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Metal-driven self assembly of C_3 symmetry molecular cages

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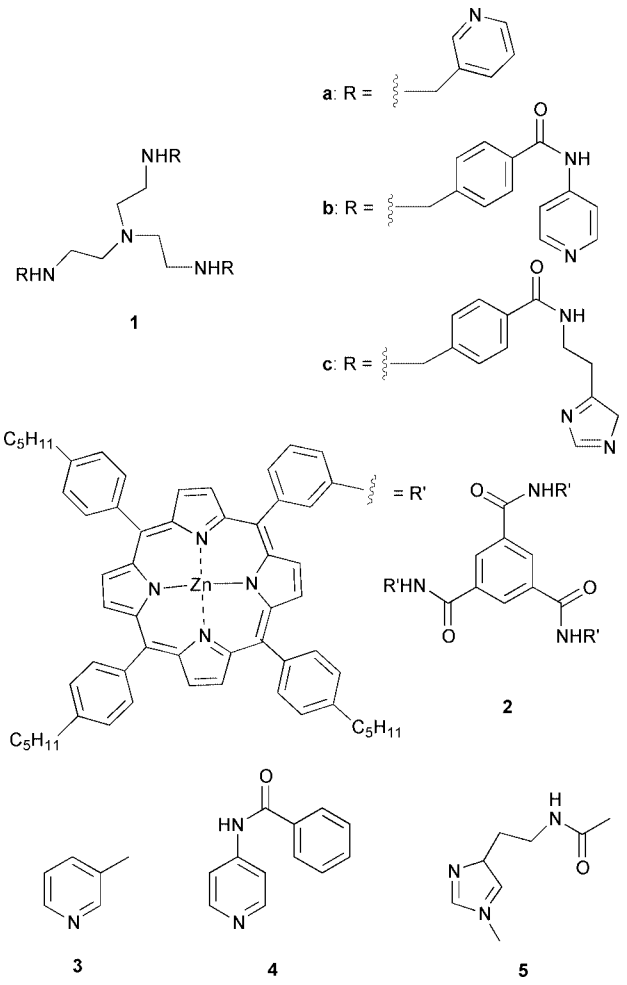
A series of tris(2-aminoethyl)amine (TREN) derivatives functionalized on the arms with pyridine or methylimidazole ligands bind very strongly to a trisporphyrin derivative *via* apical coordination, with formation of molecular cages; the strength of the binding (K_b up to $10^{8.8}$ mol^{-1} dm^3) depends on the structure of the TREN derivative as well as on its coordination to Zn(II).

The self assembly of proteins to elicit new and unique functions is a common feature in the biological world.[1] A case in point is HIV-1 protease, whose activity is dependent on a hydrogen bond-driven dimerization of two protein units.[2] The possibility of realizing molecules of controlled geometry and shape in the laboratory by assembling easily synthesized subunits is an appealing goal which is attracting enormous interest, demonstrated by the continuous flow of contributions appearing in the chemical literature.[3] Such 'supermolecules' may find useful application in molecular recognition and selective substrate transformation, sensing, signal transduction and, eventually, in the realization of miniaturized nanostructures. Metal–ligand coordination is one of the driving forces exploited for the assembly of these structures.[4] Examples are provided by the work of the Stang,[5] Fujita,[6] Hamilton,[7] Sauvage,[8] and Lehn[9] groups. Self-assembling porphyrin oligomers towards macrocycles or polymers have been reported by Hunter *et al.*,[10] while Tabushi and coworkers, as early as 1985,[11] elegantly demonstrated allosteric binding to a Zinc-gable porphyrin.

We report here on the formation of molecular cages driven by apical coordination of the terminal bases of tripodal ligands **1a**–**c** to the three zinc porphyrin units of **2**. The possibility of modifying the conformation of the tris(2-aminoethyl)amine (TREN) platform of derivatives **1a**–**c** *via* metal coordination gives the system a tunable geometry for controlling the binding to **2**.

Ligand **1a** was readily obtained by reaction of 3-pyridinaldehyde with TREN followed by reduction with $NaBH_4$. Ligands **1b**,**c** were prepared *via* condensation of TREN with the 4-formylbenzenamide derivatives, obtained by reaction of 4-formylbenzoyl chloride with 4-aminopyridine (**1b**) or methylhystamine (**1c**), followed by reduction with $NaBH_4$.† The trisporphyrin derivative **2** was prepared by coupling 1,3,5-benzene tricarbonyl trichloride with the corresponding aminoporphyrin,[12] followed by metallation with zinc acetate.† Porphyrin **2**, as well as the free bases **1a**–**c**, are soluble in chlorinated organic solvents. The solubility of the 1:1 Zn(II) complexes of the TREN derivatives in these solvents depends on the nature of the counterions: more hydrophilic nitrates are insoluble, while more lipophilic hexafluorophosphates are freely soluble in these media.

Trisporphyrin **2** shows a typical UV–vis spectrum, with maxima at 420 nm (ε = 430,000 mol^{-1} dm^3 cm^{-1}) and 550 nm (ε = 37,000 mol^{-1} dm^3 cm^{-1}), indicating that there is no intramolecular interaction between the porphyrins. Binding of an apical ligand causes a shift of these peaks to 430 and 565 nm, respectively. The very intense absorptions in the 420–430 nm region can be used for determination of the affinity constant with apical ligands and, in the present case, for the formation of cage complexes between **2** and **1**. Fig. 1 shows the changes in the absorption spectrum of **2** upon addition of increasing amounts of **1a** in CH_2Cl_2. The presence of a well-defined isosbestic point is suggestive of the formation of a single complex, and the fact that all the zinc porphyrin sites are fully complexed after the addition of one equivalent of ligand implies that a 1:1 cage complex has been formed. The complex so formed does not convert into species of different stoichiometry in the presence of up to a twofold excess of the TREN derivative, contrary to recent observations for a bisporphyrin receptor in the presence of multiarmed amines.[13] Clearly, a key role is played here by the complementary structure of the two subunits involved in the formation of the supramolecular cage complex. Analysis of the absorbance *vs.* concentration data‡ leads to a well-behaved complexation curve (Fig. 1, inset) which gives a very high binding constant (log K_b = 8.81) for the 1:1 complex. Similar curves were obtained for tripodal ligands **1b**,**c** and **1a**,**b**–Zn(II) complexes.



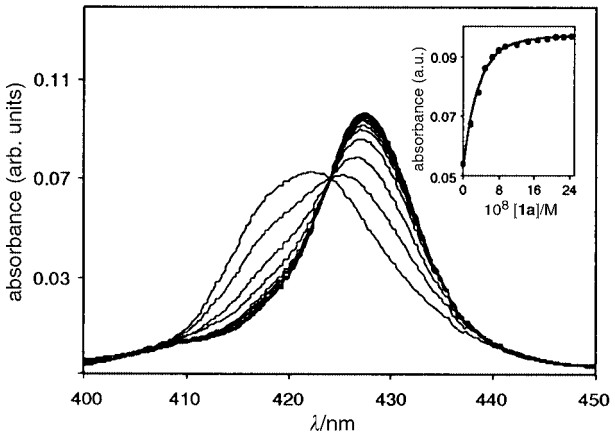


Fig. 1 Change in the absorbance of a 60 μM solution of **2** in CH_2Cl_2 upon addition of **1a**. Inset: binding isotherm of the data at 427 nm. The solid line represents the computer-generated best fit for a 1:1 complex.

The titration data are summarized in Table 1, along with the values determined for model ligands **3**–**5**. The values of the parameters EM and β are also listed in the table. EM§ corresponds to the ratio $\{(K_b)_{cage}/[(K_b)_{model}]^3\}^{0.5}$ and is the effective molarity for the intramolecular cyclizations required to form the cage. β[14] is simply the ratio $(K_b)_{cage}/(K_b)_{model}$ and gives an indication of the absolute strength of binding associated with the formation of the cage, with respect to the single apical coordination of the model compound to one porphyrin. Inspection of Table 1 reveals that tripodal ligand **1a** shows the highest binding constant to **2**, which reduces 30-fold upon Zn(II) binding to TREN. In the case of **1b**, the binding constant is lower and coordination of Zn(II) to TREN does not induce any significant change. Allowing for the stronger binding interaction of methylimidazole to the Zn-porphyrin (compared with pyridine), the least effective ligand is **1c**, with EM and β values significantly lower than those of **1a** and **1b**. The β values indicate that cooperative binding of the tripodal ligands to the three porphyrins leads to a higher affinity than single apical ligands (up to five orders of magnitude in the case of **1a**). Inspection of molecular models reveals that, in the case of **1b**, the length of the tripodal arms and their flexibility is such that coordination of Zn(II) does not significantly affect their binding geometry. However, this flexibility reduces the strength of binding with respect to **1a**, due to the freezing out of conformational mobility on complexation.[14] The disadvantage of flexibility is further evidenced by the relatively low values of EM and β for **1c**, which has even longer arms. For **1a**, the length of the arms¶ is such that apical binding to the porphyrins requires the latter to move out of the plane of the central benzene by rotation around the amide bonds pointing inwards (Fig. 2). Complexation of Zn(II) to the TREN platform further reduces the distance between the three pyridine nitrogens,

Table 1 Binding constants of trisporphyrin **2** to tripodal ligands **1a–c** and model ligands **3–5** in CH_2Cl_2[a] at 25 °C

Ligand	log K_b[b]	EM[c]	β[c]
3[d]	3.75 ± 0.02	—	—
1a	8.81 ± 0.07	6.0×10^{-2}	1.1×10^5
1a·Zn	7.36 ± 0.05	1.1×10^{-2}	4.1×10^3
4[d]	3.98 ± 0.03	—	—
1b	7.75 ± 0.09	8.0×10^{-3}	5.9×10^3
1b·Zn	7.64 ± 0.05	7.1×10^{-3}	4.6×10^3
5[d]	5.37 ± 0.07	—	—
1c[e]	7.50 ± 0.09	5.0×10^{-5}	1.3×10^2

[a] In the presence of 1% CH_3CN. [b] Binding constant are expressed in mol^{-1} dm^3. [c] See the text for the definition of EM and β. The units of EM are mol dm^{-3}, and β is dimensionless. [d] Binding constants of the model ligands are the microscopic values determined assuming independent binding to each porphyrin of **2**. [e] The binding of **1c**·Zn(II) to **2** does not follow a well behaved isotherm; for this reason it has been omitted.

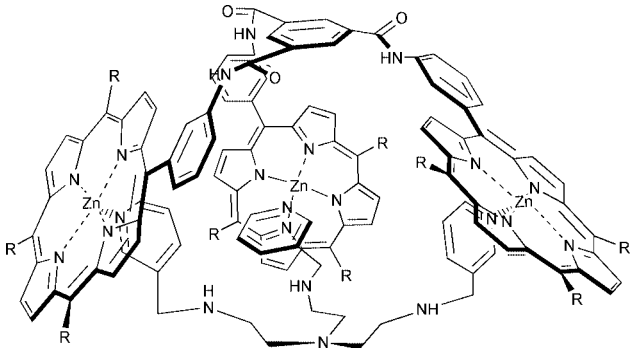


Fig. 2 Schematic diagram of the molecular cage formed by binding of **1a** to **2**.

imposing a more stringent geometric constraint for binding, resulting in a smaller binding constant.

In conclusion, we have shown that tripodal molecules, based on complementary porphyrins and pyridine or imidazole ligands, give highly symmetrical molecular cages with very strong binding constants which are potentially suitable for molecular recognition and selective transformation of substrates trapped in the cavity: work aimed at this goal is ongoing in our laboratories.

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Notes and references

† All new compounds gave the expected ^{1}H- and ^{13}C-NMR spectra and the correct elemental analyses (C, H, N).

‡ The binding isotherm was fitted using the program HOSTEST II. See: C. S. Wilcox, in *Frontiers in Supramolecular Organic Chemistry and Photochemistry*, H.-J. Schneider and H. Dürr, VCH, Weinheim, 1991.

§ In the cage formation the first binding is intermolecular (K), the second binding is intramolecular ($EM_1 \times K$) and the third binding is also intramolecular ($EM_2 \times K$). Thus, the overall observed binding constant is $EM_1 \times EM_2 \times K^3$. Assuming that $EM_1 = EM_2$, the effective molarity is the square root of the product $EM_1 \times EM_2$.

¶ Energy minimization with the HyperChem program (Hyperchem 2 for Windows, © 1991, Hypercube Inc. and Autodesk Inc.) indicates that two Zn(II) ions in the porphyrin derivative **2** are *ca.* 20 Å apart when the molecule is flat. The distance between two pyridine nitrogens of **1a** is, in the fully stretched conformation, *ca.* 15 Å.

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