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ISSN 1359–7345 CODEN CHCOFS (13) 1481–1604 (2008)

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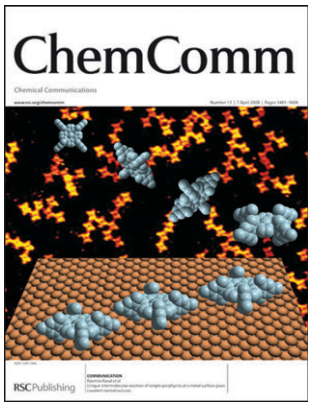
MWCNTs modified by covalent anchoring of glucose oxidase to convert glucose to H_2O_2 for use by a catalase enzyme to provide autonomous propulsion.
Image reproduced by permission of Davide Pantarotto, Wesley R. Browne and Ben L. Feringa from *Chem. Commun.*, 2008, 1533.



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Direct STM visualisation of a combinatorial mixture of covalent nanostructures created from a unique intermolecular reaction of porphyrins at a copper surface.
Image reproduced by permission of Mendel In't Veld, Patrizia Iavicoli, Sam Haq, David B. Amabilino and Rasmita Raval from *Chem. Commun.*, 2008, 1536.

CHEMICAL BIOLOGY

B25

Drawing together the 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
April 2008/Volume 3/Issue 4
www.rsc.org/chembiology

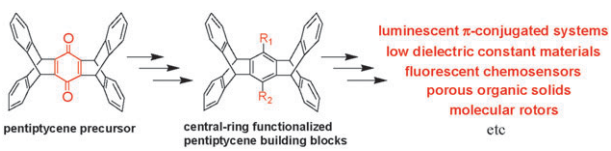
FEATURE ARTICLES

1501

Central-ring functionalization and application of the rigid, aromatic, and H-shaped pentiptycene scaffold

Jye-Shane Yang* and Jyu-Lun Yan

The progress of pentiptycene chemistry is reviewed.



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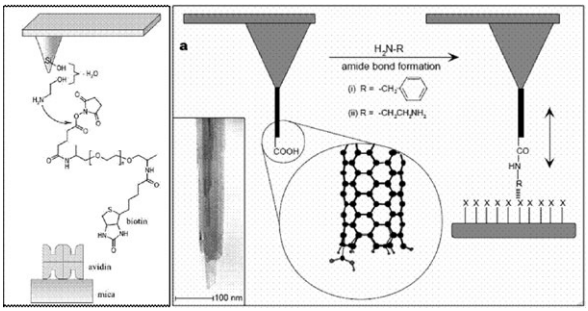
FEATURE ARTICLES

1513

Chemical modifications of AFM tips for the study of molecular recognition events

Régis Barattin and Normand Voyer*

In recent years, there has been growing interest in controlling the chemical functionalization of AFM tips to investigate important biological recognition events at the single molecule level.



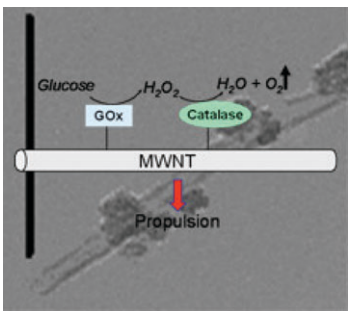
COMMUNICATIONS

1533

Autonomous propulsion of carbon nanotubes powered by a multienzyme ensemble

Davide Pantarotto, Wesley R. Browne and Ben L. Feringa*

The concerted action of glucose oxidase and catalase enzymes attached covalently to multiwalled carbon nanotubes enables autonomous motion using glucose as the chemical fuel.

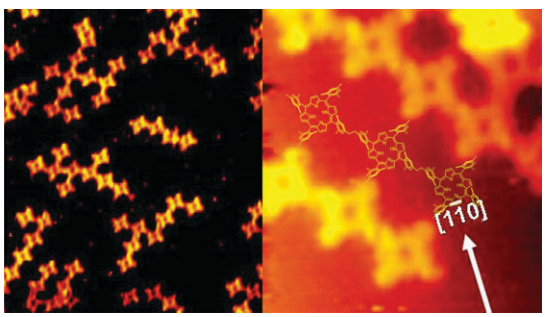


1536

Unique intermolecular reaction of simple porphyrins at a metal surface gives covalent nanostructures

Mendel In't Veld, Patrizia Iavicoli, Sam Haq, David B. Amabilino* and Rasmita Raval*

Tetra(aryl)porphyrins can be covalently linked together *via* a condensation polymerisation reaction at a Cu surface to yield a combinatorial mixture of robust molecular nanostructures at surfaces.

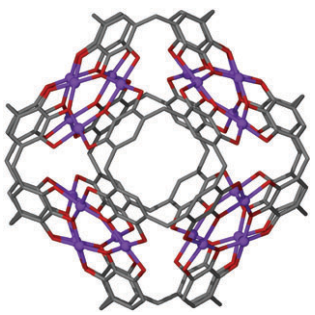


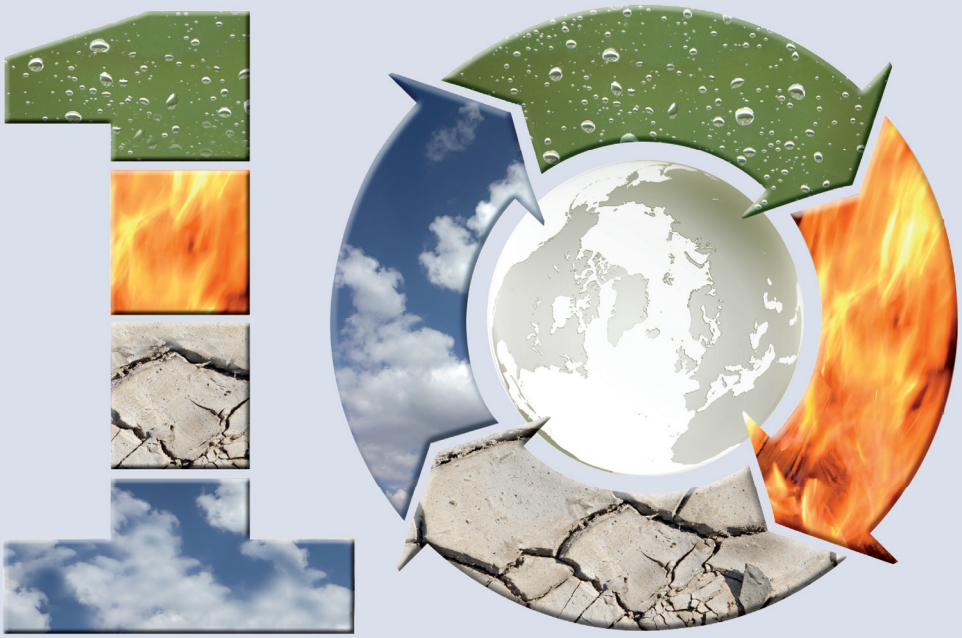
1539

Rapid formation of metal–organic nano-capsules gives new insight into the self-assembly process

Scott J. Dalgarno, Nicholas P. Power, John E. Warren and Jerry L. Atwood*

Metal–organic nano-capsules are rapidly synthesised by the addition of copper nitrate to *C*-alkylpyrogallol[4]arenes, shedding new light on the assembly process based on the formation of 96 Cu–O bonds.





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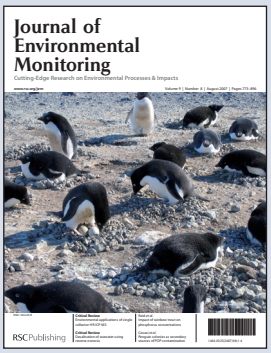

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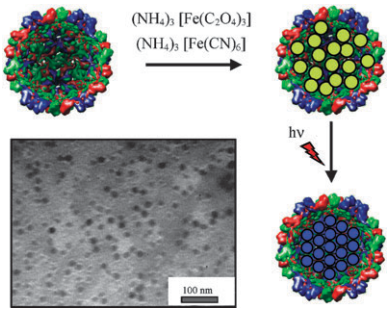
1542

Viral capsids as templates for the production of monodisperse Prussian blue nanoparticles

Andrés de la Escosura, Martijn Verwegen, Friso D. Sikkema, Marta Comellas-Aragonès, Andrei Kirilyuk, Theo Rasing, Roeland J. M. Nolte and Jeroen J. L. M. Cornelissen*

The use of a viral template has allowed the synthesis of monodisperse Prussian blue nanoparticles with a diameter of 18 ± 1.7 nm and their organization into hexagonal patterns on different surfaces.

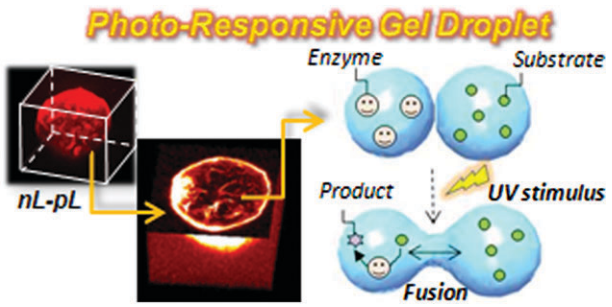


1545

Photo-responsive gel droplet as a nano- or pico-litre container comprising a supramolecular hydrogel

Shinji Matsumoto, Satoshi Yamaguchi, Atsuhiko Wada, Toshihiro Matsui, Masato Ikeda and Itaru Hamachi*

Photo-responsive gel droplets having nano- or pico-L volume that showed photo-induced gel–sol transition were successfully developed, for which the inter-droplet mass transport and the subsequent enzymatic reactions in the interior of the gel droplets were photo-triggered.

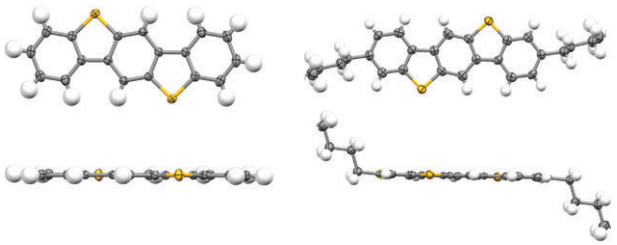


1548

Benzo[1,2-*b*:4,5-*b*′]bis[*b*]benzothiophene as solution processible organic semiconductor for field-effect transistors

Peng Gao, Dirk Beckmann, Hoi Nok Tsao, Xinliang Feng, Volker Enkelmann, Wojciech Pisula and Klaus Müllen*

Coplanar benzo[1,2-*b*:4,5-*b*′]bis[*b*]benzothiophene derivatives for application in organic field-effect transistors were synthesized by a simple two-step procedure involving triflic acid induced ring-closure reaction; such solution processed devices show a hole mobility of up to 0.01 $cm^2\ V^{-1}\ s^{-1}$.

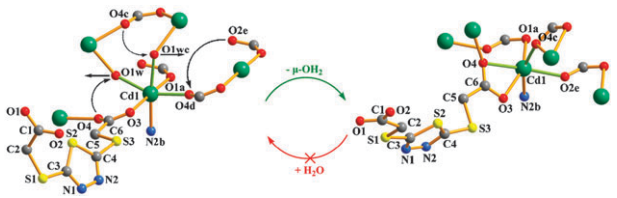


1551

Single-crystal-to-single-crystal transformation involving release of bridging water molecules and conversion of chain helicity in a chiral three-dimensional metal-organic framework

Dong-Xu Xue, Wei-Xiong Zhang, Xiao-Ming Chen* and He-Zhou Wang

A unique and drastic single-crystal-to-single-crystal transformation of dehydration within the 3-D chiral Cd(II) dicarboxylate is reported.

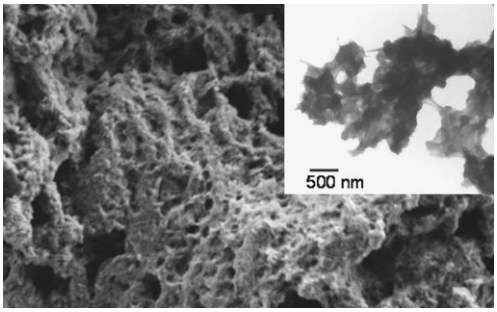


1554

Spongy gel-like layered double hydroxide–alkaline phosphatase nanohybrid as a biosensing material

Erwan Geraud, Vanessa Prevot, Claude Forano* and Christine Mousty*

Formation of new bio-nanohybrid material was obtained by immobilization of alkaline phosphatase (AlP) within a Mg_2Al layered double hydroxide by ''soft chemistry'' coprecipitation synthesis, resulting in an original spongy gel-like morphology allowing the preservation of the enzyme structure and activity even at low pH values thanks to the buffering property of the basic host structure.

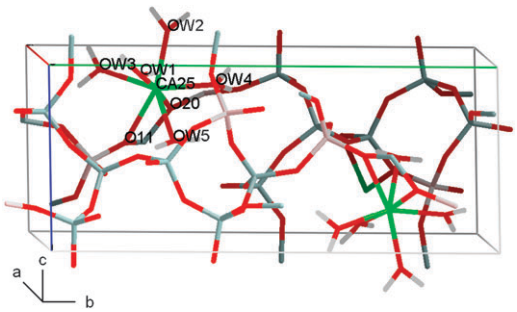


1557

Hydrogenous materials using powder neutron diffraction: full structural determination of adsorbed water molecules in a zeolite

Paul F. Henry,* Mark T. Weller and Chick C. Wilson

A full structural description, including the adsorbed water molecules, of the zeolite goosecreekite $CaAl_2Si_6O_{16} \cdot 5H_2O$, has been obtained from powder neutron diffraction data in one hour, illustrating the potential of modern instrumentation for characterization of hydrogenous materials without deuteration.

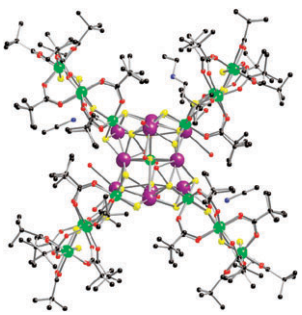


1560

Chemistry and supramolecular chemistry of chromium horseshoes

Marzio Rancan, Graham N. Newton, Christopher A. Muryn, Robin G. Pritchard, Grigore A. Timco, Leroy Cronin* and Richard E. P. Winpenny*

Supramolecular assembly of hexametallic chromium horseshoes about ammonium and sodium cations is demonstrated; cryospray mass spectrometry shows the assembly of four horseshoes and a sodium fluoride cluster is stable in solution.

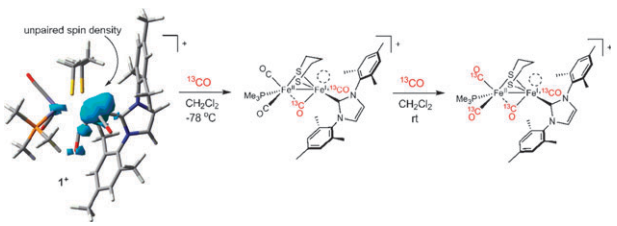


1563

Regioselective $^{12}CO/^{13}CO$ exchange activity of a mixed-valent Fe(II)Fe(I) model of the H_{ox} state of [FeFe]-hydrogenase

Christine M. Thomas, Tianbiao Liu, Michael B. Hall and Marcetta Y. Darensbourg*

Classical organometallic, radical-promoted CO-exchange chemistry in a mixed-valent Fe(II)Fe(I) model of the H_{ox} state of [FeFe]-hydrogenase mimics that observed for the enzyme active site.



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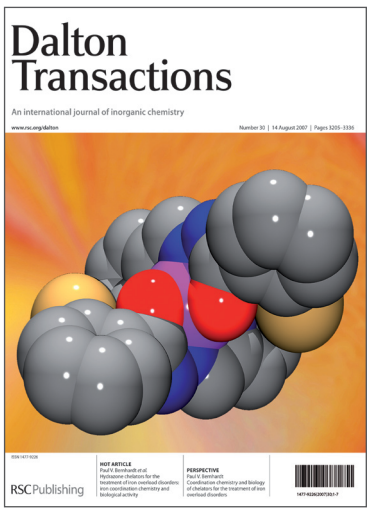

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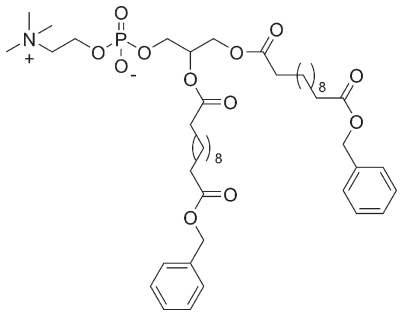
1566

A new helper phospholipid for gene delivery

Carla A. H. Prata, Yougen Li, Dan Luo, Thomas J. McIntosh, Philippe Barthelemy and Mark W. Grinstaff*

The synthesis and characterization of a new helper lipid for gene transfection is described that when used with DOTAP shows enhanced gene transfection activity.

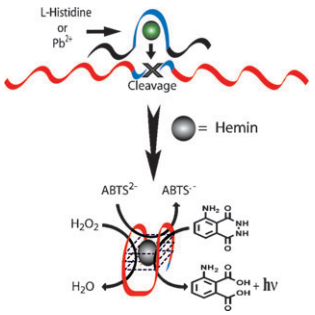


1569

A DNAzyme cascade for the amplified detection of Pb^{2+} ions or L-histidine

Johann Elbaz, Bella Shlyahovsky and Itamar Willner*

DNAzyme cascades are used for the amplified detection of Pb^{2+} or L-histidine. The Pb^{2+}- or L-histidine-dependent DNAzymes are blocked by the respective ribonucleobase substrate tethered at its ends to the horseradish peroxidase-mimicking DNAzyme. Cleavage of the substrate by Pb^{2+} or L-histidine yields the hemin-containing DNAzymes that amplify the colorimetric analysis of Pb^{2+} or L-histidine.

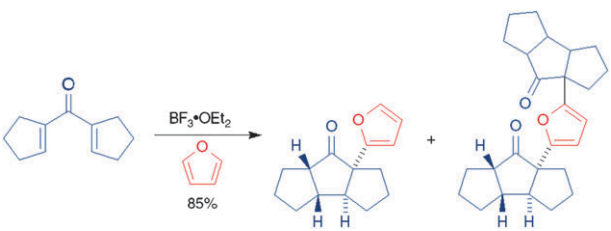


1572

Construction of aryl-substituted triquinanes through the interrupted Nazarov reaction

Curtis J. Rieder, Ryan J. Fradette and F. G. West*

The first examples of *intermolecular* trapping of the Nazarov intermediate using simple arenes is described. In one acyclic case, an unprecedented alternative product of arene Michael addition was formed in good yield.

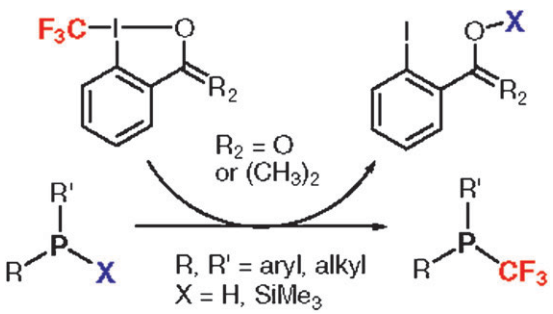


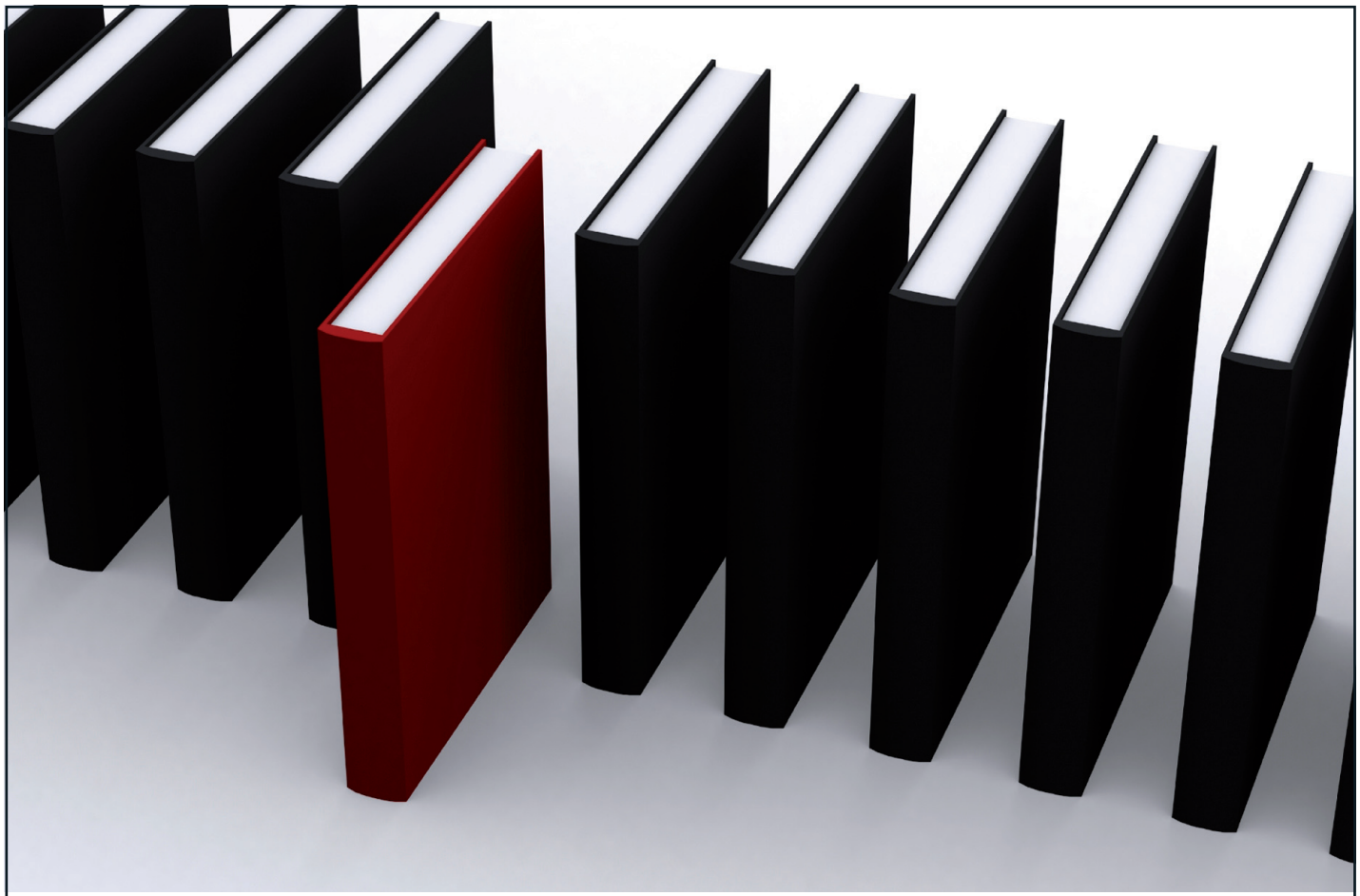
1575

Mild electrophilic trifluoromethylation of secondary and primary aryl- and alkylphosphines using hypervalent iodine(III)–CF_3 reagents

Patrick Eisenberger, Iris Kieltsch, Nicolas Armanino and Antonio Togni*

A novel and straightforward preparative access to trifluoromethylphosphines from primary or secondary phosphines is reported. The sources of the trifluoromethyl group are readily available hypervalent iodine compounds, used as electrophilic reagents.





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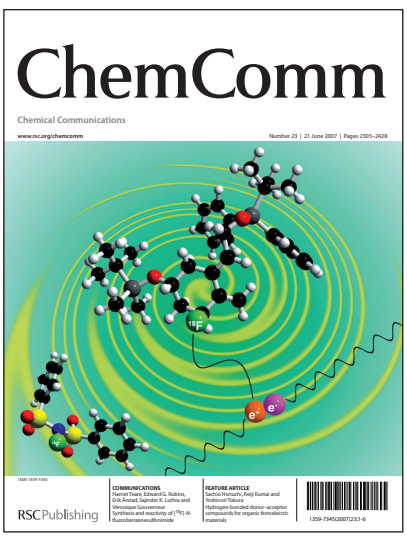

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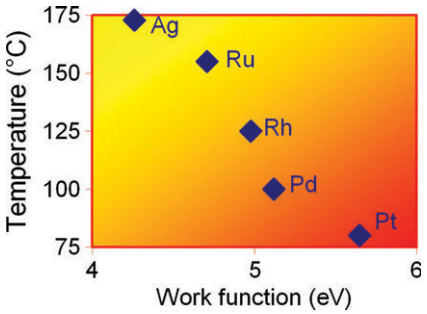
1578

A practical demonstration of electronic promotion in the reduction of ceria coated PGM catalysts

Nadia Acerbi, Shik Chi Tsang, Stan Golunski and Paul Collier*

When ceria is deposited over supported PGM catalysts its reducibility is dependent on the work function of the underlying metal.

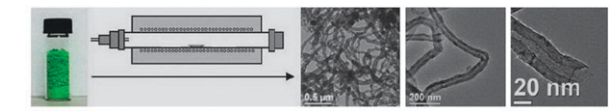


1581

One-step solid-state thermolysis of a metal–organic framework: a simple and facile route to large-scale synthesis of multiwalled carbon nanotubes

Linyun Chen, Junfeng Bai,* Chunzhao Wang, Yi Pan, Manfred Scheer and Xiaozeng You

We report a solid-state approach to large-scale synthesis of multiwalled carbon nanotubes (MCNTs) by one-step direct thermolysis of a metal–organic framework $[Ni_3(btc)_2 \cdot 12H_2O]$ (btc = benzene-1,3,5-tricarboxylato).

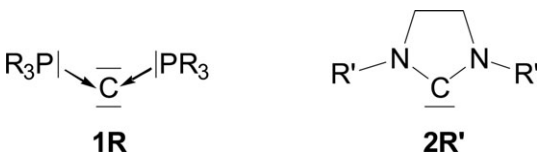


1584

Are carbodiphosphoranes better ligands than *N*-heterocyclic carbenes for Grubb's catalysts?

Ralf Tonner* and Gernot Frenking*

Theoretical investigations suggest that substitution of an *N*-heterocyclic carbene **2** by a carbodiphosphorane **1** in the Grubb's catalyst for olefin metathesis might lead to enhanced reactivity.

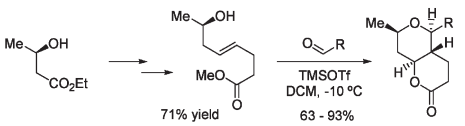


1587

Intramolecular Prins cyclisations for the stereoselective synthesis of bicyclic tetrahydropyrans

Jon D. Elsworth and Christine L. Willis*

Methyl (4*E*,7*R*)-7-hydroxyoctanoate was prepared from ethyl (*R*)-3-hydroxybutanoate and on reaction with a series of aldehydes in the presence of TMSOTf gave bicyclic oxygen heterocycles in good yields and with the creation of three new stereogenic centres in a single pot.



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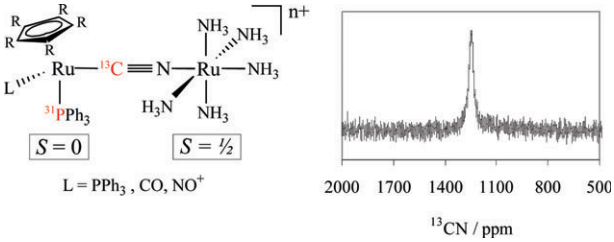
1590

Cyanide ^{13}C NMR hyperfine shifts in paramagnetic cyanide-bridged mixed-valence complexes

W. Michael Laidlaw* and Robert G. Denning

Paramagnetic (hyperfine) NMR shifts in the ^{13}C cyanide bridge and ^{31}P resonances in a set of mixed valence complexes $[(\eta^5\text{-}C_5R_5)Ru(PPh_3)L(^{13}CN)Ru(NH_3)_5]^{n+}$ (R = H; L = PPh_3, CO, NO^+; R = Me; L = PPh_3) are sensitive to the extent of intermetallic charge-transfer, and are strongly solvent dependent.

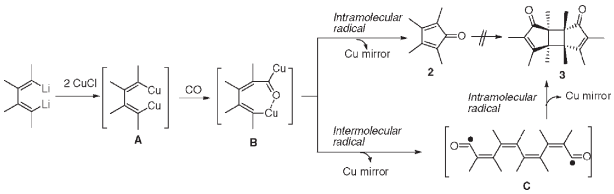


1593

CuCl-mediated tandem CO insertion and annulation of 1,4-dilithio-1,3-dienes: formation of multiply substituted cyclopentadienones and/or their head-to-head dimers

Qian Luo, Chao Wang, Wen-Xiong Zhang and Zhenfeng Xi*

Tandem CO insertion and intra/intermolecular annulation of butadienyl-di-copper reagents has been developed to afford cyclopentadienones and their head-to-head dimers.

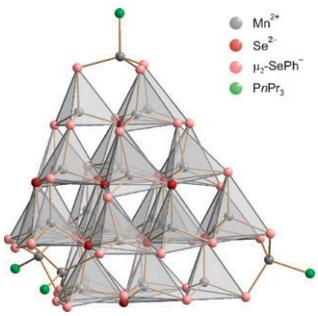


1596

Synthesis, structure and physical properties of the manganese(II) selenide/selenolate cluster complexes $[Mn_{32}Se_{14}(SePh)_{36}(PnPr_3)_4]$ and $[Na(benzene\text{-}15\text{-}crown\text{-}5)(C_4H_8O)_2]_2[Mn_8Se(SePh)_{16}]$

Andreas Eichhöfer,* Paul T. Wood, Raghavan N. Viswanath and Richard A. Mole

The first examples of pure manganese selenide cluster complexes with more than four manganese atoms have been synthesized and investigated.

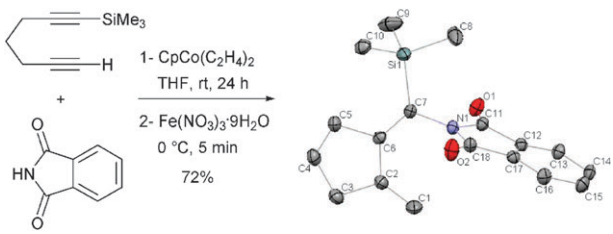


1599

Cobalt-mediated regio- and stereoselective assembly of dienamides by hydroaminative alkyne coupling of α,ω-diynes

Vincent Gandon, Corinne Aubert, Max Malacria and K. Peter C. Vollhardt*

Intermediate cobaltacyclopentadienes formed by oxidative coupling of α,ω-diynes exposed to $CpCo(C_2H_4)_2$ can be intercepted by amides with N–H activation to yield fused dienamides regio- and stereoselectively in a two step-one pot procedure.



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Chemical Biology

Is Raman spectroscopy the way to nail criminals?

The information at your fingertips

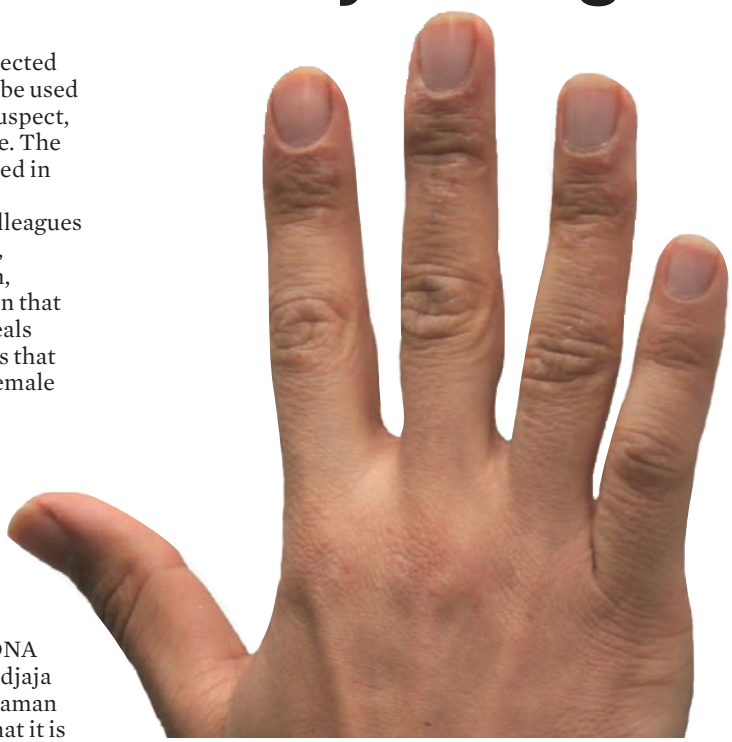
Fingernail fragments collected from a crime scene could be used to predict the sex of the suspect, say scientists in Singapore. The clippings could also be used in diagnostics, they claim.

Effendi Widjaja and colleagues at the Agency for Science, Technology and Research, Jurong Island, have shown that Raman spectroscopy reveals tiny structural differences that exist between male and female fingernails. As these differences in the Raman spectra are usually too small to see by eye the researchers used a special pattern recognition tool to enhance them.

Gender distinction is normally carried out by DNA analysis. According to Widjaja the advantages of using Raman spectroscopy instead is that it is simple, quick, non-invasive and does not require much sample preparation. It could therefore be used as a quick evaluation tool to determine the sex of the donor of fingernail fragments collected in forensic studies, said Widjaja.

Fingernail clippings can also provide scientists with information about a person's diet, race or even health, said Widjaja. 'We are planning to explore the use of Raman spectroscopy of human finger nails as a rapid and non-invasive diagnostic tool for early detection of diseases,' he said. Levels of the metabolic waste product creatinine are raised in the nail clippings of renal failure patients, for example. 'Potentially we could exploit the relationship between the nail composition and the degree of renal failure,' said Widjaja.

Sarah Corcoran



DAVID PACE / 123RF

Fingernails can provide information about a person's health

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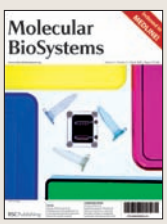
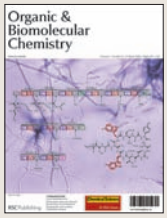




Research highlights

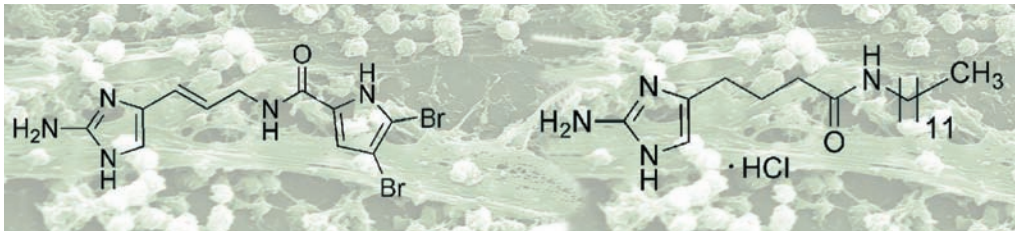
Bacterial colonies dispersed by natural product analogues

Marine inspiration for biofilm break up

Biofilms are responsible for an estimated three quarters of all microbial infections. Now, inspired by marine natural product oroidin, American scientists have developed compounds that could help fight these colonies of bacteria.

Microbes in biofilm form behave differently from those that are free-floating. This can make them up to a thousand times more resistant to antibiotics and immune systems, and so biofilms difficult to disperse once formed. Yet biofilms are ubiquitous and, as well as being a threat to health, can cause agricultural and engineering problems. 'Probably the biggest challenge facing this area,' explained Christian Melander from the research team at North Carolina State University, in Raleigh, US, 'is the lack of molecular architecture that has been identified to inhibit and disperse bacterial biofilms.'

Oroidin's documented activity against biofilm formation, together with its relatively simple structure, made it ideal for exploiting in the search for such scaffolds. Melander's team decided to reverse oroidin's amide bond, allowing easier analogue synthesis and the use of widely available amines to introduce diversity.



Oroidin's (left) amide bond is reversed in analogues (right) that disperse bacterial films

Reference
J J Richards, T E Ballard and C Melander, *Org. Biomol. Chem.*, 2008, DOI: 10.1039/b719082d

They found that some analogues were significantly better than oroidin at inhibiting biofilm formation in two strains of the pathogen *Pseudomonas aeruginosa*. The most active compound, a linear alkyl chain amide, was also able to disperse established biofilms.

According to Helen Blackwell, who carries out anti-biofilm research at the University of Wisconsin-Madison, US, these compounds are notable 'as they not only inhibit biofilm formation, but also are capable of dispersing preformed biofilms.' She added, 'this dispersion ability bodes well for this compound class for a number of biomedical and industrial applications.'

The group is now looking at further varying the most active amide's alkyl chain and also at removing the amide group entirely, as well as testing the compounds against other bacterial strains. Melander said that 'the ultimate goal is to be able to produce non-toxic compounds that are active in vivo.'
Frances Galvin

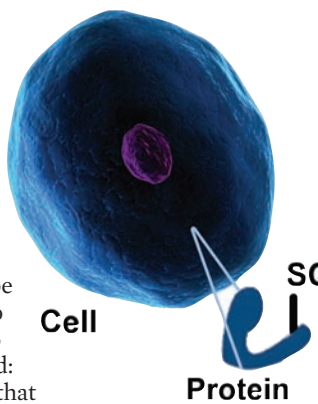
Chemical traps find oxidised proteins inside cells

The amino acid response to stress

A probe that labels oxidised sulfur atoms in proteins could help researchers studying oxidative stress in living cells. Oxidative stress has been implicated in phenomena as diverse as aging, diabetes and neurodegenerative diseases.

A group from the University of Michigan in Ann Arbor, US, has developed a probe to follow oxidation of the amino acid cysteine. Kate Carroll, who led the research team, explained: 'We know from genetic studies that bacteria and yeast have finely tuned systems to respond to oxidative assault and that these function through oxidation of pivotal cysteine residues of sentinel proteins.'

Cysteine has a complicated biochemistry, occuring in up to ten different sulfur oxidation states – or oxoforms – including sulfenic acid. 'Our goal,' said Carroll, 'is to develop approaches to investigate thiol modifications that exploit each cysteine oxoform's unique reactivity for selective recognition.'



Reference
K G Reddie *et al*, *Mol. BioSyst.*, 2008, DOI: 10.1039/b719986d

With this aim, Carroll's team developed a probe which is chemically selective for protein sulfenic acids. Leslie Poole, a specialist in sulfur biochemistry, at Wake Forest University in Winston-Salem, US, described it as 'the first probe demonstrating an ability to trap and detect sulfenic acid formation on proteins within living cells.' Poole added that 'the small size and cell permeability of this probe enable in situ labelling within cells that can then be followed by linkage to various probes to analyse the sites of modification.'

Carroll said: 'From a biological perspective we were motivated by the knowledge that numerous biological processes could be controlled through relatively modest chemical modification. Adding a single oxygen atom could control whether a cell lives or dies.'

But how cysteine oxidation is linked to disease is not yet clear. Carroll said, 'we must move beyond this stage and understand the roles of these modifications for individual proteins at a molecular level. Our long term goal is to investigate the roles that cysteine modifications play in the aging process and in the initiation and progression of disease states, such as cancer.'

The work could also lead to new chemistry. 'From a chemical standpoint, exploring and exploiting differences in reactivity between thiol, sulfenic, sulfinic and sulfonic acid states is also very challenging and exciting,' said Carroll.
Colin Batchelor

Mass spectrometry maps marine biomolecules

Therapeutic secrets of the sea

Marine organisms produce a wealth of natural products, but in the complex environment of a marine sponge it can be difficult to tell which creature should be given the credit. Now US scientists are trying to solve the mystery by pinpointing the molecules within intact organisms.

Pieter Dorrestein from the University of California, San Diego, and colleagues used a mass spectrometry approach to help them to identify potentially important biomolecules from sea creatures such as marine sponges and cyanobacteria. These natural products are an underexploited source of potential drugs, Dorrestein said. 'The compounds show unique chemistries and structures that supersede anything pharmaceutical companies or chemists can design or synthesise.'

The technique used by the team – natural product matrix-assisted laser desorption ionisation imaging (npMALDI-I) – also allows the scientists to locate exactly where these natural products are in the organism. And, since up to 40 per cent of a sponge's mass is thought to be attributed to co-existing organisms, the method could help the scientists to discover which of the organisms are responsible for making the potentially bioactive compounds.

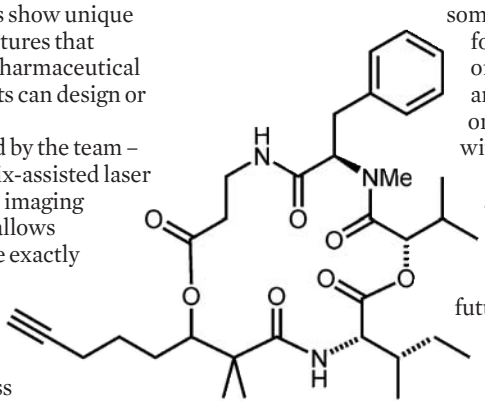
npMALDI-I can be used to locate natural products in complex marine organisms

The team found that within a cross-section of a sponge, some of the natural products were localised on the outer edges, while others were concentrated in the middle. Given that co-existing micro-organisms tend to populate specific regions of the sponge tissue, explained Dorrestein, the results suggest that the micro-organisms are responsible for at least some of the compounds.

Margo Haygood, an expert in marine systems at Oregon Health and Science University, Beaverton, US, described the work as a major advance. 'As a biologist I've always wanted to be able to see the chemistry in the complex systems we study,' she said. 'Although we have some beautiful and elegant methods for specific molecules, the virtue of this work is that it is general – any compound, even an unknown one, can be detected and mapped within the sample.'

'There is so much we can learn about the origin and function of secondary metabolites by seeing where they are located,' she added. 'When future advances improve the resolution of the imaging to something comparable to light microscopy, as I think is inevitable, it will be a dream come true.'

Sarah Corcoran



Cyanobacteria produce a wealth of natural products (here shown, yanucamide B)

Reference
E Esquenazi *et al*, *Mol. BioSyst.*, 2008, DOI: 10.1039/b720018h

News in brief

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Instant insight: Henning Schliephake discusses the state-of-the-art dental implants making their way to a dentist's surgery near you.

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A sensor that can discriminate between closely related bacteria has been developed by materials scientists in the US.

Miniature mixing inspired by nature
Dutch scientists have copied nature to develop a faster and more efficient method for mixing small volumes of liquid.

Flying high with nanomedicine
In this month's interview, Jinwoo Cheon explains how nanoparticles can be used in medical diagnostics.

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Cyclotides redirected towards alternative enzyme targets

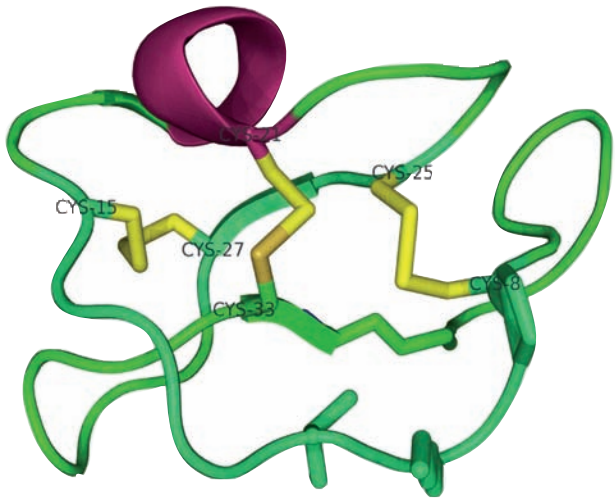
Protein activity tied in knots

UK scientists have engineered a molecular knot that inhibits an enzyme crucial to foot-and-mouth disease, an infectious disease amongst cloven-hoofed animals.

Edward Tate, Robin Leatherbarrow and colleagues from Imperial College London have looked to natural product cyclotides to create analogues that inhibit a range of protein-digesting enzymes. Among these was the first reported peptidic inhibitor of the enzyme FMDV $3C^{pro}$ – essential for the foot-and-mouth disease virus (FMDV) to replicate.

'Cyclotides are small proteins of around 30 amino acids that contain both a head-to-tail macrolactam backbone and a cystine knot, an arrangement of three disulfide bonds between pairs of cysteine residues, whereby two bonds form a loop through which the third is threaded,' said Tate. After carrying out the total synthesis of cyclotides from the MCoTI family, the UK team re-engineered the rigid and well-defined structures to create analogues with different biological activities.

MCoTI cyclotides are potent inhibitors of trypsin, a protease enzyme that breaks down proteins in the digestive system. By re-engineering the proteins, the cyclotides' inhibitory activity can be redirected towards an alternative protease target, Tate explained. This included a protease from a completely different mechanistic class: a cysteine protease from foot and mouth disease virus.



Cyclotides contain three disulfide bonds (yellow) and form a cystine knot

Whilst it is not the first FMDV protease inhibitor reported, Tate explained, 'to my knowledge, it is the most effective reported inhibitor in a controlled assay against the enzyme in isolation.' He added that, although the cyclotides were too complex for use as an animal drug, his results could help guide future non-cyclotide based inhibitor design for the FMDV enzyme.

'The more interesting thing is that the analogues can inhibit a cysteine protein at all, since this is a very different class of protease from that typically targeted by MCoTI cylotides,' said Tate. 'The ease with which these structurally complex cyclotides can now be synthesised and re-engineered will enable new studies into their biological activity, for example, as potential peptide-based drugs.'

David Craik, from the University of Queensland in Brisbane, Australia, who studies protein structures relevant to drug design, agreed: 'The work represents an exciting development in the field of cystine knot proteins. By demonstrating a high yielding chemo-enzymatic approach to their synthesis as well as the ability to engineer tailored enzyme inhibitory activity into them, it is likely to greatly enhance applications of this ultra-stable class of proteins as drug development scaffolds.' *Elinor Richards*

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Protein-passivated Fe_3O_4 nanoparticles: low toxicity and rapid heating for thermal therapy
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Integrating whole transcriptome assays on a lab-on-a-chip for single cell gene profiling
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Nanoscale structure and dynamics of DNA
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Why is the amyloid beta peptide of Alzheimer's disease neurotoxic?
Arvi Rauk, *Dalton Trans.*, 2008, 1273 (DOI: 10.1039/b718601k)

Molecular design of inhibitors against the M^{pro} protein of the severe acute respiratory syndrome (SARS) virus
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AFM for nanoscale microbe analysis
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Interview

The science of herbal remedies

Peter Houghton tells Joanne Thomson that there is still much to be learnt from traditional medicine

Peter Houghton

Peter Houghton is Professor in Pharmacognosy in the department of pharmacy at Kings College London. His research areas include substances from plants of potential use in treating central nervous system degenerative disease, cancer and for wound healing. He is also interested in the investigation of herbal medicines. Peter joined the *Natural Product Reports* editorial board at the beginning of 2008.

What inspired you to become a scientist?
I have always been intrigued by the amazing variety in nature and wondered how things work and how they were formed. I was lucky enough to grow up in the Cotswolds and my father, who was a pharmacist, pointed out many of the wild plants growing there. I guess that is where my particular interest started. However, I like exploring in all sorts of ways and enjoy working out connections between apparently unrelated facts and how we, as humans, have exploited these. I think that it is very important for us scientists not to lose a sense of wonder at the incredible complexity and beauty of the world around us and the ingenuity and skill of what humans can do.

You are interested in ethnopharmacology. Could you explain what this is and why it is important in the development of new drugs?
Ethnopharmacology is the scientific study of traditional medicines, the materials used for medicinal, pharmaceutical and toxicological purposes by different human cultures and societies. Many of these materials consist of plants or fungi and their biological activity is, of course, due to the chemical compounds contained in them. Many important drugs like morphine, digoxin and reserpine came into use because the plants containing them were known as poisons and used as medicines. In addition, active compounds can serve as lead molecules such as the local anaesthetics derived from cocaine and the muscle relaxants based on curare alkaloids. The antimalarial artemisinin and galantamine, which is used to treat symptoms of Alzheimer's disease, are recently-introduced drugs which have an ethnopharmacological basis.

Do you believe there is a place for both traditional and Western medicines in society today?
Very definitely. Medicine is increasingly realising that mixtures of compounds are often more useful in treating a disease than a single 'silver bullet' chemical. Modern approaches to chemotherapy of cancer and AIDS are examples of this. There is increasing evidence for 'polyvalence' in traditional medicines. In other words, different types of constituent are present with differing modes of action but all contributing to the overall clinical effect. Recent applications of systems biology and analysis of complex mixtures now enable the complex interplay of interactions between an extract and the body to be described and analysed scientifically. We must also not forget that, in many parts of the world, traditional remedies are the only ones within geographical or economic reach of many of the population. A scientific basis for their safe and effective use, as well as for ensuring good quality, would enable them to be viewed with greater confidence as alternatives to expensive 'Western' drugs. I believe that the increasing influence of China, with its very strong cultural heritage and current use of its traditional medicines, will accelerate a paradigm shift in Western thinking about chemotherapy of disease.

What is hot in natural products chemistry?
There is a lot of interest in the chemistry and biological activity of Chinese medicinal plants. I believe that advanced and computer-aided analytical methods for profiling extracts and their effect on metabolic systems are of great interest, since these could be used both in standardisation protocols but also in elucidating complex interactions.

What is your favourite plant?
For scent, flowers and because it is so much associated with the beautiful British countryside, I would go for the hawthorn (*Crataegus* spp.). For its name, appearance and the attention that I get when I mention it, the sausage tree (*Kigelia pinnata*) is another favourite.

What do you do in your spare time?
I enjoy cooking, natural history and exploring. My wife and I always ring-fence time to have a couple of holidays each year, usually somewhere where we can walk and see flowers and animals. I am also quite involved in my local church and am training for ordination in September 2008 in the Church of England.

What would you be if you weren't a scientist?
I think that a scientist is something that you are, even if you are not doing it as a job, so I hope that I will never lose my natural curiosity. However, I am planning to retire from full-time university life soon to spend more time helping in my church and its work – hence the ordination course. I see no real conflict between my Christian faith and scientific investigation; both follow from observing and seeking to explain things that exist and occur in the world around.

Instant insight

Reading the genome atlas

Peter Hallin, Tim Binnewies and David Ussery at the Technical University of Denmark at Lyngby examine how the BLASTatlas tool can be used to spot the differences between similar genomes

One of the central tenants of molecular biology is that biological information flows from DNA to RNA to protein. Furthermore, a protein's sequence determines its structure and the structure its function. In general, although there are many methods that attempt to predict protein structure, it is still often difficult to predict the structures of novel sequences. Currently the state of affairs is pretty much limited to homology searches – that is, if one can find a good sequence match to a protein with known structure and function, it is inferred that the unknown protein has the same function. One can question the reliability and wisdom of this, but nonetheless, this is a commonly used approach.

There has been a literal explosion at the level of sequence information. The development of fast and inexpensive methods for sequencing bacterial genomes has led to a wealth of data, often with many genomes being sequenced of the same species or of closely related organisms. Thus, there is a need for simple ways to compare these sequenced genomes. We have developed the BLASTatlas method for mapping and visualising whole genome homology of genes and proteins within a reference strain compared to one or more other strains or species of prokaryotic organisms. The map is accurate at the level of amino acid conservation – in many cases few regions of a protein will be conserved.

The figure shows a zoom of a particular region of a BLASTatlas for the main chromosome of *Clostridium botulinum* strain Langeland A, compared to 11 other *Clostridia* genomes. There are three dark blue lanes near the top, where most of the proteins are conserved, implying that these proteins probably play the same functional role in these organisms. The other genomes compared show little sequence conservation overall, and the genes contain only partial matches. So the plot answers questions not just about the presence or absence of genes, but about the degree to which they are conserved. The strong sequence conservation in the three dark blue lanes makes biological sense in that they all represent different strains of *C. botulinum*. The diversity within the genus of *Clostridium* is amongst the largest of all bacterial genera, and is as great as that between all animals.

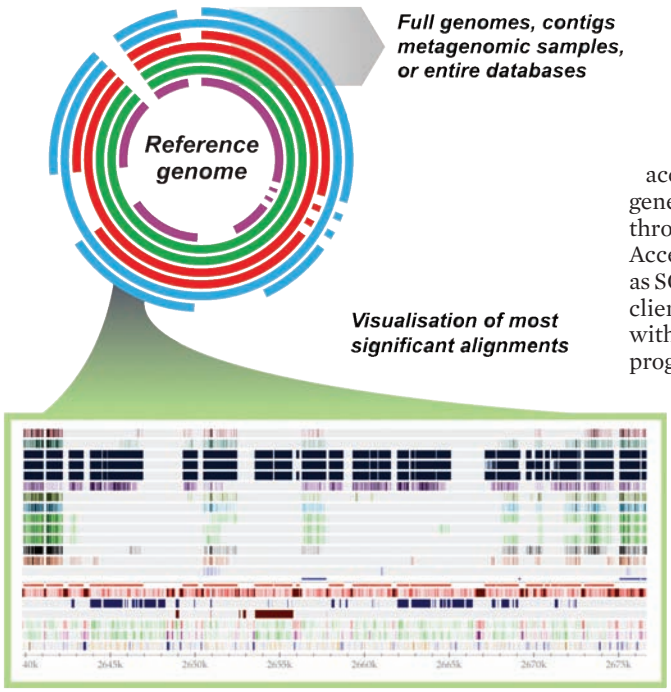
Gene regulation is controlled in part by the mechanical–chemical properties of chromosomal DNA. So we map DNA structural properties from the reference genome sequence on the same atlas, showing amino acid conservation of protein coding genes. The bottom three lanes in the figure represent DNA structural parameters that we routinely use. Stacking energy measures how easily the strands in the DNA helix separate, position preference is a measure of the DNA's anisotropic flexibility and curvature reflects the three-dimensional structure of a short region of the DNA helix. Extreme values before the start of a gene indicate the potential presence of a promoter – a region of DNA that precedes a sequence to be transcribed into RNA. At the chromosomal level, sometimes these structural parameters correlate with functional properties, such as highly variable regions, or regions containing highly expressed genes.

We allow users to directly access the tools that are used to generate these BLASTatlas maps, through the use of Simple Object Access Protocol, commonly known as SOAP. This framework allows clients to directly communicate with our server and in a programmatic fashion, thereby allowing the user's own programs to systematically examine a large number of genomes.

Read Hallin et al*'s highlight 'The Genome BLASTatlas: a GeneWiz extension for visualization of whole-genome homology' in a forthcoming issue of* Molecular BioSystems.

Reference
P F Hallin, T T Binnewies and D W Ussery, *Mol. BioSyst.*, 2008, DOI: 10.1039/b717118h

Zooming in: a BLASTatlas map allows genomes to be compared



Instant insight

A fluorescent future

B H Kim, Y J Seo and N Venkatesan at Pohang University of Science and Technology in Korea explain why quencher-free molecular beacons mean a brighter outlook for medicine

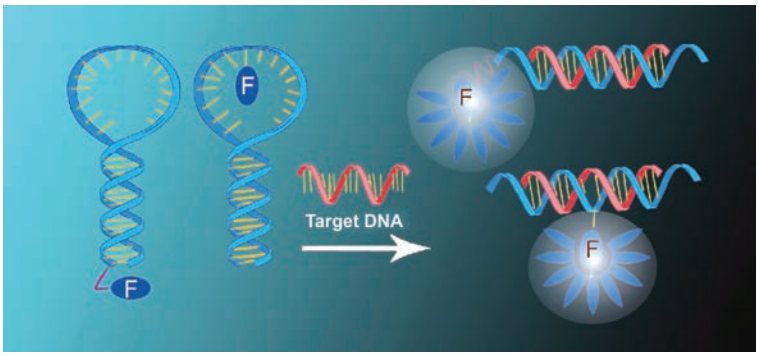
Genetic analysis underpins DNA diagnostics. Swapping just a couple of letters in an individual's genome can cause an incurable genetic disorder, so identifying genetic differences is very important to diagnose and possibly cure certain diseases.

Unravelling the 'secret of life' by completing sequencing of the human genome, has led to our better understanding of genetic differences, be it between individuals, between parents and their offspring or normal and abnormal genes in genetic disorders. Such differences are expressed in terms of single nucleotide polymorphisms (SNPs, a single base change in a DNA sequence) or copy number variations (CNVs, when the number of copies of a gene varies).

Initially, DNA analysis relied mainly on radiolabelled nucleotides. Now fluorescent techniques are being used increasingly. Analytical methods that use fluorescent probes to bind to particular DNA regions are now well-known. So-called molecular beacons (MBs), these probes are now being used during DNA amplification by polymerase chain reactions (PCR), to qualitatively as well as quantitatively estimate single or multiple gene sequences simultaneously. Similarly, different types of MBs are used in related applications such as protein analysis and to study protein–DNA interactions. In addition, MBs' suitability for probing the levels and kinetics of DNA photodamage, and as vehicles for photoinduced drug release has also been explored.

The conventional MB consists of a stable hairpin (stem–loop) oligonucleotide carrying a fluorophore at one end and a quencher at the other. In the hairpin form the fluorophore transfers its energy to the nearby quencher. When the target DNA is added, the hairpin opens out to bind to the DNA and the fluorophore is no longer quenched. So the target DNA is detected by an increase in fluorescence. This type of MB has been modified by a number of research groups to improve its detection limit, reduce its signal to noise ratio and to improve its stability against enzymes.

Quencher-free molecular beacons change fluorescence intensity as they bind to target DNA



Quencher-free molecular beacons (QF-MBs) are a recent addition to the family of modified MBs. These hairpin-shaped fluorescent oligonucleotides contain one or multiple fluorophores and can be broadly classified into two different types: mono-labelled, containing a fluorophore at the middle or one end of the oligonucleotide, and dual-labelled, containing two fluorophores at the stem or ends. In almost all, the entire or part of the hairpin's loop is complementary to the target oligonucleotide.

None of these MBs has an additional quencher, but despite this each recognises fully complementary DNA. Quenching by photoelectron transfer between a nucleobase (usually guanine) and the fluorophore and changes in the fluorophore's microenvironment are major factors behind the successful working of the mono-labelled QF-MBs. Thus when QF-MB hybridises with its target DNA this brings about a change in one or both of these factors, resulting in a fluorescence intensity change.

Mono-labelled QF-MBs can be used to reveal the nucleotide at an SNP and discriminate a fully matched target DNA from mismatched ones. The QF-MBs have notable advantages over the quencher–fluorophore MB systems. Nucleobases act as inbuilt quenchers, mono-labelled QF-MBs can be immobilised on a solid surface through the free end and, compared to the conventional MBs, preparation of mono-labelled QF-MBs is relatively easy and more economical. QF-MBs can be used in homogeneous as well as heterogeneous assay formats. Also, with one free end, the mono-labelled QF-MBs can be used as primers in PCR, to quantify target DNA levels with high sensitivity.

Researchers around the world continue to modify MBs to suit specific needs. Of these, QF-MBs are playing a significant role and, in the near future, should become one of the mainstream DNA analytical tools. Such technological advances will be the key to new diagnostic and treatment options.

Read Kim et al*'s tutorial review 'Quencher-free molecular beacons: a new strategy in fluorescence based nucleic acid analysis' in a forthcoming issue of* Chemical Society Reviews.

Reference
N Venkatesan, Y J Seo and B H Kim, *Chem. Soc. Rev.*, 2008, DOI: 10.1039/b705468h

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