7·8/2002

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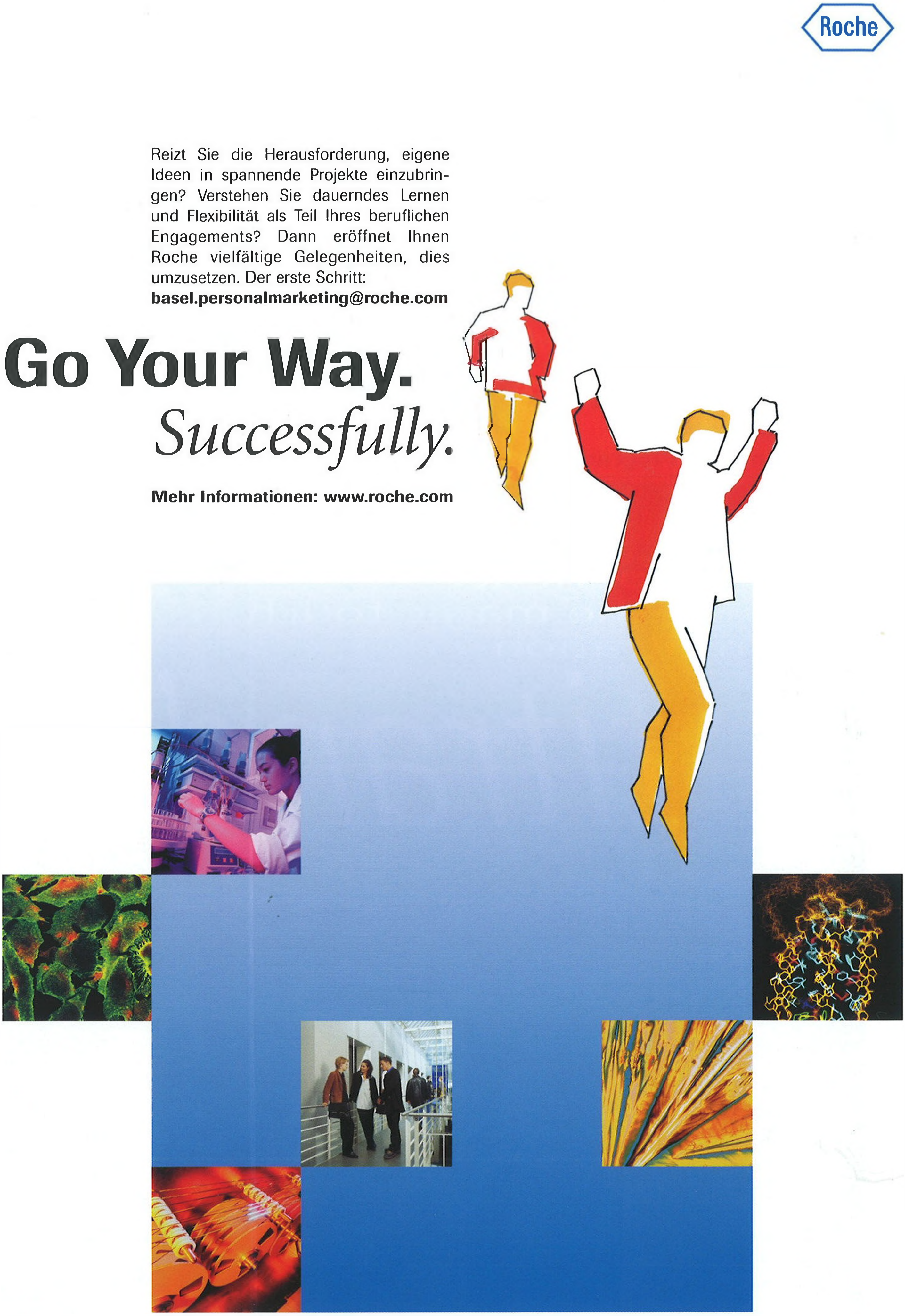
# CHIMIA

## FALL MEETING 2002
## HERBSTVERSAMMLUNG 2002
## ASSEMBLÉE D'AUTOMNE 2002

SCHWEIZERISCHE CHEMISCHE GESELLSCHAFT
SOCIETE SUISSE DE CHIMIE
SWISS CHEMICAL SOCIETY

**Enclosure:**
**r+d in life sciences**
**15 – 18 October 2002**
**Fair Information**
**and Congress Program**

CHIMIA 2002, VOLUME 56, NUMBER 7-8/02, PAGES 318–446// CHIMIAD 56(7-8) 318–446 (2002)



# CHIMIA

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**International Journal for Chemistry**
and
**Official Membership Journal**
of the Swiss Chemical Society (SCS)
and its Divisions

**Internationale Zeitschrift für Chemie**
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| SGLUC | Swiss Soc. of Food and Environmental Chemistry | SGLUC | Schweiz. Ges. für Lebensmittel- und Umweltchemie |
| SGMS | Swiss Group for Mass Spectrometry | SGMS | Schweiz. Gruppe für Massenspektrometrie |
| SGPP | Swiss Soc. of Photochemistry and Photophysics | SGPP | Schweiz. Ges. für Photochemie und Photophysik |
| SVC | Swiss Chemical Engineers FH Association | SVC | Schweizerischer Verband diplomierter Chemiker FH |
| VSN | Swiss Association of Science Teachers | VSN | Verein Schweiz. Naturwissenschaftslehrerinnen und -lehrer |

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CHIMIA 2002, 56, No. 7/8

EDITORIAL

# Invitation to Attend the Fall Meeting of the Swiss Chemical Society in Basel, on Thursday, October 17, 2002

On behalf of the Swiss Chemical Society (SCS) and the local Organizing Committee, it is our pleasure to invite you to attend the 2002 Fall Meeting of SCS. Following the tradition of alternating universities to host this event, it is now Basel's turn and we will do our best to offer you an interesting Fall Meeting in the framework of 'r+d in life sciences', International Trade Fair and Congress for Research and Development, Analytics and Diagnostics in Life Sciences and the Chemical Industry (Successor of «ilmac»).

The Fall Meeting of the SCS is the largest annual event in Switzerland where graduate chemistry students, post-docs, and chemists of all levels have the opportunity to present results they have achieved in their research projects. Again this year, there will be a jury in each session giving awards and substantial prizes to the best poster presentations, as well as to the best oral contributions.

The following pages of CHIMIA display more than 300 abstracts of scientific contributions of the Fall Meeting 2002. Please convince yourself of the diversity and outstanding creativity of chemists in Switzerland. The wealth and excellence of these contributions should lure you into participating in this meeting.

The Fall Meeting of the SCS allows all generations of scientists to exchange ideas. It stimulates future projects and discussions. Swiss chemical research participates in the frontiers of science, sharing the borders with several other disciplines such as physics, materials science, biology and the life sciences. This meeting represents the multifaceted aspects of chemistry, particularly those related to basic and applied research performed in academic institutions as well as in industry.

For the first time the 'Swiss Young Chemists' Committee' (JCFch) is taking part in the Fall Meeting with an initative to provide information about job perspectives through contacts and workshops with people already working in industry.

Everything is ready now. We therefore look forward to well-attended and lively sessions and to welcoming you in Basel, and we hope you will enjoy the 2002 Fall Meeting of the Swiss Chemical Society and participate to its success now and in the future.

Prof. Martin Quack
Chairman
Division Chemical Research

Prof. Wolf-D. Woggon
Chairman
Local organizing committee

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SCHWEIZERISCHE CHEMISCHE GESELLSCHAFT

SOCIETE SUISSE DE CHIMIE

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|---|---|---|
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| CHEMICAL RESEARCH | RECHERCHE CHIMIQUE | CHEMISCHE FORSCHUNG |
| MEDICINAL CHEMISTRY | CHIMIE THERAPEUTIQUE | MEDIZINISCHE CHEMIE |

# Fall Meeting 2002
# Herbstversammlung 2002
# Assemblée d'automne 2002

Thursday, October 17, 2002
Donnerstag, 17. Oktober 2002
Jeudi, 17 octobre 2002

**Basel**

**Convention Center – 2nd floor**
**Messeplatz 21**

## Organizing Committee

Prof. H. Berke (Subdivision Inorganic Chemistry)
Prof. A. Chougnet (Coordination-Administration)
Prof. C. Daul (Subdivision Computational Chemistry)
Dr. W. Froestl (Division Medicinal Chemistry)
PD Dr. M. Karpf (Co-Chairman)
Prof. M. Quack (Subdivision Physical Chemistry)
Prof. J. Robinson (Subdivision Organic Chemistry)
S.P. Smidt (Swiss Young Chemists' Committee)
Prof. J.-L. Veuthey (Division Analytical Chemistry)
PD Dr. R. Wenger (Division Chemical Research)
Prof. W.-D. Woggon (Chairman)
Prof. R. Zenobi (Division Analytical Chemistry)

## Secretary

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Institute of Organic Chemistry, University of Basel, St. Johanns-Ring 19, CH–4056 Basel
Tel.: +41 61 267 11 12, Fax: +41 61 267 09 76, E-mail: myrtha.kanalz@unibas.ch

## Informationen

**Keine Anmeldung erforderlich, der Eintritt ist kostenlos d.h. wird von der SCG bezahlt**

**Studierende, die Mitglied der SCG** sind, erhalten folgende Reisekosten zurückerstattet: Bahnbillet nach Basel, 2.Kl. $^1/_2$ Tax (Anreise aus dem Ausland: Rückerstattung der Reisekosten ab Schweizer Grenze). Das Bahnbillet ist dem Rückerstattungsantrag beizulegen. Der Rückerstattungsantrag ist unter Angabe der Arbeits- und Privatadresse, des Bank- oder PC-Kontos sowie womöglich unter Beilage eines Einzahlungsscheines beim Sekretariat der SCG, Frau *Lilly Etter,* SCG, c/o Novartis,WKL-136.P.71, CH-4002 Basel einzureichen.

## Informations

**L'inscription n'est pas nécessaire, l'entrée est gratuite, financée par la SSC**

**Les étudiants membres de la SSC** peuvent demander le remboursement des frais de voyage sur la base du billet de train aller et retour Bâle, 2$^{ème}$ classe, demi tarif (pour les membres qui viennent de l'étranger, seuls les frais de voyage sur le territoire suisse sont remboursés). Le billet doit être joint à la demande de remboursement. Veuillez indiquer l'adresse privée et celle du lieu de travail, les coordonnées du compte bancaire ou postal et joindre, si possible, un bulletin de versement. La demande est à adresser au Secrétariat de la SSC, Madame *Lilly Etter*, SSC, c/o Novartis, WKL-136.P.71, CH-4002 Basel.

## Location

The Fall Meeting 2002 will take place at the Basel Convention Center, next to the hotel Swissôtel Le Plaza, Messeplatz 21, 2nd floor.

## Transportation

Although the Convention Center provides parking facilities, travel by train is recommended.
From Basel main station, the Convention center can be reached by tram no. 1 or 2, direction 'Messeplatz' and 'Badische Bahnhof' (tram stop Messeplatz).

| **Morning**<br>Train from | Departure | Arrival Basel | **Evening**<br>Departure Basel | Arrival | Train to |
|---|---|---|---|---|---|
| Bern | 7:49 | 8:56 | 19:04 | 20:11 | Bern |
| Fribourg | 7:16 | 8:56 | 19:04 | 20:43 | Fribourg |
| Genève | 6:48 | 9:35 | 18:24 | 21:12 | Genève |
| Lausanne | 7:27 | 9:35 | 18.24 | 20:33 | Lausanne |
| Neuchâtel | 8:03 | 9:35 | 18:24 | 19:56 | Neuchâtel |
| Zürich | 8:37 | 9:37 | 18:20 | 19:20 | Zürich |

## Social

| | |
|---|---|
| Lunch: | Sandwiches, coffee and mineral water are served next to the poster area, in the Foyer, 2nd floor, Congress Center |
| Coffee breaks: | Coffee and mineral water will be served in the Foyer on the 2nd floor |

## Program of the Fall Meeting 2002

### 10.00–10.10 Opening Ceremony

*Room San Francisco*
Chairperson: *A. Merbach*

### 10.10 Presentation of the Werner Prizes 2002

10.10–10.30
**Prof. *Jérôme Lacour***
**Werner Prize Laureate 2002**
Department de Chimie Organique
Université de Genève
'Chiral Ion Mediated Asymmetric Chemistry'
Abstract 1

10.30–10.50
**Prof. *Werner M. Nau***
**Werner Prize Laureate 2002**
Institut für Physikalische Chemie
Universität Basel
'Biopolymer Motions Probed by Fluorescence'
Abstract 2

### 11.00–15.40 Analytical Chemistry

11.00–11.15
**General Assembly of the Members**
*Room Samarkand*

11.30–12.40
**Lectures**
*Room Samarkand*
Abstracts 3, 5–6

12.40–14.30
**Poster Session**
*Foyer 2nd floor*
Abstracts 9–43

14.30–15.40
**Lectures**
*Room Samarkand*
Abstracts 4, 7–8

### 11.00–16.00 Medicinal Chemistry

11.00–11.15
**General Assembly of the Members**
*Room Singapore*

11.15–13.00
**Lectures**
*Room Singapore*
Abstracts 44–50

13.00–14.00
**Poster Session**
*Foyer 2nd floor*
Abstracts 58–65

14.00–16.00
**Lectures**
*Room Singapore*
Abstracts 51–57

### 11.00–16.00 Chemical Research

11.00–11.15
**General Assembly of Members**
*Room San Francisco*

### 11.15–15.45 Computational Chemistry

11.15–12.45
**Lectures**
*Room Rio*
Abstracts 66–71

13.00–14.30
**Poster Session**
*Foyer 2nd floor*
Abstracts 77–87

14.30–15.45
**Lectures**
*Room Rio*
Abstracts 72–76

### 11.15–16.00 Organic Chemistry

11.00–11.15
**Lectures**
*Room Montreal*
Abstracts 88–94

11.15–13.00
**Lectures**
*Room San Francisco*
Abstracts 101–107

13.00–14.30
**Poster Session**
*Foyer 2nd floor*
Abstracts 114–179

14.30–16.00
**Lectures**
*Room Montreal*
Abstracts 95–100

14.30–16.00
**Lectures**
*Room San Francisco*
Abstracts 108–113

### 11.15–16.00 Physical Chemistry

11.15–13.00
**Lectures**
*Room Osaka*
Abstracts 180–186

13.00–14.30
**Poster Session**
*Foyer 2nd floor*
Abstracts 193–216

14.30–16.00
**Lectures**
*Room Osaka*
Abstracts 187–192

### 11.15–16.00 Inorganic and Coordination Chemistry

11.15–13.00
**Oral presentation of 12 posters**
*Room Sidney*

13.00–14.30
**Lunch and Poster Session**
*Foyer 2nd floor*
Abstracts 223–309

14.30–16.00
**Lectures**
*Room Sidney*
Abstracts 217–222

**11.15–16.00** *contactchemists.ch*
**The Swiss Young Chemists' Committee's Careers Fair**
*Foyer 2nd floor.*
Participating companies: *Actelion* (Poster 310), *Ares Serono* (Poster 311), *Bachem* (Poster 312), *Baer Management Consulting* (Poster 313), *Carbogen* (Poster 314), *Chemspeed* (Poster 315), *CibaSC* (Poster 316), *Lonza* (Poster 317), *Nestlé* (Poster 318), *Novartis* (Poster 319), *F. Hoffmann-La Roche* (Poster 320), *Syngenta* (Poster 321)

11.15–11.20 **Welcoming Remarks for *contactchemists.ch***
*Room Hongkong*

11.20–16.00 **Company Presentations**
*Room Hongkong*

**16.00–16.30** **Coffee Break**
*Foyer 2nd floor*

**16.30–16.45** **Awards for the Best Oral and Poster Presentations**
*Room Montreal*
Chairperson: *Wolf-D. Woggon*

**Analytical Chemistry**
1 poster and 1 oral presentation
Jury: *J.-L. Veuthey, R. Zenobi*

**Medicinal Chemistry**
1 poster and 2 oral presentations
Jury: *H.P. Märki, W. Fröstl*

**Computational Chemistry**
1 poster and 1 oral presentation
Jury: *C. Daul, H. Huber*

**Organic Chemistry**
2 posters and 2 oral presentations
Jury: *M. Karpf, P. Renaud, J. Robinson, H. Wennemers*

**Physical Chemistry**
1 poster and 1 oral presentation
Jury: *W. Nau, J. Wirz*

**Inorganic and Coordination Chemistry**
3 posters, 1 oral presentation, and 1 oral poster presentation
Jury: *H. Berke, T. Kaden*

**17.00** **Presentation of the Paracelsus Prize 2002**
*Room Montreal*
Chairperson: *A. Merbach*

17.05–18.00 **Lecture of the Paracelsus Prize Laureate 2002**
**Prof. *Martin Quack***
Laboratorium für Physikalische Chemie, ETH-Zurich
'Molecular Spectra, Reaction Dynamics, Symmetries and Life'

## DETAILED PROGRAM

**10.00–10.10** **Opening Ceremony**
*Room San Francisco*

**10.10** **Presentation of the Werner Prizes 2002**
Chairperson: *A. Merbach*

10.10–10.30 **Prof. *Jérôme Lacour***
**Werner Prize Laureate 2002**
Department de Chimie Organique
Université de Genève
'Chiral Ion Mediated Asymmetric Chemistry'
Abstract 1

10.30–10.50 **Prof. *Werner M. Nau***
**Werner Prize Laureate 2002**
Institut für Physikalische Chemie
Universität Basel
'Biopolymer Motions Probed by Fluorescence'
Abstract 2

## Analytical Chemistry

**11.00–11.15** **General Assembly of the Members**
*Room Samarkand*

**11.30–12.10** **Invited Lecture**
*Room Samarkand*
Chairperson: *R. Zenobi*

***B.L. Karger***
The Barnett Institute,
Northeastern University, Boston, USA
'Recent Advances in High Performance LC (1D and 2D)/Mass Spectrometry for Proteomic Analysis'
Abstract 3

**12.10–12.40** **Contributed Lectures**
*Room Samarkand*
Abstracts 5–6
Chairperson: *R. Zenobi*

12.10–12.25 ***S.D. Friess**, R. Zenobi*
Department of Chemistry, ETH-Zürich
'Intrinsic Mass Signal Intensities of Protein Digests'
Abstract 5

12.25–12.40 ***L. Geiser**, S. Cherkaoui, J.-L. Veuthey*
Laboratory of Pharmaceutical Analytical Chemistry, School of Pharmacy, University of Geneva
'Nonaqueous Capillary Electrophoresis-Electrospray-Mass Spectrometry for the Analysis of Pharmaceutical Compounds'
Abstract 6

**12.40–14.30** **Lunch and Poster Session**
*Foyer 2nd floor*
Abstracts 9–43

**14.30–15.10** **Invited Lecture**
*Room Samarkand*
Chairperson: *J.-L. Veuthey*

***G. Hopfgartner***
School of Pharmacy, University of Geneva
'New Opportunities for the Characterization of Small Molecules and Peptides using Multidimensional Chromatography and Hybrid Tandem Mass Spectrometry'
Abstract 4

**15.10–15.40** **Contributed Lectures**
*Room Samarkand*
Abstracts 7–8
Chairperson: *J.-L. Veuthey*

15.10–15.25 ***M. Guillong,*** *D. Günther*
ETH-Zürich
'LA-ICP-MS: Particle Composition and their Contribution to Sensitivity and Accuracy of the Method'
Abstract 7

15.25–15.40 ***J. Mohn,*** *L. Emmenegger, E. Sandmeier*
EMPA, Air Pollution/Environmental Technology, Dübendorf
'On-Line Gas Analysis for Process Diagnostics in Semiconductor Industries'
Abstract 8

## Medicinal Chemistry

**11.00–11.15** **General Assembly of the Members**
*Room Singapore*

**11.15–13.00** **Lectures**
*Room Singapore*
Abstracts 44–50
Chairperson: *H.P. Märki*

11.15-11.30 ***K.H. Altmann,*** *G. Bold, F. Cachoux, V. Guagnano, T. Isarno, M. Wartmann*
Novartis Pharma AG, Basel
Corporate Research and TA Oncology Research
'Design and Synthesis of Highly Potent Analogs of the Naturally Occurring Antitumor Agents Epothilones A and B'
Abstract 44

11.30–11.45 ***S. Cottens,*** *R. Baenteli, W. Bauer, C. Ehrhardt, U. Hommel, J. Kallen, G. Weitz-Schmidt*
Novartis Pharma, Basel, Transplantation Research
'Statin Derivatives as Inhibitors of the Leukocyte Function Antigen-1'
Abstract 45

11.45–12.00 *P. Furet, P. Imbach, J. Roesel, P. Fuerst, M. Lang, V. Guagnano, M. Noorani, J. Zimmermann,* ***C. Garcia-Echeverria***
Novartis Pharma AG, Basel, Oncology Research
'Non-Covalent Inhibitors of the 20S Proteasome'
Abstract 46

12.00–12.15 ***L. Calzolai,*** *D. Lysek, P. Guntert, C. von Schroetter, K. Wüthrich*
Institute of Molecular Biology and Biophysics, ETH-Zürich
'NMR Structure of the Turtle Prion Protein'
Abstract 47

12.15–12.30 ***C. Meyer***[a], *D. Meyer*[a], *T.A. Bickle*[b], *B. Giese*[a]
[a]Department of Chemistry, University of Basel
[b]Biozentrum, University of Basel
'Chemical Restriction'
Abstract 48

12.30–12.45 ***E. Goetschi,*** *P. Angehrn, H. Gmuender, P. Hebeisen, D. Kostrewa, H. Link, T. Luebbers, R. Masciadri, P. Reindl, F. Ricklin, F.P. Theil*
F. Hoffmann-La Roche Ltd, Basel, Pharma Division, Discovery Research
'From the DNA Gyrase Inhibitor Cyclothialidine to a New Class of Antibacterial Agents'
Abstract 49

12.45–13.00 ***K. Groebke,*** *L. Weber, Yu-Hua Ji, J. Ackermann, D.W. Banner, H.J. Böhm*
F. Hoffmann-La Roche Ltd, Basel
'Design of Factor VIIa Inhibitors as Safe Anticoagulants'
Abstract 50

**13.00–14.00** **Lunch and Poster Session**
*Foyer 2nd floor*
Abstracts 58–65

**14.00–16.00** **Lectures**
*Room Singapore*
Abstracts 51–57
Chairperson: *W. Froestl*

14.00–14.15 ***S. Kolczewski,*** *T.M. Ballard, T. Hoffmann, S.M. Poli, S. Röver, P. Schnider, A.J. Sleight*
F. Hoffmann-La Roche Ltd, Basel, Pharma Research
'Design and Synthesis of Potent and Selective, Orally Active $NK_1$ Receptor Antagonists'
Abstract 51

14.15–14.30 ***R. Lattmann***[a], *N. Teno*[b], *M. Missbach*[a], *E. Altmann*[a], *K. Gohda*[b], *J.A. Gasser*[a], *K. Toriyoma*[b], *J.R. Green*[a], *T. Buhl*[a], *H. Ishihara*[b], *M. Kometani*[b], *R. Gamse*[a], *C. Betschart*[b]
[a]Novartis Pharma, Basel
[b]Novartis, Tsukuba, Japan
'Identification of Orally Active Inhibitors of Cathepsin K'
Abstract 52

14.30–14.45 ***P.W. Manley***, *S.W. Cowan-Jacob, D. Fabbro, G. Fendrich, P. Furet, V. Guez, J. Liebetanz, J. Mestan, T. Meyer*
Novartis, Basel
'Molecular Interactions Between Glivec$^{\text{TM}}$ and Mutant Forms of cAbl Kinase'
Abstract 53

14.45–15.00 ***R. Sedrani***, *G. Zenke, J. Kallen*
Novartis, Basel, Pharma Research
'The Spirobicyclic Subunit of Sanglifehrin A Can Be Replaced by Structurally Simpler Moieties'
Abstract 54

15.00–15.15 ***M. Sulpizi***, *U. Röthlisberger, A. Cattaneo, P. Carloni*
Institute of Inorganic Chemistry, ETH-Zürich
SISSA/ISAS-Trieste, Italy
'Reaction Mechanism of Caspases: Insights from QM/MM Car-Parrinello Simulations'
Abstract 55

15.15–15.30 ***E. Vieira***, *J. Huwyler, S. Jolidon, F. Knoflach, V. Mutel, J. Wichmann*
F. Hoffmann-La Roche Ltd, Basel, Discovery Research
'Positive Allosteric Modulators of mGlu1 Receptors'
Abstract 56

15.30–16.00 ***G. Thoma***
Novartis Pharma AG, Basel
'A Novel Approach for the Control of Polyvalent Biological Interactions'
Abstract 57

## Chemical Research

**11.00–11.15** **General Assembly of the Members**
*Room San Francisco*

## Computational Chemistry

**11.15–12.45** **Lectures**
*Room Rio*
Abstracts 66–71
Chairperson: *C. Daul*

11.15–11.30 ***M.C. Colombo***, *J. Vande Vondele, L. Guidoni, A. Laio, U. Röthlisberger*
Laboratory of Inorganic Chemistry, ETH-Zürich
'QM/MM Study of the Copper Binding Sites of Prion Proteins'
Abstract 66

11.30–11.45 ***F. Tran***, *T.A. Wesolowsky, J. Weber*
Department of Physical Chemistry, University of Geneva
'Theoretical Study of Weakly Bound Complexes Using the Density Functional Theory Formalism Based on Electron Density Partitioning'
Abstract 67

11.45–12.00 ***U.F. Röhrig***[a], *I. Frank*[b], *L. Guidoni*[a], *A. Laio*[c], *C. Molteni*[d], *M. Parrinello*[c], *U. Röthlisberger*[a], *J. Vande Vondele*[e]
[a]Laboratory of Inorganic Chemistry, ETH-Zürich
[b]Chemistry Department, LMU Munich, Germany
[c]Swiss Center for Scientific Computing, Manno
[d]Cavendish Laboratory, Cambridge University, UK
[e]Institute of Physical Chemistry, University of Zürich
'Molecular Dynamics Simulations of Rhodopsin: Insights into the Signaling Pathway and Spectral Changes'
Abstract 68

12.00–12.15 ***S. Rey***, *A. Daina, F. Ooms, P.-A. Carrupt, B. Testa*
Institut de Chimie Thérapeutique, Université de Lausanne
'The Molecular Lipophilicity Potential and the Molecular Hydrogen-Bonding Potentials: Their Application to the Development of a Scoring Function for Virtual Ligand–Receptor Screening'
Abstract 69

12.15–12.30 ***S. Piana***, *U. Röthlisberger*
Laboratory of Inorganic Chemistry, ETH-Zürich
'A QM/MM Study of Catalytic Enantioselective Fluorination'
Abstract 70

12.30–12.45 ***M.G. Müller***, *E. Hardy, B. Kirchner, P.S. Vogt, C. Bratschi, D.J. Searles*[a], *H. Huber*
Departement Chemie der Universität Basel
[a]School of Science, Griffith University, Brisbane, Australia
'D Quadrupolar NMR Relaxation Times in $D_2O$/DMSO Mixtures Calculated by Molecular Dynamics Simulations in Combination with Quantum Chemical Calculations'
Abstract 71

**13.00–14.30** **Lunch and Poster Session**
*Foyer 2nd floor*
Abstracts 77–87

**14.30–15.45** **Lectures**
*Room Rio*
Abstracts 72–76
Chairperson: *H. Huber*

14.30–14.45 ***P. Maurer,*** *A. Laio, U. Röthlisberger*
Laboratory of Inorganic Chemistry,
ETH-Zürich
'Molecular Mechanics Force Field Parameters Derived From Mixed QM/MM Calculations'
Abstract 72

14.45–15.00 ***L. Guidoni,*** *U. Röthlisberger*
Department of Chemistry, ETH-Zürich
'Driving Chemical Reactions via Biases of Molecular Orbitals'
Abstract 73

15.00–15.15 ***C. Corminboeuf***[a], *T. Heine*[b], *M. Büehl*[c], *J. Weber*[a]
[a]Department of Physical Chemistry,
University of Geneva
[b]Inst. f. Physikalische Chemie, TU Dresden,
Germany
[c]Max-Plank-Institut für Kohlenforschung,
Mülheim, Germany
'Influence of Dynamics on NMR Chemical Shifts – Berry Pseudorotation and Diels-Alder Reaction'
Abstract 74

15.15–15.30 ***G. Bouchard***[a], *B. Walther*[b], *P.-A. Carrupt*[a], *B. Testa*[a]
[a]Institut de Chimie Thérapeutique,
University de Lausanne
[b]Technologie Servier, Orléans, France
'Affinity of 5-HT$_{1A}$ Agonists and Their Metabolites: Radioreceptor Assays and Molecular Modelling'
Abstract 75

15.30–15.45 ***D. Bas***[a], *A. Goursot*[b], *J. Weber*[a], *T. Wesolowski*[a]
[a]Department of Physical Chemistry,
University of Geneva
[b]Ecole de Chimie, Montpellier, France
'Theoretical Study of Bonding Carbon Monoxide to Alkali Metal Cations in ZSM5 Zeolite Using Orbital-Free Embedding Formalism'
Abstract 76

## Organic Chemistry

**11.15–13.00** **Lectures**
*Room Montreal*
Abstracts 88–94
Chairperson: *M. Karpf*

11.15–11.30 *E.P. Kündig,* ***C.H. Fabritius,*** *G. Grossheimann, F. Robvieux, P. Romanens, G. Bernardinelli*
Department of Organic Chemistry,
University of Geneva
'Molybdenum-Mediated Arene Transformations'
Abstract 88

11.30–11.45 ***A. Goeke,*** *S. Jork, D. Mertl*
Givaudan, Dübendorf
'Titanacyclopentene Complexes and their Application as 1,4-Dicarbanion Equivalents'
Abstract 89

11.45–12.00 *C.G. Bochet,* ***C. Helgen***
Departement de Chimie Organique,
Université de Genève
'Photochemical Acylation: Application to the Synthesis of Amides and Carbamates'
Abstract 90

12.00–12.15 *G. De Almeida, M. Bürli, G. Kälin, W. Höneise,* ***A.F. Indolese***
Rohner AG, Pratteln
'Ionic Liquids as Solvents for Metal-Catalyzed Reactions'
Abstract 91

12.15–12.30 ***M. Kessler***[a], *R. Glatthar*[a], *B. Giese*[a], *C.G. Bochet*[b]
[a]University of Basel, [b]University of Geneva
'Orthogonal Photolabile Protecting Groups in Solid Phase Synthesis'
Abstract 92

12.30–12.45 ***T. Kovac,*** *F. Villar, P. Renaud*
Department of Chemistry and Biochemistry,
University of Bern
'Synthesis of Deoxypodophyllotoxin via a Radical Cascade Reaction'
Abstract 93

12.45–13.00 ***P. Krattiger,*** *C. McCarthy, A. Pfaltz, H. Wennemers*
Institute of Organic Chemistry,
University of Basel
'A New Concept for the Combinatorial Search for Catalysis'
Abstract 94

**13.00–14.30** **Lunch and Poster Session**
*Foyer 2nd floor*
Abstracts 114–179

**14.30–16.00** **Lectures**
Room Montreal
Abstracts 95–100
Chairperson: *P. Renaud*

14.30–14.45 ***P. Kraft,*** *R. Cadalbert*
Givaudan Dübendorf AG
'Constructing Conformationally Constraint Macrobicyclic Musks'
Abstract 95

14.45–15.00 ***M. Nagel***[a], *G. Fráter*[b], *H.-J. Hansen*[c]
[a]EMPA, Dübendorf, [b]Givaudan Dübendorf AG,
[c]University of Zürich
'Novel, Short and Repeatable Two-Carbon Ring Expansion Reactions', Abstract 96

15.00–15.15 ***M. Obkircher,*** *B. Giese*
Institute of Organic Chemistry,
University of Basel

'A New Photochemical Carbon–Nitrogen Bond Formation: From Aspartic Acids to γ-Lactams'
Abstract 97

15.15–15.30 ***R.O. Schönleber***, *B. Giese*
Institute of Organic Chemistry, University of Basel
'7-Methoxycoumarin-4-yl-methyl (MCM): A New Photochemically Labile Protecting Group for Amines'
Abstract 98

15.30–15.45 *S. Elmer*, ***F. Schröder***
Givaudan Dübendorf AG
'Olfactory Profiles of the Lilial Isomers: Synthesis and Evaluation of Enantiopure *meta-t*-Butyl-Lilial'
Abstract 99

15.45–16.00 ***B. Wüstenberg***, *A. Pfaltz*
Institute of Organic Chemistry, University of Basel
'Ir-Catalyzed Asymmetric Hydrogenation: Synthesis and Application of New Heteroaromatic Substrates'
Abstract 100

**11.15–13.00** **Lectures**
*Room San Francisco*
Abstracts 101–107
Chairperson: *J. Robinson*

11.15–11.30 ***T.B. Angelov***, *O. Schärer*
Institute of Medical Radiobiology, University of Zürich
'A Chemical Approach for Investigation of DNA Interstrand Crosslink Repair'
Abstract 101

11.30–11.45 ***M. Conza***, *H. Wennemers*
Institute of Organic Chemistry, University of Basel
'Synthesis and Screening of a Diketopiperazine Receptor Library'
Abstract 102

11.45–12.00 ***G. Das***, *P. Talukdar*, *N. Sakai*, *S. Matile*
Department of Organic Chemistry, University of Geneva
'Practical Fluorimetric Sensing Applications of Rigid-Rod β-Barrel Ion Channels'
Abstract 103

12.00–12.15 ***S. Gendreizig***, *A. Keppler*, *K. Johnsson*
Institute of Molecular and Biological Chemistry, EPFL-Lausanne
'Specific and Covalent Labeling of Alkyltransferase Fusion Proteins in Living Cells'
Abstract 104

12.15–12.30 ***P. Hebeisen***, *J. Geiwiz*, *E. Goetschi*
Pharma Division, Discovery Research, F. Hoffmann-La Roche AG, Basel
'Inter- and Intramolecular Reductive Thiolation of Aromatic Aldehydes: Application to the Concise Synthesis of Cyclothialidine Analogues'
Abstract 105

12.30–12.45 ***M. Lochner***, *W.-D. Woggon*
Institute of Organic Chemistry, University of Basel
'A Crown-Capped Iron Porphyrin Mimicking the Resting State of Cytochrome $P450_{cam}$'
Abstract 106

12.45–13.00 ***M. Nold***, *M. Conza*, *H. Wennemers*
Institute of Organic Chemistry, University of Basel
'Conformational Studies on Proline-Diketopiperazines: Implications for the Binding Properties of Two-Armed Diketopiperazin Receptors'
Abstract 107

**13.00–14.30** **Lunch and Poster Session**
*Foyer 2nd floor*
Abstracts 114–179

**14.30–16.00** **Lectures**
*Room San Francisco*
Abstracts 108–113
Chairperson: *H. Wennemers*

14.30–14.45 ***M. Oberhuber***, *J. Berghold*, *B. Kräutler*
Institute of Organic Chemistry, University of Innsbruck, Austria
'A Synthetic Approach to the Products of Chlorophyll Breakdown in Higher Plants'
Abstract 108

14.45–15.00 ***L. Patiny***, *F. Monachon*, *M. Krompiec*
Institute of Molecular and Biological Chemistry, EPFL-Lausanne
'New Ways to Share and Process Chemical Information over the Internet'
Abstract 109

15.00–15.15 ***P. Tafelmeyer***, *K. Johnsson*
Institute of Molecular and Biological Chemistry, EPFL-Lausanne
'Development of a Cytochrome c Peroxidase-based Reporter System for Monitoring Protein–Protein Interactions'
Abstract 110

15.15–15.30 ***A.V. Vorogushin***[a,b], *W.D. Wulff*[a], *H.-J. Hansen*[b]
[a]Michigan State University, E. Lansing MI,USA
[b]Institute of Organic Chemistry, University of Zürich
'Central-to-Axial Chirality Transfer under Kinetic and Thermodynamic Conditions: Preparation of Either Atropisomer of Configurationally Stable Allocolchicinoids'
Abstract 111

15.30–15.45
*N. Amann, E. Pandursky, T. Fiebig,* ***H.-A. Wagenknecht***
TU Munich, Germany
'Preparation and Spectroscopic Properties of Pyrenyl-Modified Oligonucleotides as Models for Electron Injection into DNA'
Abstract 112

15.45–16.00
***Xiao-an Zhang****, G. Scherer, W.-D. Woggon*
Institute of Organic Chemistry, University of Basel
'Binding of Ortho-Vanadate Anion: Towards Mimics of Vanadium Haloperoxidase(VHPO)'
Abstract 113

## Physical Chemistry

**11.15–13.00**
**Lectures**
*Room Osaka*
Abstracts 180–186
Chairperson: *J. Wirz*

11.15–11.30
***A. Galland***[a]*, G. Bouchard*[a]*, G. Caron*[b]*, G. Plemper van Balen*[a]*, A.A. Marca Martinet*[a]*, S. Geinoz*[a]*, S. Rey*[a]*, G. Ermondi*[b]*, F. Vacondio*[c]*, M. Mor*[c]*, P.V. Plazzi*[c]*, P.-A. Carrupt*[a]*, B. Testa*[a]
[a]Institut de Chimie Thérapeutique, BEP, Université de Lausanne
[b]Dip. Scienza e Technologia del Farmaco, Torino, Italy
[c]Dip. Farmaceutico, Universita die Parma, Italy
'The 1,2-Dichlorethane/Water vers. the n-Octanol/Water System: More About Intra- or Intermolecular H-Bond Interactions'
Abstract 180

11.30–11.45
***M. Hippler****, R. Pfab, M. Quack*
Physical Chemistry, ETH Zürich
'Ionization Detected Overtone Spectroscopy of the $N$=2 CH-Chromophore of Jet-cooled Benzene Isotopomers near 6000 $cm^{-1}$'
Abstract 181

11.45–12.00
***S. Albert****, M. Quack*
Physical Chemistry, ETH Zürich
'Rovibrational Analysis of the $\nu_3$ Band of CDBrClF'
Abstract 182

12.00–12.15
D. Ferri, **T. Bürgi**, A. Baiker
Laboratory of Technical Chemistry, ETH Zürich
'Investigation of Chirally modified Pt and Pd Catalysts by *In Situ* IR spectroscopy'
Abstract 183

12.15–12.30
*M. Quack,* ***A. Sieben****, M. Willeke*
Physical Chemistry, ETH Zürich
'Effect of Isotopic Substitution on Parity Violating Energy: Influence of Anharmonic Corrections'
Abstract 184

12.30–12.45
***P. Brodard****, E. Vauthey*
Department of Physical Chemistry, University of Geneva
'Liquid–Liquid Interfaces Structure and Thickness Explored by Transient Evanescent Gratings'
Abstract 185

12.45–13.00
***M. Sulpizi****, U. Röthlisberger, P. Carloni*
Institute of Inorganic Chemistry, ETH-Zürich, SISSA/ISAS, Trieste, Italy
'TDFT and ROKS Characterization of Aminocoumarins in solution: Towards the Design of New Fluorescent Probes'
Abstract 186

**13.00–14.30**
**Lunch and Poster Session**
*Foyer 2nd floor*
Abstracts 193–216

**14.30–16.00**
**Lectures**
*Room Osaka*
Abstracts 187–192
Chairperson: *W. Nau*

14.30–14.45
***D. Schürch****, A. Currao, G. Calzaferri*
Department of Chemistry and Biochemistry, University of Bern
'The AgCl Photoanode'
Abstract 187

14.45–15.00
***C. Leiggener****, G. Calzaferri*
Department of Chemistry and Biochemistry, University of Bern
'Luminescent Silver Sulfide Clusters'
Abstract 188

15.00–15.15
***H. Maas****, S. Huber, G. Calzaferri*
Department of Chemistry and Biochemistry, University of Bern
'Trapping Energy from and Injecting Energy into Dye–Zeolite Nanoantennae'
Abstract 189

15.15–15.30
*A. Fürstenberg,* ***A. Morandeira****, E. Vauthey*
Department of Physical Chemistry, University of Geneva
'Charge Transfer in Electron Donating Solvents'
Abstract 190

15.30–15.45
***C. Dutan****, S. Choua, T. Berclaz, N. Mézailles, A, Moores, L. Ricard, P. Le Floch, M. Geoffroy*
Department of Physical Chemistry, University of Geneva
'EPR/ENDOR Spectra and DFT Calculations of the One-Electron Reduction Compound of a Di(*meta*-sylphenylenesiloxane)'
Abstract 191

15.45–16.00
***J.-D. Grundwaldt****, S. Hannemann, C. Keresszegi, M. Maciejewski, M. Ramin, A. Baiker*
Laboratory of Technical Chemistry, ETH-Zürich

'*In Situ* X-ray Absorption Spectroscopy on Heterogeneous Noble Metal Catalysts'
Abstract 192

## Inorganic and Coordination Chemistry

**11.15–13.00** **Oral Presentations of 12 Posters**
*Room Sidney*
Chairperson: *H. Berke*

**13.00–14.30** **Lunch and Poster Session**
*Foyer 2nd floor*
Abstracts 223–309

**14.30–16.00** **Lectures**
*Room Sidney*
Abstracts 217–222
Chairperson: *T. Kaden*

14.30–14.45 ***G. Ferrando-Miguel**, P. Wu, J.C. Huffman, K.G. Caulton*
Department of Chemistry and Molecular Structure Center, Indiana University, Bloomington, USA
Department of Chemistry, ETH Zürich
'New Hexacoordinate Dihydride Complexes of Ru and Os: $M(H)_2(chelate)(P^iPr_3)_2$ with Chelate *ortho*-$EC_6H_3Re'$ and E, E' = O, Nr'; R, R' = H or $CH_3$'
Abstract 217

14.45–15.00 ***M.-L. Lehaire**, R. Scopelliti, K. Severin*
Institut de Chimie Moléculaire et Biologique, EPFL-Lausanne
'Stabilization of Molecular LiF and LiFHF Inside Metallamacrocyclic Hosts'
Abstract 218

15.00–15.15 ***P. Dotta**, P.S. Pregosin*
Laboratory of Inorganic Chemistry, ETH Zürich
'3,5-Dialkyl Meta Effect in Enantioselective, Palladium Catalyzed Reactions'
Abstract 219

15.15–15.30 ***C.N. McMahon, L. Siegfried**, D. Gusmeroli, T.A. Kaden*
Department of Chemistry, University of Basel
'Novel Polytopic Ligands with Two Different Binding Sites Based on Open-Chain and Cyclic Structural Elements"
Abstract 220

15.30–15.45 ***F. Bonadio**[a], E. Rusanov[b], H. Stoeckli-Evans[b], S. Decurtins[a]*
[a]Departement für Chemie und Biochemie, Universität Bern
[b]Institut de Chimie, Université de Neuchâtel
'New Paramagnetic Complexes Using "$N_3O_2$" Macrocyclic Ligand as a Building Block'
Abstract 221

15.45–16.00 ***J. Collot**, D. Berdat, J. Gradinaru, M. Skander, T.R. Ward*
Institut de Chimie, Université de Neuchâtel
'Second-Coordination Sphere: Proteins as Host for Enantioselective Catalysis'
Abstract 222

## contact**chemists.ch**

### The Swiss Young Chemists' Committee's Career Fair

**11.15–16.00** *Foyer 2nd floor*
Participating companies: *Actelion* (Poster 310), *Ares Serono* (Poster 311), *Bachem* (Poster 312), *Baer Management Consulting* (Poster 313), *Carbogen* (Poster 314), *Chemspeed* (Poster 315), *CibaSC* (Poster 316), *Lonza* (Poster 317), *Nestlé* (Poster 318), *Novartis* (Poster 319), *F. Hoffmann-La Roche* (Poster 320), *Syngenta* (Poster 321)

11.15–11.20 **Welcoming Remarks for *contactchemists.ch***
*Room Hongkong*

11.20–12.05 **Company Presentation: Nestlé**
*Room Hongkong*

12.15–13.00 **Company Presentation: Ciba SC**
*Room Hongkong*

13.15–14.00 **Workshop: 'How to Apply' by Baer Management Consulting**
*Room Hongkong*

14.15–15.00 **Company Presentation: Ares Serono**
*Room Hongkong*

15.15–16.00 **Company Presentation:** *to be announced*
*Room Hongkong*

**16.00–16.30** **Coffee Break**
*Foyer 2nd floor*

## Awards for the Best Oral and Poster Presentations

**16.30–16.45** *Room Montreal*
Chairperson: *W.-D. Woggon*

## Presentation of the Paracelsus Prize 2002

**17.00** *Room Montreal*
Chairperson: *A. Merbach*

17.05–18.00 **Lecture of the Paracelsus Prize Laureate 2002**
**Prof. *Martin Quack***
Laboratorium für Physikalische Chemie, ETH-Zürich
'Molecular Spectra, Reaction Dynamics, Symmetries and Life'

Organic Chemistry

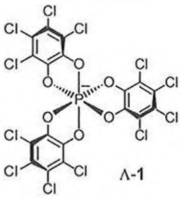
**1**

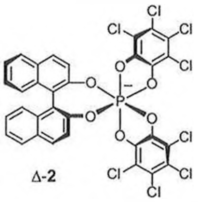
### Chiral Ion Mediated Asymmetric Chemistry.

Jérôme Lacour

Department of Organic Chemistry, Université de Genève, Switzerland

Many chemical reactions and processes involve cationic reagents or products. Cations are frequent intermediates along reaction pathways and often act as powerful electrophiles or Lewis acids. Cations are also used as templates for the efficient construction of supramolecular arrays. In many instances, the cations are *prostereogenic* or *chiral*, and *racemic* molecular or supramolecular assemblies are afforded. To obtain instead non-racemic products or reagents, we are studying projects dealing with the asymmetric chemistry of chiral anions and cations.


Λ-1


Δ-2

Previously, readily prepared hexacoordinated phosphate anions TRISPHAT **1** and BINPHAT **2** have been shown to be configurationally stable.[1] These highly lipophilic anions are efficient NMR chiral shift, resolving and asymmetry-inducing agents for organic, metallo-organic and organo-metallic species. Selected applications of these reagents will be presented [2].

[1] J. Lacour, C. Ginglinger, C. Grivet, G. Bernardinelli, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 608; J. Lacour, A. Londez, C. Goujon-Ginglinger, V. Buß, G. Bernardinelli, *Org. Lett.* **2000**, *2*, 4185.
[2] J. Lacour, L.Vial, C. Herse, *Org.Lett.* **2002**, *4*, 1351. J. Lacour, J. J. Jodry, D. Monchaud, *Chem. Commun.* **2001**, 2302. J. Lacour, C. Goujon-Ginglinger, S. Torche-Haldimann, J. J. Jodry, *Angew. Chem. Int. Ed.* **2000**, *39*, 3695.

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Physical Chemistry

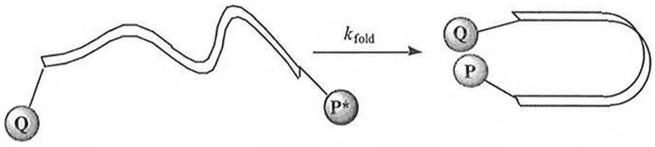
**2**

### Biopolymer Motions Probed by Fluorescence

Werner M. Nau

Departement Chemie, Universität Basel, Klingelbergstrasse 80, CH–4056 Basel, Switzerland

The fastest motions in biopolymers, e.g., intramolecular end-to-end contact formation, occur in the µs-ns time range, which is not accessible to stopped-flow studies. We have exploited the long fluorescence lifetime and the selective contact quenching mechanisms of fluorazophores (chromophores based on 2,3-diazabicyclo[2.2.2]oct-2-ene) to introduce a fluorescence-based method for monitoring intramolecular contact formation [1,2].



Quenching occurs on contact with an intrinsic quencher, either tryptophane or guanine, and the rate of quenching can be directly related to the kinetics of end-to-end contact formation ($k_{\mathrm{fold}}$). The folding kinetics provides a direct measure of the flexibility of the biopolymer. We have studied the flexibility of polypeptides and oligonucleotides as a function of the amino acid type in polypeptides and the base type in oligonucleotides. This allows us to propose „flexibility scales" for amino acids and nucleotides.

[1] R. R. Hudgins, F. Huang, G. Gramlich, W. M. Nau, *J. Am. Chem. Soc.* **2002**, *124*, 556.
[2] X. Wang, W. M. Nau, *ChemPhysChem* **2002**, *3*, 393.

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**3**

### Recent Advances in High Performance LC(1D and 2D) / Mass Spectrometry for Proteomic Analysis

Barry L. Karger
Barnett Institute
Northeastern University
Boston, MA 02115

The challenges for global identification and quantitation of complex protein mixtures continue to be great. Issues of comprehensiveness, sensitivity, dynamic range and throughput are significant. In this talk, we will first discuss the requirements for proteome analysis using one-dimension and two-dimension liquid chromatography coupled to both ESI/MS and MALDI/MS. In both cases, high-resolution separations are required, often at the trace level. We will present results on analysis of lysates using both ESI and MALDI. In particular, our recent work on vacuum deposition, followed by MALDI/TOF and MALDI/TOF-TOF will be described. This approach allows for high throughput and, at the same time, a decoupling of the separation, MS and MS/MS steps for optimum analysis. Some advances that likely will occur in this area and LC/MS in general in the coming period will also be noted. Finally, specific examples of the use of these tools will be described.

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**4**

### New opportunities for the characterization of small molecules and peptides using multidimensional chromatography and hybrid tandem mass spectrometry.

Gérard Hopfgartner

University of Geneva, 20 Bd d'Yvoy CH-1211 Geneva 4.

Triple quadrupole mass analysers are largely used for the quantification of small molecules, while ion trap mass spectrometers are more suited for drug metabolism and for proteomics. Ideally one would like to have all features of both instruments in one system. The situation becomes even more complex with hybrid instruments such as quadrupole time of flight mass spectrometers, where medium resolution and accurate mass of the precursor ions and the fragment ions can be obtained with high sensitivity. Recently a new type hybrid RF/DC quadrupole-linear ion trap mass spectrometer (QqQlinear ion trap, Q TRAP, AB/MDS Sciex) has been brought on the market (1). This instrument is based on a quadrupole ion path and is capable of all of the conventional tandem MS scan modes as well as several high-sensitivity ion trap MS scans using the final quadrupole as a linear ion trap. Also two completely new scan modes are available: the Time Delayed Fragmentation (TDF) and the Enhanced Multiply Charged (EMC) modes of operation. Selected examples in drug metabolism and proteomics will be presented to demonstrate the new possibilities of the hybrid system and how it fits in the global MS picture to solve analytical problems using multidimensional HPLC with microbore and nanobore columns.

1) J. Hager, *Rap. Commun. Mass Spectrom.*, 2002, *16*, 512.

Analytical Chemistry

**5**

## Intrinsic Mass Signal Intensities of Protein Digests

Sebastian D. Friess and Renato Zenobi

Department of Chemistry, Swiss Federal Institute of Technology, ETH
Hönggerberg, 8093 Zurich

In a tryptic digestion, the protein of interest is cleaved by trypsin adjacent to the arginine or lysine residues. A MALDI (Matrix-assisted Laser Desortion/ Ionization) mass spectrum of this peptide mixture provides a fingerprint of great specificity.

For the ideal case of full cleavage, all fragments are present in the mixture in equimolar concentrations. However, the MALDI mass spectrum usually shows some peptide fragment signals with very high intensity, whereas other fragments are represented by very small signals, and again others are fully absent. This phenomenon is well known, but not well understood. It is assumed that the diversity in signal intensity comes from different gas-phase basicities of the fragments, which in turn results in partial signal suppression. Fundamental aspects of ion formation in MALDI [1] are probably responsible for this behavior.

We address the phenomenon of different signal intensities by comparing MALDI mass spectra of individual arginine containing peptides with mass spectra from the corresponding peptide mix, recorded under exactly the same experimental conditions. Signals in a mass spectrum of a peptide mix have almost identical intensities as signals recorded from each individual peptide alone. Hence, the signal intensity observed in a peptide mix seems to be an intrinsic property of the individual peptides (such as the ionization efficiency), and not the result of suppression or promotion effects.

The topic is discussed under various aspects such as the influence of different matrix systems and introduction of peptides with obviously different ionization efficiencies.

[1] R. Zenobi, R. Knochenmuss, *Mass Spectrom. Rev.* **1998**, 17, 337-366.

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**6**

## NONAQUEOUS CAPILLARY ELECTROPHORESIS-ELECTROSPRAY-MASS SPECTROMETRY FOR THE ANALYSIS OF PHARMACEUTICAL COMPOUNDS

Laurent Geiser, Samir Cherkaoui, Jean-Luc Veuthey
*Laboratory of Pharmaceutical Analytical Chemistry, School of Pharmacy*
*University of Geneva, 20 Bd d'Yvoy, 1211 Geneva 4.*

Nonaqueous capillary electrophoresis (NACE) has encountered growing interest. Compared to aqueous buffer, organic solvents possess different physico-chemical properties: viscosity ($\eta$), dielectric constant ($\varepsilon$), polarity, auto-protolysis constant, electrical conductivity, etc. Therefore, different selectivity, high efficiency, rapid analysis time and better solubility and stability of some compounds in organic solvent than in water are the main reasons for this success. In particular, NACE has been found to be a good alternative for the analysis of pharmaceuticals and their metabolites that are difficult to separate in aqueous media.

In addition, low evaporation heat and low surface tension of acetonitrile (ACN), methanol (MeOH) and other alcohol are further properties in favor to on-line coupling of NACE with electrospray ionization mass spectroscopy (ESI-MS). Besides, other organic solvents (e.g. N-methyl formamide) could be used in NACE, showing higher $\varepsilon^2/\eta$ ratio which will result on high efficiency. But they have found only limited applications with UV detection, because of their very high optical cut-off. Therefore, hyphenation of CE with ESI-MS will certainly open new possibilities in NACE separation.

Several applications of NACE-ESI-MS are illustrated for the analysis of different drugs: anti-depressants (fluoxetine, venlafaxine and their metabolite), amphetamines and beta-blockers. Moreover phytochemicals applications are also exhibited with the analysis of some alkaloids.

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Analytical Chemistry

**7**

## LA-ICP-MS: Particle composition and their contribution to sensitivity and accuracy of the method

Marcel Guillong and Detlef Günther

Swiss Federal Institute of Technology, 8093 Zürich, Switzerland

Laser ablation-inductively coupled plasma-mass spectrometry has become one of the well-accepted analytical techniques for solid sample analysis and a large number of successful applications have shown its potential.

High speed photographic studies of wet droplets and solid particles in the ICP showed that particles and droplets are not completely vaporized and ionised [1]. It was established in previous experiments that the particle size distribution in aerosols from laser ablation is dependent on the wavelength of the ablating laser and the matrix. For silicate matrices the particle size distribution is much smaller for a 193 nm excimer system compared to a 266 nm Nd:YAG system. Using the 266 nm laser larger particles (>1 μm) are not completely ionised in the inductively coupled plasma causing non-stoichiometric signals from the MS [2]. The degree of vaporisation and ionisation on the other hand is dependent on the type of ICP [3]. One way to overcome the different excitations is to filter out larger particles before the ICP with glass wool filter in the aerosol transport tubing.

Other methods to influence the size of particles entering the ICP are cascade impactors or separation through centrifugal forces. This work describes the excitation efficiency of particles in the ICP in dependence on their size distribution. Experiments with collected large particles show that the plasma ionise particles above 0.5 μm to few percent only. However, the composition of the aerosol before entering the plasma and after the plasma was studied and indicates a contribution of the plasma to non-accurate results. The role of large and small particles to this effect will be presented.

Possibilities to increase the production of small particles (on the laser side) to enhance the degree of excitation (in the ICP) and to improve the sensitivity and accuracy of LA-ICP-MS measurements will be discussed.

[1] R. S. Houk, R. K. Winge and X. S. Chen, *J.Anal.At.Spectrom.*, 1997, **12**, 1139-1148.
[2] M. Guillong and D. Günther, *J.Anal.At.Spectrom.*, 2002, **17**, 1-8.
[3] D. Günther, *Anal.Bioanal. Chem.*, 2002, **372**, 31-32.

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Analytical Chemistry

**8**

## On-line Gas Analysis for Process Diagnostics in Semiconductor Industries

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Perfluorocompounds (PFC) are widely used in chemical vapour deposition (CVD) processes in Semiconductor industries. Their use and abatement must be optimised for economic and ecological reasons [1].

Fourier transform infrared spectroscopy (FTIR) and quadrupole mass spectrometry (QMS) were used to monitor process gas emissions during tungsten (1), tungsten silicide (2) and tetraethylorthosilicate (TEOS) (3) deposition.

$$WF_6 + 3H_2 \rightarrow W(s) + 6HF \qquad (1)$$

$$WF_6 + SiH_4 \rightarrow W_xSi_y(s) + SiF_4 + HF + other \qquad (2)$$

$$Si(OC_2H_5)_4 + 12O_2 \rightarrow SiO_2(s) + 10H_2O + 8CO_2 \qquad (3)$$

Input and output concentration profiles were determined to point out episodes of increased emissions, i.e. low efficiency of process gases. Mass balances of tungsten and silicon were calculated differentiating between tungsten/silicon deposition on wafer resp. chamber wall and output of unreacted process gases. These results are essential to optimise process conditions and reduce the cost of ownership (COO). FTIR spectroscopy was furthermore used to monitor the destruction efficiency of an abatement device for various process gases.

[1] L. Beu, P.T. Brown, J. Latt, J.U. Rapp, T. Gilliland, T. Tamayo, J. Harrison, J. Davison, A. Cheng, J. Jewett, W. Worth, *International Sematech Technology transfer* **1998**, 98053508A-TR.

Analytical Chemistry **9**

## Determination of Fuoroquinolone Antibacterial Agents in Sewage Sludge and Sludge-Treated Soil by Accelerated Solvent Extraction and Liquid Chromatography with Fluorescence Detection

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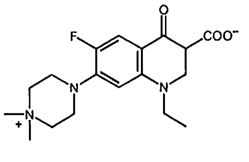
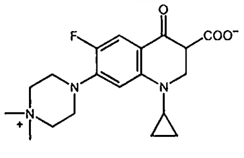
In recent years, public and scientific concern about the occurrence of pharmaceuticals in the environment has been continuously increasing. Antibacterials are the most often discussed pharmaceuticals because of their potential role in the spread and maintenance of resistance of bacterial pathogens.
A method for the determination of fluoroquinolone antibacterial agents (FQs) ciprofloxacin and norfloxacin in sewage sludge and soil samples based on reversed-phase liquid chromatography with fluorescence detection was developed. The FQs were quantitavely extracted by Accelerated Solvent Extraction at 100 °C and 100 atm with aqueous phosphoric acid / acetonitrile mixture (1:1, pH 2). A clean-up step by SPE (mixed-phase cation-exchange disk cartridges, MPC) substantially improved the selectivity of the method. Relative standard deviations varied between 8 to 11% for sludge and soil extraction and analysis. Limits of quantification were 0.45 and 0.18 mg/kg for sludge and soils, respectively. Concentrations of ciprofloxacin and norfloxacin in sludges from different wastewater treatment plants ranged from 1.40 to 2.42 mg/kg dry sewage sludge.



Norfloxacin



Ciprofloxacin

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**10**

## SEPARATION OF ISOMERIC TROPANE ALKALOIDS FROM *SCHIZANTHUS GRAHAMII* BY CAPILLARY LC-MS AND GC-MS

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Despite the availability of some sophisticated hyphenated chromatographic techniques, gas chromatography coupled to mass spectrometry with electron impact ionisation remains a technique of choice commonly employed for structural elucidation. Nevertheless due to analytical problems (eg. limited sample volatility, artefact formation during injection or degradation) a complementary technique such as LC has to be used. In this study a purified alkaline extract from the stem-bark of endemic Chilean *Schizanthus grahamii* (Solanaceae) was analysed by two orthogonal capillary chromatographic techniques, namely GC-MS and LC-MS.
Previous chemical investigations [1] have shown that this genus contains tropane alkaloids esterified with isomeric $C_5$ acids, namely angelic, tiglic and senecioic acids. This esterification leads to the formation of structural and configurational (E and Z) isomers, which are interesting challenges for analytical chemists.
Thus, GC separation of four isomeric hydroxytropane esters was achieved on a conventional HP5-MS wall-coated open-tubular column. The fragmentation pattern of these alkaloids are presented and discussed. However, only one isomer showed a distinguishable mass spectrum.
These four isomeric compounds were also separated by capillary LC on a porous graphitic carbon column. Indeed, the highly regular and planar structure of the graphitic support presents unique selectivity for geometrical isomers and shows excellent peak symmetry for basic compounds. Since all MS spectra were identical with the single quadrupole MS detector, it was also difficult to distinguish and assign these isomers. However, the ability to perform some differentiation by in-source collision-induced dissociation is demonstrated and discussed.

[1] Lounasmaa, M., Tamminen T., (1993) in: The Alkaloids (Cordell, G.A., ed.) Vol. 44, pp. 1-114, Academic Press, New York.

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Analytical Chemistry **11**

## Protonation mechanism of poly(amidoamine) (PAMAM) dendrimers

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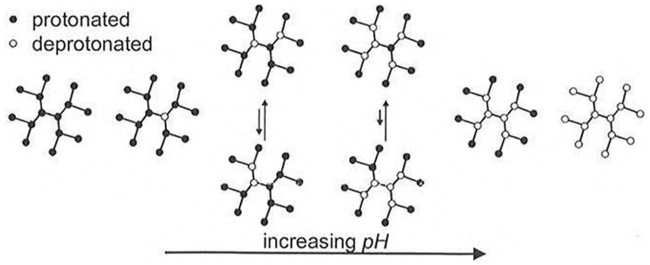
Potentiometric acid-base titrations of the first six generations of poly(amidoamine) (PAMAM) dendrimers at different ionic strengths have been carried out, using a high-precision titration setup[1]. The experimental data were fitted to a site binding model titration curves by means of a non-linear least squares procedure[2]. The applied model involves three different micro p*K*s and two different next-neighbor pair interaction energies as adjustable parameters[3].



A very good agreement between the model and the measured data was found within the whole experimentally accessible *pH* region for the lower generations of the PAMAM dendrimers. As for the higher generations, in the pH region between 6 and 10, the macro p*K*s predicted by the model lay in a slightly broader range than experimentally observed. It was possible to describe the titration curves of all generations with the same electrostatic interaction parameters, which were found not to be dependent upon ionic strength. The p*K*s were found to be dependent upon ionic strength in a fashion typical for weak bases. The site binding model allows a precise assessment of the microscopic protonation states of the PAMAM dendrimers, as shown in the above figure.

[1] Kinniburgh, D. J., Milne, C.J., Guide to the Wallingford Titrator, British Geological Survey, Technical Report WD/92/14, 1992.
[2] Borkovec, M., Koper, J. M., *Progr. Colloid Polym. Sci.*, **1998**, *109*, 142.
[3] Duijvenbode, R. C., Borkovec, M., Koper, J. -M., *Polymer*, **1998**, *39*, 2657.

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Analytical Chemistry **12**

## Dependence of fatty acids composition in cows milk from high and lowland region

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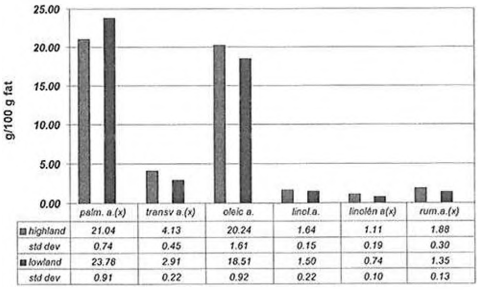
Using a very powerful gas chromatographic analytical procedure it was possible to separately measure the concentration of saturated fatty acids and of $\omega_3$ and $\omega_6$ unsaturated acids.
The results show unequivocally that milk from cows fed with grass from highland areas is low in saturated fatty acids but high in $\omega_3$ and $\omega_6$ acids. This difference is statically valid and shows the high quality of milk originary from cows fed with grass from highland.



| | palm. a.(x) | transv a.(x) | oleic a. | linol.a. | linolén a(x) | rum.a.(x) |
|---|---|---|---|---|---|---|
| ▨ highland | 21.04 | 4.13 | 20.24 | 1.64 | 1.11 | 1.88 |
| std dev | 0.74 | 0.45 | 1.61 | 0.15 | 0.19 | 0.30 |
| ■ lowland | 23.76 | 2.91 | 18.51 | 1.50 | 0.74 | 1.35 |
| std dev | 0.91 | 0.22 | 0.92 | 0.22 | 0.10 | 0.13 |

Graphic 1 : Global average of 20 milk samples of highland and 20 milk samples of lowland region
(x) indicates the existence of a significant difference between milk samples of lowland and highland regions.

This work will be continued with the aim to compare the fatty acids concentration between cheese obtained with milk from highland and milk from lowland.

Analytical Chemistry **13**

## Oligomers of Modified β-Cyclodextrin as Chiral Selector for Capillary GC

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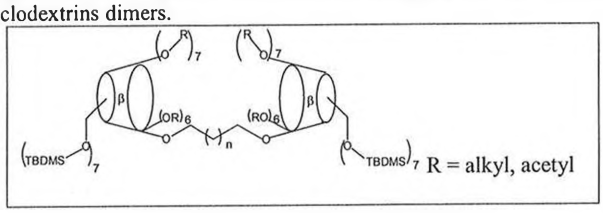
Nowadays, most volatile chiral compounds are analysed in GC by means of modified cyclodextrins diluted in polysiloxane polymers in accordance with Schurig's method [1]. Chiral discrimination is the basis of chiral chromatography. In spite of a great number of investigations [2], the separation mechanism is not fully known. This explains the great number of CSP tested to fullfil the resolution of various racemic chiral compounds.

Alkyls, acetyl in 2,3 positions and TBDMS in 6, are used as modifiers of β-Cyclodextrin. The chirals moieties were diluted in OV1701 as polymer.

The cyclodextrins dimers percentage have been optimised so as to avoid high retention and to allow us to work at lower temperature, and avoid minimum drawback for the resolution. Our aim is to obtain cyclodextrins able to produce complexes which are impossible to obtain with identical simple cyclodextrins modified in a similar way; it is the case for big size solutes. Different classes of compounds (racemic mixtures of alcohols, ketones, ...) have been analysed in order to define the application field of these new cyclodextrins dimers.



[1] V. Schurig, H.P. Nowotny, J. Chromatogr.1998, 44, 155.
[2] A. Venema, H. Henderisks, R.V. Geest, *J. High Resolut. Chromatogr.*,**1991**, *14*, 676.

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Analytical Chemistry **14**

## Determination of Association Constants of Adenylate Kinase with Noncovalent Inhibitors by ESI-MS

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Several approaches exist to determine the solution phase binding constants of noncovalent assemblies [1]. To measure solution phase parameters with a mass spectrometer, any reactions or dissociations in the analyzer itself must be prevented. For an electrospray ion source this means that the spray and ion transfer conditions have to be as gentle as possible.

With a number of control experiments we show that the measured complexes between adenylate kinase(AK) and the two inhibitors P1,P5-Di-(adenosine-5')pentaphosphate(Ap5A) and P1,P4-Di(adenosine-5')tetraphosphate(Ap4A) are noncovalent, specific and survive the ionization process.

We show with titration experiments that it is indeed possible to measure the solution phase association constants of noncovalent complexes with mass spectrometry. We estimated the association constants for AK•Ap5A (Ka=$4 \cdot 10^7 M^{-1}$) and for AK•Ap4A (Ka=$9 \cdot 10^4 M^{-1}$) (see Figure 1). The measured association constants agree very well with literature values [2].

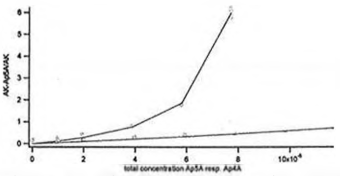

Figure 1: Titration of AK with Ap5A ($K_a$=$4.0 \cdot 10^7 M^{-1}$) and Ap4A ($K_a$=$9.0 \cdot 10^4 M^{-1}$) in 50mM $(HNEt_3)HCO_3$ and 0.5mM EDTA. The lines are the fitted data.

1. Daniel, J. M.; Friess, S. D.; Rajagopalan, S.; Wendt, S.; Zenobi, R. *Int. J. Mass Spectrom.* **2002**, *216*, 1-27.
2. Reinstein, J.; Vetter, I. R.; Schlichting, I.; Rösch, R.; Wittinghofer, A.; Goody, R. S. *Biochemistry* **1990**, *29*, 7440-7450.

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Analytical Chemistry **15**

## A near-field method to analyse the liquid-liquid interface

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Scanning near-field optical microscopy has already been successfully applied in combination with Raman spectroscopy [1]. In this way the improved resolution is combined with spectroscopic analysis to provide chemical information for the sample of interest.

Our attempt aims at applying this technique to the study of the boundary between two liquids. An important property of near-field probes is the high resolution or small depth of focus in tip direction. This means that the interface can be approached in small steps over a wide range. Gradual structural changes at variable distances from the interface can be spectrally analysed.

The exchange phenomena between two liquids and the stability of a multiphase system are mainly controlled by the properties of the interface. These can often be tuned with the addition of surface-active molecules [2]. The effect of surfactants on water/carbon tetrachloride interface will be studied. The choice of these liquids comes from the interest to analyse the interaction of water with hydrophobic fluid surfaces which plays a key role in many natural processes like protein folding, membrane formation and micellar assembly.

[1] Y. Narita, T. Tadokoro, T. Ikeda, T. Saiki, S. Mononobe, M. Ohtsu, *Appl. Spectrosc.* **1998**, *9*, 1141.
[2] F. Ravera, M. Ferrari, L. Liggieri, *Adv. Coll. Int. Sci.* **2000**, *88*, 129.

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Analytical Chemistry **16**

## Extractive FTIR On-line Gas Analysis

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Fourier Transform Infrared Spectroscopy (FTIR) for extractive on-line process gas analysis is receiving much interest because of its multicomponent analysis capability, sensitivity and time resolution [1]. Therefore, FTIR can fulfil many of the requirements set by a wide variety of applications.

Field tests were performed with a commercially available low-resolution spectrometer. For various analytical tasks, the main parameters, such as cell length, detector, reference library and spectral range were carefully optimised. Particular attention was paid to sample pre-treatment.

Validation measurements with independent analytical methods (GC, NDIR, MS, wet chemistry) have shown satisfactory quantitative results in process gases from chemical and semiconductor industries, exhaust gases of a cement kiln and agricultural ammonia emissions (Fig. 1).

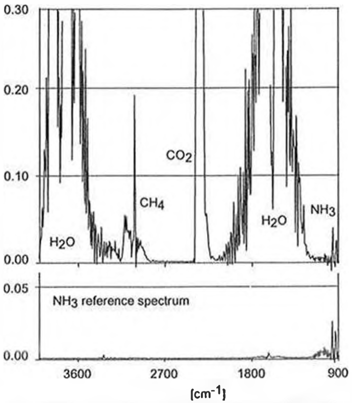

*Fig. 1:* Quantitative measurement of 17 ppm $NH_3$ in a pigsty. Concentrations of the main components: $H_2O$ 1.0 %, $CO_2$ 610 ppm, $CH_4$ 110 ppm.

[1] P.R. Griffiths, J.A. de Haseth, 'Fourier transform infrared spectrometry', John Wiley and Sons, New York, **1986**.

Analytical Chemistry **17**

### Fluorescent measurements and spectroscopy of mass-selected trapped molecular ions

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Laser induced fluorescence (LIF) spectroscopy increases in popularity as an analytical technique. It is a very sensitive and selective method, which provides detailed information on atoms and molecules from the observation of their electronic and vibrational spectra. Optical experiments are of fundamental interest as an extension of mass spectrometry's capabilities. Standard mass spectrometry techniques have yielded a wealth of details on gas-phase ion structure and protein sequencing, in particular. Fourier transform ion cyclotron resonance mass spectrometry (FTICR MS) presents a unique opportunity to combine the fluorescence measurements of gas-phase ions with high resolution mass spectra. Ions in a FTICR MS can be trapped for prolong periods of time over a large dynamic range in a precisely defined region that makes this technique ideally suited for optical spectroscopy experiments. In this work we further extend the usage of LIF/FTICR MS in a broader range of biochemistry applications.

Preliminary experiments were performed on rhodamine 6G ions. We have selected rhodamine 6G ions as a test sample due to its high fluorescence yield (0.94) and known absorption/fluorescence characteristics. The absorption maximum of rhodamine is in the 530 nm range that is well-suited with 514 nm Ar laser line. In these experiments we were able to detect laser induced fluorescence signal (S/N=5) from trapped rhodamine ions (m/z 443), pre-selected in the FTICR trap. The experiments with rhodamine allowed the optimization of both the collection optical path and the ion trapping conditions inside the FTICR cell. Note that the rhodamine fluorescence data exhibits a decay resulting from photo-fragmentation of the trapped ions. We found that the analysis of photo-fragmentation data allowed the optimization of the experimental parameters, such as excitation laser power, position of the excitation laser beam, number of ions, and conditions for ion axialization to maximize the fluorescence signal in measurements on biomolecule ions.

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Analytical Chemistry **18**

### Occurrence and fate of selected macrolide and sulfonamide antibiotics in sewage treatment

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Antibiotics are an important group of pharmaceuticals – the human consumption in Switzerland exceeds 30 t/a. In veterinary medicine approximately another 40 t are used yearly. They are of concern especially due to the possible spread of bacterial resistance. The most important groups of antibiotics in human medicine are beta-lactams (including penicillins and cephalosporins), sulfonamides, macrolides and fluoroquinolones. Whereas beta-lactams seem to be chemically instable, members of the other three groups have been detected in various aquatic compartments of the environment. Human used antibiotics, or pharmaceuticals in general, reach the aquatic environment mainly via excretion and therefore mostly after passing through a sewage treatment plant. Their fate and occurrence during the wastewater treatment is mostly unknown as well as the suitability of distinct treatment processes for their elimination. This question is thoroughly investigated in the EU project POSEIDON (www.eu-poseidon.com) which, together with engineers, tries to assess and improve the removal efficiency of waterworks. Conventional as well as advanced wastewater technologies like membrane filtration are tested for the removal rate of different pharmaceuticals including macrolides and sulfonamides. The poster gives an overview of the POSEIDON project. In addition, the analytical method applied for the determination of several macrolides and sulfonamides is presented. Solid phase extraction and liquid chromato-graphy coupled with tandem mass spectrometry are applied. First results on the occurrence of selected antibiotics in different aqueous matrices are shown.

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Analytical Chemistry **19**

### Detection of the mycotoxins Fumonisin $FB_1$ and $FB_2$ in corn by LC/MS and LC/MS/MS with Electrospray Ionization

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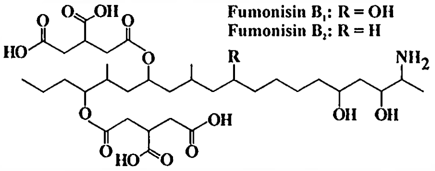
Fumonisins are a group of structurally related secondary metabolites produced mainly by the fungus *Fusarium moniliforme*. These mycotoxins are commonly found worldwide in corn and corn-based food and have been related to a variety of animal toxications. They are classified as possible carcinogens [1].

The aim of this work was to replace fluorescence detection, which is today most commonly applied [2] by MS- and $MS^n$-detection with an ion trap. The non-volatile buffer used due to the ionic behaviour of the analytes could be replaced successfully by formiate. Electrospray ionization in the negative mode and selected ion monitoring gave the lowest detection and quantification limits by MS (1 ppb ($B_1$) and 2 ppb ($B_2$) compared to 2 ppb and 40 ppb by fluorescence detection). Additionally, a typical fragmentation pattern caused by the loss of the tricarboxylic groups was observed in the $MS^n$ mode. This selective loss could be helpful when screening real samples for the presence of unknown or metabolized fumonisins. Levels of fumonisins in Swiss corn products will be presented.



[1] Musser SM, *et al.*, Appl. Environ. Microbiol., **2002**, 504, 95-105
[2] Shepard GS, *et al.*, J. Liq. Chromatogr., **1990**, 13, 2077-2087

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Analytical Chemistry **20**

### Polybrominated diphenyl ether flame retardants: Methods and first assessment in fish from Swiss rivers

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Polybrominated diphenyl ethers (PBDEs) are a class of brominated flame retardants that are starting to receive a lot of attention due to their similarity in structures to PCB and reports of their wide spread and increasing concentrations in the environment. They are additive chemicals in a myriad of products such as textiles, polyurethane foams, circuit boards and plastics. They leach out over the lifetime of these products and enter the environment. The global use of PBDEs was about 67'000 t in 1999 and is still increasing, although the penta- PBDE formulation will be banned in the EU in 2003. The less brominated congeners such as the penta-BDE have been shown to disrupt endocrine and hepatic system functions as well as compromise neurodevelopment.

Methods were developed for the determination of PBDEs is fish muscle tissue, liver and bile. The muscle tissue and liver were extracted by accelerated solvent extraction (ASE) and the bile by liquid-liquid extraction. The samples were analyzed on a Fisons 8060 GC coupled with a Fisons MD800 MSD in +EI mode using a 30 m DB-5 column. Recoveries for BDE-28, 37, 47, 66, 99, 100, 153, 154 and 183 in the bile ranged from 81-109%. Detection limits in the bile (0.5 g) ranged form 400 pg/g to 3.3 ng/g. For a 10 g dry wt fish sample the detection limits ranged from 20 to 165 pg/g and for 1 g of liver 200 pg/g to 1.6 ng/g. The method was applied to fish collected in four Swiss rivers; Necker, Venoge, Emme and Linth Binnenkanal.

Analytical Chemistry

**21**

### Detection of In-house Moulds Attacks by Analysis of Microbial Volatile Organic Compounds (MVOCs) in Indoor Air

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Identification of indoor mould attacks is mainly done by sampling and counting spores and conidia. In contrast to spore emission which is highly dependent on seasonal and environmental parameters, mould generates continuously volatile organic compounds. These so-called microbial volatile organic compounds (MVOCs) are considered to be a very good indicator for mould attack, also when hidden. Most MVOCs suitable as mould tracers are rather polar $C_6$-$C_8$ compounds such as aliphatic and aromatic aldehydes, ketones and alcohols [1].

In this work first results are presented about a passive sampling technique using active charcoal adsorbents to trap MVOCs from mould. A sampling time of 28 days allow to collect 1,5 $m^3$ of air. Solvent desorption by diethyl ether and separation by HRGC-MS in the selected ion monitoring mode give detection limits of about 3-10 ng/$m^3$ (absolute 5-15 pg) for most compounds and allow multi sampling analysis.

The separation and analysis of trace amounts of alcohols and other polar substances is still a demanding task. In opposite to splitless injection leading to peak broading on-column injection was found most suitable giving excellent peak shapes as well as minimal thermal stress. Cross-linked polyethylene glycol phases were able to separate all relevant compounds at pg-levels from other compounds present in air. Further methodological aspects and applications will be presented.

[1] Lorenz, W., *MVOC-Bestimmungen zur Erkennung mikrobieller Schäden in Gebäuden*, in *Handbuch für Bioklima und Lufthygiene*. 2001, pg. 1-20.

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**22**

Analytical Chemistry

### Determination of pesticides in groundwater by HPLC/MS at the ppt-level

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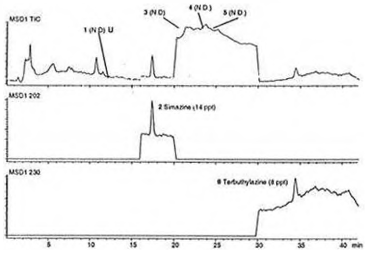
Within the framework of the project PEGASE (Pesticides in European ground waters), a detailed study of the transport processes of some pesticides from the soil surface to the groundwater table is ongoing. For monitoring this process, the analytical method must be capable of determining concentrations at the ppt level ($10^{-12}$), which is far below the pollution level.



**1** : Desethylatrazine
**2** : Simazine
**3** : Atrazine
**4** : Isoproturon
**5** : Diuron
**6** : Terbuthylazine

The method based on HPLC-MS after an SPE preconcentration uses only small quantities of sample (100 ml) and has a detection limit of 10 ppt. The simultaneous determination of the six different studied pesticides is possible.

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Analytical Chemistry

**23**

### Pharmaceuticals in the aquatic environment

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A lot of pharmaceuticals and personal care products (PPCP) enter the aquatic environment via wastewater treatment plants, since they are excreted by urine and faeces. Another possible source is the improper disposal over the toilet. As they are not fully removed in the treatment plant, they can be observed in receiving surface water. The entry of PPCPs into the environment through consumption is much higher than through production.

Pharmaceuticals are designed to cause specific biological effects at specific target organisms for a limited period of time. Furthermore they are often resistant to biodegradation, due to the importance of metabolic stability to pharmacological action. The continuous, long-term exposure of PPCPs to the environment, although at low concentration levels, may result in gradual almost hardly detectable changes.

The EU-Project Poseidon (http://www.eu-poseidon.com) researches for methods, which will reduce the uncontrolled release of PPCPs into the environment via wastewater. In addition it intends to specify the potential risks to the environment and to enhance efficient and unpolluted water supply.

Chemical analytical methods are a prerequisite to conduct field studies at scale of operating wastewater treatment plants and are needed to assess the environmental risk that pharmaceuticals could possibly pose toward aquatic and soil organisms and water quality.

This poster presents the methods for the analysis of the PPCPs Diclofenac, Ibuprofen, Diazepam, Tonalid, Galaxolid, Carbamazepine and Iopromid. Solid phase extraction, gas chromatography-mass spectrometry and liquid chromatography - tandem mass spectrometry were successfully applied. The quantification limits in wastewater effluent are around 50 to 100ng/l. Also first results of concentrations in various aqueous compartments of a wastewater treatment plant are presented.

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Analytical Chemistry

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### Determination of β-lactam antibiotics in effluents from municipal hospitals and wastewater treatment plants in Switzerland by LC/MS/MS

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Residues of persistent pharmaceuticals and personal care products have become a major public and scientific concern. It is well known that significant amounts of biologically active compounds, e.g. antimicrobials, enter the aquatic environment primarily by way of wastewater treatment plants. Great concern has been expressed that chronic exposure to trace levels of these pharmaceuticals, applied in human and veterinary medicine, may contribute to the spread of antibiotic resistance.

Thus, in several European countries research programs have been initiated in order to evaluate the levels of pharmaceuticals in wastewater, surface, ground and drinking water. In Switzerland our project HUMABRA (Occurrence of Human-Use Antibiotics and Antibiotic Resistance in the Aquatic Environment), as part of the Swiss National Research Program (NRP 49) on antibiotic resistance, aims to enlarge the knowledge on the behavior of antibiotics in hospital wastewater, wastewater treatment plants and in receiving ambient waters by trace analytical procedures.

Regarding the available consumption data in Switzerland, β-lactam antibiotics (penicillins and cephalosporines) account for about 50 %, i.e. 18 t/a, of total human consumption of antimicrobials. Nevertheless, they have not yet been found in wastewater or in the aquatic environment. Short half-lifes in aqueous matrices caused by fast degradation, e.g. hydrolysis of the β-lactam ring, might be the reason. Thus, a method based on solid phase extraction and HPLC/MS/MS has been developed for the determination of the 11 most relevant β-lactam antibiotics in Switzerland with limits of detection in the low ng/L-range. The analytical method and first results in the analysis of hospital effluents are presented.

Analytical Chemistry **25**

### A Characteristic Neutral Loss in the Ion Trap MS$^n$-Spectrum of Isoflavones

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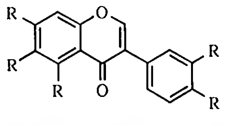
Isoflavones 1 may be phytoestrogens and occur mainly in legumes (especially soybeans [1][2]) but also in further plants. Due to the presence of many other compound classes, a method to screen plant extract for isoflavones should allow an unequivocal identification as well as open the possibility to find potential new ones. For this purpose, HPLC-MS is the method of choice, already in use to analyse isoflavones in plant and food [1][3].



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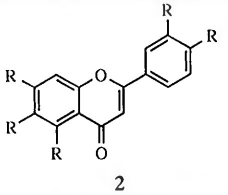

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To identify structure specific fragmentations in the mass spectra of isoflavones, mass spectra of reference isoflavone aglycones and of corresponding isomeric flavone aglycones 2 as the closest related structures were studied using an ion trap MS in the APCI or ESI mode (positive ion detection). A neutral loss was observed which is only of high abundance for isoflavones. It allowed to detect selectively isoflavones and was successfully applied to the analysis of isoflavone enriched soy flour. Its suitability for screening plant extracts for unknown isoflavones is in progress.

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[3] L. Gu, W. Gu, *Phytochem. Anal.* **2001**, *12*, 377.

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Analytical Chemistry **26**

### LA-ICP-MS: Investigation on aerosols of brass samples

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Laser ablation ICP-MS is a well-established micro-analytical technique for the determination of major and trace elements in solids. This technique is widely used in the fields of material- and environmental science, geology and chemistry. A variety of matrices such as steels, ceramics, polymers and others can be analyzed while others such as alloys of Cu and Zn (brass) lead to severe problems in their quantification. Even with matrix-matched calibration, ratios of the major components can not be determined accurately by LA-ICP-MS. A calibration curve using brass standards having different Cu/Zn ratios reveals a strong non linearity illustrating the problem determining brass samples [1]. The amount of zinc determined is always found to be too high when compared to copper [2].
Investigations of the elemental composition inside the ablation crater show that the reason for this behavior can not be only a product of a distillation process involving the melt phase generated during the ablation process. Results obtained by micro XRF show with an uncertainty of < 5% of that of the original composition of the sample is maintained inside the crater [3]. Nevertheless a distillation process between Cu and Zn having different melting and boiling points can still be part of the problem observed, but a process provoking a zinc excess of up to 100% should lead to a significant Cu accumulation, which should then be observable in the quenched melt phase on the floor of the crater. Aerosol trapping experiments using filters, followed by a dissolution and determination by solution nebulization ICP-MS show a Cu/Zn ratio being slightly higher than the ratio obtained from a direct measurement of the dissolved brass sample. This is in contrast to the measured ICP signal and leads to the conclusion that the major problem of brass analysis by LA-ICP-MS is not dominated by the ablation process. Particle size distribution obtained using different ablation wavelengths (266/193 nm) and element composition of different size fractions of the aerosol will be discussed.

[1] O.V. Borisov; X.L. Mao; A. Fernandez; M. Caetano; R.E. Russo, *Spec. Chim. Acta B* **1999**, 54, 1351-1365.
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Analytical Chemistry **27**

### Evaluation of different Dynamic Capillary Coatings for the Determination of Carbohydrate-Deficient Transferrin in Human Serum by Capillary Electrophoresis

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Serum transferrin comprises several isoforms with up to two complex oligosaccharide chains containing 0 to 8 sialic acid residues and neutral sugars. Carbohydrate-deficient transferrin (CDT) encompasses isoforms that are deficient in carbohydrate chains and consequently in sialic acid residues (including asialo-, monosialo- and disialo-transferrin) and is a well known marker for chronic alcohol abuse. Recently, capillary electrophoreses has been reported as a tool extremely effective for the simultaneous, individual, quantitative determination of the CDT isoforms. Three methods for CDT determination in human serum by capillary zone electrophoresis (CZE) that feature different dynamic capillary coatings were evaluated for CDT determination in human serum of alcohol abusers and control subjects. In all cases, CZE was performed using an alkaline borate buffer, serum samples were saturated with iron before analysis, data were evaluated as area % of disialo-transferrin in relation to tetrasialo-transferrin and peak identification was accomplished with immunosubtraction. Optimized conditions with the use of spermine, diaminobutane and commercially available, proprietary reagents that form a stable double coating were characterized in terms of robustness and reproducibility.

This work was supported by the Liver Foundation, Bern, Switzerland and by MIUR (Italian Ministry of Education, University and Research).

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### Apertureless Near-Field Scanning Probe Microscopy for Highly-Localized Raman Enhancement **28**

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Surface enhanced Raman scattering (SERS) has emerged as a highly sensitive analytical technique, offering signal enhancements of several orders of magnitude over conventional Raman scattering. However, the inherent heterogeneity of metallic SERS substrates creates variable electromagnetic field enhancement across the surface. This shortcoming limits the utility of the technique and renders quantitative measurements unreliable. As an alternative to conventional SERS, a metallized AFM tip can be brought very near a sample surface, providing highly localized signal enhancement [1-3]. This technique provides a uniform enhancement across the sample, allowing for quantitative analysis and even Raman imaging. This presentation will discuss recent advances in instrumentation, including the incorporation of a confocal laser-scanning microscope for rapid optical alignment of the laser focus with the AFM tip. Further, an external scanning stage is now being employed to provide feedback and scan the sample relative to the tip and optics, ensuring constant alignment of the laser beam and collection optics with the AFM tip. Applications of this technology for nanoscale chemical analyses will also be described.

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Analytical Chemistry **29**

### The Purity of Laboratory Chemicals with Regard to Measurement Uncertainty

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The purity P of laboratory chemicals is often declared in the form $P \geq x\%$ (e.g. $P \geq 97\%$). With a randomly chosen set of 40 compounds we found that their purity is generally closer to 100% than to the lower limit. The distribution of the purity data as found in the laboratory depends on the analytical technique used. Whereas purities determined by chromatography do not exceed 100% (because the sum of all observed peak areas is set to 100%), the purities obtained by titration can exceed 100% (because the functionality is determined). Therefore the data of these two groups need to be dealt with in different ways for measurement uncertainty purposes.

For purities based on titration we propose to use a rectangular distribution with a range r from $P_{min}$ to 101%, an expected purity value which is the mean at 0.5 r and a standard uncertainty of the purity of 0.29 r. Purities determined by chromatography can be described with a triangular distribution (ramp function). One leg of the triangle represents the range r from $P_{min}$ to 100% and the right angle is located at 100%. The expected value is the median at 0.7 r and the uncertainty is 0.24 r.

These proposals match the experimental data well. However, it is a main problem that the data found in a catalogue may have less relevance for a certain analytical problem than it seems. A purity (i.e. a functionality) found by titration is not the number needed by the analyst if the compound is used as a reference for a chromatographic analysis, and vice versa.

G. van Look, V.R. Meyer, *Analyst* **2002**, *127*, 825-829.

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Analytical Chemistry **30**

### Chemical $NO_2$-Sensor based on Iron Phthalocyanine Derivatives

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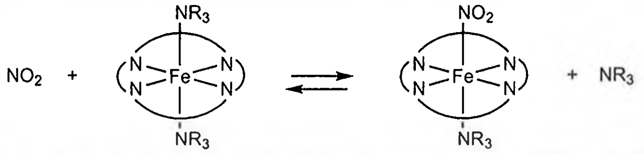
To detect selectively combustion gases, optical chemical sensors based on polymer membranes were introduced [1, 2]. Further investigations led to a new $NO_2$-sensitive membrane containing derivatives of iron phthalocyanine. Substitution at the macrocycle with alkoxy and especially with alkyl groups led to an improved solubility of the phthalocyanines within the plasticized polymer membrane.

The detection principle was based on a ligand exchange of $NO_2$ with axial-coordinated N-donor ligands of iron(II)-phthalocyanine. In this reaction the absorbance of the so-called Q band of the phthalocyanine complex decreased. This change in intensity at 650 - 670 nm was used as the measurement signal of the sensor membrane. The N-donor ligands investigated were amines and pyridines, which act simultaneously as plasticizers in the polymer layers. With this approach it was possible to selectively measure $NO_2$ in the ppb concentration range. No cross-sensitivity was observed to NO, CO, $CO_2$ and $SO_2$ with concentrations in the ppm-range.



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Analytical Chemistry **31**

### Chiral Separation of Albendazole Sulfoxide and Oxfenbendazole Enantiomers and their Analysis in Plasma

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The electrokinetic separation and analysis of the enantiomers of albendazole sulfoxide (ABZSO) and oxfenbendazole (OxBZ), sulfoxides with a sulfur stereogenic center, is reported. ABZSO and OxBZ enantiomers cannot be separated via use of common neutral cyclodextrins and negatively charged carboxymethyl-beta-cyclodextrin. With the Pirkle-type (R)-(-)-N-(3,5-dinitrobenzoyl)-alpha-phenylglycine chiral selector, ABZSO and OxBZ enantiomers do separate using an alkaline background electrolyte. The same is true employing sulfated beta-cyclodextrin and a neutral buffer. The two approaches were applied to the analysis of ABZSO enantiomers in plasma of patients under albendazole pharmacotherapy for the treatment of echinococcosis of the liver. Chiral analysis of extracts of 31 patient plasma samples revealed a mean enantiomeric (-)-ABZSO/(+)-ABZSO ratio of 0.31. These data confirm the stereoselectivity of the albendazole metabolism in man.

This work was supported by the Swiss National Science Foundation.

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Analytical Chemistry **32**

### Ion sampling efficiency in Inductively Coupled Plasma-Quadrupole Mass Spectrometry using different carrier gas combinations

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Inductively coupled plasma mass spectrometry (ICP-MS) is established as one of the most suitable analytical techniques for trace element determination in solid and liquid samples. Solid samples can be introduced into an ICP-MS by laser ablation (LA), which reduces sample preparation time. The dry ICP operating conditions associated with this technique, however, are not comparable to the standard characteristics of the ICP-MS when using solution nebulization. ICP power, sampling depth and the carrier gas flow rates are the relevant parameters that influence the ICP temperature and affect the excitation and ionization efficiency as well as the formation of interferences. For optimum operation of the LA-ICP-MS combination these parameters need to be studied in detail. This should improve analytical sensitivity offered by modern ablation systems, which allow to assess a wide range of spatial resolution (4-120 um). Optimizing these parameters and using different carrier gas compositions for the transport of laser-induced aerosols were studied on a new generation quadrupole-based ICP-MS. It is found that limits of detection are better when using helium instead of argon as aerosol carrier, which confirms the results obtained in [1, 2]. Adding a second high capacity pump to the expansion chamber improves the vacuum conditions when increasing amounts of He are used as carrier gas and leads to better ion transmission towards the mass analyzer. Furthermore, the influence of the interface geometry and the carrier gas composition on elemental sensitivity will be discussed.

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[2] D. Günther, C. A. Heinrich, *JAAS.* **1999**, *14*, 1363-1368.

Analytical Chemistry **33**

## Determination of Short-Chain Polychlorinated Paraffins in Fish Samples by HRGC-NICI-LRMS

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In recent years increasing attention has been paid to short-chained polychlorinated n-Alkanes (PCAs) because of their wide application, their persistence and their toxic potential. However, due to the complex composition of PCA mixtures (thousands of congeners) their analysis is very demanding and mainly carried out by high resolution mass spectrometry (MS). Currently, information about environmental levels of PCAs is very scarce for Western Europe [1].

To make PCA analysis more applicable, an analytical method has been developed for quantification of $C_{10}$ - $C_{13}$ PCAs in fish samples based on high-resolution gas chromatography combined with negative ion chemical ionization low resolution MS in the selected ion monitoring mode. The clean-up procedure includes fat elimination by adsorption chromatography on silica gel impregnated with concentrated $H_2SO_4$ followed by separation from other organochlorines on florisil.

Polychlorinated biphenyls could be completely separated from PCAs, also partly toxaphenes. Recoveries were between 80-90 %. The linear range was 1 - 100 ng and the limit of detection 1 ng of technical PCA mixture at a signal-to-noise ratio of 3:1. Details of the developed method and levels of PCAs in fish from the North Sea will be presented.

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Analytical Chemistry **34**

## Gas/Particle Separation and Sampling of Aromatic Oxidation Products

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As aerosol particles have important effects on human health, the formation of secondary organic aerosols (SOA) from gaseous precursors is of great current interest. The goal of this investigation is to find an appropriate system for analyzing gaseous and particulate compounds involved in SOA formation from aromatics. Two different sampling methods were characterized, one consisting of polyurethane foam (PUF) adsorbents and the other consisting of annular diffusion denuders operated along with particle filters. For the test experiments with the two sampling setups a $0.1 m^3$ bag made of Teflon™ was used. A mixture of 6 compounds (glyoxal, 2,6-dimethylbenzoquinone, glyoxylic acid, pyruvic acid, 3,5-dimethylbenzoic acid, 2,5-dimethylbenzaldehyde) that are known to be volatile aromatic oxidation products is flushed into the bag with $N_2$. The PUF arrangement consists of a Teflon™ coated quartz fiber filter (QFF) followed by two PUFs whereas the denuder system consists of two annular denuders followed by a QFF and a third backup denuder. Compounds were extracted from denuders and PUFs and derivatized [1, 2, 3]. The first PUF clearly adsorbs most of the gaseous phase (80-100%). The most volatile compounds (e.g. glyoxal) are found exclusively on PUF 1 whereas the most nonvolatile compounds are found also on the filter, leading to an overestimation of the particle phase. The results in the sampling and separation efficiency of the comparison of the denuder and PUF system will also be presented.

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**35**

## FAST LC-MS ANALYSIS OF WITHANOLIDES IN CRUDE PLANT EXTRACTS USING MONOLITHIC COLUMN.

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Liquid chromatography coupled to mass spectrometry (LC-MS) has gained wide acceptance in the field of phytochemical analysis. High sensitivity and selectivity as well as the possibility of structure elucidation make this technique a powerful tool to analyze complex samples. However, due to the complexity of plant extracts, LC often requires relatively long analysis times. Among the different approaches to reduce the analysis time without sacrificing the analytical performance, the recent introduction of monolithic columns has attracted considerable interest [1]. In fact, because of its bimodal pore structure, high flow rates can be applied maintaining high efficiency and low back-pressure. The usefulness of these columns to achieve fast analysis of pharmaceuticals, as well as drugs and metabolites has already been demonstrated[2] and the on-line combination of monolithic columns with mass spectrometry provides the fast separation power of chromatographic support and the high sensitivity and selectivity of specific detector.

In this contribution, the use of a Chromolith® column coupled to electrospray ionization mass spectrometry (ESI-MS) is presented for the qualitative and quantitative analysis of three withanolides. The latter are polar steroidal compounds, occurring almost specifically in the *Solanaceae* family. Results obtained with this new material are compared with those achieved with a conventional particulate column. Finally, method performances are evaluated and the final method is successfully applied to determine these secondary metabolites in crude plant extracts (*Iochroma gesnerioides* (Kunth) Miers (Syn. *I. coccineum* Scheidweiler)) obtained by three different extraction methods: the conventional Soxhlet extraction and two faster methods, the microwave assisted extraction and the pressurised solvent extraction.

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**36**

## RAPID ANALYSIS OF FLUOXETINE IN PLASMA BY LC-MS USING ON-LINE SAMPLE EXTRACTION.

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Fluoxetine is an oral antidepressant for oral administration and belongs to the selective serotonin reuptake inhibitor (SSRI) family. It is used to treat depression, bulimia and obsessive compulsive disorders. Through N-demethylation, fluoxetine is extensively metabolised in the liver to norfluoxetine. Therefore, because of its pharmaceutical potential and increasing popularity, reliable analytical methods for monitoring fluoxetine and its primary metabolite in biological fluids are highly desirable.

Liquid chromatography coupled to mass spectrometry (LC-MS) is nowadays considered as the method of choice for the fast, selective and sensitive analysis of drugs and metabolites in biological fluids. In order to achieve high throughput analysis, new extraction methods are developed. Among the different strategies being applied, the use of new supports with large particle size allowing the direct injection of complex matrices in the analytical system has received wide acceptance. These supports, used as a precolumn to clean and concentrate analytes of interest, can be connected to an analytical column in a column-switching set-up.

In the present investigation, a fast bioanalytical method was developed for quantitation of fluoxetine and its primary metabolite, norfluoxetine in plasma. It was based on the solid phase extraction of biological sample onto a stationary phase containing large particles coupled on-line with an analytical LC column. The extraction step was performed within an OASIS precolumn (35 x 0.3 mm; $d_p$ 30 μm) at high flow rate conditions (450 $\mu L.min^{-1}$). The separation was carried out on a Discovery HS C18 column (50 x 2.1 mm; $d_p$ 3 μm) coupled to an electrospray ionisation - mass spectrometer detector (ESI-MS). Method performances were evaluated and proved to fulfil analytical criteria. Furthermore, the developed method exhibited a sufficiently high sensitivity to monitor drug levels in the low ppb range.

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# CHARACTERIZATION OF REVERSED-PHASE STATIONARY PHASES FOR THE ANALYSIS OF BASIC COMPOUNDS

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Reversed-phase liquid chromatography (RP-HPLC) has become a powerful and widely employed technique in the analysis of a great variety of substances, in particular basic compounds. These compounds are present in various areas such as environmental, agro-industrial and pharmaceutical industries. In pharmacy it is estimated that over 80% of drugs possess a basic function.

Basic compounds can strongly interact with free silanol groups on the surface of the silica particle. These ion exchange interactions produce peak tailing which affect resolution, sensitivity and reproducibility. Thus, many new stationary phases have been designed to reduce the access to silanol groups. Therefore, the main problem facing the analyst is now to effectively select the best column for a particular type of separation.

In our previous work[1], a particular test for the characterization of base deactivated RP-HPLC stationary phases was developed. With this purpose, a set of 14 basic test substances was selected and five different chromatographic supports were tested with three isocratic mobile phases.

The aim of the present work was to simplify the methodology of the chromatographic test. Different approaches have been considered:

- reduction of the number of test compounds (on the basis of both the chromatographic and physico-chemical properties),
- reduction of the number of columns necessary to assess column and batch reproducibility,
- reduction of the number of mobile phases
- reduction of chromatographic parameters.

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Analytical Chemistry

# Elemental Fingerprinting of Historical Glass Samples

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Chemical compositions of historical glasses are possible indicators for changes in the manufacturing processes and the proveniences of raw materials (trading relations) over time [1]. In this study various glass samples from Dvin, Armenia, and dated from 5th to 14th century, were investigated. They are pieces of two to five centimeters diameter and show various colors, surfaces and shapes. An example is given in figure 1.

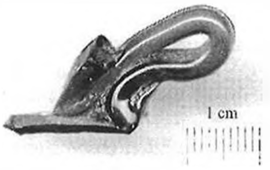

Figure 1: green glass from the 9th century

Laser ablation ICP-MS was used to determine concentrations of matrix, minor, and trace elements because of its 'quasi' non-destructive, fast and reliable analytical properties [2]. To perform quantitative multi-element analysis, matrix elements (e.g. Na, Mg, Al, Si, K, Ca, Ti, Fe) were analyzed by -XRF, ICP-OES and EPMA. After a qualitative screening, 44 elements were selected for quantitative analysis and most of them showed a reproducibility of their distribution of less than 10% RSD.

A critical evaluation of the quantification procedure and a statistical interpretation of fingerprints for the given time periods (cluster analysis, PCA) will be presented.

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Analytical Chemistry

# Therapeutic Drug Monitoring of Lamotrigine by Capillary Electrophoresis: External Quality Assessment

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Quality assurance is an important aspect in therapeutic drug monitoring (TDM). During the past five years, we have characterized the capillary electrophoresis (CE) assay for lamotrigine in human plasma and serum via analysis of samples provided by an external quality control scheme. The assay, originally reported by Shihabi and Oles [1], is based upon protein precipitation by acetonitrile and analysis of an aliquot of the acidified supernatant and has been adopted in our laboratory for routine use [2]. Experiences with this assay, including the analysis of four monthly external quality control samples whose data are directly reported to the quality control scheme, are reported. The data collected demonstrate that the CE assay is well suited for TDM of lamotrigine in a routine setting.

This work was partly supported by the Swiss National Science Foundation.

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**40**

Analytical Chemistry

# Model analytical unit for phosphate(V) ions monitoring

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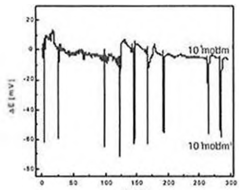
The phosphate recognition ability of some uranyl complexes [1] was investigated by potentiometry, using Ion Selective Electrodes (ISEs) and Chemically Modified Field Effect Transistors (CHEMFETs). The best potentiometric selectivity towards phosphate(V) ions was obtained for membranes with uranyl salophene complexes as ionophores [2]. The structure of salophene, belonging to the group of Schiff bases was optimized in order to obtain the highest selectivity and durability for the practical purposes [3].



The sensors of optimized construction were applied in the model analytical system, which was simulating the phosphate-determining unit, e.g. in the sewage plant. The mineral water was used as the matrix, which was doped with sodium phosphate and buffered (pH 4.5). During almost 2 weeks, the 100-times exceeding of the acceptable phosphate content was repeatedly simulated. The responses of the sensors (see fig.) were comparable and repeatable. The proper functioning of the system confirmed that it may be applied in the real conditions, e.g. for monitoring of phosphate(V) ions, combined with the automatic equipment.

[1] W. Wroblewski, K. Wojciechowski, A. Dybko, Z. Brzozka, RJ.M. Egberink, B.H.M. Snellink-Ruel and D.N. Reinhoudt, Sensors & Actuators B, **68**, 2000, 313.
[2] K. Wojciechowski, W. Wroblewski, Z. Brzozka, Mat. Sci. Eng. C, **18**, 2001, 93.
[3] W. Wroblewski, K. Wojciechowski, A. Dybko, Z. Brzozka, R.J.M. Egberink, B.H.M. Snellink-Ruel and D.N. Reinhoudt, Sensors & Actuators B, **78**, 2001, 315.

CHIMIA 2002, *56*, No. 7/8

Analytical Chemistry **41**

## Determination of Quinolone Antibiotics in Poultry Using Liquid Chromatography with Mass Spectrometric Detection

Markus Zehringer and Matthias Stöckli

State-Laboratory Basel-City, Kannenfeldstr. 2, Postfach, CH-4012 Basel

Antibiotics are widely used in animal farms to advance meat production and to batttle against infectious diseases and parasites in animals. Fluoroquinolones are utilised since a few years both as veterinarian and as human antibacterials. Numerous studies show a developing resistance of bacteria against fluoroquinolones which is the main concern about these drugs. End of January 2002 the European Union banned all imports of animal products from China due to the presence of chloramphenicol residues. In consequence of the ban some Swiss State laboratories started a rigorous control of all imports of poultry from China.

The method of choice for the analyses of fluoroquinolone residues is liquid chromatography (LC) with fluorescence detection (FL). Separation of the analytes is realized either by ion pair chromatography or reversed phase chromatography [1-2]. On the basis of a LC-FL method the State laboratory of Basel-City developed a routine method with LC/MS. After a single extraction with water/acetonitrile the analytes are separated on a RP18 column and identified by means of their typical mass fragments. The method allows the determination of 7 fluoroquinolones and two quinolones in a single run with a detection limit of 10 µg/kg. If necessary results are assured by means of daughter ions from LC-MS-MS analyses.

[1] Bauer, J.F, Howard, S. and Schmidt, A.: High-performance liquid chromatographic determination of several quinolone antibacterials in medicated fish feed. J. of Chrom. **514** (1990), 348-354.

[2] Yorke, J.C. and Froc, P.: Quantitation of nine quinolones in chicken tissues by high-performance liquid chromatography with fluorescence detection. J. of Chromatogr. **882** (2000), 63-77.

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Analytical Chemistry **43**

## Reduction of Cu(II) Used for Cationization in MALDI MS

Juan Zhang, Vladimir Frankevich, Richard Knochenmuss, Michael V. Gorshkov, and Renato Zenobi

Department of Chemistry, Swiss Federal Institute of Technology, ETH Hönggerberg, CH-8093 Zurich, Switzerland.

Divalent metal ions such as Cu(II) are used for cationization in matrix-assisted laser desorption/ionization mass spectrometry (MALDI MS). Singly charged ions are generally observed in the spectra, by reduction of Cu(II) to Cu(I). Tow different explanations of this reduction in the gas phase have been given, namely, free electron capture [1] and gas-phase charge exchange with matrix [2]. Recently, studies of the origin of the free electrons in MALDI form our laboratory have shown that in MALDI, electrons are formed by photoelectric emission from the metal/organic matrix interface [3]. In the case of non-metallic surfaces, electrons are hardly produced. According to these results, we are able to investigate the roles of free electrons and matrices as possible reducing agents in MALDI separately. Blocking the major electron source by using a non-metallic sample carrier (or metallic target with an isolation layer) provides the possibility to examine the effect of the gas-phase charge transfer between doubly charged metal ions and the matrix molecules. For investigation of the effect of the free electron capture, experiments were done under non-matrix condition by using direct laser desorption/ablation of the sample. The matrix studied in this work is nicotinic acid (NA).

[1] Karas M., Glückmann M., Schäfer J., *J. Mass Spectrom.*, 35 (2000) 1.

[2] Knochenmuss R., Stortelder A., Breuker K., Zenobi, R., *J. Mass Spectrom.*, 35 (2000) 1237.

[3] Frankevich V., Knochenmuss R., Zenobi R., *submitted to Int. J. Mass Spectrom.*

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Analytical Chemistry **42**

## Dichloromethane Enhanced Negative Ion Chemical Ionization of Polychlorinated n-Alkanes

Zdenek Zencak and Michael Oehme*

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The analysis of polychlorinated n-alkanes (PCAs) is a demanding task in analytical chemistry. The thousands of congeners present in the technical mixture make both the chromatographic separation and the mass spectrometric quantification the most demanding step towards the development of a specific analytical method.

The detection method of choice for PCAs is negative ion chemical ionization mass spectrometry (NICI-MS). Under these conditions PCAs form three main ions: $[M\text{-}HCl]^{-}$, $[M\text{-}Cl]^{-}$ and $[M+Cl]^{-}$. The relative abundances of these ions depend strongly on the degree of chlorination, the position of the chlorine atoms at the carbon chain and on the sample amount [1]. As a result, response factors of different congeneres vary by a factor of 15 which makes the accurate quantification of PCAs impossible since most single congeneres are not available on the market.

The use of dichloromethane/methane mixtures as reagent gas for NICI has been already reported for other chlorinated compounds such as chlordanes [2]. Its application to PCAs allowed to enhance the formation of the chlorine adducts and to suppress the formation of the other ions. Additionally, the response factors differed by only a factor of two or less. The detection limits of single congeneres were similar or lower than those of conventional NICI.

[1] G.T. Tomy, *et al.*, *Chemosphere* 1998, *37*, 1395.

[2] E.A. Stemmler, R.A. Hites, *Anal. Chem.* 1985, *57*, 684.

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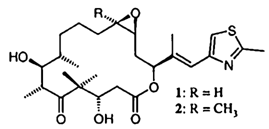
Medicinal Chemistry **44**

## Design and Synthesis of Highly Potent Analogs of the Naturally Occurring Antitumor Agents Epothilones A and B

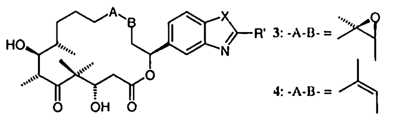
Karl-Heinz Altmann*, Guido Bold, Frédéric Cachoux*, Vito Guagnano, Thomas Isarno*, Markus Wartmann

Novartis Pharma AG, Corporate Research* and TA Oncology Research

Epothilones A (**1**) and B (**2**) are naturally occurring microtubule depolymerization inhibitors, which exhibit potent *in vitro* and *in vivo* antiproliferative activity.

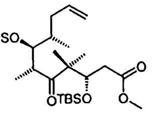


**1**: R = H
**2**: R = $CH_3$



**3**: -A-B- =
**4**: -A-B- =

As part of a synthetic program aimed at the understanding of the structural requirements for epothilone-mediated cytotoxicity and anti-tumor activity, we have identified side-chain modified analogs of type (**3**) and (**4**) as a new class of highly potent antiproliferative agents.[1] The preparation of these analogs is based on a highly convergent general strategy, which involves the stereoselective synthesis of terminal olefin (**5**) as the universal key intermediate, subsequent B-alkyl Suzuki coupling with vinyl iodides of type (**6**), and finally elaboration of the coupling products into the desired epothilone analogs. In general, analogs (**3**) and (**4**) were found to be more potent inhibitors of human cell cancer cell growth than the corresponding parent compounds epothilone B or deoxyepothilone B, respectively.



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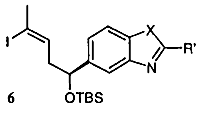


**6**

[1] K.-H. Altmann, G. Bold, G. Caravatti, A. Flörsheimer, V. Guagnano, M. Wartmann *Bioorg. Med. Chem Lett.* **2000**, *10*, 2765 - 2768.

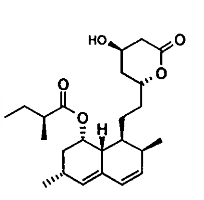
Medicinal Chemistry **45**

### Statin Derivatives as Inhibitors of The Leukocyte Function Antigen-1

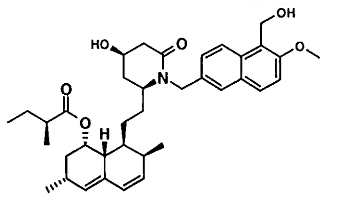
S. Cottens, R. Baenteli, W. Bauer, C. Ehrhardt, U. Hommel, J. Kallen, G. Weitz-Schmidt

Transplantation Research, Novartis Pharma AG, CH-4002, Basel

The β-2 integrin leukocyte function antigen-1 (LFA-1) plays an important role in the pathophysiology of inflammatory and autoimmune diseases. We reported that statin analogs commonly used for the treatment of hypercholesterolemia weakly but selectively block LFA-1 mediated adhesion upon costimulation of lymphocytes [1]. This effect is unrelated to the inhibition of 3-hydroxy-3-methylglutaryl coenzyme-A reductase. Using NMR spectroscopy and x-ray crystallography we could show that the statin derivatives bind to a highly conserved domain of the LFA-1 α-chain called the I-domain [2]. Subsequent optimization of the statins for LFA-1 inhibition resulted in potent and selective LFA-1-inhibitors that suppress the inflammatory response in a murine model of peritonitis. In our presentation we will describe the synthesis and a preliminary structure-activity relationship for these inhibitors.



Lovastatin



LFA703

[1] Weitz-Schmidt, G. *et al.*, *Nature Med.* 7, 687-692 (2001).
[2] Kallen, J. *et al.*, *J. Mol. Biol.* **292**, 1-9 (1999).

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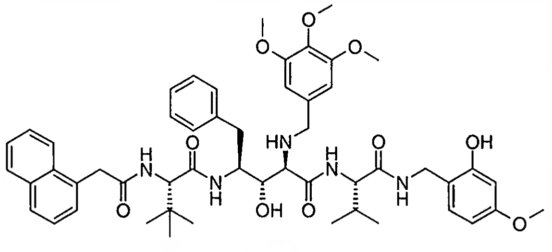
Medicinal Chemistry **46**

### Non-Covalent Inhibitors of the 20S Proteasome

P. Furet, P. Imbach, J. Roesel, P. Fuerst, M. Lang, V. Guagnano,
M. Noorani, J. Zimmermann, C. García-Echeverría

Oncology Research, Novartis Pharma AG, CH-4002 Basel, Switzerland

Proteasome inhibition has emerged in the past few years as a novel approach to cancer therapy. In particular, we are interested in modulating the chymotrypsin-like activity of the 20S proteasome by β-subunit-specific inhibitors. These compounds may trigger an anti-tumor effect by induction of cell cycle arrest and apoptosis in tumor cells. We identified by high-throughput screening (HTS) a series of 2-aminobenzylstatine derivatives that inhibit non-covalently the chymotrypsin-like activity of the 20S proteasome ($IC_{50} \approx 0.9$ μM). To optimise the *in vitro* 20S proteasome inhibition of this class of compounds, we have exploited a structural model of the human proteasome constructed by homology to the X-ray crystal structure of the yeast proteasome. This strategy in conjunction with a modular chemistry approach has allowed us the identification of 20S proteasome inhibitors with *in vitro* activities in the low nanomolar range (e.g., compound **1**, $IC_{50}$= 0.007 μM).



**1**

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**47**

### NMR structure of the turtle prion protein

Luigi Calzolai; Domenikus Lysek; Peter Guntert; Christine von Schroetter and Kurt Wuthrich.

Institute of Molecular Biology and Biophysics; ETH-Honggerberg; 8093 Zurich

Prion proteins are present in several high eucaryotes, including mammals, birds, reptiles and amphibians. Prion proteins are associated with prion diseases like BSE in cattle, scrapie in sheep and Creuzfeldt-Jacob Disease in humans. Up to now prion diseases have been found only in mammals.

To investigate how the structural motifs of prion proteins have evolved we determined the three-dimensional structure of a reptilian prion protein. We have solved, by NMR, the structure of the globular domain of the turtle prion protein and analyzed the dynamics of the full-length turtle prion protein.

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Medicinal Chemistry **48**

### Chemical Restriction

Christoph Meyer[1], Dominik Meyer[1], Thomas A. Bickle[2] and Bernd Giese[1]

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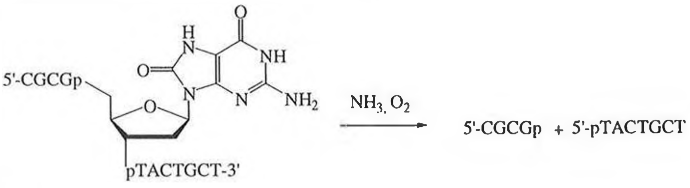
[2]Biozentrum, University of Basel, Klingelbergstrasse 50-70,
CH-4056 Basel, Switzerland

Even in the absence of enzymes site selective DNA strand cleavage reactions are possible if modified nucleotides are used. However, most of these modifications are not tolerated by polymerases or the fission does not lead to the formation of biologically active DNA. We significantly optimized the strand cleavage reaction at 8-oxoguanine in aqueous ammonia [1] saturated with oxygen.



This reaction was applied for the generation of ligatable single stranded overhangs at PCR amplified DNA. As an example, the lac Z' gene was amplified by PCR using 8-oxoguanine modified primers, restricted by ammonia treatment, ligated into a plasmid vector, transformed in *E. coli* cells and screened for blue colonies. The method guarantees efficiencies comparable to the standard cloning procedure using restriction enzymes, and furthermore it allows the design of any 3'-overhang independent of the sequence of the cloned DNA.

[1] Torres M.C., Rieger R.A., Iden C.R., *Chem. Res. Toxicol.* **1996**, *9*, 1313.

Medicinal Chemistry **49**

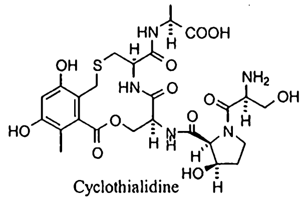
## FROM THE DNA GYRASE INHIBITOR CYCLOTHIALIDINE TO A NEW CLASS OF ANTIBACTERIAL AGENTS

E. Goetschi, P. Angehrn, H. Gmuender, P. Hebeisen, D. Kostrewa, H. Link, T. Luebbers, R. Masciadri, P. Reindl, F. Ricklin and F.-P. Theil

Pharma Division, Discovery Research, F. Hoffmann-La Roche Ltd.,
CH-4070 Basel, Switzerland

Cyclothialidine (Ro 09-1437) is a potent DNA gyrase inhibitor which was isolated from *S. filipinensis* NR0484 1). It represents a family of natural products which act by competitively inhibiting the ATPase activity exerted by the B subunit of DNA gyrase. However, cyclothialidine hardly exhibits any growth inhibitory activity against intact bacterial cells.

To explore the antibacterial potential of cyclothialidine, a flexible synthetic route was developed suitable for the systematic modification of its unique structure. From the synthesis and SAR of a large number of analogues, the minimal structural requirements for DNA gyrase inhibitory activity were found to be contained in a rather small partial structure of cyclothialidine. A modification program based on this "minimal structure" led to a great variety of new DNA gyrase inhibitors. Some of them exhibit potent antibacterial activity *in vitro* against Gram-positive bacteria and overcome resistance against antibacterial agents clinically used today. By tuning the physico-chemical properties of such compounds we were able to identify cyclothialidine congeners which showed *in vivo* efficacy.



Cyclothialidine

[1] J. Watanabe, N. Nakada, S. Sawairi, H. Shimada, S. Ohshima, T. Kamiyama and M. Arisawa, J. Antibiotics 47, 32-6, (1994).

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Medicinal Chemistry **50**

## Design of Factor VIIa Inhibitors as Safe Anticoagulants

Katrin Groebke, Lutz Weber, Yu-Hua Ji, Jean Ackermann,
David W. Banner, Hans- Joachim Böhm

F. Hoffmann-La Roche Ltd., CH-4070 Basel, Switzerland

Prevention and treatment of thromboembolic diseases represent an important medical need. In the last two decades enormous efforts have been made to find novel anticoagulants. A large number of small molecule inhibitors which intervene at different stages of the coagulation cascade, e.g. thrombin and coagulation factor Xa, have been developed. Non of these molecules have reached the market yet, which might reflect the difficulty to develop an efficacious anticougulant which does not cause bleeding complications.

Due to their selective influence on the extrinsic pathway of the coagulation cascade, inhibitors of the tissue factor/factor VIIa complex should be able to interfere with thrombotic events effectively without prolonging bleeding time and therefore should have an optimal efficacy/safety profile. This assumption could be confirmed by preclinical proof-of-concept studies [1].

To initiate the search for inhibitors of the serine protease factor VIIa lead compounds were generated by a biased combinatorial approach [2] using a novel three-component reaction. Guided by the extensive use of X-ray crystallography of enzyme/inhibitor complexes [3] and molecular modeling, small molecule factor VIIa inhibitors with low nanomolar activity and good selectivity against other proteases of the coagulation cascade were designed.

[1] Jacques Himber, Daniel Kirchhofer, Markus Riederer, Thomas B. Tschopp, Beat Steiner, Sébastien P. Roux, *Thromb. Haemost.* 1997, *78*, 1142. Jacques Himber, Canio J. Refino, Louis Burcklen, Sébastien Roux, Daniel Kirchhofer, *Thromb. Hæmost.* 2001, *85*, 475.

[2] Lutz Weber, Sabine Wallbaum, Clemens Broger, Klaus Gubernator, *Angew. Chem.* 1995, *107*, 2452. Lutz Weber, *Drug Discovery Today* 1998, *3*, 379.

[3] David W. Banner, Allan, D'Arcy, Christiane Chène, Fritz K. Winkler, Arabinda Guha, William H. Konigsberg, Yale Nemerson, Daniel Kirchhofer, *Nature* 1996, *380*, 41.

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Medicinal Chemistry **51**

## Design and Synthesis of Potent and Selective, Orally Active NK1 Receptor Antagonists

S. Kolczewski, T. M. Ballard, T. Hoffmann, S. M. Poli, S. Röver, P. Schnider, A. J. Sleight

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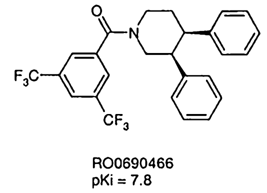
CH-4070 Basel, Switzerland

Neurokinin (NK) receptors belong to the family of G-protein coupled receptors and can be divided into three subtypes: NK1, NK2 and NK3. The endogenous ligand for NK1 receptors is the neuropeptide substance P, one of the five mammalian tachykinins. Following the discovery of the first non-peptide NK1 receptor antagonist CP-96,345, a remarkable number of small molecule NK1 receptor antagonists were identified by many pharmaceutical companies in the last decade. Moreover, recent clinical trials have demonstrated an important therapeutic application for NK1 receptor antagonists in the control of chemotherapy induced emesis and in the treatment of mood disorders such as anxiety and depression.

By rational design we discovered RO0690466 which showed moderate affinity for the NK1 receptor. In this presentation we will describe the synthesis, structure activity relationship and biological evaluation of compounds originating from this piperidine derivative which led to the identification of potent and selective, orally active NK1 receptor antagonists.



RO0690466
pKi = 7.8

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Medicinal Chemistry **52**

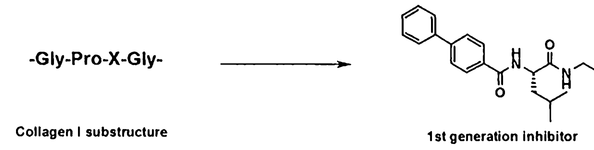
## Identification of orally active inhibitors of cathepsin K

R. Lattmann[1], N. Teno[2], M. Missbach[1], E. Altmann[1], K. Gohda[2], J.A. Gasser[1], K. Toriyama[2], J.R. Green[1], T. Buhl[1], H. Ishihara[2], M. Kometani[2], R. Gamse[1], C. Betschart[2]

[1] Novartis Pharma AG, Basel, Switzerland, [2] Novartis, Tsukuba, Japan

Cathepsin K has been shown to be highly expressed in osteoclasts and to play an essential role in bone matrix degradation. The effects of a novel class of reversible inhibitors of cathepsin K on in vitro and in vivo assays of bone resorption have been examined.

Inhibitors were identified based on a substrate analogue approach and optimisation revealed potent compounds showing specificity against cathepsins B, L and S.



Although these compounds were orally available, no pharmacological effect could be observed in rat models. The reason was attributed to a species difference between human and rat enzymes and to metabolic instability of the inhibitors.

The solution of these two issues leading to potent, extremely selective and stable inhibitors of cathepsin K, orally active in animal models will be presented.

## Molecular interactions between Glivec™ and mutant forms of cAbl kinase.

**53**

Paul W. Manley, Sandra W. Cowan-Jacob, Doriano Fabbro, Gabriele Fendrich, Pascal Furet, Valerie Guez, Janis Liebetanz, Jürgen Mestan, Thomas Meyer. Novartis, Basel, SWITZERLAND.

Bcr-Abl is a constitutively activated tyrosine kinase, present in 95% of patients with chronic myelogenous leukemia (CML) and 5-10% of adults suffering from acute leukemia. Glivec™ (STI571) is a potent inhibitor of Bcr-Abl and promises to be an effective therapy. Although in clinical trials, 96% of CML patients receiving Gleevec have shown complete haematological response, some patients develop drug resistance. Recent studies show that many resistant patients carry a point mutation in the kinase domain of Bcr-Abl (*e.g.* Thr315Ile: Gorre *et al*, *Science* 2001;**293**:876; Glu255Lys: Barthe et al, ibid:2163; Glu255Val: Hochhaus et al, ibid.: 2164; Branford et al., *Blood* 2002;99:3472). To understand the molecular mechanism by which these mutations could cause resistance to Gleevec, we have studied the three dimensional structure of a complex between Gleevec and the kinase domain (cAbl) of Bcr-Abl by X-ray crystallography and related this to the mutant proteins. Recombinant human cAbl kinase (amino acids 218 to 500) was produced using the baculovirus/insect cell expression system. A proteolytically cleavable His-tag was attached at the *N*-terminus to aid in purification. Expression in Sf9 insect cells in presence of Gleevec led to the isolation of an exclusively unphosphorylated cAbl-Gleevec complex. Crystallisation, followed by data collection using synchrotron radiation provided a high resolution (2.4 Å) molecular structure, in which the ligand induces an unusual conformational change of the *N*-terminal part of the activation loop, containing a highly conserved DFG motif. This conformation, which is unable to bind ATP, has previously been seen by Schindler *et al* (*Science* 2000;**289**:1938) for the complex between murine cAbl and aa analogue of Gleevec. It seems likely that this unusual mode of binding is key for the tyrosine kinase selectivity profile of Gleevec. In addition to making H-bond interactions between the pyridine-N and Met318, the anilino-NH and Thr315, the amide-NH and Glu286, and amide-CO and Ala380, Gleevec also makes a strong H-bond interaction between the protonated *N*-methyl piperazine and the backbone carbonyl of Ile360. This structure enables us to explain how mutants give rise to resistance: Thus in the Thr315Ile mutant, the loss of potency of Gleevec (IC50 > 10,000 nM, compared to 220 ± 30 nM for wild-type cAbl and 3,100 ± 1,100 nM for the Thr315Val) is confirmed as being due to the loss of an H-bond and steric hindrance. In the case of the Glu255Val (Gleevec IC50 3,520 ± 300 nM) and Glu255Lys mutants, the glutamic acid residue is necessary to stabilise the ligand-induced conformation of the glycine-rich loop. The loss of sensitivity of the Met244Val mutant (Gleevec IC50 680 ± 150 nM) may also be a result of an effect on the glycine-rich loop. In this communication, further details of these studies, together with additional findings will be presented.

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Medicinal Chemistry

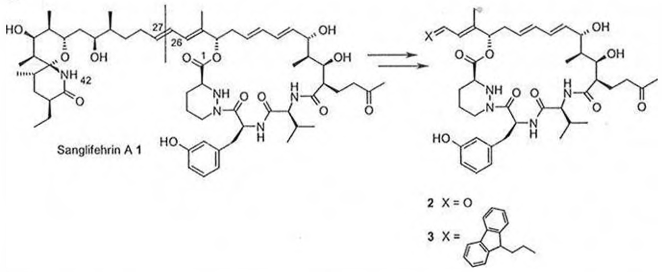
**54**

## The Spirobicyclic Subunit of Sanglifehrin A can be replaced by Structurally Simpler Moieties

Richard Sedrani, Gerhard Zenke, Jörg Kallen

Novartis Pharma Research, CH-4002, Basel, Switzerland

Sanglifehrin A **1** is a novel cyclophilin-binding, immunosuppressive natural product recently discovered at Novartis [1][2]. In the course of a chemical derivation program, we found that the C26,C27 double bond of **1** can be efficiently cleaved giving rise to the C1,C26 macrocyclic fragment **2**. The latter has a similar affinity towards cyclophilin than **1**, but is devoid of immunosuppressive activity. Fragment **2** was used to prepare derivative **3**, whose immunosuppressive activity is comparable to that of sanglifehrin A **1**.



These data demonstrate that the complete C27,N42 subunit, comprising the complex spirobicyclic system, is not required for immunosuppressive activity, and that it can be replaced by structurally much simpler groups, like the fluorenylalkyl group of compound 3.

[1] Sanglier, J.-J.; Quesniaux, V.; Fehr, T.; Hofmann, H.; Mahnke, M.; Memmert, K.; Schuler, W.; Zenke, G.; Gschwind, L.; Maurer, C.; Schilling, W. *J. Antibiot.* **1999**, *52*, 466-473

[2] Fehr, T.; Kallen, J.; Oberer, L.; Sanglier, J.-J.; Schilling, W. *J. Antibiot.* **1999**, *52*, 474-479

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Medicinal Chemistry

**55**

## REACTION MECHANISM OF CASPASES: INSIGHTS FROM QM/MM CAR-PARRINELLO SIMULATIONS

M.Sulpizi, U. Roethlisberger, A. Cattaneo, and P.Carloni

Inst. Inorg. Chem. ETHZ - Hoenggnberg Zurich, (Switzerland)
SISSA/ISAS - via Beirut 2-4 - 34014 Trieste (Italy)

Caspases are fundamental targets for pharmaceutical interventions in a variety of diseases involving disregulated apotosis. Here, we present a QM/MM (1) Car-Parrinello (2) study of key steps of the enzymatic reaction for a representative member of this family, caspase-3 (C-3). In particular, C-3 is a key enzyme in neurodegeneration of the Alzheimer Rs disease (3-4). The hydrolysis of the acyl-enzyme complex is described at the density functional (BLYP) level of theory while the protein frame and solvent is treated using the GROMOS96 force field. These calculations show that the attack of the hydrolytic water molecule implies an activation free energy of ca. 20 kcal/mol in good agreement with experimental data, and leads to a previously unrecognized gem-diol intermediate that can readily (free cneergy barrier 5 kcal/mol) evolve to the enzyme products. Our findings assist in elucidating the striking difference in catalytic activity between caspases and other structurally well-characterized cysteine proteases (papains and cathepsins) and may help in the design of novel transition-state analog inhibitors.

[1] Laio A., VandeVondele J., and Rothlisberger U.*J. Chem. Phys.*, (2002), in press

[2] Car R. and Parrinello M. *PRL* **55**, (1985), 2471

[3] Gervais F. G. et al., *Cell* **97**, (1999), 395

[4] Fasulo L., et al. *J. Neurochem.* **75**, (2000), 624.

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Medicinal Chemistry

**56**

## Positive Allosteric Modulators of mGlu1 Receptors

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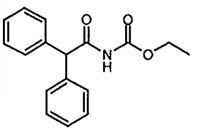
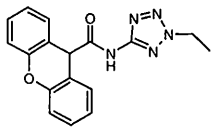
In recent years there has been a growing interest in the mGlu receptor family due to their implication in a variety of fundamental neuronal functions and they have been claimed to represent therapeutic targets for several brain diseases and disorders. In particular, group I mGlu subtypes have long been proposed to be involved in various developmental processes or in certain physiopathological states like pain, epilepsy or ischemia. However, there is still a need for selective and *in vivo* active mGlu1 receptor ligands to clarify the physiological roles mediated by this mGlu receptor subtype.

The random-screening hit **1** was identified initially by using recombinant mGlu1 receptors expressed at very high levels. In physiologically more relevant recombinant systems with a lower level of receptor expression, the compound potentiated the agonist-stimulated response without any detectable intrinsic activity. Using this screening hit as a starting point, we discovered heterocyclic derivatives like the tetrazole **2** and the oxadiazole **3**.



1



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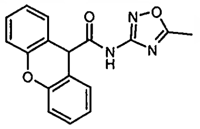

3

These compounds represent useful pharmacological tools for the study of the physiological roles mediated by mGlu1 receptors. The synthesis and the SAR of this new class of positive allosteric modulators of mGlu1 receptors will be discussed in detail.

Medicinal Chemistry **57**

### A Novel Approach for the Control of Polyvalent Biological Interactions

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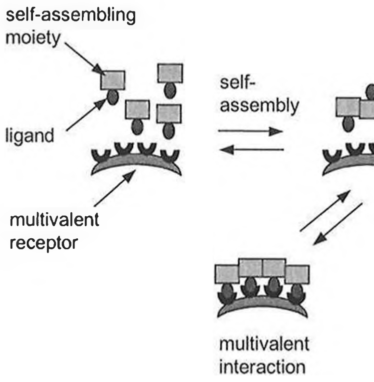
Novel molecules will be presented which comprise both a ligand and a self-assembling moiety. They dynamicly self-assemble to form non-covalent nanoparticles. These particles – not the individual molecules – function as highly potent polyvalent receptor blockers allowing for the control of physiologically relevant polyvalent interactions both in vitro and in vivo.



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Medicinal Chemistry **58**

### Structure-Activity Relationships and Molecular Modeling Studies of Coumarin Derivatives as Dual Inhibitors of Acetylcholinesterase and Monoamine Oxidase B

C. Brühlmann[a], F. Ooms[a,c], S. Rey[a], J. Wouters[b], P.A. Carrupt[a], B. Testa[a]

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[b]Institut Wiame, Bruxelles, Belgium; [c]present address: Euroscreen S.A., Bruxelles, Belgium

Alzheimer's disease (AD) is a neurodegenerative illness characterized by a progressive decline in cognitive function. Recent studies have suggested that acetylcholinesterase (AChE) inhibitors, especially inhibitors that interact with the peripheral anionic binding site of the enzyme, could potentially inhibit the formation of amyloid $\beta$-peptide. Evidence has also been presented that monoamine oxidase B (MAO-B) activity increases up to 3-fold in the brain of AD patients, which has been correlated with the development of amyloid $\beta$-peptide plaques. Since amyloid $\beta$-peptide are the main component of the senile plaques found in AD brains, any compound able to inhibit their aggregation might be regarded as potential anti-Alzheimer drug. In this context we focused on the search for dual inhibitors of AChE and MAO-B.

A number of coumarin derivatives were recently described as dual AChE and MAO-B inhibitors. Their *in vitro* screening has been extended and docking studies performed using the GOLD program to clarify structure-activity relationships. The identification of the major interactions that stabilize coumarin derivatives within the AChE binding site was performed using the molecular lipophilic potential (MLP) and the molecular hydrogen bonding potential (MHBPs). Based on these results, it was concluded that this line of research could lead to promising anti-Alzheimer drugs.

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Medicinal Chemistry **59**

### Intramolecular catalysis in the hydrolysis of basic esters

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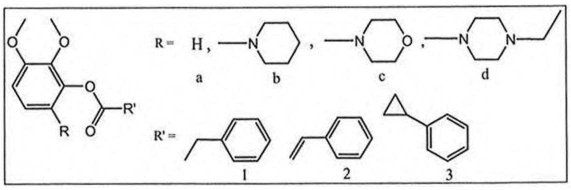
[2]Laboratoire de Synthèse, Physico-Chimie et Radiobiologie, Département de Synthèse Organique, Faculté des Sciences Pharmaceutiques, Université Paul Sabatier, Toulouse, France

While investigating the chemical degradation of a series of esters, we were intrigued by their unexpected fast degradation at physiological pH and their pH-stability profiles which suggested an intramolecular catalysis [1, 2]. Further model compounds were synthesized to elucidate the reaction mechanism. The goal of this work was to measure their physicochemical properties and their rates of chemical and enzymatic degradation. The side chains a, b, c, d, helped us to understand the influence of the basic nitrogen in the catalysis and the side chains 1, 2, 3 to assess electronic effects. The enzymes employed were pig liver carboxylesterase and horse serum cholinesterase [3].



[1] B. Testa, J.M. Mayer, *Drug. Metab. Rev. 1998, 30, 787-807.*
[2] A.R. Fersht, A.J. Kirby, *J. Am. Chem. Soc.* **1967**, 89, 4853-4863.
[3] R. Ammon, *Arzneim.-Forsch.***1977**, 27, 944-949.

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Medicinal Chemistry **60**

### Targetted MRI Contrast Agents

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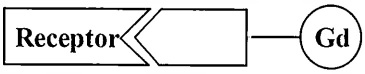
Petersgraben 4, 4031 Basel, Switzerland

Contrast agents based on Gd(III) chelates are now used in more than 50 % of the exams with Magnetic Resonance Imaging [1]. Nowadays, even if the currently available contrast agents for routine clinical examinations are safe and good enhancers, they are unspecific toward the identification of specific tissues. The main objective of this work is to attach a peptide on a contrast agent in order to obtain compounds able to identify specific tissues and thus able to target pathological sites. In analogy to our work on tumor targeting with radiolabelled regulatory peptide [2], this bioconjugate should contain a Gd(III) complex connected to a ligand able to target a given receptor.



We will present the synthesis of Gd(III) conjugates of somatostatin and biotin. Results of the study of the relaxivity of the Gd-complexes coupled to biomolecules and the impact of their interaction with biological targets will be given.

[1] S. Aime, M. Botta, M. Fasano and E. Terreno *Chem. Soc. Rev.* **1998**, *27*, 19-29.
[2] A. Heppeler, S. Froidevaux, H. R. Mäcke, E. Jermann, M. Béhé, P. Powell and M. Hennig *Chem. Eur. J.* **1999**, *5*, 1974-1981.

Medicinal Chemistry

**61**

### Synthesis of a library of selective α-mannosidase inhibitors

Sandrine Gerber Lemaire-Audoire, Florence Popowycz, Eliazar Rodríguez-García, Raynald Demange, Catherine Schütz and Pierre Vogel

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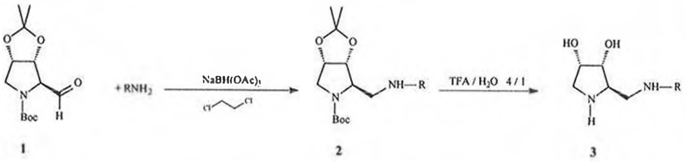
The specific inhibition of *N*-linked glycoprotein-processing glycosidases can find promising applications in the development of antibacterial, antiviral and anti-metastatic agents. The discovery of efficient and selective inhibitors of mannosidases, that are involved in the proliferation of cancer cells, could provide a useful anti-cancer strategy [1].

Here, we report the discovery of a library of 2-(aminomethyl)-3,4-dihydroxypyrrolidine derivatives **3** as selective inhibitors of α-mannosidase (*jack bean*) [2].



Following the same synthetic pathway, another family of analogues have been prepared with structural modifications on the pyrrolidine ring.

[1] White, S.L.; Nagai, T.; Akiyama, S.K.; Reeves, E.J.; Grzegorzewski, K.; Olden, K. *Cancer Commun.* **1991**, *3*, 83.

[2] Popowycz, F.; Gerber-Lemaire, S.; Demange, R.; Rodriguez-García, E.; Carmona Asenjo, A.T.; Robina, I.; Vogel, P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2489; Gerber-Lemaire, S.; Popowycz, F.; Rodriguez-García, E.; Carmona Asenjo, A.T.; Robina, I.; Vogel, P. *ChemBioChem* **2002**, *5*, 466.

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Medicinal Chemistry

**63**

### The lipophilicity behaviour of COMT inhibitors

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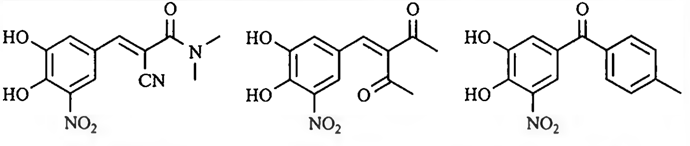
[b]Dipartimento di Scienza e Tecnologia del Farmaco, Università degli Studi di Torino, via Giuria 9, I-10125, Torino, Italy

Entacapone, nitecapone and tolcapone are inhibitors of COMT (Catechol-O-Methyl-Transferase) used in association with levo-dopa in the therapy of Parkinson's disease. This association produces a reduction of the «long term syndrome» and improves the early symptoms of the disease.



Entacapone Nitecapone Tolcapone

This study was devoted to a physicochemical characterization of these COMT inhibitors. The inhibition of brain COMT observed with entacapone is low and obtained at high doses. Nitecapone is only peripherally active. In contrast, tolcapone readily crosses the BBB (blood brain barrier) and hence also acts in the brain.

To have a better comprehension of the behaviour of these COMT inhibitors it was necessary to study the lipophilicity of both the neutral and ionized forms. The partition coefficient of the neutral forms was measured by potentiometry and that of the anions by cyclic voltammetry.

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Medicinal chemistry

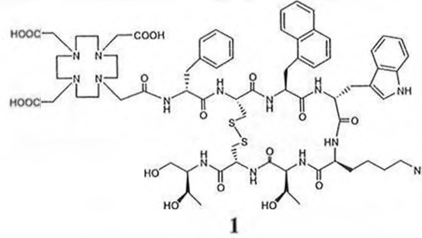
**62**

### Synthesis and Biological Activity of a New and Highly Potent Ligand for Somatostatin Receptors 2, 3 and 5

M. Ginj[1], J.S. Schmitt[1], D. Wild[1], J.C. Reubi[2], B. Waser[2], M. de Jong[3], B.F. Bernard[3], E.P. Krenning[3], H.R. Mäcke[1]

[1]University Hospital Basel, Institute of Nuclear Medicine, Radiological Chemistry, Petersgraben 4, CH-4031 Basel, Switzerland; [2]University Hospital Bern, Switzerland; [3]University Hospital Rotterdam, Netherlands

Tumor targeting with radiolabelled peptides has been of much recent interest. The prototypes are derivatives of somatostatin (SRIF) like DOTA-[Tyr$^3$]-octreotide (DOTA-TOC) [1]. Five SRIF-receptor subtypes (sstr) are known and shown to be expressed on different tumors [2]. The above mentioned peptides show high affinity mainly for sstr2 and moderate affinity to sstr 5 [3]. Using parallel solid phase synthesis we synthesized new DOTA-octapeptides based on octreotide replacing Phe$^3$ by mainly unnatural amino acids. One of them, DOTA-[1-Nal$^3$]-octreotide (DOTA-NOC) **1**, showed very good results if complexed with Y(III) or In(III).



**1**

Following the first biological results, [$^{111}$In] and [$^{90}$Y]DOTA-NOC are very promising radiopeptides for the diagnosis and peptide receptor mediated radiotherapy of a larger range of sstr expressing tumors.

[1] Heppeler A. et. al. *Curr. Med. Chem.* 7: 971-994 (2000);

[2] Forssell-Aronsson E.B. et al. *J. Nucl. Med.* **41**: 636-642 (2000)

[3] Reubi J.C. et al. *Eur.J. Nucl.Med.* **27**: 273-282 (2000)

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Medicinal Chemistry

**64**

### An Efficient Combinatorial Method for the Discovery of Glycosidase Inhibitors

Eliazar Rodríguez-García,[a] Sandrine Gerber Lemaire-Audoire,[a] Florence Popowycz,[a] Ana Teresa Carmona-Asenjo,[b] Inmaculada Robina [b] and Pierre Vogel*[a]

[a] EPFL, Institut de Chimie Moléculaire et Biologique, CH-1015 Lausanne, Switzerland.

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The specific inhibition of N-linked glycoprotein-processing α-mannosidases may provide a useful anticancer strategy [1]. Clinical trials have shown that swainsonine, an indolizidine alkaloid, acts as a reversible inhibitor of α-mannosidase [2], but its toxicity makes the discovery of new inhibitors a necessary aim. Here, we report a new method for the rapid discovery of new α-mannosidase inhibitors based on the formation of imines between diamine **1** and analogues, and a sublibrary of aldehydes in the presence of the enzyme [3]. These imines model the inhibitory activities of the corresponding amines [4].

250 µM 250 µM R = substituted aryl and heteroaryl

This strategy can also be applied to all kind of enzymes and is very useful as minute amounts of sample are required in the enzymatic assays.

[1] Asano, N. *Enzyme Inhib.* **2000**, 351.

[2] Elbein, A. D.; Molyneux, R. D. in *Iminosugars as Glycosidase Inhibitors; Nojirimycin and Beyond*, Stütz, A. E., Eds. Wiley-VCH: Weinheim, **1999**, chapter 11.

[3] Gerber-Lemaire, S.; Popowycz, F.; Rodríguez-García, E.; Carmona Asenjo, A. T.; Robina, I.; Vogel, P. *ChemBioChem* **2002**, *3*, 466.

[4] Popowycz, F.; Gerber-Lemaire, S.; Demange, R.; Rodríguez-García, E.; Carmona Asenjo, A. T.; Robina, I.; Vogel, P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2489.

65

## Evaluation of micro reactors for the generation of small molecule libraries

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Pharmaceutical industry aims to develop safe drugs displaying high impact on the alteration of disease states combined with very few or no side effects. In terms of economical benefit the chemist needs to start with an optimal lead compound for further optimization. So far, pure compound libraries even if prepared by highly automated synthesis cover only a small fraction of the possible diversity space. As long as these syntheses are carried out in macroscopic scale one will rapidly reach the point where the production of more diverse libraries becomes impossible due to huge amounts of reagents and number of products.

Microchannel flow reactors could be potentially useful for high throughput syntheses yielding a complete lab-on-a-chip when connected to other miniaturized systems for purification, analysis, and screening techniques. The combination of wet etched glass reactors with electroosmotic flow (EOF) pumping proved to be useful for rapid formation of products in otherwise slow conversions. In some experiments products were observed that could be traced back to the formation of intermediates generated electrolytically.

In this work we investigated the impact of EOF driven glass micro reactors on reaction rates and synthesis strategies in several model reactions like amide bond and heterocycle formations.

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66

## QM/MM Study of the Copper Binding Sites of Prion Proteins

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U. Röthlisberger*

*Laboratory of Inorganic Chemistry, ETH Hönggerberg-HCI, CH-8093
Zürich, Switzerland
present address : [1] Institute of Organic Chemistry, University of Zürich, CH-8093 Zürich, Switzerland
present address : [2] CSCS, CH-6928 Manno, Switzerland

Prions are proteinaceous infectious agents devoid of any nucleic acid information [1]. They play a central role in a group of fatal, neurodegenerative diseases affecting animals such as sheep (scrapie), cattle (bovine spongiform encephalopathy) and humans (e.g. Creutzfeldt-Jacob disease). The biological importance of Cu(II)-binding to prion proteins is still unclear but there is increasing evidence that the metal ion could play some role in a variety of neurodegenerative diseases such as Alzheimer, Parkinson and amyotrophic lateral sclerosis. Recent EPR-measurements on the mouse prion protein (mPrP) have indicated that, at neutral pH, a histidine residue is involved in coordination in the C-terminal structured part of the protein [2]. Since this fragment is still capable of propagating prion disease [3], Cu(II)–binding may be involved in the transition to the degenerative form. The aim of our work is to characterise potential Cu$^{2+}$-binding sites in the mPrP using molecular modelling and molecular dynamics based on the available NMR data. To properly describe the copper–protein interactions, we used a mixed Quantum Mechanics / Molecular Mechanics (QM/MM) approach based on a combination of Car-Parrinello molecular dynamics and on the GROMOS96 force field [4]. We investigated the stability and the dynamics of different structural models of the copper binding site in the vicinity of the three histidines of mPrP. Comparison between the simulations reveals putative copper binding sites and suggests targets for site-directed mutagenesis studies in order to refine their exact locations.

[1] S.B. Prusiner, *Science* **278**, 245 (1997)
[2] S. Van Doorslaer et al., *J. Phys. Chem. B*, **105**, 8 (2001)
[3] D. Shmerling et al., Cell, 93 (2) : 203-214 (1998)
[4] A. Laio et al., *J. Chem. Phys.* **116**, 6941-6947 (2002)

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Computational Chemistry 67

## Theoretical Study of Weakly Bound Complexes Using the Density Functional Theory Formalism Based on Electron Density Partitioning

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Geneva 4, Switzerland

The interaction energies of weakly bound complexes are calculated by a recently developed DFT approach based on subsystems [1][2] (Kohn-Sham Equations with Constrained Electron Density, KSCED). The ability of the KSCED approach to yield very accurate interaction energies has already been demonstrated by studying the $C_6H_6{-}X$ ($X{=}N_2$, $O_2$, or CO) complexes [3], the benzene dimer [4], and complexes involving carbazole [5]. Here we present additional results on weakly bound complexes for which CCSD(T) results are available in the literature, and, we compare the performance of the KSCED approach with the traditional Kohn-Sham one.

[1] T.A. Wesołowski, A. Warshel, *J. Phys. Chem.* **1993**, *97*, 8050.
[2] T.A. Wesołowski, J. Weber, *Chem. Phys. Lett.* **1996**, *248*, 71.
[3] T.A. Wesołowski, Y. Ellinger, J. Weber, *J. Chem. Phys.* **1998**, *108*, 6078.
[4] F. Tran, J. Weber, T.A. Wesołowski, *Helv. Chim. Acta* **2001**, *84*, 1489.
[5] T.A. Wesołowski, P.-Y. Morgantini, J. Weber, *J. Chem. Phys.* **2002**, *116*, 6411.

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Computational Chemistry 68

## Molecular Dynamics Simulations of Rhodopsin: Insights into the Signaling Pathway and Spectral Changes

Ute F. Röhrig*, Irmgard Frank†, Leonardo Guidoni*, Alessandro Laio‡,
Carla Molteni§, Michele Parrinello‡, Ursula Rothlisberger*, Joost
VandeVondele¶

*Laboratory of Inorganic Chemistry, ETH Zurich, Switzerland.
†Chemistry Department, LMU Munich, Germany.
‡Swiss Center for Scientific Computing, Manno, Switzerland.
§Cavendish Laboratory, Cambridge University, UK.
¶Institute of Physical Chemistry, University of Zurich, Switzerland.

We present classical molecular dynamics simulations of bovine rhodopsin in a membrane mimetic environment based on the recently refined X-ray structure of the photoreceptor [1]. The interactions between the protonated Schiff base and the protein moiety are explored both with the chromophore in the dark adapted 11-cis and in the photoisomerized all-trans form. Restrained molecular dynamics simulations provide evidence that the protein tightly confines the absolute conformation of the chromophore around the C12-C13 bond to a positive helicity. 11-cis to all-trans isomerization leads to an internally strained chromophore, which relaxes after a few nanoseconds by movement of the ionone ring thus adopting a more planar all-trans conformation. This movement induces in turn significant conformational changes of the protein backbone, especially in helix VI. Our results suggest a possible molecular mechanism for the early steps of signal transduction in a prototypical G-protein-coupled receptor. A QM/MM approach [2] was used to calculate the absorption spectra of the intermediates observed in the classical simulations.

[1] Palczewski et al., Science **289**, 739-745 (2000).
[2] A. Laio, J. VandeVondele, U. Rothlisberger, J. Chem. Phys. **116**, 6941-6947 (2002).

Computational Chemistry

**69**

## The Molecular Lipophilicity Potential and the Molecular Hydrogen-Bonding Potentials: Their application to the development of a scoring function for virtual ligand-receptor screening

Sébastien REY, Antoine Daina, Frédéric Ooms,
Pierre-Alain Carrupt and Bernard Testa

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The MxP fields are novel empirical tools able to compute the interactions between a target molecule and its environment based on fragmental or atomic physicochemical values. The MHBPs (Molecular Hydrogen-Bonding Potentials) determine the 3D hydrogen bonding potentials of small molecules and biological macromolecules, while the MLP (Molecular Lipophilicity Potential) determines their 3D lipophilicity properties.

A scoring function was also developed using the MxP fields to better characterize intermolecular interactions responsible for the binding of drugs to biological targets and to rank docking solutions. The so-called ScoreMxP function has yielded promising results in the study of complexes between methotrexate and dihydrofolate reductase, and between retinoic acid and cellular retinoic acid binding protein type II.

New improvements and validations with a large dataset of high resolution crystallographic ligand-protein complexes are under progress. When applied in conjunction with a docking procedure, this new empirical scoring function should be useful to screen large structural databases and help to select between different binding modes.

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## A QM/MM study of catalytic enantioselective fluorination.

**70**

Stefano Piana and Ursula Röthlisberger

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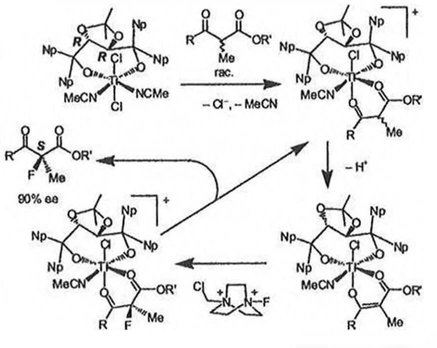
The synthesis of stereoactive organofluorine compounds is particularly challenging. Recently, the first catalytic enantioselective fluorination of β-ketoesters with F-TEDA in the presence of 5% of $TiCl_2$(TADDOLato) complexes as catalysts was presented[1]. The enantioselectivity reaches 90%.



1 (Np=1-Naphthyl, R=Et, R'=2,4,6-(*i*-Pr)$_3$C$_6$H$_2$-CH$_2$

Here we present a DFT-based QM/MM study of the reaction in acetonitrile solution.[2] Our calculations elucidate the source of the observed enantioselectivity and provide a description of the reaction mechanism that allows to rationalize a large number of experimental data.

Furthermore, comparison with the same calculations in vacuo indicates that the interaction between the solvent and the reactants plays a crucial role in modulating the reaction pathway. Low-cost and accurate QM/MM schemes are nowadays readily available, thus we expect that the simulation of quantum reactants in a classical solvent will soon become the method of choice for the theoretical study of a large number of chemical reactions.

[1] L. Hintermann, A. Togni, *Angew Chem Int Ed* **2000**, *39*, 4359-4362.
[2] S. Piana, I. Devillers, A. Togni and U Röthlisberger, *Angew Chem Int Ed* **2002**, *41*, 979-982.

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Computational Chemistry

**71**

## D Quadrupolar NMR Relaxation Times in $D_2O$/DMSO mixtures calculated by molecular dynamics simulations in combination with quantum chemical calculations

Müller M. G., Hardy E., Kirchner B., Vogt P. S., Bratschi Ch.,
Searles D. J.[#], Huber H.

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[#]School of Science, Griffith University, Brisbane, QLD 4111,

An NMR investigation of Gordalla and Zeidler [1] showed unexpected behaviour for the quadrupole coupling constant of the deuteron in a $D_2O$/DMSO mixture. It could be explained by a hydrophobic effect, but this is in contrast to other experimental evidence. Simulations of the mixture, with empirical potentials and quantum chemical calculations of clusters extracted from the simulation ensemble, did not show the experimental behaviour [2]. To obtain more information about the system, we simulated the relaxation time. In order to do this we had to assume pair-additivity for the electric field gradient (efg). We have shown [3] that this is an excellent approximation. A multidimensional pair-efg curve was obtained from quantum chemical ab initio calculations and was fitted to algebraic expressions that were implemented in the simulation program to calculate the desired time correlation functions. To date this approach (using a similar method) has only been applied to ions and rare gases, i.e. systems of spherical symmetry, which are much simpler to treat.

[1] B. C. Gordalla, M. D. Zeidler, Mol. Phys. **1986**, *59*, 817.
[2] B. Kirchner, D. J. Searles, A. J. Dyson, P. S. Vogt, H. Huber, J. Am. Chem. Soc. **2000**, *122*, 5379.
[3] M. G. Müller, B. Kirchner, P. S. Vogt, H. Huber, D. J. Searles, Chem. Phys. Lett. **2001**, *346*, 160.

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**72**

## Molecular mechanics force field parameters derived from mixed QM/MM calculations

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We present a method for deriving mechanics force field parameters from mixed QM/MM calculations. The molecule for which parameters are to be derived is treated quantum mechanically by means of density functional theory, while the surrounding solvent is treated classically.

In a first step, atomic partial charges are derived with a modified RESP scheme, which allows for a subtraction of the solute-solvent interaction. The force field parameters are then in a second step adjusted such as to reproduce best the remaining forces on the solute atoms.

Details of the fitting procedure will be discussed as well as the results of its application to aqueous solutions of i) an $H_2PO_4^-$ anion and ii) an Ala-Gly dipeptide.

Computational Chemistry **73**

## Driving Chemical Reactions via Biases of Molecular Orbitals

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Chemical reactions often have activation barriers too high to be observed on the typical picosecond timescale of first-principles dynamics simulations. To overcome these barriers, a bias potential can be applied, that drives the system toward the transition states [1]. Thermodynamic properties of the unbiased system, such as the height of the activation barrier, can thus be derived from the shorter biased dynamics runs. Density Functional Theory offers useful concepts, such as Kohn-Sham molecular orbitals, hardness, electronic and nuclear Fukui Functions [2,3], that could be used for the construction of appropriate electronic bias potentials for accelerating rare reactive events.

In the present contribution, we developed a bias potential scheme which depends only on the electronic states of the reactive system. This bias scheme is applied to the study of two different reactions in gas phase: the butadiene to cyclobutene ring closure (Fig.1) and the nucleophilic attack of a water molecule to the amide carbon of methyl-acetamide. Different reaction pathways and bias potentials for accelerating these reactions were investigated both by geometry optimization and Born-Oppenheimer molecular dynamics.

*Fig.1: Fukui f- function along the butadiene cyclization pathway.*

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Computational Chemistry **74**

## Influence of dynamics on NMR chemical shifts – Berry pseudorotation and Diels-Alder reaction

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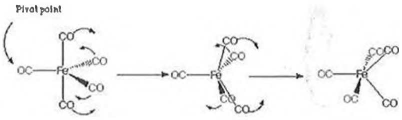
NMR chemical shift calculations have become a standard tool for structure determination of NMR characterised molecules. At present, the standard method is to calculate NMR chemical shifts on frozen gas phase geometries. In experiment, the measured chemical shifts are a time average of µs to ms taken at a finite temperature and often in solution.

Molecules capable of the so-called Berry pseudorotation, as $PF_5$ and $Fe(CO)_5$, are studied using Born-Oppenheimer Molecular Dynamics on the basis of a LCGTO-DFT scheme and Car-Parrinello-MD. Both MD methods are compared and the dynamics and its influence on the chemical shifts are studied.



Unstable quinodimethane is highly reactive in the presence of a dienophile because a Diels-Alder cycloaddition reestablishes a benzoid ring and results in aromatic stabilization. The degree of aromaticity of this benzoid ring is studied during its formation by $^{13}C$ NMR and NICS calculations along the geometries of the Diels-Alder reaction path.

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Computational Chemistry **75**

## Affinity of 5-$HT_{1A}$ agonists and their metabolites : radioreceptor assays and molecular modeling

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The relationship between the metabolism and disposition of many 5-$HT_{1A}$ ligands has been reviewed [1]. But with most of the attention focused on the parent compounds and their metabolic routes, the effect of metabolic transformation on the affinity and selectivity of metabolites for the receptor have rarely been addressed. This work was performed to determine the contribution of metabolic changes of two anxiolytic drugs (S 20499 and S 15535) to the overall affinity and hence to pharmacological responses after oral administration. Both drugs were described as 5-$HT_{1A}$ receptor agonists.

This study was performed in three phases:

1) Isolation, purification and identification of metabolites.
2) Radioreceptor assay applied to leads and to metabolites present in human plasma samples.
3) Docking study using the Molecular Lipophilicity Potential score function [2] to understand the affinities for 5-$HT_{1A}$ receptor of lead compounds and their metabolites.

[1] B. Walther, P. Vis, A. Taylor. In 'Lipophilicity in Drug Action and Toxicology', Eds. V. Pliska, B. Testa and H. van de Waterbeemd, VCH Publishers, Weinheim, 1996, pp. 253-261.
[2] P.-A. Carrupt, P. Gaillard, F. Billois, P. Weber, B. Testa, C. Meyer, S. Pérez. In 'Lipophilicity in Drug Action and Toxicology', Eds. V. Pliska, B. Testa and H. van de Waterbeemd, VCH Publishers, Weinheim, 1996, pp. 195-217.

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Computational Chemistry **76**

## Theoretical study of bonding carbon monoxide to Alkali Metal Cations in ZSM5-zeolite using orbital-free embedding formalism.

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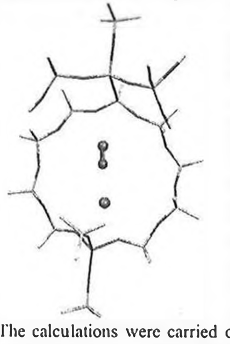
The interaction between carbon monoxide and alkali cation in ZSM5 zeolite can provide useful indications for understanding intra-zeolite processes. The different modes of coordination of this probe molecule are characterized by the change in CO stretching frequency and intensity [1].

In a previous study [2], it has been shown that the interaction between the CO molecule and the alkali cation zeolite through the C-end gives rise to a blue shift of this frequency in good agreement with experimental data.



The purpose of this work was to study the O-bonding coordination mode of the carbon monoxide in cation zeolite and to compare the calculated frequency shifts obtained with the red shift observed experimentally.

All the calculations were carried out using the orbital-free embedding formalism [3] developed in our group and implemented in the deMon program [4]. In the calculations the $M^+$...CO complex was considered as one subsystem whereas the zeolite was represented as a cluster (see figure) with frozen electron density

The cluster used comprises the atoms coordinating the $Me^+$, the channel wall opposite to the Al site and the atoms linking both parts.

The influence of the long-range electrostatic effects on the properties of CO was also studied.

The calculations were carried out for the three alkali cations ($Li^+$, $Na^+$, $K^+$). In agreement with experimental results, it was found that the $M^+$...OC complex was energetically less stable than the $M^+$...CO one and that the CO stretching vibration are red-shifted.

[1] C.O. Areán, A.A. Tsyganenko, E.E. Platero, E. Garrone, A. Zecchina, *Angew. Chem. Int. Ed.*, **1998**, *37*,3161-3163.
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Computational Chemistry **77**

## Theoretical and Experimental Study of the Racemisation of a Helical Organic Cation

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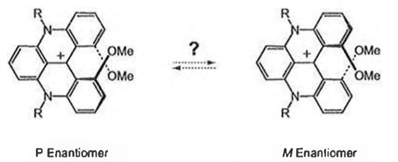
Density functional theory (DFT) calculations were performed to study the different properties of the 5H-Quino[2,3,4-kl]acridinium,1,13-dimethoxy-5,9-dipropyl-cation. This molecule, involved in the synthesis of novel triazaangulenium dyes of high chemical stability, is a chiral [4]-helicenium [1].
The theoretical study reported in this work was carried out to calculate the structural and vibrational properties of this molecule and to determine the racemisation barrier. A detailed analysis of the applicability of DFT calculations to this purpose was made preliminarily on the dimethyl cation before to study the dipropyl one. Comparisons between the calculated geometry and the X-ray diffraction data [2] reveal a good agreement between these two sets of data. We have also observed a good agreement between the theoretical and the experimental infrared spectrum. The calculated racemisation barrier (37 kcal/mol) is in good agreement with experimental estimates (at least 35 kcal/mol). Moreover, the search for the transition state made it possible to get a detailed picture of the structure changes accompanying the racemisation.



The calculations were performed using the Gaussian 98 suite of programs [3] for the *M*-enantiomer.

[1] B.W. Laursen; F.C. Krebs, *Angew. Chem. Int. Ed.*, **2000**, *39*, 3432-3434.
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[3] *Gaussian 98*, M. J. Frisch et al.

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Computational Chemistry **78**

## Prediction of electric and magnetic properties in multiferroic materials

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Multiferroic materials have ferroelectric and ferromagnetic properties in the same phase. They have both a spontaneous magnetization, which can be switched by an applied magnetic field, and a spontaneous polarization which can be switched by an applied electric field. Often these two phenomena are coupled [1]. These materials are rapidly gaining interest as they could possibly be used in data storage applications by writing data into the magnetic phase of a material and reading out the electric phase or vice versa. We are interested in predicting structures and properties of such systems [2] using a plane wave band structure code implemented in the software package Wien [3].

[1] Nicola A. Hill *J. Phys. Chem B*, **2000**, *104*, 6694-6709.
[2] Nicola A. Hill, Pio Bättig, Claude Daul, *J. Phys. Chem. B*, **2002**, *106*, 3383 -3388.
[3] P. Blaha, K. Schwarz and J. Luitz, WIEN97, A Full Potential Linearized Augmented Plane Wave Package for Calculating Crystal Properties, (Karlheinz Schwarz, Techn. Univ. Wien, Vienna 1999). ISBN 3-9501031-0-4.

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Computational Chemistry **79**

## Theoretical study of the photochemical degradation of a sulfonylurea molecule

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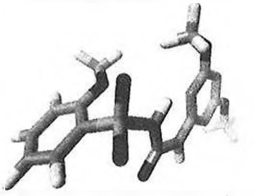
[3]Institut de Recherches sur la Catalyse, CNRS, France

The use and the number of sulfonylurea herbicides have increased since the early 1980's. A good understanding of their degradation is of ecological importance, since environmental pollutants can be issued from them. It is claimed that the chemical hydrolysis present the main degradation pathway but photodegradation can not be neglected.



Time dependent density functional theory has been used to help in the elucidation of the photochemical behavior of a sulfonylurea and derivatives. The experimental UV spectrum[1] presents three major absorption maxima below 290 nm. Two of them have been obtained theoretically and can be assigned to the cleavage of bonds at both sides of the sulfur atom. Theoretical transitions are in excellent agreement with the experimental ones.

[1] Vuillet, E.; Emmelin, C; Grenier-Loustallot, M.F.; Païsse, O.; Chovelon, J.M.; *J. Agric. Food. Chem.* 2002, 50, 1081

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Computational Chemistry **80**

## Molecular interaction fields in quantitative structure-skin permeation relationships: the VolSurf approach.

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3D-QSPeR methods define molecular properties in terms of 3D molecular interaction fields (MIFs) which can be computed from 3D-structures.

In this context, a new method called VolSurf [1], which is able to transform the information present in 3D-MIFs into a limited number of quantitative descriptors, was used to correlate 3D molecular structures of a large and heterogeneous set of compounds with skin permeation. Three different MIFs were investigated, namely GRID [2] which is based on the total energy of interaction between a probe and a target molecule, MLP [3] which is a molecular field of lipophilicity, and MHBPs [4] which take into account hydrogen-bonding capacity.

The results indicate that while the models obtained from both MxPs (MLP and MHBPs) and GRID fields are statistically equivalent, MxPs fields are better in terms of mechanistic interpretation for skin permeation.

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[2] P.J. Goodford, *J. Med. Chem.* **1985**, 28, 849.
[3] P. Gaillard, P.A. Carrupt, B. Testa, A. Boudon, *J. Comput.-Aided Mol. Design* **1994**, 8, 83.
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Computational Chemistry **81**

## Comparative Theoretical Studies of Dipeptide Solvation in Water

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We have performed Molecular Dynamics studies on the dipetide alanine-glycine in water with focus on the solvation using a range of theoretical methods; from purely classical force field simulations to fully Quantum Mechanical calculations. The classical simulations were performed within the Amber[1] scheme, we also employed a mixed Quantum Mechanical/Molecular Mechanics[2] scheme and finally a fully Quantum Mechanical scheme within Car-Parrinello Molecular Dynamics[3]. The results of theses studies show that the H-bonding pattern can differ substantially between the different levels of theory, which might have implications in other theoretical studies of peptides and proteins solvated in water.

MORE TEXT.

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[3] J. Hutter, A. Alavi, T. Deutsch, M. Bernasconi, St. Goedecker, D. Marx, M. Tuckerman, and M. Parrinello, MPI für Festkörperforschung and IBM Zürich Research Laboratory (1995-1999).

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Computational Chemistry **82**

## CURVIS – A computer program to analyze phase transition

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The design of new compounds via organic templates is an important task of modern inorganic chemistry. Organic templates exhibit an amazing variety of structures. The analysis of the structures permits to make predictions about the mechanical properties of the final products and moreover to give indications about new transient structures.
Going from a geometric problem such as the calculation of curvature of an intermediate phase, to a working computer program, takes several steps. The first step is the conversion of a geometrical problem into an algebraic one. This task has been accomplished using two different approaches: using the nodal description from Nesper and von Schnering[1], and using an exponential scale approach as given by Anderson et al.[2]. The second step is the reduction of an algebraic problem into an algorithm and finally the implementation of such algorithm into a computer program. This task introduced some approximations in the calculation but allowed an easy to perform structural analysis of the whole range structures taken into account.
The investigation of phase transitions is not simply a matter of geometry. It is possible to generate infinite intermediate structures that are reasonable from both topological and geometrical arguments. Energy is in most cases an adequate parameter to compare different possible pathways.
To quantitatively understand geometrical changes, an evaluation of shape and curvature is performed, which takes advantage from a triangular mesh representation of the surface. Measures of the surface curvature rely on the definition of gaussian (K) and mean (H) punctual curvature. The estimation of H, K, and the bending energy for a properly triangulated surface is achieved with algorithms implemented and optimised for the system. The knowledge of the energetic of a transformation of complex macroaggregates is crucial in designing new material. The visualization of geometrical and chemical properties by means of surface and volume rendering is a valid aid for extracting high level informations. A program (CURVIS) will be presented and some applications to solid state chemistry and biology will be shown.

[1] H. G. von Schnering, R. Nesper, Z. Phys. B - Condensed Matter 1991, 83, 407.
[2] M. Jacob, S. Andersson, The nature of mathematics and the mathematics of nature, Elsevier, Amsterdam, 1998.

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Computanional Chemistry **83**

## From DFT to ligand field theory

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The aim of this work is to estimate ligand field parameters using Density Functional Theory (DFT). We have shown in the past how to use DFT calculation to determine the energies of the single determinants [1]. In this work, we will use theses energies to adjust the ligand field and Racah parameters in the corresponding expressions for the single determinants within ligand field theory.
The procedure will be validated in comparing experimental, non empirical DFT data with ligand field results obtained in this way. ADF package will be used to determine the single determinants energies.

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Computational Chemistry **84**

## *Ab initio* molecular dynamics for molecules with variable number of electrons

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We have developed and implemented in the *ab initio* MD package CPMD [1] a grand canonical ensemble dynamics scheme for the simulation of systems (molecules) with fractional charge [2]. By means of this approach thermodynamic quantities such as the reaction free energy for ionization can be estimated from the partition functions of the ionic coordinates computed for the two oxidation states.
The scheme has been first tested on a simple molecule (aniline) in vacuum and subsequently applied to a more complex system of biological interest composed by the redox active fragment of NADH, the nicotinamide ring, solvated in 45 water molecules (using PBC). In this study, we also describe the ionic configurational changes and the electronic rearrangements occurring during the oxidation of nicotinamide. Of particular relevance in this respect is the computation of the Dyson orbitals (DO) [3] starting from the many-body wavefunctions of the neutral and ionic states. In order to understand the complex time evolution of the ionization potential (IP) and the discrepancy between the measured IP and the energy of the highest occupied Kohn-Sham orbital, HOMO, the calculation of DO has been extended to treat the case of periodic systems in solution.

[1] CPMD Version 3.3 written by J. Hutter, P. Ballone, M. Bernasconi, P. Focher, E. Fois, St. Goedecker, D. Marx, M. Parrinello, and M. Tuckerman at MPI fuer Festkoerperforschung and IBM Zurich Research Laboratory.
[2] I. Tavernelli, R. Vuilleumier, M. Sprik, *Phys. Rev. Lett.*, **2002**, *in press*.
[3] P.J. Duffy, D.P. Chong, M.E. Casida, and D.R. Salahub, *Phys. Rev. A*, **1994**, *50*, 4707.
D.P. Chong, O.V. Gritsenko, E.J. Baerends, *J. Chem. Phys.*, **2002**, *115*, 1760.

Computational Chemistry **85**

## Introduction of the Explicit Long-Range Nonlocality as an Alternative to the Gradient Expansion Approximation for the Kinetic-Energy Functional

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Geneva 4, Switzerland

The approximate nonempirical kinetic-energy functional proposed by Tal and Bader [1] is analyzed for polyatomic systems. The performance of this functional and the functionals derived from the gradient expansion approximation truncated to zeroth [2][3], second [4], and fourth [5] order is investigated for a testing set of 68 neutral and charged molecules [6]. It is shown that the Tal-Bader functional, despite the simplicity of the idea behind its construction, leads to significantly better total kinetic energies than the gradient expansion approximation functionals. The local behavior of the kinetic-energy density derived from the Tal-Bader functional is also discussed.

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Computational Chemistry **86**

## Implementation of the Static Nonlinear Optical Properties of Molecules in the FRIMOL Program

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Time-independent CPHF equations have been implemented to obtain some nonlinear electric and electro-magnetic properties of molecules [1] (such as $\beta^{EEB}_{ijk}$...) for the restricted Hartree-Fock wave function. These routines have been implemented in the ab-initio quantum chemistry program package FRIMOL with the same techniques as describe by Dupuis et al [2]. The 2n+1 theorem of perturbation theory was plenty used to decrease the computational effort for second and third order properties, To improve the convergence of the derivatives of the density matrix with the respect to the components of the field at each CPHF iterative cycle, different classical algorithms from SCF techniques have been tested, such as simple damping, Davidson's extrapolation/damping, and DIIS method.

In the future we will implement the time-dependent CPHF equations up to the third order properties for electric, magnetic and electro-magnetic properties, and we are looking to the computation of the mixed derivatives with respect to the electric field and to the normal coordinate [3].

[1] D.M. Bishop, S.M. Cybulski, *Molec. Phys.*, **80**, (1993), 199.
[2] M. Dupuis, S.P. Karna, *J. Comp. Chem.*, **12**, (1990), 487.
[3] O. Quinet, B. Champagne, B. Kirtman, *J. Comp. Chem.*, **22**, (2001), 1920.

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**87**

## Determination of Amino Acid Pairs in Human p53 Protein Sensitive to Mutations/Variants by means of a Random Approach

Shao-Min Yan[1], Guang Wu[2]*

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In this data-based theoretical analysis, we use the random approach to analyse the amino acid pairs in human p53 protein in order to determine which amino acid pairs are more sensitive to 190 human p53 mutations/variants (Swiss-Protein data bank, access number P04637 [1]). The rationale of this study is based on our hypothesis and findings that the harmful mutation is more likely to occur at randomly unpredictable amino acid pairs, and the un-harmful mutation is more likely to occur at randomly predictable amino acid pairs [2, 3]. This is because we argue that the randomly predictable amino acid pairs should not be deliberately evolved, whereas the randomly unpredictable amino acid pairs should be deliberately evolved with connection of protein function. The results show, for example, 93.16% of 190 mutations/variants occur at randomly unpredictable amino acid pairs. Thus the randomly unpredictable amino acid pairs are more sensitive to mutations/variants in human p53 protein. The results also suggest that the human p53 protein has the tendency to the mutation/variant.

| p53 protein | Kinds | Pairs | Mutations |
|---|---|---|---|
| Predictable | 90 (42.86%) | 124 (31.63%) | 13 (6.84%) |
| Unpredictable | 120 (57.14%) | 268 (68.37%) | 177 (93.16%) |
| Total | 210 (100%) | 392 (100%) | 190 (100%) |

[1] A. Bairoch, R. Apweiler, *Nucleic Acids Res.* **2000**, 28, 45.
[2] G. Wu, S.-M. Yan, *J. Mol. Model.* **2001**, 5, 120.
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Organic Chemistry **88**

## Molybdenum-Mediated Arene Transformations

E. Peter Kündig,* Charles-Henry Fabritius, Gabriele Grossheimann, Fabrice Robvieux, Patrick Romanens and Gérald Bernardinelli

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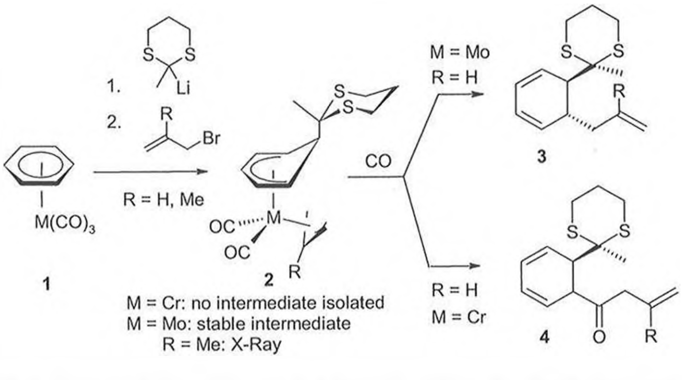
[$(\eta^6$-arene)Cr(CO)$_3$] complexes have found widespread application in organic synthesis [1]. Surprisingly no parallel development has taken place with the analogous molybdenum compounds. The labile metal arene bond in [$(\eta^6$-benzene)Mo(CO)$_3$] was used to synthesize substituted arene complexes by arene exchange. M-H and M-C bonds are stronger in Mo than in Cr-complexes and different patterns of reactivity can be expected. This hypothesis has now been confirmed and one reaction that was studied in detail *via* in situ IR analysis is shown below. Note that the analogous reaction with [$(\eta^6$-benzene)Cr(CO)$_3$] gives not **3** but the ketone product **4**.



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Organic Chemistry **89**

### Titanacyclopentene complexes and their application as 1,4-dicarbanion equivalents

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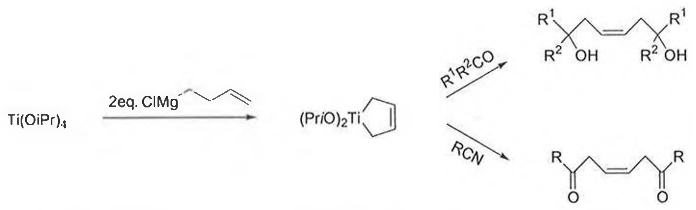
Titanium derivatives have found numerous synthetic applications. Among them, the conversion of titanium alkoxides into dicarbanionic intermediates and their synthetic use was recently reviewed in detail.[1] In a few cases, the direct conversion of ($\eta^2$-propene)Ti(OiPr)$_2$ with dienes led to the formation of titanacyclopentenes, which react as either 1,2[2]- or 1,4[3]-dicarbanions.

In this account, we report an effective formation of titanacyclopentenes which can be selectively coupled with a wide range of electrophiles. The scope and limitations of this reaction as well as some intramolecular versions will be discussed.



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[2] C. M. Williams, V. Chaplinski, P. R. Schreiner, A. de Meijere, Tetrahedron Lett. 1998, 39, 7695.
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Organic Chemistry **90**

### Photochemical Acylation : Application to the Synthesis of Amides and Carbamates

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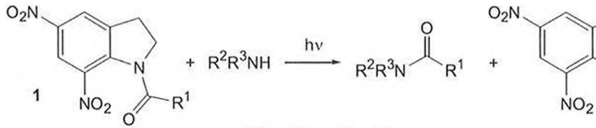
Quai Ernest-Ansermet 30, CH-1211 Genève 4

Photoprotecting groups have been widely used in the literature because of their numerous advantages; for instance, they can be removed in the absence of any chemical reagent and therefore with a high degree of selectivity. A selectivity even between two different photoprotecting groups has been achieved in our group by using different irradiation wavelengths [1].

Light can also be used, not only to cleave protecting groups, but also to generate new bonds. Thus, the irradiation of 1-acyl-5,7-dinitroindoline **1** activates the acyl group towards nucleophilic attack. This reaction can be applied to the synthesis of amides [2] and carbamates, depending on the nature of the R$^1$ group. This method has numerous advantages, such as the absence of any acid or base, high selectivity, and the possibility to trigger the reaction at exactly the desired time. Carbamates are widely used as protecting groups (for instance : Cbz, Boc or Fmoc group), so this method can be used to photochemically *protect* amines, instead of the usual photochemical deprotection.



R$^1$ = CH$_2$R, Ph, OR

[1] Bochet, C. G. *Angew. Chem. Int. Ed.* **2001**, *40*, 2071.
[2] Helgen, C.; Bochet, C. G. *Synlett* **2001**, 1968.

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Organic Chemistry **91**

### Ionic Liquids as Solvents for Metal-Catalyzed Reactions

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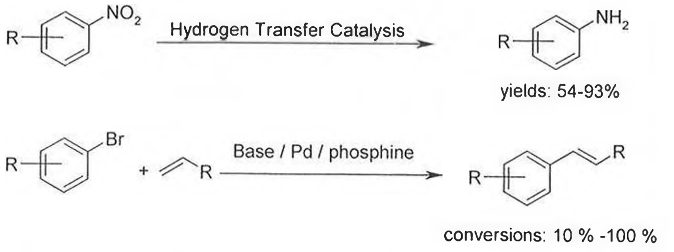
Ionic Liquids are molten salts and are composed entirely of ions.[1] These interesting new solvents are suitable for many chemical reactions and are regarded as an opportunity for cleaner productions technologies.
We used imidazolium based Ionic Liquids successfully as solvents for transition-metal catalyzed reactions such as the hydrogen transfer catalysis[2] and the Heck reaction.[3] Both reactions gave the products in high yields and improvements in selectivity was observed. However, the influence of the cation and anion has not been understood yet.



Currently, we investigate the suitability of the Ionic liquids for other catalyzed reactions such as the Suzuki reaction or the Buchwald-Hartwig amination.

[1] P. Wasserscheid, W. Keim, *Angew. Chem.* **2000**, *112*, 3926.
[2] M. Bertau, M. Bürli, *Chimica Oggi* **1999**, 49.
[3] I.P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009.

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Organic Chemistry **92**

### Orthogonal Photolabile Protecting Groups in Solid Phase Synthesis

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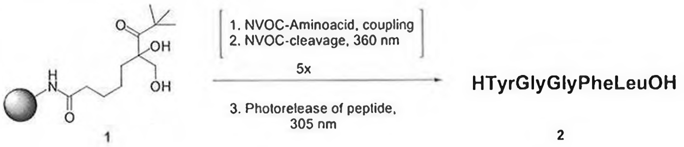
Christian G. Bochet
University of Geneva, 30 quai Ernest Ansermet, CH-1211 Geneva 4

The concept of orthogonality in protecting group strategies works with photocleavable protecting groups, if different wavelengths of light are used. No cleavage reagents are required, thus. We applied our pivaloyl anchor **1** [1] to synthesize the pentapeptide Leu-Enkephalin **2** on solid support via the corresponding *N*-nitroveratryloxycarbonyl-(NVOC)-protected amino acids. Each coupling step is followed by cleaving off the NVOC-group at 360 nm. Finally the peptide is released at 305 nm.



**1** **2**

Our present effort is to extend this method to other classes of compounds. Most recently we are improving the pivaloyllinker by means of structural modifications [2].

[1] Glatthar, R.; Giese, B. *Org. Lett.* **2000**, *2*, 2315.
[2] Keßler, M.; *Ph.D. thesis,* in preparation.

Organic Chemistry **93**

## Synthesis of Deoxypodophyllotoxin via a Radical Cascade Reaction

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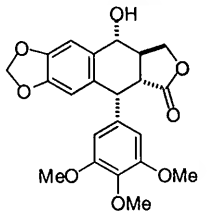
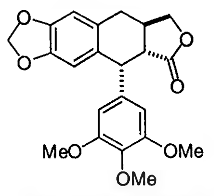
Freiestrasse 3, 3012 Bern, Switzerland

Podophyllotoxin is a plant natural product that binds to tubulin and exhibits potent antimitotic activity. Etoposide, its glucosylated C(4) epimer acts by promoting topoisomerase II-mediated DNA strand scission and is widely used for the treatment of small cell lung cancer. A flexible synthetic approach should help identifying members with high antitumor activity and low toxicity [1]. We present here a new approach for the synthesis of deoxypodophyllotoxin, a known precursor of podophyllotoxin. The key step is a tin free radical cascade reaction (5-*exo*-cyclization followed by radical arylation).



Podophyllotoxin



Deoxypodophyllotoxin

[1] R.S Ward, *Nat. Prod. Rep.* **1999**, *16*, 75.

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Organic Chemistry **94**

## A New Concept for the Combinatorial Search for Catalysts

Philipp Krattiger, Catherine McCarthy, Andreas Pfaltz
and Helma Wennemers*

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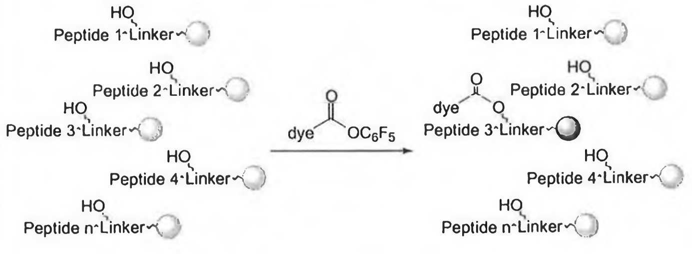
Finding new catalysts often involves the tedious testing of large numbers of compounds for their catalytic properties. We developed a new approach to test the members of a split-and-mix library for their catalytic activity in a fast and easy way. The concept has been successfully applied to develop peptidic acetylation catalysts and should be applicable to many other bimolecular reactions.

We will present details and advantages of this combinatorial approach and first results of the screening for acetylation catalysts.



Only Peptide 3 is an active catalyst

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Organic Chemistry **95**

## Constructing Conformationally Constraint Macrobicyclic Musks

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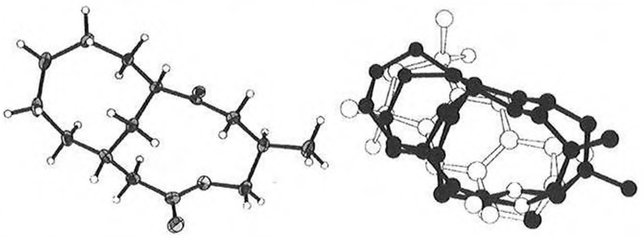
Givaudan Dübendorf AG, Fragrance Research
Überlandstrasse 138, CH-8600 Dübendorf

Is there one or are there many musk receptors? Can structure–odor correlations of polycyclic musks be applied to the design of new macrocyclic musks? — To find answers to these questions we constructed macrobicyclic molecules with some shape similarity to Galaxolide®, the odor of which is mainly due to the (4*S*)-(–)-isomers. The macrocyclic model compound was (12*R*)-12-methyl-13-tridecanolide, which possesses a clean musk odor with sandalwood accents while its enantiomer differs by a camphoraceous, animalic musk note, and 13-tridecanolide is not musky. Thus, the methyl group as well as the ring conformation are crucial in 12-methyl-13-tridecanolide.



We conformationally constrained (12*R*)-12-methyl-13-tridecanolide and 13-tridecanolide to a Galaxolide-type shape by introducing bridges between C-3 and C-8 or C-9. Syntheses started from cyclooct-2-enone or cyclohept-2-enone by Michael addition of ethyl acetoacetate, aldol condensation, decarboxylation and hydrogenation. Subsequent ring enlargement by α-alkylation with a TBS protected hydroxy halide, acid-catalyzed cyclization, oxidative cleavage of the enol ether double bond, and carbonyl reduction furnished the target structures. (1*R*,6*R*,9*R*)-(+)-6-Methyl-4-oxabicyclo[7.5.1]pentadecan-3-one was found to possess the most pronounced musk odor.

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Organic Chemistry **96**

## Novel, Short and Repeatable Two-Carbon Ring Expansion Reactions

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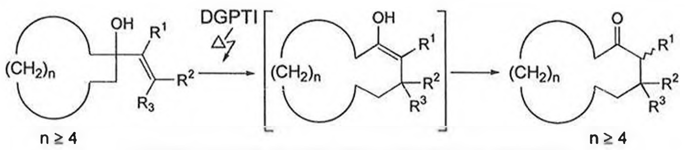
[c] University of Zürich, Winterthurerstr. 190, CH-8057 Zürich, Switzerland

1-Vinyl substituted medium and large-ring cycloalkanol derivatives **1** can be directly and efficiently transformed into the ring-expanded, bishomologous macrocyclic ketones **2** in a flow reactor system under flash vacuum pyrolysis (FVP) conditions. The cyclic ketones **2a** were then used as starting materials for subsequent analogous two-carbon ring insertion procedures [1][2].



DGPTI = Dynamic Gas Phase Thermo-Isomerization
(FVP conditions, 600 - 650°C, 1 - 4 mbar, $N_2$ flow)

| | | |
|---|---|---|
| **1a** $R^1$- $R^3$ = H | **Repeatable Ring** | **2a** $R^1$ - $R^3$ = H |
| **1b** $R^1$ - $R^3$ = H or Alkyl | **Expansion Reaction** | **2b** $R^1$ - $R^3$ = H or Alkyl |

Scope and limitations of this DGPTI reaction have also been investigated with alkyl derivatves **1b** which are transformed into the ring-expanded cyclic ketones **2b**. This novel 1,3-C shift reaction provides not only a new short access to cycloalkanones **2a** but also to many alkyl-substituted macrocyclic ketones, such as, e.g., the musk odorant (±)-muscone.

[1] M. Nagel, Dissertation, University of Zürich, Switzerland, in press.
[2] M. Nagel, H.-J. Hansen, G. Fráter, *Synlett* **2002**, 275-279 and 280-284.

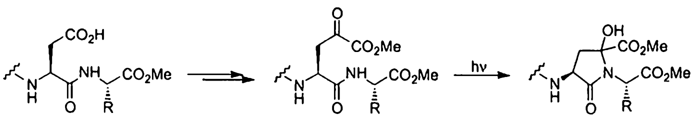
**97**

## A New Photochemical Carbon-Nitrogen Bond Formation: From Aspartic Acids to γ-Lactams

Markus Obkircher, Bernd Giese*

University of Basel, St. Johanns-Ring 19, 4056 Basel, Switzerland

Remarkably often, γ-lactams build up the core of peptide pharmaceuticals because they fix the conformation by β-turns. In previous work, such γ-lactams were formed by irradiation of peptides with a phenyl ketone modification [1]. This modification must be incorporated in the beginning of the synthesis, which is a big disadvantage. In contrast, the α-keto ester modification can be introduced as the last synthetic step into any given peptide that contains an aspartyl moiety **1** [2]. Upon irradiation of the modified peptide **2**, a new photocyclization reaction into the secondary amide was observed forming the γ-lactam **3**.



1 2 3

Right now, we are trying to apply this method to change the secondary structure of oligopeptides from an α-helix to a β-sheet.

[1] C. Wyss, R. Batra, C. Lehmann, S. Sauer, B. Giese, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2529;
[2] H. H. Wasserman, C. M. Baldino, S. J. Coats, *J. Org. Chem.* **1995**, *60*, 8231.

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Organic Chemistry **98**

## 7-Methoxycoumarin-4-yl-methyl (MCM): A New Photochemically Labile Protecting Group for Amines

Ralph O. Schönleber, B. Giese*

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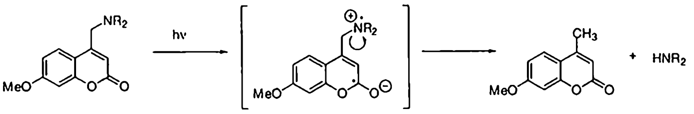
Previous work showed that coumarins are suitable photoactive protecting groups for phosphates, sulfonates and carboxylates [1-3]. We found that coumarinyl-4-yl-methyl groups can also cleave amine bonds via a hitherto unknown mechanism. Photocleavage is a two-step process in which the protected amines are released by photolytic generation of a charge-separated state by photoinduced electron transfer that undergoes spontaneous α-bond scission.



To our knowledge, all photolytical releases of amines occur over the indirect way of carbamates. With our protecting group, a more direct photolytical amine bond cleavage is possible even at wavelengths above 350 nm. The corresponding amines were obtained in good yields.

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[2] B. Schade, V. Hagen, R. Schmidt, R. Herbrich, E. Krause, T. Eckardt, J. Bendig, *J. Org. Chem.* **1999**, *64*, 9109.
[3] R. O. Schönleber, J. Bendig, V. Hagen, B. Giese, *Bioorg. Med. Chem.* **2002**, *10*, 97.

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Organic Chemistry **99**

## Olfactory Profiles of the Lilial Isomers: Synthesis and Evaluation of Enantiopure *meta-t-Butyl*-Lilial

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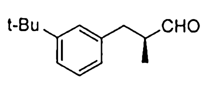
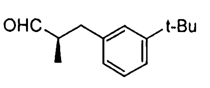
Due to their inherent instability optically active α-methyl-aldehydes are usually converted without elaborated purification into more stable derivatives [1]. The enantiomers of the fragrance classic *para*-Lilial and related olfactorily important α-methyl-aldehydes, however, require much more care during preparation, isolation, storage and evaluation [2].

We prepared both enantiomers of *meta*-Lilial via diastereoselective benzylation of N-propionyl-camphorsultame according to Oppolzer's method [3]. Subsequent reductive cleavage and oxidation furnished the *meta*-Lilial enantiomers with excellent enantiopurity.



(S)-(+)-meta-Lilial.



(*R*)-(-)-meta-Lilial.

R-(+)- and S-(-)-*meta*-Lilial have similar olfactory thresholds but different organoleptic profiles, both belonging to the "Lily-of-the-valley" family. Special measures had to be taken to prevent racemization.

[1] K.C.Nicolaou et al., *J.Am.Chem.Soc.* **1997**, *119*, 7960.
[2] a) D.Enders, H.Dyker, *Liebigs Ann.Chem.* **1990** 1107. b) A.Mosandl et al., J.W.Bats, *Z.Lebensm.Unters.Forsch.A* 1997, *205*, 76. c) A. Pfaltz et al., *Angew.Chem.* 1998, *110*, 3047.
[3] W.Oppolzer et al., Helv.Chimica.Acta. 1997, *80*, 1319.

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Organic Chemistry **100**

## Ir-Catalyzed Asymmetric Hydrogenation: Synthesis and Application of New Heteroaromatic Substrates

Bettina Wüstenberg and Andreas Pfaltz*

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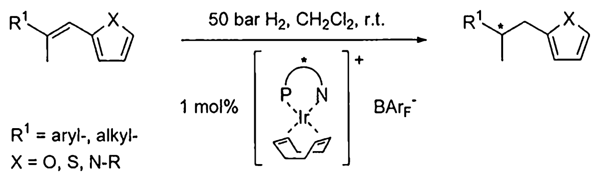
We have previously reported that Ir-complexes of P,N-ligands are efficient catalysts for the asymmetric hydrogenation of unfunctionalized carbon-carbon double bonds [1][2]. In order to increase the variety of different types of substrates, α,β-unsaturated heteroaromatic systems were studied as new target substrates. These trisubstituted alkenes containing one heteroaromatic substituent on the double bond were derived from furan, thiophene and pyrrole and have been prepared in a stereoselective synthesis.



The new substrates have been applied in the Ir-catalyzed hydrogenation with a range of different Ir/BAr$_F$-complexes of achiral and chiral P,N-ligands [3]. The effect of different substituents in R$^1$-position has been investigated as well as the influence of the heteroatom itself and its position in the heterocycle. All the new substrates can be hydrogenated with high conversion and excellent enantioselectivity.

[1] (a) A. Lightfoot, P. Schnider, A. Pfaltz, *Angew. Chem. Int. Ed.* **1998**, *37*, 2897-2899; (b) D.G. Blackmond, A. Lightfoot, A. Pfaltz, T. Rosner, P. Schnider, N. Zimmermann, *Chirality* **2000**, *12*, 442-449.
[2] (a) J. Blankenstein, A. Pfaltz, *Angew. Chem. Int. Ed.* **2001**, *40*, 4445-4447; (b) F. Menges, A. Pfaltz, *Adv. Synth. Catal.* **2002**, *344*, 40-44.
[3] R. Crabtree, *Acc. Chem. Res.* **1979**, *12*, 331-338.

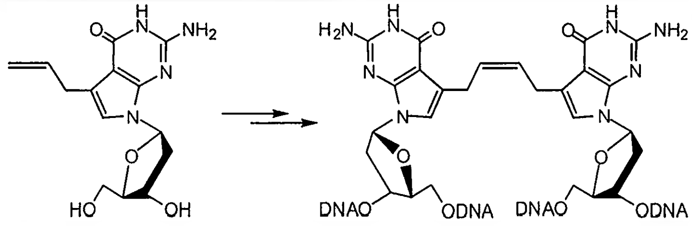
Organic Chemistry **101**

## A Chemical Approach For Investigation Of DNA Interstrand Crosslink Repair

Todor B. Angelov, Orlando Schärer*

Inst. of Medical Radiobiology, University of Zürich, August Forel Str.7,
8008 Zürich, Switzerland

Complementary DNA strands are normally kept together only by intermolecular hydrogen bonds. However some chemicals, among them many widely used anticancer drugs, are able to form covalent bridges between the two DNA strands, which blocks transcription and replication at the damaged sites. Such highly cytotoxic structures, called DNA interstrand crosslinks (ICLs), are removed in human cells, but the mechanism of this repair process and the proteins involved are still unknown. To investigate mammalian DNA ICL repair one needs appropriate substrates – oligonucleotides, containing a single, structurally defined ICL. We designed a method for the synthesis of ICLs that relies on the incorporation of modified nucleotides carrying crosslink precursor groups into complementary DNA strands, followed by catalytic induction of ICL formation. The implementation of this approach using 7-allyl- and 7-vinyl-7-deazaguanosine as crosslink precursors and the formation of ICLs using olefin metathesis will be presented. As aliphatic double bonds are not present in DNA, the olefin metathesis reaction proved to be highly specific. We are now using these synthetic ICLs to investigate ICL repair in mammalian cells using biochemical and cell biological methods.



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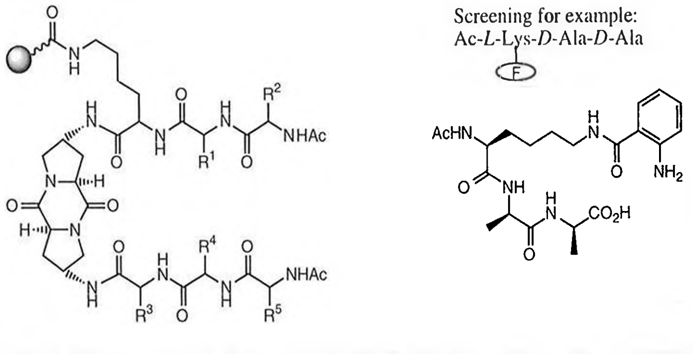
Organic Chemistry **102**

## Synthesis and Screening of a Diketopiperazine Receptor Library

Matteo Conza and Helma Wennemers*

Institute of Organic Chemistry, University of Basel
St. Johanns Ring 19, CH-4056 Basel

We have recently developed the class of two-armed diketopiperazine receptors that are able to bind to small peptides with high sequence selectivity.[1,2] These receptors consist of a rigid, structure-directing diketopiperazine backbone and two tripetides as receptors arms. Combinatorial variation of the aminoacids of the two tripeptidic arms offer the possibility of structural and functional differences. We will present the synthesis of an approximately 33.600 membered diketopiperazine receptor library and its screening against fluorophor-marked target molecules.


Screening for example:
Ac-*L*-Lys-*D*-Ala-*D*-Ala

[1] H. Wennemers, M. Conza, M. Nold, P. Krattiger, *Chem. Eur. J.* **2001**, *7*, 3342

[2] M. Conza, H. Wennemers, *J. Org. Chem.* **2002**, *67*, 2690.

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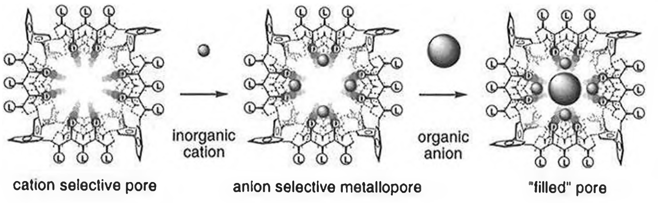
Organic Chemistry **103**

## Practical Fluorimetric Sensing Applications of Rigid-Rod β-Barrel Ion Channels

G. Das, P. Talukdar, N. Sakai, and S. Matile*

University of Geneva, Department of Organic Chemistry
1211 Geneva, Switzerland

The transformation of cation selective, doubly pH-gated pores formed by synthetic *p*-octiphenyl β-barrels [1] with internal aspartates [2] into anion permeable metallopores with internal $Mg^{2+}$-aspartate complexes which, in turn, can bind of a broad variety of organic anions including phytate ($IP_6$), heparin, thiamine phosphate and pyrophosphate, $P_i$, PP, polyphosphate, AMP, ADP, ATP, α-D-glucose 1,6-diphosphate, G-6-P, G-1-P, D-fructose 1,6-diphosphate, poly((4-phosphonophenyl)acetylene) and pyrene-1,3,6,8-tetrasulfonate will be described [3]. Practical applications toward non-invasive fluorimetric sensing will be discussed.



[1] S. Matile, *Chem. Soc. Rev.* **2001**, *30*, 158.

[2] G. Das, S. Matile, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 5183.

[3] G. Das, P. Talukdar, N. Sakai, S. Matile, unpublished results.

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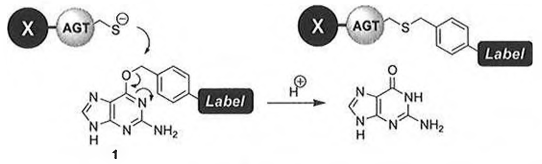
Organic Chemistry **104**

## Specific and covalent labeling of alkyltransferase fusion proteins in living cells

Susanne Gendreizig, Antje Keppler, Kai Johnsson*

Institute of Molecular and Biological Chemistry, EPFL, Switzerland

Here we present a new method for studying and manipulating proteins in living cells by labeling them specifically and covalently *in vivo* with small, synthetic molecules. The idea relies on the unusual repair mechanism of the $O^6$-alkylguanine-DNA alkyltransferase (AGT) [1]. This protein transfers the alkyl group from its substrate $O^6$-alkylguanine to its own reactive cysteine residue, leading to irreversible formation of stable *S*-alkylcysteine and thus inactivation of the enzyme. Beside alkylated DNA-molecules the AGT reacts rapidly with the small, cell-permeable molecule $O^6$-benzylguanine (BG) and accepts furthermore substitutions at the C4 position of BG derivatives [2]. This enables us to use cell-permeable BG derivatives **1** to transfer a label to AGT or AGT-X fusion proteins *in vivo* (X being any protein, label being e.g. biotin, digoxigenin or fluorescein).



This technique can be used to specifically label recombinant AGT or AGT-X fusion proteins expressed in bacteria, yeast or mammalian cells and to investigate the AGT fusion protein in the living cell.

[1] A.E. Pegg, *Mutat. Res.* **2000**, *462*, 83.

[2] R. Damoiseaux, A. Keppler, K. Johnsson, *ChemBioChem*, **2000**, *4*, 285.

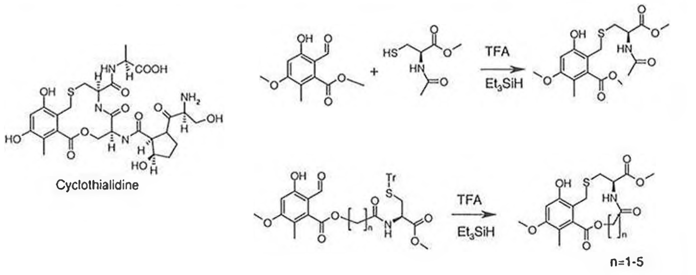
Organic Chemistry **105**

### Inter- and Intramolecular Reductive Thiolation of Aromatic Aldehydes: Application to the Concise Synthesis of Cyclothialidine Analogs

P.Hebeisen, J.Geiwiz and E.Goetschi

Pharma Division, Discovery Research, F. Hoffmann-La Roche Ltd.,
CH-4070 Basel, Switzerland

The DNA gyrase inhibitor cyclothialidine [1] was shown to be an interesting lead structure for the search of new antibacterials. During extensive SAR work [2] it was demonstrated that variation of the lactone ring size of its bicyclic core was tolerated. Indeed even *seco*-analogs exhibited DNA gyrase inhibitory activity. These derivatives were conveniently synthesized by a novel reductive thiolation approach. Application of this methodology to cyclic systems established an alternative concise and flexible synthetic access to congeners of cyclothialidine with varying ring size which so far had been prepared by lactonization of the corresponding *seco*-acids.



[1] J. Watanabe, N. Nakada, S. Sawairi, H. Shimada, S. Ohshima, T. Kamiyama, and M. Arisawa, J. Antibiotics **47**, 32-6 (1994).
[2] J. Geiwiz, E. Goetschi, P. Hebeisen, H. Link, T. Luebbers, *Pat. App.* No. EP95/675122 (1995).

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Organic Chemistry **106**

### A Crown-Capped Iron Porphyrin Mimicking the Resting State of Cytochrome P450$_{cam}$

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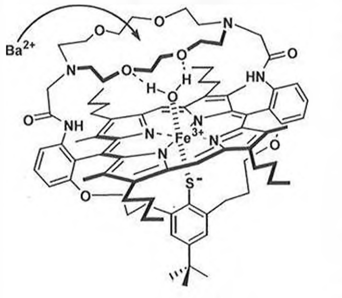
University of Basel, Institute of Organic Chemistry, St. Johanns-Ring 19,
4056 Basel, Switzerland

The crystal structure of the resting state of cytochrome P450$_{cam}$, a heme-thiolate protein, revealed a water cluster of six $H_2O$'s in the substrate binding pocket [1], one of which is coordinating to iron(III). The resting state is low-spin and changes to a high-spin system when the substrate camphor binds and $H_2O$ is removed. Concomitantly $E_o$ shifts cathodically rendering the Fe(III) reducible to Fe(II). Thus spin state changes are significant regulating the catalytic cycle of P450 and furthermore are assumed to trigger the mode/reactivity of oxygen insertion by $O{=}Fe(IV)(porph^{+\bullet})\cdots S^-$ (Cpd I) [2]. In contrast to the protein, enzyme models having a coordination $H_2O\cdots Fe(III)porph\cdots S^-$ have been shown to be high-spin [3]. We assume that this discrepancy is due to unidentified effects in the native protein: i) an electric field component of the protein and, or ii) an $HO^-$ character of the coordinating $H_2O$ due to H-bonding. Complex **1** has been prepared and investigated to study these effects.



**1**

[1] T. L. Poulos, B. C. Finzel, A. J. Howard, *Biochemistry* **1986**, *25*, 5314
[2] F. Ogliaro, N. Harris, S. Cohen, M. Filatov, S. de Visser, S. Shaik, *J. Am. Chem. Soc.* **2000**, *122*, 8977.
[3] H. Aissaoui, R. Bachmann, A. Schweiger, W.-D. Woggon, *Angew. Chemie* **1998**, *110*, 3191.

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Organic Chemistry **107**

### Conformational Studies on Proline-Diketopiperazines: Implications for the Binding Properties of Two-armed Diketopiperazine Receptors

Matthias Nold, Matteo Conza and Helma Wennemers*

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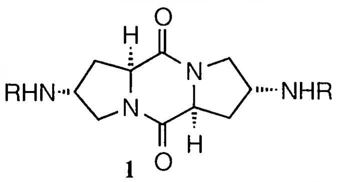
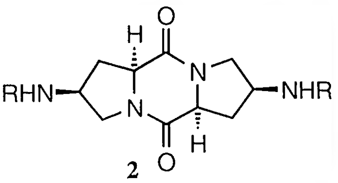
Recently we introduced the class of diketopiperazine receptors that consist of a rigid, structure directing diketopiperazine backbone bearing two peptidic arms.[1] The binding properties of the receptors towards peptides showed a high dependence on the configuration of the diketopiperazine. Namely the replacement of the *trans,trans*-diketopiperazine template **1** by the diastereomeric *cis,cis*-template **2** resulted either in different, yet quite similar peptide binding selectivities, or in some cases in a complete loss of binding ability towards peptides. Prompted by these results we analyzed the conformations of several diastereomeric aminoproline derived diketopiperazines by NMR-spectroscopy in solution as well as by crystal structure analysis in the solid state.[2]



**1**



**2**

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[1] a) H. Wennemers, M. Conza, M. Nold, P. Krattiger, *Chem. Eur. J.*, **2001**, *7*, 3342; b) M. Conza, H. Wennemers, *J. Org. Chem.* **2002**, *67*, 2690.
[2] H. Wennemers, M. Nold, M. Conza, *submitted*

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Organic Chemistry **108**

### A Synthetic Approach to the Products of Chlorophyll Breakdown in Higher Plants

Michael Oberhuber, Joachim Berghold and Bernhard Kräutler

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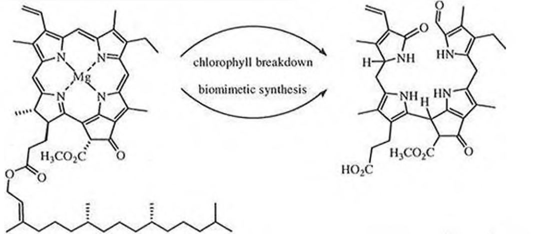
Innrain 52a – 6020 Innsbruck – Austria

When in autumn the green color of the leaves fades and bright red and yellow take its place, nature shows one of its most manifest phenomena. Nevertheless the autumnal disappearance of chlorophyll has remained enigmatic until the last decade. The most widely found breakdown products of chlorophyll could be identified as colorless linear tetrapyrroles, the so-called non-fluorescent chlorophyll catabolites (NCCs, see figure). Minute samples of several NCCs, closely related in structure, could be isolated from various plant sources. However, further chemical and mechanistic studies on the relevant catabolic transformations and intermediate products are limited by the availability material. Here we report on the first synthetic route to NCCs, which follows aspects of the presumed catabolic pathway and yielded some products of chlorophyll breakdown. The biomimetic character of this approach enabled us to gain further insight into the mechanisms of some key steps in chlorophyll breakdown.



chlorophyll a

a colorless chlorophyll catabolite (NCC)

Supported by the Austrian National Science Foundation (project no. 13505).

Organic Chemistry

**109**

### New ways to share and process chemical information over the internet

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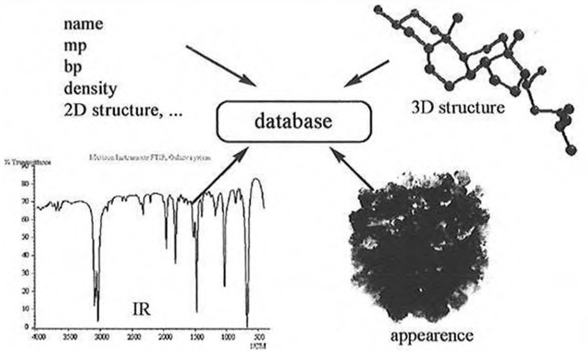
Various types of chemical information are available either in the research laboratory, on the internet or in commercially available databases. However, there is currently no freely available database on the internet where anybody can easily contribute.

Here we present an evolving database that allows anyone at any time to add new chemicals with their physical characteristics directly from a web-browser. In this database one can store anything from boiling points and melting points to NMR spectra, IR assignments, etc. Moreover it is possible to define at any time new analytical categories like the colour of the product with a corresponding picture for instance.

Providing the tool to store any kind of information to researchers all over the world is a first milestone. Even if usual queries are available, we will also present some perspectives in the search possibilities based, for example, on genetic algorithms using a user-friendly interface.



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Organic Chemistry

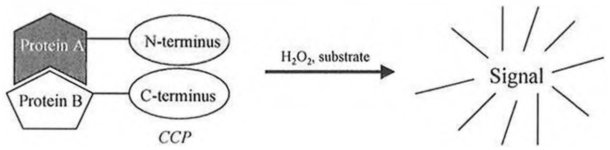
**110**

### Development of a Cytochrome *c* Peroxidase – based Reporter System for Monitoring Protein-Protein Interactions

Petra Tafelmeyer, Kai Johnsson*

Institute of Molecular and Biological Chemistry, EPFL, Switzerland

Here, I propose the development of a new system for the detection of intra- and extracellular interactions of proteins using Split-Cytochrome *c* peroxidase (CCP) as a signal protein [1]. In general, the putative interacting proteins A and B are genetically fused to two non functional fragments of the signal protein CCP. Upon interaction of the proteins A and B, a functional peroxidase is formed due to the proximity of its fragments.



Reconstituted CCP can be identified using a simple colony screen, based on the intensely colored, fluorescent or chemiluminescent products or byproducts of various peroxidase substrates. The advantage of this system would be its expected high sensitivity and its independence of cell type and compartment, compared to the yeast two-hybrid system, which is considered as a benchmark for studying protein-protein interactions, but is confined to the cell nucleus [2]. Of particular interest would be the use of this system outside of the cytoplasm, for example monitoring protein-protein interactions on the surface of a cell or in the periplasm of *E. coli*.

[1] T. L. Poulos, J. Kraut, *J. Biol. Chem.* **1980**, *255*, 8199.
[2] S. Fields, O. Song, *Nature* **1989**, *340*, 245.

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Organic Chemistry

**111**

### Central-to-Axial Chirality Transfer under Kinetic and Thermodynamic Conditions: Preparation of Either Atropisomer of Configurationally Stable Allocolchicinoids

Andrei V. Vorogushin[a,b], William D. Wulff[a], Hans-Jürgen Hansen[b]

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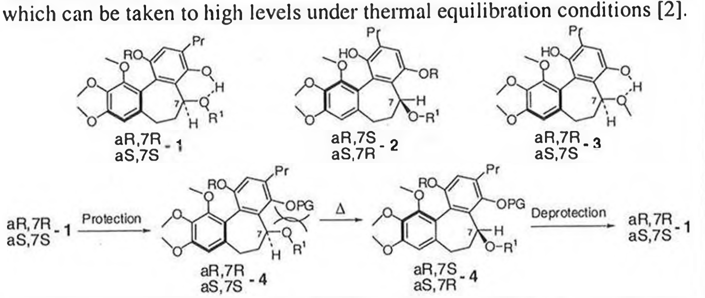
Configurationally stable allocolchicinoids [1] of type **1** are prepared from the Fischer carbene complexes and 1-pentyne with high to complete (85-100% de) diastereoselectivity. Analogous reaction with regioisomeric carbene complexes gives **2** with low to moderate (33-54% de) selectivity, which can be taken to high levels under thermal equilibration conditions [2].



Unexpectedly, opposite (aR,7R; aS,7S) atropisomer of **3** is strongly favored under thermodynamic conditions, which is likely due to the intramolecular hydrogen bonding stabilization. Because of the same effect, epimerization of (aR,7R; aS,7S)-**1** doesn't afford the opposite atropisomer (aR,7S; aS,7R)-**1**. Instead, it can be selectively prepared via **4** using protection – epimerization – deprotection routine.

[1] Vorogushin, A. V.; Wulff, W. D.; Hansen, H.-J. *Org. Lett.* **2001**, *3*, 2641.
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Organic Chemistry

**112**

### Preparation and Spectroscopic Properties of Pyrenyl-Modified Oligonucleotides as Models for Electron Injection into DNA

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Hans-Achim Wagenknecht*

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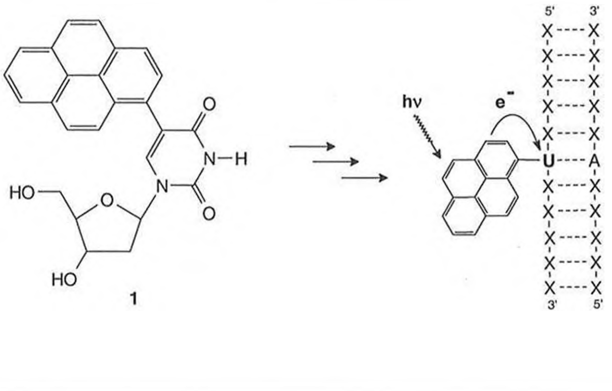
With respect to the biological relevance of DNA-charge migration, in most of the past experiments oxidative hole transfer processes have been observed resulting in oxidative guanine damage at distant sites on the nucleic acid. In contrast, reductive electron transfer through DNA duplexes is currently used extensively in DNA chip technology without understanding the mechanism of this type of charge transfer. Until now, suitable assays for the spectroscopic investigation of reductive electron transfer are elusive.

We want to present here the design, synthesis and spectroscopic properties of pyrenyl-modified nucleosides, such as **1**, and the incorporation into DNA duplexes via phosphoramidite chemistry. The nucleosides and oligonucleotides were investigated by steady-state fluorescence and femtosecond time-resolved transient absorption spectroscopy in order to elucidate the properties and dynamics of the intramolecular electron transfer and to address important key questions concerning electron injection into DNA, such as base sequence dependence and coupling to protonation.



Organic Chemistry **113**

### Binding of Ortho-Vanadate Anion: Towards Mimics of Vanadium Haloperoxidase (VHPO)

Xiao-an Zhang, Gerd Scherer, Wolf-D. Woggon*

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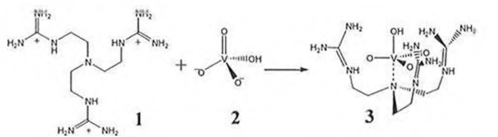
VHPO's are enzymes which are capable of halogenating a variety of organic compounds using hydrogen peroxide and halide ions as substrates. The X-ray structure of VHPO from *Curvularia inaequalis* reveals that the positively charged residues at the active site bind the orthovanadate through electronic interaction and hydrogen bonds, together with one coordinating bond from the nitrogen (NE2) of histidine 496 to vanadium. To reveal the detailed mechanism of this enzyme, it is necessary to build a model which can provide a similar binding fashion.

The vanadate receptor tris-(2-guanidinium-ethyl)amine **1** was synthesized from tris-(2-aminoethyl)amine. Its three guanidium arms can not only provide positive charges but are also hydrogen bond donors. The central nitrogen with pKa=2.48 allows the V-N coordination to accur within a broad pH window.



1 2 3

NMR titration data from $^{51}$V of vanadate and $^{1}$H of the ligand give complementary results. The ligand **1** binds vanadate **2** as 1/1 complex (see **3**) at pH 10.21 in water solution, with $K_{ass} = 10^3$ $Mol^{-1}$ . The absorption at 306 nm (UV difference spectrum) is an indication of a V-N bond in agreement with coordination in VHPO.

[1] Albrecht Messerschmidt and Ron Wever, *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 392

[2] Rokus Renrie, Wieger Hemrika, Sander R. Piersma, and Ron Wever, *Biochem.* **2000**, 39, 1133

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Organic Chemistry **114**

### Esca and Related Wood Necrosis Deseases Caused by Fungal Toxins on Grapevine

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CH-2007 Neuchâtel, Switzerland

The biological aspects of esca have been extensively investigated during the last decade in several grape-growing countries [1][2][3]. Contrary to other fungal wood diseases, which are caused by a single pathogen, esca results from the association of different fungi that act in a concomitant association or in a successive invasion by different microorganisms in the woody tissues. Two species of mitosporic fungi *Phaeomoniella chlamydospora* (*Pch*) and *Phaeoacremonium aleophilum* (*Pal*) cause the internal brown wood-streaking of branches and trunk and are considered the causal agents of a decline of young grapevines previously named "black goo" and now also known as "Petri grapevine decline". A third fungus that has a primary role in esca is the basidomycete *Fomitiporia punctata* (*Fop*). This fungus is responsible for the white rot of vine wood. The aim of this study is to characterise the secondary metabolites of *Pal* and *Fop* involved in the symptom expression of infected grapevines and to investigate the defence mechanism induced by the plants against biotic toxins.

[1] L. Mugnai, A. Graniti, G. Suricco, *Plant Disease.* **1999**, *30*, 5, 1111.

[2] P.Larignon, B. Dubos, *Eur. J. Plant Pathol.* **1997**, *103*, 147.

[3] J. Ascuna, J. Feliciano, W. D. Gubler, *Phytopathologia Mediterranea,* **2001**, *40*, S387.

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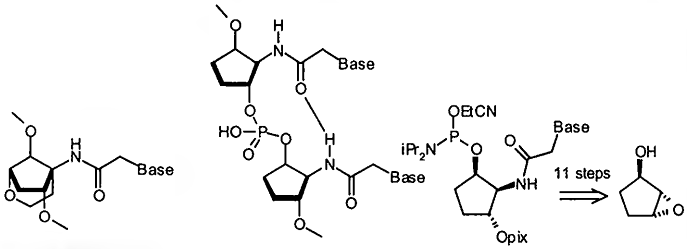
Organic Chemistry **115**

### CPA-DNA and Its Biophysical Properties

Dae-Ro Ahn, Markus Mosimann, Christian Leumann*

Department of Chemistry and Biochemistry, University of Bern, Freiestrasse 3, CH-3012 Bern, Switzerland.

Bicyclo[3.2.1]amide-DNA was designed to evaluate the effect of flexibly attached bases with an extended distance (4 instead of 3 bonds) between the base and the backbone unit [1]. Along these lines we have now investigated the cyclopentane amide-DNA (CPA-DNA) **3** from which we expect an additional favorable contribution to single-strand preorganization by interresidue hydrogen-bond formation. Starting from the known compound **1** [2], we synthesized the phosphoramidite building blocks **2** in enantiomerically pure form in 11 steps. These units were converted into oligonucleotide analogues and their complementary pairing behavior with DNA, RNA and with itself, characterized by UV-melting curves and CD-spectroscopy.



**Bicyclic [3.2.1]amide nucleotide** **3** **2** **1**

[1] Egger, A.; Leumann, C. *Synlett*, **1999**, 913-916

[2] Kawakami, T.; Shibata, I.; Baba, A.; Matsuda, H. *J.Org.Chem.* **1993**, 7608-7609

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Organic Chemistry **116**

### Synthesis and investigation of new disc-shaped conducting supramolecules

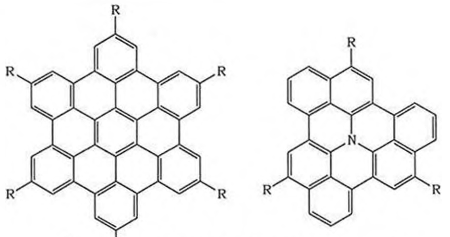
B. Alameddine, T.A. Jenny (Chemistry Department)
P. Ruffieux, O. Groening, P. Groening
and L.Schlapbach (Physics Department)

University of Fribourg, 1700 Fribourg, Switzerland

Self-assembled organic molecules have gained a lot of interest in the last two decades among others in the field of luminescence and electron emission phenomena. Such properties could be applied in the domain of materials for the fabrication of low cost flat panel displays.

The basic idea implies the deposition of large aromatic disc shaped molecules that self assemble by π-π stacking into column like ordered structures on a suitable electrode surface. Side chains are introduced to enhance solubility and stacking properties.

In extension to the known hexa-*peri*-benzocoronene (HBC) [1] system (**1**) a synthesis of the hitherto unknown nitrogen containing system **2** was devised. The trinaphthocyclazine system (**2**) is expected to show improved columnar conductivity as compared to the HBC due to lower oxidation and reduction potentials.



**1** R= alkyl. p-$C_6H_4$-alkyl,... **2**

1. J. M. W. A. M. Van de Craats, K. Müllen, Y. Geerts, J.D. Brand, *Adv. Mater.* **10**, 36 (1998).

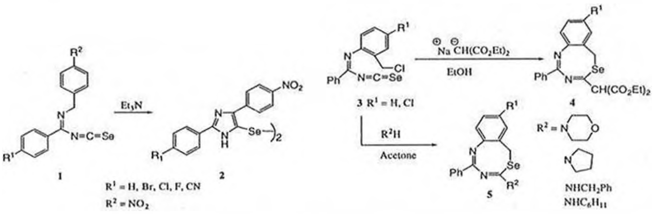
Organic Chemistry **117**

### Synthesis of Bis(2,4-diarylimidazol-5-yl) Diselenides and 6*H*-5,1,3-Benzoselenadiazocines from Imidoyl Isoselenocyanates

P. K. Atanassov, A. Linden and H. Heimgartner*

Institute of Organic Chemistry, University of Zurich
Winterthurerstrasse 190, CH-8057 Zurich

Isoselenocyanates have been used as convenient precursors for the synthesis of selenium-containing heterocycles and diselenides [1, 2, 3]. The reaction of isoselenocyanates **1** with $Et_3N$ yielded bis(imidazol-5-yl) diselenides **2**. Treatment of isoelenocyanates **3** with the sodium salt of diethyl malonate yielded diethyl 2-phenyl-6*H*-5,1,3-benzoselenadiazocin-4-yl)malonates **4**. When **3** was treated with primary and secondary amines, 4-aminobenzoselenadiazocines **5** were formed. The structures of **2**, **4**, and **5** were established by X-ray crystallography. The influence of the substituents upon the formation of the diselenides and ring closure reactions will be discussed.



[1] Y. Zhou, H. Heimgartner, *Helv. Chim. Acta*, **2000**, *83*, 539-553.
[2] Y. Zhou, H. Heimgartner, *Helv. Chim. Acta*, **2000**, *83*, 1576-1597.
[3] P. K. Atanassov, Y. Zhou, A. Linden, H. Heimgartner, *Helv. Chim.Acta*, **2002**, *85*, 1102-1117.

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Organic Chemistry **118**

### Diastereoselective 1,5-Hydrogen Abstraction

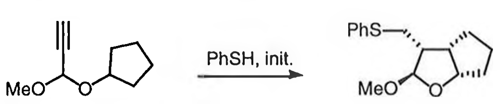
Florent Beaufils and Philippe Renaud

*Universität Bern, Departement für Chemie und Biochemie*
*Freiestrasse 3, CH-3000 Bern 9*

Isolated cases of 1,5-hydrogen transfer promoted by β-sulfanylalkenyl radicals

have been reported [1]. The stereoselectivity of these processes has never been investigated in a systematic way [2].

We present here a systematic investigation of diastereoselective 1,5-hydrogen atom transfers starting from alkyne acetals. The stereochemistry of the processis controlled by the acetal center.



[1] L. Capella, P.C. Montevecchi, M.L. Navacchia *J. Org. Chem.* **1996**, *61*, 6783.
[2] For an exception, see: C.Imboden, F. Villar, P.Renaud, *Organic Lett.* **1999**, *1*, 873.

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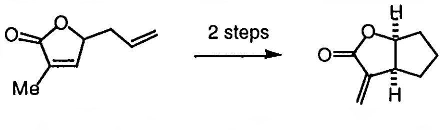
Organic Chemistry **119**

### A Novel Route to Bicyclic α-Methylene Lactones

Barbara Becattini and Philippe Renaud*

University of Bern, Department of Chemistry and Biochemistry,
Freiestrasse 3, 3012 Bern

Bicyclic α-methylene lactones represent an interesting structural motif that can be found in the skeleton of several natural products. A one-pot procedure involving hydroboration of γ-alkenyl-γ-lactones followed by intramolecular conjugate addition [1] delivers in moderate to good yields the bicyclic thiopyridyl adducts that can easily be converted into α-methylene lactones.



[1] C. Ollivier, P. Renaud, *Chem. Eur. J.* **1999**, *5*, 1468,
C. Ollivier, P. Renaud, *Angew. Chem. Int. Ed.* **2000**, *39*, 925.

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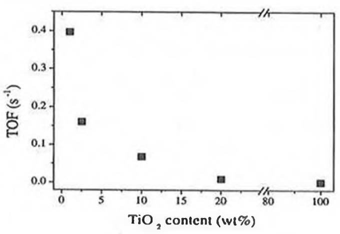
Organic Chemistry **120**

### Chemo-, Regio- and Stereoselective Epoxidation of Allylic Alcohols as a Probe for the Structure of Titania-Silica

C. Beck, T. Mallat, and A. Baiker*

Laboratory of Technical Chemistry, Swiss Federal Institute of Technology,
ETH Hönggerberg, CH-8093 Zürich



Mesoporous titania-silica aerogels are highly active and selective epoxidation catalysts [1], offering an efficient alternative to the conventional titania-on-silica and Ti-substituted zeolites. Despite the substantial effort in the past years, involving a broad range of spectroscopic methods [2], the real nature of the (various) active sites in the complex sol-gel materials remained mainly unknown. To reveal the correlation between the structural and catalytic properties, we synthesized titania-tilica aerogels in the whole concentration range. The structural changes, shown by the spectroscopic methods (BET, UV-Vis DRS, DRIFT, CP/MAS-NMR, XPS, EXAFS), are also reflected by the catalytic performance in the epoxidation of allylic alcohols: a dramatic decrease in specific activity and epoxide selectivity with increasing Ti-content (Figure). Based on the spectroscopic and catalytic results, the active Ti-sites in sol-gel mixed oxides consist of the whole range of possible Ti-O-Si and Ti-O-Ti connections, approaching isolated tetrahedral Ti in the silica matrix with decreasing Ti-content.

[1] Dusi, M., Mallat, T., Baiker, A., *Catal. Rev.- Sci. Eng.* **2000**, *42*, 213.
[2] Gao, X., Wachs, I. E., *Catal. Today* **1999**, *51*, 233.

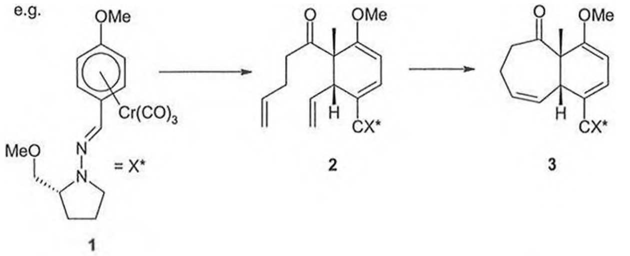
Organic Chemistry **121**

## A Rapid and Efficient Access to Enantiomerically Highly Enriched Fused Ring Compounds

Alejandro Bellido, Krishna P. Kaliappan, Andrew R. Pape,
Sylvie Radix, E. Peter Kündig*

University of Geneva, Department of Organic Chemistry,
30 Quai Ernest Ansermet, CH-1211 Geneva 4, Switzerland

Asymmetric routes to fused rings with quaternary stereogenic centers are of interest for natural product synthesis. Here we present a new, efficient way to obtain *cis*-fused bicyclic [6,5], [6,6], [6,7], and [6,8] ring compounds (e.g. **3**) from arene precursors via metal mediated dearomatization [1] followed by ring closing metathesis (RCM). The use of chiral auxiliaries (SAMP/RAMP hydrazones, chiral oxazolines) gives the intermediate substituted cyclohexadienes (e.g. **2**) with generally very high diastereoselectivity [2].



[1] A. R. Pape, K. P. Kaliappan, E. P. Kündig, *Chem. Rev.* **2000**, *100*, 2917.
[2] G. Bernardinelli, S. Gillet, E. P. Kündig, R. Liu, A. Ripa, L. Saudan, *Synthesis*, **2001**, *40*, 2040.

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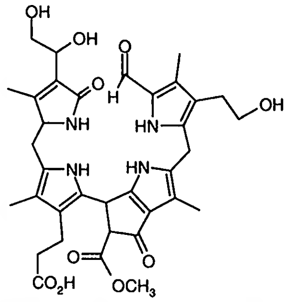
Organic Chemistry **122**

## Chlorophyll Breakdown in Spinach

Joachim Berghold[1], Kathrin Breuker[1], Michael Oberhuber[1],
Stefan Hörtensteiner[2], and Bernhard Kräutler[1]

[1] Institute of Organic Chemistry, Leopold-Franzens-Universität Innsbruck, Austria;
[2] Institute of Plant Sciences, Universität Bern, Switzerland

Nonfluorescent chlorophyll catabolites (NCC's) appear to be the final products of chlorophyll breakdown in senescent higher plants.
In extracts of degreening leaves of spinach (*Spinacia oleracea*), five colourless compounds with UV/Vis- characteristics of NCC's were separated by reversed phase HPLC. The catabolites, tentatively named *So-NCCs*, were isolated and purified by preparative HPLC, and the constitution was determined by spectroscopic means. The spectroscopic data were compared with those of natural NCC's from other sources
For example, the main catabolite in spinach (*So-NCC-2*) was formed to be the C1–epimer of *Hv-NCC-1*, the only structurally characterized NCC from barley (*Hordeum vulgare*).



So-NCC-2

Supported by the Austrian National Science Foundation (project13503)

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Organic Chemistry **123**

## Wavelength-controlled selective deprotection of functional groups

Aurélien Blanc and Christian G. Bochet*

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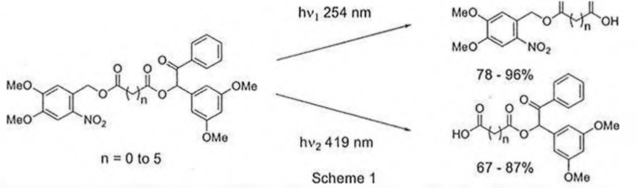
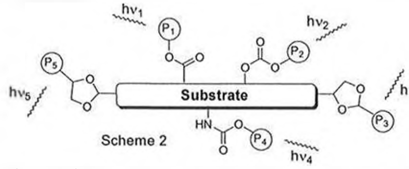
Quai Ernest-Ansermet 30, CH-1211 Genève 4

The selective activation of a functional group in presence of others is a key issue in organic synthesis. This work describes the use of light to release a desired functional group. The different groups are specifically addressed by using different wavelengths. This strategy was applied to photochemically removable protecting groups[1] and could be illustrated by the orthogonal photochemical deprotection of diacids using monochromatic light[2,3] (Scheme 1). Hence we replaced the traditional *chemical* orthogonality by a *chromatic* orthogonality.



Scheme 1

This concept could be extended to the protection of other functional groups: amines (as carbamates), alcohols (as carbonates), diols or carbonyl groups (as acetals) (Scheme 2).



Scheme 2

[1] Bochet, C. G. *J. Chem. Soc., Perkin Trans. 1*, **2002**, 125-142.
[2] Bochet, C. G. *Angew. Chem. Int. Ed.*, **2001**, *40*, 2071-2073.
[3] Blanc, A.; Bochet, C. G. *J. Org. Chem.*, **2002**, in press.

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Organic Chemistry **124**

## A Stable DNA-Duplex Containing a Non-Hydrogen-Bonding and Non-Shape-Complementary Base Couple: Interstrand Stacking as the Stability Determining Factor

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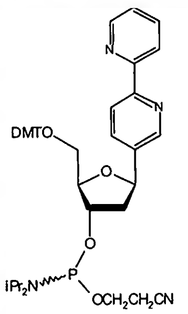
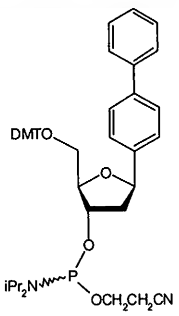
Department of Chemistry and Biochemistry, University of Bern,
Freiestrasse 3, 3012 Bern (Switzerland)

We describe the synthesis and the incorporation into oligonucleotides of the novel nucleoside building blocks **1** and **2**, carrying non-hydrogen-bonding, non-shape complementary bases. The base-modified nucleoside **1** was conceived to coordinate transition metal ions into well defined positions within a DNA double helix. Melting experiments revealed that the stability of a dBP:dBP base couple in a DNA duplex is similar to a dG-dC base-pair even in absence of transition metal ions. Since the dBP-base couple is unable to perform hydrogen-bonding, the gain in stability was initially assigned to interstrand stacking of the BP-bases[1]. On this poster we provide further experimental evidence that interstrand stacking indeed determines duplex stability in the case of non-hydrogen-bonding, non-shape-complementary-base-pairs.



1
(dBP)



2

[1] C. Brotschi, A. Häberli, C. J. Leumann; *Angew. Chem. Int. Ed.* **2001**, *40*, No.16, 3012-3014

Organic Chemistry **125**

## Dehydration of Hydroxenin Monoacetate in the Presence of Ultrasound

Fabrice Aquino, Werner Bonrath*

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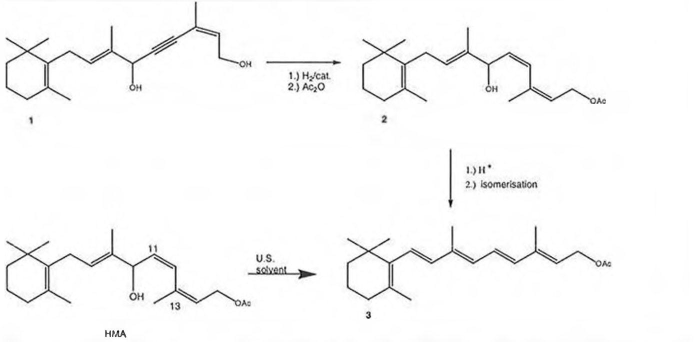
*E/Z*-Isomers of polyenes, e.g. carotenoids, are of great interest. The various reactions used for the construction of double bonds in the synthesis of the carotenoid skeleton result in (*E/Z*)-mixtures [1]. (all-*E*)-Retinyl acetate **3** is obtained after hydrogenation of the triple bond in **1** to give the (11*Z*, 13*Z*) compound, acetylation of the primary hydroxyl group, and acid catalyzed dehydration with isomerisation of the double bond into the *E* configuration [2].



Here we describe our results obtained in the *E/Z*-isomerisation of hydroxenin monoacetate (HMA, **2**) under ultrasound irradiation.

We found that in trichloromethane at 40° C HMA could be dehydrated to an *E/Z* mixture of vitamin A acetate. Without ultrasound or in other solvents the starting material remained unchanged.

### References

[1] K. Bernhard, S. Liaaen-Jensen, in 'Carotenoids', Vol. 2, Birkhäuser Verlag Basel, p. 217, 1996.
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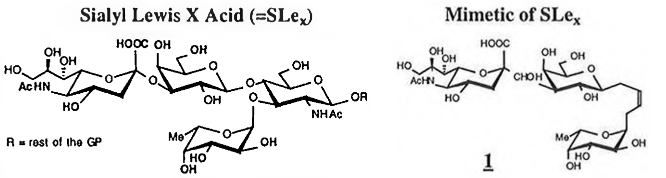
Organic Chemistry **126**

## Toward the Synthesis of a Non-hydrolysable Mimetic of Sialyl Lewis X Acid

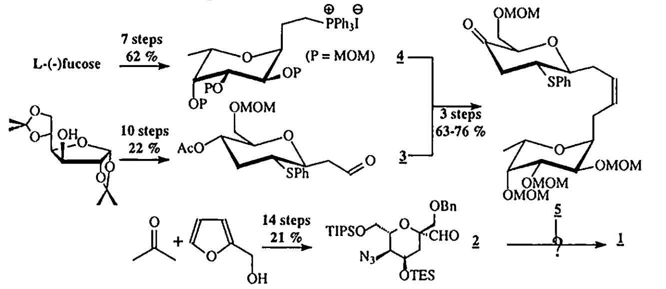
Frédéric Carrel, Pierre Vogel

ICMB, EPFL, BCH, CH-1015 Lausanne-Dorigny

Our target mimetic of Sialyl Lewis X Acid is compound **1** and analogues in which all glycosidic bridges are substituted by carbon bridges.



Our approach is based on a Wittig olefination between **3** and **4**, followed by a cross-aldolisation using **2**.



Work is underway to graft intermediates **5** and **2** through a cross-aldolisation following the Traxler-Zimmermann model.

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Organic Chemistry **127**

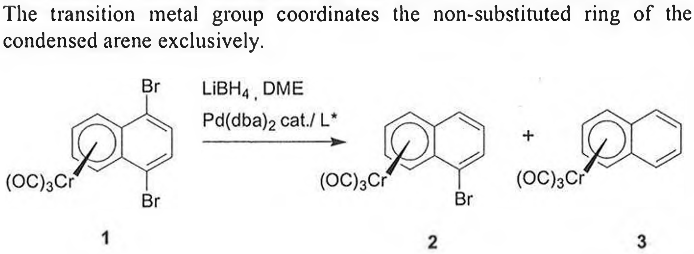
## Catalytic Enantioselective Desymmetrization of [((1-4,4a,8a-η)-5,8-Dibromonaphthalene) tricarbonylchromium(0) Complex

Piyali Datta Chaudhuri, David House and E.Peter. Kündig*

University of Geneva, 24 Quai E. Ansermet, CH-1211 Geneva 4

As part of our program on the use of [(arene)Cr(CO)$_3$] complexes in asymmetric organic synthesis we are interested in the preparation of enantiomerically enriched planar chiral complexes.[1] This contribution reports on our progress towards the synthesis of planar chiral naphthalene complexes via desymmetrization [2] of a meso-complex.

We have found that complexation of 1,4-dihalonaphthalenes to the electrophilic Cr(CO)$_3$ auxiliary provides a single regioisomer in high yield. The transition metal group coordinates the non-substituted ring of the condensed arene exclusively.



Desymmetrization of the title complex **1** to the mono bromo complex **2** via Pd catalyzed hydrogenolysis will be detailed with a comparison of the efficiency of a number of catalyst precursors / chiral ligand combinations.

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[2] (a) M. Uemura, H. Nishimura, *Tetrahedron Lett.*, **1993**, *34*, 107.
(b) B. Gotov, H.-G. Schmalz, *Org. Lett.*, **2001**, *3*, 1753.

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Organic Chemistry **128**

## Route to a Biosensor - Synthesis of Functionalized Pyrroles

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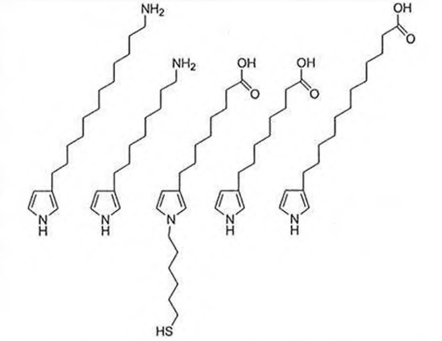
a) Department of Chemistry and Biochemistry, University of Bern, Freiestrasse 3, CH-3012, Switzerland
b) Department of Chemistry and Biochemistry, Faculty of Sciences, University of Lisbon, Campo Grande, 1749 -016 Lisboa, Portugal

The immobilization of a variety of different biological materials in electropolymerized films has become an increasingly important route for the development of biosensors [1]. One way to build a modified electrode involves the formation of a conducting polymer on the surface of the electrode by the electrochemical oxidation of a suitable monomer.

The four monosubstituted pyrrole derivatives shown in the figure were prepared from pyrrole and are suitable monomer for the construction of modified electrodes [2]. A new synthetic approach to 3-amino alkylpyrroles was developed and the method was extended to prepare the N-substituted pyrrole. The introduced funtionalization should improve the enzyme attachment and the biosensor efficiency.



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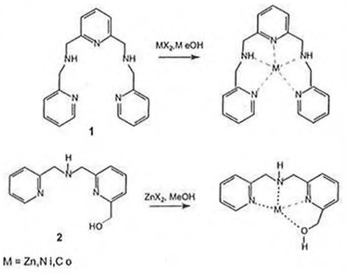
Organic Chemistry **129**

### Synthesis of zinc-, nickel- and cobalt-complexes with multidentate nitrogen ligands: New catalysts for Aldol reactions

Tamis Darbre*[a], Christian Dubs[a], Miguel Machuqueiro[a], Eduard Rusanov[b] and Helen Stoeckli-Evans[b]

a) Department of Chemistry and Biochemistry,Univ ersity of Bern, Freiestrasse 3, CH-3012, Switzerland.
b) Institut of Chemistry,Univ ersity of Neuchâtel, Avenue de Bellevaux 51, 2007 Neuchâtel, Switzerland

The ligands 2,6-Bis[((2-pyridylmethyl)amino) methyl]pyridine with a $N_5$ pattern and (6-{[Pyridin-2-ylmethyl)-amino]-methyl}-pyridin-2-yl)-methanol with a $N_3O$ pattern were synthesized. Zn(II)complexes of the two ligands could be obtained and the X-ray structure analysis of 2,6-Bis[2-pyridylmethyl)amino) methyl]pyridine zinc chloride showed Zn coordination to all five nitrogen atoms. The strong complexation of 2,6-Bis[2-pyridylmethyl)amino) methyl]pyridine and (6-{[Pyridin-2-ylmethyl)-amino]-methyl}-pyridin-2-yl)-methanol with Zn(II) were demonstrated by $^1$H-NMR studies and electrospray mass spectroscopy. Ni and Co complexes of **1** and a Co complex of **2** were also obtained and analyzed by X-ray crystallography.



The coupling of 2-hydroxy acetophenone and benzaldehyde was studied in the presence of the prepared Zn-complexes and it was shown that the coupling product was obtained at room temperature, in up to 60% yield with 7.5mol% of the zinc-catalyst.

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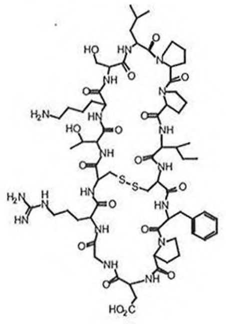
Organic Chemistry **130**

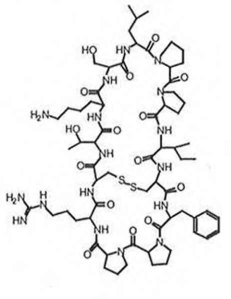
### A New Family of β-Hairpin Mimetics Based on a Trypsin Inhibitor

Anne Descours, Kerstin Moehle, Annabelle Renard and John A. Robinson
University of Zürich, Winterthurerstr. 190, CH-8057 Zürich, Switzerland

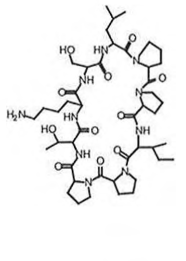
The 14 residue cyclic peptide **1** is a naturally occurring serine protease which inhibits trypsin in the nanomolar range [1]. Based on its interesting structure, we have designed a new family of inhibitors by transplanting the β-hairpin from the naturally occurring peptide **1** onto a hairpin inducing template. We present here the synthesis of two mimetics (**2** and **3**) using a L-Pro-D-Pro Template [2]. The mimetics **2** and **3** were shown to retain an inhibitory activity similar to **1**. In order to change the specificity of this ihnibitor, a library of cyclic peptides based on the 9-residue peptide **3** was then designed and produced by parallel synthesis. Some of these 9-mer mutant peptides proved to be potent inhibitors against chymotrypsin.



**1**



**2**



**3**

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[2]- A. Descours, K. Moehle, A. Renard and J.A. Robinson *Chem. Biochem.*,**200 2**,*3* , 318.

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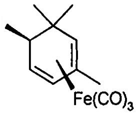
Organic Chemistry **131**

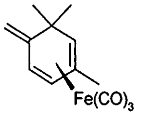
### ORGANOMETALLIC APPROACH TO THE TAXANE SKELETON INVOLVING IRON CABONYL COMPLEXES

C. Eggertswyler, T.A. Jenny*
Chemistry Department, University of Fribourg, CH-1700 Fribourg, Switzerland

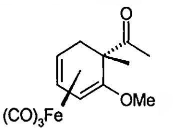
The synthetic potential of olefin iron carbonyl complexes is demonstrated by a new convergent approach in constructing the taxane skeleton.
By an unprecedented oxidation involving the Perrier reagent ($AcCl/AlCl_3$) the optically active cyclohexadiene complex **1**, accessible from (-)-β-pinene in a high yield two step synthesis [1], is transformed to the planar chiral triene complex **2**.



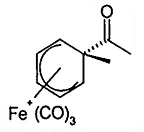
**1**



**2**

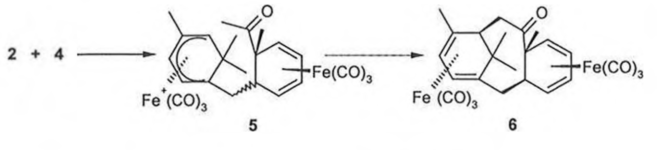


**3**



**4**

Complex **3**, obtained from 2-methoxyacetophenone, can be ionized with $H_2SO_4$ to give the cationic complex **4**. Coupling of the nucleophilic iron complex **2** with the electrophilic complex **4** yields with moderate diastereoselection the intermediate **5** which upon treatment with a sterically hindered base gives binuclear complex **6** upon ring closing alkylation.



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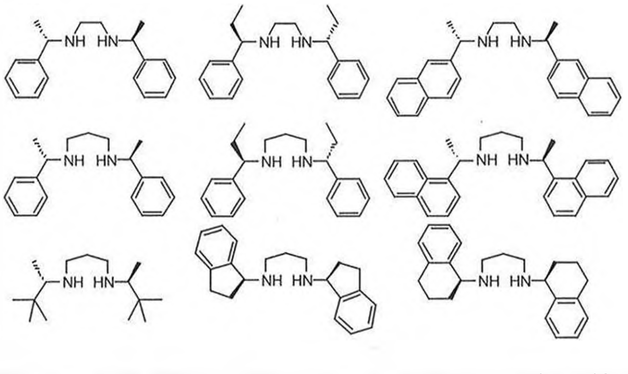
Organic Chemistry **132**

### Enantioselective Deprotonation of Cyclohexene Oxide Using New Homochiral Bis-Lithium Amide Bases

Olivier Equey, Alexandre Alexakis*

Université de Genève, quai Ernest Ansermet 30, 1211 Genève 4

High levels of asymmetric induction can be achieved for the enantioselective deprotonation of cyclohexene oxide using homochiral bis-lithium amides derived from $C_2$ symmetric homochiral diamines [1][2]. We wish to report preliminary results obtained in the enantioselective deprotonation of cyclohexene oxide using new homochiral bis-lithium amide bases :



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Organic Chemistry **133**

### The synthesis of 1,3-polyols based on sulfur dioxide cycloadditions

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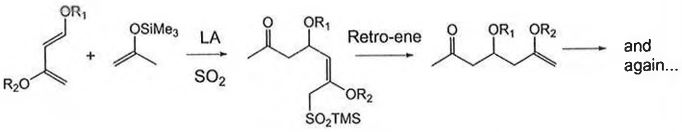
EPFL, Institut de chimie Moléculaire et Biologique, CH-1015 Lausanne, Switzerland

A great variety of natural products of biological interest includes polyketides (1,3-polyoxo, 1,3-polyols, aldols) [1] in which the polyols arrays are in an acyclic arrangement. Cyclic arrangement (in a spiroketal way) of these polyols are observable in the architecturally unique family of spongistatins possessing extraordinary cytotoxicity against chemoresistant tumor cell lines. The different approaches to the synthesis of these different building blocks have been reviewed [2].

Recently we have shown [3] that polyketides fragments can be constructed stereoselectively using cycloaddition reactions between dienes and sulfur dioxide in the presence of a Lewis acid (LA). In the light of these results it was proposed to develop a new methodology toward 1,3-polyols using iterative oxyallylation/retro-ene tandem reactions.



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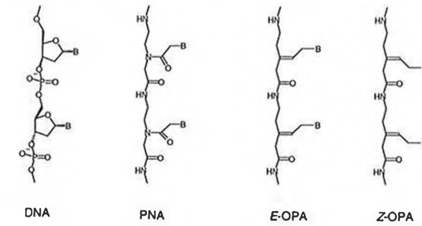
Organic Chemistry **134**

### Olefinic Peptide Nucleic Acid (OPAs)

D. Gautschi, C. Leumann*

Department of Chemistry and Biochemistry, University of Bern, Freiestrasse 3, CH-3012 Bern, Switzerland.

Polyamide or peptide nucleic acids (PNAs), first described in 1991,[1] are DNA analogues based entirely on an achiral polyamide backbone. A key structural feature of PNAs is the central amide linker between the base and the backbone. Both the *E*- and *Z*-rotameric forms of this tertiary amide functionality exist in uncomplexed PNA. In PNA/PNA, PNA/DNA and PNA/RNA duplexes, the carbonyl oxygen of the amide linker unit points uniformly to the carboxy terminus of the strand. OPA [2] was designed to remove this structural ambiguity. The central amide functionality is replaced by an isostructural, configurationally stable C-C double bond in either the *Z* or the *E* configuration. Here we report on the synthesis of the MMT-Z-A-OPA monomer in 12 steps starting from 3-Butyn-1-ol and its incorporation into a fully modified all-Z-OPA oligomer containing the Z-A- and Z-T-bases and their base-pairing properties with complementary DNA were evaluated by UV-melting experiments.



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Organic Chemistry **135**

### A general method for the synthesis of C$^8$-arylamine adducts of 2'-deoxyguanosine formed by carcinogenic amines

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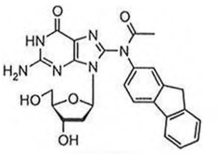
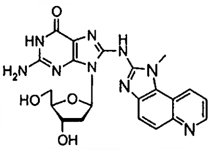
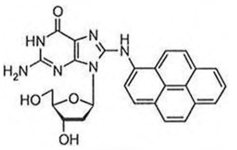
Inst. for Medical Radiobiology, University of Zürich, August Forel Str. 7, 8008 Zürich, Switzerland

A number of carcinogenic aryl-amino and -nitro compounds, present in cooked food or cigarette smoke, are known to produce C$^8$-arylamine adducts of 2'-deoxyguanosine. Syntheses of these adducts usually mimic the metabolic activation pathway by preparation of the corresponding N-hydroxy or N-acetoxy derivates and modification of DNA with these reagents. Although this method allows preparation of randomly modified DNA templates, the generation of defined single adducts could be more efficiently achieved by the site-specific incorporation of these adducts into DNA using solid phase synthesis. To achieve this goal, we have developed a general method for the synthesis of C$^8$-arylamine adducts of 2'-deoxyguanosine using a Buchwald-Hartwig coupling reaction between different arylamines and a suitably protected 8-bromo-2'-deoxyguanosine. These adducts can be selectively acetylated at the $N^8$ position and a protecting group strategy preserving the integrity of this base labile acetyl group during oligonucleotide synthesis was devised. These modified oligonucleotides will be then used to investigate their mutagenicity and their repair.


dG-AAF


dG-IQ


dG-Pyrene

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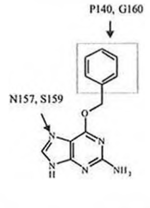
Organic Chemistry **136**

### Evolutionary approaches for the generation of human DNA-alkyltransferases (hAGT) with increased activity

Alexandre Juillerat, Thomas Gronemeyer, Kai Johnsson*

Institute of Molecular and Biological Chemistry, EPFL, Switzerland

The mechanism of the hAGT consists of the irreversible and covalent transfer of an alkyl group from the O$^6$-position of guanine in DNA to the active cysteine of the hAGT [1]. This particular mechanism was used for the covalent *in vivo* labeling of hAGT fusion proteins by addition of O$^6$-benzylguanine (BG)- derivatives [2]. Since the reaction of the hAGT with free BG is slow (600 M$^{-1}$s$^{-1}$ [1]), a hAGT mutant with increased reactivity is highly desirable. We are currently developing a screening method to select for hAGTs with increased reactivity from hAGT libraries designed by molecular modeling and created by saturation mutagenesis.



Selection for AGTs with increased reactivity is done with a phage display system based on filamentous fusion phage [3]. We showed that the the protein (hAGT) is activly presented on the surface of the phages, although the phages are assembled in the oxidizing environment of the periplasm.

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Organic Chemistry **137**

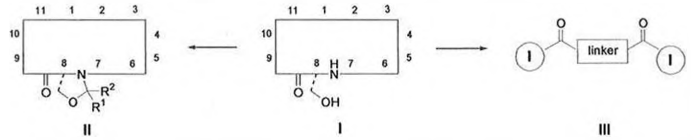
## Structure-activity studies of novel D-Ser$^8$-Cyclosporin A derivatives as potential anti-HIV compounds

Patiny L., Guichou J.-F., Lage J., Turpin O., Hamel A.,
Carrupt A. and Mutter M.

Institute of Molecular and Biological Chemistry (ICMB), EPFL,
CH-1015 Lausanne, Switzerland.

Since the discovery of the immunosuppressive activity of cyclosporin A (CsA), considerable work has been devoted to the chemical synthesis of potent analogues[1]. More recently, the finding of potential anti-HIV I activity of CsA[2] raised the interest for the design of CsA-derived compounds devoid of immunosuppressive activity[3]. With this objective, the highly immunosuppressive CsA analogue D-Ser$^8$-CsA[4] (**I**) was taken as a versatile candidate for modulating the binding mode to its receptors cyclophilin A (CypA) and calcineurin A (CnA). To this end, the functional group at position 8 is used for the chemoselective transformation of **I** to a series of derivatives including C-2 substituted pseudo-proline systems (**II**) and dimers disposing variable linkers (**III**).

The chemical synthesis, characterisation and structure-function studies will be presented. Some new derivatives exhibit CypA binding and strongly reduced CnA affinities serving as potential leads for the development of antiviral, non-immunosuppressive drugs.



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[4] Traber, R.; Hofmann, H.; Kobel, H. *J. Antibiotics* 1989, *42*, 591.

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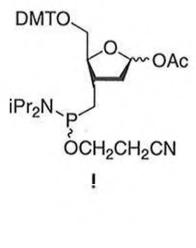
Organic Chemistry **139**

## Synthesis of a Chemically Stable Functional DNA Abasic Site Analogue

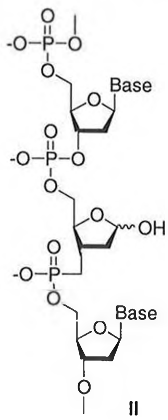
C. Hirtz, C. Leumann

Department of Chemistry and Biochemistry, University of Bern
Freiestrasse 3, CH-3012 Bern

We have developed a new synthetic abasic site analogue, in which the usual phosphodiester linkage is replaced by a phosphonate linkage. Incorporated into an oligonucleotide, we expect increased chemical stability at the abasic site, as well as inhibitory activity in the context of DNA glycosylases.



**I**



**II**

We present a straight forward synthesis of the corresponding 3'-phosphonate building block **I**, starting from (-)-2,5,-dihydrofuran-2-one, as well as its incorporation into DNA (**II**). First experiments towards its functional aspects will also be given.

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Organic Chemistry **138**

## Resolution and Configurational Stability of Novel [4]-Heliceniums

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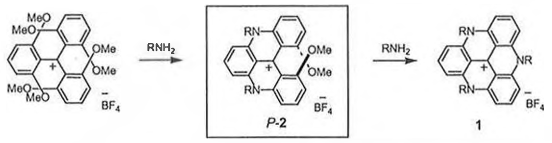
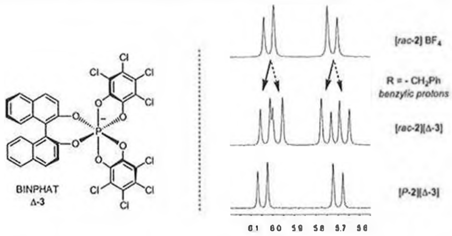
Recently, Laursen and Krebs reported the one-step synthesis of novel triazatriangulenium dyes **1**. Chiral [4]-helicenium intermediates **2** can be isolated in good yield (~70-80%) if shorter reaction times are used [1].



Herein,we report that chiral BINPHAT anion **3** [2] behaves as efficient NMR chiral shift and resolving agent for cationic dyes **2**. After association and selective precipitation, salts [(*M*)-**2**][Δ-**3**] and [(*P*)-**2**][Δ-**3**] (d.r. > 49:1) can be isolated in good yields. Racemization of **2** only occurs at high temperature and results on the configurational stability are here reported.



[1] Laursen, B. W.; Krebs, F. C. *Angew. Chem. Int. Ed.* **2000**, *39*, 3432.
[2] Lacour, J.; Londez, A.; Goujon-Ginglinger, C.; Buss, V.; Bernardinelli, G. *Org. Lett.* **2000**, *2*, 4185.

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Organic Chemistry **140**

## Equilibria of RNA Secondary Structures

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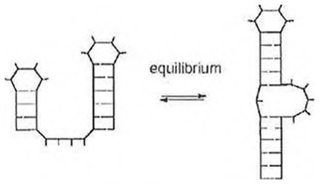
We investigate 25 to 34 nt RNA sequences, that have been designed to adopt two different secondary structures which are in thermodynamic equilibrium. Experimental evidence for the coexistence of the two conformers results from the NH-N $^1$H-NMR spectra. When compared to the NH-N $^1$H-NMR spectra of appropriate reference sequences the equilibrium position is easily quantifiable even without the demand for assignment of the individual NH resonances [1]. The reference sequences represent the several Watson-Crick base paired double helical segments, each encountered in either of the two conformers of the bistable target sequence. In addition, we rationalize the influence of nucleotide mutations on the equilibrium position of the bistable RNA sequences. The approach further allows a detailed thermodynamic analysis and the evaluation of secondary structure predictions for multistable RNAs obtained by computational methods.



[1] C. Hoebartner, M.-O. Ebert, B. Jaun, R. Micura, *Angew. Chem. Int. Ed. Engl.* **2002** ,*41* , 605-609.

Organic Chemistry

**141**

# FLUORINATED OLEFINIC PEPTIDE NUCLEIC ACID

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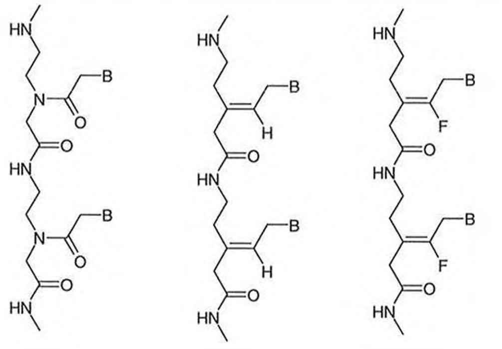
In PNA/PNA, PNA/DNA and PNA/RNA duplexes, the carbonyl oxygen of the amide linker unit in PNA points uniformly to the carboxy terminus. OPA [1] was designed to remove this structural ambiguity. The double bond mimics the amide unit of PNA. The introduction of a fluorine atom restores the original dipole moment. The fluorinated F-OPA monomers containing the bases A and T were synthesised in 13 steps starting from diethyl 3-hydroxyglutarate. The key step is a Wittig-Horner reaction in which a fluorine containing C2 synthon is introduced. These monomers were incorporated into PNA oligopeptides and their base-pairing properties with complementary DNA and RNA were evaluated by UV-melting experiments.



PNA (E)-OPA (Z)-FOPA

[1] R.Schütz, M.Cantin, C.Roberts, B.Greiner, E.Uhlmann, C.Leumann, *Angew. Chem. Int. Engl. Ed.*, **2000**, *39*, 1250.

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Organic Chemistry

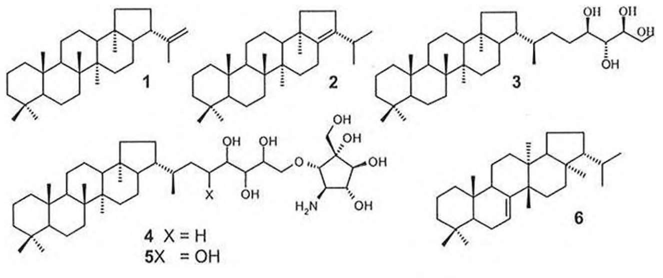
**142**

# Triterpenoids of the bacterium *Frateuria aurantia* DSMZ 6220

Cécile Joyeux, Pierre Llopiz, Serge Neunlist*

Laboratoire de Limnologie Organique, ENSCMu, Université de Haute Alsace, 3 rue Alfred Werner, 68093 Mulhouse Cedex, France.

*Frateuria aurantia* is a strain physiologically close to *Acetobacter* genus, which is known to gather good hopanoids producers [1]. Five hopanoids **1-5** and a fernene **6** were isolated from this strain, in optimum growth culture.



Diploptene **1**, hop-17(21)-ene **2** and fern-7-ène **6** were identified by GC, GC-MS and co-elution with authentic samples. The polyacetates of bacteriohopanepolyols **3**, **4** and **5** were identified by spectroscopic measurements ($^1$H- and $^{13}$C-NMR, MS, COSY, HMBC, HMQC). Bacteriohopanetetrol **3** configuration was determined by comparison with hemisynthetic diastereoisomers [2]. Carbapseudopentose moiety of **4** and **5** is the same as for the hopanoid isolated from *Zymomonas mobilis* [3].

[1] M. Rohmer, P. Bouvier-Navé, G. Ourisson, *J. Gen. Microbiol.* **1984**, *130*, 1137.
[2] P. Bisseret, M. Rohmer, *J. Org. Chem* **1989**, *54*, 2958.
[3] D. Herrmann, P. Bisseret, J. Connan, M. Rohmer, *Tetrahedron Lett.* **1996**, *37*, 1791.

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Organic Chemistry

**143**

# New chiral *P,N*-ligands for the Iridium catalyzed enantioselctive hydrogenation of unfunctionalized alkenes

Stefan Kaiser, Sebastian P. Smidt and Andreas Pfaltz*

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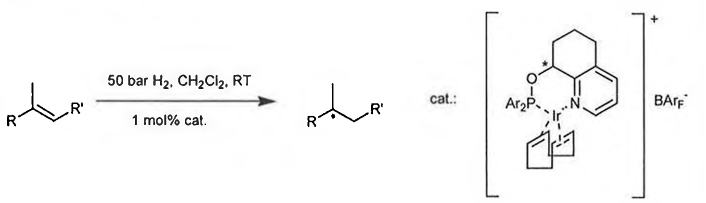
St. Johanns-Ring 19, CH-4056 Basel, Switzerland

Using chiral analogues of the Crabtree catalyst [1] we achieved remarkable results in the Iridium catalyzed enantioselective hydrogenation of unfunctionalized alkenes. Both conversion, as well as enantiomeric excess, of up to 99 % with different types of chiral phosphino-oxazoline ligands were reported. [2], [3]



In order to develop other potential ligands for Iridium catalyzed hydrogenation, our interest focused on 8-hydroxy-5,6,7,8-tetrahydroquinoline derivatives which are easy accessible. With this new class of catalyst high conversions and good enantioselectivities could be obtained in the hydrogenation of alkenes.

[1] R. Crabtree, *Acc. Chem. Res.* **1979**, *12*, 331-338.
[2] (a) A. Lightfoot, P. Schnider, A. Pfaltz, *Angew. Chem. Int. Ed.* **1998**, *37*, 2897-2899; (b) D. G. Blackmond, A. Lightfoot, A. Pfaltz, T. Rosner, P. Schnider, N. Zimmermann, *Chirality*, **2000**, *12*, 442-449.
[3] (a) J. Blankenstein, A. Pfaltz, *Angew. Chem. Int. Ed.* **2001**, *40*, 4445-4447; (b) F. Menges, A. Pfaltz, *Adv. Synth. Catal.* **2002**, *344*, 40-44.

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Organic Chemistry

**144**

# A Synthetic Application of the *Diels-Alder*/[3,3]-Sigmatropic Rearrangement Tandem Reaction: Towards a New Total Synthesis of Ibogamine

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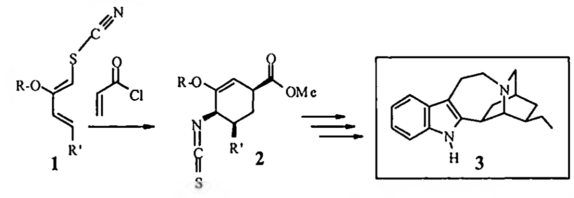
CH-2007 Neuchâtel, Switzerland

The Isoquinuclidine nucleus, a well-known precursor of the Ibogamine skeleton[1] **3**, can be obtained by a tandem process[2]. The retrosynthesis of the Isoquinuclidine skeleton leads to compound **2**, which should be obtainable *via* our tandem process *Diels-Alder* /[3,3]-sigmatropic rearrangement. In order to apply our strategy, various derivatives of the 1-thiocyanatobuta-1,3-diene **1** had to be synthesized and their efficiency in the tandem process has to be studied.



A methanesulfonyl group ( R ) has been introduced onto the diene in order to activate the position C6 of the Isoquinuclidine nucleus. The stable 1-thiocyanato-2-methanesulfonylhexa-1(Z),3(E)-diene **1** (R = $SO_2CH_3$, R' = $C_2H_5$) has been synthesized with the desired geometry.

[1] G. Büchi, D.L. Coffen, K. Kocsis, P.E. Sonnet, F.E. Ziegler, *J. Am. Chem. Soc.*, **1965**, *87*, 2073-2075.
[2] J.Schoepfer, C.Marquis, C. Pasquier and R. Neier, *J.Chem. Soc. Commun.*, **1994**, 1001-1002.

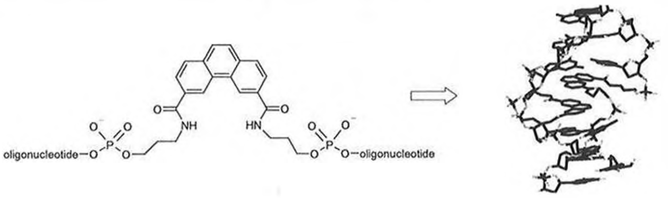
Organic Chemistry **145**

### The effect of a non-nucleosidic phenanthrene building block on DNA duplex stability

by Simon M. Langenegger and Robert Häner*

Department of Chemistry and Biochemistry, University of Bern,
Freiestrasse 3, CH-3012 Bern, Switzerland

Oligonucleotides containing a phenanthrene-derived, non-nucleosidic building block with flexible linkers were synthesized. The effect of the phenanthrene moiety on duplex stability at different positions was investigated. Placement of two phenanthrene residues in opposite positions had a slightly positive effect on duplex stability. This positive effect was further increased when two phenanthrene pairs were placed at juxtaposed positions. In contrast, introduction of a single phenanthrene unit opposite to an adenosine or a thymidine led to a destabilization of the duplex. A model of a phenanthrene-modified duplex is proposed.



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Organic Chemistry **146**

### Fluorinated Biphenyls : Potential Drugs for the Treatment of Prostate Cancer ?

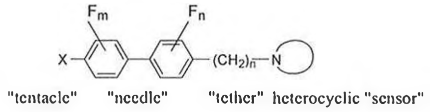
Frédéric Leroux and Manfred Schlosser

Swiss Federal Institute of Technology Lausanne, Institute of Molecular and
Biological Chemistry, BCH – LSCO, CH – 1015 Lausanne, Switzerland

17α-Hydroxylase-C17,20-lyase ($P_{450\ 17}$, CYP 17, androgen synthase,) is the key enzyme of the androgen biosynthesis. It catalyzes the hydroxylation of progesterone and pregnenolone to the 17α-products as well as the cleavage of the C17-C20 bond to give androstenedione. As androgens have been implicated in the development and progression of prostate cancer, $P_{450\ 17}$ attracted much attention as a therapeutic target.

R.W. Hartmann *et al.* have shown that *N*-imidazolylmethyl-substituted biphenyls are highly potent inhibitors of $P_{450\ 17}$ *in vitro.* [1, 2] Unfortunately, these compounds have virtually no *in vivo* activity, probably due to a rapid metabolic degradation.

As fluorine substituents may enhance the metabolic stability, we have embarked on the preparation of fluorinated analogs. The characteristics of the compounds selected as targets of synthesis are a central oligofluoro-biphenyl part which ends, on one side, with a polarizable or functional group ("tentacle") and, on the other side, with a methylene spacer (if not oligomethylene chain) bearing a nitrogen heterocycle ("sensor"). The results of first assays are promising.



[1] Wachall, B.G.; Hector, M.; Zhuang, Y.; Hartmann, R.W.; *Bioorg. Med. Chem.* **1999**, *7*, 1913 – 1924.

[2] Zhuang, Y.; Wachall, B.G.; Hartmann, R.W.; *Bioorg. Med. Chem.* **2000**, *8*, 1245 – 1252.

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Organische Chemie **147**

### Enantiopure 9-Aza-2,4-dioxa-3-phosphadecalins as Acetylcholine-Mimetics

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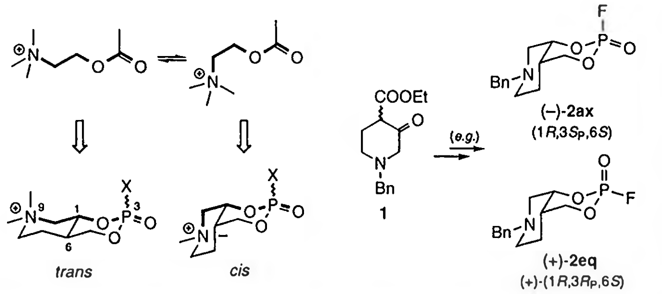
Organisch-chemisches Institut der Universität Zürich
Winterthurerstrasse 190, CH-8057 Zürich

In continuation of our studies on the irreversible inhibition of acetylcholine-esterase (AChE) by organophosphates –in particular the investigation of the physiologically active conformation of acetylcholine– we have synthesized all 8 stereoisomeric, 3-fluoro substituted title compounds ((–)-**2ax**, (+)-**2eq** as representatives) with *ee* >99%.



The heterocycles were prepared from the *cis*- and *trans*-1-benzyl-3-hydroxy-4-(hydroxymethyl)piperidines that were obtained by reductions (bakers' yeast or (*R*)- and (*S*)-BINAP-Ru/$H_2$, $LiAlH_4$) of the piperidone **1** and cyclization with $POCl_2F$.

The complete synthesis, the problems accompanied with the enantio-selective reductions and the determination of the absolute configuration as well as first results of the enzyme kinetic characterization with respect to the inhibition of AChE are presented.

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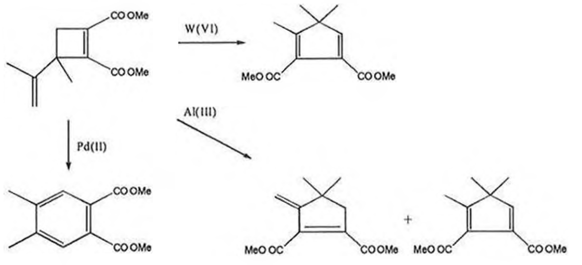
Organic Chemistry **148**

### Transition Metal Catalyzed Rearrangement of Vinylcyclobutene Dicarboxylates

Martin Lovchik and Allan Pinhas

Institute of Organic Chemistry, University of Zurich

Vinylcyclobutene derivatives rearrange in the presence of transition metal complexes to form cyclohexadienes and phthalates. Previous work in the group of Allan Pinhas [1] showed that this rearrangement could be performed with Ni(I), Ti(III), Fe(II), and Sm(II). In order to investigate these findings further, a large variety of metals was studied with respect to their use in these rearrangements. In addition these methods were applied to various derivatives of vinylcyclobutene.



It was found that Pd(II) promotes the rearrangement to yield phthalates, in the same manner as Ti(III) and Sm(II). Methyl derivatives of vinylcyclobutene, bearing a methyl substituent at the vinyl group, rearranged in the presence of W(VI) and Al(III) to form cyclopentadienes.

[1] This research was done at the University of Cincinnati in the group of Allan Pinhas. The presented results are part of the Master-thesis of Martin Lovchik (2001).

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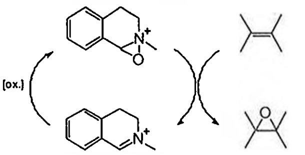
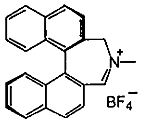
## On the Beneficial Effect of Biphasic Conditions and Anion Chirality onto the Oxaziridinium-Catalysed Epoxidation Reaction

David Monchaud, Claire Marsol, Jérôme Lacour *

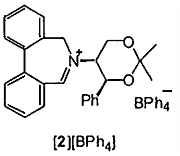
Département de Chimie Organique, Université de Genève, 1211 Genève 4

Iminium mediated epoxidation reactions of C-C double bonds have received recent attention due to the potential of the cations to react with oxone® and generate oxaziridinium species, which effectively transfer their oxygen atom to unfunctionalyzed olefins [1]. Examples of enantioselective variants of this reaction have been reported and are based on the use of non-racemic iminium precatalysts *e.g.*, **1** and **2**. $CH_3CN$ / water conditions have been used in all reported examples leading to low to good enantioselectivities.





[1][BF4]



[2][BPh4]

Herein, we report that biphasic $CH_2Cl_2$ / water conditions can lead to an improvement in the enantioselectivity of the epoxidation reaction; these conditions being rendered feasible by the combined use of TRISPHAT anions and of 18-C-6 [2]. While epoxidation of the 1-phenyl-3,4-dihydronaphthalene was performed with 41% e.e. (e.r. 2.4:1) with **[2][BPh4]**, it can now be realized with 76% e.e. (e.r. 7.2:1) with **[2][Λ-TRISPHAT]**.

[1] W. Adam, C. R. Saha-Moller, P. A. Ganeshpure, *Chem. Rev.* **2001**, *101*, 3499-3548. P. C. B. Page, G. A. Rassias, D. Barros, A. Ardakani, D. Bethell, E. Merifield, *Synlett* **2002**, 580-582.

[2] J. Lacour, C. Ginglinger, C. Grivet, G. Bernardinelli, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 608-609.

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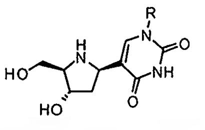
Organic Chemistry **151**

## PYRROLIDINO-DNA

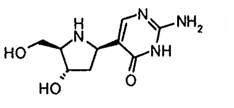
A. Häberli, A. Mayer and C. J. Leumann

Department of Chemistry and Biochemistry, University of Bern,
Freiestrasse 3, CH-3012 Bern, Switzerland.

Pyrrolidino pseudo-C-nucleosides are isosteres of natural deoxynucleosides, which are expected to carry a positive charge at nitrogen under physiological conditions. Incorporated into oligonucleotides such units may prove useful in stabilizing DNA triple helices in the parallel binding motif. The charged pyrrolidino nitrogen in a third strand is expected to form a salt bridge to an adjacent phosphate unit of the purine target strand in addition to the base-base interaction. In this poster we report on a new synthesis of the pyrrolidino-C-nucleosides 1-3[1] as well as their incorporation into DNA. We also report on the duplex- and triplex-binding properties of pyrrolidino-DNA as determined from UV-melting curves and gel retardation experiments.



**1**: R = H; pyrrolidino pseudouridine
**2**: R = $CH_3$; pyrrolidino pseudothymidine



**3**: pyrrolidino pseudoisocytidine

[1] A. Häberli, C. Leumann, Org. Lett. **2001**, 3, 489

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Organic Chemistry **150**

## TOWARDS A DNA-LIKE DUPLEX WITHOUT HYDROGEN BONDS

Gérald Mathis and Jürg Hunziker*

Department of Chemistry and Biochemistry, University of Bern,
Freiestrasse 3, 3012 Bern, Switzerland

Based on the recent observations that hydrophobic effects can be exploited in addition to complementary hydrogen bonding to create novel base pairs, we have incorporated the pentafluorophenyl- ($F^5$) and phenyl-C-deoxyribosides (P) shown below into synthetic oligonucleotides. The inverse quadrupolar moments of the phenyl and pentafluorophenyl residues are expected to lead to edge-to-edge attractive intermolecular forces. The consecutive alternating alignment of pentafluorophenyl and phenyl residues should additionally result in very strong intrastrand π-π-stacking

**Fig. 1**. The complementary charge distribution in benzene and hexafluorobenzene leads to favourable edge-to-edge (as well as stacking) contacts between these two molecules. This interaction might be exploited in a base pair between pentafluorophenyl- and phenyl-C-deoxyriboside.

When incorporated in the middle of a 10-mer DNA duplex, one or two $F^5$-P pairs lead to destabilization as judged from thermal melting profiles. However, if four consecutive pairs of alternating sequence are present, duplex stability exceeds that of the corresponding reference duplex with four A-T base pairs in the same positions.

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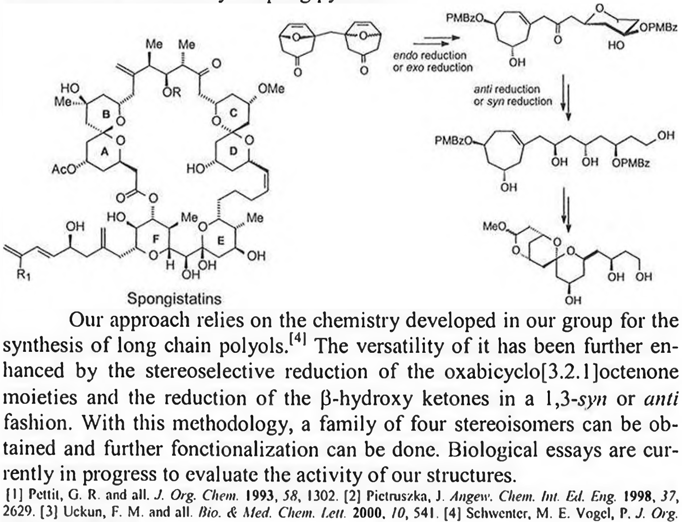
Organic Chemistry **152**

## Synthetic studies toward Spongistatins

Kai Meilert, Marc-Etienne Schwenter and Pierre Vogel*

ICMB, Ecole Polytechnique Fédérale de Lausanne
1015 Lausanne, Switzerland

Polketides are carbon chains substituted by hydroxyl groups, mainly in a 1,3-fashion. These fragments are generally linear, but in some particular cases they can be found in Nature under a cyclic form. This is the case of Spongistatins, natural products isolated from marine sponges,[1] which shows a high activity against several chemoresistant tumor cell lines (sub nanomolar growth inhibition). The AB and CD spitoketals seem to play a crucial role in the activity of spongipyrans.[3]



Our approach relies on the chemistry developed in our group for the synthesis of long chain polyols.[4] The versatility of it has been further enhanced by the stereoselective reduction of the oxabicyclo[3.2.1]octenone moieties and the reduction of the β-hydroxy ketones in a 1,3-*syn* or *anti* fashion. With this methodology, a family of four stereoisomers can be obtained and further fonctionalization can be done. Biological essays are currently in progress to evaluate the activity of our structures.

[1] Pettit, G. R. and all. *J. Org. Chem.* **1993**, *58*, 1302. [2] Pietruszka, J. *Angew. Chem. Int. Ed. Eng.* **1998**, *37*, 2629. [3] Uckun, F. M. and all. *Bio. & Med. Chem. Lett.* **2000**, *10*, 541. [4] Schwenter, M. E. Vogel, P. *J. Org. Chem.*, **2001**, 66, 7869.

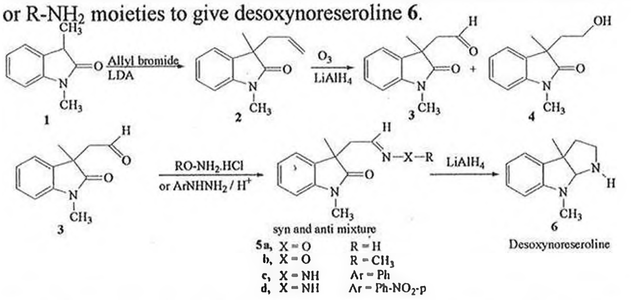
Organic Chemistry **153**

## A Novel Synthetic Approach to (+/-)-Desoxynoreseroline

Maged K. G. Mekhael and Heinz Heimgartner*

Institute of Organic Chemistry, University of Zürich
Winterthurerstrasse 190, CH-8057 Zürich

(+/-)-Desoxynoreseroline, the building unit of the pharmacologically active physostigmine alkaloid was synthesised.
Reaction of *N*-methylaniline with 2-bromopropionyl bromide followed by Friedel-Crafts alkylation afforded Julian's oxindole **1**. Further alkylation[1] of **1** using allylbromide in the presence of LDA gave 3-allyl oxindole **2** in an excellent yield. Ozonolysis of **2** followed by $LiAlH_4$ reduction of the formed ozonide[2] gave both the aldehyde **3** and alcohol **4**.
Condensation of the aldehyde **3** with hydroxylamine hydrochloride and hydrazine hydrate derivatives, respectively, gave the corresponding imine derivatives **5a-d** as a mixture of *syn* and *anti* isomers.
Reduction of this isomeric mixture with $LiAlH_4$ proceed under loss of R-OH or R-$NH_2$ moieties to give desoxynoreseroline **6**.



[1] A. D. Hughes, D. A. Price and N. S. Simpkins, *J. Chem. Soc. Perkin Trans. 1*, **1999**, 1295-1304.
[2] K. Kostova, V. Dimitrov, S. Simova and M. Hesse, *Helvetica Chimica Acta*, **1999**, *82*, 1385-1399.

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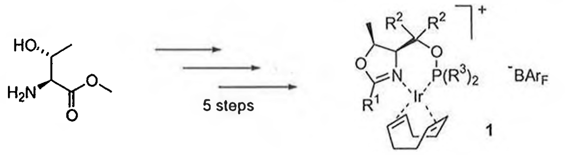
Organic Chemistry **154**

## Threonine derived Phosphinite-Oxazolines: Modular Ligands for the Catalytic Asymmetric Hydrogenation

Frederik Menges and Andreas Pfaltz*

University of Basel, St. Johanns-Ring 19, CH-4056 Basel, Switzerland

Recently we have shown that iridium-complexes of *P,N*-ligands are efficient and highly selective catalysts for the asymmetric hydrogenation [1]. With the iridium complexes of phosphino-oxazoline ligands excellent results could be obtained for some unfunctionalized olefins, such as methylstilbene-derivatives.
In our group a new class of phosphinite-oxazoline ligands has been developed and their iridium-complexes have shown to be excellent catalysts in the asymmetric hydrogenation [2].



By the use of threonine as building block for the phosphinite-oxazoline ligands **1** the selectivity in the asymmetric hydrogenation could be improved [3]. The influence of the additional substituent of the oxazoline ring on the structural properties of the iridium-complexes has been investigated.

[1] (a) A. Lightfoot, P. Schnider, A. Pfaltz, *Angew. Chem. Int. Ed.* **1998**, *37*, 2897-2899; (b) D.G. Blackmond, A. Lightfoot, A. Pfaltz, T. Rosner, P. Schnider, N. Zimmermann, *Chirality* **2000**, *12*, 442-449.
[2] J. Blankenstein, A. Pfaltz, *Angew. Chem. Int. Ed.* **2001**, *40*, 4445-4447.
[3] F. Menges, A. Pfaltz, *Adv. Synth. Catal.* **2002**, *344*, 40-44.

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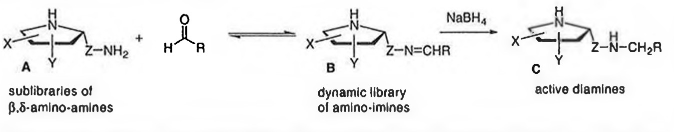
Organic Chemistry **155**

## New Diamines derived from 7-Azabicyclo[2.2.1]heptane for the Search of Glycosidase Inhibitors

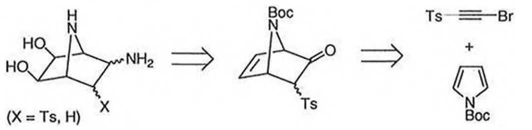
Antonio J. Moreno-Vargas and Pierre Vogel*

EPFL, Institut de Chimie Moléculaire et Biologique, CH-1015 Lausanne, Switzerland.

The search for better inhibitors implies the multi-step synthesis of a large number of analogs and derivatives and their individual testing. Vogel and coworkers have found that diamines of the type A (1,2- and 1,3-diamines) equilibrate rapidly with aldehydes to generate dynamic libraries of imines under low concentration and in the presence of glycosidases. This has led to the invention of an efficient combinatorial method for the discovery of glycosidase inhibitors [1].



Now, we present the synthesis of new bicyclic diamines imitating diamine of the type A in order to apply the former combinatorial method for the search of new glycosidase inhibitors.



[1] Gerber-Lemaire, S.; Popowycz, F.; Rodríguez-García, E.; Carmona Asenjo, A. T.; Robina, I.; Vogel, P. *ChemBioChem* **2002**, *3*, 466.

*We are grateful to the Swiss National Science Foundation, the EPFL and the Ministerio de Educación y Cultura (BQU2001-3779/)Spain. This work is part of the COST-D13-0001/99.*

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Organic Chemistry **156**

## Preparation of Sulfated Vitamin E Derivatives and Metabolites

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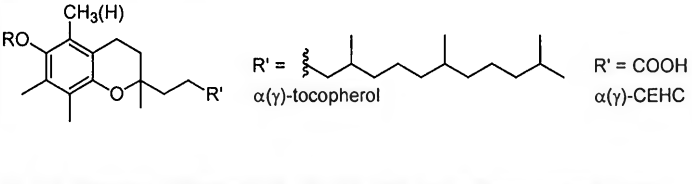
CH-4070 Basel, Switzerland

Vitamin E is essential for protection of biological cell components against oxidative damage [1]. Metabolism of fat-soluble α- and γ-tocopherol by side-chain shortening leads to highly polar degradation products, e.g. α- and γ-CEHC [2]. Conjugates like glucuronides or esters of inorganic oxo-acids are assumed to play a major role in excretion from human and animal organism. In order to provide reference material for biological testing and analytical purposes, a series of sulfuric monoesters [or their metal salts, R = $SO_3H(Met)$] has been prepared.



[1] Th. Netscher, *Chimia* **1996**, *50*, 563-567, and references cited therein.
[2] W. Stahl, P. Graf, R. Brigelius-Flohé, W. Wechter, H. Sies, *Anal. Biochem.* **1999**, *275*, 254-259, and references cited therein.

Organic Chemistry **157**

## Decarboxylative Radical Azidation: A Mild Alternative to the Schmidt Reaction

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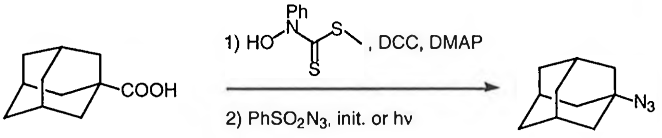
*Freiestrasse 3, CH-3000 Bern 9*

Our group recently reported the efficient azidation of radicals [1] with sulfonyl azides.

We present here, as an extension of this work, the decarboxylative radical azidation of aliphatic carboxylic acids using a modified thiohydroxamic acid as radical precursor [2]. This reaction represents a mild alternative to the Schmidt reaction.



[1] C. Ollivier and P. Renaud, *J. Am. Chem. Soc.* **2001**, *123*, 4717.
[2] For a review on radical decarboxylation, see: D. H. R. Barton, D. Crich and W. B. Motherwell, *Tetrahedron* **1985**, *41*, 3901.

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Organic Chemistry **158**

## Norpseudovitamin $B_{12}$, the New Corrinoid from *Dehalospirillum multivorans*

Wolfgang Fieber[1], Anke Siebert[2], Sigrid Ostermann[1], Karl-Hans Ongania[1], Gabriele Diekert[2]*, Bernhard Kräutler[1]*

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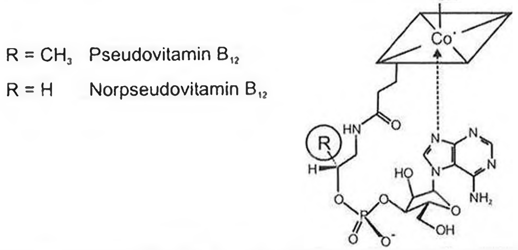
The main corrinoid from *Dehalospirillum multivorans* was extracted in its $Co_\beta$-cyano form. Analysis by HPLC and UV/Vis spectroscopy revealed the cyano-corrinoid to be "complete" but non-identical to a variety of known natural $B_{12}$-derivatives. Mass spectrometric analysis indicated the molecular formula as $C_{58}H_{81}CoN_{17}O_{14}P$, i.e. the corrinoid to be a homologue of pseudovitamin $B_{12}$.

The sample was subjected to spectroscopic analysis by UV/Vis-, CD-, and one- and two-dimensional $^1H$-, $^{13}C$- and $^{15}N$-NMR-spectroscopy. The data indicated the novel corrinoid to be 176-nor-pseudovitamin $B_{12}$ and to differ from pseudovitamin $B_{12}$ by the lack of a methyl group attached to carbon-176. This is the first example of a "complete" natural $B_{12}$-cofactor, lacking one of the methyl groups of the cobinamide moiety.



This work was supported by the Austrian Science Foundation (FWF, project 13595) and by the European Union.

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Organic Chemistry **159**

## Mechanism and New Reagents for the Radical Carboazidation of Alkenes

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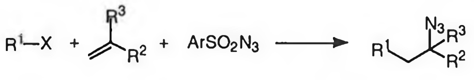
We have recently reported that radical carboazidation of alkenes with benzenesulfonyl azide works efficiently in intramolecular [1] and intermolecular [2] processes.

We report here new informations about the mechanism that depends on the nature of the radical precursor. The development of other azidation reagents that facilitates the purification of the products is also presented.



$$R^1{-}X + CH_2{=}CR^2R^3 + ArSO_2N_3 \longrightarrow R^1CH_2C(N_3)R^2R^3$$

[1] C. Ollivier and P. Renaud, *J. Am. Chem. Soc.* **2001**, *123*, 4717.
[2] P. Renaud, C. Ollivier and P. Panchaud, *Angew. Chem.* **2002**, in press.

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Organic Chemistry **160**

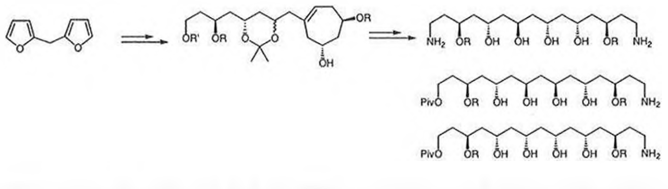
## Asymmetric Synthesis of 1-Aminopentadecane-3,5,7,9,11,13,15-heptols and of 1,15-Diaminopentadecane-3,5,7,9,11,13-hexols

Sandrine Gerber Lemaire-Audoire, Florence Popowycz, Cécile Glanzmann and Pierre Vogel

Institut de Chimie Moléculaire et Biologique, Ecole Polytechnique Fédérale de Lausanne, BCH, 1015 Lausanne, Switzerland

Long-chain polyketides with amino groups are rare natural compounds that show interesting biological properties. For instance Linearmycin A and B have been described to have antifungal and anti-bacterial activities [1] whereas Zwittermycin A produced by *Bacillus cereus* UW85 suppresses certain plant diseases [2]. Recently, our group has developed a new, non-iterative synthetic approach to long-chain polyketides [3]. The method allows the preparation of all possible pentadecan-1,3,5,7,9,11,13,15-octols and derivatives.

We have decided to exploit the method to generate a new class of long-chain aminopolyols to be tested both for their biological properties and as ligation tools.



[1] Sakuda, S.; Guce-Bigol, U.; Itoh, M.; Nishimura, T.; Yamada, Y. *J. Chem. Soc., Perkin Trans 1* **1996**, 2315.
[2] Silo-Suh, L.A.; Stabb, E. V.; Raffel, S. J.; Handelsman, J. *Curr. Microbiology* **1998**, *37*, 6; Stohl, E. A.; Milner, J. L.; Handelsman, J. *Gene* **1999**, *237*, 403.
[3] Schwenter, M. E.; Vogel, P. *Chem. Eur. J.* **2000**, *6*, 4091.

Organic Chemistry **161**

## Iron catalysts for hydrogenations and polymerizations

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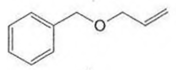
Switzerland

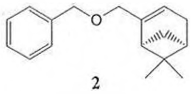
Depending on the preparation conditions a range of iron catalysts derived from iron(II) chloride were prepared which are active for the hydrogenation of olefins, the polymerization of ethylene [1] as well as for the cyclotrimerization [2] and polymerization of alkynes.

The formation of a new homogeneous precatalyst prepared from $FeCl_2$ and toluene was observed by UV spectroscopy ($\lambda_{max}$: 315 nm and 358 nm) . This precatalyst is stabilised by an additional ligand such as nitrogen or ethylene leading to the proposition of a (toluene)($N_2$)$FeCl_2$ mono- or dimeric structure.

In line with this assumption the benzyl allyl ethers **1** and **2** also complex $FeCl_2$ leading to a new type of catalyst which was first tested in olefin hydrogenation.



1



2

Active catalysts require activation of the precatalysts. Reducing agents such as DIBAH, LAH and Grignard-type reagents turned out to work best for this purpose. Depending on the exact nature of the precatalyst only a selected range of these reagents is able to generate the active catalyst.

[1] M. Qian, M. Wang, R. He, *J. Mol. Cat. A* **2000**, *160*, 243.
[2] H. tom Dieck, R. Diercks, *Angew. Chem.* **1983**, *95*, 801.

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Organic Chemistry **162**

## Chiral Relay Effect :Enantioselective Reduction of α-Ketoacetals

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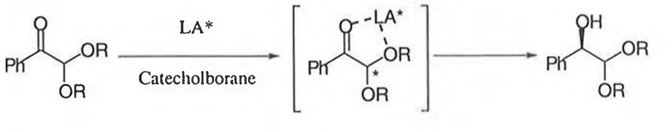
CH – 3000 Bern 9

The use of bis-oxazolines and $Zn(OTf)_2$ as chiral catalyst for asymmetric reduction of α-alkoxyketones has already been reported [1]. We present here a systematic investigation of the enantioselective reduction of α,α-ketoacetals. Results are rationalized according to a chiral relay effect because the acetal moiety becomes a chiral center upon complexation with the chiral Lewis acid.



LA* = chiral Lewis acid

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[2] (a) L. Quaranta, O. Corminboeuf, P. Renaud, *Org.Lett.* **2002**, 4, 39. (b) M.P. Sibi, L.Venkatraman, M. Liu, C.P. Jasperse, *J. Am. Chem. Soc.* **2001**, 123, 8444.

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Organic Chemistry **163**

## New Polymer-Supported Palladium Catalysts for the Suzuki Reaction

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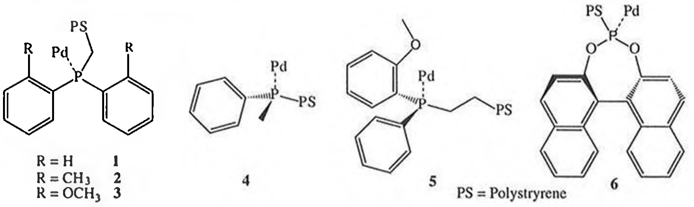
The formation of aryl-aryl bonds is a crucial step in the synthesis of many biologically active compounds. One of the most classical methods, the Suzuki cross-coupling reaction between a boronic acid and a bromoaromatic, is usually carried out with soluble palladium catalysts such as $Pd(PPh_3)_4$. Polymer-supported catalysts both retain the practical advantages of heterogenous catalysts (ease of recovery, etc...) and can successfully replace homogeneous catalysts for numerous reactions [1]. In previous studies, we have prepared catalyst 1 which proved very efficient for many Suzuki reactions [2]. We present herein the syntheses and uses of new polystyrene-supported palladium catalysts (**2-6**) possessing hindered or chiral phosphine moieties.



R = H 1
R = $CH_3$ 2
R = $OCH_3$ 3

4

5

6

PS = Polystryrene

Steric hindrance at the phosphorus center has a significant effect on the catalytic activity : for example, the yield of the coupling reaction between phenylboronic acid and 4-bromoaniline was increased from 56% to 99% when catalyst **1** was replaced by catalyst **2**.

Catalysts **4-5** were prepared from enantiomerically pure phosphine derivative and **6** from (+)-binaphthol. Unfortunately, the enantiomeric excesses obtained in attempted kinetic resolutions by Suzuki reactions catalyzed by polymers **4-6** were very low.

[1] A. Guyot, *Pure Appl. Chem.* **1988**, *60*, 365.
[2] I. Fenger, C. Le Drian, *Tetrahedron Lett.* **1998**, *39*, 4287.

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Organic Chemistry **164**

## First ROA Measurements of Biphenyls in Organic Solvents

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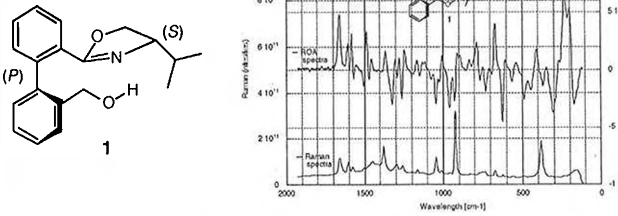
The biphenyl molecules of type **1** were investigated by ROA (Raman Optical Activity) measurements [1], to elucidate their structure in organic solvents. The influence of different conformers, present in such biphenyl structures, and the stability of hydrogen bonding (OH–N) in aprotic as well as protic solvents will be discussed. Furthermore some details of the instrumentation and measurement conditions will be given.

*Figure*. Raman and ROA spectra of **1** in acetonitrile.



[1] W. Hug, G. Zuber, A. de Meijere, A.F. Khlebnikov, H.-J. Hansen, *Helv. Chim. Acta*, **2001**,*84* , 1.

Organic Chemistry

**165**

## New, Axially Chiral ζ-Amino Alcohols Synthesized by a Ring Opening Reaction

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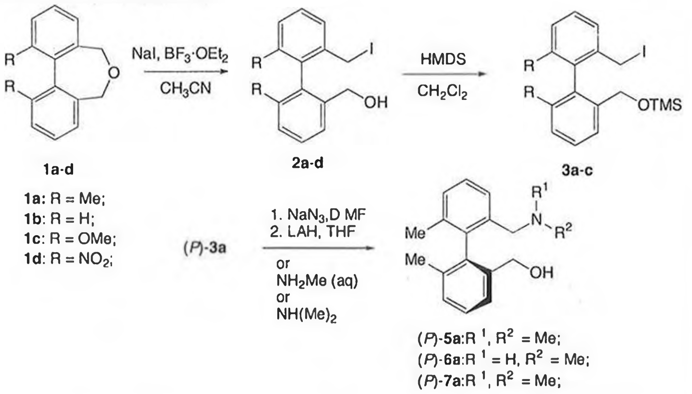
The synthesis of axially chiral ζ-amino alcohols **5** - **7**, carrying a biphenyl moiety, starting from $C_2$ symmetric biphenyl derivatives **1** by a ring opening reaction [1] as the key step is described. Although, evidence is given that enantiomerically pure (*P*)-**1a** can be transformed into (*P*)-**5a** without loss in enantiomerically purity.



Determination of the enantiomeric purity of such new amino alcohols, as well as first results as ligands in asymmetric transition-metal catalysed reactions will be provided.

[1] Vankar, Y.D.; Trinadha Rao, C. *J. Chem. Res. (S)* **1985**, 232.
[2] Mandal, A.K.; Soni, N.R.; Ratnam K.R. *Synthesis* **1985**, 274.

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Organic Chemistry

**166**

## Structural Studies by VCD of a Conformational Flexible Biphenyl

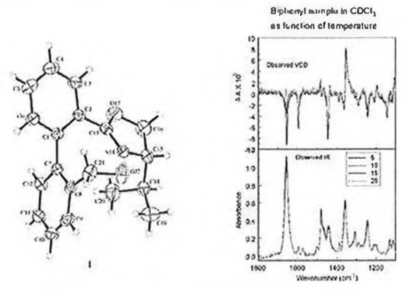
Xiaolin Cao , Teresa B. Freedman, Laurence A. Nafie

Syracuse University, 1-014 Center for Science and Technology, 13244-4100
Syracuse, New York, USA

Monica Kalbermatter, Anthony Linden, Andreas J. Rippert*

University of Zürich, Winterthurerstr. 190, CH-8057 Zürich, Switzerland

The biphenyl molecule **1** exists as one stereoisomer in the crystal with an OH···N hydrogen bond and (*P*) configuration at the chiral axis. However, in solution we measure at least two conformers. To elucidate the possible structures we performed VCD (Vibrational Circular Dichroism) measurements and calculated spectra on DFT level for all of the possible conformers [1].



The conformers that describe the measured spectra as well as temperature dependencies will be discussed.

[1] L.A. Nafie,G.-S. Yu, X. Qu, T.B. Freedman, *Farady Discuss.* **1994**, *99*, 13; L.A. Nafie, *Appl. Spectosc.* **1996**, 14A.

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Organic Chemistry

**167**

## Radical Allylation and Vinylation of Organoboranes

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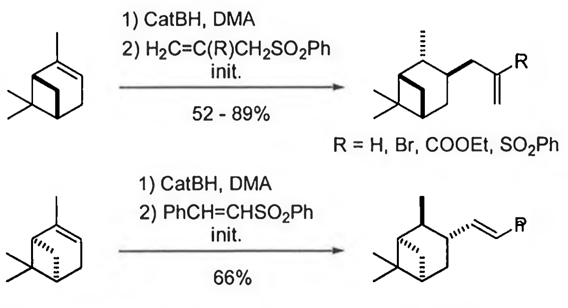
Freiestrasse 3, 3012 Bern.

Organoboranes are excellent radical precursors that are surprisingly not widely used.[1]

We report here an efficient method for the allylation and the vinylation of organoboranes. This method is based on a simple one-pot procedure involving the hydroboration of the alkene followed by reaction with allyl- and vinylsulfones.



[1] Ollivier, C.; Renaud, P. *Chem. Rev.* **2001**, *101*, 3415-3434.

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Organic Chemistry

**168**

## Towards the Total Synthesis of Lepadiformine

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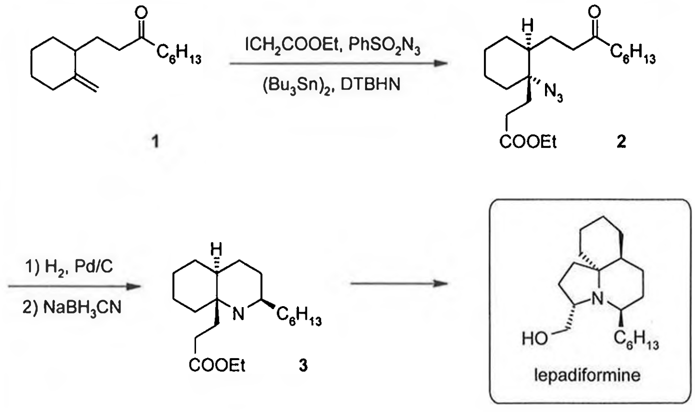
Lepadiformine is a marine alkaloid possessing interesting biological properties as well as a unique carbon skeleton [1]. By employing a novel intermolecular radical amination reaction [2, 3], we intend to achieve the shortest and most efficient synthesis so far.



[1] J.-F. Biard, S. Guyot, C. Roussakis, J.-F. Verbist, J. Vercauteren, J. F. Weber, K. Boukef, *Tetrahedron Letters* **1994**, *35*, 2691.
[2] C. Ollivier, P. Renaud, *J. Am. Chem. Soc.* **2000**, *122*, 6496.
[3] C. Ollivier, P. Renaud, *J. Am. Chem. Soc.* **2001**, *123*, 4717.

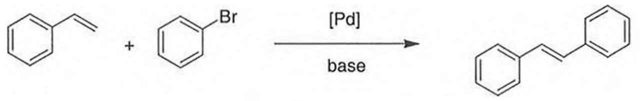
Organic Chemistry **169**

## Palladium (II) Complexes with Bidentate Ligands: Highly Active Catalysts for Heck Reactions

Thomas Schultz, Andreas Pfaltz*

University of Basel, St.-Johanns Ring 19, CH-4056 Basel, Switzerland

Although the Heck reaction is a well known reaction for the coupling of aryl halides and olefins [1], there is still the need for improved catalysts. For industrial applications it is necessary to develop catalysts of higher activity to reduce the amount of catalyst used and to enable the coupling of the less reactive but cheaper aryl chlorides. Recently palladacycles [2] and monodentate, bulky, alkyl substituted phosphine ligands [3] have been reported as highly active catalysts for the reaction of aryl bromides with olefins.



A series of bidentate ligands with two different binding sites have been synthesised. Palladium (II) complexes have been isolated and their reactivity as catalysts for the Heck reaction has been studied under various conditions. High turnover-numbers (TON) and frequencies (TOF) have been achieved with the investigated catalytic systems for different substrates.

[1] (a) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.
(b) Heck, R. F.; Nolley, J. P., Jr. *J. Org. Chem.* **1972**, *37*, 2320-2322.
[2] Herrmann, W. A.; Brossmer, C.; Reisinger, C.-P.; Riermeier, T. H.; Öfele, K.; Beller, M. *Chem. Eur. J.* **1997**, *3*, 1357-1364.
[3] Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989-7000.

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Organic Chemistry **170**

## Kinetic studies of the enantioselective hydrogenation of unfunctionalised alkenes with iridium complexes and the characterisation of intermediate hydrido species

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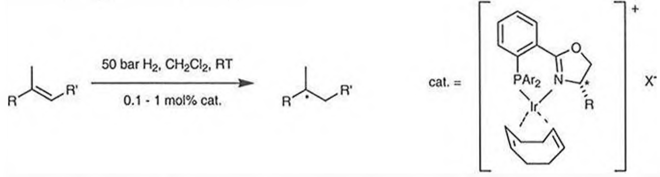
(a) University of Basel, Institute of Organic Chemistry,
St. Johanns-Ring 19, CH-4055 Basel

(b) Solvias AG, WRO-1055.6.16, Klybeckstrasse 191, CH-4002 Basel

Chiral analogues of the Crabtree catalyst [1] were developed in recent years in our group. [2] The iridium complexes of these PHOX ligands show the best results so far in activity and enantioselectivities of up to 99% for a whole range of alkene substrates.



Using hydrogen consumption measurements, the catalytic reaction with a series of catalysts with different anions was followed. Deactivation of the catalytic systems could be observed and distinguished between different conditions.

In order to gain further insight into the reaction mechanism, iridium hydrido species were analysed by NMR and a trimeric inactivated species, $[\mathrm{Ir_3(P^\wedge N)_3(H)_7}](\mathrm{PF_6})_2$, was isolated and characterised by X-ray crystallography.

[1] R. Crabtree, *Acc. Chem. Res.* **1979**, *12*, 331-338.
[2] (a) A. Lightfoot, P. Schnider, A. Pfaltz, *Angew. Chem. Int. Ed.* **1998**, *37*, 2897-2899; (b) D. G. Blackmond, A. Lightfoot, A. Pfaltz, T. Rosner, P. Schnider, N. Zimmermann, *Chirality* **2000**, *12*, 442-449.

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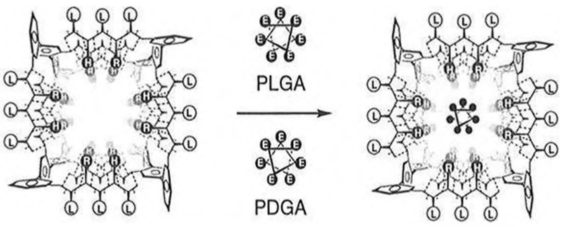
Organic Chemistry **171**

## Toward Recognition, Nucleation and Orientation of α-Helices within Rigid-Rod β-Barrels in Polarized Bilayer Membranes

N. Sordé, N. Sakai, and S. Matile*

University of Geneva, Department of Organic Chemistry
1211 Geneva, Switzerland

The usefulness of synthetic *p*-octiphenyl β-barrel ion channels [1] with internal histidine-arginine dyads to bind poly-*L*-glutamic acid (PLGA) and poly-*D*-glutamic acid (PDGA) with nanomolar dissociation constants will be described. Emphasis will be on the pH dependence of PLGA binding to study the influence of peptide charge, secondary structure, and internal α-helix nucleation as well as on the voltage dependence of PLGA binding to achieve α-helix orientation by constructive dipole-potential interactions [2].



[1] S. Matile, *Chem. Soc. Rev.* **2001**, *30*, 158.
[2] N. Sordé, N. Sakai, S. Matile, unpublished results.

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Organic Chemistry **172**

## Rigid-Rod β-Barrels with Internal "Cascade Blue" Cofactors to Catalyze Ester, Amide, and Carbonate Hydrolysis

A. Som, P. Talukdar, B. Baumeister, and S. Matile*

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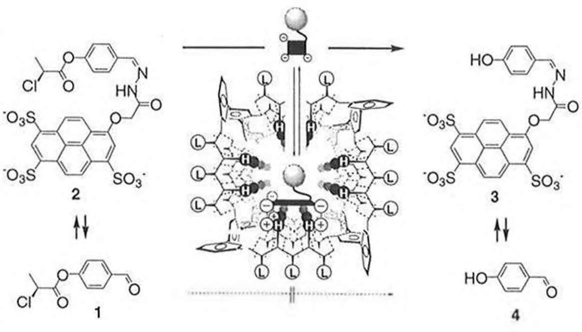
1211 Geneva, Switzerland

The "Cascade Blue" scaffold (*i.e.*, 8-X-oxy-pyrenyl-1,3,6-trisulfonates) is introduced as internal cofactor for histidine-rich *p*-octiphenyl β-barrels with ion channel [1], esterase [1], RNase [2] and fibrillogenic activity [3] to mediate binding and conversion of otherwise inaccessible benzaldehyde substrates (*e.g.*, **1**) *via* reversible hydrazone formation (*e.g.*, **2**). Up to $10^5$-fold accelerated conversions, high substrate diversity, high chemoselectivity, and poor enantioselectivity will be described [4].



[1] B. Baumeister, N. Sakai, S. Matile, *Org. Lett.* **2001**, *3*, 4229.
[2] B. Baumeister, S. Matile, *Macromolecules* **2002**, *35*, 1549.
[3] G. Das, L. Ouali, M. Adrian, B. Baumeister, K. J. Wilkinson, S. Matile, *Angew. Chem., Int. Ed.* **2001**, *40*, 4657.
[4] A. Som, S. Matile, unpublished results.

D13/0001/2002

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## SYNTHESIS OF C-DISACCHARIDES THROUGH CARBONYLATIVE STILLE COUPLING

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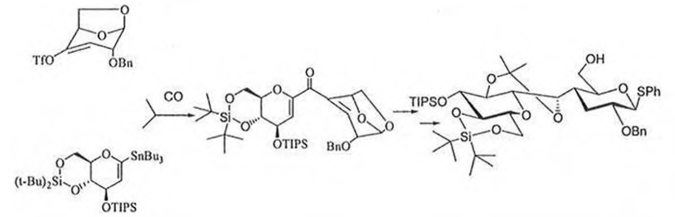
The C-glycoside analogues of O-glycosides have gained interest during the last years through their inherent stability towards hydrolysis. These new compounds are potential inhibitors of glycosyltransferases and glycosidases.[1] which are responsible for the biosynthesis of oligosaccharides, and may become non-hydrolysable mimics of epitopes (artificial vaccines).

Here, we report the synthesis of C-disaccharides through carbonylative Stille coupling.[2] The C-(1→1) and C-(1→4)-disaccharides precursors, formed through coupling, bear cross-conjugated dienone moieties. C-dissacharides can then be generated through functionalisation of these cross-conjugated dienones.



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Organic Chemistry

### 174

## Flame Retardancy of Polyacrylonitrile Fabrics byApplication a Low Pressure Plasma Process

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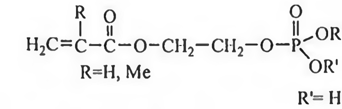
Surface modification has proved to be a particularly attractive way to flame retard polymers. Several methods have been developed, and among them low-pressure plasma processes. The advantage of this technique is that the modification is restricted to the uppermost layers of the substrates. Since flammability is controlled mainly by surface properties, modification of substrate surfaces and proper grafting of flame retardant groups such as phosphorus or phosphorus-nitrogen containing monomers would alter flammability without affecting bulk properties, furthermore is a clean environmental process.

In this paper we present the use of plasma induced graft polymerization technique to confer durable flame retardancy properties to polyacrylonitrile fabrics. For this purpose, (meth)acrylate phosphate monomers were used.



$$H_2C{=}\overset{\overset{\textstyle R}{|}}{C}-\overset{\overset{\textstyle O}{\|}}{C}-O-CH_2-CH_2-O-\overset{\overset{\textstyle O}{\|}}{P}\begin{matrix}-OR' \\ \diagdown OR'\end{matrix}$$

R=H, Me

R'= H,E t

In a first step, the kinetic of homopolymerization of monomers were studied. The grafting and the polymerization were evidenced by IR (ATR) and MEB spectrsocopies. The flame retardancy of the fabrics has been assessed by limiting oxygen measurements (LOI).

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Organic Chemistry

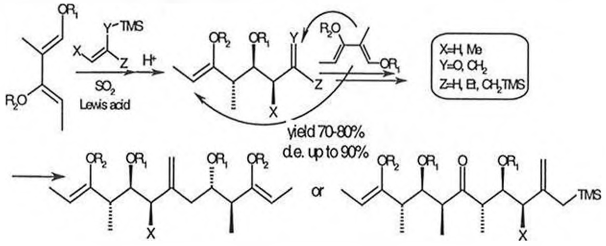
### 175

## Double Chain Elongation to Elaborate Complex Polypropionate Fragments Based on New Chemistry of Sulfur Dioxide.

Māris Turks, Pierre Vogel*

*ICMB, LGSA, EPFL, CH-1015 Lausanne-Dorigny, Switzerland.*

An interesting class of natural compounds with an exceptional profile of biological activity are polypropionates (polyketides) [1]. Many approaches have been developed to synthesize polyketide fragments. Our group has shown that simple alkyl-substituted 1,3-dienes can undergo hetero-Diels-Alder (HAD) reaction with $SO_2$ giving the corresponding 3,6-dihidro-1,2-oxatiin-2-oxides (sultines) [2]. These cycloadducts are unstable, however at low temperature in the presence of Lewis acids they could be opened to zwitterionic intermediates, which could be trapped by nucleophiles, namely enoxysilanes. Recently an asymmetric version of this oxyallylation has been proposed [3]. Here we would like to report about further development of this method using 1,3-dioxy substituted dienes. For the first time we show that different allylsilanes are also capable to undergo the oxyallylation. Representative examples are shown below.



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Organic Chemistry

### 176

## Mechanistic Studies on the Enantioselective Hydrogenation of Ketones on Cinchona Alkaloid Modified Platinum

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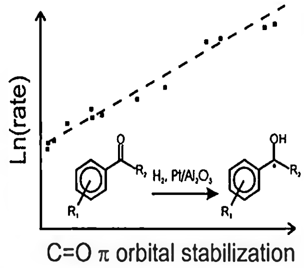
A correlation was found between the keto carbonyl orbitals energy and reaction rates of hydrogenation, in the case of a series of substituted acetophenones [1][2]. Given this insight, the mechanism proposed for the enantioselective hydrogenation of ketones on cinchona modified platinum [3] predicts a rate acceleration due to the hydrogen bonding interaction between the surface modifier and the target molecule, as the hydrogen bond stabilizes the keto carbonyl orbitals. Further studies on this mechanism of activation are persued in order to test its generality.



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[2] A. Vargas, T. Bürgi , R. Hess, M. VonArx, A. Baiker, *J. Catal.*, 2002, in press.
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Organic Chemistry

## 177

### NMR Enantiodifferentiation and Chiral Recognition of Chiral Ammonium Cations by BINPHAT Anion.

Laurent Vial, Anne Londez and Jérôme Lacour*.

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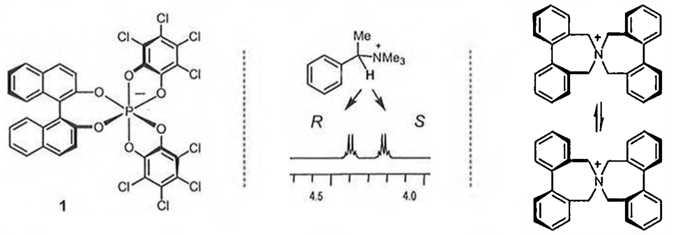
Chiral quaternary ammonium cations are the subject of much attention due to the potential of these derivatives to serve as efficient chiral phase transfer catalysts. Whereas most examples of highly stereoselective reactions have employed cations derived from the chiral pool, recent reports of successful transformations mediated by purely synthetic chiral *quats* raises the general question of the determination of their enantiomeric purity [1].



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$C_2$-symmetric hexacoordinated phosphorus BINPHAT anion **1** – of configuration controlled by a binol ligand – is readily prepared in a one-pot reaction [2]. In this poster, we show that this anion behaves as an efficient NMR chiral shift agent for quaternary ammonium cations [3]. It is also a non-covalent chiral auxiliary onto configurational labile derivatives allowing the stereoselective synthesis of the chiral species that would – otherwise – be racemic.

[1] T. Ooi, M. Kameda, K. Maruoka, *J. Am. Chem. Soc.* **1999**, *121*, 6519.

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Organic Chemistry

## 178

### Preparation of Pyrenyl-Modified Nucleosides and Oligonucleotides via Suzuki-Miyaura Cross-Coupling Reactions

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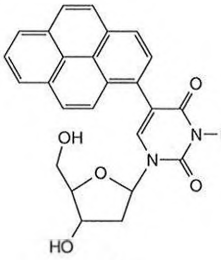
Reductive electron transfer through DNA duplexes is currently used extensively in DNA chip technology without understanding the mechanism of this type of charge transfer. Our group is currently on the way to design and prepare DNA assays based on pyrenyl-modified oligonucleotides which allow the time-resolved spectroscopic observation of reductive electron transfer through DNA.

We want to present here the preparation of pyrenyl-modified nucleosides, such as **1** and **2**, and oligonucleotides, as models for electron transfer, or hole transfer, respectively.[1] We chose to use the palladium-catalyzed Suzuki-Miyaura-type cross-coupling reaction which tolerate unprotected functional groups as well as aqueous reaction solutions. Thus, no protection of the nucleoside precursors is needed during the preparation. The protocol is very versatile and suitable for the preparation of a variety of aryl-modified nucleosides and oligonucleotides.



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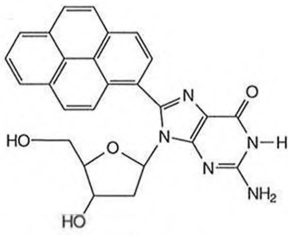

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Organic Chemistry

## 179

### Towards Total Synthesis of Cephalotaxine; Preparation of the Key Intermediate *via* Asymmetric Radical Azidation

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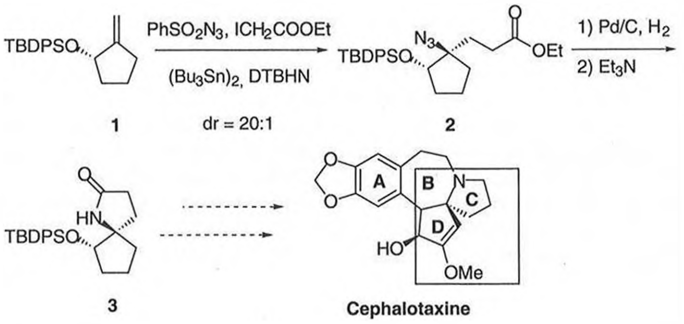
Recently we developed a novel intermolecular radical azidation reaction [1,2]. The utility of this methodology was demonstrated by preparation of various pyrrolidinone derivatives [3].



Currently we examine asymmetric version of the radical azidation reaction. During this study we prepared azaspirocyclic compound **3**, which is a key intermediate in the total synthesis of cephalotaxine.

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Physical Chemistry

## 180

### The 1,2-dichloroethane/water vs. the *n*-octanol/water system: more about intra- or intermolecular H-bond interactions.

A. Galland[1], G. Bouchard[1], G. Caron[2], G. Plemper van Balen[1],
C. A Marca Martinet[1], S. Geinoz[1], S. Rey[1], G. Ermondi[2], F. Vacondio[3],
M. Mor[3], P.V. Plazzi[3], P.-A. Carrupt[1], B. Testa[1].

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[2] Dip. Scienza e Tecnologia del Farmaco, Via Giuria 9, I-10125 Torino.
[3] Dip Farmaceutico, Università di Parma, I-43100 Parma.

Lipophilicity is a molecular property describing the relative affinity of a solute for an organic and an aqueous phase. As solvation involves interactions between the solute and the solvent, comparing the partition coefficients log P obtained in different solvent systems can generate important physicochemical information [1]. The partition coefficients of a large series of model compounds and drugs were measured in the *n*-octanol (oct)/water and in the 1,2-dichloroethane (dce)/water systems.

In a graphical representation of $\log P^N_{dce}$ *vs* $\log P^N_{oct}$, the $\alpha$ properties (H-bond donor capacity) of the solutes ($\alpha = 0$ and $\alpha > 0$) split the set into two groups. The location of more complex solutes is related to their H-bond donor capacity, which can be predicted by Systahl 1.0 [2] or by the commercial method ABSOLV [3]. A comparison between the expected and the true location on the $\log P^N_{dce}$ *vs* $\log P^N_{oct}$ graph can reveal the $\alpha$ expression in non-polar media as strongly influenced by the formation of intramolecular H-bonds.

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**181**

## Ionization detected overtone spectroscopy of the $N$=2 CH-chromophore of jet-cooled benzene isotopomers near 6000 cm$^{-1}$

Michael Hippler, Robert Pfab, and Martin Quack

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Benzene has been a prototype system for the study of molecular structure and dynamics for a long time [1], including in particular intramolecular vibrational redistribution processes [2-4]. Employing our recently introduced IR+UV double-resonance scheme for obtaining mass-resolved infrared spectra, the isotopomer selected $N$=2 CH-chromophore absorption of $^{12}C_6H_6$ and $^{13}C^{12}C_5H_6$ near 6000 cm$^{-1}$ has been recorded in a supersonic jet expansion of the benzene isotopomer mixture at natural abundance [5]. The $^{13}C^{12}C_5H_6$ spectra are the first of this kind reported in the literature. The $^{12}C_6H_6$ spectrum is compatible with a proposed model of intramolecular vibrational redistribution with a distinct hierarchy of time scales: the CH-stretching state is the IR chromophore state coupled to the IR field. With a decay time of $\tau \approx 120$ fs, vibrational excitation is redistributed to a first tier of vibrational states, probably CH-stretching/bending combination bands coupled by strong Fermi resonances. Vibrational excitation is then further redistributed with $\tau \approx 0.35$ ps to a second tier of states, possibly by weaker quartic and quintic anharmonic resonances. The observed line widths give a lower bound for the decay time into the dense background manifold, $\tau > 1.3$ ps. Although the experimental jet spectra are in qualitative agreement with calculated spectra, they clearly disagree in finer details.

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Physical Chemistry **182**

## Rovibrational analysis of the $\nu_3$ band of CDBrClF

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Laboratorium fur Physikalische Chemie, ETH Zurich,
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CDBrClF, the deuterated species of CHBrClF, is one of the simplest chiral molecules. It is of fundamental interest to demonstrate molecular parity violation [1]. In order to carry out promising experiments to prove the parity violation for this molecule the high resolved infrared spectrum has to be analyzed first. So far we have already assigned the $\nu_5$ (CCl-stretch) and $\nu_4$ (CF-stretch) region of the spectrum [2,3]. With our new Fourier transform infrared (FTIR) spectrometer Bruker IFS 120 HR (ultrahigh resolution prototype) we are now able to measure rovibrational spectra with a resolution up to 0.0007 cm$^{-1}$. Using these high resolution spectra we have assigned the $\nu_3$ (CD-bending) fundamental of CD$^{79}$BrClF ($\nu_c$=918.3715 cm$^{-1}$). We have detected local resonances for $K$>2 between $J$=75-83. The resonance partner is probably the $\nu_6+\nu_8$ state. Based on these assignments we can now propose experiments using microwave spectroscopy to detect molecular parity violation for this and heavier molecules.

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Physical Chemistry **183**

## Investigation of chirally modified Pt and Pd catalysts by *in situ* IR spectroscopy

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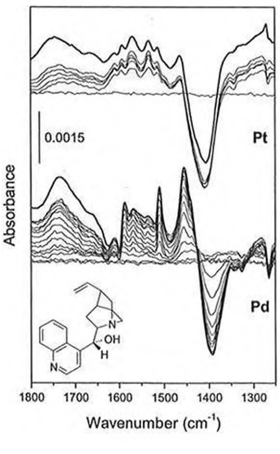
ETH Hönggerberg, 8093 Zürich

ATR-IR spectroscopy has been used to investigate the adsorption of the chiral modifier cinchonidine (CD), an efficient modifier in the enantioselective hydrogenation of C=O and C=C double bonds over chirally modified Pt and Pd catalysts [1]. ATR spectra (see Figure) recorded at 283 K in presence of $H_2$ and $CH_2Cl_2$ clearly indicate that CD adsorption on Pt and Pd is governed by the quinoline moiety and is coverage-dependent. Three species coexist on Pt/$Al_2O_3$ [2]. On Pd/$Al_2O_3$ only two species have been detected: CD oriented with the $\pi$-system nearly parallel to the metal surface and CD oriented with the $\pi$-system tilted with respect to the surface. Experimental evidence is also given that CD adsorbs weaker on Pd than on Pt at 283 K, which is attributed to the dissimilar orbital overlap between the d orbitals of Pt and Pd and the $\pi$-electrons of the quinoline moiety of CD.



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[2] D. Ferri, T. Bürgi, *J. Am. Chem. Soc.* **2001**, *123*, 12074.

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Physical Chemistry **184**

## Effect of Isotopic Substitution on Parity Violating Energy: Influence of Anharmonic Corrections

Martin Quack , Achim Sieben* and Martin Willeke
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Due to the parity violating electroweak interaction, enantiomers of a chiral molecule have slightly different energies. Fundamental consequences of this phenomenon are discussed in [**1**, **2**]. The parity violating energy $E_{PV}$ was calculated with our recently developed MC-LR approach [3]. In the present paper [4] we determined $E_{PV}$ at the minimum of the electronic Born-Oppenheimer potential for various phosphane derivatives ($PXY_2$ with X,Y=H, D, F, $^{35}$Cl, $^{37}$Cl, $^{79}$Br, $^{81}$Br ), which are chiral only by isotopic substitution. These $E_{PV}$ values were compared with $< E_{PV} >$, the vibrational averaged expectation value of $E_{PV}$. In order to get a good approximation for $<E_{PV}>$ we calculated $E_{PV}$ potentials as well as the electronic potential energy surfaces for all one dimensional (1D) normal coordinate subspaces. For these 1D subspaces accurate vibrational variational calculations were carried out, which enable us to determine individual contributions to $<E_{PV}>$ for each 1D subspace [5, 6]. In this one dimensional separable picture we also calculate $<E_{PV}>$ for vibrationally excited states. We found that especially for PDHX derivatives an anharmonic correction is essential, as $<E_{PV}>$ is up to two orders of magnitude larger than $E_{PV}$ in the examples investigated.

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Physical Chemistry **185**

# LIQUID-LIQUID INTERFACES STRUCTURE AND THICKNESS EXPLORED BY TRANSIENT EVANESCENT GRATINGS

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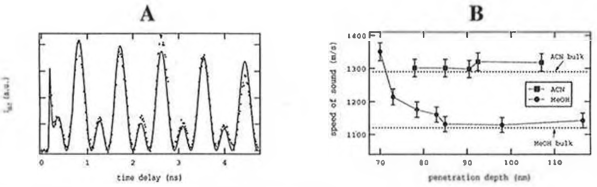
*30, Quai Ernest Ansermet, CH-1211 GENEVA 4, Switzerland*

Liquid-liquid interfaces play a major role in a broad range of applications [1] and their physico-chemical properties are known to differ strongly from those of the bulk. But due essentially to the difficulty to investigate them selectively, they are far from being completely understood.

Since the acoustic properties of materials are strongly related to their structure, we have undertaken their measurement using transient density phase gratings [2] selectively at liquid-liquid interfaces by evanescent probing or pumping.



*A interfacial TDPG signal in ACN; **B** penetration depth dependance of the speed of sound*

We have found that in protic solvents the speed of sound becomes faster and faster approaching the interface, whereas no correlation was found in aprotic solvents. Moreover, the electrostrictive nonlinear response near the interface seems to be substantially larger than in the bulk.

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Physical Chemistry **186**

# TDFT and ROKS Characterization of Aminocoumarins in solution: towards the design of new fluorescent probes

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The aminocoumarins are an important group of laser dyes in the blue-green region. In biology their spectroscopic properties have been recently exploited to monitor the enzymatic activities of several classes of proteases. In these probes aminocoumarins are linked to specific peptide recognition sequences. Enzymatic proteolysis determines changes in the substrate emission wavelength allowing a determination of the enzymatic activity. However, the domain of application of these compounds is hampered by a variety of factors since the spectra are dramatically affected by temperature and protein environment. Full undestanding of the spectral properties of the coumarins is of crucial importance for the design of new and more efficient substrates with large Stoke's shifts for an optimal separation of absorption and fluorescence bands. We performed TDFT [1] and ROKS [2] calculations on a class of coumarins for which experimetal data are available [3] in order to quantify the chemical substituent effects. Solvent and protein effects are included through a QM/MM approach [4] and their effects on the spectral properties are discussed. Our approach is able to give quantitative informations on spectral shifts and can be a useful instrument towards a rational design new and more specific probes.

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# THE AgCl PHOTOANODE **187**

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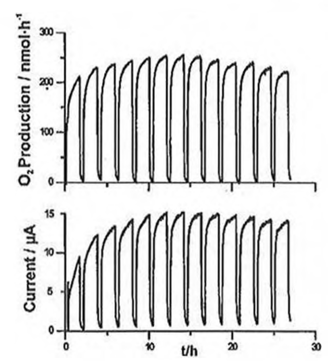
Thin AgCl layers photocatalytically oxidize water to $O_2$ under UV/Vis illumination in the presence of a small excess of silver ions [1]. The light sensitivity in the visible part of the spectrum is due to self-sensitization caused by reduced silver species [2]. Anodic polarization allows the reoxidation of said silver species. An improvement in layer sensitivity has been realized by enlarging the electrode surface area [2] and by adding sensitizers such as bromide [3], see figure. The AgCl photoanode was characterized by a number of techniques including in situ diffuse reflectance spectroscopy, surface photovoltage spectroscopy (SPS) and electron microscopy. Much insight was gained on the compositional and/or morphological changes as well as changes in electronic structure as a result of the photoreaction.



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# Luminescent Silver Sulfide Clusters **188**

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By using the well-defined cavities of zeolites we developed a method of synthesizing quantum-sized silver sulfide clusters. The preparation is based on the observation that $Ag^+$-loaded zeolite A can be reversibly activated at room temperature.[1] Its reaction with $H_2S$ leads to the formation of silver sulfide clusters in the α-cage.[2] These are the first silver sulfide species for which luminescence in the visible range of the spectrum has been observed. The color of the silver sulfide–zeolite composites ($Ag_2S$–CaA-$x$, where $x$ denotes the number of $Ag^+$ per α-cage) ranges from colorless ($0.01 < x < 0.5$) to yellow ($0.5 < x < 2$) to brown ($x > 2$). The cluster size can be varied by adjusting the initial amount of $Ag^+$ inside the zeolite. A low silver sulfide content is characterized by a blue-green luminescence and distinct absorption bands, caused by $Ag_2S$ in the α-cage. Samples with medium silver sulfide content show an orange-colored luminescence which comes from larger silver sulfide clusters e.g. $Ag_4S_2$.

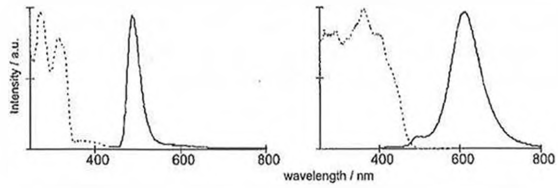

**Figure:** Luminescence (solid; excitation at 320 nm) and excitation (dot) spectra of $Ag_2S$–CaA-0.01 (left) and $Ag_2S$–CaA-2 (right) at 80 K.

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Physical Chemistry **189**

## Trapping Energy from and Injecting Energy into Dye-Zeolite Nanoantennae

Huub Maas, Stefan Huber, Gion Calzaferri*

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Efficiently working antenna systems could greatly enhance the absorptivity of future solar cells. We have shown in the past that efficiently working antennae can be made by using zeolite L crystals as a matrix for organic dyes. The systems transport electronic excitation energy through the crystal channels by fast radiationless energy migration [1, 2, 3].

We now advanced these light harvesting systems by attaching stopcock dyes on the outer surface of nano sized zeolite L crystals. The dyes preferably adsorb on the top and bottom edges of the cylindrical crystals and are too large to enter the open free diameter of the channels of zeolite L. We think they partly enter the channels because of their shape.

These stopcock dyes enable us to trap and inject electronic excitation energy at the outer surface of our antennae [4]. This opens a wide range of applications for these host-guest systems. One of the things we are interested in is to sensitise a semiconductor surface with our dye-loaded zeolite L crystals by energy transfer [5]. This will lead to a brand new type of dye sensitised solar cell, where the dyes would not have to be regenerated.

[1] S. Megelski, G. Calzaferri, *Adv. Funct. Mater.* **2001**, *11*, 277.
[2] M. Pauchard, S. Huber, R. Méallet-Renault, H. Maas, R. Pansu, G. Calzaferri, *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 2839.
[3] G. Calzaferri, H. Maas, M. Pauchard, M. Pfenniger, S. Megelski, A. Devaux in *Advances in Photochemistry, Vol 27* (Ed.: D. C. Neckers), Wiley-VCH, Winheim, **2002**, in press.
[4] H. Maas, G. Calzaferri, *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, in press
[5] G. Calzaferri, M. Pauchard, H. Maas, S. Huber, A. Khatyr, T. Schaafsma, *J. Mater. Chem.* **2001**, *12*, 1.

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Physical Chemistry **191**

## EPR/ENDOR spectra and DFT calculations of the one-electron reduction compound of a di (meta - sylphenylenesiloxane)

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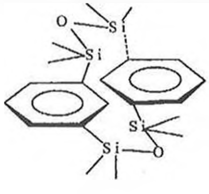
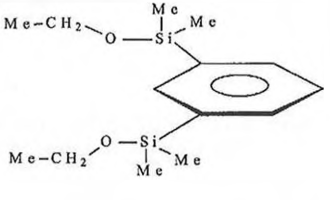
The EPR/ENDOR spectra obtained after reduction of a solution of **A**[1] in THF on a K mirror are similar to the spectra of a reduced solution of **B** and are characterized by a 20 MHz coupling with two protons, which is consistent with the localisation of the extra electron on a single ring of **A**. The reduction of **A** at low temperature in the presence of an equimolar amount of crown ether leads to a spectrum characterized by couplings of *c.a.* 10 MHz with four protons and indicate that embedding the counterion in crown-ether provokes the delocalisation of the unpaired electron on the two phenyl rings of **A**. The measured hyperfine interactions agree with those calculated by DFT for the optimised structure of $\mathbf{A}^{\bullet-}$. The structure of $\mathbf{A}^{\bullet-}$ appears as the transition state of an electron transfer reaction (inner-sphere mechanism) between the two metadisilylphenyl moieties.



**A**



**B**

[1] Zhang, R.; Pinhas,A.R.; Mark, J.E. *Polym. Prep. (Am. Chem. Soc., Div. Polym. Chem.)* **1998**, 39, 607

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Physical Chemistry **190**

## Charge Transfer in Electron Donating Solvents

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Studying intermolecular electron transfer (ET) processes in liquid donor solvents has the main advantage of suppressing the diffusion limit, making possible the measurement of the intrinsic rate constant of the reaction. We report here on the investigation of the dynamics of electron transfer from various donating solvents (aniline derivatives, aliphatic amines) to perylene (Pe) and 3-cyanoperylene (CNPe) in their lowest singlet excited state. Measurements were done using multiplex transient grating, which monitors both the decay of the excited precursor and the formation of the ionic product, and fluorescence up-conversion techniques.

The observed decay kinetics show a highly non-exponential behaviour and depend strongly on the studied system. Observed rate constants spread from hundred of fs (CNPe in small aniline derivatives) to hundred of ps (Pe in bulky aniline derivatives). The main observed trends are:

-The observed ET rate constants do not exhibit significant free energy dependence, apart from weakly exergonic reactions
-ET is remarkably faster with CNPe than with Pe
-The observed ET rate constants decrease with increasing bulkiness of the donor
-The decay of the excited acceptor is, in some cases, markedly faster than the formation of the charged product
-Strong exciplex emission is observed with the tertiary aniline derivatives

Each of these features will be discussed in detail and a model will be proposed.

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Physical Chemistry **192**

## *In situ* X-ray absorption spectroscopy on heterogeneous noble metal catalysts

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M. Ramin, Alfons Baiker

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ETH Hönggerberg, CH-8093 Zürich, Switzerland

X-ray absorption spectroscopy (XAS) is a valuable tool for understanding heterogeneous catalysts because it is element specific and important structural information on small particles, clusters or amorphous structures can be gained [1]. In addition, one of the inherent advantages is that the technique can be used *in situ* during activation of a catalyst or under reaction conditions (e.g. [1,2]). A major challenge is the design of an *in situ* cell, which allows to gain information on the structure under conditions that resemble as close as possible those during activation and reaction.

In the present study we show examples from *in situ* studies on heterogeneous Ir and Pd based noble metal catalysts, which are efficient catalysts, *i.e.* in the catalytic combustion of methane, the removal of $NO_x$, the hydrogenation of $CO_2$, and the oxidation of CO (e.g. [3,4]). The studies were performed both under static and dynamic (variation of temperature, gas composition) conditions. In order to combine the structural investigation by XAS with the catalytic activity of the catalysts, on-line product analysis was performed by mass spectrometry. A pre-reduced $Pd/ZrO_2$ catalyst, used for methane combustion, was *i.e.* oxidized when the reaction started.

[1] Iwasawa, Y. *X-ray absorption fine structure for catalysts and surfaces*; World Scientific: Singapore, 1996.
[2] Grunwaldt, J.-D.; Clausen, B. S. Topics Catal. **2002**, *18*, 37.
[3] Müller, C. A.; Maciejewski, M.; Koeppel, R. A.; Tschan, R.; Baiker, A. J. Phys. Chem. **1996**, *100*, 20007.
[4] Wögerbauer, C.; Maciejewski, M.; Baiker, A. J. Catal. **2002**, *205*, 157.

Physical Chemistry **193**

### Barrelenephosphines. A new class of air stable, crystalline, primary phosphines

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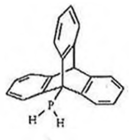
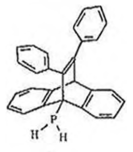
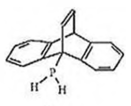
A new set of phosphorous compounds containing the $PH_2$ moiety attached to the rigid framework of barrelene was synthesised. These compounds form a new class of air stable, crystalline, primary phosphines. The derivatives of barrelene were synthesised via a Diels-Alder addition of various substituants on the 9-bromoanthracene and a subsequent introduction of the phosphorous at the bridgehead position[1]. All the phosphines (**1-5**) are crystalline, air stable, yellow or white solids.



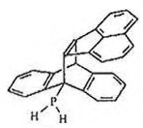
**1**



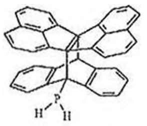
**2**



**3**



**4**



**5**

Recently, we reported several EPR studies on the hindered rotation of the PH fragment in a X-irradiated, single crystals of phosphines **1**[2],**2**[3] and **3**[4]. The dynamics of rotation of the $PH_2$ group in the diamagnetic molecules **4** and **5**, and the dynamics of rotation of the paramagnetic fragment PH obtained by the X-irradiation of the corresponding diamagnetic molecules, are currently under investigation.

[1] M. Brynda, M. Geoffroy, G. Bernardinelli, *Chem. Commun.* **1999**, 961.
[2] G. Ramakrishnan, A. Jouati, M. Geoffroy, *J. Chem. Phys.* **1996, 100**, 10861.
[3] M. Brynda, T. Berclaz, M. Geoffroy, G. Bernardinelli, *J. Phys. Chem. A* **1998**, 8245.
[4] M. Brynda, T. Berclaz, M. Geoffroy, *Chem. Phys. Lett.*, **2000, 323**, 474.

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Physical Chemistry **194**

### Electronic and Vibrational Spectra of Fluorenone in Zeolite L

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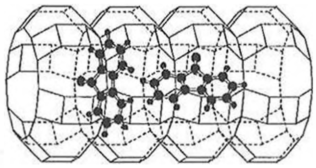
Fluorenone was successfully inserted into the channels of zeolite L following a method described in [1]. The size, the structure, and the stability of fluorenone are well suited for the study of the interaction of the molecule with the zeolite framework. The FT-IR, Raman, luminescence emission and excitation spectra of this system were recorded in order to study this. Normal coordinate analysis and EHMO calculations were performed to gain a better understanding of the system. An extensive analysis on spherosiloxanes was done in a previous work [2].



The FT-IR spectrum of fluorenone in zeolite shows only a significant shift of the C=O stretching band compared to the spectrum in KBr. The emission spectra of fluorenone in different solutions and their temperature dependence have been studied extensively [3][4]. Upon insertion into the zeolite, the emission spectra of the dye change considerabely.

[1] M. Pauchard, A. Devaux, G. Calzaferri, *Chem. Eur. J.* **2000**, *6*, 3456
[2] C. Marcolli, G. Calzaferri, *J. Phys. Chem. B*, **1997**, *101*, 4925
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[4] L. Biczók, T. Bérces, *J. Phys. Chem.* **1988**, *92*, 3842

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Physical Chemistry **195**

### Phenol adsorption by carbons

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University of Neuchâtel, Chemistry Institute, CH-2007 Neuchâtel.

Adsorption of phenol and phenolic compounds from aqueous solution is one of the most studied of liquid-phase applications of carbon adsorbents. The adsorption process depends on many factors (pH of solution, surface area of the adsorbent and its surface chemistry).

On non-porous and microporous carbons, it appears that phenol adsorption from dilute solutions is limited to a monolayer. The specific enthalpy of transfer from the liquid to the surface of ≈ –30 kJ mol$^{-1}$ indicates a similar adsorption mechanism for both types of carbon. Moreover, the adsorption isotherm follows the Dubinin-Radushkevich-Kaganer equation for adsorption on open surfaces where the adsorption potential A = RT ln($p_s$/p), $N_{am}$ the monolayer capacity of the surface and E the characteristic energy:

$$N_a = N_{am} \exp[-(A/E)^2] \qquad \text{DRK}$$

On the other hand, immersion of activated carbons into concentrated phenol solutions corresponds to a volume filling process. Adsorption of phenol vapour near and above room temperature follows the Dubinin-Radushkevich equation for volume filling of micropores, where W is the adsorbed volume and $W_o$ the micropore volume of the adsorbent.

$$W = W_o \exp[-(A/E)^2] \qquad \text{DR}$$

In all cases, the oxygen content has an influence on the adsorption of phenol.

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Physical Chemistry **196**

### Electrochemical Characterization of Heat Treated Graphite

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Paul Scherrer Institute, Laboratory for Electrochemistry, CH-5232 Villigen PSI

Lithium-ion cells often contain graphite as the negative electrode material for reasons of low cost and good cycle performance. It is well known that the graphite electrode is always covered by a thin protective film called the Solid Electrolyte Interphase (SEI). The film formation consumes lithium ions and thus, the energy density of the cell decreases. The quality of the SEI strongly depends on material parameters of the graphite, subsequent graphite treatment, and the composition of the electrolyte solution.

To study the influence of graphite modification by heat treatment on the SEI formation we oxidized TIMREX SLX 50 graphite in air at different temperatures for 1 h. Significantc hanges in electrochemical behaviour were observed in an electrolyte containing ethylene carbonate and dimethyl carbonate (1:1) with 1M $LiPF_6$ as the conducting salt. We found an extended potential plateau at about 0.5 – 0.7 V vs. Li/$Li^+$ fors amples with the heat treatment temperature above 700 °C. The plateau arises due to the electrochemical decomposition of components of the electrolyte solution. Thus,t he graphite heat treatment temperature should not exceed 700 °C.

The electrochemical experiments were supplemented with the determination of the cristallite size $L_a$ of surface oxidized graphites using Raman spectroscopy and the equation of Tuinstra and Koenig [1]. We have seen that $L_a$ increases with an increase in the oxidation temperature, but there is no obvious correlation of $L_a$ with electrochemical data.

*We acknowledge the support of Prof. A.W okaun (PSI) and Dr.M . E. Spahr (TIMCAL SA. Bodio).*

[1] F. Tuinstra,J .L . Koenig, *J. Chem. Phys.* 53 (1970) 1126.

Physical Chemistry **197**

## Electroweak Parity Violation in the Chiral Molecule 1,3-Difluoroallene

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In contrast to the traditional view, electroweak quantum chemistry predicts enantiomers of chiral molecules to differ in energy. Moreover, for typical, stable chiral molecules with high energetic barriers against interconversion between enantiomers, parity violation should as a rule dominate the dynamics of chirality [1,2]. We report the first computational results for parity violation in 1,3-difluoroallene, which is a chiral molecule in its equilibrium geometry. We calculated the parity-violating potential as a function of the dihedral angle using our recently introduced multiconfiguration linear response approach [3]. In particular we applied the CASSCF-LR method, which is suited to describe biradicals and biradicaloids, to the calculation of twisted 1,3-difluoroallene. The P enantiomer of 1,3-difluoroallene is calculated to be more stable than the M enantiomer by about 1 x $10^{-12}$ J $mol^{-1}$. Additional calculations of the potential energy surfaces of the first excited states of 1,3-difluoroallene will be presented. We have also synthesized it and measured its infrared spectra as it may prove useful for the spectroscopic detection of molecular parity violation by ultrahigh resolution techniques [4,5].

[1] R. Berger, M. Gottselig, M. Quack, M. Willeke, *Angew. Chem. Int. Ed.*, 2001, *40*, 4195.
[2] M. Gottselig, D. Luckhaus, M. Quack, J. Stohner, M. Willeke, *Helv. Chim. Acta*, 2001, *84*, 1846.
[3] R. Berger, M. Quack, *J. Chem. Phys.*, 2000, *112*, 3148.
[4] M. Quack, *Chem. Phys. Lett.*, 1986, *132*, 147.
[5] M. Quack, *Angew. Chem.*, 1989, *101*, 588; *Nova Acta Leopoldina NF*, 1999, *81*, 137.

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Physical Chemistry **199**

## *In situ* XANES study on $TiO_2$-$SiO_2$ aerogels and flame made materials

J.-D. Grunwaldt[1], C. Beck[1], W. Stark[1,2], A. Hagen[3], Alfons Baiker

[1]Laboratory of Technical Chemistry, Swiss Federal Institute of Technology, ETH Hönggerberg, CH-8093 Zürich, Switzerland
[2]Laboratory of Process engineering, Swiss Federal Institute of Technology, ETH Zentrum, CH-8092 Zürich, Switzerland
[3]Interdisciplinary Research Center for Catalysis, Technical University of Denmark, DK-2800 Lyngby, Denmark

Heterogeneous catalytic epoxidation of functionalized olefines in the liquid phase can be catalyzed by supported and mixed oxides, framework-substituted molecular sieves/zeolites, layered-type materials, and heterogenized homogeneous catalysts. One of the applications is the epoxidation of allylic alcohols by tert-butylhydroperoxide on Ti-based catalysts. Recently, we have studied the epoxidation of 2-cyclohexene-1-ol over $TiO_2$-$SiO_2$ based aerogels and flame-made materials [1,2].

In this study we have applied X-ray absorption near edge structure (XANES) at the Ti K-edge to further understand the difference in performance between aerogel and flame made catalysts. Apart from other techniques, it is a useful technique to identify the structure (symmetry, coordination number, oxidation state) of Ti in the solid matrix.

The studies show that tetrahedral titanium sites are the favoured sites at low $TiO_2$ concentration, while octahedral species dominate at high $TiO_2$ concentrations. *In situ* XANES during dehydration of the catalyst revealed that the coordination geometry of low loaded aerogels changed from octahedral to tetrahedral upon heating. In contrast, the flame-made materials contain Ti mainly in tetrahedral coordination geometry, similar to TS-1, even without dehydration. This can be attributed to the hydrophobic character of the flame made materials and ameliorates the catalytic performance, *i.e.* the selectivity.

[1] Beck, C.; Mallat, T.; Bürgi, T.; Baiker, A. J. Catal. **2001**, *204*, 428.
[2] Stark, W. J.; Pratsinis, S. E.; Baiker, A. J. Catal. **2001**, *203*, 516.

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Physical Chemistry **198**

## EPR study of the one electron oxidation compound of some phosphine substituted Tetrathiafulvalene and their iron compounds

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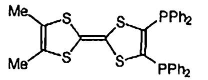
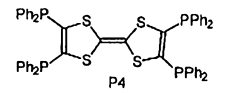
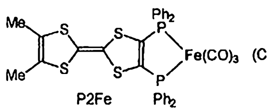
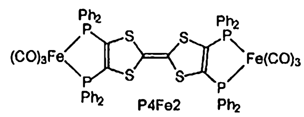
A one electron oxidation [1] of the diphosphine 3,4-dimethyl-3',4'-bis(diphenylphosphino)tetrathiafulvalene (**P2**) and the tetraphosphine tetrakis(diphenylphosphino)tetrathia-fulvalene (**P4**) was performed in situ in the EPR cavity by means of an electrochemical cell (optimised from the one described in ref. [2]). The EPR spectra exhibit hyperfine coupling with six equivalent protons for **P2**, and no hyperfine structure for **P4**. Spin densities were compared with those obtained by DFT calculation. All these results clearly show that the oxidation site is localised on the methylated double bond for **P2**, and the central double bond for **P4**.

The one electron oxidation of the iron complexes $P2Fe(CO)_3$ (**P2Fe**) and $P4[Fe(CO)_3]_2$ (**P4Fe2**) was performed under the same conditions. As shown by the $^{31}P$ coupling and the g anisotropy, the oxidation site is located on the metal, and no delocalisation occurs over the organic moiety.


P2


P4


P2Fe


P4Fe2

[1] N. Avarvari, D. Martin, M. Fourmigue, *J. Organomet. Chem.*,**2002**,*643-644*,292-300
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Physical Chemistry **200**

## THE NH- and ND-STRETCHING FUNDAMENTALS OF $^{14}ND_2H$.

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HANS HOLLENSTEIN and MARTIN QUACK, Physical Chemistry, ETH Zürich, CH-8093 Zürich

The hindered inversion at the pyramidal nitrogen atom is among the classic problems in intramolecular dynamics and in particular tunneling dynamics including the possibility of molecular chirality with appropriate substitution. The present investigation is part of a project dedicated to a complete characterization of the potential hypersurface and tunneling dynamics of ammonia. This project includes high resolution investigations of the fundamental vibrations of the deuterated ammonia isotopomers $ND_3$[1], $ND_2H$[2] and $NH_2D$[2]. We report high resolution FTIR-measurements (Bomem DA002 spectrometer, 0.004 $cm^{-1}$ instrumental band width) of the NH-stretching fundamental ($\nu_1$) and of the ND-stretching fundamentals ($\nu_{3a}, \nu_{3b}$) of $ND_2H$. The spectra were analyzed using a Watson-type S-reduced rotational Hamiltonian for the inversion-vibrational states involved. In addition, the introduction of particular inversion-rotation coupling terms proved important.The analysis yielded well determined spectroscopic parameters including up to sextic constants. The inversion-vibrational (tunneling) terms values obtained are ($s$ and $a$ distinguish between symmetric and antisymmetric tunneling states):

$T(s) = 3404.238(5)$ and $T(a) = 3404.316(5)$ $cm^{-1}$ for $\nu_1$
$T(s) = 2430.7990(7)$ and $T(a) = 2434.6222(8)$ $cm^{-1}$ for $\nu_{3a}$
$T(s) = 2559.8069(8)$ and $T(a) = 2559.9630(9)$ $cm^{-1}$ for $\nu_{3b}$

The results represent important benchmarks for testing and improving of the multidimensional potential energy hypersurface of ammonia.

[1] M.Snels, L.Fusina, H.Hollenstein and Martin Quack, *Mol. Phys.*, 2000, *98l*, 837.
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CHIMIA 2002, 56, No. 7/8

**201**

## Time-Resolved Fluorescence Spectroscopy on Organic-Inorganic Photonic Antenna Composites

Stefan Huber*, Michel Pfenniger, Marc Meyer, Mikalai M. Yatskou, Gion Calzaferri

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We showed in previous work that it is possible to insert various dyes into the channels of zeolite L[1-3]. Due to geometric restrictions of these channels, the dyes are organised in a supramolecular manner.

By inserting donor molecules in the middle part of the zeolite L channels and acceptor dyes at the ends of the channels, energy migration and transfer between the dyes can be studied by steady-state and time-resolved fluorescence spectroscopy[4].

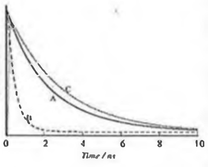

**Fig 1: A)** Luminescence decay measurement of a one dye reference zeolite L composite,
**B)** luminescence decay of the same dye in presence of an acceptor dye and
**C)** rise and decay of the luminescence of the acceptor dye.

For a one dye zeolite L composite system, a monoexponantial fluorescence decay is expected with a decay time close to that of the monomeric dye in solution. We showed this for the first time in a composite with low dye loading and for a higher loading after sample purification. Our conclusion is that non-intentional traps are responsible for the deviation of monoexponential fluorescence decay.

[1] S. Megelski, G. Calzaferri, *Adv. Functional Mater,* **2001**, 11, p. 277-286
[2] M. Pauchard, A. Devaux, G. Calzaferri,*Chem. Eur. J.*, **2000**, 6,p.3456-70
[3] G. Calzaferri, M. Pauchard, H. Maas, S. Huber, A. Khatyr, T. Schaafsmaa, *J. Mater. Chem.*, **2002**, 12(1), p. 1 - 13
[4] M. Pauchard, S. Huber, R. Méallet-Renault, H. Maas, R. Pansu, G. Calzaferri,*Angew. Chem. Int. Ed.*, **2001**, 113, p. 2921-2924

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Physical Chemistry **202**

## On the Role of Oxygen in the Aerobic Oxidation of Alcohols on Palladium

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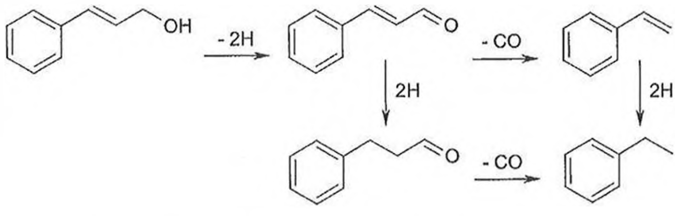
The mechanism of alcohol oxidation [1] has been investigated using the conversion of cinnamyl alcohol as a sensitive test reaction. Studies in a slurry reactor revealed that dehydrogenation and oxidative dehydrogenation follow the same reaction pathways. Hydrogenation and hydrogenolysis type side reactions evidenced the presence of surface hydrogen even during aerobic oxidation reactions. Catalyst deactivation in Ar is attributed to decarbonylation reactions and site blocking by CO. Strong adsorption of CO and its rapid removal by oxygen have been corroborated by *in situ* ATR-IR spectroscopy [2].



All these obervations are conform to a model according to which oxidation of primary and activated alcohols follows the classical dehydrogenation mechanism. The major role of oxygen is the continuous oxidative removal of CO from the metallic sites.

[1] T. Mallat and A. Baiker, Catal. Today, **1994**, 19, 247
[2] D. Ferri, T. Buergi and A. Baiker, J. Phys. Chem. B., **2001**, 105, 3187.

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Physical Chemistry **203**

## Fractional Layer Crystallization for Refining of Organics

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Sulzer Chemtech Ltd., Industriestrase 4, CH-9471 Buchs SG

Numerous Organics are purified by layer crystallization which relies upon freezing out crystalline layers of a component to be purified on cooled surfaces out of a molten crude mixture and melting them down, subsequently, after drainage of the residual, non-crystallized melt. The crystallization may occur out of a stagnant or agitated (i. e. falling film) melt. The morphology of the crystal layers generally depends on the impurities content in the crude melt, on the diffusion coefficients of the impurities components and on the layer growth rates. The layers are compact and have rather smooth surfaces if the initial impurity content is low (Fig. 1). The falling film crystallization can then be applied which allows faster crystal growth rates. If the impurity content is high the crystal layers tend to dendritic growth and exhibit rather lower mechanical stability(Fig. 2). In such cases crystallization out of stagnant melt is more suitable. To cover wide ranges of impurity contents for a given product the combination of falling film and stagnant melt crystallization has been applied in industrial processes.

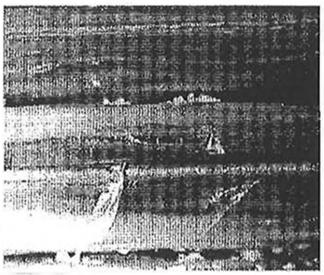

Fig. 1

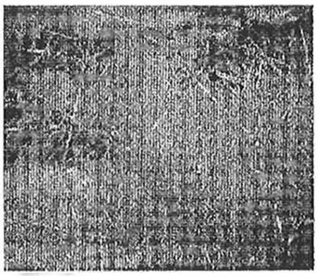

Fig. 2

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Physical Chemistry **204**

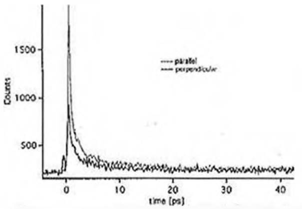
## Investigation on the ultrafast reorientational dynamics of Excited Donor/Acceptor complexes

E. Eckstein, O. Nicolet, E. Vauthey

Department of Physical Chemistry, 30 Quai Ernest-Ansermet, CH – 1211 Geneva 4,Switzerland

Although the back electron transfer reaction in donor/acceptor complexes (DACs) composed of pyromellitic dianhydride (PMDA) as acceptor and different methoxy-benzenes as donor was thoroughly studied [1], the structure of these complexes is not really known. A good way to learn more about the structure of the DACs is to investigate their reorientational dynamics.

Indeed the reorientational time depends on the molecular volume. As it also depends on the interactions with the environment, information on the DACs solvation can be obtained as well.



*Anisotropic fluorescence dynamics of PMDA/Anisol in decaline*

The reorientational times were determined by measuring the decay of the fluorescence polarisation anisotropy of the excited DACs using the up conversion technique .

The dependence of the measured reorientational times on solvent viscosity and polarity will be discussed.

[1] O. Nicolet and E. Vauthey, J.Phys. Chem. A, 2002, 106, in print.

CHIMIA **2002**, *56*, No. 7/8

Physical Chemistry **205**

## Ultrafast pump probe experiment on a photogenerated transient geminate ion pair

Stéphane Pagès, Bernhard Lang and Eric Vauthey

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30, Quai Ernest Ansermet, CH-1211 GENEVE 4, Switzerland

A charge transfer process between an electron donor and an electron acceptor results in the formation of a geminate ion pair (GIP). As demonstrated by Weller [1] and coworkers several types of intermediates are involved : exciplexes, Contact Ion Pairs (CIP), Loose Ion Pairs (LIP), Free Ions (FI) etc. The main goal of our work is to get structural informations on these intermediates. The formation of intermolecular complexes can be expected to affect the low frequency modes of the transient species and thus we are developping an original time resolved vibrational spectroscopy suitable for detecting low frequency modes. This technique is based on a pump/pump-probe experiment. We first photochemically induce the formation of a geminate ion pair using a 100fs pulse at 400 nm and then we perform a pump probe experiment on this transient applying a pair of 30 fs pulse. Controlling the time delay between the generation of the transient and the pump-probe experiment allows us to probe the differents structures of the ion pair as they evolve with time.
During the first picoseconds the signal due to ground state recovery dynamics is modulated by the propagation of low frequency vibrational wavepackets. A low frequency vibrational spectrum is obtained.

[1] Weller, A, Z. *Pure & Appl. Chem.* **1982,** Vol. 54, No. 10, p. 1885.
[2] E. Vauthey, A. W. Parker, B. Nohova and D. Phillips
*J. Am. Chem. Soc.* **1994,**116, 9182.

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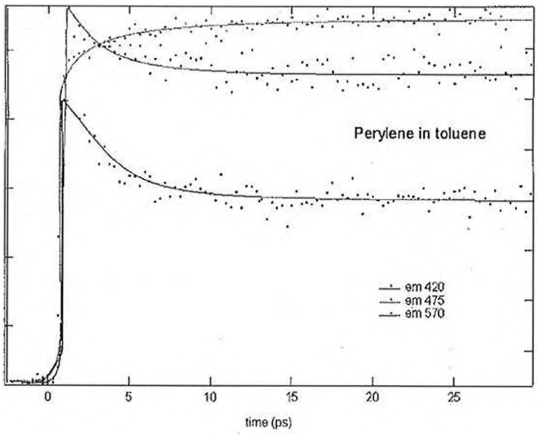
Physical Chemistry **206**

## Dynamics of Vibrational Cooling of Aromatics Hydrocarbons

Anatolio Pigliucci and Eric Vauthey

Department of Physical Chemistry, University of Geneva, 30 quai Ernest Ansermet, CH-1211 Geneva, Switzerland

As shown in the figure below, the early fluorescence dynamics of Perylene excited at 400 nm in solution is strongly wavelength dependent. This process is due to vibrational cooling, i.e. to the transfer of an excess of excitation energy to the environment. In order to understand the details of this process and in particular the role of the solvent and solute structures, ultrafast time-resolved fluorescence measurements have been carried out with Perylene and its derivatives in different solvent and with different excitation wavelength. The effect of these parameters on the cooling dynamics will be discussed.(The figure represents the Time-resolved fluorescence of Perylene in Toluene at 420,475 amd 570 nm)



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Physical Chemistry **207**

## Femtosecond Multiphoton Excitation and Ionization of Aniline Vapour

Vitaly Krylov*, Edouard Miloglyadov*, Martin Quack and Georg Seyfang

Physical Chemistry, ETH-Zürich, CH-8093 Zürich, Switzerland
*permanent address: State Optical Institute, St.Petersburg, Russia

Aniline is an ideal model system to study intramolecular vibrational energy redistribution (IVR) after IR-overtone excitation both by high resolution spectroscopy [1,2] and by time resolved techniques using tunable femtosecond laser pulses as well. The combination of these two conceptually completely different approaches will give a more detailed understanding of intramolecular energy redistribution [3]. To investigate the IVR by time resolved methods the behavior of aniline under the influence of strong laser fields has to be known in more detail.
In our experiments we have measured the ion signal from two plate electrodes in a reaction cell filled with an aniline pressure of 30 – 50 Pa. For NIR laser pulses with 100 – 150 fs pulse duration and a maximum laser intensity of 200 GWcm$^{-2}$ or more aniline is ionized efficiently for photon energies around 8000 cm$^{-1}$. If the laser is tuned from 8500 to 8900 cm$^{-1}$ the vibrational structure of the low resolution gas phase UV-spectrum is reproduced by the measured ion yields, showing the importance of the electronically excited $S_1$-state for the multiphoton ionization process. For lower NIR laser intensities a strong three photon ionization signal (2 UV + 1 NIR) has been measured for UV-photon energies between 28'600 – 31'750 cm$^{-1}$. If the NIR laser is delayed with respect to the UV laser an asymmetric correlation function is obtained which may be understood by the relaxation of highly electronically excited states. For UV photon energies above 32'000 cm$^{-1}$ the aniline is ionized by the absorption of two photons.

[1] B.Fehrensen, M.Hippler, M.Quack, *Chem. Phys. Lett.* **1998**, *298*, 230.
[2] B.Fehrensen, D.Luckhaus, M.Quack, *Z. Phys.Chem. NF*, **1999**, *209*, 1.
[3] M.Quack, *in Femtosecond Chemsitry, Vol. 2, edited by J.Manz and L.Woeste, Verlag Chemie Weinheim*, **1995**, p781.

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Physical Chemistry **208**

## Assignment of the π* and σ* States of Pyrrole Determined by Electron Impact spectroscopy

Tomáš Skalický and Michael Allan

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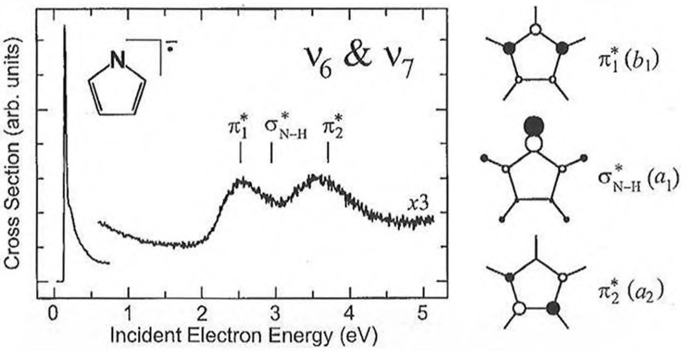
The selectivity of vibrational excitation by electron impact has been used to clarify the negative ion states of pyrrole.



The excitation function of the overlapping vibrations $\nu_6$ and $\nu_7$ , both totally symmetric $a_1$ ring vibrations, exhibits two prominent bands peaking at 2.54 eV resp. 3.60 eV. This identifies them as a temporary electron capture to the $b_1$ and $a_2$ π* orbitals, in agreement with calculation (vertical bars). Our results show that pyrrole anion has an unusual electronic structure. The π* states lie high in energy and therefore close to the σ* state, in contrast to most anions, where π* states lie substantially below σ*.

Physical Chemistry **209**

## Multidimensional Anharmonic Couplings and their Influence on Parity Violating Effects in CDBrClF

Martin Quack and Jürgen Stohner

Physical Chemistry, ETH Zurich (Hönggerberg), CH-8093 Zurich

Parity violation in molecules (e.g., see [1]) causes rovibrational frequency shifts in infrared and microwave spectra of enantiomers. In our earlier theoretical investigations of those frequency shifts for fundamentals and overtones [2,3], for their changes upon isotopic substitution [4] as well as on changes in equilibrium constants for racemization caused by parity violation [4,5], simple harmonic and anharmonic adiabatic approximations were used which assumed that the vibrational potential as well as the parity violating potential are separable in normal coordinates.

In the present work we investigate in detail the influence of nonseparable anharmonic couplings on vibrational frequency shifts in CDBrClF caused by the parity violating potential. We use the strongly coupled four dimensional CD- and CF-chromophore subspaces and discuss how relative frequency shifts are influenced by coupling in the pure vibrational potential as well as in the parity violating potential. Therefore, a four dimensional parity violating potential energy hypersurface has been determined ab initio within the multiconfigurational linear-response random phase approximation (MC-LR RPA) [7] and fitted to a polynomial expansion. We calculated eigenvalues and eigenfunctions of the molecular Hamiltonian $\widehat{H}_{\mathrm{mol}}$ and determined the frequency shifts caused by parity violation from four dimensional expectation values of the parity violating potential $V_{\mathrm{pv}}$.

[1] M. Quack, Angew. Chem. Int. Ed. Engl. (1989), **28**, 571
[2] M. Quack and J. Stohner, Phys. Rev. Lett. (2000), **84**, 3807
[3] M. Quack and J. Stohner, Z. Physik. Chemie (2000), **214**, 675
[4] M. Quack and J. Stohner, CHIRALITY (2001), **13**, 745
[5] R. Berger, M. Quack and J. Stohner, Angew. Chem. Int. Ed. Engl. (2001), **40**, 1667
[7] R. Berger and M. Quack, *J.* Chem. Phys. (2000), **112**, 3148

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Physical Chemistry **210**

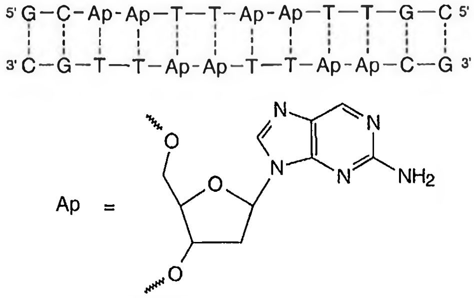
## 2-Aminopurine as a Fluorescent Probe for Energy Transfer and Excimer Formation in DNA

Manuela Rist, Torsten Fiebig,* Hans-Achim Wagenknecht*

Technical University of Munich, Lichtenbergstr. 4, 85747 Garching, Germany

Understanding the electronic properties of DNA has been the goal of various experimental and theoretical studies over the last decades. With respect to the biological consequences, by far the most efforts were spent on the investigation of charge migration processes through the base stack. Although photoinduced charge transfer is initiated by electronic excitation, no clear picture has yet emerged how to describe excitation energy in duplex DNA.

We present a new experimental approach to investigate these subjects by using specifically designed DNA assemblies where adenine (A) is replaced selectively by 2-aminopurine (Ap). Through this simple synthetic "trick", it was possible to perform these investigations by optical spectroscopy at room temperature. Our study shows that excitonic coupling between adjacent bases leads to delocalized excitation between identical bases. As a result, we observe a new emission band which is red-shifted with respect to the typical Ap fluorescence and which can be considered as excimer emission.



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Physical Chemistry **211**

## Stereomutation Dynamics and Parity Violation in Hydrogenthioperoxide Isotopomers

Martin Quack[a], Martin Willeke[a], and Gisbert Winnewisser[b]

[a] : Physical Chemistry, ETH Zurich, CH-8093 Zurich, [b] : Physikalisches Institut, Universität Köln, Zülpicher Str. 77, D-50937 Köln

Hydrogenthioperoxide H-S-O-H is a nonplanar chiral molecule analogous to the well known $H_2O_2$, $H_2S_2$, and $Cl_2S_2$ molecules. Recently the latter molecules have been investigated both experimentally and theoretically with respect to their mode selective full dimensional stereomutation wavepacket dynamics and with respect to parity violation [1-6].

We present in this paper theoretical results on mode selective stereomutation dynamics and parity violation in XSOX with X=H, D, T [7]. Parity violating potentials were calculated with our recent multiconfiguration linear response approach in the random phase approximation [8]. The torsional tunneling stereomutation dynamics are investigated with the quasiadiabatic channel quasiharmonic reaction path Hamiltonian approach which treats the torsional motion anharmonically in detail and all the other coordinates as harmonic (but anharmonically coupled to the reaction coordinate) [4]. Our results will be discussed in relation to recent experiments and in relation to results for the other molecules.

[1] M. Quack, *Angew. Chem. Int. Ed. Engl.* (1989), *28*, 571.
[2] M. Quack, *Nova Acta Leopoldina* (1999), NF *81*, 137.
[3] A. Bakasov and M. Quack, *Chem. Phys. Lett.* (1999), *303*, 547.
[4] B. Fehrensen, D. Luckhaus, and M. Quack, *Chem. Phys. Lett.* (1999), *300*, 312.
[5] M. Gottselig, D. Luckhaus, M. Quack, J. Stohner, and M. Willeke, *Helv. Chim. Acta* (2001), *84*, 1846.
[6] R. Berger, M. Gottselig, M. Quack, and M. Willeke, *Angew. Chem. Intl. Ed.* (2001), *40*, 4195.
[7] M. Quack, M. Willeke, G. Winnewisser, *to be published.*
[8] R. Berger and M. Quack, *J. Chem. Phys.* (2000), *112*, 3148.

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Physical Chemistry **212**

## *Ab initio* calculations of mode selective tunneling dynamics in $^{12}CH_3OH$ and $^{13}CH_3OH$

Benjamin Fehrensen[a], David Luckhaus[b], Martin Quack[a], Martin Willeke[a], and Thomas R. Rizzo[c]

[a] Physical Chemistry, ETH Zurich, CH-8093 Zurich, [b] Universität Göttingen, Tammanstr. 6, D-37077 Göttingen, [c] Institut de Chimie Moléculaire et Biologique, EPF Lausanne, CH-1015 Lausanne

Although methanol is one of the simplest asymmetric top molecules exhibiting large amplitude internal rotation, its torsion-rotation-vibration energy level structure is rather complicated and a challenge for spectroscopy and theory.

In this paper [1] we present our new formulation [2] of the harmonic reaction path Hamiltonian (RPH) approach [3] combined with high level *ab initio* calculations to determine mode specific tunneling splittings in $^{12}CH_3OH$ and $^{13}CH_3OH$. The experimentally observed pure torsional spectrum is reproduced very well, as are the few known isotope shifts. The mode specific tunneling splitting is investigated for the excitation of fundamentals as well as OH stretching overtone modes with and without simultaneous excitation of torsional motion, where recent experimental data are available [4-5]. Except for excitations of modes which are perturbed by anharmonic resonances an excellent agreement between experiment and our RPH model is obtained. This is true even for modes where inverted tunneling splittings (E level below A level) are observed.

[1] B. Fehrensen, D. Luckhaus, M. Quack, M. Willeke, and T. R. Rizzo, to be published
[2] B. Fehrensen, D. Luckhaus, and M. Quack, *Chem. Phys. Lett.*, **1999**, *300*, 312; *Z. Phys. Chem. N. F.*, **1999**, *209*, 1.
[3] W. H. Miller, N. C. Handy, and J. E. Adams, *J. Chem. Phys.*, **1980**, *72*, 99.
[4] O. V. Boyarkin, D. S. Perry, and T. R. Rizzo, *J. Chem. Phys.*, **1999**, *110*, 11359.
[5] D. Rueda, O. V. Boyarkin, T. R. Rizzo, I. Mukhopadhyay, and D. S. Perry, *J. Chem. Phys.*, **2002**, *116*, 91.

Physical Chemistry **213**

### Probing enantiospecificity of chiral interfaces by modulation spectroscopy

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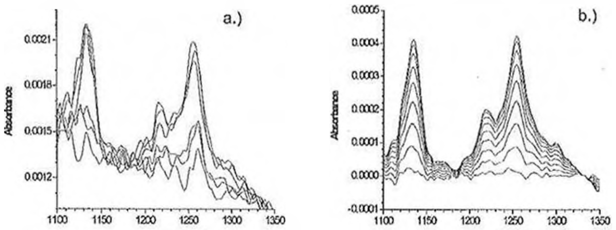
Laboratory of Technical Chemistry, Swiss Federal Institute of Technology, ETH Hönggerberg, 8093 Zürich

Enantiospecificity of chiral solid-liquid interfaces plays a crucial role in nature and technology, for example in separation processes and heterogeneous catalysis. We have implemented a technique, based on ATR infrared spectroscopy, which selectively probes enantiospecific interactions at chiral solid-liquid interfaces, such as chiral stationary phases (CSP).



The difference in the spectra of the two adsorbed enantiomers of a chiral compound, which represents the enantiospecificity, is usually small compared to the absolute signal from either one of the enantiomers. We overcome this problem by periodically admitting the two enantiomers to the CSP in a flow-through cell. The time-resolved signals (Figure a) are demodulated by a digital phase-sensitive detection (PSD, Figure b). The resulting spectra represent the enantiospecificity of the interaction between probe molecule and the CSP. The Figure shows D-ethyl lactate on a CSP.

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Physical Chemistry **214**

### In situ investigation of interface reactions between different electrolyte solutions and electrode materials for lithium–ion batteries

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Paul Scherrer Institute, Laboratory for Electrochemistry, CH-5232 Villigen PSI

For the performance of lithium-ion batteries the formation of an electronically insulating film on the surface of the electrodes during the first charge step is essential. The film called solid electrolyte interphase (SEI) protects the electrolyte from further decomposition. During the formation of the SEI gases like hydrogen, ethylene, propylene, and carbon dioxide could be detected by differential electrochemical mass spectrometry (DEMS) [1]. Both, cathodic and anodic electrode materials can be investigated with this method. Using a new developed DEMS cell we analyzed different electrolyte solutions together with different graphites and oxides. Because of its low gas evolution γ-butyrolactone is one of the most interesting solvents for electrolytes [2,3]. We were able to detect the gas evolution on graphites and oxides using this solvent together with $LiPF_6$, $LiBF_4$, and $LiClO_4$ as electrolytes. We could recognize that the behavior during the first cycle and the overall performance of the electrochemical cell among others depends on the kind of electrolyte used. By using DEMS measurements it was possible to correlate the differences in the behaviors with the gas evolution.

*We acknowledge the support of Prof. R. Nesper and Prof. A. Wokaun.*

[1] R. Imhof, P. Novak, *J. Electrochem. Soc.*, 145 (1998) 1081.
[2] M. Lanz, P. Novak, *J. Power Sources*, 102 (2001) 227-282
[3] D. Goers, M. Lanz, P. Novák, *Chimia*, 55, 649 (2001)

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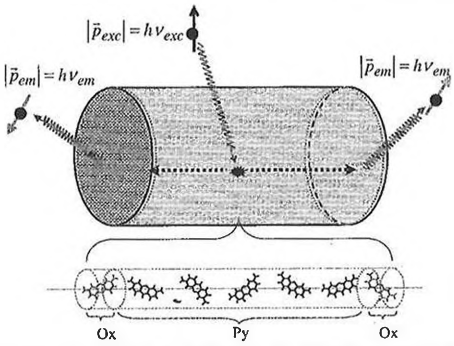
Physical Chemistry **215**

### Excitation Energy Migration in a Photonic Dye-Zeolite Antenna

Mikalai M. Yatskou, Michel Pfenninger, Marc Meyer, Stefan Huber, Gion Calzaferri *

University of Bern, Freiesstr. 3, CH-3012 Bern, Switzerland

Excitation energy migration (EEM) within assemblies of dyes embedded in hexagonal crystals of cylinder morphology is an attractive phenomenon for the construction of a photonic antenna [1]. Monte Carlo (MC) simulation-fitting method has been used to investigate the mechanism and properties of the EEM in a photonic dye-zeolite antenna [2]. Using this computational technique the complex time-resolved fluorescence of pyronine (Py) and oxonine (Ox) guest dyes in the zeolite crystals has been analyzed.



The energy transfer parameters obtained by MC simulation of the EEM in the photonic Py,Ox-zeolite L antenna are in agreement with the results of Markoff chain calculations using the Förster theory and the point dipole-dipole model [3].

[1] G. Calzaferri et al., *J. Mater. Chem.* **2002**, *12*, 1.
[2] M.M. Yatskou et al., *J. Phys. Chem. A* **2001**, *105*, 9498.
[3] N. Gfeller, G. Calzaferri, *J. Phys. Chem. B* **1997**, *101*, 1396.

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Physical Chemistry **216**

### Measurements of Associative Electron Detachment Spectra in Low-Energy $Cl^-$ + H Collisions

S. Živanov[§], F. A. U. Thiel[†], H. Hotop[†] and M. Allan[§]

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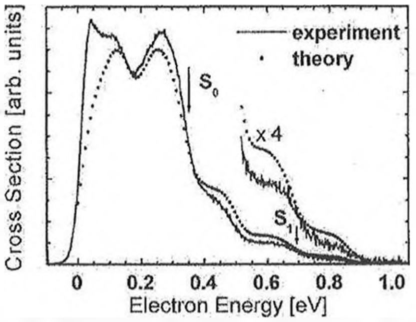
[†]Department of Physics, University of Kaiserslautern, D-67653 Kaiserslautern, Germany

In this paper we present experimental data for associative electron detachment processes in low energy collisions between atomic hydrogen and chlorine anions ($H + Cl^- \rightarrow HCl(v,J) + e^-(\varepsilon)$). We constructed a new instrument to measure the energies of the detached electrons. Our experimental results (see Figure) confirm the predictions of the recently developed nonlocal resonance theory [1], in particular steps $S_0$ and $S_1$ which were absent in simpler local models.



[1] M. Čížek, J. Horáček, F. A. U. Thiel and H. Hotop, *J. Phys. B: At. Mol. Opt. Phys.*, **2001**, 34, 6.

Inorganic and Coordination Chemistry **217**

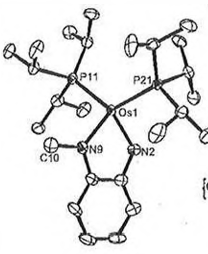
### New Hexacoordinate Dihydride Complexes of Ru and Os: $M(H)_2(chelate)(P^iPr_3)_2$ with Chelate *ortho*-$EC_6H_3RE'$ and E, E' = O, NR'; R, R' = H or $CH_3$.

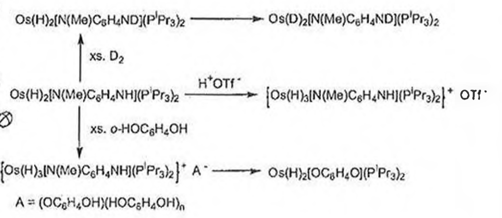
German Ferrando-Miguel, Peng Wu, John C. Huffman, and Kenneth G. Caulton*
Department of Chemistry and Molecular Structure Center, Indiana University, Bloomington IN 47405-7102, USA.
Department of Chemistry, ETH Zürich, Zürich CH-8093, Switzerland.

The synthesis and characterization of $Ru(H)_2$(*ortho*-$OC_6H_4E)(P^iPr_3)_2$ (E = NH, O) show these to be dihydrides with a nonoctahedral structure. The former compound reacts with $H_2$ to give $Ru(H)_3(OC_6H_4NH_2)(P^iPr_3)_2$, which hydrogenates $^tBuHC{=}CH_2$, but fails to hydrogenate ketones.

$$H_2 + H_2C{=}CH^tBu \xrightarrow[C_6D_6,\ 20^\circ C.]{5\ \%\ \text{cat.}} CH_3CH_2^tBu$$

Osmium analogs are available from $Os(H)_3Cl(P^iPr_3)_2$. These new molecules are fully or partially fluxional depending on the sterics of the N-substituent. The compound $Os(H)_2[N(Me)C_6H_6NH](P^iPr_3)_2$ exchanges $D_2$ into the NH site faster than into the OsH sites without further reactivity. Triflic acid protonates $Os(H)_2[N(Me)C_6H_6NH](P^iPr_3)_2$ to give a trihydride. Catechol replaces the *ortho*-diamido to give $Os(H)_2(OC_6H_4O)(P^iPr_3)_2$.





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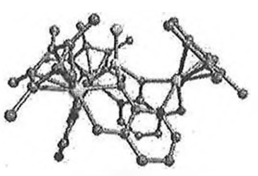
Inorganic and Coordination Chemistry **218**

### Stabilization of Molecular LiF and LiFHF inside Metallamacrocyclic Hosts

Marie-Line Lehaire, Rosario Scopelliti, Kay Severin*

Institut de Chimie Moléculaire et Biologique, Ecole Polytechnique Fédérale de Lausanne, BCH , CH-1015 Lausanne, Switzerland

Trimeric organometallic complexes of the general formula $[L_nM(C_5H_3NO_2)]_3$ ($L_nM$ = Cymene-Ru **1**, Cp*Rh **2** or Cp*Ir **3**) can be synthesized in a single step and in good yield by reaction of the corresponded chloro-bridged complex $[L_nMCl_2]_2$ with 3-hydroxy-2-pyridone in the presence of base [1][2][3]. These analogues of 12-crown-3 were shown to bind alkali metal halides as an ion pair with remarkable affinity and selectivity, which brought us to investigate the possibility to use them to stabilize molecular LiF and LiFHF. In fact although structures of other alkali metal halides are very common, compounds containing molecular LiF and LiFHF were up to now unknown. The difficulty to stabilize these salts arises from their very high lattice energy, which makes LiF and LiFHF thermodynamic traps. Due to their very low solubility in organic solvents our strategy was then to prepare complexes of these salts in situ. For this purpose we have first synthesized the LiBF4 adducts. The weekly bound $BF_4^-$ anion was then exchanged either with $F^-$ or $FHF^-$. The successful anion exchange was confirmed by the NMR data and by single crystal X-ray analysis [4]. On the basis of these results, we have also constructed a highly selective chemosensor **3** that allows the detection of fluorine anions by electrochemical means, even in protic solvents [3].



**3 · LiF**

[1] H. Piotrowski, G. Hilt, A. Schulz, P. Mayer, K. Polborn, K. Severin, *Chem. Eur. J.* **2001**,*7(15)*, 3196.
[2] H. Piotrowski, K. Polborn, G. Hilt, K. Severin, *J. Am. Chem. Soc.* **2001**, *123*, 2699.
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[4] M.-L. Lehaire, R. Scopelliti, K. Severin, submitted.

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Inorganic and Coordination Chemistry **219**

### 3,5-Dialkyl meta effect in enantioselective, Palladium catalyzed reactions

Pascal Dotta and Paul S. Pregosin

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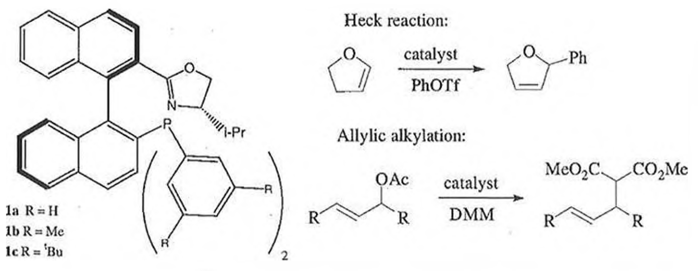
The meta-dimethyl-ligand **1b** shows significantly increased ee's in the Heck and allylic alkylation reactions compared with the results obtained with ligand **1a** [1]. This prompted us to investigate the possibility of amplifying this effect by introducing bulky *tert*-butyl (instead of methyl) groups, which led to the synthesis of ligand **1c**.



Results obtained with ligand **1c** in the Heck and allylic alkylation reactions will be presented. The complex $PdCl_2$(**1c**), **2**, and a series of $Pd^0$-olefin complexes bearing ligand **1c** were studied by x-ray-diffraction (for **2**) and two-dimensional NMR measurements (olefin complexes). The data will be interpreted in terms of structural and electronical differences between the analogous complexes containing ligands **1a** and **1b**.

NMR measurements on isolated Palladium-allyl-complexes with ligand **1c** offer an explanation with respect to how **1b** and **1c** differ.

[1] Selvakumar, K;Valentini, M; Pregosin, P.S.; *Organometallics* **2000**, *19*, 1299-1307.

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Inorganic and Coordination Chemistry **220**

### Novel Polytopic Ligands with Two Different Binding Sites Based on Open-Chain and Cyclic Structural Elements

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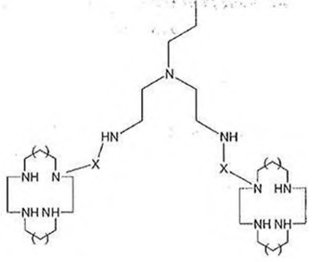
The novel chelating ligands, shown on the right, consist of three macrocyclic units bound by carbon chains of various lengths to a central tren unit. When excess metal ions are added to these ligands they can bind to the macrocycles and tren giving 3:1 or 4:1 species. Which species can form depends on chain length and ring size of the macrocycles and these effects will be discussed. Potentiometric titrations of $M_3\mathbf{L}^{6+}$ and $M_4\mathbf{L}^{8+}$ show the formation of both protonated (at low pH) and hydroxide-bridged species (at high pH). The spectra of $Cu_3\mathbf{L}_1^{6+}$ also indicates that the amino groups of the side chain ligands can bind axially to the metal ions at neutral conditions. Formation of $Cu_4(\mathbf{L}_1)^{8+}$ from $Cu_3(\mathbf{L}_1)^{6+}$ is reversible upon addition of acid. The relative stability of copper and zinc complex formation will also be discussed.



$L_1$ has X = $(CH_2)_2$ with cyclam-14
$L_2$ has X = $(CH_2)_3$ with cyclam-14
$L_3$ has X = *m*-xylyl with cyclam-14
$L_4$ has X = $(CH_2)_3$ with cyclen-12

Inorganic and Coordination Chemistry **221**

## New Paramagnetic Complexes Using "$N_3O_2$" Macrocyclic Ligand as a Building Block

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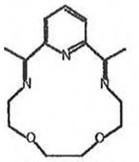
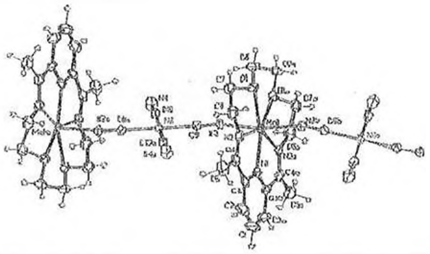
A ligand such the "$N_3O_2$" macrocyclic ligand prepared via the Schiff-base condensation of 2,6-diacetylpyridine with 3,6-dioxaoctane-1,8-diamine is a good example of a pentadentate ligand, which is able to co-ordinate to different kinds of metal-ions[1]. We are currently exploiting the chemistry of this class of building blocks and working towards the preparation of new molecule based magnetic materials. In particular our interest is focus on using axial binding cyanide ligands as linkers for additional paramagnetic transition metal ions, like $Mn^{II}$, $Ni^{II}$, $Fe^{III}$.



Ligand "$N_3O_2$"



[1] S. M. Nelson, P. D. A. McIlroy, C. S. Stevenson, E. König, G. Ritter, J. Waigel, *J. Chem. Soc., Dalton Trans.*, **1986**, 991 ; M. G. B. Drew, A. H. Othman, S. G. McFall, P. D. A. McIlroy, S. M. Nelson, *J. Chem. Soc., Dalton Trans.*, **1977**, 1173.

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Inorganic and Coordination Chemistry **222**

## Second-Coordination Sphere : Proteins as Host for Enantioselective Catalysis

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In the field of enantioselective catalysis, there is ample evidence that the second-sphere coordination (solvent, counter ion, etc.) often dramatically influences the properties of a catalyst. To take advantage of the weak interactions which govern second-coordination sphere, we embed an achiral catalyst precursor into a protein, thus offering a well-defined chiral environment around the catalyst. [1-3] Rather than covalently anchoring the catalyst to a protein, we exploit the biotin-avidin technology to incorporate the catalyst into the host protein as illustrated in Scheme 1. The resulting hybrid bio-organometallic catalysts display very promising properties. A chemogenetic approach allows to optimize the enantioselectivity of the catalyst (ee > 90 % for the hydrogenation of dehydro-aminoacids).

**Scheme 1.** Result of a docking simulation between [(+)-biotin-$NHCH_2CH_2O$(diphenylphosphino-propane)RhClCO] and avidin.

[1] Whitesides et. al. *J. Am. Chem. Soc.* **1978**, *100*, 306, [2] Chan et. al. *Tetrahedron Asym.***1999**, *10*, 1887, [3] Distefano et. al. *Chem. Rev.* **2001**, *101*, 3081.

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Inorganic Chemistry **223**

## Dithienylethene switching system containing metal complex

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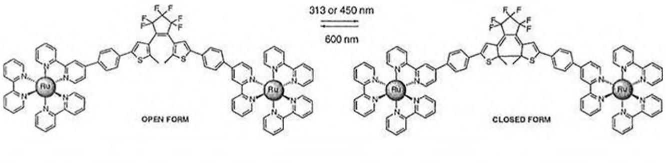
Photochromism is referred as a reversible photoisomerization between two isomers having different absorption spectra. Among a number of photochromic compounds, dithienylethenes are the most promising compounds for applications to optical memories and switches because of their thermally irreversible and fatigue resistant photochromic performance [1]. Irradiation of such compounds with light of well-separated wavelengths allows the interconversion between a nonconjugated (open form, colorless) isomer and a conjugated (closed form, deeply colored) one. The introduction of a metal complex is very interesting with respect to their photophysical properties.



The depicted photochromic complex displays a reversible discrimination of the metal centered fluorescence between the open and the closed form that can be used for optical memory device. In the present work, we describe the synthesis and photochromic behaviors of the dinuclear ruthenium metal complex.

[1] M. Irie, *Chem. Rev.*, **100**, 1685 (2000).

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Inorganic and Coordination Chemistry **224**

## Chelated Iridium(III) Bis-Carbene Complexes: Air-Stable Catalysts for Transfer Hydrogenation

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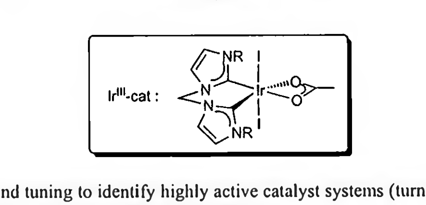
Yale Chemistry Department, 225 Prospect Street, New Haven, CT 06520, USA

*N*-heterocyclic carbenes have been attracting great attention recently as new ligands for homogeneous catalysis, where they are often considered as phosphine analogues [1]. Particularly interesting for catalytic applications are their facile synthesis and their high stability towards air and moisture, which allows versatile ligand tuning and convenient manipulations. Since chelation usually increases the stability of the corresponding transition metal complexes, we were interested in developing metal carbene catalysts containing a metal-carbon bond that is intramolecularly supported by bi- or polydentate ligand bonding. We will present methodologies for the preparation of chelated iridium(III) biscarbene complexes via a direct metallation protocol [2]. Moreover, we report on the catalytic performance of these iridium complexes in the transfer hydrogenation of ketones (see Scheme) with respect to both, activity and selectivity.



We used ligand tuning to identify highly active catalyst systems (turnover frequencies > 50 000 $h^{-1}$) that are resistant towards air and moisture.

[1] D. Bourissou, O. Guerret, F. P. Gabbai, G. Bertrand, *Chem. Rev.* **2000**,*10 0*, 39; W. A. Herrmann, C. Köcher, *Angew. Chem. Int. Ed.***19 97**,*36* , 2162.
[2] M. Albrecht, R. H. Crabtree, E. Peris, J. Mata, *Chem. Commun.***20 02**, 32.

Inorganic and Coordination Chemistry **225**

## PGSE Diffusion measurements to study anion effects using Ru-complexes as models.

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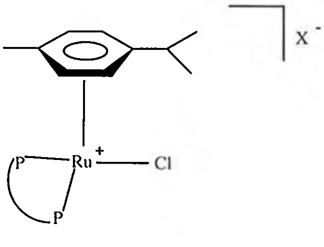
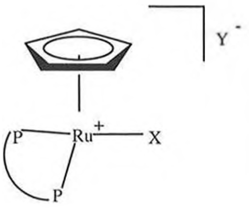
Anion effects on structure are studied by PGSE-Diffusion [1] and $^{19}F$, $^{1}H$ HOESY NMR methods. These methods allow a unique approach to understanding ion-pairing in cationic catalysts in organic solvents. Data for the model complexes **1** and **2** [2] will be presented.



1

X = Cl, $BF_4$, $SbF_6$, OTf, BArF
P-P = BINAP



2

X = Acetone
Y = $BF_4$, BArF
P-P = Biphop-F

[1] M.Valentini, H.Ruegger, P.S.Pregosin, *Helv. chim. Acta.*, **2001**, *84*, 2833.
[2] E.P.Kundig, C.M.Saudan, G.Bernardinelli, *Angew. Chem. Int. Ed.* **1999**, *38*, 9, 1220-1223.

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Inorganic and Coordination Chemistry **226**

## Crosslinked LPEI, a basic and coordinating hydrogel

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LPEI (linear polyethyleneimine) is crosslinked with 1,4 –Butandiol-diglycidylether in MeOH at RT. The macroscopic properties of the obtained hydrogels depend strongly on the ratio N : gycidyl in the reaction mixture. For a ratio of N : glycidyl = 10 : 1 stable hydrogels are obained, which can easily be cast in transparent films. The basic hydrogels and their hydro chlorides swell strongly ca 100 – 500 times in water, depending on their composition.. For a ratio 10 : 1 the swelling is maximal. The reaction of the protonated hydrogel with NaOH is sur-prisingly slow (Fig. 1). This is due to a slow relaxation of the gel after each addition of base. The rate of the relaxation is roughly proportional to the pH of the solution. This indicates, that the pH gradient between the solution and the interior of the gel is the main driving force. The hydrogel is also a good ligand for the binding of transition metals. The formation and stability are investigated at the moment.

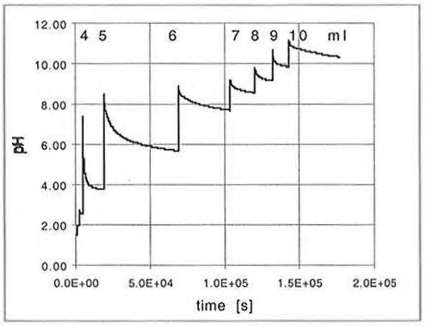

Fig.1. Relaxation of the pH during the titration of LPEI hydrogel with NaOH. In each titration step ca 0.1 equ. base are added

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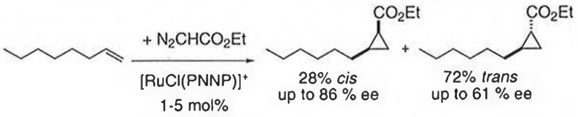
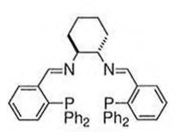
## Asymmetric Cyclopropanation of Olefins Catalyzed by [RuCl(PNNP)]⁺ Complexes

Stephan Bachmann, Cristina Bonaccorsi and Antonio Mezzetti *

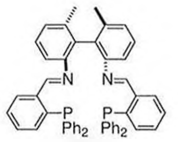
Department of Chemistry, ETH Hönggerberg, CH-8093 Zürich

We recently reported the highly *cis*-selective cyclopropanation of styrene derivatives with [RuCl(**1a**)]⁺ as the catalyst [1], [2]. Most cyclopropanation catalysts are less active with aliphatic olefins than with aromatic ones. Contrary to this, we find now that [RuCl(**1 b**)]⁺ and [RuCl(**1c**)]⁺ cyclopropanate 1-octene in moderate to high yields (65-90%) and with 72 % *trans*-selectivity. The enantioselectivites are in the range 51-61% ee for the *trans*-product and 82-86% ee for the *cis* one and are comparable to those found by Aratani using *l*-menthyl diazoacetate and a chiral Cu(II) catalyst [3]. To the best of our knowledge, this is the first example of an enantioselective cyclopropanation of 1-octene that uses ethyl diazoacetate.

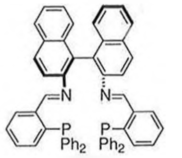




(*S,S*)-**1a**



(*S*)-**1b**



(*S*)-**1c**

Further examples with other [RuCl(PNNP)]⁺ complexes will be reported.

[1] S. Bachmann, M. Furler, A. Mezzetti, *Organometallics* **2001**, *20*, 2102.
[2] S. Bachmann, A. Mezzetti, *Helv. Chim. Acta* **2001**, *84*, 3063.
[3] T. Aratani; Y. Yoneyoshi; T. Nagase, *Tetrahedron Lett.* **1982**, *23*, 685.

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Inorganic Chemistry **228**

## Thermodynamics and Kinetics of Self-assembled Complexes Based on Bis-bipyridinyl-pyrazine

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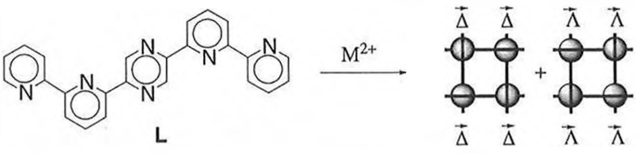
University of Fribourg, Pérolles, CH-1700 Fribourg, Switzerland

Ligand 2,5-bis-(bipyridine-6-yl)pyrazine (**L**) yields chiral, tetrameric complexes with transition metals of octahedral co-ordination geometry [1]. The formation of the corresponding tetranuclear zinc complex was followed by NMR, and the trimeric form of the complex was found to be an important intermediate in this reaction.



The tetrameric iron(II) complex could be resolved into enantiomers. The kinetics of the racemisation of the enantiopure form was investigated, in order to establish a reaction mechanism.

[1] T. Bark, M. Düggeli, H. Stoeckli-Evans, *Angew. Chem. Int. Ed.*, **2001**, *40*, 2848.

Inorganic and Coordination Chemistry **229**

### Tailor made $NS_3$-ligands for $^{111}Ag$ complexation and applications in radioimmunotherapy

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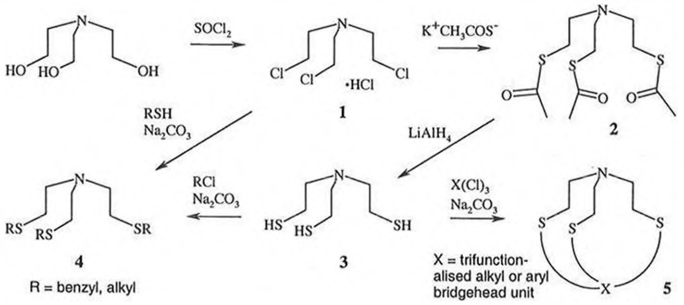
The radiation properties of the radioisotope $^{111}Ag$ like half life time ($t_{1/2}$= 7.45d) and type/energy of decay ($E_{max}(\beta^-)$ = 1.05MeV; $E(\gamma)$ = 0.34MeV) predestinate this isotope for applications in radioimmunotherapy.[1] Stable and inert complexes of the labile Ag(I) ion are most likely to be achieved with tailor made cages, which efficiently shield the Ag(I) ion from competing ligands and thus prevent transmetallation in the organism.[2] We focused on the ethylene bridged $NS_3$-moiety for Ag(I) coordination. After performing DFT calculations on potential complexes, we synthesised promising cage compounds 5 incorporating this donor set of atoms.[3] (Caution! 1 is a strong vesicant)



Scheme: Synthetic pathways to NS3-open chain and cage compounds

Crystal structures of the free ligands and their Ag(I) complexes will be discussed. A high stability constant was measured for a $NS_3$-cyclophane ligand with an unusual coordination behaviour towards Ag(I). J.M.B. thanks Prof. P.A. Schubiger, Paul Scherrer Institute, Villigen, Switzerland for valuable support.

[1]Schubiger, P.A.; Alberto, R.; Smith, A. Bioconjugate Chem. 1996, 7, 165-179
[2]Alberto, R. et al. J. Chem. Soc., Chem. Commun. 1999, 16, 1513-1514.
[3]Baumeister, J.M.; Alberto, R.; Kaden, Th.A. submitted, JCS, Dalton Trans.

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Inorganic and Coordination Chemistry **231**

### Solution Structure of Metal ion Complexes Formed with Guanosine 5'-Diphosphate ($GDP^{3-}$)

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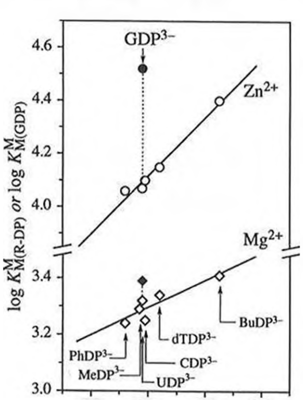
Nucleotides participate in biological reactions usually in form of their metal ion ($M^{2+}$) complexes [1]; therefore it is important to know the stabilities and structures of their complexes in solution. To this end we studied $M(GDP)^-$ complexes by potentiometric pH titrations in aqueous solution (25 °C; $I$ = 0.1 M, $NaNO_3$). Their stability is higher than expected for a simple diphosphate monoester (R-$DP^{3-}$) coordination (see Figure; $PhDP^{3-}$ = phenyl diphosphate, etc.) [2]. The stability enhancement (log $\Delta$; vertical dotted lines) can be quantified and attributed to macrochelate formation between the diphosphate-bound $M^{2+}$ and N7 of the guanine residue; this agrees with $^1H$ NMR shift experiments previously carried out with GDP and $Zn^{2+}$ or $Cd^{2+}$ [3]. The formation degree of the macrochelated species amounts to 21 ± 9%, 42 ± 9%, 63 ± 4% and 75 ± 2% for the $GDP^{3-}$ complexes of $Mg^{2+}$, $Mn^{2+}$, $Zn^{2+}$ and $Cd^{2+}$, respectively.



*Supported by the Swiss National Science Foundation.*

[1] G. H. Reed, R. R. Poyner, *Met. Ions Biol. Syst.* **2000**, *37*, 183-207; J. D. Crowley, D. A. Traynor, D. C. Weatherburn, *ibid.* **2000**, *37*, 209-278.
[2] S. A. A. Sajadi, B. Song, F. Gregáň, H. Sigel, *Inorg. Chem.* **1999**, *38*, 439-448.
[3] K. H. Scheller, H. Sigel, *J. Am. Chem. Soc.* **1983**, *105*, 5891-5900.

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Inorganic and Coordination Chemistry **230**

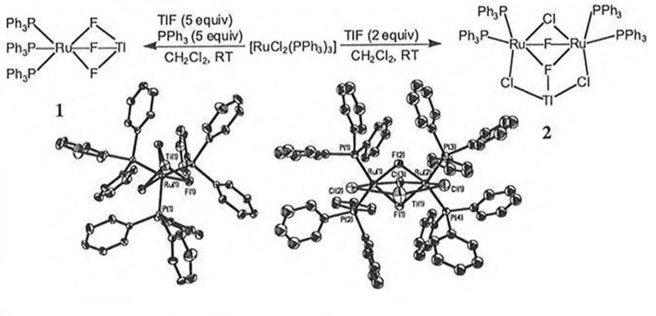
### Fluoro Complexes of Late Transition Metals and their Application in Halide Exchange Reactions with Alkyl Halides

Claus Becker and Antonio Mezzetti*

Department of Chemistry, ETH Zürich, CH-8093 Zürich, Switzerland

Fluoro complexes of late transition metals are still very rare and, therefore, interesting because of their potential application in catalysis. Some of these complexes were found to perform halide exchange with activated alkyl halides such as dichloromethane [1]. We have reported a catalytic version of this fluoride-transfer reaction using five-coordinate Ru(II) complexes as catalysts [2,3].

We report here the new fluoro complexes **1** and **2**, which were prepared from $[RuCl_2(PPh_3)_3]$ and TlF. Their chemistry and their ability of transferring fluoride to organic substrates will be discussed.



[1] V.V. Grushin, *Chem. Eur. J.* **2002**, *8*, 1006.
[2] P. Barthazy, A. Togni, A. Mezzetti, *Organometallics* **2001**, *20*, 3472.
[3] A. Togni, A. Mezzetti, P. Barthazy, C. Becker, I. Devillers, R. Frantz, L. Hintermann, M. Perseghini, M. Sanna, *Chimia* **2001**, *55*, 801.

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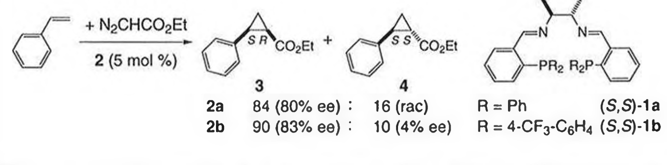
Inorganic and Coordination Chemistry **232**

### Electron-deficient PNNP Ligands in the Ruthenium-catalyzed Asymmetric Cyclopropanation of Olefins

Cristina Bonaccorsi, Stephan Bachmann and Antonio Mezzetti

Department of Chemistry, ETH Zürich, CH-8093 Zürich, Switzerland

The asymmetric cyclopropanation of *para*-substituted styrenes catalyzed by $[RuCl(PNNP)]^+$ [1] shows strong substrate-based electronic effects suggesting that an electrophilic carbene intermediate is involved in the reaction [2]. Thus, we have undertaken the electronic tuning of the PNNP ligands by introducing electron-withdrawing groups into the aromatic substituents of the P atoms.
Although ligand-based electronic effects are generally modest, preliminary results with the ether adducts $[RuCl(OEt_2)(PNNP)]^+$ (**2a**, PNNP = **1a**; **2b**, PNNP = **1b**) as the catalysts indicate that the $CF_3$-substituted complex **2b** is more active than the unsubstituted one, **2a**, in the cyclopropanation of styrene with diazoacetate. Thus, the overall yields of the cyclopropane derivatives (**3** + **4**) is 54% for **2b** and 28% for **2a**. The introduction of the $CF_3$ substituent also improves the cis- and enantioselectivity:



We are preparing and testing the corresponding five-coordinate complex $[RuCl(\mathbf{1b})]^+$, which is expected to give higher selectivities than its ether adduct **2b** [1], as well as other electron-deficient PNNP ligands.

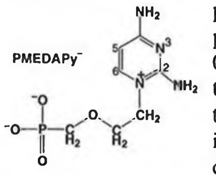
[1] S. Bachmann, M. Furler, A. Mezzetti, *Organometallics* **2001**, *20*, 2102.
[2] S. Bachmann, A. Mezzetti, *Helv. Chim. Acta*, **2001**, *84*, 3063.

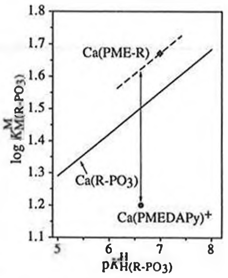
Inorganic and Coordination Chemistry **233**

### Coordinating Properties of the Acyclic Nucleotide Analogue 1-[2-(Phosphonomethoxy)ethyl]-2,4-diaminopyrimidine (PMEDAPy)

Alfonso Fernández-Botello,[a,b] Antonín Holý,[c] Virtudes Moreno,[b] Helmut Sigel[a,*]

[a]Inst. of Inorg. Chemistry, University, Spitalstr. 51, CH-4056 Basel, Switzerland; [b]Inorg. Chem. Dept., University, E-08028 Barcelona, Spain; [c]Inst. of Org. Chem. and Biochem., Acad. of Sciences, CZ-16610 Prague, Czech Republic





Several acyclic nucleotides show remarkable antiviral activity [1] and at least in those instances where the biological effect involves nucleic acid polymerases also metal ions are important [2]. At present we study (pot. pH titrat.; aq. sol.; 25°C; $I$ = 0.1 M, $NaNO_3$) the metal ion ($M^{2+}$) binding properties of PMEDAPy⁻ (synthesis: [1]) to reveal the influence of the positively charged pyrimidine residue on the coordinating properties of the -$PO_3^{2-}$ group. For the evaluation of the measured constants we use the log $K^{M}_{M(R-PO_3)}$ *versus* $pK^{H}_{H(R-PO_3)}$ straight-line plots from our phosph(on)ate (R-$PO_3^{2-}$) studies [3] as well as the stabilities of the M(PME-R) species involving chelate formation with the ether O atom [2]; PME-$R^{2-}$ is a derivative of (phosphonomethoxy)ethane with a 'non-interacting' residue R. Our preliminary results for the $M(PMEDAPy)^+$ complexes of $Ca^{2+}$ (Fig.), $Co^{2+}$ and $Zn^{2+}$ indicate that the stability inhibition amounts to about 0.4 log unit.

*Supported by the Swiss Nat. Science Found. and via COST D20 by the Swiss Fed. Off. for Educ. & Science and the Ministry of Educ. of the Czech Republic.*

[1] A. Holý, M. Buděšínský, J. Podlaha, I. Císařová, *Collect. Czech. Chem. Commun.* **1999**, *64*, 242-256; and refs therein.
[2] H. Sigel, *Pure Appl. Chem.* **1999**, *71*, 1727-1740; and refs therein.
[3] H. Sigel, *Coord. Chem. Rev.* **2000**, *200-202*, 563-594.

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**Inorganic and Coordination Chemistry** **234**

### SPIROPYRAN BASED MOLECULAR SWITCHES

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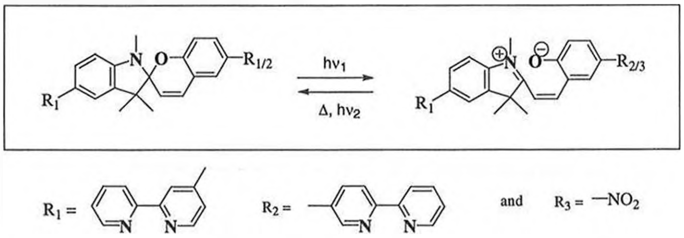
The photochromic properties of spiropyranes (SP) have attracted attention because of their potential application in the development of optical filters, optical and chiroptical switching molecules, electronically conducting wires, and molecular level logic gates. [1]



Metal complexes: $[(bpy)_2Ru(R_n)]^{2+}$, $[(bpy)_2Os(R_n)]^{2+}$, $(R_n)Re(CO)_3Cl$, n=1,2

We have developed a new series of spiropyrans containing covalently bounded 2,2'-bipyridine co-ordinating sites. Further complexation between the new ligands and photoactive metal centres (Ru(II), Os(II), and Re(I)) extends the molecular structure by the introduction of a chemical bounded photosensitizer. By irradiation into the $^1$MLCT band of the sensitizer an energy transfer can occur to the spiropyran switching unit. Such an energy transfer process can induce molecular modifications (opening or closing the SP). Furthermore depending upon the state of the switching unit, this energy transfer can tune the properties of the dinuclear switch.

[1] Photochromism Molecules and Systems; Eds. H. Dürr, H. Bouas-Laurent, Elsevier, Amsterdam (**1990**).

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Inorganic and Coordination Chemistry **235**

### High Resolution EPR Spectroscopy with Water Stable Rh(0) and Ir(0) Complexes

F. Breher, C. Böhler, G. Frison, H. Grützmacher, J. Harmer, A. Schweiger

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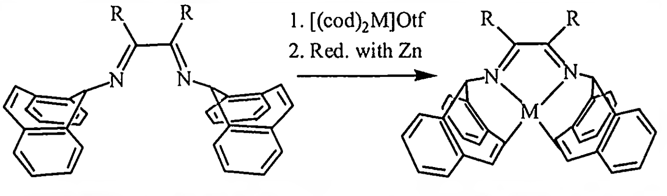
During the last years, there has been an increasing interest in the use of chelating bidentate nitrogen ligands [e.g. bipy, tmeda] in transition metal catalysis. The advantage of these ligands is their stability against oxidation, but, however, these complexes are often unstable. We therefore investigated chelating ligands which have additional binding sites suitable to stabilise late transition metal complexes of rhodium and iridium. These tropdad$^R$ ligands contain a diazadiene[1],[2] (dad) unit to which tropylidene (trop) groups attached via the nitrogen atoms (see below).



tropdad$^R$ ligands (R=H, Me) $[(tropdad^R)M^0]$ with M=Rh, Ir

The cationic transition metal complexes of Rh(I) and Ir(I) of tropdad$^R$ ligands show unusual low redox potentials and even zinc is sufficient as reducing agent leading to water and air stable $d^9$-configurated $[(tropdad^R)Rh^0]$ and $[(tropdad^R)Ir^0]$ complexes. These paramagnetic species were investiganted by a various number of different EPR techniques (e.g. ENDOR, matched-HYSCORE).

[1] Elsevier *et al.*, *Organometallics* **1997**, *16*, 317.
[2] Kaim *et al.*, *Z. Anorg. Allg. Chem.* **2001**, *627*, 620.

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Inorganic and Coordination Chemistry **236**

### Pseudo $C_2$-Symmetric Chiral Monophosphines Bearing two Ferrocenyl Units

Diego Broggini and Antonio Togni

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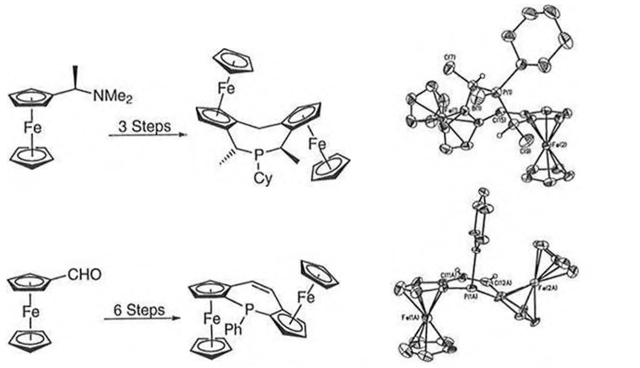
Although monodentate chiral phosphines are overshadowed by the more popular chelating diphosphines, they find some interesting applications in homogeneous catalysis [1]. We report here the synthesis of a new type of cyclic, chiral monodentate phosphines bearing two ferrocenyl moieties [2].



Structural and conformational aspects, as well as reactivity features shall be reported.

[1] F. Lagasse, H. B. Kagan, *Chemical & Pharmaceutical Bulletin* **2000**, *48*, 315.
[2] D. Broggini, A.Togni, Manuscript in preparation.

Inorganic and Coordination Chemistry **237**

## Photo- and Electrochemical Investigations on Novel Binuclear Rhodium-Ruthenium-Olefin Complexes and Their Mononuclear Subunits

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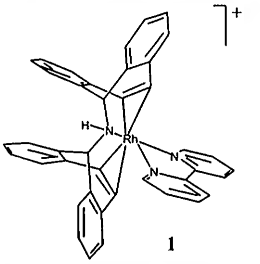
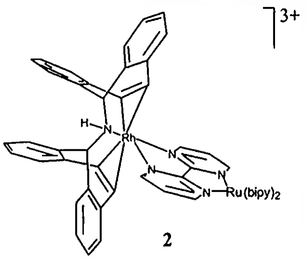
The mononuclear 5 coordinated amine-olefin complex of Rhodium(I) **1** shows interesting reaction patterns in electrochemical studies. Upon reduction the neighboring amine proton reacts with the Rhodium(0) centre. It was shown by Nocera et al.[1] that such species are capable of releasing Hydrogen. The product of this reaction pathway is the corresponding Rh-amide complex which was isolated and characterized.



**1**



**2**

Preliminary work[2] showed that reduction of similar Rh(I) complexes can be achieved using mild reducing agents. For that reason photoreduction of the Rh(I) centre should be possible.
Synthesis of the binuclear Ru-Rh complex **2** was successful and first photophysical investigations showed complete quenching of the luminescence supporting that fact. Electrochemical data of **2** will be presented.

[1] A. F. Heyduk, D. G. Nocera, *Science* **2001**, 293, 1639
[2] S. Deblon, H. Rüegger, H. Schönberg, S. Loss, V. Gramlich, H. Grützmacher, *New Journal of Chemistry* **2001**, *25*, 83

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Inorganic and Coordination Chemistry **238**
COST D18

## Macro(bi)cyclic Eu(II) Complexes as Potential MRI Contrast Agents

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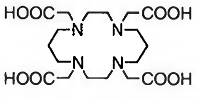
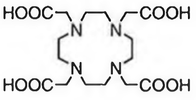
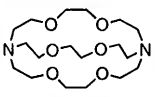
Current developments on contrast agents for Magnetic Resonance Imaging go towards the examination of the physical-chemical state of tissues. These specific contrast agents, called responsive or "smart" contrast agents, can report on important physiological parameters like partial oxygen pressure, pH, temperature, ion distribution in the intra- and extracellular space, metabolite concentration or enzymatic activity. One powerful candidate as redox responsive contrast agent could be the $Eu^{III}/Eu^{II}$ redox system in which the $Eu^{II}$ has seven unpaired electron and high relaxation enhancement effect, similarly to $Gd^{III}$, while $Eu^{III}$ has only a small influence on proton relaxivity. In this perspective, the parameters that influence the water proton relaxivity (rate of water exchange, rotation and electronic relaxation) were determined earlier for the Eu(II) aqua ion and some other Eu(II) poly(amino carboxylate) complexes by $^{17}O$ NMR, EPR and $^{1}H$ NMRD measurements at variable field and temperature.[1] Recently we have investigated three macrocyclic Eu(II) complexes, $[Eu(TETA)]^{2-}$, $[Eu(DOTA)(H_2O)]^{2-}$ and $[Eu(2.2.2)(H_2O)_2]^{2+}$, containing different number of water molecules in the inner coordination sphere.



$H_4TETA$



$H_4DOTA$



(2.2.2)

[1] É. Tóth, L. Burai and A. E. Merbach, *Coord. Chem. Reviews*, **2001**, *216-217*, 363.

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Inorganic and Coordination Chemistry **239**

## Towards a dinuclear tweezer-like metal complex .

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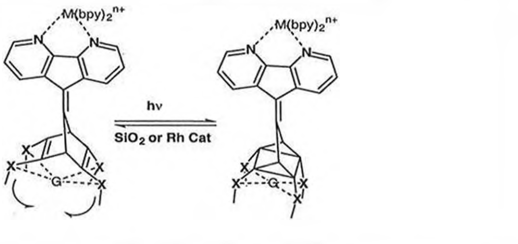
CH-1700 Fribourg, E-mail: yoel.chriqui@unifr.ch

Norbornadiene (NB) can be photochemically isomerized to its quadricyclane (Q) form. Due to the absence of an energetically low-lying absorption band, the photochemical bond-forming process needs normally UV-light. By incorporation of a photo sensitizer into the switching part, the process could be shifted to the visible region (about 450 nm).



A possible application could be found in the field of energy storage. A further interesting property of the planned molecular device is their ability to act as a tweezer. The four anchoring groups X in the norbornadiene molecule are widespread. In the quadricylane molecule they are close together like in an excavator(1). With such a device we can build up a new type of transport molecule in which the guest (G) can be catched and released by a light stimulus.
In order to find the best host, we will try to incorporate different substituents on the NB↔Q part like methoxy, cyano or acetoxy groups.

(1) F. Starck, P.G. Jones, R. Herges; *Eur. J. Org. Chem* **1998**, 2533-39.

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Inorganic and Coordination Chemistry **240**

## Chiral ligands containing different donor groups and their complexes. Synthesis and Characterisation

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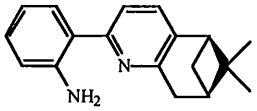
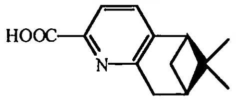
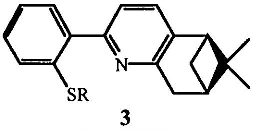
The synthesis of metal complexes with predeterminated chirality at metal center has been the subject of widespread interest in coordination chemistry over recent years [1]. We describe the synthesis and characterisation of the chiral ligands **1, 2, 3** containing different donor groups such as $-NH_2$, $-COO^-$, $-SR$ ($R = H, CH_3, C_2H_5$), having as feature a pinene-pyridine fragment.



**1**



**2**



**3**

The "coordinating capacity" of the new introduced groups is investigated by preparing and characterising their complexes.

This work is supported by the Swiss National Science Foundation.

[1] U. Knof, A. von Zelewsky, *Angew. Chem.*, **1999**, 111, 312.

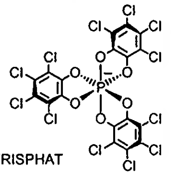
Inorganic and Coordination Chemistry **241**

## Ion-Pair Mediated Stereoselective Synthesis of a Configurationally Stable Mononuclear Tris(diimine)Iron(II) Complex

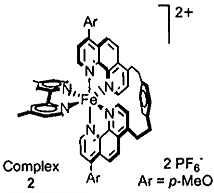
Samuel Constant, David Monchaud, Jérôme Lacour*

Département de Chimie Organique, Université de Genève, 1211 Genève 4

Cationic transition metal complexes are often chiral and many of their applications, reactions or processes yield racemic molecular or supramolecular assemblies. To afford instead non-racemic or enantiopure products, we are studying projects dealing with their asymmetric ion pairing.



TRISPHAT
Δ-1



Complex
2

2 $PF_6^-$
Ar = *p*-MeOPh

Previously, readily prepared tris(tetrachlorobenzenediolato)phosphate(V) anion **1** (or TRISPHAT) was shown to be configurationally stable[1]. This anion is an efficient NMR chiral shift and resolving agent for cationic transition metal complexes. In collaboration with the group of J.-P. Sauvage (Strasbourg, Fr.), we now report on the resolution and on the asymmetric synthesis of a *configurationally stable* mononuclear iron(II) complex **2**; the high diastereoselectivity (d.e. > 90%) coming only from non-covalent interactions with chiral anions **1**[2].

[1] J. Lacour, C. Ginglinger, C. Grivet, G. Bernardinelli, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 608.

[2] D. Pomeranc, V. Heitz, J.-C. Chambron, J.-P. Sauvage, *J. Am. Chem. Soc.* **2001**, *123*, 12215. D. Monchaud, J. J. Jodry, D. Pomeranc, V. Heitz, J.-C. Chambon, J.-P. Sauvage, J. Lacour., *Angew. Chem. Int. Ed.* in press.

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## Complexation and Protonation Behaviour of Chiral Tetradentate Polypyridines Derived from α-Pinene

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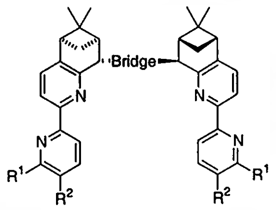
Self-assembly of helicates with labile metal centres has been recently a subject of great interest in the field of supramolecular chemistry. [5,6]-CHIRAGEN[*p*-xyl] **L1b** spontaneously forms a sixfold, circular helicate with Ag(I) and Cu(I).[1]



**L1:** $R^1 = R^2 = H$
**L2:** $R^1$ = *p*-MeO-Ph, $R^2$ =H
**L3:** $R^1$ = H, $R^2$ =*p*-MeO-Ph
bridge: **a** = 0, **b** = *p*-xyl

[5,6]-CHIRAGEN-ligands such as **L2a-b**, **L3a-b** have been synthesised and structurally characterised. We are investigating the formation of coordination compounds by self-assembly with several labile metal ions.

Thanks to the methoxy-groups of these ligands they can be used as precursors for the formation of macrocyles, especially **L3a**.

The protonation of [5,6]-CHIRAGEN[0] **L1a** is another subject of interest. The signal intensity of the CD-spectra changes dramatically upon protonation. This big increase of the intensity is explained by the change of the exciton coupling of the two bipyridine-units, which is comparable to the complexation of **L1a** with other cations such as silver(I) or copper(I).[2] This means, the proton plays the role of a coordinated cation, which makes the ligand to change its conformation.

This work is supported by the Swiss National Science Foundation.

[1] O. Mamula, A. von Zelewsky, G. Bernadinelli, *Angew. Chem. Int. Ed.* **1998**, *37*, 289-293.

[2] O. Mamula, A. von Zelewsky, T. Bark, H. Stoeckli-Evans, A. Neels, G. Bernardinelli, *Chem Eur. J.* **2000**, *6*, 3575-3585.

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Inorganic and Coordination Chemistry **243**

## Mechanistic investigation of the dependence of water exchange rate versus lanthanide ionic radii for a series of polyaminoamide complexes

Frank A. Dunand[a], Shanrong Zhang[b], A. Dean Sherry[b], André E. Merbach*[a]

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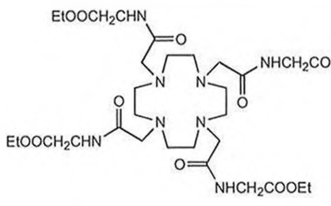
frank.dunand@epfl.ch
[b] Department of Chemistry, University of Texas at Dallas, P.O.Box 830688, Richardson, TX 75083, USA

Next to the use of Gd(III) complexes as contrast agents for the Magnetic Resonance Imaging (MRI), lanthanides complexes have shown interesting properties for their use as CT (Magnetisation Transfer) or CEST (Contrast Enhancement through Saturation Transfer) agents. Very recently a important dependence of the water exchange rate on the complexes of DOTA-tetraamide ligand **1** along the lanthanide series was observed.[1]



*Molecular structure of 1*

We present here variable pressure NMR investigations performed in order to understand the mechanistical reasons for the non-regular variation of the water exchange rate along the lanthanide series.

[1] S. Zhang, K. Wu, D.A. Sherry, *J. Am. Chem. Soc.* **2002**, *124*, 4226-4227.

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Inorganic and Coordination Chemistry **244**

## Solution Studies on $Cu^{2+}$-Complexes with Pyrazole- and Triazole-Based Chelating Ligands

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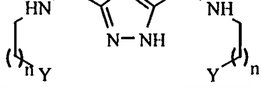
A series of pyrazole- and triazole-based ligands were synthesized in a similar manner as described in the literature [1]. The stability of the $Cu^{2+}$-complexes with these ligands were determined by solution at 25°C and I= 0.5 ($KNO_3$). The calculations, performed with the program TITFIT [2], indicate that mononuclear $[MLH_n]$ (n= 3,2,1,0 and -1) and dinuclear species $[M_2LH_m]$ (n= 0, -1 and -2) are performed as well as the dimeric species $[M_2L_2H_x]$ (x= 2, 1) depending on the nature of the side chains.



X= CH, N
Y= $-NH_2$, $-NH(CH_3)$, $-N(CH_3)_2$
n= 1, (2)

The following results were determined :

For nearly all species the triazole-based $Cu^{2+}$-complexes are less stable than the analogous pyrazole-based ones. Lengthening the side chain by introduction of an extra methylene-group results in a decrease of stability. The ligands with Y= $-N(CH_3)_2$ give less stable 2:1 species than those with Y= $-NH_2$ or Y= $-NH(CH_3)$. Because of steric interactions the ligands with Y= $-N(CH_3)_2$ give no dimeric species $M_2L_2H_x$.

[1] T. Kamiusuki, H. Ōkawa et al., *J. Chem. Soc. Dalton Trans.*,**1990**, 195

[2] A.D. Zuberbühler, and T.A. Kaden, *Talanta* **1982**, 29, 201

Inorganic and Coordination Chemistry **245**

## New catalyst for the hydroamination of activated olefins: Ni(II)-PPP Complexes

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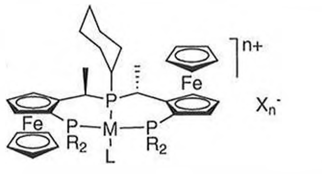
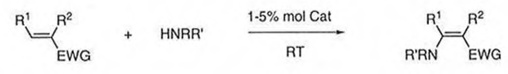
Complexes of the type $[M(PPP)L]X_n$ (M = Ni, Pd, Pt; L = solvent or $Cl^-$; X = $ClO_4^-$, $PF_6^-$, $BF_4^-$, $OAc^-$) containing tridentate ferrocenyl ligands [1] have been prepared, characterized and tested for catalytic olefin hydroamination.



Medium to high activities were generally observed for the Pd-complexes. Only in the case of activated olefins the Ni(PPP)-complexes displayed higher activity than corresponding Pd complexes, as predicted by DFT calculations [2] (TON between 15 and 50, TOF up to 2.0 $h^{-1}$).



$R^1, R^2$ = Me, H
EWG = CN, COOR

[1] Barbaro P., Bianchini C., Togni A., *Organometallics* **1997**, *16*, 3004.
[2] Senn H.M., Blöchl P.E., Togni A., *J. Am. Chem. Soc.* **2000**, *122*, 4098.

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Inorganic and Coordination Chemistry **247**

## BABAR-Phos Complexes: Synthesis and Homogeneous Catalysis

Gionata Frasca, Nicola Pé, Florian Läng, Prof. Dr. Hansjörg Grützmacher

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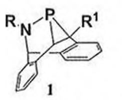
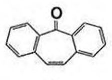
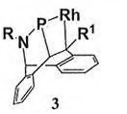
The polycyclic phosphiranes **1** (BABAR-Phos) are not oxidized by $O_2$, sulfur, strongly alkylating agents, and resist aqueous acids and bases. Starting from the dibenzoannelated tropolone **2** led to gram quantities of the amino-substituted phosphiranes in excellent yields. Their small sum of bond angles at the phosphorus centre should make them good π acceptors which in turn should make them interesting ligands for hydrosilylation and hydroboration catalysts.



**1**
**BABAR-Phos**



**2**



**3**
**"Park"**

Rhodium complexes with BABAR-Phos ligands are active catalysts and all catalysts show activity comparable to other rhodium complexes. Most Babar-Phos-Rhodium complexes show good selectivity in hydroboration reactions of styrene with cathecol borane. A product distribution of 2-phenylethanol (15-35%) and 1-phenylethanol (65-85 %) is achieved which is comparable to the Wilkinson-catalyst. Furthermore, our system has major advantages in comparison to the classical analogue. The activity of Babar-Phos does not drop in subsequent catalytic cycles while $[RhCl(PPh_3)_3]$ almost shows no activity. The catalytically active rhodium(+1) centre may be "parked" as Rh(+3) **3** within the ligand skeleton after consumption of substrate and be reactivated by addition of substrate.
Introducing groups R and R1 at the Babar-Phos-Ligand improves the performance of the catalysts in hydroboration and hydrosilylation. We also present a chelating BABAR-Phos ligand.

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Inorganic Chemistry **246**

## Structure and Magnetic Properties of $Mn^{II}Mn^{IV}(CN)_6 \cdot 2.5\ H_2O$

Patrick Franz*, Helen Stöckli–Evans, Silvio Decurtins

University of Bern, Department of Chemistry and Biochemistry,
Freiestrasse 3, CH-3012 Bern

Compounds of the type $M'M''(CN)_6 \cdot x\ H_2O$ are very interesting with respect to the structural and magnetic point of view. They crystallize in a cubic space group and can show magnetic ordering phenomena. Unfortunately, these compounds are very difficult to crystallize. Nevertheless, many researchers make an effort to synthesize and characterize new compounds of this type, which we call Prussian Blues.
We were able to crystallize a bimetallic transparent red–orange μ–cyano bridged 3–dimensional network compound of stoichiometry $Mn^{II}Mn^{IV}(CN)_6 \cdot 2.5\ H_2O$, which exhibits a ferrimagnetic phase transition at 34 K. The structure and the temperature dependence of the magnetic susceptibility are given in figure 1 and figure 2, respectively.

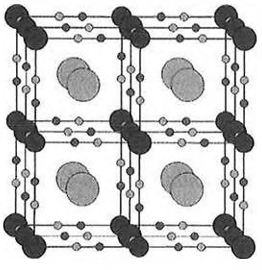

Figure 1: Crystal Structure

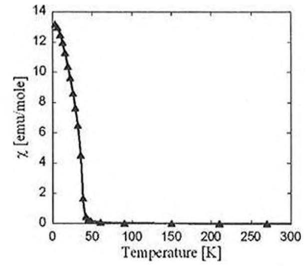

Figure 2: Magnetic susceptibility in an applied field of 1000 Gauss

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Inorganic and Coordination Chemistry **248**

## Oxygen donor stabilized alkaline earth metal iodides

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University of Geneva, Dépt de Chimie Minérale, Sciences II, 30 Quai E.-Ansermet,
CH-1211 Geneva, Switzerland

From a classical standpoint, taking into account the differences in electronegativity of the elements between alkali or alkaline earth metals on one hand and halogens on the other, the alkali and alkaline earth metal halides can be classified as ionic compounds in the solid state. However, the binding situation seems to be influenced by the external conditions and neighbourhood. Isolating, for instance, a NaI-unit in the gas phase reveals a resonance behavior of the bond which converts from being covalent into being ionic.[1] Theoretical *ab initio* calculations confirm the covalent character of the bonds in some alkaline earth metal halides and pseudo-halides, such as $BaBr_2$, that exhibit bent structures in the gas phase, whereas a linear arrangement is expected from the VSEPR model [2] leading to a reformulation of the latter.[3]
The structures of the zero-dimensional compounds $[CaI_2(L)_4]$ (L = thf, $H_2O$), $[MI_2(thf)_5]$ (M=Sr, Ba) and $[CaI_2(DME)(diglyme)]$ (Fig. 1), derived from alkaline earth metal halides, will be presented in their solid state. The packing of the compounds in the solid state will be discussed in the context of ionicity or covalency.

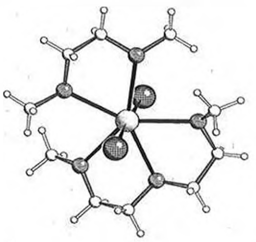

Figure 1

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Inorganic and Coordination Chemistry **249**

## Facile Access to Ruthenium-Hydrides with functionalised Arenes Their Performance in Transfer-Hydrogenation Catalysis

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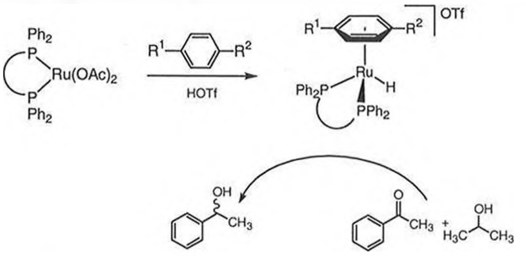
Chiral ruthenium hydride complexes play an important role in various catalytic processes of which the enantioselctive transfer-hydrogenation of ketones has recently attracted considerable interest and the exact mechanism is still under discussion. [1]

We describe here a route to chiral bisphosphine hydrido-complexes bearing substituted arenes and report their kinetic and enatioselective performance as transfer-hydrogenation catalysts.



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Inorganic and Coordination Chemistry **250**

## A close look to the Dichlorophenylphosphane-Sodium-System

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With the reduction of dichlorophenylphosphane by sodium metal in a new solvent system a very easy entry into the chemistry of phenylpolyphosphanids was found. Three sodium compounds, namely $Na_2P_2Ph_2$, $Na_2P_3Ph_3$ and $Na_2P_4Ph_4$ were isolated and their solid state structures established by x-ray crystallography. While the tri- and tetraphosphanediides in form of their tmeda complexes adopt monomeric cage structures, the disodium diphenyldiphosphanediide forms with the ligand dme an intriguing salt lattice composed of $[Na(dme)_3]^+$-cations and trimeric fivecapped trigonal prismatic sodium-at anions $[Na_5(dme)_3(P_2Ph_2)_3]^-$, which are stable also in solution as indicated by nmr spectroscopy.

[1] M. Baudler, D. Koch, E. Tolls, K.M. Diedrich, B. Kloth, *Z. anorg. allg. Chem.* **1976**, *420*, 146.
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Inorganic and Coordination Chemistry **251**
COST B12

## Structure and reactivity of aquacarbonyl complexes of Ru(II), Re(I) and Tc(I)

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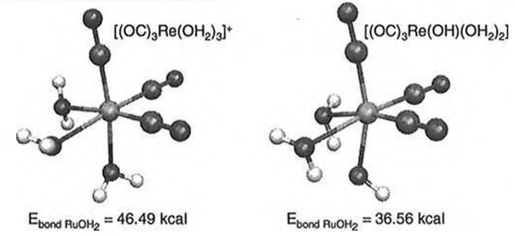
The water exchange rate on $[(OC)_nM(OH_2)_{6-n}]$ with n = 1-3 for M = $Ru^{2+}$ [1], and n = 3 for M = $Re^+$, $Tc^+$ have been investigated by $^{17}O$ NMR spectroscopy. Variable acidity measurements on the triscarbonyl complexes have shown that the water exchange on the monohydroxo species $[(OC)_3M(OH)(OH_2)_2]$ with M = $Ru^{2+}$, $Re^+$ is faster than on the $[(OC)_3M(OH_2)_3]$ analogs.

DFT calculations of both complexe types (carbonyl and monohydroxocarbonyl) have been performed to correlate the kinetic data with the bond lengths, the bonding energies and electronic density distribution. The satisfactory agreement are found beetwen lability of the water molecules and the corresponding bonding energies.



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Inorganic and Coordination Chemistry **252**
COST B12

## High-pressure NMR investigation of ligand exchange on *fac*-$[(OC)_3Re(OH_2)_3]^+$

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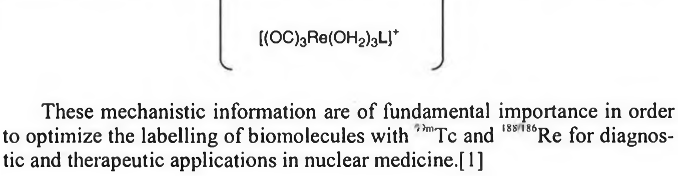
Kinetic studies of complex formation between *fac*-$[(OC)_3Re(OH_2)_3]^+$ and several N, O, or S bearing ligands show that the nature of the donor atom has only a weak influence on the reaction rate indicating that the exchange seems to be dissociatively activated. Determining the activation volume by high pressure measurements for these reactions allows to assign the correct mechanism.



These mechanistic information are of fundamental importance in order to optimize the labelling of biomolecules with $^{99m}$Tc and $^{188/186}$Re for diagnostic and therapeutic applications in nuclear medicine.[1]

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Inorganic and Coordination Chemistry **253**

### Novel alkali mixed-ligand metal clusters

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The preparation of novel alkali metal clusters was achieved by reaction of metallation of a wide range of O-donor ligands from s-block elements. [1,2] Thus, more than dealing with unusual structural chemistry, useful structural information about reaction intermediates or by-products in organic syntheses could be determined.

Syntheses of new alkali mixed-ligand compounds are presented here and characterised by a combination of all the available methods. [3] For instance, reactions of *p-tert*-butylcalix[4]arene with alkali metals *tert*-butoxides in tetrahydrofuran afford dimerics polymetallated calixarenes species $[M_4(p\text{-}tert\text{-butylcalix[4]arene-4H})(thf)_x]_2 \cdot nTHF$ (M = Li, K; *n* = 1 or 6; *x* = 4 or 5), leading to novel crystal structures in which the four independent alkali ions are each coordinated differently (Figure 1).

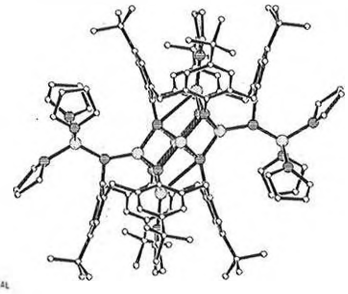

Figure 1: Crystal structure of $[Li_8(p\text{-}tert\text{-butylcalix[4]arene})_2(thf)_8]$

[1] K. M. Fromm, E. D. Gueneau, H. Goesmann, *Chem. Commun.*, **2000**, 2187.
[2] K. M. Fromm, E. D. Gueneau, G. Bernardinelli, H. Goesmann, J. Weber, M. -J. Mayor-López, P. Boulet, T. Tybell, J. -Y. Genoud, H. Chermette, **2002**, *submitted*
[3] E. D. Gueneau, K. M. Fromm, H. Goesmann, **2002**, *submitted*

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Inorganic and Coordination Chemistry **255**

### Vanadium complexes as catalysts for the electrophilic fluorination of β-ketoesters

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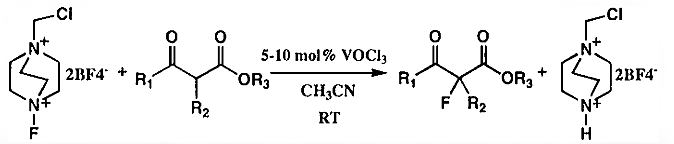
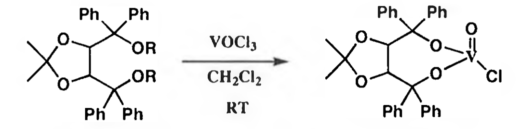
The first catalytic enantioselective fluorination in the presence of Ti(TADDOLate) complexe was recently reported [1-3] from our laboratory. In order to further develop this reaction we explored different early transition metal Lewis acids as possible catalysts and found that $VOCl_3$ is comparable to $TiCl_4$ in promoting the fluorination of β-ketoesters with F-TEDA.



New chiral Vanadium (V) have been prepared by the reaction of $VOCl_3$ with TADDOL silylethers.



R= $-SiMe_3$, -H

K3

[1] L.Hintermann, A.Togni, *Angew. Chem. Int. Ed.* **2000**, *39*, 4359-4362.
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Inorganic Chemistry **254**

### A DNA-Intercalating Complex of a Pyrene Derivative with the $^{188}Re(CO)_3$-Moiety as a Potentially Improved Radiotherapeutic Drug

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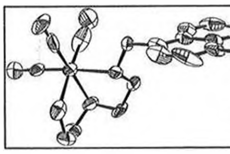
8057 Zürich, Switzerland

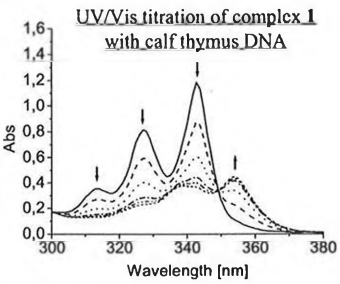


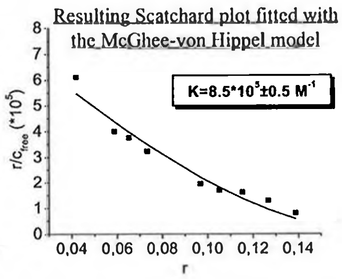
1

N-(2-Amino-ethyl)-N'-pyren-1-yl-methyl-ethane-1,2-diamine (P) reacts in water within 30 minutes at 90°C with the $[^{188}Re(CO)_3(H_2O)_3]^+$ precursor to form in quantitative yield the complex $[^{188}Re(CO)_3(P)]^+$ **(1)**, whose crystal structure is shown on the right.

When transported into the nucleus of a cancer cell by an adequate carrier (e.g. peptide), the $^{188}Re$ complex **1** should readily intercalate into its DNA and induce, through its highly energetic β-particles, DNA double strand breaks that should be lethal to the cancerous cell.

A value of $8.5*10^5$ $M^{-1}$ for the intercalation constant of complex **1** in calf thymus DNA could be determined by UV/Vis titration with DNA and subsequent fitting of the resulting Scatchard plot with the McGhee-von Hippel model [1] (data shown below)





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Inorganic and Coordination Chemistry **256**

### NMR Evaluation of the Configurational Stability of $[Cu(diimine)_2]^+$ Complexes

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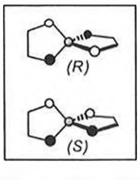
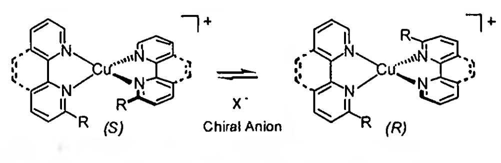
1,10-Phenanthrolines, 2,2'-bipyridines and 2-iminopyridines have been widely used as ligands for Cu(I). The derived tetrahedral complexes are usually sensitive to oxidation and bulky substituents are introduced in positions adjacent to the N-coordinating atoms to provide steric inhibition to the geometric reorganization that occurs upon oxidation. The ligands are often unsymmetrical and their complexation to a copper(I) atom results in the formation of chiral $[CuL_2]^+$ adducts [1]. VT-NMR evaluation of the configurational stability of these complexes was reported using ligands that evidenced nonequivalent signals upon complex formation [2]. Herein, we report another method using a chiral counterion [3] as the source of NMR differentiation. This allows the use of simple bpy, phen and iminopyridine ligands, and the direct comparison of the configurational stability of their chiral adducts.





[1] A. Von Zelewsky *Stereochemistry of Coordination Compounds,* John Wiley and Sons, Chichester, UK, **1996**.
[2] E. Riesgo, Y. Z. Hu, F. Bouvier, R. P. Thummel *Inorg. Chem.* **2001**, *40*, 2541; G. C. Van Stein, G. Van Koten, B. Debock, L. C. Taylor, K. Vrieze, C. Brevard *Inorg. Chim. Acta* **1984**, *89*, 29.
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Inorganic and Coordination Chemistry **257**

### The influence of $CO_2$ on the peroxynitrite-mediated oxidation of oxymyoglobin and oxyhemoglobin

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Institute of Inorganic Chemistry, ETH Hönggerberg, CH-8093 Zurich

Peroxynitrite ($ONOO^-$), a strong oxidizing and nitrating species generated *in vivo* from the diffusion controlled reaction between $NO^{\cdot}$ and $O_2^{\bullet -}$, has been shown to be able to cross the red blood cell membrane and react with hemoglobin [1]. We have recently determined that the rate constants for the oxidation of oxymyoglobin ($MbFeO_2$) and oxyhemoglobin ($HbFeO_2$) by peroxynitrite ($ONOO^-/HOONO$) are $(5.4 \pm 0.2) \times 10^4$ $M^{-1}s^{-1}$ and $(8.4 \pm 0.4) \times 10^4$ $M^{-1}s^{-1}$, respectively [2]. The reactions proceed in two steps via the formation of the ferryl ($Fe^{IV}=O$) forms of the proteins [2].

As it has been shown that under physiological conditions $ONOO^-$ reacts rapidly with $CO_2$ to yield 1-carboxylato-2-nitrosodioxidane ($ONOOCO_2^-$), a stronger nitrating agent than peroxynitrite, we have studied the influence of $CO_2$ on the rate and the mechanism of the peroxynitrite-mediated oxidation of $MbFeO_2$. Here we show that the reaction still proceeds in two steps and that the rate of the first step of the reaction, the oxidation of $MbFeO_2$ to $MbFe^{IV}=O$, increases with increasing $CO_2$ concentration. This effect is pH dependent, larger rates are obtained at higher pH. In contrast, the second-order rate constant for the second step, the reduction of $MbFe^{IV}=O$ to $MbFe^{III}OH_2$, does not change significantly in the presence of an excess of $CO_2$. Under physiological conditions (pH 7.4 and ca. 1.2 mM $CO_2$) the rate constant for the oxidation of $MbFeO_2$ by peroxynitrite is $3 \times 10^5$ $M^{-1}s^{-1}$. Possible mechanisms for this reaction will be discussed.

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[2] M. Exner, S. Herold, *Chem. Res. Toxicol.* **2000**, *13*, 287.

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Inorganic Chemistry **259**

### Electron microscopic characterization of carbon nanostructures from acetylene decomposition.

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Carbon nanotubes were synthesized by decomposition of acetylene on metal catalysts. We varied the temperature (500 – 1000 °C) and the metal type (Fe, Co, Ni, steel). Products were characterized by X-ray powder diffraction (XRD) and electron microscopy techniques (TEM, EDX, SEM, ESI).

All powders are well graphitisied and contain the reflection 002, with a d-value of about 3.3Å. Metals could be dissolved by acid treatment. Nevertheless, reflections of catalysts appear in the XRD patterns, indicating metal nanoparticles intercalated in carbon material.

Transmission electron microscopy images of different carbon nanostructures and nanoforms will be presented. Curved forms, mosaic structures, carbon blacks, and graphite whiskers were typical products. Moreover, carbon fibers were produced on a relatively large-scale [1]. Giant fullerenes, onions, loops, ribbons were found in a number of samples, whereas fullerenes, microbamboo carbon, multiwall nanotubes and singlewall nanotubes are only rarely observed. Of great interest are situations of transitions from amorphous carbon to curved graphite-like forms and finally to flat graphite layers.

[1] A.Ivantchenko, R.Nesper, F.Krumeich, C.Frei, *Chimia*, **2001**, *55*, *7/8*, 620.

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Inorganic and Coordination Chemistry **258**

### Synthesis and characterization of tetranuclear copper(II) complexes with the chiral ligand 1,2-bis(1-methyl-benzimidazolyl)ethanediol

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We have previously shown that 1,2-bis(1-methyl-benzimidazolyl)ethanediol (Bzimed) acts as a facially coordinating tridentate ligand forming mononuclear complexes $[Me(ligand)_2]^{2+}$ (Me: Co(II), Ni(II), Cu(II), Zn(II))[1]. At low ligand:metal ratios the ligand can form polynuclear complexes with the deprotonated alcohol function bridging two or more metal ions. With copper(II) a ligand to metal ratio of 1/1 leads to the formation of $[Cu_4(\mathit{RR}\text{-}Bzimed)_4(-4H)(ClO_4)_2](NO_3)_2(H_2O)_4$ (Figure 1). We report X-ray structure and magnetic susceptibility measurements of this compound in the solid state. By virtue of the spin-coupling of the copper(II) atoms well resolved hyperfine shifted $^1H$-NMR signals are observed. Thus $^1H$-NMR spectroscopy enables the characterization of the tetrameric complex $[Cu_4(\mathit{RR}\text{-}Bzimed)_4(-4H)]^{4+}$ and its tetramer-dimer dissociation equilibrium in solution. Besides magnetic measurements in solution will be discussed.

Figure 1: X-ray structure of $[Cu_4(\mathit{RR}\text{-}Bzimed)_4(-4H)]^{4+}$

[1] Katharina Isele, Vanessa Broughton, Craig J. Matthews, Alan F.Williams, Gérald Bernadinelli, Patrick Franz and Silvio Decurtins, Dalton Transactions, in press.

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Inorganic Chemistry **260**

### New reactions of sodium acetylide.

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Sodium acetylide, $NaHC_2$, was synthesized by adding a blue solution of the metal in liquid ammonia under stirring to a solution of acetylene in liquid ammonia ($T \approx -50°C$) [1]. The product was characterized by X-ray powder diffraction.

Voltage-current measurements were carried out with different ammonia solutions: pure ammonia, with sodium, and with sodium acetylide. The voltage varied between 0-12V, and the data collection was performed by a EG&G PARC 273A instrument (Pt electrodes). Data for ammonia and alkali metals in solution are in a good agreement with those given in the literature. In the range 2-6 V, $NaHC_2$ has a peak centered near 4V. At more than 8V, heating of the solution was observed.

Furthermore, $NaHC_2$ was heated with transition metal catalysts at 1000 °C. X-ray powder diffraction and transmission electron microscopy together with energy dispersive x-ray spectroscopy measurements of the product showed the presence of metal particles embedded in graphite-like carbon. Curved carbon nanostructures and graphite whiskers appear, too. We present magnetic measurements (SQUID) of the product.

[1] T.H.Vaughn, G.F.Hennion, R.R.Vogt, J.A.Niewland, *Journal of Organic Chemistry*, **1938**, *2*, 1.

Inorganic and Coordination Chemistry **261**

## Quantification of the contribution of electronic asymmetry in enantioselective catalysis

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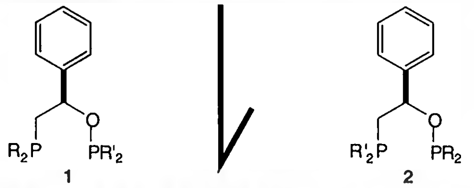
Electronically asymmetric chiral bidentate ligands have received increasing attention in recent years [1-3]. In an attempt to dissect the steric from electronic contributions, we have designed two *pseudo*-enantiomeric ligands **1** and **2**. These were tested in the rhodium-catalyzed asymmetric hydrogenation of olefins.



**1** **2**

R, R' = *o*-anisyl, cyclohexyl, phenyl, pyrrol, phenyl, *o*-tolyl.

The difference in ee (defined as {[R]-[S]}/{[R]+[S]}) obtained for the *pseudo*-enantiomeric catalysts derived from **1** and **2** can be used to quantify the energetic contribution ($\delta\Delta G^{\neq}_{1}$–$\delta\Delta G^{\neq}_{2}$) of the electronic asymmetry in enantioselective catalysis. For R=Ph, R'=*o*-An, the highest ee obtained for the hydrogenation of olefins is 80% (which corresponds to a $\delta\Delta G^{\neq}_{1} = 1.30$ kcal·mol$^{-1}$), whereas for R=*o*-An, R'=Ph, the corresponding ee is –22% ($\delta\Delta G^{\neq}_{2}=0.27$ kcal·mol$^{-1}$). Therefore the contribution of electronic asymmetry corresponds to $\delta\Delta G^{\neq}_{1}-\delta\Delta G^{\neq}_{2} = 1.03$ kcal.mol$^{-1}$.

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[2] T. V. RajanBabu, A. L. Casalnuovo, *J. Am. Chem. Soc.* **1996**, 118, 6325.
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Inorganic and Coordination Chemistry // COST D20/0002/00 **263**

## Stability Constants of Metal Ion ($M^{2+}$) Complexes Formed with N3-Deprotonated Uridine, $(Urd–H)^-$, or Uridine 5'-*O*-Thiomonophosphate, $(UMPS–H)^{3-}$

Bernd Knobloch,[a,b] Carla P. Da Costa,[a] Wolfgang Linert,[b] Andrzej Okruszek,[c] Helmut Sigel[a,]*

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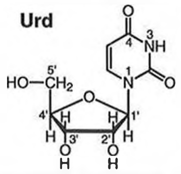
[b]Inst. of Appl. Synth. Chemistry, Tech. University, A-1060 Vienna, Austria;
[c]Dept. of Bioorg. Chemistry, Acad. of Sciences, PL-90-363 Lódź, Poland

The uracil moiety is one of the important nucleobase residues occurring in nucleotides and nucleic acids [1]. Since the metal ion affinity of this pyrimidine derivative is only poorly characterized, we decided to study the metal ion-binding properties of uridine (Urd), which may be deprotonated at its (N3)H site with $pK_a = 9.19 \pm 0.05$ [2] to give $(Urd–H)^-$. Presently we attempt to measure (pot. pH titrat.; aq. sol.; 25 °C; $I = 0.1$ M, $NaNO_3$) the stability constants of several $M(Urd–H)^+$ complexes. Such studies are hampered by $M^{2+}$-hydroxo complex formation, but up to now we obtained the following preliminary results (log $K^{M}_{M(Urd-H)}$ is given in parenthesis): $Mg(Urd–H)^+$ (0.70 ± 0.15), $Co(Urd–H)^+$ (1.60 ± 0.10), $Ni(Urd–H)^+$ (1.76 ± 0.06) and $Cd(Urd–H)^+$ (3.16 ± 0.10). We intend to compare these data with the stabilities of the complexes formed between $M^{2+}$ and $M(UMPS–H)^-$, i.e., with a $(UMPS–H)^{3-}$ species which has one $M^{2+}$ coordinated at its thiophosphate group but which should be able to bind a further one at its $(N3)^-$ site giving $M_2(UMPS–H)^+$. Such comparisons should facilitate understanding of the UMPS systems.

**Urd**



*Supported by the Swiss Nat. Science Found. and via COST D20 by the Swiss Fed. Off. for Educ. & Science and the State Comm. for Scientific Res., Poland.*

[1] *Metal Ions in Biological Systems,* Vol. 32: *Interactions of Metal Ions with Nucleotides, Nucleic Acids, and Their Constituents*; Eds: A. Sigel, H. Sigel; Dekker, New York & Basel, **1996**, pp. 1-678.
[2] H. Sigel, *Chem. Soc. Rev.* **1993**, 22, 255-267.

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Inorganic and Coordination Chemistry **262**

## Investigation on Low Molecular Iron(III) Coordination Compounds, Their Stability and Reduction Behaviour Against Ascorbate and Superoxide

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Our current research focuses on the reduction of iron(III) coordination compounds with citrate and adenosine triphosphate (ATP) by ascorbate and superoxide. Both complexes are considered possible biorelevant species in the labile iron pool. Ascorbate and superoxide are potential physiologically significant reductants. The experiments with ascorbate are carried out under anaerobic conditions, whereas the ones with superoxide are induced by pulse radiolysis.

For the iron(III) citrate complex, cyclovoltammetric measurements show a high inertness and only a small potential difference of approx. 0.2 V to ascorbate. No observable reduction occurs. Also the reaction with superoxide by pulse radiolysis seems to occur only to a minor extent.

The iron(III) ATP complex can be reduced by ascorbate, but the reaction is too slow ($t_{1/2} \geq 500$ s) to be biorelevant as stopped flow experiments suggest. The reduction by superoxide occurs faster, but given the low physiological concentrations of superoxide and a bimolecular pathway, reaction rates drop to a nonrelevant magnitude.

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## Synthesis of a New Semi-Flexible Nonadentate Covalent Tripod and its Complexing Properties with Trivalent Lanthanides **264**

Sylvain Koeller, Gérald Bernardinelli and Claude Piguet*

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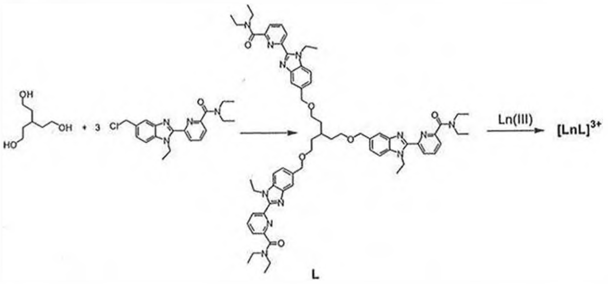
The nonadentate podand tris-{2-[2-(6-diethylcarbamoyl-pyridin-2-yl)-1-ethyl-1H-benzoimidazol-5-ylmethoxy]-ethyl}-methane (L) has been prepared according to a multistep strategy using the flexible 3-(2-hydroxyethyl)-pentane-1,5-diol covalent tripod. In solution, a dynamically averaged $C_{3v}$-symmetrical structure is observed and the absence of any Nuclear Overhauser Effects (NOEs) between the pyridinic protons and the ethyl moiety implies a *trans* conformation of the coordinating pyridine and benzoimidazole nitrogen atoms. Reactions of L in an ionic buffer ($Bu_4NClO_4$) with $Ln(ClO_4)_3$ or $Ln(OTf)_3$ (Ln = La-Lu) produce stable 1:1 podates $[Ln(L)]^{3+}$ in acetonitrile.



L

The Eu complex crystallizes in the trigonal *R*3*c* group and thus exhibits a crystallographic $C_3$-symmetry. Particular attention has been focused on the structural conditions required for the regular wrapping of the extended covalent tripod, a crucial point for the design of directional light-converting devices [1].

[1] Renaud, F.; Decurnex, C.; Piguet, C.; Hopfgartner, G. *J. Chem. Soc., Dalton Trans.* **2001**, 1863-1871.

CHIMIA 2002, 56, No. 7/8

Inorganic and Coordination Chemistry

**265**

## Electron Microscopy Characterisation of Silica Nanotubes

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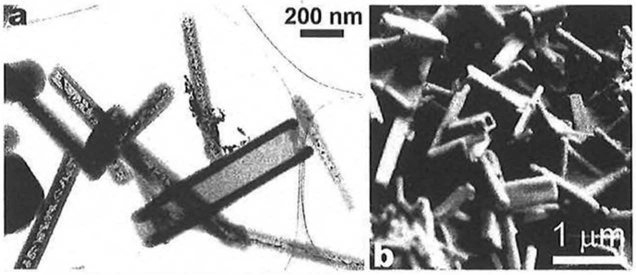
[2] Institute for Physical Chemistry and Electrochemistry, University of Hanover, D-30167 Hanover, Germany

For the synthesis of silica nanotubes, well-developed, self-organised nanofibers of $[Pt(NH_3)_4](HCO_3)_2$ are used as templates [1]. The surface of these fibers is coated with silica produced by a sol-gel reaction starting with $Si(OEt)_4$. The precursors are arranged on top of the nanofibers via hydrogen bonds. After condensation to the amorphous silica walls, the Pt-salt nanofibers are thermally decomposed and auto-reduced to metallic Pt nanoparticles. SEM and TEM investigations (figure) of the product confirm the fabrication of silica nanotubes in high yield. Unexpectedly, distinct tube variants exist that differ with respect to the morphology as well as to the filling with Pt particles. In rare cases, even Pt nanowires are formed.



(a) Transmission electron microscopy and (b) scanning electron microscopy images of silica nanotubes.

[1] C. Hippe, M. Wark, E. Lork, G. Schulz-Ekloff, *Microp. Mesop. Mater.* **1999**, *31*, 235.

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Inorganic Chemistry

**266**

## $Eu_5Mg_{18}Si_{13}$- a new phase in the Eu/Mg/Si-system

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Up to now only the phase EuMgSi is known in the ternary system Eu/Mg/Si. EuMgSi crystallizes with the NiTiSi-type and contains isolated $Si^{4-}$- anions [1].

Recently, the new phase $Eu_5Mg_{18}Si_{13}$ was obtained by ampoule syntheses from the pure elements. $Eu_5Mg_{18}Si_{13}$ (P-62m; a=14.368(1) Å; c=4.360(1) Å) crystallizes with the $Ba_5Mg_{18}Si_{13}$ structure type and is isostructural to $Sr_{6.33}Mg_{16.67}Si_{13}$ and $Ba_5Mg_{18}Ge_{13}$ [2-4]. The structure contains isolated $Si^{4-}$ -anions and $Si_4^{10-}$ -stars (Fig. 1), which are stacked ecliptically along [001].

It can formally be described by the formulation $(Eu^{2+})_5(Mg^{2+})_{18}[Si_4^{10-}][Si^{4-}]_9$ in complete accord with the Zintl-Klemm concept. However, the $Si_4^{10-}$-stars are not planar and can be better rationalized with a situation being isostructural and isoelectronic to $PCl_3$.

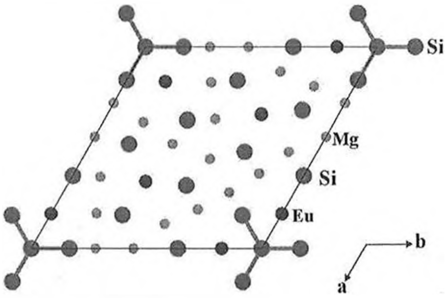

**Fig. 1:** The crystal structure of $Eu_5Mg_{18}Si_{13}$

[1] F. Merlo, M. Pani, M. L. Fornasini; *J. Alloys Comp.* **1993**, *196*, 145
[2] S. Wengert; *PhD Thesis ETH No. 12070*, Zürich 1997
[3] A. Currao; *PhD Thesis ETH No. 11747*, Zürich 1996
[4] F. Zürcher; *PhD Thesis ETH No. 12546*, Zürich 1998

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Inorganic Chemistry

**267**

## A new phase in the Yb/Si-system

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In the binary system Yb/Si, the four phases YbSi, $YbSi_{2-x}$, $Yb_3Si_5$, $Yb_5Si_3$ are known [1-3]. In the course of systematic thermochemical investigations of the binary system Yb/Si, the new phase $YbSi_{1.41}$ could be obtained by reacting the pure elements under inert conditions. $YbSi_{1.41}$ crystallizes in the orthorhombic space group *Cmcm* (a=4.159(1) Å; b=23.510(5) Å; c=3.775(1) Å). It contains planar infinite all-trans silicon chains, which are stacked ecliptically along the b-direction. The main structural building blocks are trigonal $Yb_6$-prisms, which are centered by silicon atoms. Furthermore, there is electron density in the adjacent $Yb_6$-prisms, which can only be assigned to a partially occupied silicon site (41%, cf. Fig. 1). Weak superstructure reflections were found in the electron diffraction patterns and the results of HRTEM investigations indicate a partial ordering of these silicon atoms.

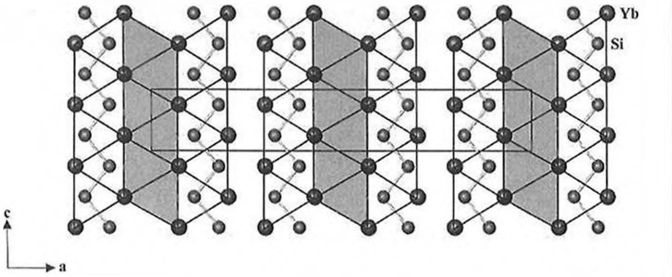

**Fig. 1:** The structure of $YbSi_{1.41}$; the trigonal $Yb_6$-prisms are highlighted with black lines and the partially occupied $Yb_6$-prisms are shaded in grey.

[1] F. Merlo, M. L. Fornasini, *J. Less-Common Met.* **1967**, *13*, 603
[2] A. Iandelli, A. Palenzona, G. L. Olcese, *J. Less-Common Met.* **1979**, *64*, 213
[3] I. Mayer, I. Shidlovsky, *Inorg. Chem.* **1969**, *8(6)*, 1240

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Inorganic and Coordination Chemistry

**268**

## The Potential of Peroxynitrous Acid Determined by Linear Sweep Voltammetry

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Peroxynitrite is formed *in vivo* from the diffusion-controlled reaction of $NO^{\bullet}$ with $O_2^{\bullet-}$. Peroxynitrous acid (ONOOH) is a strong oxidant and reacts with a wide variety of biomolecules. The instability and reactivity of peroxynitrous acid makes it difficult to determine the reduction potential of this biological harmful species. We measured by linear sweep voltammetry the decay of peroxynitrous acid at pH 5.6. From the decay kinetic we determined a signal corresponding to peroxynitrous acid. The reduction potential was determined by Feldberg simulation. Additionally we estimated the reduction potential by extrapolation of the sweep rate by the formula $E_P = E^{0'} - \frac{RT}{\alpha n_a F}\left[0.78 + \ln\left(\frac{D_0^{1/2}}{k^0}\right) + \ln\sqrt{\frac{\alpha n_a F v}{RT}}\right]$ [1]. We obtained with both procedures a reduction potential of about 1.2 V. The oxidized product is $NO_2^{\bullet}$.

[1] A.J. Bard, L.R. Faulkner, Electrochemical Methods; John Wils & Sons Inc.: 1980

Inorganic and Coordination Chemistry **269**

## A Novel Ligand Scaffold for Two-Metal Catalysis?

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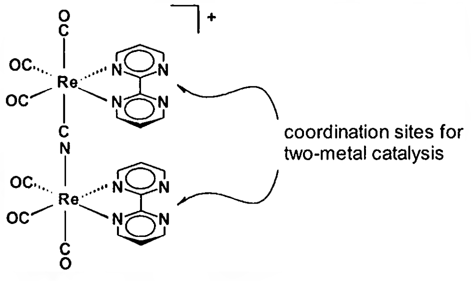
University of Zürich, Winterthurerstr. 190, CH-8057 Zürich, Switzerland

Molecular assemblies in which two active metal centres are fixed close to one another are attractive systems for catalysis. Thus far work in this field was mainly focused on ligands that rigidly fix the positions and orientations of the two metal sites towards each other. Here we present the preparation of the binuclear, cyanide-bridged Rhenium complex $[(CO)_3(bpm)Re\text{-}CN\text{-}Re(bpm)(CO)_3](NO_3)$ **1** (bpm=2,2'-bipyrimidine) as a novel ligand scaffold for two-metal catalysis.



**1**

NMR studies indicate that the two bpm- subunits rotate freely around the Re-CN-Re axis. Two catalytically active metal centers coordinated to the vacant bpm-sites would be held in close proximity by the Re-CN-Re backbone of the complex while different rotational conformations of the assembly as a whole are still possible. It is our task now to find suitable metal units that form stable but still active tetranuclear complexes with **1** and test their catalytic properties.

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Inorganic and Coordination Chemistry **270**

## Synthesis and Coordination Chemistry of very robust Phosphiranes

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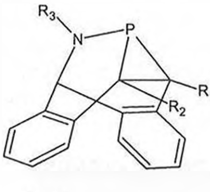
Due to their special electronic properties phospiranes are interesting Ligands for homogenous catalysis. Various exceedingly stable phosphiranes (1 a-f) with its cyclic $PC_2$ unit embedded in a polycyclic carbon framework were synthesized in good yields starting from dibenzosuberenone. These BABAR-Phos called phosphiranes are not sensitive towards oxygen and readily form complexes with rhodium and platinum.



a: R1=H, R2=Ph, R3=iPr
b: R1=H, R2=Naphtyl, R3=iPr
c: R1=H, R2=o-Anisyl, R3=iPr
d: R1=H, R2=Ph, R3= 3,5-CF3-Ph
e: R1=H, R2=Ph, R3=(+)-C(CH3)(Ph)H
f: R1=Ph, R2=Ph, R3=iPr

1 a-f

BABAR-Phos Ligands show high activity in Rh-catalyzed hydroboration of styrene. The regeoselectivity of the catalytic reaction can be influenced by modification of the substituents at either the N-Atom or at the C-Atoms of the $PC_2$ heterocycle. C-substituents were introduced by simple Suzuki coupling reactions of 10-Bromodibenzosuberenone with arene boronic acids. Substition of only one C-atom leads to formation of two enantiomers i.e. introduces chiral information to the Ligand.

[1] Hansjörg Grützmacher, Jürgen Liedtke, Gionata Frasca, Florian Läng, Nicola Pè, *Phosphorous, Sulfur and Silicon*. **2002**, *177*, 1.

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Inorganic and Coordination chemistry **271**

## Evaluation of ligand strain on the properties of rhodium and iridium complexes by electrochemical investigations

Cécile Laporte, Carsten Böhler, Frank Breher, Hartmut Schönberg, Hansjörg Grützmacher

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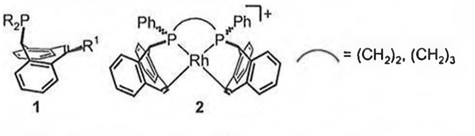
Rhodium and iridium complexes with the $R^1$-tropp$^R$ ligand system **1** (tropp = tropylidene phosphane; IUPAC 5-diphenylphosphanyl-dibenzo[a,d]cycloheptene) are reversibly reduced in two successive single electron transfer steps at remarkably low negative potential.



Because the redox steps are reversible, tropp complexes are ideally suited to study the effects of R and $R^1$ on the thermodynamic properties. Especially for M = Rh or Ir, such investigations may be helpful to understand substituent effects on the performance of catalysts. In order to investigate effects from restraints on the conformational freedom of organometallics, we synthesised chelating bis(tropp) ligands and prepared with them complexes such as **2**. For example, with the meso form [*R*,*S*-bis(tropp$^{Ph}$)], the rhodium(I) complex $[Rh\{$*R*,*S*-bis(tropp$^{Ph}$)$\}]PF_6$ [**2a**: ∩= $(CH_2)_2$] was obtained.

The redox chemistry was studied in order to determine the influence of the strain energy imposed by the ligand. Complex **2a** is reduced reversibly in THF at stronger negative potentials as other tropp complexes ($E^1_{1/2}$ = -1.405 V and $E^2_{1/2}$ = -1.772 V vs. Ag/AgCl ) which we attribute to the built up of a considerable strain energy (30 kJ.mol$^{-1}$) in the redox process.

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Inorganic and Coordination Chemistry **272**

## Design and Synthesis of Novel Functionalised TTF Derivatives

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Since 1985, the syntheses of new functionalized tetrathiafulvalene (TTF) derivatives have paved the way for the use of the TTF system as a building block within the wider context of supramolecular and materials chemistry [1]: for example, as redox-active components in Langmuir-Blodgett (LB) films, molecular sensors, molecular shuttles and switches, wires, multi-stage assemblies and dendritic macromolecules. As a consequence, considerable attention has been paid to molecular systems containing a redox-active functionality, as well as a host unit capable of cation binding [2]. Recently we have been exploring an approach to design and synthesize suitably functionalized bis(ethylenedithio)tetrathiofulvalene(BEDT-TTF) derivatives (Figure 1) in order to prepare novel organic conducting materials featuring TTF moieties within metal binding ligand systems [3]. Here, single crystal structures of some novel functionalized BEDT-TTF derivatives, together with a study of their binding ability to transition metal ions are described.

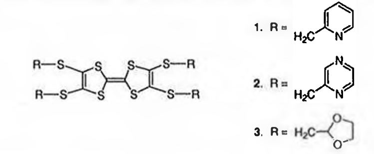

**Figure 1**. Structures of some functionalised BEDT-TTF derivatives

[1] J.L. Segura, N. Martín, *Angew. Chem. Int. Ed.* **2001**, *40*, 1372.
[2] M.R. Bryce, W. Davenport, L.M. Goldenberg, C. Wang, *Chem. Comm.* **1998**, 945.
[3] S-X Liu, S. Dolder, M. Pilkington and S. Decurtins, *J. Org. Chem.* **2002**, *67*(9), 3160.

Inorganic Chemistry **273**

## Determination of the Association Constants between Biotinylated Coordination Complexes and Avidin

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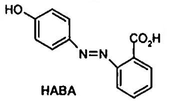
The biotin-avidin technology is based on the extraordinary affinity of biotinylated compounds for avidin. The affinity of biotin for avidin has been estimated to $K_a$ = ca. $10^{14}$ $M^{-1}$. It is generally assumed that derivatization of the valeric acid side chain of biotin does not significantly decrease the corresponding $K_a$. Our group exploits the enantiopure chiral environment provided by avidin in enantioselective catalysis wih achiral biotinylated catalyst precursors. In order to ensure quantitative localization of the catalyst precursor within the avidin binding pocket, we have set out to determine the association constant of various biotinylated coordination compounds. As these constants were found to be too large to be determined precisely ($K_a > 10^8$ $M^{-1}$), we rely on a two-step procedure to determine the association constants as illustrated below:

$$\text{Avidin} + \text{HABA} \overset{K_{d(HABA)}}{\rightleftharpoons} \text{Avidin} \cdot \text{HABA}$$

$$K_{d(HABA)} = \frac{[\text{Avidin}][\text{HABA}]}{[\text{Avidin} \cdot \text{HABA}]}$$



HABA

$$\text{Avidin} \cdot \text{HABA} + \text{Biotin-catalyst} \overset{K'_{d(biotin\text{-}cat)}}{\rightleftharpoons} \text{Avidin} \cdot \text{Biotin-catalyst} + \text{HABA}$$

$$K'_{d(biotin\text{-}cat)} = \frac{[\text{Avidin} \cdot \text{HABA}]\,[\text{biotin-cat}]}{[\text{Avidin} \cdot \text{biotin-cat}]\,[\text{HABA}]}$$

$$K_{d(biotin\text{-}cat)} = K_{d(HABA)}K'_{d(biotin\text{-}cat)} = \frac{[\text{Avidin}][\text{biotin-cat}]}{[\text{Avidin} \cdot \text{biotin-cat}]}$$

This procedure was exploited for different complexes with various geometries, steric bulk and charges, yielding precise association constants. It appears that although the large coordination complexes are located within the binding pocket of avidin as assessed by circular dichroism, the $K_a$ remain very high ($K_a > 10^{10}$ $M^{-1}$).

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Inorganic and Coordination Chemistry **274**

## The Design and Synthesis of Novel Aza-Phthalocyanines With Peripheral Binding Sites

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Silvio Decurtins

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The diverse repertoire of coordination chemistry and electronic properties of phthalocyanines, arising from their large π-conjugated systems, together with their outstanding propensity to assemble into cofacially-stacked arrays make them interesting for applications in the fields of liquid crystals, Langmuir-Blodgett films and therapeutic agents in pharmacology [1].
In recent years, much attention has focused upon the peripheral substitution of the phthalocyanine skeleton, in particular, since this affords new materials with diverse chemical and physical properties. One of the major difficulties facing chemists working in this field is a lack of suitable synthetic routes for the preparation of functionalised phthalocyanine derivatives in reasonable yields. In an attempt to address this problem we are currently focusing our attention on the preparation of novel aza-phthalocyanines.
In this context, we present new phthalocyanine derivatives with additional peripheral binding sites [2]. The study of these molecules is particularly interesting with a view to the preparation of novel molecule-based optical, conducting and magnetic materials. Furthermore, exploiting the coordination chemistry of the additional binding sites provides us with an alternative strategy for controlling the structural topology, which in turn should enable us to tune the physical properties of this new class of phthalocyanine derivatives.

[1] N.B. McKeown "Phthalocyanine Materials: Synthesis, Structure and Function" **1988**, Cambridge University Press, Cambridge.
[2] J. Rusanova, M. Pilkington and S. Decurtins, *J. Chem. Soc. Chem. Commun.* **2002**, *in prep.*

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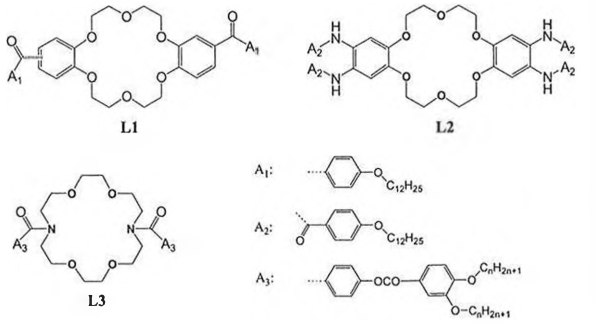
Inorganic and Coordination Chemistry **275**

## Lanthanide complexes of promesogenic macrocyclic ligands and their optical behaviour

Olimpia Mamula[1], Stéphane Suárez[1], Claude Piguet[2], Jean-Pierre Rivera[2] and
Jean-Claude Bünzli[1]*

[1]Institute of Molecular and Biological Chemistry, Federal Institute of Technology, 1015-Lausanne, Switzerland; [2]Department of Inorganic, Analytical and Applied Chemistry, Sciences II, University of Geneva, 1211 Geneva 4, Switzerland

Sustained efforts have drawn hefty attention recently to obtain metal-containing liquid crystals (metallomesogens) in view of potential applications. In order to combine the unique physical properties of lanthanide cations (*i.e.* Eu(III)/Eu(II) luminescence) and their known binding affinities for macrocycles, we synthesized the ligands **L1**,**L 2**,**L 3**.



The optical, thermal (TGA, DSC), mesogenic (polarized microscopy) properties of **L1**, **L2**, **L3** and their complexes with Eu(III) and La(III) will be presented.

[1] K. Binnemans *et al.*,*J. Am. Chem. Soc.*, **2000**, *122*, 4335-4344.
[2] C. Piguet *et al.*,*Ino rg. Chem.*,**20 00**,*39* , 5286-5298.

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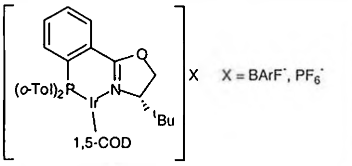
Inorganic and Coordination Chemistry **276**

## $^1$H, $^{19}$F, $^{31}$P and $^{35}$Cl-PGSE Diffusion Measurements in Organometallic Chemistry. Structure of a Cationic Polyhydrido Ir Cluster Complex

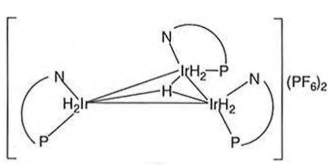
P. S. Pregosin*, H. Rüegger, E. Martinez-Viviente and A. Albinati

Laboratory of Inorganic Chemistry. ETH HCI Hönggerberg. CH-8093.
Zürich. Switzerland

$^1$H and $^{19}$F Pulsed Gradient Spin Echo (PGSE) diffusion data can be useful in determining molecular volumes and inter-ionic interactions in metal complexes.[1] They suggest that the higher hydrogenation activity of the BArF$^-$ salt of catalyst **1** with respect to the $PF_6^-$ salt is due to increased mobility of the $PF_6^-$ anion, which allows ready deactivation of the catalyst via trimerization to **2**.[2] We have isolated and fully characterized **2**, and will describe its NMR data and crystal structure.

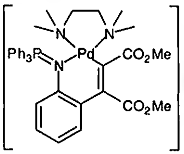


**1**



**2**

We have extended the PGSE diffusion methodology to include $^{31}$P and $^{35}$Cl. These were used in the study of **3**, and allow diffusion studies on molecules which do not show suitable $^1$H-NMR signals or which have a $ClO_4^-$ anion.



**3**

[1] M. Valentini, H. Rüegger and P. S. Pregosin. *Helv. Chim. Acta.* **2001**, *84*, 2833.
[2] D. Drago, P. S. Pregosin and A. Pfaltz. *Chem. Commun.* **2002**, 286.

Inorganic and Coordination Chemistry

**277**

## Selective release of technetium complexes from a solid phase due to C-N bond cleavage upon metal coordination

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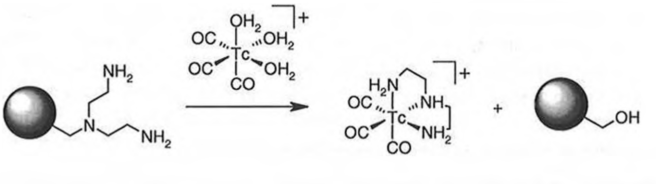
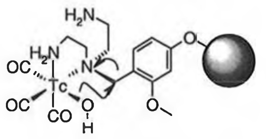
The last step in the preparation of $^{99m}$Tc-radiolabeled biomolecules is the complex formation. Due to the short half life time of $^{99m}$Tc, this reaction has to be done immediately before administration to patients. To ensure complete binding of the $^{99m}$Tc precursor, high excess of the biomolecule-chelator conjugate is usually applied. This entails the risk of side effects due to unlabeled biomolecules in vivo. Here we describe a new labeling method using solid phase technology, which allows the separation of unlabeled from labeled bioactive molecules by simple filtration.



We discovered a very specific cleavage reaction, initiated by the formation of $[Tc^{I}(CO)_3L]$-complexes. Chelators with tertiary amino groups are prone for C-N bond cleavage if the corresponding methylene group is bound to an arylic system. Based on kinetic data and on investigations on model compounds, we propose an intramolecular mechanism for this reaction. As the tertiary amino group coordinates to the cationic Tc-center, it becomes partially positive and the adjacent carbon is therefore activated for nucleophilic attack. A remaining hydroxy ligand attacks the methylene group of the chelator and induces C-N bond cleavage. The third donator site of the chelator coordinates to the Tc-center, and the product complex is released into solution.



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Inorganic and Coordination Chemistry

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## Peroxynitrite and Transition Metals

Martin Merkofer, Patrick K. Wick, Thomas Nauser, Reinhard Kissner, and Willem H. Koppenol

Institute of Inorganic Chemistry, ETH Hönggerberg, CH-8093 Zurich

Peroxynitrite is a cytotoxic species. Its decomposition is catalyzed by iron and manganese porphyrin complexes. Given the observation of an unstable Fe–ONOO$^-$ complex in haemoglobin [1], the question has arisen whether it would be possible to stabilize peroxynitrite, or to catalyze its decay by complexation to a metal. We analysed the catalytic decomposition of peroxynitrite by Cu(II), Ni(II) and Zn(II) complexes. All three metals enhance the decay rate, as expected for Lewis acids in general. In the presence of Cu(II), we observed a reaction faster than that proposed for homolysis of ONOO$^-$ to NO$^\bullet$ and $O_2^{\bullet-}$, 0.017 $s^{-1}$ [2]. Therefore, homolysis is not the main reaction. This is supported by the observation that Zn(II) complexes also enhance the decay, though such complexes cannot be reduced by superoxide. Cu(II)-nta enhances the formation of $NO_3^-$ when [ONOO$^-$] < [ML]. No formation of Cu(I) could be observed, which argues against homolysis of ONOO$^-$. We propose a mechanism which involves an isomerization within the coordination sphere. When [ONOO$^-$] > [Cu] the decomposition to $NO_2^-$ and $O_2$ is catalyzed.
We reported that a stable $[Co(CN)_5ONOO]^{3-}$ complex can be isolated [3]. The Co(III) complex has a spectrum in which the absorption of peroxynitrite is blue-shifted, similar to that of the unstable Cu-complex. We also have some evidence for a side-on peroxynitrite-titanium(IV) complex at pH = 0.

[1] S. Herold, *FEBS Letters* **1999**, *443*, 81.
[2] Merényi, G., and Lind, J., *Chem. Res. Toxicol.* **1998**, *11* , 243.
[3] P.K. Wick, R. Kissner, W.H. Koppenol, W. H., *Helv. Chim. Acta* **2001**, *84*, 3057; **2000**, *83*, 748

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Inorganic Chemistry

**279**

## Study of the Structural and Electronic Properties of Five-Coordinate [Ni(acac)$_2$(py)] Type Complexes

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and

Maja Gruden-Pavlovic and Sonja Grubisic

*Chemistry Department, University of Belgrade, Belgrade, Yugoslavia*

Intramolecular rearrangement between a square pyramidal (SQP) and two distinct trigonal bipyramidal (TBP) configurations of [Ni(LL)$_2$(py)] (LL = acac$^-$ or Me$_2$acac$^-$) has been studied by molecular mechanics (MM), angular overlap model (AOM) and density functional (DFT) approaches in a complementary fashion.

In MM double-well potential functions were used to describe the angle bending deformations around the metal atom in the course of SQP↔TBP interconversion.

MM analysis is complemented with AOM to assess the steric and electronic factors which control the SQP↔TBP rearrangement. To that end we have developed a new fully integrated MM/AOM program capable of treating steric and electronic effects in an unified way.

Finally, the DFT approach was used: (1) to set a framework for quantitative understanding of the intramolecular rearrangements in [Ni(LL)$_2$(py)], and (2) to provide a basis for the parameterization of the MM force field applicable to five coordinate structures in general.

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†Roche Research Foundation Fellow, 2001-2002.

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Inorganic Chemistry

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## Crystal structure of CaSiN$_2$

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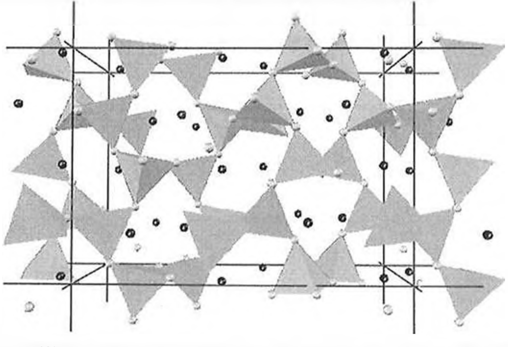
Although the preparation of a substance with the composition $CaSiN_2$ is known since 1909 [1], the crystal structure of $CaSiN_2$ has not been clarified yet. Crystals of transparent, orange $CaSiN_2$ were obtained as a by-product of the synthesis of $Ca_7Si_4N_{10}$ [2] starting from $CaSi_2$ and $Ca_3N_2$ at temperatures of 1400 °C in sealed niobium ampoules. The surplus of calcium metal acts as a flux and enables the formation of large single crystals.



$CaSiN_2$ crystallizes orthorhombic in the space group P b c a (a=5.129(3) Å, b=10.224(1) Å, c=14.821(4) Å, Z=1, R(Fo)=0.0341) isotypic to $KGaO_2$ containing a 3-dimensional network of $SiN_4$-tetrahedra forming sechser rings. All Si-N[2] distances are within the usual range for nitridosilicates between 1.719 (6) - 1.778 (6) Å [3].

[1] C. Eichel, *Diss. Dresden T.H.* **1909**, 53.
[2] F. Ottinger, R. Nesper, *Chimia* **2001**, *55*, 620.
[3] H. Huppertz, W. Schnick, *Chem. Eur. J.* **1997**, *3*, 679.

Inorganic and Coordination Chemistry **281**

### 2,3,5,6-Tetrakis-(2-amino-ethylsulfanylmethyl)-pyrazine: Synthesis and Complexations Studies

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The goal of this research was to synthesise a new thiomethyl tetrasubstitued pyrazine ligand: 2,3,5,6-tetrakis-(2-amino-ethylsulfanylmethyl)-pyrazine. The next step involves the complexation of this ligand with transition metals. X-ray diffraction and UV spectrometry were used to characterise the different compounds obtained and to study and compare the affinity of the ligand towards selected metals ions.

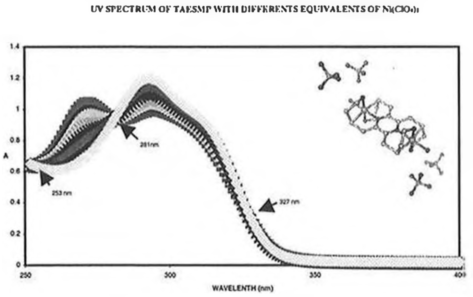

Fig. 1: X-Ray structure and UV spectrometric studies of a $Ni^{2+}$ complex

[1] Teixidor, F.; Escriche, L.; Rodriguez, I.; Casabò, J.; Rius, E.; Molins, E.; Martinez, B.; Miravitles C. *J. Chem. Soc. Dalton Trans.*, **1989**, 1381.

[2] Constable, E.C.; Sacht, C.; Palo, G.; Tocher, D.A.; Truter M.R. *J. Chem. Soc. Dalton Trans.*, **1985**,1307

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Inorganic and Coordination Chemistry **282**

### Synthesis of New Chiral Bis-Bipyridine and Terpyridine Ligands, their Use in Supramolecular Chemistry: When Chemistry Meet Topology

Laure-Emmanuelle Perret-Aebi and Alexander von Zelewsky

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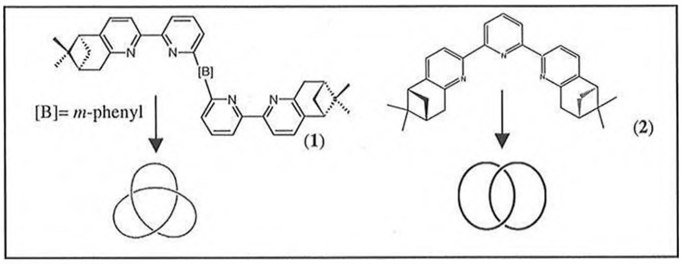
Chiral 2,2'-bis-bipyridines, where the two bipyridine moieties are connected through various bridging groups ([B]= *m*-phenyl, *p*-phenyl, thiophene, stilbene) are obtained by Suzuki cross-coupling reactions. The resulting metal chelators represent a new variety in the class of the CHIRAGEN ligands (1)[1]. These new ligands and also a chiral terpyridyl ligand (2) [2] are used for the synthesis of topological objects such as molecular knot and catenane in a predetermined configuration due to the pinene moieties.



This work is supported by the Swiss National Science Foundation and the CERC3 program.

[1] Perret-Aebi, L.-E., von Zelewsky, A., *Synlett*, **2002**, 5, 773-774.
[2] Ziegler, M. et al., *J. Chem. Soc., Dalton Trans.*, **1999**, 667-675.
[3] Frisch, H. L., Wasserman, E. J., *J. Am. Chem. Soc.*, **1961**, 83, 3789-3795.
[4] Dietrich-Buchecker, C. O., Sauvage, J.-P., *Angew. Chem.,Int. Ed.*, **1989**, 28, 1154-1156.
[5] Rapenne, R., Dietrich-Buchecker, C. O., Sauvage, J.-P. *J. Am. Chem. Soc.*, **1996**, 10932-10933.

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### Anisotropic Nanoscale Design: Oxidic Nanorods

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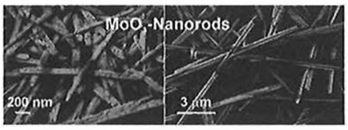
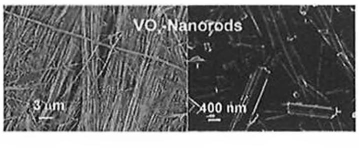
ETH Zürich, Switzerland

**Nanorod Design:**
For a future nanotechnology, the design of anisotropic nanomaterials such as oxidic nanorods is mandatory – but many technologically applicable syntheses remain to be developed. This systematic study provides the production of molybdenum- and vanadium-based nanorods from flexible solvothermal synthetic routines. Starting from a standard and reliable procedure, a multitude of different materials can be transferred into anisotropic nanomodules.[1, 2]

**Single-precursor Solvothermal Procedures: $MoO_x$-Nanorods**
Starting from molybdic acid, $MoO_3$-nanorods of controlled size and shape can be designed by parameter adjustment of a one-step reaction:



**Additive-controlled Solvothermal Routines: $VO_x$-Nanorods**
Readily available inorganic additives such as hydroxides or fluorides of the alkali and earth alkali metals provide maximum morphology and phase control together with minimum experimental effort.



[1] G. R. Patzke, F. Krumeich, R. Nesper, *Angew. Chem.*, in print.

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### Catalytic enantioselective fluorination. New substrates provide mechanistic understanding

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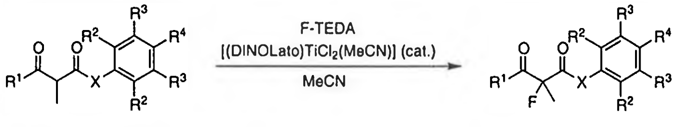
ETH Hönggerberg, CH-8093 Zürich, Switzerland

In view of elucidating mechanistic aspects of the recently reported catalytic and enantioselective fluorination [1], different approaches have been undertaken.
Thus, a series of phenylesters and phenyl thioesters have been prepared and fluorinated, confirming the general observation that the selectivity is strongly controlled by steric factors (examples shown below).



X = O, $R^1$ = Et, $R^2$ = $R^3$ = $R^4$ = H: 86% e.e.
X = S, $R^1$ = Et, $R^2$ = $R^3$ = $R^4$ = H: 84% e.e.
X = O, $R^1$ = Et, $R^2$ = $R^3$ = H, $R^4$ = OMe: 86% e.e.
X = O, $R^1$ = Me, $R^2$= $R^4$ = Me, $R^3$ = H: 66% e.e.

High enantioselectivities have been reached despite their reduced steric hindrance, compared with benzyl ester tested previously. Moreover, the best results for phenylesters were obtained with the less sterically demanding substrates.

[1] (a) L. Hintermann, A. Togni, *Angew. Chem. Int. Ed.* **2000**, *39*, 4359.
(b) A. Togni, A. Mezzetti, P. Barthazy, C. Becker, I. Devillers, R. Frantz, L. Hintermann, M. Perseghini, M. Sanna, *Chimia* **2001**, *55*, 801.
(c) S. Piana, I. Devillers, A. Togni, U. Röthlisberger, *Angew. Chem. Int. Ed.* **2002**, *41*, 979.

Inorganic Chemistry **285**

### $NO_x$ storage over Pt-Ba/$Al_2O_3$ studied byPulse Thermal Analysis

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Laboratory of Technical Chemistry, ETH-Hönggerberg, CH-8093 Zurich, Switzerland

The new generation of lean burn engine technology (air to fuel ratio A/F = 25:1) has been developed to decrease the fuel consumption and carbon dioxide emission. Conventional three-way catalysts are not efficient in removal of $NO_x$ in an oxygen rich exhaust; therefore $NO_x$ storage reduction (NSR) catalysts have been developed. The NSR catalyst is used in an engine that operates alternatively under lean and rich conditions: during lean cycle the $NO_x$ present in the exhaust gas is stored on the catalyst, while during rich cycle period the stored $NO_x$ is reduced to $N_2$ by $H_xC_y$. A typical NSR catalyst is Pt(1)-Ba(20)/$Al_2O_3$(100). Gas-solid reactions occurring in the catalytic system such as adsorption of NO on the support and its reaction with the barium component, formation of barium nitrate and its reduction by propene were investigated in situ by Pulse Thermal Analysis technique (Pulse TA®). This technique provides the opportunity to simultaneously monitor changes in the composition of the gas and solid phase during the course of the reaction. Pt-Ba/$Al_2O_3$ was characterized by XRD, TEM, EDX and chemisorption analysis and its storage activity was investigated by conventional thermal analysis and Pulse TA®. We have also investigated the reduction of newly formed barium nitrate by propene, carbon monoxide and hydrogen in an oxidizing atmosphere. The aim was to explain the role that each component of the catalyst plays during $NO_x$ storage/reduction cycle. The studies indicate that the Ba containing alumina supported catalysts show a high $NO_x$ storage capacity due to the conversion of $BaCO_3$ into crystalline $Ba(NO_3)_2$ phase. Also the thermal stability of supported barium salts is distinctly lower compared to corresponding unsupported salts and in the absence of barium no crystalline nitrate phases are formed.

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### NEW CHIRAL BUILDING BLOCKS CONTAINING FERROCENE AND THEIR REACTIONS IN SELF-ASSEMBLY

Boris Quinodoz and Alexander von Zelewsky

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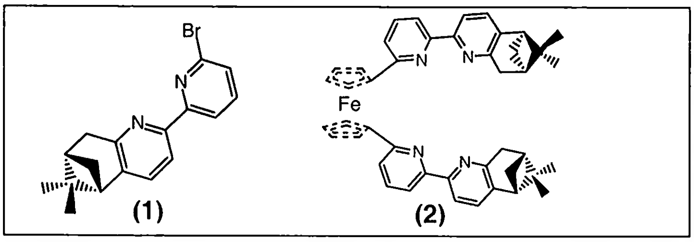
During the past few years, chiral ligands used as building blocks have been synthesised in order to predetermine the configuration at the metal center. Recently a new compound (1), was synthesised as a new variety of the CHIRAGEN ligand family. [1] One example is (2) containing a ferrocene moiety as bridge, thereby increasing the flexibility of the ligand due to the potential rotation of the ferrocene.



This new ligand could lead to intersting phenomena in supramolecular structure due to its redox active site.

This work is supported by the Swiss National Science Foundation.

[1] A. von Zelewsky, *Coord. Chem. Rev.*, **1999**, 190-192, 811-825.

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### New catalysts for the Kharasch reaction by fast screening of homo- and heterobimetallic complexes

Laurent Québatte, Rosario Scopelliti and Kay Severin*

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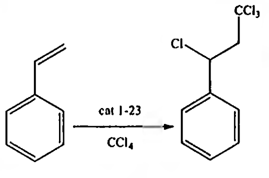
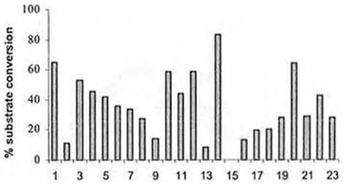
High throughput screening methods are increasingly being used for the discovery of new homogeneous catalysts. So far, this method has not been applied to heterobimetallic catalysts, probably due to the difficulty to obtain a large pool of structurally defined complexes. Recently we have shown that bimetallic complexes, in which two different metal fragments are connected by halogeno-bridges, can easily be synthesized using metathesis reactions [1].





We have investigated the possibility to use these types of complexes as catalysts for atom transfer radical additions. As the benchmark reaction we have employed the addition of $CCl_4$ to styrene. Testing bimetallic complexes containing various combinations of Pd(II), Pt(II), Rh(I), Rh(III), Ir(I), Ir(III), Ru(II) and Ru(IV) in a parallel screening, we have identified a Ru-Rh complex with an exceptionally high activity.

[1] S. Kay, *CHEMISTRY*, **2002**, *8*, (7), 1514-1518

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Inorganic and Coordination Chemistry **288**

### Toward low dimensional supramolecular polymers

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Département de chimie inorganique, minérale et appliquée
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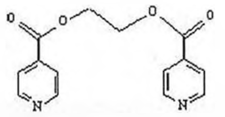
The aim of this work is the synthesis of low-dimensional supramolecular polymers via metal ion complexation and hydrogen bonding. The influence of the ligand and some mechanisms of generation of inorganic polymers have been established for systems containing alkaline earth metal ions [1], [2]. We now wish to use other metals as transition metals ($M^{m+}$), implementing for metal complexation and hydrogen bonding sites within a single ligand.
Firstly, a ligand **$L_1$** with two N-donor groups for metal ion complexation was designed in order to control the dimensionality of the final compound, depending on the metal ion.



**$L_1$** : 4,4'-bis(4-pyridyl)butanedinate

Thus, for $Ag^+$, a one dimensional compound is expected, the ester groups remaining available for hydrogen bonding or further complexation of different metal.

[1] K. M. Fromm, G. Bernardinelli, H. Goesmann, *Polyhedron*, **2000**, *19*, 1783-1789.
[2] K. M. Fromm, *Chem. Eur. J.*, **2001**, *7(10)*, 2236-2244

Inorganic and Coordination Chemistry **289**

### Formation of S-nitrosothiols From Hemoglobin and Nitrogen Monoxide

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Institute of Inorganic Chemistry, ETH Hönggerberg, CH-8093 Zurich

The very fast reaction between oxyhemoglobin ($HbFeO_2$) and nitrogen monoxide ($k \approx 10^7$ $M^{-1}s^{-1}$) [1] has long been proposed to represent a sink for $NO^•$ in the blood vessels and to yield methemoglobin ($HbFe^{III}OH_2$) and $NO_3^-$. However, it has recently been proposed that *in vivo* $NO^•$ rather reacts with the very small amount of deoxygenated heme (deoxyHb) to form an iron(II)-nitrosyl complex ($HbFe^{II}NO$) [2]. In addition, it has been suggested that the " NO group" can be transferred, by a yet unclear mechanism, to the surface thiol Cysβ93 to form S-nitrosohemoglobin (SNO-Hb) [2].

Here we present the results of our studies of the dependence of the mixing procedure and the relative ratio of $NO^•$ and $HbFeO_2$ on the yield of SNO-Hb. We first studied the reaction between a dilute $HbFeO_2$ solution (50 μM) and different amounts of a $NO^•$ saturated solution (2 mM). Then we compared the yield of SNO-Hb obtained when equal volumes of $NO^•$ and $HbFeO_2$ solutions were mixed. The largest yields (ca. 15% expressed relative to the amount of added $NO^•$) were obtained when an equivalent volume of a $NO^•$ solution was slowly added to a $HbFeO_2$ solution. The yields of SNO-Hb obtained when deoxyHb was allowed to react with $NO^•$ under similar conditions were slightly larger, but still lower than the previously reported data [1].

The reaction between $NO^•$ and hemoglobin has been proposed to represent an important mechanism to store $NO^•$ and to provide selective delivery of $NO^•$ to oxygen-depleted tissues. The data presented here question this hypothesis. Alternative mechanisms for SNO-Hb formation and their *in vivo* relevance will be discussed.

[1] S. Herold, M. Exner, T. Nauser Biochemistry **2001**, *40*, 3385.
[2] J.R. Pawloski, D.T. Hess, J.S. Stamler, *Nature* **2001**, *409*, 622.

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Inorganic and Coordination Chemistry **290**

### Overcrowded Alkenes as Chiroptical Switches

**S. Roma, M. Querol Sans and P. Belser**

Department of Chemistry, University of Fribourg,
1700- Pérolles Switzerland

Cis/trans isomerism processes and heliochromism in overcrowded alkenes has been extensively studied towards the development of molecular switches and molecular motors. The performances of these kind of systems are mainly based on a stilbene-like cis/trans photoisomerization [1,2]. One of the main drawback of these systems is the use of irradiation wavelengths in the UV region and this may produce fatigue photoresistance.

One way to improve the above mentioned approach could be the introduction of a metal complex, covalently bounded to the switching unit in order to induce a sensitized photoisomerization.

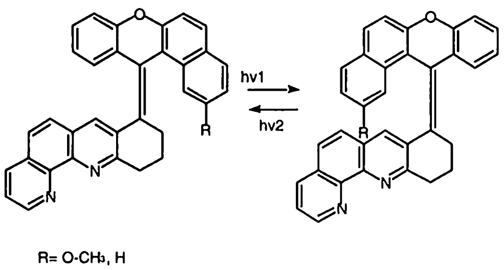

**Figure 1**

The present communication gives the preliminary results towards the synthesis and characterization of highly overcrowded alkenes bearing chelating sites able to build up photosensitized chiroptical switches (see Figure 1).

[1] Ben L. Feringa, Acc. Chem. Res., **2001**, *34*, 501-513.
[2] N. Koumura, E. M.Geertsema, M. B. van Gelder, A. Meetsma and Ben L. Feringa, J. Am. Chem. Soc , **2002**, *124*, 5037-5051.

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### Synthesis of Supramolecular Dyads by Utilizing Functionalized Ru(II), Os(II) Complexes as Building Blocks

Peter Belser and Nunzio Salluce

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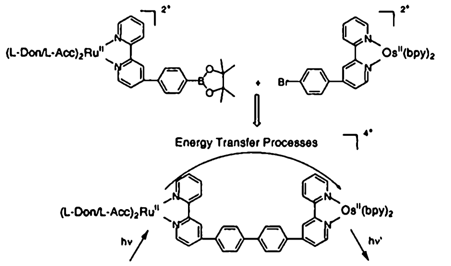
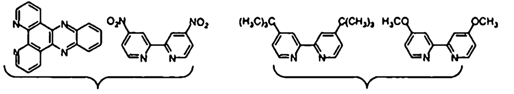
Photoactive dinuclear metal complexes have been synthesised by Suzuki-coupling reaction using functionalized Ru(II), Os(II) complexes as building blocks.



This system is an example of a molecular device performing photoinduced energy or electron transfer processes and it could perform functions such as charge separation and conversion of light into chemical energy [1]. To study the directional energy transfer processes we have modified the Ru(II) sensitizer unit by incorporating electron acceptor or donor groups on the auxiliary ligands.

The rate costants of the above mentioned process (energy transfer) depends upon the nature of the donor (L-Donor) or acceptor (L-Acc) ligands used:



[1] F. Barigelletti, L. Flamigni, *Chem. Soc. Rev.* **2000**, 29, 1-12.

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Inorganic and Coordination Chemistry **292**

### Further development of catalytic enantioselective fluorination

Maria Sanna and Antonio Togni.

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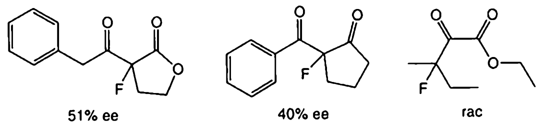
ETH Hönggerberg, CH-8093 Zürich, Switzerland.

The first catalytic and enantioselective C-F bond-forming reaction uses Ti(TADDOLato) complexes as effective catalysts and monosubtituted β-keto esters as enolizable substrates [1].

The catalytic system has been successfully extended to other classes of substrates, such as keto-lactones,1,3 diketones, α-keto esters [2], although usually the enantioselectivities observed are lower than for β-keto esters.



Also Cu(II)Bis(oxazoline) complexes are shown to be effective for the catalytic fluorination of dicarbonyl substrates. So far the enantioselectivities are up to 10%.

[1] Hintermann, L.; Togni, A. Angew. Chem. Int.Ed. **2000**, *39*, 4359.
[2] Sanna, M.; Devillers, I.; Frantz, R.; Hintermann, L.; Perseghini, M.; Togni, A.; manuscript in preparation.

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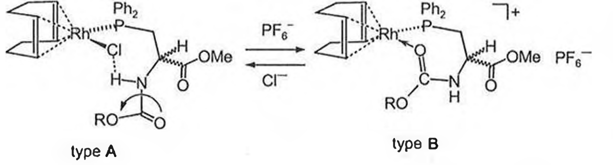
### The Coordination Chemistry of Phosphinated Amino Acids towards Rh(I)

Markus Scherer, Christian Meyer, Sandra Loss, Heinz Rüegger, Hansjörg Grützmacher

Labor für Anorganische Chemie, ETH Hönggerberg, CH-8093 Zürich,

Organohalides, $R^1$-Hal, can easily be transformed into the corresponding organophosphanes $R^1$-$PR^2_2$ by treating them with a copper(I)-phosphanide complex $[Cu(PR^2_2]L_n]$. We tested this approach with protected brominated serine derivatives $^{R}$Ser*Br* (R = Cbz, Boc) and the dipeptide $^{Z}$AlaSer*Br* (R = $^{Z}$Ala) to give the phosphanes $^{R}$Ser*phos* and $^{Z}$AlaSer*phos*, respectively. These phosphanes react with 0.5 equivalent of $[Rh_2(\mu_2\text{-}Cl)_2(cod)_2]$ to form neutral Rh(I)-phosphane complexes of the type **A**. X-ray structure analyses show that with both phosphanes seven membered rings containing the Rh(I)-Cl and the P-$CH_2$-CH-NH unit of the serine derivative are formed. The amide proton binds strongly to the chlorine at the Rh atom. NMR studies showed, that this conformation of the complexes is maintained in solution. Replacing the chlorine atoms by a non-coordinating anion like $PF_6^-$ leads to a severe structural change: rotation around the amide linkage –HN-CO- occurs and a new seven membered heterocycle Rh-P-$CH_2$-CH-NH-C-O (type **B**) involving the C=O group is obtained with both ligands $^{Z}$AlaSer*phos* and $^{R}$Ser*phos*. Upon addition of $Cl^-$ to type **B**, this process is reversed giving type **A**. Detailed NMR and IR experiments show that type **A** structures containing the amino acids in an α-helix type conformation are considerably more rigid than the second type of structures containing the amino acids in a β-sheet conformation.



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Inorganic and Coordination Chemistry

**294**

### Formylation with Compressed $CO_2$: Highly Efficient Catalytic Synthesis of *N*-Formylmorpholine

Leo Schmid, Michael S. Schneider, A. Baiker*

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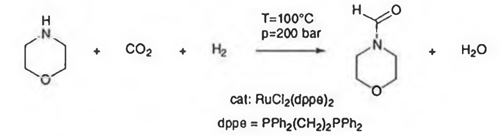
Carbon dioxide fixation has gained considerable attention due to environmental considerations and its large-scale availability at low cost [1]. Replacement of environmentally harmful C1-building units used in chemical synthesis by non-toxic and easy to handle $CO_2$ represents an interesting challenge for green chemistry.



We show that formylation of morpholine in compressed $CO_2$ using a bidentate ruthenium catalyst $RuCl_2(dppe)_2$, which has been applied recently in the synthesis of *N,N*-dimethylformamide [2], affords very high *N*-formylmorpholine production rate at almost 100% selectivity. *N*-formylmorpholine is used in large scale amounts in industry for BTX extraction [3].

Phase behaviour studies during the reaction revealed a complex multiphase system, which strongly influences the efficiency of the reaction.

[1] M. Halmann, Chemical Fixation of Carbon Dioxide: Methods for Recycling $CO_2$, CRC Press, Boca Raton, Florida, **1993**; A. Baiker, *Appl. Organometal. Chem.*, **2000**, 14, 751.
[2] O. Kröcher, R.A. Köppel, A. Baiker, *Chimia*, **1997**, 51, 48.
[3] E. Cinelli, S. Noe, G. Paret, *Hydrocarbon Process.*, **1972**, 51(4), 141.

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**295**

### Ruthenium (II) Complexes with 3,3'-Disubstituted-2,2'-Bipyridine

Maria-Cristina Senna[a], Andreas Hauser[b], Antonia Neels[c], Helen Stoeckli-Evans[c], Silvio Decurtins[a]*

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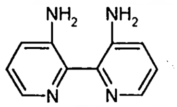
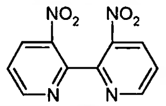
[c]Institut de Chimie, Université de Neuchâtel, Avenue Bellevaux 51, CH-2007 Neuchâtel, Switzerland.

We have recently studied the coordination chemistry of 3,3'-diamino-2,2'-bipyridine (**1**) and its dication [1]. We report here on the synthesis of the heteroleptic complexes $[Ru(bipy)_2(bipy')](PF_6)_2$ with bipy=2,2'-bipyridine and bipy'=3,3'-diamino-2,2'-bipyridine (**1**) or 3,3'-dinitro-2,2'-bipyridine (**2**). These complexes were characterized on the basis of elemental analyses, $^1H$ NMR and FAB mass spectral data. The optical absorption and luminescence spectra, and the electrochemical behavior of the Ru(II) complexes in comparison to $[Ru(bipy)_3]^{2+}$ are reported. The $[Ru(bipy)_2(\mathbf{1})](PF_6)_2$ complex was also characterized by single crystal X-ray diffraction measurements.


**(1)**


**(2)**

This work was supported by the Swiss National Science Foundation through Project No. 2000-061641.00 and the TMR Research Network ERBFMRXCT 980181 of the European Union, entitled: “Molecular Magnetism: From Materials towards Devices”.

[1] C.R. Rice, S. Onions, N. Vidal, J.D. Wallis, M.-C. Senna, M. Pilkington and H. Stoeckli-Evans, *Eur. J. Inorg. Chem.* **2002**, in press.

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**296**

### Peroxynitrite-mediated Nitration of Tyrosine and Tryptophan Residues in Myoglobin and Hemoglobin

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Peroxynitrite ($ONOO^-$), a strong oxidizing and nitrating agent generated *in vivo* from the diffusion controlled reaction between $NO^\bullet$ and $O_2^{\bullet-}$, reacts with hemoproteins to generate high valent iron forms and/or nitrated tyrosyl residues. We have recently shown that the reactions of peroxynitrite with oxyhemoglobin ($HbFeO_2$) and oxymyoglobin ($MbFeO_2$) proceed in two steps with the formation of the ferryl species $HbFe^{IV}$=O and $MbFe^{IV}$=O [1]. Here we present extensive analysis of hemoglobin and myoglobin after treatment with different amounts peroxynitrite in the presence of $CO_2$ at different temperatures. Nitrotyrosine was identified by HPLC after acid hydrolysis and enzymatic digestion as well as through nitrotyrosine antibodies. Our results show that very low quantities of nitrotyrosine are formed when equivalent amounts of peroxynitrite are allowed to react with the oxy- and met-forms of these proteins even in the presence of physiologically relevant amounts of $CO_2$. Significant larger yields were observed with apoMb, suggesting that the heme center of myoglobin may act as an efficient scavenger of peroxynitrite. In addition, we have found that tryptophan residues of Mb and Hb are also nitrated to a detectable extent. Though 6-$NO_2$-Trp seems to be the predominant isomer, 5- and 4-$NO_2$-Trp could also be identified unambiguously in Mb and 4-$NO_2$-Trp in Hb. The role of nitrotryptophan as a biomarker for nitrosative stress will be discussed.

[1] M. Exner, S. Herold, *Chem. Res. Toxicol.* **2000**, *13*, 287.

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COST D10

**297**

## Correlation between experimental data and structural and electronic parameters from DFT studies of Ru(II) aquacomplexes

Elena Sidorenkova,[a] Pascal V. Grundler,[a]
Jacques Weber,[b] André E. Merbach[a]

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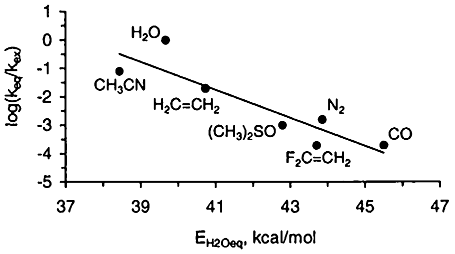
[b]Département de Chimie Physique, Université de Genève, CH-1211 Genève
elena.sidorenkova@epfl.ch

The complexes $[Ru(OH_2)_5L]^{2+}$ with L = CO, $C_2H_4$, $CF_2CH_2$, $H_2$, $N_2$, $CH_3CN$ and DMSO are easily synthesised from $[Ru(OH_2)_6]^{2+}$, and their reactivity was extensively studied by multinuclear NMR spectroscopy. Kinetic parameters were obtained from variable pressure and variable temperature experiments.[1]

DFT calculations were performed, leading to a set of structural and electronic data. Correlations between the calculated and the experimental data for series of the monosubstituted ruthenium aqua complexes allow us to make prediction on properties that are yet not experimentally accessible for some of the complexes.



[1] P.V. Grundler, G. Laurenczy, A. E. Merbach *Helv. Chim. Acta.* **2001**, *84*, 2854-2867 and references therein.

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**298**

## Dinuclear Metal Complexes as Z-DNA Selective Binders?

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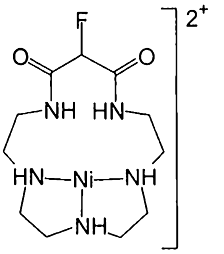
In Z-DNA, the N7 atoms of the guanine nucleobases are extremely well accesible to the solvent. Not surprisingly, X-ray DNA structures exist where metal atoms are bound to that very position: either as an outer-sphere Magnesium or an inner-sphere Cobalt(II) coordination compound [1]. Complex 1 was shown to induce a B to Z DNA transition at a concentration of 30 µM [2].



In order to find a metal complex which would selectively bind to Z-DNA, we combined the 2 above mentioned building motifs. We will present the design and synthesis of dimetallic complexes. Their interactions with poly d(CG) double-stranded DNA, studied by CD spectroscopy, will be shown.

We thank the Swiss National Science Foundation and the University of Zürich for generous support.

[1] Gao, Y.-G.; Sriram, M.; Wang, A. H.-J. *Nucleic Acids Res.* **1993**, *21*, 4093-4101.
[2] Shih, H.-C.; Tang, N.; Burrows, C. J.; Rokita, S. E. *J. Am. Chem. Soc.* **1998**, *120*, 3284-3288.

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**299**

## Flame Synthesis of Heterogeneous Catalysts

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Aerosol synthesis of titania-silica in a methane/oxygen flame afforded mixed oxide nanoparticles with excellent selectivity for the catalytic epoxidation of 2-cyclohexenol by tert.-butylhydroperoxide. To make the catalysts accessible to industrial scale testing, a pilot-scale set-up was constructed, delivering up to 500 g catalyst per hour in a continuous process. This increase in production rate over two orders of magnitude did not affect the catalytic performance showing that flame aerosol synthesis can be applied on an application scale for the production of titania/silica catalysts.

Spectroscopic methods (FTIR and XANES) revealed the high content of catalytically active tetrahedral Ti sites in the flame-made material. While most conventional materials show strong surface hydration, the gas-phase made oxides exhibit very low affinity to water. Controlled doping of trace amounts of transition metals into the titania-silica catalysts allowed to asses the role of impurities for catalytic performance. Even at 30 ppm metal content, chromium heavily affected the performance of the material. Since precursor materials are vaporized prior to feeding into the flame, reactor residence times stay within seconds and no liquids come in contact with the product, mixed oxide materials with high purity (less than 3 ppm transition metals) can be prepared without taking special precautions. In the case of sensitive reactions such as selective oxidations, this high purity is of crucial importance.

[1] Wendelin J. Stark, Sotiris E. Pratsinis, Alfons Baiker, *J. Catal.* **2001**, *203*, 516.

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**300**

## Large metal redox potential shift by deprotonation of complexes containing an imidazole moiety

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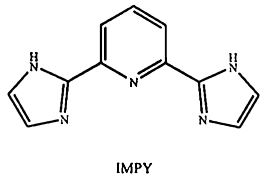
University of Geneva, Quai Ansermet 30
CH-1211 Geneva 4, Switzerland

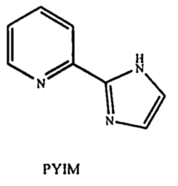
Complexes of cobalt(II) and ruthenium(II) with 2.6-Bis-(1*H*-imidazol-2-yl)-pyridine (IMPY) and 2-(1*H*-imidazol-2-yl)-pyridine (PYIM) have been prepared and characterised.

Deprotonation of the coordinated imidazole by NaOH led to the spontaneous oxidation of the metals and modifies significantly its spectral and redox properties. Cyclic voltametry studies show a large shift between the protonated and the deprotonated forms corresponding to approximately 300 mV/$H^+$. For example the metal redox potential for $Ru^{+3/+2}$ in impy complexes is shifted from +645mV to - 622mV (*vs* SCE) after deprotonation, thereby offering a means to stabilize high oxidation states.

The crystal structure of $[Co(impy\text{-}H)_2]_2.(Ph_3PNPh_3).Na_2.OH.(H_2O)_2.MeOH$ shows that $Na^+$ ions are bound to the deprotonated imidazolate ions.



IMPY



PYIM

Inorganic and Coordination Chemistry

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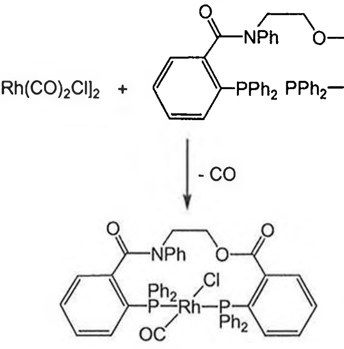
### New Diphosphine Ligands Containing Ethyleneglycol and Aminoalcohol Spacers for the Rhodium-Catalyzed Carbonylation of Methanol

C. M. Thomas,* R. Mafua, B. Therrien, H. Stœckli-Evans, G. Süss-Fink*

Institut de Chimie, Université de Neuchâtel, C.P. 2, CH-2007 Neuchâtel

New diphosphine ligands have been designed by means of suitable spacer units which impose *trans* coordination to rhodium and iridium centres.



(7)

$$CH_3OH + CO \xrightarrow[7]{H_2O,\ CH_3I} CH_3COOH$$

The complexes thus obtained catalyse efficiently the carbonylation of methanol and allow, in the case of complex **7**, the recovery of the unchanged catalyst.

[1] C. M. Thomas, R. Mafua, B. Therrien, E. Rusanov, H. Stoeckli-Evans, G. Süss-Fink, *Chem. Eur. J.*, **2002**, in the press

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**302**

### Dendritic Systems Based on Dinuclear Ruthenium or Rhodium Units Generating Peripheral Catalytic Sites

F. Chérioux, C. M. Thomas, B. Therrien and G. Süss-Fink

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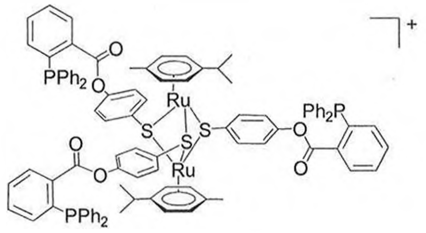
A series of dendritic cations containing $Ru_2S_3$ or $Rh_2S_3$ units either in the core or in the dendrons has been synthesized and characterized. The X-ray crystal structure analysis shows a trigonal bipyramidal $Rh_2S_3$ core with propeller-like *para*-hydroxiphenyl substituents at the sulfur atoms.



(5)

$$CH_3OH + CO \xrightarrow[5,\ [Rh(CO)_2Cl]_2]{CH_3I,\ H_2O} CH_3COOH$$

Reaction of the peripheral OH groups with diphenylphosphino benzoic acid results in the formation of phosphine-functionalized dendritic cations. The ruthenium-containing cation with three $PPh_2$ functions at the periphery (**5**) acts as ligand for rhodium(I) and enhances significantly the catalytic activity of $[Rh(CO)_2Cl]_2$ for the carbonylation of methanol.

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**303**

### New approaches for designing lanthanide-containing metallomesogens : hexacatenar and dendritic tridentate receptors

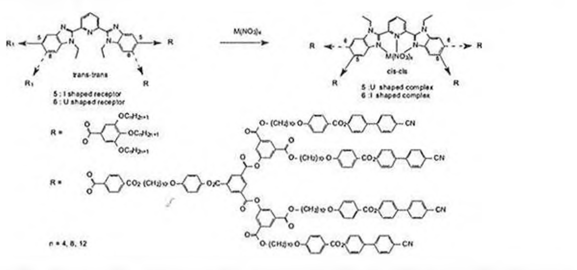
Emmanuel Terazzi,[a] Gérald Bernardinelli,[a] Jean-Pierre Rivera,[a] Claude Piguet,[a,]* Bertrand Donnio,[b] Daniel Guillon[b] and Robert Deschenaux[c]

[a] Department of Inorganic Chemistry, University of Geneva, CH-1211 Geneva 4.

[b] Institut de Physique et Chimie des Matériaux de Strasbourg, F-67037 France

[c] Institute of Chemistry, University of Neuchâtel, CH-2000 Neuchâtel

Aromatic tridentate 2,6-bis(benzimidazol-2yl)pyridine ligands fonctionalised at the 5- and 6-positions by hydroxyls groups are used to give I- and V-shaped receptors.[1] Subsequent reactions with gallic acid derivatives leads to mesogenic hexacatenar materials . The systematic variation of the length of the terminal aliphatic chains provides a complete library of lipophilic tridentate receptors which have been tested for their capacity to form metallomesogens (i.e. metal-containing liquid crystals) with lanthanide metal ions. Another approach is to incorporate the receptors at the focal point of a third generation dendritic structure which is known to induce mesogenic properties.[2]



[1] Nozary H., Piguet C., Rivera J.-P., Benardinelli G, Tissot P., Vulliermet N., Weber J. and Bünzli, J.-C.. *Inorg. Chem.* **2000**, *39*, 5286-5298.

[2] Dardel B., Guillon D., Heinrich B., and Deschenaux R. *J. of Mater. Chem.* **2001**, 2814-2831.

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Inorganic and Coordination Chemistry
COST D10

**304**

### Oligomerisation of ethylene in aqueous medium: $[Ru(H_2O)_6]^{2+}$ Mediator Implication

Bernadette Ugurtas, Fabrice Riblet, André E. Merbach

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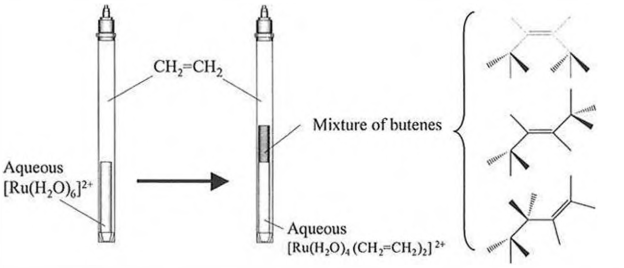
Bernadette.ugurtas@epfl.ch Fabrice.riblet@epfl.ch

Aqueous solution of ruthenium(II) hexaaquaion pressurized with ethylene yields to well identified mono- and *cis*,bis-complexes.[1] Overreaction occurs and a supernatant layer of butenes is observed under pressure ([Z-but-2-ene]:[E-but-2-ene]:[but-1ene] 1:2.2:2.2). This astonishing result has stimulated mechanistic investigations using $^1H$ NMR sapphire tube technique.



An intramolecular mechanism involving the bis complex is strongly suggested since no deuterium insertion has been observed in the products. Furthermore new butene complexes were identified during the catalytic process. Such compounds were also obtained by reaction of $[Ru(H_2O)_6]^{2+}$ with butenes. These species might be involved in further catalytic steps that have recently lead to the observation of a liquid hexenes mixture.

[1] G.Laurenczy, A.E.Merbach, *J.Chem.Soc.Chem.Commun.* **1993**, 2, 187-189

Inorganic and Coordination Chemistry **305**

### Zintl Phase Double Salts: An Overview

Johannes B. Willems, Reinhard Nesper*

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We investigate earth alkaline halides with respect to their use as solvents for Zintl phases. The research in the Ba/Si/I and Ba/Si/Br phase systems, respectively, leads to the discovery of several new ternary double salt phases.[1, 2]

| $Ba_3SiI_2$ | $Ba_4Si_3Br_2$ | $Ba_2Si_2I$ | $Sr_5Si_6I_2$ |
|---|---|---|---|
| *isolated [$Si^{4-}$]-ions* | *cyclotrisilicide units* | *infinite chains of cis-trans conformation* | *infinite chains of six-membered rings* |

Table 1: New Zintl phase / halide double salts

The silicon partial structure herein ranges from isolated [$Si^{4-}$]-anions to infinite chains of six membered rings in the case of $Sr_5Si_6I_2$. The $Ba_3SiI_2$ structure type turned out to be very flexible. Up to now it was possible to synthesize four new isostrucural compounds.[1] The next goal is the investigation of solid solutions in this system.

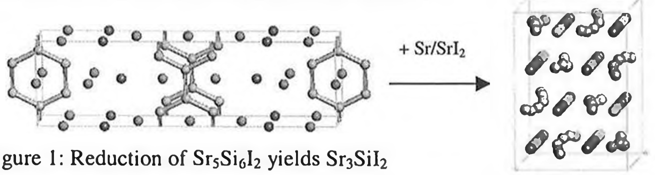

Figure 1: Reduction of $Sr_5Si_6I_2$ yields $Sr_3SiI_2$

A further research topic concentrates on the chemical reactivity of double salts, in particular the reduction and ion exchange of the compounds $Ba_4Si_3Br_2$ and $Ba_3SiI_2$ according to figure 1.

[1] S. Wengert, R. Nesper, *J. Solid State Chem.* **2000**, *152*, 460.
[2] S. Wengert, J. B. Willems, R. Nesper, *Chem. Eur. J.* **2001**, *7*, 3209.

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### A New Zintl Phase Synthesized via Thermal Decomposition

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A new Zintl compound $BaLiGe_2$ was synthesized via thermal decomposition of $BaMg_2Li_2Ge_2$ at high vacuum. The structure was refined in space group Pnma. The result indicates that $BaLiGe_2$ crystallizes into a layered structure with planar Zintl anions (Figure 1). The Zintl anion is a 1-dimensional chain with an all-cis-conformation, which is different from those of known compounds $CaLiSi_2$ and $CaLiGe_2$ [1], which have a one-dimensional zintl anion chain with all-trans-conformation, and it is also different from the structures of $Ca_2LiSi_3$ and $Ca_2LiGe_2$ [2], which have a one-dimensional Zintl anion chain with a cis-trans-trans conformation.

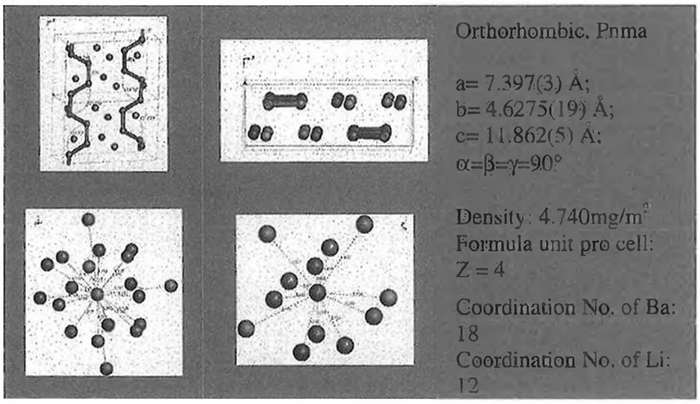

Figure 1 Crystal structure of $BaLiGe_2$

[1] W. Müller, H. Schäfer, A. Weiss; *Z. Naturforsch;* **1971,** 26b, 5.
[2] W. Müller, H. Schäfer, A. Weiss; *Z. Naturforsch;* **1971,** 26b, 534.

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COST D18

### Molecular Dynamics Simulations of $Gd^{3+}$ complexes

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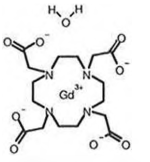
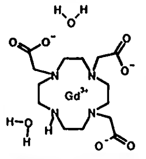
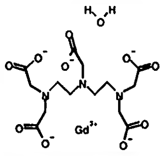
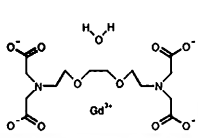
de Lausanne, EPFL - BCH, 1015 Lausanne, Switzerland
Fabrice.Yerly@epfl.ch

Stable polyaminocarboxylate complexes of the highly paramagnetic $Gd^{3+}$ are used as magnetic resonance imaging (MRI) contrast agents. In order to develop new complexes with higher efficiency, one has to better understand the relationships between the molecular structure and its consequences on the water proton relaxation. Structural and dynamic information that are unavailable experimentally can be obtained using the molecular dynamics simulations. This is possible through the very recent development of a new force field describing the $Gd^{3+}$ ion.[1]


[Gd(DOTA)($H_2O$)]⁻


[Gd(DO3A)($H_2O$)$_2$]


[Gd(DTPA)($H_2O$)]$^{2-}$


[Gd(EGTA)($H_2O$)]⁻

We show here the potentiality of this new force field for a series of complexes, including cyclic and acyclic ligands, variable hydration number of the metal and variable global charge.

[1] F. Yerly, K.I. Hardcastle, L. Helm, S. Aime, M. Botta, A.E. Merbach *Chem. Eur. J.* **2002**, *8*, 1031-1039 .

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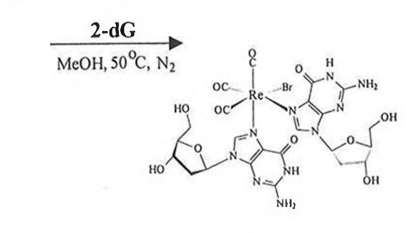
Inorganic and Coordination Chemistry **308**

### Rhenium(I) Complexes of Nucleo-Purines and Purine Analogs

Fabio Zobi, Roger Alberto*, Bernhard Spingler, and Thomas Fox

University of Zürich, Winterthurerstr. 190, CH-8057 Zürich, Switzerland

Although cisplatin is a very effective anticancer drug, it has undesirable side effects, and inherent and acquired resistence reduces its clinical efficacy [1]. These limitations combined with the extraordinary success of cisplatin and closely related platinum antitumor agents, has stimulated the search of new inorganic complexes having cytotoxic properties.



To this end we have employed the $[Re(H_2O)_3(CO)_3]^+$ ion in the synthesis rhenium(I) complexes of nucleo-purines and purine analogs. This new class of compounds shows remarkable chemical similarities to platinum complexes.

[1] Jamieson, E. R.; Lippard, S. J. *Chem. Rev.* **1999**, 99, 2467-2498.

Inorganic and Coordination Chemistry **309**

### New media for teaching inorganic chemistry

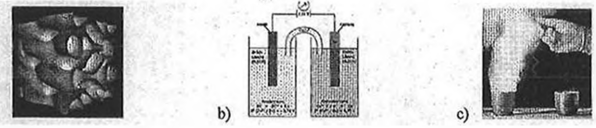
Anke Zürn, Stefano P. Piotto, Wolfram Uhlig, Christian Mensing,
Bruno Rüttimann, Reinhard Nesper

ETH Zürich, Wolfgang-Pauli-Strasse 10, CH-8093 Zürich, Switzerland

The rapid development of chemistry with consequently additional important teaching contents as well as new basic conditions led to profound changes in the higher education of chemistry. Often old teaching/learning structures or materials do not match any longer new contents and tasks. On the other side important "old" contents are not any longer taught due to temporal, economic, ecological or health reasons.

The learning of university students can be highly improved by the help of integrated web lessons, videos, and schematic animations. The target now is the preparation of completely new teaching materials and training forms rather than a simple transfer of old print based teaching materials in on-line ones. Here the crucial question is: Which is the medium that transfers optimally the content to be taught in respect to specific conditions?

One of the new media most challenging possibilities is to investigate and teach the dynamics of chemical processes (e.g. chemical reaction or phase transition) and complicated spatial structures more effectively than before. Inside the framework of CCN [1] the use of new technologies for research and education in solid state chemistry is investigated. The results in merging commercial and newly designed tools will be presented as: 3D - animations of spatial complex structures for tutorials of basic solid-state chemistry and crystallography, as well as for advanced lectures on topological relationships of crystal structures and 3D periodic surfaces, as i.e. PNS [2]. Vector based (Flash) teaching elements for schematic representations as complex temporal reactions and processes, reaction mechanism or experimental setups. Videos of chemical experiments support lectures of general and inorganic chemistry, allow to revive online original live experiments and enable the perception of experiments difficult to perform because they are too expensive, dangerous, or ecologically questionable [3].



Examples: a) 3D-animations, b) schematic animations, c) videos of chemical experiments.

[1] CCN - the Chemistry Contact Network, URL: http://www.ccn.ethz.ch
[2] H.G. von Schnering, R. Nesper, *Z. Phys. B - Condensed Matter* **1991**, *83*, 407-412
[3] CCI - Creative Chemistry on the Internet, URL: http://www.cci.ethz.ch

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EUROPEAN COOPERATION
IN THE FIELD OF SCIENTIFIC
AND TECHNICAL RESEARCH

# Third Swiss COST Chemistry Symposium

**(http://www.swiss-chem-soc.ch/DCR/cost_symposium/)**

**Friday, October 18th, 2002**

r+d in life sciences
Convention Center of the Basel Fair
Messeplatz 21
Basel, Switzerland
Room ‘Montreal’, 2nd Floor

**Organizer:**

Prof. Alan Williams
Université de Genève
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CH-1211 Genève 4, Switzerland
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## REGISTRATION

Registration is required in order to enter the 'r+d in life sciences' area. More information will be given in CHIMIA issue 9 and on the web (*http://sgich1.unifr.ch/oc/cost/main-page.html*).

## WHAT IS COST?

COST (a French acronym for 'Coopération Européenne dans le domaine de la recherche Scientifique et Technique') was set up in 1971 to stimulate and to structure European cooperation in the field of science and technology. This forum of research now brings together a total of 33 European countries including the fifteen members of the European Union. COST is oriented towards pre-competitive research. COST activities are currently covering the following areas: computer sciences, telecommunications, transports, oceanography, materials, environment, meteorology, agriculture-biotechnology, food technology, social sciences, medical research, urban civil engineering, chemistry, forests-forestry products, physics and nanosciences.

## COST CHEMISTRY

Chemistry is a central science with a distinguished history and many recent successes in Europe (23 *Nobel* prize winners since 1960 are European). The chemical industry is one of Europe's most competitive and successful industries and contributes to the prosperity and quality of life of modern European society. In order to maintain and to improve this position, it was decided to use the COST forum to elaborate a strategic scientific scheme for basic research in chemistry in Europe. With this aim, a Technical Committee (TC) in chemistry was set up in 1990. In 1992, on the basis of a proposition from the TC, COST decided to launch seven Actions in the field of chemistry. There are now 23 COST actions at various stages of their life cycle involving over a hundred working groups and associating several hundred European research groups. The COST system is characterized by the bottom-up approach (the initiative comes from the researcher) and by the fact that the funding of the research is national. In Switzerland the main sources of funding for COST CHEMISTRY are the Office of Education and Science, and the Swiss National Science Foundation. Full details of COST chemistry may be obtained from the COST Chemistry web site (*http://www.unil.ch/cost/chem/*).

## WHY A THIRD SWISS COST CHEMISTRY SYMPOSIUM?

The object of this symposium is to present some of the chemical research taking place in Switzerland and in Europe within the COST framework. With 23 current actions it has not been possible to cover everything, and so we have invited ten eminent scientists active in the themes of COST chemistry to give lectures in the general field of chemistry applied or applicable to life sciences, ranging from fundamental chemical research to chemical studies inside biological systems.

A poster session will also allow the Swiss groups involved in COST programs to present their recent results, and fifteen different actions are represented by more than 60 posters.

# Scientific Program

Convention Center, Messeplatz 21, Room 'Montreal', 2nd floor

| | |
|---|---|
| 9.30 | Welcome: **Prof. *Alan Williams***<br>Introduction: **Dr. *Eva Klaper***<br>Federal Office of Science and Education, Bern |

## Session 1: Modern Synthetic Methods

| | |
|---|---|
| 9.50 | **Prof. *Philippe Renaud***<br>University of Bern<br>'Novel Radical Reactions for the Synthesis of Natural Products' |
| 10.20 | **Prof. *Martyn Poliakoff*, FRS**<br>University of Nottingham, United Kingdom<br>'Supercritical Fluids: Clean Solvents for Green Chemistry' |
| 10.50 | **Coffee Break, Poster Session**<br>(outside lecture hall) |
| 11.10 | **Prof. *Peter Chen***<br>ETH Zürich<br>'High Throughput Screening of Organometallic Catalysts' |
| 11.40 | **Prof. *David Reinhoudt***<br>Twente University, The Netherlands<br>'Supramolecular Chirality' |
| 12.10–14.00 | **Poster-Sandwich Session** |

## Session 2: Linking Molecules to Biological Sites

| | |
|---|---|
| 14.00 | **Prof. *Silvio Aime***<br>University of Torino, Italy<br>'Paramagnetic Lanthanide Complexes in MRI: From Extracellular Contrast Agents to Probes in Molecular Imaging' |
| 14.30 | **Prof. *Roger Alberto***<br>University of Zürich<br>'Binding Technetium to Biomolecules' |
| 15.00 | **Prof. *Gerard van Koten***<br>University of Utrecht, The Netherlands<br>'Anchoring of Organometallics to Biological Supports: Biomarkers and Water-soluble Catalysts' |
| 15.30 | **Coffee and Posters** |

## Session 3: Chemistry in Biological Systems

| | |
|---|---|
| 16.00 | **Prof. *Wolf-Dieter Fessner***<br>Technical University of Darmstadt, Germany<br>'Enzyme Specificity for Carbohydrate Diversity' |
| 16.30 | **Prof. *Horst Vogel***<br>EPF Lausanne<br>'Elucidating Biochemical Networks by Micro- and Nanotechnology' |
| 17.00 | **Prof. *Jean-Louis Reymond***<br>University of Bern<br>'The Chemical Language of Enzymes: Design, Inhibition, and Screening' |
| 17.30 | **Concluding Remarks** |

## Cost Actions Represented by Posters at the Symposium:

| | |
|---|---|
| D10 | Innovative Methods and Techniques for Chemical Transformations |
| D11 | Supramolecular Chemistry |
| D12 | Organic Transformations: Selective Processes and Asymmetric Catalysis |
| D13 | New Molecules for Human Health Care |
| D14 | Functional Molecular Materials |
| D15 | Interfacial Chemistry and Catalysis |
| D18 | Lanthanide Chemistry for Diagnosis and Therapy |
| D19 | Chemical Functionality Specific to the Nanometer Scale |
| D20 | Metal Compounds in the Treatment of Cancer and Viral Diseases (MCCV) |
| D21 | Metalloenzymes and Chemical Biomimetics |
| D24 | Sustainable Chemical Processes: Stereoselective Transition Metal-Catalysed Reactions |
| D25 | Applied Biocatalysis:<br>Stereoselective and Environmentally Friendly Reactions Catalysed by Enzymes |
| D26 | Integrative Computational Chemistry |
| D28 | Natural Products as a Source for Discovery, Synthesis and Application of Pharmaceuticals |
| D29 | Sustainable/Green Chemistry and Chemical Technology |

**D10-1**

Inorganic and Coordination Chemistry

## Structure and reactivity of aquacarbonyl complexes of Ru(II), Re(I) and Tc(I)

Pascal V. Grundler,[a] Elena Sidorenkova,[a]
Roger Alberto,[b] André E. Merbach[a]

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[b] Anorganisch-Chemisches Institut, Universität Zürich,
Winterthurerstrasse 190, 8057 Zürich, Switzerland
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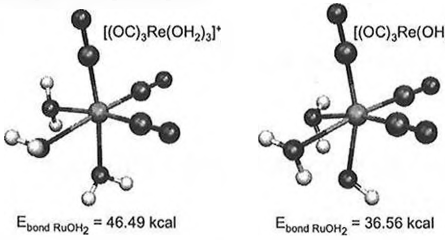
The water exchange rate on $[(OC)_nM(OH_2)_{6-n}]$ with n = 1-3 for M = $Ru^{2+}$ [1], and n = 3 for M = $Re^+$, $Tc^+$ have been investigated by $^{17}O$ NMR spectroscopy. Variable acidity measurements on the triscarbonyl complexes have shown that the water exchange on the monohydroxo species $[(OC)_3M(OH)(OH_2)_2]$ with M = $Ru^{2+}$, $Re^+$ is faster than on the $[(OC)_3M(OH_2)_3]$ analogs.

DFT calculations of both complexe types (carbonyl and monohydroxocarbonyl) have been performed to correlate the kinetic data with the bond lengths, the bonding energies and electronic density distribution. The satisfactory agreement are found beetwen lability of the water molecules and the corresponding bonding energies.



[1] U. Meier, R. Scopelliti, E. Solari, A. E. Merbach *Inorg. Chem.* **2000**, *39*, 3816-3822.

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**D10-2**

Inorganic and Coordination Chemistry

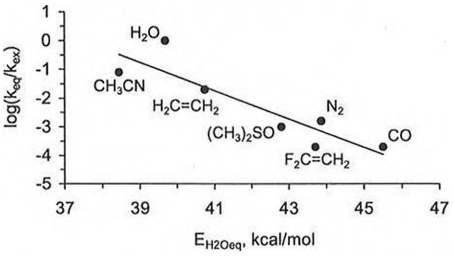
## Correlation between experimental data and structural and electronic parameters from DFT studies of Ru(II) aquacomplexes

Elena Sidorenkova,[a] Pascal V. Grundler,[a]
Jacques Weber,[b] André E. Merbach[a]

[a]Institut de Chimie Moléculaire et Biologique, Ecole Polytechnique Fédérale de Lausanne, EPFL - BCH, CH-1015 Lausanne, Switzerland
[b]Département de Chimie Physique, Université de Genève, CH-1211 Genève
elena.sidorenkova@epfl.ch

The complexes $[Ru(OH_2)_5L]^{2+}$ with L = CO, $C_2H_4$, $CF_2CH_2$, $H_2$, $N_2$, $CH_3CN$ and DMSO are easily synthesised from $[Ru(OH_2)_6]^{2+}$, and their reactivity was extensively studied by multinuclear NMR spectroscopy. Kinetic parameters were obtained from variable pressure and variable temperature experiments.[1]

DFT calculations were performed, leading to a set of structural and electronic data. Correlations between the calculated and the experimental data for series of the monosubstituted ruthenium aqua complexes allow us to make prediction on properties that are yet not experimentally accessible for some of the complexes.



[1] P.V. Grundler, G. Laurenczy, A. E. Merbach *Helv. Chim. Acta.* **2001**, *84*, 2854-2867 and references therein.

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**D10-3**

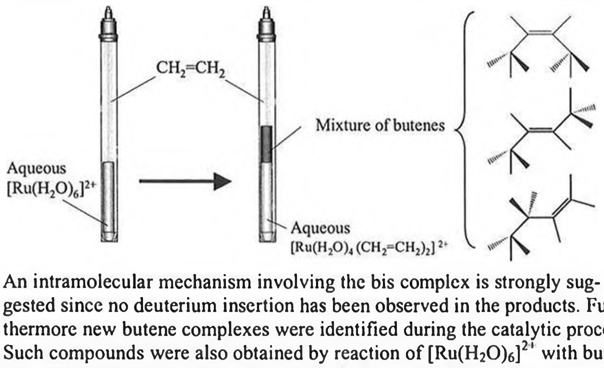
Inorganic and Coordination Chemistry

## Oligomerisation of ethylene in aqueous medium: $[Ru(H_2O)_6]^{2+}$ Mediator Implication

Bernadette Ugurtas, Fabrice Riblet, André E. Merbach

Institut de Chimie Moléculaire et Biologique, Ecole Polytechnique Fédérale de Lausanne, BCH CH-1015 Lausanne (Switzerland)
Bernadette.ugurtas@epfl.ch Fabrice.riblet@epfl.ch

Aqueous solution of ruthenium(II) hexaaquaion pressurized with ethylene yields to well identified mono- and *cis*,bis-complexes.[1] Overreaction occurs and a supernatant layer of butenes is observed under pressure ([Z-but-2-ene]:[E-but-2-ene]:[but-1ene] 1:2.2:2.2). This astonishing result has stimulated mechanistic investigations using $^1H$ NMR sapphire tube technique.



An intramolecular mechanism involving the bis complex is strongly suggested since no deuterium insertion has been observed in the products. Furthermore new butene complexes were identified during the catalytic process. Such compounds were also obtained by reaction of $[Ru(H_2O)_6]^{2+}$ with butenes. These species might be involved in further catalytic steps that have recently lead to the observation of a liquid hexenes mixture.

[1] G.Laurenczy, A.E.Merbach, *J.Chem.Soc.Chem.Commun.* **1993**, 2, 187-189

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**D10-4**

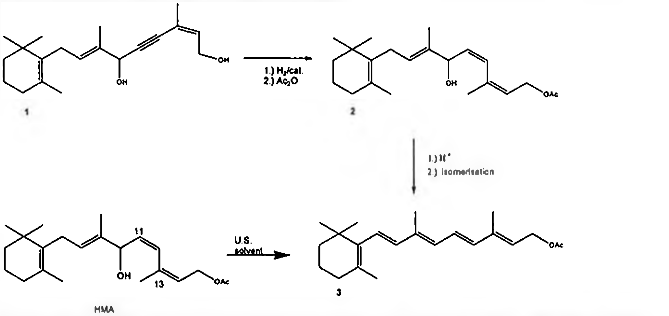
Organic Chemistry

## Dehydration of Hydroxenin Monoacetate in the Presence of Ultrasound

Fabrice Aquino, Werner Bonrath*

Roche Vitamins Ltd., Grenzacherstr., CH-4070 Basel, Switzerland

*E/Z*-Isomers of polyenes, e.g. carotenoids, are of great interest. The various reactions used for the construction of double bonds in the synthesis of the carotenoid skeleton result in (*E/Z*)-mixtures [1]. (all-*E*)-Retinyl acetate **3** is obtained after hydrogenation of the triple bond in **1** to give the (11*Z*, 13*Z*) compound, acetylation of the primary hydroxyl group, and acid catalyzed dehydration with isomerisation of the double bond into the *E* configuration [2].



Here we describe our results obtained in the *E/Z*-isomerisation of hydroxenin monoacetate (HMA, **2**) under ultrasound irradiation.

We found that in trichloromethane at 40° C HMA could be dehydrated to an *E/Z* mixture of vitamin A acetate. Without ultrasound or in other solvents the starting material remained unchanged.

**References**
[1] K. Bernhard, S. Liaaen-Jensen, in 'Carotenoids', Vol. 2, Birkhäuser Verlag Basel, p. 217, 1996.
[2] M. John, W. Hähnlein, in Ullmanns Encyclopedia of Industrial Chemistry, Vol. A27, p. 453, 1996.

CHIMIA 2002, 56, No. 7/8

**D10-5**

Inorganic and Coordination Chemistry

### Hydrogenation with Ruthenium(arene)phosphine Catalysts in Water

Henrietta HORVÁTH[1,2], Ágnes KATHÓ[2], Ferenc JOÓ[2],
Gábor LAURENCZY[1]

[1]EPFL, ICMB, Lausanne, Switzerland; [2]University of Debrecen, Hungary

[$\{RuCl_2(TPPMS)_2\}_2$] (TPPMS= monosulfonated triphenylphosphine) and [$RuCl_2(PTA)_4$] (PTA= 1,3,5-triaza-7-phosphaadamantane) are active catalysts for the hydrogenation of bicarbonates in aqueous solution [1]. Coordinative saturation in [$RuCl_2(PTA)_4$] was shown to result in a slow reaction with $H_2$ [2]. Therefore we studied the reductions with [$\{(C_6H_6)RuCl_2\}_2$] and [$\{$(p-cymene)$RuCl_2\}_2$] as precursors of less-substituted Ru(II)-phosphine complexes in the aqueous hydrogenation of $CO_2$. The reaction of [$\{(C_6H_6)RuCl_2\}_2$] and [$\{$(p-cymene)$RuCl_2\}_2$] with PTA, TPPMS and TPPTS (TPPTS= trisulfonated triphenylphosphine) afforded the complexes of the general formula [(arene)$RuCl_2$(P)]. The solid state structures of [$(C_6H_6)RuCl_2$(PTA)] and [$(C_6H_6)RuCl_2$(TPPMS)] were determined by X-ray diffraction [3]. Under $H_2$ (P>25 bar) these complexes initially yielded the monohydrides [(arene)RuH$(P)_2]^+$. The reaction of [$(C_6H_6)RuCl_2$(PTA)] resulted in the hydrogenation of the benzene ligand, and in an excess of PTA the known [$RuHX(PTA)_4$] and [$RuH_2(PTA)_4$] were formed [2].
The half-sandwich [(arene)$RuCl_2$(PTA)] complexes were studied in the hydrogenation of bicarbonate using medium-pressure sapphire NMR tubes in order to follow *in situ* the formate formation, the sole product of the reaction. In $D_2O$ a high proportion of $DCO_2^-$ was formed in addition to $HCO_2^-$.

The authors are grateful for the support through the following grants: Swiss National Science Foundation, 2100-061653.00/1 (G.L.); OTKA, Hungary, T029934 (F.J.). H.H. thanks the EPFL for the scholarship.

[1] F. Joó, G. Laurenczy, L. Nádasdi and J. Elek, *Chem. Commun.* 1999, 971.
[2] G. Laurenczy, F. Joó and L. Nádasdi, *Inorg. Chem.*, 2000, *39*, 5083.
[3] Á. Kathó, A.C. Bényei, F. Joó, M. Sági, *Adv. Synth. Catal.*, 2002, in press.

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**D10-6**

Inorganic and Coordination Chemistry

### Substitution Reactions on $[Ru(H_2O)_6]^{2+}$ with Water Soluble Phosphines

József KOVÁCS[1,2], Ferenc JOÓ[2], Gábor LAURENCZY[1]

[1]EPFL, ICMB, Lausanne, Switzerland; [2]University of Debrecen, Hungary

Replacement of a water molecule with a ligand L in $[Ru(H_2O)_6]^{2+}$ leads to $[Ru(H_2O_{ax})(H_2O_{eq})_4L]^{2+}$. These complex formation reactions with various ligands are known, the kinetic parameters for the substitutions with MeCN[1], $F_2C{=}CF_2$[1], $Me_2SO$[1], CO[2], $NMP^+$[1], $N_2$[3], $H_2C{=}CH_2$[4], $Cl^-$, $Br^-$, $I^-$[5] were determined. However, there is no information about structures, kinetics, or mechanisms with phosphorus containing ligands.
In order to obtain an insight into complex formation of $[Ru(H_2O)_6]^{2+}$ with catalytically important water soluble phosphines, we studied its reaction with TPPMS (*m* and *p* mono-sulphonated triphenylphosphine), TPPTS (tri-sulphonated triphenylphosphine), DPPETS (tetra-sulphonated bis-diphenylphosphino ethane), PTA (1,3,5-triaza-7-phosphaadamantane) and MPTA (1-methyl-1-azonia-3,5-triaza-7-phosphaadamantane). These are standard phosphine ligands in aqueous organometallic catalysis [6].
We report our results on the kinetics of formation of the Ru(II)-aqua-phosphine complexes. The structures of the compounds were determined by $^{31}P$, $^1H$, $^{17}O$ solution NMR and single crystal X-ray diffraction, the kinetics of the reactions were followed by UV-VIS spectrophotometry.

The authors thank the Swiss National Science Foundation (2100-061653.00; G. L.), and the OTKA (T029934; F. J.), Hungary for financial support.

[1] N. Aebischer, E. Sidorenkova, M. Ravera, G. Laurenczy, D. Osella, J. Weber, A. E. Merbach, *Inorg. Chem.*, **1997**, *36*, 6009
[2] G. Laurenczy, L. Helm, A. Ludi, A. E. Merbach, *Helv. Chim. Acta*, **1991**, *74*, 1236
[3] G. Laurenczy, L. Helm, A. E. Merbach, *Inorg. Chim. Acta*, **1991**, *189*, 131
[4] G. Laurenczy, A. E. Merbach, *Chem. Comm*, **1993**, 187
[5] T. W. Kallen, J. E. Early, *Inorg. Chem.*, **1971**, *10*, 1149
[6] F. Joó, *Aqueous Organometallic Catalysis*, Kluwer, Dordrecht, **2001**

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**D11-1**

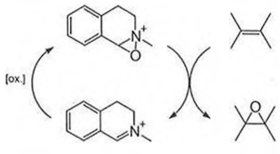
Organic Chemistry

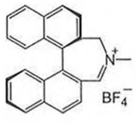
### On the Beneficial Effect of Biphasic Conditions and Anion Chirality onto the Oxaziridinium-Catalysed Epoxidation Reaction

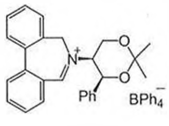
David Monchaud, Claire Marsol, Jérôme Lacour *

Département de Chimie Organique, Université de Genève, 1211 Genève 4

Iminium mediated epoxidation reactions of C-C double bonds have received recent attention due to the potential of the cations to react with oxone® and generate oxaziridinium species, which effectively transfer their oxygen atom to unfunctionalyzed olefins [1]. Examples of enantioselective variants of this reaction have been reported and are based on the use of non-racemic iminium precatalysts *e.g.*, **1** and **2**. $CH_3CN$ / water conditions have been used in all reported examples leading to low to good enantioselectivities.




[**1**][$BF_4$]


[**2**][$BPh_4$]

Herein, we report that biphasic $CH_2Cl_2$ / water conditions can lead to an improvement in the enantioselectivity of the epoxidation reaction; these conditions being rendered feasible by the combined use of TRISPHAT anions and of 18–C–6 [2]. While epoxidation of the 1-phenyl-3,4-dihydronaphthalene was performed with 41% e.e. (e.r. 2.4:1) with [**2**][$BPh_4$], it can now be realized with 76% e.e. (e.r. 7.2:1) with [**2**][Λ-TRISPHAT].

[1] W. Adam, C. R. Saha-Moller, P. A. Ganeshpure, *Chem. Rev.* **2001**, *101*, 3499-3548. P. C. B. Page, G. A. Rassias, D. Barros, A. Ardakani, D. Bethell, E. Merifield, *Synlett* **2002**, 580-582.
[2] J. Lacour, C. Ginglinger, C. Grivet, G. Bernardinelli, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 608-609.

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**D11-2**

Inorganic and Coordination Chemistry

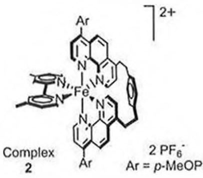
### Ion-Pair Mediated Stereoselective Synthesis of a Configurationally Stable Mononuclear Tris(diimine)Iron(II) Complex

Samuel Constant, David Monchaud, Jérôme Lacour*

Département de Chimie Organique, Université de Genève, 1211 Genève 4

Cationic transition metal complexes are often chiral and many of their applications, reactions or processes yield racemic molecular or supramolecular assemblies. To afford instead non-racemic or enantiopure products, we are studying projects dealing with their asymmetric ion pairing.


TRISPHAT
Δ-**1**


Complex
**2**

Previously, readily prepared tris(tetrachlorobenzenediolato)phosphate(V) anion **1** (or TRISPHAT) was shown to be configurationally stable[1]. This anion is an efficient NMR chiral shift and resolving agent for cationic transition metal complexes. In collaboration with the group of J.-P. Sauvage (Strasbourg, Fr.), we now report on the resolution and on the asymmetric synthesis of a *configurationally stable* mononuclear iron(II) complex **2**; the high diastereoselectivity (d.e. > 90%) coming only from non-covalent interactions with chiral anions **1**[2].

[1] J. Lacour, C. Ginglinger, C. Grivet, G. Bernardinelli, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 608.
[2] D. Pomeranc, V. Heitz, J.-C. Chambron, J.-P. Sauvage, *J. Am. Chem. Soc.* **2001**, *123*, 12215. D. Monchaud, J. J. Jodry, D. Pomeranc, V. Heitz, J.-C. Chambon, J.-P. Sauvage, J. Lacour., *Angew. Chem. Int. Ed.* in press.

**D12-1**

Organic Chemistry

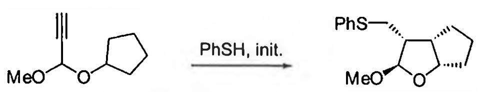
## Diastereoselective 1,5-Hydrogen Abstraction

Florent Beaufils and Philippe Renaud

*Universität Bern, Departement für Chemie und Biochemie*
*Freiestrasse 3, CH-3000 Bern 9*

Isolated cases of 1,5-hydrogen transfer promoted by β-sulfanylalkenyl radicals have been reported [1]. The stereoselectivity of these processes has never been investigated in a systematic way [2].

We present here a systematic investigation of diastereoselective 1,5-hydrogen atom transfers starting from alkyne acetals. The stereochemistry of the processis controlled by the acetal center.



[1] L. Capella, P.C. Montevecchi, M.L. Navacchia *J. Org. Chem.* **1996**, *61*, 6783.
[2] For an exception, see: C.Imboden, F. Villar, P.Renaud, *Organic Lett.* **1999**, *1*, 873.

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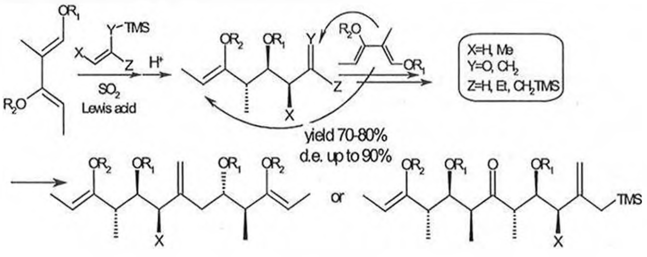
**D12-2**

## Double Chain Elongation to Elaborate Complex Polypropionate Fragments Based on New Chemistry of Sulfur Dioxide.

Māris Turks, Pierre Vogel*

*ICMB, LGSA, EPFL, CH-1015 Lausanne-Dorigny, Switzerland.*

An interesting class of natural compounds with an exceptional profile of biological activity are polypropionates (polyketides) [1]. Many approaches have been developed to synthesize polyketide fragments. Our group has shown that simple alkyl-substituted 1,3-dienes can undergo hetero-Diels-Alder (HAD) reaction with $SO_2$ giving the corresponding 3,6-dihidro-1,2-oxatiin-2-oxides (sultines) [2]. These cycloadducts are unstable, however at low temperature in the presence of Lewis acids they could be opened to zwitterionic intermediates, which could be trapped by nucleophiles, namely enoxysilanes. Recently an asymmetric version of this oxyallylation has been proposed [3]. Here we would like to report about further development of this method using 1,3-dioxy substituted dienes. For the first time we show that different allylsilanes are also capable to undergo the oxyallylation. Representative examples are shown below.



[1] Hoffmann, R. W. *Angew. Chem. Int. Ed.* **2000**, *39*, 2054.
[2] Fernandez, T.; Sordo, J. A.; Monnat, F.; Deguin, B.; Vogel, P. *J. Am. Chem. Soc.* **1998**, *120*, 13276.
[3] Narkevitch, V.; Megevand, S.; Schenk, K.; Vogel, P. *J. Org. Chem.* **2001**, *66*, 5080.

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**D12-3**

Organic Chemistry

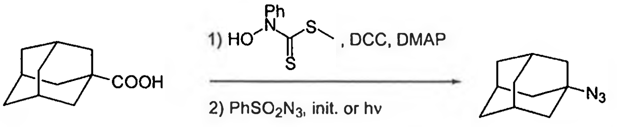
## Decarboxylative Radical Azidation: A Mild Alternative to the Schmidt Reaction

Erich Nyfeler and Philippe Renaud

*Universität Bern, Departement für Chemie und Biochemie*
*Freiestrasse 3, CH-3000 Bern 9*

Our group recently reported the efficient azidation of radicals [1] with sulfonyl azides.

We present here, as an extension of this work, the decarboxylative radical azidation of aliphatic carboxylic acids using a modified thiohydroxamic acid as radical precursor [2]. This reaction represents a mild alternative to the Schmidt reaction.



[1] C. Ollivier and P. Renaud, *J. Am. Chem. Soc.* **2001**, *123*, 4717.
[2] For a review on radical decarboxylation, see: D. H. R. Barton, D. Crich and W. B. Motherwell, *Tetrahedron* **1985**, *41*, 3901.

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**D12-4**

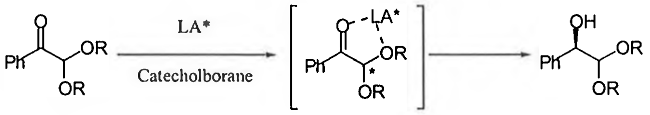
Organic Chemistry

## Chiral Relay Effect :Enantioselective Reduction of α-Ketoacetals

Andrea Romagnoli and Philippe Renaud

Universität Bern, Departement für Chemie und Biochemie, Freiestrasse 3,
CH – 3000 Bern 9

The use of bis-oxazolines and $Zn(OTf)_2$ as chiral catalyst for asymmetric reduction of α-alkoxyketones has already been reported [1]. We present here a systematic investigation of the enantioselective reduction of α,α-ketoacetals. Results are rationalized according to a chiral relay effect because the acetal moiety becomes a chiral center upon complexation with the chiral Lewis acid.



LA* = chiral Lewis acid

[1] M. Bandini, P.G. Cozzi, M. deAngelis, A. Umani-Ronchi, *Tetrahedron Lett.* **2000**, 41, 1601.
[2] (a) L. Quaranta, O. Corminboeuf, P. Renaud, *Org.Lett.* **2002**, 4, 39. (b) M.P. Sibi, L.Venkatraman, M. Liu, C.P. Jasperse, *J. Am. Chem. Soc.* **2001**, 123, 8444.

**D12-5**

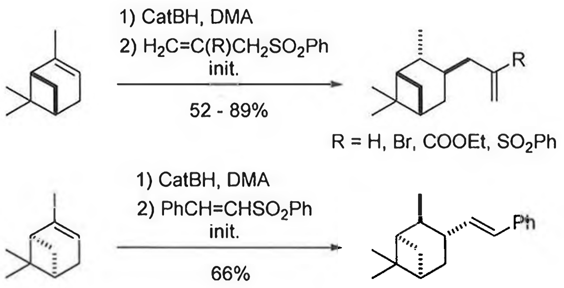
## Radical Allylation and Vinylation of Organoboranes

A.P. Schaffner and P. Renaud*

University of Bern, Department of Chemistry and Biochemistry,
Freiestrasse 3, 3012 Bern.

Organoboranes are excellent radical precursors that are surprisingly not widely used[1].

We report here an efficient method for the allylation and the vinylation of organoboranes. This method is based on a simple one-pot procedure involving the hydroboration of the alkene followed by reaction with allyl- and vinylsulfones.



[1] Ollivier, C.; Renaud, P. *Chem. Rev.* **2001**, *101*, 3415-3434.

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**D12-6**

Organic Chemistry

## A Novel Route to Bicyclic α-Methylene Lactones

Barbara Becattini and Philippe Renaud*

University of Bern, Department of Chemistry and Biochemistry,
Freiestrasse 3, 3012 Bern

Bicyclic α-methylene lactones represent an interesting structural motif that can be found in the skeleton of several natural products. A one-pot procedure involving hydroboration of γ-alkenyl-γ-lactones followed by intramolecular conjugate addition [1] delivers in moderate to good yields the bicyclic thiopyridyl adducts that can easily be converted into α-methylene lactones.

[1] C. Ollivier, P. Renaud, *Chem. Eur. J.* **1999**, *5*, 1468,
C. Ollivier, P. Renaud, *Angew. Chem. Int. Ed.* **2000**, *39*, 925.

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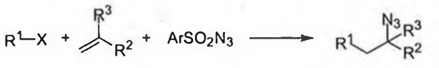
**D12-7**

## Mechanism and New Reagents for the Radical Carboazidation of Alkenes

Philippe Panchaud and Philippe Renaud*

University of Bern, Freiestrasse 3, CH-3012 Bern, Switzerland

We have recently reported that radical carboazidation of alkenes with benzenesulfonyl azide works efficiently in intramolecular [1] and intermolecular [2] processes.
We report here new informations about the mechanism that depends on the nature of the radical precursor. The development of other azidation reagents that facilitates the purification of the products is also presented.



[1] C. Ollivier and P. Renaud, *J. Am. Chem. Soc.* **2001**, *123*, 4717.
[2] P. Renaud, C. Ollivier and P. Panchaud, *submitted for publication.*

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**D12-8**

Organic Chemistry

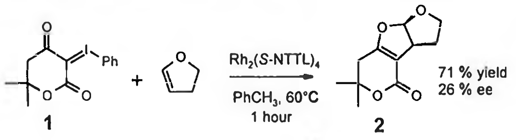
## Enantioselective 1,3-Dipolar Cycloaddition of Cyclic Rhodium Carbenoids using Chiral Dirhodium(II) Catalysts

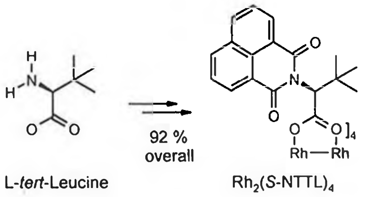
Yves Allenbach, Paul Müller*

University of Geneva - Department of Organic Chemistry
30 Quai Ernest-Ansermet,
CH-1211 Geneva, Switzerland

Rhodium-mediated decomposition of suitable carbenoid precursors has become an important methodology in organic synthesis. Cyclic 1,3-dicarbonyl iodonium ylides are decomposed by rhodium carboxylates in the presence of furane or 2,3-dihydrofurane to generate interesting polyheterocyclic frameworks.

The aim of our research is to find a chiral metal-based catalyst able to achieve both high enantioselectivities and good yields. Up to now, $Rh_2$(*S*-NTTL)$_4$ has proven to be the best catalyst for the conversion of iodonium ylide **1** with 2,3-dihydrofurane to yield tricyclic adduct **2** in 71 % yield and 26 % enantiomeric excess.





**D12-9**

Organic Chemistry

### Desymmetrization of *meso*-Aziridines

Paul Müller* and David Riegert

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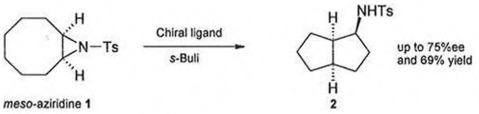
30, Quai Ernest-Ansermet,
CH-1211 Geneva, Switzerland

*N*-Sulfonated *meso*-aziridines have been desymmetrized by reaction with *s*-butyllithium in the presence of a chiral ligand. The reaction proceeds *via* enantioselective α-deprotonation and subsequent α-elimination to afford a carbene which inserts in an appropriately oriented CH-bond, in analogy to that of epoxides.[1]

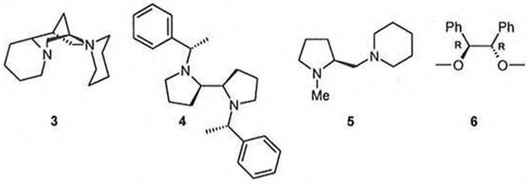
Thus, desymmetrization of *N*-toluenesulfonylimine **1** with ligands **3** to **6** proceeds with up to 75% ee to the bicyclic sulfonamide **2**.[2]



*meso*-aziridine **1** **2**

*scheme 1*

Chiral ligands:



**3** **4** **5** **6**

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[1] D. M. Hodgson, G. P. Lee, J. Witherington, *J. Chem. Soc., Perkin trans. 1*, **1998**, 2151-2161.

[2] P. Müller, P. Nury, *Helv. Chim. Acta*, **2001**, *84*, 662-677.

**D12-10**

Organic Chemistry

### Enantioselective Intramolecular C-H Insertion of Silylated Diazoacetates by Chiral Dirhodium(II) Catalysts

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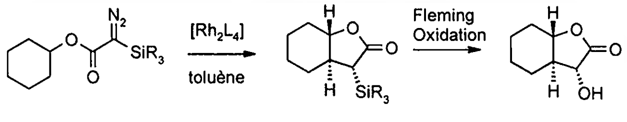
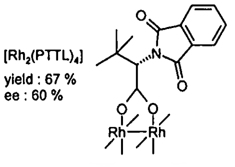
30 Quai Ernest-Ansermet
CH-1211 Geneva, Switzerland

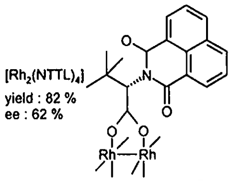
C-H Insertion reactions are widely studied in catalytic enantioselective synthesis. This work implies the use of α-(triorganylsilyl)-diazoacetate (**1**) . The C-H insertion of **1** (R=Et) with $[Rh_2(PTTL)_4]$ or $[Rh_2(NTTL)_4]$ proceeds with up 62 % ee to the silylated lactone **2**. Fleming oxidation [1] of **2** (R=$Me_2Ph$) affords the α-(hydroxy)-γ-lactone **3**.



**1** **2** **3**



$[Rh_2(PTTL)_4]$
yield : 67 %
ee : 60 %



$[Rh_2(NTTL)_4]$
yield : 82 %
ee : 62 %

[1] I. Fleming, R. Henning, D. C. Parker, H. E. Plaut, P. E. J. Sanderson, *J. Chem. Soc., Perkin Trans 1*, **1995**, 317-337.

**D12-11**

Organic Chemistry

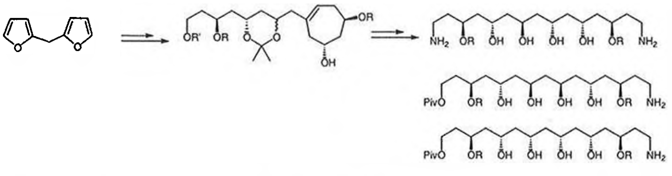
### Asymmetric Synthesis of 1-Aminopentadecane-3,5,7,9,11,13,15-heptols and of 1,15-Diaminopentadecane-3,5,7,9,11,13-hexols

Sandrine Gerber Lemaire-Audoire, Florence Popowycz, Cécile Glanzmann and Pierre Vogel

Institut de Chimie Moléculaire et Biologique, Ecole Polytechnique Fédérale de Lausanne, BCH, 1015 Lausanne, Switzerland

Long-chain polyketides with amino groups are rare natural compounds that show interesting biological properties. For instance Linearmycin A and B have been described to have antifungal and anti-bacterial activities [1] whereas Zwittermycin A produced by *Bacillus cereus* UW85 suppresses certain plant diseases [2]. Recently, our group has developed a new, non-iterative synthetic approach to long-chain polyketides [3]. The method allows the preparation of all possible pentadecan-1,3,5,7,9,11,13,15-octols and derivatives.

We have decided to exploit the method to generate a new class of long-chain aminopolyols to be tested both for their biological properties and as ligation tools.



[1] Sakuda, S.; Guce-Bigol, U.; Itoh, M.; Nishimura, T.; Yamada, Y. *J. Chem. Soc., Perkin Trans 1* **1996**, 2315.

[2] Silo-Suh, L.A.; Stabb, E. V.; Raffel, S. J.; Handelsman, J. *Curr. Microbiology* **1998**, *37*, 6; Stohl, E. A.; Milner, J. L.; Handelsman, J. *Gene* **1999**, *237*, 403.

[3] Schwenter, M. E.; Vogel, P. *Chem. Eur. J.* **2000**, *6*, 4091.

**D12-12**

Organic Chemistry

### Fluorinated Biphenyls : Potential Drugs for the Treatment of Prostate Cancer ?

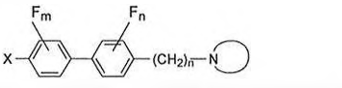
Frédéric Leroux and Manfred Schlosser

Swiss Federal Institute of Technology Lausanne, Institute of Molecular and Biological Chemistry, BCH – LSCO, CH – 1015 Lausanne, Switzerland

17α-Hydroxylase-C17,20-lyase ($P_{450\ 17}$, CYP 17, androgen synthase,) is the key enzyme of the androgen biosynthesis. It catalyzes the hydroxylation of progesterone and pregnenolone to the 17α-products as well as the cleavage of the C17-C20 bond to give androstenedione. As androgens have been implicated in the development and progression of prostate cancer, $P_{450\ 17}$ attracted much attention as a therapeutic target.

R.W. Hartmann *et al.* have shown that *N*-imidazolylmethyl-substituted biphenyls are highly potent inhibitors of $P_{450\ 17}$ *in vitro*.[1, 2] Unfortunately, these compounds have virtually no *in vivo* activity, probably due to a rapid metabolic degradation.

As fluorine substituents may enhance the metabolic stability, we have embarked on the preparation of fluorinated analogs. The characteristics of the compounds selected as targets of synthesis are a central oligofluoro-biphenyl part which ends, on one side, with a polarizable or functional group ("tentacle") and, on the other side, with a methylene spacer (if not oligomethylene chain) bearing a nitrogen heterocycle ("sensor"). The results of first assays are promising.



[1] Wachall, B.G.; Hector, M.; Zhuang, Y.; Hartmann, R.W.; *Bioorg. Med. Chem.* **1999**, *7*, 1913 – 1924.

[2] Zhuang, Y.; Wachall, B.G.; Hartmann, R.W.; *Bioorg. Med. Chem.* **2000**, *8*, 1245 – 1252.

**D12-13**

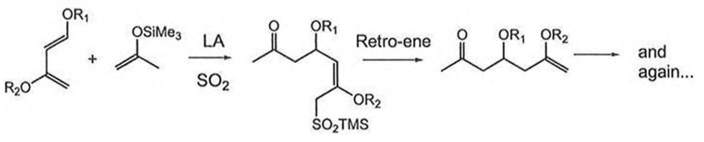
Organic Chemistry

## The synthesis of 1,3-polyols based on sulfur dioxide cycloadditions

Freddy Fonquerne, Pierre Vogel*

EPFL, Institut de chimie Moléculaire et Biologique, CH-1015 Lausanne, Switzerland

A great variety of natural products of biological interest includes polyketides (1,3-polyoxo, 1,3-polyols, aldols) [1] in which the polyols arrays are in an acyclic arrangement. Cyclic arrangement (in a spiroketal way) of these polyols are observable in the architecturally unique family of spongistatins possessing extraordinary cytotoxicity against chemoresistant tumor cell lines. The different approaches to the synthesis of these different building blocks have been reviewed [2].
Recently we have shown [3] that polyketides fragments can be constructed stereoselectively using cycloaddition reactions between dienes and sulfur dioxide in the presence of a Lewis acid (LA). In the light of these results it was proposed to develop a new methodology toward 1,3-polyols using iterative oxyallylation/retro-ene tandem reactions.



[1] Omura, S.; Tanaka, H. *Macrolide Antibiotics: Chemistry, Biology and Practice; Academic Press, New-York* **1984**, 351-404.
[2] (a) Pietruszka, J. *Angew. Chem. Int. Ed.*, **1998**, *37*, 2629-2636. (b) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021-2040. (c) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041-2114.
[3] Narkevitch, V.; Schenk, K.; Vogel, P. *Angew. Chem. Int. Ed.*, **2000**, 39, 1806-1808.

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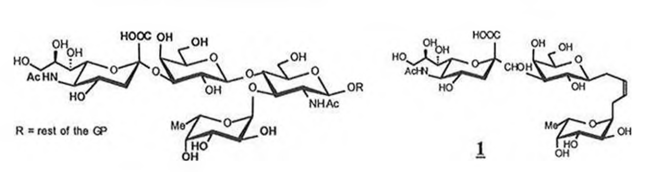
**D13-2**

## Toward the Synthesis of a Non-hydrolysable Mimetic of Sialyl Lewis X Acid

Frédéric Carrel, Pierre Vogel,
ICMB, EPFL, BCH, CH-1015 Lausanne-Dorigny

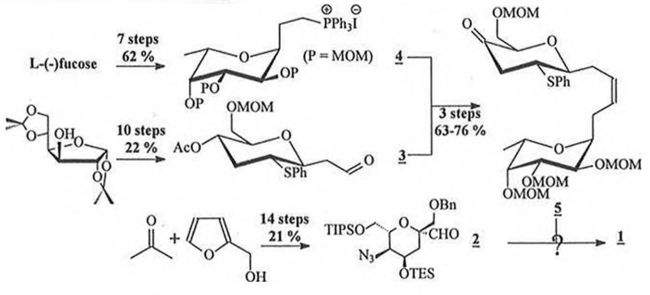
Our target mimetic of Sialyl Lewis X Acid is compound 1 and analogues in which all glycosidic bridges are substituted by carbon bridges.


**Sialyl Lewis X Acid (=SLe$_x$)**

**Mimetic of SLe$_x$**

1

Our approach is based on a Wittig olefination between 3 and 4, followed by a cross-aldolisation using 2.



Work is underway to graft intermediates 5 and 2 through a cross aldolisation following the Traxler-Zimmermann model.

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**D13-1**

Inorganic and Coordination Chemistry

## High-pressure NMR investigation of ligand exchange on *fac*-$[(OC)_3Re(OH_2)_3]^+$

Pascal V. Grundler,[a] Sonia Cayemittes-Shematsi,[a] Bernadette Ugurtas,[a] Roger Alberto,[b] André E. Merbach[a]

[a]Institut de Chimie Moléculaire et Biologique, Ecole Polytechnique Fédérale de Lausanne, EPFL - BCH, CH-1015 Lausanne, Switzerland
[b] Anorganisch-Chemisches Institut, Universität Zürich, Winterthurerstrasse 190, 8057 Zürich, Switzerland
Pascal.Grundler@epfl.ch

Kinetic studies of complex formation between *fac*-$[(OC)_3Re(OH_2)_3]^+$ and several N, O, or S bearing ligands show that the nature of the donor atom has only a weak influence on the reaction rate indicating that the exchange seems to be dissociatively activated. Determining the activation volume by high pressure measurements for these reactions allows to assign the correct mechanism.

$$[(OC)_3Re(OH_2)_3]^+ \longrightarrow \left\{\begin{matrix} [(OC)_3Re(OH_2)_2\circ\,]^+ \\ [(OC)_3Re(OH_2)_2\cdots(\mathbf{OH_2,L})]^+ \\ [(OC)_3Re(OH_2)_3\mathbf{L}]^+ \end{matrix}\right\}^{\ddagger} \longrightarrow [(OC)_3Re(OH_2)_2\mathbf{L}]^+$$

These mechanistic information are of fundamental importance in order to optimize the labelling of biomolecules with $^{99m}$Tc and $^{188/186}$Re for diagnostic and therapeutic applications in nuclear medicine.[1]

[1] R. Alberto, R. Schibli, R. Waibel, U. Abram, A.P. Schubiger, *Coord. Chem. Rev.* **1999**, *190-192*, 901-919.

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**D13-3**

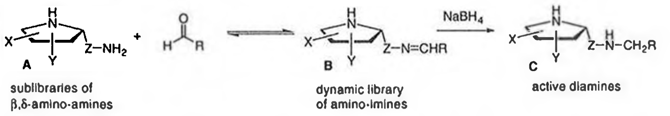
Organic Chemistry

## New Diamines derived from 7-Azabicyclo[2.2.1]heptane for the Search of Glycosidase Inhibitors

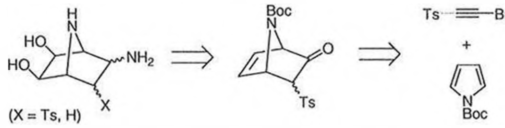
Antonio J. Moreno-Vargas and Pierre Vogel*

EPFL, Institut de Chimie Moléculaire et Biologique, CH-1015 Lausanne, Switzerland.

The search for better inhibitors implies the multi-step synthesis of a large number of analogs and derivatives and their individual testing. Vogel and coworkers have found that diamines of the type A (1,2- and 1,3-diamines) equilibrate rapidly with aldehydes to generate dynamic libraries of imines under low concentration and in the presence of glycosidases. This has led to the invention of an efficient combinatorial method for the discovery of glycosidase inhibitors [1].



Now, we present the synthesis of new bicyclic diamines imitating diamine of the type A in order to apply the former combinatorial method for the search of new glycosidase inhibitors.



[1] Gerber-Lemaire, S.; Popowycz, F.; Rodríguez-García, E.; Carmona Asenjo, A. T.; Robina, I.; Vogel, P. *ChemBioChem* **2002**, *3*, 466.

*We are grateful to the Swiss National Science Foundation, the EPFL and the Ministerio de Educación y Cultura (BQU2001-3779/)Spain. This work is part of the COST-D13-0001/99.*

**D13-4**

Medicinal Chemistry

### An Efficient Combinatorial Method for the Discovery of Glycosidase Inhibitors

Eliazar Rodríguez-García,[a] Sandrine Gerber Lemaire-Audoire,[a] Florence Popowycz,[a] Ana Teresa Carmona-Asenjo,[b] Inmaculada Robina [b] and Pierre Vogel*[a]

[a] EPFL, Institut de Chimie Moléculaire et Biologique, CH-1015 Lausanne, Switzerland.
[b] Departamento de Química Orgánica, Facultad de Química, Universidad de Sevilla, 41071, Sevilla, Spain.

The specific inhibition of N-linked glycoprotein-processing α-mannosidases may provide a useful anticancer strategy [1]. Clinical trials have shown that swainsonine, an indolizidine alkaloid, acts as a reversible inhibitor of α-mannosidase [2], but its toxicity makes the discovery of new inhibitors a necessary aim. Here, we report a new method for the rapid discovery of new α-mannosidase inhibitors based on the formation of imines between diamine **1** and analogues, and a sublibrary of aldehydes in the presence of the enzyme [3]. These imines model the inhibitory activities of the corresponding amines [4].

1

250 µM 250 µM R = substituted aryl and heteroaryl

This strategy can also be applied to all kind of enzymes and is very useful as minute amounts of sample are required in the enzymatic assays.

[1] Asano, N. *Enzyme Inhib.* **2000**, 351.
[2] Elbein, A. D.; Molyneux, R. D. in *Iminosugars as Glycosidase Inhibitors; Nojirimycin and Beyond*, Stütz, A. E., Eds. Wiley-VCH: Weinheim, **1999**, chapter 11.
[3] Gerber-Lemaire, S.; Popowycz, F.; Rodríguez-García, E.; Carmona Asenjo, A. T.; Robina, I.; Vogel, P. *ChemBioChem* **2002**, *3*, 466.
[4] Popowycz, F.; Gerber-Lemaire, S.; Demange, R.; Rodríguez-García, E.; Carmona Asenjo, A. T.; Robina, I.; Vogel, P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2489.

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**D13-5**

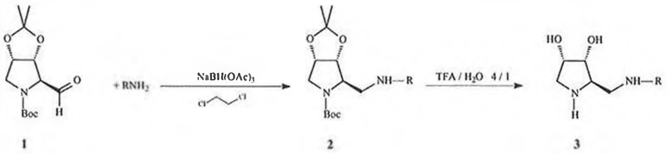
Medicinal Chemistry

### Synthesis of a library of selective α-mannosidase inhibitors

Sandrine Gerber Lemaire-Audoire, Florence Popowycz, Eliazar Rodríguez-García, Raynald Demange, Catherine Schütz and Pierre Vogel

Institut de Chimie Moléculaire et Biologique, Ecole Polytechnique Fédérale de Lausanne, BCH, 1015 Lausanne, Switzerland

The specific inhibition of *N*-linked glycoprotein-processing glycosidases can find promising applications in the development of antibacterial, antiviral and anti-metastatic agents. The discovery of efficient and selective inhibitors of mannosidases, that are involved in the proliferation of cancer cells, could provide a useful anti-cancer strategy [1].
Here, we report the discovery of a library of 2-(aminomethyl)-3,4-dihydroxypyrrolidine derivatives **3** as selective inhibitors of α-mannosidase (*jack bean*) [2].



Following the same synthetic pathway, another family of analogues have been prepared with structural modifications on the pyrrolidine ring.

[1] White, S.L.; Nagai, T.; Akiyama, S.K.; Reeves, E.J.; Grzegorzewski, K.; Olden, K. *Cancer Commun.* **1991**, *3*, 83.
[2] Popowycz, F.; Gerber-Lemaire, S.; Demange, R.; Rodriguez-Garcia, E.; Carmona Asenjo, A.T.; Robina, I.; Vogel, P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2489; Gerber-Lemaire, S.; Popowycz, F.; Rodriguez-Garcia, E.; Carmona Asenjo, A.T.; Robina, I.; Vogel, P. *ChemBioChem* **2002**, *5*, 466.

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**D14-1**

**Organic Chemistry**

### NEW ORGANIC CHEMISTRY OF SULFUR DIOXIDE ONE-POT THREE AND FOUR COMPONENT SYNTHESIS OF SULFONES

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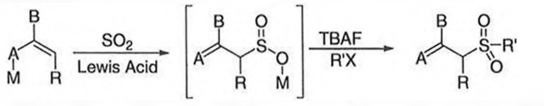
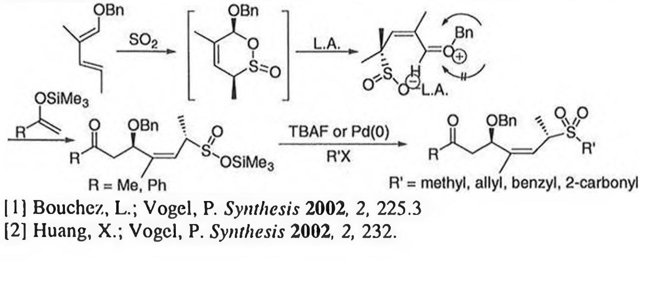
Silyl enol ethers of esters, of ketones, as well as allylstannane and allylsilanes react with sulfur dioxide activated with ($t$-Bu)$Me_2SiOSO_2CF_3$ to give sulfinates that can be reacted in the same pot with a variety of electrophiles generating the corresponding polyfunctional sulfones. The silyl sulfinate intermediates are formed via ene-reactions following probably concerted mechanism. [1]



Other sulfinate intermediates could be generated as well, reacting (E,E)-1-benzyloxy-2-methylpenta-1,3-diene with trimethylsilyl enol ethers derived from acetone or acetophenone in presence of $SO_2$ precomplexed with Lewis acids such as $Yb(OTf)_3$ or $(CF_3SO_2)_2NH$. A variety of electrophiles could be employed to afford the corresponding polyfunctional sulfones in a one-pot operation. [2]



[1] Bouchez, L.; Vogel, P. *Synthesis* **2002**, *2*, 225.3
[2] Huang, X.; Vogel, P. *Synthesis* **2002**, *2*, 232.

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**D15-1**

### Electrochemical and Scanning Probe Investigations of Electrodes coated with Vitamin $B_{12}$ Derivatives

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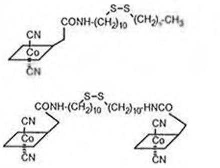
'University of Lisbon, Faculty of Science, Dep. of Chemistry, 1749 Lisboa

While the basic reactivities of corrinoids and porphinoids, key compounds for various important biological transformations, are known from in-vivo and in-vitro investigations, important mechanistic aspects of the involved biological transformations are not yet well understood. One approach to further enhance our understanding of their activity involves the study of reactions at electrodes that are surface modified with these electrocatalytically active systems.

In this contribution, we report on surface-modified poly- and monocrystalline gold electrodes coated with a Vitamin $B_{12}$ derivative bearing an alkane disulfide side chain.



ESCA and TOF-SIMS investigations of the modified electrodes suggest that the $B_{12}$ derivative is connected to the gold substrate at the disulphide group [1]. Ex-situ and in-situ STM experiments performed at $B_{12}$-modified electrodes prepared by surface modification of flame-annealed Au(111) and Au(100) substrates, show pronounced differences in their nm-scale morphology compared to the bare gold substrates [2]. First voltammetric investigations [2] of the modified electrodes suggest that the surface layer remains stable in a relatively wide potential range. The investigated system is considered of high interest as a model system to study locally and at high resolution its electrocatalytic reactivity.

[1] R. Luginbühl, R. Keese, J. Mendonca, N. Simic, H. Siegenthaler, in preparation
[2] L. Abrantes, R. Keese, R. Luginbühl, J. Mendonca, H. Siegenthaler, in preparation.

**D18-1**

Medicinal Chemistry

## The Role of Radio-Lanthanides in Radiopharmaceutical Development: The Potential of the Alpha-emitting $^{149}$Tb in TAT

Beyer, G.J.[1], Soloviev, D.[1], Morel, C.[1], Zaidi, H.[1], Miederer, M.[2], Čomor[3], J.J., Vranješ[3], S., Mäcke, H.[4] and the ISOLDE Collaboration[5]

[1]HUG, Cyclotron Unit, CH-1211 Geneva, [2]TU Munich, Clinic of Nuclear Medicine, Munich, D, [3]Vinča Institute, 11001 Belgrade, Yu, [4]University Hospital Basel, Div. of Radiological Chemistry, CH-4031 Basel
[5]CERN, PPE Division, 1211-Geneva 23, Switzerland

The radio-lanthanides are of special interest for bio-medical research and application: they are three-valent metallic radionuclides which show any radiation properties suitable for SPECT, PET and different aspects of Radio-Immuno Therapy. They provid the unique possibility to study relationships between molecule parameters and a biological response without changes in the basic tracer molecule. For our studies we produced the radionuclides via spallation reaction of 1 GeV at the ISOLDE (on-line isotope separator) facility at CERN. Gamma spectroscopy was applied to measure simultaneously the biodistribution of $^{141}$Ce, $^{145}$Sm, $^{149}$Gd, $^{167}$Tm and $^{225}$Ac in tumor bearing nude mice. The radionuclides were injected as free chelates with citrate, EDTMP, or bound to backbone DTPA-conjugated mab and peptides. Our first experiments with $^{149}$Tb (alpha emitter) labeled antibodies in vitro and in vivo will be described. PET studies were performed with rabbits using $^{142}$Sm EDTMP and with phantoms using the positron emitters $^{134}$Ce/$^{134}$La, $^{138}$Nd/$^{138}$Pr, $^{140}$Nd/$^{140}$Pr, $^{142}$Sm/$^{142}$Pm, $^{149}$Tb and $^{152}$Tb.

Results of our systematic in vitro and in vivo studies will be described [1]. CHX-DTPA antibodies were labeled with the alpha emitting $^{149}$Tb. The yield was instantaneously better than 95 % and a specific activity of 250 MBq/mg mab was obtained. High cytotxic effects for single cell targeting was measured and confirmed in vivo. The positron emitters $^{134}$Ce/La, $^{138}$Nd/Pr, $^{140}$Nd/Pr and $^{142}$Sm/Pm show excellent PET imaging properties.

[1] Beyer, G.J., *HI*. **2000**, *129*, 529-553

The work was support by the Swiss National Science Foundation, Nr. 3100-053672.98.

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**D18-2**

Medicinal Chemistry

## Targetted MRI Contrast Agents

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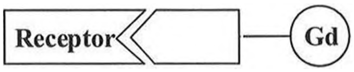
Contrast agents based on Gd(III) chelates are now used in more than 50 % of the exams with Magnetic Resonance Imaging [1]. Nowadays, even if the currently available contrast agents for routine clinical examinations are safe and good enhancers, they are unspecific toward the identification of specific tissues. The main objective of this work is to attach a peptide on a contrast agent in order to obtain compounds able to identify specific tissues and thus able to target pathological sites. In analogy to our work on tumor targeting with radiolabelled regulatory peptide [2], this bioconjugate should contain a Gd(III) complex connected to a ligand able to target a given receptor.



We will present the synthesis of Gd(III) conjugates of somatostatin and biotin. Results of the study of the relaxivity of the Gd-complexes coupled to biomolecules and the impact of their interaction with biological targets will be given.

[1] S. Aime, M. Botta, M. Fasano and E. Terreno *Chem. Soc. Rev.* **1998**, *27*, 19-29.

[2] A. Heppeler, S. Froidevaux, H. R. Mäcke, E. Jermann, M. Béhé, P. Powell and M. Hennig *Chem. Eur. J.* **1999**, *5*, 1974-1981.

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**D18-3**

Inorganic and Coordination Chemistry

## Synthesis of new polyaminocarboxylate synthons to be used as medical MRI contrast agents

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Gadolinium(III) complexes are widely used as contrast agents in medical magnetic resonance imaging (MRI). To achieve a high relaxivity, the complexes must reach two important features. One is the fast water exchange rate that polyaminocarboxylate ligands are capable to yield ; The other one is the slow rotation of the chelate, which can be achieved by synthesizing rigid heavy molecules

We focused on the synthesis of five new polyaminocarboxylate synthons that can coordinate a Gd(III) ion. The coordinating unit of the TTAHA ligand[1] complexes the lanthanide ion in four of these five synthons, whereas the last one carries an iminodiacetate moiety. Three molecules have a xylene backbone, the remaining two a phenanthroline one.

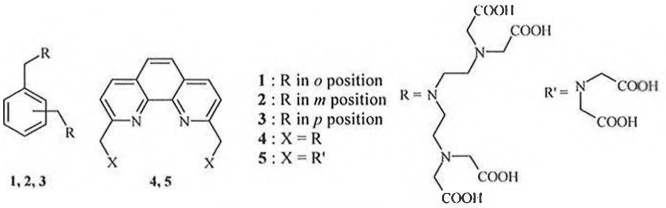

Figure 1: Structure of the five synthons

[1] R. Ruloff, R.N. Muller, D. Pubanz, A.E. Merbach, *Inorg. Chim. Acta*, **1998**, *275-276*, 15-23.

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**D18-4**

Inorganic and Coordination Chemistry

## XAFS Structural Study of Eu$^{2+}$ Solvation

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[b] Institute of Solid State Physics, University of Riga, Latvia
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Structural parameters of the Sr$^{2+}$ and, for the first time, of the redox unstable Eu$^{2+}$ ions were determined by the X-ray Absorption Fine Structure (XAFS) method in water [1], DMF, DMSO and MeCN solutions. Unexpected differences in coordination number and metal-to-solvent distances have been observed between the two supposedly isostructural ions.

| Solvent | $H_2O$ | | DMF | | DMSO | | MeCN | |
|---|---|---|---|---|---|---|---|---|
| Salt | *N* | *R* (Å) | *N* | *R* (Å) | *N* | *R* (Å) | *N* | *R* (Å) |
| $Sr(O_3SCF_3)_2$ | 8.0(3) | 2.600(3) | 6.9(3) | 2.555(5) | 7.0(3) | 2.540(7) | 8.1(8) | 2.665(6) |
| $Eu(O_3SCF_3)_2$ | 7.2(3) | 2.584(5) | 6.0(5) | 2.541(3) | 6* | 2.525* | 7.9(4) | 2.640(4) |

For both Eu$^{2+}$ and Sr$^{2+}$ ions, a decrease in coordination number (N) and metal-to-solvent distances (R) was found along the increasingly solvating MeCN<$H_2O$<<DMF<DMSO solvent series.

Smaller coordination numbers are observed for the Eu$^{2+}$ ion in O-coordinating solvents. The ionic radii of both Sr$^{2+}$ and Eu$^{2+}$ ions are very similar, but the slightly softer character of the Eu$^{2+}$ ion leads to shorter M-N and longer M-O bonds.

[1] G. Moreau, L. Helm, J. Purans, A. E. Merbach, *J. Phys. Chem. A*, **2002**, *106*, 3034.

**D18-5**

Inorganic and Coordination Chemistry

### Macro(bi)cyclic Eu(II) Complexes as Potential MRI Contrast Agents

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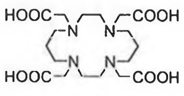
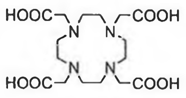
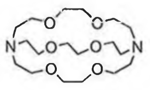
Current developments on contrast agents for Magnetic Resonance Imaging go towards the examination of the physical-chemical state of tissues. These specific contrast agents, called responsive or "smart" contrast agents, can report on important physiological parameters like partial oxygen pressure, pH, temperature, ion distribution in the intra- and extracellular space, metabolite concentration or enzymatic activity. One powerful candidate as redox responsive contrast agent could be the $Eu^{III}/Eu^{II}$ redox system in which the $Eu^{II}$ has seven unpaired electron and high relaxation enhancement effect, similarly to $Gd^{III}$, while $Eu^{III}$ has only a small influence on proton relaxivity. In this perspective, the parameters that influence the water proton relaxivity (rate of water exchange, rotation and electronic relaxation) were determined earlier for the Eu(II) aqua ion and some other Eu(II) poly(amino carboxylate) complexes by $^{17}O$ NMR, EPR and $^{1}H$ NMRD measurements at variable field and temperature.[1] Recently we have investigated three macrocyclic Eu(II) complexes, $[Eu(TETA)]^{2-}$, $[Eu(DOTA)(H_2O)]^{2-}$ and $[Eu(2.2.2)(H_2O)_2]^{2+}$, containing different number of water molecules in the inner coordination sphere.



$H_4TETA$



$H_4DOTA$



(2.2.2)

[1] É. Tóth, L. Burai and A. E. Merbach, *Coord. Chem. Reviews*, **2001**, *216-217*, 363.

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**D18-6**

Inorganic and Coordination Chemistry

### Isomers of Hydroxylated $Gd(DTPA)(H_2O)^{2-}$ Derivatives A Water Echange Study

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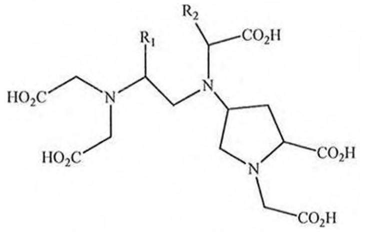
In the past few years a lot of efforts have been made to functionalize the DOTA and DTPA ligand in order to gain notably in water exchange rate, a parameter which becomes particularly limitative for proton relaxivity if the Gd(III) chelate of the considered ligand is engaged in macromolecules [1]. Here we have studied the water exchange of hydroxylated $Gd(DTPA)(H_2O)^{2-}$ derivatives [2].



$R_1 = H$ or $CH_2OH$

$R_2 = CH_2OH$ or H

$^{17}O$ NMR measurements have been performed to show how the hydroxymethyl substituent and the conformational constraint of the pyrrolidine ring influence the water exchange.

[1] In *The Chemistry of Contrast Agents in Medical Magnetic Resonance Imaging*, Eds.: A. E. Merbach and E. Toth, Wiley **2001**.
[2] I.F. Pickersgill, H. Rapoport, *J. Org. Chem.* **2000**, *65*, 4048.

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**D18-7**

Inorganic and Coordination Chemistry

### New Gd-loaded PAMAM dendrimer for MRI

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Éva Tóth, André E. Merbach

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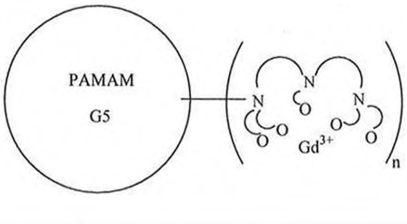
Macromolecular Gd(III) chelates are widely investigated as MRI contrast agents [1]. Their slow rotation allows for increased water proton relaxivities, hence higher efficiency, as compared to low molecular weight Gd(III) complexes. Dendrimers are a very attractive class of macromolecule as they are highly rigid and almost monodisperse.

We have synthesized a new dendrimeric Gd(III) complex based on generation 5 polyamidoamine (PAMAM) dendrimer. The surface of this cascade polymer has been modified by covalently attaching a new polyaminopolycarboxylate ligand via a thiourea linker.



We present the synthesis and characterization of this dendrimer and its corresponding Gd(III) complex. We show that the Gd(III) complex of this cascade polymer presents a remarkably high relaxivity.

[1] The chemistry of contrast agents in medical magnetic resonance imaging, A.E. Merbach, É. Tóth (Eds), John Wiley & Sons, Chichester, **2001**.

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**D18-8**

Inorganic and Coordination Chemistry

### Fullerols - highly water soluble fullerene derivatives

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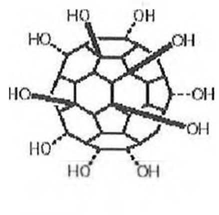
Chemically modified fullerenes are currently being investigated for application in the fields of biology and medicine [1]. One important objective of such derivatization is to make fullerenes water soluble allowing them therefore to be biologically available. We have synthesized highly hydroxylated fullerenes (fullerols) by using quaternary ammonium hydroxides as catalysts [2].



The fullerols have been characterized by a series of physico-chemical techniques, such as IR, thermogravimetry, MS, elemental analysis, as well as by $^{13}C$ and $^{17}O$ NMR. The acid-base behaviour of fullerols in aqueous solution was studied by pH-potentiometry and NMR titration in the absence and in the presence of metal ions.

[1] L.J. Wilson, *Interface.* **1999**, 8, 24.
[2] J. Li, A. Takeuchi, M. Ozawa, X. Li, K. Saigo, K. Kitazawa, *J. Chem. Soc. Chem. Commun.* **1993**, 1784.

**D18-9**

Inorganic and Coordination Chemistry

### New Albumin Binding Gadolinium Complexes for MRI

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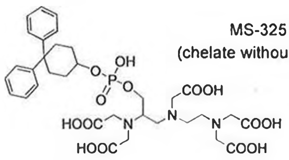
MS-325 is a Gd(III)-based blood pool contrast agent for magnetic resonance imaging (MRI) currently undergoing clinical tests [1]. The chelate is a phosphodiester of 4,4-diphenylcyclohexanol and the functionalized poly(amino carboxylate) DTPA (see formula). The high efficiency of MS-325 as contrast agent is explained by its significant binding to human serum albumin in blood plasma.



MS-325
(chelate without $Gd^{3+}$)

We have synthesized new derivatives of MS-325 by modifying the poly(amino carboxylate) unit in the aim of influencing the first coordination sphere of the gadolinium ion. We have investigated the consequences of the modifications on the efficiency as MRI contrast agent. The syntheses and the results of the physico chemical characterization of the new compounds will be presented in detail.

[1] P. Caravan, N.J. Cloutier, M.T. Greenefield, S.A. McDermid, S.U. Dunham, J.W.M. Bulte, J.C. Amedio, Jr., R.J. Looby, R.M. Supkowski, W.DeW. Horrocks, Jr., T.J. McMurry, R.B. Lauffer, *J. Am. Chem. Soc.* **2002**, *124*, 3152.

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**D18-10**

Medicinal chemistry

### Synthesis and Biological Activity of a New and Highly Potent Ligand for Somatostatin Receptors 2, 3 and 5

M. Ginj[1], J.S. Schmitt[1], D. Wild[1], J.C. Reubi[2], B. Waser[2], M. de Jong[3], B.F. Bernard[3], E.P. Krenning[3], H.R. Mäcke[1]

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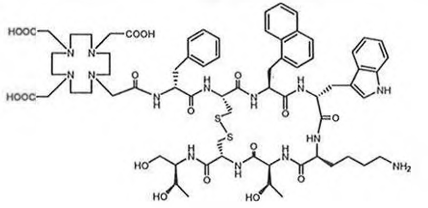
Tumor targeting with radiolabelled peptides has been of much recent interest. The prototypes are derivatives of somatostatin (SRIF) like DOTA-[$Tyr^3$]-octreotide (DOTA-TOC) [1]. Five SRIF-receptor subtypes (sstr) are known and shown to be expressed on different tumors [2]. The above mentioned peptides show high affinity mainly for sstr2 and moderate affinity to sstr 5 [3]. Using parallel solid phase synthesis we synthesized new DOTA-octapeptides based on octreotide replacing $Phe^3$ by mainly unnatural amino acids. One of them, DOTA-[1-$Nal^3$]-octreotide (DOTA-NOC) **1**, showed very good results if complexed with Y(III) or In(III).



**1**

Following the first biological results, [$^{111}$In] and [$^{90}$Y]DOTA-NOC are very promising radiopeptides for the diagnosis and peptide receptor mediated radiotherapy of a larger range of sstr expressing tumors.

[1] Heppeler A. et. al. *Curr. Med. Chem.* **7**: 971-994 (2000);
[2] Forssell-Aronsson E.B. et al. *J. Nucl. Med.* **41**: 636-642 (2000)
[3] Reubi J.C. et al. *Eur.J. Nucl.Med.* **27**: 273-282 (2000)

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**D18-11**

Inorganic and Coordination Chemistry

### Molecular Dynamics Simulations of $Gd^{3+}$ complexes

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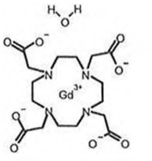
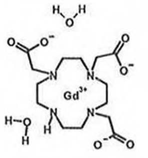
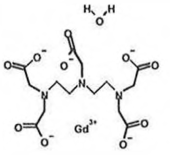
Stable polyaminocarboxylate complexes of the highly paramagnetic $Gd^{3+}$ are used as magnetic resonance imaging (MRI) contrast agents. In order to develop new complexes with higher efficiency, one has to better understand the relationships between the molecular structure and its consequences on the water proton relaxation. Structural and dynamic information that are unavailable experimentally can be obtained using the molecular dynamics simulations. This is possible through the very recent development of a new force field describing the $Gd^{3+}$ ion.[1]



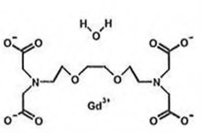
$[Gd(DOTA)(H_2O)]^-$



$[Gd(DO3A)(H_2O)_2]$



$[Gd(DTPA)(H_2O)]^{2-}$



$[Gd(EGTA)(H_2O)]^-$

We show here the potentiality of this new force field for a series of complexes, including cyclic and acyclic ligands, variable hydration number of the metal and variable global charge.

[1] F. Yerly, K.I. Hardcastle, L. Helm, S. Aime, M. Botta, A.E. Merbach *Chem. Eur. J.* **2002**, *8*, 1031-1039 .

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**D18-12**

Inorganic and Coordination Chemistry

### Simultaneous Analysis of 17O/1H NMR and EPR Data of GD(III) Complexes in Solution Using an Improved Theory for Electronic Spin Relaxation.

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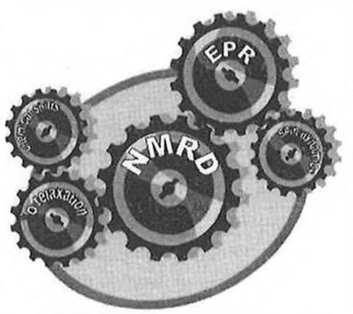
The recent model developed for the analysis of EPR data gives a powerful tool for establish a relation between the molecular structure and the electron spin relaxation [1][2]. This theory has been used successfully to analyze the EPR spectra of a number of complexes, but its consequences on 1H and 17O NMR were still unclear. Using the aquo ion [Gd(H2O)] as a first example, we performed the simultaneous analysis of 17O-NMR, 1H NMR and EPR relaxation data using this rigorous theory. The better understanding of the electron spin relaxation obtained through the recent EPR studies allows us to fix several parameters to physically reasonable values, decreasing the number of degrees of freedom of our statistical system. All the values we calculate for the adjustable parameters can be analyzed from the point of view of their physical meaning, and we find them to be satisfactory.



The simultaneous analysis of 1H, 17O NMR and EPR removes some of the statistical problems due to the interdependence of some parameters. Different experiments impose different constraints on the parameters, allowing a better determination of their values.

[1] S. Rast, A. Borel, L. Helm, E. Belorizky, P.H. Fries, A. E. Merbach, *J. Am. Chem. Soc.* **2001**, *123*, 2637-2644.
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**D18-13**

Inorganic and Coordination Chemistry

## Mechanistic investigation of the dependence of water exchange rate versus lanthanide ionic radii for a series of polyaminoamide complexes

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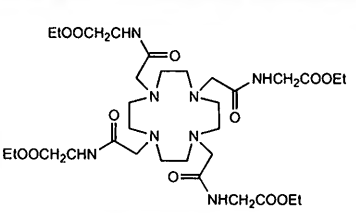
Next to the use of Gd(III) complexes as contrast agents for the Magnetic Resonance Imaging (MRI), lanthanides complexes have shown interesting properties for their use as CT (Magnetisation Transfer) or CEST (Contrast Enhancement through Saturation Transfer) agents. Very recently a important dependence of the water exchange rate on the complexes of DOTA-tetraamide ligand **1** along the lanthanide series was observed.[1]



*Molecular structure of 1*

We present here variable pressure NMR investigations performed in order to understand the mechanistical reasons for the non-regular variation of the water exchange rate along the lanthanide series.

[1] S. Zhang, K. Wu, D.A. Sherry, *J. Am. Chem. Soc.* **2002**, *124*, 4226-4227.

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**D19-1**

## Preparation and optical properties of $TiO_2$-polymer nanocomposites

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$TiO_2$, in particular in its rutile modification, offers a unique combination of high refractive index, transparency in the optical and absorption in the UV wavelength range, and chemical stability. In contrast to related composites containing larger particles, light scattering is virtually absent when nano-sized particles are used. Hence, nanocomposites of comprised of a polymer matrix and rutile are of potential interest in areas such as lenses or protection of polymers from UV light. We have prepared nanocomposite films via *in-situ*-synthesis of colloidal rutile in aqueous solution followed by addition of a water-soluble polymer, casting, and drying. The resulting materials indeed absorb UV radiation close to the visible wavelength range and are essentially completely transparent between 400 and 800 nm. Another synthetic route is based on the synthesis of surface-modified rutile particles which can be isolated and redispersed as optically transparent dispersions in organic solvents. After dissolution of a polymer in these dispersions and solvent evaporation, again transparent nanocomposite films were obtained which were found to absorb UV light and are optically tansparent in the visible wavelength range. These films, however, did not exhibit the above mentioned color change upon prolonged UV radiation. Further studies with these materials, e.g. refractive index determinations, are in progress.

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**D20-1**

## Intramolecular Equilibria in Complexes of an Adenosine 5'-Monophosphate ($AMP^{2-}$) Analogue: 9-(5-Phosphonopentyl)adenine ($dPEEA^{2-}$)

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Francisco González-Vílchez,[b] Helmut Sigel[a,*]

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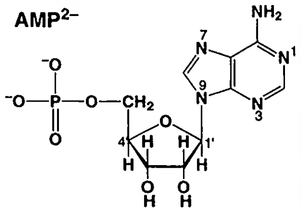
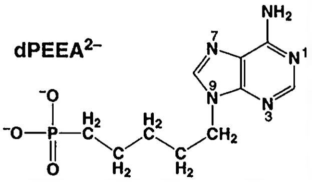
**$AMP^{2-}$**



**$dPEEA^{2-}$**



The stability constants of several M(dPEEA) complexes, with, e.g., $M^{2+} = Mg^{2+}$, $Ni^{2+}$, $Cu^{2+}$, $Zn^{2+}$or $Cd^{2+}$, have been determined by potentiometric pH titrations in aqueous solution (25 °C; $I$ = 0.1 M, $NaNO_3$). Application of previously determined [1,2] log $K^{M}_{M(R\text{-}PO_3)}$ *vs* p$K^{H}_{H(R\text{-}PO_3)}$ straight-line plots for simple phosph(on)ate ligands, R-$PO_3^{2-}$ (where R has no affinity for $M^{2+}$), proves that the primary binding site of $dPEEA^{2-}$ is the -$PO_3^{2-}$ group. However, in several instances also macrochelate formation occurs with N7 of the adenine residue as is reflected by an increased stability. The formation degree of the macrochelates is 28 ± 10%, 46 ± 12%, 42 ± 28%, and 42 ± 9%, for the M(dPEEA) species with $Ni^{2+}$, $Cu^{2+}$, $Zn^{2+}$, and $Cd^{2+}$, respectively. $Mg^{2+}$ and $Ca^{2+}$ form only open isomers. These results are similar to those observed for the corresponding complexes of the natural nucleotide $AMP^{2-}$ [1].

*Supported by the Swiss Nat. Science Found. and via COST D20 by the Swiss Fed. Off. for Educ. & Science and the Ministry of Educ. of the Czech Republic.*

[1] H. Sigel, B. Song, *Met. Ions Biol. Syst.* **1996**, *32*, 135-205.
[2] H. Sigel, D. Chen, N. A. Corfù, F. Gregáň, A. Holý, M. Strašák, *Helv. Chim. Acta* **1992**, *75*, 2634-2656.

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**D20-2**

## Intramolecular Stacking Interactions in Ternary Complexes Formed by 2,2'-Bipyridine (Bpy) or 1,10-Phenanthroline (Phen), Copper(II), and the Quaternary 1-(2-Phosphonomethoxy)ethyl Derivative of 2,4-Diaminopyrimidine ($PMEDAPy^-$)

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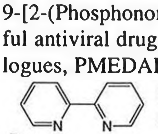
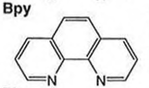
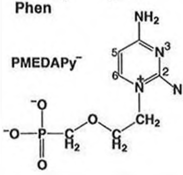


Bpy



Phen

PMEDAPy⁻



9-[2-(Phosphonomethoxy)ethyl]-2,6-diaminopurine (PMEDAP) is a powerful antiviral drug (refs in [1]); in the search for other active nucleotide analogues, $PMEDAPy^-$ was synthesized [1]. Such compounds can be diphosphorylated in the cell, becoming nucleoside triphosphate analogues, and in their complexed form these may inhibit nucleic acid polymerases [2]. Since the anchoring process in the active-site of an enzyme often involves aromatic-ring stacking [2], we tested this property of the positively charged pyrimidine residue by binding $PMEDAPy^-$ via $Cu^{2+}$ to Bpy or Phen (= Arm), which gives then ternary $Cu(Arm)(PMEDAPy)^+$ complexes allowing intramolecular stack formation. This should be reflected [3] by an increased stability compared to that expected for the coordination of $Cu(Arm)^{2+}$ to the -$PO_3^{2-}$ group of a simple R-$PO_3^{2-}$ ligand where R represents a non-interacting group. Indeed, stability enhancements correspond to 0.51 and 0.63 (±0.08) log units with Bpy or Phen, respectively. This indicates that the formation degree [3] of the stacked isomers reaches about 70% or more.

*Supported by the Swiss Nat. Science Found. and via COST D20 by the Swiss Fed. Off. for Educ. & Science and the Ministry of Educ. of the Czech Republic.*

[1] A. Holý, M. Buděšínský, J. Podlaha, I. Císařová, *Collect. Czech. Chem. Commun.* **1999**, *64*, 242-256; and refs therein.
[2] H. Sigel, *Pure Appl. Chem.* **1999**, *71*, 1727-1740; and refs therein.
[3] H. Sigel, *Coord. Chem. Rev.* **1995**, *144*, 287-319; and refs therein.

**D20-3**

Inorganic and Coordination Chemistry

### Stability Constants of Metal Ion ($M^{2+}$) Complexes Formed with N3-Deprotonated Uridine, $(Urd–H)^-$, or Uridine 5'-*O*-Thiomonophosphate, $(UMPS–H)^{3-}$

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Andrzej Okruszek,[c] Helmut Sigel[a,]*

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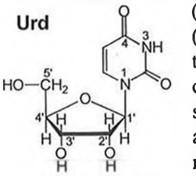
The uracil moiety is one of the important nucleobase residues occurring in nucleotides and nucleic acids [1]. Since the metal ion affinity of this pyrimidine derivative is only poorly characterized, we decided to study the metal ion-binding properties of uridine (Urd), which may be deprotonated at its (N3)H site with p$K_a$ = 9.19 ± 0.05 [2] to give $(Urd–H)^-$. Presently we attempt to measure (pot. pH titrat.; aq. sol.; 25 °C; $I = 0.1$ M, $NaNO_3$) the stability constants of several $M(Urd–H)^+$ complexes. Such studies are hampered by $M^{2+}$-hydroxo complex formation, but up to now we obtained the following preliminary results ($\log K^{M}_{M(Urd-H)}$ is given in parenthesis): $Mg(Urd–H)^+$ (0.70 ± 0.15), $Co(Urd–H)^+$ (1.60 ± 0.10), $Ni(Urd–H)^+$ (1.76 ± 0.06) and $Cd(Urd–H)^+$ (3.16 ± 0.10). We intend to compare these data with the stabilities of the complexes formed between $M^{2+}$ and $M(UMPS–H)^-$, i.e., with a $(UMPS–H)^{3-}$ species which has one $M^{2+}$ coordinated at its thiophosphate group but which should be able to bind a further one at its $(N3)^-$ site giving $M_2(UMPS–H)^+$. Such comparisons should facilitate understanding of the UMPS systems.

**Urd**



*Supported by the Swiss Nat. Science Found. and via COST D20 by the Swiss Fed. Off. for Educ. & Science and the State Comm. for Scientific Res., Poland.*

[1] *Metal Ions in Biological Systems,* Vol. 32: *Interactions of Metal Ions with Nucleotides, Nucleic Acids, and Their Constituents*; Eds: A. Sigel, H. Sigel; Dekker, New York & Basel, **1996**, pp. 1-678.
[2] H. Sigel, *Chem. Soc. Rev.* **1993**, *22*, 255-267.

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**D21-1**

Organic Chemistry

### Structural Aspects of Nucleosides: Protonated and Complexed Adenosines

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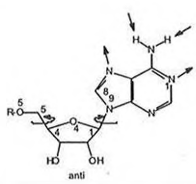
The A-T and C-G base pairs are the most important structural motifs of DNA. Their association is due to hydrogen bonds which lead to rather small structural changes in these bases and the adjacent ribose moieties. These results are inter alia based on the structural details of the corresponding nucleosides which have been elucidated in great detail [1]. In contrast analogous analyses of the protonated congeners have hithertoo not found the appropriate attention. In view of the importance of the acid catalyzed cleavage reactions of nucleosides and DNA the possible structural consequences of the protonation of the bases for the structure of the ribose and adjacent bonds are of interest.



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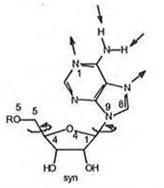

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In order to gain insight into the structural consequences exerted by protonation of the base, the structures of adenosines and their protonated (complexed) congeners were retrieved from the CSD file and examined for changes in bond lengths, bond and torsional angles around the ribose ring [2]. According to a statistical evaluation, the structural differences around the ribose moiety between the protonated and free adenosines are insignificant. These results are used as basis for a discussion of the structure of the adenosyl moiety in coenzyme $B_{12}$ where the atom C(5') is directly bonded to the Co(III) of the corrin ring. It may be concluded that the homolysis of the Co-C(5') bond is activated by other factors than protonation of the adenine moiety.

[1] W. Saenger, Principles of Nucleic Acid Structure, Springer Verlag, 1984.
[2] J. Hauser, R. Keese, manuscript submitted for publication.

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**D21-2**

Inorganic and Coordination Chemistry

### Formation of S-nitrosothiols From Hemoglobin and Nitrogen Monoxide

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Institute of Inorganic Chemistry, ETH Hönggerberg, CH-8093 Zurich

The very fast reaction between oxyhemoglobin ($HbFeO_2$) and nitrogen monoxide ($k \approx 10^7\ M^{-1}s^{-1}$) [1] has long been proposed to represent a sink for $NO^\bullet$ in the blood vessels and to yield methemoglobin ($HbFe^{III}OH_2$) and $NO_3^-$. However, it has recently been proposed that *in vivo* $NO^\bullet$ rather reacts with the very small amount of deoxygenated heme (deoxyHb) to form an iron(II)-nitrosyl complex ($HbFe^{II}NO$) [2]. In addition, it has been suggested that the " NO group" can be transferred, by a yet unclear mechanism, to the surface thiol Cysβ93 to form S-nitrosohemoglobin (SNO-Hb) [2].

Here we present the results of our studies of the dependence of the mixing procedure and the relative ratio of $NO^\bullet$ and $HbFeO_2$ on the yield of SNO-Hb. We first studied the reaction between a dilute $HbFeO_2$ solution (50 μM) and different amounts of a $NO^\bullet$ saturated solution (2 mM). Then we compared the yield of SNO-Hb obtained when equal volumes of $NO^\bullet$ and $HbFeO_2$ solutions were mixed. The largest yields (ca. 15% expressed relative to the amount of added $NO^\bullet$) were obtained when an equivalent volume of a $NO^\bullet$ solution was slowly added to a $HbFeO_2$ solution. The yields of SNO-Hb obtained when deoxyHb was allowed to react with $NO^\bullet$ under similar conditions were slightly larger, but still lower than the previously reported data [1].

The reaction between $NO^\bullet$ and hemoglobin has been proposed to represent an important mechanism to store $NO^\bullet$ and to provide selective delivery of $NO^\bullet$ to oxygen-depleted tissues. The data presented here question this hypothesis. Alternative mechanisms for SNO-Hb formation and their *in vivo* relevance will be discussed.

[1] S. Herold, M. Exner, T. Nauser Biochemistry **2001**, *40*, 3385.
[2] J.R. Pawloski, D.T. Hess, J.S. Stamler, *Nature* **2001**, *409*, 622.

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**D21-3**

Inorganic and Coordination Chemistry

### Peroxynitrite-mediated Nitration of Tyrosine and Tryptophan Residues in Myoglobin and Hemoglobin

Kalinga Shivashankar and Susanna Herold

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Peroxynitrite ($ONOO^-$), a strong oxidizing and nitrating agent generated *in vivo* from the diffusion controlled reaction between $NO^\bullet$ and $O_2^{\bullet-}$, reacts with hemoproteins to generate high valent iron forms and/or nitrated tyrosyl residues. We have recently shown that the reactions of peroxynitrite with oxyhemoglobin ($HbFeO_2$) and oxymyoglobin ($MbFeO_2$) proceed in two steps with the formation of the ferryl species $HbFe^{IV}{=}O$ and $MbFe^{IV}{=}O$ [1]. Here we present extensive analysis of hemoglobin and myoglobin after treatment with different amounts peroxynitrite in the presence of $CO_2$ at different temperatures. Nitrotyrosine was identified by HPLC after acid hydrolysis and enzymatic digestion as well as through nitrotyrosine antibodies. Our results show that very low quantities of nitrotyrosine are formed when equivalent amounts of peroxynitrite are allowed to react with the oxy- and met-forms of these proteins even in the presence of physiologically relevant amounts of $CO_2$. Significant larger yields were observed with apoMb, suggesting that the heme center of myoglobin may act as an efficient scavenger of peroxynitrite. In addition, we have found that tryptophan residues of Mb and Hb are also nitrated to a detectable extent. Though 6-$NO_2$-Trp seems to be the predominant isomer, 5- and 4-$NO_2$-Trp could also be identified unambiguously in Mb and 4-$NO_2$-Trp in Hb. The role of nitrotryptophan as a biomarker for nitrosative stress will be discussed.

[1] M. Exner, S. Herold, *Chem. Res. Toxicol.* **2000**, *13*, 287.

**D21-4**

Inorganic and Coordination Chemistry

### The influence of $CO_2$ on the peroxynitrite-mediated oxidation of oxymyoglobin and oxyhemoglobin

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Peroxynitrite ($ONOO^-$), a strong oxidizing and nitrating species generated *in vivo* from the diffusion controlled reaction between $NO^{\bullet}$ and $O_2^{\bullet-}$, has been shown to be able to cross the red blood cell membrane and react with hemoglobin [1]. We have recently determined that the rate constants for the oxidation of oxymyoglobin ($MbFeO_2$) and oxyhemoglobin ($HbFeO_2$) by peroxynitrite ($ONOO^-$/HOONO) are $(5.4 \pm 0.2) \times 10^4$ $M^{-1}s^{-1}$ and $(8.4 \pm 0.4) \times 10^4$ $M^{-1}s^{-1}$, respectively [2]. The reactions proceed in two steps via the formation of the ferryl ($Fe^{IV}$=O) forms of the proteins [2].
As it has been shown that under physiological conditions $ONOO^-$ reacts rapidly with $CO_2$ to yield 1-carboxylato-2-nitrosodioxidane ($ONOOCO_2^-$), a stronger nitrating agent than peroxynitrite, we have studied the influence of $CO_2$ on the rate and the mechanism of the peroxynitrite-mediated oxidation of $MbFeO_2$. Here we show that the reaction still proceeds in two steps and that the rate of the first step of the reaction, the oxidation of $MbFeO_2$ to $MbFe^{IV}$=O, increases with increasing $CO_2$ concentration. This effect is pH dependent, larger rates are obtained at higher pH. In contrast, the second-order rate constant for the second step, the reduction of $MbFe^{IV}$=O to $MbFe^{III}OH_2$, does not change significantly in the presence of an excess of $CO_2$. Under physiological conditions (pH 7.4 and ca. 1.2 mM $CO_2$) the rate constant for the oxidation of $MbFeO_2$ by peroxynitrite is $3 \times 10^5$ $M^{-1}s^{-1}$. Possible mechanisms for this reaction will be discussed.

[1] A. Denicola, et al. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 3566.
[2] M. Exner, S. Herold, *Chem. Res. Toxicol.* **2000**, *13*, 287.

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**D21-5**

Inorganic and Coordination Chemistry

### Investigation on Low Molecular Iron(III) Coordination Compounds, Their Stability and Reduction Behaviour Against Ascorbate and Superoxide

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Our current research focuses on the reduction of iron(III) coordination compounds with citrate and adenosine triphosphate (ATP) by ascorbate and superoxide. Both complexes are considered possible biorelevant species in the labile iron pool. Ascorbate and superoxide are potential physiologically significant reductants. The experiments with ascorbate are carried out under anaerobic conditions, whereas the ones with superoxide are induced by pulse radiolysis.

For the iron(III) citrate complex, cyclovoltammetric measurements show a high inertness and only a small potential difference of approx. 0.2 V to ascorbate. No observable reduction occurs. Also the reaction with superoxide by pulse radiolysis seems to occur only to a minor extent.

The iron(III) ATP complex can be reduced by ascorbate, but the reaction is too slow ($t_{1/2} \geq 500$ s) to be biorelevant as stopped flow experiments suggest. The reduction by superoxide occurs faster, but given the low physiological concentrations of superoxide and a bimolecular pathway, reaction rates drop to a nonrelevant magnitude.

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**D21-6**

Inorganic and Coordination Chemistry

### The Potential of Peroxynitrous Acid Determined by Linear Sweep Voltammetry

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Peroxynitrite is formed *in vivo* from the diffusion-controlled reaction of $NO^{\bullet}$ with $O_2^{\bullet-}$. Peroxynitrous acid (ONOOH) is a strong oxidant and reacts with a wide variety of biomolecules. The instability and reactivity of peroxynitrous acid makes it difficult to determine the reduction potential of this biological harmful species. We measured by linear sweep voltammetry the decay of peroxynitrous acid at pH 5.6. From the decay kinetic we determined a signal corresponding to peroxynitrous acid. The reduction potential was determined by Feldberg simulation. Additionally we estimated the reduction potential by extrapolation of the sweep rate by the formula $E_P = E^{0'} - \frac{RT}{\alpha n_a F}\left[0.78 + \ln\left(\frac{D_0^{1/2}}{k^0}\right) + \ln\sqrt{\frac{\alpha n_a F v}{RT}}\right]$ [1]. We obtained with both procedures a reduction potential of about 1.2 V. The oxidized product is $NO_2^{\bullet}$.

[1] A.J. Bard, L.R. Faulkner, Electrochemical Methods; John Wils & Sons Inc.: 1980

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**D21-7**

Inorganic and Coordination Chemistry

### Peroxynitrite and Transition Metals

Martin Merkofer, Patrick K. Wick, Thomas Nauser, Reinhard Kissner, and Willem H. Koppenol

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Peroxynitrite is a cytotoxic species. Its decomposition is catalyzed by iron and manganese porphyrin complexes. Given the observation of an unstable Fe–$ONOO^-$ complex in haemoglobin [1], the question has arisen whether it would be possible to stabilize peroxynitrite, or to catalyze its decay by complexation to a metal. We analysed the catalytic decomposition of peroxynitrite by Cu(II), Ni(II) and Zn(II) complexes. All three metals enhance the decay rate, as expected for Lewis acids in general. In the presence of Cu(II), we observed a reaction faster than that proposed for homolysis of $ONOO^-$ to $NO^{\bullet}$ and $O_2^{\bullet-}$, 0.017 $s^{-1}$ [2]. Therefore, homolysis is not the main reaction. This is supported by the observation that Zn(II) complexes also enhance the decay, though such complexes cannot be reduced by superoxide. Cu(II)-nta enhances the formation of $NO_3^-$ when $[ONOO^-] < [ML]$. No formation of Cu(I) could be observed, which argues against homolysis of $ONOO^-$. We propose a mechanism which involves an isomerization within the coordination sphere. When $[ONOO^-] > [Cu]$ the decomposition to $NO_2^-$ and $O_2$ is catalyzed.
We reported that a stable $[Co(CN)_5ONOO]^{3-}$ complex can be isolated [3]. The Co(III) complex has a spectrum in which the absorption of peroxynitrite is blue-shifted, similar to that of the unstable Cu-complex. We also have some evidence for a side-on peroxynitrite-titanium(IV) complex at pH = 0.

[1] S. Herold, *FEBS Letters* **1999**, *443*, 81.
[2] Merényi, G., and Lind, J., *Chem. Res. Toxicol.* **1998**, *11*, 243.
[3] P.K. Wick, R. Kissner, W.H. Koppenol, W. H., *Helv. Chim. Acta* **2001**, *84*, 3057; **2000**, *83*, 748

**D24-1**

Inorganic and Coordination Chemistry

### Facile Access to Ruthenium-Hydrides with functionalised Arenes Their Performance in Transfer-Hydrogenation Catalysis

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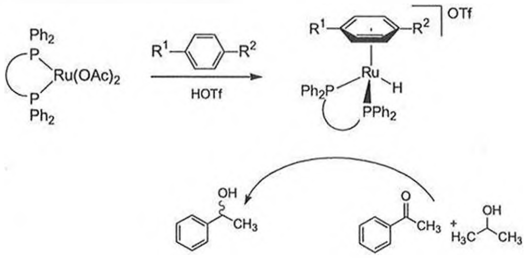
CH-8093 Zürich

Chiral ruthenium hydride complexes play an important role in various catalytic processes of which the enantioselctive transfer-hydrogenation of ketones has recently attracted considerable interest and the exact mechanism is still under discussion. [1]

We describe here a route to chiral bisphosphine hydrido-complexes bearing substituted arenes and report their kinetic and enatioselective performance as transfer-hydrogenation catalysts.



1. Alonso D. A., Nordin S. J.-M., Roth P., Tarnai T., Andersson P. G., Thommen M., Pittelkow U. *J. Org. Chem.* **2000**, *65*, 3116 – 3122; Gao J-X., Ikariya T., Noyori R. *Organometallics* **1996**, *15*, 1087 – 1089.

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**D25-1**

Medicinal Chemistry

### On the Functional Requirements of Fucosyltransferase III

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Klingelbergstrasse 50, CH-4056 Basel, Switzerland

Fucosyltransferases regio- and stereospecifically catalyze the transfer of fucose from GDP-fucose to specific hydroxy groups of their substrates. The resulting oligosaccharides, e.g. Le$^{a/x}$ and sLe$^{a/x}$ play key roles in regulatory pathways of cell-adhesion and developmental processes [1].

Our interest in glycosyltransferases for the preparative synthesis of carbohydrate mimetics [2] prompted us to study the acceptor tolerance of recombinant fucosyltransferase III (EC 2.4.1.65 ). Soluble FucT III was expressed in *SF9* insect cells in a protein-A chimeric form. Modified type I and type II oligosaccharides containing replacements of Glc*N*Ac and/or sialic acid by a variety of non-carbohydrate moieties were used as acceptor substrates.

The kinetic parameters ($v_{max}$, $K_m$) of the transfer reactions indicated a remarkable flexibility of fucosyltransferase III in respect to the acceptance of modified substrates. The structure activity relationship (SAR) obtained in our investigation showed a broad applicability of FucT III for the synthesis of Le$^{a/x}$ and sLe$^{a/x}$ mimetics. To elucidate the interactions of the fucose accepting hydroxy groups of the type I & II substrates with the active site, the corresponding deoxygenated analogs have been synthesized. Surprisingly, neither of the analogs showed an inhibitory effect on FucT III but rather acted as acceptors leading to blood group antigens.

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[2] B. Ernst, B. Wagner, G. Baisch, A. Katopodis, T. Winkler, R. Öhrlein, *Can. J. Chem.*, **2000**, *78*, 892; B. Ernst, R. Öhrlein, *Glycoconj. J.* **1999**, *16*, 161.

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**D25-2**

Medicinal Chemistry

### Expression and Preparative Use of Recombinant Human α(2-3)-Sialyl Transferase

Oliver Schwardt, Tamara Visekruna, Said Rabbani, and Beat Ernst*

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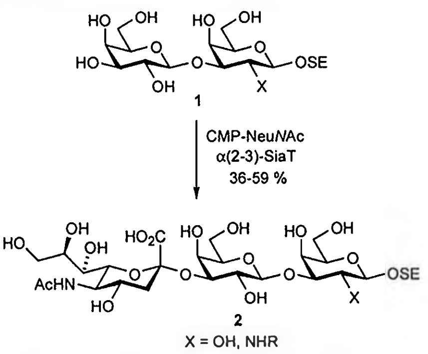
Klingelbergstrasse 50, CH-4056 Basel, Switzerland

Recombinant human α(2-3)-sialyl transferase (EC 2.4.99.) was expressed from baculo virus infected insect cells and purified by affinity chromatography on CDP-fractogel.

The α(2-3)-sialyl transferase was applied for enzymatic sialidation using several natural and non-natural disaccharides, e.g. Gal-β(1-3)-Gal **1**, as acceptors and CMP-sialic acid as donor.



Our investigations are aiming at the use of sialyl transferases in preparative scale. To achieve this goal, expression levels and storage conditions of sialyl transferases were optimized and substrate tolerances elucidated. The results of these investigations will be presented.

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**D26-1**

Computational Chemistry

### Theoretical study of bonding carbon monoxide to Alkali Metal Cations in ZSM5-zeolite using orbital-free embedding formalism.

Delphine Bas[1], Annick Goursot[2], Jacques Weber[1] and Tomasz Wesolowski[1]

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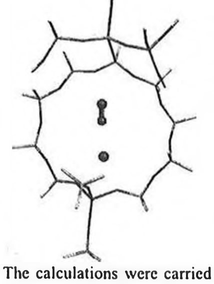
[2]Ecole de Chimie, 8 rue de l'Ecole Normale, 34296 Montpellier, Cedex 5, France

The interaction between carbon monoxide and alkali cation in ZSM5 zeolite can provide useful indications for understanding intra-zeolite processes. The different modes of coordination of this probe molecule are characterized by the change in CO stretching frequency and intensity [1].

In a previous study [2], it has been shown that the interaction between the CO molecule and the alkali cation zeolite through the C-end gives rise to a blue shift of this frequency in good agreement with experimental data.



The purpose of this work was to study the O-bonding coordination mode of the carbon monoxide in cation zeolite and to compare the calculated frequency shifts obtained with the red shift observed experimentally.

All the calculations were carried out using the orbital-free embedding formalism [3] developed in our group and implemented in the deMon program [4]. In the calculations the $Me^+$...CO complex was considered as one subsystem whereas the zeolite was represented as a cluster (see figure) with frozen electron density

The cluster used comprises the atoms coordinating the $Me^+$, the channel wall opposite to the Al site and the atoms linking both parts.

The influence of the long-range electrostatic effects on the properties of CO was also studied.

The calculations were carried out for the three alkali cations ($Li^+$, $Na^+$, $K^+$). In agreement with experimental results, it was found that the $Me^+$...OC complex was energetically less stable than the $Me^+$...CO one and that the CO stretching vibration are red-shifted.

[1] C.O. Areán, A.A. Tsyganenko, E.E. Platero, E. Garrone, A. Zecchina, *Angew. Chem. Int. Ed.*, **1998**, *37*,3161-3163.
[2] T.A. Wesolowski, A. Goursot, J. Weber; *J. Chem. Phys.*, **2001**, *115*, 4791.
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**D26-2**

Computational Chemistry

## Influence of dynamical effects on NMR chemical shifts

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[1]Department of Physical Chemistry, University of Geneva, Switzerland,
[2]Inst. f. Physikalishe Chemie, TU Dresden, Germany

NMR measurements are a powerful tool to characterise molecular structures. The calculation of molecular chemical shifts has become a standard tool in theory in the past 10 years. However, discrepancies between experiment and theory can be found especially for flexible compounds with a lot of conformers. This can be rationalised with the experiment having a long time-scale, which is not assembling the simple picture of a static calculation of the minimum geometry.

We address this problem using Born-Oppenheimer molecular dynamics together with a sampling over a variety of NMR calculations of snapshot geometries. The approach will be applied to a variety of small organic and inorganic molecules.

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**D28-2**

Organic Chemistry

## Towards Total Synthesis of Cephalotaxine; Preparation of the Key Intermediate *via* Asymmetric Radical Azidation

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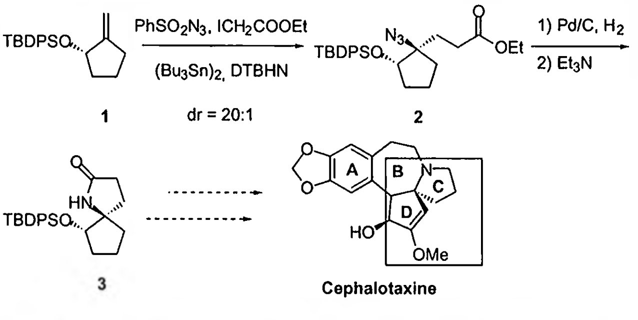
Freiestrasse 3, 3012 Bern, Switzerland

Recently we developed a novel intermolecular radical azidation reaction [1,2]. The utility of this methodology was demonstrated by preparation of various pyrrolidinone derivatives [3].



Currently we examine asymmetric version of the radical azidation reaction. During this study we prepared azaspirocyclic compound **3**, which is a key intermediate in the total synthesis of cephalotaxine.

[1] Ollivier, C.; Renaud, P. *J. Am. Chem. Soc.* **2000**, *122*, 6496.
[2] Ollivier, C.; Renaud, P. *J. Am. Chem. Soc.* **2001**, *123*, 4717
[3] Renaud, P.; Ollivier, C.; Panchaud, P. *submitted for publ.*

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**D28-1**

Organic Chemistry

## Towards the Total Synthesis of Lepadiformine

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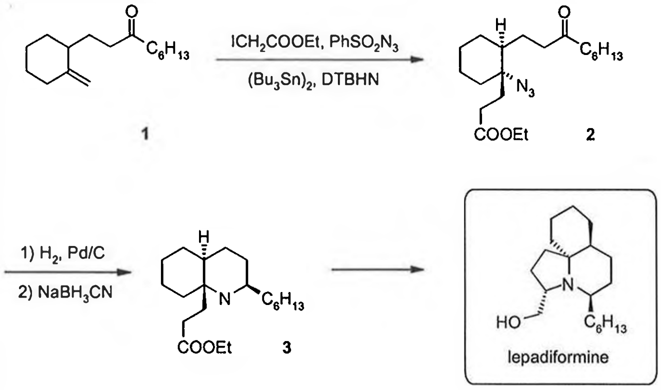
Lepadiformine is a marine alkaloid possessing interesting biological properties as well as a unique carbon skeleton [1]. By employing a novel intermolecular radical amination reaction [2, 3], we intend to achieve the shortest and most efficient synthesis so far.



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[2] C. Ollivier, P. Renaud, *J. Am. Chem. Soc.* **2000**, *122*, 6496.
[3] C. Ollivier, P. Renaud, *J. Am. Chem. Soc.* **2001**, *123*, 4717.

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**D28-3**

Organic Chemistry

## Synthetic studies toward Spongistatins

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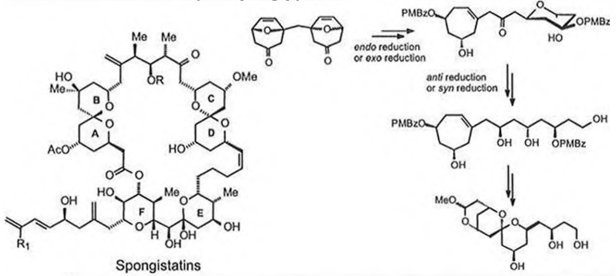
1015 Lausanne, Switzerland

Polketides are carbon chains substituted by hydroxyl groups, mainly in a 1,3-fashion. These fragments are generally linear, but in some particular cases they can be found in Nature under a cyclic form. This is the case of Spongistatins, natural products isolated from marine sponges,[1] which shows a high activity against several chemoresistant tumor cell lines (sub nanomolar growth inhibition). The AB and CD spitoketals seem to play a crucial role in the activity of spongipyrans.[3]



Our approach relies on the chemistry developed in our group for the synthesis of long chain polyols.[4] The versatility of it has been further enhanced by the stereoselective reduction of the oxabicyclo[3.2.1]octenone moieties and the reduction of the β-hydroxy ketones in a 1,3-*syn* or *anti* fashion. With this methodology, a family of four stereoisomers can be obtained and further fonctionalization can be done. Biological essays are currently in progress to evaluate the activity of our structures.

[1] Pettit, G. R. and all. *J. Org. Chem.* **1993**, *58*, 1302. [2] Pietruszka, J. *Angew. Chem. Int. Ed. Eng.* **1998**, *37*, 2629. [3] Uckun, F. M. and all. *Bio. & Med. Chem. Lett.* **2000**, *10*, 541. [4] Schwenter, M. E. Vogel, P. *J. Org. Chem.*, **2001**, 66, 7869.

CHIMIA 2002, 56, No. 7/8

**D29-1**

Inorganic and Coordination Chemistry

### Aqueous Carbon Dioxide Reduction Using Ru(NO)Phosphine Catalysts

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[1]EPFL, ICMB, BCH, CH-1015 Lausanne, Switzerland
[2]University of Debrecen, Debrecen, Hungary

Water soluble analogs of $[RuCl_3(NO)(PPh_3)_2]$ [1] were synthesized in the reaction of $K_2[RuCl_5NO]$ with stoichiometric amount of mono-and trisulfonated triphenylphosphines (*m*TPPMS and *m*TPPTS). $[RuCl_3(NO)(PTA)_2]$ was also prepared but the compound has limited solubility in water despite PTA itself being highly soluble (PTA = 1,3,5-triaza-7-phosphaadamantane). In an excess PTA, the known $[RuCl_2(PTA)_4]$ was obtained. In case of sulfonated phosphines, $[RuCl(NO)(TPPMS)_3]$ or $[RuCl(NO)(TPPTS)_3]$ were formed having trigonal bipyramidal structures as identified by NMR measurements. In the presence of $H_2$ (P = 100 bar) these are transformed to the $[RuH(NO)(TPPMS)_3]$ or $[RuH(NO)(TPPTS)_3]$ species which are similar to $[RuH(NO)(PPh_3)_3]$ [2]. The hydrides proved to be catalytically active in the hydrogenation of $CO_2/HCO_3^-$ in aqueous solution. The formation of the product, $HCOO^-$ was followed by in situ NMR measurements under pressure. The effect of pH, $CO_2$ and $H_2$ pressure, or the concentration of the catalyst on the reaction rate were studied, and the findings were compared to the results of the reduction of $CO_2/HCO_3^-$ catalysed by $[\{RuCl_2(TPPMS)_2\}_2]$ [3].

The authors are grateful for the support through the following grants: Swiss National Science Foundation, 2100-061653.00/1 (G.L.); OTKA, Hungary, T029934 (F.J.). Zs. O. thanks the EPFL for the scholarship. L. Nádasdi is thanked for his valuable help in the medium pressure NMR measurements.

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## Author Index

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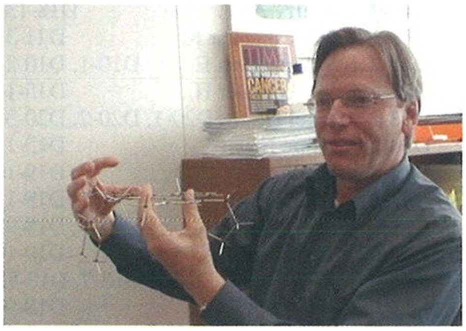
# Glivec: A New Treatment Modality for CML: A Case History

Jürg Zimmermann*
Sandmeyer Prize Winner 2002

*Abstract:* Glivec (the brand name in the US is Gleevec™) is a protein-tyrosine kinase inhibitor which potently inhibits the Abl tyrosine kinase *in vitro* and *in vivo*. The compound specifically inhibits proliferation of *v-abl* and *bcr-abl* expressing cells, suggesting that it is not a general antimitotic agent. In addition, Glivec is a potent inhibitor of the platelet-derived growth factor receptor kinase (PDGF-R) and of the receptor kinase for stem cell factor (SCF), c-Kit, and inhibits PDGF- and SCF-mediated biochemical events. In contrast, it does not affect signal transduction mediated by other stimuli including epidermal growth factor (EGF), insulin and phorbol esters. Pharmacokinetic studies in various animal species demonstrate that pharmacologically relevant concentrations are achieved in the plasma following oral administration of the drug. STI571 shows antitumor activity as a single agent in animal models at well-tolerated doses. On May 10, 2001, the U.S. Food and Drug administration announced the fast track approval of Gleevec™ (imatinib mesylate), our treatment for patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase or chronic phase after failure of interferon-alpha therapy. The FDA approval came in just over 10 weeks after Novartis filed its New Drug Application, and just two months after the FDA notified us that it had granted Glivec a priority review.

**Keywords**: Bcr-abl Protein kinase · Chronic myeloid leukemia (CML) · Glivec (Gleevec™) · Lead optimisation · Phenylamino pyrimidines · Philadelphia chromosome



**Jürg Zimmermann**

*Jürg Zimmermann* was born on 5th May 1957 in Adelboden, Switzerland. After an apprenticeship as a laboratory technician he studied chemical engineering at the Engineering School in Burgdorf, Switzerland. He then studied organic chemistry at the ETH in Zürich, where he attained his PhD under the supervision of Professor Dieter Seebach. Afterward he joined as a postdoctoral fellow Professor Beckwith's group at the Australian National University for the study of the cyclization of radicals and afterward Professor Lown's group at the University of Alberta in Edmonton for the design and synthesis of DNA-binding ligands. In 1990, he joined the Oncology Research Department of Ciba-Geigy in Basel. He headed various protein kinase projects and during this period he invented the active ingredient of Glivec (the US brand name is Gleevec™). He moved then to Core Technology of Novartis to become head of combinatorial chemistry in 1998. He was awarded the Max-Lüthi medal (1982), the Dolphin Prize (1993), the Sandmeyer Prize (2002), the Bruce-Cain Memorial Award (2002) and the Inventor of the Year Award (2002).

## 1. Introduction, Chronic Myeloid Leukemia (CML)

Chronic myeloid leukemia (CML) is one of the four most common types of leukemia. In the United States, there are approximately 20,000–23,000 patients with CML at any given time. Worldwide, CML has an incidence of one to two cases per 100,000 population per year, and is responsible for 15 to 20% of all adult cases of leukemia. CML is a hematological stem cell disorder caused by an acquired or induced abnormality in the DNA of the stem cells in bone marrow. This abnormality results in a gene that produces an abnormal protein. This protein disrupts the bone marrow's normally well-controlled production of white blood cells. The resulting proliferation of white blood cells leads to a massive increase in their concentration in the blood.

CML progresses through three distinct phases: the chronic phase (typically lasting from four to six years), the accelerated phase (typically lasting from six to twelve months), and blast crisis (typically lasting from three to six months), which are marked by a progressive increase in the

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number of white blood cells. As a patient moves through these stages, the disease becomes biologically more complex, making it increasingly refractory to therapy and, therefore, more difficult to treat.

The current treatment options include an allogeneic bone marrow transplant – using healthy stem cells from the bone marrow of a closely matched donor – which currently offers patients with CML the best hope for a cure. However, only about 20% of patients are eligible for such a transplant, either because a suitable donor cannot be located, because of advanced age, or because of other complicating medical factors. Another option for some patients is an autologous bone marrow transplant using the patient's own blood stem cells after they have undergone intensive chemotherapy and radiation treatment. Although this therapy prolongs survival, almost all patients eventually relapse, in part because their bodies still harbor malignant CML cells.

A range of drugs is used in the treatment of CML, including interferon-alpha, hydroxyurea, cytarabine, bisulfan. Although it is not a cure, interferon (given by injection) may prolong the survival of some CML patients. It has been shown in some patients to elicit both a hematological response and, to a lesser extent, a cytogenetic response. However, as CML becomes more aggressive, many patients become refractory to interferon therapy.

In CML, the genetically altered stem cell is distinguished by the presence of the Philadelphia (Ph) chromosome [1], which is detected in most patients. The Philadelphia chromosome (so-called because University of Pennsylvania researchers identified it) is created by an exchange of parts between two chromosomes. A detached portion of chromosome 9 shifts to chromosome 22, and a section of chromosome 22 shifts to chromosome 9 in a phenomenon known as 'translocation' [2]. This cytogenetic alteration is detected in 95% of patients with CML and is the hallmark of the disease (Fig. 1).

The Philadelphia chromosome produces an enzyme that plays a central role in aberrant cell growth and division. This enzyme, a tyrosine kinase known as Bcr-Abl [3][4], changes the cell's normal genetic instructions, jamming the signal that tells the body to stop producing white blood cells. The result is that while a cubic millimeter of blood from a healthy person contains 4,000 to 10,000 white blood cells, the same volume of blood from a CML patient contains 10 to 25 times this number. The massive increase in the number of white blood cells characterizes CML. The fact that the expression of Bcr-Abl in mice could induce a disease resembling CML, provided strong evidence that the Bcr-Abl protein was indeed one of the mayor driving forces in the pathophysiology of CML [5]. Thus, an inhibitor of the Abl protein tyrosin kinase would be predicted to be an effective and selective therapeutic agent for this leukemia (Fig. 2).

## 2. Medicinal Chemistry

The starting point for every medicinal chemistry project is a lead compound with a given pharmacological activity. The biological activity of a molecule however must be complemented by other properties that make the molecule a good drug substance. It is estimated that a large proportion of molecules fail in late stages of drug development due to reasons of drug–drug interaction or poor ADME (absorption, distribution, metabolism, and excretion) features. Failure to detect these liabilities early in the drug discovery process can be extremely costly and time consuming. On the basis of physical and calculated properties for known drugs, criteria for 'drug-likeness' have been established [6].

In the case of Glivec (the US brand name is Gleevec™), a lead compound was identified in a screen for inhibitors of protein kinase **C** (PKC), (see Fig. 3). A high cellular activity was obtained in derivatives bearing a 3'-pyridyl group at the 3-position of the pyrimidine, the phenylamino pyrimidine core was absolutely essential for PKC inhibitory activity (Fig. 4). During the optimization of this structural class on the inhibition of PKC, a serine/threonine kinase, it was observed that the presence of an amide group on the phenyl ring gives rise to inhibition also of tyrosine kinases, such as the bcr-abl kinase (**A**, Fig. 5). The amide bond is required to be stable towards hydrolysis because the release of an unprotected diamino phenyl moiety has to be avoided in order to avoid mutagenicity. In fact a high stability against hydrolysis could be achieved with derivatives bearing a phenyl group at the amide bond (**B**, Fig. 5). The low selectivity was the next hurdle to overcome since this type of compound is a dual inhibitor of PKC and Bcr-Abl.

At this point a key observation was made from analysis of the structure-activity relationships: substituents at position

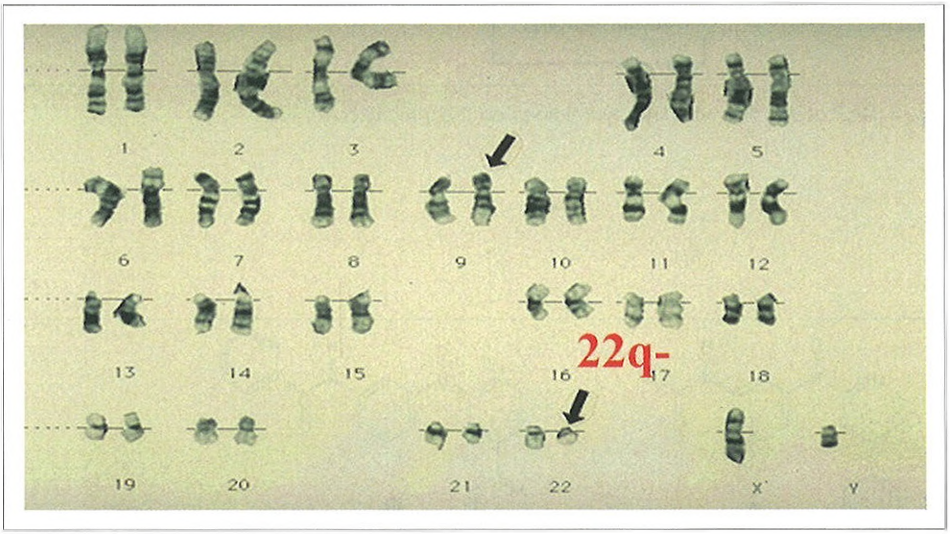


Fig. 1. Philadelphia chromosome 22

- **Bcr-Abl is detected in 95 % of patients with CML**
- **Bcr-Abl is the causative abnormality of CML**
- **Bcr-Abl tyrosine kinase is constitutively activated intracellularly**
- **Tyrosine kinase activity is required for CML cell function**
- **Abl null mice are viable**

Fig. 2. Bcr-abl as a theraputic target for CML

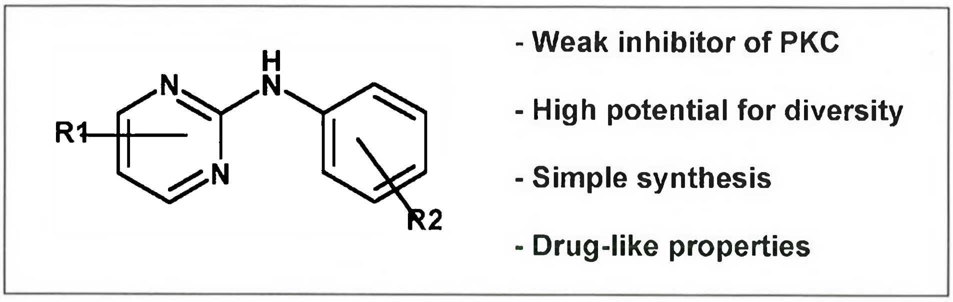


Fig. 3. Lead compound: Phenylamino pyrimidine

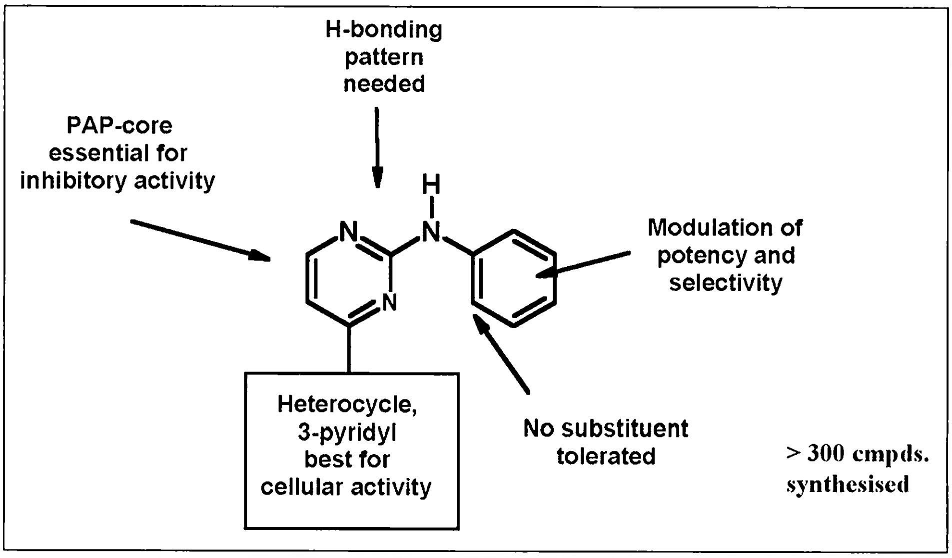


Fig. 4. SAR of the phenylamino pyrimidines on the inhibition of PKC

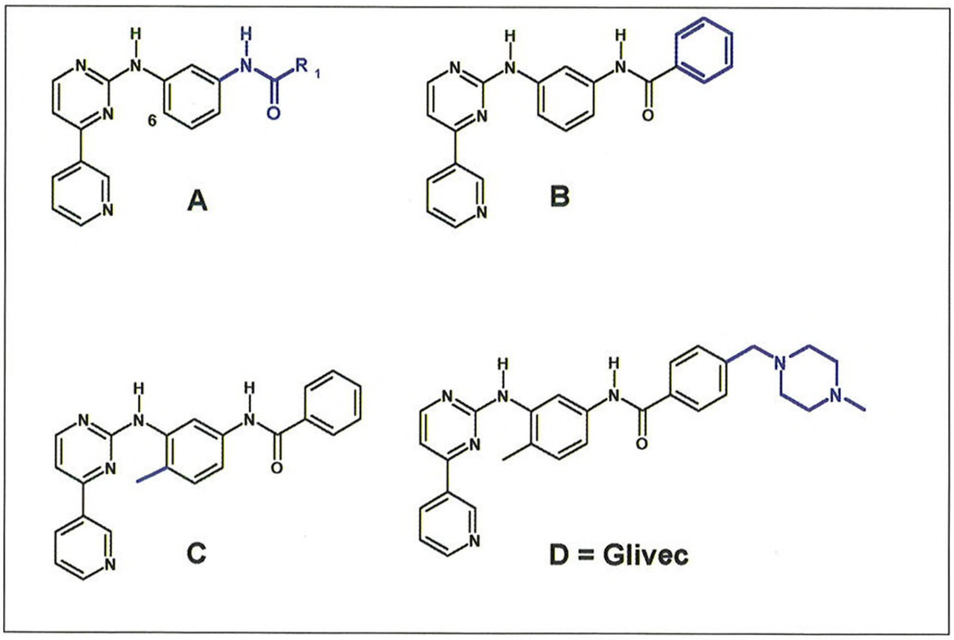


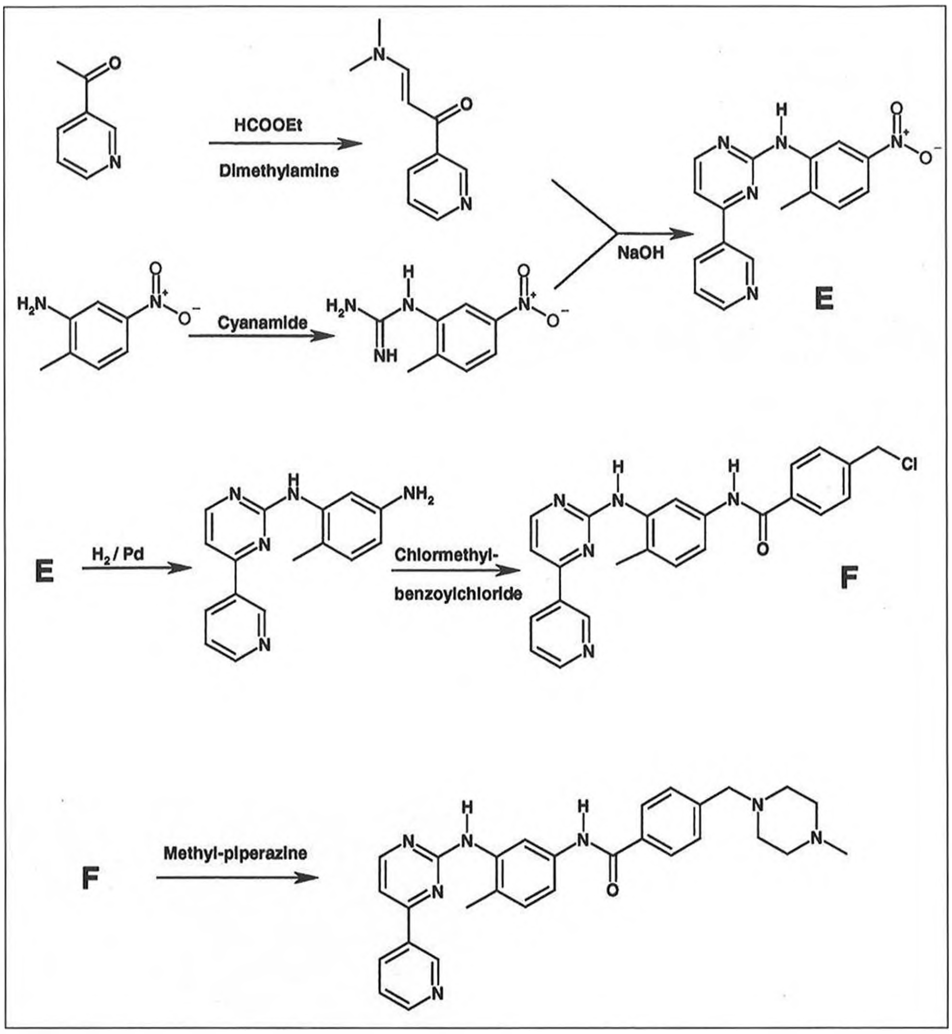
Fig. 5. Chemical formulaes of the compounds mentioned in the text

6 of the diamino phenyl ring were not tolerated for PKC inhibition (Fig. 4). Indeed, the introduction of a simple 'flag-methyl' led to loss of activity against PKC, while the activity against Bcr-Abl could be retained or even enhanced (**C**, Fig. 5). Unfortunately, the first series of selective inhibitors originally prepared showed poor oral bioavailability and low solubility in water. This drawback was eventually circumvented by the introduction of a solubilizing side chain in a region of the molecule that does not interfere with the binding capability to the targeted enzyme. The attachment of basic groups at the 4-position did not significantly alter the potency but dramatically improved aqueous solubility. Again the 'aniline-alert' (mutagenic potential) had to be avoided; this was done in this case by the introduction of a spacer between the phenyl ring and the nitrogen atom. The best compound from this series was the methyl-piperazino derivative **D** [7] which was selected as the most promising candidate for clinical development. The synthesis starts from the acetyl-pyridine, which is converted to an enaminone. The condensation with a guanidine, prepared from the corresponding aniline with cyanamide, yields the phenylamino pyrimidine in high yield. Catalytic reduction of the nitro group, acylation, and benzylic substitution with N-methyl piperazine eventually gives the active ingredient of Glivec (Scheme).

X-ray crystallography [8] showed that binding of a derivative of Glivec occurs at the ATP binding site by binding with high specificity to an inactive form of the kinase. The need for the kinase to adopt this unusual conformation favoring binding may contribute to the high selectivity of the compound.

## 3. Pharmacological Profile and Clinical Development

The compound inhibits the v-Abl kinase with an IC50 of 38 nM but is inactive against serine/threonine kinases. The compound does not inhibit the kinase activity of the receptor for the epidermal growth factor (EGF)-receptor, the vascular endothel growth factor (VEGF-R1 and VEGF-R2) and the fibroblast growth factor (FGF-R1). Tie-2 (Tek), c-Met and the kinase activity of the Src-family (c-Scr, c-Fgr., c-Lyn, Lck) are all also not inhibited. At the cellular level an inhibition of the PDGF-R-K (platelet derived growth factor receptor coupled kinase) and c-kit, the receptor coupled kinase for the stem cell factor (SCF) are inhibited. Glivec showed a strong antiproliverative



Scheme. Synthesis of the active ingredient of Glivec

effect on cell lines which express Bcr-Abl. A selective inhibition on the CML-colony formation was shown in *ex vivo* samples derived from patients. A validation of the antiproliverative effect was also done *in vivo*, a once-daily i.p. dose of 2.5 and 50 mg/kg showed a dose-dependent inhibition of the growth of the bcr-abl transformed cells on syngenic mice. Pharmacokinetic studies showed a rapid uptake upon p.o. administration to give a pharmacologically relevant blood level in the plasma [9]. These data prompted us to start an evaluation of the drug in CML patients. The first trial with Glivec was a phase I study in patients with chronic phase and subsequently also with blast phase CML. The dose given was 25 to 1000 mg, no maximal tolerated dose was identified. At a dose of 300 mg and higher, 98% of patients showed a hematological response with moderate side effects. In later trials in newly diagnosed patients in early chronic phase, data show that use of Glivec can result in high cytogenetic response rates. Complete cytogenetic response, the elimination of the cells that characterise CML, is regarded as the ultimate goal of CML treatment. The rates reported are significally higher than those historically documented with other CML therapies in the same disease setting. Taken together, all these findings have established Glivec as a safe and effective therapy in all stages of CML and have been the basis for the marketing approval by the FDA on May 10, 2001, *i.e.* less than three years after the start of the first phase I. On March 2002 the FDA approved Glivec also for the treatment of patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GISTs).

In summary, Glivec has shown that a rationally designed, molecularly targeted therapy based on the specific abnormality present in human malignancy can be a very efficient therapy. It represents a new paradigm in cancer drug development and will hopefully be followed by a new generation of specific, targeted therapies in oncology.

***Acknowledgment:***

Dr. Alex Matter and Dr. Nick Lydon are acknowledged as the originators of this research program. Dr. Elisabeth Buchdunger was responsible for the cellular characterization of this compound. Dr. Brian Druker is acknowledged for his preclinical and clinical work and his enthusiasm. The work of many more colleagues at Novartis is also gratefully acknowledged.

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# CONFERENCE REPORT

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# 37th ESF/EUCHEM Conference on Stereochemistry

## Bürgenstock (Switzerland), April 13 to 19, 2002

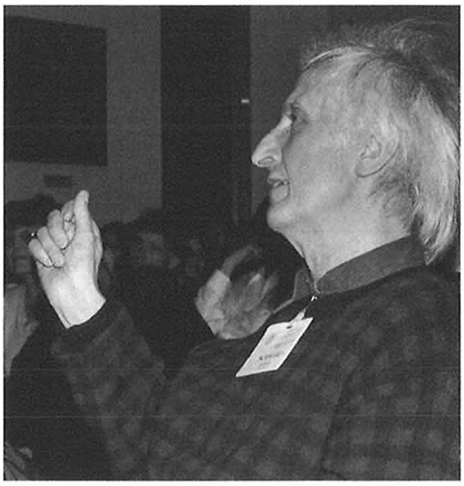
Kay Severin* and Kai Johnsson

**Keywords:** Bürgenstock · EUCHEM · Interdisciplinary Chemistry & Biology · Stereochemistry

In the middle of April, 141 chemists from 23 different countries had gathered at the Bürgenstock to attend the legendary ESF/EUCHEM Conference on Stereochemistry. Apart from the slightly larger number of participants, the organizers of the 37th Bürgenstock conference followed tradition: only a few high-class speakers were invited, the names of whom were kept secret up until the first day. Given that many other conferences can only survive with the help of heavy public relations in combination with prominent plenary speakers, it may be surprising that this concept works. But it certainly does! This year's president ***Lia Addadi*** (Weizman Institute of Science, Israel) together with the local organizing committee *Hans-Beat Bürgi* (University of Bern), *François Diederich* (ETH Zürich), *E. Peter Kündig* (University of Geneva) and *Klaus Müller* (Hoffman-La Roche, Basel) succeeded in attracting 14 excellent speakers. Fortunately, due to financial support from the *European Science Foundation*, the *Swiss National Science Foundation* and industry, they were also able to invite 23 promising young scientists who were allowed to present their work in the poster sessions.

Lia Addadi (President)

Jan E. Bäckvall (Vice President)



Helmut Schwarz (Guest of Honor)

The first day of the conference focused on ordered assemblies in biological systems. The talk by ***Dorit Hanein*** (Burnham Institute, USA) gave an introduction into actin-based motility in biology and the characterization of these processes by electron cryomicroscopy (Fig. 1). Motile cells are important in a variety of different biological processes, ranging from embryonic development, immune response, wound healing and nerve cells to less desired processes such as metastasis and bacterial infections. Molecular electron cryomicroscopy is a powerful technique as its resolution allows it to bridge light microscopy and crystallography. In addition, the rapid cooling necessary for the preparation of the samples allows snapshots to be taken of a

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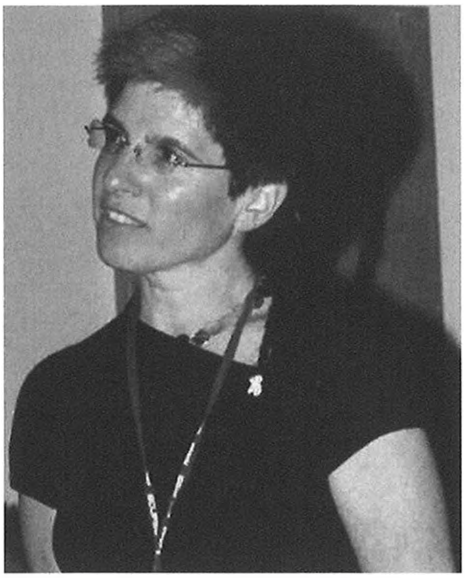
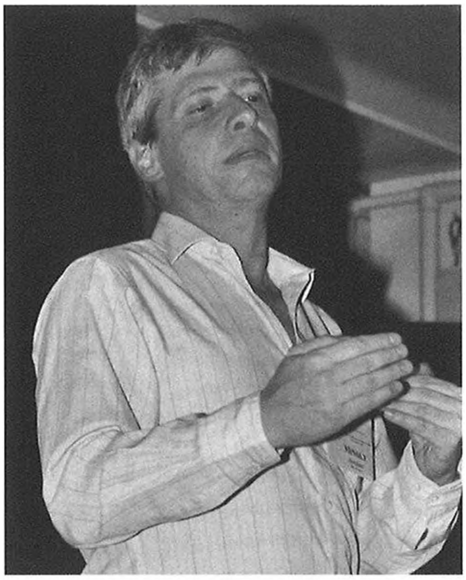
macromolecular assembly, a crucial point when dynamic processes are to be evaluated. One of the processes of actin-based motility investigated in detail by the group of Hanein using electron cryomicroscopy was protrusion by actin polymerization as observed in the budding of yeast. Here, their pioneering studies showed how the protein complex Arp2/Arp3 choreographs the formation of branched actin networks in a highly specific manner [1].

This presentation was followed by a fascinating talk by ***Avi Minski*** (Weizmann Institute, Israel) on the interplay of stress and order in living systems. Two different modes of orders can be observed in living systems: dynamic order and equilibrium order. Dynamic order may be present in systems that exist far from thermodynamic equilibrium by consuming energy. It is a characteristic property of all living systems. Under conditions of stress, however, living systems can induce a transfer from a dynamic order into an equilibrium order. One example that shows such a transition is the formation of crystalline DNA in starved bacteria (Fig. 2), a process in which the *DNA-binding protein under stress* (DPS) has been shown to play an important role. The crystalline DNA phase, which can be easily detected by electron microscopy, protects the DNA against damage [2].



Dorit Hanein



Avi Minsky

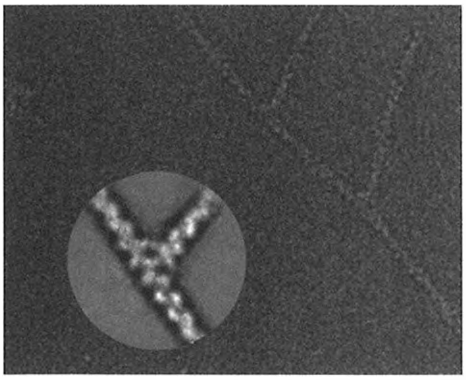


Fig. 1. Two-dimensional reconstruction of a branch junction using electron cryomicroscopy. Branch junctions are the building blocks of the machinery that pushes the cell forward. The reconstruction was obtained by first imaging single branch junctions (two of them shown in the background) that were then aligned and averaged (foreground). The leading edge of the cell is facing towards the top of the figure (the picture was kindly provided by D. Hanein).

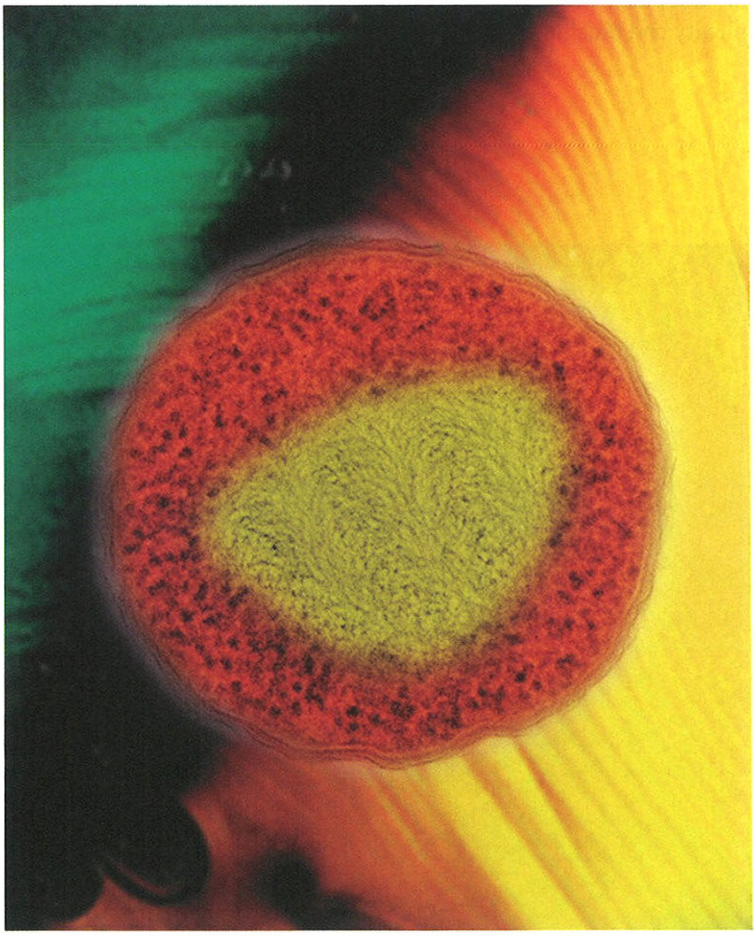
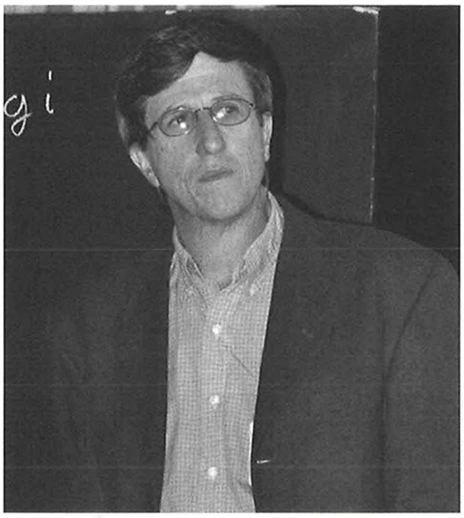


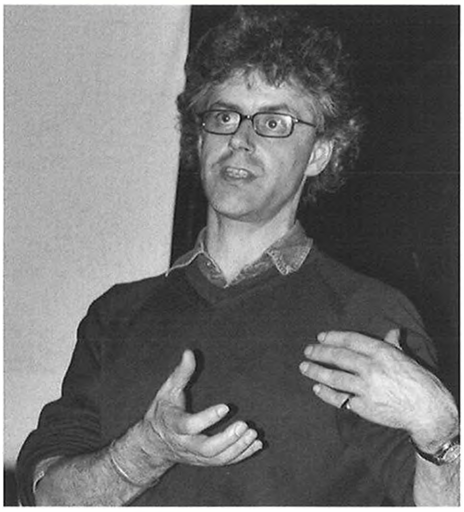
Fig. 2. Electron micrograph of a partially ordered liquid crystalline DNA structure formed in the center of a starved *Escherichia coli* cell in which DPS has been knocked out. The background is a polarized light micrograph of a liquid crystalline phase of purified bacterial DNA (the picture was kindly provided by A. Minski).

The first poster session on Sunday afternoon was opened after four short oral presentations by *Rainer Haag* (University of Freiburg, Germany, 'pH-Responsive Molecular Nanocapsules for Drug Delivery'), *Florian Hollfelder* (University of Cambridge, UK, 'Microcin B17 Synthetase – Mechanism of Formation of a Peptide Antibiotic and Characterization of Microcin Action'), *Michael Keller* (Imperial College London, UK, 'The Collapse of the Titan: The Mixer Decides it All') and *Thomas R. Ward* (University of Neuchâtel, 'Second-Sphere Coordination: Proteins as Host for Enantioselective Catalysis').

In the evening session, an introduction into the topic of biomineralization was given by ***Steve Weiner*** (Weizmann Institute, Israel) and ***Jeremy Young*** (Natural History Museum, UK). The morphological complexity that can result from the anisotropic mineral nucleation and growth through biological control was highlighted by Jeremy Young in discussing the biomineralizations of *Coccolithophorids*, unicellular marine plant plankton with a calcareous skeleton that form a major component of the oceanic microplankton in past and present oceans (Fig. 3). In these organisms, mineral and polymorph control, shape control, stabilization of normally unstable phases, the orientation of crystallographic axes as well as the size of the objects leads to the construction of structures, which are both of high complexity and breathtaking beauty [3].



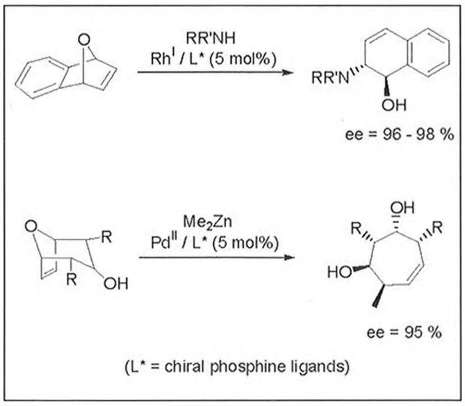
Steve Weiner



Jeremy R. Young

On Monday morning, two lectures were devoted to new methodologies in organic synthesis with the focus on selective transition metal catalyzed transformations. This year's Vice President *Jan E. Bäckvall* first introduced ***Mark Lautens*** (University of Toronto, Canada) who described the efforts of his group to develop stereoselective ring-opening reactions for oxabicyclic compounds. Using Pd(II) and Rh(I) complexes in combination with chiral phosphine ligands they were able to obtain carbocyclic products with high enantioselectivity (Scheme 1). Products of this kind represent interesting chiral ligands for transition metal catalysts and useful building blocks for natural product synthesis (*e.g.* Callystatin A) [4].

Mark Lautens



Scheme 1. Enantioselective ring-opening reaction of oxabicyclic compounds to give versatile building blocks for organic synthesis.

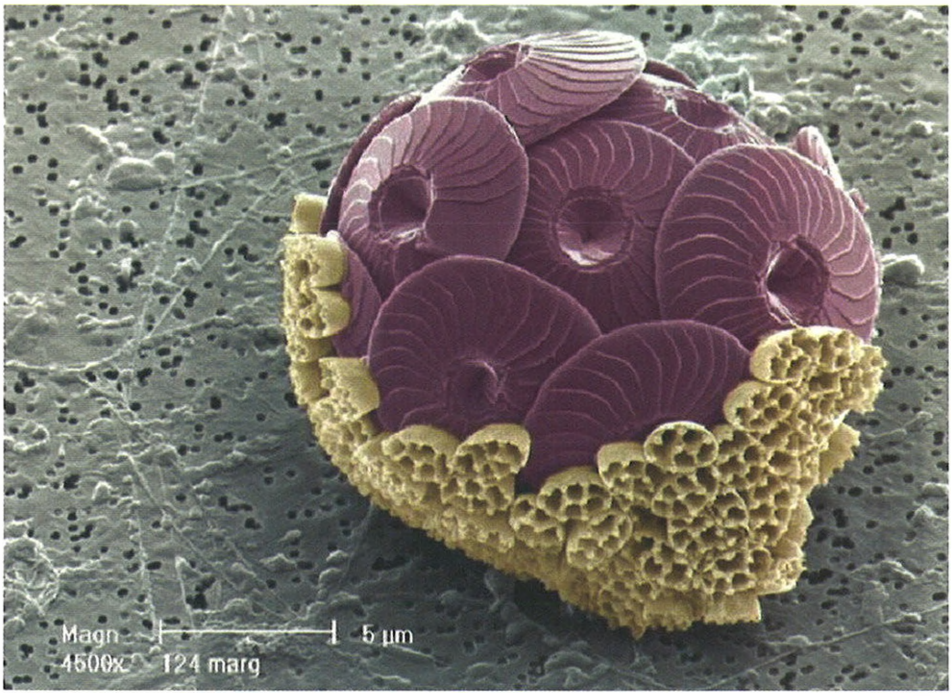


Fig. 3. Coccospheres of *Calcidiscus leptoporus*, which belongs to the familiy of *Coccolithophorids* (the image was obtained by electron microscopy and kindly provided by J.R. Young).

The tremendous impact of modern olefin metathesis catalysts is evidenced by the vast number of papers which have appeared over the last years. It is therefore not surprising that two of the overall fourteen lectures were entirely devoted to this topic. ***Siegfried Blechert*** (TU Berlin, Germany) showed that the ruthenium based catalysts **1**–**3** as well as the permanently immobilized catalyst **4** are highly active for ring-closing, ring-opening, ring-rearrangement, and cross-metathesis reactions (Fig. 4). It was pointed out that the optimal catalyst depends on the actual synthetic problem. Although the chiral complex **3** gave no induction in asymmetric ring-closing metathesis, its stability and activity in ring-closing metathesis reactions proved to be superior to that of **1** and **2** [5].

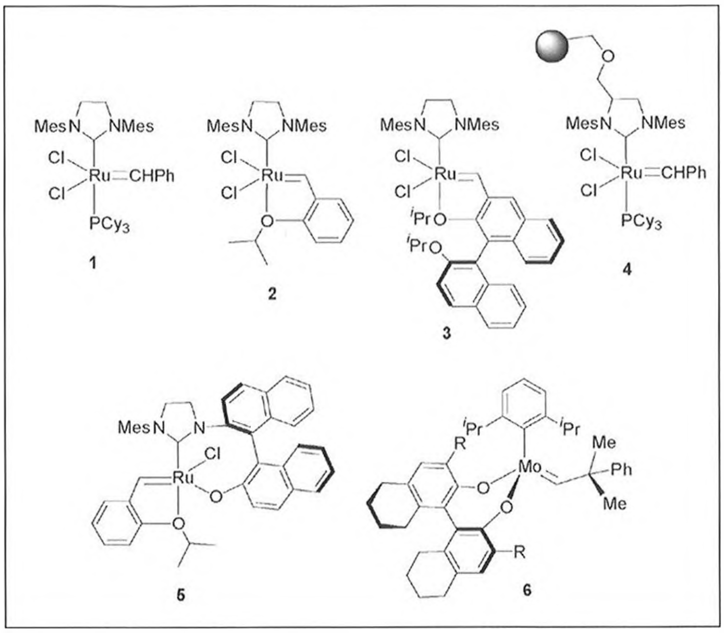
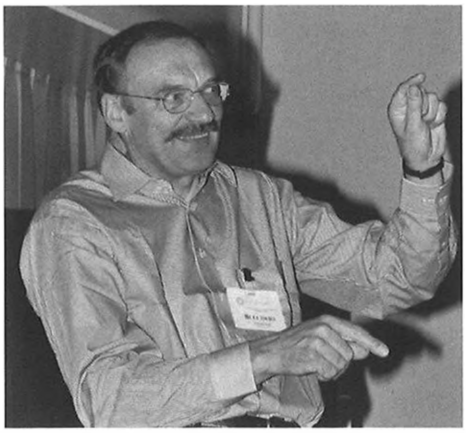


Fig. 4. Achiral and chiral catalysts for olefin-metathesis.



Siegfried Blechert

Takuzo Aida

Poster session

As the day before, the poster session in the afternoon turned out to be very stimulating with long discussions on a broad range of topics. Four selected posters were summarized in short oral presentations by *Karol Grela* (Polish Academy of Sciences, Poland, 'New Applications of Ruthenium-Based Metathesis Catalysts Bearing N-Heterocyclic Carbene Ligands'), *Marcel Mayor* (Forschungszentrum Karlsruhe, Germany, 'Electric Current through Single Molecules'), *Stefan Pitsch* (EPFL, 'Total Synthesis of Aminoacylated t-RNAs') and *Mark S. Searle* (University of Nottingham, UK, 'Peptide Models of Protein β-Sheets: Insight into Stabilising Weak Interactions and Protein Folding').

The evening lecture was given by ***Takuzo Aida*** (University of Tokyo, Japan) who presented highly original results in the field of supramolecular chemistry (Fig. 5). The topics discussed ranged from the generation of polyethylene nanofibers within mesoporous silica *via* CdSe nanoclusters stabilized by tubular proteins to dendritic multiporphyrin arrays and synthetic receptors for fullerenes [6].

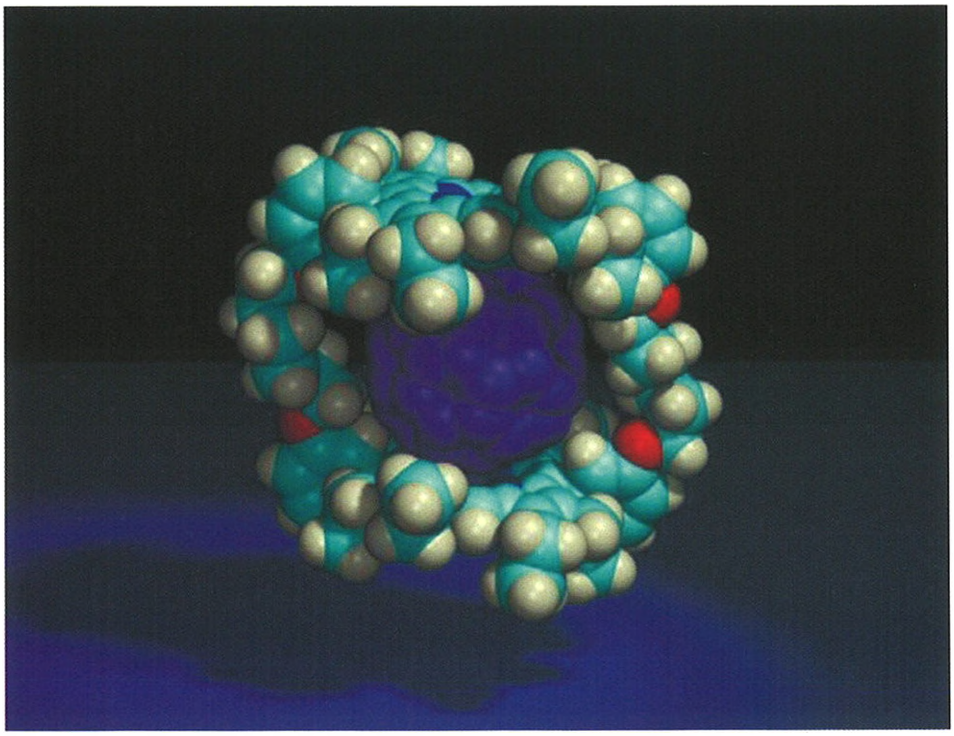


Fig. 5. Graphic representation of a supra-molecular inclusion complex of $C_{60}$ within a zinc porphyrin cyclic dimer, based on crystallographic data (the image was kindly provided by T. Aida).

The Tuesday morning session began with a talk from ***David Tirrell*** (Caltech, USA) on the genetically directed synthesis of novel macromolecules. In particular, he demonstrated how the incorporation of unnatural amino acids (Fig. 6) with unique chemical properties can be used to generate proteins with novel properties. One such example is the replacement of leucine side chains with hexafluoroleucine side chains to obtain coiled-coil proteins which are significantly more stable than their natural counterparts. Another example presented was the site-specific incorporation of *p*-acetylphenylalanine into a recombinant protein in *Escherichia coli* by employing a rationally designed mutant form of the phenylalanyl-tRNA synthetase of the host. The recombinant protein carrying the ketone functionality can be chemoselectively ligated with hydrazide reagents or other reagents possessing selectivity for this functional group [7].

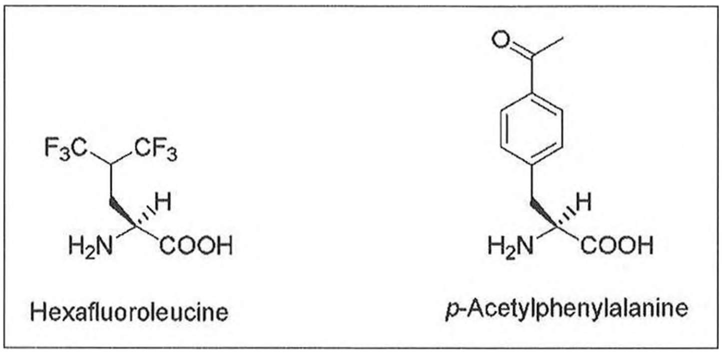


Fig. 6. Unnatural amino acids incorporated *in vivo* intro proteins.

David A. Tirrell

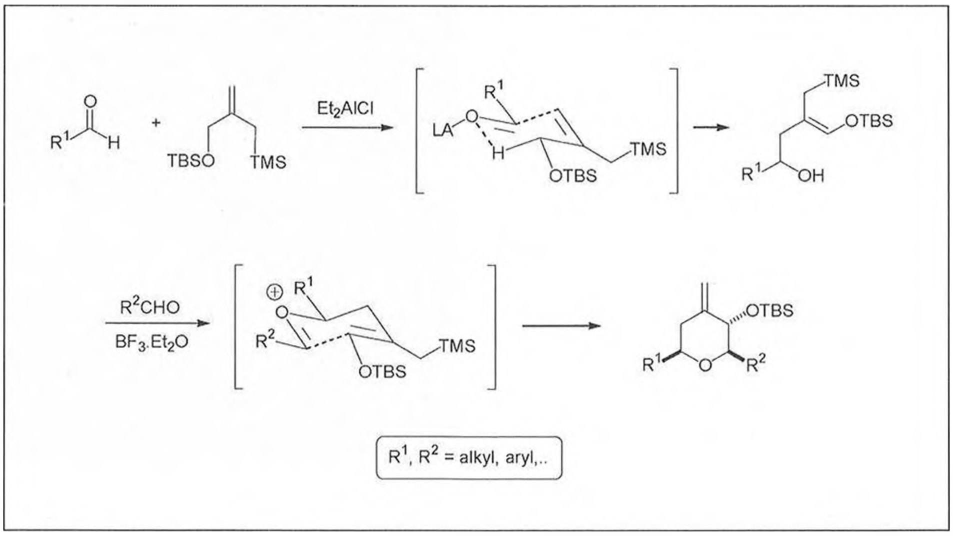
In the subsequent lecture by ***Thomas V. O'Halloran*** (Northwestern University, USA), recent findings about the cellular inorganic chemistry of Cu(II) and Zn(II) were described. His group has determined the concentration of 'free' copper and zinc ions in the cell which was found to be less than one ion per cell although the overall concentration of these metals can be as high as $10^5$ ions per cell ($Zn^{2+}$). This points to the fact that intracellular traffic of these metal ions is precisely controlled by a variety of metalloregulatory proteins [8].

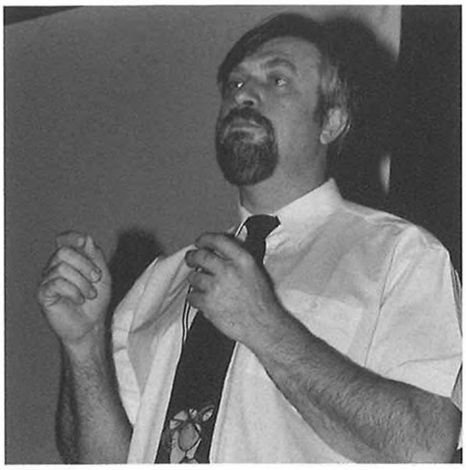
Thomas V. O'Halloran

By tradition, Tuesday evening was devoted to chamber music. The well-known Aura String Quartet from Basel (Antonio Núñez, Roger Pyne, Christian Vaucher, Conrad Wyss), together with the guitarist Walter Feybli, delighted the audience with music from Boccherini, Dvorak, and Castelnuovo-Tedesco. A joyful reception followed the concert.

On Wednesday, the talk of ***Istvan Markó*** (Université Catholique de Louvain, Belgium) focused on the development of new methodologies for total synthesis. A particularly elegant approach that has been developed by his group is the use of an ene reaction followed by an intramolecular silyl-modified Sakurai reaction for the efficient assembly of various target molecules (Scheme 2). Applications of this and related approaches in total synthesis were discussed, including their work on the syntheses of pseudomonic acid, ambrucitin and amphinitol [9].

Scheme 2. Application of an ene reaction followed by an intramolecular silyl-modified Sakurai reaction for the elegant and efficient assembly of carbon scaffolds.





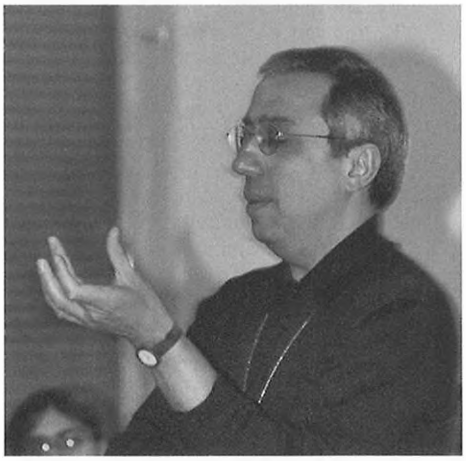
Istvan Markó

In the following session, ***Dieter Enders*** (RWTH Aachen, Germany) gave an overview of his endeavors in asymmetric organic synthesis, spanning an enormous variety of different approaches and target molecules. His talk covered work by his group on α-silyl ketone controlled asymmetric synthesis and its application in the Mannich synthesis, his work on the total synthesis of callystatin A, $TiCl_4$-mediated asymmetric aldol reactions, the iterative synthesis of protected anti-1,3-polyols, asymmetric nucleophilic acylations, the use of stable carbenes in asymmetric catalysis of a benzoin condensation, iron-mediated chirality transfer, asymmetric synthesis of ferrocenyl ligands with planar and central chirality as well as the asymmetric epoxidation of enones using oxygen [10].

Dieter Enders

The final poster session was held on Wednesday afternoon. The decision of the organizing committee to have three sessions with only 16 posters each proved to be of advantage since there was enough time for scientific exchange. Four oral 'appetizers' were presented by *Mercedes Crego-Calama* (University of Twente, The Netherlands, 'Noncovalent Synthesis of Chiral Hydrogen-Bonded Assemblies'), *Frank-Gerrit Klärner* (University of Essen, Germany, 'Molecular tweezers and Clips as Synthetic Receptors; Molecular Recognition and Dynamics in Receptor-Substrate Complexes'), *Kay Severin* (EPFL, 'Self-Assembled Organometallic Receptors for Small Ions') and *Nico A.J.M. Sommerdijk* (Eindhoven University of Technology, The Netherlands, 'Efficient Nucleation and Precise Control over Calcium Carbonate Growth using Poly(isocyanide) Based Templates').

One of most significant recent advances in olefin metathesis is the development of chiral catalysts for asymmetric reactions. In the evening lecture, ***Amir H. Hoveyda*** (Boston College, USA) summarized the contributions of his group in this area. A new ruthenium catalyst (**5**) (Fig. 4) was described that is able to efficiently promote asymmetric ring-opening/cross metathesis reactions. The catalyst is stable enough to allow the reactions to be carried out in undistilled solvents without an inert gas atmosphere. Mo-based catalysts such as **6** (Fig. 4), on the other hand, display an enhanced activity but are more sensitive and may lead to unwanted side reactions such as polymerization of the substrate [11].



Amir H. Hoveyda

The science and technology of 'smart materials' has just started to emerge and tremendous advances can be expected for the future. With this statement, ***Samuel I. Stupp*** (Northwestern University, USA) opened his lecture on Thursday morning about new materials by self-assembly and templating. Using short triblock copolymers consisting of stiff rod-like segments and flexible coil-like segments, Stupp's group was able to obtain nanostructures with defined size and shape. These self-assembled materials show unique physical properties. Towards the fabrication of materials that resemble bone, nanostructured fibrous scaffolds were generated using peptide-amphiphiles as the building block. Fibers of this kind can be stabilized by chemical cross-linking und act as a template for the mineralization of hydroxyapatite [12].

Samuel I. Strupp

Amphiphilic block copolymers are also key components in the research projects of ***Galen D. Stucky*** (University of California, Santa Barbara, USA). In the second lecture about material science on Thursday morning, he explained how these polymers can be used as structure-directing agents to obtain mesoporous silica with pore sizes of up to 300 Å. This technique can also be applied to other metal oxides such as $TiO_2$, $Al_2O_3$, $Ta_2O_5$ and $SiTiO_4$. Currently, his group is investigating potential applications such as optical sensing [13].

Galen D. Stucky

The final lecture on Thursday evening was given by ***Ruth Duncan*** (Cardiff University, UK). She described the advantages but also the problems of polymer-drug conjugates. The attachment of anti-tumor ac-

Ruth Duncan and Helmut Ringsdorf

tive compounds to water-soluble polymers or dendrimers can result in more selective targeting of tumor cells. Of crucial importance, however, is the nature and the stability of the drug-polymer linkage and the biocompatibility of the polymer. Several polymeric drugs conjugates are presently in clinical trials and – as she pointed out – many more are expected for the future [14].

The last day with its topics spanning from self-assembly in material science to the use of polymers in medicinal chemistry is typical for the broad range of fields discussed at Bürgenstock conferences. This mixture of cutting-edge science covering all aspects of chemistry is certainly one of the main attractions of these unique meetings. The choice of the highly distinguished Swedish chemist *Jan E. Bäckvall* as next years president (April 26 to May 2, 2003) secures that this tradition will continue.

Received: June 4, 2002

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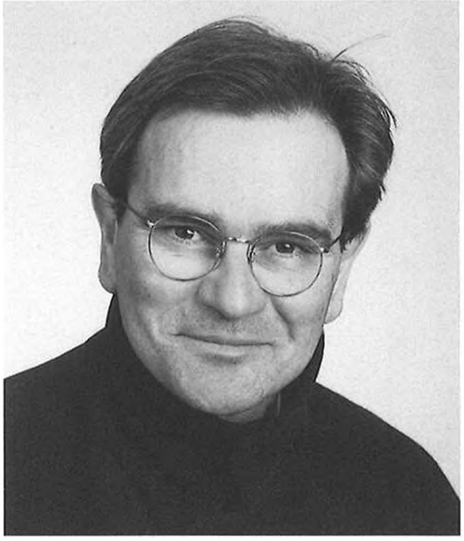
# Prof. Wolf Woggon zum 60. Geburtstag



Wolf Woggon

*In einer kleinen Pfanne bei Mittelhitze 15 g Butter zergehen lassen, die gehackten Zwiebeln hineingeben und 5 Minuten garen, bis sie glasig, aber noch nicht braun sind. Das Brot wird zerbröckelt und mit Sahne, Zwiebeln, Hackfleisch, Anschovisfilet, Petersilie, Eier, Zitronenschale, Salz und schwarzem Pfeffer gut vermischt. Anschliessend durch den feinsten Einsatz eines Fleischwolfes geben. Man feuchtet die Hände leicht mit kaltem Wasser an und formt aus dem Teig acht grosse Kugeln von ungefähr 5 cm Durchmesser...'*

So beginnt das von Wolf Woggon verfeinerte Rezept seines Lieblingsgerichtes: Königsberger Klopse. Nicht in der alten preussischen Krönungsstadt sondern in Berlin wurde Wolf Woggon vor 60 Jahren geboren und er blieb dort, nach einem Ausflug in die Geologie, bis zum Chemie-Diplom an der Freien Universität. Danach wechselte er von der Spree an die Limmat und fertigte bei Hans Schmid seine Doktorarbeit zur Biosynthese von Cantharadin (Fig. 1) an. Vielleicht war es seine Lust, im Experiment intellektuelle und sinnliche Qualitäten zu vereinigen, die Wolf Woggon auch weiterhin an diesem Thema faszinierte. So klärte er, nach seiner Postdoktorandenzeit bei Allan Battersby, die Chemie und Biologie des Cantharidins – neben der anderer Arthropoden-Inhaltstoffe – in seiner Habilitationsarbeit an der Universität Zürich auf. Cantharidin ist ein Lockstoff des Käfers *Lytta vesicatoria*, den er in Sizilien habhaft machte. Die entscheidenden biologischen Studien wurden aber in der Schweiz durchgeführt, weil sich Zürich als ein besseres Pflaster für kopulierende Käfer herausstellte als Palermo.

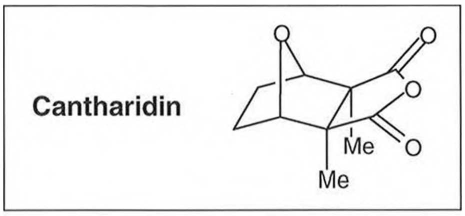


Fig. 1

Dem Gebiet der bioorganischen Chemie blieb Wolf Woggon auch nach seiner Berufung an die Universität Basel treu. Bahnbrechende Arbeiten wurden zur Chemie der Enzyme Cytochrom P450, der Tocopherol Cyclase, der β,β-Carotendioxygenase sowie den Chloroperoxidasen angestellt. So ist im Arbeitskreis von Wolf Woggon das erste P450 Enzymmodell synthetisiert worden, das $O_2$ spaltet und nicht-

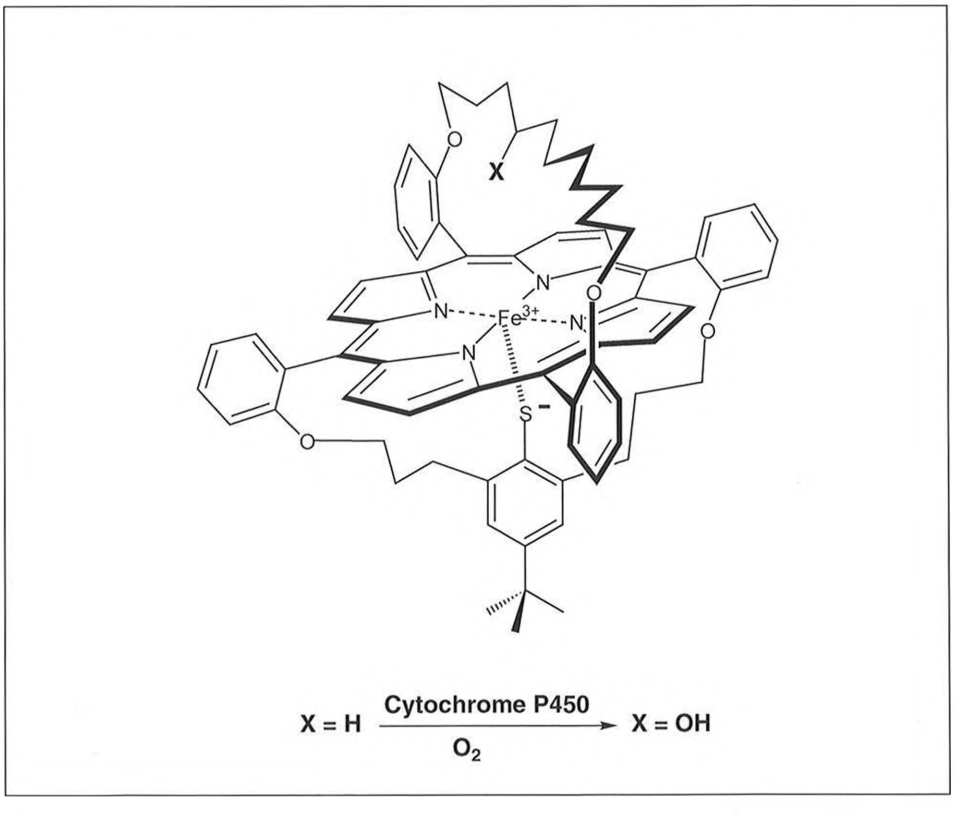


Fig. 2

aktivierte C,H-Bindungen intramolekular hydroxyliert (Fig. 2).

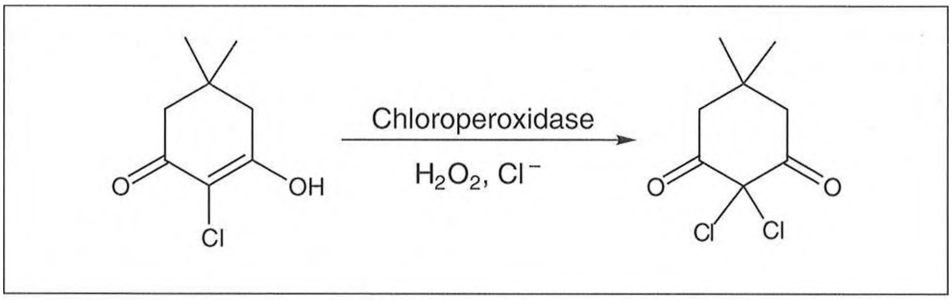
Weitergehende Studien belegten den wichtigen Einfluss des Thiolat-Liganden auf das Redoxpotential des Eisenkomplexes. Auch die strukturverwandten Chloroperoxidasen, die anstelle einer OH-Gruppe ein Cl-Atom in das organische Substratmolekül einführen (Scheme 1), wurden in der Woggon-Gruppe intensiv untersucht.

Weitere Highlights aus der Woggon-Gruppe sind die Identifizierung, Reinigung und Aufklärung des Reaktionsmechanismus der Tocopherol Cyclase (Scheme 2) sowie der kürzlich erfolgte Nachweis, dass eine 'Dioxygenase' für β-Carotin in Wahrheit eine Monoxygenase ist.

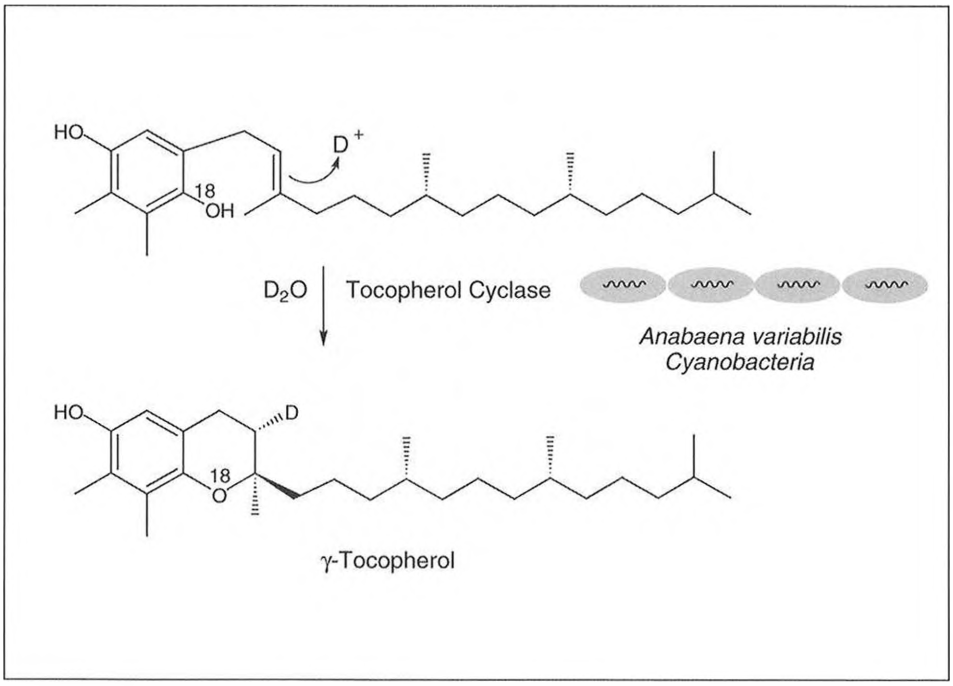
Neben der Forschung gilt Wolfs Zuneigung ganz besonders schnellen Italienerinnen (Lancia), der modernen Kunst (bemerkenswert sind seine Photographien) und dem Kochen (s.o.). Eines fehlt noch an dem Bild: 'No sports'.

Lieber Wolf, im Namen aller Kollegen gratulieren wir sehr herzlich und wünschen Dir weiterhin viel Erfolg und Spass innerhalb und ausserhalb der Chemie.

*Bernd Giese und Andreas Pfaltz*



Scheme 1



Scheme 2

FH – HES Fachhochschulen – Hautes Ecoles Spécialisées

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# «Labormanagement»: Ein Konzept für einen neuen, interdisziplinären Lehrgang an der HTA Burgdorf

Iris Smid* und Ruth Weber

## Laboratory Management: A Concept for a New Interdisciplinary Course of Studies at the Burgdorf School of Engineering and Architecture

*Abstract:* This article presents the concept of a new study course in laboratory science and management. Target groups are the female-dominated professions of laboratory technician, pharmaceutical assistant and druggist. The interdisciplinary and modular course is designed to be particularly attractive for these mainly female target groups.

**Keywords:** Interdisciplinary course of studies · Laboratory management · Laboratory science · University of Applied Sciences

Statistiken zeigen, dass Frauen an schweizerischen Fachhochschulen im Technik- und Ingenieurbereich deutlich untervertreten sind. Dies liegt zu einem wesentlichen Teil daran, dass die technischen Fachhochschulen zu einseitig auf Männer als Zielpublikum ausgerichtet sind. Zu der sich daraus ergebenden Chancenungleichheit kommt hinzu, dass es für manche frauendominierte Berufsgruppen überhaupt keine geeigneten weiterführenden Ausbildungsmöglichkeiten weder an technischen noch an nicht-technischen Fachhochschulen gibt. Zu diesen Berufsgruppen zählen insbesondere medizinische Laborant/innen, Drogist/innen und Pharmassistent/innen. Für diese ist deshalb der Anreiz sehr klein, überhaupt die für ein Fachhochschulstudium notwendige Berufsmaturität zu erwerben. Die Chancenungleichheit zwischen Frauen und Männern wird dadurch weiter verstärkt.

Die Folge ist, dass sowohl die Anzahl der Berufsabschlüsse im Laborbereich als auch die Anzahl neuer Studienanwärter/innen für eine Laborberufsausbildung stetig abnimmt. Potenziell technik- und naturwissenschafteninteressierte Schulabgänger/innen kehren diesen 'Sackgassenberufen' zunehmend den Rücken.

Sofortiges Handeln ist vonnöten: Im Rahmen des Förderungsprogrammes 'Chancengleichheit von Frauen und Männern an den Fachhochschulen' vom Bundesamt für Berufsbildung und Technologie (BBT) wurde deshalb an der Hochschule für Technik und Architektur (HTA) Burgdorf, einer Teilschule der Berner Fachhochschule, ein Konzept zur Einrichtung eines neuen interdisziplinären Lehrganges in Labormanagement ausgearbeitet. Zielgruppen sind biologische, chemische und medizinische Laborant/innen, sowie Drogist/innen und Pharmassistent/innen.

Mit diesem Konzept wird das Ziel verfolgt, ausgesprochen frauendominierten Berufsgruppen erstmals in der Schweiz einen attraktiven interdisziplinären Lehrgang an einer technischen Fachhochschule anzubieten, mehr weibliche Berufspersonen für eine Berufsmaturität zu motivieren, die Anzahl weiblicher Studierender an den technischen Fachhochschulen zu steigern und mehr Studierende für einen Berufsbereich (Laborbereich) zu gewinnen, der dringend qualifizierte Fachleute benötigt.

## Berufsprofil der Absolventinnen und Absolventen des Lehrganges

Labormanagerinnen und -manager sind als Fachpersonen in leitender Stellung primär in den Gebieten Gesundheit, Ernährung und Umwelt tätig. Mit ihren fachspezifischen Kompetenzen in den Bereichen Technik, Informatik, Qualitätssicherung, Betriebswirtschaft und Personalmanagement sind sie befähigt, Spitzenqualität im Betrieb eines Labors zu gewährleisten und deren Kontinuität zu sichern.

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Labormanagerinnen und -manager

- 'beherrschen' sowohl das Instrumentarium als auch die Methoden der chemischen, biologischen und medizinischen Analytik
- kontrollieren und sichern die Laborqualität
- verstehen Informatikkonzepte und sind mit Spezialsoftware zur Erfassung und Auswertung von Messdaten, zum Recherchieren von Informationen in Datenbanken und zur Verwaltung von Daten vertraut
- kommunizieren problemlos mit Spezialisten aus der Labortechnik- und Informatikbranche
- können professionell dokumentieren
- evaluieren und beschaffen Geräte und Laboreinrichtungen
- können Projekte planen und durchführen sowie die Ergebnisse kundengerecht präsentieren
- verfügen über professionelle Kenntnisse im Führen und Coachen des Laborpersonals und denken betriebswirtschaftlich.

Ihre wichtigsten Einsatzbereiche sind medizinische und nicht-medizinische Privatlabors, Laboratorien von Spitälern, Pharmaunternehmen und der Lebensmittelbranche, Umweltlabors und kantonale Laboratorien.

## Studienkonzept und Leitideen

Der Lehrgang Labormanagement ist vom Konzept her modular aufgebaut und interdisziplinär. Technisch-naturwissenschaftliche und wirtschaftswissenschaftliche Module werden mit einer Ausbildung in Führungs- und Management-Kompetenzen kombiniert, um der Neigung von Frauen zu personenorientierten Tätigkeiten entgegenzukommen.

Das Studium umfasst drei Studienjahre (Fig.) mit anschliessender zehnwöchiger Diplomarbeit. Die technisch-naturwissenschaftlichen Inhalte umfassen etwa 80% der Grundausbildung (1. Studienjahr), 60% der Fachausbildung (2. Studienjahr) und noch etwa 50% der Vertiefung (3. Studienjahr).

Es ist vorgesehen, im ersten und zweiten Studienjahr vom Angebot des Studienganges Chemie zu profitieren. Um Unterschiede in der Vorbildung der Studierenden auszugleichen, sollen Stützkurse angeboten werden. Ausbildungsschwerpunkte des Lehrganges sind: Laboranalytik, Laborinformatik, Laborqualität, Führen und Coachen sowie Betriebswirtschaftliches Denken, wobei die Module in Laboranalytik, Laborinformatik und Laborqualität disziplinär, die Module im Bereich Führen und Coachen sowie Betriebswirtschaftliches Denken disziplinenübergreifend ausgerichtet sind.

Leitideen des Lehrganges sind

- eine ganzheitliche Ausbildung anzubieten (*ca.* ein Drittel des Studiums umfasst sprachliche, wirtschaftliche und persönlichkeitsbildende/sozialwissenschaftliche Inhalte)
- die Lerninhalte modular zu strukturieren und mögliche Synergien mit anderen Abteilungen bzw. Ausbildungsstätten zu nutzen
- die Laboranalytik- und Laborinformatikveranstaltungen didaktisch und inhaltlich auf die spezifischen Voraussetzungen und Lernbedürfnisse der mehrheitlich weiblichen Studierenden auszurichten
- Fähigkeiten im Projektmanagement auszubilden und schon im Studium zu üben
- stark berufsfeldbezogene und marktnahe Lehrveranstaltungen anzubieten
- das Selbstvertrauen in bezug auf technische Kompetenz sowie die Sozialkompetenz (Kommunikations-, Team- und Konfliktfähigkeit) zu fördern
- auch schon während dem Studium den direkten Kontakt der Studierenden mit erfahrenen und engagierten Berufsfrauen im Laborbereich zu fördern.

| | | | | |
|---|---|---|---|---|
| 3. Jahr (V) | **Laboranalytik, Laborinformatik und Laborqualität**<br>Analysentechniken/Instrumentalanalytik (chemische Analytik, medizinische Spezialanalytik, Umweltanalytik, Nukleinsäureanalytik, PCR-Technologie) II<br>Informatik III (v.a. medizinische Informatik, Bioinformatik, Umweltdatenbanken)<br>Laborqualität II | **Führen und Coachen**<br>Mitarbeiterselektion<br>Mitarbeiterförderung u. –beurteilung<br>Konfliktmanagement<br>Stressbewältigung | **Betriebswirtschaftliches Denken**<br>Marketing II<br>Öffentlichkeitsarbeit | **Exkursionen**<br>Besuch von frauengeführten (Labor-) Betrieben |
| 2. Jahr (FA) | **Laboranalytik, Laborinformatik und Laborqualität** (z.T. gemeinsame Ausbildung mit Chemiker/innen)<br>Englisch II<br>Analysentechniken/Instrumentalanalytik (chemische Analytik, medizinische Spezialanalytik, Umweltanalytik, Nukleinsäureanalytik, PCR-Technologie) I<br>Informatik II (v.a. Informationssysteme)<br>Laborqualität I | Teambildung und -entwicklung<br>Projektmanagement | Marketing I<br>Kostenwesen | |
| 1. Jahr (GA) | (gemeinsame Ausbildung mit Chemiker/innen)<br>Kommunikation<br>Englisch I<br>Mathematik/Statistik<br>Chemie/Biochemie<br>Biologie/Mikro-/Molekularbiologie<br>Informatik I | Grundlagen der Kommunikationstechniken<br>Arbeitsorganisation (inkl. Zeitmanagement) | Einführung | |

Fig. Struktur des interdisziplinären Lehrganges Labormanagement. GA=Grundausbildung, FA=Fachausbildung, V=Vertiefung.

## Bedürfnisnachweis

Zur Abklärung des Bedarfs der Wirtschaft und des Gesundheitswesens an Absolventinnen und Absolventen des vorgeschlagenen Studienganges wurden je eine bis zwei Fachpersonen in leitender Stellung aus den Bereichen öffentliches Gesundheitswesen, private medizinische und nicht-medizinische Grosslabors, Umweltingenieurunternehmen und Industrie befragt. Das Konzept zur Einrichtung des Lehrganges wurde ohne Ausnahme sehr begrüsst und die Berufsaussichten von Labormanagerinnen und -manager auf dem Arbeitsmarkt als sehr gut beurteilt.

Eingegangen am 4. Juli 2002

# SCHWEIZERISCHE CHEMISCHE GESELLSCHAFT
# SOCIETE SUISSE DE CHIMIE
# SWISS CHEMICAL SOCIETY

www.swiss-chem-soc.ch

## DIC Division Industrielle Chemie

### Bericht zur Mitgliederversammlung 2002 mit Firmenbesuch vom 13.06.2002 bei den Firmen CIMO in Monthey und Orgamol in Evionnaz

Visp, 18.06.2002

Liebe Mitglieder der Division Industrielle Chemie

Zur Jahresversammlung 2002 der Division Industrielle Chemie trafen sich 42 Mitglieder bei der Firma CIMO in Monthey. Nach dem Empfang mit Kaffee und Gipfeli wurden wir durch Herrn M.G. Overney herzlich empfangen. Herr Overney gab uns einen kurzen Überblick auf den Standort Monthey und die dort vertretenen Firmengruppen.

Vorgängig der Mitgliederversammlung hatten wir erstmals die Gelegenheit zwei Fachvorträgen zu lauschen:

– Frau Claudia Nitschke, Projektleiterin Roche AG, Sisseln hielt einen Vortrag zum Thema **'Erfolgsfaktoren bei der Realisierung von Projekten'.** Die Referentin hat es sehr gut verstanden, auf wesentliche Grundprinzipien des Projektmanagement bei komplexen chemisch-technischen Problemstellungen hinzuweisen.

– Herr Olivier Loiseleur, Novartis Pharma AG, Basel stellte uns in seinem Referat **'The Story of the Development of Glivec'** die Entwicklungsgeschichte eines erfolgreichen und innovativen medizinal-chemischen Forschungsprojektes im Bereich der Krebstherapie dar. Er sprach stellvertretend für Dr. Jürg Zimmermann, dem für die massgebenden Beiträge in der Entwicklung von Glivec der Sandmeyerpreis 2002 der SCG verliehen wurde.

Anschliessend an den fachlichen Teil wurde durch den Präsidenten der DIC H.R. Dettwiler die Mitgliederversammlung mit folgender Traktandenliste eröffnet und abgewickelt:

- Rückblick auf das Geschäftsjahr 2001
- Jahresrechnung 2001
- Budget des Geschäftsjahres 2002
- Entlastung des Vorstandes
- Vorschläge für neue Vorstandsmitglieder
- Beschlussfassung bez. neuem Reglement der DIC
- Zukünftige Veranstaltungen
- Projekte des Vorstandes, Information zum Skill Inventory
- Varia, Verdankungen, Schluss der Versammlung

Der Jahresbericht 2001 der Division wurde im Rahmen des Rechenschaftsberichtes der SCG in der CHIMIA **2002**, *56*, 36 veröffentlicht.

Für die Aktivitäten der DIC äusserte sich der Präsident in seinen rückblickenden und vorausschauenden Ausführungen zu folgenden Themen:

Das **Geschäftsjahr 2001** hat sich bezüglich sichtbarer Aktivitäten in ruhigen Bahnen bewegt. Für die Mitglieder war im Berichtsjahr nur die Mitgliederversammlung 2001 der DIC vom 4.5.2001 bei der Firma Carbogen/Neuland in Hunzenschwil als aktive Veranstaltung spürbar.

Anderseits hat sich der Vorstand in mehreren Sitzungen und einem Workshop intensiv mit der Organisation von zukünftigen Aktivitäten und Dienstleistungen beschäftigt.

**Die Weiterentwicklung des Informationskonzepts** konzentrierte sich auf den Ausbau der Homepage der DIC und deren Abgleichung innerhalb der Homepage der SCG. Dieses Medium stellt heute unser wichtigstes Kommunikationsmittel dar und bietet den Mitgliedern eine Reihe von Informationen und Links zum Fachgebiet der Industriellen chemischen Produktion. Die DIC wird innerhalb dieser Rahmenbedingungen ihre Informationspraxis überarbeiten und am Konzept der Gesellschaft aktiv mitgestalten.

Die Auswertung des Fragebogens zur **Erhebung der Bedürfnisse** der Mitglieder hat klar ergeben, dass diese in der Fachinformation und im Anbieten von Ausbildungsveranstaltungen liegen. Dementsprechend wird sich der Vorstand zukünftig schwerpunktmässig mit der Organisation von Fachseminaren, Symposien und dem Thema 'Weiterbildung' beschäftigen.

Es besteht neu die Möglichkeit zur Abgabe einer **CD zum Thema 'Thermal Safety Tutorial'** an die Mitglieder. Diese kann über unser Vorstandsmitglied Walter Jucker bezogen werden und ist über eine beschränkte Zeit kostenlos verfügbar.

**Das Nachdiplomstudium in chemischer Verfahrensentwicklung und Produktion,** angeboten durch die Hochschule für Technik und Architektur Fribourg nimmt konkrete Formen an. Die DIC hat im Aufbau eine Beiratsfunktion wahrgenommen. Dieser Studiengang wird speziell für die Aus- u. Weiterbildung von produktionsorientierten Chemikern von Nutzen sein. Es wird auf einen klaren Praxisbezug grosses Gewicht gelegt. Die DIC wird orientieren sobald die Ausschreibung des ersten Ausbildungsmoduls gestartet wird.

Das **Skill Inventory** bezweckt die gegenseitige Nutzbarmachung der Fachkompetenz der Mitglieder der Division. Es ist seit letztem Herbst in unserer Homepage aufgeschaltet und für die Mitglieder verfügbar. Die Nutzung durch die Mitglieder ist noch zaghaft. Eine online Demonstration durch Vorstandsmitglied Walter Jucker diente der Bekanntmachung dieses Instruments zur Nutzbarmachung des Fachwissens der Mitglieder. Wir möchten allen wärmstens empfehlen ihr Profil im Skill-Inventory zu hinterlegen.

Der **Kassenbericht 2001** wurde in ausführlicher und kompetenter Weise vom Kassier Dr. Kurt Käser erläutert. Der Revisor, Dr. Joyeux, bestätigte die korrekte Rechnungsführung. Die Versammlung konnte damit dem Kassier einstimmig Entlastung erteilen und die Arbeit mit Applaus verdanken. Unser Vermögen von rund Fr. 100 000.- gibt uns wesentlichen Spielraum zur Organisation qualitativ guter Veranstaltungen. Ebenfalls das Budget 2002 konnte auf das Wohlwollen der Versammlung zählen. Auf die spezielle Präsentation der Zahlen wird an dieser Stelle verzichtet.

Wir müssen Rücktritte aus dem Vorstand zur Kenntnis nehmen. Es sind dies Christof Buxtorf, der neu die Funktion als Treasurer in der IUPAC wahrnimmt und Christian Favez, der in den Vorstand der SCG berufen wurde. Wir verdanken den Vorstandskollegen die konstruktive und kollegiale Mitarbeit in unserem Leitungsgremium und wünschen ihnen viel Erfolg in den neuen Funktionen.

Es geht der Appell an die Mitglieder, sich spontan zu melden, falls Interesse an der Vorstandarbeit besteht, oder uns allenfalls behilflich zu sein, falls wir neue Mitglieder im Vorstand suchen.**Das Reglement der DIC** wurde innerhalb des Vorstandes überarbeitet und dem Vorstandsausschuss der SCG zur Vernehmlassung unterbreitet.

Nach einigen formalen Anpassungen konnte dieses durch den Vorstand der SCG genehmigt werden. Die Mitgliederversammlung der DIC verzichtete auf eine weitere Vernehmlassung innerhalb unserer Division und genehmigte das überarbeitete Reglement mit Akklamation. Das Dokument ist auf der Homepage einsehbar.

Bezüglich **zukünftiger Veranstaltungen** ist auf folgendes hinzuweisen:
– Wir möchten Sie auch darauf aufmerksam machen, dass die Messe Basel aus der ehemaligen Fachmesse ILMAC im Sinne einer Neuorientierung zwei neue Fachmessen kreiert hat. Es sind dies die auf wissenschaftliche Bedürfnisse ausgerichtete **'r+d in life sciences'** und die produktionsorientierte **'REACH for Process Solutions'**. Beide Messen finden parallel statt und sind festgelegt auf **Dienstag, 15. Oktober – Freitag, 18. Oktober 2002.** Einzelheiten zum Konzept sind über *www.rdfair.ch* und *www.reachfair.ch* abrufbar. Die Schweizerische Chemische Gesellschaft wird mit ihren Divisionen für den begleitenden Wissenschaftskongress verantwortlich sein.

Unsere Sektion wird am 16. Oktober 2002 ein **Seminar** zum Thema **'Simulation Tools and Their Application in Chemical Manufacturing'** organisieren. Der Zugang zu diesem Seminar ist im Messeeintritt inbegriffen. Weitergehende Informationen zur Messe und zum Kongress sind unter obenstehenden Internetadressen sowie aus der CHIMIA ersichtlich.

– Der Vorstand beschäftigt sich bereits mit der Organisation des **6. Freiburger Symposium 2003 am 25./26. September 2003.** Der voraussichtliche Themenbereich lautet 'Sichere Prozessführung in der Chemischen Industrie'. Wir bitten die Mitglieder sich dieses Datum bereits vorzumerken.

Im Anschluss an die Mitgliederversammlung offerierte uns CIMO das Mittagessen wobei auch der firmenübergreifenden Fachdiskussion Raum geboten werden konnte.

Mit unseren Privatfahrzeugen verschoben wir uns anschliessend nach Evionnaz, wo wir durch Herrn Jean-Paul Surbeck, Directeur Général von Orgamol empfangen wurden. Herr Surbeck stellte uns in einer Präsentation seine Firma eingehend vor. Ein Rundgang unter Führung von kompetenten Mitarbeitern durch Teile des Werkes in Evionnaz gab uns gute Einblicke in die Tätigkeiten und Technologien von Orgamol.

Für die in der Entwicklung und Produktion tätigen Chemiker und Chemieingenieure sind diese Einblicke in andere Betriebe und die damit verbundenen Diskussionen wichtig. Die Möglichkeit zum Erfahrungsaustausch bringt doch immer wieder Erkenntnisse und Erfahrungen, die für das Gesamtwohl der produzierenden chemischen Industrie in der Schweiz wichtig sind. Der gute Eindruck bei Orgamol bestätigt, dass auch relativ kleine Unternehmen im zunehmend schwierigeren Geschäft der Lohnproduktion ihre Chance wahrnehmen können.

Wir verdanken der Firma Orgamol diesen sehr informativen und lehrreichen Einblick in ihr Fachgebiet und die erwiesene Gastfreundschaft beim abschliessenden Apéro recht herzlich und hoffen, uns im nächsten Jahr in einer ähnlich angenehmen Umgebung wieder treffen zu können.

Der Präsident DIC
H.R. Dettwiler

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# Schweizer Jungchemikerforum
# Club des Jeunes Chimistes Suisses
# Swiss Young Chemists' Committee

## The Swiss Young Chemists' Committee – An Opportunity for Young Chemists

Under the sponsorship of the Swiss Chemical Society (SCS) and the Basler Chemische Gesellschaft, a Swiss Young Chemists' Committee (SYCC) was founded in Basel in Spring 2001. It aims to foster greater contact between students, PhD students and post-docs in Swiss universities and young chemists in the Swiss chemical industry. This project is being piloted in Basel with the hope that further regional groups will follow.

### Activities of the SYCC Basel

In Basel, we are organising a series of presentations by young chemists from industry and academia in order to give students an insight into the careers available to chemists. Of course, we aim to cover all relevant fields of work in the chemical industry. A chance for informal discussion after these talks is available during a reception or during dinner. So far, we have had presentations by young industry chemists from Novartis Pharma (twice), Hoffmann La Roche, and Chemspeed. Also, two diploma theses from the Department of Chemistry in Basel were presented. To learn about university careers, a recent presentation was held by a Privatdozent from Karlsruhe (Germany) who had only passed his habilitation two weeks before he came to Basel.

Representatives of the SYCC Basel were present at the Spring and Fall meetings of the SCS in order to inform young chemists firstly about our activities and secondly to motivate them to set up regional committees in their cities. The first event organised for chemists from all over Switzerland and from the neighbouring regions of France and Germany will be *contactchemists.ch*, held on 17th October 2002 during the Fall Meeting of the SCS in the Messe Basel. It is a careers fair that will give a selected number of companies the chance to present themselves and describe what their jobs entail. PhD students and postdocs will present their research in public during the SCS Fall Meeting so that company representatives can learn about the scientific profile of the candidates. This concept underlines one of the aims of the committee, the possibility for both companies and students to benefit.

### Why Should Your University Have a Regional Committee?

Last but not least, greater contact between students of the Swiss universities can be established – but this depends on YOU: We strongly encourage the foundation of other local groups of the Swiss Young Chemists' Committee! We would be pleased to help you with information on how to do this. Please check our websites *http://www.swiss-chem-soc.ch/jcf_home.html* and *http://www.contactchemists.ch* or e-mail to *jcf_basel@gmx.ch*.

Dipl.-Chem. Sebastian P. Smidt,
Speaker of the Swiss Young Chemists' Committee

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## FECS Lectures 2002

Prof. *Ivano Bertini*, (University of Florence)
at the 8th FECS Conference on Chemistry and the Environment
Athens, 31 August – 4 September 2002
'A Structural Genomics Approach to Metal Ion Homeostasis, Resistance, and Reduction'

Prof. *Ed Southern*, (University of Oxford)
at Euroanalysis 12
Dortmund, 8–13 September 2002
'DNA Microarrays: Small Chemistry, Big Biology'

## New Members

Choudhary, Muhammad Iqbal, Prof., PK-75270 Karachi
Collot, Jerome, 2000 Neuchâtel
Constant, Samuel, F-74400 Chamonix
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# INFORMATION

## News

### Novartis erhält internationalen Prix Galien 2002 für innovatives Krebsmedikament Glivec®

Basel, 3. Juni 2002 – Novartis ist erstmals mit dem renommierten internationalen Prix Galien für therapeutische Innovationen ausgezeichnet worden. Der Preis wurde für das innovative Medikament Glivec® (Imatinib) (in den USA: Gleevec™ (Imatinibmesylat)) verliehen, ein auf molekularem Weg wirkendes Medikament für Krebspatienten mit einer bestimmten Form von chronisch-myeloischer Leukämie (CML). Glivec, ein Signalübertragungshemmer, ist eines der ersten Krebsmedikamente, das mit Hilfe von rationalem Arzneimitteldesign entwickelt wurde. Es nutzt neueste Kenntnisse der Funktionsweise von Krebszellen. In den letzten zwei Jahren wurde die Novartis Forschung insgesamt neunmal für therapeutische Innovationen mit einem Prix Galien ausgezeichnet.

Die Auszeichnung folgt unmittelbar auf die ermutigenden neuen Daten, die auf der Jahrestagung 2002 der American Society of Clinical Oncology in Orlando, Florida (USA), präsentiert wurden, sowie auf die durch die Europäische Kommission erteilte Zulassung von Glivec für die Behandlung von Patienten mit Kit (CD 177)-positivem oder nicht operierbarem und/oder metastasierendem, malignem gastrointestinalem Stromatumor (GIST).

Der internationale Prix Galien wird alle zwei Jahre verliehen. Er zeichnet innovative Medikamente aus, die eine wesentliche Therapieverbesserung ermöglichen. Medikamente, die bereits auf nationaler Ebene ausgezeichnet wurden, kommen in die internationale Ausscheidung. In diesem Jahr hat Glivec den nationalen Prix Galien in folgenden Ländern bekommen: Belgien, Kanada, Frankreich, Luxemburg, die Niederlande und Portugal. Die Beratungen für den internationalen Prix Galien fanden in Madrid unter dem Patronat der Pressegruppe MediMedia Spain statt. Der internationalen Jury gehörten 13 renommierte Wissenschaftler an, welche die nationalen Jurys vertraten. Die Übergabe des Preises erfolgt am 17. Oktober 2002 in Madrid.

### '50 Jahre Schweizerischer Nationalfonds'

Bern, 2. Juli 2002. *Am 1. August 2002 wird der Schweizerische Nationalfonds zur Förderung der wissenschaftlichen Forschung (SNF) sein 50. Jubiläum feiern. Diese vom Bund finanzierte, doch von Wissenschaftlern und Wissenschaftlerinnen geführte Einrichtung hat die Forschungslandschaft Schweiz in den letzten fünf Jahrzehnten massgeblich geprägt. Ein Überblick.*

Vor 1952 war die Finanzierung der Forschung in der föderalistischen Schweiz Sache der Kantone. Der daraus resultierende 'Flickenteppich' bewog viele entmutigte Forscher und Forscherinnen, ins Ausland zu ziehen, wo sie in den Genuss einer umfangreicheren, national geregelten Finanzhilfe kamen.

Nach mehrjährigen Debatten gelang es jedoch Alexander von Muralt, Physiologie-Professor an der Universität Bern, die Interessen der Wissenschaft mit jenen der Politik unter einen Hut zu bringen. Im Jahr 1950 stellte er dem Bundesrat das Projekt für einen Schweizerischen Nationalfonds zur Förderung der wissenschaftlichen Forschung vor. Die vom Bund finanzierte aber von Wissenschaftlern geführte Institution wurde am 1. August 1952 offiziell aus der Taufe gehoben.

#### Forschungsförderung und Professionalisierung

Nach den ersten Jahren der Konsolidierung, die stark von der Atomforschung geprägt waren, unterteilte der SNF in den sechziger Jahren seinen nationalen Forschungsrat. Die Projekte aus den Geistes- und Sozialwissenschaften, aus den Natur- und exakten Wissenschaften sowie aus der Biologie und Medizin werden seither in drei 'Abteilungen' beurteilt. In den Sechzigerjahren hatte der SNF auch vor, eigene Forschungszentren zu führen, diese Idee wurde aber aus Kostengründen nicht umgesetzt. Mit dem schweizerischen Hochschulförderungsgesetz setzte 1969 eine Entwicklung zur Institutionalisierung der Wissenschafts- und Hochschulpolitik ein. Beim SNF wurde die Forschungsförderung professionalisiert. Während der Wirtschaftskrise in den Siebzigerjahren erhielt der SNF den Auftrag, Nationale Forschungsprogramme (NFP) durchzuführen, die neue Erkenntnisse zur Lösung von Problemen von nationaler Tragweite liefern sollen. 1976 wurde die neue Abteilung IV mit der Leitung der bis heute 54 NFP beauftragt.

#### Auch international am Ball

Mit dem Forschungsgesetz von 1984 wurde der SNF als Forschungsorgan des Bundes offiziell bestätigt. Auf internationaler Ebene verstärkte der SNF, der 1974 zu den Gründungsmitgliedern der 'European Science Foundation' gehörte, sein Engagement in den Achtziger- und Neunzigerjahren zunehmend, unter anderem mit den aktuellen Forschungspartnerschaften in Osteuropa und in den südlichen Entwicklungsländern. Zugleich wurde ab 1992 die nationale Programmforschung mit den heute fast abgeschlossenen Schwerpunktprogrammen (SPP) verstärkt. Ihnen folgen seit 2001 die Nationalen Forschungsschwerpunkte (NFS), deren Ziel die nachhaltige Stärkung des Forschungsplatzes Schweiz in strategisch wichtigen Gebieten von der Genetik bis zur Klimaforschung ist. In den Neunzigerjahren rückten auch die wesentlichen Aufgaben des SNF – die Förderung der freien Grundlagenforschung und des wissenschaftlichen Nachwuchses – wieder stärker in den Blickpunkt. Unter anderem lancierte der SNF ein Programm für Förderprofessuren an den Schweizer Hochschulen und ETHs und leitete spezielle Massnahmen zur Frauenförderung ein.

**Berühmte Nobelpreisträger**

Für sein Jubiläum kann der SNF eine sehr positive Bilanz seiner Tätigkeit für die Forschung in der Schweiz ziehen. Einige Beispiele: In den Sozial- und Geisteswissenschaften ist dank seiner Beiträge an Jean Piaget und Bärbel Inhelder in Genf ein Psychologiezentrum von Weltruf entstanden. Im Bereich der Mathematik, Natur- und Ingenieurwissenschaften haben Forschende aus Physik und Chemie Grundbeiträge zum Verständnis der Materie erarbeitet, welche die Entwicklung von höchst aktuellen Forschungszweigen wie Nanowissenschaften oder Mikroelektronik ermöglichten. Auf dem Gebiet der Biologie und der Medizin ist der Aufschwung der Molekularbiologie seit den Sechzigerjahren eng verknüpft mit dem SNF, der die Beobachtung von Viren mit dem Elektronenmikroskop seit 1952 unterstützt hat. Auch haben mehrere Nobelpreisträger von der Förderung des Schweizerischen Nationalfonds profitiert, unter ihnen Werner Arber, Richard R. Ernst und Rolf Zinkernagel.

**Der SNF heute**

Im Auftrag des Bundes gewährt der Schweizerische Nationalfonds zur Förderung der wissenschaftlichen Forschung (SNF) Beiträge für Forschungsarbeiten und fördert den wissenschaftlichen Nachwuchs. Ihm steht für das Jahr 2002 ein Budget von 400 Mio. Franken zur Verfügung, die in erster Linie zur Finanzierung von ungefähr 3000 Forschungsprojekten bestimmt sind.

Neben der Grundlagenforschung leitet der SNF zurzeit 18 Nationale Forschungsprogramme, ein Schwerpunktprogramm, 14 Nationale Forschungsschwerpunkte, zwei internationale wissenschaftliche Kooperationsprogramme, die schweizerische Beteiligung an den europäischen Programmen, sowie zehn Stipendien- und Austauschprogramme für angehende Forschende. Zudem finanziert er jedes Jahr die Publikation von rund 120 wissenschaftlichen Werken.

Im Jahr 2001 flossen 19% der bewilligten Kredite in die Geistes- und Sozialwissenschaften, 39% in die Mathematik, Natur- und Ingenieurwissenschaften und 42% in die Biologie und Medizin. 79% der unterstützten Forschenden sind unter 35 Jahre alt, 38% sind Frauen. Der SNF finanziert derzeit etwa Hundert Förderungsprofessuren an den Schweizer Hochschulen.

## Honors / Ehrungen

Prof. *Erick Carreira*, Laboratorium für Organische Chemie, ETH Zürich, is to be awarded the Thieme-IUPAC Prize 2002 in recognition of his outstanding achievements in the field of synthetic organic chemistry. He will be presented with the prize at ICOS-14 in Christchurch, New Zealand on 16 July, 2002.

Prof. *François Diederich*, Laboratorium für Organische Chemie, ETH Zürich, wurde von der Berlin-Brandenburgischen Akademie der Wissenschaften zum ordentlichen Mitglied der Mathematisch-Naturwissenschaftlichen Klasse gewählt.

Prof. *Dieter Seebach*, Laboratorium für Organische Chemie, ETH Zürich, wurde vom International Scientific Committee des International Symposium on Chirality als Preisträger der Chirality Medal auserkoren.

Prof. Dr. *Manfred Hesse*, Organisch-chemisches Institut der Universität Zürich, wurde für seine Arbeiten in organischer Chemie und für seine persönlichen Beiträge zur Ausbildung hochqualifizierter Spezialisten in Bulgarien, am 10. Juli 2002 in der Berner Botschaft der Republik Bulgarien, die höchste Auszeichnung der Bulgarischen Akademie der Wissenschaften, die Ehrenmedaille 'Marin Drinov am Band' und die Auszeichnung 'Für besondere Beiträge zu Wissenschaft und Kultur' überreicht.

Professor Marin Drinov (1838–1906), nach Studien in Russland und Forschungsaufenthalten in Prag, Wien, Paris, Genf, Neapel und Rom, Gelehrter von europäischem Rang für Byzantinistik und die Geschichte der Balkanvölker, war Gründer und erster Präsident (1869) der 'Bulgarischen Gelehrtengesellschaft', die 1911 zur Bulgarischen Akademie der Wissenschaften umgestaltet wurde. Er gehört zu den grossen Identifikationspersönlichkeiten der bulgarischen Nation im 19. Jahrhundert.

## Congresses – Conferences – Workshops

PSI PAUL SCHERRER INSTITUT

### 17th One-Day Symposium

**Electrochemistry**
**Auditorium WHGA/001, PSI-West, Villigen**
**September 11th, 2002, 09.45 – 16.00 h**

### Carbons for Electrochemical Applications

**Programme**

| | |
|---|---|
| 09.45 – 10.30 | Welcome Gathering (Coffee) |
| 10.30 – 11.15 | **Carbons for Electrochemical Applications – An Overview of Material Properties**<br>Prof. Dr. *J.O. Besenhard*, Technische Universität Graz, A |
| 11.15 – 11.45 | **Physico-Chemical Characterization of Carbons**<br>Dr. *F. Fischer*, ex TIMCAL, Sins, CH |
| 11.45 – 12.15 | **Carbon Nanotubes, Synthesis, Properties and Applications**<br>Dr. *A. Zuettel*, Universität Fribourg, CH |
| 12.15 – 12.45 | **Diamond Film Electrodes for Electrochemical Processes**<br>Dr. *T. Lehmann*, INFRACOR GmbH, Marl, D |
| 12.45 – 14.00 | Lunch Buffet |
| 14.00 – 14.30 | **Optimized Graphite Powders in Electrochemical Cells**<br>Dr. *M.E. Spahr*, TIMCAL SA, Bodio, CH |
| 14.30 – 15.00 | **Activated Carbons for Double Layer Capacitors**<br>Dr. *M. Reimerink*, NORIT, Amersfoort, NL |
| 15.00 – 15.30 | **Carbons for Fuel Cells: Support for Precious Metal Catalysts**<br>Dr. *J. Koehler*, OMG AG, Hanau, D |
| 15.30 – 16.00 | **New Developments for Carbon Fuel Cell Components**<br>Dr. *N. Berg*, SGL TECHNOLOGIES GmbH, Meitingen, D |

→ Anmeldung erbeten an: Frau I. Kalt, Tel.: 056 310 29 19
oder isabella.kalt@psi.ch

# CHIMIA-REPORT

Bitte an die Inserenten

Richten Sie Ihre Beiträge für die Rubrik CHIMIA-REPORT nicht an die Redaktion, sondern ausschliesslich an: Kretz AG, Postfach, CH–8706 Feldmeilen Besten Dank!

## Neu: IGO 150 CELLlife von Jouan

Jouan, die ideale Marke für das biologische Labor mit seinen Zentrifugen, Evaporatorzentrifugen, Brut- und Trockenschränken, präsentiert neu seinen $CO_2$-Brutschrank IGO 150 CELLlife™ mit den idealen Wachstumsbedingungen für Ihre Zellkulturen:

- unschlagbare Erholzeit für das $CO_2$-Niveau: weniger als 3 Minuten
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- $CO_2$-Kontrolle mit UV-Detektor – die genauste Methode für das Wohl Ihrer Kulturen
- keine versteckten Ecken für Infektionsherde.

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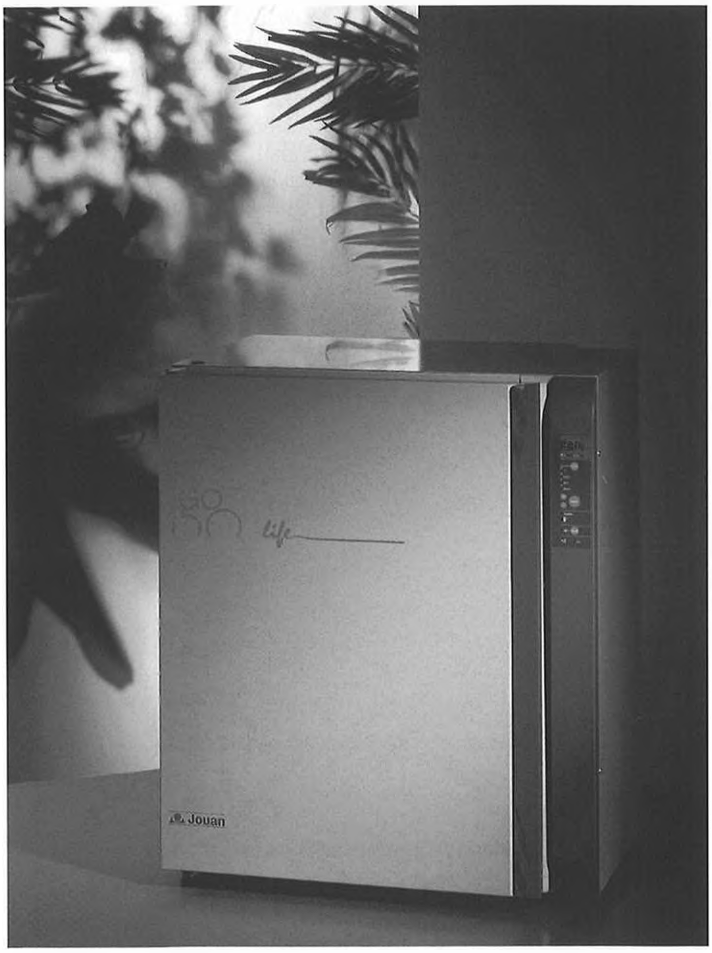
'The Influence of Culture Parameters on Cell Development' mit vielen Hinweisen zu den optimalen Lebensbedingungen für Ihre Lieblinge aus der Serie 'Jouan Cell Culture Training'

Detaillierte Auskünfte und eine kompetente Beratung erhalten sie bei:

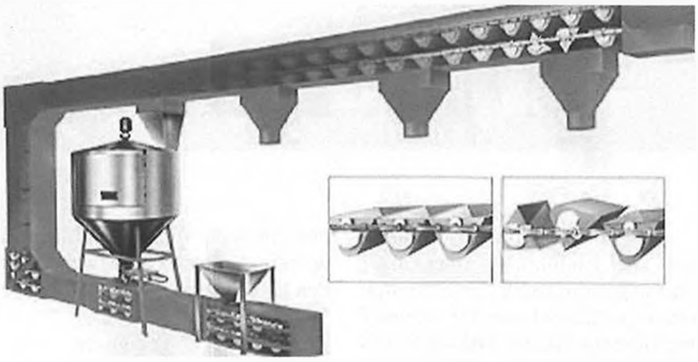
- IG Instrumenten-Gesellschaft AG
  Räffelstrasse 32
  CH-8045 Zürich
  Telefon 01 456 33 33
  Telefax 01 456 33 30
  E-Mail igz@igz.ch

Das gesamte Lieferprogramm kann auch im Internet abgefragt werden unter *www.igz.ch*

*Leserdienst Nr. 2*



## Pendelbecherwerke – schonendste Förderung von Schüttgütern



Pendelbecherwerke gelten als das schonendste Fördersystem für Schüttgüter. Beim Fördern von hochwertigen bruch- und abriebempfindlichen Produkten ist die Produktequalität entscheidend. Ohne Entmischung können die Produkte von mehreren Aufgabestellen zu verschiedensten Empfangsstellen transportiert werden. Namhafte Produzenten von Teigwaren aller Art, Pommes Chips und Müesli haben sich dieses einzigartige Fördersystem zu Nutze gemacht. Mehrere Pendelbecherwerke werden in diesen Anlagen zur Verteilung und zum Transport der Produkte zu verschiedenen Behältern und diversen Abfüll- und Verpackungsanlagen eingesetzt. Entscheidend für die Wahl des Systems sind häufig auch die variablen Bauformen mit einer individuellen Anzahl Aufgabe- und Entleerstationen. Ebenso dürfte die perfekte Reinigung der Becher mittels speziellen, integrierten Waschanlagen von grösster Bedeutung sein. Aber auch für eine Vielzahl von weiteren Anwendungen wie z.B. für Getreideflocken, Reis-Crispies, Waschmittel, Bonbons oder für abrasive Produkte im Umweltschutzbereich, hat sich die robuste Konstruktion bestens bewährt.

Wie erwähnt, stehen integrierbare Wasch- und Trocknungsstationen für die Reinigung der Becher und des Innenschachtes zur Verfügung, wobei auch ein späterer Einbau jederzeit möglich ist. Damit wird ein einwandfreier, hygienischer Betrieb ermöglicht. Weitere Informationen erhalten Sie bei:

- WISAG
  Oerlikonerstrasse 88
  CH-8057 Zürich
  Tel. 01 317 57 57
  Fax 01 317 57 77
  *Internet: www.wisag.ch*
  E-Mail: info@wisag.ch

*Leserdienst Nr. 3*

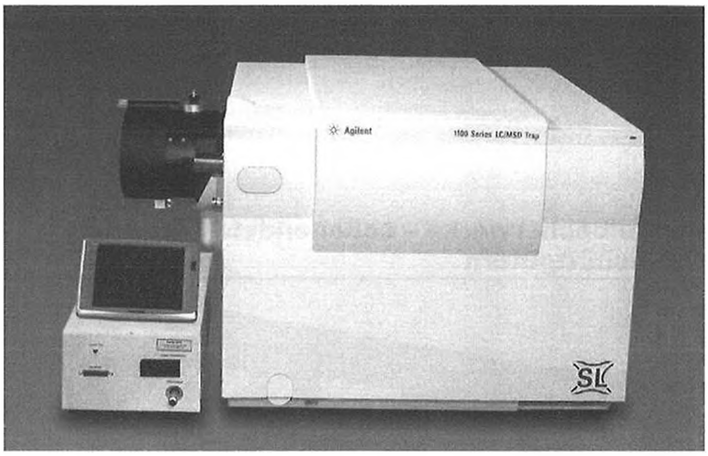
## TURCK neu bei Bachofen AG

TURCK, eine der global führenden Unternehmensgruppen der Industrieautomation und der Sensortechnik, wird in der Schweiz neu durch die Bachofen AG in Uster vertreten. Das Sensorprogramm umfasst u.a. induktive, magnetinduktive, kapazitive und optoelektronische Sensoren. Dabei bilden die induktiven uprox®-Faktor 1 Sensoren einen besonderen Produkteschwerpunkt. Aus den Bereichen interface- und Feldbustechnik bietet TURCK effektive Produktelösungen für die Industrie an. Eine Vielfalt an busstop®-Komponenten für die am weitesten verbreiteten Feldbussysteme und Schalt- und Überwachungsgeräte für den Ex-Bereich runden das Angebot ab.

- Bachofen AG
  Ackerstrasse 42
  CH–8610 Uster
  Tel. 01 944 11 11
  Fax 01 944 12 33
  *www.bachofen.ch*
  info@bachofen.ch

*Leserdienst Nr. 4*

## Agilent Technologies führt eine unter Atmosphärendruck arbeitende MALDI-Quelle für die Proteomforschung ein



Agilent Technologies Europe gab die Einführung einer unter Atmosphärendruck arbeitenden matrixgestützten Laser-Desorptions/Ionisierungs-Quelle (AP-MALDI) bekannt, die gemeinsam mit dem LC/MSD Trap SL Ionenfallen-Massenspektrometer der Serie Agilent 1100 eingesetzt werden soll. Diese AP-MALDI-Quelle wurde in Kooperation mit der MassTech Inc. aus Burtonsville, Maryland, USA, entwickelt. Sie sorgt für eine sanfte Ionisierung, die sich besonders gut zur Analyse von Peptiden und verwandten Substanzen eignet, die für Wissenschaftler in der Proteomforschung interessant sind.

**Hervorragend geeignet zum schnellen Screening**

Da die AP-MALDI-Quelle unter Atmosphärendruck arbeitet, kann ein Probenträger innerhalb von Sekunden eingesetzt werden, was die Bedienung vereinfacht und den Probendurchsatz enorm steigert. Ein mit der AP-MALDI-Quelle ausgestattetes LC/MSD Trap SL eignet sich somit hervorragend für das schnelle Screening von Proben, die von Proteinen stammen. Die 96-Well-Probenteller sind mit den automatischen Probenauftragssystemen kompatibel, was zu einer weiteren Steigerung des Probendurchsatzes beiträgt.

**Aussergewöhnliche Empfindlichkeit**

Ein mit der AP-MALDI-Quelle ausgestattetes LC/MSD Trap SL der Serie Agilent 1100 zeigte bei der Auftragung von Probenmengen im Subfemtomolbereich auf den Probenträger eine hervorragende Empfindlichkeit. Für AP-MALDI-Analysen wird nur ein Bruchteil der insgesamt aufgetragenen Probe verbraucht, sodass die Probenträger für weitere Analysen aufbewahrt werden können.

**Zur Recherche geeignete MS/MS-Spektren**

Das AP-MALDI-System von Agilent erzeugt schnell und problemlos zur Bibliothekssuche geeignete MS- und MS/MS-Spektren von Proteinaufschlüssen. Das auf den Probenträger gerichtete angewärmte Trockengas soll die Bildung von Matrix-Clustern vermindern und zu einem saubereren Massenspektrum führen. Die Spezifität der MS/MS-Daten senkt den Bedarf an hoher Komplementarität und sorgt für schlüssigere Übereinstimmungen mit der Datenbank.

**Äusserst vielseitig**

Für die AP-MALDI-Quelle wird das Standard-Ionenquellen-Montagesystem von Agilent verwendet. Ein Wechsel zwischen der AP-MALDI-Quelle und den ESI-, APCI- und APPI-Quellen, die bereits für die LC/MSD Trap zur Verfügung stehen, nimmt nur Minuten in Anspruch. Für die in der Proteomforschung tätigen Wissenschaftler heisst dies, dass sie die AP-MALDI-Quelle für ein schnelles Vorscreenen verwenden und dann das System für eine eingehendere LC/MS/MS-Analyse der sie interessierenden Proben rasch auf den Elektrospray-Ionisierungsmodus (ESI) umstellen können.

- Agilent Technologies
  (Schweiz) AG
  Chemical Analysis Group
  In der Luberzen 29
  CH-8902 Urdorf
  Tel. 0848 80 35 60
  Fax 01 735 97 00

*Leserdienst Nr. 5*

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## Heraeus® HERAsafe® KS – new standard in safety and ergonomics

**The new Class II Heraeus® HERAsafe® KS safety cabinets from Kendro Laboratory Products provide optimum product and personnel protection with an ergonomically superior design. The slanted front window, the rear-cabinet-wall digital eye-level-display, and the use of a remote control for parameter setting combine to make our new generation of safety cabinets unmatched in the industry.**

The rear-cabinet-wall eye level display allows parameter and operating functions to be conveniently monitored from a seated position. The information displayed includes downflow rate, total operating hours, time of day, and optional UV-C irradiators operating time. The display also offers a stop-watch function.

For the first time, all parameters are set via a remote control. For contamination prevention, the remote control can be used with a sealed SAFEbag. No need to take your hands out of the clean air atmosphere when you want to change the settings of your cabinet. This eliminates the risk of contamination from the outside going into the work area or from the inside to the outside environment. Now glove changes are a thing of the past.

The unique patented aerosol-tight front window with its frameless edge offers an unobstructed view of the work area and optimum contamination protection – even in stand-by mode. The slanted front window design favors a relaxed working posture. The large work aperture with a height of more than 250 mm ensures ease of handling.

The tried and tested safety concept of the Heraeus® HERAsafe® lives on in this new generation. Cleaning and disinfection are child's play with the new HERAsafe® KS. The working surfaces consist of scratch-proof and acid-resistant stainless steel. Powerful UV-C irradiators are available to aid efficient disinfection. Cross-beam UV-C irradiation illuminates the entire work area, effectively avoiding any shadows.

Kendro Laboratory Products, Inc., is a global leader in products and services for Life and Materials Science, Drug Discovery and Bioprocessing. The company, with world-renowned brands including SORVALL® and Heraeus®, designs, manufactures and markets a wide range of equipment for sample storage, preparation and processing. Recently acquired by SPX Corporation, Kendro Laboratory Products employs more than 1700 associates around the world. The company serves its customers through an extensive network of direct sales and service representatives and distribution partners in over 150 countries.

- Kendro Laboratory Products AG
  Räffelstrasse 32, Postfach
  CH–8045 Zürich
  Telefon 01 454 12 12
  Telefax 01 454 12 99
  e-mail:
  kendro-ag@swissonline.ch

*Leserdienst Nr. 6*

## DuPont Nylon steigt in den Glutarsäuremarkt ein

Der Geschäftsbereich Nylon Zwischenprodukte von DuPont hat ein weltweites Programm zur Marktentwicklung für seine Glutarsäure gestartet. Den Schwerpunkt legt das Unternehmen zunächst auf Glutarsäure-Lösungen, prüft für bestimmte Marktsegmente aber auch die Herstellung in fester Form (Schuppen/Pulver). Derzeit ist Glutarsäure als 50%ige wässerige Lösung sowie als Pulver zu Testzwecken lieferbar, soll aber noch in diesem Jahr auch in Industrie-Mengen verfügbar sein. Haupteinsatzgebiete sind derzeit Aktivatoren in Lötflussmitteln sowie Zwischenprodukte für die Arzneimittelherstellung.

Glutarsäure – eine Divarbonsäure mit fünf Kohlenstoffatomen – löst sich sehr gut in Wasser und ist dadurch leicht handhabbar. Unter den Dicarbonsäuren hat Glutarsäure den niedrigsten Schmelzpunkt. Sie ist in der europäischen Richtlinie 90/128/EISC für Substanzen im Kontakt mit Lebensmitteln aufgeführt und darf daher in Kunststoffen für Lebensmittelverpackungen eingesetzt werden.

Darüber hinaus gibt es weitere vielversprechende Einsatzgebiete für Glutarsäure:

- Reinigungsmittel – Dank ihrer guten Wasserlöslichkeit bietet Glutarsäure vielfältige Formulierungsmöglichkeiten für wasserbasierende Reinigungsmittel. Gleichzeitig hat sie virentötende Wirkung und ist ein guter Chelatbildner, d.h. sie bindet effizient Ionen, die Wasserhärte verursachen sowie Metalloxide. Daher bieten sich Anwendungsgebiete an, wie die Nachbearbeitung und Reinigung von Metallen sowie die Reinigung von Geräten, z. B. Boilern, oder harten Oberflächen, z.B. Böden und Wände.

- Waschmittel – Glutarsäure ist sehr mild und führt nicht zur Korrosion von Reinigungsgeräten wie Geschirrspüler oder Waschmaschinen.

- Elektronik – Mit ihren guten elektrolytischen Eigenschaften bei hohen Temperaturen eignen sich Glutarsäuresalze sehr gut als Kondensator-Elektrolyte. Dank ihrer chelatbildenden Eigenschaften und ihrer guten Wasserlöslichkeit kann Glutarsäure auch für verschiedene Lötflussmittel eingesetzt werden, z.B. 'No-Clean'-Lötflussmittel (Rückstände müssen nicht entfernt werden) sowie 'Aqueous-Clean'-Lötflussmittel (Rückstände lassen sich mit Wasser entfernen).

- Lebensmittel – Glutarsäure ist ein natürlicher Bestandteil von Zuckerrüben und lässt sich in Wasserextrakten aus Rohwolle nachweisen. Sie hat ein angenehmes Fruchtsäure-Aroma und ausserdem vorteilhafte Säuerungsmittel-Eigenschaften. Nach einer Zulassung durch die Food and Drug Administration könnte Glutarsäure in zahlreichen Lebensmitteln als Ersatz für Zitronen- oder Maleinsäure dienen.

- Arzneimittel – Neben dem Einsatz als Puffersubstanz oder als Zwischenprodukt für Arzneimittel deuten Untersuchungen darauf hin, dass sich Glutarsäure auch für die Herstellung von kontrolliert dosierbaren, schwerlöslichen basischen Wirkstoffen eignet.

- Kunststoffe – Glutarsäure kann als Basis für eine Vielzahl von PVC-Weichmachern dienen. Diese bieten sehr gute Eigenschaften bei tiefen Temperaturen und verhalten sich ähnlich wie Adipate.

'Wir haben in jüngster Zeit auf verschiedenen Gebieten erfolgreich neue Produkte eingeführt' so Dr. Ingo Ganz, Market Development Manager des Geschäftsbereichs Nylon Zwischenprodukte von Du-Pont für Europa.

'Jetzt werden wir unsere Divarbonsäurepalette ausbauen und diejenigen Marktsegmente erschliessen, in denen die einzigartigen Eigenschaften der Glutarsäure herausragende Vorteile gegenüber anderen Säuren bieten.'

- Du Pont de Nemours
  (Deutschland) GmbH
  Du Pont Strasse 1
  D-61343 Bad Homburg v.d.H.
  Tel. ++ 49 (0) 61 72 – 87-0

*Leserdienst Nr. 7*

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**'Neue Lösungen' in der Chemie**

## 1. Internationale Konferenz 'Green Solvents for Catalysis'

## 13.–16. Oktober 2002 in Bruchsal

Die Entwicklung umweltfreundlicher chemischer Verfahren steht hoch im Kurs. Dabei kommt es vor allem darauf an, schon während des Prozesses die Umweltbelastung so gering wie möglich zu halten. Auf der 1. internationalen Konferenz 'Green Solvents for Catalysis – Environmentally Benign Reaction Media' vom 13.–16. Oktober 2002 in Bruchsal bei Heidelberg werden dazu innovative Lösungswege aufgezeigt. Die Veranstaltung wird von der DECHEMA e.V. (Gesellschaft für Chemische Technik und Biotechnologie), Frankfurt am Main, organisiert. Internationale Spitzenwissenschaftler aus Industrie und Hochschule sowie Nachwuchsforscher präsentieren und diskutieren hier an drei Tagen neue wissenschaftliche Ergebnisse.

Derzeit forschen weltweit Wissenschaftler an unterschiedlichen alternativen Lösungsmittelkonzepten, wie z.B. überkritischen Fluiden und ionischen Flüssigkeiten. Neben ökologischen Vorteilen gegenüber herkömmlichen Lösungsmitteln eröffnen die neuen Reaktionsmedien auch andere Wege der Prozessführung. So ermöglichen sie in homogenkatalytischen Reaktionen z.B. ein effektives Recycling der meist teuren Metallkatalysatoren.

Im Vordergrund stehen der Vergleich unterschiedlicher alternativer Lösungsmittel und deren Anwendungen in der homogenen Katalyse. Die Präsentationen werden verschiedene Reaktionstypen, wie z.B. Oxidation, Hydrierung, Hydroformylierung behandeln, aber auch industrielle Anwendungen und Zukunftsperspektiven der 'neuen Lösungen' aufzeigen. Unter den Plenarvortragenden sind so bekannte Namen wie Paul T. Anastas, wissenschaftlicher Berater des amerikanischen Präsidenten, Chris J. Adams vom Institute of Applied Catalysis, UK, und Hans-Ulrich Blaser, Solvias AG, CH. Das attraktive Vortragsprogramm wird durch Posterpräsentationen und eine begleitende Firmenausstellung ergänzt.

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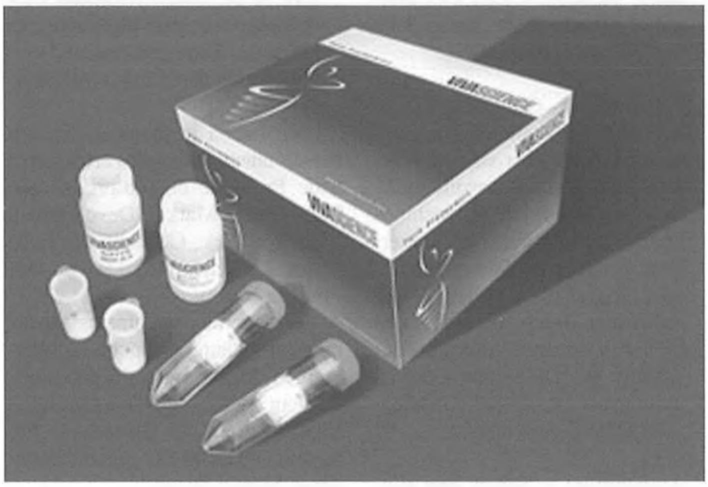
*Leserdienst Nr. 8*

## Vivascience AG stellt neue Kits zur Protein-Aufreinigung vor



Vivascience AG, eine 100%ige Tochter der Sartorius AG, entwickelt und produziert Filtrations-Einheiten zur Aufreinigung von Proteinen. Jetzt werden die ersten drei einer neuen Produktlinie von gebrauchsfertigen Vivapure™ Kits für die Protein-Aufreinigung eingeführt. Die vivapure Kits sind für einen weiten Bereich von Anwendungen in der biologischen und biomedizinischen Forschung geeignet und sind gegenüber den herkömmlichen Methoden der Protein-Aufreinigung deutlich schneller und kostengünstiger.

Vivascience unterstreicht die langfristige Ausrichtung der Sartorius AG auf die Biotechnologie und ist eines der ersten Unternehmen, die sich ganz auf Proteomics spezialisiert haben.

Durch patentierte Technologien ist die Firma bestens positioniert, sich an diesem rasch entwickelnden Markt zu beteiligen, der sich aus dem wachsenden Interesse der wissenschaftlichen Gemeinschaft an Proteinforschung ergibt.

Die besondere Konstruktion der Vivascience Ultrafiltrations-Einheiten ermöglicht zuvor nicht erreichbare Verarbeitungs-Geschwindigkeiten und einfachste Handhabung. Merkmale dieses aussergewöhnlichen Konzepts sind die vertikal eingebauten Membranen unter Nutzung der weitaus grösseren Zentrifugalkraft an Stelle von Schwerkraft. Ausgesuchte Materialien mit niedriger Bindungsneigung gewährleisten hohe Ausbeuten, während eingebaute Sicherheitsmerkmale die wertvollen Proben schützen. Es ist diese Kombination, die dem Anwender ein Optimum an Schnelligkeit, Proben-Reinheit und maximaler Rückgewinnung bietet.

Die **Vivapure Acidic and Basic Protein Purification Kits** sind gebrauchsfertige Sets zur Aufreinigung von sauren oder basischen Proteinen, also für einen sehr weiten Bereich von Anwendungen. Der **Vivapure Albumin Removal Kit** trennt Albumin aus Blut oder anderen albuminhaltigen Proben ab und der **Vivapure DNA Removal Kit** enffernt schliesslich kontaminierende DNA aus Protein-Lösungen.

**Die drei neuen Protein Aufreinigungskits im Detail:**

Die neuen **Vivapure Acidic and Basic Protein Purification Kits** basieren auf den Vivapure Zentrifugensäulen als zentralem Werkzeug für Protein-Aufreinigung. Die Vivapure Produkte verwenden eine innovative und sehr leistungsstarke Membrantechnologie, die das bewährte Prinzip des Ionenaustauschs in Zentrifugensäulen einsetzt. Die Vivapure Basic and Acidic Protein Purifisation Kits beinhalten von Anfang bis Ende alles was zur raschen Aufreinigung von Proteinen benötigt wird:

Zentrifugensäulen zur ersten Klärung der Probe, gefolgt von dem eigentlichen Ionenaustauschschritt für das Zielprotein und eine abschliessende Ultrafiltration, um das gewonnene Protein zu konzentrieren. Die Zusammenstellung der Kits ist so gewählt, dass neben den Vorteilen von gebrauchsfertigen Kits auch die gebotene experimentelle Flexibilität gewährleistet ist, die für die Arbeit mit Proteinen zwingend erforderlich ist.

Mit dem neuen **Vivapure Albumin Removal Kit** wird der Gehalt von einem der Hauptbestandteile von Serum herabgesetzt. Dadurch wird die Empfindlichkeit von vielen Analyse-Methoden verbessert, die Ausbeute der nachfolgenden Aufreinigungs-Schritte erhöht und der Nachweis von selten vorkommenden Proteinen erleichtert. Das neue **Vivapure DNA Removal Kit** zielt auf einen kritischen Punkt bei der Protein Aufreinigung aus biologischem Material: das Vorhandensein von Nukleinsäuren mit hohem Molekulargewicht. Das Vivapure DNA Removal Kit entfernt störende DNA und erleichtert damit die Protein Aufreinigung. Dies ist besonders bei der Herstellung von rekombinanten Proteinen von Bedeutung, die für weitergehende Anwendungen frei von kontaminierenden Nukleinsäuren sein müssen.

Alle Kits werden mit den benötigten Puffern, laminierten 1-2-3 Protokoll-Karten und einem umfassenden Handbuch über Protein Aufreinigung geliefert. Vivapure Kits sind in zwei Grössen erhältlich: Mini Kits für Probenvolumen von bis zu 400 µl und Maxi Kits für grössere Volumina von bis zu 19 ml je Beladungsschritt. Noch grössere Volumina können durch wiederholtes Beladen verarbeitet werden.

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  Internet: *www.vivascience.com*

*Leserdienst Nr. 9*

## Der neue Thermo Finnigan UltraFast TRACE™ GC maximiert die Produktivität

Der neue UltraFast TRACE GC von Thermo Finnigan ist ein Gaschromatograph mit Direkt-Säulen Beheizung was zu einer Heizrate von bis zu 1200 °C führt. Dadurch wird die Analysenzeit drastisch reduziert und die Produktivität erheblich gesteigert.

Das UltraFast TRACE GC System kombiniert schnellste Temperatur Programmraten mit kurzen, engen (0.1 mm i.d.) Kapillarsäulen – dies führt zu sehr schnellen Resultaten mit sehr hoher Genauigkeit. Das System ist ausserdem so ausgelegt dass Proben mit kleinem Splitverhältnis aufgegeben werden können und somit ist die schnelle GC erstmals auch für die Spurenanalytik einsetzbar.

Als Detektoren stehen entweder ein sehr schneller Flammen Ionisations Detektor (FID) oder das schnellste Massenspektrometer von Thermo Finnigan, das leistungsfähige TEMPUS™ Time-of-flight GC/MS System zur Verfügung.

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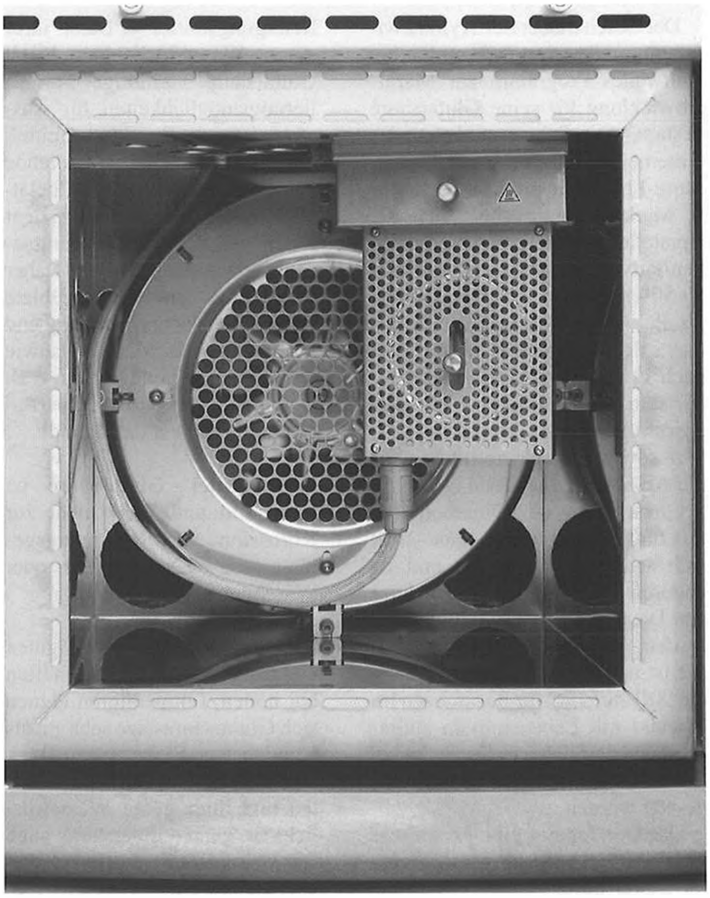
  *Web: www.brechbuehler.ch*

*Leserdienst Nr. 10*



## Neuer Rotor für sehr hohes Probenaufkommen

Die Rotorfamilie der Eppendorf Centrifugen 5810 und 5810 R wurde erweitert. Das neueste Mitglied ist der Ausschwingrotor A-4-81, der sich durch sehr hohe Kapazität und Flexibilität auszeichnet.

Dieser hochvolumige, vielseitige Qualitätsrotor erhöht das Fassungsvermögen der Centrifugen 5810 und 5810 R auf 1600 ml und ist ideal einsetzbar in allen medizinischen und biotechnologischen Laboratorien, in denen ein hoher Probendurchsatz anfällt.

In 4 Rechteckbechern können alle handelsübliche Gefässe von 1, 5 bis 400 ml, wie z. B. Vacutainer, Glasröhrchen und bis zu 20 x 50 ml Falcon®-Gefässe bei einer max. Drehzahl von 4000 l/min (max. RZB: 3250 x g) zentrifugiert werden.

Zusammen mit dem modularen Adaptersystem runden Kappen für die aerosoldichte Zentrifugation das umfangreiche Zubehörprogramm ab. Ausserdem sind Rotor, Becher und Kappen sowie Adapter autoklavierbar (20 min, 121 °C).

Der Rotor ist auch als A-4-81-MTP für die Zentrifugation unterschiedlichster Plattenformate erhältlich.

- Vaudaux-Eppendorf AG
  im Kirschgarten 30
  CH-4124 Schönenbuch/Basel
  Tel. 061 482 14 14
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*Leserdienst Nr. 11*

## Kontaminationsprävention ohne Kompromisse: Neue Features für den Heraeus® HERAcell® 240 $CO_2$-Inkubator

**Der Heraeus® HERAcell® 240 $CO_2$-Inkubator von Kendro überzeugt mit zwei neuen Standardfeatures und drei neuen Optionen. Ab sofort ist das Gerät standardmässig mit einem patentierten selbstabgleichenden $CO_2$-Messsystem (auto-zero) und einem neuartigen Wasserstands-Alarmsystem ausgerüstet. Drei neue Optionen runden das Angebot ab: $CO_2$/$O_2$-Kontrolle in zwei Konzentrationsbereichen, ein neuartiger IR-$CO_2$-Sensor sowie eine Flaschendrehvorrichtung. Alle Inneneinbauten und Sensoren bleiben während der hochwirksamen 90 °C Dekontaminationsroutine ContraCon im Gerät.**

**Der Heraeuse $CO_2$-Inkubator HERAcell® 240 ist ideal für den Einsatz in der Zell- und Gewebekultur.**

HERAcell® 240 bietet ab jetzt zwei $O_2$-Regelbereiche als Option. Von 1 bis 21% Sauerstoffgehalt für hypoxische Applikationen zur Simulation physiologischer $O_2$-Konzentrationen. Der Bereich von 5 bis 90 % $O_2$ bietet grösstmögliche Flexibilität. Der Zirkoniumoxid-Sensor ist wartungsfrei, wird automatisch abgeglichen (autocal) und bleibt während der 90 °C ContraCon-Dekontaminationsroutine im Inkubator.

Zur Regelung des $CO_2$-Gehaltes besteht nun die Wahl zwischen dem bewährten WLD (Wärmeleitfähigkeits-Detektor) oder dem neuen, einzigartigen IR-$CO_2$-Sensor. Beide Sensoren sind mit einer auto-zero Funktion ausgestattet.

Dadurch wird die Langzeit-Stabilität der $CO_2$-Konzentrationen gewährleistet und somit konstante pH-Werte für optimale Wachstumsbedingungen.

Beide Sensoren bleiben während der 90 °C ContraCon Dekontaminationsroutine im Inkubator und werden ebenfalls dekontaminiert. Dadurch entfällt die manuelle Reinigung, d.h. Zeitersparnis und verringertes Kontaminationsrisiko.

Ab sofort kann der HERAcell® 240 mit bis zu vier Flaschendrehvorrichtungen für Rollerflaschen von 58 bis 186 mm Durchmesser ausgestattet werden. Die Drehzahl für jede Ebene wird unabhängig voneinander eingestellt. Auch hier kommt die 90 °C ContraCon Dekontaminationsroutine zuverlässig zum Einsatz. So gehört die manuelle Reinigung und Dekontamination von Flaschendrehvorrichtungen der Vergangenheit an.

Standardmässig ist der HERAcell® 240 mit einem neuartigen Wasserstands-Alarmsystem ausgerüstet. Dieser alarmiert rechtzeitig optisch und akustisch, wenn das Wasserreservoir nachgefüllt werden muss. Eine gleichmässig hohe Feuchtigkeit, die die Kulturen vor Austrocknung bewahrt, ist somit gewährleistet. Der Sensor dieses Systems wird während der 90 °C ContraCon-Routine dekontaminiert.

Kendro ist ein weltweit führender Anbieter von Produkten und Dienstleistungen auf den Gebieten Life und Materials Science, Drug Discovery und Biotechnologie. Kendro entwickelt, produziert und vertreibt Produkte der bekannten Marken SORVALL® und Heraeus für die Probenlagerung, -vorbereitung und weiterverarbeitung. Das Unternehmen beschäftigt seit seiner Übernahme durch die US-amerikanische SPX Corporation über 1700 Mitarbeiter. Kendro betreut seine Kunden durch ein umfangreiches Vertriebs- und Servicenetzwerk und durch Distributionspartner in über 150 Ländern.

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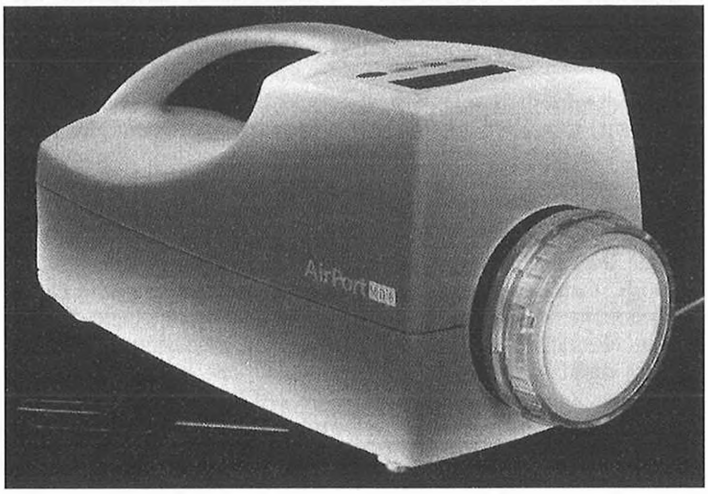
*Leserdienst Nr. 12*

## Sicherheit im Lufbraum: AirPort MD8 – den Keimen auf der Spur



Der neue Luftkeimsammler AirPort MD8 der Sartorius AG, Göttingen, ist für den Einsatz in der Pharmazeutischen Industrie, in der Biotechnologie sowie der Nahrungsmittel und Getränkeindustrie bestimmt. Des weiteren kommt er in Krankenhäusern, im Umweltschutz und in der Arbeitssicherheit zum Einsatz.

In Verbindung mit Gelatinefilter-Einwegeinheiten weist das portable Luftkeimsammelgerät Mikroorganismen und Viren in Reinräumen nach. Das tragbare und netzunabhängige System garantiert dabei sichere, reproduzierbare und quantitative Ergebnisse. Tragbar und akkubetrieben, eignet sich der AirPort MD8 insbesondere für den mobilen und universellen Einsatz.

Während der Luftkeimsammlung, beispielsweise bei der Kontrolle von Reinräumen, stellt die Akkuzustandsanzeige eine konstante Leistung des Gerätes sicher. Neben der 3-stufigen Einstellmöglichkeit des Volumenstroms ist auch das Probenvolumen von 10 bis 2000 Liter frei wählbar. Die jeweils zuletzt am Gerät eingestellten Parameter bleiben auch nach Ende der Messung erhalten.

Die benutzte Gelatine-Membranfilter-Methode – welche auch beim MD8 airscan zum Einsatz kommt und sich weltweit bewährt hat – garantiert zuverlässige und genaue Messergebnisse. Neben einer hohen Rückhalterate für Mikroorganismen wirkt die Restfeuchtigkeit des Filters einem Austrocknen der gesammelten Organismen entgegen. Die Löslichkeit des Gelatine-Filters eröffnet nach der Sammlung eine Vielzahl weiterer Anwendungsmöglichkeiten, wie z.B. die Kombination mit Schnelltest-Systemen, die Vierensammlung oder aber die Messung von höheren Keimkonzentrationen.

Der Luftkeimsammler ist ergonomisch geformt und leicht zu reinigen. Eine fünfsprachige Displayanzeige sowie die Möglichkeit, das Gerät direkt vor Ort kalibrieren zu können, bieten dem Anwender weitere Vorteile. Die austauschbaren Stecker des im Lieferumfang enthaltenen Ladegerätes erlauben ferner einen weltweiten Einsatz des nur 2,5 kg schweren und sehr geräuscharm arbeitenden AirPort MD8.

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  D-37070 Göttingen
  Tel. 0551 308 37 02
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  *www.sartorius.com*

*Leserdienst Nr. 13*

## ARL OPTIM'X: Wieder ein innovatives RF-Produkt von Thermo ARL

Getreu seiner Tradition der innovativen und zeitgemässen RF-Technologie stellt Thermo ARL, ein Thermo Electron-Unternehmen (NYSE:TMO), mit Stolz sein neuestes WDRF-Produkt vor. Dieses kompakte, neue System, das ARL OPTIM'X, hat mehrere einzigartige Leistungsmerkmale für optimalen Einsatz bei spezifischen Anwendungen. Das ARL OPTIM'X reiht sich in die bereits gut eingeführte Familie von Thermo ARL RF-Geräten ein: die ARL ADVANT'X und die ARL 9800 Reihe.

Das neue Gerät ist für folgende Anwendungen und Industriebereiche ausgelegt:

- Petrochemische Industrie (besonders Raffinerien), für die Analyse von S und Pb entsprechend ISO 14596 und ASTM D2622.
- Haupt- und Neben-Oxide in Kalkstein, Sand, Bauxit und anderen Bergbau-Bereichen.
- Haupt- und Neben-Oxide in Sanitärporzellan, feuerfesten Materialien, Schlacken und Sintern.
- Mineralische Nährstoffe in der Nahrungsmittel-Industrie.
- Anstriche, Papier, Bleche und andere Produkte, in denen einige Haupt- und Neben-Elemente überwacht werden müssen.

Das Gerät braucht weder interne noch externe Wasserkühlung, und kann mit gasdichten Detektoren ausgestattet werden, so dass auch eine externe Gasversorgung entfällt. Feste, flüssige und pulverförmige Proben können zur Analyse manuell oder automatisch eingegeben werden. Einige seiner einzigartigen Vorteile sind:

- Es kann mit Multichromatoren™ für Simultan-Analysen, einem SmartGonio™ für sequentielle Analysen, oder mit beidem ausgestattet werden.
- Mindestens 8 bis 10 mal bessere spektrale Auflösung, als die der meisten EDRF-Geräte.
- Hohe Zuverlässigkeit und Genauigkeit im Vergleich zu anderen WDRF-Klein-Geräten auf dem Markt.
- Bessere Leistung als gleichwertige EDRF-Geräte, bis hinunter zu Natrium.
- Eng gekoppelte Optik und vollständiges Ausnutzen der Röntgenröhren-Strahlung.
- Optisch gesteuertes, miniaturisiertes SmartGonio™ mit voneinander unabhängiger Theta-Zwei-Theta-Drehung von Kristall und Detektor.
- Ausgezeichnetes Preis/Leistungs-Verhältnis für spezifische Anwendungen.

Das ARL OPTIM'X ist die richtige Wahl für zuverlässige, genaue, optimale Analysen von ausgewählten Haupt- und Neben-Elementen oder Oxiden in organischen und anorganischen Matrizes. Es kann herkömmliche nasschemische Methoden ersetzen – bei bedeutender Analysen-Kostenersparnis.

Das ARL OPTIM'X kann auch eine Laborausstattung für Röntgen-Diffraktion, FT-IR und andere Gefügeuntersuchungs-Methoden ergänzen. Schliesslich kann es auch als Sicherheits-Reserve-Gerät dienen, in Labors, die schon mit Hochleistungs-Röntgen- OE- und anderen spektrometrischen Techniken zur ElementAnalyse ausgerüstet sind.

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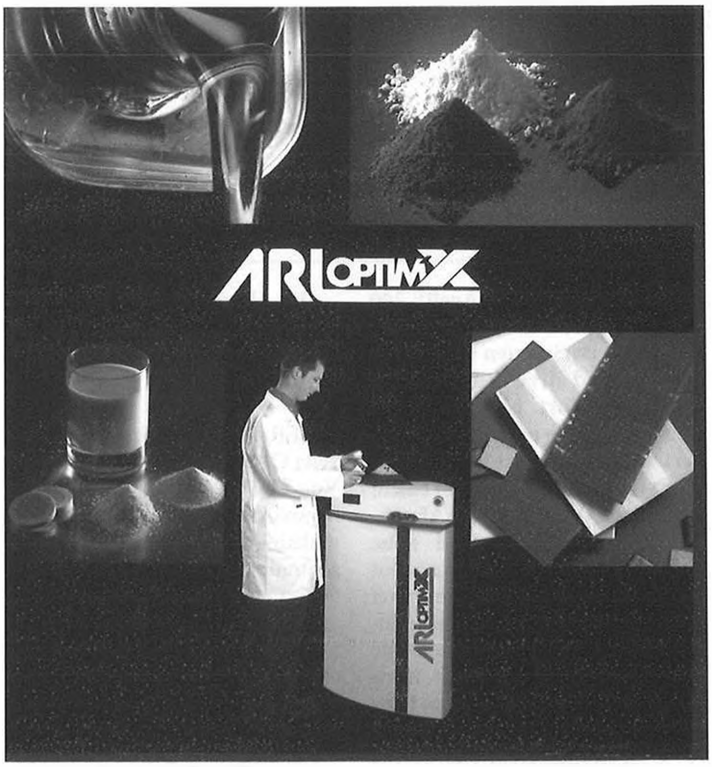
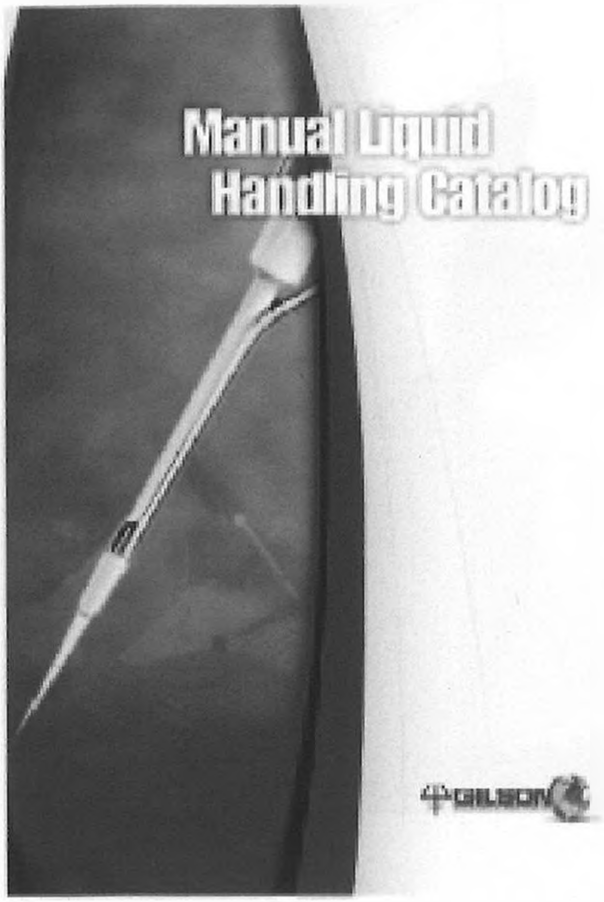
*Leserdienst Nr. 14*



## Pipetten Katalog 2002 von GILSON



Der übersichtlich Katalog illustriert das gesamte **Pipettensortiment** mit Zubehör.

Besonders interessant ist das **TowerPack™** Refillsystem für **GILSON** Spitzen. Es setzt in den Bereichen Sparsamkeit (Platzbedarf, Abfall) und Preis neue Massstäbe für Spitzen in Boxen. Die original **DIAMOND™** Spitzen bilden mit unserem **PIPETMAN®** ein optimales Pipettiersystem für die professionelle Anwendung.

Im **GILSON** Liquid Handling Katalog 2002 sind neben **PIPETMAN®** auch der **MICROMAN®** (positive displacement), der **DISTRIMAN™** (Repetierpipette) sowie die gesamte Zubehörpalette detailliert erläutert. Die informative Broschüre ermöglicht die schnelle Wahl des jeweils richtigen Pipettiersystems.

Den neuen **GILSON** Pipetten Katalog 2002 erhalten Sie kostenlos bei:

- GILSON (Schweiz) AG
  Untere Bahnhofstrasse 14
  CH-8932 Mettmenstetten
  Tel. 01 768 56 00
  E-mail: info-ch@gilson.com

*Leserdienst Nr. 15*

## JUMO IMAGO 500 – Mehr als ein Prozessregler

Durch die einfache und intuitive Bedienung macht es Spass, mit dem JUMO IMAGO 500 zu arbeiten. Die Bedienerführung wird durch die übersichtliche Darstellung von Bildern, Symbolen, Texten und Farben unterstützt.

Sein grosser hintergrundbeleuchteter Farbbildschirm mit einem 100 mm x 134 mm Sichtfeld bietet Ihnen einen sehr hohen Bedienkomfort.

Durch seine zwei getrennten Schnittstellen kann der JUMO IMAGO 500 Konfigurationsparameter- oder Programmdaten übertragen und gleichzeitig mit einer Visualisierungssoftware kommunizieren. Es ist damit aber auch möglich, die eingebaute Teleservicefunktion zu nutzen oder über die PROFIBUS-DP-Schnittstelle mit einer SPS Prozessdaten auszutauschen. Vier unabhängige Regler mit acht Parametersätzen lassen sich im JUMO IMAGO 500 verwalten, womit auch komplexere Regelaufgaben, wie z.B. die Kaskaden-Regelung realisiert werden können. Mit einer Zykluszeit ab 50ms ist das Gerät auch gut für schnelle Regel-strecken, z.B. Druckregelung geeignet.

Acht Mathematik- und Logikmodule ermöglichen die Einbindung von analogen oder digitalen Werten in mathematische oder logische Formeln, die beispielsweise für Verhältnis-, Differenzbegrenzungs- und Feuchteregelungen zur Verfügung stehen.

Ist das Gerät als Programmregler programmiert, stehen Ihnen vier Zeitplanprogramme mit 50 Programmen und insgesamt 1000 Abschnitten zur Verfügung. Acht Steuerspuren ermöglichen zu jedem Abschnitt das Schalten von zusätzlichen Steuerorganen. Selbstverständlich sind auch Funktionen wie Zyklusprogrammierung, Toleranzüberwachung oder Parametersatzanwahl vorhanden.

Zur Prozessüberwachung oder Steuerung hat das Gerät max. 16 Grenzwertschalter mit acht verschiedenen Funktionen sowie Ein- und Ausschaltverzögerung, Wischfunktion oder Selbsthaltung zur Auswahl.

Weitere Besonderheiten des JUMO IMAGO 500 sind eine Registrierfunktion, grafische Programmdarstellung und eine Ereignisliste.

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  Seestrasse 67
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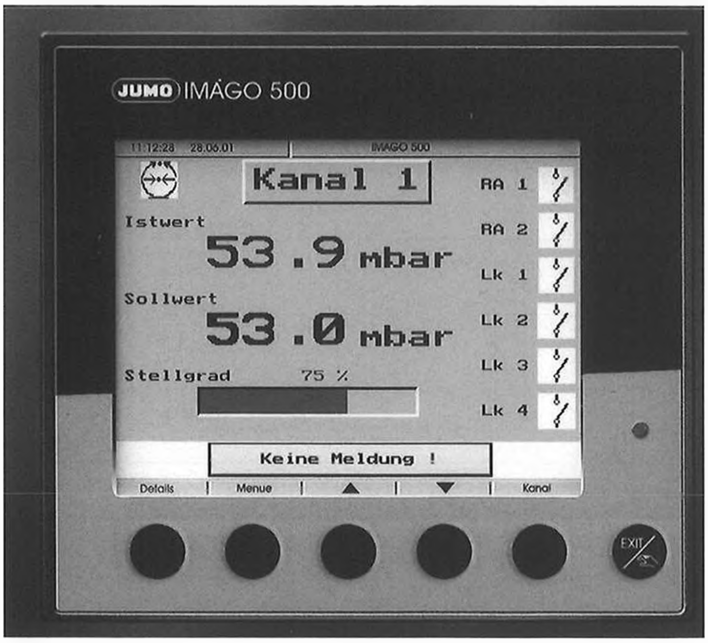
*Leserdienst Nr. 16*



## Neu: Hightech-Stereomikroskope Leisa MZ16 und MZ16 A

Eine Weltneuheiten in der Stereomikroskopie: höchste Auflösung 840 Lp/mm, höchste Vergrösserung 230x, Motorzoom, automatische Funktionen (Messen), Digitalanzeige. Nie zuvor konnten dreidimensionale Objekte mit einem Stereomikroskop so hoch aufgelöst beobachtet werden wie mit den neuen Stereomikroskopen Leica MZ16 und MZ16 A von Leica Microsystems. Zum erstem Mal sind mit einem Stereomikroskop 0,6 Mikron feine Strukturen sichtbar. Mit Objektivrevolver können Objekte in einem Vergrösserungsbereich von 7,1x bis 230x mit einer Auflösung bis 840 Lp/mm in kürzester Zeit durchgemustert werden. Laborversuche haben bewiesen: Das bisher extrem zeitraubende Vorsortieren, Auslesen, Charakterisieren, Auswerten wird um das Fünffache verkürzt.

Das neue Leica MZ16 A ist das erste Stereomikroskop mit motorischem Zoom, das sich ebenso wie der optionale Motorfokus bequem, sehr schnell und sehr genau steuern lässt – mit feinen, leichten Fingerbewegungen, mit den Füssen oder computergesteuert. Sie sparen viel Zeit und Kraft und sind produktiv wie noch nie.

Bei jedem Zoomwechsel zeigt Ihnen das Leica MZ16 A sofort die aktuelle Vergrösserung und die Messwerte in mm, Inch oder tausendstel Inch an. Überzeugen Sie sich, wie viel Zeit Sie für die wichtigen Dinge gewinnen.

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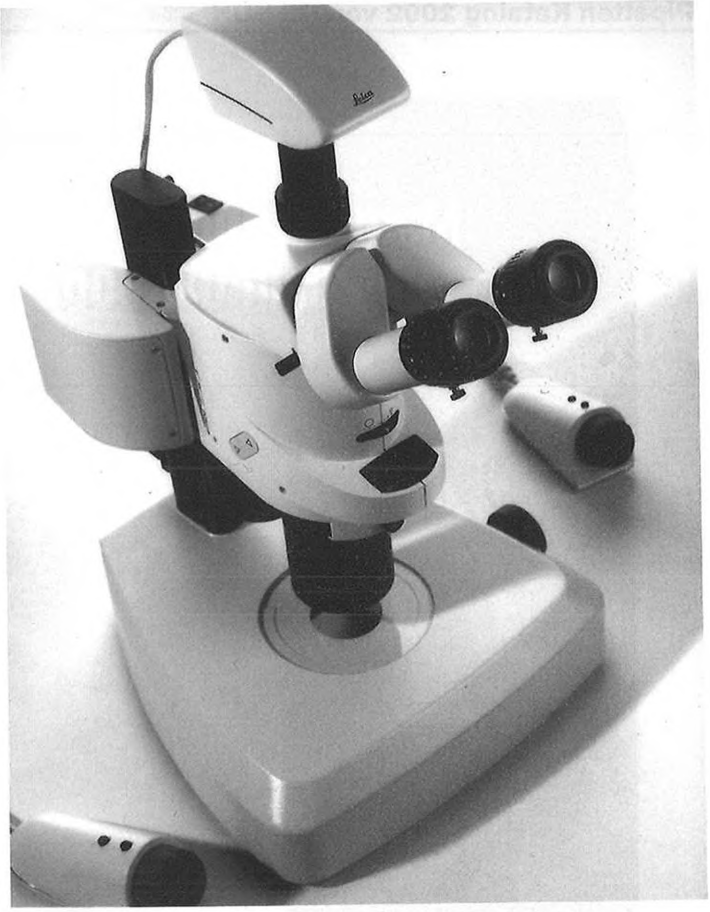

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## CHIMIA-Leserdienst Heft 7/8/2002

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Das Informationszentrum Chemie Biologie der ETH Zürich sucht per 1. Januar 2003 eine/einen

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**Aufgabenbereich:**
Das Informationszentrum Chemie Biologie ist eine Informationsstelle der Departemente Chemie und Biologie der ETH Zürich (vgl. www.infochembio.ethz.ch). Sie dient allen ETH Hochschulangehörigen und auswärtigen Benützer, welche biologische und chemische Literatur benötigen. Die weit gehende, auch rückwirkende elektronische Verfügbarkeit der Primärliteratur führt zusammen mit bereits vorhandenen Datenbanken zu einer nahezu völligen Verschiebung der Nutzung vom Ort der Bibliothek zum Arbeitsplatz. Die steigenden Kosten dafür erzwingen eine effiziente Nutzung und eine enge Zusammenarbeit mit den übrigen bibliothekarischen Einrichtungen der ETH und schweizweit. Erstes Ziel ist es daher, die Informationsnutzung für Lehre und Forschung durch fachspezifische nutzerorientierte Informationsaufbereitung und der Betreuung, Schulung und Ausbildung der zukünftigen Chemiker und Biologen zu optimieren. Schwerpunkte dabei bilden sowohl Vorlesungen, Kurse und persönliche Beratung, als auch die Anpassung und Ergänzung des Bibliothekssystems mit Portalfunktion und Multimedia Unterrichtsmaterial. Als Leiter/in sind Sie zusammen mit Ihrem Team von 8 Personen, das in naher Zukunft mit 2-3 zusätzlichen Stellen erweitert wird, für die Planung und Entwicklung des Informationszentrums, für die Bestandesentwicklung und den Bestandesnachweis, für Recherchen und Dokumentbeschaffung sowie für die Ausbildung und Schulung der Studenten und Mitarbeitenden verantwortlich. Sie erfüllen diese Aufgaben in naher Zusammenarbeit mit der ETH Bibliothek. Auf eine hohe Webpräsenz wird dabei Wert gelegt.

**Anforderungen:**
Sie verfügen über ein abgeschlossenes Hochschulstudium (Naturwissenschaft). Weiter besitzen Sie Leitungs- und Führungserfahrung und verstehen es, Aufgaben zu delegieren, damit die Verantwortungsbereiche der Angestellten eine interessante Herausforderung darstellen. Ihre kommunikativen Fähigkeiten ermöglichen Ihnen einen guten Kontakt zu Departementsangehörigen (Professoren, Forschern, Studenten), ETH Dienststellen und anderen Hochschulen. Fundierte Kenntnisse in verschiedensten EDV-Anwendungen sowie sehr gute Englischkenntnisse werden vorausgesetzt.

**Leistungsangebot:**
Bei dieser sehr selbständigen Tätigkeit bieten wir Ihnen die Herausforderung, die Organisations- und Führungsstruktur auf zukünftige Anforderungen auszurichten und die Schnittstellen zwischen Forschern, Lehrern, Studenten und auswärtigen Benützern auszubauen.

**Ihre Bewerbung:**
Bitte senden Sie Ihre vollständigen Bewerbungsunterlagen bis Ende August unter Kennwort **LEIT-INFZ** an ETH Zürich, Frau Tanja Gloor, Personalchefin, ETHZ, 8092 Zürich. Für weitere Auskünfte wenden Sie sich bitte an:
Herr Josef Meienberger, Tel. 01 632 30 67,
Email: meienberger@chem.ethz.ch

**Weitere Stellen finden Sie unter www.pa.ethz.ch.**

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La Faculté des sciences de l'Université de Genève ouvre une inscription pour un poste de

## MAÎTRE D'ENSEIGNEMENT ET DE RECHERCHE
**en chimie analytique pharmaceutique**

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| **Charge** | Il s'agit d'un poste à charge complète comprenant une charge de cours ainsi que l'organisation des travaux pratiques de l'analyse pharmaceutique pour les étudiants en pharmacie. Collaboration à des projets interdisciplinaires de recherche, plus particulièrement dans le domaine de l'électrophorèse capillaire et de la chromatographie en phase liquide. |
| **Titre exigé** | – Diplôme de pharmacien ou titre jugé equivalent.<br>– Doctorat en sciences pharmaceutiques ou titre jugé équivalent. |
| **Entrée en fonction** | 1^er^ janvier 2003 ou date a convenir. |

Les dossiers de candidature doivent être adressés avant le 27 septembre 2002, au professeur Jean-Luc Veuthey, président de la Section de pharmacie, Quai Ernest-Ansermet 30, CH-1211 Genève 4, auprès duquel les renseignements complémentaires peuvent être obtenus sur le cahier des charges et les conditions.

Désirant associer tant les femmes que les hommes à l'enseignement et a la recherche, l'Université souhaite recevoir davantage de candidatures féminines.

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