

Kevin Burgess
Texas A&M University, US

Biomedical

Cell permeable peptides

Two nicely complementary studies on cell-permeable peptides have been published by Giralt *et al* (*J. Am. Chem. Soc.*, 2015, 137, 7357), and by Kessler and co-workers (*Chem. Eur. J.* doi:chem.201501600).

Giralt and co-workers had previously studied (N-MePhe)₄ as a carrier to attach to molecules and ferry them across the blood brain barrier (BBB), and identified the (N-MePhe)₄ molecule (1) as a promising carrier. In their latest work, they made more rigid analogs of this system based on the (PhePro)₄ system (2). Using the PAMPA assay, based on synthetic membrane coated with a lipid mixture, they found the (PhePro)₄ systems to be more efficient by a factor of 7 with a relevant cargo.

Perhaps more surprising is the fact that stereoisomers of the (PhePro)₄ system showed different rates of permeation. They explain this observation in terms of corresponding stereochemical features in the way the lipid membranes pack on the membrane surface. The cargoes studied are physiologically relevant: L-DOPA, which has limited BBB permeability, and is used for treatment of Parkinson's, and nipecotic acid, which has considerable potential for treatment of neurological conditions, but has little tendency to cross the BBB.

Kessler and co-workers made a complete series of cyclic pentapeptides (5) that were systematically N-methylated, except that the permethylated peptide could not be obtained. Significantly, they studied these peptides in both the PAMPA assay, and a natural Caco-2 cell barrier.

In contrast to the research above, none of their peptides were significantly permeable in the PAMPA assay. Permeation through Caco-2 cells did not correlate with conformational homogeneity of the

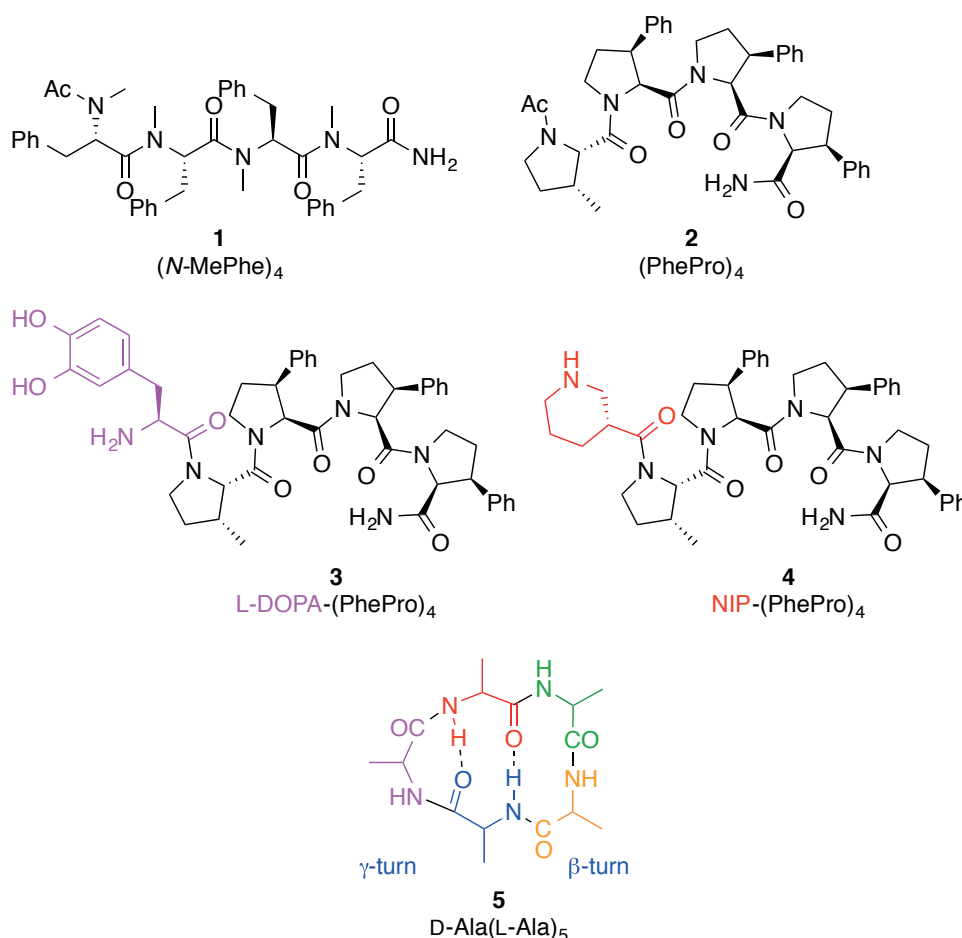
peptides or extent of methylation. However, they noticed that there did seem to be a correlation between permeability and *cis*-amide bonds in the structures. Therefore, they suggested that transport of compounds (5) could be carrier mediated.

Together the Giralt and Kessler work highlights how little is really understood regarding the vital processes of permeation through the BBB. However, it does highlight the fact that the generic model of membranes consisting of lipid bilayers with neatly aligned linear hydrocarbon chains is clearly inadequate. Stereochemically defined branching in lipids probably neither

random nor accidental, and lipids probably self assemble into preferred secondary and tertiary structures that favor and deter certain passive diffusion processes. We do not consider these structures often because they are not easily identified by NMR, but that is a little bit like hiding under the sheets and hoping the monster will go away.

Selective imaging of MAO-B in live cells

Yao, in a collaboration involving his group in Singapore, and others in China and Korea, have been selectively mating FDA-approved drugs for Parkinson's disease: selegiline and rasagiline (*Angew.*



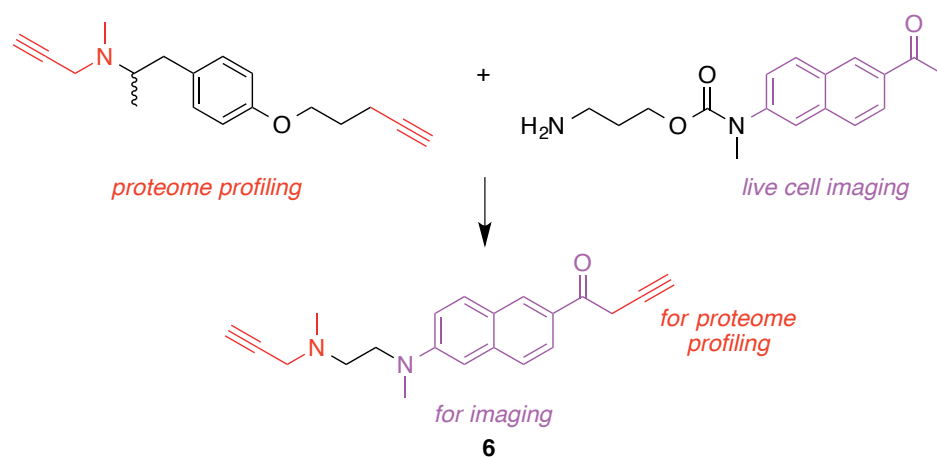
Chem. Int. Ed., 2015, 54, 10821). Both these substances bind monoamine oxidases (MAOs), but neither is selective for the -A or -B isoforms, and neither is fluorescent.

After one generation (published previously) they arrived at the second compound (**6**), shown on right. Probe (**6**) fortuitously has considerable selectivity for MAO-B. This group used this probe to follow MAO-B expression levels in a variety of living cells via blotting and confocal microscopy.

This work sets the foundation for correlating prognosis and progression of Parkinson's disease with levels of expression of MAO-A and -B enzymes.

Analysis of helical tertiary structures in protein-protein interactions (PPI)

Arora has analysed the occurrence of three different tertiary structure motifs that feature helices at PPI



interfaces: (i) helix dimers; (ii) coiled-coils within one protein interacting with one or more other proteins; and, (iii) coiled coil where the constituent helices are donated by more than one protein (*J. Am. Chem. Soc.*, doi: jacs.5b5527).

Having divided the library of these tertiary structures into these

three classes, it simplifies the process of analysing differences. Thus they looked at amino acid composition, and rationalised how this varies overall, and analysed for hot-spots at the surface residues. This work may assist studies involving stapled helical mimics to perturb biological interactions.

Arno Kraft
Heriot-Watt University, Edinburgh, UK

Advanced materials

Magnetic stirring bars from nanoparticles

Effective mixing is essential for fast mass transport in chemical reactions and in ensuring an acceptable reaction rate.

Most chemists favour magnetic stirring for mixing volumes in the range of a few mL to about 1000mL, or more powerful mechanical stirrers for larger volumes. Stirring smaller volumes can be much more of a challenge.

Microdroplets on a microtiter plate or in micelles, or liquids inside microfluidic devices are just too small for most conventional stirring methods as the size of any commercial magnetic stirrer bar would be out of proportion to the volume to be stirred.

C. Cao, W. Song and co-workers came up with the idea of making a miniaturised version of a magnetic stirrer bar from nanoparticles (*Angew. Chem. Int. Ed.*, 2015, 54, 2661).

The authors started off by synthesising Fe₃O₄ magnetic nanoparticles with uniform diameters of about 250nm. The nanoparticle clusters were first broken up by ultrasound, then coated *in situ* with a polymer which acted as an adhesive and prevented further aggregation. This procedure created oblong chains of Fe₃O₄ spheres (Figure 1).

The polymer coating had two other benefits. It inhibited corrosion of the iron oxide when exposed to acidic conditions, and it provided an anchor for fixing Pd nanoparticles onto the surface of the nanochains. The resulting iron oxide-polymer-Pd nanochains could serve as small-scale magnetic stirring bars that also provided catalytically active sites for the hydrogenation of styrene and other alkenes.

The iron oxide-polymer-Pd nanochains turned out to be as efficient as a conventional Pd/C hydrogenation catalyst. Hydrogenation of styrene was

fast and took just 1-2min at room temperature. Unlike Pd on charcoal, which can only be dispersed in solution and often needs centrifugation to be recovered, the iron oxide-polymer-Pd nanochains were readily separated from the reaction mixture with the help of a magnet. The nanochains were equally successful for the hydrogenation of methylene blue in microdroplets where their performance even exceeded that of Pd/C.

Recyclable cross-linked rubber

Both natural and synthetic rubber are made elastic by a process called vulcanisation, which involves the treatment of the rubber precursor, typically an amorphous high-molecular-weight polymer containing lots of residual double bonds, with sulfur.

The result is a slightly cross-linked amorphous material, which is rubber-elastic above its glass

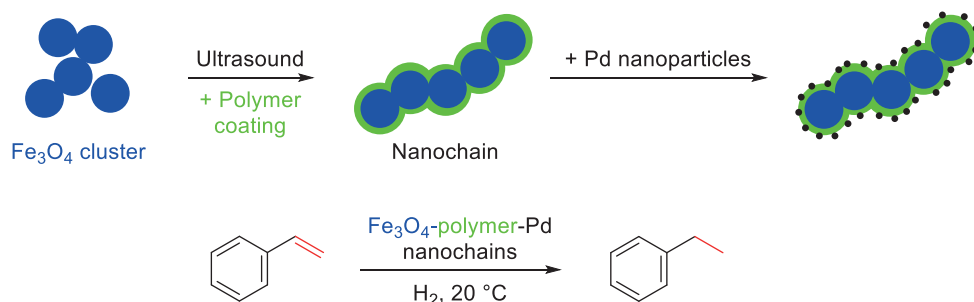


Figure 1 Preparation of iron oxide-polymer-Pd nanochains for the catalytic hydrogenation of styrene

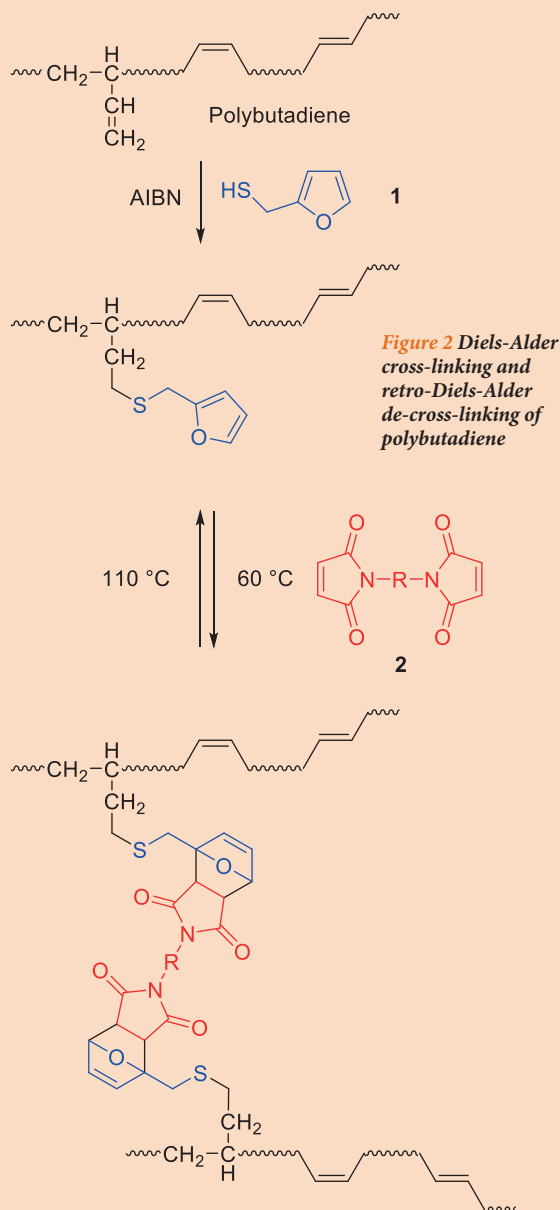


Figure 2 Diels-Alder cross-linking and retro-Diels-Alder de-cross-linking of polybutadiene

transition, usually well below room temperature.

Rubber tyres contain about 50% of cross-linked rubber, the remainder consisting of carbon black filler, steel mesh, stabilisers, activators and left-over reagents from the vulcanisation.

The complexity of the mixture makes recycling of used rubber tyres extremely challenging. Since vulcanised rubber is a cross-linked polymer, it can no longer be reshaped, re-moulded or easily recycled.

A. Gandini and co-workers have considered introducing thermally reversible crosslinks as the means of making rubber recyclable (*Adv. Mater.*, 2015, 27, 2242).

The authors first reacted a commercial polybutadiene with furfuryl thiol (1) in the presence of a radical initiator (Figure 2). Under these conditions, any radicals formed along the polymer chain reacted with thiol (1).

In a second step, the dangling furan groups then underwent a Diels-Alder reaction with a bis-maleimide crosslinker (2) at 60°C, which resulted in a gelled material within several hours.

The network structure is crucial for obtaining rubber elasticity. Dynamic mechanical analysis provided evidence for a glass transition at -80°C and an extended rubbery plateau between -60°C and +100°C. At temperatures above 100°C, a retro-Diels-Alder reaction led to de-cross-linking of the polymer network.

The overall idea of a recyclable rubber by introducing reversible cross-links is relatively simple; however, more testing will be needed to decide whether or not the material properties are good enough for technical applications.

Atom-thick semiconducting films

The manufacture of modern computer chips demands ever smaller integrated circuits. The ultimate goal will be to make high-performance transistors, diodes and photodetectors that are only one atomic layer thick. Graphene is the paradigm case of such a monolayer semiconducting material. Its only drawback is that the graphene sheets cannot be grown on a substrate but need to be manually transferred.

Two recent papers have looked at alternatives to graphene. Silicene is a silicon analogue of graphene and can be made by epitaxial growth on Ag(111) thin films on a mica substrate (L. Tao *et al.*, *Nat. Nanotech.*, 2015, 10, 227).

Silver helps to stabilise silicene, as well as act as a contact electrode. The metal is also readily etched away using an iodine/iodide solution that does not damage the silicene. Considering that silicon is the semiconductor par excellence, silicene's carrier mobilities for holes and electrons is somewhat disappointing and of the order of only 100cm²/Vs, which makes them noticeably lower than those of graphene. Since silicon prefers a three-dimensional diamond lattice, it is not surprising that the two-dimensional silicene is unstable in air and has a tendency to buckle, making it much more difficult to handle.

Certain transition metal dichalcogenides, such as MoS₂ and WS₂, also remain semiconducting down to an atomically thin level (K. Kang *et al.*, *Nature*, 2015, 520, 656). The authors managed to grow 3-atom-layer thin films of these semiconducting materials on silicon dioxide over a 4-inch wafer scale by a technique called metal-organic chemical vapour deposition, which uses metal carbonyls, diethyl sulfide and hydrogen, together with argon as carrier gas (Figure 3). Films could be patterned by standard photolithography and an oxygen plasma. A low partial pressure of the metal carbonyl was crucial to ensure the growth of a uniform monolayer over a large area.

The structural continuity of the films was confirmed by transmission electron microscopy and X-ray

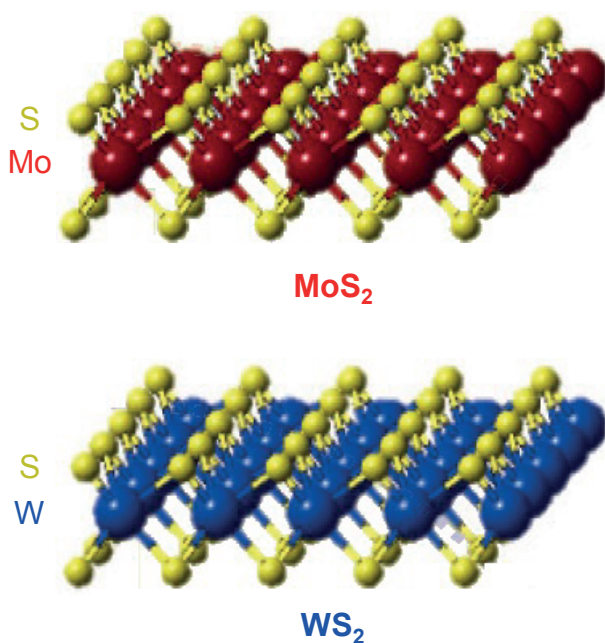


Figure 3 Structure of 3-atom-thick molybdenum and tungsten disulfide

photoelectron spectroscopy. Electron mobilities were around 30 cm²/Vs at room temperature. The authors managed to make a series of field-effect transistors with a device yield of 99%, on different substrates, eg aluminium oxide, SiN, and even to

stack them vertically.

Although there is still a long way to go, the two papers illustrate some of the potential of atomically thin integrated circuits.

Ultralow-fatigue NiTiCu shape-memory alloy films

Shape-memory alloys, such as nickel-titanium (NiTi), have found extensive use as actuators in miniaturised electromechanical devices that can be stimulated by an electrical current which produces enough heat to trigger the thermal shape-memory transition. The materials rely on a reversible solid-state transformation from a metastable crystalline austenite to the thermodynamically more stable martensite phase. The phase transition is accompanied by a hysteresis, which finds use in small solid-state refrigerators. Superelasticity is another prominent property of shape-memory materials.

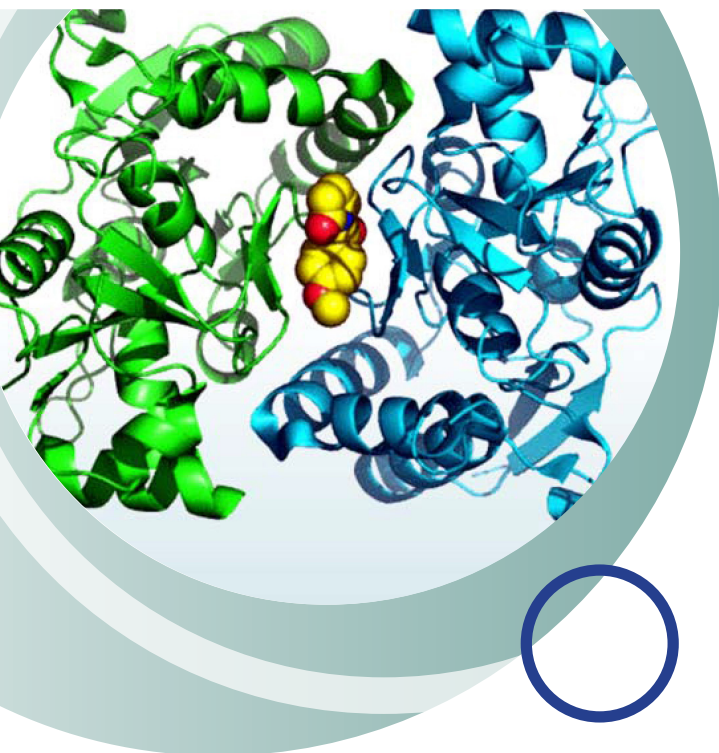
The NiTi alloy further features in biomedical applications, most notably stents that are initially compressed but expand upon warming to body temperature when a surgeon inserts

them into an artery of a patient.

Most shape-memory alloys, especially the binary NiTi, suffer from fatigue when cycled repeatedly, which can culminate in a change in transformation temperature, a reduction of the superelastic plateau and the build-up of residual martensite phase.

A recent paper has demonstrated that replacing part of the Ni positions with Cu generates an ultralow-fatigue shape-memory material (C. Chluba *et al.*, *Science*, 2015, **348**, 1004).

A particular Ti-rich alloy was estimated to be virtually fatigue-free for at least 10⁷ transformation cycles based on accelerated fatigue tests. Films of the new material were obtained by magnetron-sputtering. Further structural investigations revealed the presence of Ti₂Cu precipitates, which seemed to be responsible for the improved reversibility of the stress-strain curves of the material. The findings open up the possibility that other shape-memory alloys, such as TiNiAg, might exhibit a similar boost in performance characteristics.



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