Synthesis of a Cyclic Porphyrin Trimer with a Semi-rigid Cavity

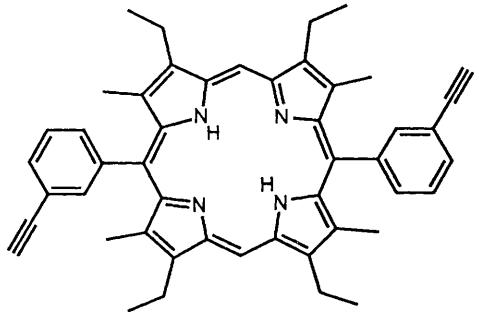
Harry L. Anderson and Jeremy K. M. Sanders*

University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.

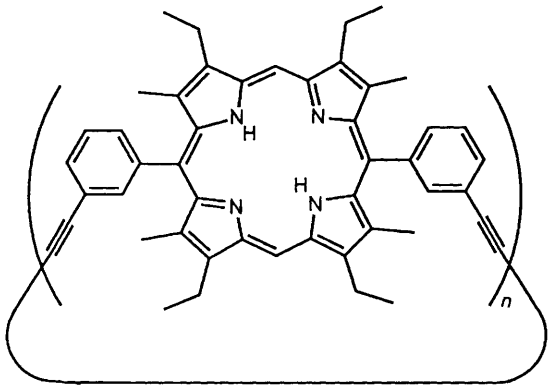
A cyclic trinuclear porphyrin host has been synthesised; its binding properties show that it has a spacious cavity which prefers an open conformation but which can close around small bidentate ligands such as 4,4'-bipyridyl.

The ability to bind two guest molecules so as to force them into close proximity is an essential feature of many enzymes and is also likely to be of value in the design of supramolecular devices. Most of the oligotopic co-receptor molecules[1] hitherto synthesised are either too small to bind any but the simplest guests, or they are too flexible to enforce useful proximity between separate bound species.[1,2] We report here the synthesis of an oligotopic receptor with a cavity which is spacious enough to accommodate more than one organic guest, rigid enough to exhibit a pre-organised non-collapsable cavity, and yet flexible enough to bind guest molecules even when they do not fit the relaxed cavity.

The bisacetylenic porphyrin (**1**)† was synthesised in 77% yield by reaction of 3-ethynylbenzaldehyde[3] with 3,3'-diethyl-4,4'-dimethyldipyrromethane followed by oxidation of the porphyrinogen with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.[4] Attempts at obtaining cyclic Glaser coupling products from (**1**) or its zinc derivative (**Zn1**) using conventional procedures[5] resulted in formation of insoluble material and copper-metallated products. However, when a 0.5 mM solution of (**Zn1**) in pyridine was stirred with a large excess of copper(I) chloride (120 equivs.) under air at room temperature for 24 h, coupling went to completion before porphyrin transmetallation became significant. At least 90% of the crude product was soluble in chloroform; no terminal acetylene groups were detected by FTIR and NMR. The main product was the cyclic trimer (**$Zn_3$2**) which was isolated, after conversion to (**2**) with dilute acid, in 47% yield. The cyclic tetramer (**$Zn_4$3**) was also formed in about 20% yield but we have not yet been able to separate this compound cleanly from small amounts of cyclic pentamer (**$Zn_5$4**).‡



(**1**)



(**2**) $n = 3$
(**3**) $n = 4$
(**4**) $n = 5$

Metallation of diaryl porphyrins with zinc results in a large increase in their chromatographic mobility on silica. Thus partial reaction of the free base (**2**) with zinc acetate in chloroform enabled us to isolate the dimetallated species (**$Zn_2$2**) in near-statistical yield. This compound is valuable as a ditopic host in its own right and as a potential synthetic precursor to a wide range of heterometallic receptors.

Molecular mechanics calculations (MM2) predict that the trinuclear porphyrin (**2**) and its metallo derivatives have a regular triangular geometry with a distance of 16 Å between porphyrin centroids. ^{1}H NMR and UV spectra confirm that the molecule is predominantly in an open conformation: the upfield chemical shifts experienced by all proton resonances of each porphyrin due to the ring currents of the other two are small (0.05—0.10 p.p.m.), and no exciton coupling[6] between porphyrin chromophores can be detected.

Further insight into the conformational behaviour of these structures was gained by investigating their binding to a range of pyridine ligands, using UV absorption and ^{1}H NMR

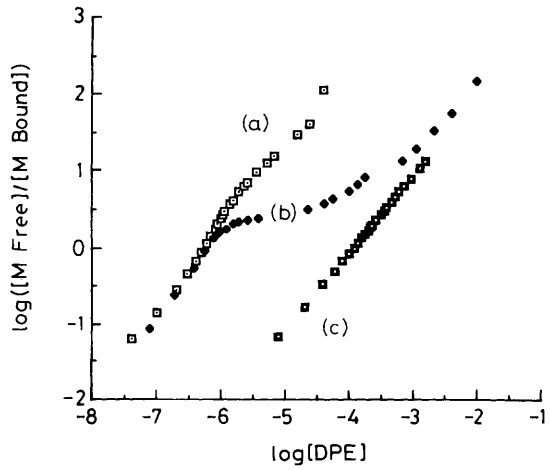


Figure 1. Hill plots for binding of metalloporphyrins (M) to DPE in CH_2Cl_2 at ambient temperature: (a) (**$Zn_2$2**), (b) (**$Zn_3$2**), (c) (**Zn1**).

† All new compounds gave satisfactory NMR and high resolution FAB mass spectra.

‡ All the cyclic porphyrin oligomers give characteristic FAB mass spectra containing molecular ion clusters for $M^{+\cdot}$, $M^{2+\cdot}$, and $M^{3+\cdot}$.

Table 1. Microscopic binding constants.[a]

Ligand	Porphyrin	K_1	K_2	K_3
Pyridine	(**Zn1**)	2.8×10^3		
	(**$Zn_2$2**)	2.6×10^3	2.6×10^3	
	(**$Zn_3$2**)	2.6×10^3	2.6×10^3	2.9×10^3
Bipy	(**Zn1**)	2.4×10^3		
	(**$Zn_2$2**)	1.6×10^4		
	(**$Zn_3$2**)	2.0×10^4	2.7×10^3	
DPE	(**Zn1**)	4.3×10^3		
	(**$Zn_2$2**)	4.5×10^6		
	(**$Zn_3$2**)	4.3×10^6	2.8×10^3	
TPyT	(**Zn1**)	1.3×10^3		
	(**$Zn_2$2**)	4.4×10^7		
	(**$Zn_3$2**)	$>10^9$		

[a] In $dm^3\ mol^{-1}$, measured in CH_2Cl_2 at ambient temperatures.

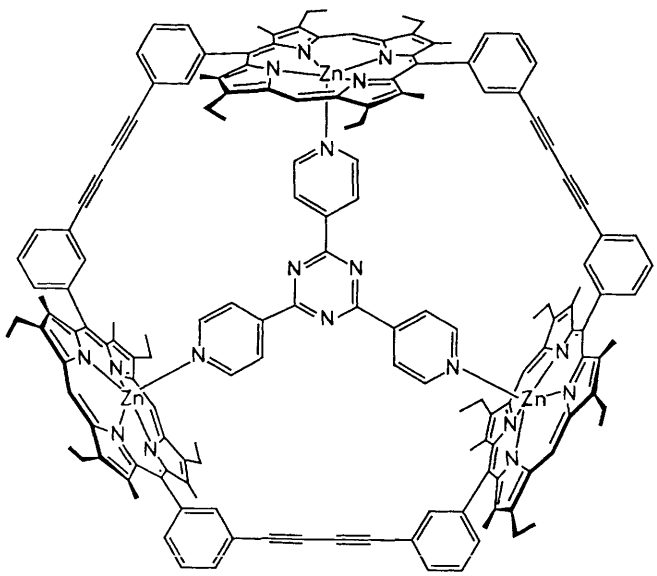


Figure 2. Structure of (**$Zn_3$2**)·TPyT complex.

spectroscopy and FAB mass spectrometry. Simulation analysis of UV titration curves[7] with pyridine, 4,4′-bipyridine (Bipy), 1,2-di-(4-pyridyl)ethane (DPE), and 2,4,6-tri-4-pyridyl-s-triazine[8] (TPyT) was used to obtain empirical binding constants, which were divided by their statistical weightings to give the microscopic binding constants[9] shown in Table 1. The cyclic species (**$Zn_2$2**) and (**$Zn_3$2**) show microscopic binding constants to pyridine which are identical, within experimental error, to that of the monomer (**Zn1**), which demonstrates that both the inside and the outside of the cavity are freely accessible to pyridine binding and that binding to each zinc site occurs independently.

The binding curves for co-ordination of bidentate ligands to (**$Zn_3$2**) are biphasic, as seen most clearly from the Hill plots[10] for DPE binding, Figure 1. At low ligand concentration one ligand molecule binds across two zinc atoms with binding constant K_1, despite the fact that this must cause a significant distortion of the host geometry; at higher concentrations a second ligand molecule binds to the third zinc site with a binding constant K_2 which is similar to K_1 for (**Zn1**). Only the first binding process is observed with (**$Zn_2$2**). The K_1 values for bifunctional ligands would be expected to be larger than the square of the binding constant to (**Zn1**) as a result of the chelate effect.[11] The fact that they are less than this reflects the strain associated with binding. This induced-fit strain is greatest for the smaller Bipy ligand because it requires more host distortion. Free base porphyrins are generally more flexible than metalloporphyrins[12] and yet there is no significant difference between K_1 values for (**$Zn_3$2**) and (**$Zn_2$2**), which implies that host distortion does not involve deformation of the unbound porphyrin.

TPyT has good size and shape complementarity with the cavity of these hosts and binds extremely strongly. Its binding constant to (**$Zn_2$2**) is greater than the square of its binding constant to (**Zn1**)§ and its 1 : 1 complex with (**$Zn_3$2**) is so stable that it can be observed directly by FABMS and is in slow exchange on the ^1H NMR timescale even in the presence of excess (**$Zn_3$2**) or TPyT. Analysis of ring current induced chemical shift changes shows that the complex has the structure shown in Figure 2, the pyridyl groups lying flat in the plane of the three zinc atoms. Its stability constant is too large for direct measurement from UV titration curves, which yield a lower limit of $10^9\ dm^3\ mol^{-1}$. Observation of exchange broadening between free and bound (**$Zn_3$2**) in high temperature ^1H NMR spectra at 250 MHz and 400 MHz in $C_2D_2Cl_4$ solution gives an estimate of 75 kJ mol^{-1} for $\Delta G^{\ddagger}$ at 370 K. This corresponds to an upper limit of *ca.* $10^{10}\ dm^3\ mol^{-1}$ for the binding constant at 298 K.

In summary, we have developed a direct synthetic route to a new range of tritopic hosts and shown that these molecules have the correct conformational properties to mimic some aspects of enzymic binding. Work is now in progress towards use of these systems to mimic enzymic catalysis.

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References

1 J. M. Lehn, *Angew. Chem., Int. Ed. Engl.*, 1989, **27**, 89.
2 C. A. Hunter, M. N. Meah, and J. K. M. Sanders, *J. Chem. Soc., Chem. Commun.*, 1989, 692 and 694.
3 R. M. Acheson and G. C. M. Lee, *J. Chem. Soc., Perkin Trans. 1*, 1987, 2321.
4 M. J. Gunter and L. N. Mander, *J. Org. Chem.*, 1981, **46**, 4792.
5 O. M. Behr, G. Eglinton, A. R. Galbraith, and R. A. Raphael, *J. Chem. Soc.*, 1960, 3614; F. Sondheimer and R. Wolovsky, *J. Am. Chem. Soc.*, 1962, **84**, 260; D. O'Krongly, S. R. Denmeade, M. Y. Chiang, and R. Breslow, *ibid.*, 1985, **107**, 5544; C. O. Diedrich-Buchecker, A. Khemiss, and J. P. Sauvage, *J. Chem. Soc., Chem. Commun.*, 1986, 1376.
6 C. A. Hunter, J. K. M. Sanders, and A. J. Stone, *Chem. Phys.*, 1989, **133**, 395.
7 C. A. Hunter, P. Leighton, and J. K. M. Sanders, *J. Chem. Soc., Perkin Trans. 1*, 1989, 547.
8 H. Biedermann and K. Wichmann, *Z. Naturforsch, Teil B*, 1974, **29**, 360.
9 K. A. Connors, 'Binding Constants,' 1987, Wiley, p. 51.
10 A. V. Hill, *J. Physiol. London*, 1910, **40**, IV—VII.
11 A. R. Fersht, 'Enzyme structure and mechanism,' 1977, W. H. Freeman, p. 231.
12 R. A. Freitag, J. A. Mercer-Smith, and D. G. Whitten, *J. Am. Chem. Soc.*, 1981, **103**, 1226.

§ The increased binding for (**$Zn_2$2**) corresponds to an effective molarity of *ca.* 27 for the ligand within the cavity.