

nature chemistry

JANUARY 2012 VOL 4 NO 1
www.nature.com/naturechemistry

NANOPARTICLE ASSEMBLY

Opening the toolbox

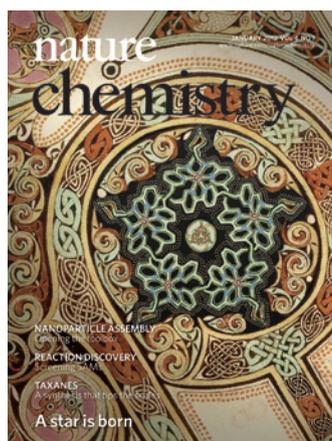
REACTION DISCOVERY

Screening SAMs

TAXANES

A synthesis that tips the scales

A star is born



COVER IMAGE

The cover image features the interlaced 'rho' character from Matthew 1:18 in the Lindisfarne Gospels as a backdrop for the X-ray crystal structure of the most complex non-DNA molecular knot synthesized so far. A team led by David Leigh prepared the 160-atom-long pentafoil knot in a one-step reaction from ten organic building blocks and five iron(II) cations. They use a single chloride anion as a template, which, in the solid-state structure, is located at the centre of the pentafoil knot and exhibits ten $\text{CH}\cdots\text{Cl}^-$ hydrogen bonds. Article p15; News & Views p7

IMAGE: JIM CALLAGHAN (EVOLUTION DESIGN)
BASED ON AN IMAGE ©THE BRITISH LIBRARY
BOARD, (COTTON NERO D. IV, F.29)

COVER DESIGN: ALEX WING



nature publishing group

Nature Chemistry (ISSN 1755-4330) is published monthly by Nature Publishing Group (Porters South, 4 Crinan Street, London N1 9XW, UK). Editorial Office: Porters South, 4 Crinan Street, London N1 9XW, UK. Telephone: +44 (0)20 7833 4000. Fax: +44 (0)20 7843 4563. Email: nchem@nature.com. North American Advertising: Nature Chemistry 75 Varick Street, Fl 9, New York, NY, 10013-1917, US. Telephone: +1(212) 726-9200. Fax: +1(212) 696-9006. European Advertising: Nature Chemistry Porters South, 4 Crinan Street, London N1 9XW, UK. Telephone: +44 (0)20 7833 4000. Fax: +44 (0)20 7843 4749. New subscriptions/renewals/changes of address/back issues and all other customer service questions should be addressed to - North America: Nature Chemistry Subscription Dept, PO Box 5054, Brentwood, TN 37024-5054, USA. Outside North America: Subscriptions Department, Brunel Road, Basingstoke, Hants. RG21 6XS, UK. Telephone: +44 (0)1256 329242; Fax: +44 (0)1256 812358. Annual subscription rates: US/Canada US\$3520, Canada add 5% GST (institutional/corporate), US\$99, Canada add 5% GST (individual making personal payment); UK/Rest of World (excluding Europe and Japan) £1806 (institutional/corporate), £51 (individual making personal payment); Europe €2795 (institutional/corporate), €79 (individual making personal payment). Japan: contact Nature Asia-Pacific, Chiyoda Building, 2-37 Ichigayatamachi, Shinjuku-Ku, Tokyo, 162-0843, Japan. Telephone +81 3 3267 8751. For single back issue prices contact the publisher. Nature Chemistry (ISSN 1755-4330) is published monthly by Nature Publishing Group, c/o Mercury Airfreight International Ltd, 365 Blair Road, Avenel, NJ 07001, USA. Periodicals postage is paid at Rahway NJ. Postmaster: send address changes to Nature Chemistry, c/o Mercury Airfreight International, 365 Blair Road, Avenel, NJ, USA. Reprints: Nature Chemistry Reprints Department, Porters South, 4 Crinan Street, London N1 9XW, UK. Subscription information is available at the Nature Chemistry homepage at <http://www.nature.com/naturechemistry>. Postmaster: send address changes to Nature Chemistry Subscriptions Department, Brunel Road, Basingstoke, Hants. RG21 6XS, UK or Nature Chemistry Subscriptions Department PO Box 5054, Brentwood, TN 37024-5054, USA. © 2012 Macmillan Publishers Limited. All rights reserved.

A synthetic molecular pentafoil knot

Jean-François Ayme¹, Jonathon E. Beves¹, David A. Leigh^{1*}, Roy T. McBurney¹, Kari Rissanen² and David Schultz¹

Knots are being discovered with increasing frequency in both biological and synthetic macromolecules and have been fundamental topological targets for chemical synthesis for the past two decades. Here, we report on the synthesis of the most complex non-DNA molecular knot prepared to date: the self-assembly of five bis-aldehyde and five bis-amine building blocks about five metal cations and one chloride anion to form a 160-atom-loop molecular pentafoil knot (five crossing points). The structure and topology of the knot is established by NMR spectroscopy, mass spectrometry and X-ray crystallography, revealing a symmetrical closed-loop double helicate with the chloride anion held at the centre of the pentafoil knot by ten CH...Cl hydrogen bonds. The one-pot self-assembly reaction features an exceptional number of different design elements—some well precedented and others less well known within the context of directing the formation of (supra)molecular species. We anticipate that the strategies and tactics used here can be applied to the rational synthesis of other higher-order interlocked molecular architectures.

Knots are important structural features in DNA¹, are found in some proteins^{2–5} and are thought to play a significant role in the physical properties of both natural and synthetic polymers^{6,7}. Although billions of prime knots are known to mathematicians⁸, to date the only ones to have succumbed to chemical synthesis using building blocks other than DNA are the topologically trivial unknot (that is, a simple closed loop without any crossing points) and the next simplest knot (featuring three crossing points), the trefoil knot^{9,10}. A pentafoil knot—also known as a cinquefoil knot or Solomon's seal knot (the 5₁ knot in Alexander–Briggs notation¹¹)—is a torus knot¹² with five crossing points, is inherently chiral, and is the fourth prime knot (following the unknot, trefoil knot and figure-of-eight knot) in terms of number of crossing points and complexity^{8,11,12}.

Sauvage reported the first molecular knot synthesis¹³, using a linear metal helicate¹⁴ to generate the three crossing points required for a trefoil knot. Although other syntheses of trefoil knots have been reported^{15–22} (as have composites of trefoil knots²³ and other molecular topologies such as catenanes^{24–28} and Borromean links²⁹), higher-order molecular knots remain elusive. Here, we report on the synthesis of a molecular pentafoil knot that combines the use of metal helicates to create crossover points³⁰, anion template assembly to form a cyclic array of the correct size^{31–33}, and the joining of the metal complexes by reversible imine bond formation^{34–37} aided by the gauche effect³⁸ to make the continuous 160-atom-long covalent backbone of the most complex non-DNA molecular knot prepared to date.

So far, attempts to make molecular knots with more than three crossing points by extending the linear helicate strategy of Sauvage to ligands with more coordination sites have proved unsuccessful³⁰, probably because joining the ends of each strand with the required connectivity becomes increasingly difficult as helicate length increases. An alternative way to use helicates (which generate the necessary crossing points) to make higher-order topologies could be to use cyclic structures or grids, where there is no requirement for there to be long distances between the ends of the strands that are to be connected. To generate the five crossing points required for a pentafoil knot, we modified a motif for generating

cyclic metal helicates discovered by Lehn in the mid-1990s^{31–33}. Lehn found that double-stranded circular helicates of various sizes could be obtained using Fe(II) or Ni(II) ions with tris(bipyridine) ligands with very short inter-bipyridine spacers that destabilized the normally preferred three-metal-ion linear triple helicate. The presence of chloride ions in the reaction mixture led to the selective formation of the five-metal-ion cyclic double helicate. To have the potential to covalently connect the organic ligands to form a knot, we envisioned replacing two of the three bipyridine groups in Lehn's original building blocks with formylpyridine groups, then use their reversible reaction with amines to form imines and generate tris(bidentate) ligand strands. A decade ago we introduced reversible metal–imine bond coordination as an effective means of assembling mechanically interlocked molecules under thermodynamic control^{34,35}. This provides a mechanism for correcting 'mistakes' in connectivity that occur during the covalent-capture step of mechanical bond formation and has been widely adopted for this purpose ever since^{10,29,36,37}.

The reaction conditions (ethylene glycol, 170 °C)^{31–33} used to form cyclic helicates with tris(bipyridine) ligands are not compatible with imine bond formation. Because the product distribution between cyclic double helicate, linear triple helicate and polymer is a delicate thermodynamic balance that could change significantly depending on the structure of the building blocks, reaction conditions, solvent and the nature and stoichiometry of the metal and anions, we first investigated whether it was possible to translate the self-assembly chemistry of the tris(bipyridine) ligands to an imine system.

Results and discussion

Treatment of bis-aldehyde **1** with 1-aminohexane **2a** in the presence of FeCl₂ in *d*₆-dimethylsulfoxide (CD₃SOCD₃, Fig. 1) afforded a purple solution with an initially complex ¹H NMR spectrum (see Supplementary Information), indicative of the presence of a range of different monomeric, oligomeric and polymeric species. However, on heating at 60 °C, the ¹H NMR spectrum of the reaction mixture gradually simplified until, after 24 h, only a single, highly symmetrical species appeared to be present in solution. The

¹School of Chemistry, University of Edinburgh, The King's Buildings, West Mains Road, Edinburgh EH9 3JJ, UK, ²Department of Chemistry, Nanoscience Center, University of Jyväskylä, P.O. Box 35, 40014 JYU, Finland. *e-mail: david.leigh@ed.ac.uk

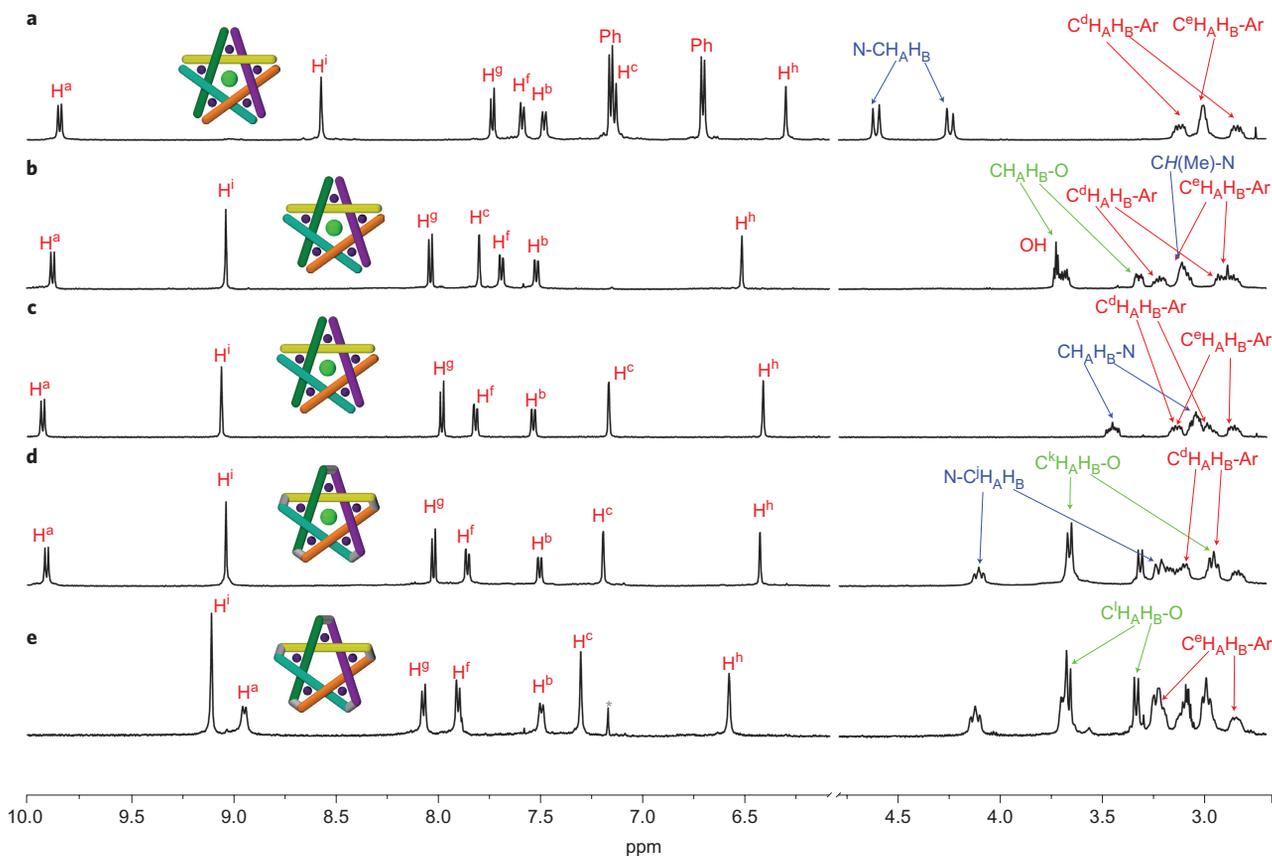


Figure 2 | Partial ^1H NMR spectra (500 MHz, CD_3CN , 298 K) of cyclic double helicates and the chloride-complexed and 'empty cavity' pentafoil knot. **a**, 4-Methylbenzylamine-derived pentameric cyclic helicate $[\mathbf{3b}]\text{Cl}(\text{PF}_6)_9$. **b**, (*R*)-2-amino-propanol-derived pentameric cyclic helicate of single handedness (*M*)- $[\mathbf{3g}]\text{Cl}(\text{PF}_6)_9$. **c**, Hexylamine-derived pentameric cyclic helicate $[\mathbf{3a}]\text{Cl}(\text{PF}_6)_9$. **d**, Pentafoil knot $[\mathbf{6}]\text{Cl}(\text{PF}_6)_9$. **e**, 'Empty cavity' pentafoil knot $[\mathbf{6}](\text{PF}_6)_{10}$ in the presence of excess AgPF_6 . The simplicity of each spectrum is indicative of a symmetrical, cyclic (no endgroups) molecular structure. The AB systems observed for certain resonances (for example, $\text{N-CH}_A\text{H}_B$) are characteristic of methylene groups in asymmetric environments (as conferred by a helix). The differences between the chemical shifts of H^f , H^g and H^h in some of the helicates probably reflect small changes in geometry at the metal centres with the different ligands. The absence of chloride in the 'empty cavity' pentafoil knot $[\mathbf{6}](\text{PF}_6)_{10}$ is signalled by the large shift in H^g (**e**) compared to the other complexes (**a-d**) in which the H^g protons are involved in strong $\text{CH}\cdots\text{Cl}^-$ hydrogen bonding. The proton assignments correspond to the lettering shown in Figs 1 and 3.

monoamine starting material with a diamine (Fig. 3). Although simple alkyl chain diamines of various lengths (**4**) gave complex mixtures of oligomers and polymers under these conditions, the use of diamine **5** led to the formation of a molecular pentafoil knot, $[\mathbf{6}]\text{Cl}(\text{PF}_6)_9$ (Fig. 3). The ^1H NMR spectrum of the reaction mixture took longer to simplify than with most monoamines, but after two days showed the presence of essentially a single low-molecular-weight species (although some polymers are probably also present, consistent with the broad uneven baseline of the ^1H NMR spectrum of the crude reaction mixture, see Supplementary Information). After anion exchange and workup, $[\mathbf{6}]\text{Cl}(\text{PF}_6)_9$ was isolated in 44% yield. The yield of the knot is very sensitive to the stoichiometry of reactants used, with the best results obtained using a 1:1.1:1.1 ratio of 1:5:FeCl₂. Using strictly equimolar amounts of iron and diamine is particularly important, with even a 10% excess of amine decreasing the yield of the knot by up to half (see Supplementary Information).

Many of the signals in the ^1H NMR spectrum of pristine $[\mathbf{6}]\text{Cl}(\text{PF}_6)_9$ (Fig. 2d) occur at very similar chemical shifts to the equivalent protons in the hexylamine-derived helicate $\mathbf{3a}^{10+}$ (Fig. 2c), suggesting that the knot and this helicate are structurally very similar about the iron centres. ESI-MS revealed a series of *m/z* fragments corresponding to $[(\text{Fe}_5\text{L})\text{Cl}][\text{PF}_6]_n^{(9-n)+}$ (where L is the organic framework pentafoil knot) for $n = 2, 3, 4, 5$ and 6 ,

indicating that signals are observed for the molecular knot losing between two and six PF_6^- ions in the mass spectrum (see Supplementary Information).

Single crystals of $[\mathbf{6}]\text{Cl}(\text{PF}_6)_9$ were obtained by slow diffusion of diethyl ether vapour into a solution of the knot in acetonitrile:toluene (3:2) and the solid-state structure was determined by X-ray crystallography using the Diamond synchrotron source (see Supplementary Information). The crystal structure (Fig. 4) confirms the topology and symmetry of the molecular pentafoil knot. The single organic ligand weaves a continuous path about the five co-planar iron centres, the loop passing over and under itself each time it wraps around a metal ion. At the centre of the structure is the chloride anion, held in place by ten $\text{CH}\cdots\text{Cl}^-$ hydrogen bonds that are presumably responsible for it not being exchanged during treatment with KPF_6 (Fig. 4a). Interestingly, the chloride anion is displaced by ~ 1.30 Å from the least-squares plane defined by the five Fe(II) ions (Fig. 4b). Given the symmetry of the ^1H NMR spectrum, in solution the chloride anion must oscillate rapidly on the NMR timescale between the different sides of the molecular knot, accompanied by significant conformational changes in the overall framework of the structure.

The conformations of the groups used to link the metal centres suggest why the pentafoil knot is not favoured using simple alkyl chain diamines (Fig. 4a). To connect each metal centre to the

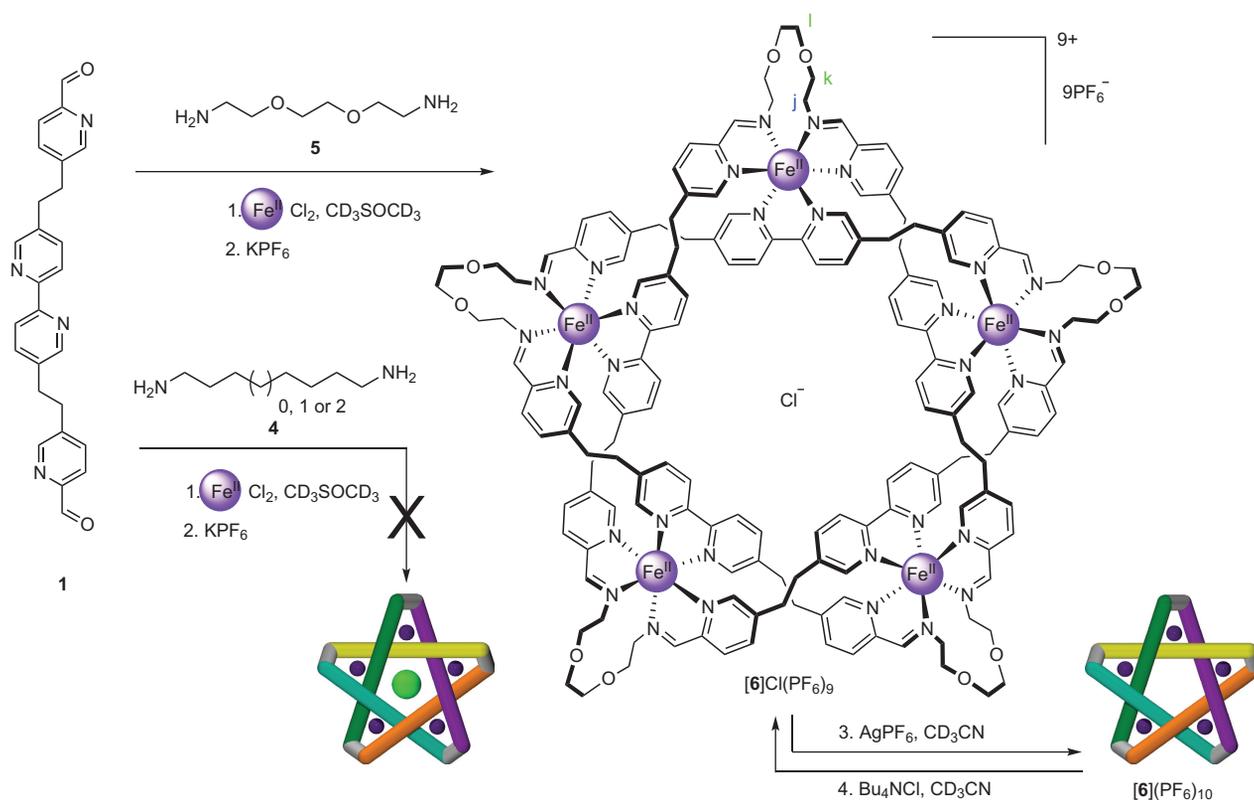


Figure 3 | Synthesis of molecular pentafoil knot $[6]\text{Cl}(\text{PF}_6)_9$ and 'empty cavity' pentafoil knot $[6](\text{PF}_6)_{10}$. Reaction conditions: 1. d_6 -dimethylsulfoxide, 60°C , 48 h. 2. Excess saturated aqueous KPF_6 . Yield of $[6]\text{Cl}(\text{PF}_6)_9$ from **1**, 44%. 3. AgPF_6 (90 equiv.), CD_3CN , 30 min (>98%). 4. Bu_4NCl (1 equiv.), CD_3CN , 5 min (>98%).

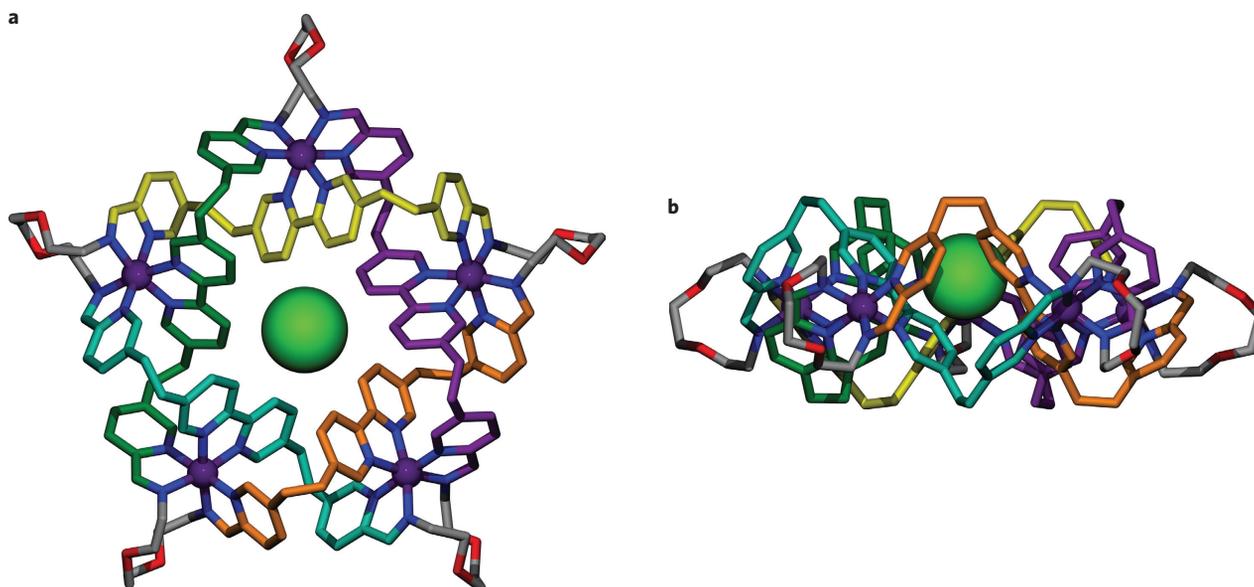


Figure 4 | X-ray crystal structure of molecular pentafoil knot $[6]\text{Cl}(\text{PF}_6)_9$. Iron ions shown at 50% van der Waals radius. Chloride anion shown at 100% van der Waals radius. All other atoms shown in framework representation: nitrogen atoms, blue; oxygen atoms, red; carbon atoms originating from the diamine building block (**5**), grey; carbon atoms originating from the five dialdehyde building blocks (**1**), yellow, orange, dark green, purple and turquoise. PF_6^- anions, solvent molecules and hydrogen atoms are omitted for clarity. **a**, View from above the plane of the five octahedral $\text{Fe}(\text{II})$ ions, showing the symmetry and topology of the 160-atom-loop pentafoil knot with the chloride ion at the centre. $\text{CH}^{\text{a}}\cdots\text{Cl}^-$ distances (\AA): 2.70, 2.69, 2.71, 2.70, 2.76, 2.76, 2.71, 2.70, 2.69, 2.76. $\text{C}-\text{H}^{\text{a}}-\text{Cl}^-$ angles (deg): 177, 176, 176, 172, 179, 173, 176, 170, 177, 170. $\text{O}-\text{C}-\text{O}$ torsion angles (deg): 77(2), 64(3), 60(3), 56(3), 57(3). **b**, Side view showing the displacement of the chloride ion above the plane of the $\text{Fe}(\text{II})$ ions and the interwoven double helix of the ligand. Crystallographic data and experimental details of the structural refinement for $[6]\text{Cl}(\text{PF}_6)_9$ are provided in the Supplementary Information.

next, the bis-amine spacer must form a loop that allows its two amine groups to form imine bonds that coordinate to the same metal ion. Sequences of $-\text{CH}_2-$ groups prefer antiperiplanar arrangements of carbon atoms (that is, 180° C–C–C torsional angles), and forcing a chain to turn back on itself brings some of the C–H groups into pseudo-1,3-diaxial steric clashes. In contrast, the lowest energy conformation of $-\text{XCH}_2\text{CH}_2\text{O}-$ (X=O, N) units has the carbon-heteroatom bonds at 60° to each other, a gauche conformation that is favoured for stereoelectronic reasons³⁸, producing a low-energy turn. The lack of hydrogen atoms on the oxygen atoms also minimizes the steric interactions that occur as a consequence of the turn. Although the energetic cost of each of these effects may be individually small, multiplying them fivefold, as would be required to assemble a molecular pentafoil knot from alkyl chain diamines, is sufficient to tip the thermodynamic balance away from the cyclic-helicate knot to other oligomeric and polymeric products.

Treatment of $[\text{6}]\text{Cl}(\text{PF}_6)_9$ with a large excess (90 equiv.) of AgPF_6 in CD_3CN (298 K, 30 min, Fig. 3) caused significant changes in parts of the ^1H NMR spectrum (Fig. 2e). The H^a protons, heavily deshielded in $[\text{6}]\text{Cl}(\text{PF}_6)_9$ due to $\text{CH}\cdots\text{Cl}^-$ hydrogen bonding (Fig. 2d), were shifted to 8.95 ppm (Fig. 2e), indicating that the final chloride anion had been exchanged for hexafluorophosphate (confirmed by mass spectrometry), generating the empty cavity pentafoil knot $[\text{6}](\text{PF}_6)_{10}$ (Fig. 3). Treatment of $[\text{6}](\text{PF}_6)_{10}$ with Bu_4NCl smoothly regenerates $[\text{6}]\text{Cl}(\text{PF}_6)_9$ (Fig. 3), but the ^1H NMR spectrum of the empty pentafoil knot shows no changes upon addition of other tetrabutylammonium salts (for example, Bu_4NBr , and Bu_4NI), demonstrating that $[\text{6}](\text{PF}_6)_{10}$ is a selective cavitand for the chloride ion.

Conclusions

The one-step synthesis of molecular pentafoil knot $[\text{6}]\text{Cl}(\text{PF}_6)_9$ assembles five metal cations, five bis-aldehyde and five bis-amine building blocks about one chloride anion, in 44% isolated yield. The number of different design features that are combined to assemble the knot is exceptional: the system uses octahedral metal-ion helicate formation to generate entwined ligand strands, short linkers between chelating groups to favour cyclic double helicates over linear triple helicates, anion template synthesis to select the correct number of crossing points, and reversible imine bond formation to join the complexes with the required strand-to-strand connectivity. Macrocyclization to form the covalent backbone of the pentafoil knot makes use of stereoelectronic effects to favour the required turns in the linking units and ligand–ligand interactions to promote mechanical bond formation over polymer formation. The symmetry of the cyclic helicate structures means that even individually rather weak interactions can significantly perturb the product distribution in the reaction mixture, in some cases usefully (for example, to form cyclic helicates of a particular handedness) and in others detrimentally (for example, to disfavour knot formation).

The pentafoil knot has symbolic significance in many ancient and modern cultures and religions (as does its two-dimensional projection, the pentagram) and features as the central emblem on the present-day flags of both Morocco and Ethiopia. The practical significance of its preparation in molecular form includes the lessons learned from the multitude of different structural design features¹⁰ used in its assembly and the potential for the synthesis of higher-order structures with precisely defined knotted architectures that may enable the role of entanglements in molecular materials to be elucidated and exploited.

Methods

Preparation of molecular pentafoil knot $[\text{6}]\text{Cl}(\text{PF}_6)_9$. A d_6 -dimethylsulfoxide solution of anhydrous FeCl_2 (250 μl of a 210 mM solution, 52 μmol , 1.1 equiv.) was added to dialdehyde **1** (20 mg, 47 μmol , 1 equiv.) in 10 ml d_6 -dimethylsulfoxide.

The resulting purple solution was sonicated in an ultrasonic bath for 10 min and heated at 60°C for 30 min to ensure complete dissolution of the dialdehyde. A d_6 -dimethylsulfoxide solution of 2,2'-(ethylenedioxy)bis(ethylamine) (1.00 ml of a 52 mM solution, 52 μmol , 1.1 equiv.) was added to the mixture. The resulting dark purple mixture was heated at 60°C for 2 days. After cooling to room temperature, excess saturated aqueous KPF_6 was added (~ 5 ml). A fine suspension of a purple material formed, which was collected on Celite, thoroughly washed with water, ethanol, dichloromethane and diethyl ether. The purple solid was dissolved in acetonitrile and concentrated under reduced pressure to give $[\text{6}]\text{Cl}(\text{PF}_6)_9$ as a purple powder (18 mg, 4.2 μmol , 44%). ^1H NMR (500 MHz, CD_3CN) δ 9.90 (d, $J = 8.2$ Hz, 10H, H^a), 9.04 (s, 10H, H^b), 8.03 (d, $J = 7.9$ Hz, 10H, H^c), 7.86 (d, $J = 7.7$ Hz, 10H, H^d), 7.50 (d, $J = 7.9$ Hz, 10H, H^e), 7.20 (s, 10H, H^f), 6.43 (s, 10H, H^g), 4.15–4.06 (m, 10H, C^aH_A), 3.66 (d, $J = 9.6$ Hz, 20H, C^bH_A and C^cH_A), 3.32 (d, $J = 9.3$ Hz, 10H, C^dH_B), 3.23 (d, $J = 13.9$ Hz, C^eH_B), 3.19–3.15 (m, 10H, C^dH_B), 3.15–3.07 (m, 10H, C^eH_B), 3.03–2.89 (m, 20H, C^fH_B and C^gH_B), 2.88–2.80 (m, 10H, C^dH_A). ^{13}C NMR (126 MHz, CD_3CN) δ 174.0 (C^a), 157.2 (N–C– C^b), 156.8 (N–C– C^c), 154.1 (C^b), 153.4 (C^c), 140.9 (C^d – C^e)/ C^f – C^g), 140.7 (C^e – C^f)/ C^g – C^h), 140.3 (C^e), 138.9 (C^f), 129.5 (C^g), 125.5 (C^h), 71.4 (C^i), 68.9 (C^j), 61.4 (C^k), 31.0 (C^l), 30.2 (C^m). High-resolution electrospray ionization mass spectrometry (HRESI-MS): $m/z = 713.5736$ [$\text{M}-4(\text{PF}_6)$] $^{5+}$ (calcd. for $\text{C}_{160}\text{H}_{170}\text{ClF}_{24}\text{Fe}_5\text{N}_{30}\text{O}_{10}\text{P}_4$, 713.5750). The proton and carbon assignments correspond to the lettering shown in Figs 1 and 3. Further details of the characterization can be found in the Supplementary Information.

The synthesis, characterization and spectroscopic information for all compounds, including those prepared in the synthetic route to building block **1**, can be found in the Supplementary Information.

Received 15 September 2011; accepted 3 October 2011;
published online 6 November 2011

References

- Wasserman, S. A. & Cozzarelli, N. R. Biochemical topology: applications to DNA recombination and replication. *Science* **232**, 951–960 (1986).
- Taylor, W. R. A deeply knotted protein structure and how it might fold. *Nature* **406**, 916–919 (2000).
- Taylor, W. R. & Lin, K. Protein knots: a tangled problem. *Nature* **421**, 25 (2003).
- Wagner, J. R., Brunzelle, J. S., Forest, K. T. & Vierstra, R. D. A light-sensing knot revealed by the structure of the chromophore-binding domain of phytochrome. *Nature* **438**, 325–331 (2005).
- Taylor, W. R. Protein knots and fold complexity: some new twists. *Comput. Biol. Chem.* **31**, 151–162 (2007).
- Saitta, A. M., Soper, P. D., Wasserman, E. & Klein, M. L. Influence of a knot on the strength of a polymer strand. *Nature* **399**, 46–48 (1999).
- Arai, Y. *et al.* Tying a molecular knot with optical tweezers. *Nature* **399**, 446–448 (1999).
- Menasco, W. W. & Thistlethwaite, M. B. (eds) *Handbook of Knot Theory* (Elsevier, 2005).
- Fenlon, E. E. Open problems in chemical topology. *Eur. J. Org. Chem.* 5023–5035 (2008).
- Beves, J. E., Blight, B. A., Campbell, C. J., Leigh, D. A. & McBurney, R. T. Strategies and tactics for the metal-directed synthesis of rotaxanes, knots, catenanes, and higher order links. *Angew. Chem. Int. Ed.* **50**, 9260–9327 (2011).
- Alexander, J. W. & Briggs, G. B. On types of knotted curves. *Ann. Math.* **28**, 562–586 (1926–1927).
- Adams, C. C. *The Knot Book* (American Mathematical Society, 2004).
- Dietrich-Buchecker, C. O. & Sauvage, J.-P. A synthetic molecular trefoil knot. *Angew. Chem. Int. Ed. Engl.* **28**, 189–192 (1989).
- Piguat, C., Bernardinelli, G. & Hopfgartner, G. Helicates as versatile supramolecular complexes. *Chem. Rev.* **97**, 2005–2062 (1997).
- Ashton, P. R. *et al.* Molecular meccano 27. A template-directed synthesis of a molecular trefoil knot. *Liebigs Ann. Recueil* 2485–2494 (1997).
- Rapenne, G., Dietrich-Buchecker, C. & Sauvage, J.-P. Copper(i)- or iron(ii)-templated synthesis of molecular knots containing two tetrahedral or octahedral coordination sites. *J. Am. Chem. Soc.* **121**, 994–1001 (1999).
- Safarowsky, O., Nieger, M., Fröhlich, R. & Vögtle, F. A molecular knot with twelve amide groups—one-step synthesis, crystal structure, chirality. *Angew. Chem. Int. Ed.* **39**, 1616–1618 (2000).
- Lukin, O. & Vögtle, F. Knitting and threading of molecules: chemistry and chirality of molecular knots and their assemblies. *Angew. Chem. Int. Ed.* **44**, 1456–1477 (2005).
- Feigel, M., Ladberg, R., Engels, S., Herbst-Irmer, R. & Fröhlich, R. A trefoil knot made of amino acids and steroids. *Angew. Chem. Int. Ed.* **45**, 5698–5702 (2006).
- Fenlon, E. E. & Ito, B. R. The thread & cut method: syntheses of molecular knot precursors. *Eur. J. Org. Chem.* 3065–3068 (2008).
- Guo, J., Mayers, P. C., Breault, G. A. & Hunter, C. A. Synthesis of a molecular trefoil knot by folding and closing on an octahedral coordination template. *Nature Chem.* **2**, 218–222 (2010).
- Barran, P. E. *et al.* Active metal template synthesis of a molecular trefoil knot. *Angew. Chem. Int. Ed.* <http://dx.doi.org/10.1002/anie.201105012> (2011).

23. Carina, R. F., Dietrich-Buchecker, C. & Sauvage, J.-P. Molecular composite knots. *J. Am. Chem. Soc.* **118**, 9110–9116 (1996).
24. Fujita, M., Ibukuro, F., Hagihara, H. & Ogura, K. Quantitative self-assembly of a [2]catenane from two preformed molecular rings. *Nature* **367**, 720–723 (1994).
25. Wang, L., Vysotsky, M. O., Bogdan, A., Bolte, M. & Böhmer, V. Multiple catenanes derived from calix[4]arenes. *Science* **304**, 1312–1314 (2004).
26. Lam, R. T. S. *et al.* Amplification of acetylcholine-binding catenanes from dynamic combinatorial libraries. *Science* **308**, 667–669 (2005).
27. Ronson, T. K. *et al.* Stellated polyhedral assembly of a topologically complicated Pd₄L₄ ‘Solomon cube’. *Nature Chem.* **1**, 212–216 (2009).
28. Hasell, T. *et al.* Triply interlocked covalent organic cages. *Nature Chem.* **2**, 750–755 (2010).
29. Chichak, K. S. *et al.* Molecular Borromean rings. *Science* **304**, 1308–1312 (2004).
30. Dietrich-Buchecker, C., Colasson, B., Jouvenot, D. & Sauvage, J.-P. Synthesis of multi-1,10-phenanthroline ligands with 1,3-phenylene linkers and their lithium complexes. *Chem. Eur. J.* **11**, 4374–4386 (2005).
31. Hasenknopf, B., Lehn, J.-M., Kneisel, B. O., Baum, G. & Fenske, D. Self-assembly of a circular double helicate. *Angew. Chem. Int. Ed. Engl.* **35**, 1838–1840 (1996).
32. Hasenknopf, B. *et al.* Self-assembly of tetra- and hexanuclear circular helicates. *J. Am. Chem. Soc.* **119**, 10956–10962 (1997).
33. Hasenknopf, B., Lehn, J.-M., Boumediene, N., Leize, E. & Van Dorsselaer, A. Kinetic and thermodynamic control in self-assembly: sequential formation of linear and circular helicates. *Angew. Chem. Int. Ed.* **37**, 3265–3268 (1998).
34. Leigh, D. A., Lusby, P. J., Teat, S. J., Wilson, A. J. & Wong, J. K. Y. Benzylic imine catenates: readily accessible octahedral analogues of the Sauvage catenates. *Angew. Chem. Int. Ed.* **40**, 1538–1543 (2001).
35. Hogg, L. *et al.* A simple general ligand system for assembling octahedral metal–rotaxane complexes. *Angew. Chem. Int. Ed.* **43**, 1218–1221 (2004).
36. Hutin, M., Schalley, C. A., Bernardinelli, G. & Nitschke, J. R. Helicate, macrocycle, or catenate: dynamic topological control over subcomponent self-assembly. *Chem. Eur. J.* **12**, 4069–4076 (2006).
37. Price, J. R. *et al.* Copper(I)-templated synthesis of a 2,2′-bipyridine derived [2]catenane: synthetic, modelling, and X-ray studies. *Aust. J. Chem.* **62**, 1014–1019 (2009).
38. Murcko, M. A. & DiPaola, R. A. *Ab initio* molecular orbital conformational analysis of prototypical organic systems. 1. Ethylene glycol and 1,2-dimethoxyethane. *J. Am. Chem. Soc.* **114**, 10010–10018 (1992).
39. Ohsawa, Y., DeArmond, M. K., Hanck, K. W. & Moreland, C. G. A proton NMR study of reduced paramagnetic tris(2,2′-bipyridine) complexes of iron(II), ruthenium(II) and osmium(II). *J. Am. Chem. Soc.* **107**, 5383–5386 (1985).
40. Mamula, O., von Zelewsky, A. & Bernardinelli, G. Completely stereospecific self-assembly of a circular helicate. *Angew. Chem. Int. Ed.* **37**, 290–293 (1998).
41. Krämer, R., Lehn, J.-M. & Marquis-Rigault, A. Self-recognition in helicate self-assembly: spontaneous formation of helical metal complexes from mixtures of ligands and metal ions. *Proc. Natl Acad. Sci. USA* **90**, 5394–5398 (1993).
42. Albrecht, M. ‘Let’s twist again’—double-stranded, triple-stranded, and circular helicates. *Chem. Rev.* **101**, 3457–3497 (2001).
43. Nitschke, J. R. Construction, substitution, and sorting of metallo-organic structures via subcomponent self-assembly. *Acc. Chem. Res.* **40**, 103–112 (2007).

Acknowledgements

The authors thank the Diamond Light Source (UK) for synchrotron beamtime on I19 (XR029), the Engineering and Physical Sciences Research Council (EPSRC) National Crystallography Service for data collection, and the EPSRC National Mass Spectrometry Service Centre (Swansea, UK) and C.L. Mackay (SIRCAMS, University of Edinburgh) for high-resolution mass spectrometry. J.E.B. and D.S. are Swiss National Science Foundation postdoctoral fellows. This research was funded by the EPSRC and the Academy of Finland (K.R., projects 212588 and 218325).

Author contributions

J.-F.A., J.E.B., R.T.M. and D.S. carried out the synthesis and characterization studies, helped plan the experiments, and participated in the preparation of the manuscript. K.R. solved the crystal structure. D.A.L. helped plan the experiments and prepare the manuscript.

Additional information

The authors declare no competing financial interests. Supplementary information and chemical compound information accompany this paper at www.nature.com/naturechemistry. Reprints and permission information is available online at <http://www.nature.com/reprints>. Correspondence and requests for materials should be addressed to D.A.L.

INTERLOCKED MOLECULES

One-pot pentaknot

The most complex non-DNA synthetic molecular knot so far has been made in a single step by combining a number of reversible chemical interactions, including metal-directed self-assembly, anion templation and imine bond formation.

Michaele J. Hardie

Knots are commonly encountered in everyday life, but their significance extends far beyond their obvious practical utility of being able to bind objects together. As well as serving as decorative motifs — most notably in some illuminated manuscripts such as the *Book of Kells* — the symbolism often associated with some knots' intricate interwoven structures has seen them used to represent countries, religious ideals and concepts such as unity. Knots have also long fascinated mathematicians with an interest in topology. Mathematically speaking, however, a knot is only considered to be a true knot if it cannot be undone without breaking it.

Chemists have long sought to tie molecules into knots¹. This interest in making knots partly stems from the inherent beauty of such structures and the considerable synthetic challenge they represent. The appeal of knots goes well

beyond the aesthetic, however, because functional biomolecules including DNA and some proteins are known to form knotted structures. Both natural and synthetic polymers may form knots and this has a marked effect on their physical properties, with a knot weakening a polymer strand and making it more likely to break².

Most examples of molecular knots made by chemists have been the simplest of the true knots, the trefoil knot. Now, writing in *Nature Chemistry*, David Leigh and his team report the synthesis of the first non-DNA molecular knot of higher order, namely the pentafoil or cinquefoil knot³. Their rational strategy for making a molecular pentafoil knot combines many aspects of modern supramolecular chemistry, including metal-directed assembly, anion templation and reversible covalent bond formation.

Using metal cations to direct how organic ligands come together has had a

rich recent history in creating topologically complex chemical architectures¹. Such strategies require crossover points, either between different circuits, such as in a chain-like link (a catenane) or in the Borromean rings, or within a single circuit, such as in a knot. Researchers led by Jean-Pierre Sauvage demonstrated in the late 1980s that the three crossover points required to ultimately generate a trefoil knot can be introduced through a helicate⁴. Helicates consist of multiple ligand strands that wrap around metal cations in a helical fashion. Sauvage recognized that a two-stranded helicate with two metal centres will contain the three crossover points required for a trefoil knot. If the ends of the ligands in the helicate are linked together in the appropriate fashion a knot will ensue (Fig. 1a). Although extending the length of the ligand strands and increasing the number of metal cations should, in theory,

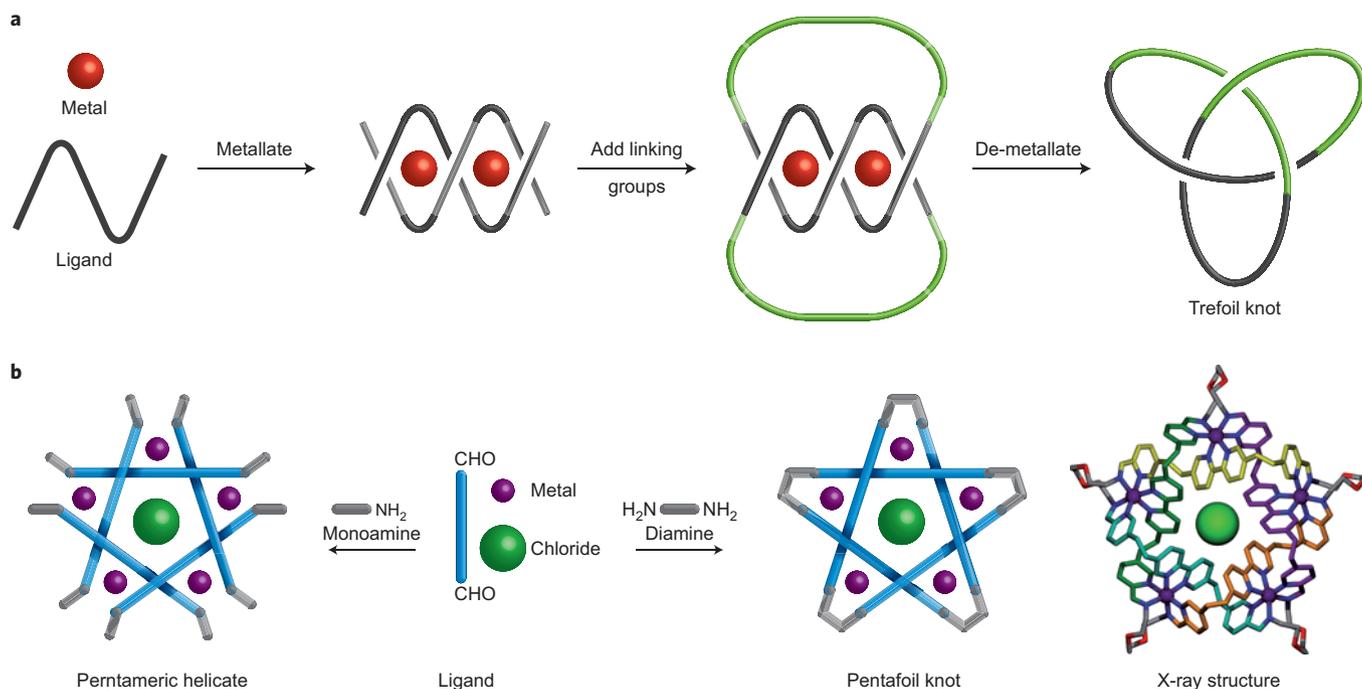


Figure 1 | Making molecular knots. **a**, A schematic representation of Sauvage's step-wise synthesis of a trefoil knot. **b**, Leigh's one-pot synthesis of pentameric helicates (left) and a pentafoil knot (right) including X-ray crystallographic analysis that confirms the knotted topology.

result in more crossover points and hence lead to higher knots, such an approach has not proved successful in the laboratory.

Leigh and his team approached the problem of making a higher-order knot by using a special class of helicates, known as circular helicates, which were first reported by Lehn and co-workers⁵. Here, the twisted ligand strands form a disconnected ring by templation around an anion template. Chloride anions guide the formation of a circular pentameric helicate — comprising five ligands and five metal ions — that contains five crossover points, exactly the number required for a pentafoil knot. Connecting the ends of the ligand strands together in the correct manner would give the desired molecular pentafoil. Instead of doing this in a labour-intensive step-wise procedure, Leigh and colleagues pursued a one-pot method where all of the required chemical transformations occur in the same mixture.

Another crucial aspect of the design strategy was the choice of reversible bond-forming reactions. Reversible imine formation combined with labile metal–ligand bond formation has been previously shown by Leigh⁶ and the groups of Stoddart⁷ and Nitschke⁸ to be a powerful approach to synthesizing highly complex architectures, including catenanes and Borromean rings. Unfortunately, imine bonds are not stable under the fairly harsh conditions that were originally used to make these circular helicates. To begin with, therefore, Leigh and co-workers showed that they could form circular helicates using a modified approach compatible with imine bond formation.

This new strategy required simultaneous formation of the metal-binding groups at the ends of the ligand strands along with

metal binding itself. This was achieved by reacting the aldehyde at each end of the ligand strands with a monoamine (Fig. 1b, left). Next the team tackled the even more challenging task of making the pentafoil knot using a similar one-pot procedure, but using diamine linkers to join the ligands together in a continuous strand (Fig. 1b, right). In a final complication, the choice of linking molecule proved crucial to ensure the correct conformational twist to enable complete closure of the cyclic structure. Ultimate proof of the success of this approach came from the crystal structure of the metallated pentafoil knot (Fig. 1b).

This chemistry is a beautiful illustration of the self-assembly processes that underpin many aspects of chemistry and biology. Many different products are possible, such as oligomers or simpler helicates, but the system continues to break and make chemical bonds until only a single product of the lowest energy is reached. The chemist designs the components, puts them together, and then allows the system to sort itself out, perhaps with a bit of encouragement through heating. With gentle heating, Leigh's circular helicates form themselves in around 24 hours from an initial complex mixture of products. The pentafoil knot, which requires the formation of ten imine bonds and fifteen metal–chelate interactions all in a specific pattern and with specific molecular conformations, took a mere two days to sort itself out.

For a number of decades, the trefoil knot was the highest-order knot that synthetic chemistry could lay claim to, but that is now beautifully superseded by the pentafoil knot. Given that larger anions such as sulfate can template even larger six-fold circular helicates, is a sexafoil now just round the corner? This

pentafoil knot contains five iron cations, but to be truly considered a knot — that is a self-entangled single circuit — it needs to be demonstrated that it can withstand removal of the metal centres. This has proved possible in other metal-templated systems.

More generally, two of the most complex synthetic chemical topologies to date, the Borromean rings and the pentafoil knot, have employed a convergent multi-reversible bond-formation strategy and the latter raises the bar by also including anion templation effects. This illustrates that supramolecular chemists are becoming more sophisticated in their approaches to complex architectures, and can successfully employ multiple and simultaneous bond-forming and structure-directing strategies. Although biology is said to use a small chemical 'toolbox' with a high degree of complexity, chemists have available a much larger chemical toolbox but are considerably less sophisticated in its use. Nevertheless, this is another step towards the chemist's control of very highly complex systems indeed. □

Michaele J. Hardie is at the School of Chemistry, University of Leeds, Leeds LS2 9JT, UK.
e-mail: M.J.Hardie@leeds.ac.uk

References

1. Forgan, R. S., Sauvage, J.-P. & Stoddart, J. F. *Chem. Soc. Rev.* **111**, 5434–5464 (2011).
2. Saitta, A. M., Soper, P. D., Wasserman, E. & Klein, M. L. *Nature* **399**, 46–48 (1999).
3. Ayme, J.-F. *et al. Nature Chem.* **4**, 15–20 (2012).
4. Dietrich-Buchecker, C. O. & Sauvage, J.-P. *Angew. Chem. Int. Ed. Engl.* **28**, 189–192 (1989).
5. Hasenknopf, B., Lehn, J.-M., Kneisel, B. O., Baum, G. & Fenske, D. *Angew. Chem. Int. Ed. Engl.* **35**, 1838–1840 (1996).
6. Leigh, D. A., Lusby, P. J., Teat, S. J., Wilson, A. J. & Wong, J. K. Y. *Angew. Chem. Int. Ed.* **40**, 1538–1543 (2001).
7. Chichak, K. S. *et al. Science* **304**, 1308–1312 (2004).
8. Hutin, M., Schalley, C. A., Bernardinelli, G. & Nitschke, J. R. *Chem. Eur. J.* **12**, 4069–4076 (2006).

EXCITON DYNAMICS

Electrons take an unexpected turn

Traditional wisdom suggests that excited electrons will move towards positively charged parts of a molecule. Advanced time-domain calculations show that the conventional picture breaks down in the ultrafast regime, providing key insights into photo-activated, attosecond processes.

Heather M. Jaeger and Oleg V. Prezhdo

Decreasing resources and environmental concerns have turned the world's attention to alternative energy supplies. And with solar power expected to provide a major proportion of our energy in the future, chemists are taking a closer look at the photo-induced processes that drive the conversion of light into usable energy. Regardless of the

end product — electrical current, chemical fuel or biomass — photo-conversion relies on the generation and evolution of excitons. In a practical sense, an exciton is an electron–hole pair that is created on photo-excitation. They must be separated from one another to generate an electrical potential; however, negatively charged electrons and positively

charged holes interact, creating a barrier to such exciton dissociation. To best utilize photovoltaic and photosynthetic devices, one must understand the conditions that promote charge separation and exciton diffusion. However, truly understanding the evolution of excitons in molecular systems is far from trivial given their quantum mechanical