that is too short or too rigid will restrict coordination, forcing one ligand to wrap around only one of the metal centres and the remaining two to fold around the two metal ions in a double-helical structure (instead of a triple-helical one). Incorporating a rigid stereocentre within a ligand’s bridge can lead to enantiopure helicates.

The challenges in isolating stereochemically pure complexes, and in tuning them without disturbing their structure, mean that although chiral assemblies of multidentate organic ligands have been previously reported, their applications in biological systems have remained limited. Scott and colleagues have now circumvented the issue by adopting a different approach: preparing monometallic complexes from optically pure ligands, and connecting them together through linkers (Fig. 1b). An optically pure diamine in which the two amino groups (red in Fig. 1b) are connected through a diether linker (blue) is first prepared, then reacted with a pyridine-carbox-aldehyde end-group (green) and the metal centres. The compounds obtained are optically pure, non-racemizing triple-stranded helices. In this approach, the stereochemistries of the two metal centres (both shown in Δ conformation in Fig. 1) are pre-determined independently through ligand design, rather than coupled to each other during the assembly process with a rigid linker. This represents a very different chirality induction process that introduces a greater flexibility in the design of the metallo-helical compounds, where various types of end groups and bridges can be used — not just rigid ones. Several analogues were prepared, with different functional groups and either zinc or iron (one of the least toxic metals) as metal centres in a variety of stereochemistries.

Scott and colleagues refer to the resulting compounds as ‘flexicates’, a term that reflects their resemblance to helicates as well as the differences in their preparation. These flexicates offer a simplicity and an elegance of design that should be a source of inspiration for future studies. One advantage is that they can be constructed from fairly benign components such as benzylcic alcohols, phenylglycinol and picolinaldehydes. One of the bridging units that was used is related to pentamidine, an antimicrobial medication given for the treatment of pneumocystis, a form of pneumonia. Furthermore, these molecules may be easily tuned to explore structure–function relationships that are crucial in biological applications. This is in stark contrast to the largely aromatic amines used so far, which were necessary to ensure the rigidity required to construct previously reported helicates — for example, 4,4’-methyleneedianiline, a common building block, is known to be a carcinogen.

The researchers observed that π-stacking interactions (visible in Fig. 1c) occurred between the ligands, contributing to the diastereoselectivity of the assembly process. Furthermore, this interaction is hydrophobic and also imparts the complexes with unusually good stability in water.

The flexicates are particularly suited to studies in biological media and for in vivo pharmacokinetics and transport. They are soluble and stable in aqueous media, readily available on a practical scale, and synthetically flexible so that their properties can be tuned or optimized. Indeed, Scott and colleagues demonstrate binding with DNA through investigations using linear dichroism. In particular, the iron-based flexicate complex with both iron centres in the Δ conformation (ΔFe, ΔFe) shows a significant interaction with DNA, consistent with a binding in an orientation that suggests that the complexes target the grooves (Fig. 1c). Furthermore, this complex also shows good antibiotic activity against Gram-positive but also, unusually, Gram-negative bacterial strains (methicillin-resistant Staphylococcus aureus (MRSA) and Escherichia coli, respectively) as well as low toxicity to Caenorhabditis elegans (typically used as a model organism in toxicity studies). All these attributes suggest that flexicates have the potential to develop into a family of cost-effective antibiotics.

Although these possible applications are promising, they depend on further developments. Yet this study on flexicates already offers a practical outcome: a straightforward approach to producing optically pure metallo-helical complexes. This should facilitate research in various areas that involve helical compounds, so widespread in biological systems yet so challenging to access synthetically.

Janice R. Aldrich-Wright is in the Nanoscale Organisation and Dynamics Group, School of Science and Health, University of Western Sydney, Penrith, New South Wales 2751, Australia. e-mail: j.aldrich-wright@uws.edu.au

References

BIOMIMETIC CHEMISTRY

Merging the old with the new

The classic organometallic compound ferrocene has been combined with a unique diiron unit in the latest synthetic analogue of an enzyme active site, achieving the three functionalities needed for a working model of diiron hydrogenase, itself of ancient origin.

Marcetta Y. Daresbourg and Ryan D. Bethel

In the past 15 years, as protein crystallographers, spectroscopists and biochemists reached consensus on the structure of the active site of a hydrogen-producing metalloenzyme, the diiron ([FeFe]-) hydrogenase, a new coterie of chemists, synthetic organometallic chemists in fact, have been drawn into the realm of natural product synthesis. They have addressed the active sites of three known hydrogenases, widely distributed in nature, and particularly important in microorganisms of ancient origin when hydrogen was the energy vector on an oxygen-deficient earth. Two of them, the [NiFe]- and [FeFe]-hydrogenases, reversibly mediate the anaerobic oxidation of H2 to protons and electrons (H2 ↔ 2H+ + 2e−), a
hydrogenases, the [NiFe]- and the [FeFe]-hydrogenase, contain several 4Fe4S clusters, positioned to conduct electrons in and out of the active sites according to the direction of their hydrogen processing. One of these in the [FeFe]-hydrogenase is a 4Fe4S cluster ‘hard-wired’ to the 2Fe active site, suggesting an additional role, perhaps to delocalize various redox levels.

The challenge of connecting a synthetic 4Fe4S cluster to the simple 2Fe parent complex (Fig. 1b) has been met by Pickett and colleagues, utilizing Holm’s approach of encapsulating three irons of the cubane by a supramolecular trithiolate, connecting the fourth iron to the diron carbonyl by a simple thiolate bridge. Although a heroic synthetic endeavour, the functional aspect of the 2Fe subsite was not further developed, presumably because of the fragility of the construct.

In Rauchfuss and Camara’s assembly (Fig. 1c) the redox activity or redox-buffering effect of the 4Fe4S cluster is mimicked by a ferrocenyl derivative, well-known to be redox-tunable and, when attached to the phosphorus that binds to iron, producing a redox-active ligand stable in two oxidation states, Fe

Yet another critical design element matched by Rauchfuss and Camara’s complex is the inverted square pyramidal structure of the distal iron, with the available site as represented by the dashed circle in Fig. 1c. The geometry of a functional diron model compound should include a kinetically feasible H

The natural [FeFe]-hydrogenase electrocatalyst differs from all other known enzyme active sites in that its components are reminiscent of fundamentally simple paradigms of organoiron chemistry: carbon monoxide and cyanide as ligands, a latent Fe–Fe bond, and a bridging dithiolate (Fig. 1a). The simplest of organoiron complexes, (μ-S(CH)

myriad modifications have provided a steady advance towards a structural, spectroscopic and functional model of the two-iron subsite of the overall 6Fe hydrogen-producing cluster (Fig. 1a). The latest in this effort is shown in Fig. 1c, an assembly reported by Rauchfuss and Camara in Nature Chemistry that gives a high-fidelity model of the [FeFe]-hydrogenase active site that makes simultaneous use of functionalities dedicated to binding, atom management and redox management.

Requirements for matching enzyme active site and model are detailed by the coloured arrows that link natural and synthetic components in Fig. 1. In green is the diphosphine ligand that mimics the electron enrichment by the cyanide ligands, necessary to stabilize the oxidized form of the diron unit. Blue denotes the built-in pendant base installed on the dithiolate sulfur-to-sulfur bridgehead, and positioned to facilitate proton shuttling to and from the available site on the pentacoordinate distal iron (the iron furthest from the 4Fe4S cluster in the enzyme). This design feature of nature has proved effective in the nickel catalysts of DuBois and colleagues, wherein such a proton relay built into a diphosphine ligand provides electrocatalysis of hydrogen production at rates and conditions rivalling the [FeFe]-hydrogenase.

The red component shown in Fig. 1c is the newest feature in a working model of the [FeFe]-hydrogenase. Both redox-active
Relieving PEGylation

A new type of protein–polymer conjugate provides improved stability without detrimentally affecting bioactivity, and thus offers great potential for the development of new peptide-based drugs.

Matthew C. Parrott and Joseph M. DeSimone

Currently, there are over 130 protein- or peptide-based therapeutics approved for clinical use. Insulin is probably the most well-known protein therapeutic — it is currently used by 171 million people worldwide for glucose regulation. Protein therapeutics cause little or no immune response. Furthermore, they exhibit high disease specificity, and are usually effective at producing a positive outcome for most patients. With such a positive combination of desirable properties the recent increase in the popularity of protein- and peptide-based therapeutics is easily understood. These advantages can be attributed to a structure built from commonly occurring biological molecules that are well tolerated by the body, and its ability to perform specific functions without interfering with normal biological processes. Consequently, protein therapeutics has tremendous potential to manage and cure a number of complicated diseases.

Hindering the rapid progression of this field are the inherent sensitivities associated with proteins, including: thermal instability, rapid excretion from the body, degradation by proteolysis, and low solubility. A common method used to evade these limitations is the covalent attachment of poly(ethylene glycol) (PEG) to the protein — a technique known as PEGylation. PEG is widely known as an amphiphilic polymer (that is, having both hydrophilic and hydrophobic parts) that can improve water solubility, and increase native protein stability while simultaneously decreasing non-specific protein adsorption. This extends a protein’s circulation time in the body, and the added steric bulk minimizes protein–protein interactions, which reduces the possibility of degradation. The practice of PEGylation is generally regarded as the standard approach used to enhance protein properties, and is the basis for many approved peptide-based therapeutics. A new type of protein–polymer conjugate provides improved stability without detrimentally affecting bioactivity, and thus offers great potential for the development of new peptide-based drugs.

Marcetta Y. Darenbourg and Ryan D. Bethel are in the Department of Chemistry, Texas A&M University, College Station, Texas 77843, USA. e-mail: marcetta@chem.tamu.edu; rbethel@mail.chem.tamu.edu

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