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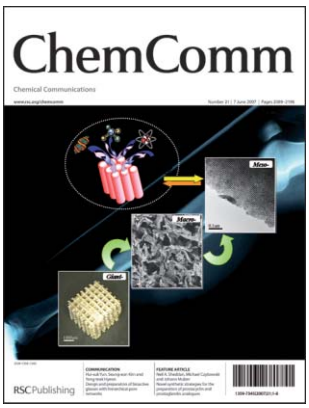
IN THIS ISSUE

ISSN 1359-7345 CODEN CHCOFS (21) 2089–2196 (2007)



Cover

See Hui-suk Yun, Seung-eon Kim and Yong-teak Hyeon, page 2139.
The image shows novel functional scaffolds used for tissue regeneration with hierarchically 3D giant-, macro-, and meso-pore structures. Image reproduced by permission of Hui-suk Yun, Seung-eon Kim and Yong-teak Hyeon, from *Chem. Commun.*, 2007, 2139.

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

June 2007/Volume 2/Issue 6

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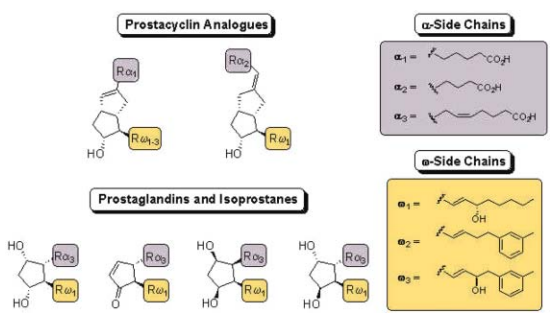
FEATURE ARTICLE

Novel synthetic strategies for the preparation of prostacyclin and prostaglandin analogues – off the beaten track

Neil A. Sheddan,* Michael Czybowski and Johann Mulzer*

Various strategies for the preparation of prostacyclin, prostaglandin and isoprostane analogues are discussed, with particular focus on novel approaches developed in our own laboratories.



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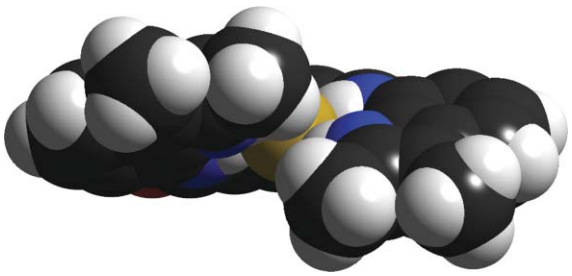

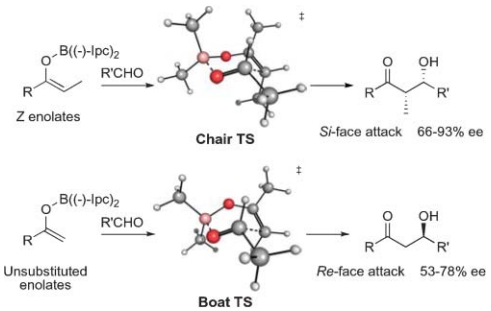

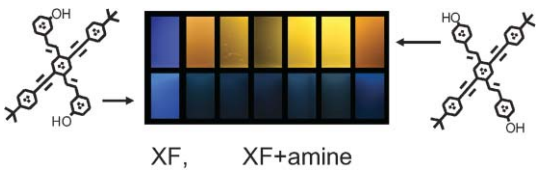

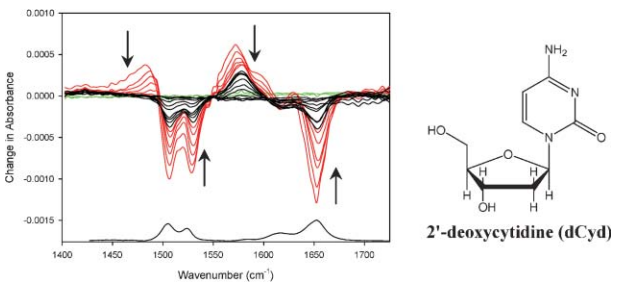

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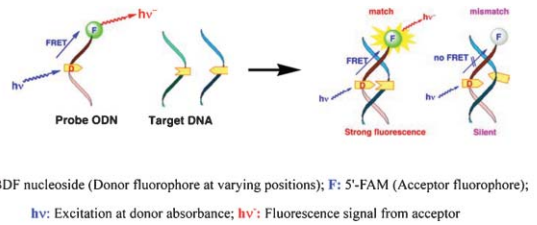


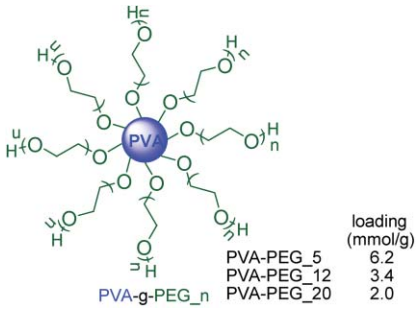
D: BDF nucleoside (Donor fluorophore at varying positions); F: 5'-FAM (Acceptor fluorophore);
hν: Excitation at donor absorbance; hν': Fluorescence signal from acceptor

Dual-labeled oligonucleotide probe for sensing adenosine *via* FRET: A novel alternative to SNPs genotyping

Yoshio Saito,* Subhendu Sekhar Bag, Yuichi Kusakabe, Chiharu Nagai, Katsuhiko Matsumoto, Erika Mizuno, Satoshi Kodate, Isamu Suzuka and Isao Saito*

Distance dependent selectivity in sensing the opposite base from its target DNA sequence *via* FRET with a BDF nucleoside was demonstrated.

2136

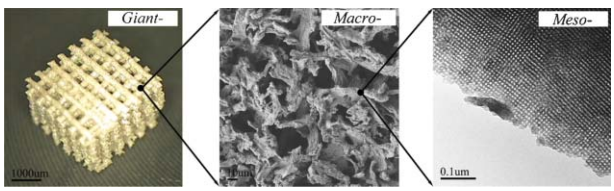


Poly(vinyl alcohol)-*graft*-poly(ethylene glycol) resins and their use in solid-phase synthesis and supported TEMPO catalysis

Juntao Luo, Christophe Pardin, William D. Lubell* and X. X. Zhu*

PVA-*g*-PEG resins with high loading and good swelling are prepared *via* anionic polymerization of ethylene oxide onto PVA beads. They are used in solid-phase synthesis, supported catalysis and high-resolution NMR spectral analysis.

2139

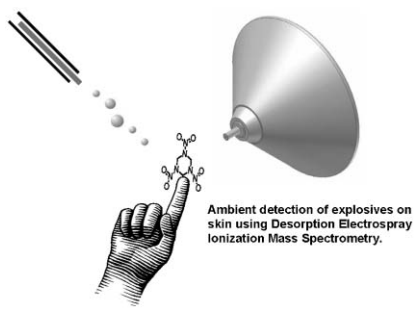


Design and preparation of bioactive glasses with hierarchical pore networks

Hui-suk Yun,* Seung-eon Kim and Yong-teak Hyeon

Hierarchically 3D porous bioactive glass scaffolds with good bone-forming bioactivity *in vitro* have been synthesized by using a combination of the sol–gel, polymer templating, and rapid prototyping techniques.

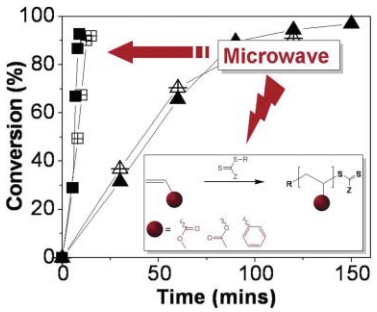
2142

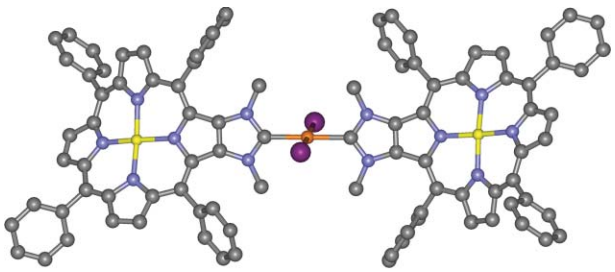


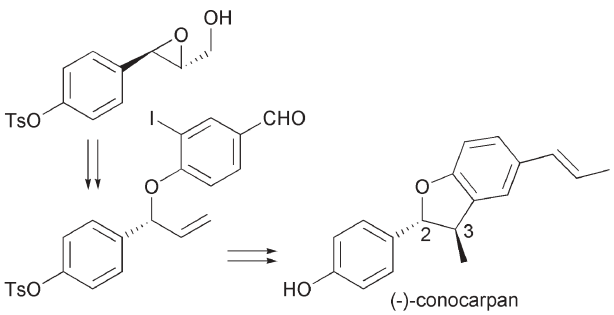
Detection of explosives on skin using ambient ionization mass spectrometry

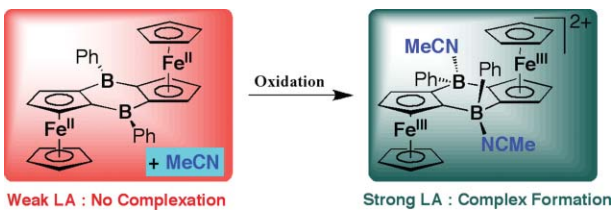
Dina R. Justes, Nari Talaty, Ismael Cotte-Rodriguez and R. Graham Cooks*

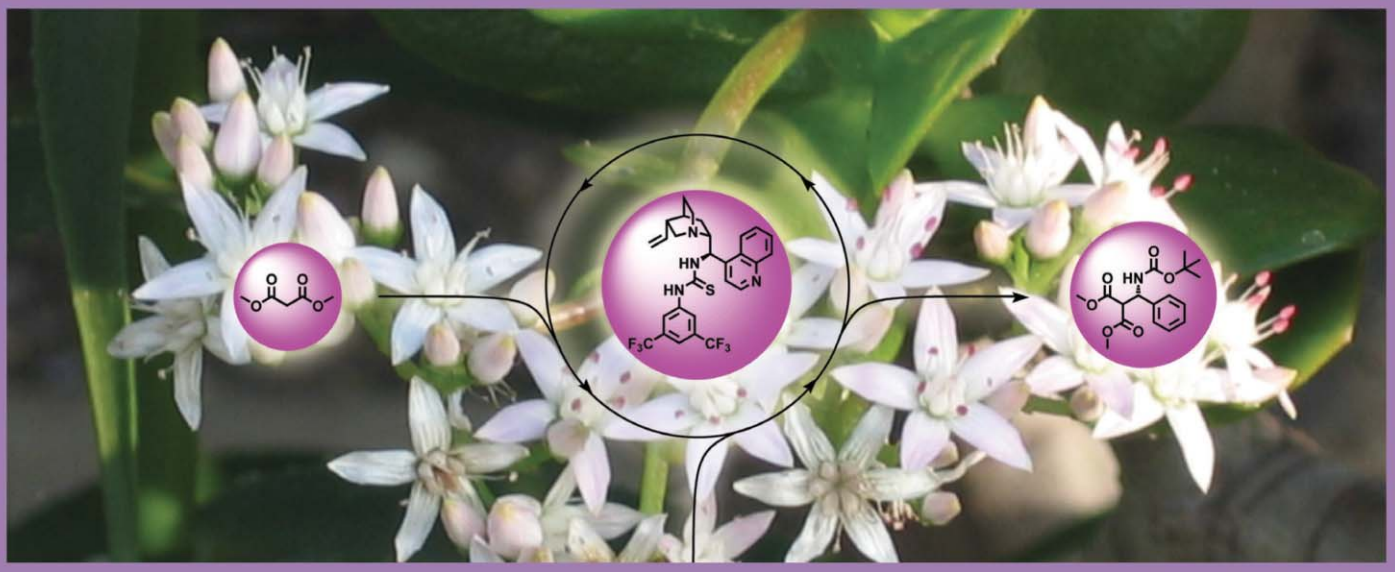
Ambient detection of explosives on skin using desorption electrospray ionization mass spectrometry.











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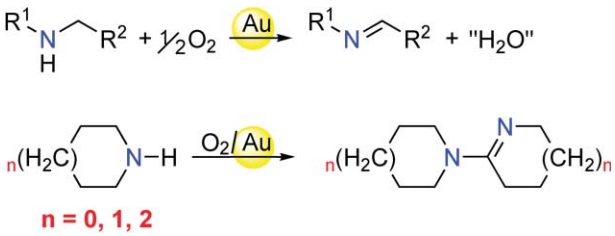
Non-nanogold catalyzed aerobic oxidation of secondary amines to imines

Bolin Zhu and Robert J. Angelici*

Bulk gold powder ($\sim 10^3$ nm particle size) is a highly active catalyst for the oxidative dehydrogenation of secondary amines to imines under the mild conditions of 1 atm O_2 and 60–100 °C.



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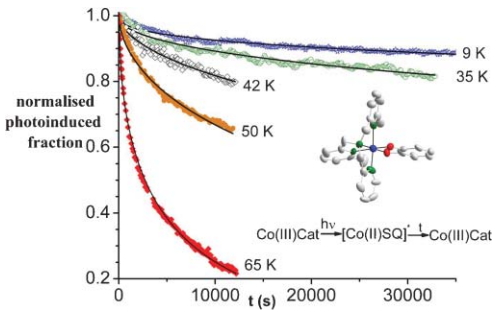
Unprecedented optically induced long-lived intramolecular electron transfer in cobalt–dioxolene complexes

Alessandra Beni, Andrea Dei,* Mario Rizzitano and Lorenzo Sorace

We report very long lifetimes for the photoinduced metastable states of two cobalt–dioxolene complexes undergoing valence tautomer interconversion, a result which opens new research perspectives for the possible use of these systems as memory devices.



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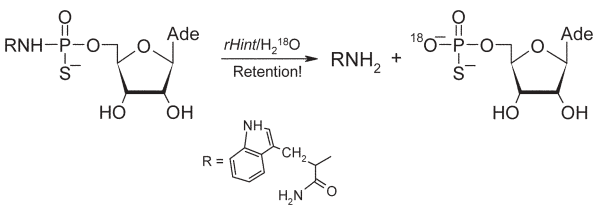
Stereochemistry of rHint1 hydrolase assisted cleavage of P–N bond in nucleoside 5′-*O*-phosphoramidothioates

Agnieszka Krakowiak, Renata Kaczmarek, Janina Baraniak, Michał Wieczorek and Wojciech J. Stec*

The Hint-1 hydrolase assisted cleavage of the P–N bond in adenosine-5′-*O*-[*N*-(tryptophanylamide)] phosphoramidothioate proceeds with retention of configuration at the phosphorus atom which is consistent with the formation of a covalent enzyme–substrate complex.

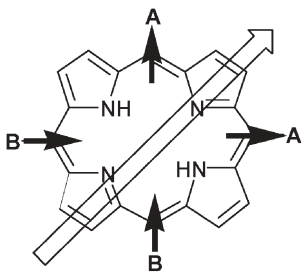


2166

A_2B_2-type *push–pull* porphyrins as reverse saturable and saturable absorbers

Eleni G. A. Notaras, Marijana Fazekas, James J. Doyle, Werner J. Blau and Mathias O. Senge*

The nonlinear optical response of A_2B_2-type *push–pull* porphyrins is characterized by reverse saturable absorption (RSA) at lower intensity levels and saturable absorption (SA) at higher intensity levels.



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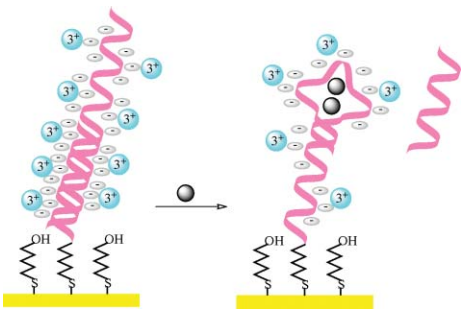

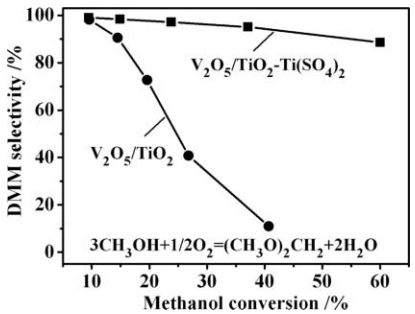

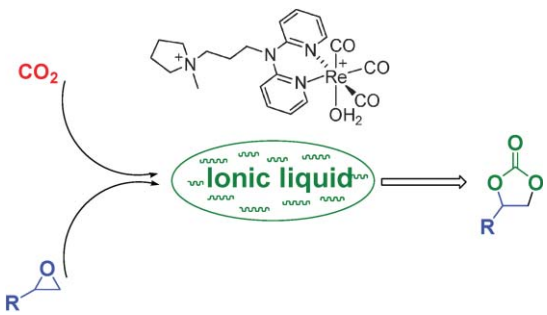

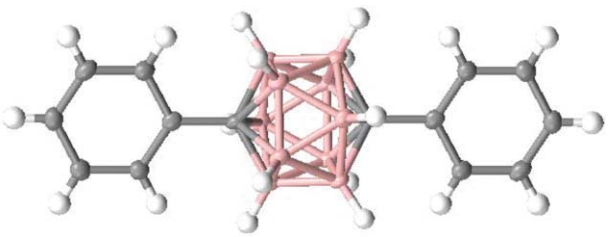

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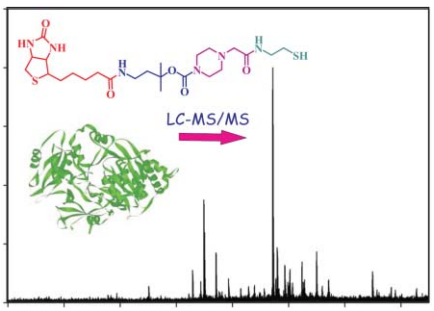

CILAT – a new reagent for quantitative proteomics

Shuwei Li* and Dexing Zeng

A new type of reagent, called CILAT (Cleavable Isobaric Labeled Affinity Tag), can enrich tyrosine-containing peptides from proteolytic peptide mixtures for quantitative proteomic assays with LC–MS/MS.

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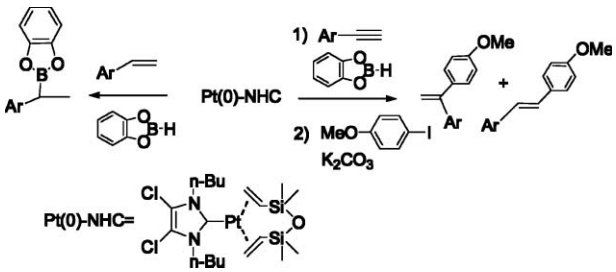

The active role of NHC ligands in platinum-mediated tandem hydroboration–cross coupling reactions

Vanesa Lillo, Jose A. Mata, Anna M. Segarra, Eduardo Peris* and Elena Fernandez*

Pt(0)–N-heterocyclic carbene complexes catalyse the regioselective hydroboration of C=C and promote tandem H–B addition on C≡C/cross coupling reaction.

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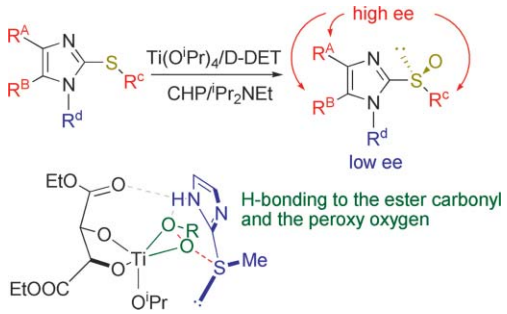

Factors influencing the selectivity in asymmetric oxidation of sulfides attached to nitrogen containing heterocycles

Muthu Seenivasaperumal, Hans-Jürgen Federsel, Anne Ertan and Kálmán J. Szabó*

Asymmetric oxidation of heterocyclic sulfides were studied using a tartrate/Ti(^{i}OPr)$_4$ catalyst system. We concluded that the smallest heterocyclic substituent on sulfur required for the high level of enantioselection is the imidazole ring.

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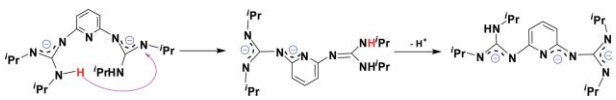

Synthesis and structural characterization of lanthanide complexes with the di- or tri-anionic diguanidinate ligand: new insight into the flexibility and distinct reactivity of the linked diguanidinate ligand

Chengfu Pi, Zhenyu Zhu, Linhong Weng, Zhenxia Chen and Xigeng Zhou*

Unprecedented disproportionation and deprotonation of the diguanidinate ligand have been established, demonstrating, for the first time, that the number and distribution of negative charges on the diguanidinate ligand are tunable.

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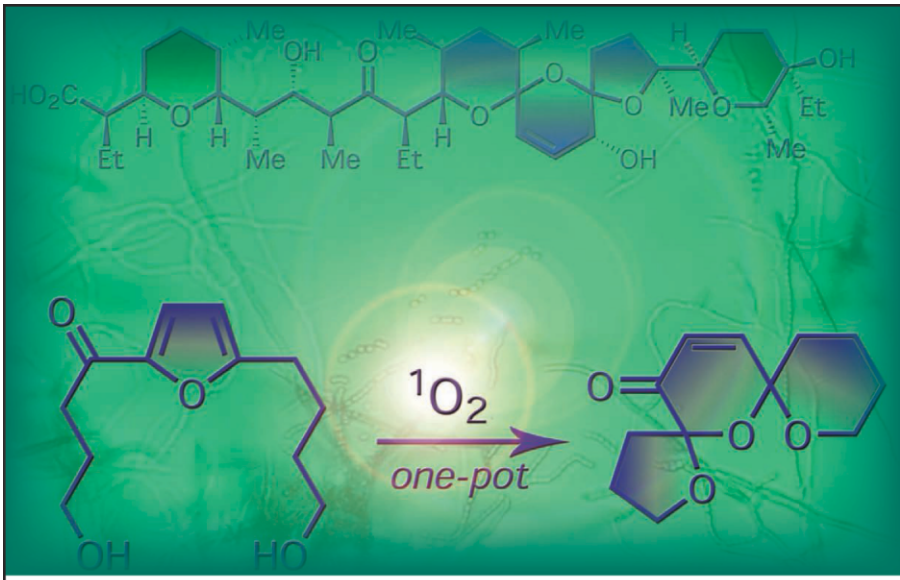

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"*O*-Acyl isopeptide method" for peptide synthesis: synthesis of forty kinds of "*O*-acyl isodipeptide unit" Boc-Ser/Thr(Fmoc-Xaa)-OH

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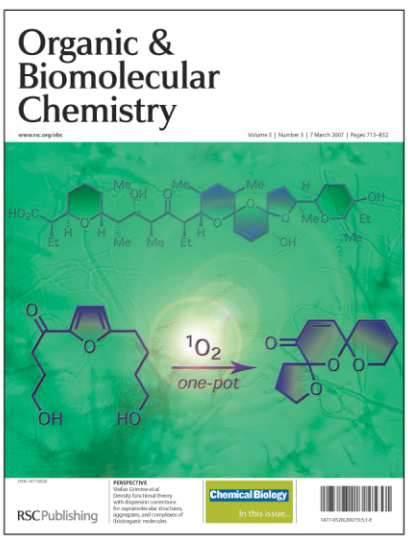

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Chemical Biology

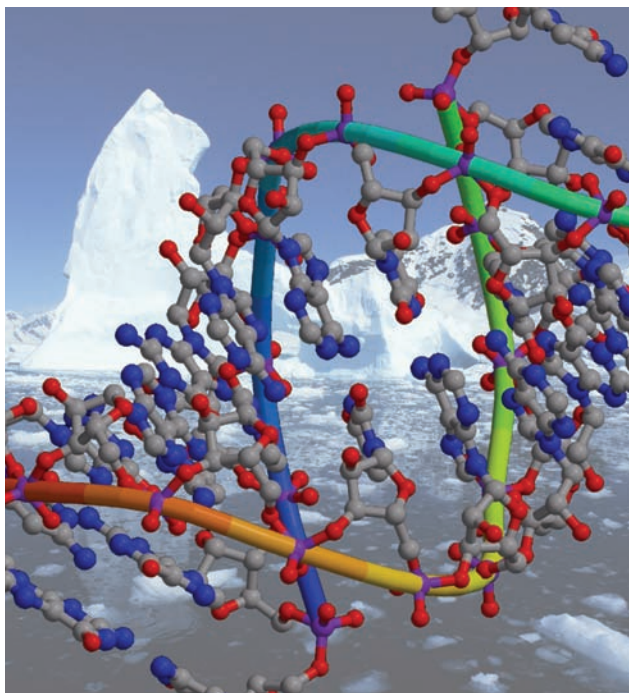
Freezing temperatures aid enzyme-free nucleotide replication

RNA on ice

Life could have begun at the poles according to researchers in Germany. Clemens Richert and Stephanie Vogel of the University of Karlsruhe have found that steps in the spontaneous replication of RNA are possible without the usual enzymes, even for the most difficult sections of the strand. 'The notion of spontaneous replication, perhaps the very reaction that defines the beginning of life from inanimate material, is fascinating,' said Richert. 'All attempts to demonstrate this phenomenon *in vitro* have thus far failed.'

Today, nucleic acid replication is catalysed by polymerases inside cells, but at some point in prebiotic evolution replication must have begun without these enzymes. 'It is likely that RNA was the first encoding system,' said Richert. But, the problem is that sequence stretches of multiple adenosine residues do not support spontaneous replication, he added.

RNA replication is assisted by three factors in Richert's system: promoters to aid nucleotide extension; helper RNA to assist in the replication of adenosine regions; and a low temperature, which helps to improve the yield of copied nucleotide. Even in the team's worst case situation, a stretch of three adenosine residues, the conditions allowed successful enzyme-free replication in a frozen mixture.

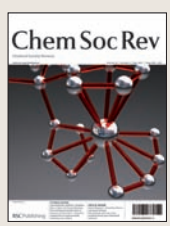


Ice-caps: a perfect environment for spontaneous RNA replication?

According to Richert, the results suggest that the earliest life forms could have benefited from freezing environments. Chris Greenwell, an expert in prebiotic chemistry at the University of Wales in Bangor, UK, agrees. 'These experiments overcome the obstacle to replication presented by adenosine residues, lending support to theories that prebiotic replication occurred in polar ice-cap regions, where sea ice formation concentrates reactants,' he said. *Michael Spencelayh*

Reference
S R Vogel and C Richert, *Chem. Commun.*, 2007, 1896

In this issue



Research highlights

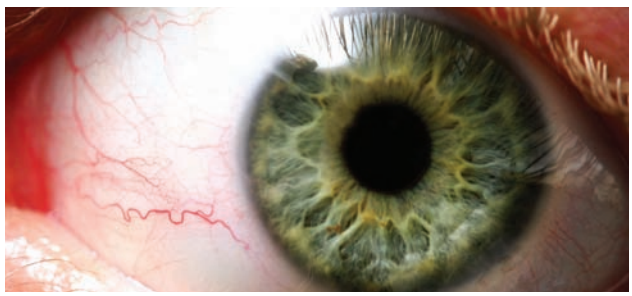
Contact lens material provides framework for cell growth

Retinal repair

Polymer scaffolds could one day be used to fix damaged eyes. A team of US researchers has developed a plastic scaffold for retinal cells, which can be implanted in the eye and used to replace diseased or damaged cells.

The retina is a layer of cells across the back of the eye, which collects light and sends signals to the brain. If it becomes damaged, through accident, illness or aging, then sight is impaired or lost. The new, 1mm wide scaffold holds a layer of retinal progenitor cells, which can differentiate into the types of cell needed to make a new section of retina. It rests against the back of the eye, allowing the cells to grow gradually outwards into the retina and replace old, damaged cells.

The scaffold is made of the same material as hard contact lenses, poly(methyl methacrylate), and is only 6μm thick. Previous attempts to repair retinas in this way have used scaffolds more than twenty times thicker, and implanting them has often caused more damage than they have been able to repair.



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New for old: implant helps replace cells at the back of the eye

Further reading
Read more about tissue engineering in the June special issue of *Lab on a Chip*: 'Cell and Tissue Engineering Microsystems.'

The group behind the research, led by Tejal Desai at the University of California in San Francisco, tested both flat scaffolds and scaffolds containing a regular grid of pores. They found that cells stay attached to porous scaffolds more easily, making them a better way to transport the cells to the back of the eye.

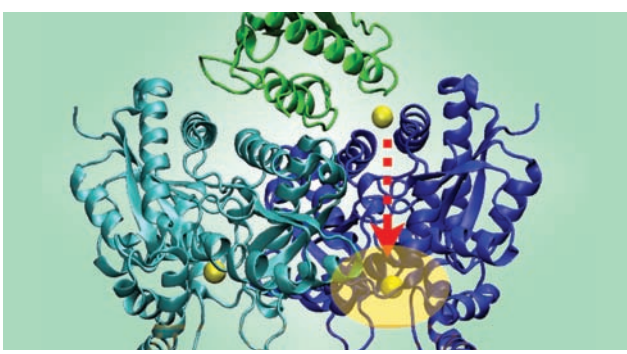
Desai believes that scaffolds are the most promising method to fix retinal damage. 'Retinal progenitor cells alone are insufficient to recreate the complex structure of the retina, particularly when multiple retinal layers have been lost or disrupted,' she said. 'Our scaffolds influence retinal progenitor cell attachment, promote differentiation and provide a physical guide for normal anatomical organisation of the cells.'

Clare Boothby

Reference
S Tao *et al*, *Lab Chip*, 2007, DOI: 10.1039/b618583e

Protein chaperones metal towards heme assembly line

Iron taxis



Frataxin (green, top) delivers iron (yellow) before its transport to the enzyme active site (yellow oval)

Scientists are one step closer to understanding a progressive neurodegenerative disease thanks to a study into the role of an essential human protein, frataxin.

Frataxin has been implicated in iron transport in the body. In Friedreich's ataxia (FRDA), an inherited disorder that causes increasing deterioration of the nervous system and affects about 1 in 50 000 people, the body is unable to make frataxin. The resulting protein deficiency affects the cells' ability to control and use iron, with debilitating consequences. According to Timothy Stemmler a structural biologist at Wayne State University, Detroit, US: 'If scientists can understand what frataxin does and how to help FRDA patients make it, we can go a long way to developing new drugs to treat or even cure these patients.'

Further reading
Read more about hemes in the July special issue of *Natural Product Reports:* 'The chemistry and biochemistry of heme proteins.'

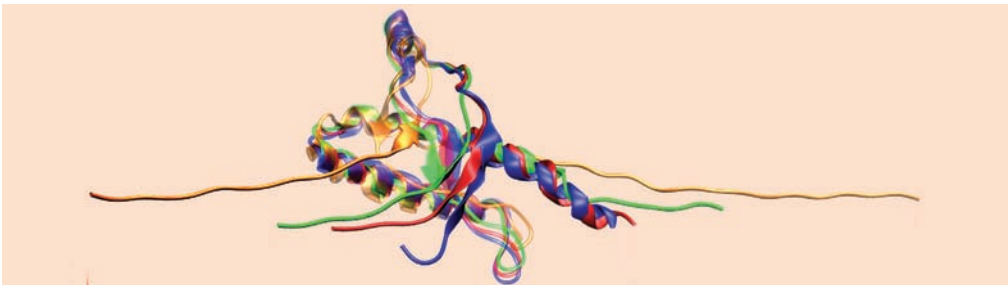
Working towards this goal, Stemmler and his colleagues in the US and Mexico, investigated frataxin's role in the production of heme – an iron-containing protein cofactor that controls cellular processes ranging from energy production to oxygen transport. Using a combination of x-ray absorption and nuclear magnetic resonance spectroscopies, the team showed that frataxin operates as a molecular chaperone to iron, delivering the metal to ferrochelatase, the enzyme involved in assembling heme.

Andrew Dancis, an expert in iron transport at the University of Pennsylvania, US, explained that the iron delivery step in the ferrochelatase synthesis of heme has been completely mysterious until now. 'Frataxin is in the right place to play a role in this process,' he said. 'Stemmler sheds light on this process by defining the human ferrochelatase binding surface with iron and frataxin, and by proposing a pathway for the iron delivery.'

Stemmler suggested that, 'if we can understand all the steps involved in the different cellular iron regulation pathways at the protein level, we can provide a universal understanding of how cells control the chemistry performed by this highly reactive element. This insight should help not only in treating FRDA,' he continued, 'but the growing number of metal regulation related human disorders as well.' *Kathryn Lees*

Reference
K Z Bencze *et al*, *Chem. Commun.*, 2007, 1798

Unravelling the prion mystery



Tiny differences between mammalian and non-mammalian prion proteins could be responsible for transmissible spongiform encephalopathies (TSEs) such as Creutzfeld–Jacob disease, say Italian scientists. TSEs are generally accepted to be caused by prions in the brain folding into an abnormal form; this triggers other prions to refold, creating plaques and tangles.

Carmelo La Rosa at the University of Catania and colleagues used molecular dynamics simulations to probe the difference between prion proteins in two mammals, humans and Syrian hamsters, and two non-mammals, chickens and turtles. TSEs have not been reported in chickens or turtles.

Simulations imply that mammalian prions do not refold efficiently

The group used the simulations to model the prions, to see how far they could stretch and still refold into their native state. They found that a greater force was needed to unfold the mammalian prions. However, once unfolded, these prions refolded into the native state less efficiently than the turtle or chicken proteins, adopting metastable configurations instead.

La Rosa hopes that mechanistic research such as this will lead to treatments for TSEs. 'The detailed characterisation of the metastable states in the early steps of prion misfolding is a promising prerequisite for anti-prion molecule design,' he said.

Colin Batchelor

Reference
M Pappalardo *et al*, *New J. Chem.*, 2007, DOI: 10.1039/b700764g

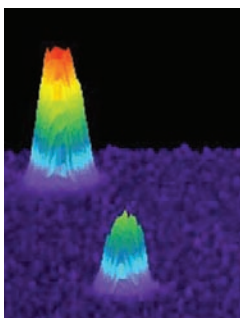
Illuminating infection

To detect a parvovirus you just need to lighten up, say Italian scientists.

Aldo Roda and co-workers at the University of Bologna have developed an ultrasensitive way of detecting parvovirus B19 infections. The virus is responsible for a range of syndromes in humans, including aplastic crisis. Aplastic crisis causes suppression of red blood cell production and is a particular threat to children with sickle cell disease, for whom infection can result in severe anaemia.

By exploiting three detection techniques in combination, Roda's team has engineered a system that they claim is more sensitive than any previously developed *in situ* assays. The method is sensitive enough to detect the virus within cells and at early stages of infection.

In Roda's assay, infected cells are exposed to short strands of a synthetic version of DNA: peptide nucleic acid, or PNA. The PNA strands bind to the viral nucleic acids and are then labelled with an enzyme (alkaline phosphatase) using a linker already on the PNA.



Chemiluminescence is used to detect viral nucleic acids

The key to the new system is chemiluminescence, light produced by a chemical reaction. Used in detection, it is extremely sensitive and the signal can be quantified. By adding a substrate that chemiluminesces on binding to the enzyme label, the PNA and hence viral nucleic acids can be detected.

Importantly, Roda's method does not require amplification or extraction of the viral nucleotides from the cells, reducing sample handling and potentially shortening assay times. According to the team, the system could eventually be used to monitor persistent low-level viral replication in chronic infections and to study the effects of antiviral drugs. *Freya Mearns*

Reference
F Bonvicini *et al*, *Analyst*, 2007, DOI: 10.1039/b701664f

Protein unfolding step-by-step

UK scientists have developed a more sensitive technique for studying how peptides unfold. They expect that the method will be useful in fundamental research on protein structure and in understanding conditions such as Alzheimer's disease.

Ewan Blanch from the University of Manchester and his colleagues used Raman spectroscopy to analyse protein model poly(glutamic acid) as it unfolded in response to increasing pH. The scientists discovered two distinct phases as poly(glutamic acid) goes from the helical to the disordered state. They speculate that this is because the end and central helix regions have different thermodynamic stabilities.

The group combined normal and chiral Raman spectroscopies to examine the protein model. Both methods have been used for some years to study protein unfolding, but correlating the two techniques has proved to be advantageous for two reasons, said Blanch. 'Firstly, you get much better spatial resolution, allowing you to resolve smaller spectral bands,' he said. 'Secondly, you can see which bands in a spectrum behave in the same way as experimental conditions change. If we know the origins of these bands we can map out the series of changes that occurs during an experiment and learn something new about the mechanisms involved.'

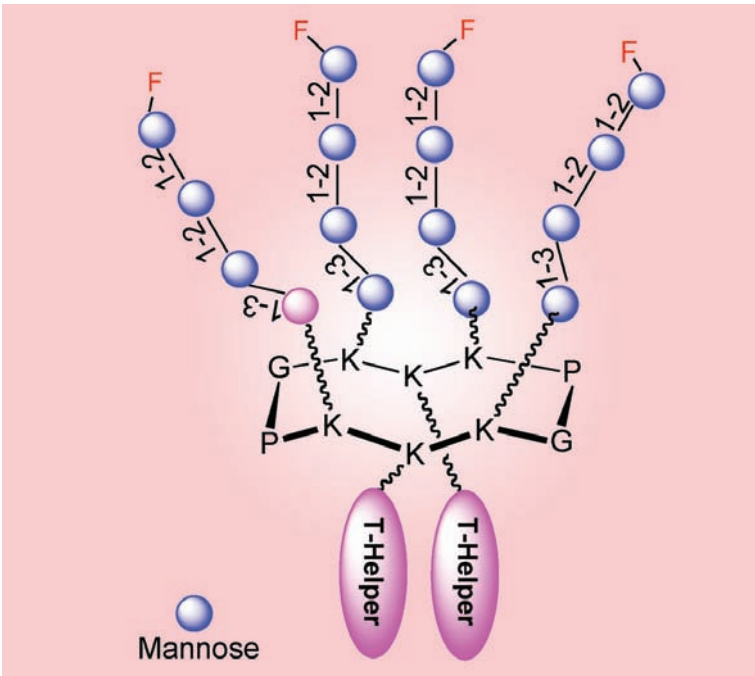
The technique can be applied to more complex systems, said Blanch; co-worker Lorna Ashton has used it to study the unfolding of real proteins. The group will also use the method to investigate RNA unfolding and the formation of amyloid fibrils, protein aggregates associated with Alzheimer's disease. 'We are just beginning to explore the potential of Raman and correlation analysis,' said Blanch.

Danièle Gibney

Reference
L Ashton *et al*, *Analyst*, 2007, **132**, 468

Synthetic carbohydrate cluster shows its vaccine potential

Sugar solution for HIV?



Wang's mannose-rich cluster molecule resembles the target for an HIV-1 antibody

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

Lai-Xi Wang and colleagues at the University of Maryland in Baltimore have made a compound based on the target of a human antibody known as 2G12. The target is a cluster of carbohydrate chains, rich in the sugar mannose, found on a glycoprotein on the HIV-1 virus surface. 2G12 binds to the cluster and neutralises the virus, so a synthetic compound that mimics this target could stimulate 2G12 production in the body and work as an HIV vaccine.

Wang explained, 'HIV-1 is a smart virus that has developed a number of defence mechanisms to evade immune surveillance and carbohydrates play some essential roles in HIV-1 infection and transmission.' The mannose-containing glycoprotein cluster is 'unique' to the virus and not found on normal human glycoproteins, he added. 'This forms the basis for developing a carbohydrate-based vaccine.'

The group made its compound by attaching four carbohydrate chains to one face of a peptide ring. These formed the cluster that 2G12 could recognise and Wang and his colleagues were able to show that 2G12 does bind the new compound. The team also included two peptide chains on the other face of the ring – as these chains also cause an immune response, the aim was to give longer-lasting antibodies.

Ben Davis, a chemist at the University of Oxford, UK, welcomed the research. '2G12 is an intriguing antibody and a number of groups are looking at how we might exploit our understanding of its mode of sugar-binding as a way of developing HIV vaccines. The next key step will be to see if these new clusters can induce the desired immune response,' he said.

Rachel Warfield

Reference
J Wang *et al*, *Org. Biomol. Chem.*, 2007, **5**, 1529

In the current issue of Research Articles...

Read more at www.rsc.org/chembiology

Interview

Light and life

Are lawnmowers a thing of the past? Pill-Soon Song explains all to Celia Clarke

Pill-Soon Song

Pill-Soon Song is a professor of photobiology at the Cheju National University, Korea. He is Editor-in-Asia for *Photochemical and Photobiological Sciences*. His research interests are in the interactions between light and organisms, in particular the effect of light on plant development.

What motivated you to study photobiology?

I've always been interested in looking at life and living processes from chemical and physical points of view. To some extent by coincidence and to some extent by design, I became interested in living processes associated with light. There are processes of living systems that are absolutely dependent on light, like photosynthesis in plants and vision in animals. So, I became interested in the photobiological aspects of living processes, which is a combination of biology and physics.

Which is the most likely outcome of artificial photosynthesis, a fix for increasing CO_2 levels or a new energy source?

There are several ways to harness solar energy by directly fixing CO_2 and reducing it to the level of carbohydrates – in other words mimicking or improving plant photosynthesis. Probably the most direct way is to increase the CO_2 fixation efficiency of plants, for example, by genetic engineering. This is an important approach to harness solar energy more efficiently. But for more artificial harnessing of solar energy, for example for solar cells, the most common system is the photochemical splitting of water to generate hydrogen as a fuel source. Many laboratories around the world are working in this major research area.

What are you working on at the moment?

I am working on how plants respond to light by regulating their growth and development. Plants are not able to move around so they have to adapt to environmental situations. For example, if plants are in the shade they cannot photosynthesise efficiently and, since they cannot move into brighter daylight, they respond to the shade light at the molecular level. The shade light causes a set of genes to make the plants grow upwards in search of light and that's called the shade avoidance response.

Plants have light-absorbing visual pigments, like our rhodopsin, called phytochromes. In bright daylight the major component of light is 660nm wavelength red light, and upon absorbing this light, one phytochrome form transforms into another, physiologically active form. This activates certain genes involved in growth and development and it can be switched off by absorbing longer wavelength, 730nm, shade light. So, you have an on-and-off switching system in plants that means they can dynamically respond to their light environment.

You have a project involving lawn grass. What is this about?

We are applying our understanding of the shade-avoidance mechanism to biotechnological and commercial uses. Lawn grass grows in a compact situation – this dense growth creates shadow on its neighbours and triggers the grass to grow vertically as fast as it can, to avoid the shade. So, you have to mow the lawn more often. Also, if lawn grass is kept in the shade it doesn't develop chlorophylls so it cannot photosynthesise. We are trying to make the plants tolerate and not avoid the shade. And by tolerance, I mean that the plants remain green and can absorb and use the shade light to regulate their growth so that they don't have to grow as tall.

And you do this by chemically and genetically modifying the plants' phytochromes. The phytochrome absorbs 660nm light, so it cannot effectively absorb the 730nm shade light – as far as the plant is concerned, when it is in the shade, it is in the dark. So we are changing the wavelength of absorption of the phytochrome toward the wavelength of shade light. Then, when you introduce a genetically engineered phytochrome gene into lawn grass, the grass in the shade sees the shade light more effectively and it grows slower. It also means that you're using up less water because you're not having such rapid growth and, since a lot of water is good for fungal infections, you can minimise disease too.

What lies in the future for photobiology?

I think there will be two major avenues of research. One is the fundamental area – to understand how light affects living systems and processes. The other avenue is applied aspects – the lawn grass is a minor example, but a more important issue is the energy problem we are facing on the planet. One way to improve energy production by plants is to cut down on shade avoidance. You can shorten the stems of rice plants and corn, and this will result in more starch in the grains. Applied photobiology could lead to increased energy production from crop plants. There is also an area of extremely active research called photodynamic therapy: using light in combination with a light-absorbing, so-called photosensitiser, compound to treat cancer and skin diseases.

And finally, if you weren't a scientist, would you do?

I'd probably be a medical doctor. I like the idea of an eye doctor – an ophthalmologist – which is to do with photobiology. Or a skin doctor – a dermatologist – it's also related to photobiology, skin photobiology.

Instant insight

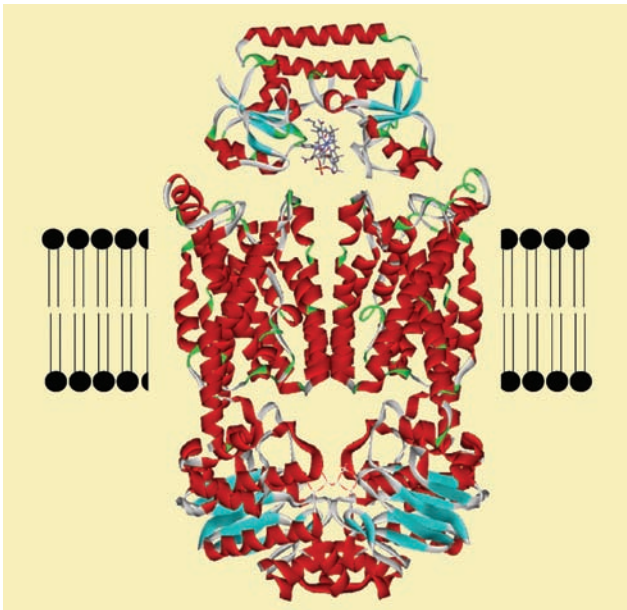
Essential metals

Xiangyang Liang, Dominic Campopiano and Peter Sadler at the University of Edinburgh, UK, examine how and why metals cross membranes

Cell membranes are natural barriers, surrounding the cytoplasm and cell compartments and separating them from the external environment. They comprise a lipid bilayer with transmembrane proteins and proteins attached to the membrane surface. These membrane proteins perform various functions, serving as channels, pumps, transporters, enzymes and receptors (sensory proteins). Metal ions are essential in many of these biological processes.

Membrane proteins can be involved in transporting metal ions (and sometimes their associated ligands) through membranes. Ion channels are transmembrane proteins that form pores that allow ions to cross into or out of a cell. Ions crossing ion channels always flow in the same direction as diffusion: from a more to a less concentrated solution, or from positive to negative potential. The channel pores are gated. For ligand-gated channels, the gates open or close in response to a ligand such as Ca(II), a guanine nucleotide binding protein (G-protein), or glutamate; for voltage-gated channels, the gates respond to a change in membrane potential. These channels are highly selective and recognise only certain ions and allow them to pass through.

A metal ion's passage across a membrane can be passive, without energy requirement, or active, with energy supplied from adenosine triphosphate (ATP) hydrolysis. Ion pumps and transporters transfer metal ions against the direction of diffusion using this energy of hydrolysis. These include P-type ATPase pumps, enzymes that catalyse the conversion of ATP to adenosine diphosphate (ADP). The released phosphate is transferred to an aspartate residue to form a phosphorylated (P) intermediate, hence the term P-type. Ion transporters are a very large and diverse family of membrane proteins, including ATP-binding cassette transporters, the Zip family of zinc transporters, the cation diffusion facilitator family, the copper transporters Ctr and COPT and iron-regulated transporters, which also actively transport various metal ions, as is apparent from their names.



Transmembrane proteins allow metal ions and complexes to cross cell membranes

PAUL BILTON, EDINBURGH, UK

'Metal ions are essential in many biological processes'

Receptors are also transmembrane proteins. Binding of signalling molecules to a receptor on one side of the membrane initiates a response on the other side. These proteins play important roles in cellular communication and signal transduction, the transfer of signals from outside to inside the cell. G-protein-coupled-receptors (GPCRs) with 7 transmembrane helices are bound to G-proteins on the inner side of the cell membrane. Over 800 genes are known to encode such proteins and members of this superfamily include receptors for many hormones, neurotransmitters, chemokines (small proteins involved in cell migration) and calcium ions, as well as sensory receptors for various odorants, bitter and sweet taste, and even photons. GPCRs are thought to be the protein targets in around 40% of all therapeutic interventions.

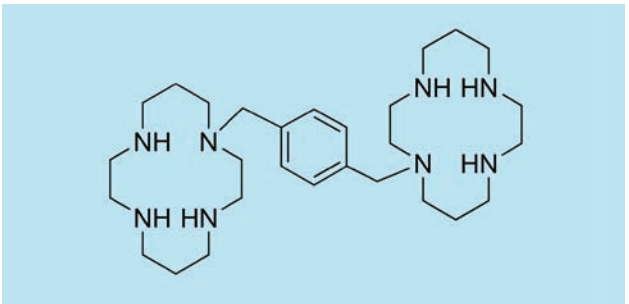
There is a variety of other enzymes in membranes, including receptor-like kinases and respiratory enzymes. Kinases are a class of enzymes that phosphorylate substrates by transferring phosphate onto them. Metal ions such as Mg^{2+} or Mn^{2+} are essential for the phosphorylation process. Receptor-like kinases play dual roles, acting as both receptors and kinases. Respiratory enzymes are mainly metalloproteins, containing metals such as iron and copper. In the inner membrane of cell mitochondria, electrons are passed along a series of respiratory enzyme complexes. These electrons are generated from NADH (reduced nicotinamide adenine dinucleotide), produced by oxidation of nutrients such as glucose, and are ultimately transferred to molecular oxygen. The passage of electrons between the complexes releases energy that is stored in the form of a proton gradient across the membrane and is then used by ATP synthase to make ATP from ADP and phosphate.

With their many roles in metal transport, cell signalling and energy release, membrane proteins can be drug targets. Membranes can also play important roles in the action of therapeutic and diagnostic metal complexes. For example, the thermodynamics and kinetics of metal reactions such as ligand substitution and redox reactions, are highly dependent on the medium. Reactions of metal complexes within membranes can differ significantly from those in media with higher dielectric constants, such as more aqueous extracellular fluids.

Targeting metals to membrane sites and controlling their reactivity in these sites therefore presents considerable challenges.

Metal ion affinity for ligands in a lipid environment can differ from that in aqueous media (extra- and intracellular environments). The thermodynamically-preferred binding sites for metal ions in membranes cannot easily be predicted given current knowledge of metal–ligand stabilities, since most have been determined for aqueous solutions only. Seemingly poor ligands could bind tightly to metal ions in protein cavities with low dielectric constants. Understanding the interactions of metals with transmembrane proteins will aid the design of more effective metallodrugs.

For example, the long-established use of organomercurials as diuretics has now been correlated with the compounds' ability to bind to aquaporins (water channels) and inhibit water transport through them. The new anti-leukaemia drug arsenic trioxide, which is largely the neutral molecule $As(OH)_3$ at physiological pH, enters cells through aquaglyceroporin, which facilitates transport of glycerol. High affinity copper transport proteins containing methionine-rich sequences have recently been associated with the uptake of the platinum drug cisplatin; Pt(II) is known to have a high affinity for the sulfur atom of methionine.



Binding to metal ions means antiviral drug AMD3100 shows higher affinity for its target

GPCRs have a negatively-charged electrostatic surface directed towards the cell membrane exterior and are strong potential targets for metal ions. The affinity of the antiviral drug AMD3100 for its target, the chemokine receptor CXCR4, is enhanced by binding to Cu(II), Ni(II) or Zn(II). In models, metal ions bound in the macrocyclic rings of AMD3100 can coordinate to specific aspartic and glutamic acid carboxylate groups in the extracellular loops of CXCR4 and amine groups in the macrocycles can form hydrogen bonds to CXCR4 side-chains. Also, hydrophobic interactions between the indole rings of tryptophan residues in CXCR4 and the carbon backbone of the bicyclam are possible. It should be possible to design new generations of metal complexes that will bind specifically to different GPCRs based on such interactions.

These examples provide a stimulus for further exploration of the chemistry of metal ions in membranes and offer promise for the discovery of drugs with novel modes of action.

Reference
X Liang, D J Campopiano and P J Sadler, *Chem. Soc. Rev.*, 2007, DOI: 10.1039/b617040b

Essential elements

Pioneering RSC work on RSS feeds

First came enhanced HTML in electronic journal articles in the first phase of Project Prospect – now further developments means RSC Publishing has become the first ever publisher to enhance RSS feeds with structured subject and compound information.

Journal RSS feeds from RSC Publishing were the first from a scientific publisher to include the graphical abstract. This latest innovation means that RSS feeds from RSC journals will also display ontology terms and compound details, including the 2D image. Users will be able to see at a glance whether the paper is relevant to their research. In addition, hidden coding within the RSS feed allows the metadata to be read by machine – another step towards the 'semantic web'.

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hyperlinked compound information within the HTML, links to terms from the IUPAC Gold Book, plus links from ontology terms to definitions and related papers. Enthusiastically received by authors and readers, feedback since launch has also resulted in improvements to the Toolbox from which these enhancements are available.

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To see for yourself, look out for the Project Prospect icon in RSC journal contents lists that identifies enhanced articles. So far, 500 articles have been published that feature these enhancements.

Find out more at: www.projectprospect.org

Article breaks new ground

Research from across four institutions, in two countries, and involving eight researchers published in *Molecular BioSystems* has become the first RSC Open Science paper. Authors from the UK and US collaborated on the work, which involved screening chemical compounds and monitoring changes in tissue during early skeletal development in zebrafish.

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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The RSC is continually aiming to provide both scientists in the lab and those working in industry with reliable and high-quality reference material. Three recently published titles focus on industry-related topics and make excellent reading:

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Freeze-Drying of Pharmaceuticals and Biopharmaceuticals (F Franks) – Describes the technology with particular emphasis on the properties of the material to be processed.

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