

# Organic & Biomolecular Chemistry

An international journal of synthetic, physical and biomolecular organic chemistry  
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## IN THIS ISSUE

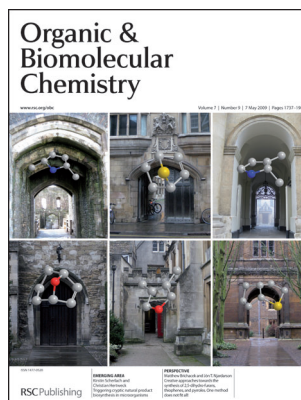
ISSN 1477-0520 CODEN OBCRAK 7(9) 1737–1988 (2009)



### Cover

See Jennifer R. Hiscock *et al.*, pp. 1781–1783.  
The fluorescence of a carbazolylurea based anion receptor is selectively quenched upon addition of benzoate anions to the receptor in DMSO- $d_6$ -water solution.

Image reproduced by permission of Philip A. Gale from *Organic & Biomolecular Chemistry*, 2009, **7**, 1781.



### Inside cover

See Matthew Brichacek and Jón T. Njardarson, pp. 1761–1770.  
As a metaphor for the various synthetic approaches one can use to assemble a desired target structure, the cover shows pictures of six different entry ways. Pictures are courtesy of Betsy Eigenberg.

Image reproduced by permission of Jón T. Njardarson from *Organic & Biomolecular Chemistry*, 2009, **7**, 1761.

## CHEMICAL BIOLOGY

### B33

Drawing together research highlights and news from all RSC publications, *Chemical Biology* provides a ‘snapshot’ of the latest developments in chemical biology, showcasing newsworthy articles and significant scientific advances.

## Chemical Biology

May 2009/Volume 4/Issue 5

[www.rsc.org/chembiology](http://www.rsc.org/chembiology)

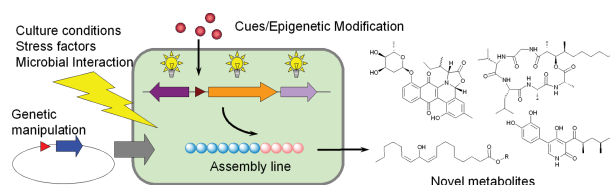
## EMERGING AREA

### 1753

#### Triggering cryptic natural product biosynthesis in microorganisms

Kirstin Scherlach and Christian Hertweck\*

Often valuable microbial products are overlooked because their biosynthetic pathways are only activated under specific conditions. This report gives an overview on the strategies to yield “cryptic natural products”.



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# Organic & Biomolecular Chemistry

An international journal of synthetic, physical and biomolecular organic chemistry

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Organic & Biomolecular Chemistry brings together molecular design, synthesis, structure, function and reactivity in one journal. It publishes fundamental work on synthetic, physical and biomolecular organic chemistry as well as all organic aspects of: chemical biology, medicinal chemistry, natural product chemistry, supramolecular chemistry, macromolecular chemistry, theoretical chemistry, and catalysis.

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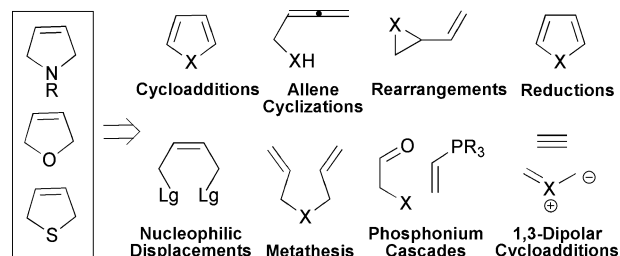
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1761

### Creative approaches towards the synthesis of 2,5-dihydrofurans, thiophenes, and pyrroles. One method does not fit all!

Matthew Brichacek and Jón T. Njardarson\*

A review of synthetic approaches that provide access to 2,5-dihydrofuran, thiophene and pyrrole building blocks is presented, their limits demonstrating that a single method is insufficient.



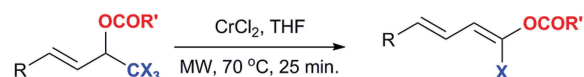
## COMMUNICATIONS

1771

### Highly stereoselective synthesis of (*Z,E*)-1-halo-1,3-dienol esters *via* rearrangement of Fischer chromium chloro-carbenes using microwave irradiation

Dhurke Kashinath, Charles Mioskowski, J. R. Falck, Mohan Goli, Stéphane Meunier,\* Rachid Baati\* and Alain Wagner

Functionalized (*Z,E*)-1-halo-1,3-dienol esters are synthesized in a highly stereoselective manner *via* CrCl<sub>2</sub>-mediated rearrangement of allylic trihalomethylcarbinol esters induced by microwave irradiation.



R = alkyl, aryl, heteroaryl  
R' = Me, Ph, 2-thienyl, 2-pentenyl  
X<sub>3</sub> = Cl<sub>3</sub>, Br<sub>2</sub>F

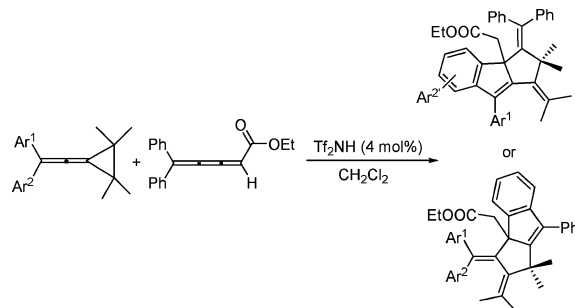
(*Z,E*)-1-halo-1,3-dienol esters  
X = F, Cl  
64–92 %

1775

### Triflic imide-catalyzed cascade cycloaddition and Friedel–Crafts reaction of diarylvinylenecyclopropanes with ethyl 5,5-diarylpenta-2,3,4-trienoate

Wei Li and Min Shi\*

A cascade cycloaddition and Friedel–Crafts reaction of diarylvinylenecyclopropanes with ethyl 5,5-diarylpenta-2,3,4-trienoates provided a variety of novel polycyclic ester derivatives in moderate to good yields in the presence of triflic imide under mild conditions.

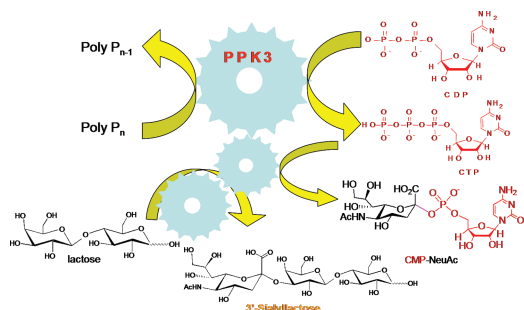


1778

### Enzymatic synthesis of sialylation substrates powered by a novel polyphosphate kinase (PPK3)

Jozef Nahálka\* and Vladimír Pátoprstý

A novel energy protein, PPK3, which effectively transfers macroergic phosphate bonds from soluble polyphosphates to nucleoside diphosphates, was applied in the enzymatic synthesis of cytidine monophosphate *N*-acetylneuraminic acid and 3'-sialyllactose. The enzyme was immobilized *in vivo* into inclusion bodies.



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## Perspective:

### Chemical approach toward efficient DNA methylation analysis

Akimitsu Okamoto, *Org. Biomol. Chem.*, 2009, **7**, 21

DOI: 10.1039/b813595a

## Emerging Area:

### Mechanistic approaches to palladium-catalyzed alkene difunctionalization reactions

Katrina H. Jensen and Matthew S. Sigman, *Org. Biomol. Chem.*, 2008, **6**, 4083

DOI: 10.1039/b813246a

## Communications:

### 3- and 5-Functionalized BODIPYs via the Liebeskind-Srogl reaction

Junyan Han, Oswaldo Gonzalez, Angelica Aguilar-Aguilar, Eduardo Peña-Cabrera and Kevin Burgess, *Org. Biomol. Chem.*, 2009, **7**, 34

DOI: 10.1039/b818390b

### Stereoselective synthesis of the hormonally active (25S)- 7-dafachronic acid, (25S)- 4-dafachronic acid, (25S)-dafachronic acid, and (25S)-cholestenoic acid

René Martin, Frank Däbritz, Eugeni V. Entchev, Teymuraz V. Kurzchalia and Hans-Joachim Knölker, *Org. Biomol. Chem.*, 2008, **6**, 4293

DOI: 10.1039/b815064h

## Papers:

### Cyclic tetraureas with variable flexibility – synthesis, crystal structures and properties

Denys Meshcheryakov, Françoise Arnaud-Neu, Volker Böhmer, Michael Bolte, Julien Cavaleri, Véronique Hubscher-Bruder, Iris Thondorf and Sabine Werner  
*Org. Biomol. Chem.*, 2008, **6**, 3244

DOI: 10.1039/b808773c

### Recognition and discrimination of DNA quadruplexes by acridine-peptide conjugates

James E. Redman, J. M. Granadino-Roldán, James A. Schouten, Sylvain Ladame, Anthony P. Reszka, Stephen Neidle and Shankar Balasubramanian,  
*Org. Biomol. Chem.*, 2009, **7**, 76

DOI: 10.1039/b814682a

### Indium and zinc-mediated Barbier-type addition reaction of 2,3-allenals with allyl bromide: an efficient synthesis of 1,5,6-alkatrien-4-ols

Wangqing Kong, Chunling Fu and Shengming Ma, *Org. Biomol. Chem.*, 2008, **6**, 4587

DOI: 10.1039/b812869c

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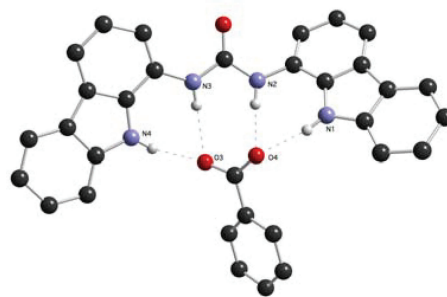
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1781

### Fluorescent carbazoylurea anion receptors

Jennifer R. Hiscock, Claudia Caltagirone, Mark E. Light, Michael B. Hursthouse and Philip A. Gale\*

A series of fluorescent carbazoylurea base anion receptors have been synthesised that show a high affinity for oxo-anions (particularly bicarbonate and acetate). The fluorescence of dicarbazoylurea (**1**) is quenched upon addition of benzoate anions in DMSO–0.5% water.



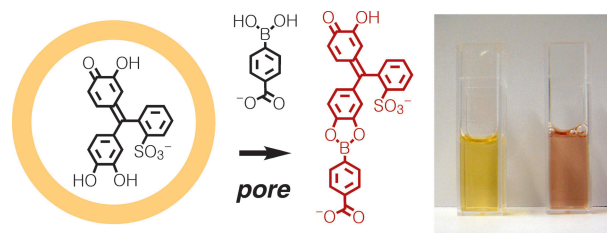
## PAPERS

1784

### Colorful methods to detect ion channels and pores: intravesicular chromogenic probes that respond to pH, pM and covalent capture

Sara M. Butterfield, Andreas Hennig and Stefan Matile\*

Indicators that respond to chemical stimulation are adapted to the colorimetric detection of the activity of ion channels, transporters and pores as well as their ability to select among different ions or to sense various analytes.

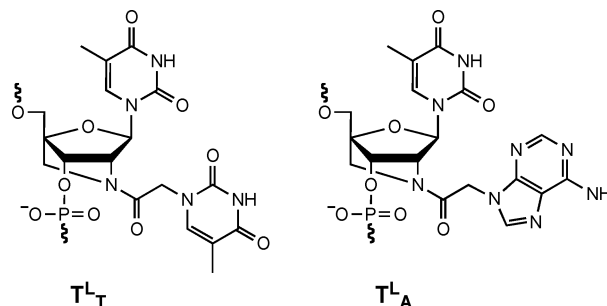


1793

### Functionalization of 2'-amino-LNA with additional nucleobases

Tadashi Umemoto, Jesper Wengel and Andreas Stahl Madsen\*

Oligonucleotides containing “double-headed” LNA monomers with an additional thymine or adenine moiety show increased thermal stability when forming duplexes with complementary DNA, even allowing multiple incorporations.

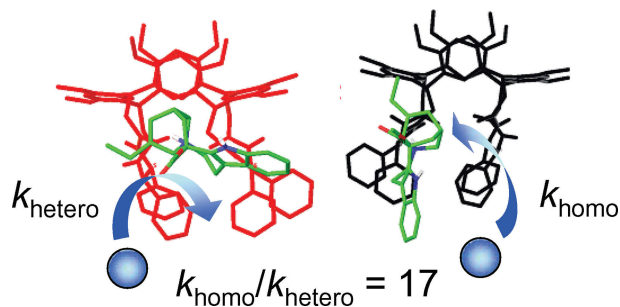


1798

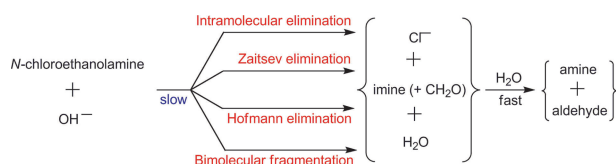
### Interactions of vinca alkaloid subunits with chiral amido[4]resorcinarenes: a dynamic, kinetic, and spectroscopic study

Bruno Botta,\* Caterina Frascchetti, Francesca R. Novara, Andrea Tafi, Fabiola Sacco, Luisa Mannina, Anatoli P. Sobolev, Jochen Mattay, Matthias C. Letzel and Maurizio Speranza\*

The gas-phase amine-induced displacements of (+)-catharanthine (**C**) from chiral amido[4]resorcinarenes (**M**) exhibit larger or smaller kinetic enantioselectivities, depending on the functional groups present in the **M** hosts.



1807

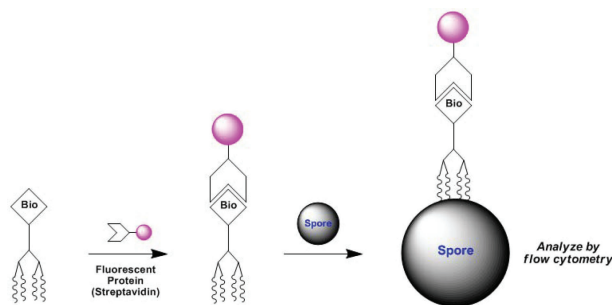


### A theoretical study on the mechanism of the base-promoted decomposition of *N*-chloro,*N*-methylethanolamine

Daniel R. Ramos, Raquel Castillo, Moisés Canle L., M. Victoria García, Juan Andrés and J. Arturo Santaballa\*

The pathways involved in the first step of the base-promoted decomposition of *N*-chloro,*N*-methylethanolamine in aqueous solution are investigated at the MP2/6-31++G(d,p) computing level. The common feature of the four reaction paths is the proton transfer to HO<sup>-</sup> being more advanced than all other molecular events, whereas imine formation is delayed.

1815

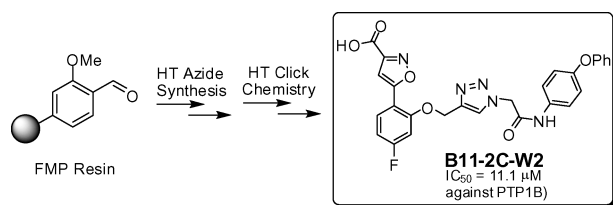


### Refined multivalent display of bacterial spore-binding peptides

Sabrina Lusvarghi, Jenny Morana Kim, Yehuda Creeger and Bruce Alan Armitage\*

A tetravalent scaffold was used to display a peptide that binds specifically to bacterial spores. Flow cytometry demonstrated binding of the tetravalent peptide at low nanomolar concentrations, with progressively lower affinity for di- and monovalent analogues.

1821

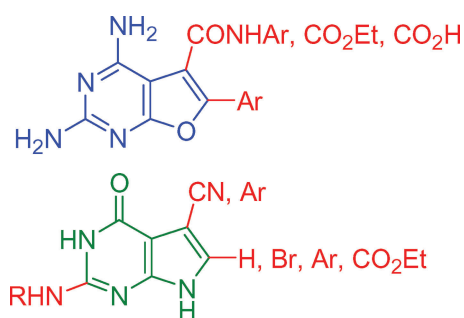


### High-throughput synthesis of azide libraries suitable for direct “click” chemistry and *in situ* screening

Rajavel Srinivasan, Lay Pheng Tan, Hao Wu, Peng-Yu Yang, Karunakaran A. Kalesh and Shao Q. Yao\*

We report herein a highly robust and efficient strategy for high-throughput synthesis of a 325-member azide library, which was subsequently “clicked” to generate the corresponding bidentate inhibitors against PTP1B.

1829



### Diversity oriented syntheses of fused pyrimidines designed as potential antifolates

Colin L. Gibson, Judith K. Huggan, Alan Kennedy, Lionel Kiefer, Jeong Hwan Lee, Colin J. Suckling,\* Carol Clements, Alan L. Harvey, William N. Hunter and Lindsay B. Tulloch

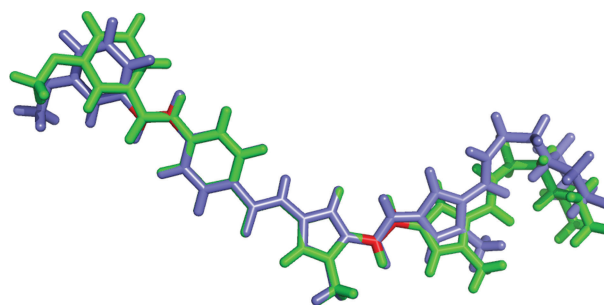
Furo[2,3-*d*]pyrimidines and pyrido[2,3-*d*]pyrimidines have been prepared by routes leading to diversity in the red substituents; several compounds were found to have significant inhibitory activity against the parasite, *Trypanosoma brucei brucei* in cellular assays and against pteridine reductase 1, a key antiparasitic target, in purified enzyme assays.

1843

### A new synthesis of alkene-containing minor-groove binders and essential hydrogen bonding in binding to DNA and in antibacterial activity

Nahoum G. Anthony, David Breen, Gavin Donoghue, Abedawn I. Khalaf, Simon P. Mackay, John A. Parkinson and Colin J. Suckling\*

Using novel synthetic minor-groove binders based upon distamycin, both hydrophobic interactions and specific hydrogen bonds are shown to be important in obtaining highly potent antibacterial compounds.

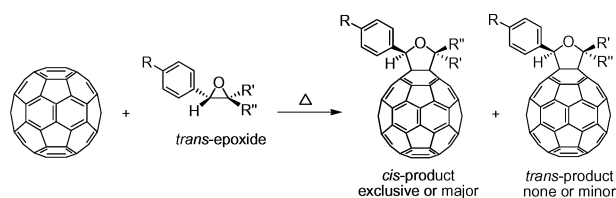


1851

### Reaction of [60]fullerene with *trans*-epoxides: a theoretical study

Guan-Wu Wang,\* Ping Wu and Hai-Tao Yang

The experimentally obtained exclusive or predominant *cis*-products from the reaction of C<sub>60</sub> with carbonyl ylides generated from *trans*-epoxides can be explained well by computational investigation of the proposed reaction mechanism; the ring opening of the *trans*-epoxides, which is the rate-determining step, should be included in the whole reaction profiles to explain all experimental phenomena.

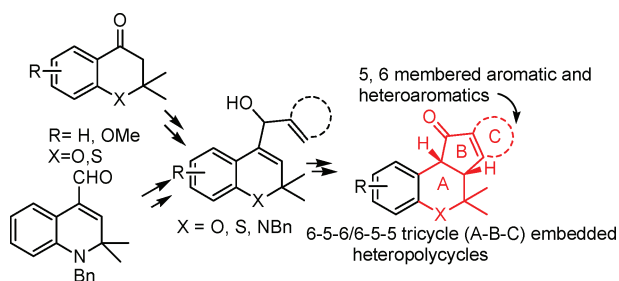


1858

### Application of Nazarov cyclization to access [6-5-6] and [6-5-5]tricyclic core embedded new heterocycles: an easy entry to structures related to Taiwaniaquinoids

Ritesh Singh, Maloy Kumar Parai and Gautam Panda\*

A concise and general route to synthesize a new class of [6-5-6] and [6-5-5]tricyclic core embedded polyheterocycles has been accomplished through diastereoselective Nazarov cyclization using triflic acid with an overall yield of 35–40%.

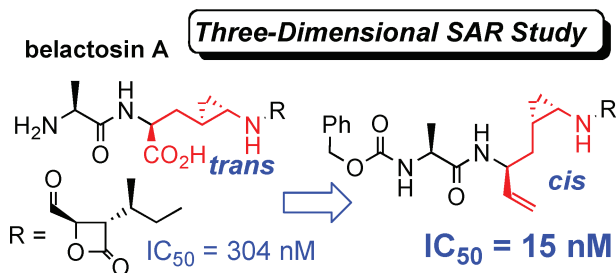


1868

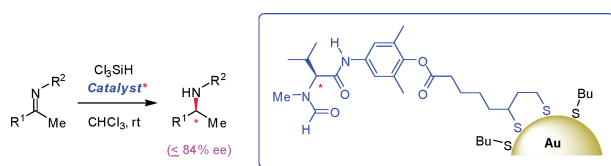
### Three-dimensional structure-activity relationship study of belactosin A and its stereo- and regioisomers: development of potent proteasome inhibitors by a stereochemical diversity-oriented strategy

Keisuke Yoshida, Kazuya Yamaguchi, Akira Mizuno, Yuka Unno, Akira Asai, Takayuki Sone, Hideyoshi Yokosawa, Akira Matsuda, Mitsuhiro Arisawa and Satoshi Shuto\*

A highly potent proteasome inhibitor, which is the unnatural *cis*-cyclopropane analog of belactosin A, was identified based on the stereochemical diversity-oriented strategy using a conformationally rigid cyclopropane structure.



1878

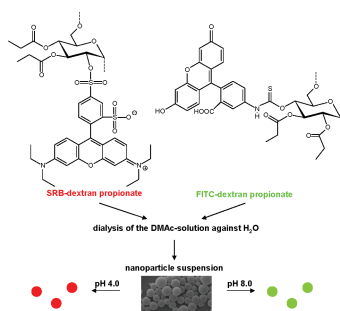


### Organocatalysts immobilised onto gold nanoparticles: application in the asymmetric reduction of imines with trichlorosilane

Andrei V. Malkov,\* Marek Figlus, Graeme Cooke,\* Stuart T. Caldwell, Gouher Rabani, Mark R. Prestly and Pavel Kočovský\*

Gold nanoparticles functionalised with a valine-derived formamide, have been developed as an effective catalyst for the asymmetric reduction of ketimine **1** with trichlorosilane ( $\leq 84\%$  ee).

1884

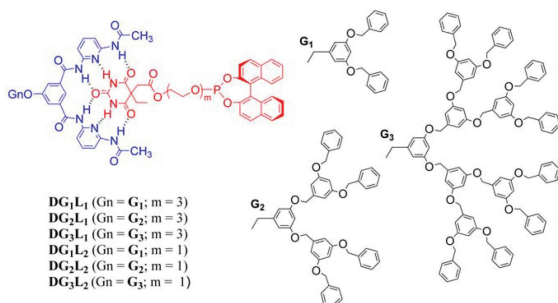


### Evaluation of fluorescent polysaccharide nanoparticles for pH-sensing

Anja Schulz,\* Stephanie Hornig, Tim Liebert, Eckhard Birkner, Thomas Heinze and Gerhard J. Mohr\*

Dextran nanoparticles covalently labeled with a fluorescent pH-indicator dye (fluorescein isothiocyanate) and a reference dye (sulforhodamine B) are investigated for their suitability as pH-sensor materials. The nanosensors are stable during autoclaving, exhibit low cross-reactivity to ionic strength and the dextran matrix protects the immobilized dyes from oxidation.

1890

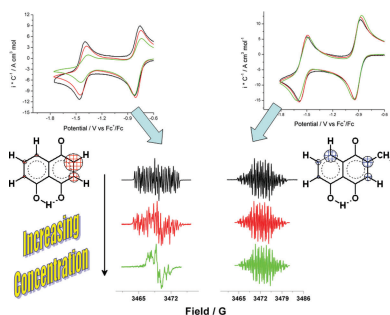


### Supramolecular chiral dendritic monophosphites assembled by hydrogen bonding and their use in the Rh-catalyzed asymmetric hydrogenation

Yong Li, Yan-Mei He, Zhi-Wei Li, Feng Zhang and Qing-Hua Fan\*

Novel supramolecular chiral dendritic monophosphite ligands are prepared and successfully applied in an Rh-catalyzed asymmetric hydrogenation. The catalyst could be easily recycled *via* solvent precipitation.

1896



### Towards a molecular-level understanding of the reactivity differences for radical anions of juglone and plumbagin: an electrochemical and spectroelectrochemical approach

Lindsay S. Hernández-Muñoz, Martín Gómez, Felipe J. González, Ignacio González and Carlos Frontana\*

An electrochemical and spectroelectrochemical strategy is presented for evaluating reactivity differences, due to self-protonation processes in the semiquinone anions from naturally occurring quinones juglone and plumbagin.

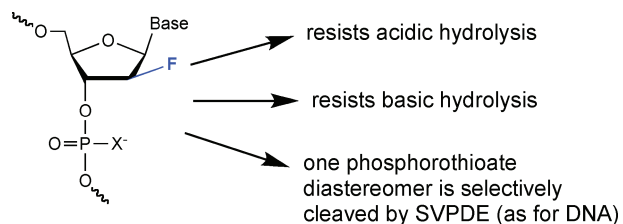


1904

### Studies on the hydrolytic stability of 2'-fluoroarabinonucleic acid (2'-F-ANA)

Jonathan K. Watts, Adam Katolik, Júlia Viladoms and Masad J. Damha\*

The stability of 2'-F-ANA to acidic and basic hydrolysis was explored for the first time. 2'-F-ANA was highly stable to acid and was also quite stable to base. This is also the first study of the stereochemistry of nuclease cleavage of PS-2'-F-ANA.



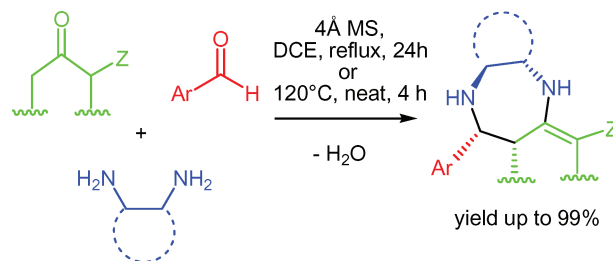
1911



### User-friendly stereoselective one-pot access to 1,4-diazepane derivatives by a cyclodehydrative three-component reaction with 1,3-dicarbonyls

Enrique Sotoca, Christophe Allais, Thierry Constantieux\* and Jean Rodriguez\*

An efficient, user-friendly solvent- and catalyst-free multicomponent reaction of 1,3-dicarbonyls with 1,2-diamines and aromatic aldehydes is described for the direct stereoselective synthesis of 1,4-diazepane derivatives.



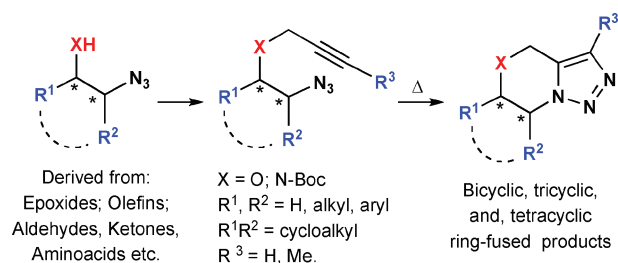
1921



### Intramolecular azide-alkyne [3 + 2] cycloaddition: versatile route to new heterocyclic structural scaffolds

Rongti Li, Daniel J. Jansen and Apurba Datta\*

A systematic investigation of the intramolecular azide-alkyne [3 + 2] cycloaddition, leading to a variety of structurally unique heterocycles is described.



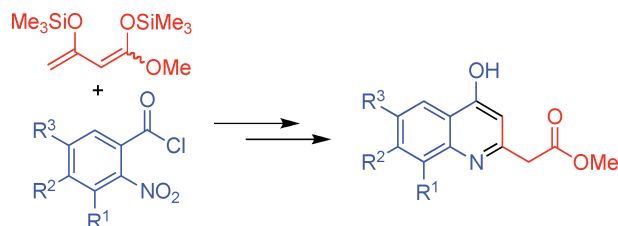
1931



### Synthesis of chromones and 4-hydroxyquinolines based on uncatalyzed condensations of 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene with 2-alkoxy- and 2-nitrobenzoyl chlorides and related reactions

Thomas Rahn, Bettina Appel, Wolfgang Baumann, Haijun Jiao, Armin Börner, Christine Fischer and Peter Langer\*

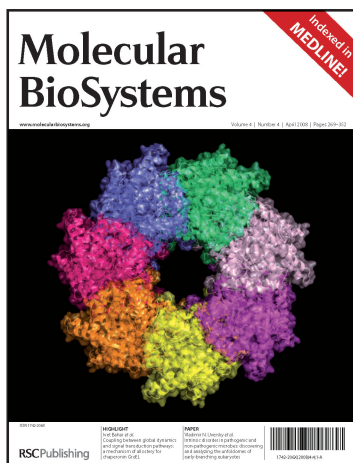
Functionalized 2-hydroxychroman-4-ones, chromones, and 4-hydroxyquinolines were prepared based on the reaction of 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene with 2-methoxy- and 2-nitrobenzoyl chlorides.



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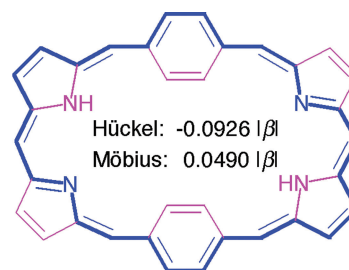
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1939

### Macrocyclic aromaticity in Hückel and Möbius conformers of porphyrinoids

Jun-ichi Aihara\* and Hideki Horibe

Degrees of macrocyclic aromaticity and associated main macrocyclic conjugation pathways in Hückel- and Möbius-type porphyrinoids were predicted successfully using our recently proposed method based on calculated bond resonance energies.



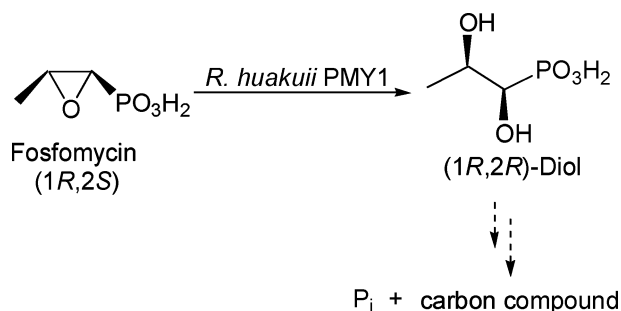
Superaromatic Stabilization Energies

1944

### Studies on the biodegradation of fosfomycin: Growth of *Rhizobium huakuii* PMY1 on possible intermediates synthesised chemically

John W. McGrath, Friedrich Hammerschmidt,\*  
Werner Preusser, John P. Quinn\* and Anna Schweifer

The clinically used antibiotic fosfomycin is degraded by *R. huakuii* via the (1*R*,2*R*)-diol with release of P<sub>i</sub>.

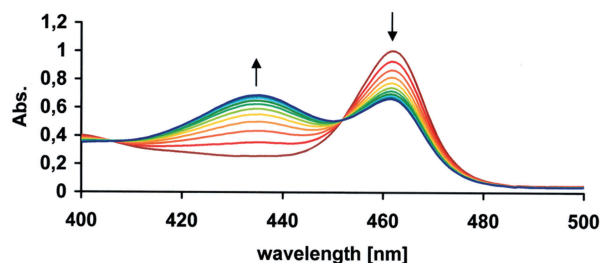


1954

### New insights into the *S*-nitrosothiol–ascorbate reaction. The formation of nitroxyl

Michael Kirsch,\* Anna-Marie Büscher, Stephanie Aker,  
Rainer Schulz and Herbert de Groot

The *S*-nitrosothiol–ascorbate reaction, *i.e.*, the converting reaction of the popular so-called “biotin-switch technique”, yields both a thiol function and the thiol-depleting intermediate nitroxyl.



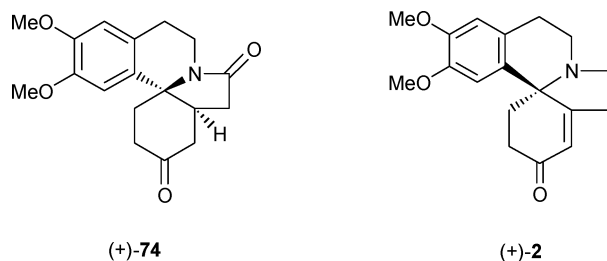
1963



### New approaches for the synthesis of erythrinan alkaloids

Fengzhi Zhang, Nigel S. Simpkins\* and Alexander J. Blake

The synthesis of erythrinan systems has been addressed using either asymmetric synthesis approaches with chiral lithium amide bases, or by using (*L*)-malic acid as a chiral pool starting material. Chiral starting materials were elaborated to final compounds such as keto-amide **74**, and 3-demethoxyerythratidinone (**2**), and others, by ring closures involving radicals or *N*-acyliminium ions as intermediates, or by alkene metathesis.





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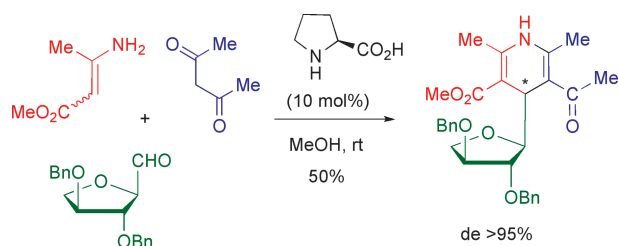
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Dr. Andrew Phillips, UC Boulder

1980

**Dihydropyridine C-glycoconjugates by organocatalytic Hantzsch cyclocondensation. Stereoselective synthesis of  $\alpha$ -threofuranose C-nucleoside enantiomers**

Diogo R. B. Ducatti, Alessandro Massi,\* Miguel D. Nosedá, Maria Eugênia R. Duarte and Alessandro Dondoni\*

The proline-catalyzed three-component Hantzsch reaction of rare C-glycosyl aldehydes affords dihydropyridine C-glycoconjugates in a fully stereoselective manner.



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# Organic & Biomolecular Chemistry

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#### Design and synthesis of phosphole-based systems for novel organic materials

Yoshihiro Matano and Hiroshi Imahori, *Org. Biomol. Chem.*, 2009, DOI: 10.1039/b819255n

### Emerging Area:

#### Metal-catalysed halogen exchange reactions of aryl halides

Tom D. Sheppard, *Org. Biomol. Chem.*, 2009, DOI: 10.1039/b818155a

### Communication:

#### Highly enantioselective asymmetric autocatalysis using chiral ruthenium complex-ion-exchanged synthetic hectorite as a chiral initiator

Tsuneomi Kawasaki, Toshiki Omine, Kenta Suzuki, Hisako Sato, Akihiko Yamagishi and Kenso Soai, *Org. Biomol. Chem.*, 2009, DOI: 10.1039/b823282b

### Paper:

#### Ruthenium-based metallacrown complexes for the selective detection of lithium ions in water and in serum by fluorescence spectroscopy

Sébastien Rochat, Zacharias Grote and Kay Severin, *Org. Biomol. Chem.*, 2009, DOI: 10.1039/b820592b

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# Chemical Biology

Polymer-based test for proteins proves sensitive, selective and simple

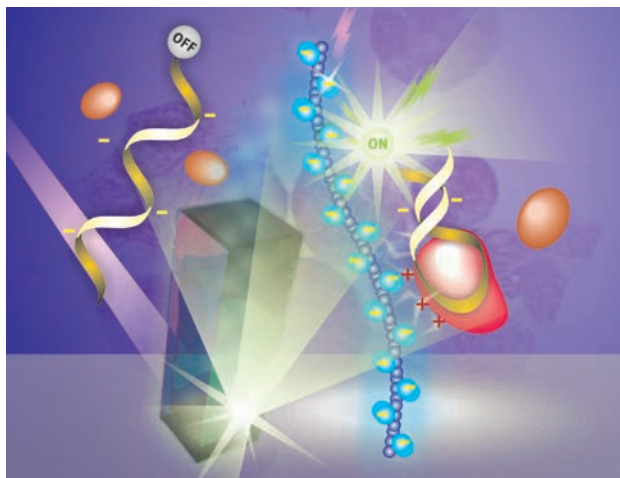
## The beginning of the end for ELISA?

A polymer-based test for proteins has proved sensitive, selective and much simpler than a traditional assay.

Proteins can act as markers for diseases, so it is important to be able to detect them easily and quickly. They are conventionally detected in clinics using immunoassays called enzyme-linked immunosorbent assays, or ELISAs. Now Jing Wang and Bin Liu from the National University of Singapore have developed a test for proteins that is simpler and faster to use.

Whilst ELISAs are sensitive they are time-consuming. The assays use antibodies on a solid substrate to bind the protein of interest so the test requires numerous surface modification and washing steps as well as detection. Wang and Liu's test uses aptamers instead of antibodies and protein detection occurs in solution rather than at a surface, which makes their assay quicker.

Aptamers are typically oligonucleic acids or peptides and bind a specific target molecule, which can be a protein. Wang and Liu used an



aptamer specific for lysozyme – a protein that is widely present in cells. To detect the protein they modified the aptamer molecules with a dye and combined them in solution with a conjugated polymer.

In Wang and Liu's system, both the polymer and aptamer molecules are negatively charged and repel each other in solution. However, when a

positively charged protein specific to the aptamer – lysozyme in this case – is present, the aptamer binds the protein and its surface charge switches to be positive too. It is therefore attracted to the conjugated polymer. Shining light on the solution excites the polymer which transfers energy to the dye on the bound aptamer, causing it to fluoresce.

Wang and Liu found the test's sensitivity was comparable to an ELISA. The test could be used to detect protein selectively in urine, saliva and serum, although the sensitivity does decrease as the sample complexity increases.

Shengqi Wang, an expert on clinical diagnostic techniques from the Beijing Institute of Radiation Medicine, China, says the method 'offers a new way of detecting protein.' Although much work is needed before the method could seriously rival the robustness, sensitivity and repeatability of ELISAs, 'the method is easy to manipulate and saves time,' adds Shengqi Wang. *Freya Mearns*

**Wang and Liu's polymer –aptamer mixture fluoresces if lysozyme enzyme is present**

#### Reference

J Wang and B Liu, *Chem. Commun.*, 2009, DOI: 10.1039/b820001g

## In this issue

### Unlocking the mysteries of mitochondria

Caged chemical probe offers spatial control in study of the body's power plants

### Lab-on-a-tube for brain monitoring

A spiral sensor sandwich could help patients with traumatic brain injury

### Elemental evolution

Ariel Anbar talks about fossils, Star Trek and life on Mars

### What is metallomics?

This month's Instant insight introduces the relative newcomer in the '-omics' fields



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# Research highlights

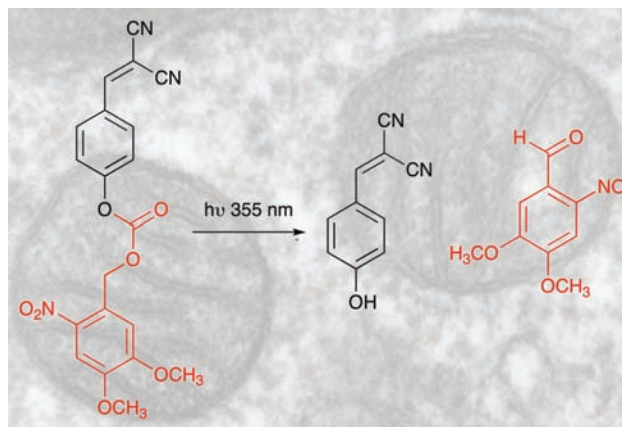
## Caged chemical probe offers spatial control in mitochondrial function study

# Unlocking the mysteries of mitochondria

The body's power plants are being probed by a multidisciplinary collaboration of UK scientists.

Mitochondria are the energy power houses of cells, generating the ATP (adenosine triphosphate) used as fuel in biological processes. Yet, despite their importance, mysteries still surround how mitochondria work. Scientists investigating these structures often treat them with AG10, a compound that destroys mitochondrial activity, allowing their function to be studied. But AG10 acts indiscriminately throughout a cell. Now, researchers at the Universities of Oxford, Strathclyde and St Andrews have modified AG10 to generate a new spatially-selective mitochondrial probe.

The probe works thanks to a nitrobenzyl 'cage' group attached to a phenol group on AG10. The cage prevents AG10 exerting its biologically active properties, that is until laser light is applied to unlock



**AG10 (black) is released from its nitrobenzyl cage (red) using laser light**

#### Reference

N Avlonitis *et al.*, *Mol. BioSyst.*, 2009, DOI: 10.1039/b820415m

the cage. 'The advantage of this is two fold,' says Stuart Conway who led the collaboration with John McCarron. 'Not only can we decide when to release these compounds but we can also decide where we release them.'

By testing the caged compound in muscle cells the researchers demonstrated that laser photolysis

releases caged AG10 only in regions of the cell near the photolysis site, enabling AG10 to go on to locally knock-out mitochondrial activity.

'The key benefit of the work is in providing chemical tools that offer the prospect of high-resolution investigation of mitochondrial function for the first time,' says James Dowden, an expert in the design and synthesis of chemical probes for biological systems, from the University of Nottingham, UK.

The UK team says it expects the probe to allow researchers to look at the role mitochondria play in calcium signalling, an integral part of many physiological processes, including learning and memory, in more detail than ever before. Towards this, they now plan to apply the cage concept to investigate protein complexes involved in an intracellular messenger system linked to calcium signalling.

*Jennifer Newton*

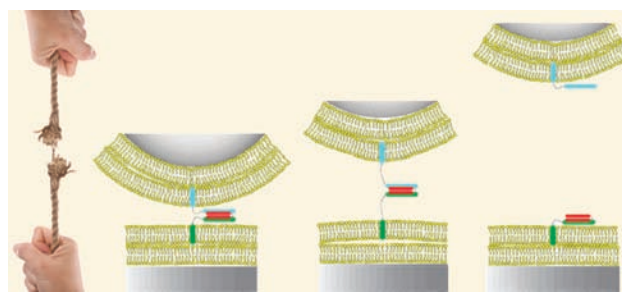
## Following the proteins that pull cell membranes together as they run in reverse

# The strength of protein SNAREs

Pulling a protein complex apart has allowed US scientists to unravel some of the secrets of membrane fusion.

Membrane fusion is an important biological event involved in a range of cellular processes including egg fertilisation and waste transport. It is also the mechanism by which some pathogens enter cells. Now, Vincent Moy from the University of Miami, Florida, US, and colleagues have used atomic force microscopy (AFM) to measure the force required to pull apart SNARE complexes, protein complexes involved in the membrane fusion process.

When membranes fuse, SNARE proteins from different membranes combine to form a complex that helps pull the membranes together. SNARE complex formation 'exerts a mechanical force which is transmitted to the membranes, bringing them together and disrupting them,' explains Midhat Abdulreda, who worked



**A SNARE complex resembles a rope linking two cell membranes, pulling them together**

#### Reference

M H Abdulreda *et al.*, *Integr. Biol.*, 2009, 1, 301 (DOI: 10.1039/b900685k)

on the project. The membranes' hydrophobic nature ensures that the disrupted membranes fuse together.

The US team's approach assumes that the unbinding process as the SNARE complex is pulled apart is the reverse of the binding process, effectively allowing the researchers to monitor SNARE complex formation – in reverse.

Using the AFM approach, Moy's team showed that the pulling force exerted on the membranes by the SNARE complex facilitates

membrane hemifusion – where only the outer membranes are mixed and the inner membrane remains intact – and that it also increases the likelihood of complete membrane fusion.

The researchers were also able to show for the first time that there is a direct correlation between the strength of the SNARE interaction and SNARE-mediated membrane fusion. Further studies of the complexes revealed that two energetically different steps govern SNARE complex formation.

Tanya Dahms, an expert in physical biochemistry, at the University of Regina, Saskatchewan, Canada, welcomes the research. The experimental system is well-designed, she says, and the group has used this in a powerful combination with AFM spectroscopy to understand biological processes at the molecular level.

*Russell Johnson*



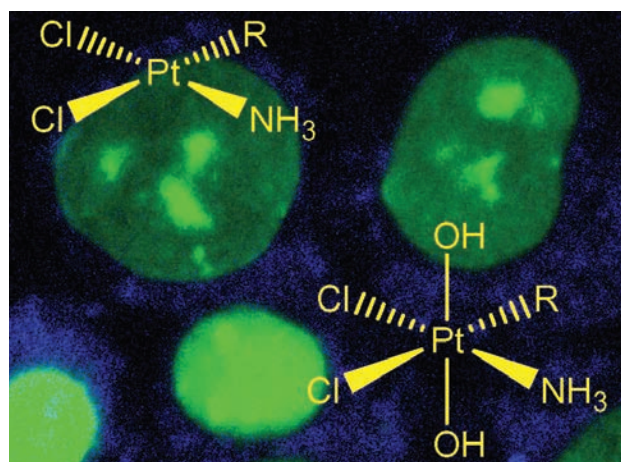
Reduced-state drugs offer brighter outlook for anticancer therapy

## Illuminating the cell response to platinum

A technique for studying anticancer drugs inside cells could help in the search for better-targeted cancer therapies.

Trevor Hambley and co-workers from the University of Sydney, Australia, have used their new coordination-sensitive fluorescence technique to monitor platinum drugs of different coordination state – Pt(II) and Pt(IV) – inside cells. Their aim is to track the differences in how the complexes are handled by cells.

‘Platinum drugs work by binding to DNA but they do so in healthy cells as well as tumour cells, causing toxicity,’ explains Hambley. So whilst Pt(II) complexes such as cisplatin are active against cancer, their toxicity to healthy cells can also lead to side effects. The advantage of Pt(IV) complexes is that they are much less reactive than Pt(II), but they reduce to form the highly active Pt(II) species. If Pt(IV) drugs could be reduced to Pt(II) only once they are inside a tumour, they should be effective against cancer while having low toxicity.



**Platinum complexes with different coordination states show different fluorescence properties which can be used to locate them within cells**

**Reference**  
E J New *et al*, *Dalton Trans.*, 2009, DOI: 10.1039/b821603g

But, as Ulrich Bierbach, who researches platinum anticancer drugs at Wake Forest University, North Carolina, US, explains, little is known about how these drugs act in the cell, despite many years of intense research. Approaches such as Hambley’s help to trace the pathways these complexes take inside cancer cells so the method ‘will ultimately

help improve the pharmacological properties of current and future platinum-based therapies,’ says Bierbach.

Hambley’s group made Pt(II) and Pt(IV) complexes containing a fluorescent ligand and treated cancer cells with them. By using confocal fluorescence microscopy to study the fluorescence in the cells, the researchers found that the Pt(II) complexes showed higher fluorescence than Pt(IV), and when Pt(IV) is reduced to Pt(II) there is an increase in fluorescence. ‘We used differences between the images to gather information on how the compounds are handled by the cells,’ explains Hambley.

Hambley says that he hopes to track where in the cell Pt(IV) complexes are reduced to Pt(II), by monitoring fluorescence changes over time. The group is also working on strategies for restricting Pt(IV) complex reduction to the tumour environment.  
*Fay Riordan*

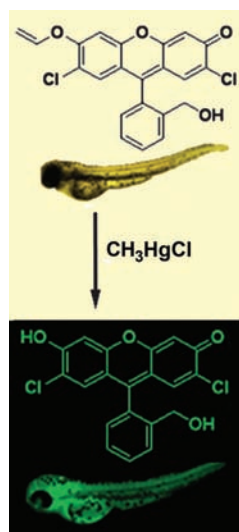
Probe highlights inorganic and organic mercury forms for organ imaging

## Making fish fluoresce for mercury detection

Scientists in South Korea have developed a new probe for mercury that can be used for imaging organs in living organisms.

Mercury is a highly toxic and widespread pollutant. But whilst a number of fluorescence probes exist for mercury most detect only its inorganic forms; there are few reports of probes for organic mercury species such as methylmercury. Yet, the element is commonly found in organic forms, which are more toxic than inorganic mercury as their lipophilicity allows them to cross biological membranes. Consequently, new ways of detecting these mercury species, particularly in organisms, is of crucial importance.

Now, Kyo Han Ahn of Pohang University of Science and Technology, Injae Shin of Yonsei University, Seoul, and colleagues have addressed this need. They have developed a



**Ahn and Shin’s probe reacts with mercury compounds to release a fluorescent compound**

structurally simple probe which reacts with both organic and inorganic mercury to give a fluorescent product. They have used the probe to monitor mercury species in mammalian cells and zebrafish organs incubated with organic mercury.

While previous probes for inorganic mercury used sulfur-based ligands, Ahn and Shin’s approach takes advantage of different chemistry, as Amirla de Silva, an expert in fluorescent sensors at Queen’s University, Belfast, UK, explains. ‘Ahn and his colleagues have taken inspiration from the field of oxymercuration reactions. This is a nice conceptual advance.’ De Silva adds that as the reaction between the probe and mercury is irreversible, the probe is essentially a chemodosimeter – or reagent – rather than a sensor. ‘Nevertheless, a chemodosimeter for methylmercury is an important step

in permitting the monitoring of this severe poison in life forms.’

Ahn agrees and says the probe could be vital to the study of mercury poisoning. ‘Now we have a molecular probe that can be used for studying and tracing notoriously toxic methylmercury in living species. By using the probe, we may study the distribution and fate of methylmercury in organisms,’ he explains.

The next step is to develop a probe that is more discriminating. ‘One of the most challenging issues in mercury sensing is to discriminate inorganic mercury from methylmercury,’ says Ahn. ‘We do not have such a molecular probe yet but we are working on it.’  
*Edward Morgan*

**Reference**  
M Santra *et al*, *Chem. Commun.*, 2009, DOI: 10.1039/b900380k

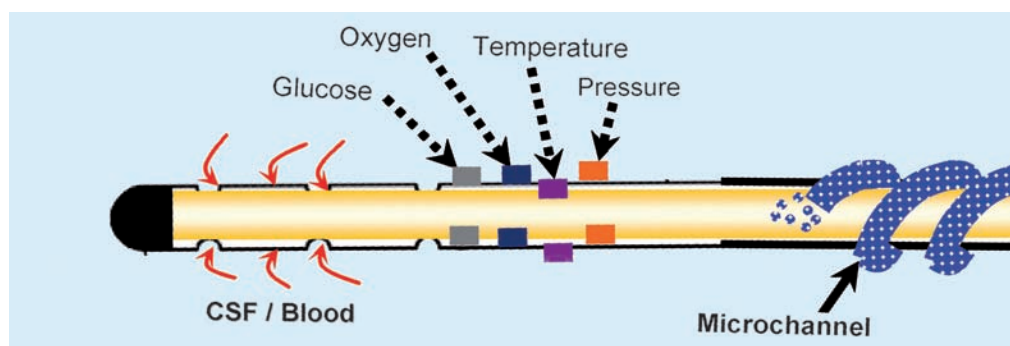
## Sensor system monitors glucose, oxygen, temperature and pressure

# Lab-on-a-tube for brain monitoring

A spiral sensor sandwich could help patients with traumatic brain injury. The new device allows continuous monitoring of key physiological and biological parameters affected by TBI.

TBI is caused by direct impact or by acceleration alone. Often little can be done to reverse the initial brain damage so clinicians focus on stabilising the patient and preventing further injury due to, for example, insufficient oxygen in the brain. But physiological indices such as brain glucose are commonly assessed only intermittently, even though they are known to affect patient outcomes. This is partly due to the lack of a simple, comprehensive and inexpensive monitoring device.

The lab-on-a-tube system developed by Chunyan Li and colleagues at the University of Cincinnati, US, comprises a film containing a microchannel sandwiched between two polymer films, one including a pressure sensor and the other containing glucose, oxygen and temperature sensors. The system is rolled into a spiral to form a tube which can be inserted into the brain. The tube is connected to a multimodal monitor, which shows results from the four sensors, and a cerebrospinal fluid drainage bag as the tube can also



be used to drain (and monitor) the fluid to lower intracranial pressure.

The device addresses a vital clinical need since, according to Raj Narayan, a member of the US team, 'the technology for monitoring severely-ill patients is woefully inadequate.' Li's device has several advantages over existing approaches as it is less invasive – only one hole needs to be drilled into the skull – and is less traumatic as its diameter can be adjusted to lie safely in place. It is also cheaper and easier to use than multiple individual sensors. The tube could be used to deliver drugs through the microchannel that delivers calibration solution to the biosensors.

The significance of the device is emphasised by Ross Bullock, a TBI researcher at the University

**The tubular device can measure key parameters affected by TBI and could be used to deliver drugs to the brain through the microchannel**

of Miami, US, who says that multimodality sensors of this type would 'represent a very major step forward in our ability to monitor neurosurgical patients.'

Possible future developments are suggested by Justin Williams, an expert in neurochemistry and neurobiology at the University of Wisconsin-Madison, US, who says that 'the multifaceted fabrication approach makes it possible to integrate numerous other types of sensors as well as electrical stimulation and even drug delivery.'

Having tested its device with patient samples in vitro, the team is now testing the system in vivo. 'We need to pass this translation process,' says Narayan. 'Interactions with tissues are often unanticipated even to those experienced in the field.' Ziva Whitelock

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# Elemental evolution

*Ariel Anbar talks to May Copsey about fossils, Star Trek and life on Mars*



**Ariel Anbar**

**Ariel Anbar is a biogeochemist in the department of chemistry and biochemistry and the school of earth & space exploration at Arizona State University, US, and a member of the *Metalomics* editorial board. His research is focused on the chemistry of transition elements in the environment, and understanding how changes in bioessential elements during Earth's history have affected evolution.**

## **What was it that inspired you to be a scientist?**

I grew up in a scientific family. My father was an academic and a chemist, so to have an interest in chemistry was natural. I became interested in the evolution of the Earth, and chemistry applied to that, on a college geology field trip. I cracked open a rock to find a fossil and had the awe-inspiring realisation that no living thing had laid eyes on the remains of this for a couple of hundred million years. I started to become intrigued by the questions of evolution and ancient environments and, as I was majoring in chemistry, it was natural for me to think about how to blend those two subjects.

## **Could you tell me about what is going on in your lab at the moment?**

The core research in my group is geochemical and focuses on the development and application of novel methods for measuring natural variations in the concentrations and isotope compositions of transition metals in geological materials. Our major focus is to use such measurements to try to understand ancient environments and how the environment has changed with time. For example, we look at the isotopes of molybdenum in two and half billion year old rocks and measure how their abundances differ from those in similar rocks today. Those variations tell us about differences in chemical processes in the environment, such as the extent to which molybdenum interacted with oxygen in the atmosphere and oceans. To decipher how those changes in isotopic composition relate to the amount of oxygen or other variables, you have to do laboratory experiments to figure out what it is that causes the isotopes to fractionate in plausible natural conditions.

## **You've recently been looking at the oxygen content in the oceans, can you tell me more about that?**

Molybdenum is an unusually redox-sensitive metal in the environment and so its concentrations and isotope compositions in ancient oceans vary as a function of oxygen. This has interesting implications beyond the use of molybdenum as a tracer of ancient oxygen. For example, today, among the transition metals, molybdenum is the most abundant in the oceans. However, it was much more scarce in ancient oceans. Molybdenum is important in many enzymes, so you can start to ask whether or not molybdenum scarcity affected the biosphere in the past.

## **You've recently obtained funding from NASA, is that work related to looking at possible life on Mars?**

I'm the leader of a NASA Astrobiology Institute (NAI) team at Arizona State University. The theme of our team is 'Follow the Elements'. For about a decade, in searching for habitable environments beyond those on Earth, NASA has had the mantra of 'Follow the Water'. But it's not enough to know if there was water there. That's a necessary condition, but not sufficient. What else makes a place habitable? One of the criteria, in addition to water, is the presence of the elements required for biology. Therefore, if you think that there was an ancient groundwater system in some location on Mars, we need to ask what we can infer about the nitrogen budget there, or the availability of phosphorus in that environment or in those ancient waters.

## **Looking back, what do you consider to be your most rewarding achievements?**

When I started my independent career I gambled on this idea that transition metal isotopes would fractionate in the environment to a degree that was measurable. Many of my seniors told me I was a little crazy! The technology to measure the consequences of isotope sensitivities for carbon and oxygen has existed for 50 years. However for transition metals, the challenge is that the difference in mass between isotopes as a percentage of the total mass is much smaller, so the size of fractionation is much smaller. So I took this gamble that the development of ICP mass spectrometry combined with multiple detectors had matured to the point that we could make sufficiently precise measurements, and that an assistant professor could actually build a career doing this. That gamble has paid off very nicely and I'm pretty proud of the role I played being one of the early leaders in this field.

The other thing that I'm proud of is helping to build this bridge between bioinorganic chemistry and geochemistry. Metal abundances have varied with time in the environment. In many cases these metals are essential in biology – as in the case of molybdenum. There have to be consequences for evolution or for the function of the biosphere. This is an area that, when I got started as an independent academic, had not been truly investigated.

## **What do you like doing when you're not in the lab?**

I'm a simple person – I enjoy hanging out with my family. I have an eight year old and five year old, so I can often be found watching an old *Star Trek* episode with them. I was a *Star Trek* fan as a kid. That definitely influenced my choice of career!

# Call for Papers

# Metallomics

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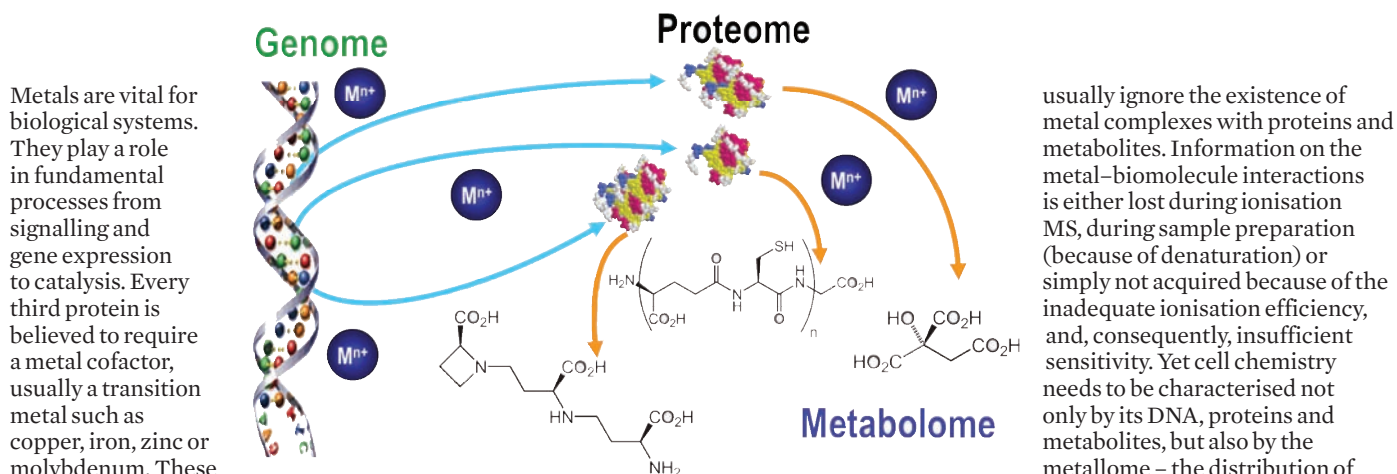
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# What is metallomics?

Amongst the ‘-omics’ fields, metallomics is a relative newcomer.

Ryszard Lobinski and colleagues at the National Research Council of France (CNRS), Pau, provide their definition



Metals are vital for biological systems. They play a role in fundamental processes from signalling and gene expression to catalysis. Every third protein is believed to require a metal cofactor, usually a transition metal such as copper, iron, zinc or molybdenum. These proteins include metallothionein, crucial in maintaining the body's equilibrium and in detoxification processes, metallochaperones, which protect and direct metal ions through the cell, and extracellular proteins albumin and transferrin – essential for metal transport in human blood. Metal ions are also responsible for controlling the expression of these proteins in cells.

As some metals are crucial for the body to function, not having enough of these elements can result in disease. But so too can the excessive presence of others: for example, arsenic, chromium and nickel have been linked to cancer and immune system malfunction, mercury to foetal death or malformation, and aluminium, mercury and manganese to neurological disorders.

Organisms sense and store metals and manufacture metal-containing enzyme active sites in response to environmental signals and stress. Given the essential roles of metals and their implications in disease, understanding the mechanisms involved in these processes is of paramount importance. This is where ‘metallomics’ will help.

As scientists have decoded the complete genetic blueprints of an

**Metal ions play an essential role in the body where they interact with genes, proteins and metabolites**

increasing number of organisms, many different ‘-omics’ disciplines have emerged. The aim of these is to analyse a particular class of components of a living organism.

The first of these to develop was genomics, the study of the full set of an organism's genes: the genome. The genome contains information that allows us to predict the primary sequences of all proteins which can be (but not necessarily are!) expressed. The discrepancy between proteins that can be and proteins that are made is the fundament of another ‘-omics’ discipline: proteomics. This is the study of the complete set of proteins produced in a cell, tissue or organism, their localisation, structure, stability, and interaction.

Proteomics has gone through an exponential development in the past decade, made possible by the invention of soft ionisation mass spectrometry (MS) techniques. Advances in molecular MS are also at the origin of the spectacular progress of metabolomics – the study of the entire set of metabolites of an organism.

But the analytical approaches to proteomics and metabolomics

usually ignore the existence of metal complexes with proteins and metabolites. Information on the metal–biomolecule interactions is either lost during ionisation MS, during sample preparation (because of denaturation) or simply not acquired because of the inadequate ionisation efficiency, and, consequently, insufficient sensitivity. Yet cell chemistry needs to be characterised not only by its DNA, proteins and metabolites, but also by the metalloome – the distribution of metals and metalloids among the different species and cell compartments.

Metallomics is the systematic study of metalloomes and the interactions and functional connections of metal ions and their species with genes, proteins, metabolites and other biomolecules within organisms and ecosystems. Characterising metalloomes, and their interactions, requires dedicated analytical approaches to detect, locate, identify and quantify metal species, as well as revealing their function in the body. The ultimate goal of metallomics is to provide a global and systematic understanding of the metal uptake, trafficking, role and excretion in biological systems, potentially to be able to predict all of these *in silico* using bioinformatics.

Metallomics is an emerging field. As it develops, this transdisciplinary research area has the potential to impact on fields from biogeochemistry, to clinical chemistry and pharmacology, plant and animal physiology, and nutrition.

Read more in the critical review ‘Metallomics: the concept and methodology’ in issue 4, 2009, of Chemical Society Reviews.

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# Essential elements

## Lab on a Chip goes YouTube™

Are you interested in watching the latest advances in microfluidics on video? The new *Lab on a Chip* YouTube™ video channel makes it possible by visualising all the latest scientific research in the field of miniaturisation. 'Many of the articles we receive for *Lab on a Chip* include video footage. These videos are currently captured on our journal website together with the scientific article, but we felt it was essential to share all this interesting information, not only with the scientists who regularly read *Lab on a Chip* but with the wider scientific community,' states Harp Minhas, editor of the journal.

One of the videos included

illustrates how researchers at the University of St Andrews, UK, use the unusual curving properties of laser beams to hurl microparticles and cells over walls. The scientists were looking into optically redistributing microparticles and cells between microwells.



'I think it is a great idea to establish such a video channel, in particular within the field of microfluidics where the vast majority of results are recorded

and presented as video files,' comments Jörg Baumgartl, who led the research. The associated article is published in *Lab on a Chip* as an advance article at [www.rsc.org/loc](http://www.rsc.org/loc).

'All scientists are keen to increase the visibility and impact of their work and this ties in with the RSC goal to communicate the chemical sciences as widely as possible and engage a wide audience,' adds Harp Minhas. 'Videos are a universal language and aid the understanding of scientific work on an international level. YouTube™ represents the perfect medium to help us achieve this goal.'

To find out more go to [www.youtube.com/labonachipvideos](http://www.youtube.com/labonachipvideos)

## Out and about

The Third *ChemComm* International Symposium on Organic Chemistry was held in February in China. The RSC partnered with three universities – Peking University, Sichuan University and the Shanghai Institute of Organic Chemistry – to host the three one-day meetings. With over 700 delegates attending and key speakers from across the world, the symposium was a huge success.

Sarah Thomas, editor of *ChemComm* comments: 'The lectures presented during the symposium were of outstanding quality and covered the whole breadth of organic chemistry from transition metal asymmetric catalysis, organocatalysis,

mechanistic studies to the synthesis of both natural and non-natural products.' Abstracts of the research presented at the symposium, and biographies of the presenters can be found at [www.rsc.org/chemcommsymposia](http://www.rsc.org/chemcommsymposia)

The RSC is also organising the 42nd IUPAC Congress which will be held in Glasgow, UK, in August. The programme features around 50 symposia, which will demonstrate the impact of the chemical sciences, highlighting

exciting innovations with an overall focus on 'Chemistry Solutions'. Key themes for this event are: Analysis & Detection, Chemistry for Health, Communication & Education, Energy & Environment, Industry & Innovation, Materials and

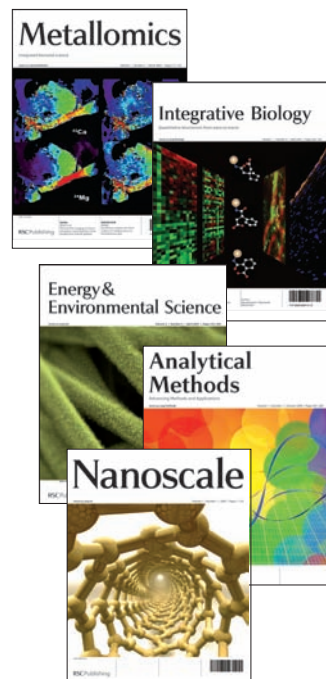
Synthesis & Mechanism. An early bird discount of £50 is available for those who register for the meeting before 5 June 2009.

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