VIP Giant Conjugated Macrocycles

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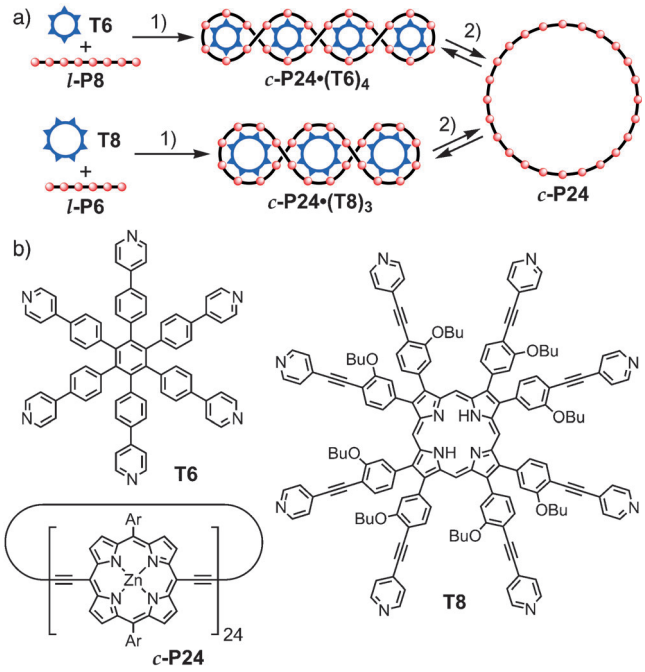
Two Vernier-Templated Routes to a 24-Porphyrin Nanoring**

*Dmitry V. Kondratuk, Luis M. A. Perdigao, Melanie C. O'Sullivan, Simon Svatek, Gareth Smith, James N. O'Shea, Peter H. Beton, and Harry L. Anderson**

Dedicated to Professor Fraser Stoddart on the occasion of his 70th birthday

Ingenious new template-directed strategies make it possible to synthesize an increasingly wide range of molecular architectures, which would otherwise be inaccessible.[1–12] Recently, we developed the concept of Vernier templating—the use of noncommensurate combinations of templates and building blocks to direct the formation of cyclic oligomers, such that the number of binding sites in the product is the lowest common multiple of the numbers of sites in the template and the starting material.[12d] This principle allows a small template to direct the formation of a much larger macrocycle. Previously, we illustrated this idea with the synthesis of a 12-porphyrin nanoring, ***c*-P12**, from a linear zinc porphyrin tetramer, ***l*-P4**, and a hexapyridyl template, **T6**. Here we report the synthesis of a 24-porphyrin ring, ***c*-P24**, by two Vernier-templated routes: a) coupling the linear porphyrin octamer ***l*-P8** in the presence of hexapyridyl template **T6**, and b) coupling the linear porphyrin hexamer ***l*-P6** in the presence of the octapyridyl template **T8** (Scheme 1). The 24-porphyrin nanoring can be prepared in yields of up to 25%. It has a diameter of 10 nm, as confirmed by scanning tunneling microscopy (STM), and a molecular weight of 26 kDa, thus placing it in the size range of a typical protein. This flexible macrocycle can be locked into a planar π-conjugated conformation by the cooperative self-assembly of a 2:24 double-strand complex with the linear diamine ligand 1,4-diazabicyclo[2.2.2]octane (DABCO).

The representation of the two routes to ***c*-P24** in Scheme 1 overlooks the fact that complexes such as (***l*-P8**)$_3$·(**T6**)$_4$ and



Scheme 1. a) Vernier-templated synthesis of the nanoring ***c*-P24**. Reagents: 1) [PdCl$_2$(PPh$_3$)$_2$], CuI, benzoquinone, *i*Pr$_2$NH; 2) pyridine. b) Structures of **T6**, **T8**, and ***c*-P24**; Ar = 3,5-bis(octyloxy)phenyl.

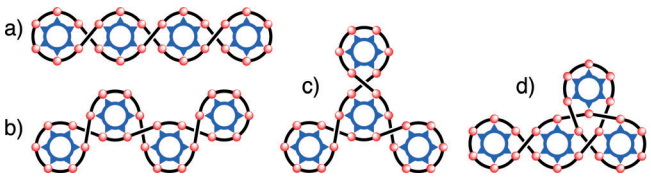


Figure 1. Four examples of possible isomers of ***c*-P24**·(**T6**)$_4$.[13]

***c*-P24**·(**T6**)$_4$ have many possible isomers, as illustrated in Figure 1. However, the formation of these isomeric intermediates should not detract from the efficiency of the Vernier-templated synthesis, because removal of the template will convert all these isomers into the same ***c*-P24** open ring (except for knotted structures, for example, Figure 1 d[13]).

Palladium-catalyzed oxidative coupling of the linear porphyrin octamer ***l*-P8**[12a] in the presence of the hexapyridyl template **T6**[12b,c] gave the expected product ***c*-P24**, together with the 16-porphyrin ring ***c*-P16**[14] and linear polymers, all as complexes with **T6**. The polymeric by-products were removed

[*] D. V. Kondratuk, Dr. M. C. O'Sullivan, Prof. H. L. Anderson
Department of Chemistry, University of Oxford
Chemistry Research Laboratory
Oxford OX1 3TA (UK)
E-mail: harry.anderson@chem.ox.ac.uk
Homepage: http://hla.chem.ox.ac.uk/
Dr. L. M. A. Perdigao, S. Svatek, Dr. J. N. O'Shea, Prof. P. H. Beton
School of Physics & Astronomy, University of Nottingham
Nottingham, NG7 2RD (UK)
G. Smith
School of Chemistry, University of Manchester
Manchester, M13 9PL (UK)

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using a short column of alumina and the mixture of ring complexes was separated by size-exclusion chromatography. The ***c*-P24**/***c*-P16** ratio depends on the amount of **T6** present during the reaction. Use of a slightly substoichiometric amount of template ([**T6**]/[***l*-P8**] < 4:3) shifts the product distribution towards ***c*-P24**·(**T6**)$_4$, while use of more than 4:3 equivalents of **T6** favors formation of ***c*-P16**. Coupling ***l*-P8** in the presence of one equivalent of **T6** gave ***c*-P24**·(**T6**)$_4$ as the main cyclic product (14% yield of isolated product; see Section B2 of the Supporting Information). Treatment of the template complexes with an excess of pyridine resulted in quantitative conversion into the free nanorings ***c*-P16** and ***c*-P24**.

Coupling of the linear porphyrin hexamer ***l*-P6**[12b,c] in the presence of the octapyridyl template **T8**[12a] gave a mixture of the cyclic products ***c*-P12**, ***c*-P18**, and ***c*-P24** and linear polymers (all as complexes with **T8**).[14] Removal of **T8** by size-exclusion chromatography in the presence of pyridine afforded the corresponding free nanorings ***c*-P12**, ***c*-P18**, and ***c*-P24**, as well as linear polymers, which were separated by gel-permeation chromatography to give ***c*-P24** as the main cyclic product, isolated in 25% yield.

When starting materials ***l*-P6** or ***l*-P8** were coupled under the same conditions, except in the absence of any template, only linear polymers were formed. Thus, the formation of macrocyclic by-products (***c*-P16** from ***l*-P8**/**T6**, and ***c*-P12**/***c*-P18** from ***l*-P6**/**T8**), must be template-directed.[14] Further work will be required to understand the formation of these unexpected products, which appear to originate from higher-order complexes of the starting materials.

The 24-porphyrin ring ***c*-P24** was characterized by matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS; Figure 2a); the expected molecular ion $[M]^+$ is the dominant signal (found: 26.124 kDa; calcd: 26.035 kDa).[15] The ^{1}H NMR spectrum of ***c*-P24** shows just two β-proton doublets, which reflects the D_{24h} symmetry (Figure 2b). The structure of the 24-porphyrin nanoring was confirmed by STM. Molecules were deposited using an electrospray source on to a Au(111) surface in an ultrahigh vacuum.[12d,16] In Figure 2c,d, several nearly circular ***c*-P24** molecules are shown adsorbed on a gold surface; in the case of the small-area image (Figure 2d), it is possible to count 24 porphyrin subunits. The average diameter of the nanorings, of about 10 nm, matches the expected Zn···Zn diameter of 9.7 nm.

UV/Vis/NIR and NMR spectroscopic titrations showed that ***c*-P24** forms a very stable 2:24 sandwich complex with DABCO (Figure 3a), similar to the 2:12 complex formed by ***c*-P12**.[17] Self-assembly of these double-strand complexes is a promising strategy for planarizing and rigidifying large nanorings, just as ladder formation amplifies electronic coupling in linear porphyrin wires.[18] The formation of (***c*-P24**)$_2$·(DABCO)$_{24}$ is in slow exchange on the ^{1}H NMR timescale and the complex exhibits the expected singlet at −4.1 ppm (integration 288 H), corresponding to DABCO molecules sandwiched between two porphyrin units. The inequivalence between the two faces of the porphyrins is evident from splitting of the resonances of the *ortho* protons of the meso-aryl substituents, but the inequivalence between the inner and outer rims of the nanorings is unresolved, probably because the ring is so large that the environments on its rims are similar.[17] UV/Vis/NIR titrations of ***c*-P24** with DABCO gave an end-point after addition of 12 equivalents of DABCO (see Figure S21 in the Supporting Information). Addition of a large excess of DABCO results in disassembly of the sandwich complex into two single-strand rings. The almost isosbestic behavior (Figure 4a) and the sharp, sigmoidal denaturation curve (Figure 4b) suggest a two-state equilibrium between (***c*-P24**)$_2$·(DABCO)$_{24}$ and (***c*-P24**)·(DABCO)$_{24}$.[19] This equilibrium was modeled by the thermodynamic cycle in Figure 3b to give the calculated binding isotherms plotted in Figure 4b.[20] Denaturation is extremely cooperative, with a Hill coefficient of $n_H = 11.7$ and a switching window of $c_R = 1.5$.[21,22] To the best of our knowledge this is the highest cooperativity observed for a synthetic supramolecular system;[23] however, the cooperativity is not as high

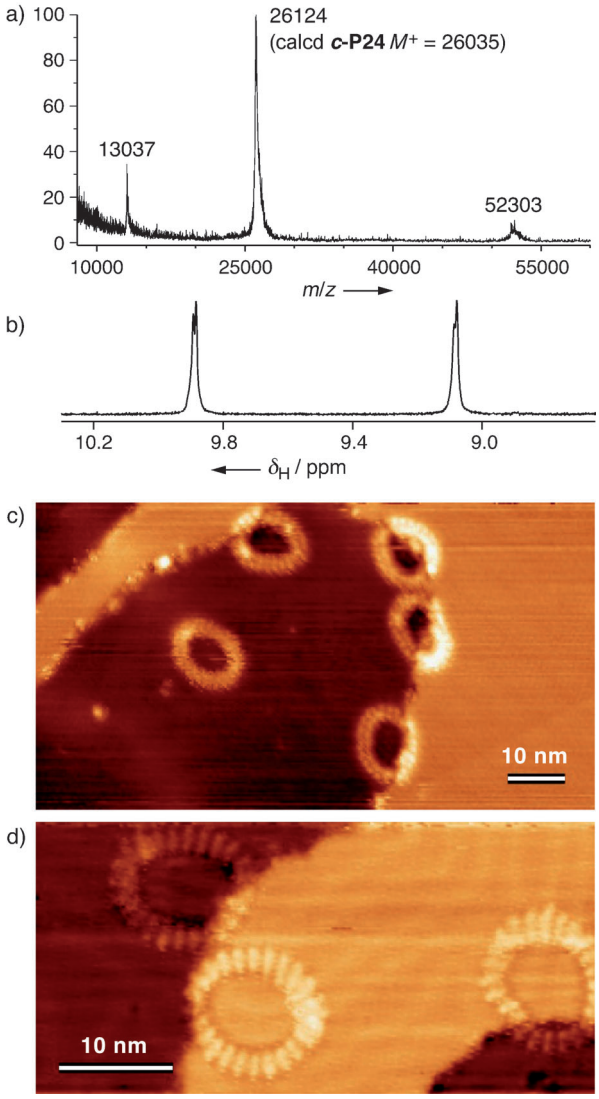

Figure 2. Characterization of the nanoring ***c*-P24**: a) MALDI-TOF mass spectrum, b) partial ^{1}H NMR spectrum (β-pyrrole protons region; $CDCl_3$/1% C_5D_5N, 298 K, 500 MHz), and c,d) STM images of ***c*-P24** molecules on a gold surface.

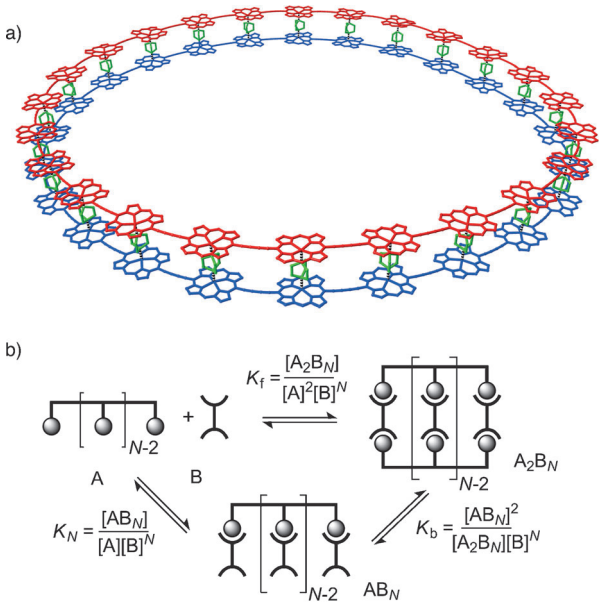

Figure 3. a) Structure of (***c*-P24**)$_2$·(DABCO)$_{24}$ calculated using the MM+ force field (HyperChem). Aryl side groups and hydrogen atoms are omitted for clarity. b) Generic thermodynamic cycle for the formation of double-strand complexes using a bidentate ligand.

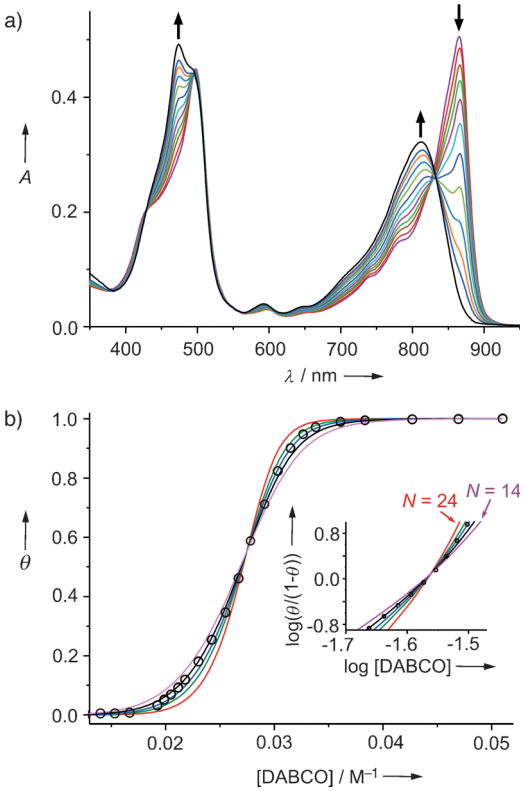

Figure 4. UV/Vis/NIR titration of DABCO into (***c*-P24**)$_2$·(DABCO)$_{24}$ (c = 0.2 μM, $CHCl_3$, 298 K). a) Absorption spectra over the course of the titration. Arrows indicate changes on addition of DABCO. b) Mole fraction of single-strand (***c*-P24**)·(DABCO)$_{24}$ (θ) derived from the absorption at 864 nm (black dots), fitted to the calculated curves for N = 14 (pink line), 16 (black line), 18 (blue line), 20 (green line), and 24 (red line) binding sites. The inset shows the Hill plot with the fits for the same values of N.

as expected for a two-state equilibrium with this stoichiometry. The simulated Hill coefficient for a process of the type shown in Figure 3b with N = 24 is n_H = 15.9, and the experimental value of 11.7 corresponds to an apparent number of binding sites of N = 16–18 (Figure 4b). Thus, denaturation of the (***c*-P24**)$_2$·(DABCO)$_{24}$ complex does not appear to be a completely all-or-nothing process; there is some population of partially bound species which broadens the denaturation curve.

In conclusion, we have prepared a 10 nm diameter butadiyne-linked, π-conjugated 24-porphyrin nanoring ***c*-P24** by Vernier-templated synthesis from a linear porphyrin octamer ***l*-P8**, and also from a linear porphyrin hexamer ***l*-P6**. The ring has been characterized using ^{1}H NMR spectroscopy, MALDI-MS, and STM imaging. Although there are a few reports of larger π-conjugated macrocycles[24] and larger cyclic porphyrin oligomers,[25] ***c*-P24** is the largest molecular ring to have been synthesized by a template-directed strategy, and this strategy should be applicable to the selective synthesis of even larger macrocycles. The observation that ***c*-P24** can be locked into a planar conjugated tertiary structure by formation of the (***c*-P24**)$_2$·(DABCO)$_{24}$ sandwich complex indicates that it is a promising system for exploring molecular Aharonov–Bohm effects.[24,26]

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[13] We have not yet detected the formation of knotted products of the type shown in Figure 1 d.

[14] The identities of ***c*-P16** and ***c*-P18** were demonstrated by ^{1}H NMR spectroscopy, MALDI TOF MS, and STM imaging; see the Supporting Information.

[15] The MALDI mass spectrum of ***c*-P24** in Figure 2 a exhibits minor signals at half and twice the expected mass. The resolution is not sufficient to determine whether these signals arise from $[M]^{2+}$ and $[M_2]^+$ of ***c*-P24**, or from traces of ***c*-P12** and ***c*-P48**.

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[19] The spectral changes associated with denaturation of (***c*-P24**)$_2$·(DABCO)$_{24}$ are similar to those for denaturation of (***c*-P12**)$_2$·(DABCO)$_{12}$; however, the band for (***c*-P24**)$_2$·(DABCO)$_{24}$ at $\lambda_{max} = 864$ nm is red-shifted compared with that of (***c*-P12**)$_2$·(DABCO)$_{12}$ at $\lambda_{max} = 850$ nm, thus reflecting the greater π conjugation in the larger ring. The absorption band of (***c*-P24**)$_2$·(DABCO)$_{24}$ is also broader, indicating that the larger nanoring is more flexible.

[20] The following expression for the mole fraction of the complex formed can be deduced from the generic thermodynamic cycle in Figure 3 b:

$$\theta = \left(-K_b[\mathrm{B}]_0^N + \sqrt{K_b^2[\mathrm{B}]_0^{2N} + 8K_b[\mathrm{B}]_0^N[\mathrm{A}]_0}\right)/(4[\mathrm{A}]_0)$$

where $[B]_0$ is the total concentration of the bidentate ligand, and $[A]_0$ is the total concentration of the *N*-site zinc porphyrin oligomer.

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[22] The switching window c_R is defined as the factorial increase in ligand concentration required to change the bound/free ratio from 1:10 to 10:1 (see Ref. [21]).

[23] Compared with denaturation of (***c*-P24**)$_2$·(DABCO)$_{24}$, denaturation of (***c*-P12**)$_2$·(DABCO)$_{12}$ is less cooperative and gives a Hill coefficient of $n_H = 9.5$ and a switching widow of $c_R = 1.8$. The (***c*-P12**)$_2$·(DABCO)$_{12}$ complex is also less stable; the DABCO concentration required to achieve 50 % denaturation is 5.8 mM, compared with 27 mM for (***c*-P24**)$_2$·(DABCO)$_{24}$.

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