Tetrahedron Letters, Vol.27, No.7, pp 807-810, 1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

DESIGN AND SYNTHESIS OF A NEW CLASS OF HYDROPHOBIC BINDING SITES

Michael A. Petti[1a], Timothy J. Shepodd[1b] and Dennis A. Dougherty*[1c]

Contribution No.7330 from the Laboratories of Chemistry
California Institute of Technology
Pasadena, California 91125

Abstract: The design, synthesis and basic aggregation and binding behavior of a new class of water-soluble molecules with hydrophobic binding sites are reported.

The binding of organic molecules within the hydrophobic cavities of synthetic water-soluble macrocycles is a topic of considerable current interest.[2] Several general host structures based on cyclophane skeletons have been shown to include non-polar guest molecules within their cavities and thus transport them into aqueous solution.[3,4] We set out to improve on these designs by building a new class of structures incorporating ethenoanthracenes as rigid, chiral hydrophobic units. When assembled into a macrocycle this structure can produce hosts of helical symmetry with rigid dissymmetric binding sites. Our design also places water-solubilizing groups exterior to and thus isolated from the well-defined, central cavity. Also, the synthesis of these structures is short, efficient and flexible, allowing predictable control of the binding site topography.

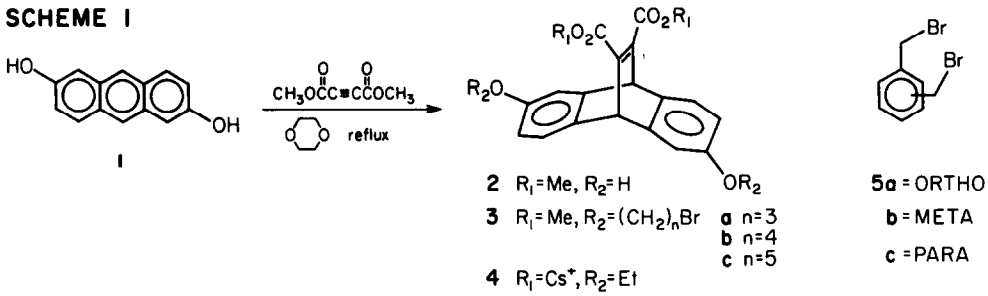
Our synthetic approach is summarized in Scheme I. Dimethyl acetylenedicarboxylate addition[5] to 2,6-dihydroxyanthracene[6] (**1**) (dioxane, 100°C, 48 h, pyrogallol, 60%) affords the racemic ethenoanthracene derivative, **2**. For the aliphatic series, diol **2** is alkylated with an excess of 1,n-dibromide (acetone, Cs_2CO_3, reflux, 12 h, 65-70%) giving the dibromides **3a-c**. The macrocycles **III**, **IV**, **V** (R = Me) are formed by reaction of **3a-c** with another equivalent of **2**, (Cs_2CO_3, DMF, 0.001 M, 4 days, 60° C).[7] For the aromatic series, 2 equivalents each of diol **2** and **5a-c** are combined (Cs_2CO_3, DMF, 0.001 M, 1 week, 50° C)[7] giving the macrocycles **O**, **M**, **P** (R = Me). The isolated yields for the macrocycles (Scheme 1) are much higher than usually observed for the formation of such large rings. These yields attest to the rigid, concave shapes of **2** and **3**. In each series the two diastereomers formed in the cyclization were separated by preparative HPLC and the esters hydrolyzed (excess CsOH, DMSO, H_2O, 50° C, 8 h). Cation exchange for NH_4^+, lyophilization and subsequent neutralization with CsOD/D_2O gives solutions of the very water-soluble tetra Cs^+ salts which were used in all binding studies.

In the coupling reaction of racemic **2/3**, two diastereomers are formed in essentially equal yields. The **meso** compound (C_{2h} symmetry) arises from heterochiral[8] coupling of the two "half molecules". The chiral (**d,l**) isomer (D_2 symmetry) arises from the homochiral[8] coupling of two half molecules. In this isomer, the hydrophobic cavity is helical, with an overall right- (or left-) handedness. We feel this could be an exceptionally favorable topography for achieving enantioselective host-guest interactions. The diastereomers of **III** and **V** were identified by ^{1}H NMR at the tetraester stage. In the chiral isomer, the methylene hydrogens of the middle CH_2 group of the polymethylene chain are homotopic, whereas in the **meso** isomer they are diastereotopic. Decoupling the hydrogens adjacent to this methylene group leads to a singlet for one diastereomer and to an AB quartet for the other, allowing the assignment to be made easily. For the other macrocycles, the identity of the diastereomers was determined by relative HPLC elution order using **III** and **V** as references. The ^{1}H NMR and ^{13}C NMR spectra of all these macrocycles are consistent with their high symmetry structures. In addition, EIMS, FABMS, and vapor phase osmometry confirm these structures to be those shown in Scheme I.

Molecules such as the tetra Cs^+ salts can act as surfactants and aggregate. To exclude these aggregation effects we have performed all binding studies well below the critical micelle concentration (CMC) of these molecules. The CMCs were determined by monitoring the chemical shifts of the protons of the host as a function of concentration.[9] Above 1 mM the signals of all the hosts broaden and undergo substantial changes in chemical shift (see Figure 1). We therefore assume monomeric hosts for concentrations significantly below 1 mM.

As expected,[2-4] these structures effectively bind aromatic guests. A variety of solid-liquid and liquid-liquid extraction studies shows significant binding of anthracene and pyrene.[10] For example, Figure 2 shows the UV spectrum of an aqueous solution of the host-guest complex between **P-dl** (R = Cs^+) and pyrene. The bathochromic shifts (from 320 nm to 328 nm and 334 nm to 344 nm) and the reduced value of the extinction coefficient of the pyrene relative to pyrene in isooctane are consistent with the pyrene being bound in the hydrophobic cavity of the host. By comparison, a previously reported host[3a] shifts the same bands to 323 nm and 339 nm. Fluorescence studies show the bound pyrene to be monomeric and the amount solubilized to be far greater than the intrinsic water solubility. Similarly, NMR studies of the interactions of our hosts with a variety of water-soluble, aromatic guests show the upfield shifts of the guest signals that are characteristic of binding by encapsulation. Most importantly, in all such studies the control molecule, **4**, shows no significant binding interaction.

SCHEME I

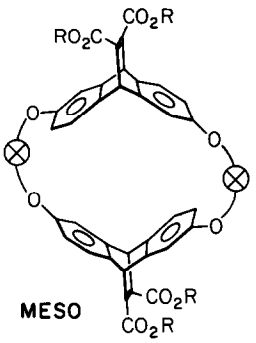


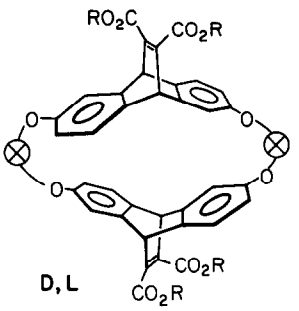
2 R_1=Me, R_2=H

3 R_1=Me, R_2=$(CH_2)_n$Br **a** n=3, **b** n=4, **c** n=5

4 R_1=Cs^+, R_2=Et

5a = ORTHO **b** = META **c** = PARA





MACROCYCLIZATION YIELDS

3a + 2 →	III-MESO	III-DL	24%
3b + 2 →	IV-MESO	IV-DL	51%
3c + 2 →	V-MESO	V-DL	32%
2 [**5a** + 2 →	O-MESO	O-DL	24%
2 [**5b** + 2 →	M-MESO	M-DL	36%
2 [**5c** + 2 →	P-MESO	P-DL	18%

⊗: III = $(CH_2)_3$; IV = $(CH_2)_4$; V = $(CH_2)_5$; O =  ; M =  ; P = 

FIGURE 1

CMC DETERMINATION P-meso and V-dl

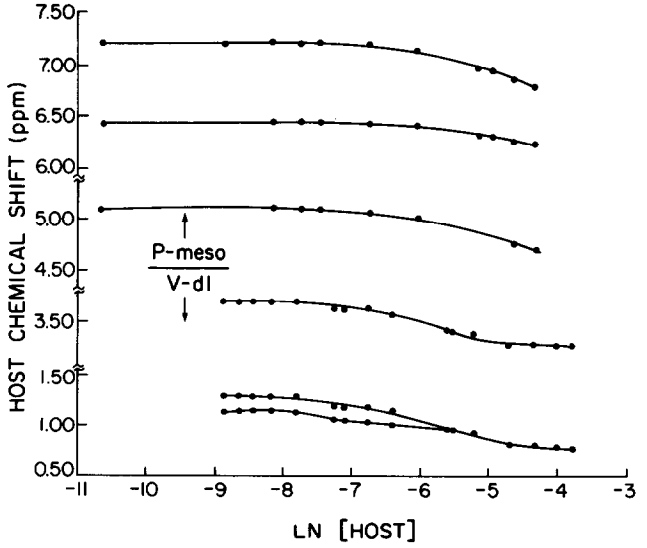
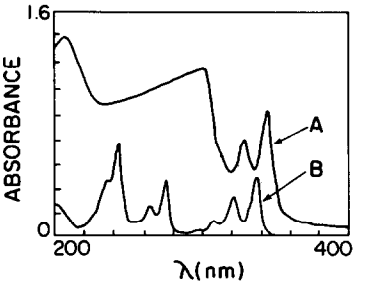


FIGURE 2



A: UV spectrum of host-guest complex (**P-dl**, pyrene). Bands below 300 nm due to free host. K_a (determined by back extraction) is 2 x 10^6 M^{-1}. The initial host concentration = 1.3 x 10^{-4} M.

B: UV spectrum of pyrene in isooctane.

Further studies on the use of these structures for catalysis and enantiomer discrimination are in progress.

Acknowledgements: We thank the 3M Corporation and the ARCO Foundation for partial support of this work.

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10. Association constants are in the range 10^3-10^7 M^{-1} for different host-guest combinations. However, in our hands the precision of these extraction studies is such that only order of magnitude estimates of binding constants can be obtained.

(Received in USA 2 December 1985)