Enzyme mimics based on cyclic porphyrin oligomers: strategy, design and exploratory synthesis

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A strategy is set out for the design and synthesis of a series of cyclic porphyrin oligomers which should be able to bind two or more substrate molecules, catalyse a reaction between them and release the product(s). Exploratory syntheses and some spectroscopic properties of butadiyne-linked cyclic dimer, trimer and tetramers of two *meso*-diaryl porphyrins are described in detail.

Introduction

This paper is the first of a series[1-5] describing in detail our project to create enzyme mimics based on oligomeric porphyrins. The ultimate aim is to create systems which are capable of binding two or more substrates within a cavity, catalysing reaction between them and releasing the product(s). The long-term aim is *not* to mimic any particular natural enzyme. However, inspired by the example of nature, we want to understand the principles of how to design and create homogeneous catalytic systems. Although we are still a long way from achieving that goal, the key porphyrin trimer described in this paper effectively and stereoselectively accelerates an intermolecular Diels–Alder reaction[6,7] and catalyses acyl transfers,[7,8] proving that the basic concept is viable. Since completion of the work described in this series, the basic design has undergone further evolution in several directions.[9]

In this paper we set the scene at the outset of this work in 1987, describe our overall strategy, discuss our molecular and synthetic design, give details of early syntheses of the butadiyne-linked cyclic porphyrin oligomers which were our initial targets,[10] and present spectroscopic evidence in support of the extraordinary structures created. These exploratory syntheses generated sufficient material for the ligand-binding studies which form the basis of the second paper in the series.[1] The resulting ligand-templated syntheses of oligomers ranging from dimers to an octamer are described in the following two papers,[2,3] while the remaining papers in the series cover oligomers which are extended by platinum- or octatetrayne-links.[4,5]

Background and strategy

The concept of model enzymes has a long history:[11,12] Breslow,[13] Cram[14] and Lehn[15] amongst others have created catalytic systems by attaching reactive groups to the peripheries of binding pockets, while many simple models of Cytochrome p450 have also been described.[16] Many asymmetric homogeneous catalysts such as the Sharpless–Katsuki allylic epoxidation system[17] and Kagan's hydrogenation catalyst[18] might also be categorised as model enzymes of this type. Each of these binds a single substrate and uses the proximity of a reactive group on the catalytic molecule.

We set ourselves a rather different goal: to create a system with two convergent binding sites positioned in such a way that two substrate molecules can be held in close proximity, or a single substrate can be held at two ends. Such an enzyme has no need of discrete catalytic sites and can catalyse reactions simply by virtue of its binding properties. Conceptually this approach is closely related to the use of catalytic antibodies, where a supposed transition state analogue is used to generate an 'ideal' binding site.[19] Our approach has the advantage of designed receptors whose properties are under synthetic control and whose binding can be dissected in detail, while the catalytic antibody approach has the advantage of sampling many more possible receptors for any given reaction. A detailed comparison of the merits of the two approaches must await the experimental investigation of many more systems and reactions.

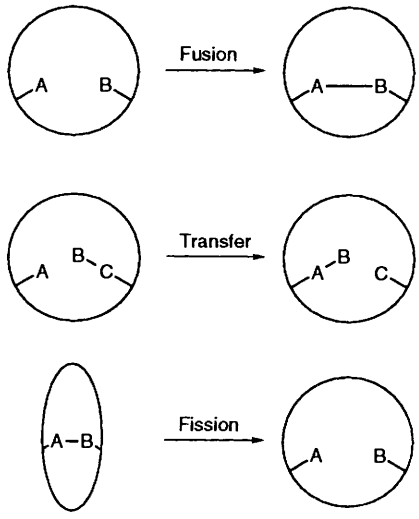

Fig. 1 Schematic view of possible fusion, transfer and fission processes catalysed within the cavity of an enzyme mimic

Three classes of reaction which could be catalysed by a suitable receptor are fusion, transfer and fission; these are illustrated schematically in Fig. 1. Strictly speaking, fusion and fission are just two sides of the same coin since any isolated enzyme must behave reversibly, but it is easier to consider them separately. Fusion and transfer reactions would be expected to be accelerated simply by the proximity of the two substrates; in effect, the unfavourable entropy of activation is reduced, or paid for, by the favourable enthalpy of binding. By contrast the driving force for the fission reaction illustrated in Fig. 1 would be relief of the mechanical strain induced in the host by bidentate substrate binding. Our Diels–Alder[6,7] and acyl transfer[7,8] reactions are examples of fusion and transfer reactions, respectively. We know of no clear experimental examples of the strain-induced fission illustrated, although the cobalt porphyrin dimer dioxygen reduction catalysts of

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Collman and of Chang[20] may gain some of their efficiency this way.

It was clear at the outset that any host system capable of catalysing interesting reactions would have to enclose a large volume and, therefore, if it was to be synthetically readily accessible, it would have to be constructed from large active building blocks. At an early stage we chose the porphyrin unit as one of our primary building blocks.† Porphyrins are ideal building blocks for assembly of large host architectures because of their central binding sites, nominally planar geometry, stability, ease of synthesis and spectroscopic eloquence deriving from the delocalised π-system. Their properties can also be fine tuned by varying the complexed metal atom. Porphyrins have an intense chromophore which facilitates their chromatographic purification and enables even nanogram quantities to be characterised by their absorption and emission spectra. The wavelength of metalloporphyrin absorption is sensitive to axial ligand coordination and exciton coupling alters the absorption of proximal porphyrins in a way which can be accurately predicted.[23] The large diamagnetic ring-current of porphyrins dominates their ^{1}H NMR spectra and enables detailed structural information to be obtained from the chemical shifts of bound species.

Our strategy therefore was to design and construct cyclic porphyrin dimers and trimers that enclose a large open cavity. The ligand-binding properties of these systems would then be investigated with two complementary aims in view: (a) development of ligand-templated syntheses of specifically desired oligomers and (b) understanding of what types of ligands might be substrates for intracavity catalysis. Multifunctional ligands which might bind several monomeric porphyrins and then direct oligomer synthesis in a desired direction by templating can be also viewed as transition state analogues for reactions between several monofunctional ligands within preformed cavities. The complementarity or symmetry relating these two processes can be summarised as templating outwards from inside, and inwards from outside.

The first generation of porphyrin dimers prepared by our group with these aims suffered from several disadvantages, including inefficient synthesis, poor solubility, multiple diastereoisomers resulting from low molecular symmetry, and collapsed cavities due to a combination of flexible linkages and porphyrin–porphyrin attraction.[24,25] Those molecules gave a useful insight into the nature of π–π interactions,[26] but were unsuitable for their intended purpose. The lessons learnt from that first generation led to the design criteria and successful second generation of molecules described in the present series of papers.

Molecular and synthetic design

The needs for efficient synthesis, high symmetry, relatively rigid linkers and an open accessible cavity led us to the *meso*-diarylporphyrin as basic building block, with linkers placed at the *meta*-position of the aryl group (Fig. 2). This substitution pattern directs the linker perpendicular to the plane of the porphyrin, generates a large cavity and avoids the need to separate atropoisomers.‡ Furthermore, simple geometrical considerations show that the cyclic trimer should be strain-free

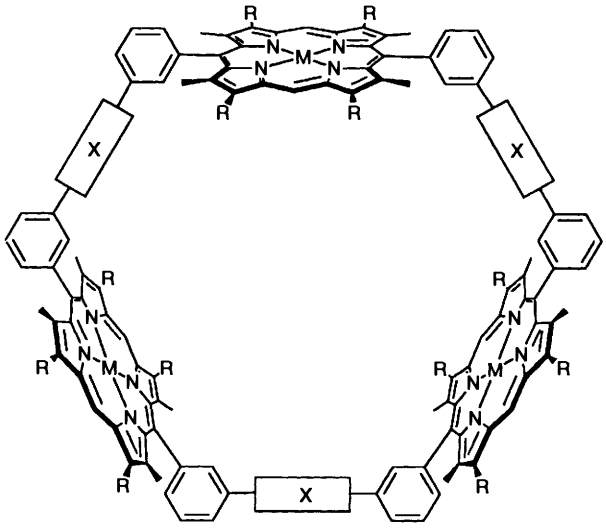


Fig. 2 Schematic view of the cyclic porphyrin trimers. M = Zn or H_2, X = –C≡C–C≡C– (for **c-Tri1**), R = Et (for **c-Tri1a**) or $CH_2CH_2CO_2Me$ (for **c-Tri1b**). Similar nomenclature is used for cyclic porphyrin dimers (*e.g.* **Zn_2-c-Dim1b**), cyclic tetramer (*e.g.* **Zn_4-c-Tet1b**), and cyclic pentamer (*e.g.* **Zn_2-c-Pen1b**).

if a linear linker is used. The attractions of a trimer include the large working volume available and the possibility of termolecular chemistry, although at the price of complex binding and kinetics. Methyl β-pyrrole substituents were used adjacent to the aryl groups, to reduce steric compression at the porphyrin periphery, because this can lead to complications associated with porphyrin non-planarity.[29] Large non-polar substituents were desirable at the other β-pyrrole positions to improve the solubility: we looked at two series of compounds, with R as ethyl (as in **Zn_3-c-Tri1a**) and as $CH_2CH_2CO_2Me$ (as in **Zn_3-c-Tri1b**).§ The ester functionalised series proved slightly more difficult to make (see below) but has the great advantage that the solubility characteristics of any oligomer can be tuned simply by transesterification with appropriate alcohols. The ability to control solubility at will, and independently of oligomer synthesis, has proved to be vital in the later stages of this and related work.[1–3,8,30]

We decided in the first instance to use butadiyne linkers generated by Glaser coupling of a terminal alkyne:

$$\text{Ar–C}\equiv\text{C–H} + \text{H–C}\equiv\text{C–Ar} \longrightarrow \text{Ar–C}\equiv\text{C–C}\equiv\text{C–Ar}$$

This reaction has been used to construct many large macrocycles, because it generally goes in good yield under mild conditions.[31–35] These design considerations, and the well-precedented synthesis of diaryl porphyrins,[27,36–38] led to a target porphyrin trimer through the highly convergent synthesis illustrated in Fig. 3: trimer (and other oligomers) should be accessible from readily available starting materials in three key steps. Model building and molecular mechanics calculations indicated that the butadiyne-linked trimer should enclose a cavity where the metal–metal distance is around 15 Å, while in the dimer the metal–metal distance is around 12 Å. The overall design was such that use of a range of linear linkers would generate analogous cavities which differ in size but not shape:

† Following the pioneering work of Burrows and of Davis,[21] our group has also found cholic acid to be a versatile building block for binding and catalytic systems. The concave shape and hydrogen-bonding features of cholic acid complement well the properties of porphyrins described here.[22]

‡ The rotation rate of *meta*-substituted *meso*-aryl groups is slow (*ca.* 1 Hz) on the NMR chemical shift time-scale at room temperature whereas rotation of *ortho*-substituted *meso*-aryl groups is so slow that atropoisomers only interconvert on heating.[27,28]

§ The system of abbreviated formulae used to refer to hosts in this paper is summarised in Fig. 2. For example in **Zn_3-c-Tri1a**: **Zn_3** means three porphyrins metallated with zinc; **-c-** means cyclic oligomer; **Tri** means trimer; **1** means the butadiyne linked series; **a** means ethyl side chains. The monomer from which **Zn_3-c-Tri1a** is synthesised is **Zn-Mon1a** (Fig. 3). This system of nomenclature is continued and expanded in the following papers in this series.

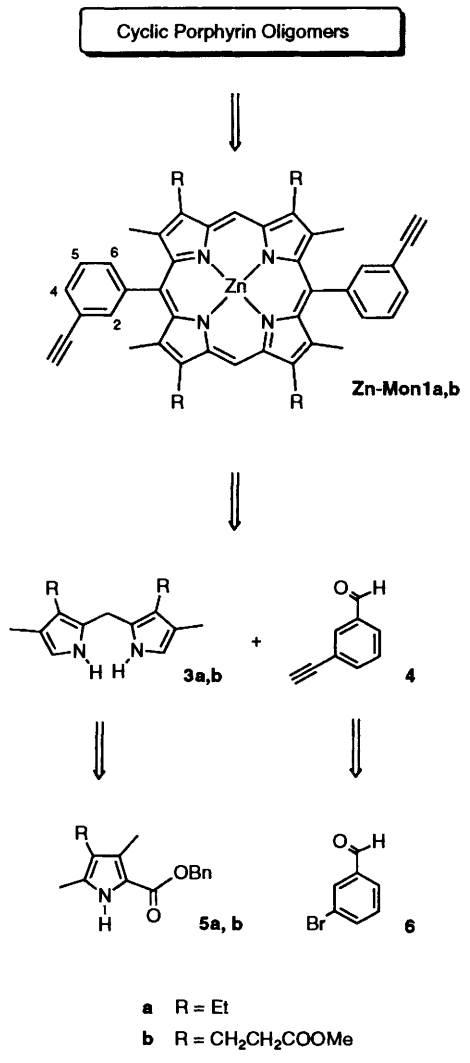


Fig. 3 Convergent synthetic plan for the target cyclic porphyrin oligomers

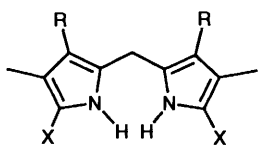
later papers in this series describe larger analogues with platinum[4,39] and octatetrayne[5] links.

Initially we decided to concentrate on zinc porphyrins for the following reasons: they are diamagnetic so are readily studied by NMR; they are easy to prepare from free-base porphyrins and are readily demetallated with dilute acid but they are stable to moisture, air and silica; they are neutral so avoid the complications associated with counter anions; they form five-coordinate 1:1 complexes with amines which have suitable binding constants for measurement by NMR or UV titration; they do not normally form six-coordinate 1:2 complexes with amines, while complexes with O, S and P donor ligands are much less stable than those with amines; the structure of zinc porphyrin–pyridine complexes is known accurately from X-ray diffraction studies,[40,41] zinc porphyrins are fluorescent whereas heavier metal porphyrins are not. Binding to zinc porphyrins has little effect on the reactivity of a ligand but, in principle, other metalloporphyrins can be used to activate bound species.

Results and discussion

Synthesis

The dihydrodipyrrins **1a**, **b** were synthesised using literature procedures[27,42–44] and quantitatively converted into **2a**, **b** by



palladium–carbon-catalysed hydrogenolysis. Decarboxylation of **2a** to give **3a** was initially carried out using aqueous alkali,[27] but later we found the yield could be improved by using refluxing 2-aminoethanol.[45,46] Treatment of a 1:1 mixture of **3a** and 3-ethynylbenzaldehyde,[47] **4**, with methanolic toluene-*p*-sulfonic acid (Gunter's conditions[37]) gave a white precipitate of porphyrinogen, which was filtered off and treated immediately with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in THF, generating the bisacetylenic porphyrin, **H_2-Mon1a** in 77% isolated yield after recrystallisation.

Attempted preparation of **3b** by decarboxylation of **2b** in 2-aminoethanol failed; presumably the amine reacts with the ester groups. This problem was circumvented by a one-pot decarboxylation and porphyrin synthesis procedure; **3b** was generated by acid catalysed decarboxylation of **2b** and the acid also catalysed condensation with **4** when it was added to the reaction mixture. **H_2-Mon1b** was isolated in 55% yield after DDQ oxidation. Both **H_2-Mon1a** and **H_2-Mon1b** are easily prepared on the gram scale, providing plenty of material with which to explore the feasibility of coupling. Metallated derivatives such as **Zn-Mon1a**, **b** were prepared in near quantitative yield using zinc acetate in chloroform.

Oxidative coupling of **H_2-Mon1a**, **b** would be expected to give linear butadiyne-linked intermediates which could cyclise to give dimers, **H_4-c-Dim1a**, **b**, trimers, **H_6-c-Tri1a**, **b**, and higher cyclic oligomers. Numerous procedures have been published for performing Glaser coupling,[34–35] but most proved not to be practical with our system. We found that Glaser coupling occurs extremely rapidly in pyridine at room temperature, if a very large excess of copper(I) chloride is used with air as the oxidant and that copper metallation of zinc porphyrins is quite slow under these conditions. Thus reaction of 0.5 mmol dm^{-3} **Zn-Mon1a** with 60 mmol dm^{-3} CuCl in pyridine for 24 h gave **Zn_3-c-Tri1a** as the main product. Zinc was removed from the porphyrins after coupling, with dilute acid, to facilitate chromatographic separation of the oligomers. The trimer was isolated, after conversion to **H_6-c-Tri1a**, in 35–45% yield. Cyclic tetramer **Zn_4-c-Tet1a** was also produced in about 15–20% analytical yield, but it was difficult to separate it from small amounts of cyclic pentamer so that the isolated yield of pure **H_8-c-Tet1a** was only about 5%. The reaction also produced some insoluble material which appeared to contain dimer, **Zn_2-c-Dim1a**: FAB MS of a solution of the precipitate in trifluoroacetic acid gave a peak at the correct mass for cyclic dimer. **Zn-Mon1b** reacted in a similar way to **Zn-Mon1a**. Under the same conditions it gave 35–40% yields of **H_6-c-Tri1b** as well as higher oligomers. However, unlike the case with **Zn-Mon1a** all the products from **Zn-Mon1b** were soluble, including **Zn_2-c-Dim1b** which was isolated, after conversion into **H_4-c-Dim1a**, in 25–35% yield.

At the time of this work only one other trimer-forming Glaser coupling reaction was known, that of Sondheimer,[33] and there was no precedent for such efficient trimerisation. However, there have since been many other examples of this type of reaction reported.[48–52] The fact that such very large ring compounds can be prepared efficiently must be attributed in part to the efficiency of the Glaser coupling process. But it is also a result of rigidity of the bisacetylenic precursors, which reduces the unfavourable entropy associated with supermacrocyclisation by limiting the conformational freedom of the

intermediates; these reactions are *structure directed*. In the third paper of this series we describe how the cyclic dimer and trimer can be synthesised even more efficiently when their formation is both structure-directed and template-directed.

When **H_6-c-Tri1a** is stirred with zinc acetate in chloroform, the progressive metallation of the trimer can be followed by TLC. First **ZnH_4-c-Tri1a** starts to appear, then **Zn_2H_2-c-Tri1a** and, finally, **Zn_3-c-Tri1a**. All the material is eventually converted into this permetallated compound, but the rise and fall in the concentration of each intermediate can be seen clearly because the chromatographic mobilities increase with increasing metallation. This experiment provided compelling evidence for the trimeric nature of **H_6-c-Tri1a**. It also enabled hosts such as **Zn_2H_2-c-Tri1a** to be prepared, by chromatography of the reaction mixture before complete reaction. **Zn_2H_2-c-Tri1a** is an interesting host because of the relationship between its binding properties and those of **Zn_3-c-Tri1a**. It is also a potentially valuable precursor to heterometallated trimers. The chromatographic mobilities of the methyl-ester functionalised porphyrins are much less affected by metallation; their R_Fs are dominated by the ester groups so we did not attempt to prepare partially metallated forms of these hosts.¶

The ester functionalised cyclic oligomers **H_4-c-Dim1b** and **H_6-c-Tri1b** obviously have potential for conversion into water-soluble hosts, either by saponification to polycarboxylic acid salts or by attaching large water-solubilising groups by amide or ester links. This is not an area which we have pursued in any detail. However, a single hydrolysis experiment with **Zn_3-c-Tri1b** yielded a potassium salt which is sparingly soluble in water; its UV spectrum can easily be recorded in pure water but the ^{1}H NMR spectrum required use of D_2O–[$^2H_4$]methanol (1 : 1)

NMR spectroscopy

The spectra of **H_2-Mon1b** and **H_6-c-Tri1b** are almost identical except for the absence of the terminal acetylene proton in **H_6-c-Tri1b** and the fact that all the resonances in **H_6-c-Tri1b** are shifted upfield by ~0.1 ppm. This shift is due to the trans-cavity ring-current and its low value is evidence that the porphyrin units are far apart and that the cavity is predominantly open. Comparison of the spectrum of **H_4-c-Dim1b** with that of **H_2-Mon1b** (Fig. 4) shows that, as expected, the dimer has larger trans-cavity ring-current induced shifts (~0.25 ppm) than the trimer. The pattern of the aromatic resonances of **H_2-Dim1b** is also different; the internal *ortho* proton is shifted upfield by 1 ppm whereas the external *ortho* proton is shifted downfield by 0.45 ppm. This indicates that the aryl groups bend out-of-the-plane of the porphyrin to relieve strain in the butadiyne links. In a simple diaryl porphyrin, the *ortho*-aromatic protons lie near the boundary between the shielding and deshielding regions of the porphyrin ring-current. As the aryl groups bend out-of-the-plane of the porphyrin, the internal *ortho* protons move into the shielded region and the external protons move into the deshielded region.

The ^{1}H NMR spectrum of the unfunctionalised trimer, **H_6-c-Tri1a**, and also the metallated forms of both series, show similar *trans*-cavity ring-current shifts and aromatic resonance patterns to those of their analogues in Fig. 4. The spectra of partially metallated species such as **Zn_2H_2-c-Tri1a** are essentially identical with those of corresponding mixtures of fully metallated and unmetallated hosts because metallation has little effect on the porphyrin ring current or molecular shape. The

¶ Recently we have found that replacement of the methyl esterifying group by isodecyl groups restores the dominance of metallation state in chromatographic properties and allows separation of partially-metallated dimers and trimers on alumina (R. S. Wylie, E. G. Levy and J. K. M. S., unpublished)

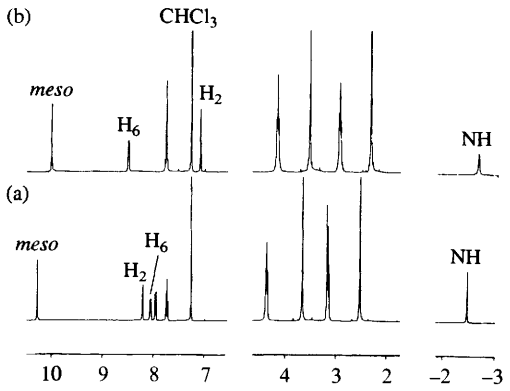


Fig. 4 ^{1}H NMR spectra of (a) monomer **H_2Mon1b** and (b) dimer, **H_4-c-Dim1b** in $CDCl_3$ solution

^{1}H NMR spectrum of **Zn_4-c-Tet1a** is more complicated than that of the smaller cyclic oligomers as a result of slow conformational equilibria; the spectrum of this host can only be understood by comparison with those of its complexes, so it is discussed in the following paper.[1]

The *J*-modulated spin echo ^{13}C spectra of **Zn_3-c-Tri1a** and **Zn-Mon1a** show the same number of resonances and are virtually identical except for one signal: the resonance due to the terminal acetylenic carbon of **Zn-Mon1a** is shifted, inverted and reduced in intensity on conversion into **Zn_3-c-Tri1a**, indicating formation of butadiyne links.

IR and electronic spectra

As expected, the absorptions at 3304 cm^{-1} due to the terminal acetylene groups of **Zn-Mon1a** and **b** disappear on formation of the cyclic porphyrin oligomers. This is a sensitive test for completion of coupling because the terminal acetylene resonance is very intense and can be detected in low concentrations by FT IR. We have been unable to detect signals due to the butadiyne moiety in these compounds which is not surprising because symmetrical butadiynes give very weak IR bands.

The UV–VIS absorption spectra of **Zn_3-c-Tri1a**, **Zn-Mon1a** and diphenylbutadiyne show useful similarities and differences. The Soret and *Q* bands of the two porphyrins are superimposable: no exciton coupling can be detected in the spectrum of **Zn_3-c-Tri1a**, showing that the porphyrin chromophores are well separated in space. This is also true of the free-base forms and ester-functionalised trimers, but the dimers, **Zn_2-c-Dim1b** and **H_4-c-Dim1b** show very slight exciton coupling, their Soret bands being red-shifted by *ca* 1 nm. This is close to the predicted shift for two parallel chromophores 10 Å apart. The cyclic porphyrin oligomers also exhibit a band due to the butadiyne chromophore in the 300–400 nm region. This signal was very useful for estimating the extent of Glaser coupling while developing the synthesis of these compounds.

FAB mass spectra

Positive ion FAB mass spectra of the cyclic oligomers show intense peaks which closely match the accurate mass isotopomer distributions expected for M^+ and M^{2+} (and M^{3+} for trimers). For example, Fig. 5 shows a spectrum of **H_6-c-Tri1a**. Peaks arising from multiply charged ions are readily distinguished from those of lighter singly charged molecules by inspection of their isotopic peak distribution and observation of fractional masses. Higher oligomers such as the tetramer, **H_8-c-Tet1a**, and pentamer, **H_{10}-c-Pen1a**, also gave intense molecular ions by FAB MS. The unusually high intensity of multiply charged ions in these oligomers is a reflection of (a) the ease of oxidation of individual porphyrin units, and (b) the electronic

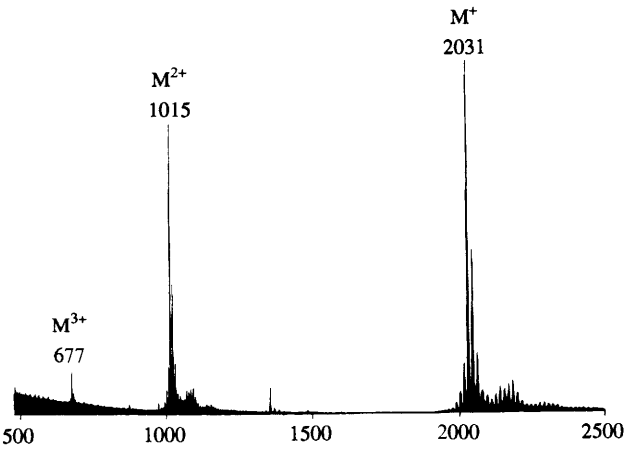


Fig. 5 FAB mass spectrum of trimer **H_6-c-Tri1a**

isolation of those units in the oligomers; one would not expect second and third ionisations to be easy where the first charge was delocalised over the whole molecule.‖ The ester-functionalised hosts gave much less intense molecular ions than the ethyl series, presumably as a result of their greater polarity. We were able to use the sensitivity of FAB MS to **H_6-c-Tri1a** to establish that the protonated form of this host is able to bind giant anions such as $[PW_{12}O_{40}]^{3-}$, $[SiW_{12}O_{40}]^{4-}$ and $[Os_{10}C(CO)_{24}]^{2-}$ [53]

Conclusion

This paper describes the design principles for a new range of host structures with very spacious open cavities, and establishes the viability of a direct and efficient synthetic route to these new structures. Crucial features of the design strategy include the ability to control solubility independently of the synthesis and the potential to create analogous series of receptors with the same cavity topology but different cavity size and rigidity. In addition, detailed spectroscopic evidence has been assembled to support both the covalent structures claimed and to provide preliminary evidence on cavity shapes. The following paper [1] provides further detailed evidence for both structure and cavity topology through ligand binding studies, while two recent crystal structures provide the ultimate proof of structure for **Zn_3-c-Tri1a** and **Zn_4-c-Tet1b**.[54,55] Since this exploratory synthesis was carried out, numerous minor improvements have been made; for example it is most efficient to keep a TMS group on the alkyne until after porphyrin synthesis. The current best synthesis of the oligomers described here is given in the third paper of the series.[2]

These molecules have proved to be versatile objects for molecular recognition and catalysis,[6-8] and the understanding obtained in this work has laid the basis for the development of a further generation of hosts with more finely tuned properties.[9] Since we embarked on this work, several groups have described a variety of synthetic systems that use binding energy to accelerate reactions between two substrate molecules.[56-59]

Experimental

All column chromatography was carried out using 60 mesh silica gel. Deuteriochloroform was de-acidified before use by storage over anhydrous potassium carbonate overnight. NMR spectra were recorded on Bruker AM-400 or Bruker WM-250 spectrometers. Fast atom bombardment (FAB) mass spectra were obtained using a *meta*-nitrobenzyl alcohol matrix either in Cambridge (on a Kratos MS-50 instrument) or in Swansea, by the S. E. R. C. mass spectrometry service. IR spectra were recorded in chloroform using a Perkin-Elmer 1710 instrument in Fourier transform mode. Microanalyses were carried out by the University Chemical Laboratory Microanalysis Department in Cambridge. UV spectra were recorded in dichloromethane. In cases where ^{13}C NMR spectra have been partially assigned by *J* modulation this is indicated by (+), for quaternary/secondary signals or (−) for primary/methyl signals, following the chemical shifts. Free-base porphyrins were converted into zinc complexes in near quantitative yield by treatment with zinc acetate dihydrate in refluxing chloroform (10 min). Excess of zinc acetate was removed using a short column of silica, eluting with chloroform.

The final purification step in all porphyrin preparations was crystallisation by layered addition of methanol to a chloroform solution of the compound, followed by drying *in vacuo*. This gave solvent-free material, even with zinc porphyrins. Filtration through a 0.45 μm membrane prior to recrystallisation greatly facilitated the preparation of microanalytically pure material.

5,15-Di(3-ethynylphenyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin H_2-Mon1a[37]

Toluene-p-sulfonic acid monohydrate (200 mg, 1.05 mmol) was added to a solution of 3,3′-diethyl-4,4′-dimethyldihydrodipyrrin **3a** (1.00 g, 4.35 mmol) and 3-ethynylbenzaldehyde **4** (566 mg, 4.35 mmol) in methanol (30 cm^3) and the mixture deoxygenated and stirred under argon for 15 min. A white precipitate formed. The mixture was stored for 6 h at room temperature and then overnight at 5 °C. The white precipitate (porphyrinogen) was filtered off, washed in methanol (5 cm^3) and redissolved in THF (50 cm^3) to form a pale pink solution. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone, DDQ (1.6 g, 7 mmol) was added to the solution causing immediate intense colouration. The mixture was stirred for 1.5 h and then treated with triethylamine (2 cm^3) and evaporated. Purification of the residue by flash chromatography, eluting with chloroform, gave a main red band which was collected, concentrated to 50 cm^3 and crystallised to yield the title porphyrin (1.14 g, 77%) (Found: C, 84.0; H, 6.8; N, 8.1. $C_{48}H_{46}N_4$ requires C, 84.9; H, 6.8; N, 8.2%); δ_H(250 MHz; $CDCl_3$) −2.48 (2 H, s), 1.76 (12 H, t), 2.51 (12 H, s), 3.16 (2 H, s), 4.01 (8 H, q), 7.71 (2 H, t), 7.93 (2 H, d), 8.07 (2 H, d), 8.23 (2 H, s) and 10.23 (2 H, s); ν_{max}/cm^{-1} 3304 (CH); λ_{max}/nm 405, 505, 540, 574 and 625; *m*/*z* 678 (M^+).

[5,15-Di(3-ethynylphenyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrinato(-2)-N^{21},N^{22},N^{23},N^{24}]zinc Zn-Mon1a

(Found: C, 77.5; H, 6.0; N, 7.5. $C_{48}H_{44}N_4Zn$ requires C, 77.7; H, 6.0; N, 7.5%); δ_H(250 MHz; $CDCl_3$) 1.57 (12 H, t), 2.32 (12 H, s), 3.06 (2 H, s), 3.82 (8 H, q), 7.51 (2 H, m), 7.76 (2 H, d), 7.90 (2 H, d), 8.09 (2 H, s) and 9.96 (2 H, s); δ_C(100 MHz; $C_2D_2Cl_4$–C_5D_5N) 15.3 (−), 17.3 (−), 20.0 (+), 77.4 (−), 84.4 (+), 97.2 (−), 117.9 (+), 121.5 (+), 127.3 (−), 131.7 (−), 134.0 (−), 137.2 (+), 137.4 (−), 144.4 (+), 145.1 (+), 146.3 (+) and 147.9 (+); ν_{max}/cm^{-1} 3305 (CH); λ_{max}/nm 409, 539 and 572; *m*/*z* 740.3 (M^+).

5,15-Di(3-ethynylphenyl)-2,8,12,18-tetra(2-methoxycarbonylethyl)-3,7,13,17-tetramethylporphyrin H_2-Mon1b[44]

Palladium-on-carbon (10%; 140 mg) was added to a solution of 5,5′-dibenzyloxycarbonyl-3,3′-di(2-methoxycarbonylethyl)-4,4′-dimethyl-2,2′-dihydrodipyrrin **1b** (2.46 g, 4.0 mmol) in THF (100 cm^3) containing 1% triethylamine and the mixture was stirred under hydrogen for 1 h, by which time *ca.* 200 cm^3 (8 mmol) of gas had been consumed. The catalyst was filtered off and the solution of **2b** evaporated. TFA (argon-saturated; 25 cm^3) was added under argon at 0 °C to generate a solution of

‖ This electronic isolation is also apparent in the electrochemical properties of the oligomers, which are essentially identical with those of the monomer.

3b. After 20 min a solution of 3-ethynylbenzaldehyde **4** (520 mg, 4.0 mmol) in methanol (argon-saturated; 100 cm^3) was cannulated into the mixture which was then stirred for a further 2 h. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (1.36 g, 6 mmol) in THF (50 cm^3) was then added to the mixture after which it was stirred for a further 2 h. Triethylamine (20 cm^3) was then added to the mixture and the solvent removed by evaporation. Flash chromatography of the residue (SiO_2–$CHCl_3$, R_F 0.18) followed by recrystallisation yielded the title porphyrin (1.005 g, 55%); δ_H(400 MHz; $CDCl_3$) −2.48 (2 H, s), 2.52 (12 H, s), 3.15 (8 H, t), 3.18 (2 H, s), 3.65 (12 H, s), 4.36 (8 H, t), 7.73 (2 H, t), 7.95 (2 H, d), 8.04 (2 H, d), 8.20 (2 H, s) and 10.28 (2 H, s); ν_{max}/cm^{-1} 3304 (CH) and 1732 (C=O); λ_{max}/nm 408, 506, 539, 574 and 627; *m/z* 911 (M^+)

[5,15-Di(3-ethynylphenyl)-2,8,12,18-tetra(2-methoxycarbonylethyl)-3,7,13,17-tetramethylporphyrinato(−2)-N^{21},N^{22},N^{23},N^{24}]-zinc Zn-Mon1b. (Found: C, 69.1; H, 5.3; N 5.7. $C_{56}H_{52}N_4O_8Zn$ requires C, 69.0; H, 5.4; N, 5.7%); δ_H(400 MHz; $CDCl_3$) 2.47 (12 H, s), 3.13 (8 H, t), 3.16 (2 H, s), 3.67 (12 H, s), 4.31 (8 H, t), 7.77 (2 H, t), 7.95 (2 H, d), 8.05 (2 H, d), 8.20 (2 H, s) and 10.19 (2 H, s); λ_{max}/nm 410, 538 and 575; *m/z* 973 (M^+).

Unfunctionalised porphyrin trimer H_6-c-Tri1a

Zn-Mon1a (50 mg, 67 mmol) and copper(I) chloride (freshly prepared; 800 mg, 8.1 mmol) were dissolved in pyridine (150 cm^3) and the solution was stirred under dry air for 24 h. After this it was diluted with chloroform (200 cm^3) and washed with water until the aqueous layer was colourless (3 × 500 cm^3). The mixture was then treated with acetic acid until dark green (200 cm^3) after which it was washed with water (4 × 500 cm^3), evaporated and passed through a silica column, eluting with chloroform, to remove insoluble and polar by-products. The crude product was then chromatographed a second time, eluting with dichloromethane. (Fast purple–red bands of **Cu_2H_2-c-Tri1a** and **CuH_4-c-Tri1a** were occasionally observed, followed by the main red band of **H_6-c-Tri1a**.) Tetramer and higher oligomers remained on the column until eluted with 5% chloroform in dichloromethane; 15 mg of crude tetramer were thus obtained. The first band was recrystallised to yield the free-base trimer (20 mg, 45%). (The above procedure was also conducted on four times this scale; 200 mg of **Zn-Mon1a** yielded 85 mg, 48%, of **H_6-c-Tri1a** and 60 mg of crude **H_8-c-Tet1a**); δ_H(250 MHz; $CDCl_3$) −2.67 (6 H, s), 1.65 (36 H, t), 2.42 (36 H, s), 3.90 (24 H, q), 7.70 (6 H, t), 7.96 (6 H, d), 8.06 (6 H, d), 8.12 (6 H, s) and 10.10 (6 H, s); λ_{max}/nm 315, 334, 408, 506, 540, 573 and 625; *m/z* 2031 (M^+), 1015 (M^{2+}) and 677 (M^{3+}).

Zn_3-c-Tri1a. (Found: C, 77.8; H, 5.7; N, 7.6. $C_{144}H_{126}N_{12}Zn_3$ requires C, 77.9; H, 5.7; N, 7.6%); δ_H(250 MHz; $CDCl_3$) 1.65 (36 H, t), 2.39 (36 H, s), 3.90 (24 H, q), 7.70 (6 H, t), 7.97 (6 H, d), 8.06 (8 H, d), 8.12 (8 H, s) and 10.06 (6 H, s); δ_C(100 MHz; $C_2D_2Cl_4$–C_5D_5N; 50 °C) 15.5 (−), 17.7 (−), 20.0 (+), 82.5 (+), 97.0 (−), 99.7 (+), 117.0 (+), 120.8 (+), 127.6 (−), 131.9 (−), 134.3 (−), 137.0 (+), 137.3 (−), 144.8 (+), 144.9 (+), 146.0 (+) and 147.5 (+); λ_{max}/nm 315, 334, 409, 539 and 572; *m/z* 2220.9 (M^+), 1109.9 (M^{2+}) and 738.3 (M^{3+}).

Unfunctionalised porphyrin tetramer Zn_4-c-Tet1a

Crude **H_8-c-Tet1a** (100 mg; from several runs of the above **H_6-c-Tri1a** preparation, containing pentamer by FAB MS) was purified by repetitive flash chromatography (5% $CHCl_3$ in CH_2Cl_2), rechromatographing only the fastest non-trimer band from each column. After six repetitions no further change could be detected by TLC or ^1H NMR. The solution of partly purified tetramer was recrystallised from dichloromethane and treated with an excess of zinc acetate (50 mg) in chloroform (20 cm^3) to convert it into the zinc complex; it was then recrystallised again from dichloromethane to yield **Zn_4-c-Tet1a** (*ca.* 5 mg). This purified material is almost totally insoluble in dichloromethane, and is only sparingly soluble in chloroform even in the presence of pyridine; δ_H(400 MHz; $CDCl_3$–C_5D_5N) 1.63 (48 H, t), 2.41 (48 H, m), 3.89 (32 H, m), 7.57–8.24 (32 H, m) and 10.0 (8 H, m); λ_{max}/nm 315, 334, 409, 539 and 572; *m/z* 2960.6 (M^+). [This compound was also characterised as its *meso*-tetra(4-pyridyl)porphyrin complex (see next paper): **Zn_4-c-Tet1a·H_2-Py_4P**; δ_H(400 MHz; $CDCl_3$) −4.86 (2 H, s), 1.67 (48 H, br t), 2.24 (8 H, d), 2.41 (48 H, s), 3.97 (32 H, m), 5.67 (8 H, d), 6.91 (8 H, s), 7.67 (8 H, t), 7.91 (8 H, d), 8.01 (8 H, d), 8.44 (8 H, s) and 10.03 (8 H, s).]

Functionalised dimer (H_4-c-Dim1b) and trimer (H_6-c-Tri1b)

The above procedure was used with **Zn-Mon1b** (65 mg, 67 μmol) instead of **Zn-Mon1a**. The first column was run using chloroform as above, but the second column was eluted with chloroform–dichloromethane (1:1) instead of dichloromethane. An initial band of **H_4-c-Dim1b** was followed by **H_6-c-Tri1b** which tailed into higher oligomers.

H_4-c-Dim1b. Yield 15 mg, 30%; R_F($CHCl_3$) 0.13; δ_H(400 MHz; $CDCl_3$) −2.63 (4 H, s), 2.34 (24 H, s), 2.95 (16 H, t), 3.53 (24 H, s), 4.17 (16 H, t), 7.08 (4 H, s), 7.74 (8 H, m), 8.49 (4 H, d) and 10.01 (4 H, s); ν_{max}/cm^{-1} 1732 (C=O); λ_{max}/nm 407, 507, 540, 575 and 627; *m/z* 1818 (M^+).

Zn_2-c-Dim1b. (Found: C, 67.4; H, 5.0; N, 5.4. $C_{112}H_{100}N_8O_{16}Zn_2$ requires C, 69.2; H, 5.2; N, 5.8%); δ_H(400 MHz; $CDCl_3$) 2.30 (24 H, s), 2.90 (16 H, m), 3.55 (24 H, s), 4.10 (16 H, t), 7.01 (4 H, s), 7.72 (8 H, m), 8.50 (4 H, d) and 9.87 (4 H, s); δ_C(100 MHz; $CDCl_3$–C_5D_5N) 15.4, 21.6, 36.8, 51.2, 74.0, 82.3, 96.5, 116.9, 120.7, 126.7, 129.6, 132.5, 138.1, 138.8, 141.0, 143.7, 145.1, 147.0 and 173.2; λ_{max}/nm 316, 336, 410, 540 and 576; *m/z* 1945.7 (M^+).

H_6-c-Tri1b. Yield 20 mg, 40%; R_F($CHCl_3$) 0.11; δ_H(400 MHz, $CDCl_3$) −2.66 (6 H, s), 2.43 (36 H, s), 3.04 (24 H, t), 3.55 (36 H, s), 4.23 (24 H, t), 7.72 (6 H, t), 7.98 (6 H, d), 8.02 (6 H, d), 8.07 (6 H, s) and 10.16 (6 H, s); ν_{max}/cm^{-1} 1733 (C=O); λ_{max}/nm 408, 506, 539, 574 and 627; *m/z* 2726 (M^+) and 1364 (M^{2+}).

Zn_3-c-Tri1b. (Found: C, 68.9; H, 5.2; N, 5.7. $C_{168}H_{150}N_{12}O_{24}Zn_3$ requires C, 69.2; H, 5.2; N, 5.8%); δ_H(400 MHz; $CDCl_3$) 2.38 (36 H, s), 2.95 (24 H, t), 3.52 (36 H, s), 4.15 (24 H, t), 7.72 (6 H, t), 7.99 (6 H, d), 8.05 (6 H, d), 8.06 (6 H, s) and 10.00 (6 H, s); δ_C(100 MHz; $CDCl_3$–C_5D_5N) 15.5, 21.9, 37.0, 51.5, 74.1, 81.8, 96.8, 117.5, 120.8, 127.6, 131.9, 133.9, 136.8, 138.1, 141.0, 144.4, 145.8, 147.2 and 173.5; λ_{max}/nm 315, 335, 411, 539 and 575; *m/z* 2917 (M^+) and 1458 (M^{2+}).

Monofreebase dizinc unfunctionalised trimer (Zn_2H_2-c-Tri1a)

Zinc acetate dihydrate (3 mg, 14 μmol) was added to a stirred solution of **H_6-c-Tri1a** (10 mg, 5 μmol) in chloroform (50 cm^3) at room temperature and the reaction was monitored by TLC at 2 min intervals. The formation of partly metallated species was clearly observed; first **ZnH_4-c-Tri1a** started to appear, then **Zn_2H_2-c-Tri1a**, and finally **Zn_3-c-Tri1a**. After 14 min the main component was **Zn_2H_2-c-Tri1a** so the reaction mixture was immediately eluted through a column of silica with chloroform (to remove unchanged zinc) then flash chromatographed a second time, eluting with dichloromethane, to yield **Zn_2H_2-c-Tri1a** (2 mg, 19%). The other bands were treated with zinc acetate to give **Zn_3-c-Tri1a** (5 mg, 45%); δ_H(400 MHz; $CDCl_3$) −2.69 (2 H, s), 1.64 (36 H, t), 1.39 (24 H, s), 1.42 (12 H, s), 3.88 (24 H, m), 7.70 (6 H, m), 7.96 (6 H, d), 8.06 (6 H, d), 8.09 (2 H, s), 8.12 (4 H, s), 10.04 (4 H, s) and 10.10 (2 H, s); λ_{max}/nm 315, 334, 408, 506, 540, 573 and 624; *m/z* 2157.1 (M^+).

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