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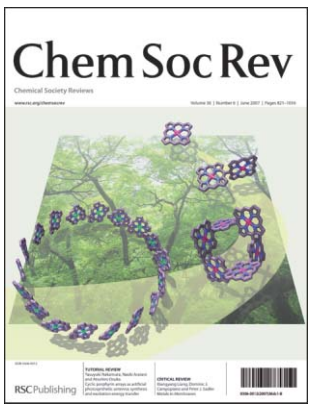

Cover

See Yasuyuki Nakamura, Naoki Aratani and Atsuhiro Osuka, page 831.

The cover picture represents the evolution of our pigments towards the antenna system with the background of fresh green at Kiyomizu temple in Kyoto, Japan.

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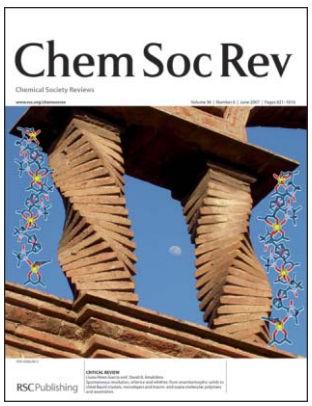

Inside cover

See Lluïsa Pérez-García and David B. Amabilino, page 941.

The spontaneous resolution of chemical systems, from the nanometer to the macroscopic level, is often unpredictable, beautiful and intriguing, as indicated by the presence of the moon.

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CHEMICAL SCIENCE

Drawing together the research highlights and news from all RSC publications, *Chemical Science* provides a 'snapshot' of the latest developments across the chemical sciences showcasing newsworthy articles, as well as the most significant scientific advances.

Chemical Science

June 2007/Volume 4/Issue 6

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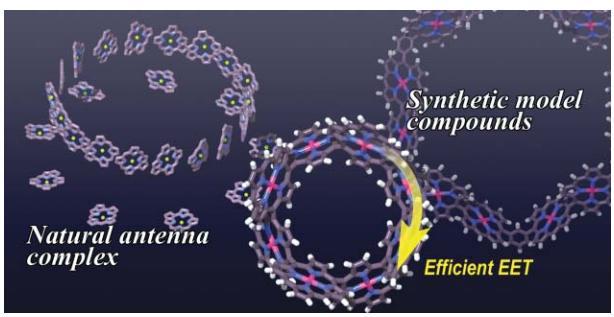
TUTORIAL REVIEWS



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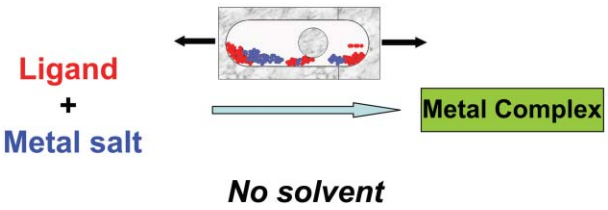

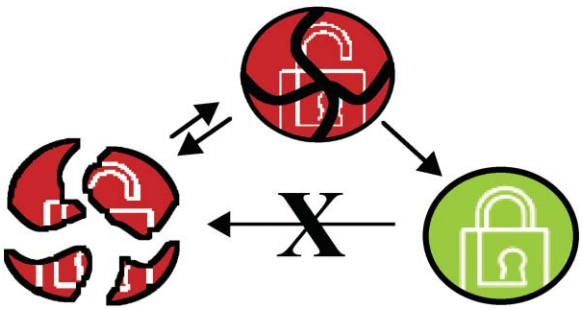

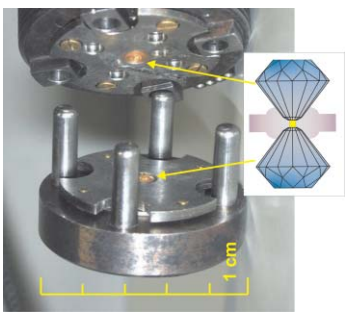

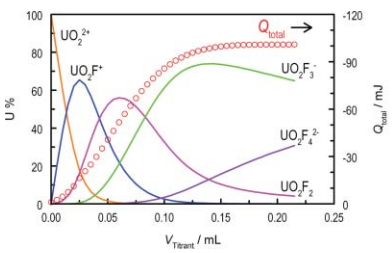

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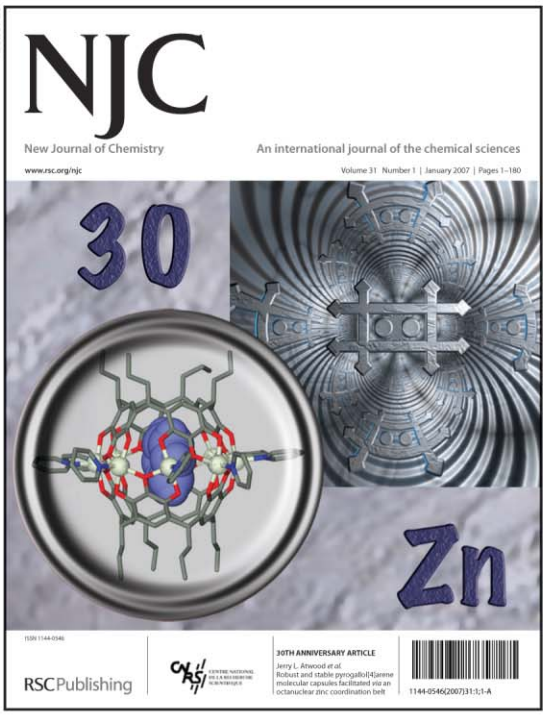

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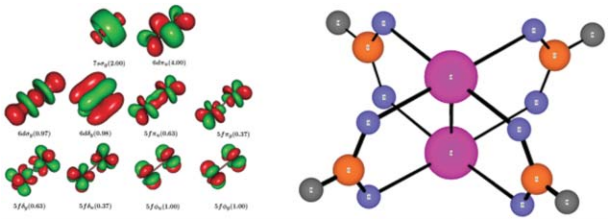

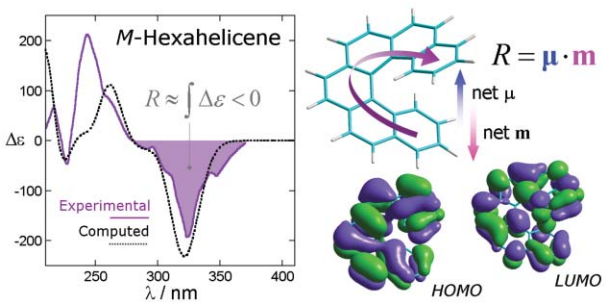

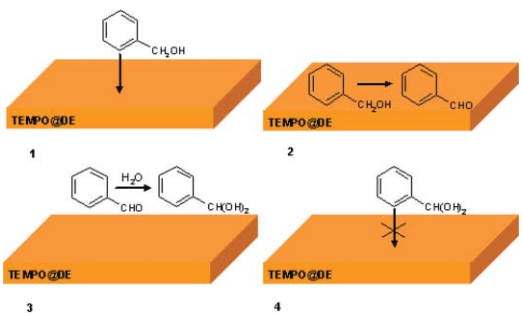

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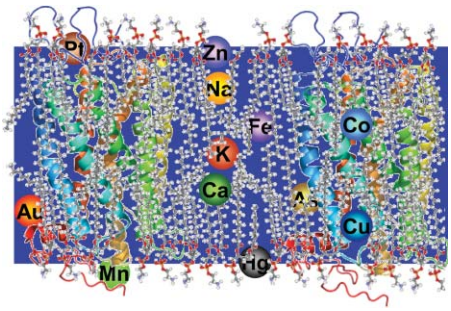

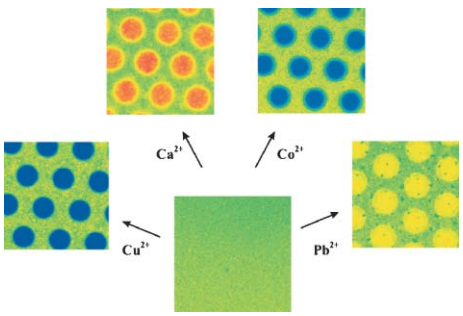

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June 2007 / Volume 4 / Issue 6 / ISSN 1478-6524 / CSHCBM / www.rsc.org/chemicalscience

Chemical Science

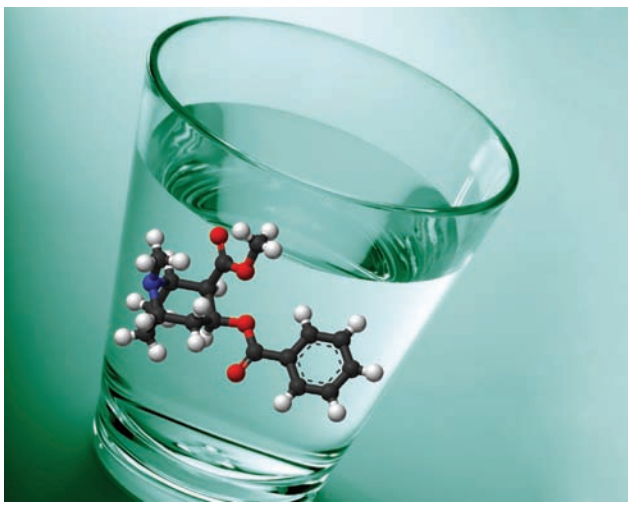
Wastewater sampling indicates significant cocaine usage amongst Dubliners

Something in the water

How much cocaine is going up Dublin's nose? The answer lies in the output from the city's wastewater treatment plants, according to research carried out at Dublin City University by Brett Paull and colleagues. The researchers estimated the levels of consumption of substances such as cocaine and morphine by measuring their concentrations, and the concentrations of their metabolites, in effluent and surface water.[1]

'There are currently very few ways to non-invasively assess community consumption of illicit drugs,' said Paull. 'Social survey data, although useful, is often subject to sampling bias, whereas environmental forensic approaches such as this, when subject to stringent quality assurance and controls, could provide a more accurate assessment.'

Previously, Paull's team surveyed drug contamination on euro banknotes in Dublin.[2] 'However, as an indicator of societal abuse, such samples provide only limited information,' said Paull. But water treatment plants accurately record the volume of water flow and serve a known number of people, allowing total consumption to be estimated.



Cocaine is just one of the illicit drugs flowing through Dublin's water treatment plants

Using samples taken from the water plant that serves 1.7 million people within the Dublin metropolitan area, the researchers calculated that more than 220 grams of cocaine flowed through the plant per day. Taking into account the way cocaine is metabolised in the body, this equates to the total consumption of more than 2200 grams of cocaine. The researchers estimate that this is equivalent to a consumption level of about 1.4 grams per 1000 people per day.

'The problem of cocaine consumption is not wholly confined to the capital city,' said Paull. Similar measurements on wastewater treatment plants that serve small towns just outside Dublin revealed consumption levels at about one fifth that of the metropolitan area.

The researchers believe that their method could be used for the routine monitoring of cocaine consumption within a community, revealing any usage trends, such as increases during weekends and public holidays.

Colin Batchelor

References

1 J Bones, K V Thomas and B Paull, *J. Environ. Monit.*, 2007, DOI: 10.1039/b702799k

2 J Bones, M Macka and B Paull, *Analyst*, 2007, **132**, 208

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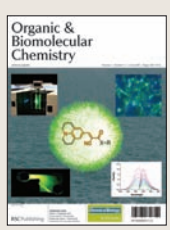
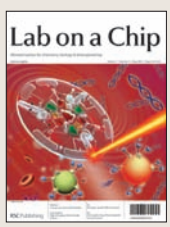
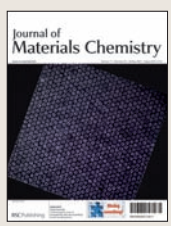




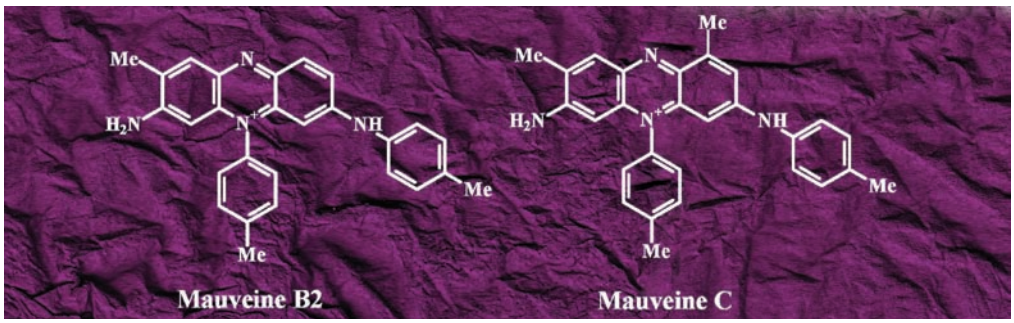


A snapshot of the latest developments from across the chemical sciences

Research highlights

Perkin proved right as puzzling purple yields its secrets

Revealing the mysteries of mauve



Two new compounds have been identified in an original sample of mauveine dye that was made by Sir William Perkin over 150 years ago.

Mauveine, with its characteristic purple colour, was the first synthetic dye molecule, and its production is thought by many to mark the beginning of the modern organic chemical industry. Now, a team of researchers led by João Seixas de Melo at the University of Coimbra and Maria João Melo at the New University of Lisbon, both in Portugal, has discovered two new compounds during its analysis of a historic sample of the dye from the Science Museum in London.[1]

Mauveine dye was already known to contain mauveine A (with two methyl groups) and mauveine B (with three methyl groups).[2] The components discovered by Seixas de Melo and colleagues are mauveine B2, a structural isomer of mauveine B, and a structure with four methyl groups, called mauveine C.

Tony Travis, an expert in the history of chemistry and technology at the Hebrew University of Jerusalem, Israel, welcomed the findings. 'Perkin thought that the commercial mauve dye consisted of more than one component,' said Travis. 'This work shows that even though Perkin was unable to establish the structures of these components, he was correct.'

Using the same starting materials and procedure as Perkin, Seixas de Melo's team made a fresh mauveine sample and compared its composition with that of the historical sample. The different molecular components were separated using high performance liquid chromatography. The chromatograms showed that mauveine B2 and mauveine C were present in both samples.

Advances in chromatography have allowed previously unknown components of mauveine dye to be revealed

Seixas de Melo believes the identities of these mauveine constituents have only now been uncovered as a result of the more efficient chromatographic techniques that are available.

'Perkin would be delighted...he spent years trying to establish the constitution and structure of the mauve dye both as a scientific puzzle and because he believed that the constitution would suggest how new derivatives might be made,' said Travis. 'These newly available structures suggest why Perkin failed to prepare a series of derivatives, as had been the case for aniline red.'

Seixas de Melo hopes to extend the study to look at other ancient dyes including indigo and dracoflavylium, a major constituent of the resin known as dragon's blood. *Alison Stoddart*

Reference
1 J Sexias de Melo *et al, Chem. Commun.*, 2007, DOI: 10.1039/b618926a
2 O Meth-Cohn and M Smith, *J. Chem. Soc., Perkin Trans. 1*, 1994, 5

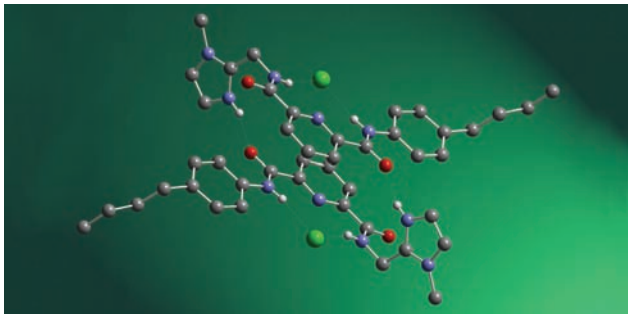
Natural product mimic helps hydrogen chloride to cross membranes

Double ion carriers offer drug lead

Synthetic molecules that can simultaneously transport two different ions across a membrane could lead to a new class of drugs.

The prodigiosin family of natural products has a variety of therapeutic effects including toxicity to micro-organisms and killing tumour cells. These beneficial activities are linked to the simultaneous transport – known as symport – of hydrogen and chloride ions across a cell membrane. Replicating this co-transport with synthetic molecules opens up the possibility of creating symport based drugs.

Now, a team of researchers led by Phil Gale, at the University of Southampton, UK, and Bradley Smith at the University of Notre Dame, Indiana, US, has managed to do just that. The researchers designed prodigiosin mimics that can efficiently co-transport hydrogen chloride out of vesicles. The team used a pyridine ring modified with two amide groups in the core of the carrier molecule to increase the chloride affinity. The design of the carrier molecule also allowed it to adopt a more organised structure, increasing the efficiency.



Chloride ions (green) fit snugly into the hydrogen bonding pocket of the carrier molecule

'Potentially, this line of research could lead to new therapeutic agents' said Gale. 'The future challenge will be to achieve tissue specificity,' he added. *Russell Johnson*

Reference
P A Gale *et al, Chem. Commun.*, 2007, 1736

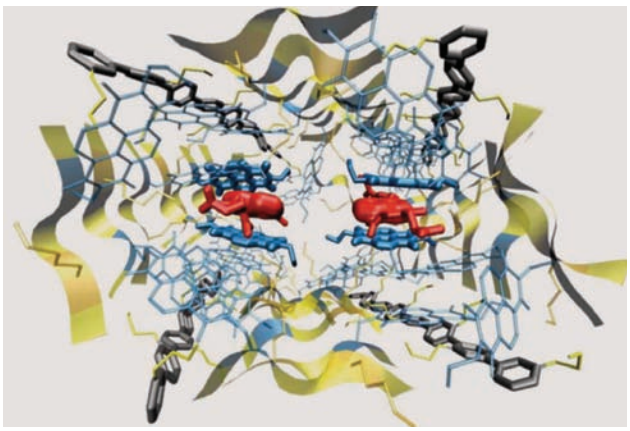
Pores in a cell membrane inspire a new kind of biosensor

Pores for thought

Researchers in Switzerland have made artificial membrane pores that can recognise nucleotides.

Pores in cell membranes are channel-like structures, made from proteins, which allow specific molecules to pass into and out of the cell. These pores can also act as sensors, such as those found in taste receptor cells in the human tongue. Natural sensors like these usually rely on ion-pairing interactions to recognise different molecules.

But the synthetic pore, made by Stefan Matile and colleagues at the University of Geneva, uses a different kind of interaction altogether. Matiles' pore is made from rigid rods functionalised with pentapeptides, which self-assemble into a barrel structure, just like that of a natural pore. The pentapeptides are themselves functionalised with electron-poor naphthalenediimide molecules. A pair of these electron-poor molecules can act as a clamp, sandwiching an electron-rich analyte such as a nucleotide – a sub-unit of DNA.



Electron-poor clamps (blue) recognise electron-rich analytes (red)

'The pores are bioinspired, but it is wonderful to achieve this small victory over nature in utilising this kind of interaction,' said Matile. 'It may even give us access to new analytes.'

Jean-Marie Lehn, an expert in molecular recognition from Louis Pasteur University, Strasbourg, France, said, 'this work will be very important in understanding how natural pores work, and for designing new types of sensor based on this technology.'

Matile says there are many potential applications for this kind of system, which could lead to diagnostic sensors for cholesterol, inhibitor screens for drug discovery, or even a synthetic tongue that could 'taste' the difference between sweet, sour and umami. 'The next step is to convince potential investors that this is a viable proposition,' he said.

The synthesis of the pore is not easy, but Matile believes the effort pays off; the high activity of these sensors means that hundreds of thousands of assays can be performed using only milligram quantities of pores. 'Potentially, all that is required in order to realise new applications is the appropriate functionalisation of the pentapeptide with the right type of clamp,' said Matile.

Stephen Davey

Reference
H Tanaka *et al*, *Org. Biomol. Chem.*, 2007, **5**, 1369

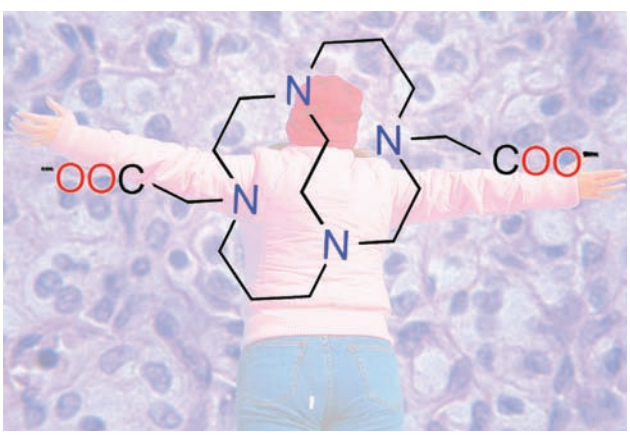
Radiopharmaceuticals reach their target with shorter arms

New cancer therapy within reach

Long arms may be useful for reaching the biscuit tin but scientists in the US have shown that shorter arms are better for radiopharmaceuticals.

A team of chemists led by Edward Wong and Gary Weisman at the University of New Hampshire, Durham, and Carolyn Anderson at the Washington University School of Medicine, Missouri, has been investigating molecules that combine with copper to make radiopharmaceuticals. Radioisotopes such as ^{64}Cu can be used for both the diagnosis and targeted therapy of cancer, but a carrier is needed to get the copper to where it is needed.

Wong's team had previously found a molecule that chelates (or binds to) copper(II) extremely strongly. The molecule consists of a 14-membered ring, known as a macrocycle, that has carboxylic acid groups dangling on pendant arms. Now the scientists have investigated how varying the lengths of the ligand arms of the molecule altered its properties.



Shorter arms make for a more stable complex

The results showed that having longer arms made it easier to reduce the copper complex to copper(I), which results in the metal breaking free from the ligand in a process called demetallation. The longer armed molecules also proved to be less stable during in vivo testing.

The researchers plan to work on improving the binding kinetics of the complexes and reducing the harsh conditions currently needed to make the radiopharmaceuticals. They also intend to expand the work to other metals. 'Although radio-copper chelation has been a major goal, we anticipate that other radiometals such as gallium and indium will also form very robust complexes with this family of chelators and expand their application potential,' said Wong.

Laura Howes

Reference
K J Heroux *et al*, *Dalton Trans.*, 2007, 2150

News in brief

Golden glue
Theoretical chemists predict that gold atoms could serve as a versatile glue to stick molecules together.

Hydroxy-cruciforms
Cross-shaped molecules that change colour when exposed to amines could be used to detect compounds used in the manufacture of drugs, pesticides, dyes, preservatives and disinfectants.

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This month in *Chemical Technology*

The clean art of conservation
Supercritical carbon dioxide cleans up ancient textiles without damaging them.

Mild green ionic liquids
Washing with eutectic solvents cleans up biodiesel - and produces glycerol.

Hot-wiring enzymes for fuel cells
Using anthracene to link laccase to electrodes delivers electrons straight to the active site.

See **www.rsc.org/chemicaltechnology** *for full versions of these articles*

This month in *Chemical Biology*

RNA on ice
Life could have begun at the poles according to researchers in Germany.

Retinal repair
Polymer scaffolds could one day be used to fix damaged eyes.

Sugar solution for HIV?
Sugars could be the basis for future HIV vaccines, according to researchers in the US.

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Nanobombs away!

South Korean scientists have developed a porous silicon nanobomb that heats up with near-infrared irradiation and could cause cancer cells in the body to explode.

Recent research into a new kind of photodynamic therapy has concentrated on using single-walled carbon nanotubes, combined with near-infrared light, to generate heat to kill cancer cells. Now, Chongmu Lee and colleagues from Inha University, Korea, have substituted the carbon nanotubes with a porous silicon nanomaterial, which they claim can generate as much heat as the carbon nanotubes, with the added bonus of producing much smaller amounts of reactive oxygen species.

Cancer-killing reactive oxygen species (ROS), generated with traditional photodynamic therapy techniques, can cause a range of side effects in patients undergoing cancer treatment including sensitivity to light, blistered, red or swollen skin if exposed to bright light, feeling or being sick, a metallic taste in the mouth and soreness on swallowing. The ROS accumulated in human bodies might also react with biological molecules to accelerate aging, weaken immunity and eventually cause a number of degenerative diseases.

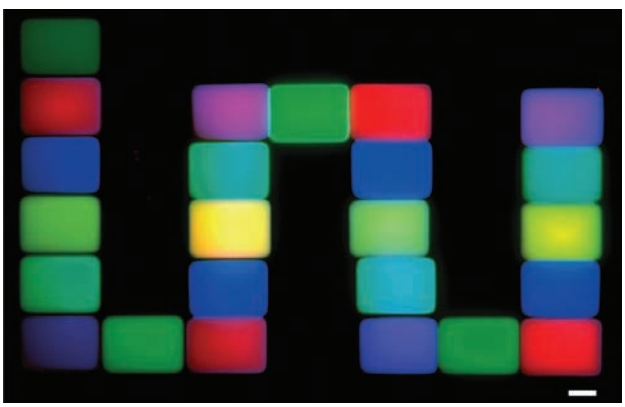
Lee is hopeful that this work can be developed for cancer treatment, but he admits that there is still a long way to go. 'Although the preliminary results in this work show the feasibility of porous silicon as a new therapeutic agent, it is obvious that much work including teratoma tests and experiments on human bodies is necessary before cancer therapy based on porous silicon is realised,' he said.

Elinor Richards

Porous silicon combined with near-infrared light is a cancer killer

Reference
C Lee *et al*, *J. Mater. Chem.*, 2007, DOI: 10.1039/b700892a

Fluid approach to 3D microstructures



Each coloured block represents a different polymer. (Scale bar is 200 micrometers)

US scientists have developed a cheaper and quicker way of making three-dimensional microstructures.

Samuel Sia's team at Columbia University, New York, used light from a microscope to polymerise specific areas of a fluid inside a microfluidic channel. This process, which causes the fluid to harden and stick to the surface of the channel, is known as photocuring. The unpolymerised material was then washed away and a second material was injected into the channel to be photocured. By repeating this process, Sia built up a three-dimensional microstructure made up of 24 different materials in less than one hour, far quicker than conventional methods.

Sia says that the technique, which combines microscopy with microfluidics, will be useful for studying cell behaviour because the microstructures can mimic complex biological tissues.

Victor Ugaz, an expert in microfluidics at Texas A&M University, College Station, US, welcomes this development. 'This technique allows you to polymerise different materials to create structures with spatial variations in material properties. This may be the most exciting aspect; there is a lot of interest in patterning cells in microenvironments that incorporate these kinds of variations since they may more closely mimic in vivo conditions.'

Sia believes the technique has many potential applications. 'An important next step will be to exploit this capability to make new discoveries, for example in cell-cell communication for the patterning of biocompatible hydrogels,' he said.

Joanne Thomson

Reference
Y K Cheung *et al*, *Lab Chip*, 2007, **7**, 574

Interview

The crystal ball game

Is polymorphism crystal clear? Nicola Nugent asks Ashwini Nangia...

Ashwini Nangia

Ashwini Nangia is a professor of chemistry at the University of Hyderabad, India, and he is a member of the editorial board for *CrystEngComm*. His research interests are focused on crystal engineering and supramolecular chemistry.

How did you become interested in chemistry?
Organic chemistry sparked my interest – I had a good teacher at school. Also, I was fascinated with the periodic table – it's a blend of patterns and order on one hand, and then a bundle of exceptions on the other. This combination of method and madness in the same subject is what made me interested in chemistry.

What kind of research do you do now?
When I first joined the University of Hyderabad, I worked on organic synthesis. About that time, several articles appeared by Dieter Seebach, Fraser Stoddart and George Whitesides. These articles, combined with inspiration from my colleague, Gautam Desiraju, who is a pioneer in crystal engineering, made me look beyond the making of molecules and look at how molecules self-assemble. Since then, my research group has looked at several topics, including host-guest inclusion compounds. We have studied the Cambridge Structural Database to look for recurring patterns and used them in our crystal design approaches. Now, we are focusing on polymorphism and pseudo polymorphism, which is not only an academic challenge, but has great relevance for the pharmaceutical industry.

Is polymorphism becoming more predictable?
I think we are still very far away from predicting polymorphism. We have a better understanding within families of structures, but not globally. Even the simplest of molecules can be polymorphic, while the most complex structure you can design, based on your logic driven ideas of what should be polymorphic, will turn out to have only a single form. If we start from the basics, a pathway may evolve from which we will understand why certain molecules are polymorphic and how many forms will exist. It goes back to the point I mentioned at the beginning – there is a method, but then there are exceptions, and that's what fuels the curiosity.

What do you think will be the next big breakthrough in your field?
The major challenges today are: polymorphism, crystal structures with multiple Z' (number of molecules in the asymmetric unit) and crystal structure prediction. We are blending experiment with computation. The blending of these ideas will help us understand what really goes into crystallisation, because it's essentially a one step process – you start with a compound, dissolve it and the next morning, if you are lucky, you get good single crystals. We know the beginning and end of the process, but like any reaction mechanism, we want to know the middle. There have been several recent studies in this area. Hopefully, in the next ten years we'll have a better understanding of what crystallisation really is and how it proceeds.

What is the secret to running a successful research group?
I think the success of any research group, is down to the students. You can have good ideas, but what drives the idea to reality, at least for experimental chemists, is the student who implements the idea. I have a good group of research students who are able to see the plan or vision that I have when I suggest a problem. Like all research plans, I will be frank enough to admit that many of them don't see reality, but the students are able to get the sense that if one thing doesn't work, something else has to be tried.

What is the most rewarding aspect of your work?
It has always been my dream to work in a contemporary area of research. Being realistic about the facilities in my department, it's pleasing that we are able to do something close to where the latest developments in crystal engineering are happening. I may have been able to do a different type of chemistry, perhaps more instrument based chemistry, if I was working overseas, but it makes me very happy to do the research and produce our results in India.

What challenges face researchers in India?
The main challenge is attitude. The school system puts emphasis on achieving good grades rather than encouraging innovative thinking and risk taking. The students are wedded to the fact that whatever they do should work, and the first setback they face in research is that most things don't work. But a negative result is not always a bad thing in science. One negative result today may lead to a positive result tomorrow. A shift in thinking is really the biggest challenge.

What advice would you give to a young scientist?
For any scientist at any point in their life, the most important thing is to do something innovative and challenging. And most of all, whatever you do, you should enjoy it.

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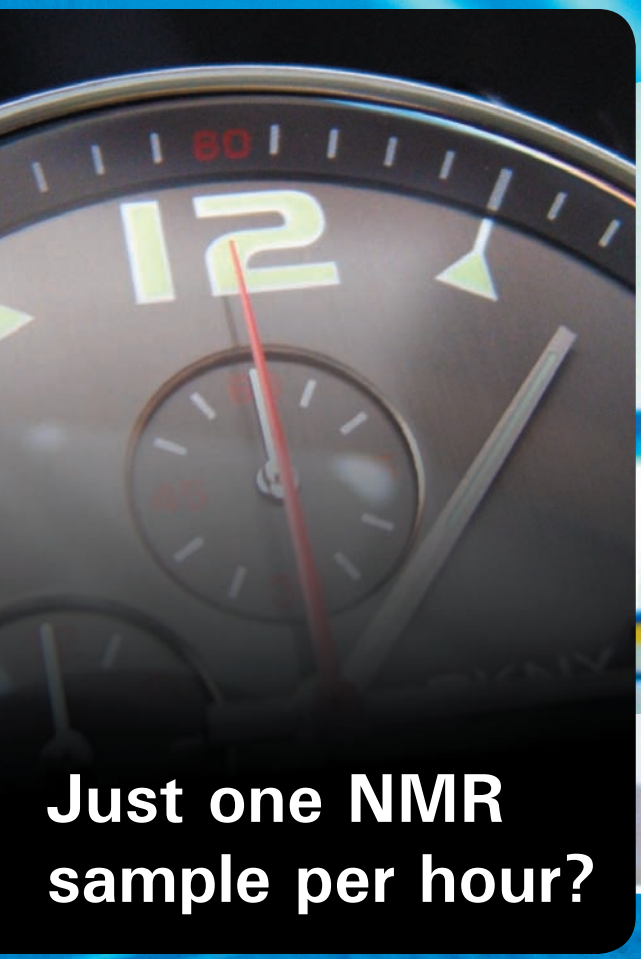

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In from the cold

Bill Baker from the University of South Florida, Tampa, US, extols the virtues of cold-water marine natural products

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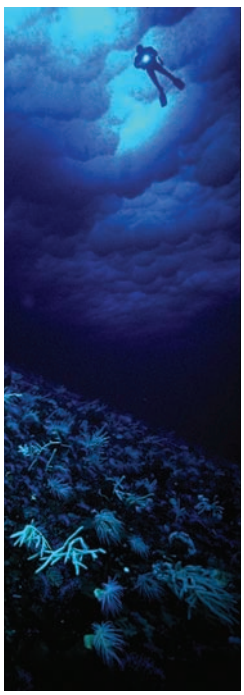
The words coral and sponge might conjure up pleasant thoughts of warm tropical waters and colourful fishes. The organic chemists among us may think of terpenes and polyketides, while pharmacologists might reflect on anti-inflammatory or anti-cancer agents. That these disparate images are not incongruous is testament to the growing role of marine organisms as sources of biomedically important chemical diversity. Yet much remains to be discovered. With more than 70 per cent of the earth covered by oceans, marine natural products represent only 10 per cent of natural products described to date.

Now modify that word association with the adjectives Antarctic, Arctic, or deep sea. Thoughts of tropical islands flee, along with them chemical or biomedical connotations. Icebergs, abyssal depths and sea water hovering within a few degrees of zero seem at first incompatible with corals and sponges, terpenes and polyketides, and the treatment of human disease. And perhaps for good reason, as these extreme cold regions have traditionally been thought to be lacking in animal life and the accompanying ecological pressure to drive the evolution of chemical defenses. Additionally, the cold-water diving, lack of diving support services and sheer remoteness of many of these habitats renders them difficult to rationalize as practical sources of biological or chemical diversity.

Nonetheless, accumulating biological and chemical research points to a rich cold-water flora and fauna and an active ecology, as dependant upon chemical defenses as many lower latitude habitats. Among bioactivity-producing organisms, sponge biodiversity in Antarctica is as high as that found at temperate latitudes, and deep sea microbial fauna are among the most diverse known. Recent studies have also shown cold-water invertebrate-associated microbe communities are robust.

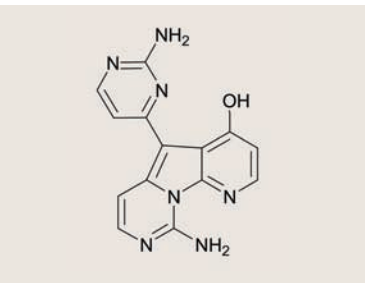


Diving under ice: not your routine scuba trip

From the chemical laboratory, unique structural motifs have emerged, as have biological activity profiles that have caught the attention of the pharmaceutical industry. Variolin B, for example, is a structurally unique cyclin-dependent kinase inhibitor from an Antarctic sponge, which is in clinical development as an anti-cancer drug. Meridianins and palmerolides derive from Antarctic tunicates and have advanced in synthetic and pharmacological studies. Meridianins have similar activity to variolin B, while palmerolide A, a potent inhibitor of the enzyme vacuolar-ATPase, targets melanoma. Cold-water natural products are also known to act as antibiotic, antiviral, antifouling, hemolytic, serotonergic, and ion channel modulating agents, as well as inhibitors for a number of specific enzymes.

Besides the accumulating evidence for the biomedical potential of cold-water natural products, the statistics are also encouraging. If the marine realm is largely understudied as a source of chemical diversity, the cold-water habitats are truly unstudied. Consider that 90 per cent of the biosphere is marine, and that a significant portion of that habitat is found at the extreme low end of liquid water's temperature range, yet only 0.3 per cent of natural products reported to date have been isolated from species originating in these environments.

What's not to like about cold-water bioprospecting? To be sure, these studies are difficult. Diving under the ice is not your routine scuba diving operation and deep water habitats can only be sampled by ship-based equipment. In polar regions, it is not unusual to have one to three meters of sea ice between diver and ocean, requiring extraordinary measures to gain access to the water. Thermal gear, while quite satisfactory at keeping the diver warm, often weighs as much as, if not more, than the diver, rendering graceful egress from the water impossible. Deep sea trawls, while less physically demanding than scuba diving, present mountains of fragrant biodiversity that must be sorted, often in difficult sea and weather conditions, and are environmentally damaging. Further, while advances in sampling devices have made some deep sea sediments accessible, the abyss remains very difficult to sample.



Antarctic sponges supply variolin B

So the cold-water chemical diversity story has yet to unfold, but the case is compelling. While sampling will always be more challenging in these environments, there is little doubt that chemical rewards of cold-water biodiversity await the intrepid bioprospector.

Read Bill Bakers review on 'Cold-water marine natural products' in an upcoming issue of Natural Product Reports.

Reference
M D Lebar, J L Heimbegner and B J Baker, *Nat. Prod. Rep.*, 2007, DOI: 10.1039/b516240h

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The study is an excellent example of research carried out at the chemistry–biology interface, which is a prime focus of the *Molecular BioSystems* journal.

Zebrafish embryos can be monitored relatively easily outside of the uterus and are transparent, so changes can be clearly observed. They serve as models in the study of Menkes disease in humans, a developmental disease associated with copper metabolism.

In the study, mercapto-pyridine-*N*-oxide (MCP) was found to affect the development of the notochord, an important tissue involved in early skeletal development. Results suggested that MCP targets the copper-dependent enzyme lysine oxidase.

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