

Photochemical & Photobiological Sciences

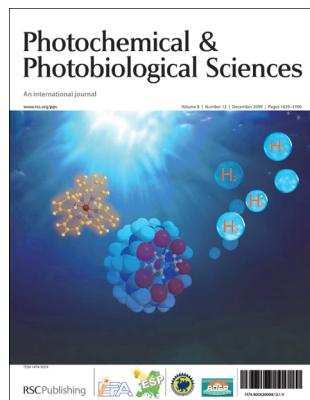
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Cover

See C. G. Silva, M. de Miguel, B. Ferrer, M. Álvaro and H. García, pp. 1650–1654.

Photocatalytic hydrogen production from water becomes more efficient if punking-like hollow capsules (cucurbiturils) are present in the system.

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B89

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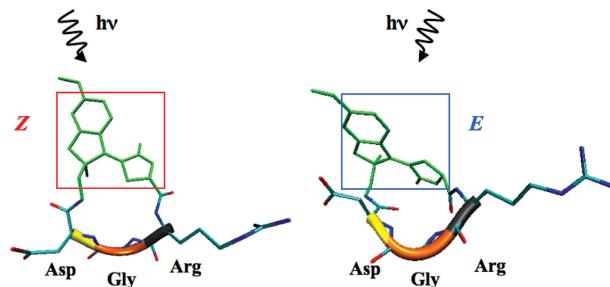
PERSPECTIVE

1639

A novel biomimetic photochemical switch at work: design of a photomodulable peptide

Adalgisa Sinicropi,* Caterina Bernini, Riccardo Basosi and Massimo Olivucci

Structural and spectroscopic properties of a novel cyclic peptidomimetic, formed by a biomimetic Z/E photoisomerizable switch conjugated to the biologically active RGD peptide, are investigated in aqueous solution by means of molecular dynamics and quantum-mechanical/molecular-mechanic (CASPT2//CASSCF/AMBER) computations.



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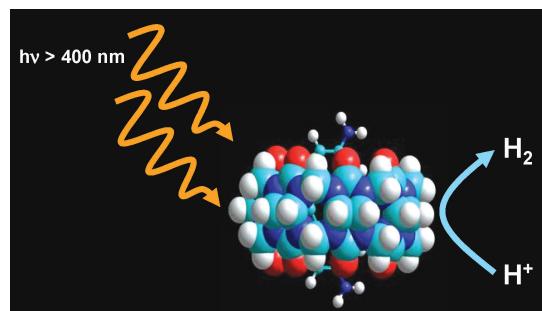
PAPERS

1650

Enhanced efficiency of the visible-light photocatalytic hydrogen generation by the ruthenium tris(2,2'-bipyridyl)-methyl viologen system in the presence of cucurbit[n]urils

Cláudia Gomes Silva, Maykel de Miguel, Belén Ferrer, Mercedes Álvaro and Hermenegildo García*

The efficiency of photocatalytic H₂ generation increases when cucurbiturils are present in solution. The efficiency enhancement is CB[6] < CB[7] < CB[8].

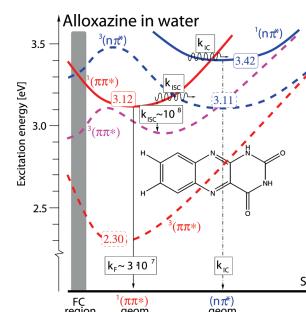


1655

The photophysics of alloxazine: a quantum chemical investigation in vacuum and solution

Susanne Salzmann and Christel M. Marian

We show that the decay mechanism of the optically bright ¹(π_Hπ_L*) state of alloxazine depends strongly on the polarity and hydrogen-bonding ability of the solvent. For the gas-phase and in nonpolar solvents we predict complete quenching of the fluorescence, whereas in aqueous solution a competition between fluorescence and intersystem crossing to the *T*₂ and *T*₃ states is found.

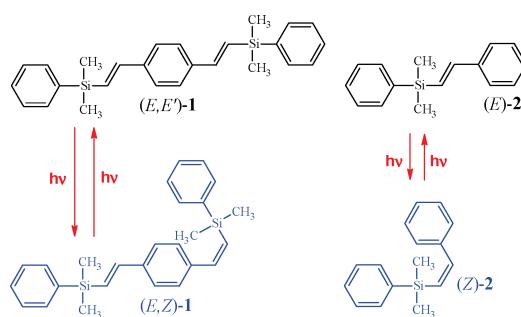


1667

Kinetics of reversible photoisomerization: determination of the primary quantum yields for the *E*-*Z* photoisomerization of silylenephenylenevinylen derivatives

Małgorzata Bayda, Gordon L. Hug, Jakub Lukaszewicz, Mariusz Majchrzak, Bogdan Marciniec and Bronisław Marciniaik*

A method is presented for determining the primary photochemical quantum yields in photoreversible reactions. With this method it is possible to get both forward and reverse quantum yields starting with either isomer.

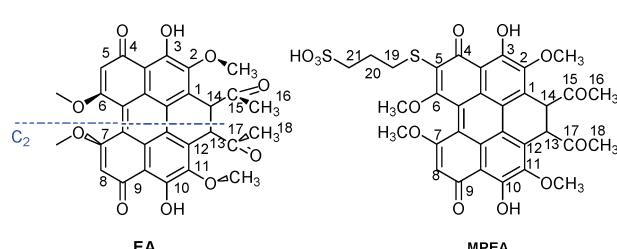


1676

A novel elsinochrome A derivative: a study of drug delivery and photodynamic activity

Yang Zhang, Jie Xie, Luyong Zhang, Cong Li, Hongxia Chen, Ying Gu* and Jingquan Zhao*

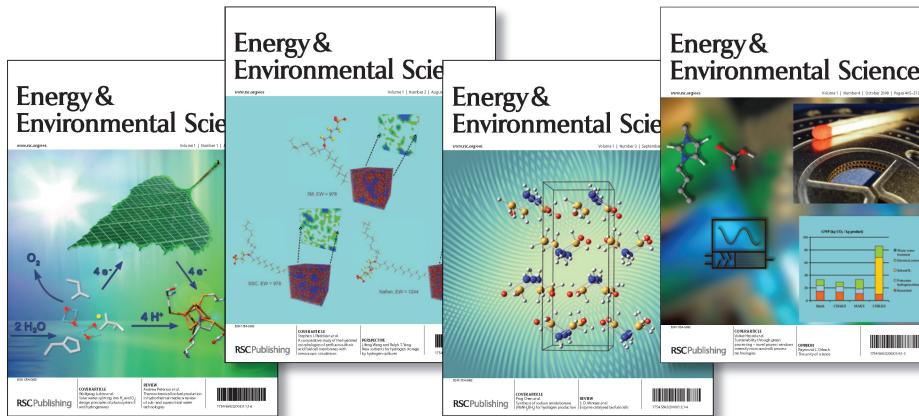
A novel elsinochrome A (EA) derivative, 5-(3-mercaptopropanesulfonic acid)-substituted elsinochrome A (MPEA), with an amphiphilicity was designed and synthesized by considering drug delivery and biological activity requirements.



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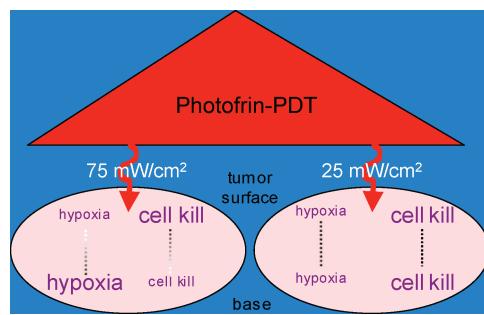
PAPERS

1683

 Fluence rate-dependent intratumor heterogeneity in physiologic and cytotoxic responses to Photofrin photodynamic therapy

Theresa M. Busch,* Xiaoman Xing, Guoqiang Yu, Arjun Yodh, E. Paul Wileyto, Hsing-Wen Wang, Turgut Durduran, Timothy C. Zhu and Ken Kang-Hsin Wang

Photofrin PDT at 75 mW cm^{-2} produces greater hypoxia and protection from cell kill at the base *vs.* surface of intradermal tumors. This heterogeneity is overcome by treatment at lower (25 mW cm^{-2}) fluence rate.

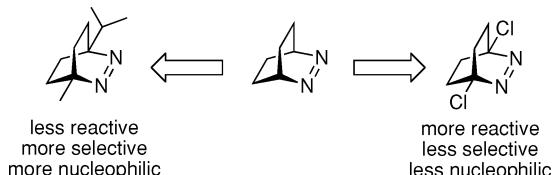


1694

Effect of bridgehead substitution on the fluorescence quenching of 2,3-diazabicyclo[2.2.2]oct-2-enes by solvents and antioxidants

Roland Meyer, Xiangyang Zhang and Werner M. Nau*

Simple bridgehead substitution in bicyclic azoalkanes allows the fine-tuning of fluorescent probes for antioxidants with respect to their reactivity, selectivity, and nucleophilicity.

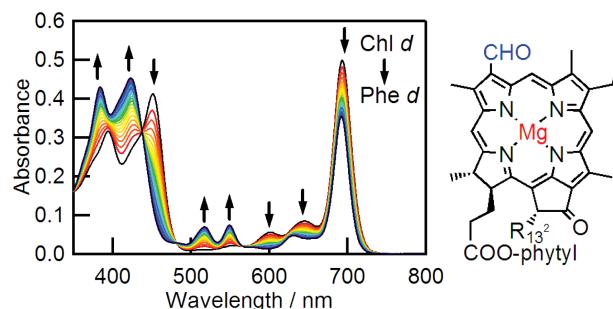


1701

Demetalation kinetics of natural chlorophylls purified from oxygenic photosynthetic organisms: effect of the formyl groups conjugated directly to the chlorin π -macrocycle

Yuki Hirai, Hitoshi Tamiaki, Shigenori Kashimura and Yoshitaka Saga*

Demetalation kinetics of chlorophyll (Chl) *d* possessing 3-formyl group was slower than that of Chl *a* possessing 3-vinyl group, but faster than that of Chl *b* possessing 7-formyl group.

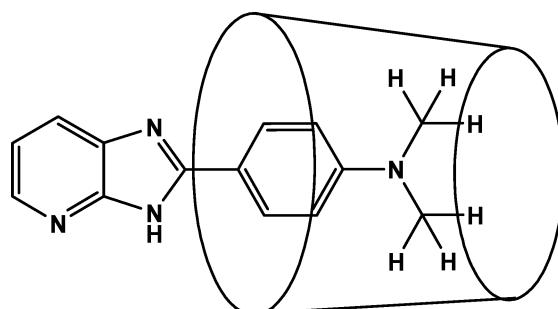


1708

 Encapsulation of 2-(4'-*N,N*-dimethylamino)-phenylimidazo[4,5-*b*]pyridine in β -cyclodextrin: effect on H-bond-induced intramolecular charge transfer emission

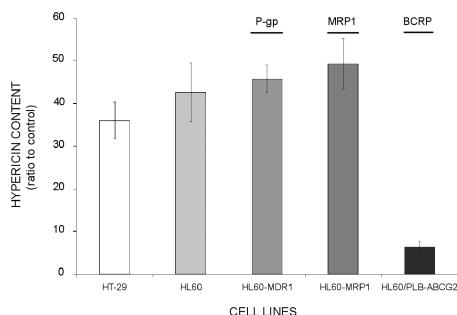
Nihar Dash, Francis A. S. Chipem and G. Krishnamoorthy*

DMAPIP- β -CD inclusion complex emits dual fluorescence with enhanced normal and ICT emission due to reduced polarity experienced by DMAPIP- β inside the cavity and hydrogen bonding of pyridine nitrogen with water.



PAPERS

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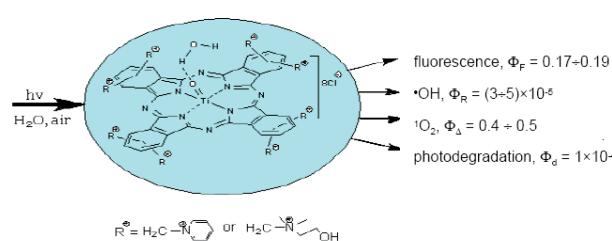


Drug efflux transporters, MRP1 and BCRP, affect the outcome of hypericin-mediated photodynamic therapy in HT-29 adenocarcinoma cells

Rastislav Jendželovský, Jaromír Mikeš, Ján Koval', Karel Souček, Jiřina Procházková, Martin Kello, Veronika Sačková, Jiřina Hofmanová, Alois Kozubík and Peter Fedoročko*

Stimulation of MRP1 and BCRP expression by hypericin *per se* affected its accumulation and therefore HY-PDT efficiency, however this undesired effect was eliminated by pre-treatment with proadifen.

1724

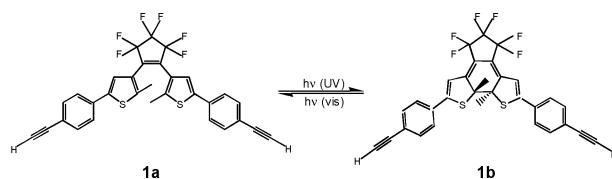


Photophysical properties and photodynamic activity of octacationic oxotitanium(IV) phthalocyanines

Nina Kuznetsova,* Dmitry Makarov, Olga Yuzhakova, Anton Strizhakov, Yana Roumbal, Ludmila Ulanova, Alexander Krasnovsky and Oleg Kaliya

Both singlet oxygen and hydroxyl radicals participate in bacterial cell killing and oxidation of organic substrates photosensitized by octacationic oxotitanium phthalocyanines in aqueous solutions.

1734

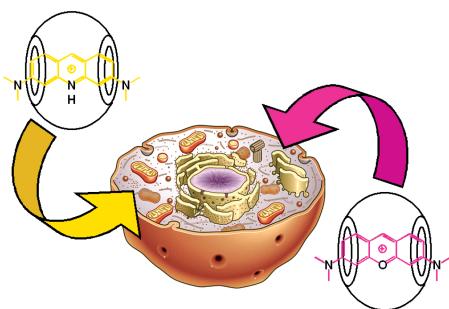


Photochemical investigation of a photochromic diarylethene compound that can be used as a wide range actinometer

André Ribeiro Santos,* Roberto Ballardini, Peter Belser, Maria Teresa Gandolfi, Vijay Mahadevan Iyer and Luca Moggi*

The thermally stable isomers **1a** and **1b** interconvert photochemically in acetonitrile. The photochemistry, wide spectral absorption range (240–700 nm) and high fatigue resistance make **1** suitable as a simple reusable chemical actinometer, especially for the visible (400–620 nm), where few other actinometers are available.

1743



Cucurbituril complexes cross the cell membrane

Pedro Montes-Navajas, María González-Béjar, J. C. Scaiano* and Hermenegildo García*

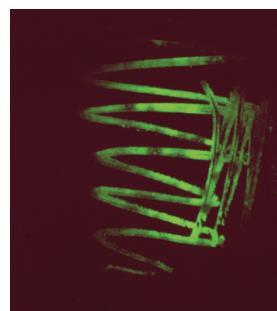
Host-guest complexes based on CB[7] and CB[8] with strong binding constants can enter tumoral cells as determined by fluorescence microscopy.

PAPERS

1748

***Pyrearinus termitilluminans* larval click beetle luciferase: active site properties, structure and function relationships and comparison with other beetle luciferases**A. J. Silva Neto, V. Scorsato, F. G. C. Arnoldi and
V. R. Viviani*

The green-emitting *Pyrearinus termitilluminans* larval click beetle luciferase was expressed, purified and characterized. Among beetle luciferases, it displays the most blue-shifted bioluminescence spectrum, as well as a high catalytic constant, thermal stability and sustained luminescence.



ADDITIONS AND CORRECTIONS

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Additions and corrections for 2009

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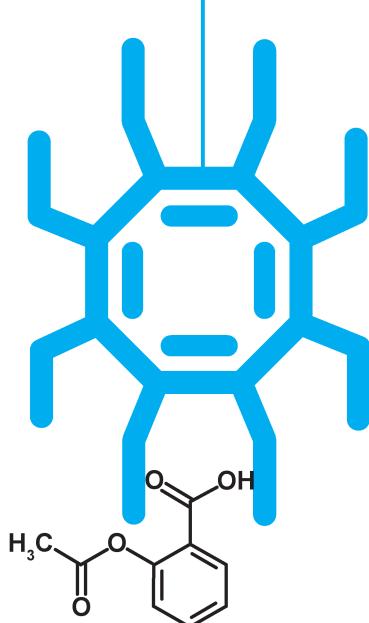
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Highlights in

Chemical Biology

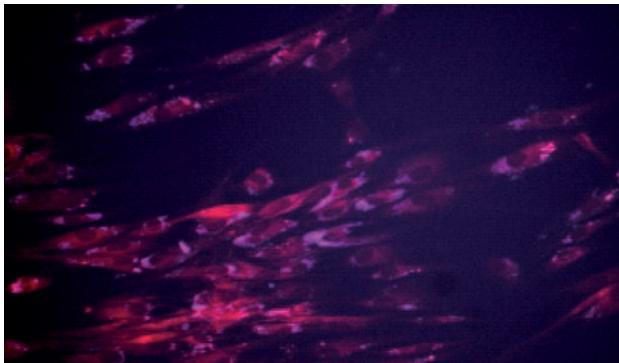
Surprising result as water-swollen gels help move cells from A to B

Sticky polymers for wound healing

Temperature-responsive gels are showing promise for tissue regeneration therapy, according to researchers in the UK.

Stephen Rimmer of the University of Sheffield and colleagues have modified a water-swollen polymer gel with a cell-adhesive peptide. The gel can be used to pick up skin cells and move them to a new substrate, where they can then be gently detached. Rimmer explains that a motivation for the team was the gel's potential applications in wound healing, as the second substrate could potentially be a damaged tissue. 'Cell therapy for regenerating tissues requires transporting the cells to the desired wound bed,' he says.

Rimmer's gel works by binding to surface proteins on cells grown in a normal culture, thus removing them from the substrate. In the next step, cooling the swollen gel from the 37°C cell culture temperature to below 34°C causes it to swell even further, which has the effect



of reducing cell adhesion. This releases the bound cells and can be used to deposit them at a new location.

In current methods, the protein-hydrolysing enzyme trypsin can be used to detach cells from their culture dish but this can result in damage. Using temperature-responsive polymers to transport cells avoids this problem and these have been used in the past. However, in these cases it is

Skin cells can be picked up by the polymer and gently deposited on a new substrate

usually necessary to grow the cells on the polymer itself, which can be challenging according to the researchers. Rimmer's approach avoids this requirement and can be used with commercially available culture substrates.

Fred Grinnell, a cell biologist at the University of Texas, Dallas, US, is impressed. 'I would have said this work was impossible if someone had asked me in advance,' he says. 'The Rimmer group has added a competitive cell adhesion functionality to temperature sensitive polymers and used a physiologically normal mechanism to transfer cells. A very surprising outcome!'

'We believe that this will be a key tool in the transfer of many cells, including stem cells,' says Rimmer, outlining how he expects the gel to be used in the future. 'One of our goals is to find a partner for commercialisation of the materials for transferring delicate cell types,' he adds. *Michael Spencelayh*

Reference
S Hopkins *et al*, *Soft Matter*, 2009, DOI: 10.1039/b909656f

In this issue

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Strategic screening for drugs

High-throughput assay finds small molecule inhibitors of transferase enzymes

Taking fleas for a spin

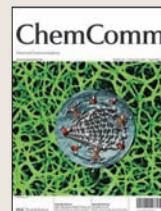
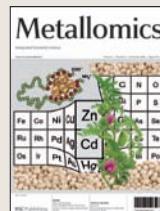
Magic angle NMR allows metabolomic profiling of aquatic organism

Instant insight: Reactions in droplets

Microfluidic droplets could become the reaction vessels of choice for biological research say Yolanda Schaerli and Florian Hollfelder

Interview: Sweet science

David Jakeman talks about carbohydrates, drugs and Darwin



Research highlights

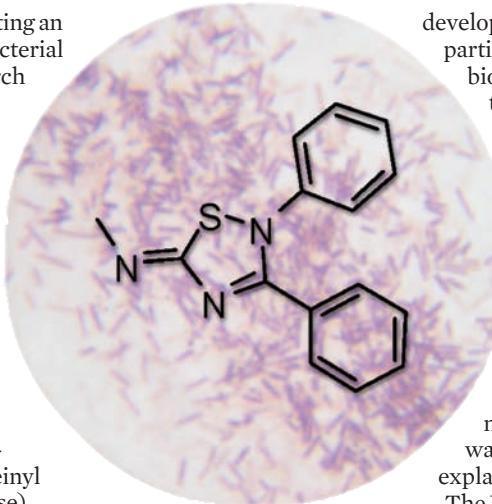
High-throughput assay finds small molecule inhibitors of transferase enzymes

Strategic screening for drugs

US scientists are targeting an enzyme essential to bacterial metabolism in the search for new antibiotics.

Michael Burkart of the University of California, San Diego, and Anton Simeonov from the National Institutes of Health, Bethesda, and coworkers have developed a high-throughput kinetic assay to screen small molecules as inhibitors of surfactin-type phosphopantetheinyl transferase (Sfp-PPTase) enzymes.

Transferases are among a group of enzymes that can add and remove groups from proteins after their polypeptide backbone has been built – a process known as post-translational modification. The enzymes are of biological and pharmaceutical interest as their inhibitors have been suggested as avenues for antibacterial, antifungal and anticancer therapeutic



Thiadiazole SCH-202676 was the most active inhibitor of a *Bacillus subtilis* PPTase

development. Sfp-PPTases in particular are known to activate biosynthetic pathways towards virulence factors in pathogens and so finding small molecules that reduce the enzymes' activity is of interest to researchers pursuing novel antibiotics. 'But transferase enzymes have been resistant to the development of simple methods for activity determination that do not require centrifugation, washing or separation steps,' explains Simeonov.

The US researchers built upon their previous work which uses PPTases to transfer a fluorescent substrate analogue onto a protein. The protein contains a fluorescence quenching group, meaning that the PPTase activity can be monitored by observing a fluorescence decrease as the reaction proceeds. The team has now incorporated the reaction into an assay which identifies PPTase inhibitors by their effect on the fluorescence decrease. They

were able to validate the new assay in a pilot screen of approximately 1200 bioactive molecules and found several potential PPTase inhibitors.

Hirotada Mori, of the Nara Institute of Science and Technology, Ikoma City, Japan, who specialises in bioinformatics, says that the development 'will help a lot in this field, by helping in the discovery of new chemical inhibitors. Such inhibitors will be the tools that allow further research into these enzymes,' he adds, 'so this work will open the gate to further research into PPTases.'

'We will be conducting a high throughput screen of the molecular libraries small molecule repository, a diverse collection of around 300 000 small molecules,' says Simeonov. 'With access to chemical probes of PPTase enzymes, we hope to gain a further understanding of phosphopantetheinyl transfer events in a range of organisms from bacteria to humans. We also speculate that the methodology may be adaptable to other transferase enzyme classes,' he adds.

Mary Badcock

Specific DNA sequences can be detected using a fluorescent probe

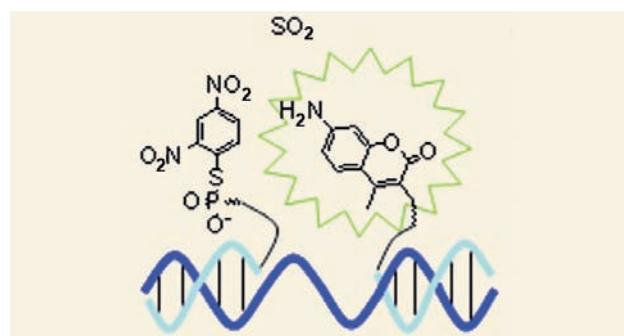
Single-base RNA resolution

A fluorescent probe sensitive to differences at the single-base-level of DNA has been created by researchers in Japan.

Hiroshi Abe and colleagues at the Riken Advanced Science Institute, Saitama, Japan developed a system for detecting specific nucleotide sequences in DNA.

Many fluorescent probes use a pair of quencher and fluorescence dyes, but a detection method with a higher sensitivity is still required to monitor gene expression, explains Abe.

Abe's method uses two probe DNA molecules, one is attached to a coumarin dye and the other to a nucleophilic group. The two probes bind to adjacent sequences on target DNA or RNA strands, bringing



A nucleophilic substitution reaction on the DNA template causes the fluorescence emission

Reference
A Shibata, et. al, *Chem. Commun.*, 2009, DOI: 10.1039/b912896d

the coumarin and the nucleophile together. 'The two groups form an intermediate complex, which quickly decomposes to give an unmasked amino group on the coumarin accompanied by the transfer of a dinitrobenzene. Thereby, the probe emits a

fluorescence signal,' explains Abe.

Reaction-triggered fluorescent compounds for nucleotide sensing have been described before. But, Abe's system offers high signal and very low background fluorescence under biological conditions and is able to discriminate even single base differences. '[The previous methods] have drawbacks, such as the instability of probes in biological conditions, the requirement for a catalyst and the toxicity of the compounds used,' he notes.

'Our future aim is the detection of RNA species in living cells and simple gene diagnosis that is carried out by simply mixing the probe with cells,' concludes Abe.
Michael Spencelayh

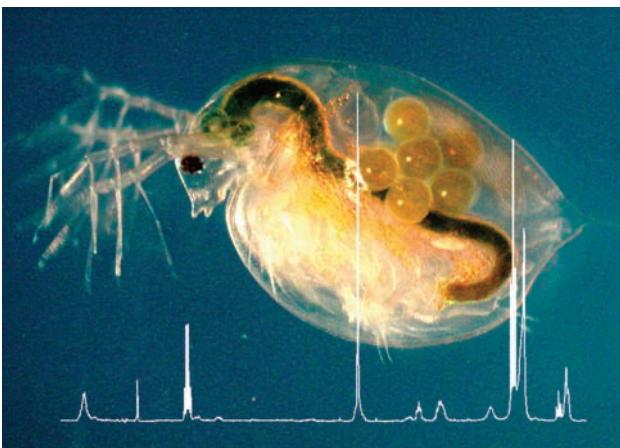
Magic angle NMR allows metabolomic profiling of aquatic organism

Taking fleas for a spin

French scientists have taken nuclear magnetic resonance spectra of live water fleas, a step which could have implications for environmental studies.

In a collaboration between the Research Center of the Armed Forces' Health Service in La Tronche, and Cemagref, Lyon, Andrei Bunescu and colleagues used proton high resolution magic-angle spinning (HRMAS) NMR to provide a metabolomic profile of the freshwater organism, *Daphnia magna*. Although proton NMR has previously been used for similar studies, the broad signals meant the spectra were very difficult to quantify. By spinning the samples at the so-called magic angle of 54.7°, Bunescu and colleagues were able to obtain higher resolution spectra and detect lipids within the fleas.

The team determined the optimum parameters that would allow the water fleas to remain unaffected by the procedure. They



NMR spectra show that water fleas have increased lipid levels just before egg laying

Reference
A Bunescu et al, *Mol. BioSyst.*, 2010, DOI: 10.1039/b915417e

found that anaesthetising the organisms and spinning the samples at speeds of 2000Hz or less for a maximum of three hours resulted in a survival rate comparable to control samples. 'The surviving daphnids presented a normal life cycle, as they developed eggs and embryos as the control organisms did,' explains

Bunescu.

The group compared NMR spectra of 1 and 7-day-old daphnids. They observed higher lipid levels in the spectra from older fleas, which they attributed to the presence of eggs in these organisms. 'Lipids play an important role in the reproduction capability of daphnids,' explains Bunescu. 'The lipid level inside daphnids is the highest just before egg laying.'

The team suggests that the procedure may provide information on the effects of chemicals on the *Daphnia magna*. And Steve Williams, an expert in imaging science from the University of Manchester, UK, suggests that this information could prove useful in environmental studies. 'As an important creature in the aquatic food chain, the metabolomic status of this organism may be a barometer of the effect of pollution on the aquatic environment,' he says.

Elizabeth Davies

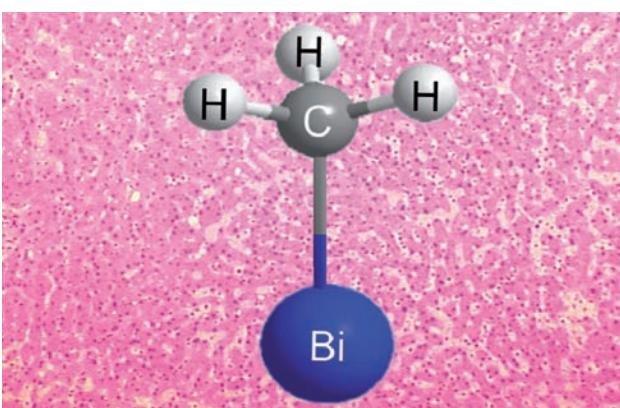
Liver cells show species selective uptake of inorganic bismuth

A piece in the puzzle of bismuth toxicology

Liver cells transform inorganic bismuth into potentially toxic methylated species, according to observations from scientists in Germany.

Inorganic bismuth is known to have low toxicity and is often used as a lead substitute, for example in paints and alloys; it is even used in medicine as an antigastric and antiulcer agent. However, there is evidence that intestinal microflora can convert inorganic bismuth compounds into multiply-methylated species, which are highly toxic and can cause brain dysfunction. Now Markus Hollmann and colleagues, at the University of Duisberg-Essen, have shown that human hepatic cells can also convert inorganic bismuth to organic bismuth.

The researchers incubated the cells with various bismuth complexes and trapped the resulting volatile bismuth species by mixing the cell lysate with



Hepatic cells could play a role in bismuth methylation in vivo

Reference
M Hollmann et al, *Metallomics*, 2010, DOI: 10.1039/b911945k

sodium tetraethylborate to form heavier ethylated derivatives. They could then analyse the mixture using a combined gas chromatography–mass spectrometry technique. They found that some bismuth species were methylated but bismuth glutathione was not, indicating that cell uptake of bismuth is species-

dependent.

'As far as we know, this study is the first to show bismuth methylation using mammalian cells and our work provides another piece in the puzzle of bismuth toxicology and bismuth metabolism,' says Hollmann.

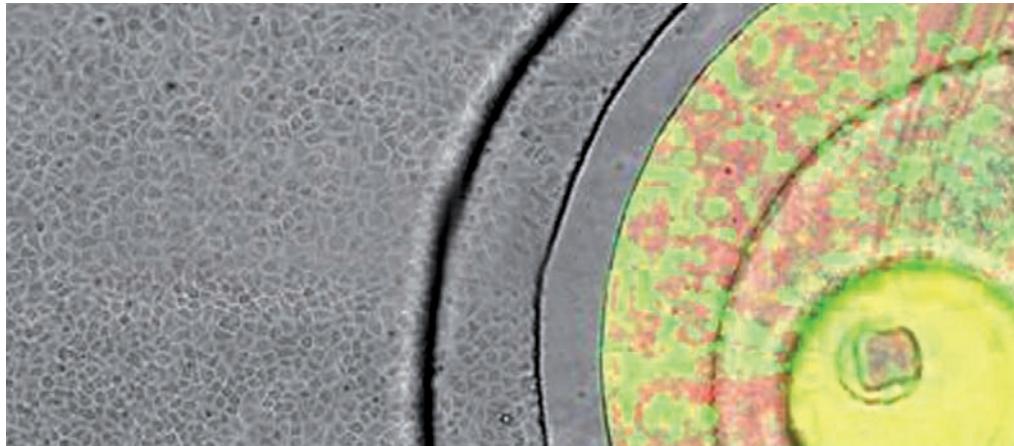
Yasumitsu Ogra, an expert in chemical toxicology from Showa Pharmaceutical University, Tokyo, Japan, agrees. 'The evidence for bismuth methylation may give novel toxicological insight,' he says. 'The technique paves a road to speciation of other volatile metal/metalloid-containing metabolites in biological samples,' he adds.

The German team plans to pursue several avenues in future research. These include investigating the methylation process and its time dependency and kinetics, and eventually the cellular distributions of the bismuth compounds.

Carl Saxton

Lab-on-a-chip co-cultures different cell types of the human gut

Culture clash for good and bad bacteria



The human gut is home to a hundred trillion 'good' bacteria that are essential for it to function. But 'bad' bacteria can upset this balance, resulting in infection. US scientists have now found a way to mimic this environment in a lab-on-a-chip device, making it easier to investigate why some pathogenic bacterial strains are so virulent.

Communities of 'good' – or commensal – bacteria in the gut interact closely with the endothelial cells that line it. Up to now, studying these systems *in vitro* has been very difficult because bacteria multiply much faster than endothelial cells.

Arul Jayaraman and colleagues at Texas A&M University, College Station, have now developed a microfluidic system that grows the colonies separately before allowing them to interact in a manner very similar to what happens in the gut.

The system consists of a polymer template that is lowered onto a glass surface to create an isolated island. The researchers seeded commensal *Escherichia coli* bacteria into the island, and endothelial cells outside, with nutrients allowed to flow in (and waste to flow out) through microfluidic channels. Once the colonies reached maturity, the team

Good bacteria (green) and pathogenic bacteria (red) grow in an island separated from endothelial cells (grey) before they are allowed to mix to replicate conditions in the gut

Reference
J Kim, M Hedge and A Jayaraman, *Lab Chip*, 2009, DOI: 10.1039/b911367c

introduced a pathogenic strain of *E. coli* into the commensal colony, removed the template, and monitored the death of the endothelial cells as the pathogenic bacteria moved across the boundary.

Mike Shuler, Chair of Biomedical Engineering at Cornell University, Ithaca, US, says that 'this is a very clever microfluidic device. The work is an important first step to the broad problem of understanding bacterial interactions with the gastrointestinal tract.' He adds that it would be interesting to study cell types that produce mucus and hence more closely resemble those present in the gut.

Jayaraman explains that the set-up is 'true to life' because it creates bacterial aggregates called biofilms rather than disorganised colonies. Previous studies, he says, have just added pathogenic bacteria into colonies of endothelial cells, which does not replicate the cellular interactions and chemical signals present in the gut. Their device, he says, will aid rapid screening of probiotic strains, such as those used as dietary supplements, because it allows the culture conditions for each strain to be optimised separately.

David Barden

In the current issue of Research Articles...



Signature peptides of influenza nucleoprotein for the typing and subtyping of the virus by high resolution mass spectrometry
Alexander B Schwahn *et al*, *Analyst*, 2009, **134**, 2253 (DOI: 10.1039/b912234f)

Site-selective scission of human genome by artificial restriction DNA cutter

Kenichiro Ito *et al*, *Chem. Commun.*, 2009, 6542 (DOI: 10.1039/b911208a)

Inhibition of the histone lysine demethylase JMJD2A by ejection of structural Zn(II)

Rok Sekirnik, *Chem. Commun.*, 2009, 6376 (DOI: 10.1039/b916357c)

Droplet-based compartmentalization of chemically separated components in two-dimensional separations

X Z Niu, *et al*, *Chem. Commun.*, 2009, 6159 (DOI: 10.1039/b918100h)

Towards a human-on-chip: Culturing multiple cell types on a chip with compartmentalized microenvironments

Chi Zhang, *et al*, *Lab Chip*, 2009, **9**, 3185 (DOI: 10.1039/b915147h)

Lab-on-Chip for fast 3D particle tracking in living cells

Houssam Hajjouli, *et al*, *Lab Chip*, 2009, **9**, 3054 (DOI: 10.1039/b909016a)

Global analysis of the yeast osmotic stress response by quantitative proteomics

Boumediene Soufi *et al*, *Mol. BioSyst.*, 2009, **5**, 1337 (DOI: 10.1039/b902256b)

Expanding the borononucleotide family: synthesis of borono-analogues of dCMP, dGMP and dAMP

Anthony R Martin, *Org. Biomol. Chem.*, 2009, **7**, 4369 (DOI: 10.1039/b912616c)

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Interview

Sweet science

David Jakeman talks about carbohydrates, drugs, and Darwin.
Interview by Nicola Wise



David Jakeman

David Jakeman is an associate professor at Dalhousie University, Halifax, Canada. His research focuses on discovering tools to develop new antibiotic and anticancer drugs using synthetic chemistry, protein engineering and microbial fermentation. He is a member of the *Natural Product Reports* editorial board.

Your research focuses on carbohydrate enzymology and medicinal chemistry directed towards novel antibacterial and anticancer agents. Could you explain this in layman's terms?

We are interested in designing new carbohydrate-containing molecules as carbohydrates often impart unique biological properties to small molecules. Many natural products and proteins have carbohydrates attached to them through a process known as glycosylation. If we can understand how glycosylation occurs we may be able to alter the process and change the way the molecule interacts with biological systems. There are a number of important medicines that are glycosylated and the carbohydrate functionality is crucial for bioactivity.

What projects are you working on at the moment?

We are designing ways to glycosylate natural drug-like molecules. This can be synthetically challenging, so we are using enzymes to perform this chemistry. Enzymes are the catalysts nature uses, and by protein engineering you can change the way the enzymes function. As a result different sugars with different stereochemistry and functionalities can be added to the molecules. This has the potential to improve biological properties such as strengthening interactions with a biological target or modifying the metabolism of a molecule.

How did you become involved in medicinal chemistry?

In the final year of my undergraduate course, I took a course by Mike Blackburn (who I went on to do a PhD with) on biological chemistry which I found interesting as he provided real world applications of chemistry and what you can do with it, such as making molecules and using it to explain biological processes. That is what we do - we modify enzymes and try to use them to explain what goes on in a particular system. The aim is that you have something which has improved biological activity.

Having studied in the UK, and worked in both America and Canada what do you think are the main differences between the UK and North America with respect to research and academia?

As an undergraduate I had little appreciation of what it was like to be an academic in the UK, but as a postdoctoral researcher in the US I got an

inclination as to what my supervisor (Jeremy Evans, Washington State University) did, and a much greater insight when I was in Canada working with Stephen Withers (University of British Columbia).

I don't think there are many differences, especially as the UK education system is becoming more like North America in its approach to both undergraduate and graduate training. Many people in the UK are rethinking how their first year courses are taught due to changes in the A-level curriculum.

What advice would you give to a young scientist wanting to pursue a career in science?

They should volunteer in the lab and the sooner the better, because then they will know at the earliest opportunity whether or not it is something they want to do. I didn't and I wish I had!

What do you love about your job?

The people and the flexibility! I can structure my day in any way I choose. Although the downside is that I have a long to-do list which never gets any shorter!

Do you remember your first experiment?

It was probably with a home chemistry set that my parents bought me when I was 11 or 12. After that I remember finding books in the school library on experiments that you can do, such as the glycerine and potassium permanganate experiment, and seeing school demonstrations, such as the reaction of alkali metals in water. Basically I loved anything that burned/popped/made noise – the standard things that stick in people's minds.

Which historical scientific figure would you most like to have dinner with and why?

I'd quite like to know Charles Darwin's thoughts on creationism - I think that would make an interesting conversation.

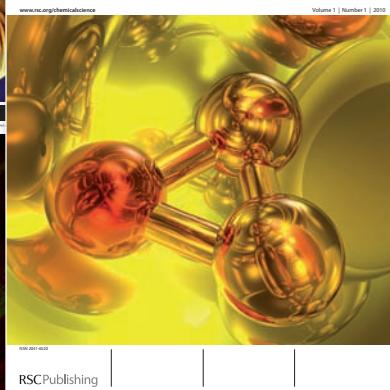
And finally, if you weren't a chemist, what would you be?

I think I would still be a scientist but in a different discipline, maybe marine biology. When you see television documentaries describing the researchers' exploits swimming with dolphins in tropical climates, it seems more appealing than watching bacteria grow in the lab... although I'm sure the reality is very different!



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Reactions in droplets

Small in size, but with a large array of uses, microfluidic droplets could become the reaction vessels of choice for a significant fraction of biological research say Yolanda Schaeerli and Florian Hollfelder of the University of Cambridge, UK

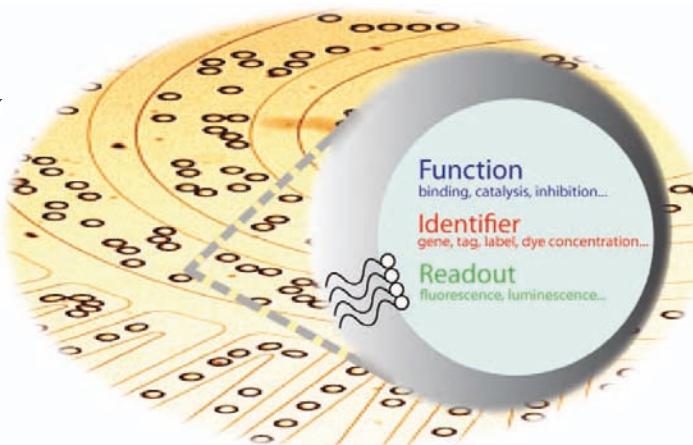
Contemporary biology increasingly demands high-throughput experiments. Only these can provide the vast amounts of information needed to study cell populations, and DNA, protein and small molecule libraries appropriately. Practically, such a format should be highly economical, consuming minimal amounts of reagent and operating at the lowest cost per assay, which means running experiments on the microscale.

Compartmentalisation provides a system to address these requirements. This uses a stream of water-in-oil emulsion droplets as an extremely small equivalent of an array of test tubes: droplets can have femto- to nanolitre volumes. Up to 10^{10} droplet reactors will fit into a millilitre and an equivalent number of experiments can be carried out simultaneously.

Water-in-oil emulsion droplets are easily made by mixing oil and an aqueous phase using a stirrer, homogeniser or extruder. But researchers wanting the best quality droplets can use a microfluidic device to create drops of more uniform size, which allow the most precise quantitative experiments. Devices have recently been built that can generate up to 10 000 highly monodisperse aqueous droplets per second (typically 10–200 μm in diameter).

The microfluidic format can be used not only to form droplets but also to process them in a variety of ways. Droplets can be divided, fused, incubated, analysed, sorted and broken up. Integrating and automating these steps could potentially lead to systems for biological experimentation with a level of control akin to experiments on the macroscopic scale.

A droplet compartment is not only small, but it can also be smart. It can



Droplets combine the function of a molecule with information on its identity and a readout indicating how well it performs its function

combine the function of a molecule (such as the catalytic activity of an enzyme), with information on its identity (for example the DNA sequence encoding the protein) and a readout to assess how well the molecule performs its function. Thus, the droplet contains everything needed to assess and decode a particular experiment or profile a library member.

The droplet principle is used in various applications. The most commercially successful use of compartmentalisation is in the emulsion polymerase chain reaction (ePCR), which uses a polymerase enzyme to amplify DNA held within droplets. For ePCR compartmentalisation provides monoclonality: a complex mixture can be divided into droplets containing a single DNA template. The DNA in each droplet is thus amplified bias-free, whereas in a mixture one DNA strand might be amplified to a greater extent than another. The result is a PCR reaction suitable for a number of applications, most importantly high-throughput DNA sequencing.

Droplets can also be used to link genotype (DNA or RNA) and phenotype (an observable trait, such as binding or catalytic activity) just like a cell. In directed evolution a gene library is diluted

so that, as in ePCR, each droplet contains no more than one copy of DNA. Genes are transcribed and translated to yield proteins of which improved variants are selected via a procedure tailored to their characteristic trait, such as turnover of a substrate to yield a fluorescent product. This phenotype–genotype linkage is essential to mimic natural selections in the laboratory to create proteins or nucleic acids with improved or new functions.

But cells themselves can also be compartmentalised in droplets. By holding back any substance released by a captured cell, cell-based directed evolution experiments relying on detecting product formation have become possible. Additionally, being able to trap cells with additional external stimuli paves the way for studies into the mechanisms that control a cell's response to its environment at the single cell level. Resolving a mixture of cells into individuals will also allow access to other information that has been unavailable from conventional experiments with cell populations.

Microfluidic droplets are becoming well-established tools in the lab, in approaches such as ePCR, for example. Directed evolution and cell-based assays are now in advanced stages of development and proof-of-principle experiments are appearing for a whole range of applications from diagnostics, cellomics, proteomics, to drug discovery and synthetic biology. Extrapolation of these approaches towards more highly integrated systems may change the way biological experiments are designed and carried out.

Read more in Schaeerli and Hollfelder's review in a themed issue on Computational and Systems Biology in Molecular BioSystems.

Reference

Y Schaeerli and F Hollfelder,
Mol. BioSyst., 2009,
DOI: 10.1039/b907578j

Essential elements

A new generation of conferences



Does the chemistry community really need more events with several hundred international events already available in a tempting (and not so tempting) choice of venues?

Any new event has to offer something different - which is precisely what this new generation of conferences from the RSC does. Launching in 2010 to support the launch of the new RSC flagship journal *Chemical Science* and in association with *ChemComm* and *ChemSocRev*, the International Symposia

on Advancing the Chemical Sciences (ISACS) is a significant new global symposia series. Ambitious in its scale and comprehensive in its coverage, the first three symposia will be held on three continents, over three sequential weeks in July 2010 and have already attracted support from some of the leading names in the respective fields.

Dr Richard Pike, Chief Executive of the RSC, is excited by the scale and high quality of the series: 'Each ISACS event will present a unique

opportunity to hear from a new generation of dynamic, internationally renowned speakers. High quality presentations will review cutting edge developments and highlight future challenges in each research area. The global scale and wide coverage of this symposia series is very much aligned to the mission of the RSC, namely to 'advance the chemical sciences'.

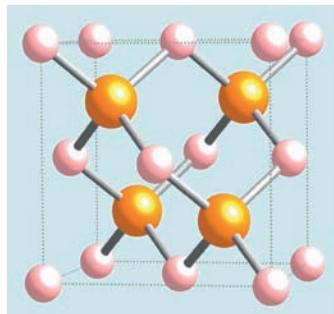
Each ISACS event will feature a single stream of a minimum of eighteen plenary lectures complemented by extensive poster sessions with plenty of time dedicated to networking. The chance for young researchers to present their work alongside that of some of the leading and emerging names in the field is an opportunity not to be missed.

Sign up for news updates and find out more at www.rsc.org/isacs

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Currently only available for Word 2003/2004 operated on a PC, the CIF Data Importer is a Beta version for testing, and the RSC would welcome any feedback from users. Find out more at www.rsc.org/CIFdata.

Plus, look out for live links from CCDC and PDB structure references in RSC online articles to the relevant webpages of the WebCSD and Protein Data Bank where the structures can be visualised.

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schedule has been devised to ensure all journals are moved across smoothly to the new system.

If you're an existing referee or author you will receive some more information about the new system shortly. In the meantime if you have any specific enquires please email the publishing department at rscpublishing@rsc.org

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