Sugar-Coated Metalated Macrocycles

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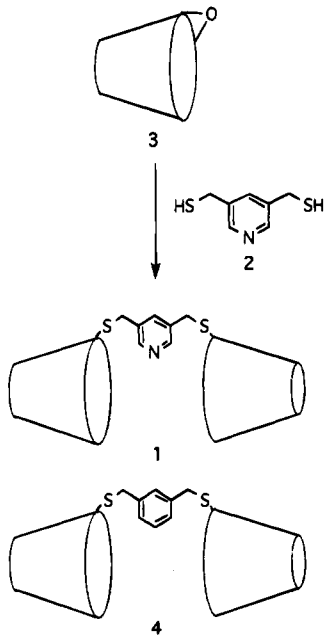
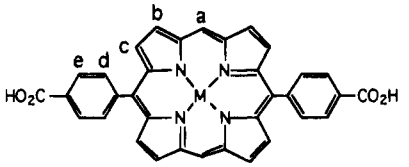
We have previously described a self-assembly-based approach for the construction of heme-dependent protein mimics.[1] These species contain a heme moiety noncovalently embedded within two β-cyclodextrin derivatives. In this context, we have recently reported the synthesis of a pyridine-linked cyclodextrin dimer (**1**).[2] We now demonstrate that the water-soluble host **1** coordinates a diverse assortment of metalated macrocyclic compounds in aqueous solution. In addition, unlike the majority of cyclodextrin dimers that have been reported to date,[3] this species contains individual cyclodextrin units that are covalently attached to one another via their secondary faces. This type of arrangement provides a structurally well-defined groove that circumscribes the metal binding site of appropriately embedded metal-containing ligands.[1]



The cyclodextrin dimer **1** is designed to recognize and coordinate lipophilic compounds (or lipophilic regions of compounds) that possess a centrally positioned metal ion. We previously described the preparation of **1** via the reaction of the dimercaptopyridine **2** with the monoepoxide of β-cyclodextrin **3**.[2,4] For comparative purposes, we also synthesized the benzene-linked cyclodextrin dimer **4**, which lacks a coordinating nitrogen atom and therefore should be unable to ligate the central metal atom of metalated macrocyclic compounds. We have found that **1** exhibits an enhanced ability (relative to **4**) to encapsulate a variety of metal-ion-containing guests, including metalloporphyrins, metallocyclams, metallosalens, and other metalated macrocycles.

1. Metalloporphyrins. We first examined the complexation behavior of **1** with the free base porphyrin **5** and its metalated counterparts **6**−**8**. The structure of the complex **1**·**6** was



5 H,H
6 Zn(II)
7 Mn(III)
8 Co(III)

examined in detail by NMR spectroscopy, and as expected, appropriate NOEs were observed between the porphyrin and cyclodextrin components.[5] The association constants for this complex and those involving related metalated porphyrins are provided in Table 1. The cyclodextrin dimer exhibits a greater affinity for the metalated porphyrins **6**−**8** than for the unmetalated species **5**. In order to determine if this behavior is a consequence of the presence of the pyridine bridge, we examined the binding properties of the benzene-linked analog **4**. As expected, both hosts **1** and **4** bind the free base porphyrin **5** with equal affinity. Furthermore, the benzene-linked dimer **4** exhibits no special affinity for metalloporphyrins **6**−**8** versus porphyrin **5**. This strongly implies that the pyridine bridge in **1** coordinates the central metal ion of metalloporphyrins. This interaction enhances the affinity of **1** (relative to **4**) for metalated porphyrins by up to *4 orders of magnitude*.

2. Metallocyclams. Metalated cyclams not only have been employed as metalloenzyme mimics[6] but in addition have recently been shown to function as potent inhibitors of the human immunodeficiency virus.[7] The Cu- and Ni-containing cyclams **9** and **10** serve as guests for the pyridine-linked cyclodextrin dimer with association constants in the range of 2

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(4) The addition of mercaptans to cyclodextrin epoxide results in a conformational inversion of the modified glucose unit. The remaining unmodified six glucose moieties are conformationally unaffected. See ref 2 and the following: Breslow, R.; Czarnik, A. W. *J. Am. Chem. Soc.* **1983**, *105*, 1390−1391.

(5) The protons attached to C-3 and C-5 of the glucose moieties in **1** are directed into the interior of the cyclodextrin moiety, whereas those attached to C-2 and C-4 are positioned on the exterior of the dextrin units. The following NOEs were observed: irradiation of the C-3 protons on the cyclodextrin [porphryin protons (see **5**−**8**): a (0%); b (−10.6%); c (−18.7%); d (−22.9%); e (−18.5)]; irradiation of the C-5 protons on the cyclodextrin [porphyrin protons: a (0%); b (0%); c (0%); d (−12.5%); e (−10.2%)]; irradiation of the C-2 and C-4 protons on the cyclodextrin [porphyrin protons: a (0%); b (0%); c (0%); d (0%); e (0%)].

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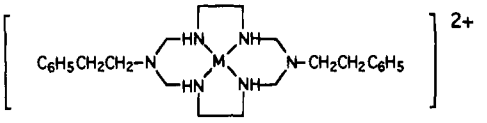
Table 1. Association Constants of Metalated Macrocyclic Compounds with Cyclodextrin Dimers **1** and **4**[a]

guest	binding constant (M^{-1}) host **1**	host **4**
5	$(2.5 \pm 0.1) \times 10^4$	$(1.7 \pm 0.1) \times 10^4$
6	$(3.4 \pm 0.2) \times 10^6$	$(1.9 \pm 0.2) \times 10^4$
7	$(7.6 \pm 0.3) \times 10^6$	$(1.0 \pm 0.1) \times 10^4$
8	$(1.7 \pm 0.2) \times 10^8$	$(1.3 \pm 0.2) \times 10^4$
9	$(2.1 \pm 0.2) \times 10^4$	*b*
10	$(2.4 \pm 0.2) \times 10^4$	$(1.8 \pm 0.2) \times 10^3$
11	$(6.3 \pm 0.4) \times 10^4$	$(5.6 \pm 0.3) \times 10^4$
12	$(1.3 \pm 0.2) \times 10^5$	*b*
13	$(1.5 \pm 0.2) \times 10^5$	*b*
14	$(3.3 \pm 0.3) \times 10^5$	$(5.0 \pm 0.2) \times 10^4$
15	$(1.4 \pm 0.1) \times 10^4$	$(1.3 \pm 0.1) \times 10^4$
16	$(1.7 \pm 0.2) \times 10^4$	$(1.2 \pm 0.1) \times 10^4$
17	$(2.2 \pm 0.2) \times 10^4$	*b*
18	$(2.6 \pm 0.2) \times 10^4$	*b*
19	$(6.9 \pm 0.5) \times 10^4$	*b*

[a] Metalloporphyrins,[11] metallocyclams,[12] metallosalens,[13] and the lanthanide-containing species,[14] were prepared according to literature protocols. Assays were thermostated at 25 °C and utilized a 200 mM phosphate pH 7.0 buffer. All measurements were performed in quadruplicate as previously described.[2] With the exception of compounds **5**–**8**, association constants were obtained via competitive binding experiments with the fluorescent indicator 2-(*p-tert*-butylanilino)naphthalene-6-sulfonic acid ("BNS").[3f] For compounds **5** and **6**, formation constants were obtained by directly monitoring the change in Soret band absorbance as a function of variable concentration of host. The association constants for **7** and **8** were obtained in an analogous fashion, but in the presence of the competitive BNS guest due to the large binding constants associated with these metalloporphyrins. [b] Not determined.

$\times 10^4$ M^{-1}. In the case of the Ni-containing species, this

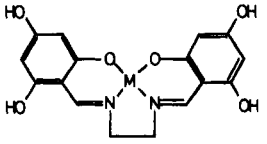


9 Cu(II)

10 Ni(II)

represents an order of magnitude enhancement in binding affinity relative to the benzene-linked host **4**.

3. Metallosalens. Metalated salens have received considerable attention as catalysts for the asymmetric epoxidation of olefins as well as DNA-modifying agents.[8,9] The three metalated achiral species **12**–**14** exhibit slightly greater association constants with **1** than does the unmetalated derivative **11**.



11 H,H

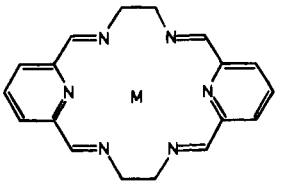
12 Ni(II)

13 Zn(II)

14 Co(II)

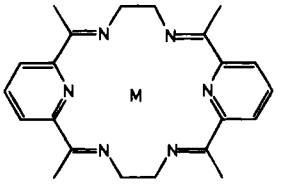
Furthermore, the Co-salen displays an enhanced affinity for the pyridine-linked dimer **1** versus that of the benzene-bridged derivative **4**. While these results imply that the pyridine moiety of **1** does interact with the metal ions in these salens, the modest difference in complexation behavior between the metalated and unmetalated macrocycles suggests that the pyridine moiety is not especially tightly coordinated to the metal ion.

4. Other Metalated Macrocycles. Morrow and her colleagues have recently shown that lanthanide macrocyclic complexes serve as efficient catalysts for the hydrolytic cleavage of RNA.[10] These species offer several advantages over the metal-ion-promoted cleavage of nucleic acids, including the elimination of diffusible oxygen-derived radicals. Complexes **15**–**18** coordinate to the cyclodextrin dimer **1** and exhibit binding constants similar to those observed for the metalated cyclams. Furthermore, the affinities displayed by guests **15** and



15 Ba(II)

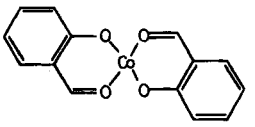
16 La(III)



17 Eu(III)

18 La(III)

16 for both the benzene- and pyridine-bridged hosts are nearly identical. These results are not especially surprising since the lanthanides are hard acids and, therefore, relatively soft bases (e.g., pyridine) would not be expected to coordinate tightly to these ions. In short, in those instances where pyridine should serve as a strong ligand, there is a dramatic enhancement in binding affinity. In contrast, in those cases where pyridine should behave as a weak ligand, there is little or no change in binding affinity. Finally, the Co-containing salicylaldehyde complex **19** forms an inclusion complex with **1** as well.



19

Many of the metallomacrocycles described in this study have been previously demonstrated to exhibit interesting chemical and biochemical properties. However, one can envision that these properties can be substantially altered by "sugar-coating" the metalated macrocycles with dimer **1**. For example, the latter is extraordinarily water-soluble and therefore could potentially serve as a water-soluble carrier of otherwise water-insoluble guests. In addition, upon association of the metallomacrocycles with **1**, a groove is generated that circumscribes the central metal ion. This rudimentary active site should exhibit a special affinity for substrates possessing structural attributes that complement those of the groove itself. In short, the pyridine-linked cyclodextrin dimer offers an unusually flexible approach for the construction of structurally well-defined, water-soluble, metalloenzyme mimics.

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