the secured wireless network SSID: “UofT” with the following credentials:

Username: isbomc12
Password: utsc2012
Special Journal of Organometallic Chemistry (JOMC) Issue

As a part of the ISBOMC’12 symposium, there will be a special issue of Journal of Organometallic Chemistry (JOMC) as we have done for each of the previous conferences. All conference participants are invited to contribute. Manuscripts should be submitted electronically at http://www.journals.elsevier.com/journal-of-organometallic-chemistry/. All submitted manuscripts will be peer reviewed. The deadline for submission of manuscripts is September 30, 2012.
ISBOMC Advisory Board

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List of Local ISBOMC’12 Organizers

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PLENARY SPEAKERS

Prof. Takashi HAYASHI
Professor of Chemistry
Faculty of Engineering
Department of Applied Chemistry
Osaka University
2-1 Yamadaoka, 565-0871, Suita
Japan
E-mail: thayashi@chem.eng.osaka-u.ac.jp

Background Info

Professor Hayashi obtained his BA, MA and PhD in Engineering from Kyoto University. Specifically, his PhD work was conducted under the supervision of Professor Yoshihiko Ito and focused on the use of chiral ferrocenylphosphine metal complexes to catalyze a range of asymmetric synthesis reactions. His outstanding work in this field led to his immediate appointment to an Assistant Professor within the Faculty of Engineering of Kyoto University following the completion of his Doctorate Degree. He was later promoted to an Associate Professor in Kyushu University, during which time he served as project leader on the Precursory Research for Embryonic Science and Technology (PREST) at the Japan Science and Technology Corporation (JST). He currently resides at the University of Osaka serving as a Professor for the Faculty of Engineering. He serves on the editorial boards for the Journal of Porphyrins and Phthalocyanines as well as the Journal of Inorganic Biochemistry. His key research interests involve the engineering of porphyrin-based hemoproteins with enhanced structure and reactivities by the incorporation of functionalized, artificial heme derivatives.
**Prof. Bernhard K Keppler**

*Professor of Inorganic Chemistry*
*Head of the Institute of Inorganic Chemistry*
*Faculty of Chemistry*
*Institute of Inorganic Chemistry*
*University of Vienna*
*Waehringer Strasse 42, 1090 Vienna*
*Austria*

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**Background Info**

Professor Keppler received his BA in Chemistry from the University of Heidelberg, where he would later complete a PhD in the fields of both Chemistry and Medicine. Presently, he serves as a Professor and Head of the Institute of Inorganic Chemistry at the University of Vienna, Austria. Professor Keppler is a world-renowned expert on bio-inorganic chemistry, coordination compounds and has dedicated his career to discovering several novel anti-cancer compounds. He discovered NKP-1339, a transferring-targeted small molecule that down regulates GRP78, a key regulator of mis-folded protein processing and a tumor survival factor. His findings have been published in over 450 research articles in peer-reviewed journals and several books. He is also on the editorial boards of several scientific journals including: Anticancer Research, Chemical Monthly, Bioinorganic Chemistry and Applications, Journal of Inorganic Biochemistry (2005- 2009) and Current Chemical Biology.
Background Info

Professor Romão received his PhD in Chemistry in 1979 from the Technical University of Lisbon (Universidade Técnica de Lisboa, UTL). His primary research interests in the field of organometallic chemistry focus on the synthesis of new metal derivatives of carbon monoxide (CO) to be used for potential applications in the production of renewable and sustainable energy as well as a novel class of drugs based on the therapeutic activities of CO observed at sub-toxic dosages.
**Prof. Peter Sadler**  
*Professor of Chemistry*  
*Department of Chemistry*  
*University of Warwick*  
*Coventry CV4 7AL*  
*UK*  
*E-mail: P.J.Sadler@warwick.ac.uk*

**Background Info**

Peter Sadler obtained his Bachelor’s, Master’s and Doctorate Degree at the University of Oxford followed by two years as a Medical Research Council Research Fellow in Molecular Pharmacology at the University of Cambridge and the National Institute for Medical Research. In 1973 he was appointed as a lecturer in Chemistry at Birkbeck College, University of London, where he subsequently became reader in Biological Inorganic Chemistry, and professor of Chemistry. In 1996 he was appointed to the Crum Brown chair of Chemistry at the University of Edinburgh, and in June 2007 took up a chair in Chemistry at the University of Warwick where he is also Head of Department. He is a fellow of the Royal Society of Edinburgh (FRSE) and the Royal Society of London (FRS). His research interests focus on the design and chemical mechanism of action of therapeutic metal complexes, including organometallic arene anticancer complexes, photo-activated metal anticancer complexes (for photochemotherapy), metallomacrocycles as anti-virals and stem-cell-mobilizing agents, and metalloantibiotics.
Background Info

Professor Severin was born in Germany in 1967. He earned his BA in Chemistry at the University of Munich (Ludwig-Maximilians-Universität Munich, LMU). In 1996, he completed his Doctorate Degree at LMU (summa cum laude) working in the group of Professor W. Beck with a dissertation in Bioorganometallic Chemistry. Subsequently, he joined the group of Professor M. R. Ghadiri, Scripps Research Institute, USA, as a postdoctoral fellow. In 1997, he returned to the University of Munich and started independent research projects ("Habilitation") at the Department of Chemistry. He was a visiting professor at the University of Vienna (Austria) from March to June 2001. Later that year, he became assistant professor at the Institute of Chemical Sciences and Engineering at the Swiss Federal Institute of Technology, Lausanne (EPFL). In 2009, he was promoted to a full Professor at this same institute. In the Severin group, they investigate dynamic combinatorial libraries of metal complexes with the objective to create adaptive chemical systems, which can be used as versatile sensors for biologically interesting analytes such as sugars, amino acids and peptides.
Prof. Rudolf K. Thauer
Emeritus Professor
Max Planck Institute for Terrestrial Microbiology
Emeritus Group Biochemistry
Karl-von-Frisch-Strasse 10, D-35043 Marburg
Germany
E-mail: thauer@mpi-marburg.mpg.de

Background Info

Professor Thauer obtained his PhD in Biochemistry from the University of Freiburg in Germany, and did postdoctoral work with Karl Decker in Freiburg and Harland Wood at Case Western Reserve. Until 1976, he was an Associate Professor of Biochemistry at the Ruhr-University Bochum, Germany. From 1976 to 2005, he was Professor of Microbiology at the Philipps University, Marburg, Germany. From 1991 to 2007, he was director at the Max Planck Institute for Terrestrial Microbiology in Marburg, Germany, where he now heads an emeritus group within the same institution. During his career, he has extensively studied the energy metabolism of Clostridia, sulphate-reducing bacteria and methanogenic archaea. His observation that methanogenic archaea require nickel for growth led to the discovery of numerous novel nickel enzymes and of the nickel porphinoid cofactor coenzyme F430. He is best known for his review on "Energy Conservation in Chemotrophic Anaerobic Bacteria," which was published in 1977 in Bacteriological Reviews and has been cited more than 1,600 times.
Prof. Anne Vessières-Jaouen
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Paris Cedex 05
France
E-mail: a-vessieres@chimie-paristech.fr

Background Info

Dr. Vessières-Jaouen attended the University of Rennes in France where she received her BA in both Chemistry and Biochemistry. She later completed her PhD in Organometallic Chemistry at the same University working under the guidance of Professor P. Dixneuf. Subsequently, she would go on to complete a second PhD in Biochemistry working with Professor P. Jouan. She serves as a Coordinator of the Department Charles Friedel at the ENSCP (L’ École Nationale Supérieure de Chimie de Paris). Her main area of focus is the field of bioorganometallic chemistry. Specifically, she is involved in the synthesis and structure-activity relationship studies of novel organometallic anti-cancer drugs as well as the development of non-isotopic immunoassays termed Carbonyl Metallo Immunoassays (CMIA) that uses metal carbonyl units as tracers with IR spectroscopy as a detection method.
Conference Program
ISBMOOC’12 at a glance!!!!

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<td>Lectures</td>
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<td>Tour of Niagara Falls and Niagara winery</td>
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| 16:00 – 18:00       | 16:30     | 17:00 – 19:00 | 9:00 – 12:45 |
| Registration        | Tour of Toronto | Posters     | Lectures   |

| 18:00               |           |           |           |
| Welcome Mixer       |           |           |           |

|         |           |           |           |
| 19:00   |           |           |           |
| BBQ Dinner |           |           |           |
Sunday July 8, 2012

16:00 – 18:00 Conference registration (in front of the Ralph Campbell Lounge)

18:00 Welcoming Mixer (Ralph Campbell Lounge)

Monday July 9, 2012

Session I - Bioorganometallic Supramolecular Systems

9:00 – 9:45 Plenary Lecture (PL-1)
K. Severin
Institut des Sciences et Ingénierie Chimiques, Ecole Polytechnique Fédérale de Lausanne (EPFL)

Organometallic Receptors and Sensors for Biologically Interesting Molecules

9:45 – 10:05 B. Therrien (OP-1)
University of Neuchatel, Institute of Chemistry, Ave de Bellevaux 51, CH-2000 Neuchatel, Switzerland

Drug Delivery by Water-Soluble Organometallic Cages

10:05 – 10:45 Coffee Break

10:45 – 11:30 Plenary Lecture (PL-2)
R. Thauer
Max Planck Institute for Terrestrial Microbiology

Organometallic Chemistry Involved in CO₂ Reduction with H₂ to Methane in Methanogenic Archaea

11:30 – 11:50 K. Ma (OP-2)
Department of Biology, University of Waterloo

Thermostable Iron- and Zinc-containing Alcohol Dehydrogenases

11:50 – 12:10 FLASH PRESENTATIONS

M. Salmain (PP-1)
Laboratoire Charles Friedel, Chimie ParisTec

Design of Artificial Metalloenzymes Resulting from the Functional Mutation of Papain

S. Martic (PP-2)
Department of Physical and Environmental Sciences, University of Toronto Scarborough

Monitoring Copper-Tau Interactions Electrochemically

12:10 – 13:40 LUNCH
Session 2 - Medicinal Organometallic Chemistry

13:40 – 14:25  Award Lecture (PL-3)
A. Vessières
Laboratoire Charles Friedel, Chimie ParisTech

The Ferrocifen Family and Metal Carbonyl Tracers: Two Facets of Bioorganometallic Chemistry

14:25 – 14:45  C.D. Hartinger (OP-3)
School of Chemical Sciences, The University of Auckland

Exploring Tumor Targeting Strategies with Organometallic Agents

14:45 – 15:05  D. Plażyński (OP-4)
Department of Organic Chemistry, University of Łódź

Biotin and its Derivatives as Acylating Agents in the Friedel-Crafts Reaction. Avidin Affinity, Anticancer Activity of Ferrocenyl Compounds and Fluorescence Properties of Pyrene Derivatives

15:05 – 15:25  L. Oehninger (OP-5)
Institute of Medicinal and Pharmaceutical Chemistry, Technische Universität Braunschweig

Ruthenium(II) N-heterocyclic Carbene Complexes as Enzyme Inhibitors and Antiproliferative Agents

15:25 – 15:45  G.S. Smith (OP-6)
Department of Chemistry, University of Cape Town

Antiplasmodial Activity of Ferrocenyl Thiosemicarbazone Complexes

16:30  Guided Bus Tour of Toronto and self-guided tour
Return busses will leave at 22:30 and 23:00 to return to the University of Toronto Scarborough

Tuesday July 10, 2012

Session 3 - Medicinal Organometallic Chemistry

9:00 – 9:45  Plenary Lecture (PL-4)
P. Sadler
Department of Chemistry, University of Warwick
Organometallic Anticancer Complexes

9:45 – 10:05  W.H. Ang (OP-7)
Department of Pharmacy, National University of Singapore

Selective Release of Platinum(IV) Prodrugs Entrapped within Multiwalled Carbon Nanotubes by Chemical Reduction

10:05 – 10:45  Coffee Break

10:45 – 11:30  Plenary Lecture (PL-5)
B. Keppler
Institute of Inorganic Chemistry, University of Vienna
Preclinical and Clinical Advances with Anticancer Metal Compounds

11:30 – 11:50
C. M. Clavel (OP-8)
Institute des Sciences et Ingenierie Chimiques, EPFL

Thermoresponsive Organometallic Arene Ruthenium Derivatives for Tumor Targeting

11:50 – 12:10
FLASH PRESENTATIONS

M.-A. Richard (PP-3)
Laboratoire Charles Friedel, Chimie ParisTec

Comparative Mechanistic Study of Two Series of Ferrocifens

J.J. Cazares-Marinero (PP-4)
Laboratoire Charles Friedel, Chimie ParisTec

SAHA-Ferrocifen Hybrid and Related Compounds with Anticancer Activity

12:10 – 13:30
LUNCH

Session 4 - BioOrganometallics

13:30 – 13:50
T. Moriuchi (OP-9)
Department of Applied Chemistry, Osaka University

Design of Bioorganometallic Guanosine-Based Gold Complexes

13:50 – 14:10
R.H. Fish (OP-10)
Lawrence Berkeley National Laboratory, University of California

The Chemoselective Reactions of Tyrosine Containing G-Protein-Coupled Peptides with [Cp*Rh(H2O)3](OTf)2, Including 2D NMR Structures and the Biological Consequences

14:10 – 14:30
P. Buglyó (OP-11)
Department of Inorganic and Analytical Chemistry, University of Debrecen

Interaction of [Ru(η6-p-cym)(H2O)3]2+ with an Important Serum Component, Citrate: A Solution Equilibrium and Solid State Study

14:30 – 14:50
T.P. Curran (OP-12)
Department of Chemistry, Trinity College

β-Sheets Bearing an Organometallic Moiety: Peptide Derivatives of 2-Amino-2'-carboxyphenylacetylene Coordinated to Tungsten

14:50 – 15:20
Coffee break

15:20 – 15:40
I.S. Butler (OP-13)
Department of Chemistry, McGill University

Mechanobioorganometallic Chemistry
15:40 – 16:00  
D. Can (OP-14)  
Institute of Inorganic Chemistry, University of Zürich  

*Organometallic Inhibitors with $^{99m}$Tc-Labeled Cyclopentadienyl Derivatives*

16:00 – 16:20  
S. Martic (OP-15)  
Department of Physical and Environmental Sciences, University of Toronto Scarborough  

*Bioorganometallic Probes for Kinase-Catalyzed Phosphorylation Reactions*

16:20 – 16:40  
L. Paul (OP-16)  
Department of Chemistry and Biochemistry, University of Berne  

*Comparison of the Stability and Reactivity Towards Biological Ligands of Different Ruthenium-Hexacationic Cages Using NMR Spectroscopy*

17:00 – 19:00  
POSTER SESSION

19:00  
BBQ Dinner

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**Wednesday July 11, 2012**

**Session: Interactions and Applications of Biological Molecules**

9:00 – 9:45  
Plenary Lecture (PL-6)  
T. Hayashi  
Department of Applied Chemistry, Osaka University  

*Heme Pocket Is an Attractive Cavity for Bioorganometallic Reaction Centers*

9:45 – 10:05  
J. Tucker (OP-17)  
School of Chemistry, University of Birmingham  

*New Approaches and Directions in the Modification of Nucleobases with Ferrocene Unit*

10:05 – 10:45  
Coffee Break

10:45 – 11:05  
R. Gobetto (OP-18)  
Department of Chemistry, University of Torino  

*Hyperpolarized $^{13}$C-MRI*

11:05 – 11:25  
M. Milne (OP-19) (OP-19)  
Department of Chemistry, Western University  

*Development and Evaluation of ParaCEST MRI Contrast Agents Possessing Highly Shifted Amide Proton Signals*

11:25 – 11:45  
X.-A. Zhang (OP-17) (OP-20)  
Department of Physical and Environmental Sciences, University of Toronto Scarborough  

*Manganese Porphyrin Based MRI Contrast Agents*
11:45 – 12:05  **E. Rosenberg (OP-21)**  
Department of Chemistry, University of Montana  

*Kinetic Studies of Pt(en)Cl(NHR) to Guanine Monophosphate*

12:05 – 12:25  **K. J. Kilpin (OP-22)**  
Institut des Sciences et Ingénierie Chimiques, EPFL  

*Rational Design of Ruthenium(II) Arene Complexes as Cancer Targeting Agents*

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**Thursday July 12, 2012**

**Session: CO-Releasing Molecules**

9:00 – 9:45  **Plenary Lecture (PL-7)**  
**C.C. Romao**  
Instituto de Tecnologia Quimica e Biologica da Universidade Nova de Lisboa  

*Metal Carbonyls for CO Therapy: Successes and Challenges*

9:45 – 10:05  **I.J.S. Fairlamb (OP-23)**  
Department of Chemistry, University of York  

*Therapeutically Viable Organometallic CO-Releasing Molecules (CO-RMs) – from Thermal to Photochemical Releasers*

10:05 – 10:45  **Coffee Break**

10:45 – 11:05  **F. Zobi (OP-24)**  
Institute of Inorganic Chemistry, University of Zürich  

*Chemistry and Biology of Biocompatible Transition Metal-Based CO-Releasing Molecules on Cobalamin Scaffolds*

Department of Chemistry, University of York  

*Mechanistic and Synthetic Insight into the Behaviour of Carbon Monoxide-Releasing Molecules*

11:25 – 11:45  **A. E. Pierri (OP-27)**  
Department of Chemistry and Biochemistry, University of California Santa Barbara  

*Photoactive CO Releasing Moieties (photoCORMs) Based on Ruthenium Diimine Carbonyls for Use in Therapeutic Applications and For In Vitro Imaging*
11:45 – 12:05  **H.-G. Schmalz (OP-28)**  
Department of Chemistry, University of Cologne  

*Enzyme-Triggered CO-Releaseing Molecules (ET-CORMs)*

12:05 – 12:20  Closing Remarks and announcement of ISBOMC’14
PLENARY LECTURES
Organometallic Complexes as Receptors and Sensors

Kay Severin

*Institut des Sciences et Ingénierie Chimiques, Ecole Polytechnique Fédérale de Lausanne (EPFL), 1015 Lausanne, Switzerland. E-mail: kay.severin@epfl.ch*

The lecture summarizes attempts to make receptors and sensors for biologically interesting analytes using (mostly) organometallic transition metal complexes. I will describe rhodium and ruthenium complexes which are able to selectively bind and detect small ions (fluoride, chloride, lithium), complex bio-ligands such as peptides, and gases. Furthermore, I will discuss possibilities to improve the discriminative power of sensors by using pattern recognition techniques. In particular, I will focus on indicator displacement assays, which are well suited for pattern-based analysis methods.

References


Organometallic Chemistry Involved In CO₂ Reduction With H₂ To Methane In Methanogenic Archaea

K. Thauer

Max Planck Institute for Terrestrial Microbiology, Emeritus Group Biochemistry, Karl-von-Frisch-Strasse 10, D-35043 Marburg

Estimates are that about 1 billion tonnes of methane are generated per year in anoxic environments via the action of methanogenic archaea. About one third of the methane is produced by reduction of CO₂ with 4 H₂ to methane. This exergonic process (∆G° = -131 kJ/mol) is coupled with the conservation of energy in the form of ATP. Most of the methanogenic archaea growing on H₂ and CO₂ are autotrophs, i.e. they can use CO₂ as their sole carbon source. Autotrophic CO₂ fixation proceeds via the Wood-Ljungdahl pathway involving carbon monoxide as intermediate in acetyl-CoA synthesis.¹

Hydrogenotrophic methanogens generally contain three types of [NiFe]-hydrogenases and one [Fe]-hydrogenase. In the active site of the [NiFe]-hydrogenases the iron carries one cyanide and two CO ligands. The iron in the [Fe]-hydrogenase is ligated by two CO and an unique acyl group.² The reduction of CO₂ to methane proceeds via methyl-cob(III)alamine³ and most probably methyl-Ni(III)F₄₃₀ as intermediates.³-⁶ The involvement of methyl-Ni(III)F₄₃₀ is still disputed. The reduction of CO₂ into the methyl group of acetyl-CoA proceeds via methyl-cob(III)alamine, and a methyl-Ni(III) and an acetyl-Ni(III) intermediate. The involved nickel is part of a protein bound [NiNi]-center bridged via a thiolate to a [4Fe4S] cluster. The oxidation state of the proximal Ni, which accepts the methyl group from the methylated corrinoid protein, is still disputed.⁷

References

PL-3

The Ferrocifen Family and Metal Carbonyl Tracers: two facets of Bioorganometallic Chemistry

Anne Vessières

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Our contribution to the domain of Bioorganometallic Chemistry is mainly focused on two different topics, namely the development of new organometallic drugs and the use of metal carbonyl complexes for infrared quantification of minute amount of tracers.1 2 Regarding the first topic, we have prepared a large series of molecules possessing the ferrocenyl-diphenyl-butadiene skeleton 1, and recently their corresponding [3]ferrocenophane complexes 2. All these complexes show a significant antiproliferative effect on cancers cells (10 µM< IC50 >32nM on 60 cell lines).3 However, they seem to act via different mechanisms that will be discussed. In vivo experiments performed with 1B on 9L rat gliosarcoma have shown that its formulation in lipid nanocapsules led to almost total disappearance of implanted tumors.4

Concerning the second topic, we have recently synthesized antibodies multilabelled with metal carbonyl tracers.5 They open the way for the development of a full solid phase carbonyl metallo immunoassay (CMIA) based on their quantification by infrared. Finally, the subcellular imaging of a Re(CO)3 complex, in a single cell, by photothermal infrared spectromicroscopy will be presented. This cutting edge technique uses a set-up coupling atomic force microscopy (AFM) and a tunable pulsed infrared laser. Precise localisation of the rhenium complex in the cell nucleus is obtained using detection of the characteristic \(\nu(CO)\) bands of the complex.6

References
Organometallic Anticancer Complexes with New Mechanisms of Action

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I will describe our recent work on the design and mechanism of action of low-spin d⁶ ruthenium(II)¹ and osmium(II)² arene and iridium(III)³ cyclopentadienyl anticancer complexes. As is the case for organometallic catalysts (e.g. olefin metathesis and transfer hydrogenation), both the metal and the ligands can play critical roles in activity.⁴ The kinetics and thermodynamics of ligand substitution and metal- or ligand-based redox reactions need to be controlled to allow transport and delivery to the target site, followed by controlled activation for interaction with targets.

Monofunctional RuII arene complexes can distort DNA by specific interactions with G bases, sometimes dual-mode involving also arene intercalation.⁵ More inert complexes can be activated by ligand-centred redox reactions, including azopyridine OsII arene complexes which are highly active both in vitro and in vivo.²

Analysis of NCI 60-cell-line data,⁶ reveals strong cell selectivity, a surprising similarity in the mechanisms of action of OsIII and IrIII complexes, and multitargeting mechanisms of action, different from platinum drugs. These may include modulation of the redox status of cancer cells via catalytic hydride transfer from coenzyme NADH to the metal.⁷

Additional mechanisms of targeting complexes include incorporation of cell-penetrating and receptor-binding peptides and activation by visible light.⁸⁻⁹

Acknowledgements

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References

Preclinical and clinical advances with anticancer metal compounds

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Considerable progress has been made recently in the development of metal-based anticancer compounds, both non-platinum and platinum, as will be exemplified by the early phases of clinical evaluation of the ruthenium(III) complex NKP-1339 and the advanced preclinical development of oxaliplatin derivatives. NKP-1339 has recently entered the phase IIa part of a clinical study in cancer patients, led by Daniel Von Hoff, Virginia G. Piper Cancer Center (Scottsdale, AZ, USA), and Howard Burris III, Sarah Cannon Research Institute (Nashville, TN, USA). Preliminary results of the phase I (dose escalation) part had been presented at the Annual Meeting of the American Society of Clinical Oncology 2011, and in the meantime phase I was completed at the maximum tolerated dose. Anticancer activity was observed in patients with gastro-intestinal neuroendocrine tumors, accompanied by substantially improved quality of life. This finding is particularly remarkable as this malignancy is extremely difficult to treat and efficacious new drugs are urgently needed. Activity was also noted in a variety of other solid tumors, all of them heavily pretreated. The lack of common chemotherapy-related toxicities, the interference with homeostasis of the endoplasmic reticulum as well as synergies with various established anticancer drugs make NKP-1339 a proper candidate for combination therapies.

Among a series of oxaliplatin derivatives, methyl-substituted analogues were identified as being more active and better tolerable than the parental drug in preclinical settings. Synthesis of an enantiomerically pure compound could be established, and in vivo studies revealed distinct advantages of this derivative, in particular reduced impairment by resistance mechanisms, reduced dependence on immunogenic cell death induction, lower systemic toxicity and markedly reduced signs of the dose-limiting neuropathy typically associated with oxaliplatin treatment. Final preclinical developmental steps are currently being planned with the prospect of a clinical study in the very near future.

These and other examples, such as gallium and lanthanum compounds as well as platinum complexes targeted to bone tissue, illustrate the great potential still inherent in the development of anticancer metallopharmaceuticals.

References

Hemoproteins have one or several heme cofactors within the interior, the so-called “heme pocket”. In a series of heme cofactors, heme $b$, protoporphyrin IX iron complex, is found in the ubiquitous hemoproteins and bound in the heme pocket via the combination of multiple non-covalent interactions as well as a direct coordination between heme iron and one or two axial ligand(s). The heme $b$ cofactor in the corresponding hemoproteins is usually removable under acidic conditions, and then replaceable with an artificially modified heme moiety. Even in the case of cytochrome $c$ where heme $c$ is linked to the heme pocket via covalent linkage, it is known that the heme $c$ cofactor is also removable. These processes suggest that a heme pocket will provide an attractive cavity or concave as a binding site not only for native or modified heme but also for an organometallic complex. Over the last decade, our group has mainly focused on the insertion of various artificially generated prosthetic groups such as iron porphycene, iron corrole or modified protoheme IX into the apoproteins from myoglobin, horseradish peroxidase, and P450cam to modulate those chemical properties. In a series of these works, it is found that the interaction between a prosthetic group and heme pocket is essential for the regulation of these hemoprotein functions.$^1$ Furthermore, we have recently started to insert several organometallic species as an artificial prosthetic group into apoproteins to create a new bioorganometallic catalyst (Figure 1). Here, I introduce three kinds of reconstituted hemoproteins with organometallic complexes; (1) [FeFe]-hydrogenase model was constructed by apocytochrome $c$ with a diiron carbonyl cluster to generate $H_2$ in the presence of a Ru-complex as a photosensitizer. In this system, the diiron carbonyl cluster is bound in the heme pocket via two cysteine side chains and exhibits the $H_2$ evolution activity in the complete aqueous condition.$^2$ (2) Cobalt corrin will be an attractive complex as a vitamin B$_{12}$ model. Myoglobin reconstituted with tetradehydrocorrin cobalt(II) complex was prepared and characterized by X-ray crystal structure analysis, suggesting that the cobalt complex is completely located in the myoglobin heme pocket. Furthermore, the cobalt(I) and cobalt(III)–$CH_3$ species in the heme pocket were clearly detected by UV-vis spectroscopy upon the addition of dithionite and $CH_3$I, respectively. Interestingly, the methyl group was found to transfer to the His93 imidazole nitrogen in the distal heme pocket. This seems to be a functional model of methionine synthase. (3) It is found that the apoprotein of nitrobindin still remains a stable $\beta$-barrel structure which seems to be an attractive reaction cavity. Therefore, to create a new biocatalyst, a rhodium complex was introduced into the barrel structure via covalent linkage. The organometallic complex is found to exhibit the catalytic activity toward phenylacetylene polymerization with the stereostructure regulation of poly-phenylacetylene due to the hemoprotein matrix.

Figure 1. Representative scheme of hemoprotein reconstitution with an artificial metal complex.

References

Metal Carbonyls for CO Therapy: Successes and Challenges

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Carbon Monoxide (CO), is well-established as a signaling molecule with important physiological and cytoprotective properties. Accordingly, inhalation of CO gas elicits beneficial therapeutic effects on a variety of disease situations, namely those with inflammatory component, like organ transplant, myocardial infarct, rheumatoid arthritis and many others. Since the intrinsic and practical limitations of therapeutic inhalation of CO are easily recognizable, the use of pro-drugs that can deliver CO in sub-toxic, therapeutically effective amounts was envisaged. Transition metal carbonyl complexes were proposed in 1995, but the first examples of biologically active CO-Releasing Molecules (CORM-2 and CORM-3) were reported in 2002 and 2003 by Motterlini and Mann. These complexes of the type [RuII(CO)3L3] and a few other of the type [Mo(CO)xL(6-x)] have indeed recapitulated the biological and therapeutic effects of CO in a large variety of in vitro and in vivo models. Organic CO-RMs were also studied, but one decade of systematic search at Alfama Ltd. still considers [M(CO)xL_y]± complexes the most flexible source of CO-RMs.

In spite of the many positive results and important proofs-of-concept obtained with these experimental CO-RMs, their chemical properties preclude their pharmaceutical use. For example, their rapid decomposition in circulation strongly hampers pharmacokinetic studies, prevents tissue targeting and compromises the understanding of their mode of action.

In order to overcome this situation CO-RMs must be equipped with drug-like properties that enable the control and monitoring of their ADME profile, pharmacokinetics and tissue specificity. They must be soluble, stable in air and in plasma and targeted to reach the diseased tissues, and deliver CO where it is needed. In other words, they must be tailor-made for particular, specified indications.

The methodology required to reach this end and bring CO-RMs to the clinic will be discussed and exemplified by the recent data acquired at Alfama Inc on a lead CO-RM designed for the treatment of acute liver failure.

References

ORAL PRESENTATIONS
Drug Delivery by Water-Soluble Organometallic Cages

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The last decade has seen the field of metalla-assemblies moving towards applications. Not only are we still seeing beautiful new two and three-dimensional constructions appearing in the literature at regular pace, but nowadays, we are observing as well metalla-assemblies with functions. Indeed, they have been used as micro-reactors, sensors or as molecular flasks, to name just a couple of examples. Nevertheless, in recent years, another application for metalla-assemblies capable of encapsulating guest molecules has emerged. The ability of some metalla-assemblies to act as water-soluble containers to solubilise and protect guest molecules in biological media has been exploited, thus offering new opportunities in the fascinating field of coordination-driven self-assembly.1-3

References
Thermostable Iron- and Zinc-containing Alcohol Dehydrogenases

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Anaerobic hyperthermophilic microorganisms, such as *Thermotoga* and *Thermococcus* can grow on carbohydrates and peptides to produce ethanol as an end product. Alcohol dehydrogenase (ADH) is a key enzyme catalyzing the production of alcohols. Several iron- and zinc-containing alcohol dehydrogenases are characterized from hyperthermophilic archaea and bacteria, but it is still not known how the choice for iron or zinc is made. It appears that both iron- and zinc-containing ADHs in archaea represent the most thermostable ADHs.\(^1\)\(^2\) A highly active ADH from hyperthermophilic archaeon *Thermococcus guaymasensis* was purified to homogeneity and was found to be a homotetramer with a subunit size of 40 ± 1 kDa. Metal analyses revealed that this NADP\(^+\)-dependent enzyme contained 0.9 ± 0.03 g atom zinc per subunit. It was a primary-secondary ADH and exhibited a substrate preference for secondary alcohols and corresponding ketones. There was no observation about the loss of zinc and the half-life at 95 °C was 24 hours, representing the most thermostable ADH. Anaerobic hyperthermophilic bacteria could also have iron- and zinc-containing ADHs, but they seem to be less stable. An ADH was purified from *Thermotoga hypogea*, and it contained 1.020.06 g-atoms of iron per subunit. The enzyme was a homodimer with a subunit molecular mass of 401 kDa. It had a half-life of about 10 hours at 70°C, and its catalytic activity increased along with the rise of temperatures up to 95°C. It was oxygen sensitive, however, loss of enzyme activity could be recovered by incubation with dithiothreitol and ferrous iron. When the iron was lost upon exposure to oxygen, zinc was incorporated, resulting in an inactive enzyme, which may be caused by the different coordinating ligands that might change the binding site stereo-structure leading to the loss of its catalytic activity. This was further supported by the fact that its activity was proportional to its iron content and it was reciprocal to its zinc content. Both enzymes were oxygen-sensitive and were successfully cloned and over-expressed in *E. coli*. The recombinant ADHs had indistinguishable properties from the native ones. Sequence analyses showed that they were difference groups of ADHs from archaea and bacteria. The nature of the ligand coordination for both iron and zinc requires further investigation.

References
Platinum complexes are among the most widely applied anticancer chemotherapeutics. However, they have low selectivity for tumor tissue, which results in adverse effects and limits the deliverable dose. Therefore, we are aiming for the development of targeted and targeting drugs, designed to interact selectively with a biomolecular target or to be selectively transported to and accumulated in the tumor, respectively. Ruthenium coordination compounds with low general toxicity have shown promising anticancer activity in clinical trials. More recently, organometallic ruthenium(arene) complexes have moved into the focus of interest and it was shown that the ligand sphere strongly influences their chemical and biological properties.

We have prepared a series of Ru(arene) compounds functionalized with flavonoids, maleimide or peptides in order to obtain either compounds that can inhibit topoisomerase, or enrich selectively in cells or cell compartments. Two synthetic approaches will be presented that include the functionalization of the arene or employing hydroxypyrones as bioactive and carrier ligands. These data will be complemented by studies on the reactivity to different biomolecules, with characterization of the adducts by spectroscopic and separation methods. The anticancer activity of the compounds as compared to established chemotherapeutics and drug candidates will be discussed.

References

Biotin and its Derivatives as Acylating Agents in The Friedel-Crafts Reaction. Avidin Affinity, Anticancer Activity of Ferrocenyl Compounds and Fluorescence Properties of Pyrene Derivatives

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The biotin-(strept)avidin system, based on the extremely high affinity of biotin and biotinylated molecules for the proteins avidin or streptavidin (Kd~10^{-13}–10^{-15} M), is widely used in bioanalysis, drug delivery and materials science.

The biotin moiety is usually attached to biomolecules, spacers or reporter groups using C–N bond forming reactions. The conjugates obtained in this way display relatively high affinity to (strept)avidin (although usually markedly lower than the affinity of parent biotin). We reported a conceptually novel approach to the biotinylation of electron-rich reporter molecules such as redox-active ferrocene and rutenocene and luminescent pyrene via formation of carbon-carbon bond. This approach is based on the Friedel-Crafts reaction using D-biotin or biotin-derived long-chain carboxylic acids as acylation agents.

It is well known that cancer cell lines overexpress many tumor-specific receptors, e.g. biotin. The biotin is taken up from the intestinal content via Sodium-Dependent Multivitamin Transporter (SMVT) – a product of Slc5a6 gene – expressed in the apical region of the epithelial cells. Thus we selected three different human intestine-derived cell lines: COLO-205 (colorectal adenocarcinoma), HCT116 (colorectal carcinoma) and SW620 (colorectal adenocarcinoma) to check whether they differ in response to ferrocenyl derivatives of biotin.

In this presentation we disclose synthesis of a new biotin derivatives of ferrocene, rutenocene and pyrene, their affinity for avidin, fluorescence properties of pyrene derivatives, and anticancer activities of ferrocenyl compounds.

References

Ruthenium(II) \(N\)-heterocyclic Carbene Complexes as Enzyme Inhibitors and Antiproliferative Agents

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Since the successful application of ruthenium derivatives like KP1019 and NAMI-A as anticancer drugs, ruthenium based complexes have been widely synthesized and studied as bioactive compounds.\(^1\) Based on this fact and on recent promising results from our group concerning \(N\)-heterocyclic carbene (NHC) gold(I) complexes\(^2\) as well as Grubbs catalysts,\(^3\) we synthesized a series of NHC ruthenium(II) derivatives and performed a biological screening. The new complexes showed an effective inhibition of selenocysteine and cysteine containing enzymes (e.g. thioredoxin reductase (TrxR) and cathepsin B), which are overexpressed in cancer cells. In the case of TrxR one of the derivatives showed an EC\(_{50}\) value in the low nanomolar range. We also evaluated the effects on the proliferation of cultured tumor cells as well as the influence on tumor cell metabolism (e.g. cell morphology and oxygen consumption, see figure). It was demonstrated that ruthenium(II) NHC complexes are able to trigger distinct biological effects related to cancer chemotherapy. The enzyme inhibitory as well as antiproliferative activity were dependent on the \(N\)-residues of the benzimidazol-2-ylidene core.

References

Antiplasmodial Activity of Ferrocenyl Thiosemicarbazone Complexes

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Polyamines such as putrescine, spermidine and spermine are simple natural organic scaffolds occurring in polycationic form, and are widely distributed in animals and plants. Polyamines are involved in diverse biological processes including cell proliferation and differentiation, regulation of gene expression, translation, modulation of cell signalling and membrane stabilization. Thiosemicarbazones are a class of compounds noted for their wide range of pharmacological properties and are known to act through the chelation of endogenous metals required for cell function. We recently reported on the biological properties of a series of cyclopalladated thiosemicarbazones and on the synthesis of ruthenium-arene complexes coordinated to a poly(propyleneimine) dendritic scaffold, showing a clear correlation between the size of the compound and the cytotoxicity. It is the multivalent nature of these branched polyamine scaffolds which often leads to an increased interaction between a dendrimer-drug conjugate and a target bearing multiple receptors. Conjugation of chemotherapeutic drugs to polyamines has been reported to yield enhanced efficacy and selectivity towards tumour cells.

With the known potent activity of the antimalarial agent, ferroquine, and following the targeted approach to introduce multifunctionalities, we set out to prepare ferrocenylthiosemicarbazone functionalised polyamine scaffolds. In this presentation, we report on a series of ferrocenyl thiosemicarbazone complexes and their antiplasmodial activity against the malaria parasite P. falciparum.

References

Selective release of platinum(IV) prodrugs entrapped within multiwalled carbon nanotubes by chemical reduction

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Platinum-based anticancer drugs constitute some of the most effective chemotherapeutic regimes but they are limited by high toxicities and severe side-effects arising from premature aquation and non-specific interactions. Macromolecular delivery agents can be used to shield platinum drugs from adventitious binding and as a platform to attach targeting groups, as a strategy to mitigate some of these limitations. We conceived of an approach to utilise carbon nanotubes as a protective shell for stable platinum(IV) prodrugs entrapped within its inner cavities. An inert and highly hydrophobic platinum(IV) complex was designed to be entrapped within multiwalled carbon nanotubes via hydrophobic-hydrophobic interactions. Upon chemical reduction, the drug was converted to its cytotoxic and hydrophilic form and released from the carrier, via a drastic reversal in hydrophobicity, for DNA-binding. This simple method of hydrophobic entrapment and controlled release by chemical reduction and hydrophobicity reversal, exploiting the platinum(IV) scaffold as a prodrug, could form the basis of other target delivery strategies into cancer cells.

References

Thermoresponsive Organometallic Arene Ruthenium Derivatives for Tumour Targeting

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Many of the most widely applied anticancer agents exhibit severe side-effects, including in extreme cases, secondary cancers that are only detected a long time after administration of the drug has ceased. A promising approach to overcome non-selectivity relies on drug enhancement by the application of external techniques, such that the toxicity of the drug is low until it is activated at the tumour site. One such combination approach is to combine chemotherapy with hyperthermia at the tumour site. Indeed, the cytotoxicity of some anticancer drugs is enhanced under mild hyperthermia (40-42°C), even though the drugs also work under normal conditions, and were not intentionally designed for this application. 1 The thermosensitivity of small molecule drugs can be enhanced by attaching them to thermosensitive macromolecules, e.g. liposomes drug carriers, that are insoluble at 37°C and become soluble under hyperthermia and cross the cell membrane. However, the development of low molecular weight thermosensitive drugs that exclude macromolecular carriers would be attractive. As a first proof-of-concept, we synthesized thermoactive molecular derivatives of chlorambucil (CLB), that are essentially inactive at 37°C, and are activated by mild hyperthermia (41°C) in vitro. 2 This behavior, referred to as thermoactivity, was achieved by covalently linking perfluorinated 'pony tails' to CLB, as perfluorinated compounds were shown to be highly thermoresponsive in the field of catalysis. Herein, we describe the extension of thermoresponsive derivatization to a series of new organometallic arene ruthenium complexes. These complexes include a pyridine ligand derivatized with perfluorinated pony tails and their corresponding hydrocarbon analogues. They were screened in various cancer cell lines (A2780 ovarian carcinoma cisplatin-sensitive and resistant, MCF-7 and MDA-MBA-231 breast carcinomas, A549 human lung carcinoma, SW40 colon cancer) and two compounds exhibit thermoresponsive cytotoxicity towards cancerous cells. We have shown that organometallic ruthenium complexes modified with a perfluorinated chain can exert thermoresponsive behavior to target tumour tissue. The concept uses hyperthermia to trigger drug cytotoxicity inside heated tumour cells. This discovery opens the way towards the rational design of other thermoactive organometallic anticancer drugs.

References

Bioorganometallic chemistry is a rapidly growing research field at the interface of various disciplines. Conjugation of organometallic compounds with biomolecules such as DNA, amino acids, and peptides is envisioned to provide novel systems depending on the properties of both components. Nucleobases of DNA possess acceptors and donors for hydrogen bonding, which permits self-association into various nano-architectures. A variety of modified nucleobases with fluorescent, electrical, magnetic, and metal ion binding properties have been reported to expand the scope of their applications. A typical example is the assembly of guanosines and their derivatives to octameric or polymeric species in the presence and absence of a cation. Herein, we report the design, synthesis, and characterization of new type bioorganometallic compounds bearing guanosine and gold complexes.

A guanosine-based Au(I) isonitrile complex $\text{GAu(I)}$ and cyclometallic Au(III) complex $\text{GAu(III)}$ were obtained from 8-bromoguanosine. $\text{GAu(I)}$ was demonstrated to serve as the reliable G-octamer scaffold via self-assembly, wherein the quartet and octamer were formed in the absence and presence of a potassium ion, respectively, exhibiting a switchable emission based on Au(I)-Au(I) interaction. $\text{GAu(III)}$ was also performed to form the empty quartet, octamer, and polymeric columnar aggregate depending on the presence of a potassium ion.

References
The Chemoselective Reactions of Tyrosine Containing G-Protein-Coupled Receptor Peptides with [Cp*Rh(H2O)3](OTf)2, Including 2D NMR Structures and the Biological Consequences

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The bioconjugation of organometallic complexes with peptides has proven to be a novel approach for drug discovery. Therefore, we report a new paradigm for the facile and chemoselective reaction of tyrosine containing G-protein-coupled receptor (GPCR) peptides with [Cp*Rh(H2O)3](OTf)2, in water, at room temperature, and at pH 5-6. We have focused on three important GPCR peptides; namely, [Tyr1]-leu-enkephalin, [Tyr4]-neurotensin(8-13), and [Tyr3]-octreotide, each of which, has a different position for the tyrosine residue, together with competing functionalities. Importantly, all other functional groups present; i.e., amino, carboxyl, disulfide, phenyl, and indole, were not prominent sites of reactivity by the Cp*Rh tris aqua complex. Furthermore, the influence of the Cp*Rh moiety on the structure of [Tyr3]-octreotide, was characterized by 2D NMR, resulting in the first representative structure of an organometallic-peptide complex. The biological consequences of these Cp*Rh-peptide complexes, with respect to GPCR binding and growth inhibition of MCF7 and HT29 cancer cells, will be presented for the [(η6-Cp*Rh-Tyr1)-leu-enkephalin](OTf)2, and [(η6-Cp*Rh-Tyr3)-octreotide](OTf)2, complexes.

References

Interaction of [Ru(η⁶-p-cym)(H₂O)₃]²⁺ with an Important Serum Component, Citrate: A Solution Equilibrium and Solid State Study

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Half-sandwich type ruthenium(II) complexes with promising antiproliferative activity are attracting increasing attention.¹ When administered, depending upon the thermodynamic stability and kinetic inertness, these compounds may not remain intact in the body and after partial or complete dissociation of the coordinated ligand(s) it is very likely that the ruthenium containing half-sandwich cation will interact with different serum components. Therefore, for a better understanding the existing differences in the antiproliferative activity of these ruthenium compounds their biotransformation processes in the body also need to be considered.

For this purpose and in continuation of our work on this field,² the interaction between [Ru(η⁶-p-cym)(H₂O)₃]²⁺ and an important low molecular weight serum component, citric acid, was studied with the aid of combined pH-potentiometric, ¹H-NMR and ESI-TOF-MS methods in aqueous solution. For comparative purposes propane-1,2,3-tricarboxylic acid without an alcoholic-OH group in position 2 was also investigated.

In this contribution stoichiometries, stability constants and the most plausible solution structures of the complexes formed in the systems will be presented. Depending upon the pH, citrate was found to coordinate to the metal ion via [COO⁻, COO⁻, OH] or [COO⁻, COO⁻, O⁻] fashion yielding mononuclear complexes with high stability. As a consequence at physiological pH the hydrolysis of the metal ion is completely hindered even at 1:1 metal to ligand ratio. Crucial role of the alcoholic/alcoholate function of the citric acid in [Ru(η⁶-p-cym)(H₂O)₃]²⁺ binding is reflected in the low stability of the species formed with tricarballylic acid. The X-ray crystal structures of [Ru(η⁶-p-cym)(citrH)]·H₂O·CH₃OH (1) (Scheme) and 2[Ru(η⁶-p-cym)(citrH)]·3H₂O (2) being the first published structures of an organometallic Ru(II)-citrate and both featuring a [COO⁻, COO⁻, OH] coordinated ligand, will also be reported.

References

Acknowledgements
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β-Sheets Bearing an Organometallic Moiety: Peptide Derivatives of 2-Amino-2′-carboxyphenylacetylene Coordinated to Tungsten

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Nearly 20 years ago Kemp and Li reported that peptide derivatives (1) of 2-amino-2′-carboxyphenylacetylene (2) adopt β-sheet conformations.1 One of the key structural elements in 1 is the central alkyne.

Given our ongoing interest in probing possible uses of tungsten-alkyne coordination to generate peptides with defined three-dimensional conformations,2 we have prepared and examined several peptide derivatives like 1. Our work with these derivatives has confirmed the earlier conclusions by Kemp and Li that these molecules adopt β-sheet conformations in solution. We have also observed that as longer peptides are attached to 2 the resulting species aggregate in solution. We have also prepared mono-alkyne complexes (3) by reacting peptide derivatives like 1 with one equivalent of W(CO)₃(dmtc)₂. Conformational analysis of these monoalkyne complexes shows that the β-sheet conformation is maintained after coordination to tungsten. Finally, we have attempted to form the corresponding bis-alkyne complexes (4) by reacting two equivalents of peptide derivatives like 1 with W(CO)₃(dmtc)₂. Problems encountered in the synthesis of these bis-alkyne complexes will be presented.

References

Mechanobioorganometallic Chemistry

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Mechanochemistry is the term applied to bond-breaking reactions that are induced by grinding materials together in ball mills. This is actually an old area that is now attracting considerable attention because such “solventless” reactions can be considered to be “green chemistry” and provide opportunities different to those in conventional solution-based (including solvothermal) syntheses.¹ Since grinding materials in a ball mill produces local heating and possibly even melting, mechanochemistry can also be considered to be closely related to chemistry in the melt phase.² We have now initiated a broad examination of the possibilities of mechanochemistry in the solid-state synthesis of bioorganometallic compounds. Preliminary work has been done on the reactions of caffeine, theobromine and other pharmaceutically-relevant derivatives with metal carbonyls and ferrocenes and the results of these initial studies will be presented.

References

Organometallic Inhibitors with $^{99m}$Tc-Labeled Cyclopentadienyl Derivatives

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Organometallic complexes with bioactive ligands are nowadays interesting for both, the noninvasive imaging of biological features and the therapeutic treatment of diseases. While several transition metals across the periodic table are frequently used for therapy, $^{99m}$Tc is the most prominent nuclide in nuclear medicine.[1, 2] Tridentate $\sigma$- or $\pi$-donors, coupled to targeting vectors are popular ligand systems for the $\text{fac-}[^{99m}\text{Tc}(\text{CO})_3]^+$ core.[3] Whereas widely used in synthetic organometallic chemistry, Cyclopentadiene (Cp) is for bioinorganic imaging an uncommon ligand. Missing any polarizing heteroatoms, the molecule is hydrophobic and therefore in fact unsuitable for aqueous syntheses, which is a key criterion for $^{99m}$Tc-chemistry. Moreover Cp and many derivatives are unstable as a monomer and undergo Diels-Alder polymerisation. Meggers et al. outlined with protein kinase inhibitors that organometallic complexes, as compared to organic compounds, can have the property of enhanced three dimensional population of chemically relevant biological space, such as binding cavities of proteins.[4] Such molecules therefore can achieve high selectivity for specific targets. We lately demonstrated with organometallic carbonic anhydrase inhibitors (CAi), that compounds containing [(Cp)Re(CO)$_3$] truly follow this concept.[5] Moreover, [(Cp)Re(CO)$_3$] structurally can be introduced into bioactive substances by replacing phenyl rings.[6] Combining these two fundamental observations, bioorganometallic complexes containing this moiety exhibit therefore a high potential as therapeutic and as diagnostic agents.

We will present recent results on organometallic carbonic anhydrase inhibitors and a new labeling strategy, which allows the generation of two different bioactive imaging probes in one pot and from one substrate. This will enable the targeting of two different biological relevant functions, which will increase the diagnostic information. Furthermore, we demonstrate with the example of new organometallic analogues of well-known HDAC inhibitors, that the principle of replacing phenyl rings by [(Cp)Re(CO)$_3$] is consistent to a large extent.

References
Bioorganometallic Probes for Kinase-Catalyzed Phosphorylation Reactions

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Protein kinases catalyze the phosphorylation of proteins and modulate fundamental cellular function including cell regeneration and death.¹ Hyperactivity of some kinases is recognized as a molecular cause for diseases, including some cancers and tauopathies.² As a result, signal pathways involving protein kinases are currently undergoing intense studies. In an effort to develop an alternative to commonly used methodologies towards monitoring the kinase-catalyzed phosphorylations and inhibitor screening, we designed 5'-γ-ferrocenyl (Fc)-adenosine triphosphate (Fc-ATP) and demonstrated its utility for the electrochemical detection of kinase-catalyzed phosphorylations of the surface-bound peptides.³ Here we describe how we utilize anti-ferrocene antibodies (Fc-Ab₁) as a versatile bioanalytical tool for developing a new biosensing strategy able to monitor phosphorylation reactions of Tyr/Thr/Ser residues in peptides and proteins on surface and in solution.⁴ In a biochemical assay, we apply the Fc-Ab₁ / Ab₂ system for visualization of the protein kinase-driven transfer of the γ-Fc-phosphate group from Fc-ATP to the hydroxyl group of a peptides or proteins, and compare the reaction kinetics of Fc-ATP versus ATP. In addition, we carry out a head-to-head comparison of the Fc-ATP conjugate and its performance in cell lysate with the standard [γ-3²P]ATP radiolabel. We demonstrate the generality of the Fc-Ab₁ for detection of a range of protein kinase activities and inhibitor screening in a versatile immunoarray format.

References

Comparison of stability and reactivity towards biological ligands of different ruthenium-hexacationic cages using NMR spectroscopy

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Ruthenium-based anticancer drugs have received much attention over the last decades since they are known to possess less severe side effects than the well-used platinum drugs.1–3 Recently, we and other groups have designed different ruthenium metalla-assemblies, especially hexacationic metalla-prisms, which can encapsulate various planar molecules either permanently or reversibly. This property makes the metalla-cages useful in drug delivery, since they can act as “Trojan Horses” to deliver drugs into cancer cells.4,5

The aim of our work is to determine the behaviour of different metalla-cages under physiological conditions, with or without a guest molecule encapsulated, using various NMR techniques and thereby find possible biological targets for these complexes in biological media. To identify these targets the interactions of the metalla-assemblies with amino acids, nucleotides, glutathione, and other selected biomolecules like glucose, lactic acid or ascorbic acid have been monitored.

Chart 1. The three different metalla cages used for investigation.

References
New Approaches and Directions in the Modification of Nucleobases with Ferrocene Units

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The tagging of ferrocene to nucleic acids and their components is a topical theme, not least due to continued interest in the electrochemical sensing of various biomolecules and biological units. Ferrocenes are commonly connected to nucleosides (i.e. base plus sugar) via derivatisation at a carbon atom on the base, which allows incorporation into a nucleic acid strand by standard automated chemical synthesis. We are interested in an alternative approach of connecting ferrocenes directly to nucleobases (i.e. base minus sugar), in order to generate versatile building blocks relevant to the design of bioorganometallic H-bonding assemblies and compounds that show biological activity.

This talk will give an overview of our initial findings in the area and will include various synthetic approaches to the functionalisation of nucleobases (e.g. adenine, shown below) and a discussion of their various applications and redox properties.¹

Figure 1. The structure of a ferrocene derivative substituted with two adenine groups and the H-bonded sheet it forms in the solid-state

Reference

Transfer of para-H\textsubscript{2} spin order to the products of hydrogenations with parahydrogen yields extraordinary enhancements of the NMR signals which, in theory, may reach values as high as 10\textsuperscript{5} times the signal intensity of the corresponding derivatives obtained with normal H\textsubscript{2}.\textsuperscript{1} The possibility of polarizing heteronuclear resonances in molecules obtained from hydrogenation using parahydrogen is of huge interest for in vivo studies by MRI. In particular the high signal/noise ratio that can be achieved on heteronuclei such as \textsuperscript{13}C allows to obtain molecules that can be traced in vivo due to the complete absence of those signals in biological tissues leading to images in which the background signal derives uniquely from instrumental noise.

Hyperpolarization is transferred from protons to heteronuclei through scalar coupling by using organometallic complexes and several studies deal with systems containing \textsuperscript{13}C-carbonyl resonances that are characterized by long T\textsubscript{1} values.\textsuperscript{2} In order to produce a \textsuperscript{13}C hyperpolarized contrast agent using this approach, an unsaturated substrate is necessary (usually a triple bond containing molecule, that is efficiently para-hydrogenated in the presence of a suitable organometallic catalyst), with an adjacent carbonyl group to which hyperpolarization is transferred due to its coupling with para-hydrogen protons. To tackle the issue associated to the non-biocompatibility of the hydrogenation catalyst, its removal through a passage on a ion-exchange resin may cause a dramatic polarization loss, as the temporary immobilization of the substrate on the resin may result in markedly enhanced relaxation rates.

Herein a new approach based on the use of precursors of the hyperpolarized substrates of interest is presented.\textsuperscript{3} Both the precursor and the catalyst are not water soluble, and the reaction with para-H\textsubscript{2} is carried out in an organic solvent to yield a product that, upon contact with water, transforms into the water soluble hyperpolarized substrate of interest.

References
Development and Evaluation of ParaCEST MRI Contrast Agents Possessing Highly Shifted Amide Proton Signals

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Over half of all magnetic resonance images (MRI) use some form of exogenous contrast agent. Currently all clinically available MRI contrast agents are based on a chelated gadolinium ion (Gd³⁺) which functions as T1 relaxation agents. A new field of agents are being developed that rely on paramagnetic chemical exchange saturation transfer (ParaCEST) process to produce a contrast. The benefit of this new class of agents is the increase in environmental sensitivity, which current agents are lacking. The ability to monitor small changes in both pH and temperature may permit more ready identification of cancerous tissues which possess lower pH and higher temperatures compared to normal tissue. The ParaCEST technique requires a pre-saturation pulse to excite the frequency of interest (| >> 0 ppm) which through chemical exchange generates contrast by causing diminishment of the bulk water signal ( = 0 ppm) (Figure a). The drawback of using a pre-saturation pulse is the magnetisation transfer (MT) that can arise from saturation of endogenous biological molecules which ultimately can diminish the observable signal and lower the amount of contrast and signal-to-noise ratio (Figure b). To overcome the inherent MT effects that are present when performing a ParaCEST scan, we have begun to develop a class of agents that possess signals that are outside the range of biological MT (t-butyl Figure a,b). These agents show signals out to -100 ppm, compared to bulk water. We have effectively shifted the signal outside any background effects, giving rise to the best possible signal to noise ratio, which ultimately leads to more sensitive agents that will support the use of lower agent concentrations.

References

Manganese Porphyrin Based MRI Contrast Agents

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As a noninvasive imaging modality with high resolution, magnetic resonance imaging (MRI) is increasingly applied in clinical diagnosis and basic biomedical research. Conventional \textit{in vivo} MRI are mainly based on the \textsuperscript{1}H-NMR signal of water, the most abundant molecule present in tissue. The contrast and sensitivity of MRI can be enhanced by paramagnetic MRI contrast agent (CA), which can alter the relaxation time ($T_1$ or $T_2$) of the \textsuperscript{1}H NMR signal.\textsuperscript{1} The current clinical MRI CAs are predominantly based on low molecular weight gadolinium (Gd) complexes, which typically exhibit lower relaxivity at higher magnetic fields.\textsuperscript{1} Recently, several Gd CAs have been implicated in nephrogenic systemic fibrosis (NSF), a severe side effect related to Gd toxicity.\textsuperscript{2} To overcome these limitations, we initiated a program to develop Gd-free $T_1$ CAs based on Mn-porphyrin-platform, which was chosen due to its anomalously high relaxivity and flexibility for structural modification. We systematically optimize a series of molecular parameters in order to achieve high relaxivity and low toxicity. I’ll present our recent efforts in design, synthesis and characterization of new water-soluble Mn(III)porphyrins, and focus on the impact of reorientational correlation time ($\tau$) on $T_1$ relaxivity. In addition, the potential of developing manganese porphyrin based MRI sensors for molecular imaging\textsuperscript{3} will also be discussed.

References

Kinetin studies of Pt(en)Cl(NHR) to guanine monophosphate

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It has been suggested for a long time that electron microscopy could be a cheaper and faster way to sequence DNA. The use of base selective heavy atom labels is a direct way to visualize the individual bases by electron microscopy. In order for this approach to be successful rapid and complete reaction of the base selective label must be realized. Recently, it has been reported that complexes of the type (en)PtCl(NH2R) (R= fluorescent probe) selectively bind to guanine. However, these studies did not address the efficiency of binding or the rate of binding of the complex to guanine. A preliminary study with the complex (en)PtCl(NH2R) (R=C8H9NO2 (benzo[d][1,3]dioxol-5-ylmethylamine) showed that this complex bound well to guanine and that the Pt atoms could be visualized by electron microscopy bound to an ssDNA-oligo GATC repeat. Although the data proved inadequate get sequence data it prompted us to pursue an investigation of the efficiency and selectivity of binding to DNA of a range of these complexes with different length tethers and different end groups (see Chart 1). It was found that complexes with longer tethers reacted faster and that there was a significant difference in the rate of reaction between DGMP and DAMP. In a separate but related study we investigated the reactivity of a Pt complex tethered to a triosmium cluster. This was inspired by our prior work on the selective labelling of guanine with an alkyne mesylate and quinoline-4-carboxaldehyde triosmium clusters. The obvious advantage of the trinuclear cluster is its ease of visualization by electron microscopy. The Pt complex was conjugated to NH2CH2CH2(Ph)2PO3(CO)10 and its reaction with DGMP studied. Although reaction was detected the rate was much slower than for the organic anions shown in Chart. Future directions in this work will be presented.

References
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Rational Design of Ruthenium(II) Arene Complexes as Cancer Targeting Agents

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A major drawback of inorganic drugs currently used in the clinic to treat cancer is their inability to discriminate between healthy and cancerous cells. As a result, there has been a substantial increase in efforts towards developing compounds which specifically target cancer cells, thus limiting the undesirable side-effects associated with chemotherapy.

One metal that is beginning to show promise as an anti-tumour agent is ruthenium. Since the initial discovery that the ruthenium(II) arene complex RAPTA-C has cytotoxic properties, a number of structural modifications have been made to the RAPTA scaffold in an attempt to introduce groups to overcome drug resistance and target tumor cells. Recent efforts have been directed towards targeting enzymatic processes involved in cancer by incorporating specific inhibitors into the structure. Current developments in this area will be presented.

References

Therapeutically Viable Organometallic CO-Releasing Molecules (CO-RMs) – from Thermal to Photochemical Releasers

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The development of carbon monoxide–releasing molecules (CO-RMs) has become an exciting target for therapeutic intervention.1 Since 2003 several organometallic-based CO-RMs have been developed in York. Our rational design strategies, synthetic chemistry and CO-releasing ability of various thermo-CO-RMs will be described in this presentation.2 The CO-RM structures are shown below.

Emphasis will be placed on accurately determining CO-release rates from CO-RMs by a deoxy-myoglobin carbonmonoxy-myoglobin UV-vis assay.3 Furthermore our results detailing the cell viability of our CO-RM structures will be described, including vasodilatory and anti-inflammatory effects of selected CO-RMs.

Our recent results on photo-CO-RMs containing water-solubilising and biocompatible ligand systems, using LED technologies (irradiation at 400 and 465 nm), will be presented.

References

In the last decade, the use of carbon monoxide (CO) as a cytoprotective and homeostatic molecule has received increasing attention in medicine due to its documented beneficial therapeutic effects. There are three main areas where CO is evaluated as a clinically valuable medical agent: 1) inflammation, 2) cardiovascular diseases and 3) organ preservation and transplantation. The anti-inflammatory properties of CO have been corroborated in a large number of animal models while the protective effects of CO as vasodilator have been successfully evaluated on several cardiovascular diseases including pulmonary arterial hypertension, for which there is no cure. Carbon monoxide proved effectiveness in prolonging organ graft survival, particularly in heart and kidney transplants for which CO inhalation (3 mg per Kg for 1 hour) has entered Phase II clinical trials.

Since the discovery of the therapeutic potentials of CO, design, identification and characterization of CO-releasing molecules (CORMs) has become an active field of research. In this context we have described a family of 17-electron dicarbonyl ReII-based CORMs which show a number of acceptable properties as required for a medical drug. In this contribution we will discuss our recent progress in the development of biocompatible-site specific metal based CORMs conjugated to vitamin B12.

References
Mechanistic and Synthetic Insight into the Behaviour of Carbon Monoxide-Releasing Molecules

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Carbon monoxide–releasing molecules (CO-RMs) have become an exciting target for therapeutic intervention. CO generated in mammals is responsible for a variety of important physiological functions and is a fundamental signalling mediator. CO gas also elicits a range of beneficial therapeutic effects, although the associated toxicity and inherent poor selectivity of CO in its naked form is clearly not ideal. The method of choice for taking advantage of the beneficial role of CO is to utilise a CO-RM, such as a metal carbonyl complex, which acts as a source of CO in biological systems. Although the biological effects of CO (and CO-RMs) are now well established, there is little understanding of the precise requirements needed for transition metal carbonyl compounds to act as effective therapeutic agents. We have therefore undertaken a systematic study in order to elucidate the factors that may control CO-release. Insight into the solution-state behaviour of the complexes has been obtained from both in situ spectroscopic studies and an assay based on CO-capture by myoglobin.

This presentation will describe the CO-releasing properties of a range of metal carbonyls from Groups 5-10 of the periodic table and from all three rows of transition metals. The CO-release behaviour of metal complexes with a range of oxidation states, coordination environments, nuclearity and carbonyl ligands has been probed. This has allowed for the establishment of different mechanistic pathways for the initiation of CO-release, including hydrolysis of halide ligands, as well as thermal and photochemical CO-dissociation. This work has subsequently informed the design and synthesis of a number of new potential CO-RMs containing biologically-inspired ligands, such as those in 1-3.

References

Nano-sized Carriers for CO-Releasing Molecules

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The use of nanoparticles (NPs) for biomedical applications is a continuously rapid growing research field, with heavy emphasis on imaging and drug delivery. The unique properties of NP based systems hold strategic advantages over small molecular drugs.1 NPs in this sense can be synthetic or biological polymers, dendrimers and micelles as well as metallic or oxidic particles. Advances of NPs for drug delivery are e.g. high drug load, conjugation of hardly soluble drugs to a soluble NP carrier and use of multiple targeting devices on a NP scaffold for targeted drug delivery. Furthermore, drug carrier systems at the nano-scale are ideally suited to target sites of inflammatory and distinct cancerous tissues due to their enhanced permeability and retention (EPR) effect.2

Although macromolecular scaffolds are long known in NO release,3 only a few examples of CO-releasing nano-sized scaffolds are known.4 We recently described 2-hydroxypropylmethacryl amide based polymers functionalized by Mn(CO)3 complexes which act as photoactivatable CO-releasing molecules (photoCORMs).4a

The NPs not only can act as scaffolds for further functionalization and decoration, but also can be used as triggers for CO release. The very elegant light-induced CO release can so far only be used in treatment of surface tissues as the light used does not penetrate deeply into tissues. Here we report on our on-going work to modify the CO-release characteristics of so-called “spontaneous” CORMs by incorporation into nano-scale composites. The composite should consist of a NP core, CORMs attached and additional polymer coating and/or further decoration with cell-targeting molecules. We used different iron oxide NPs (IONPs) as scaffolds to attach CORMs on their surface. IONPs are regarded as the most biocompatible NPs and easily decorated. For decoration of the IONPs we developed a L-DOPA derived CORM-3 analog. IONPs functionalized with L-DOPA give very stable dispersions in aqueous solutions. The IONPs functionalized with CORM-3 analogs show temperature and pH-dependent CO release.

References
Photoactive CO Releasing Moieties (photoCORMs) Based on Rhenium Diimine Carbonyls for Use in Therapeutic Applications and For In Vitro Imaging

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Carbon monoxide is a biologically relevant, endogenously produced small molecule. Studies have shown CO to promote many physiological effects, such as stimulating wound healing, preventing ischemia/reperfusion injury, and preventing organ graft rejection. Here, we describe the photoactive CO releasing moiety (photoCORM), [Re(CO)₃(bpy)(thmp)]⁺ (I), an air-stable, water-soluble rhenium(I) carbonyl complex of bipyridine and tris(hydroxymethyl) phosphine. Irradiation of I in an aqueous buffer solution results in the release of one equivalent of carbon monoxide. Additionally, I has a long-lived phosphorescence, the wavelength of which shifts to lower energy upon loss of CO. In vitro uptake of I into cells from the human carcinoma cell line PPC-1 was confirmed by observing this phosphorescence through a confocal fluorescence microscope, and CO photorelease was verified through the shift of emission wavelength. Thus, I serves as both a photoactive carbon monoxide releasing moiety, and an imaging agent to visualize cellular CO release.

References
In search of new CO-releasing molecules which deliver their gaseous load to a target tissue only after activation of a specific release mechanism, we have recently introduced acyloxybutadiene-Fe(CO)₃ complexes as enzyme-triggered CO-releasing molecules (ET-CORMs). The earlier observation that enol complexes of type 2 are air-sensitive suggested their suitability as CORMs (Scheme 1). As stable (and “storable”) precursors we devised the corresponding esters, e.g. acyloxydiene complexes of type 1, which are sufficiently stable under physiological conditions but are readily converted to the “active” species 2 by means of enzymatic hydrolysis. Thus, once a complex of type 1 enters a cell, cleavage of the ester function by an intracellular esterase triggers the desired CO-release by generating the labile enol complex 2. The oxidative decomposition of this intermediate (presumably via a 16-VE species of type 3) leads to the liberation of the enone ligand and to the release of up to three molecules of CO.

In the course of our project, we have synthesized and characterized a whole series of differently acylated η⁴-dienol-Fe(CO)₃ derivatives using a novel protocol. The enzyme-triggered CO release from these compounds was monitored (detection of CO through GC and/or by means of a myoglobin assay) and the anti-inflammatory effect of the compounds was assessed by a cellular assay based on the inhibition of NO-production by inducible NO synthase (iNOS) using the murine macrophage cell line RAW264.7. It was demonstrated that the properties (rate of esterase-triggered CO release, iNOS inhibition, cytotoxicity) of the complexes strongly depend on the substitution pattern of the π-ligand and the nature of the acyloxy substituent. Moreover, the cytoprotective effect of some of the compounds was demonstrated using HUVEC cells.

References
POSTER PRESENTATIONS
Design of Artificial Metalloenzymes Resulting from the Functional Mutation of Papain

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The discovery of effective enzyme catalysts for organic synthesis has drawn attention due to their high activity and selectivity. Enzymes outperform synthetic catalysts by employing highly efficient substrate recognition and orientation together with stabilization of reactive intermediates. On the other hand, metal catalysts span a large range of important chemical reactions. Introduction of metal complexes with known catalytic properties into proteins should combine the advantages of both catalytic strategies. Herein a “step process” approach to design artificial metalloenzymes was applied to the enzyme papain.

Papain from *carica papaya* (EC 3.4.22.2) is a member of the cysteine endoproteinases family. It is a monomeric protein of 212 residues with a molecular weight of 23 422 Da. The X-ray structure (fig. 1) shows that the polypeptide folds into two domains, which are divided by a catalytic site of 15 Å wide by 25 Å long. The catalytically essential residues His 159 and Cys 25 are located in the groove on the opposite domains. We took advantage of the high nucleophilicity of the single free cysteine residue of papain (Cys 25) to site-selectively anchor catalytically active metal cofactors in a covalent fashion.

These cofactors containing either Ru(II) or Rh(III) metal ions coordinated by N-maleimide functionalized dipyridylamine-type ligands were synthesized in several steps (fig. 2). Site-specific anchoring to papain was assessed by irreversible loss of its hydrolytic activity. The newly acquired catalytic activity of the resulting hybrid species was tested on the reduction of the cofactors NAD(P)H and the transfer hydrogenation of ketones in aqueous media. In this latter case, modest enantiomeric excesses were measured on selected substrates.

References

Monitoring Copper/Tau Interactions Electrochemically

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The neurodegenerative diseases, such as Alzheimer’s disease and tauopathies, are linked to aging, protein malfunction, oxidative damage and heavy metal ions. Among metal ions, copper plays a pivotal role and has been extensively explored with respect to amyloid-β peptide aggregation but little is known about the interactions of copper ions with tau proteins. Copper is found at micromolar concentrations in neurofibrillary tangles of tau which are the biomarkers of the neurodegenerative disease. Moreover, toxic neurofibrillary tau tangles are largely hyperphosphorylated. Here, we explore electrochemically the interactions of copper ions and two isoforms of tau protein, by monitoring the signal related to the redox-active copper species. In addition, the effects of the post-translational modifications of tau, such as phosphorylation or ferrocene-phosphorylation, on metal-ion/tau interactions were also addressed. The two isoforms of tau protein (3R and 4R) differ in the number of repeat domain (R) in the C-terminal half of the protein. The repeats consist of ~ 31 residues and have recently been identified as the predominant sites of the metal ion binding. The structural and electronic effects, due to tau phosphorylation, on metal ion interactions are less known. Hence, the effects of the protein type, pH, and protein modification on the Cu(II)/tau protein interactions were investigated. In addition, tau aggregation was probed as a function of metal ions and aging time.

References

Comparative Mechanistic Study of Two Series of Ferrocifens

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The ability of cancer cells to adapt and survive current treatments constrains researchers to discover new drugs and this constitutes a major challenge for the 21st century. A few years ago, the Jaouen’s group evidenced that the introduction of a ferrocenyl fragment in the organic frame of tamoxifen provides an unexpected activity: whereas tamoxifen (through its active metabolite hydroxytamoxifen 1) is a potent hormonotherapeutic agent for the treatment of ER+ breast tumours, hydroxyferrocifen 2 proved to be active against both ER+ and ER- breast cancer cells.1 The antiproliferative activity of 2 is supposed to be due to the in situ formation of a quinone methide (QM) 3.2 We are now investigating the reactivity of such QMs in order to identify potential biological targets. Besides the identification of a cyclisation resulting in an indenic compound 4, we managed to synthesize and characterize adducts with several -model and biologically relevant- thiol compounds. Interestingly, some adducts were found to keep antiproliferative effects.

Additionally, the replacement of the ferrocenyl group in compound 5 by a ferrocenophanyl moiety -compound 6- was found to dramatically increase the antiproliferative effect of the molecule.3 If we were able to generate QMs when there are four (7) or five (8) carbons on the bridge, 6 was apparently not oxidized into QM, suggesting that it follows another mechanism of action.

References
SAHA-Ferrocifen Hybrid and Related Compounds with Anticancer Activity

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Organometallic compounds have been found to be good candidates as anticancer agents. Our group has shown that replacing one of the phenyl groups of tamoxifen by ferrocene afforded complexes with high antiproliferative activity, not only against hormone-dependent breast cancer cell lines, as tamoxifen does, but also against hormone-independent ones: the Ferrocifen series. We have now prepared a new family of hybrid compounds derived from Ferrocifen and suberoylanilide hydroxamic acid (SAHA). Pure organic analogs were synthesized for comparison.

In addition of genetic defects, it has been recently proposed that cancer establishment and progression can be carried out by non genetic mechanisms –epigenetic aberrations– involved in genetic regulation. Histone deacetylases inhibitors (HDACi) are one of the most important classes of epigenetic drugs. HDACi prevent histone deacetylation in order to maintain DNA accessible to transcription factors. HDAC inhibition represents an exploitable mechanism for the design of new antitumor agents. Thus, based on the fact that SAHA, one of the most studied HDACi, is able to make synergy with other drugs to increase the antitumor effects, we suggest that the combination of SAHA with selected organometallic moieties may be a good alternative to create hybrid bifunctional drugs. For this reason we have replaced the cap group of SAHA (Scheme 1) with the 4-(2-ferroceny1-1-phenylbut-1-en-1-yl)phenyl group of aniline 1a.

We suppose that the activity of the resulting product and its derivatives may be attributable to the following features: (i) the increased lipophilicity of compound that favors the membrane crossing, (ii) the presence of units capable of binding cellular receptors, (iii) the organometallic antenna conjugated with aromatic systems which is sensitive to redox phenomena, (iv) the structure of ferrocene which allows to fill spaces in the cavity of active sites more efficiently than planar aromatic groups and (v) the chain length which may bring the ferrocifen pharmacophore close to the histone receptor allowing it to exert its cytotoxic effect.

The cytotoxic activity of all compounds was evaluated against both breast cancer cell lines, hormone-dependent (MCF-7) and hormone-independent (MDA-MB-231) and prostate cancer cell line (PC-3). Comparing both hybrid series pure organic and organometallic compounds, it clearly appears that Ferrocifen-SAHA derivatives are the most effective.

References

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In recent years the use of ferrocene in the field of bioorganometallic chemistry has been growing rapidly. Ferrocene’s stability, low toxicity and redox activity make it an ideal candidate for incorporation into drug molecules. The main focus of research to date has been in anti-cancer agents.$^{1a,b}$

Previously we have prepared a series of $N$-(6-ferrocenyl-2-naphthoyl) dipeptide and amino acid esters.$^{2a,b}$ These were evaluated in H1299 non small cell lung cancer cell lines. They displayed excellent activity with the most active derivative, $N$-(6-ferrocenyl-2-naphthoyl) glycine glycine ethyl ester, having an IC$_{50}$ value lower than that of the platinum(II) based cancer drug, Cisplatin, in the H1299 cell line. These compounds consist of three components, (i) an electroactive core, (ii) a conjugated linker that lowers the oxidation potential of the ferrocene moiety and (iii) a peptide derivative which can interact with other molecules via hydrogen bonding. We are currently extending the structure-activity relationship (SAR) of the compounds.

The $N$-(6-ferrocenyl-2-naphthoyl) dipeptide esters were characterised by a combination of spectroscopic techniques. These have been evaluated in H1299 and A549 lung cancer cell lines and the results will be presented.

\[
\text{R} = \text{CH}_3, \text{C}_2\text{H}_5, \text{C}_3\text{H}_7, \text{C}_4\text{H}_9, \text{CH}_2(\text{C}_6\text{H}_5).
\]

References

A biological evaluation of novel N-(6-ferrocenyl-2-naphthoyl) glycine-glycine methyl and ethyl esters as anticancer agents in melanoma cell lines

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Ferrocene is a particularly attractive candidate for incorporation into biomolecules and biologically active compounds due to its aromatic character, redox properties and low toxicity. The medicinal application of ferrocene derivatives are as antifungal, antibacterial, antimalarial and anti-cancer agents.

Previously we have reported the anti-cancer activity of N-(6-ferrocenyl-2-naphthoyl) amino acid and dipeptide ester derivatives.

Here we present a biological evaluation of the effects of N-(6-ferrocenyl-2-naphthoyl) glycine-glycine methyl and ethyl esters on three melanoma cell lines, HT-144, Lox-IMVI and Malme-3M, including IC50 values as well as cell cycle analysis and apoptosis induction by TUNEL assay.

References:
Synthesis, structural characterization and *in vitro* anti-cancer activity of novel ferrocenyl bioconjugates

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Bioorganometallic chemistry is a field devoted to the synthesis and study of organometallic species of biological and medicinal interest. Notably, the field of medicinal chemistry has benefited considerably from the incorporation of organometallic moieties into potential drug molecules, with ferrocene receiving particular interest due to its aromatic character, redox properties, stability and low toxicity. Our laboratory has published *in vitro* biological results for *N*-ferrocenyl benzoyl dipeptide esters and *N*-(6-ferrocenyl-2-naphthoyl) amino acid and dipeptides ethyl esters against the H1299 non small lung cancer cell line and the Sk-Mel-28 malignant melanoma cancer cell line1-6. We now report the synthesis of novel ferrocenyl based bioconjugates which consist of four key moieties (i) an electroactive core (ii) an ethynyl moiety (iii) three different aromatic linkers and (iv) a series of dipeptide esters. The ferroceny1 bioconjugates were characterized by a combination of spectroscopic techniques including: $^1$H, $^{13}$C, DEPT-135 and HMOC NMR spectroscopy, IR, UV-Vis and mass spectrometry. The biological activity of selected compounds from *in vitro* proliferation assays in various cancer cell lines will be presented.

![Diagram](image)

References

Structures, Redox Properties and Complexation of Polyaniline-Unit Molecules Bearing Amino Acid Pendant Groups

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Polyaniline is one of promising electrically conducting polymers with chemical stability. The introduction of the amino acid pendant groups into polyaniline is considered to be a convenient strategy to induce chirality into π-conjugated backbones. We have already demonstrated this strategy by using phenyl-capped aniline oligomer derivatives\(^1\) as a unit molecule of polyaniline. Phenylenediamine derivative 1\(\text{red-L}\) bearing amino acid pendant groups was designated to investigate its structural and redox properties.\(^2\) In the CD spectrum of 1\(\text{red-L}\), Cotton effect based on the chirality-organized structure was observed, indicating that chiral induction of π-conjugated moiety is achieved through intramolecular hydrogen bonding with the amino acid pendant groups. The phenylenediamine 1\(\text{red-L}\) was oxidized with a chemical oxidant to the quinonediimine 1\(\text{ox-L}\), wherein the chirality-organized structure was also formed through intramolecular hydrogen bonding. The radical anion species could be generated by chemical reduction of 1\(\text{ox-L}\), which was characterized spectroscopically. Interestingly, preservation of the chirality-organized structure and stabilization of the radical species are achieved by the intramolecular hydrogen bonding.

Polyaniline was reported to form d,π-conjugated system through complexation.\(^3\) Chiral complex 2\(\text{-L}\) was obtained by the reaction of quinonediimine 1\(\text{ox-L}\) as a ligand with palladium salt. The crystal structure of 2-L exhibited the coordination to the imines of the quinonediimine and amino acid moieties. Furthermore, induced circular dichroism (ICD) was observed with the coordination to the π-conjugated moiety.

References

Highly-ordered molecular assemblies are constructed in bio-systems to fulfill unique functions as observed in enzymes, receptors, etc. Introduction of functional complexes into highly-ordered biomolecules is considered to be a convenient approach to novel biomaterials, bio-inspired systems, etc. Architectural control of molecular self-organization is of importance for the development of functional materials. The non-covalent bonding is a powerful tool in the construction of architectural molecular assemblies. Regulation of hydrogen bonding is a key factor in the design of various molecular assemblies by virtue of its directionality and specificity. Utilization of self-assembling properties of nucleobases in bio-inspired systems offers the flexibility of exploiting four different binding motifs. On the other hand, square-planar d8 transition metal complexes possess the intriguing photophysical and photochemical properties. In particular, luminescent platinum(II) complexes with oligopyridine and cyclometalating ligands have attracted much attention because of their luminescence properties based on metallophilic interaction through d2•••d2 and/or π-π interactions. A combination of luminescent platinum(II) complexes with nucleobases is allowed to design novel biomolecules. We herein report the synthesis of the organoplatinum(II) complexes having 1-octyluracil and emission property based by assembling of the platinum(II) complexes.

The platinum(II) complex Pt-U6 was prepared by the reaction of cyclometalated 6-phenyl-2,2'-bipyridyl (pbp) platinum(II) chloride with 6-ethynyl-1-octyluracil moiety. A molecular scaffold having the complementary hydrogen bonding sites was designed and synthesized to assemble Pt-U6 through hydrogen bonds. The reaction of 1,8-diiodonaphthalene with 2,6-diamidopyridine derivative afforded the molecular scaffold ND. The emission spectrum of PtU6 in CH2Cl2 showed emission at 590 nm, which in ascribed to a triplet metal-to-ligand charge transfer (3MLCT) and/or a triplet ligand-to-ligand charge transfer (3LLCT). Interestingly, PtU6 was found to exhibit a new emission band based on synergistic effect at around 730 nm in the presence of the molecular scaffold ND. This emission band is assignable to a triplet metal-metal-to-ligand charge transfer (3MMLCT) based on Pt-Pt and π-π interactions of the ligands (pbp). The molecular scaffold ND was found to play an important role in assembling PtU6 into ND-PtU6 (1:2) through complementary hydrogen bonding and π-π interaction between the ligands in a solution state.

Figure 1. Emission spectra of PtU6 (dashed line) and ND-PtU6 (1:2) (solid line) in CH2Cl2. (λex = 530 nm) ([PtU6] = 1.0 x 10^{-3} M).
The Influence of RAPTA Moieties on the Antiproliferative Activity of Peripheral-Functionalised Poly(salicyldiminato) Metallo dendrimers

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Ruthenium complexes are generally less toxic than platinum-based anticancer drugs.1 As a consequence, the field of ruthenium-arene chemistry is gaining considerable attention in biomedical applications.2 The use of metallo dendrimers, functionalised on the periphery with ruthenium-arene moieties, as potential anticancer agents is scarce. We have recently published a series of monodentate (N-donor) and chelating bidentate (N,N- and N,O-) ruthenium(II) arene (arene = p-cymene or hexamethylbenzene) first- and second-generation metallo dendrimers, based on poly(propyleneimine) dendritic scaffolds and investigated their in vitro cytotoxicity.3 The chelating ruthenium(II) arene metallo dendrimers show superior activity, with the octanuclear cationic N,N-ruthenium(II) hexamethylbenzene complex found to be the most active. The complexes showed a clear correlation between the size dependency of the metallo dendrimer, DNA damage and cytotoxicity. Moreover, the chelating N,N- and N,O-ruthenium(II) arene metallo dendrimers appear to operate via a different mechanism to cisplatin.

In this presentation, we report the synthesis of a series cationic N,O- chelating, ruthenium(II) arene metallo dendrimers, modified on the periphery with PTA moieties, and evaluate their antiproliferative activity against the A2780 and A2780cisR human ovarian cancer cells.

IC50 = 0.8 μM

IC50 > 200 μM

IC50 > 200 μM

IC50 > 200 μM

IC50 > 200 μM

IC50 > 200 μM

References

Peptide and Protein Complexes of Re(CO)$_3^+$

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The bioinorganic chemistry of the Re(CO)$_3$(H$_2$O)$_3^+$ ion continues to receive much attention. First discovered in 1994, this species and its derivatives are of interest as models for next-generation technetium imaging agents, as well as cold analogues of rhenium and $^{188/186}$Re therapeutic radionuclide complexes.

We have explored various aspects of the chemistry of this species including the binding of amino acid conjugates by formation of diimines with pyridine-2-carboxaldehyde.$^1$

More recently we have found that reactions with dipeptides produce two separate types of complexes. His-His-OH yields a stable complex that models the reactivity of His-tags.$^2$ Dipeptides without a coordinating side group produce $C_2$-symmetric dimers with the formula [Re(CO)$_3$(k$_3$-dipeptide')]$_2$. Two examples have been crystallized and characterized.

We have also explored the reaction of Re(CO)$_3$(H$_2$O)$_3^+$ with lysozyme and found that a complex is produced with a water molecule replaced by a histidine imidazole from His15. NMR, IR, X-ray, and MS data elaborate theses finding.$^3$, $^4$

References

Synthesis, Electrochemistry and H-Bonding of 1,1’-Homo-disubstituted Ferrocenes Containing Adenine and Thymine Nucleobases

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The electrochemical sensing of biomolecules and the tagging of ferrocene to nucleic acids have been a subject of interest in the recent years. In order to widen the scope of ferrocene-containing biomolecules, we have prepared four different conjugated/unconjugated ferrocene-linked nucleobases (1-4). Adenine and thymine were coupled in the first place to a 1,1’-bis-carboxaldehyde ferrocene via a Horner-Wittig reaction. This afforded conjugated ferrocenyl derivatives 3 and 4. Subsequent H2/Pd catalyzed reduction led to the formation of two saturated ferrocene bis-nucleobases 1 and 2.

Electrochemical analysis indicated a strong influence of the nature of the linker group on the ferrocene-centered redox-potentials. Furthermore, X-Ray crystallography studies revealed interesting H-bonding assemblies in the solid state. Further studies are in progress to connect ferrocene to other bases to achieve a better understanding of organometallic nucleobase assemblies.

References
Monitoring the Effect of Tyrosine Phosphorylation on Tau Protein Aggregation
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Tau, a microtubule associated protein, has been implicated in the formation of neurofibrillary tangles (NFTs), a characteristic finding in Alzheimer’s disease.¹ In a healthy individual a partially phosphorylated Tau is responsible for assembly and stabilization of microtubules through sequence motifs that associate with tubulin and mechanisms such as phosphorylation. In the case of Alzheimer’s disease, hyperphosphorylation of serine, threonine and tyrosine residues decrease and weaken tubulin binding, and therefore destabilize microtubules, leading to the formation of NFTs.²³ It is currently unknown which phosphorylation event is pivotal in the formation of these tangles, but it appears that the degree to which Tau is phosphorylated in a particular region, and at what residues, are determining factors. This hyperphosphorylation has very strong kinase activity dependence, and therefore monitoring this activity is vital in determining the manner in which these tangles form. This research aims to monitor the effect of tyrosine phosphorylation on Tau protein hyperphosphorylation utilizing Ferrocene-ATP bioconjugates.⁴⁶ Sequential phosphorylations using a number of tyrosine kinases have been performed and monitored through use of surface electrochemistry, electron microscopy and surface plasmon resonance. By varying the tyrosine kinase used in these reactions, additional information can be gained as to a critical phosphorylation event and site, leading to the formation of the NFTs. The additional interactions probed by this research, both steric and kinase dependent could provide insight into the structure and folding of hyperphosphorylated Tau.

References:
Monitoring Surface-Immobilized Tubulin Polymerization/Depolymerization and Effect of Additives on Biopolymer Stability

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α- and β-tubulin, members of the tubulin family of proteins, polymerize under physiological conditions to form microtubules, the primary structural components of the cellular cytoskeleton. Microtubule stability can be modulated by many factors, including salt concentration, microtubule-associated proteins, and the presence of small-molecule drugs such as paclitaxel. A particular microtubule-associated protein, tau, has been shown to have its microtubule-stabilizing properties attenuated upon phosphorylation. This destabilization of microtubules by tau phosphorylation is hypothesized to play a role in the neurodegeneration pathological to Alzheimer’s disease. In this study, tubulin polymerization and depolymerization has been monitored on gold surfaces by electrochemical impedance spectroscopy (EIS). Quartz crystal microbalance and surface plasmon resonance were used as confirmatory techniques. The effects of additives on the rate of depolymerization of tubulin has also been examined by these methods. Additives studied include paclitaxel, calcium, and phosphorylated and unphosphorylated tau protein. We also report on the effects of ferrocene-phosphorylations on the tau protein's microtubule stabilizing properties.

References
The Contrasting Chemical Reactivity of Potent Isoelectronic Iminopyridine and Azopyridine Osmium(II) Arene Anticancer Complexes

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A wide variety of steric and electronic features can be incorporated into transition metal coordination complexes, offering the prospect of rationally-designed therapeutic agents with novel mechanisms of action. Here we compare the chemical reactivity and anticancer activity of organometallic OsII complexes $[\text{Os}(\eta^6\text{-arene})(XY)Z\text{PF}_6]$ where arene = p-cymene or biphenyl, $XY = N,N^\prime$-chelated phenyliminopyridine or phenylazopyridine derivatives, and $Z = \text{Cl}$ or I.

In a similar manner to the azopyridine complexes we reported recently, some iminopyridine complexes are also potently active towards cancer cells (nM IC$_{50}$ values). However we show that, unlike the azopyridine complexes, the iminopyridine complexes can hydrolyse in aqueous solution, bind to the nucleobase guanine, and oxidize coenzyme nicotine adenine dinucleotide (NADH). We report the first detection of an Os-hydride adduct in aqueous solution ($^1$H $-4.2$ ppm). Active iminopyridine complexes induced a dramatic increase in the levels of reactive oxygen species (ROS) in A549 lung cancer cells. The anticancer activity may therefore involve interference in the redox signalling pathways in cancer cells by a novel mechanism.

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References


Correlation between Cytotoxicity, Hammett Constants and Lipophilicity for a Family of Bridged Trithiophenolato Dinuclear Arene Ruthenium Complexes

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Ruthenium complexes possess interesting anticancer activity and few side effects compared to platinum complexes and may be strong candidates for rational drug design.1 However, for most of these systems, the mode of action, uptake and biological processes are still poorly understood. We have synthesized first a family of highly cytotoxic trithiolato-bridged dinuclear arene Ru-complexes, with IC50 values against A2780 and A2780cisR cellular lines being in the submicromolar range,2 of the general formula [(p-cymene)2Ru2(SPh-p-R)3]+ and analysed their interaction with amino acids, nucleotides and glutathione under physiological conditions. Surprisingly, these compounds remained inert against nucleotides and amino acids, and we discovered that they can actually act as efficient catalyst for the oxidation of the cysteinyl group of GSH to the glutathione disulphide form (GSSG).3 Preliminary results obtained with o-, m-, and di- substituted thiol groups as ligands, and in particular tentative correlations between Hammett’s constants (σp), IC50 and lipophilicity (logP), will be also presented provide a first insight into the possible mode of action of these Ru-complexes.4

Chart 1. 3-D representation of the correlation between IC50 values, Hammett constants (σp) and lipophilicity (logP) for a series of trithiolato-bridged dinuclear arene Ru-complexes

References

Self-assembly of Ferrocene-peptides

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Molecular self-assembly is an important strategy for the construction of functional supramolecular structures. Self-assembly is generally directed by non-covalent interactions including hydrogen bonding, hydrophobic and π-π interactions among others. In this context, synthetic peptides serve as building blocks toward the design of nano- and micro-scale functional structures such as nanotubes, nanofibers and vesicles. Introduction of molecular scaffold such as Ferrocene (Fc), as a part of peptide scaffold contributes to the stability and conformational rigidity of the system and often controls and directs the secondary structure through intramolecular and intermolecular hydrogen bonding interactions. Examples of self-assembly of Fe-peptide into β-barrel-like structure and chirality organized systems have been previously reported. Here, we studied hierarchical self-assembly of disubstituted ferrocene (Fc)–peptide conjugates containing Gly-Val-Phe and Gly-Val-Phe-Phe peptides and their growth into macroscopic objects. Self-assembly of Fc-peptides through intra- and intermolecular interactions led to the formation of nanofibers, large fibrous crystals and twisted ropes depending on the peptide sequence and solvent composition.

References:

Development of High Relaxivity Gd-free MRI T₁ Contrast Agents

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Magnetic Resonance Imaging (MRI) offers exquisite anatomical information but is limited by its intrinsic low sensitivity and contrast. To mitigate this drawback, MRI contrast agents (CAs) are frequently administered to improve the image quality. However, due to the low relaxivity (relaxation efficiency of the CA) of clinical MRI CAs, high dosage is required. Since the commonly used MRI CAs are Gd-based, the adverse effect of Gd toxicity such as Nephrogenic Systemic Fibrosis (NSF) becomes a major issue.

To overcome these challenges, we aim to develop new Gd-free T1 CAs with high relaxivity and low toxicity via a systematic synthetic approach. Mn-porphyrin is chosen as our building block as Mn-porphyrin (MnTPPS), 1, exhibits high relaxivity at high magnetic field while Gd-based CAs is shown decrease relaxivity with increase magnetic field above 0.05T. According to the Solomon, Bloembergen and Morgan (SBM) model, it is known that low tumbling rate (t₀) fosters more efficient proton nuclei-paramagnetic ion interaction, favouring high relaxivity. Thus, we expanded the size of MnTPPS by synthesizing a novel dimeric manganese porphyrin, 2, which should have a lower tumbling rate. The nuclear magnetic resonance dispersion (NMRD) profile was measured at a variable magnetic field from 0T – 1T and 2 exhibits significantly higher relaxivity per Mn than 1. We also synthesized a tetracarboxylate derivative (MnTCP), 3, and as expected, due to its smaller size (higher tumbling rate), the relaxivity is lower than 1 and 2, nevertheless, still higher than typical Gd-CAs.

The development of dimers of different linking lengths and orientations are also in progress as their effects on relaxivity can guide future MRI CA design. In vivo studies will be performed to determine the efficiency of 1, 2 and 3 as a Gd-free blood pool agent.

References

Biological Investigation of Cytotoxic Ti(IV) Complexes

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In the last decades two titanium based drugs (titanocene dichloride and budotitane) reached clinical trials but failed because of decreased hydrolytical stability and formulation problems. Based on these promising works and with the aim of improving cytotoxicity and hydrolytic stability better stabilized titanium-containing compounds, e.g. Titanocene Y, and a new class of non-Cp Ti(IV) complexes were synthesized and seem to hold a high potential for anticancer therapy.1,2

In our study the mentioned lead structures were investigated biologically in comparison to known titanocenes. Very interesting properties for the novel class of diamino bis(phenolato) “salan” Ti(IV) complexes (see figure 1) could be obtained and may be a step forward in target identification of titanium-based anticancer drugs.

![Fig. 1: Titanium complexes: (a) Titanocene dichloride, (b) Titanocene Y, (c) Salan-Ti(IV) complex](image)

The lead compound of new diamino salan-Ti(IV) complexes has an improved cytotoxicity and cellular uptake into MCF-7 breast cancer and HT-29 colon carcinoma cell lines compared to known titanocenes. A relationship between the antiproliferative activity, the cellular accumulation and the protein binding ability of the tested Ti-containing compounds was noted. In addition, the toxicity of titanium-based compounds in zebrafish embryos3 was studied and no toxic effects could be observed up to a concentration of 20 µM. The presented results indicate that the novel titanium complexes possibly have overcome the disadvantages of titanocene dichloride. Further investigations were performed on the DNA-binding efficacy, the nuclear drug content and the drugs accumulation in mitochondria.

References

Metallo-carbonyl-Gold-Antibody Bioconjugates for Mid-IR Optical Immunosensing

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Gold nanoparticles are widely employed in a variety of areas including optical devices, electronics, catalysis, biotechnology and medicine. Many of the reported applications of colloidal gold involve functionalization of gold nanoparticles to prepare a new generation of labels for molecular detection. Recently we described the labeling of gold nanoparticles of various diameters with CpFe(CO)2 (Fp) moieties by reaction with compound Fp-SS-Fp. The Fp derivative displays specific and intense absorption bands in the mid-IR spectral range (between 1800 and 2150 cm⁻¹) which is usually free from biomolecules absorption. This feature made it useful as IR-detectable marker to monitor biochemical processes as hormone–receptor or antigen–antibody associations.

Fig. 1. Metallo-carbonyl-gold-antibody bioconjugate

Herein we present the Fp-labeled gold nanoparticles derivatized with a polyclonal anti-mouse IgG antibody. These immunoprobes were able to detect a monoclonal mouse IgG chemisorbed to a planar gold-coated glass sensor by mid-IR surface analysis.

References

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