LETTER

doi:10.1038/nature09683

# Vernier templating and synthesis of a 12-porphyrin nano-ring

Melanie C. O'Sullivan[1]*, Johannes K. Sprafke[1]*, Dmitry V. Kondratuk[1], Corentin Rinfray[1], Timothy D. W. Claridge[1], Alex Saywell[2], Matthew O. Blunt[2], James N. O'Shea[2], Peter H. Beton[2], Marc Malfois[3] & Harry L. Anderson[1]

**Templates are widely used to arrange molecular components so they can be covalently linked into complex molecules that are not readily accessible by classical synthetic methods[1–7]. Nature uses sophisticated templates such as the ribosome, whereas chemists use simple ions or small molecules. But as we tackle the synthesis of larger targets, we require larger templates—which themselves become synthetically challenging. Here we show that Vernier complexes can solve this problem: if the number of binding sites on the template, $n_T$, is not a multiple of the number of binding sites on the molecular building blocks, $n_B$, then small templates can direct the assembly of relatively large Vernier complexes where the number of binding sites in the product, $n_P$, is the lowest common multiple of $n_B$ and $n_T$ (refs 8, 9). We illustrate the value of this concept for the covalent synthesis of challenging targets by using a simple six-site template to direct the synthesis of a 12-porphyrin nano-ring with a diameter of 4.7 nm, thus establishing Vernier templating as a powerful new strategy for the synthesis of large monodisperse macromolecules.**

The principle behind all Vernier systems is the formation of a moiré pattern. Moiré patterns are observed on a wide range of length scales whenever two non-commensurate periodicities are superimposed. In the simplest case, two sets of parallel lines, with different spacings, produce a striped pattern with a periodicity that is the lowest common multiple of those of the two components, like the beat pattern generated by adding two sine waves of slightly different wavelengths (Fig. 1a). Engineers use moiré patterns and Vernier scales to amplify small mismatches in separation that would otherwise be difficult to resolve. Similarly in chemistry, the formation of a Vernier complex between components with different numbers of binding sites provides a way to amplify the molecular length scale, generating precisely defined assemblies (Fig. 1b). Although the idea of molecular Vernier systems has been discussed for more than 20 years[10], only two examples have been investigated experimentally[8,9]. The idea that the formation of Vernier complexes between a template and a molecular building block can serve as a powerful strategy for the synthesis of large macrocycles (Fig. 1c) is based on the realization that Vernier complexes do not need to be linear. A template with six binding sites, T6, binds to a building block with four binding sites, *l*-P4, to form the Vernier complex $(l\text{-P4})_3\bullet(T6)_2$, which probably consists of two isomers. The *l*-P4 units can then be coupled together covalently to give a figure-of-eight complex, $c\text{-P12}\bullet(T6)_2$. Displacement of the template gives the free macrocycle *c*-P12. Vernier templating allows simple templates to be used to direct the formation of complex monodisperse targets.

We have demonstrated the concept of Vernier templating (Fig. 1c) by synthesizing a butadiyne-linked, π-conjugated 12-porphyrin nano-ring (Fig. 2a). Palladium-catalysed oxidative coupling of the linear porphyrin tetramer *l*-P4 in the presence of the hexapyridyl template T6 gave the figure-of-eight complex $c\text{-P12}\bullet(T6)_2$ in 39% isolated yield (the only other products are insoluble polymers). Treatment of this complex with an excess of pyridine, as a competing ligand, resulted in quantitative conversion to the free 12-porphyrin nano-ring *c*-P12 (isolated in 96% yield). Both $c\text{-P12}\bullet(T6)_2$ and *c*-P12 were fully characterized by $^1$H NMR and matrix-assisted laser desorption/ionization mass spectrometry (Supplementary Information). The $^1$H NMR spectrum of $c\text{-P12}\bullet(T6)_2$ (Fig. 2b, top), is fully consistent with the expected $D_2$ symmetry, with 24 β-pyrrole doublets and 12 *t*-butyl singlets. The resonances from the porphyrin units near the central crossing point are spread over a wide range of chemical shifts. We have assigned most of these resonances using a variety of two-dimensional NMR techniques, and observed nuclear Overhauser enhancements between resonances of the proximate porphyrin units at the centre of the structure (Supplementary Fig. 20). The $^1$H NMR spectrum of *c*-P12 is extremely simple, with just two sharp β-pyrrole doublets, two aromatic signals and one *t*-butyl singlet, demonstrating its $D_{12h}$ symmetry. The structures of $c\text{-P12}\bullet(T6)_2$ and *c*-P12 are supported by solution-phase small-angle X-ray scattering (SAXS) data. Recently this technique has emerged as a valuable method for characterizing synthetic supramolecular architectures[11]. The experimental SAXS electron density pair-distribution functions, obtained from dilute solutions of $c\text{-P12}\bullet(T6)_2$ and *c*-P12 in toluene, match the simulated pair-distribution functions for calculated geometries (Fig. 3a, b). The free nano-ring, *c*-P12, is quite flexible in

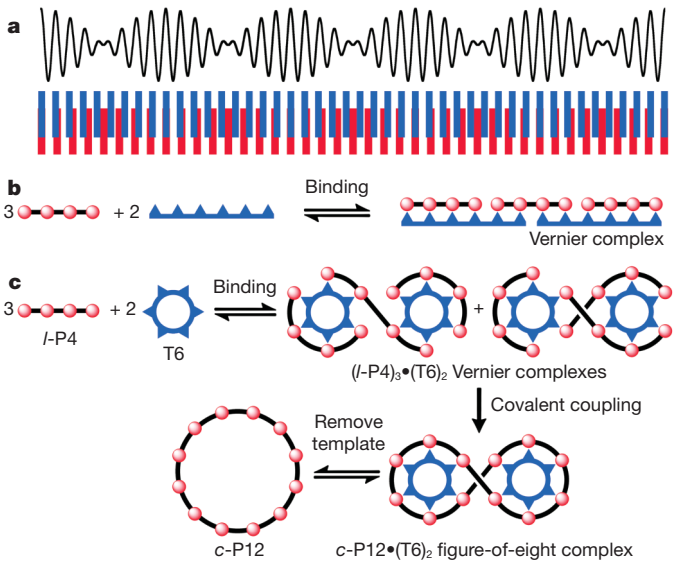


**Figure 1 | Vernier templating.** **a**, The basis of a Vernier measuring device is illustrated by the moiré pattern arising from the summation of two sine waves, or two stripes, with a periodicity ratio of 8:9. **b**, Formation of a molecular 3:2 Vernier complex. **c**, Vernier templating: the use of Vernier complex formation to direct the formation of a 12-site macrocycle, *c*-P12, using a 6-site template, T6.

[1]Department of Chemistry, Oxford University, Chemistry Research Laboratory, Mansfield Road, Oxford OX1 3TA, UK. [2]School of Physics & Astronomy, University of Nottingham, Nottingham, NG7 2RD, UK. [3]Diamond Light Source Ltd, Harwell Science and Innovation Campus, Didcot OX11 0DE, UK.
*These authors contributed equally to this work.

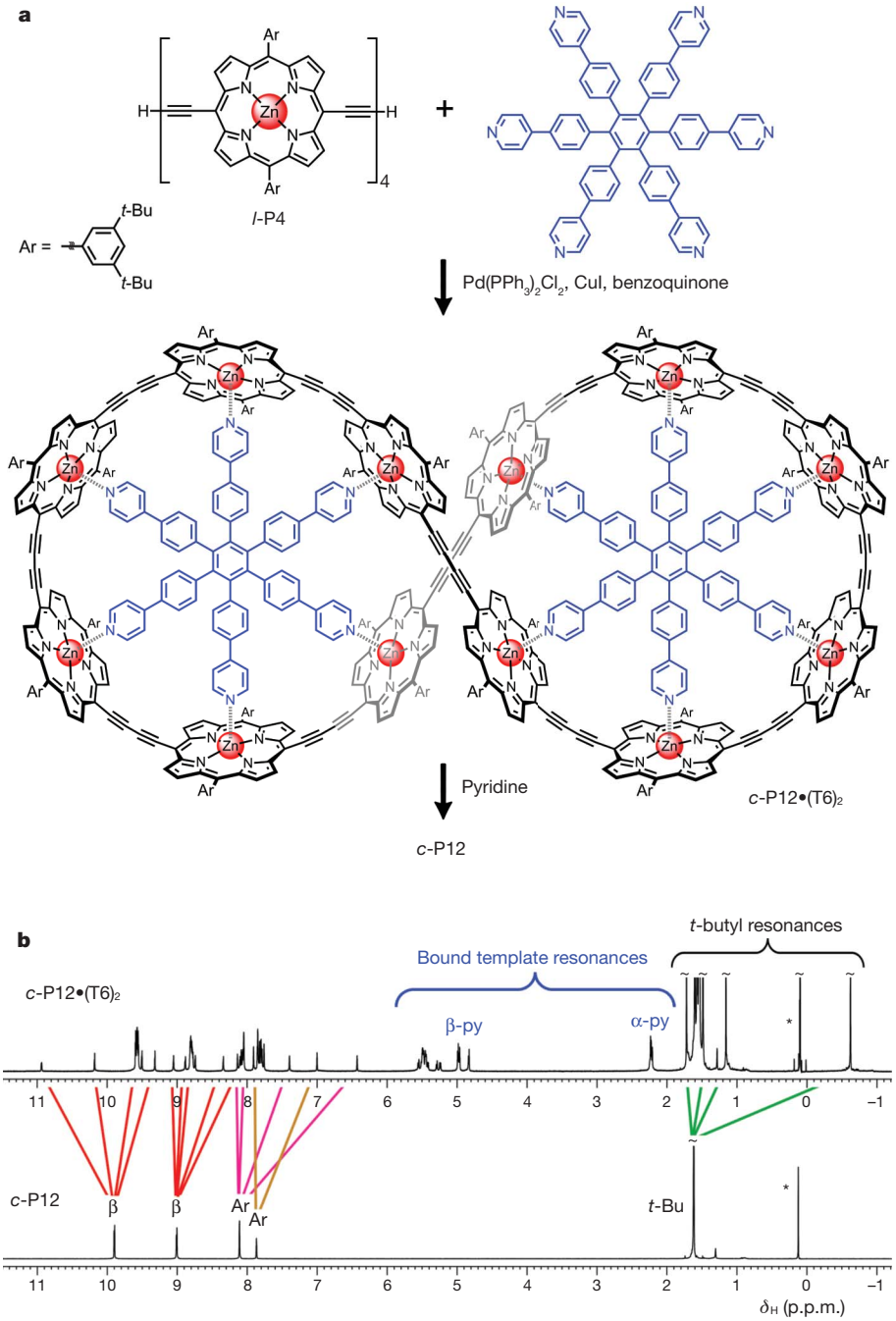


**Figure 2 | Synthesis and NMR characterization of the 12-porphyrin nano-ring. a**, Vernier-templated synthesis of *c*-P12 through the formation of a figure-of-eight complex, *c*-P12•$(T6)_2$. **b**, $^1$H NMR spectra of *c*-P12•$(T6)_2$ in $CDCl_3$ and *c*-P12 in $CDCl_3/C_5D_5N$. The coloured lines show how the spectrum of *c*-P12•$(T6)_2$ collapses on removal of the template (700 MHz, 298 K; diffusion-edited to exclude solvent signals; *silicon grease impurity; Ar, aryl; β, β-pyrrole; Bu, butyl; $\delta_H$, chemical shift; py, pyridine).

solution and its SAXS data could only be adequately simulated by using a combination of several elliptical conformations. The structure of the 12-porphyrin nano-ring was also confirmed by scanning tunnelling microscopy (STM). Molecules were deposited using an electrospray source, on a Au(111) surface in ultrahigh vacuum[12]. In Fig. 3c, several nearly circular *c*-P12 molecules are shown adsorbed at a gold step edge (the line running diagonally across the image); in each case, it is possible to count the 12 porphyrin subunits (see also Supplementary Figs 39 and 40).

We also synthesized the nano-ring *c*-P12 by a 'classical' template-directed route (Fig. 4). Palladium-catalysed oxidative coupling of the linear porphyrin tetramer *l*-P4 in the presence of the dodecapyridyl template T12 gave *c*-P12•T12 in 35% isolated yield; treatment of this complex with pyridine results in quantitative conversion to the free 12-porphyrin nano-ring *c*-P12. The efficiency of this classical templating route is similar to that of the Vernier route. However, it is more difficult to purify samples of *c*-P12 prepared using T12, and the T12 template is only available in small amounts from a low-yielding ten-step synthesis, whereas T6 is accessible in two steps from commercial materials[6]. This illustrates the tremendous advantage of Vernier templating as a way to gain access to large, complex targets using readily available templates.

Control experiments showed that oxidative coupling of *l*-P4 in the absence of a template gives linear polymers without forming any detectable *c*-P12. Coupling of the corresponding porphyrin monomer and dimer (*l*-P1 and *l*-P2) in the presence of template T6 yields the cyclic hexamer *c*-P6 together with small amounts of *c*-P12 (Supplementary

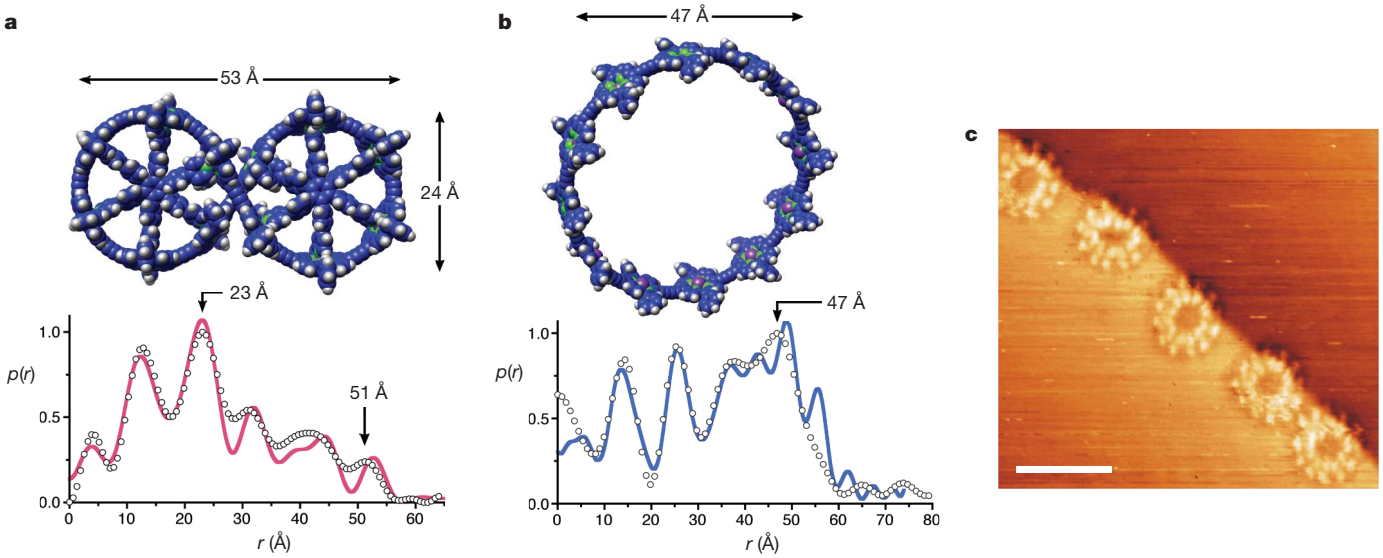


**Figure 3 | Characterization of the 12-porphyrin nano-ring by SAXS and STM.** **a**, **b**, SAXS pair-distribution data for *c*-P12•$(T6)_2$ in toluene (**a**) and *c*-P12 in toluene–pyridine (**b**); experimental points and simulated curves from the calculated structures are shown. $p(r)$, pair-distribution function for electron density at separation $r$. **c**, STM image of *c*-P12 on a gold surface. The version of *c*-P12 used in this STM experiment had octyloxy side chains instead of *t*-butyls. STM scanning parameters: sample voltage, −1.8 V; tunnel current, 30 pA. Scale bar, 50 Å.

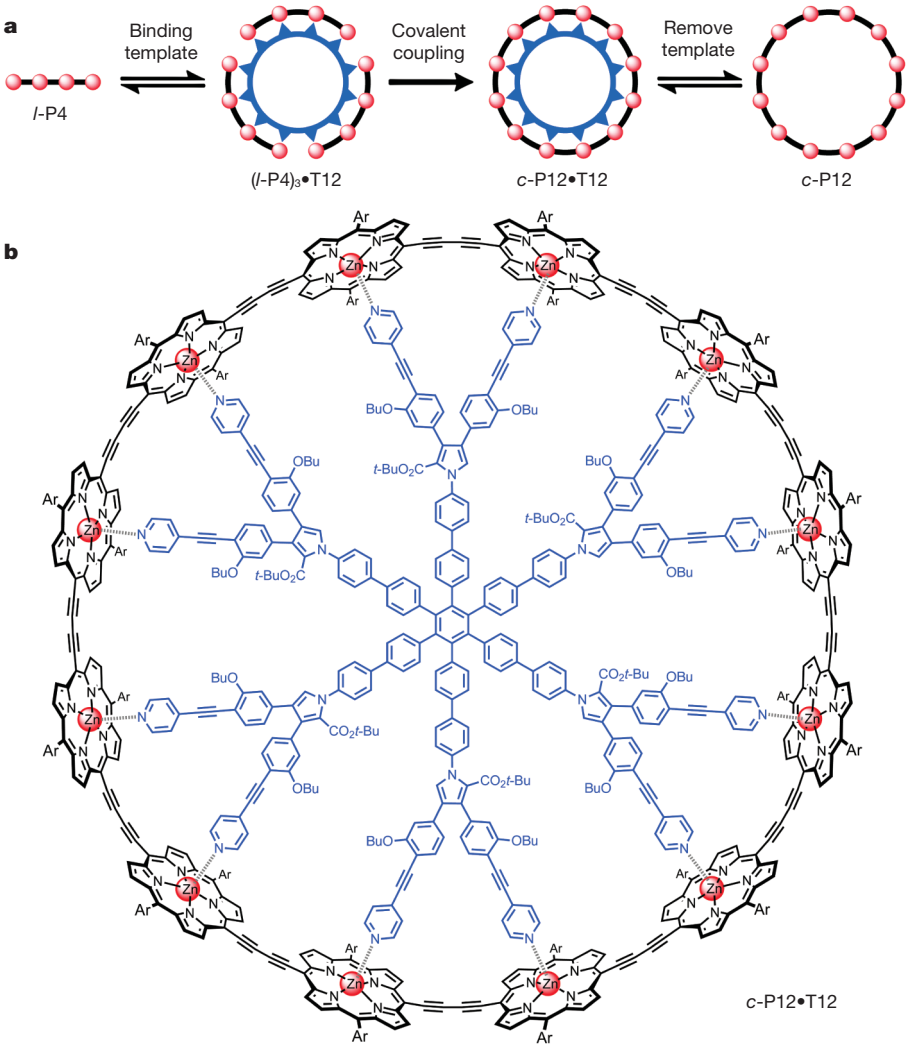


**Figure 4 | Classical template-directed synthesis of nano-ring *c*-P12.** **a**, Palladium-catalysed oxidative coupling of *l*-P4 in the presence of T12, followed by treatment with pyridine, yields *c*-P12. **b**, Structure of *c*-P12•T12 (Ar = 3,5-bis(*t*-butyl)phenyl).

Table 1); the yields of *c*-P12 from these routes are much lower than from Vernier templating.

The 12-porphyrin nano-ring *c*-P12, with a diameter of 4.7 nm, is among the largest π-conjugated macrocycles ever synthesized[5–7,13–15]. It will be interesting to investigate whether molecules of this type can support persistent ring currents analogous to those observed in mesoscopic metal rings[13,16]. Nano-rings of chromophores such as *c*-P12 are also a focus of attention because of their resemblance to natural light-harvesting chlorophyll complexes[11,17–21].

The results reported here indicate that Vernier templating will provide access to even larger cyclic chromophore arrays. For example, coupling a five-porphyrin building block, *l*-P5[22], in the presence of T6 should give *c*-P30, by way of a Vernier complex of stoichiometry $(l\text{-P5})_6\bullet(\text{T6})_5$. Formation of a stable Vernier complex is not essential for Vernier templating. The main role of the template may be to favour cyclization when a linear chain intermediate is produced with a number of binding sites, $n_P$, which is the lowest common multiple of $n_B$ and $n_T$. Thus, in the Vernier synthesis of *c*-P12 (Figs 1c and 2a), the template could work simply by binding *l*-P12 (formed by oligomerization of *l*-P4) in such a way as to accelerate its cyclization. Vernier templating should be applicable to any template-directed cyclization reaction in which the components have well-defined binding sites, such that a precise mismatch can be set up between $n_B$ and $n_T$. This strategy seems to be a general approach to the synthesis of monodisperse macromolecules of a size not previously accessible.

## METHODS SUMMARY

**Vernier-templated synthesis of *c*-P12•$(\text{T6})_2$.** The template T6 (19.5 mg, 19.6 μmol) and the linear porphyrin tetramer *l*-P4 (61.0 mg, 19.1 μmol) were dissolved in $CHCl_3$ (88 ml) by sonication for 1 h (bath sonicator). A catalyst solution was prepared by dissolving $Pd(PPh_3)_2Cl_2$ (17.7 mg, 25.2 μmol), Cu(I) iodide (24.2 mg, 0.127 mmol) and 1,4-benzoquinone (56.1 mg, 0.52 mmol) in $CHCl_3$ (12 ml) and diisopropylamine (610 μl). The catalyst solution was added to the solution of *l*-P4 and T6, stirred for 1 h at 20 °C and then stirred for 1.5 h at 50 °C. The mixture was passed through a plug of alumina using $CHCl_3$ as eluent, and purified by size-exclusion chromatography (Biobeads SX-1, toluene). Recrystallization by layer addition of MeOH to a solution in $CH_2Cl_2$ yielded *c*-P12•$(\text{T6})_2$ as a dark-brown solid (29.0 mg, 39%). See Supplementary Information for full details of the characterization of *c*-P12•$(\text{T6})_2$ and related compounds.

**Synchrotron radiation SAXS.** A solution of the sample in toluene, or toluene and 1% pyridine (concentration, ~0.1 mM) was placed in a cell with mica windows. Data were collected on beamline I22 at the Diamond Light Source (UK), with the detector at a distance of 1.25 m from the sample cell; the momentum transfer range was $0.03\ \text{Å}^{-1} < q < 1.0\ \text{Å}^{-1}$ ($q = 4\pi\sin(\theta)/\lambda$, where $2\theta$ is the scattering angle and $\lambda = 1.00$ Å is the X-ray wavelength). The data were normalized to the intensity of the incident beam, and scattering due to the solvent was subtracted.

**Scanning tunnelling microscopy.** A solution of *c*-P12 (with octyloxy side chains) in toluene–methanol (3:1 by volume, with 5% pyridine; concentration, 200 μg $\text{ml}^{-1}$) was deposited on the substrate (gold on mica) by electrospray. Images were acquired in ultrahigh vacuum using electrochemically etched tungsten tips, in constant-current mode at 20 °C.

**Received 8 September; accepted 9 November 2010.**

1. Diederich, F. & Stang, P. J. (eds) *Templated Organic Synthesis* (VCH-Wiley, 1999).
2. Anderson, S., Anderson, H. L. & Sanders, J. K. M. Expanding roles for templates in synthesis. *Acc. Chem. Res.* **26,** 469–475 (1993).
3. Chichak, K. S. *et al.* Molecular Borromean rings. *Science* **304,** 1308–1312 (2004).
4. Crowley, J. D. *et al.* An unusual nickel-copper-mediated alkyne homocoupling reaction for the active-template synthesis of [2]rotaxanes. *J. Am. Chem. Soc.* **132,** 6243–6248 (2010).
5. Jung, S.-H. *et al.* A conjugated polycarbazole ring around a porphyrin. *Angew. Chem. Int. Ed.* **45,** 4685–4690 (2006).
6. Hoffmann, M. *et al.* Enhanced π-conjugation around a porphyrin[6] nanoring. *Angew. Chem. Int. Ed.* **47,** 4993–4996 (2008).
7. Hoffmann, M., Wilson, C. J., Odell, B. & Anderson, H. L. Template-directed synthesis of a π-conjugated porphyrin nanoring. *Angew. Chem. Int. Ed.* **46,** 3122–3125 (2007).
8. Kelly, T. R., Xie, R. L., Weinreb, C. K. & Bregant, T. A molecular vernier. *Tetrahedr. Lett.* **39,** 3675–3678 (1998).
9. Hunter, C. A. & Tomas, S. Accurate length control of supramolecular oligomerization: Vernier assemblies. *J. Am. Chem. Soc.* **128,** 8975–8979 (2006).
10. Lindsey, J. S. Self-assembly in synthetic routes to molecular devices. Biological principles and chemical perspectives: a review. *N. J. Chem.* **15,** 153–180 (1991).
11. Kelly, R. F. *et al.* Intramolecular energy transfer within butadiyne-linked chlorophyll and porphyrin dimer-faced, self-assembled prisms. *J. Am. Chem. Soc.* **130,** 4277–4284 (2008).
12. Saywell, A. *et al.* Conformation and packing of porphyrin polymer chains deposited using electrospray on a gold surface. *Angew. Chem. Int. Ed.* **49,** 9136–9139 (2010).
13. Mayor, M. & Didschies, C. A giant conjugated molecular ring. *Angew. Chem. Int. Ed.* **42,** 3176–3179 (2003).
14. Zhang, F., Götz, G. & Winkler, H. D. F. Schalley, C. A. & Bäuerle, P. Giant cyclo[*n*]thiophenes with extended π-conjugation. *Angew. Chem. Int. Ed.* **48,** 6632–6635 (2009).
15. Nakao, K. *et al.* Giant macrocycles composed of thiophene, acetylene, and ethylene building blocks. *J. Am. Chem. Soc.* **128,** 16740–16747 (2006).
16. Bleszynski-Jayich, A. C. *et al.* Persistent currents in normal metal rings. *Science* **326,** 272–275 (2009).
17. McDermott, G. *et al.* Crystal structure of an integral membrane light-harvesting complex from photosynthetic bacteria. *Nature* **374,** 517–521 (1995).
18. Roszak, A. W. *et al.* Crystal structure of the RC-LH1 core complex from *Rhodopseudomonas palustris*. *Science* **302,** 1969–1972 (2003).
19. Nakamura, Y., Aratani, N. & Osuka, A. Cyclic porphyrin arrays as artificial photosynthetic antenna: synthesis and excitation energy transfer. *Chem. Soc. Rev.* **36,** 831–845 (2007).
20. Hajjaj, F. *et al.* Assemblies of supramolecular porphyrin dimers in pentagonal and hexagonal arrays exhibiting light-harvesting antenna function. *J. Am. Chem. Soc.* **128,** 4612–4623 (2006).
21. Chang, M.-H., Hoffmann, M., Anderson, H. L. & Herz, L. M. Dynamics of excited-state conformational relaxation and electronic delocalization in conjugated porphyrin oligomers. *J. Am. Chem. Soc.* **130,** 10171–10178 (2008).
22. Taylor, P. N. & Anderson, H. L. Cooperative self-assembly of double-strand conjugated porphyrin ladders. *J. Am. Chem. Soc.* **121,** 11538–11545 (1999).

**Supplementary Information** is linked to the online version of the paper at www.nature.com/nature.

**Acknowledgements** We thank the Engineering and Physical Sciences Research Council (EPSRC), the Diamond Light Source, the European Commission (EU-contract: MRTN-CT-2006-036040, THREADMILL) and the Clarendon Fund for support; the EPSRC mass spectrometry service (Swansea) for mass spectra; and B. Odell for help with NMR spectroscopy.

**Author Contributions** H.L.A. designed the project and wrote the manuscript. J.K.S., M.C.O., D.K. and C.R. carried out most of the experimental work. T.D.W.C. provided expertise with NMR analysis. STM was performed by A.S. and M.O.B., supervised by J.N.O. and P.H.B. SAXS analysis was performed by J.K.S. and H.L.A. with help from M.M. All authors edited the manuscript.

**Author Information** Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Readers are welcome to comment on the online version of this article at www.nature.com/nature. Correspondence and requests for materials should be addressed to H.L.A. (harry.anderson@chem.ox.ac.uk).