Porphyrin Clips Derived from Diphenylglycoluril. Synthesis, Conformational Analysis, and Binding Properties

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With the aim to construct synthetic systems that function according to the principles of enzymes, molecular clips based on diphenylglycoluril were covalently attached to (metallo)porphyrins. Two different porphyrin clips, **1** and **2**, were synthesized that differ in the length and position of the linker between the clip and the porphyrin. This resulted in a great difference in flexibility of the cavity molecules, which had remarkable consequences for their binding properties in organic solution. The physical properties of the free base and zinc porphyrin clips have been studied in detail with NMR techniques and by the host−guest binding of viologen, dihydroxybenzene, and pyridine derivatives.

Introduction

The complexity encountered in natural enzymatic systems hampers to a great extent the understanding of their exact working mechanisms. One of the key aims of supramolecular chemistry, therefore, is to design simplified enzyme mimics that still possess the properties of the natural systems.[1] To be an efficient enzyme mimic, the designed molecule has to possess a binding cavity or cleft that can selectively recognize and complex a substrate. This substrate is then converted at a catalytic center in the direct proximity of the binding site. With natural enzymes as an inspiration, several synthetic catalysts have been developed that contain such a binding site that recognizes substrates.[2]

As part of our studies to create a cytochrome P450 mimic,[3] we are interested in developing substrate-selective porphyrin receptor molecules. In the literature, there are numerous examples of porphyrins connected to receptor-like molecules. Capped metalloporphyrins have been applied for the study of O_2 and CO binding, but these cannot bind substrate molecules. Some tetraphenyl porphyrins have been synthesized that are equipped with functional and directed binding groups attached to their *meso*-phenyl groups, allowing them to recognize quinones,[4a] amino acid esters,[4b] and carbohydrates.[4c] There are, however, relatively few porphyrins that are provided with a well-defined cavity, which is able to selectively recognize substrates and is furthermore able to shield the porphyrin from its direct environment. A simple approach toward enzyme mimics is to connect a known cavity moiety, i.e., a cyclodextrin or calixarene, to a porphyrin. In this way, Mn(III) and Fe(III) porphyrins functionalized with one, two, or four cyclodextrins have been described that catalyze oxidation reactions and display a certain regio- or stereoselectivity.[5] Substrate binding in these systems is, however, mainly based on hydrophobic interactions in water and not on directed binding. Some calixarene-capped porphyrins have been reported that bind salts[6a] or small aza-heterocycli.[6b] A novel approach is to construct porphyrin arrays in which the porphyrins themselves form the cavity. Along this line, cyclic cavity-forming porphyrin systems have been synthesized in which substrates containing metal−ligand functions can be bound to the metal−porphyrin and can be coupled to each other.[7] Binding of organic substrates without the aid of a metal complexed in the porphyrin is rarely documented. The steroid-capped porphyrins of Sanders[8a] and the cyclophane-bridged porphyrin of Diederich[8b] are examples of such receptors that can complex substrates without the help of the porphyrin metal.

In this paper, we present the synthesis and physical properties of two new "porphyrin clips", **1** and **2**, which possess defined cavities with directed substrate binding sites. The influence of the shape and size of the cavity on the substrate-binding behavior of the clip molecules has been studied in detail and will be discussed. The catalytic properties of the new metallohosts will be reported elsewhere.[9]

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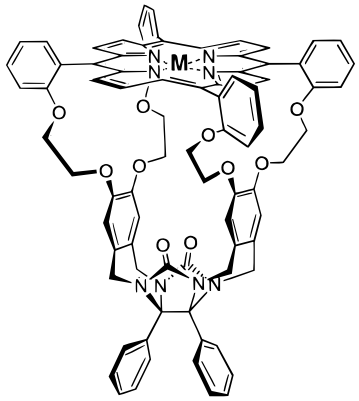
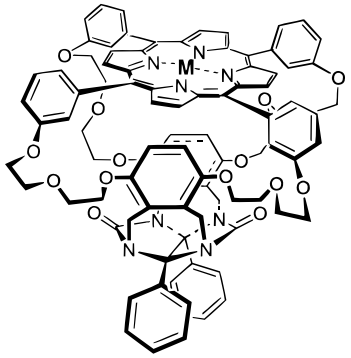
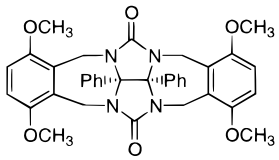
Chart 1



H_2-1 M = 2H
Zn-1 M = Zn



H_2-2 M = 2H
Zn-2 M = Zn



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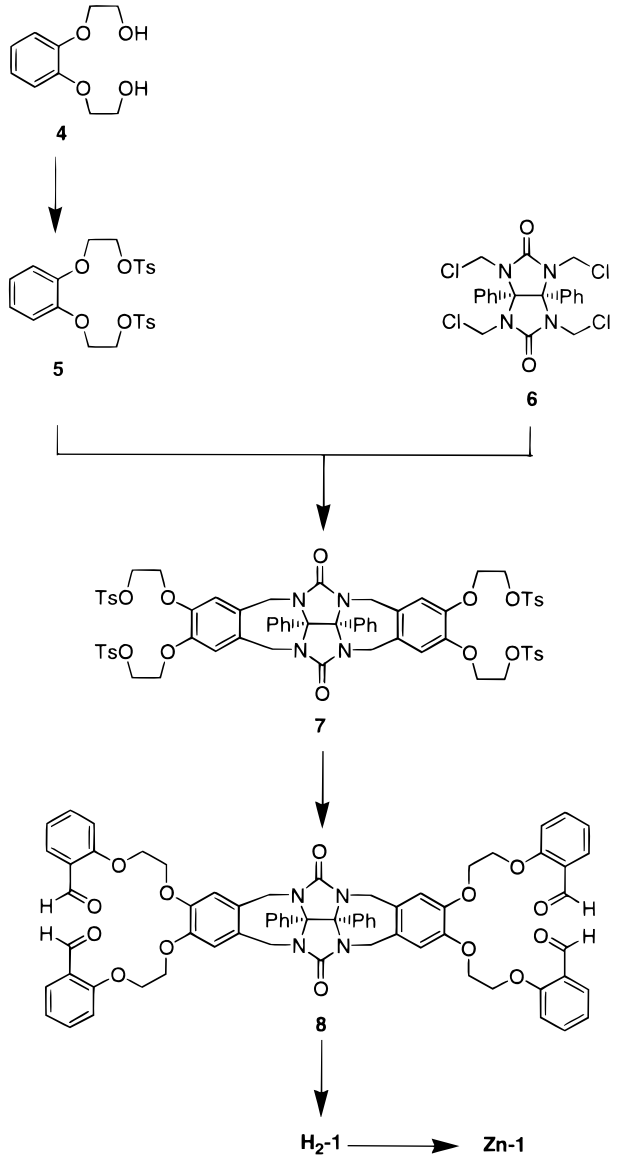
Results and Discussion

Design. The receptor component of our porphyrin hosts is the well-documented molecular clip **3** (Chart 1). Previous studies have shown that derivatives of this U-shaped molecule are able to bind (dihydroxy)benzene[10a,b] and viologen[10c] derivatives in organic solution. Other work revealed that a derivative of **3** functionalized with a Rh(I) phosphite center situated above the cavity can act as a substrate-selective hydrogenation and isomerization catalyst,[11] showing features similar to those encountered in enzymes, such as Michaelis−Menten kinetics, product inhibition, and rate enhancement by cooperative binding.

Scheme 1



Clip molecules were therefore designed which have a metal−porphyrin molecule situated *above* the receptor cavity. It was decided to use oxyethylene spacers of various length to connect the porphyrin molecule to the clip. In this way, the size and rigidity of the metallohost can be easily varied. By the use of CPK models and molecular modeling calculations, two target molecules were designed; one (**1**) has four short spacers that are placed "on top" of the clip side walls, and the other (**2**) has four long oxyethylene spacers that are connected to the "sides" of the walls.

Synthesis. The synthesis of **1** (Scheme 1) started with the treatment of diol **4** with *p*-toluenesulfonyl chloride in pyridine, yielding the ditosyl compound **5** in 90% yield. This compound was attached to tetra(chloromethyl)-diphenylglycoluril **6**[12] by a Friedel-Crafts alkylation reaction in 1,2-dichloroethane, using $SnCl_4$ as a catalyst. As side-products of this reaction, a monowalled clip compound and derivatives of **7** that had lost one or more tosyl groups were formed. This mixture could be purified

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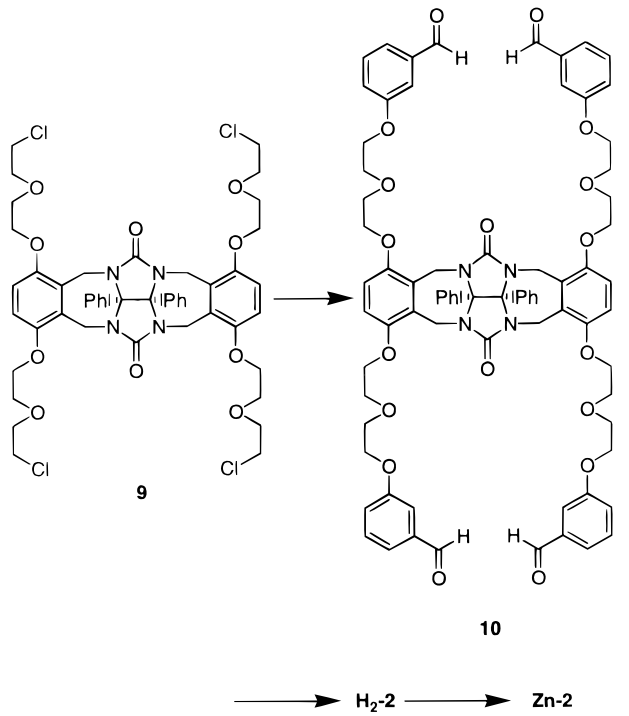
Scheme 2



by recrystallization from toluene to give 62% of pure **7**. The latter compound was then reacted with salicylic aldehyde in acetonitrile using K_2CO_3 as a base to give the tetra-aldehyde clip molecule **8** in 59% yield after column chromatography. Finally, condensation of **8** with 4 equiv of pyrrole in dichloromethane and subsequent oxidation of the formed porphyrinogen with *p*-chloranil gave porphyrin clip **H_2-1** in 6% yield after purification by column chromatography and several precipitations of the product in *n*-hexane.

The starting compound for porphyrin cavity **2** was tetrapodand **9**[12] (Scheme 2). This compound was reacted with *m*-hydroxybenzaldehyde under Finkelstein conditions in acetonitrile using K_2CO_3 as a base to give tetra-aldehyde clip molecule **10** in 64% yield after purification by column chromatography. Porphyrin clip **H_2-2** was synthesized from **10** in 4% yield in the same manner as described for **H_2-1**.

H_2-1 and **H_2-2** were converted into their corresponding zinc derivatives **Zn-1** and **Zn-2** by a reaction with excess zinc(II) acetate dihydrate in a mixture of chloroform and methanol (2:1, v/v). This metal was complexed instead of the paramagnetic Mn(III), which is needed for the catalytic oxidation reactions,[9] to be able to use NMR spectroscopy in the structural analysis of the compounds.

Structural Analysis. The structures of the porphyrin receptors in chloroform solution were investigated with ^{1}H NMR spectroscopy (500 MHz). Nearly all proton resonances in the spectra could be assigned with the help of COSY and 2D NOESY techniques (Figures 1 and 2). CPK models, molecular modeling, and 2D NOESY ^{1}H NMR spectroscopy indicated that in **1** the four short spacers force the porphyrin to be located symmetrically above the clip, thus forming a rigid and defined cavity with a diameter of ≈9 Å (Figure 3a). This rigidity is supported by the observation of well-separated, sharp resonances for every oxyethylene proton in the NMR spectrum (Figure 1). Insertion of a Zn(II) ion in the porphyrin caused no significant changes in the NMR spectrum or thus in the 3-dimensional structure of **1**.

In **2**, the spacers between the porphyrin and the clip are longer, and molecular modeling suggested that the porphyrin has considerable freedom of movement with regard to the cavity. These spacers are too short to allow the porphyrin to be situated on the convex side of the clip. The NMR spectra (Figure 2) indeed revealed that **H_2-2** and **Zn-2** are far more flexible than **1**, displaying interesting conformational behavior. The strong upfield shifts of the resonances of the cavity side-wall protons H-5 and of the nearby crown ether protons H-6a and H-6b of **H_2-2** indicate that these protons are in the direct neighborhood of the center of the porphyrin.

To get more insight into the 3-dimensional structure of the molecule, a 2D NOESY experiment was recorded on **H_2-2**. Several NOE contacts were observed between the porphyrin and the cavity part of this molecule, viz., between the side-wall protons H-5 and the *β*-pyrrole protons H-14, between H-5 and the pyrrole NH protons H-16, and between all of the crown ether protons (H-6 to

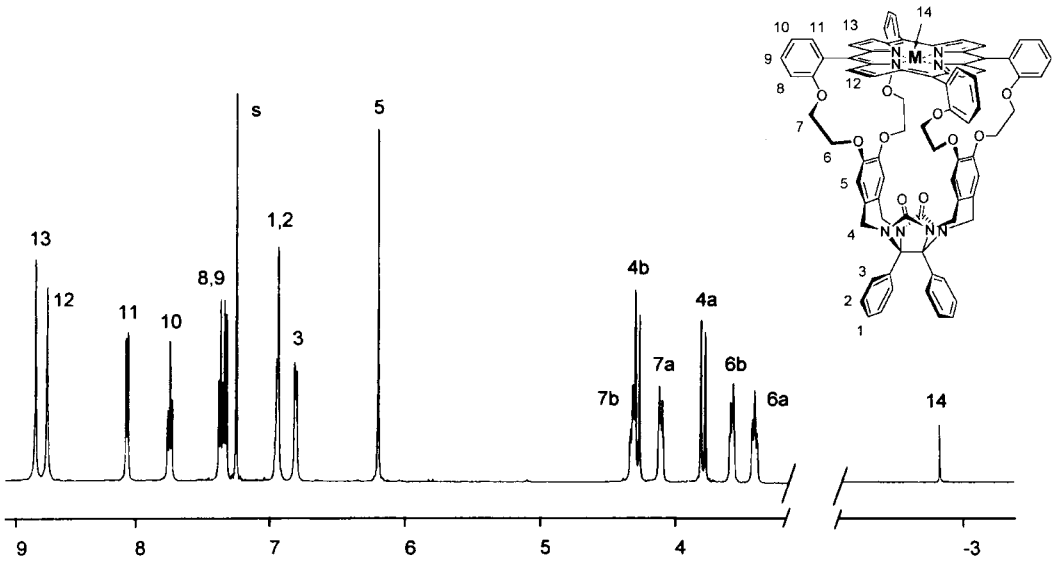


Figure 1. Proton assignments in the 500 MHz ^{1}H NMR spectrum of **H_2-1** in $CDCl_3$.

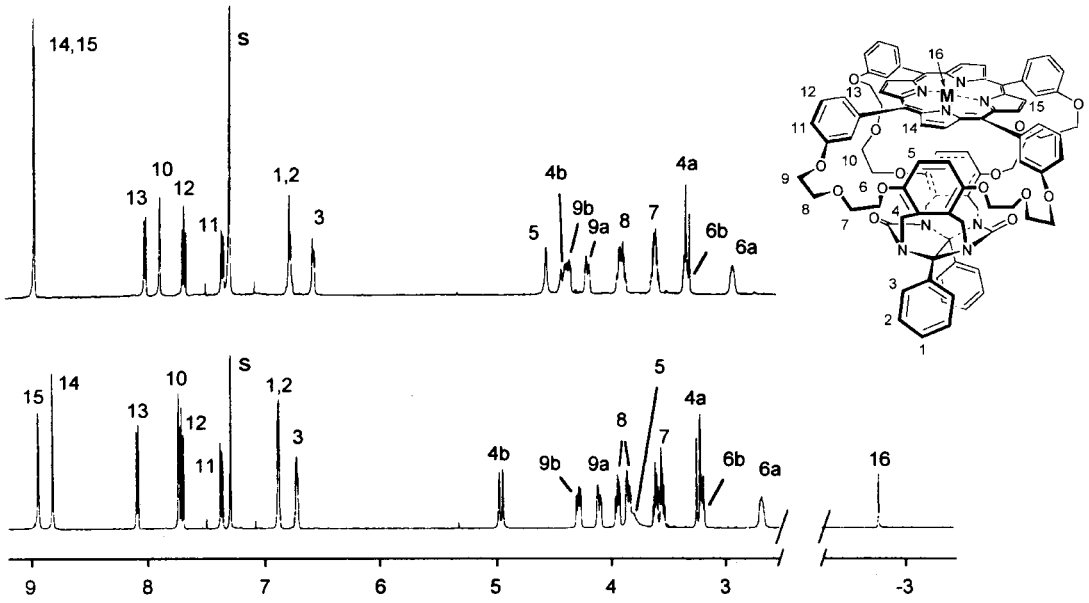


Figure 2. Proton assignments in the 500 MHz ^{1}H NMR spectra of **H_2-2** (bottom) and **Zn-2** (top) in $CDCl_3$.

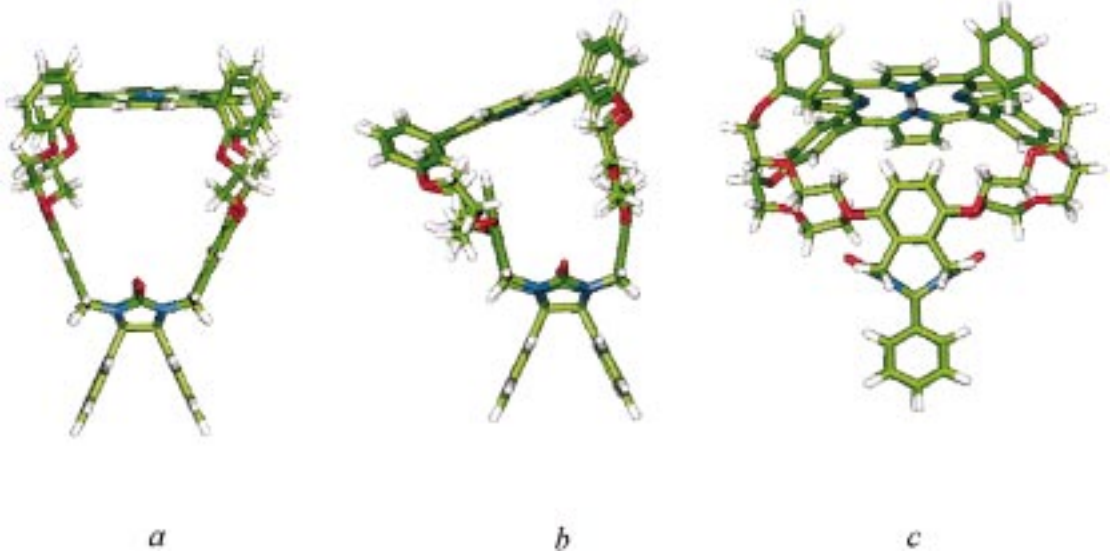


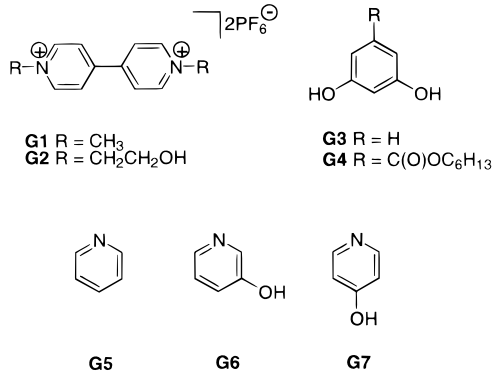
Figure 3. Computer-calculated structures of porphyrin clips, based on the NOE constraints in the 2D NOESY spectra. (a) **H_2-1**. (b) **H_2-2**, side view. (c) **H_2-2**, front view.

H-9) and H-10/H-14. The combination of the observed upfield shifts and NOE contacts suggests that the center of the porphyrin is situated directly above the cavity side-walls. This is also evident from the fact that the observed shift of H-5 (3.8 ppm) is an *average* value. If the porphyrin were locked in its position near the cavity side-wall, the chemical shift of the side-wall protons would be expected to be at ~1 ppm ($\Delta\delta \approx 5.5-6$ ppm). Because for the side-wall protons (H-5) only one, broadened, signal is observed at room temperature, it can be concluded that **H_2-2** apparently exists in (at least) two identical conformations that are interconverting rapidly on the NMR time scale. In each of these the porphyrin is located in a more or less edge-to-face geometry on one of the side-walls of the clip molecule (Figure 3b). The sharp and well-resolved resonances for all oxyethylene protons confirms that these geometries are very well-defined.

The insertion of a Zn(II) ion in **H_2-2** to give **Zn-2** led to some remarkable changes in the ^{1}H NMR spectrum (Figure 2). The resonances of the side-wall protons H-5 significantly sharpened and shifted downfield to 4.5 ppm ($\Delta\delta \approx +0.7$ ppm). The signals of the oxyethylene protons H-6a and H-6b and the *meso*-phenyl proton H-10 also shifted downfield by +0.27, +0.14, and +0.14 ppm, respectively. In the 2D NOESY spectrum of **Zn-2**, NOE contacts between the porphyrin protons H-14 and the wall protons H-5 were not observed anymore. Taken together with the downfield shifts of the resonances of H-5, H-6, and H-7, this suggests that the center of porphyrin moiety in **Zn-2** is not sitting as directly over the cavity side-walls as it is in **H_2-2**.

The dynamics of the conformational behavior of compounds **2** were studied with variable temperature (VT) NMR (500 MHz). A solution of **H_2-2** in $CDCl_3$ was cooled to 213 K, at which temperature the resonances of all protons on the inside of the cavity (H-5, H-6 to H-9, and H-10) severely broadened but did not yet coalesce. Subsequently, the solution was heated from 213 to 328

Chart 2



K. Over this temperature range, several resonances displayed large downfield shifts, e.g., those of the wall protons H-5 (+0.77 ppm), the crown ether protons H-6a (+0.47 ppm), and the pyrrole NH protons H-16 (+0.16 ppm). These shifts are in line with a loosening of the interaction between the porphyrin and the cavity side-wall. Remarkably, the NMR spectrum of a solution of **Zn-2** in $CDCl_3$ which was cooled to 240 K strongly resembled the spectrum of **H_2-2** at 328 K.

Combining all results, it is clear that at room temperature and below an attractive edge-to-face interaction must exist between the porphyrin plane and the cavity side-walls of compounds **2**. At higher temperatures, this interaction becomes weaker, and the porphyrin is, on average, further away from the cavity side-wall. In **Zn-2**, the abovementioned interaction between porphyrin and side-wall is at room temperature apparently weaker than in **H_2-2**. It is as yet unclear why this interaction becomes weaker when a Zn(II) ion is complexed in the porphyrin.

Binding Properties. Porphyrin receptors **1** and **2** both possess a cleft that can bind guests by a variety of interactions, viz., by hydrogen bonding with the carbonyl functions, by $\pi-\pi$ interactions with the walls, by hydrogen bonding and dipole interactions with the crown ether spacers, and in the case of a Zn(II) ion porphyrin, by complexation of ligands to the metal center. The host–guest binding properties of these porphyrin cavities with a variety of guest molecules (Chart 2) were therefore investigated to study the influence of the differences in cavity size and flexibility between **1** and **2** on their complexation behavior and to establish what type of substrates would be suitable for future catalysis experiments.

Binding of Viologen Derivatives.[13] A first series of binding experiments was carried out with viologen derivatives (*N*,*N*′-disubstituted 4,4-dipyridinium compounds). It has been reported before that these guests form strong charge-transfer complexes with crown ether functionalized derivatives of **3**,[10c] and crown ether strapped porphyrins have also been found to be efficient receptors for them.[14] NMR and UV measurements revealed that **1** forms exceptionally strong 1:1 complexes with viologens **G1** and **G2** in acetonitrile/chloroform (1:1, v/v) solution (see Table 1).

Table 1. Association Constants K_a (M^{-1}) and Binding Free Energies ΔG (KJ mol^{-1}, in brackets) between Porphyrin Clips and Various Guests at 298 K

	H_2–1	**Zn-1**	**H_2–2**	**Zn-2**	**3**[a]
G1[b]	6.0×10^5 [f] (−32.9)	8.6×10^5 [f] (−33.8)	1100[e] (−17.4)	5800[e] (−20.2)	
G2[b]	7.4×10^6 [g] (−39.2)	*h*	3500[e] (−20.2)	1×10^4 [f] (−22.8)	
G3[c,e]	2200 (−19.1)	1400 (−17.9)	1400 (−17.9)	440 (−15.1)	2600 (−19.5)
G4[c,e]	520 (−15.5)	800 (−16.6)	2100 (−19.0)	4500 (−20.8)	1.7×10^4 (−24.1)
G5[d]		1.1×10^5 [f] (−28.8)		1.4×10^4 [f] (−23.6)	
G6[d]		3.0×10^7 [g] (−42.7)		4.8×10^6 [g] (−38.1)	
G7[d]		2.5×10^4 [f] (−25.1)		8.0×10^4 [f] (−28.0)	

[a] Values taken from ref 10b. [b] In $CHCl_3/CH_3CN$ 1:1 (v/v) or $CDCl_3/CD_3CN$ 1:1 (v/v). [c] In $CDCl_3$. [d] In $CHCl_3$, from UV titrations. [e] Estimated error 10%. [f] Estimated error 30%. [g] Estimated error 50%. [h] No reliable value could be determined, probably because the coordination of the OH-groups of **G2** to the Zn(II)-ion interfers with the normal mode of binding.

Table 2. Selected Calculated Complexation Induced Shift Values (ppm) of Host Protons upon Binding of Viologens and Dihydroxybenzenes by H_2-1 and H_2-2[a]

		guest			
host	proton[b]	**G1**[c]	**G2**[c]	**G3**[d]	**G4**[d]
H_2–1	H-5	−0.16	−0.12	−0.06	−0.02
	H-6a	−0.69	+0.60	−0.72	−0.28
	H-6b	−0.16	+0.41	−0.57	−0.02
	H-7a	0	+0.43	−0.66	−0.13
	H-7b	0	+0.67	−0.55	−0.09
	H-12	+0.24	+0.14	+0.10	+0.15
	H-13	+0.15	+0.13	+0.05	+0.02
	H-14	−0.17	−1.16	+0.20	−0.02
H_2–2	H-5	+0.40	+1.10	−0.73	*e*
	H-6a	+0.19	+0.45	−0.26	*e*
	H-6b	+0.05	+0.29	−0.02	*e*
	H-10	−0.07	−0.08	+0.16	+0.22
	H-14	0	0	−0.09	−0.17
	H-15	+0.07	+0.14	−0.09	−0.11
	H-16	−0.20	−0.46	−0.23	−0.32

[a] Calculated from ^1H NMR titration experiments (500 MHz, 298 K). [b] For proton numbering, see Figures 1 and 2. [c] In $CDCl_3/CD_3CN$ 1:1 (v/v). [d] In $CDCl_3$. [e] Value could not be determined because of broadening of the signal.

The positive charge distributed on the nitrogen atoms, the α-protons of the bipyridine ring and the first *N*-methylene moiety can interact with the crown ether spacers, and extra stabilization can be obtained when the *N*,*N*′-substituents of the guest (**G2**) can form hydrogen bonds with the carbonyl groups of the diphenylglycoluril framework.[15] The geometry of the guest in the host–guest complex was found to be strongly dependent on the *N*,*N*′-substituent. This was concluded from the observed strong upfield shifts (Table 2) of the pyrrole NH protons in the 1:1 complex of **H_2-1** and **G2**, compared to the only small upfield shifts of these protons in the complex of **H_2-1** with **G1**. We therefore propose that the bipyridinium part of **G2** is oriented parallel to the porphyrin, whereas **G1** is oriented perpendicular to it and clamped between the cavity side-walls (Figure 4a,b). The presence of a Zn(II) ion in the porphyrin did not result in significant changes in binding strength or geometry.

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(15) This is indicated by an observed downfield shift of the OH protons of **G2** upon complexation in hosts **1** and **2**.

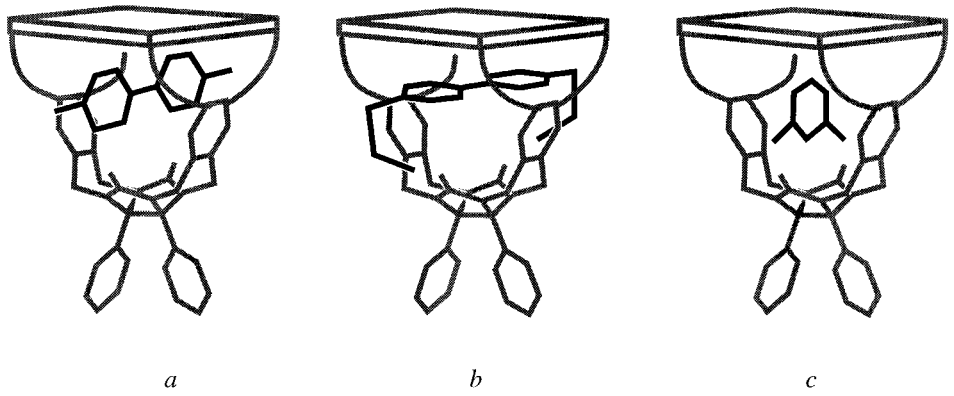

Figure 4. Schematic structure of the complex between (a) hosts **1** and **G1**, (b) **1** and **G2**, and (c) **1** and **G3**.

In contrast to the very strong binding of viologens in host **1**, host **2** proved to be a relatively poor binder for this type of guest molecules (Table 1). Binding of these guests in hosts **2** appears to occur by an *induced fit* mechanism: in all cases, the signals of the crown ether protons H-6a and H-6b shifted strongly downfield (Table 2), as did the signal of the wall protons (H-5). This is an indication that the porphyrin is lifted from the cavity side-walls upon binding of the guest. It can clearly be seen from the calculated complexation-induced shift values that in the complex of **H_2-2** with **G2** the porphyrin is situated more centrally over the cavity. The fact that **G1** and **G2** are bound weaker in **H_2-2** than in **Zn-2** is attributed to the stronger interaction between the porphyrin and side-wall in the former host.

The fact that **1** binds viologens several orders of magnitude stronger than **2** can be attributed to several factors. First, **1** is a better preorganized host for these guests than **2**, which upon binding has to undergo conformational changes at the expense of binding energy. Second, the electron-rich crown ether oxygen atoms in **1** are in closer proximity to the positive charges in the guest than the oxygen atoms in **2**. Finally, "cavity effects" may also play a role because **1** has a smaller cavity than **2**, which is better filled by the guest (vide infra).

Binding of Dihydroxybenzene Derivatives. Binding experiments were also carried out with 1,3-dihydroxybenzene derivatives as guests. In previous studies, these compounds were found to be ideal guests for receptors derived from **3**. NMR titrations revealed that in chloroform all porphyrin clips formed weaker host−guest complexes with 1,3-dihydroxybenzene (**G3**) than reference compound **3** (Table 1). The complexation-induced shift values (Table 2) indicate that the binding geometry is the same as in **3**, viz., with the OH-groups hydrogen bonded to the carbonyl groups of the receptor. The downfield shift of the pyrrole NH protons of **H_2-1** suggests that the aromatic ring of **G3** is oriented in an edge-to-face geometry to the porphyrin (Figure 4c), whereas the upfield shift of the NH protons in the complex of **H_2-2** with **G3** is explained by a more face-to-face geometry (Figure 5).

An explanation for the weaker binding of **G3** in **1** and **2** as compared to **3** might be the presence of the porphyrin above (in the case of **1**) or near (in the case of **2**) the cavity, which hinders the guest from adopting an ideal binding geometry in the host−guest complex.[16] Intuitively, the K_a for **G3** in **1** would be expected to be smaller than in **2**, because the guest is expected to be more hindered by the porphyrin in the former host than in the latter. However, it is clear that the cavity of **1** is large enough to accommodate **G3**, and the additional interactions with the porphyrin roof and probably also a cavity effect[10b] result in a better binding than in **2**.

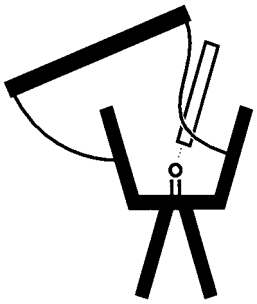

Figure 5. Schematic structure of the complex between **H_2-2** and **G3**.

Table 1 shows that substituting **G3** on the 5-position with a hexyl ester group (**G4**) leads to a lower K_a with hosts **1**, simply because the guest is now too large to give a good fit in the cavity. In hosts **2**, this effect is not present and does therefore not decrease the K_a values, which, because of the electron-withdrawing ester group,[10b] now are higher than the K_a values of **2** with **G3**. Addition of **G4** to **2** resulted in severe broadening of the NMR signals of the protons lining the inside of the cavity. This might point to hindering of the exchange between the two conformations of the host. The alkyl tail of the guest probably can act as a kind of "supramolecular brake".

It is remarkable that **Zn-1** and **Zn-2** bind **G3** more weakly than their free-base analogues. The opposite is observed for the binding of **G4** in **Zn-1** and **Zn-2** as compared to the binding in **H_2-1** and **H_2-2**. In the case of **G4** an extra coordinative interaction between the carbonyl group of the guest and the Zn(II) ion is presumed to be present but could not be demonstrated by UV−vis or IR spectroscopy.[17]

Binding of Pyridine Derivatives. To investigate the binding properties of the porphyrin hosts and the influence of the metallo center further, 1:1 host−guest com-

(16) The ideal binding geometry between a dihydroxybenzene derivative and a molecular clip is in an offset manner, in which the aromatic ring of the guest is located parallel but partly above the cavity side-walls, see ref 10b.

(17) It is well-known that a ligand (i.e., water, methanol, an aldehyde) can axially coordinate to a Zn(II) porphyrin. The increase in K_a going from **G3** to **G4** in **Zn-2** is significantly larger than for **H_2-2** and host **3**, implying some additional interaction.

plexes of **Zn-1** and **Zn-2** with pyridine (**G5**) were prepared. In both complexes, a redshift of the Soret band in the UV−vis spectrum was observed, indicating that the guest coordinates to the Zn(II) ion. NMR spectroscopy furthermore clearly showed that this complexation predominantly took place inside the cavity. UV−vis titrations were carried out, from which high K_a values were calculated (see Table 1). When these values are compared with the K_a of **G5** bound to Zn(II)-tetra(*meso*-phenyl)-porphyrin (K_a = 1000 M^{-1} in $CDCl_3$), it is clear that a cavity-effect is operative. This cavity-effect is more pronounced for **Zn-1** than for **Zn-2** and is probably due to a the aforementioned better preorganization of the former host as compared to the latter. The measured K_a for the **Zn-1-G5** complex is one of the highest observed in organic solvents.[18]

In a subsequent series of binding experiments, hydroxy-substituted pyridine guests that can have extra hydrogen bonding interactions with the host were used. For both **Zn-1** and **Zn-2** extremely high K_a values were found with **G6**. In contrast, the K_a values of 4-hydroxypyridine (**G7**) with the two hosts were found to be much lower. This may be partly the result of an electronic effect; however, it is striking that this guest forms a weaker host−guest complex with **Zn-1** than with **Zn-2** and also a weaker complex than **G5** with **Zn-1**. CPK models and molecular modeling revealed that **G7** in **Zn-1** cannot coordinate to the zinc ion and at the same time form a good hydrogen bond with one of the carbonyl groups. In **Zn-2** the spacers between the clip and the porphyrin are longer and more flexible allowing coordination of **G7** to the Zn(II) ion, while a weak hydrogen bond can still be formed between the hydroxy group of this guest and one of the carbonyl groups of the host.

Conclusions

The results described above clearly demonstrate that the location and orientation of the porphyrin ring with regard to the receptor, imposed by the spacers between these components, has a great impact on the conformational and complexation behavior of the new host molecules. Because of its rigid and preorganized cavity clip **1** is a far better host for viologen guests than clip **2**. The latter receptor is, as a result of its flexible structure, a somewhat more versatile host than **1** because it can adjust its conformation upon complexation of a guest (induced-fit binding). Both hosts display a so-called cavity-effect which leads to higher binding constants under certain conditions. For host **1**, which possesses the most rigid and preorganized cavity, this effect is more pronounced than for host **2**.

Experimental Section

Materials and Methods. All syntheses were carried out under an inert nitrogen or argon atmosphere. Diethyl ether and *n*-hexane were distilled under nitrogen from sodium−benzophenone ketyl. Chloroform and acetonitrile were distilled from $CaCl_2$. Dichloromethane, 1,2-dichloroethane, and methanol were distilled from CaH_2. Deuteriochloroform used in the NMR titrations was vacuum distilled from P_2O_5 and stored under nitrogen. Ethyl acetate and *n*-hexane used for column chromatography were rotary evaporated prior to use. Pyridine was dried over KOH and freshly distilled. Pyrrole was vacuum distilled at room temperature immediately prior to use. Salicylic aldehyde was vacuum distilled, and *m*-hydroxybenzaldehyde was recrystallized from water. $MgSO_4$, Na_2CO_3, K_2CO_3, and NaI were dried in an oven (150 °C). All other solvents and chemicals were commercial materials and used without purification. Merck silica gel (60H) was used for column chromatography, and Merck silica gel F254 plates were used for thin-layer chromatography. Molecular modeling calculations were performed on a Silicon Graphics Indigo II work station using the CHARMm force field.[19]

Syntheses. 2-[2-(2-Hydroxy-ethoxy)-phenoxy]-ethanol (4). This compound was synthesized according to a literature procedure.[20]

Ditosyl Compound 5. To a cooled solution (0 °C) of **3** (7.0 g, 37 mmol) in pyridine (25 mL) was added in small portions *p*-toluenesulfonyl chloride (14.8 g, 78.2 mmol). The mixture was stored overnight at 4 °C and then poured onto ice (100 g). After the ice had melted, aqueous 6 N HCl (25 mL) was added, and the product was extracted with CH_2Cl_2 (2 × 50 mL) The combined organic layers were dried ($MgSO_4$), filtered, and evaporated to dryness. The residue was recrystallized from toluene to yield 16.0 g (90%) of **5** as a white solid: mp 86 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, 4H, ^3J = 8.3 Hz), 7.33 (d, 4H, ^3J = 8.3 Hz), 6.93−6.87 (m, 2H), 6.84−6.78 (m, 2H), 4.33−4.30 (m, 4H) 4.17−4.14 (m, 4H), 2.43 (s, 6H) ppm; ^{13}C-{^{1}H} NMR ($CDCl_3$, 75 MHz) δ 148.42, 145.01, 132.85, 129.92, 127.91, 122.60, 116.33, 68.22, 67.30, 21.59 ppm; MS (EI) *m*/*z* 506 $(M)^+$. Anal. Calcd for $C_{24}H_{26}O_6S_2$: C, 56.90; H, 5.17; S, 12.66. Found: C, 56.95; H, 4.94; S, 12.80.

1,3,4,6-Tetrakis(chloromethyl)tetrahydro-3a,6a-diphenyl-imidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*-dione (6). This compound was synthesized according to a literature procedure.[12]

Tetra-Tosyl Clip Molecule 7. Compounds **5** (5.0 g, 10 mmol) and **6** (2.2 g, 4.5 mmol) were dissolved in 1,2-dichloroethane (100 mL). $SnCl_4$ (4 mL, 32 mmol) was added, and the mixture was refluxed for 16 h. After cooling, aqueous 6 N HCl (25 mL) was added, and the mixture was refluxed for another 10 min. After cooling, CH_2Cl_2 (75 mL) was added, and the organic layer was washed with aqueous 1 N HCl (3 × 100 mL) and water and subsequently evaporated to dryness. The crude product was recrystallized from toluene to yield 3.8 g (62%) of **7** as a white solid: mp 110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, 4H, ^3J = 9.0 Hz), 7.17 (d, 4H, ^3J = 9.0 Hz), 7.12 (br s, 10H), 6.67 (s, 4H), 4.65 (d, 4H, ^2J = 15.8 Hz), 4.21 (t, 8H, ^3J = 7.3 Hz), 4.09 (d, 4H, ^2J = 15.8 Hz), 4.01−3.85 (m, 8H), 2.36 (s, 6H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ 157.70, 146.77, 144.87, 133.52, 132.62, 130.07, 129.82, 128.91, 128.73, 128.19, 127.81, 117.11, 85.39, 68.22, 66.78, 44.73, 21.58 ppm; MS (FAB) *m*/*z* 1355 $(M + H)^+$. Anal. Calcd for $C_{68}H_{66}N_4O_{18}S_4$: C, 60.25; H, 4.91; N, 4.13; S, 9.46. Found: C, 60.12; H, 4.87; N, 4.22; S, 9.12.

Tetra-Aldehyde Clip Molecule 8. A suspension of **7** (2.1 g, 1.6 mmol), salicylic aldehyde (0.82 g, 6.7 mmol), and K_2CO_3 (0.85 g, 6.2 mmol) in freshly distilled acetonitrile (100 mL) was refluxed for 16 h. After cooling, the mixture was filtered, and the filtrate was evaporated to dryness. The residue was dissolved in CH_2Cl_2 (50 mL). This solution was washed with aqueous 0.5 N NaOH (2 × 100 mL) and evaporated to dryness. The residue was purified by column chromatography ($CHCl_3$/MeOH 197:3 v/v). The resulting off-white product was dissolved in a minimal amount of $CHCl_3$, and this solution was added dropwise to stirred diethyl ether (100 mL). After filtration, the product was dried under vacuum to yield 1.10 g (59%) of **8** as a white solid: mp 107 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.30 (s, 4H), 7.70 (dd, 4H, ^3J = 7.9 Hz, ^4J = 1.8 Hz), 7.43 (td, 4H, ^3J = 7.9 Hz, ^4J = 1.8 Hz), 7.21−7.07 (m, 10H), 6.95−6.70 (m, 8H), 6.89 (s, 4H), 4.76 (d, 4H, ^2J = 15.9 Hz), 4.24−4.17 (m, 4H), 4.17 (d, 4H, ^2J = 15.9 Hz), 4.15−4.08 (m, 4H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ 189.71, 160.99, 157.81, 147.38, 135.83, 133.50, 131.05, 128.89, 128.73, 128.24, 127.98, 125.04, 120.99, 116.80, 113.10, 85.45, 67.68, 67.41, 44.81 ppm; MS (FAB) *m*/*z* 1155 $(M + H)^+$. Anal. Calcd for

(18) Similar high values were found for the binding of pyridine to Zn(II) picket fence porphyrins in toluene solution. Imai, H.; Kyuno, E. *Inorg. Chem.* **1990**, *29*, 2416.

(19) CHARMm version 22.0, Revision 92.0911, Resident and Fellows of Harvard College, 1984, 1992, with the use of template charges.

(20) Landini, D.; Montanari, F.; Rolla, F. *Synthesis* **1978**, 223.

$C_{68}H_{58}N_4O_{14}.0.5CHCl_3$ C, 67.72; H, 4.85; N, 4.61. Found: C, 67.83; H, 4.86; N, 4.89.

5,7,12,13b,13c,14-Hexahydro-1,4,8,11-tetrakis[2-(2-chloroethoxy)-ethoxy]-13b,13c-diphenyl-6*H*,13*H*-5a,6a,12a,-13a-tetraazabenz[5,6]-azuleno[2,1,8-*ija*]benz[*f*]azulene-6,13-dione (9). This compound was synthesized according to a literature procedure.[12]

Tetra-Aldehyde Clip Molecule 10. A mixture of **9** (0.50 g, 0.50 mmol), Na_2CO_3 (1.6 g, 15 mmol), NaI (5.0 g, 33 mmol), and *m*-hydroxybenzaldehyde (0.50 g, 4.1 mmol) in freshly distilled acetonitrile (100 mL) was refluxed for 10 days. After cooling, the mixture was filtered, and the filtrate was evaporated to dryness. Water (100 mL) was added, and the resulting suspension was extracted with $CHCl_3$ (3 × 50 mL). The organic layer was washed with aqueous 0.5 N NaOH (2 × 100 mL), filtered, and evaporated to dryness. After column chromatography ($CHCl_3$/EtOH 97:3 v/v), 0.43 g (64%) of **10** was obtained as a white solid: mp 212 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.95 (s, 4H), 7.43 (d, 4H, ^3J = 7.5 Hz), 7.39 (s, 4H), 7.38 (t, 4H, ^3J = 7.5 Hz), 7.19−7.13 (m, 4H), 7.09−7.01 (m, 10H), 6.63 (s, 4H), 5.59 (d, 4H, ^2J = 15.8 Hz), 3.74 (d, 4H, ^2J = 15.8 Hz), 4.08−3.81 (m, 32H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ 192.21, 159.41, 157.80, 150.72, 137.76, 133.83, 129.96, 128.55, 128.33, 128.14, 122.97, 121.96, 114.25, 113.55, 85.28, 70.47, 69.73, 67.81, 37.02 ppm; MS (FAB) *m*/*z* 1331 (M + H)$^+$. Anal. Calcd for $C_{76}H_{74}O_{18}N_4 \cdot CH_3CH_2OH$: C, 68.01; H, 5.85; N, 4.07. Found: C, 68.19; H, 6.06; N, 4.08.

Porphyrin Clip H_2-1. To CH_2Cl_2 (250 mL) were added compound **8** (0.30 g, 0.26 mmol) and pyrrole (70 mg, 1.0 mmol). The solution was purged with argon for 15 min and excluded from light, and $BF_3 \cdot OEt_2$ (50 mg, 0.35 mmol) was added. The mixture was stirred for 16 h at room temperature. 4-Chloranil (0.17 g, 0.75 mmol) was added and the mixture was refluxed for 1 h. After the mixture cooled, the solvent was evaporated, and the residue was purified by column chromatography (2×, first CH_2Cl_2/EtOH 95:5 v/v, then $CHCl_3$/MeOH 99:1 v/v). The product was dissolved in a minimal amount of $CHCl_3$ and precipitated in stirred *n*-hexane (25 mL) to yield, after centrifugation and drying under vacuum, 20 mg (6%) of **H_2-1** as a dark red solid: mp > 400 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (s, 4H), 8.66 (s, 4H), 8.07 (d, 4H, ^3J = 7.3 Hz), 7.75 (t, 4H, ^3J = 8.0 Hz), 7.37 (t, 4H, ^3J = 7.4 Hz), 7.34 (d, 4H, ^3J = 8.4 Hz), 6.97−6.91 (m, 6H), 6.83−6.78 (m, 4H), 6.20 (s, 4H), 4.30−4.20 (m, 4H), 4.24 (d, 4H, ^2J = 15.8 Hz), 4.09−4.01 (m, 4H), 3.74 (d, 4H, ^2J = 15.8 Hz), 3.53−3.43 (m, 4H), 3.37−3.30 (m, 4H), −2.72 (br s, 4H) ppm; ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 158.76, 156.99, 146.60, 135.75, 133.63, 131.90, 129.82, 129.57, 128.45, 128.10, 119.82, 115.21, 111.93, 84.76, 67.43, 66.87, 44.39; MS (FAB) *m*/*z* 1345 (M + H)$^+$; UV−vis ($CHCl_3$) λ/nm (log(ϵ/M^{-1} cm^{-1})) 418 (5.63), 485 (3.44), 515 (4.27), 548 (3.82), 587 (4.02), 639 (3.70). Anal. Calcd for $C_{84}H_{64}N_8O_{10}$: C, 74.97; H, 4.79; N, 8.33. Found: C, 74.84; H, 4.93; N, 8.32.

Porphyrin Clip Zn-1. To a degassed solution of **H_2-1** (20 mg, 0.015 mmol) in a mixture of $CHCl_3$ (2 mL) and MeOH (1 mL) was added $Zn(OAc)_2 \cdot 2H_2O$ (8.0 mg, 0.036 mmol). The mixture was refluxed for 3 h. After the mixture cooled, the solvent was evaporated, and the product was dissolved in CH_2Cl_2 (10 mL) The organic layer was washed with water (2×) and concentrated in vacuo. After purification by column chromatography (CH_2Cl_2/MeOH 97:3, v/v) 20 mg (95%) of **Zn-1** was obtained as a purple solid: mp > 400 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89 (s, 4H), 8.77 (s, 4H), 8.10 (d, 4H, ^3J = 6.6 Hz), 7.74 (t, 4H, ^3J = 7.2 Hz), 7.38 (t, 4H, ^3J = 7.5 Hz), 7.34 (d, 4H, ^3J = 8.2 Hz), 7.00−6.92 (m, 6H), 6.85−6.74 (m, 4H), 6.17 (s, 4H), 4.27−4.15 (m, 4H), 4.19 (d, 4H, ^2J = 15.6 Hz), 4.09−3.99 (m, 4H), 3.72 (d, 4H, ^2J = 15.6 Hz), 3.57−3.47 (m, 4H), 3.35−3.23 (m, 4H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ 158.87, 150.13, 149.88, 146.63, 135.56, 133.66, 132.72, 131.44, 130.89, 129.90, 129.36, 128.50, 128.11, 119.87, 116.14, 115.41, 112.16, 84.76, 67.50, 67.02, 44.33 ppm; UV−vis ($CHCl_3$) λ/nm (log(ϵ/M^{-1} cm^{-1})) 420 (5.6), 545 (4.1). No satisfactory elemental analysis could be obtained.

Porphyrin Clip H_2-2. From **10** (0.30 g, 0.23 mmol) and pyrrole (61 mg, 0.91 mmol) in CH_2Cl_2 (250 mL) using $BF_3 \cdot OEt_2$ (50 mg, 0.35 mmol) and 4-chloranil (0.17 g, 0.75 mmol), this compound was synthesized as described for **H_2-1**. The crude product was purified by column chromatography (2×, first $CHCl_3$/MeOH 97:3 v/v, then gradient elution EtOAc/*n*-hexane 1:1 v/v to EtOAc/*n*-hexane 3:1 v/v). The resulting compound was dissolved in a minimal amount of $CHCl_3$ and precipitated in stirred *n*-hexane (25 mL). After centrifugation and drying under vacuum, 12 mg (4%) of **H_2-2** was obtained as a dark red solid: mp > 400 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.92 (s, 4H), 8.80 (s, 4H), 8.06 (d, 4H, ^3J = 7.3 Hz), 7.71 (br s, 4H), 7.68 (t, 4H, ^3J = 7.9 Hz), 7.35 (dd, 4H, ^3J = 8.2 Hz, ^4J = 2.3 Hz), 6.85 (m, 6H), 6.70 (m, 4H), 4.92 (d, 4H, ^2J = 16.1 Hz), 4.24 (m, 4H), 4.09 (m, 4H), 3.85 (m, 8H), 3.8 (br s, 4H), 3.55 (m, 8H), 3.21 (d, 4H, ^2J = 16.1 Hz), 3.20 (m, 4H), 2.68 (m, 4H), −2.70 (br s, 2H) ppm; ^{1}H NMR (500 MHz, $CDCl_3$/CD_3CN 1:1, v/v) δ 8.92 (s, 4H), 8.85 (s, 4H), 8.03 (d, 4H, ^3J = 7.3 Hz), 7.82 (br s, 4H), 7.71 (t, 4H, ^3J = 7.9 Hz), 7.34 (dd, 4H, ^3J = 8.2 Hz, ^4J = 2.3 Hz), 6.85 (m, 6H), 6.70 (m, 4H), 4.65 (d, 4H, ^2J = 16.1 Hz), 4.35 (m, 4H), 4.16 (m, 4H), 3.85 (m, 12H), 3.55 (m, 8H), 3.16 (d, 4H, ^2J = 16.1 Hz), 3.16 (m, 4H), 2.64 (m, 4H), −2.78 (br s, 2H) ppm; ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 158.00, 156.90, 149.35, 143.30, 133.86, 132.91, 129.83, 128.18, 127.97, 127.56, 127.14, 126.02, 121.69, 120.18, 116.37, 111.56, 84.52, 70.74, 69.76, 68.74, 68.11, 36.40 ppm; MS (FAB) *m*/*z* 1521 (M + H)$^+$; UV−vis ($CHCl_3$) λ/nm (log(ϵ/M^{-1}cm^{-1})) 420 (5.6), 515 (4.2), 549 (4.0), 588 (3.7), 644 (3.6). No satisfactory elemental analysis could be obtained.

Porphyrin Clip Zn-2. This compound was prepared from **H_2-2** (20 mg, 0.013 mmol) and $Zn(OAc)_2 \cdot 2H_2O$ (7.2 mg, 0.032 mmol) as described for **Zn-1**. After purification by column chromatography (EtOAc/*n*-hexane 2:1 v/v) 20 mg (96%) of **Zn-2** was obtained as a purple solid: mp > 400 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.96 (s, 4H), 8.94 (s, 4H), 7.98 (d, 4H, ^3J = 7.4 Hz), 7.85 (br s, 4H), 7.65 (t, 4H, ^3J = 7.5 Hz), 7.33 (dd, 4H, ^3J = 8.3 Hz, ^4J = 2.3 Hz), 6.71 (m, 6H), 6.51 (m, 4H), 4.59 (s, 4H), 4.32 (m, 4H), 4.28 (d, 4H, ^2J = 15.6 Hz), 4.18 (m, 4H), 3.85 (m, 8H), 3.55 (m, 8H), 3.30 (d, 4H, ^2J = 15.6 Hz), 3.34 (m, 4H), 2.95 (m, 4H) ppm;^{1}H NMR (500 MHz, $CDCl_3$:CD_3CN 1:1, v/v) δ 8.97 (s, 4H), 8.92 (s, 4H,), 8.01 (d, 4H, ^3J = 7.4 Hz), 7.96 (br s, 4H), 7.70 (t, 4H, ^3J = 7.5 Hz), 7.34 (dd, 4H, ^3J = 8.3 Hz, ^4J = 2.3 Hz), 6.88 (m, 6H), 6.72 (m, 4H), 4.76 (s, 4H), 4.72 (d, 4H, ^2J = 15.6 Hz), 4.56 (m, 4H), 4.27 (m, 4H), 3.88 (m, 8H), 3.58 (m, 8H), 3.20 (d, 4H, ^2J = 15.6 Hz), 3.15 (m, 4H), 3.00 (m, 4H) ppm; ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 157.22, 156.89, 150.23, 149.62, 134.28, 132.11, 131.92, 127.84, 127.62, 127.31, 126.61, 121.68, 120.96, 115.83, 112.44, 84.36, 70.74, 70.02, 68.62, 36.49 ppm; MS (FAB) *m*/*z* 1585 (M + H)$^+$; UV−vis ($CHCl_3$) λ/nm (log(ϵ/M^{-1}cm^{-1})) 420 (5.6), 546 (4.2). No satisfactory elemental analysis could be obtained.

(*N*,*N*′)-Dimethyl-4,4′-bipyridinium Dihexafluorophosphate (G1). This compound was prepared from the commercially available dichloride salt by anion exchange with NH_4PF_6.

(*N*,*N*′)-Di(2-ethanol)-4,4′-bipyridinium Dihexafluorophosphate (G2). 4,4′-Bipyridine (3.7 g, 24 mmol) and 2-bromoethanol (16 g, 0.13 mol) were refluxed in acetonitrile (75 mL) for 24 h. After the mixture cooled, the precipitate was filtered off, washed with diethyl ether, and dried under vacuum. The product was dissolved in a minimal amount of water, and this solution was then added to a saturated aqueous NH_4PF_6 solution to yield, after filtration and drying under vacuum, 6.0 g (47%) of **G2** as a white solid: mp 185 °C; ^{1}H NMR (300 MHz, CD_3CN) δ 9.39 (d, 4H, ^3J = 7.2 Hz), 8.85 (d, 4H, ^3J = 7.2 Hz), 5.05 (t, 4H, ^3J = 5.1 Hz), 4.68 (t, 2H, ^3J = 5.2 Hz), 4.24−4.17 (m, 4H) ppm; MS (FAB) *m*/*z* 391 (M − PF_6)$^+$. Anal. Calcd for $C_{14}H_{18}N_2O_2P_2F_{12}$: C, 31.36; H, 3.38; N, 5.22. Found: C, 31.18; H, 3.39; N, 5.18.

Hexyl 3,5-Dihydroxybenzoate (G7). This compound was synthesized according to a literature procedure.[10b]

Supporting Information Available: ^{1}H NMR peak assignments for all compounds and protocols for determining association constants using ^{1}H NMR and UV titrations. This material is available free of charge on the Internet at http://pubs.acs.org.

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