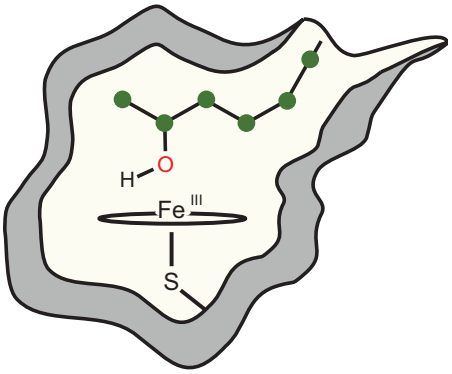
CYTOCHROME P450

Caught in the act

Science **330,** 933–937 (2010)



The cytochrome P450 family of enzymes are widespread in nature and involved in the bioactivation and metabolism of the majority of pharmaceuticals. They are of further interest to chemists because of their ability to hydroxylate C–H bonds, which remain stable and unreactive in lab-based organic chemistry. Although the highly reactive intermediate suggested to be responsible for these reactions, known as compound I, is thought to be an iron(IV)oxo species, it has so far proved elusive to full detection and characterization.

Now, Jonathan Rittle and Michael Green from Pennsylvania State University have been able to perform a spectroscopic and kinetic study on compound I as it hydroxylates a C–H bond in lauric acid. They were able to generate compound I in high yields from a very pure sample of the cytochrome P450 enzyme CYP119 from a thermophilic species *Sulfolobus acidocaldarius*. Rittle and Green were then able to study the elusive intermediate in action using a range of spectroscopic techniques, including Mössbauer spectroscopy, electron paramagnetic resonance and optical absorption. Mössbauer studies confirmed that compound I contains an iron(IV) oxo centre exchange-coupled to a radical porphyrin ligand.

The kinetic characterization revealed that the rate constant for the oxidation of lauric acid was 1.1×10^7 M^{-1} s^{-1}, which Rittle and Green call 'remarkably efficient'. A large kinetic isotope effect was measured, supportive of values and a suggested mechanism from previous studies.

MASS SPECTROSCOPY

Investigating intermediates

Angew. Chem. Int. Ed. **50,** 250–254 (2011)

Desorption electrospray ionization (DESI) used in conjunction with mass spectrometry has become an important technique for chemical analysis in ambient conditions. Mass spectrometry requires the analyte to be charged and this is achieved in DESI by aiming an electrically charged aqueous mist at an analyte deposited on a surface. This extracts the analyte from the surface, creating ionized droplets from which detectable gas-phase ions eventually form. Now Richard Zare and colleagues at Stanford University have used the short desorption and ionization timescales involved in DESI to detect transitory reaction intermediates[1].

To test the technique the researchers studied the synthesis of ruthenium catalysts, which are used for the asymmetric reduction of ketones through transfer hydrogenation. One such catalyst can be synthesized through the reaction of the diruthenium complex $[\{RuCl_2(p\text{-cymene})\}_2]$ with 1-amino-2-indanol. This reaction was examined by depositing the former on a surface and including the latter in the charged mist used to ionize the analyte. The reactions of three other amino alcohols — all ethyl benzene derivatives — were also studied. Significant mass spectra signals were observed that correspond to short-lived coordination species between the diruthenium complex and the two β-amino alcohols studied, but equivalent signals were not observed for those amino alcohols in which the amine and hydroxyl groups were further apart.

The researchers could not unambiguously determine the structures of the intermediates, but the spectra were enough to highlight the importance of the relative positions of the amine and hydroxyl groups to the reactivity of the amino alcohols and, more generally, the potential of the DESI technique for studying reaction intermediates.

WATER OXIDATION

Catalysis in a drought

J. Am. Chem. Soc. **132,** 17670–17673 (2010)

One thrust of research aimed at cleanly reducing the increasing gap between our energy needs and energy stores is to mimic the chemical processes of photosynthesis. The aim for artificial photosynthesis is to use sunlight and water to produce hydrogen and oxygen, and to do so, catalysts that efficiently 'split' water are needed. An initial step in this process is the oxidation of water and this is carried out in nature by a manganese–oxo cluster within photosystem II. This occurs in a hydrophobic environment with water as a limiting reagent, but previous experiments to mimic this process have been carried in aqueous solution, with water obviously in abundance.

Now, Thomas Meyer and colleagues at the University of North Carolina at Chapel Hill have studied the water oxidation reaction catalysed by a ruthenium complex in a non-aqueous environment — with water as a limiting reagent. The catalyst used was a ruthenium complex coordinated by both bipyridine and a tridentate ligand made up of two benzimidazol ligands covalently linked through pyridine.

From cyclic voltammograms of the catalyst in propylene carbonate — at varying concentrations of water — the team calculated a rate enhancement for water oxidation of a factor of about 300 relative to the same catalyst in aqueous solution at pH 1. The results from Meyer and colleagues also provide evidence for a different reaction pathway compared with that in aqueous solution, supporting a direct oxygen transfer to water to give a hydrogen peroxide intermediate, rather than oxygen attack alongside simultaneous proton transfer.

ALZHEIMER'S DISEASE

Binding screens

J. Am. Chem. Soc. **132,** 17015–17022 (2010)

The misfolding and aggregation behaviour of the amyloid-β (Aβ) protein — in particular the isoform Aβ42 — is known to be involved in Alzheimer's disease. Early, intermediate, aggregates are now thought to be the most toxic species to cells, rather than fully formed amyloid plaques, but their precise structure remains elusive, rendering the search for aggregation inhibitors difficult. Aggregation enhancers have therefore been suggested as potential alternative drugs, because they reduce the presence of these early intermediates by forming the plaques much more quickly. The lack of structural information has hindered traditional approaches either to design specific inhibitors or to screen molecules for their influence on the aggregation behaviour of Aβ.

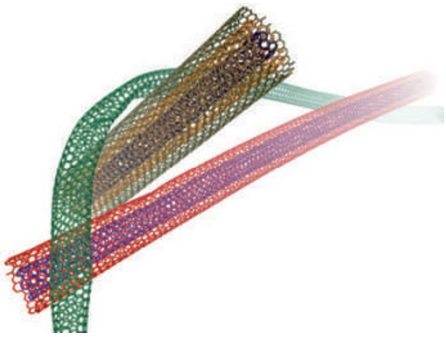
Now, Michael Hecht from Princeton University and co-workers have screened potential drugs based solely on their ability to bind to the Aβ peptide. A small-molecule microarray was prepared by attaching a wide variety of compounds to a glass slide through isocyanate groups. Each slide, which contained thousands of compounds, is probed with an Aβ monomer, fluorescently labelled so the species that bind to it can be detected by fluorescence.

Seventy-nine molecules were identified that bind to the Aβ peptide from this highly sensitive, high-throughput assay, and were subsequently tested for their ability to prevent Aβ42-induced killing of a cell line. Fifteen of these increased the survival of cells incubated with Aβ42 by more than 30%. Further investigations with one of these compounds suggested that it enhanced Aβ42 aggregation. This microarray method shows promise for the identification of therapeutic leads, regardless of their action mechanism.

CARBON NANOTUBES

At a stretch

Science **330,** 1364–1368 (2010)



Viscoelastic materials are both viscous (they can dissipate energy) and elastic (they can reversibly deform and reform). Their uses are widespread and range from biological tissues through to everyday objects such as mattresses, to high-performance materials such as vibration isolators. One drawback of many of these materials, however, is the limited temperature range of their optimal performance. Outside these temperatures, they are either brittle or they degrade.

Now, a team from the Japanese National Institute of Advanced Industrial Science and Technology led by Kenji Hata and Don Futaba have created a material from carbon nanotubes (CNTs) that is viscoeleastic between −196 °C and 1,000 °C. To create as many physical connections between CNTs as possible, they made randomly oriented, long and clean CNTs, which they then compressed. This quadrupled the density of the material, and scanning electron microscopy revealed a complex structure of interconnected CNTs. The stress–strain behaviour of the compressed material showed that it possessed viscoelastic properties, with stiffness and damping similar to silicone rubber — a known viscoelastic material with the previous best thermal stability.

Comparing the two materials over a large temperature range, however, showed that the silicone rubber degraded at 200 °C, whereas the CNT material's properties did not change at all up to 600 °C. Similarly, the silicone material hardens at −55 °C, but the CNTs maintain their properties down to −140 °C. Repeated stress–strain experiments (even up to one million times) showed that the material has excellent fatigue resistance — Hata, Futaba and colleagues suggest that it dissipates energy through the zipping and unzipping of the tubes at points where two are in contact.

ENANTIOMER SEPARATION

Selective soap films

J. Am. Chem. Soc. **132,** 18045–18047 (2010)

Enantiomer separation is big business — worldwide sales of single-enantiomer drugs, for example, reached $147 billion in the year 2001 and enantiomer separation has been used both to obtain enantiopure starting materials and to separate racemic mixtures of the final product. Now, Purnendu Dasgupta from the University of Texas at Arlington and co-workers from Chiang Mai University in Thailand have introduced a new enantiomer-separation method — selective permeation through a chirally doped soap film.

Soap films are ultrathin liquid membranes formed by surfactant molecules, and consist of two layers separated by a solution of micelles. They are known to be gas-permeable, and can dissolve a wide range of substances. Dasgupta and co-workers created soap films doped with α-cyclodextrin — a cyclic oligosaccharide widely used in chiral separations — and then showed that one enantiomer of gaseous α-pinene (a chiral bicyclic hydrocarbon) passed through the film faster than the other, leading to its enrichment. Interestingly, it is the (+)-enantiomer that is enriched despite it being the one that binds most weakly to α-cyclodextrin, showing that, in fact, such binding slows down the permeation of the membrane.

As yet, the selectivity of the enrichment is small: (+)-α-pinene permeates the membrane about 1.6 times faster than the (−)-enantiomer. The demonstration, however, that a stable film containing a chiral dopant can be formed is an important first step, and the enrichment factor corresponds well to the difference in binding constant of the two enantiomers of α-pinene to the chiral dopant. Ultimately, complete chiral separations could be achieved by the use of multiple membranes.

The definitive versions of these Research Highlights first appeared on the *Nature Chemistry* website, along with other articles that will not appear in print. If citing these articles, please refer to the original web version.

blogroll

Taking the P

An arsenic-loving bacterium sent the blogosphere into overdrive.

It started quietly enough. NASA announced a press conference "to discuss an astrobiology finding that will impact the search for evidence of extraterrestrial life" to be published in *Science*. Some people put two and two together but didn't get four: Jason Kottke, for example, suggested that NASA had "discovered arsenic on Titan and maybe even detected chemical evidence of bacteria utilizing it for photosynthesis" (http://go.nature.com/7gdq6m). When the paper came out you could almost feel the hype deflating, but plenty of people still found the 'Bacterium that can grow by using arsenic instead of phosphorus' interesting (http://go.nature.com/fjHeOg).

The press coverage was intense, but people were reading the paper carefully and critically. To take just one prominent example, blogging (micro)biologist Rosie Redfield concluded on RRResearch "Lots of flim-flam, but very little reliable information" (http://go.nature.com/DDeSJW). As the blogosphere's reaction continued, science writer Carl Zimmer contacted 13 experts, all of whom gave the paper a thumbs-down in an article for Slate (http://www.slate.com/id/2276919/).

Responding to the comments, the paper's first author, Felisa Wolfe-Simon, issued a statement that the authors "welcome lively debate" but that they "invite others to read the paper and submit any responses to *Science* for review so that we can officially respond" (http://www.ironlisa.com/gfaj/). Indeed, the backlash against the backlash was supported by Dr Isis, who forthrightly told those critical of the work to "Put your experiment where your mouth is! [...] The language of those discussions needs to be data" (http://go.nature.com/r6TDCn). The episode caused many blogs to question the roles of peer-review, press conferences and blogging — too many to list.

And finally...if you're worried about the future of peer-review after this, why not read some of *Environmental Biology*'s funniest reviewers' quotes (http://go.nature.com/mvwwCY).