A Synthetic Receptor Which Uses Multiple Edge−Face Interactions To Bind Aromatic Guests

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Host **1** binds bicyclic aromatic guests such as 6-nitro-2-naphthol **2**, serotonin mimic **3**, and stilbene-derivative **4** with high affinity. Competition studies were performed to determine the association constants for complexation of **2**−**4** by **1**. Lower-affinity host **14** lacked the structural requirements to form edge−face contacts with guests **2**−**4** and served as the competitive host. For each guest, evaluation of the geometry of the host−guest interaction by low-temperature NMR experiments revealed two edge−face interactions between the face of the anthracene bridge of **1** and the edge of the guest. The results reported in this paper suggest that the observed edge−face interactions stabilize the complexes formed by host **1**. The synthesis of host **1** and the complexation of **2**−**4** by this host are described.

Introduction

In an edge−face interaction, the positively polarized hydrogen atoms of one aromatic ring interact with the π-electrons of another aromatic ring. Edge−face interactions in benzene were predicted many years ago, but the optimal orientation of two aromatic rings is still widely discussed.

Several computational papers have addressed the issue of the stabilizing effect of edge−face interactions, and all of the calculations indicate that the edge−face benzene dimer is a minimum and that edge−face interactions are stabilizing.[1] In proteins, edge−face interactions between aromatic side chains of the residues in the interior of the protein have been proposed to play a significant role in stabilizing the native state.[2] Although much experimental evidence for edge−face interactions in the solid state has been provided,[3] evidence for edge−face interactions in solution is scarce.[4]

A few examples of synthetic organic receptors designed to study edge−face interactions have been presented. In studies by Hunter and Sanders,[5] porphyrin dimers were examined. A flexible system in which aryl groups could exist either in a face−face arrangement or in the edge−face motif was provided by Gellman et al.[6] Hamilton et al. demonstrated that thymine receptors containing naphthalene units exhibited either face−face or edge−face binding with 1-butylthymine depending on the electronic properties of the naphthalene.[7] Wilcox et al. developed a model system to calibrate the preference of phenyl rings for edge−face interactions.[8] Recently, Hunter et al. developed host−guest systems containing zero, one, or two possible edge−face interactions and found that, for this system, an edge−face interaction increased the stability of the complex by 1.4 ± 0.8 kJ/mol.[9]

In this paper, we report the synthesis and complexation behavior of a synthetic receptor **1**, which contains an anthracene unit that is capable of forming multiple edge−face interactions to large aromatic guests such as 6-nitro-2-naphthol **2**, serotonin mimic **3** (methyl 5-hydroxy-3-indolecarboxylate, Figure 1), and *trans*-4-hydroxy-4′-nitrostilbene **4** when they are incavitated by the host. The rigid cavity in **1** was specifically designed for the complexation of aromatic guests that incorporate a hydrogen bond donating substituent.[10] The hydrogen bond donor of the guest forms a hydrogen bond to the pyridine-derived bridge of the host; the pyridine nitrogen points into the host's cavity. The two naphthalene rings that form the floor and ceiling of the host's cavity have a center-to-center separation of 7 Å, enabling π-stacking interactions between the host and the guest with an optimal 3.5 Å distance between the guest and each naphthalene. We suggest that the formation of multiple

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(5) (a) Hunter, C. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1990**, *112*, 5525. (b) Hunter, C. A. *Chem. Soc. Rev.* **1994**, 101.

(6) (a) Schladetzky, K. D.; Haque, T. S.; Gellman, S. H. *J. Org. Chem.* **1995**, *60*, 4108. (b) Newcomb, L. F.; Haque, T. S.; Gellman, S. H. *J. Am. Chem. Soc.* **1995**, *117*, 6509.

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(8) Paliwal, S.; Geib, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1994**, *116*, 4497.

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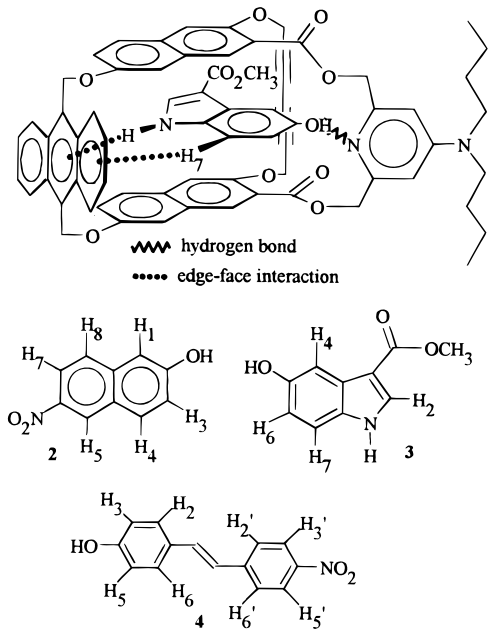
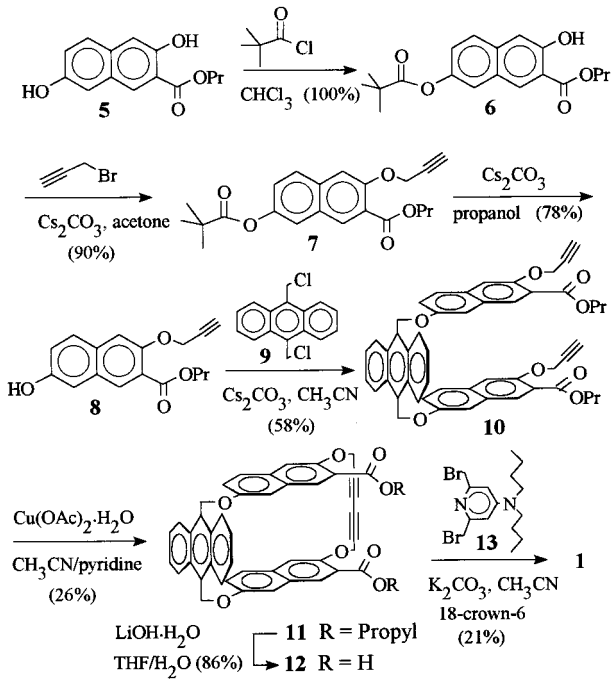


Figure 1. Proposed solution state binding motif for the **1**−**3** complex; structures of **2**−**4**.

Scheme 1. Synthesis of 1



noncovalent interactions between the host and the guest allows for very tight binding of **2**−**4** by **1**. Furthermore, the large association constants (K_as) obtained for this host and the observation of multiple edge−face interactions suggest that the edge−face interaction is stabilizing.

Results and Discussion

Synthesis of Host 1. The synthesis of host **1** is shown in Scheme 1. Propyl 3,7-dihydroxy-2-naphthoate **5** was reacted with pivaloyl chloride to give propyl 3-hydroxy-7-propargyloxy-2-naphthoate **6** quantitatively.[11] The 3-hydroxyl group of **6** was propargylated using propargyl bromide and Cs_2CO_3 in acetone to give the diester ether **7**. Deprotection of the 7-hydroxyl group using Cs_2CO_3 in propanol gave propyl 7-hydroxy-3-propargyloxy-2-naphthoate **8** in 70% overall yield from **5**. Alkylation of **8** with 9,10-bis(chloromethyl)anthracene **9** (CH_3CN, Cs_2CO_3, 2 days) gave a 58% yield of precyclophane **10**.

From precyclophane **10**, the crucial macrocyclization reaction was performed using 5 equiv of $Cu(OAc)_2 \cdot H_2O$ in 75% CH_3CN:25% pyridine.[12] Although traditionally this reaction is carried out in pyridine,[13] the solvent mixture offered the advantage of allowing the reaction to be conducted at a concentration of 2 mM rather than the 1 mM concentration that is required for pyridine alone. In addition, the mixed solvent system allowed for much easier workup. Although the yield of cyclophane **11** is not high (26%) with either the pyridine or the pyridine/CH_3CN procedure, it is similar to or better than many published results for this procedure.[14]

Hydrolysis of the propyl esters to give cyclophane diacid **12** was successful in a 60/40 mixture of THF/H_2O with 17 equiv of $LiOH \cdot H_2O$ at 40 °C. The reaction of **12** with 2,6-bis(bromomethyl)-4-dibutylaminopyridine **13** in CH_3CN (1.5 mM in **12**) with 8 equiv of K_2CO_3 and 10 equiv of 18-crown-6 afforded host **1** (21%).[15]

Complexation of 6-Nitro-2-naphthol (2). The ^1H NMR spectra at different stages of the titration are shown in Figure 2.[16] After 1 equiv of guest had been added, the host appeared to be essentially all bound, as the peaks were not shifted upon addition of more guest. Analysis of the aromatic region of the spectrum was very complicated, however, since the naphthyl protons from the host and the guest appeared in the same region of the spectrum and the guest peaks were broadened until excess guest had been added.

Slow exchange broadening was observed for host **1** upon addition of **2**, with maximum broadening after 0.5 equiv of guest had been added. Further additions of **2** caused the peaks to sharpen. Overlap of the broad guest peaks with the sharpened host peaks occurred until excess guest was present. Then, the guest peaks also sharpened or shifted downfield out of the most congested area. The observed pattern of slow exchange broadening suggested that the K_a for complexation of **2** was high.

That the guest was bound inside the cavity of host **1** was indicated by the sharpening of the anthracene ring signals of **1** as the amount of **2** was increased. The broadening of peaks in the spectrum of free **1** was attributed to the rotation of the anthracene ring through the cavity of the host, and this was eliminated upon addition of an equivalent of **2**.[17] The freezing out of rotation through the cavity at room temperature sug-

(11) Because the reaction of **5** with **9** was unsuccessful under a wide variety of alkylation conditions, the described protection/deprotection strategy was invoked. For further details, see ref 23.

(12) Berscheid and Vogtle (*Synthesis* **1992**, 58) reported a modified Eglinton coupling using 5 equiv of $Cu(OAc)_2 \cdot H_2O$ in CH_3CN.; only precyclophane **10** was recovered using these conditions.

(13) Eglinton, G.; McCrae, W. *Adv. Org. Chem.* **1963**, *4*, 225 (and references therein).

(14) For some examples, see: (a) Diederich, F.; Rubin, Y. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1101 (and references therein). (b) Hebert, N.; Beck, A.; Lennox, R. B.; Just, G. *J. Org. Chem.* **1992**, *57*, 1777. (c) Eglinton, G.; Galbraith, A. R.; *Proc. Chem. Soc.* **1958**, 350.

(15) 18-Crown-6 was added to solubilize the salt of diacid **13**.

(16) All room-temperature titration studies were performed as described in the Experimental Section and analyzed using the program K12 which was written using the SIMPLEX algorithm according to ref 15c. Program K12 uses several complexation cases and has an attached Post Script and graphical user interface that produces plots interactively. The source (Turbo C) was written by H. W. Whitlock.

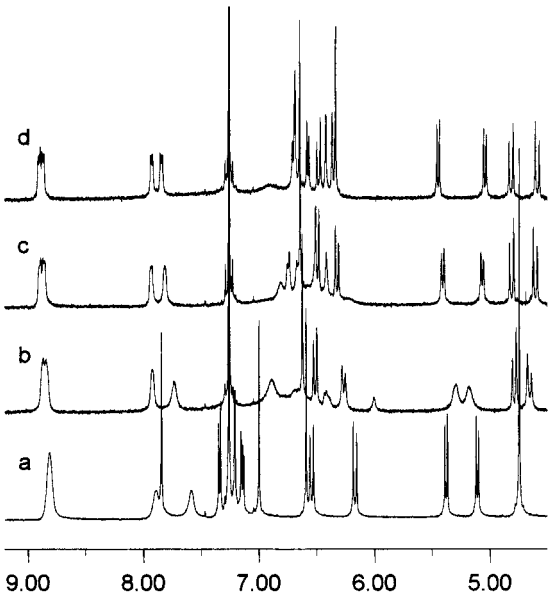
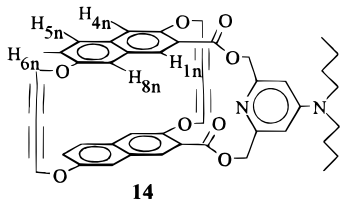


Figure 2. ^{1}H NMR spectra showing the addition of **2** to **1** (500 MHz, $CDCl_3$, 298 K): (a) **1** + 0.0 equiv of **2**. (b) **1** + 0.5 equiv of **2**. (c) **1** + 1.0 equiv of **2**. (d) **1** + 2.2 equiv of **2**.

gested that binding occurred inside the cavity and that the K_a was high.



14

To determine the K_a for complexation of **2**, a competition study using host **14**[18] as the competitor was carried out.[10a,c,19] Previous experimental results with a host similar to **14** and comparison of the calculational information for **1** and **14** (vide supra) suggests that the difference in rigidity and flexibility between **1** and **14** will be minimal.[10d,e] Although the anthracene bridge of **1** is about 0.9 Å shorter than the diyne linker which could result in a difference in π-stacking affinity, the largest difference in the two hosts is clearly the inability of **14** to form edge−face interactions.

A $CDCl_3$ solution containing a mixture of **1**, **14**, and **2** in a 1:1:1.2 ratio was prepared, and the ^{1}H NMR spectra at 298 and at 215 K were obtained. Host **14** was found to be 6% bound, and host **1** was found to be 76% bound. Insertion of these values for percent bound into eq 1 gave $K_{rel} = 48$.

$$K_{rel} = [1/(\%\ \text{bound}\ H_1 \div 100) - 1]/[1/(\%\ \text{bound}\ H_2 \div 100) - 1] \quad (1)$$

Since the K_a for complexation of **2** by **14** had been predetermined to be 320 M^{-1}, the K_a for complexation of 6-nitro-2-naphthol by **1** could be calculated to be 15 400 M^{-1}.

(17) When a sample of **1** in $CDCl_3$ was heated, the anthracene signals in the ^{1}H NMR sharpened. When the sample was cooled, a sharply resolved signal was visible for each $H_{1a,4a}$ and for each $H_{2a,3a}$. Estimated free energy values are given in ref 18.

(18) Cloninger, M. J. Ph.D. Thesis, University of Wisconsin−Madison, 1996.

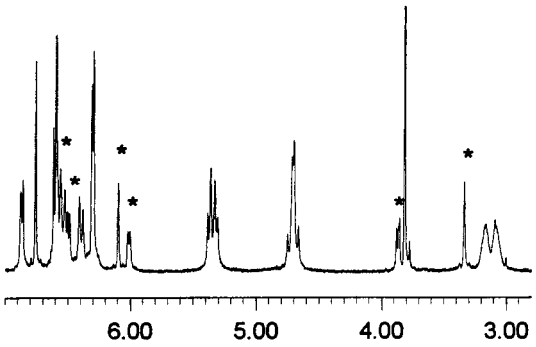


Figure 3. ^{1}H NMR spectrum of bound 6-nitro-2-naphthol **2** at 215 K (500 MHz, $CDCl_3$). Signals from **2** are marked with *.

Table 1. Changes in Chemical Shift for 2 upon Complexation by 1

peak	δ free	δ bound	$\Delta\delta$ (free − bound)
H_1	7.24	6.10	1.14
H_3	7.76	6.50	1.26
H_4	7.95	3.87	4.08
H_5	8.74	3.35	5.39
H_7	8.20	6.57	1.63
H_8	7.24	6.02	1.22
OH	5.29	11.69	−6.4

The orientation of **2** within the cavity of **1** was determined from ^{1}H NMR spectra of a $CDCl_3$ solution of **1** and **2** (1.2 equiv) at 215 K. The relevant part of the spectrum showing the signals assigned to complexed **2** is shown in Figure 3.

To assign each proton in the low-temperature spectrum of the complexed guest, a series of labeling and decoupling experiments was performed. A sample of **1** and d_1-6-nitro-2-naphthol[18] in $CDCl_3$ was prepared, and the ^{1}H NMR spectrum was obtained at 215 K. Since the singlet at δ 6.10 was not present in this spectrum, the singlet at δ 3.35 was due to H_5 while the singlet at δ 6.10 was due to H_1.

The assignment of the four doublets was made using correlated spectroscopy (COSY). A COSY experiment on a sample containing **1** and **2** in $CDCl_3$ at 215 K showed cross-peaks due to coupling between the doublets at δ 6.57 and 6.02 and between the doublets at δ 6.50 and 3.87. A long-range COSY (fixed delay of $\Delta = 0.12$ s) identified the cross-peaks connecting the singlet at δ 6.1 to the doublet at δ 6.50 and connecting the singlet at δ 3.35 to the doublet at δ 6.57.

The assignment of protons for complexed **2** and the changes in chemical shift upon complexation are summarized in Table 1. H_5 and H_4 were shown to move farthest upfield: 5.39 ppm upfield and 4.08 ppm upfield, respectively. This indicated that larger guests such as 6-nitro-2-naphthol are indeed able to form multiple edge−face interactions to the face of the anthracene ring.[20] The orientation of **2** within the cavity of **1** as indicated using ^{1}H NMR techniques is shown in Figure 4.

(19) Wilcox, C. S. Design, Synthesis, and Evaluation of an Efficacious Functional Group Dyad. Methods and Limitations in the Use of NMR for Measuring Host−Guest Interactions. In *Frontiers in Supramolecular Chemistry*; Schneider, H.-J., Durr, H., Eds.; VCH: New York, 1991; p 123.

(20) As expected, complexation induced a small downfield shift of the protons on the anthracene ring of **1**. The naphthalene protons of **1** were shifted about 0.5 ppm upfield by the π-field of the guest.

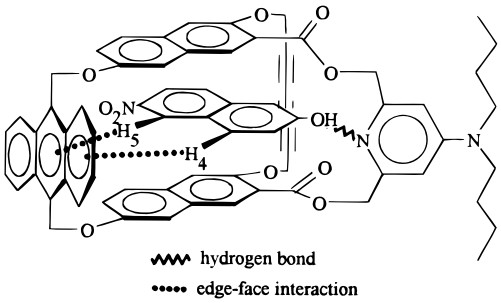


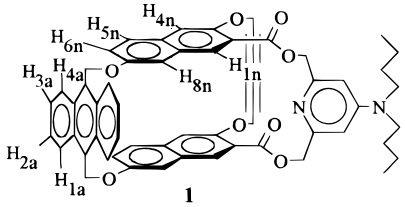
Figure 4. Proposed solution state binding motif for the **1**−**2** complex.

Complexation of Methyl 5-Hydroxy-3-indolecarboxylate 3. Macromodel calculations predicted that **3** would be bound well by **1**.[21] **3** was an especially interesting guest both because it may be regarded as a serotonin mimic and because it differs from **2** in the placement of substituents and the shape of the aromatic unit. It was hoped that the difference between the naphthyl and the indoyl ring systems would provide a measure of the variations allowed in guests that could be bound with high affinity by **1**. Furthermore, the electron-withdrawing substituent in **3** was a vinylogous carbamate rather than a nitro group, and the effect of this change would also help to identify the amount of change allowed while still retaining the high affinity of **1** for a guest.

A room-temperature ^{1}H NMR titration study was performed using a $CDCl_3$ solution of **1** to which aliquots of a stock solution of **3** were added such that the amount of guest varied between 0.18 and 2.33 equiv.

During the titration, exchange broadening was observed in the host signals, and the host peaks sharpened as the amount of guest approached 1 equiv. The signals for the anthracene protons of **1** sharpened as the amount of **3** in the solution was increased, but it was not until an excess of guest had been added that the characteristic second-order coupling pattern could be observed. Thus, although the rotation of the anthracene ring through the cavity was eventually halted (on the NMR time scale) by the incavitation of the guest, more guest was needed in the case of **3** than when the guest was 6-nitro-2-naphthol. This observation was assumed to reflect a lower binding affinity of **1** for the indole-derived guest.

The K_a was calculated from the room-temperature titration study. Three host protons, H_{4n}, H_{5n}, and H_{8n}, were followed to give calculated K_as of 3361, 5663, and 5483 M^{-1}, respectively. The average K_a for **1** with **3** was 4840 ± 1280 M^{-1}, where the standard deviation of the three values is reported as the range or error in K_a. The reported range is relatively large but is not really surprising when the line broadening and large degree of spectral overlap are considered.



1

K_a for the complexation of **3** by **1** was also determined in a competition study using **14**. For the competition study, a $CDCl_3$ solution containing a 0.6:1:0.7 ratio of **1** to **14** to **3** was prepared and the ^{1}H NMR spectrum at 298 K was obtained. Host **14** was determined to be 7% bound, and **1** was found to be 55% bound. Insertion of the two values for percent bound into eq 1 gave K_{rel} = 15. Since the K_a for complexation of **3** by **14** was known to be 280 ± 40 M^{-1}, the K_a for complexation of **3** by **1** was calculated to be 4480 ± 560 M^{-1}. This value is within experimental error of the K_a determined in the titration study.

Table 2. Changes in Chemical Shift for 3 upon Complexation by 1

peak	δ free	δ bound	$\Delta\delta$ (free − bound)
OCH_3	3.93	3.18	0.75
NH	8.70	3.24	5.46
H_2	7.29	5.36	1.93
H_4	7.08	5.53	1.55
H_6	6.94	6.13	0.81
H_7	7.08	3.43	3.65
OH	5.15	11.60	−6.44

To evaluate the binding motif for the indole-based guest, the ^{1}H NMR spectrum of the complex was obtained at 215 K and the guest signals were identified. All five of the aromatic protons were visible as separate signals with the two most upfield signals at 3.24 and 3.43 ppm. The other three signals were farther downfield at δ 5.36, 5.53, and 6.13. The methyl groups appeared as separate signals for the free and the complexed guest, with the signal for the free guest at δ 3.93 and the signal for the bound guest at δ 3.18.

To assign each proton in the low-temperature spectrum of the complexed guest, a series of homonuclear decoupling (HOMODEC) experiments was carried out. In Table 2, the most reasonable assignments for the complexed protons as derived from the HOMODECs are given, and the change in shift between the free and complexed guest signals is reported. The inferred solution state geometry is shown in Figure 1.

Complexation of *trans*-4-Hydroxy-4′-nitrostilbene 4. Macromodel calculations and CPK models predicted that *trans*-4-hydroxy-4′-nitrostilbene **4**[21] would not only fit well in the cavity of **1** but also would be bound so that one of the protons on the double bond and one of the protons in the phenol ring could participate in edge−face interactions with anthracene.

A room-temperature ^{1}H NMR titration study similar to those described above was carried out using a $CDCl_3$ solution of **1**. In the ^{1}H NMR spectra that were acquired upon addition of guest, slow exchange broadening was again observed, and the spectra became sharper as the amount of guest in solution approached 1 equiv. The peaks did not completely sharpen until 1.4 equiv of **4** had been added. The anthracene signals sharpened upon addition of guest, further indicating that the association between **4** and host **1** was strong. It was also interesting to note that the anthracene signals for $H_{2a,3a}$ at about 8 ppm were overlapped with a sharp doublet assigned to be the two protons ortho to the nitro group on the stilbene-derived guest **4**. The sharp anthracene host peaks indicated that the guest was bound within the host cavity in order to stop rotation of anthracene through the cavity, but the sharp downfield doublet observed for the guest indicated that the guest did not fit completely into

(21) MacroModel V3.5 (MM2* force field): Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

Table 3. Changes in Chemical Shift for 4 upon Complexation by 1

peak	δ free	δ bound	$\Delta\delta$ (free − bound)
$H_{3',5'}$	8.20	8.00	0.20
$H_{2',6'}$	7.59	6.03	1.56
H_6	7.45	6.01	2.44
H_5	6.86	5.53	1.33
H_3	6.86	5.41	1.45
H_2	7.45	2.65	4.80
C=CH	7.23, 7.00	4.86, 2.86	2.37, 4.14[a]
OH	4.95	12.70	−7.75

[a] Minimum values.

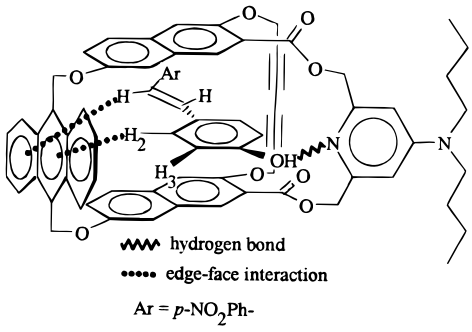


Figure 5. Proposed solution state binding motif for the **1**−**4** complex.

the cavity. If the guest were completely within the host cavity, then all guest signals would be expected to be broadened and shifted upfield. Rather, part of **4** appeared to dangle out the back of the cavity.

To determine the association constant for complexation of **4** by **1**, a competition study similar to those described above was done. A $CDCl_3$ solution containing a 1:1:0.6 ratio of **1** to **14** to **4** was prepared, and the ^{1}H NMR spectra at 298 and at 215 K were obtained. **14** was determined to be 2% bound, and **1** was determined to be 78% bound by integration of the signals at 215 K. Substitution of these values for percent bound into eq 1 provided a K_{rel} of 158. Since the K_a for **14** with **4** was determined via a room-temperature ^{1}H NMR titration study to be 500 ± 110 M^{-1}, the K_a for **1** with **4** was determined to be 78 800 ± 17 400 M^{-1}.

To determine the orientation of **4** within the cavity of **1**, a ^{1}H NMR spectrum of the complex was obtained at 215 K. In the low-temperature spectrum, eight signals were observed for the two sets of four aromatic protons and the two protons on the double bond. The two protons on the double bond were assigned to the broad doublets at δ 2.86 and 4.86 (J = 13.0 Hz). Integration revealed that the downfield doublet (δ 8.00) and the broad singlet at δ 6.03 were each due to two guest signals, while the other six peaks integrated to one proton each. A series of HOMODECs was obtained, and the resulting assignments of protons and the chemical shift of the free and complexed stilbene-derived guest are shown in Table 3. The orientation of the host−guest complex as it was determined from ^{1}H NMR experiments is shown in Figure 5.

Computational Simulations of Host−Guest Complexation. Because crystallography-grade crystals could not be obtained, we have examined the complexation of 5-hydroxyindole and β-naphthol by a combination of molecular dynamics and molecular mechanics. The results suggest that complexation of both bicyclic aromatics is exothermic and driven primarily by van der Waals attractive forces. We conclude that the cavity of the anthracene host is large enough to accommodate these guests with no net steric repulsion.

Molecular dynamics were done at 300 and 600 K for 100 ps, using the standard MacroModel 5.0 molecular dynamics package at constant temperature.[21] The AMBER force field was employed for the molecular dynamics. The final structure was minimized with both the AMBER and MM2* force fields, and the final "best" complex is pictured in Figure 6 as a stereoview.

The orientation of this complex is in strikingly good agreement with the NMR results and shows that H_5 of the naphthol is shielded appreciably more than H_4. (See Figure 1 for the proton numbering scheme.) The cant of the naphthol in the complex is required for formation of the hydrogen bond to the pyridine bridge. Estimation of $\Delta H°$ of complexation was achieved by moving the naphthol 14 Å away and minimizing. Values of −136 kJ/mol (AMBER) and −94 kJ/mol (MM2*) were obtained. When the naphthol was placed 7 Å from the cavity, repeated minimization caused it to move spontaneously into the cavity to give a metastable conformation slightly higher in energy than that pictured (26 kJ/mol). Ten picosecond of molecular dynamics (300°) then caused it to relax to the conformation shown.

From these results we may draw two conclusions. First, from a simple steric perspective, the calculations show that the cavity of this host is large enough to accommodate a naphthalene or an indole ring. The numbers cited above are not to be taken as serious estimates of $\Delta H°$, since the usual 0 K gas phase conditions apply. Second, multiple energy minima are associated with rocking and flopping of the aromatic host within the cavity. This is dramatically apparent on playing the "movie" of the molecular dynamics calculations and also from the spontaneous "docking" process.

Conclusions

Host **1** was shown to bind 6-nitro-2-naphthol **2**, methyl 5-hydroxy-3-indolecarboxylate **3**, and 4-hydroxy-4′-nitrostilbene **4** with high affinity. The association constants for complexation were determined via competition studies with a weaker binding host (**14**) to be 15400 ± 2700, 4480 ± 560, and 78800 ± 17400 M^{-1} respectively in $CDCl_3$.

In the indole system, a vinylogous carbamate was present rather than a nitro group. The roughly 3-fold lower affinity of **1** for **3** relative to **2** may be due mainly to the change in strength of the electron-withdrawing substituent. Shape complementarity may also be a factor.

For **2**−**3**, two edge−face interactions were observed. In the low-temperature ^{1}H NMR spectra of the complexed guests, the protons of the guest that were positioned over the anthracene ring of the host were shifted an average of 4.7 ppm upfield. The other aromatic protons of the guest were shifted only an average of 1.3 ppm upfield upon complexation.

Hosts similar to **1** have shown a substantial preference for guests such as *p*-nitrophenol which have a pK_a near 7. Phenol (pK_a = 10) is essentially not bound by these naphthalenophanes.[10] Although **4** has a pK_a of 9.95,[22] it

(22) Sheridan, R. E. Ph.D. Thesis, University of Wisconsin−Madison, 1988.

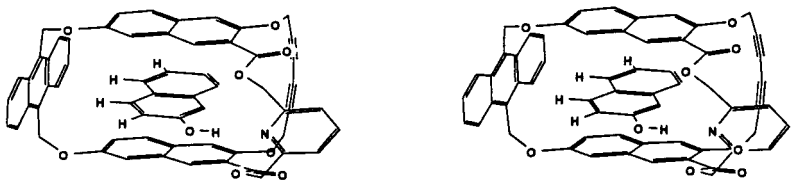


Figure 6. Stereoview of **1**-*β*-naphthol.

is bound well by **1**. The high pK_a indicates that there is not a lot of extended conjugation (i.e., that the stilbene system is bent), and the binding of **4** was predicted to be relatively weak. That the binding affinity of **1** for **4** was high despite the nonoptimal pK_a of **4** supports the proposition that edge−face interactions lend stability to complexation.[23] The relatively weak binding by **14** of **2**, **3**, and **4** is further indication that the multiple edge−face interactions present with **1** are at least partly responsible for the high affinity of **1** for these guests.

A major difference in the interactions of hosts **1** and **14** with guests **2**−**4** is the possibility of edge−face interactions in complexes of **1**. For each guest, K_{rel} was found to be between 15 and 158. Therefore, binding interactions between host **1** and the guests are stronger by 1.6−3.0 kcal/mol relative to host **14**. The simplest interpretation of these relationships is that the edge−face interactions in complexes of host **1** make significant contributions to binding.

Experimental Section

General Techniques. 9,10-Bis(chloromethyl)anthracene **9** was either synthesized as described or purchased from Acros and used without further purification. The numbering scheme for proton assignments for all compounds is consistent with that shown for **1**; tetramethylsilane (TMS) was used to reference all the spectra.

***n*-Propyl 3-Hydroxy-7-pivaloxy-2-naphthoate (6).** Naphthoate ester **5** (10.0 g, 41 mmol) was dissolved in 14 mL of $CHCl_3$. Pivaloyl chloride (5.8 mL, 46.7 mmol, 1.2 equiv) was added, and the reaction was stirred at 70 °C for 15 h. After 15 h, the reaction was no longer releasing HCl gas. The excess pivaloyl chloride and the $CHCl_3$ were removed (Kugelrohr, vacuum pump) to give 13.7 g (102%) of pale yellow solid **6**. For characterization, a sample was chromatographed (SiO_2: 5% hexane/$CHCl_3$) and recrystallized ($CHCl_3$/hexane): mp = 88−91 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.52 (s, −OH), 8.45 (s, 1H, H_1), 7.69 (d, J = 9 Hz, 1H, H_5), 7.53 (d, J = 2 Hz, 1H, H_8), 7.32 (s, 1H, H_4), 7.22 (dd, J = 9, 2 Hz, 1H, H_6), 4.39 (t, J = 7 Hz, 2H), 1.85 (sextet, J = 7 Hz, 2H), 1.40 (s, 9H), 1.08 (t, J = 7 Hz, 3H); ^{13}C NMR (62.4 MHz, $CDCl_3$) δ 170.44, 156.89, 156.73, 147.65, 136.13, 132.04, 127.94, 127.29, 124.87, 119.64, 115.21, 111.97, 67.16, 38.74, 26.68, 21.44, 9.85; HRMS calcd for $C_{19}H_{22}O_5$ m/e = 330.1467, found m/e = 330.1457. Anal. Calcd: C, 69.06; H, 6.72. Found: C, 69.34; H, 6.79.

***n*-Propyl 7-Pivaloxy-3-propargyloxy-2-naphthoate (7).** Acetone (35 mL) was added to 10.5 g (32 mmol) of **6**. Propargyl bromide (4.5 mL, 51 mmol, 1.6 equiv) and Cs_2CO_3 (11.5 g, 35 mmol, 1.1 equiv) were added, and the reaction was stirred at reflux under N_2 for 24 h. The reaction mixture was cooled to room temperature, and 50 mL of $CHCl_3$ was added. Then 5% HCl was added until the aqueous layer was acidic (litmus). The organic layer was dried ($MgSO_4$), and the solvent was removed in vacuo to give 11.7 g (100%) of brown oil. This oil was filtered through a plug of silica gel ($CHCl_3$ eluent) to give 10.5 g (90%) of light yellow oil which solidified after drying for several days. A small sample was recrystallized ($CHCl_3$/hexane) for characterization: mp = 51−54 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.24 (s, 1H, H_1), 7.73 (d, J = 9 Hz, 1H, H_5), 7.53 (d, J = 2 Hz, 1H, H_8), 7.34 (s, 1H, H_4), 7.23 (dd, J = 9, 2 Hz, 1H, H_6), 4.85 (d, J = 2 Hz, 2H), 4.31 (t, J = 7 Hz, 2H), 2.55 (t, J = 2 Hz, 2H), 1.80 (m, J = 7 Hz, 2H), 1.39 (s, 9H), 1.05 (t, J = 7 Hz, 3H); ^{13}C NMR (62.4 MHz, $CDCl_3$) δ 177.32, 166.07, 153.40, 147.95, 133.40, 131.94, 128.02, 127.86, 123.47, 123.13, 118.88, 108.96, 77.72, 75.72, 66.17, 56.02, 38.24, 26.20, 21.11, 9.57; HRMS calcd for $C_{22}H_{24}O_5$ m/e = 336.1624, found m/e = 368.1618. Anal. Calcd: C, 71.71; H, 6.57. Found: C, 71.25; H, 6.56.

***n*-Propyl 7-Hydroxy-3-propargyloxy-2-naphthoate (8).** Propanol (25 mL) and **7** (12.4 g, 34 mmol) were combined. Cs_2CO_3 (13.2 g, 40 mmol, 1.2 equiv) was added, and the reaction was stirred under N_2 for 20 h. The reaction was diluted with 100 mL of $CHCl_3$ and washed with 5% HCl until the aqueous washings were acidic (litmus). The organic layer was dried ($MgSO_4$) and the solvent was removed in vacuo to give 13.0 g (135%) of brown oil. Chromatography (SiO_2: 30% EtOAc/hexane) gave 7.8 g (78% yield) of yellow solid **8**. A pure sample was obtained for analysis by recrystallization (benzene/hexane): mp 102−103 °C.; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.1 (s, 1H, H_1), 7.61 (d, J = 8 Hz, 1H, H_5), 7.28 (s, 1H, H_4), 7.19 (dd, J = 8, 3 Hz, 1H, H_6), 7.16 (1H, H_8, partly obscurred by H_6), 6.47 (br s, 1H, OH), 4.80 (d, J = 2 Hz, 2H), 4.33 (t, J = 7 Hz, 2H), 2.51 (t, J = 2 Hz, 1H), 1.81 (m, J = 7 Hz, 2H), 1.05 (t, J = 7 Hz, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 166.93, 153.38, 151.44, 130.96, 130.52, 129.00, 128.05, 122.15, 120.83, 110.14, 109.56, 78.27, 75.85, 66.94, 56.61, 21.85, 10.42; HRMS calcd for $C_{17}H_{16}O_4$ m/e = 284.1049, found m/e = 284.1041. Anal. Calcd: C, 71.80; H, 5.68. Found: C, 71.97; H, 5.76.

9,10-Bis(chloromethyl)anthracene (9). Paraformaldehyde (4.3 g, 48 mmol) and 63 mL of glacial acetic acid were combined to form a white slurry. HCl gas was bubbled through a glass frit into the stirred suspension until the solution was clear (about 3 min). Anthracene (9.9 g, 55 mmol) and another 63 mL of glacial acetic acid were added to the flask. The reaction was stirred at 60 °C under N_2 for 20 h and then poured over ice. The resulting bright yellow solid was filtered and dried over P_2O_5 in vacuo for several hours to give 14.0 g (92%) of **10**. Upon recrystallization (benzene), bright yellow needles formed: mp decomposed at 214 °C (lit.[24] mp decomposed at 204−205 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.37 (m, 4H), 7.64 (m, 4H), 5.59 (s, 4H); ^{13}C NMR (125.8 MHz, $CDCl_3$-d_6-DMSO) δ 128.95, 128.09, 126.88, 126.16, 125.35, 123.01, 120.45, 37.52; HRMS calcd for $C_{16}Cl_2H_{12}$ m/e = 275.0350, found m/e = 2755.0369.

Precyclophane (10). 9,10-Bis(chloromethyl)anthracene **9** (1.021 g, 3.7 mmol) and **8** (2.000 g, 7.0 mmol, 2.0 equiv) were taken up in 40 mL of CH_3CN to form a bright yellow slurry. Cs_2CO_3 (2.4 g, 7.4 mmol, 2.0 equiv) was added, and the reaction mixture was stirred under N_2 for 2 d. It was then diluted with 100 mL of $CHCl_3$ and washed with 5% HCl until the water washings were acidic (litmus). The organic layer was dried ($MgSO_4$), and the solvent was removed in vacuo to give 2.5 g (88%) of tan solid. Chromatography (SiO_2: 5% hexane/$CHCl_3$) gave 1.652 g (58%) of bright yellow solid **10**. Recrystallization (ethylene dichloride/hexane) gave an analytically pure sample: mp 195−197 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.38

(23) The K_a for complexation of **2** by a host containing a substituted xylene ring instead of anthracene was on the same order of magnitude as the K_a for complexation of **2** by **14**.

(24) (a) Badger, G. M.; Cook, J. W. *J. Chem. Soc.* **1939**, 802. (b) Miller, M. W.; Amidon, R. W.; Tawney, P. O. *J. Am. Chem. Soc.* **1955**, *77*, 2845.

(m, 2H, $H_{1a,4a}$), 8.34 (s, 1H, H_{1n}), 7.72 (d, J = 9 Hz, 1H, H_{5n}), 7.59 (d, J = 3 Hz, 1H, H_{8n}), 7.57 (m, 2H, $H_{2a,3a}$), 7.39 (s, 1H, H_{4n}), 7.27 (dd, J = 9, 3 Hz, 1H, H_{6n}), 6.11 (s, 2H), 4.89 (d, J = 2 Hz, 2H), 4.36 (t, J = 7 Hz, 2H), 2.56 (t, J = 2 Hz, 1H), 1.86 (m, J = 7 Hz, 2H), 1.10 (t, J = 7 Hz, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$, one quaternary carbon missing) δ 171.59, 166.75, 156.95, 152.83, 131.85, 131.32, 129.54, 128.85, 126.80, 125.15, 123.56, 122.28, 110.55, 107.99, 78.90, 76.34, 67.31, 63.37, 57.53, 22.59, 11.13; DEPT 135 (67.9 MHz, $CDCl_3$) CH and CH_3 δ 131.4, 128.3, 126.3, 124.6, 121.7, 110.0, 107.5, 10.6; CH_2 66.8, 62.8, 57.0, 22.1; FABMS calcd for $C_{50}H_{42}O_8$ M = 770, found M + 1 = 771.

Cyclophane (11). Pyridine (245 mL) and CH_3CN (735 mL, dried over 4 Å MS (molecular sieves) overnight) were combined and heated to reflux (84 °C). Precyclophane **10** (1.506 g, 2.0 mmol) and $Cu(OAc)_2 \cdot H_2O$ (1.953 g, 9.8 mmol, 5.0 equiv) were added to the refluxing solvent, and the reaction was refluxed for 1 h. The reaction was quenched with ice, diluted with 400 mL of $CHCl_3$, and washed with ice cold 5% HCl in a 2 L separatory funnel until the water washings were acidic (litmus). The organic layer was dried with $MgSO_4$, and the solvent was removed in vacuo to give 1.4 g (93%) of tan solid. Chromatography (SiO_2: 2% EtOAc/$CHCl_3$) gave 400 mg (26%) of a bright yellow solid. Recrystallization by slow diffusion of ethylene dichloride/heptane at room temperature gave an analytically pure sample for analysis: mp decomposed at 228−229 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (m, 2H, $H_{1a,4a}$), 7.92 (s, 1H, H_{1n}), 7.58 (m, 2H, $H_{2a,3a}$), 7.29 (d, J = 2 Hz, 1H, H_{8n}), 7.08 (d, J = 9 Hz, 1H, H_{5n}), 6.98 (s, 1H, H_{4n}), 6.67 (dd, J = 9, 2 Hz, 1H, H_{6n}), 6.30 (s, 2H), 4.79 (s, 2H), 1.76 (m, J = 7 Hz, 2H), 1.02 (t, J = 7 Hz, 3H); ^{13}C NMR (62.4 MHz, $CDCl_3$) δ 156.94, 155.24, 151.76, 131.63, 131.35, 130.74, 130.18, 129.32, 128.31, 126.38, 125.28, 123.21, 121.28, 112.55, 110.78, 74.46, 71.25, 66.61, 63.98, 56.66, 21.62, 10.02; FABMS calcd for $C_{50}H_{40}O_8$ M = 768, found M + 1 = 769.

Cyclophane Diacid (12). Cyclophane **11** (368 mg, 0.5 mmol) was dissolved in 50 mL of THF. A solution of LiOH·H_2O (350 mg, 8.3 mmol, 17.4 equiv) in 32 mL of H_2O (Millipore) was added, and the reaction was stirred under N_2 at 40 °C for 24 h. The reaction mixture was then diluted with 40 mL of $CHCl_3$ and washed with 40 mL of saturated $NaHCO_3$ solution. The aqueous layer was cooled in an ice bath, acidified with 5% HCl to pH = 3 (litmus), and extracted with 2 × 75 mL of $CHCl_3$. The final organic layer was dried with $MgSO_4$, and solvent was removed in vacuo to give 282 mg (86%) of **12** as a yellow-orange solid. All attempts at recrystallization resulted in product decomposition. **12**: ^{1}H NMR (300 MHz, $CDCl_3$-d_6−DMSO) δ 8.78 (m, 2H, $H_{1a,4a}$), 7.86 (s, 1H, H_{1n}), 7.67 (m, 2H, $H_{2a,3a}$), 7.33 (d, J = 2 Hz, 1H, H_{8n}), 7.23 (d, J = 9 Hz, 1H, H_{5n}), 7.03 (s, 1H, H_{4n}), 6.84 (dd, J = 9, 2 Hz, 1H, H_{6n}), 6.37 (s, 2H), 4.90 (s, 2H); FABMS calcd for $C_{44}H_{28}O_8$ M = 684, found M + 1 = 685.

Dibutylaminopyridine-Bridged Host (1). Cyclophane diacid **12** (145 mg, 0.21 mmol, 2.0 mM) was dissolved in 105 mL of CH_3CN. 2,6-Bis(bromomethyl)-4-dibutylaminopyridine **13** (81 mg, 0.21 mmol, 2.0 mM) and K_2CO_3 (247 mg, 1.79 mmol, 17.0 mM, 8.6 equiv) and 18-crown-6 (640 mg, 2.42 mmol, 23.1 mM, 11.7 equiv) were added, and the reaction was stirred under N_2 in the dark for 5 d. The reaction mixture was then diluted with 200 mL of $CHCl_3$ and washed with 2 × 200 mL of H_2O. The organic layer was dried ($MgSO_4$), and the solvent was removed in vacuo to give 516 mg of yellow oil (mainly product and 18-crown-6). Chromatography (SiO_2: 30% hexane/EtOAc) gave 56 mg (30%) of pale yellow solid. Recrystallization by slow diffusion with ethylene dichloride/heptane at room temperature gave (40 mg, 21%) of analytically pure material. **1**: mp decomposed at 207−210 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (m, 2H, $H_{1a,4a}$), 7.90 (m, 1H, $H_{2a,3a}$), 7.84 (s, 1H, H_{1n}), 7.60 (m, 1H, $H'_{2a,3a}$), 7.33 (d, J = 9 Hz, 1H, H_{5n}), 7.20 (d, J = 2 Hz, 1H, H_{8n}), 7.13 (dd, J = 9,2 Hz, 1H, H_{6n}), 6.99 (s, 1H, H_{4n}), 6.59 (s, 1H, H_{py}), 6.54, 6.16 (ABq, J_{AB} = 14 Hz, 2 H), 5.38, 5.11 (ABq, J_{AB} = 11 Hz, 2 H), 4.74 (s, 2H, diyne methylene), 3.32 (t, J = 8 Hz, 2H), 1.60 (m, J = 8 Hz, 2H), 1.39 (m, J = 8 Hz, 2H), 0.99 (t, J = 8 Hz, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 166.11, 154.95, 154.44, 153.84, 150.93, 130.98, 130.46, 130.23, 129.96, 129.54, 129.33, 127.94, 127.03, 125.99, 125.58, 124.50, 123.76, 121.71, 112.71, 108.83, 106.63, 73.09, 69.90, 68.63, 62.41, 57.86, 50.22, 43.44, 29.09, 20.27, 13.98; FABMS calcd for $C_{59}H_{50}N_2O_8$ M = 914.3569, found M + 1 = 915.3645. Anal. Calcd (host **1** plus one molecule of ethylene dichloride): C, 72.31; H, 5.38. Found: C, 71.90; H, 5.53.

Determination of Association Constants. (A) Titration Method. A 400 μL solution of host in $CDCl_3$ was titrated with appropriate amounts of guest so that the amount of guest varied between 0.1 and 10 equiv. A best fit for the plot of chemical shift versus guest:host concentration was obtained using nonlinear least-squares analysis.[15c]

(B) Competition Method. Host **1** and host **14** were combined in $CDCl_3$ in about a 1:1 ratio. About 1 equiv of the guest was added and K_{rel} was calculated using eq 1.

Supporting Information Available: General NMR experimental procedures, tables, and graphs for the K_as for complexation of **2**, **3**, and **4** by **14** and for complexation of **3** by **1** are given. COSY and LR COSY spectra for **2** + **1** and HOMODECS for **3** + **1** and for **4** + **1** are shown. Stackplots showing the addition of increasing amounts **3** to **1** and **4** to **1** and spectra showing **3** and **4** complexed by **1** at 215 K are given (21 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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