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Highly shape-selective guest encapsulation in the precisely defined cavity of a calix[4]arene-capped metalloporphyrin†

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We developed a metalloporphyrin-based molecular container capped with a calix[4]arene, and its rigid cavity distinguished the slight structural differences in the aromatic guests.

In nature, the highest levels of molecular recognition events are found, and include substrate recognitions by an enzyme, ligand–acceptor interactions and antigen–antibody reactions. The development of an artificial host, capable of binding certain guest molecules with high specificity, has received considerable attention with the goal of understanding the mechanism of biomolecular recognition.[1] However, there are a very limited number of examples in the literature where clear-cut selectivity and specificity for recognition are equal to those of an enzymatic system.[2] Although a number of calixarene–porphyrin hybrids that mimic cytochrome P-450 have been created, the selectivity for their guest recognitions was not comparable with that in nature.[3,4] Herein, we report the synthesis and the unusual guest selectivity of the new molecular container **1Zn** composed of calix[4]arene and Zn(II)-porphyrin (Fig. 1).

The synthesis of calix[4]arene-capped porphyrin **1Zn** is shown in Scheme 1. Treatment of methyl 2-formylbenzoate **2**[5] with excess pyrrole under acidic conditions gave phenyldipyrromethane derivative **3**. Condensation of **3** with benzaldehyde in the presence of a catalytic amount of trifluoroacetic acid, followed by oxidation with DDQ, afforded free-base porphyrin **4**. Hydrolysis of **4** gave 5,15-bis(2-carboxy-1-benzyl)-10,20-diphenylporphyrin, which was converted to acid chloride **5** using oxalyl chloride. The coupling of **5** and diaminocalix[4]arene **6**[6] furnished the desired calix[4]arene-capped porphyrin $\mathbf{1H_2}$, which was treated with excess amount of $Zn(OAc)_2$ to give Zn(II)-porphyrin derivative **1Zn**.

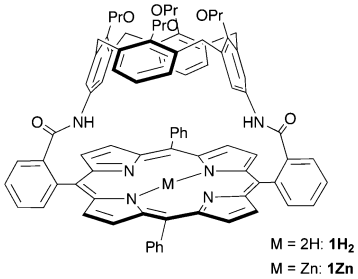
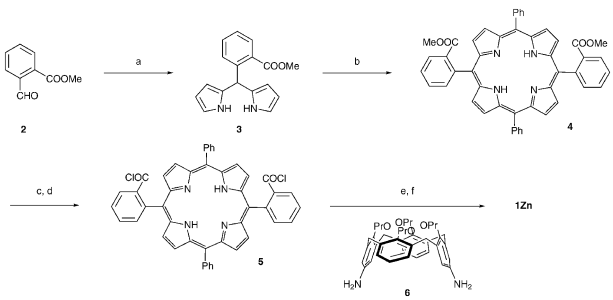


Fig. 1 Calix[4]arene-capped porphyrin.

To investigate the guest-binding ability of calix[4]arene-capped porphyrin **1Zn** and Zn(II)-*meso*-tetraphenylporphyrin, **ZnTPP**, titration experiments with *N*-containing aromatic compounds in chloroform were carried out using electronic absorption spectroscopy. The association constants (K_as)[7] and binding free energies (ΔGs) for pyridine (**7**), 4-methylpyridine (**8**), imidazole (**9**) and *N*-methylimidazole (**10**) were determined (Table 1).

Surprisingly high guest selectivity is found for **1Zn**. The binding abilities of **7** and **9** are extremely higher than those of **8** and **10**. Since the free energy differences ($\Delta\Delta G$s) of 19.6 and 35.8 kJ mol^{-1} are particular for **7** *vs.* **8** and **9** *vs.* **10** upon complexation, the presence of the methyl groups on the guest aromatic rings leads to the significant reduction of the guest binding abilities. By contrast, no particular selectivity is claimed in the guest complexation of **ZnTPP**. It is obvious that the calix[4]arene moiety is responsible for developing the shape selective discrimination of the host **1Zn**.[8]



Scheme 1 *Reagents and conditions*: (a) pyrrole, TFA, 40%; (b) benzaldehyde, TFA, CH_2Cl_2; then DDQ, CH_2Cl_2, 17%; (c) LiOH, THF, H_2O, 92%; (d) $(COCl)_2$, CH_2Cl_2; (e) **6**, Et_3N, CH_2Cl_2, 2 steps 22%; (f) $Zn(OAc)_2$, MeOH, $CHCl_3$, 74%.

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† Electronic supplementary information (ESI) available: Experimental section, NMR spectra of new compounds, the results of UV-Vis titration, a NOESY and an EXSY spectrum of a mixture of **1Zn** and pyridine, and atomic coordinates of **1Zn** with pyridine or imidazole. See DOI: 10.1039/c1cc14739k

Table 1 Association constants K_a (M^{-1}) and binding free energies ΔG (kJ mol^{-1}) in $CHCl_3$ at 298 K and volumes ($Å^3$) of guest molecules

		1Zn		**ZnTPP**	
Guest	Volume	K_a	$-\Delta G$	K_a	$-\Delta G$
Pyridine (**7**)	74	53 400 ± 800	27.0	2700 ± 700	19.6
4-Methylpyridine (**8**)	87	20 ± 1	7.4	6000 ± 230	21.6
Imidazole (**9**)	64	1 920 000 ± 400 000	35.8	7600 ± 300	22.1
N-Methylimidazole (**10**)	77	n.d.[a]	0	6800 ± 300	21.9

[a] Association constant was too small to be determined.

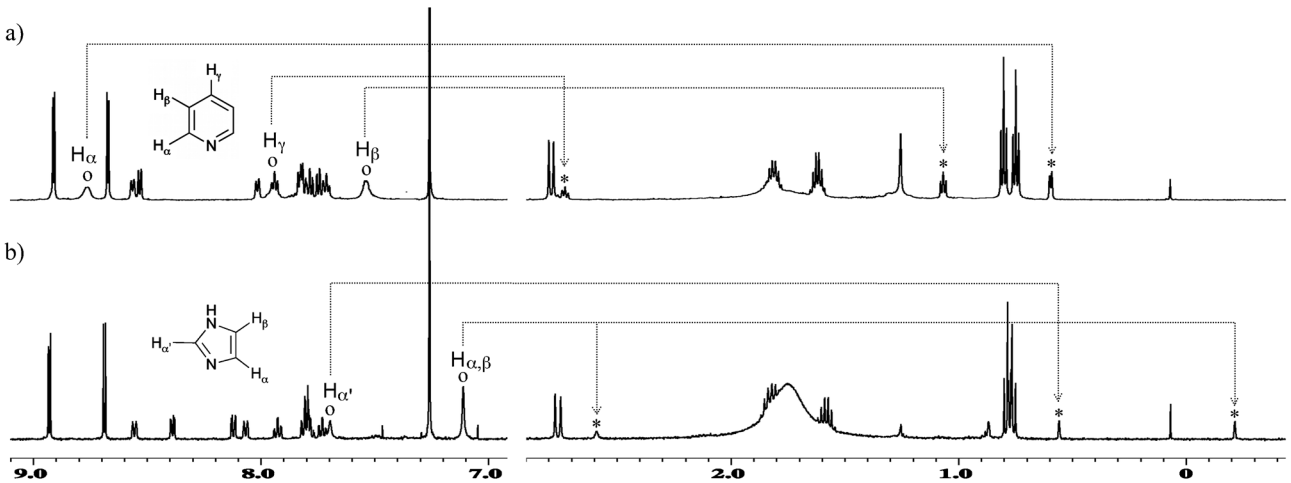

Fig. 2 ^{1}H-NMR spectra (600 MHz) in chloroform-*d* at 298 K. (a) **1Zn** (1.33 mM) and pyridine (**7**) (2.66 mM); (b) **1Zn** (1.47 mM) and imidazole (**9**) (4.41 mM). The signals of the free and encapsulated guests are marked with o and *, respectively.

To obtain a detailed understanding of the unusual shape selectivity of **1Zn**, the complex structures of the calix[4]arene-capped porphyrin **1Zn** with **7**, **8**, **9** and **10** were examined by ^{1}H-NMR titration. The ^{1}H-NMR spectra of **7** and **9** in the presence of **1Zn** showed two sets of the aromatic signals, which were assigned to the protons of the free and bound guests (Fig. 2a and b), whereas the protons of **8** and **10** slightly shifted upfield to bring the time-averaged signals, arising from a rapid exchange of the free and bound states (see ESI†). The large complexation induced upfield shifts were observed only for the protons of **7** and **9** (**7**: −8.2, −6.5 and −5.3 ppm for H_α, H_β and H_γ; **9**: −7.3, −7.3 and −4.5 ppm for H'_α, H_α, and H_β, respectively), and were obviously larger than those observed for the guests bound to **ZnTPP**.[9,10] The calix[4]arene-capped face is more shielded than the other side; thus, these large upfield shifts place the guests inside the cavity. The close contact of **7** and the calix[4]arene was proven by the intermolecular NOEs (see ESI†).

The in–out guest exchange rate constants for pyridine were determined by an exchange (EXSY)[11] NMR experiment. $\Delta G^{\ddagger}$s of 49.9 and 74.9 kJ mol^{-1} for the uptake and release of the encapsulated guest are unexpectedly high. Accordingly, **1Zn** selectively encapsulates **7** within the cavity, which is released through the small portals of the host, even though the uncapped face of the porphyrin ring is sterically accessible for the guest coordination.

To discuss the unusual shape selectivity of **1Zn**, the molecular modeling of the complexes was carried out by DFT calculation using M06-2X/LANL2DZ.[12] The volumes of the guests were estimated to be 64–87 $Å^3$.[13] **1Zn** recognizes the tiny changes of the guest shapes. The strict shape selectivity for the guest encapsulation can be rationalized using the calculated structures of the host–guest complexes in Fig. 3. The two aromatic rings connected to the porphyrin ring lean inward to squeeze the planar guest, while the other two aromatic rings are tilted outward. The two 3-position protons of the pyridine ring face toward the aromatic ring that is tilted outward, resulting in CH–π interactions. The calculations of complexes show that pyridine coordination inside the host cavity is energetically more preferable than that from outside of the cavity ($\Delta\Delta H$ = 73.67 kJ mol^{-1}). Thus, van der Waals attractive interactions in the cavity play an important role in the face selectivity.[14,15] The H_γ of the pyridine is positioned close to the oxygen atoms of the calix[4]arene lower rim. When a methyl group is substituted for the proton H_γ, the methyl group should create the serious steric interactions against the oxygen atoms of the

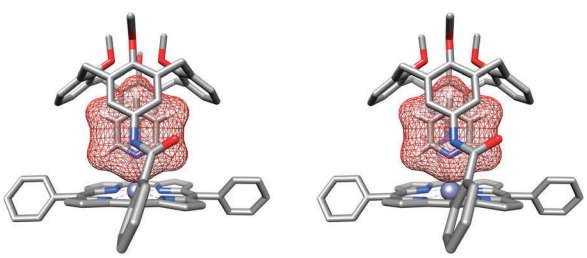

Fig. 3 Stereoplot of the optimized structure of the encapsulation complex with **1Zn** and pyridine. To simplify and clarify the calculation, *n*-propyl groups were replaced with methyl groups.

calix[4]arene that probably result in a large reduction of the host–guest association.

In summary, axial ligands, such as pyridine and imidazole, are known to bind to Zn(II)-porphyrins to give five-coordinated complexes.[16] In the case of capped porphyrins, axial ligands can bind from either side of the porphyrin to give positive association constants. Calix[4]arene-capped porphyrin **1Zn** offers a guest-binding environment in its cavity to show high guest selectivity. The guests that are shaped in a way that is complementary to the confined cavity are capable of fitting into and binding to the cavity by van der Waals attractive interactions. This type of high shape selectivity is obviously unusual in an artificial molecular host.

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8 Host molecules in ref. 3 and 4 are obviously more flexible and bigger than our host molecule **1Zn**; therefore, they might show better selectivities to Me-substituted guests and broader selectivities to *N*-containing aromatic guests than **1Zn**.

9 Complexation induced shifts of pyridine with **ZnTPP** were estimated to be −6.1, −1.8 and −1.4 ppm for H_α, H_β and H_γ, respectively.

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