Synthesis and Molecular Recognition Properties of a β-Cyclodextrin Tetramer

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The synthesis and binding properties of a cyclodextrin tetramer are described. This species is composed of four individual cyclodextrin subunits covalently appended to a central aromatic core. The tetramer is prepared from β-cyclodextrin in five steps in an overall 14% yield. We have performed a preliminary survey of the binding properties of this species. The structure of tetramer–tetraarylporphryin complexes was examined by both NMR and mass spectrometry. The results are consistent with a 1:1 stoichiometry in which the aromatic substituents of the porphyrin moiety are incorporated into the individual cyclodextrin subunits of the tetramer. The cyclodextrin tetramer exhibits a high affinity for both tetraarylporphyrins and metalloporphyrins, with binding constants as large as 10^8 M^{-1}. Finally, we have compared and contrasted the behavior of the tetrameric species with that of two related cyclodextrin dimers. While all of these hosts bind both porphyrins and metalloporphyrins, the tetramer exhibits a special affinity for those guests that contain a neutral inner porphyrin core.

A large array of covalently modified cyclodextrin derivatives have been prepared over the course of the last 25 years.[1-3] These species have been utilized for a variety of purposes, such as simple models of complex biochemical processes,[4-6] as well as water-soluble agents for the delivery of medicinally useful compounds.[7-9] A hydrophobic interior encased within a water-soluble framework is the structural characteristic that renders cyclodextrins and their derivatives so appealing. However, the ability of parent cyclodextrins to bind hydrophobic compounds in aqueous solution is not an attribute characterized by a high degree of specificity. Consequently, a significant effort has been devoted to the creation of derivatives that exhibit a special affinity for specific guest compounds. For example, Breslow and his colleagues have constructed modified cyclodextrins that contain an "intrusive floor" on the primary face.[10] These species exhibit enhanced activity toward substrates whose molecular structures conform to that of the altered cyclodextrin interior. In addition, a variety of cyclodextrin dimers have been described that display unusually high association constants for specific hydrophobic compounds.[11-30] We recently prepared a pyridine-linked cyclodextrin dimer that exhibits a profound specificity for certain metalated macrocyclic complexes.[29-30] In this report, we describe the first example of a cyclodextrin tetramer (**1**).

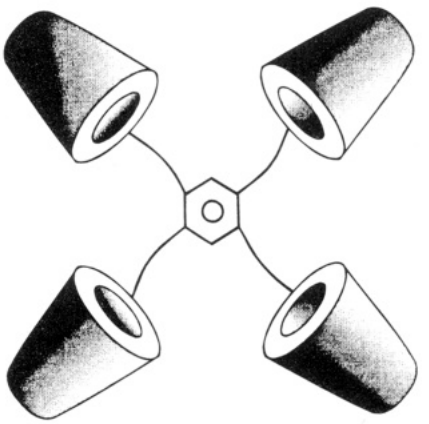

Figure 1. Schematic representation of the cyclodextrin tetramer **1**.

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Experimental Section

Unless otherwise stated, all chemicals were obtained from commercial sources and used without further purification. ^1H and ^{13}C NMR experiments for all compounds except tetramer **1** were performed at 400 and 75.5 MHz, respectively, and are reported relative to TMS (tetramethylsilane) or TSP [the sodium salt of 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid]. ^1H and ^{13}C NMR experiments for tetramer **1** were performed at 500 and 100.6 MHz, respectively, and are reported relative to TSP. Nuclear Overhauser enhancement difference spectra were obtained by subtracting the spectra obtained with the decoupler placed on each of the proton resonances from the spectra acquired with the decoupler set on the base line. The power was adjusted to perturb a narrow band of the selected proton resonance, and the experiments were run at 25 °C. Laser desorption and electrospray mass spectrometry were performed at the Yale School of Medicine Mass Spectrometry Facility. All steady-state fluorescence measurements were made on an SLM 4800 MHF (Aminco, Inc.; Rochester, NY) multifrequency phase-modulation fluorescence spectrometer.

Synthesis of Thioether 4. A 3.0 g (6.7 mmol) amount of 1,2,4,5-tetrakis(bromomethyl)benzene (**2**) (Aldrich) and 2.2 g of thiourea (28.9 mmol) were dissolved in 25 mL of 95% ethanol. The resultant solution was heated to reflux for 15 min, after which time aqueous NaOH (1.3 g in 10 mL) was added. After 15 min at reflux, the solution was allowed to cool to room temperature, neutralized with 2 M H_2SO_4, and extracted with $CHCl_3$. The extract was dried and removed *in vacuo* to yield 1.7 g (95% yield) of the tetramercaptan **3**. This product was immediately alkylated with 1-bromo-6-chlorohexane (7.0 g, 35 mmol) in $CHCl_3$ under Ar. A deoxygenated ethanolic solution of NaOH (1.2 g, 30 mmol; in 15 mL) was subsequently slowly added into the reaction vessel. After stirring at room temperature for 5 h, the solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column (eluent: $CHCl_3$/hexanes = 1:1 to 3:2) to furnish 2.9 g of tetrathioether **4** (60% yield). ^1H NMR ($CDCl_3$): 7.26 (s, 2H), 3.83 (s, 8H), 3.53 (t, 8H), 2.48 (t, 8H), 1.76 (m, 8H), 1.59 (m, 8H), 1.41 (m, 16H). ^{13}C NMR ($CDCl_3$): 135.9, 133.2, 70.8, 66.4, 45.2, 33.6, 32.3, 28.3, 25.8. FAB MS: *m/e* calculated for $C_{34}H_{58}Cl_4S_4$ = 736.5; found: 735.7 (M^+).

Synthesis of Sulfone 5. A 30% aqueous hydrogen peroxide (3.0 g) solution was added to thioether **4** (1.0 g, 1.4 mM) dissolved in 10 mL of acetic acid. The solution was stirred at 80 °C for 5 h. The solvent was removed *in vacuo*, and the resulting solid residue was extensively washed with water and subsequently lyophilized to yield 1.2 g (98% yield) of the desired pure (as assessed by TLC and NMR) product. ^1H NMR ($CDCl_3$): 7.39 (s, 2H), 4.57 (s, 8H), 3.54 (t, 8H), 3.05 (t, 8H), 1.87 (m, 8H), 1.79 (m, 8H), 1.40 (m, 16H). ^{13}C NMR ($CDCl_3$): 137.5, 129.3, 55.2, 51.6, 43.8, 31.2, 26.7, 25.3, 20.7. FAB MS: *m/e* calculated for $C_{34}H_{58}Cl_4O_8S_4$ = 864.5, found 865.3 (M + H^+).

Synthesis of Tetraiodide 6. A 1.0 g amount of sulfone **5** (0.8 mmol) and 1.0 g of NaI (6.7 mmol) were dissolved in 20 mL of dry acetone, and the resulting solution was heated at reflux for 10 h. The solvent was removed *in vacuo*, and the resulting solid residue was sequentially washed with 5% aqueous sodium sulfite and water and then subsequently lyophilized to yield 1.4 (98% yield) of desired pure (as assessed by TLC and NMR) product. ^1H NMR ($CDCl_3$): 7.39 (s, 2H), 4.56 (s, 8H), 3.19 (t, 8H), 3.04 (t, 8H), 1.83 (m, 16H), 1.47 (m, 16H). ^{13}C NMR (DMSO-d_6): 139.6, 129.9, 54.8, 51.5, 32.7, 29.4, 26.6, 20.9, 8.6. FAB MS: *m/e* calculated for $C_{34}H_{58}I_4O_8S_8$ = 1230.3, found 1231.4 (M + H^+).

Synthesis of Tetramer 1. A 1.0 g amount of 3-monomercaptocyclodextrin (0.88 mmol, prepared from β-cyclodextrin in four steps with an overall 32% yield; see reference 16 and papers cited therein) and 200 mg of tetraiodide **6** (0.16 mmol) were dissolved in 15 mL of deoxygenated DMF. K_2CO_3 (200 mg) was added, and the solution was heated to 60 °C and maintained at this temperature for 6 h. Upon cooling to room temperature, the solvent was removed *in vacuo*, the solid residue dissolved in 10 mL of water, and the resulting solution neutralized with 2 N HCl. This solution was directly loaded onto a Sephadex G-50 column (2.5 cm × 120 cm; 450 mL of swelled resin). The product was eluted from the column with distilled water. Fractions were analyzed for the presence of cyclodextrin tetramer via TLC [1:1:1:1 ethyl acetate:2-propanol:ammonium hydroxide:water; silica gel plates; anisaldehyde/ethanol/H_2SO_4/acetic acid spray followed by heating (R_f = 0.53)]. The fractions containing the product were combined, and the total volume was then reduced to 15 mL by vacuum evaporation. This solution was then loaded onto a Sephadex G-25 column (2.5 cm × 120 cm; 450 mL of swelled resin). Once again, the fractions containing cyclodextrin were combined, and the volume was reduced to 15 mL. This material was loaded onto a Sephadex G-15 column (2.5 cm × 120 cm; 450 mL of swelled resin) and eluted with distilled water to furnished 390 mg (45% yield) of pure, colorless tetramer **1**. ^1H NMR (D_2O): 7.62 (s, 2H), 4.75 (s, 8H), 3.23 (t, 8H), 2.60 (t, 8H), 1.83 (m, 8H), 1.50 (m, 8H), 1.26 (m, 8H), 1.24 (m, 8H); cyclodextrin protons are not listed here but are the same as those of a previous fully characterized cyclodextrin dimer (see reference 29). ^{13}C NMR (D_2O): 139.1, 130.6, 53.3, 51.2, 33.7, 29.6, 28.2, 28.1, 22.1; cyclodextrin carbons are not listed here but are the same as those of a previous fully characterized cyclodextrin dimer (see reference 29). Laser desorption MS: *m/e* calculated for $C_{202}H_{334}O_{144}S_8$ = 5323.3, found 5360.6 (M + H^+ + $2H_2O$).

Porphyrin **12** was prepared as previously described.[31] Zn(II) and Sn(IV) were inserted into the commercially available porphyrin **9** via the method of Adler et al.[32]

Determination of Formation Constants for Porphyrins 9–12 with the β-Cyclodextrin Tetramer 1. The formation of complexes of **1**:**9** (measured at 645–655 nm; excited at 420 nm), **1**:**10** (measured at 602–616 nm, excited at 420 nm), **1**:**11** (measured at 600–610 nm, excited at 426 nm), and **1**:**12** (measured at 650–660 nm, excited at 424 nm) was monitored via a fluorescence spectrophotometer equipped with a thermostated cell compartment maintained at 25 °C. All measurements were performed with quartz cuvettes. The stock solutions of porphyrins contain 1.5 mM of **9**, 1.5 mM of **10**, 30 mM of **11** in 200 mM pH 7 phosphate buffer and 1.5 mM of **12** in 10 mM pH 3 citric acid buffer. Three stock solutions (3 mM, 30 mM, 300 mM in buffer solution) of the β-cyclodextrin tetramer were employed. The order of addition of the component solutions was buffer, guest stock, and β-cyclodextrin tetramer stock. The final concentrations of guests were 5 nM **9**, 5 nM **10**, 100 nM **11**, and 5 nM **12**. The cyclodextrin tetramer concentration was varied from 5 nM (for **9**, **10**, **12**) or 100 nM (for **11**) up to saturation (i.e. no further change of fluorescence intensity). The resultant mixtures were preincubated for 3 min at 25 °C prior to fluorescence measurements. All measurements were performed triplicate. Formation constants were computed by the Scatchard treatment.[33]

Results and Discussion

Cyclodextrins are cyclic oligomers of six (α), seven (β), eight (γ), or more α-D-glucopyranose subunits linked in a 1-to-4 fashion.[1-3] One of the unique attributes of these water-soluble molecules is their hydrophobic interior cavity. In a very general sense, this structural feature is reminiscent of that found in many proteins where an otherwise hydrophobic active site is rendered water-

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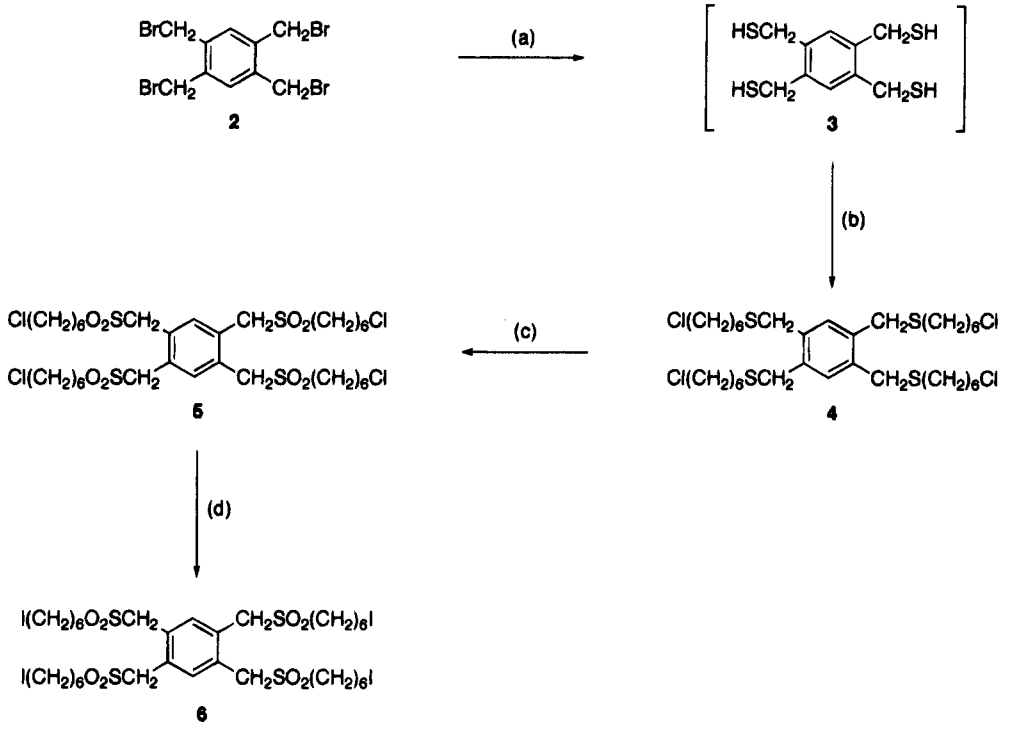
Scheme 1.[a] Synthesis of the Tetraiodide 6 from 1,2,4,5-Tetrakis(bromomethyl)benzene



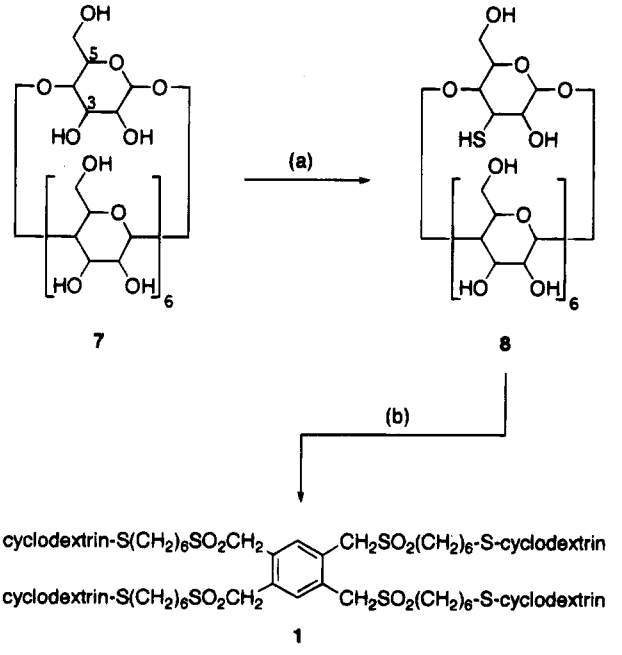
[a] (a) (i) Thiourea/ethanol/reflux/15 min, (ii) NaOH/H_2O/reflux/15 min; (b) 1-bromo-6-chlorohexane/$CHCl_3$/NaOH/ethanol/room temperature/5 h (60% overall yield from **2**); (c) H_2O_2/H_2O/acetic acid/80 °C/5 h (98% yield); (d) NaI/acetone/reflux 10 h (98% yield).

soluble by the presence of lipophilic functionality on the protein surface. Not surprisingly, cyclodextrins, and their modified counterparts, have been extensively employed in a wide variety of studies designed to mimic the activity of proteins. In this regard, we have previously synthesized and characterized β-cyclodextrin dimers and demonstrated their extraordinary affinity for metalloporphyrins and other metalated macrocycles.[29,30] We now report the synthesis and binding properties of a β-cyclodextrin tetramer. This species contains four individual β-cyclodextrin subunits that are linked, via their secondary face, to a single aromatic residue.

The synthesis of the β-cyclodextrin tetramer **1** proceeds in a highly convergent fashion via alkylation of the mercaptocyclodextrin derivative **8** with the tetraiodide **6** (Scheme 1).[34] The tetrabromomethyl derivative **2** was converted to the corresponding tetrathiol **3** in 95% yield by sequential treatment with thiourea and aqueous base. However, we typically do not isolate **3**, but rather directly alkylate it *in situ* with 1-bromo-6-chlorohexane to furnish the thioether **4** (60% yield). The thioether was then oxidized to the sulfone **5** (in nearly quantitative yield) in order to reduce the nucleophilicity of the thioether moiety. The requisite tetraiodide **6** was obtained by heating **5** to reflux in the presence of sodium iodide in acetone.

The mercaptocyclodextrin derivative **8** has been previously described by Breslow and his colleagues (Scheme 2).[16] In brief, **8** is obtained from β-cyclodextrin **7** in four

Scheme 2.[a] Synthesis of Cyclodextrin Tetramer 1



[a] (a) Conversion of β-cyclodextrin to 3-mono-mercaptocyclodextrin **8** by previously described protocols (see references 16, 23, and 26); (b) **6**/DMF/K_2CO_3/60 °C/6 h (45% yield).

steps: (1) tosylation at the C-2 hydroxyl (40%),[35] (2) conversion to the epoxide in aqueous base (100%), (3) epoxide ring opening with benzylmercaptan (80%), and (4) reductive cleavage to the mercaptan with Na/NH_3 (100%). Finally, treatment of the mercaptocyclodextrin with the tetraiodide **6** for 6 h in K_2CO_3/DMF afforded the coveted cyclodextrin tetramer (a schematic of **1** is

(34) We initially attempted to prepare cyclodextrin tetramers containing comparatively short tethers (i.e. five atoms or less) between the aromatic nucleus and the cyclodextrin substituents. Unfortunately, the compounds obtained under these circumstances possess three or fewer cyclodextrin subunits. Unfavorable steric interactions may preclude the formation of the desired tetrameric species in these short chain systems.

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provided in Figure 1) in 45% yield. This species was purified via gel filtration and characterized by laser desorption mass spectrometry and NMR spectroscopy. We have previously described the complete NMR characterization of a closely-related monosubstituted cyclodextrin derivative (the strategy employed for this detailed analysis is outlined in reference 23).

A preliminary survey of the binding properties of tetramer **1** was performed with a series of porphyrins and metalloporphyrins. The following questions were addressed: (1) What is the structure of the tetramer–porphyrin complex? (2) How effective is the β-cyclodextrin tetramer as a complexing agent? (3) How is the interaction between host and guest affected by changes in the structure of the latter? (4) How does the behavior of **1** compare to related cyclodextrin derivatives? The task of addressing these issues was relatively straightforward due to the sharp enhancement in fluorescence exhibited by the porphyrin guests in the presence of an aqueous solution of β-cyclodextrin tetramer.

Structure of the Tetramer–Porphyrin Complexes. We assessed the stoichiometry of complexation via Job's method (data not shown).[36] As expected, porphyrins **9-11** form 1:1 inclusion complexes with the tetrameric host. In addition, the solution structure of **1**:**9** was analyzed by NMR spectroscopy. Nuclear Overhauser enhancement experiments were performed, and the results are consistent with the notion that the tetracarboxyporphyrin **9** is bound within the carbohydrate framework of the tetramer. The protons attached to C-3 and C-5 of the glucose sugars in the cyclodextrin subunits of **1** are directed into the interior of each dextrin cavity. Molecular models suggest that the four aryl substituents protruding from the porphyrin nucleus can be readily accommodated within the four individual cyclodextrin moieties. Indeed, irradiation of the C-3 protons of the cyclodextrin produced NOEs (see structures **7** and **9**) of −10.7% (protons a) and −8.8% (protons b). Irradiation of the C-5 protons elicited NOEs of −6.0% (protons a) and −6.7% (protons b). In contrast, the protons associated with C-2 and C-4 of the glucose subunits lie on the surface of the cyclodextrin cone and are oriented out and away from the inner cavity. Consistent with this structural feature, irradiation of either of these protons failed to produce any effect on the signals associated with protons a or b of **9**. Finally, we successfully obtained a mass spectrum of tetramer **1** complexed to the tetraaminoporphyrin **12**. The latter is not soluble in aqueous solution under neutral or basic conditions, but does dissolve readily when the pH is less than 4. However, in the presence of slightly more than 1 equiv of tetramer, porphyrin **12** remains in solution, even when the pH is raised above 9.0. Apparently, under these conditions, a 1:1 complex between **1** and **12** forms. Indeed, lyophilization of an aqueous solution of tetramer and tetraaminoporphyrin produced a solid residue that was analyzed by electrospray mass spectrometry. Peaks corresponding to the molecular ion of the 1:1 complex (6232.0) as well as a fragment missing a single cyclodextrin subunit (5096.0) are in evidence (supporting information). In short, the tetramer produces 1:1 complexes with various porphyrin guests and NOE experiments indicate that the aryl substituents are inserted into the cyclodextrin cavities of **1**.[37]

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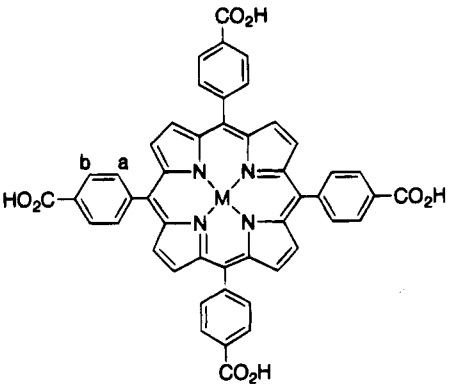
(37) However, at this point we cannot categorically state that all four aryl substituents of the porphyrin are simultaneously interred within the four individual cavities of **1**.

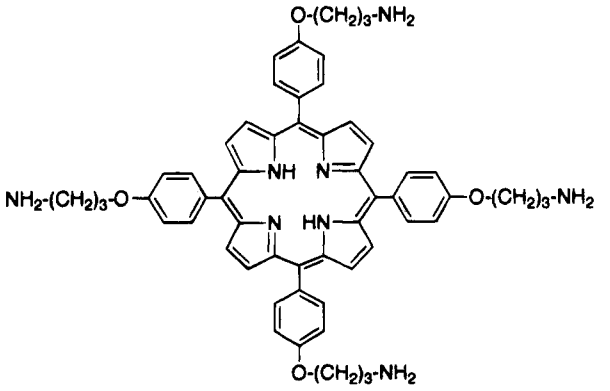


9 H,H

10 Zn

11 Sn(IV)

1 Exhibits a High Affinity for Porphyrins and Metalloporphyrins. Tetramer **1** exhibits an impressive affinity for both porphyrins and metalloporphyrins. Interestingly, **9** [$(2.9 \pm 0.2) \times 10^8$ M^{-1}] and its Zn(II) derivative **10** [$(3.0 \pm 0.2) \times 10^8$ M^{-1}] display nearly identical formation constants with **1**. This is not particularly surprising given the fact that both guests contain a neutral porphyrin nucleus. In marked contrast, the Sn(IV)-porphyrin **11** is a positively charged species that is significantly less hydrophobic than **9** or **10**. Indeed, the binding constant [$(4.1 \pm 0.2) \times 10^6$ M^{-1}] associated with the formation of the **1**:**11** complex is nearly two orders of magnitude weaker than those affiliated with the unmetalated porphyrin (**9**) and its Zn(II) counterpart (**10**). This implies that a hydrophobic environment is created upon interaction of the tetramer with the porphyrin guests. This supposition is consistent with the results obtained for the tetraaminoporphyrin **12** as well. The association constants for **9-11** were obtained at pH 7.0. However, porphyrin **12** is not water-soluble under these conditions. Consequently, we determined the affinity of this species for **1** at pH 3.0. At this pH, the inner pyrrole nitrogens are protonated rendering the porphyrin nucleus positively charged. As expected, **12** is a less effective guest [$(1.0 \pm 0.1) \times 10^7$ M^{-1}] than its neutral counterparts **9** and **10**.



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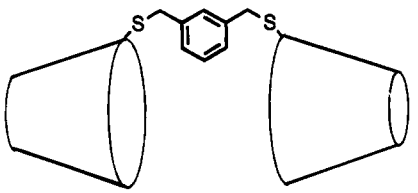
The Binding Properties of Tetramer 1 Differs from Those of Related Cyclodextrin Derivatives. We previously described the synthesis and binding properties of the cyclodextrin dimers **13** and **14**.[29,30] These species, like that of **1**, bind porphyrins and metalated porphyrins. However, the quantitative be-

havior of these hosts differs from that of **1** in a profound sense. Both the benzene-linked dimer **13** and the pyridine derivative **14** display association constants of 10^4 M^{-1} toward various diarylporphyrin guests (e.g. **15**).



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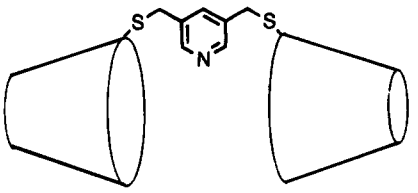

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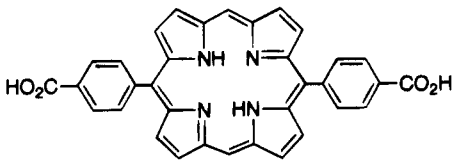

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These formation constants are four orders of magnitude less than that obtained for tetramer **1** with the analogous tetraarylporphyrin guest **9**. The pyridine-linked dimer binds metalloporphyrins more efficiently than free base porphyrins [e.g. the formation constant for Co(III)−**15** is 10^8 M^{-1}], presumably through coordination of the pyridine nitrogen to the central metal atom. In contrast, tetramer **1** is a less efficient host for positively charged porphyrins and metalloporphyrins. In short, these results indicate that it is possible to modify the bridge that links multiple cyclodextrin subunits in order to create closely-related species that exhibit remarkably different behavior toward virtually identical guest compounds.

In summary, we have prepared the first example of a tetrameric cyclodextrin species. This host exhibits an extraordinarily high affinity for porphyrins and metalloporphyrins. Based upon differences in binding constants with the Sn(IV) and tetraaminoporphyrin derivatives, it appears likely that a hydrophobic environment is created upon encapsulation of the porphyrin guests by the tetramer host. Further studies on the properties of **1** and related cyclodextrin derivatives will be reported in due course.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of **1** and **4**−**6**; laser desorption spectrum of **1**; electrospray mass spectrum of the **1**/**12** complex (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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