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IN THIS ISSUE

ISSN 1359–7345 CODEN CHCOFS (45) 5857–6060 (2008)

Cover
See Timothy C. Lillestolen and Richard J. Wheatley pp. 5909–5911.
Using a simple new algorithm, molecules can be divided into atoms with chemically intuitive charges and shapes.
The image was generated with the kind assistance of Dr Samantha Tang.
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Inside cover
See Graeme Cooke *et al.* pp. 5912–5914.
The synthesis, solid-state and preliminary solution properties of a flavin-based [2]catenane.
Image reproduced by permission of Stuart T. Caldwell, Graeme Cooke, Brian Fitzpatrick, De-Liang Long, Gouher Rabani and Vincent M. Rotello from *Chem. Commun.*, 2008, 5912.

CHEMICAL BIOLOGY

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.

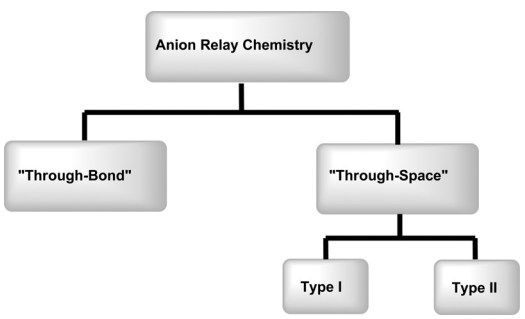
Chemical Biology
December 2008/Volume 3/Issue 12
www.rsc.org/chembiology

FEATURE ARTICLES

Evolution of multi-component anion relay chemistry (ARC): construction of architecturally complex natural and unnatural products

Amos B. Smith, III* and William M. Wuest

Efficient construction of architecturally complex natural and unnatural products is the hallmark of organic chemistry. Anion relay chemistry has the potential to provide the chemist with a powerful synthetic tactic, enabling efficient, rapid elaboration of structurally complex scaffolds in a single operation with precise stereochemical control.



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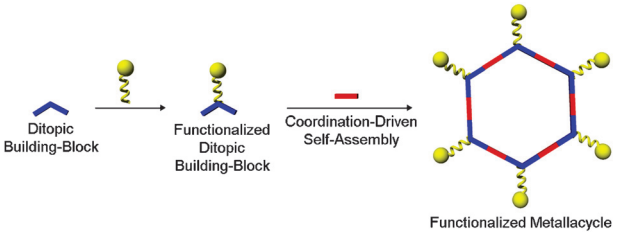
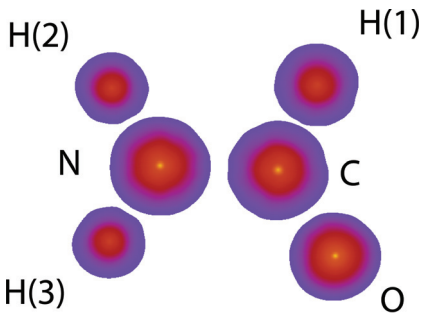
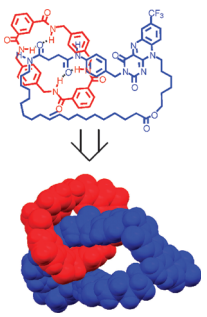
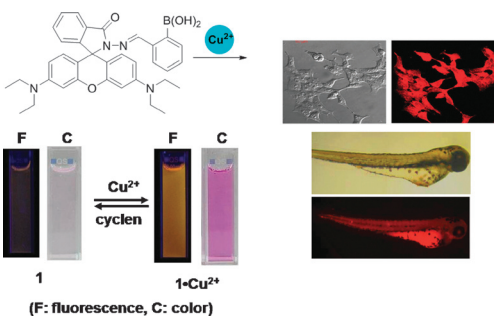
FEATURE ARTICLES



COMMUNICATIONS







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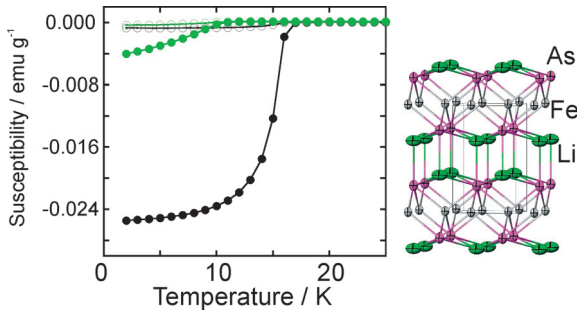
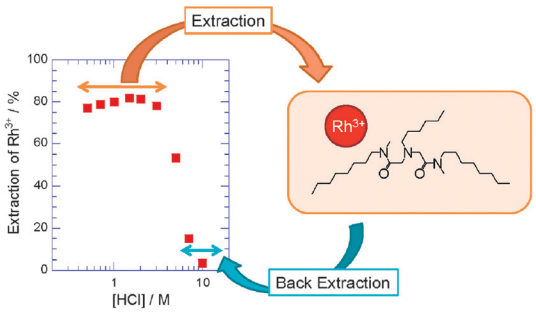


Structure and superconductivity of LiFeAs

Michael J. Pitcher, Dinah R. Parker, Paul Adamson, Sebastian J. C. Herkelrath, Andrew T. Boothroyd, Richard M. Ibberson, Michela Brunelli and Simon J. Clarke*

Superconductivity in LiFeAs samples demonstrates that superconducting anti-PbO-type $[FeAs]^{-}$ anionic layers occur with a wide range of As–Fe–As bond angles.

5921

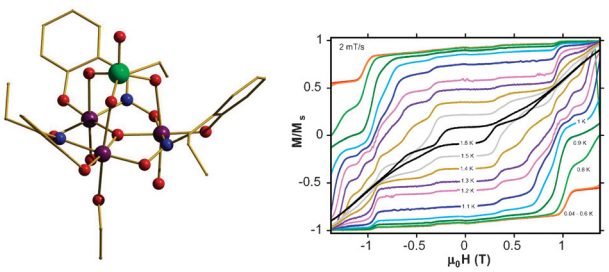


The first effective extractant for trivalent rhodium in hydrochloric acid solution

Hirokazu Narita,* Kazuko Morisaku and Mikiya Tanaka

The tertiary amine compound containing two *N*-disubstituted amide groups, *N*-*n*-hexyl-bis(*N*-methyl-*N*-*n*-octylethylamide)amine (HBMOEAA), can effectively extract and back-extract Rh^{3+} from hydrochloric acid solution.

5924

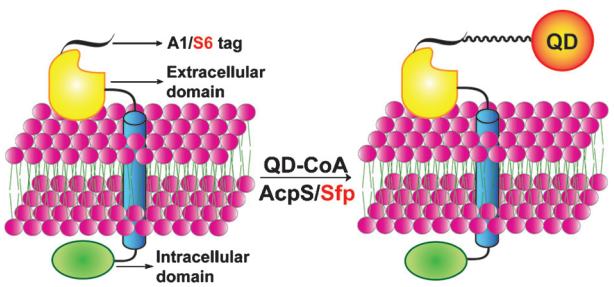


Enhancing SMM properties *via* axial distortion of Mn^{III}_3 clusters

Ross Inglis, Leigh F. Jones, Georgios Karotsis, Anna Collins, Simon Parsons, Spyros P. Perlepes, Wolfgang Wernsdorfer* and Euan K. Brechin*

Replacement of carboxylate and solvent with facially capping tripodal ligands helps to enhance the SMM properties of ferromagnetic $[Mn^{III}_3]$ triangles.

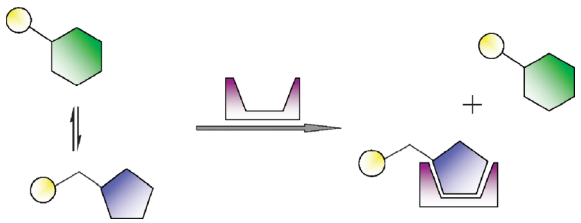
5927

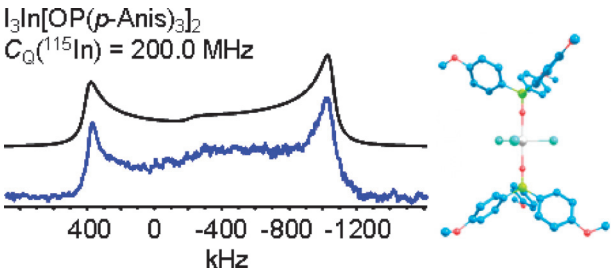


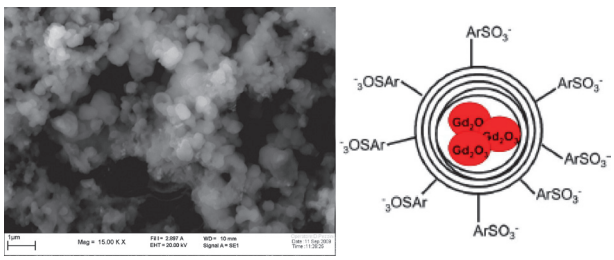
Enzyme catalyzed site-specific protein labeling and cell imaging with quantum dots

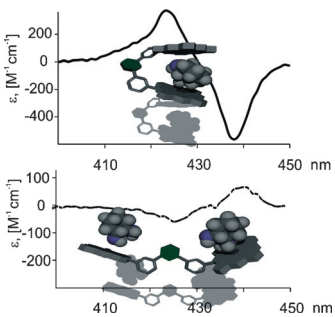
Murat Sunbul, Michelle Yen, Yekui Zou and Jun Yin*

We have developed an efficient method for one-step covalent labeling of cell surface proteins with quantum dots based on enzyme catalyzed site-specific modification of short peptide tags.









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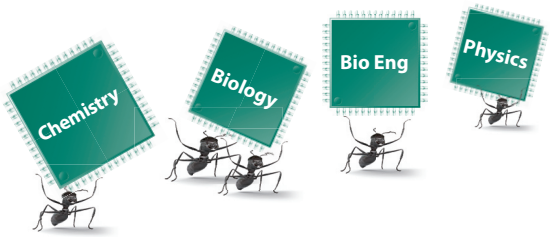

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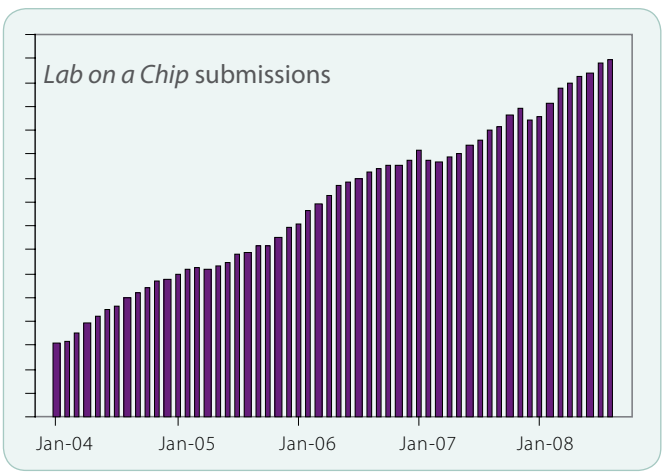

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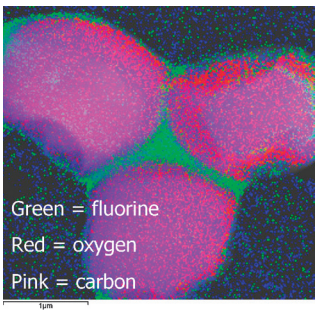

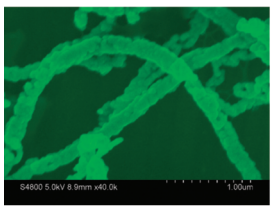

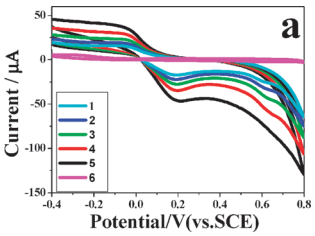

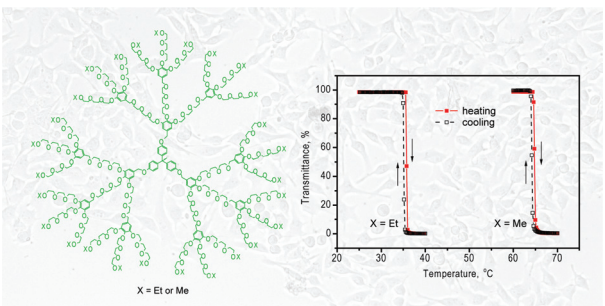

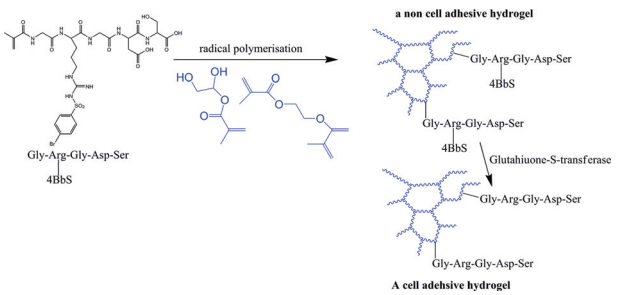

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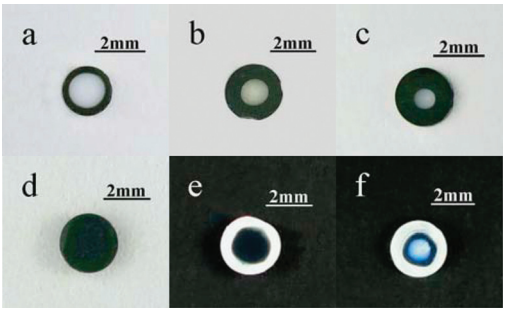
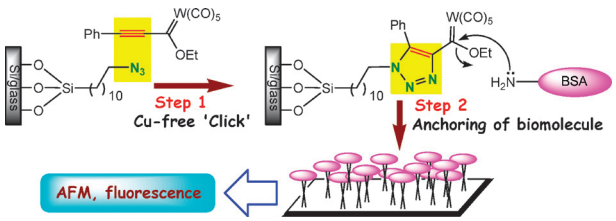


New method for the preparation of nonuniform distributed Co/SiO_2 catalysts

Jingwei Li, Yunjie Ding,* Xianming Li, Guiping Jiao, Tao Wang, Weimiao Chen and Hongyuan Luo

Egg-shell, egg-yolk and egg-white types of Co/SiO_2 catalysts were prepared by reducing the capillary pressure driving force in the impregnation process and utilizing the entrapped air to inhibit the entrance of impregnation or leaching solution into the cores of catalyst pellets during the preparation procedure.

5957

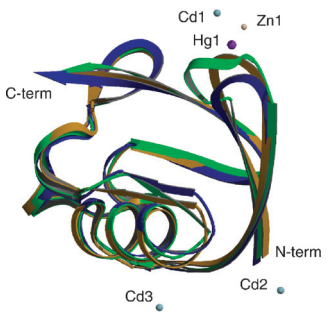


A new bio-active surface for protein immobilisation *via* copper-free 'click' between azido SAM and alkynyl Fischer carbene complex

Sudeshna Sawoo, Piyali Dutta, Amarnath Chakraborty, Rupa Mukhopadhyay, Othman Bouloussa and Amitabha Sarkar*

A Fischer carbene complex grafted on an azido-terminated monolayer by copper-free 'click' reaction (step 1) permits a convenient, instantaneous and covalent anchoring of BSA (step 2) to SAMs.

5960

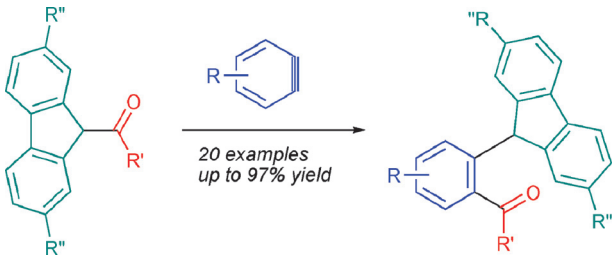


Structural probing of Zn(II), Cd(II) and Hg(II) binding to human ubiquitin

Giuseppe Falini,* Simona Fermani, Giovanna Tosi, Fabio Arnesano and Giovanni Natile

A structural investigation performed on adducts of human ubiquitin with group-12 metal ions reveals two preferential anchoring sites, His68 and Met1. The protein aggregation stereochemistry appears to be driven by the clustering of deshielded backbone hydrogen-bond patches, and metal ions foster this process.

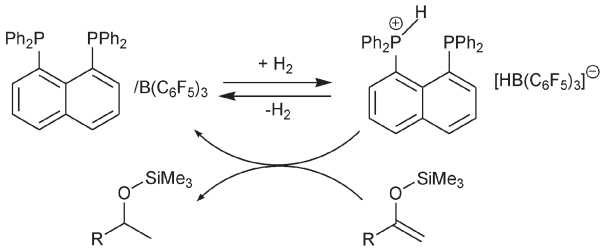
5963

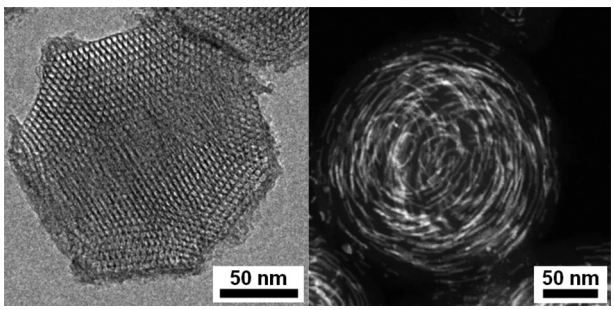


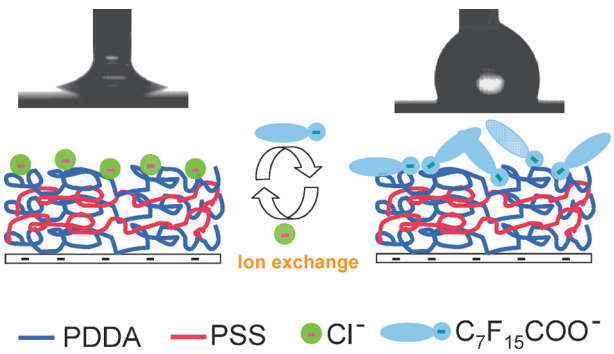
Fluorenes as new molecular scaffolds for carbon–carbon σ-bond cleavage reaction: acylfluorenylation of arynes

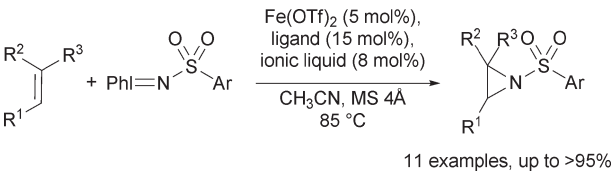
Hiroto Yoshida,* Takeshi Kishida, Masahiko Watanabe and Joji Ohshita

Synchronous installation of acyl and fluorenyl moieties into adjacent positions of aromatic skeletons has been achieved. The ease of formation of fluorenyl anions, being attributable to their aromatic stabilization, is the key to the successful reaction.









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Ben L Feringa, University of Groningen
Sir Harold Kroto, Florida State University
Klaus Müllen, Max-Planck Institute for Polymer Research
Sir J Fraser Stoddart, Northwestern University
Vivian W W Yam, The University of Hong Kong
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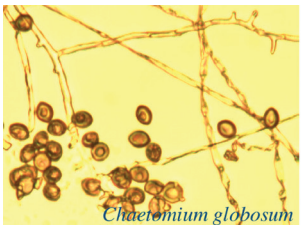

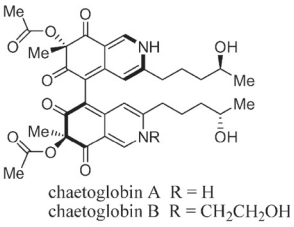

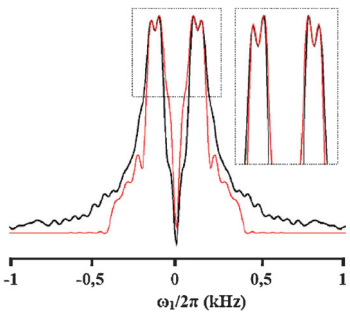

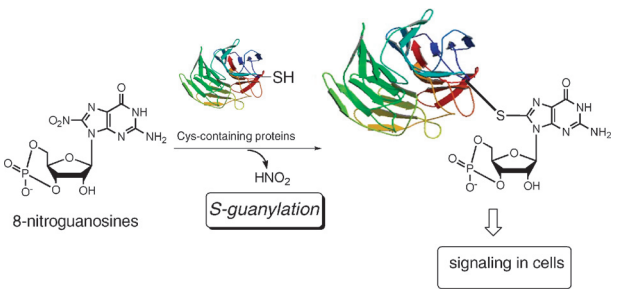

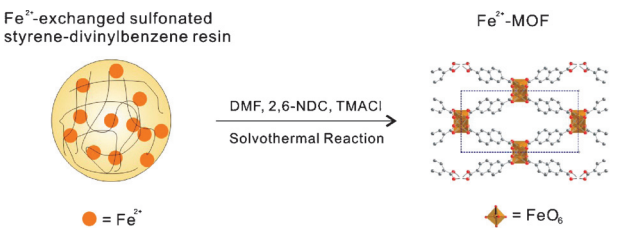

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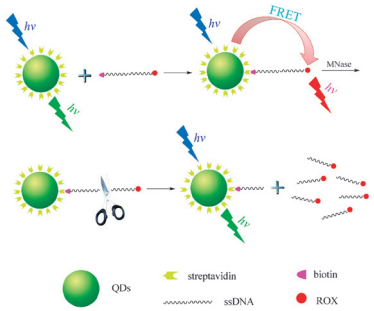
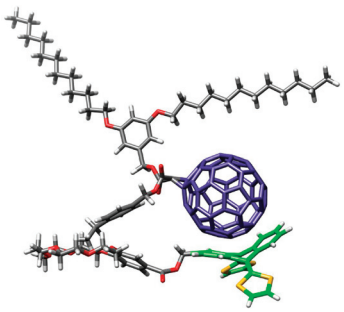


A high sensitive and specific QDs FRET bioprobe for MNase

Shan Huang, Qi Xiao, Zhi Ke He,* Yi Liu, Philip Tinnefeld, Xiong Rui Su and Xiao Niu Peng

A simple and rapid method to detect MNase with high sensitivity and specificity based on the new QD-FRET bioprobe has been developed, which can be extended to the realistic diagnostic assay conditions.

5993

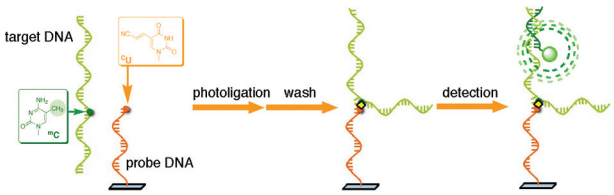


Cooperativity between π–π and H-bonding interactions–a supramolecular complex formed by C_{60} and exTTF

José Santos, Bruno Grimm, Beatriz M. Illescas, Dirk M. Guldi* and Nazario Martín*

Cooperative π–π and H-bonding interactions afford a supramolecular complex from C_{60} and exTTF exhibiting exceptional stability ($K_a \approx 10^6$ M^{-1}); upon photoexcitation, a short living radical–ion pair ($\tau = 9.3$ ps) is formed.

5996

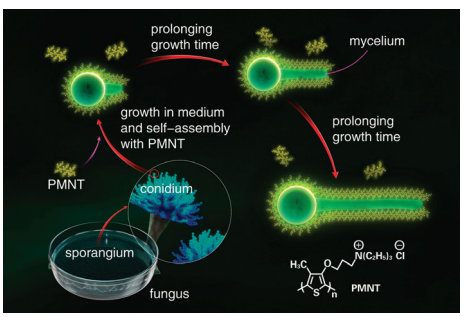


Highly selective detection of 5-methylcytosine using photochemical ligation

Masayuki Ogino, Yuuta Taya and Kenzo Fujimoto*

The authors report the nonenzymatic detection of 5-methylcytosine by using template-directed photoligation through 5-cyanovinyl-2′-deoxyuridine (^{C}U) with high selectivity. A new methylation detection method using a photoligation-based DNA chip assay is presented.

5999



Microorganism-based assemblies of luminescent conjugated polyelectrolytes

Libing Liu, Xinrui Duan, Huibiao Liu, Shu Wang* and Yuliang Li

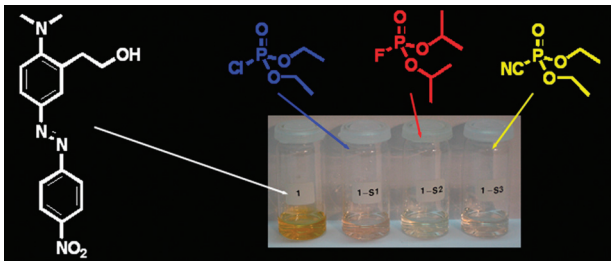
A novel approach was developed for the assembly of fluorescent conjugated polyelectrolytes into tubes on the micrometre scale of tunable length using fungi as living templates.

6002

Chromogenic detection of nerve agent mimics

Ana M. Costero,* Salvador Gil, Margarita Parra, Pedro M. E. Mancini, Ramón Martínez-Máñez,* Félix Sancenón and Santiago Royo

A new chromogenic reagent for the detection of warfare agent simulants in vapour and neutral mixed aqueous environments is reported.

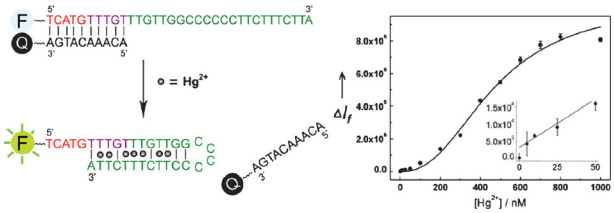


6005

Highly sensitive "turn-on" fluorescent sensor for Hg^{2+} in aqueous solution based on structure-switching DNA

Zidong Wang, Jung Heon Lee and Yi Lu*

A simple design of "turn-on" fluorescent sensor for mercury was demonstrated based on structure-switching DNA with a low detection limit of 3.2 nM and high selectivity.

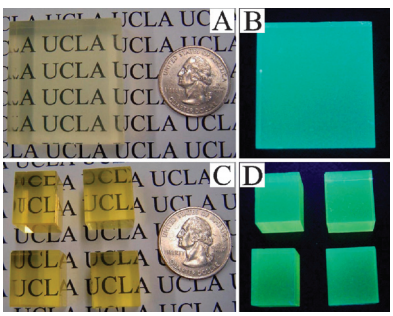


6008

A facile route to bulk high-Z polymer composites for gamma ray scintillation

Yong Sheng Zhao, Zhibin Yu, Ali Douraghy, Arion F. Chatziioannou, Yueqi Mo and Qibing Pei*

Bulk transparent polymer composites for gamma ray detection were prepared from liquid solution formulations. The composites exhibit fluorescence resonance energy transfer from the high-Z compounds to a conjugated polymer also admixed in the composites.

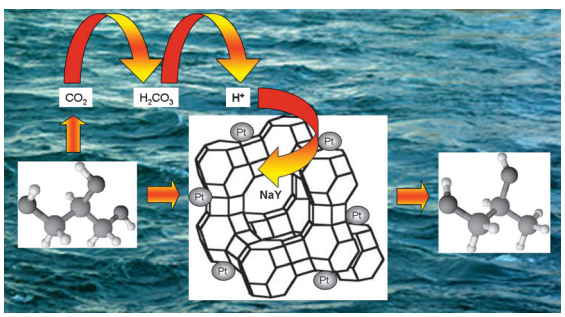


6011

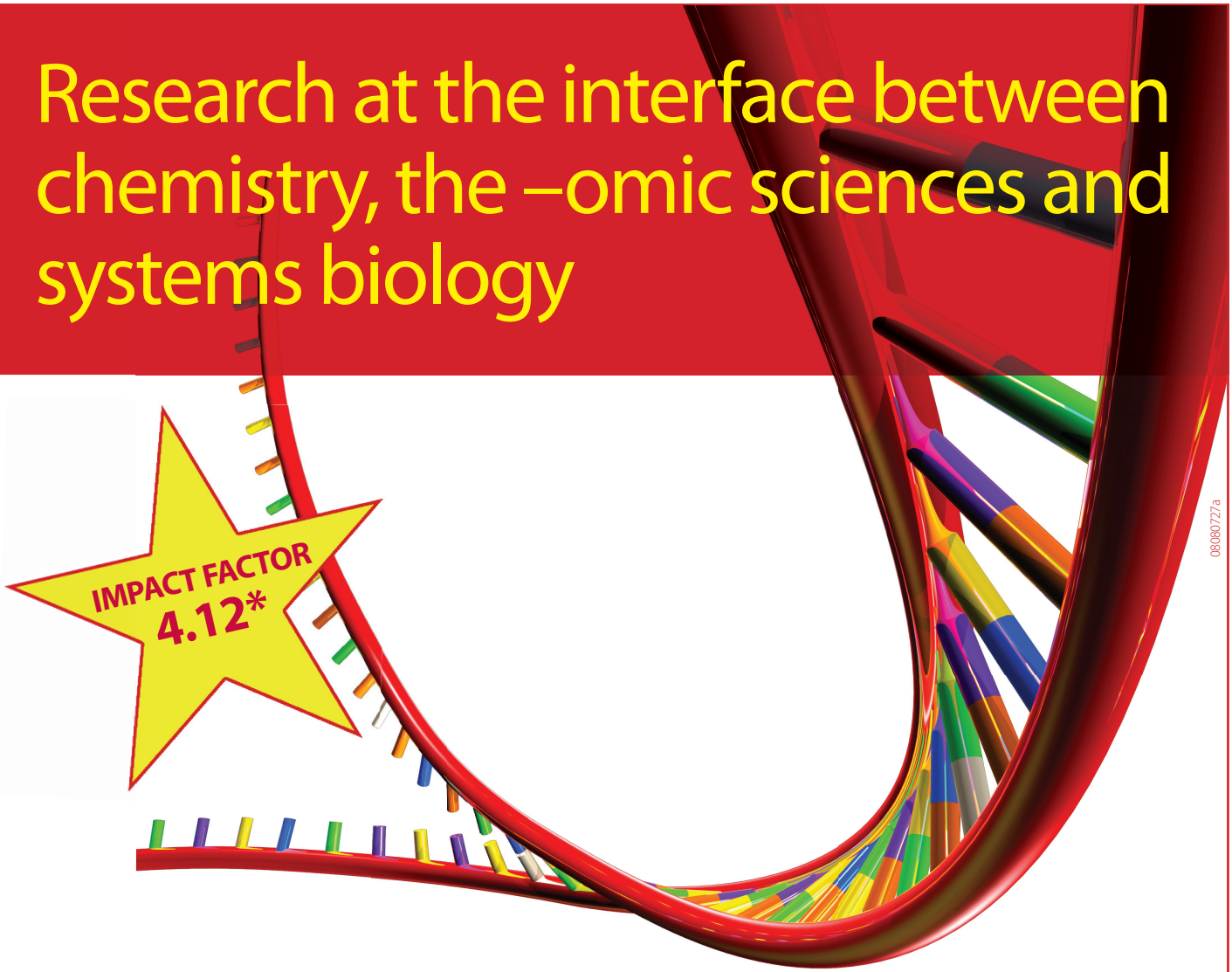
Catalytic glycerol conversion into 1,2-propanediol in absence of added hydrogen

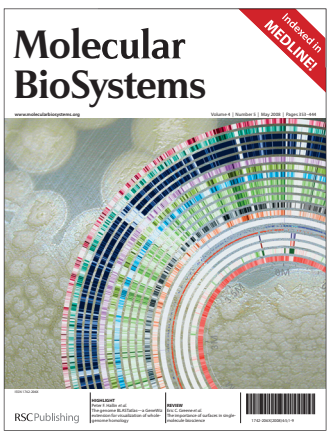
Els D'Hondt, Stijn Van de Vyver, Bert F. Sels and Pierre A. Jacobs*

Conversion of glycerol into high yields of 1,2-propanediol in absence of added hydrogen is possible with Pt impregnated NaY zeolite characterized by extra-zeolitic metal particles combined with zeolite Brønsted acidity.



Research at the interface between chemistry, the –omic sciences and systems biology





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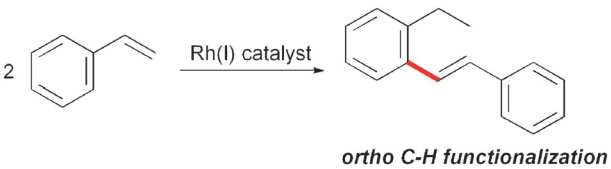
6013

Rhodium-catalysed anomalous dimerization of styrenes involving the cleavage of the *ortho* C–H bond

Mamoru Tobisu,* Isao Hyodo, Masahiro Onoe and Naoto Chatani*

The dimerization of styrene derivatives in the presence of a rhodium catalyst proceeds to give stilbene derivatives, in which the *ortho* C–H bond of styrenes is cleaved and functionalized.

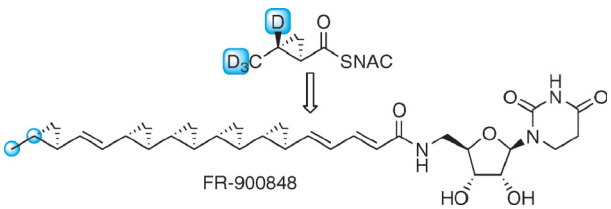


6016

Unprecedented biological cyclopropanation in the biosynthesis of FR-900848

Tetsuo Tokiwano,* Hiroaki Watanabe, Takashi Seo and Hideaki Oikawa*

We were able to show the predominant incorporation of a single enantiomer and intact incorporation of multiply labelled synthetic diketide precursors, which established the intermediacy of cyclopropanated diketide in the biosynthesis of FR-900848.

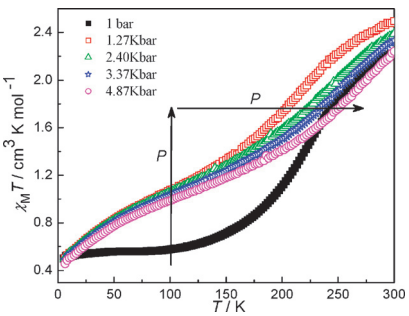


6019

The effects of pressure on valence tautomeric transitions of dinuclear cobalt complexes

Bao Li, Feng-Lei Yang, Jun Tao,* Osamu Sato, Rong-Bin Huang and Lan-Sun Zheng

The effects of pressure on valence tautomeric transition of two complexes, $[\{Co(tpa)\}_2(dhbq)]\cdot(PF_6)_3$ (**I**$\cdot(PF_6)_3$) and $[\{Co(dpqa)\}_2(dhbq)]\cdot(PF_6)_3$ (**II**$\cdot(PF_6)_3$) were investigated. The results show that external pressure makes the SC + ET transition process of the two complexes into a general SC process only.

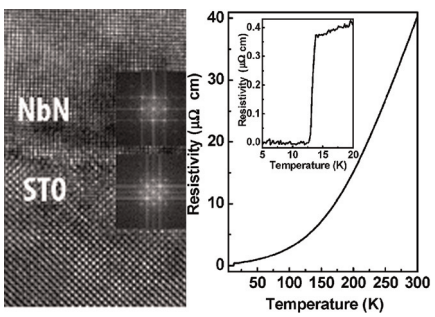


6022

Ultrathin epitaxial superconducting niobium nitride films grown by a chemical solution technique

Guifu Zou,* Menka Jain, Honghui Zhou, Hongmei Luo, Scott A. Baily, Leonardo Civale, Eve Bauer, T. Mark McCleskey, Anthony K. Burrell and Quanxi Jia*

Ultrathin epitaxial superconducting NbN (18 nm) films, exhibiting a superconducting transition temperature of 14 K, were grown on $SrTiO_3$ (STO) by a chemical solution technique, polymer assisted deposition (PAD).



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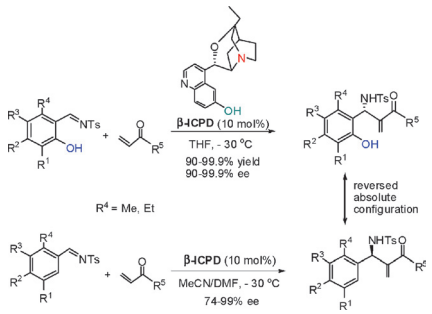
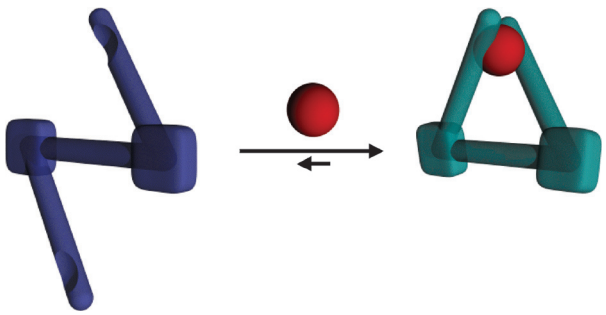


Asymmetric catalytic aza-Morita–Baylis–Hillman reaction (aza-MBH): an interesting functional group-caused reversal of asymmetric induction

Min Shi,* Ming-Juan Qi and Xu-Guang Liu

A highly efficient aza-Morita–Baylis–Hillman reaction (aza-MBH reaction) of *N*-tosyl salicylaldehyde imines with α,β-unsaturated ketones has been achieved by using β-isocupreidine (β-ICPD) as the catalyst (10 mol%) to give the corresponding adducts in good to high yields (90%–quant.) and excellent ee's (up to 99% ee).

6028

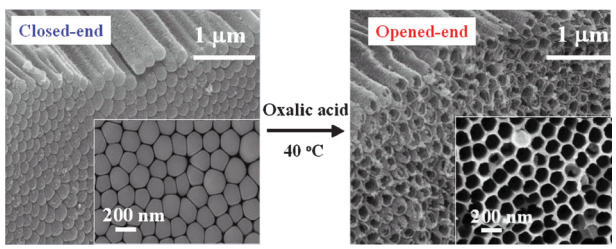


Torsionally restricted tetradentate fluorophore: a swivelling ligand platform for ratiometric sensing of metal ions

Xuan Jiang, Byung Gyu Park, Justin A. Riddle, Bong June Zhang, Maren Pink and Dongwhan Lee*

Restricted swivelling motions around a rigid molecular axle allows a new [n,π]-conjugated molecule to function as a tight metal chelator as well as a ratiometric fluorescence sensor.

6031

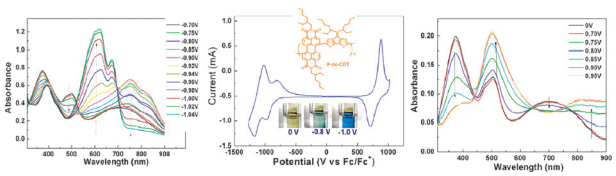


Fabrication of open-ended high aspect-ratio anodic TiO_2 nanotube films for photocatalytic and photoelectrocatalytic applications

Chin-Jung Lin, Wen-Yueh Yu, Yen-Tien Lu and Shu-Hua Chien*

A facile process is introduced to chemically remove the bottom caps of anodic TiO_2 nanotube arrays that exhibit high photocatalytic activity and photoelectrocatalytic efficiency.

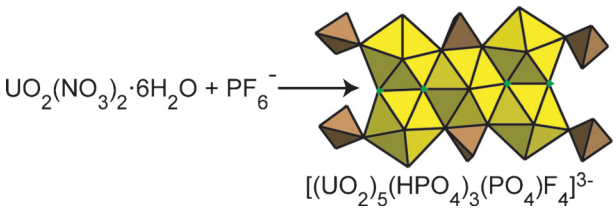
6034

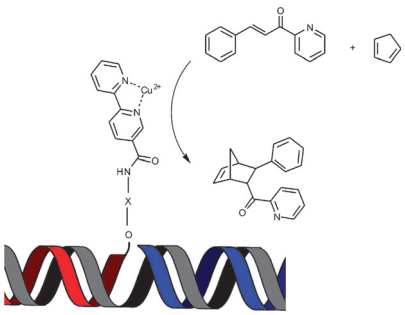


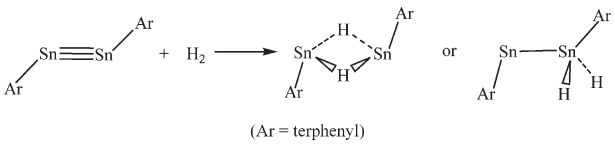
A new n-type low bandgap conjugated polymer P-co-CDT: synthesis and excellent reversible electrochemical and electrochromic properties

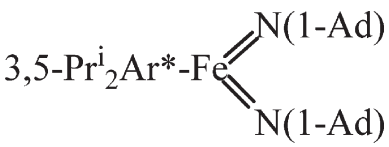
Jianhui Hou,* Shaoqing Zhang, Teresa L. Chen and Yang Yang*

A n-type low bandgap conjugated polymer based on perylene diimide and cyclopenta[2,1-*b*:3,4-*b*′]dithiophene, which exhibits excellent reversible electrochemical properties in both n-doping/dedoping and p-doping/dedoping processes, was designed, synthesized and characterized.









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Chemical Biology

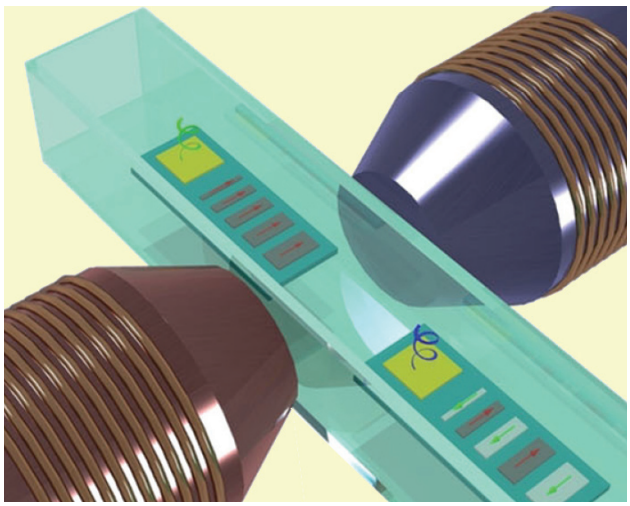
Miniature magnetic tags used to track DNA samples in chip systems

The barcode and the bioassay

Barcodes have been used to track many things, from airline luggage to parcels. Now they are being used to label and track samples in microfluidic, high-throughput systems.

Jong-Ryul Jeong's group at the University of Cambridge, UK, is working towards one of the big goals in biological science: a DNA sequencing technology that can sequence the human genome in one day. But to achieve this they need to create new microfluidic systems and realised they required a labelling technique to track samples through the small devices. Their solution was tiny magnetic barcodes that can be attached to the samples and tracked.

The magnetic barcodes consist of a small strip of plastic, smaller than the average human cell, onto which strips of cobalt are attached. The cobalt can be magnetised in two different directions, to give either a plus one or minus one signal, much like the black and white strips of a conventional barcode. These barcodes can then be read quickly as labelled samples pass a detector, just like being swiped at the checkout.



Barcoded DNA samples can be scanned much like food at the supermarket checkout

Jeong explains that the main advantages of this technology are that the tags can be coded after they have been applied to a sample, reducing the likelihood of mislabelling. They can also be coded remotely and even rewritten if needed, he adds.

Samuel Sia of Columbia University, New York, US, works on creating low cost lab-on-a-chip diagnostic devices. He says that the technique is a 'potentially useful concept' that could be used in high-throughput biological assays.

Jeong has recently set up a spin-out company to explore the opportunities that the technology presents and to develop it further. He admits that there are challenges ahead, both in improving the barcode detection speed and in developing high-throughput assays to exploit the technique. Nevertheless, he points out, the concept 'is generic enough to be applied to a variety of biological assays.'

Laura Howes

Reference
J-R Jeong *et al*, *Lab Chip*, 2008, **8**, 1883 (DOI: 10.1039/b807632d)

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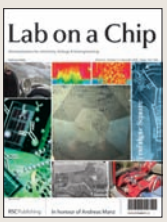

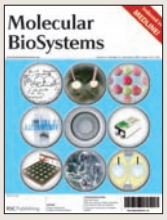

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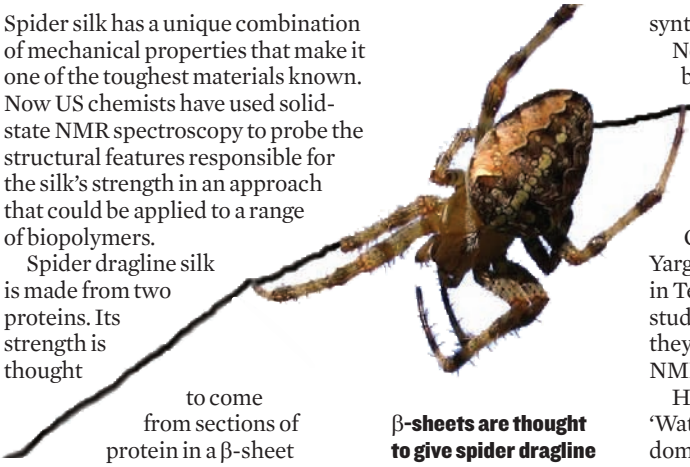
Research highlights

Solid-state NMR spectroscopy used to probe cause of spider silk's strength

INADEQUATE coverage of silky sheets

Spider silk has a unique combination of mechanical properties that make it one of the toughest materials known. Now US chemists have used solid-state NMR spectroscopy to probe the structural features responsible for the silk's strength in an approach that could be applied to a range of biopolymers.

Spider dragline silk is made from two proteins. Its strength is thought to come from sections of protein in a β-sheet conformation, while the elasticity comes from helical regions. Knowing the relative proportions of these conformations, and how this correlates to the amino acid sequence, is important for understanding the silk's mechanical properties and for developing synthetic silk.



β-sheets are thought to give spider dragline silk its strength

Reference
G P Holland *et al*, *Chem. Commun.*, 2008, 5568 (DOI: 10.1039/b812928b)

Normally, spider silk produces broad unresolved NMR signals. When the silk is treated with water, the fibres swell in diameter and shorten by approximately 50 per cent.

Gregory Holland and Jeffery Yarger at Arizona State University in Tempe, and their colleagues were studying this supercontraction when they noticed that water affected the NMR response of the helical regions.

Holland explains the process: 'Water penetrates the helical domains and causes them to become mobile, resulting in a sharpening of their NMR resonances and an increase in resolution. In contrast, water does not penetrate the β-sheet domains so they remain rigid on NMR timescales and the resonances resemble those of dry silk.'

The team used an incredible natural abundance double quantum transfer experiment (INADEQUATE) NMR method to analyse spider silk. By exploiting the difference between the NMR spectra of wet and dry silk they could differentiate the signals from the helical and sheet structures and quantify the amino acid levels in each. They concentrated on the amino acids glycine and alanine, which make up 60–70 per cent of spider silk, and found that 28 per cent of the silk's glycines and 82 per cent of the alanines are in the β-sheet conformation.

Holland and Yarger say that fully understanding the properties of spider dragline silk requires characterising the rest of its structure and the interactions between the two proteins. They are continuing to investigate these areas.

Michael Townsend

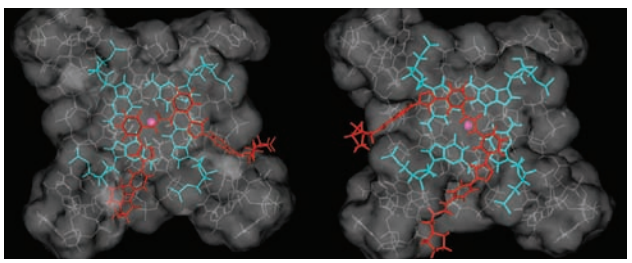
Ureas shun the double helix to bind quadruplex DNA

Quadruplex binding clicks into place

Small molecules selectively targeting four-stranded DNA could lead to anticancer drugs without the toxic side-effects, say scientists in the UK.

Quadruplex DNA is a four-strand form of the biomolecule and is associated with cancer cell replication. Stephen Neidle and William Drewe at the University of London designed a series of diphenyl urea-based structures that bind strongly to quadruplex DNA but have low affinity for duplex DNA – the two strand double helix. This selectivity means the molecules aren't toxic to healthy cells, and could specifically knock out cancer cell growth, says Neidle.

Guanine-rich DNA quadruplexes (G4s) can be found in many telomeres, end sections of chromosomes which in healthy tissue gradually degrade until the cell can no longer divide. But in cancer cells, telomeres are continually maintained by telomerase – an enzyme switched off in most healthy adult tissue – effectively making cancer cells immortal. Neidle and Drewe's molecules are designed to disrupt telomerase from binding to the quadruplex.



Molecular modelling studies suggested that diphenyl ureas would bind to guanine-rich DNA quadruplexes

Reference
W C Drewe and S Neidle, *Chem. Commun.*, 2008, 5295 (DOI: 10.1039/b814576h)

'The defining characteristic of most drugs is that they are toxic to most cells, including healthy ones,' says Neidle. 'We're looking for molecules that don't kill cells, but have a telomerase blocking mechanism.' While a number of molecules have been found to bind G4 DNA, these molecules have typically been unselective, and too large to be useful as drug molecules. 'The idea was to move away from polycyclics and develop a much more drug-like framework,' he adds.

Neidle and Drewe used click chemistry to link a biaryl urea core to two azide side chains, which modelling studies had suggested would bind strongly to G4 DNA. This synthetic strategy uses reliable reactions to join small units together, meaning that a variety of related compounds could be synthesised quickly for testing.

'Designing a drug-like quadruplex binder that really doesn't bind to duplex DNA is a pretty big step forward,' says Mark Searcey, who studies DNA quadruplex binding at the University of East Anglia, Norwich, UK. 'You're trying to target one DNA quadruplex among hundreds of thousands of duplexes, so you need very high selectivity,' he adds.

Having shown that the compounds selectively bind G4 DNA, and are not toxic to cells, Neidle is currently testing the compounds' ability to curb cancer cell growth.

James Mitchell Crow

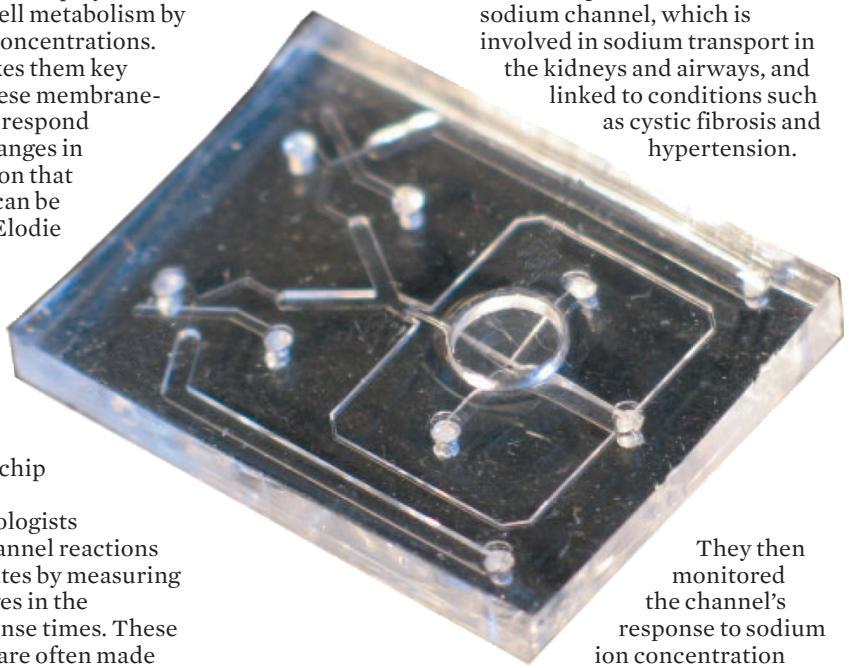
Order-of-magnitude improvement for ion channel studies

Chip measures channel currents

By allowing ions into and out of cells, ion channels play a crucial role in cell metabolism by regulating ion concentrations. Whilst this makes them key drug targets, these membrane-spanning pores respond so rapidly to changes in ion concentration that studying them can be difficult. Now, Elodie Dahan at the Swiss Federal Institute of Technology in Lausanne, and colleagues have addressed the problem using lab-on-a-chip technology.

Electrophysiologists evaluate ion channel reactions to drug candidates by measuring resulting changes in the channels' response times. These measurements are often made using the two electrode voltage clamp method, in which the cell is pierced with two microelectrodes to record the membrane cell potentials. Although automated versions are available, the impaling is time-consuming and may harm the cell. Also the measurements can be limited by the time it takes to replace the solution surrounding the cell. If these are much longer than the response time the cell will have already responded before the measurement can be taken.

The Swiss team's answer is a disposable chip for non-invasive electrophysiological measurements. Two different solutions flow into the chip mixing at the centre of a Y-junction. The mixed solution then flows towards a cell held inside the chip and the ion current across the cell membrane is measured. The chip design enables the user to change the solution flowing to the cell whilst maintaining a continuous flow, avoiding abrupt changes in shear force and stress effects on the cell membrane.



The disposable chip allows non-invasive electrophysiological measurements

The team modified frog egg cells to express ENaC, a human sodium channel, which is involved in sodium transport in the kidneys and airways, and linked to conditions such as cystic fibrosis and hypertension.

They then monitored the channel's response to sodium ion concentration by placing the egg cells in the chip and rapidly exchanging a sodium-free solution for a sodium ion solution and recording the current across the membrane over time. The device showed an order of magnitude improvement over conventional techniques.

Daniel Irimia of Massachusetts General Hospital, Boston, US, who develops microfluidic devices for biological and clinical sciences, says the device is a 'wonderful example of how emerging technologies based on microfluidic principles enable more precise, quantitative measurements in biology.'

Dahan explains that the chip's design should allow other, more complicated experiments to investigate other ion channels. 'The possibility of investigating fast kinetic events of drug receptors with increased throughput overcomes classical bottlenecks and will open the way for such systems to be used in pharmacological laboratories,' she says.

Vikki Chapman

Reference
E Dahan *et al*, *Lab Chip*, 2008, **8**, 1809 (DOI: 10.1039/b806404k)

News in brief

This month in *Chemical Science*

A total mismatch
In this month's interview, Penny Brothers, associate professor at the University of Auckland, New Zealand, tells Michael Brown about porphyrins and their potential role in neutron capture therapy.

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Egg whites have found a novel use as a template for making inorganic nanotubes, thanks to Chinese scientists.

Underperforming yeasts opt out of life
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Christelle Guillo and Michael G Roper, *Analyst*, 2008, **133**, 1481 (DOI: 10.1039/b808735k)

Controlling the activity of peptides and proteins with smart nucleic acid–protein hybrids
Lars Röglin and Oliver Seitz, *Org. Biomol. Chem.*, 2008, **6**, 3881 (DOI: 10.1039/b807838f)

Long-range chromosomal interactions and gene regulation
Adriana Miele and Job Dekker, *Mol. BioSyst.*, 2008, **4**, 1046 (DOI: 10.1039/b803580f)

Tissue engineering with nano-fibrous scaffolds
Laura A Smith *et al*, *Soft Matter*, 2008, **4**, 2144 (DOI: 10.1039/b807088c)

Carbon nanotube micro-electrodes for neuronal interfacing
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Carbohydrate–protein recognition probed by density functional theory and *ab initio* calculations including dispersive interactions
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Chemopreventive effects of natural dietary compounds on cancer development
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Design of a novel molecular beacon: modification of the stem with artificially genetic alphabet
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Luminescent rare earth nanomaterials for bioprobe applications
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FACT and the reorganized nucleosome
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Stimuli-responsive surfaces for bio-applications
Paula M Mendes, *Chem. Soc. Rev.*, 2008, **37**, 2512 (DOI: 10.1039/b714635n)

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Interview

Fired up about fungi

Russell Cox discusses with Nina Notman his fiery introduction to chemistry, his work on polyketide biosynthesis and Bristol's ChemLabS programme

Russell Cox

Russell Cox is a reader in organic and biological chemistry at the University of Bristol, UK, and a Bristol ChemLabS University Teacher Fellow. He is currently investigating programming in fungal iterative polyketide synthase, by applying molecular genetics, enzymology and synthetic chemistry.

Do you remember your first experiment?
As a young child, while living in Southampton, I remember filling an air-raid shelter in a friend's garden half an inch deep with methylated spirits and setting fire to it [Ed: we don't recommend you try this!]. This was definitely an experiment, but more designed to see whether the friend's mother would notice, or not. She didn't!

What attracted you to research in biological chemistry?
Being in the right place at the right time. It was David O'Hagan who attracted me towards biological chemistry. I started a PhD with him combining synthesis and fungal biology and was hooked from then. I have always been grateful to have studied chemistry – the ability to synthesise and analyse compounds has underpinned all the advances in my area of research, but the questions of biology remain the biggest.

What are you working on at the moment?
Our biggest project is investigating programming in fungal iterative polyketide synthases. These enzyme systems are responsible for the biosynthesis of a huge range of biologically active compounds. The enzymes responsible are true nano-machines that are programmed to perform a choreographed sequence of reactions. We can change the reactions – but not yet rationally. We are applying molecular genetics, enzymology and synthetic chemistry to investigate this problem. At the moment we are attempting to shuffle genes encoding proteins with closely related programmes in order to dissect the programmes and discover which parts of the proteins are involved.

What are the wider aims of Bristol's new ChemLabS other than the teaching of the university's undergraduates?
ChemLabS is a truly innovative programme. We were lucky enough to win funding from the Higher Education Funding Council for England to set up a centre of excellence in teaching and learning focussed on practical chemistry. We have invested in our teaching labs to make them world-class, and have brought the level of infrastructure and equipment up to industrial standards. Simultaneously, we have rebuilt all of our practical teaching material and developed a fully integrated digital system (called the Dynamic Laboratory Manual, DLM) to support all of our practical teaching. Students now are encouraged to use simulations of techniques, equipment and individual experiments before they go into the labs. We now use this methodology at all levels in the School of Chemistry at Bristol, but we are expanding with commercial partners, to make a DLM for AS and A level study.

What advice would you give to a young researcher who wants to forge a career in biological chemistry research?
Move to Germany or the US! The UK has a truly great history of scientific discoveries, especially in biological chemistry, and some great scientists, but we make life difficult for ourselves. Researchers in British universities have to fit research interests in around a full schedule of teaching and administration so time is at a premium, and the funding situation for chemistry is pretty tough in the UK at the moment.

You are a keen and successful teacher of undergraduates (having recently won the Faculty of Science Teaching Prize at Bristol), and were heavily involved in the launch of ChemLabS. What do you view as the necessary ingredients to be a good teacher?
The ability to see problems from different perspectives – our students vary tremendously in their backgrounds and approaches to learning. I am lucky to be working with a very skilled and experienced team at Bristol, and I have learned as much, or more, by being a teacher as any other aspect of my career.

What do you like to do in your spare time?
I've given up setting fire to air-raid shelters, but I still like knocking things down. I am currently working on my house in the Mendips, knocking bits down and building new bits. I recently sawed a huge oak beam out of the loft to create space for a new room, and I enjoy plumbing, wiring and carpentry. I have two young sons and we spend a lot of time together, fishing, sailing and even doing the odd scientific experiment.

Finally, if you weren't a scientist what would you be?
I'd be a gardener. Chemistry and gardening have much in common: one has to have a plan and vision and see far ahead. Gardens require patience, nurture and constant attention, and the results are very rewarding – but you don't need to write grant applications!

Instant insight

The path of least resistance

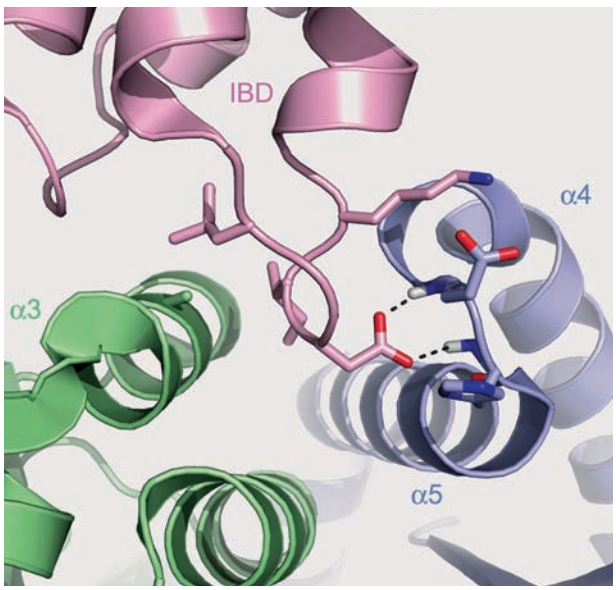
If targeting a virus directly promotes drug resistance, why not take a different approach? Zeger Debyser and colleagues at the Catholic University of Leuven, Flanders, Belgium, suggest an alternative

Until very recently, the prospect of using small molecules to block specific protein–protein interactions was viewed with much skepticism. But protein–protein interactions play a key role in most biological processes and therefore are an important class of therapeutic targets. These interactions were overlooked for a long time, since developing drugs against the traditional targets such as enzymes and receptors was more cost effective. Since the cost of developing these classical drugs is increasing rapidly and pipelines are running dry, research into protein–protein interactions is becoming feasible and warranted.

This idea can be applied to the human immunodeficiency virus type 1 (HIV-1). The virus relies on several cellular proteins to replicate, proteins referred to as cofactors. Not only does understanding the interaction between HIV proteins and cellular cofactors shed light on the virus's effects but it provides new strategies for antiviral therapy.

Developing drugs to target cellular cofactors constitutes a paradigm shift in antiviral research as present day antivirals typically target viral proteins. In the case of chronic viral infection this specificity for the viral target comes at a cost since viruses, with their high mutation rate, can become resistant to the antiviral drugs. The answer could be to develop drugs that target specific virus protein–cofactor interactions.

The conserved nature of cellular proteins may provide a critical advantage in the struggle against antiviral resistance. The virus may find more difficulties in developing resistance against drugs targeting interactions between invariable cellular proteins and conserved viral protein domains. Also, since a specific protein–protein interaction is targeted and not the cellular protein per se, this should circumvent cellular toxicity. Moreover, outside the field of infectious diseases, drugs can target cellular targets in a non-toxic way.



Targeting protein–protein interactions such as that between HIV-1 integrase (green and blue) and the cellular cofactor LEDGF/p75 (purple) could lead to new antiviral drugs

One of the major obstacles to finding small molecule protein–protein interaction inhibitors (SMPPIIs) is the flat nature of the protein–protein interface. X-ray structures have shown that a large part of the interaction area is buried, with atoms closely packed together, implying a lack of available cavities for small molecule binding. Yet, it has become clear that some protein–protein interfaces have a well-defined compact area, commonly referred to as a hot spot, which plays a major role in the interaction. These hot spots define potential targets for SMPPII development.

Returning again to the HIV example, our group discovered the cellular cofactor LEDGF/p75 which plays a crucial role in HIV replication. The cofactor is essential to the viral enzyme HIV integrase, which helps incorporate the viral DNA into regions of the host cell where it will be transcribed. LEDGF/p75 had previously been reported as a cellular stress response factor and a variant, p52, as a transcriptional coactivator but the link with HIV was unexpected. The interaction with integrase is specific for the p75 form; LEDGF/p52 lacks the integrase binding domain (IBD).

A crystal structure of the dimeric catalytic core domain of HIV-1 integrase complexed to the IBD of LEDGF is available (see figure). An interhelical loop of the IBD protrudes into a pocket at the interface of the integrase core. This pocket classifies as a hot spot for interaction and a suitable drug target. We have established an assay to detect SMPPIIs for the integrase–IBD interaction. Early hits with micromolar activity in vitro and in cell culture have raised our hopes that we can effectively and safely block this protein–protein interaction in HIV infected patients in the future.

Read more in Debyser et al*'s review 'In search of small molecules blocking interactions between HIV proteins and intracellular cofactors' in* Molecular BioSystems.

Reference
K Busschots *et al, Mol. BioSyst.*, 2008, DOI: 10.1039/b810306b

Instant insight

Life at the extremes

There are miniature natural product libraries to be found in the most unexpected places. Zoe Wilson and Margaret Brimble of the University of Auckland, New Zealand, delve deeper

A microorganism that survives extreme environments can be classified as either extreme-tolerant, if it grows best under more moderate conditions, or extremophilic, if it grows optimally under these extraordinary conditions. In order to survive in such settings, microorganisms have developed unique defences, and this has frequently led them to produce novel molecules. This has made them a mine for natural product chemists. But whilst the first extremophilic organism was isolated in the 1860s, it took over a century for scientists to realise that the number of these organisms is significant, leading to a rapid growth in research in this area.

Traditionally, the extremes of life are considered to be high and low temperature (inhabited by thermophiles and psychrophiles respectively), high pressure (piezophiles/barophiles), high and low pH (alkaliphiles and acidophiles), and high salt (halophiles). Many extremophiles actually thrive in environments which are extreme in two or more aspects. For example, the *Shewanella violacea* strain DSS12, which produces a novel violet pigment, was isolated from the Ryukyu trench in the Philippine Sea, at a depth of 5110m. This bacterium is a barohalopsychrophile – growing optimally at 30MPa, 8°C and in the presence of 3 per cent sodium chloride.

To date the largest number of novel molecules from extreme dwelling microorganisms have been isolated from thermophiles. Several of these molecules are thought to play a role in survival at extreme temperatures, such as ether linked lipids, modified nucleosides and a variety of polyamines which are thought to stabilise DNA at high temperatures by reducing flexibility.

Geysers and geothermal sites are just two of the many unlikely environments where microorganisms have been found

The term psychrophile was first used in 1902. Representatives of all the major taxa have been found inhabiting temperatures below 0°C, making this is one of the more diverse branches of the extremophiles. To date however the only novel molecules first isolated from psychrophilic or psychrotolerant microorganisms are secondary metabolites, which are largely based on modified peptides. These include mixirins A–C, three cyclic peptides isolated from the psychrotolerant *Bacillus* sp. strain MIX-62, which have been shown to inhibit human colon tumour cell growth.

Piezophiles (barophiles) are typically isolated from the bottom of the ocean and the majority of secondary metabolites isolated from these extremophiles are cyclic. Notably, a series of cyclic secondary metabolites that halt cell replication in mouse tsFT210 cells were isolated from *Aspergillus fumigatus* strain BM939, a fungus isolated from the sea bottom of the Oi river, Sizuoka prefecture, Japan.

Halophiles have to survive osmotic stress. One survival mechanism they use is to accumulate small molecules known as osmolytes, with eight novel osmolytes being first isolated from halophilic or halotolerant microorganisms.

Enzymes from alkaliphilic or alkali-tolerant microorganisms have made a large impact due to their industrial applications in biological detergents. But, to date, relatively few novel molecules have been isolated from these microorganisms. Among them are novel carbohydrates and an unusual lipid from bacteria of the *Halomonas* species.

Microorganisms capable of surviving low pH have been isolated from a range of sources around the world, both natural, for example acidic hot springs, and man-made, such as Berkeley Pit Lake (an abandoned copper mine which filled with acidic water). These microorganisms produce diverse secondary metabolites with a range of biological activities. For example, thirteen of the molecules isolated from Berkeley Pit Lake microorganisms inhibit protein-cleaving enzymes caspase-1 and matrix metalloproteinase-3.

When the large number of reported extremophiles is considered, very few have been screened for novel secondary metabolite production. Despite nearly 150 years in the public domain, this rich source of novel molecules remains largely untapped.

Read more in 'Molecules derived from the extremes of life' in issue 1, 2009, of Natural Product Reports.

Reference
Z E Wilson and M A Brimble, *Nat. Prod. Rep.*, 2009, DOI: 10.1039/b800164m

Essential elements

Board member wins Nobel Prize

The Nobel Prize in Chemistry 2008 has been awarded to Roger Tsien (below right), University of California, San Diego, US, a member of the editorial board for the upcoming RSC journal *Integrative Biology* (to be launched in January 2009), and colleagues for their work in the development of the gene marker green fluorescent protein (GFP).

Harp Minhas, editor of *Integrative Biology*, says: 'Congratulations to Professor Tsien, from all of us at the RSC. We are all immensely pleased that 2008 Nobel Prize winner Roger Tsien is an editorial board member for *Integrative Biology*; his work typifies the quality of material we are seeking in the development of biology through new tools and technologies.'

Derivatives of GFP are used in experiments to observe cell dynamics and behaviour – their fluorescent glow allows scientists to visualise processes inside cells.

Furthermore, as it is non-toxic to cells it can be used in live cell (in vitro) studies meaning that real time analysis of cells is possible.

GFP is a protein first extracted from the jellyfish *Aequorea victoria* in the 1960s by Osamu Shimomura, who was jointly awarded this year's prize with Tsien and Martin Chalfie. Variants of GFP can fluoresce in different colours, allowing several different proteins in a cell to be studied simultaneously.

Find out more about our new journal Integrative Biology *at www.rsc.org/ibiology*

Announcing *Lab on a Chip* prize winners

Lab on a Chip, the miniaturisation journal for chemistry, biology and bioengineering, has yet again shown extensive community support by sponsoring some of the most prestigious prizes in the miniaturisation field. At this year's μ-TAS meeting in San Diego the journal, together with Corning Inc., awarded the 'Pioneers in Miniaturisation Prize' to Patrick Doyle, professor at the department of chemical engineering at MIT, US. Jean-Louis Viovy from the Institute Curie comments on Doyle's work: '[Patrick] developed the "stop-flow lithography" technological platform, which I consider a major breakthrough in microfluidics.'

Lab on a Chip also awarded the 'Widmer Young Researcher Poster Award' to Maged Fouad for best poster and presentation. Among 589 candidates, this poster titled 'Nanotechnology meets plant biotechnology: carbon nanotubes deliver DNA and incorporate into the plant cell structure' caught the judges' eyes.

A new award named 'Art in Science' recognised the aesthetic value in scientific illustrations. 'The winner, Yu Wen Huang (Texas A & M University) clearly understood the principles of this award and produced an image that was reminiscent of a tall city building seen in an early morning fog. The picture is an optical effect generated by concentrated double-stranded DNA in the vicinity of a 50 micrometre wide electrode inside a microchannel,' comments Harp Minhas, editor of *Lab on a Chip*, who proudly presented all awards to the winners.

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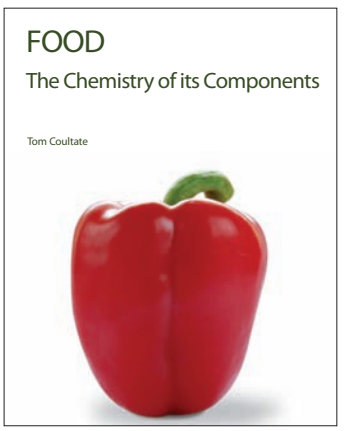

This textbook has been fully revised and updated and includes a foreword written by Heston Blumenthal. Look out for other exciting new food science books in 2009 such as *Kitchen Chemistry* (new volume), *Handbook of Culture Media for Food* and *Water Microbiology and Nanotechnologies in Food*.

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