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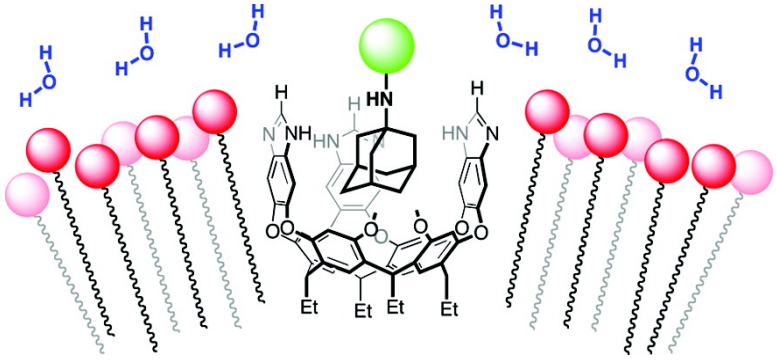
J. Am. Chem. Soc., **2007**, 129 (31), 9773-9779• DOI: 10.1021/ja0723378 • Publication Date (Web): 18 July 2007



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Guest Recognition with Micelle-Bound Cavitands

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Abstract: We report that a benzimidazole cavitand is incorporated in aqueous phosphocholine (PC) micelles, folds into the vase conformation, and functions as small-molecule host. As a micelle-bound host it has the ability to sequester selective hydrophobic guest "anchors" into its interior. These anchors include cycloalkanes, adamantanes, and nitrogen heterocycles that compete favorably with the large excess of PC alkyl side-chains that make up the micelle interior. The adamantyl anchor was further functionalized with a fluorophore, and in another instance a dipeptide and both guests retain their recognition properties with the micelle-bound cavitand. Additionally, we report that variations in the cavitand periphery and rim are well-tolerated under our experimental conditions. We find that enhanced binding toward certain guests in both micelles as well as in solution occurs in response to titration with base; this previously unknown property of benzimidazole cavitands is reported in detail.

Introduction

Resorcinarenes have proven to be a useful platform on which to develop a variety of cavitands.[1−4] The deeper cavitands served as small-molecule hosts that demonstrated guest selectivity,[2] slow guest exchange,[5] and acceleration[6,7] or even catalysis of reactions.[8,9] Some deep cavitands have even exhibited these functions in water, despite their seemingly overwhelming amount of exposed π surface.[10−13] The deepened hydrophobic interiors facilitate sequestration of both neutral[14] and charged[15] organic molecules from bulk solution, most commonly *via* the hydrophobic effect.[16−20] In addition to recognition, a water soluble cavitand was demonstrated to entice long surfactant molecules to adopt helical conformations within its interior.[21] This role reversal of induced-fit recognition, where the guest adapts in response to a rigid host, has been recently reviewed.[22] The concentration of surfactant was found to determine its ability to form kinetically stable complexes in the cavitands. Above the critical micelle concentration (cmc) the water-soluble cavitand was shown to migrate into the micelle and became the guest rather than the host.[23] In an effort to develop a general cavitand for guest recognition in micelles we prepared hydrophobic cavitand **1** (Figure 1) and report here our experiences.

Results and Discussion

We synthesized benzimidazole cavitand **1** in three linear steps following well-established procedures.[24,25] These prior reports indicated the necessity of four interleaved HOR (R = H, Me, Et, C = OR′) molecules to effect folding and stabilization of a vase conformation in $CDCl_3$ solution. Water was directly observed in a similar calixarene imidazole cavitand *via* NOE,[26] and we will continue to include these helper molecules in our depictions. The ^{1}H NMR spectra in wet DMSO-d_6 or THF-d_8: D_2O and high-resolution MS provided unambiguous characterization of **1** and demonstrated that under these conditions **1** exists in a (time-averaged) C_{4v} vase conformation. Although **1** features no striking water solubilizing features, it was slightly soluble in pure D_2O and gave sharp NMR signals (Figure 2A) characteristic of an unfolded "kite" conformation, exhibiting either C_{2v} or D_{2d} symmetry (for a monomeric or dimeric

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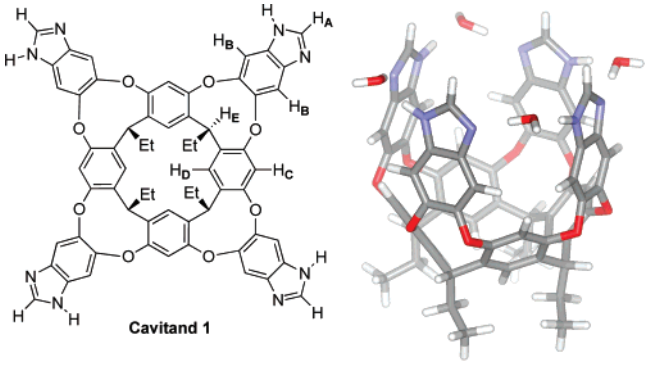

Figure 1. The ethyl-footed benzimidazole cavitand **1** and minimized representation of **1** with four interleaved water molecules (PM3, Spartan '04).[29]

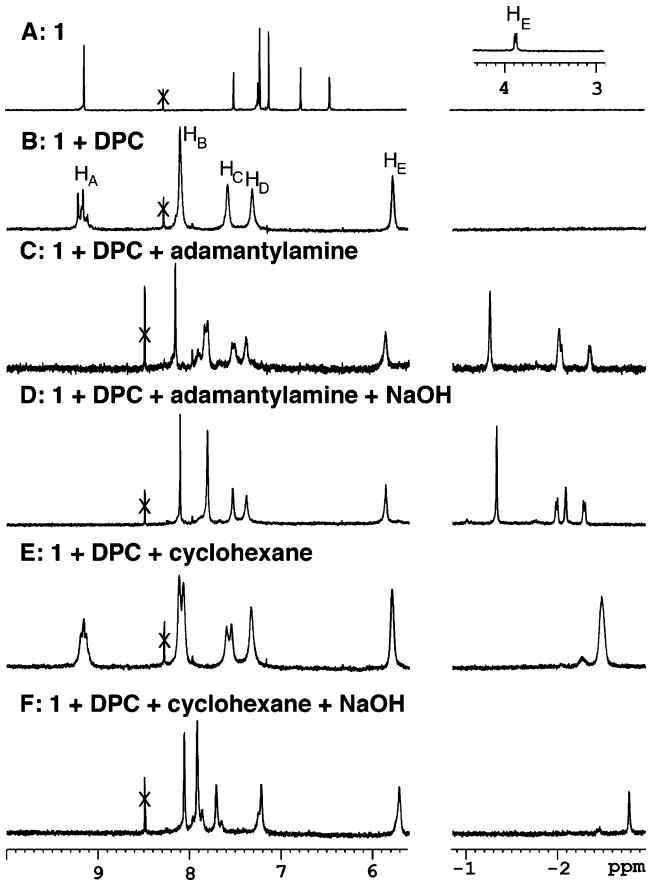

Figure 2. 600 MHz ^{1}H NMR (D_2O, 600 μL) of (A) 3 mM cavitand **1**, (B) cavitand **1** + 40 mM DPC, (C) B + 30 mM adamantylamine, (D) C + 10 μL 3% NaOH, (E) B + 30 mM cyclohexane, (F) E + 10 μL 3% NaOH. Traces of DMF marked with "X."

complex respectively).[27,28] Most characteristic is the methine resonance (H_E), that occurs at 3.9 ppm in this kite conformation. Electrospray ionization MS gave a series of peaks with the correct isotopic distribution for a singly positive charged dimer (dimer + H^+ found = 2115), confirming that cavitand **1** forms a dimeric velcrand in water.[11] Presumably the kite dimer presents a smaller surface area to the water solvent; indeed, if the cavitand was prepared as a stoichiometric complex with cyclohexane (forcing the host into the folded C_{4v} vase conformation), no dissolution in water was detected.

1. Behavior of 1 in Lipid Micelles. The geometry of cavitand **1** in water changed drastically with the addition of dodecylphosphocholine (DPC) above the cmc. Here the ^{1}H NMR spectrum reveals that cavitand **1** adopts the vase conformation (Figure 2B) even in the absence of added guest, and that this previously insoluble conformation had been coaxed into water by the micelle. The methine proton (H_E) now appears at 5.7 ppm. This initial finding indicated that the hydrophobic interior of DPC micelles effected folding of **1**. No peaks for bound phosphocholine were observed,[23] most probably due to weak binding with rapid in/out exchange. Surprisingly, cavitand **1** was not soluble in sodium dodecyl sulfate (SDS) above the cmc despite reports that the water-soluble tetracarboxylate analogue was soluble.[23]

1.1. Guest−Host−Micelle Interactions. Suitable guests adamantylamine and cyclohexane showed strong binding in micelle-bound cavitand **1**, as was obvious from the upfield region of the ^{1}H NMR spectra (Figure 2 C,E). The guests were able to compete with a sea of long chain alkyl groups of the surfactant in which **1** is submerged. The ^{1}H NMR spectra allow the observation of guest binding, as the guest shows large upfield shifts due to the preorganized aromatic rings of the cavitand creating a magnetically shielded environment, a phenomenon that micelles do not exhibit due to their construction from magnetically docile saturated hydrocarbon chains. ^{1}H NMR does not exclusively prove that the host−guest complex is located inside the micelle (although the solubility of the complex provides compelling evidence). Diffusion ordered spectroscopy (DOSY)[30] was able to show the presence of one multicomponent system. The signals for host (7.6×10^{-11} m^2/s), guest (8.4×10^{-11} m^2/s) and micelle (8.4×10^{-11} m^2/s) displayed diffusion coefficients indicating the presence of one unified molecular assembly (see Supporting Information for raw data; HOD was measured to be 1.8×10^{-9} m^2/s). These results are in agreement with literature reports.[31]

The addition of inorganic base to the guest−host−micelle assemblies had a marked effect on guest binding. With no added guest (Figure 2B) or with bound cyclohexane (E) the downfield aromatic residues of cavitand **1** were essentially unchanged. Proton H_A of the cavitand (Figure 1) resonates at 9.2 ppm in both cases. Addition of NaOH to the system with bound cyclohexane (Figure 2F) resulted in the upfield shift of cavitand peaks (e.g., H_A $\Delta\partial = -1.10$ ppm) as well as those of guest (cyclohexane $\Delta\partial = -0.29$ ppm). In the process the binding affinity of cyclohexane for **1** decreased. Adamantylamine, on the other hand, did not display the same drastic changes upon addition of NaOH. In this case, the guest is itself basic, and so the downfield cavitand peaks seen in Figure 2C are more akin to those in F (+NaOH) than those in neutral media (B, E). On the basis of integrations, adamantylamine shows only 50% binding. Addition of external NaOH (D) did not cause a large change in host or guest chemical shifts, but sharpened the signals significantly and increases binding affinity; integration reveals a 1:1 host−guest complex. The broadened, split peaks in B and E are due to multiple or flexible cavitand conformations; these peaks sharpen dramatically as seen in D and F where it appears

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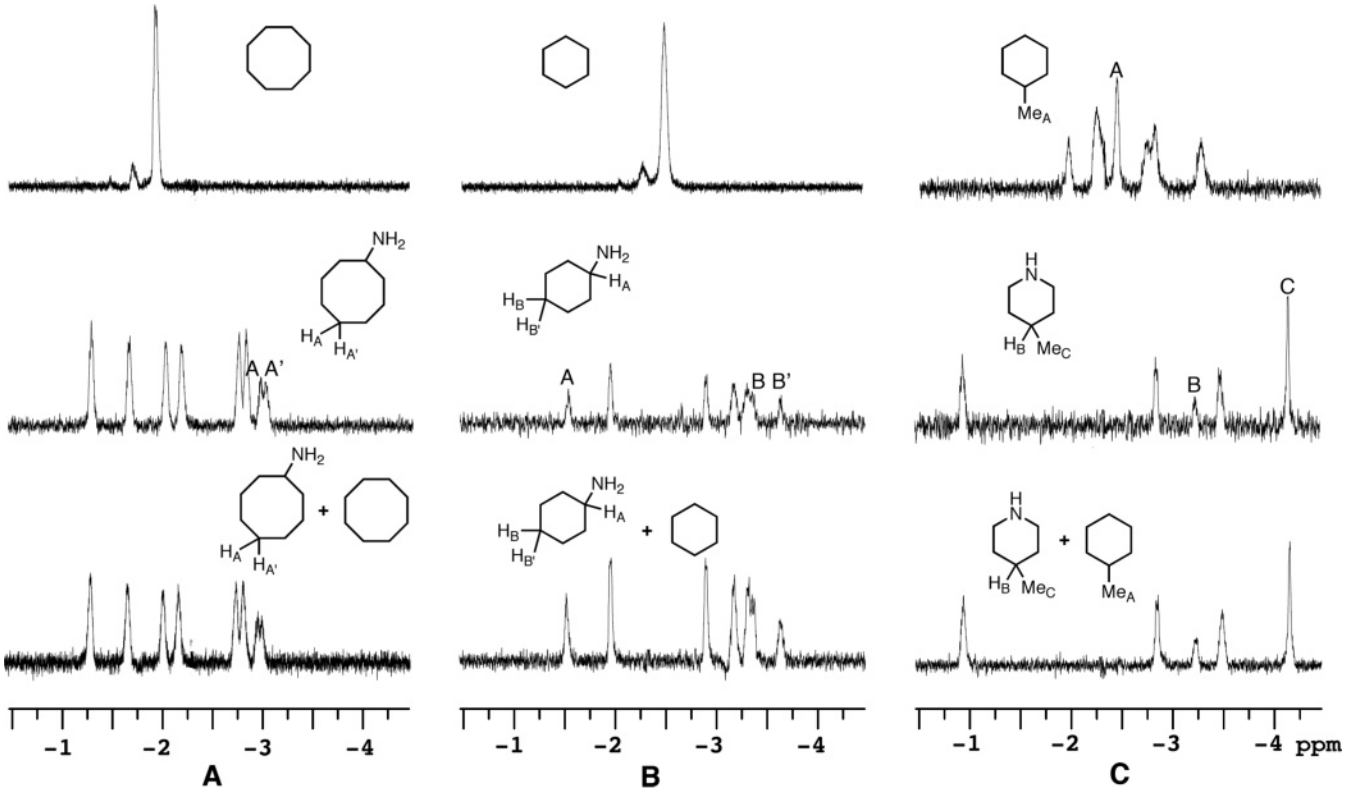
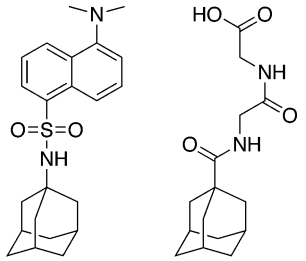


Figure 3. ^{1}H NMR competition of encapsulated hydrocarbons (3 mM **1**, 41 mM DPC, 45 mM of each guest in D_2O). Column A: cyclooctane, cyclooctylamine, and cyclooctane/cyclooctylamine. Column B: cyclohexane, cyclohexylamine, and cyclohexane/cyclohexylamine. Column C: methylcyclohexane, 4-methylpiperidine, and methylcyclohexane/4-methylpiperidine.

that NaOH has slowed the kinetic motion of the cavitand on the NMR time scale.

1.2. Guest Selectivity. Cavitand **1** formed stable complexes with several other small molecules in DPC micelles including *trans*-decalin, *trans*-1,4-dimethylcyclohexane, cyclohexane, methylcyclohexane, cyclooctane, cyclohexylamine, cyclooctylamine, cyclooctanol, and 4-methylpiperidine. A few ostensibly compatible species exhibited either weak affinity for the cavitand (e.g., 4-*tert*-butylaniline, adamantylmethylamine, 1,1,4-trimethylcyclohexane), or none at all (e.g., adamantylacetic acid, adamantanecarbonitrile). On the basis of these initial results, we conducted a series of competition experiments to probe the role of both the shaped anchor (hydrocarbon ring) as well as heteroatom substitution. The hydrocarbons cyclooctane, cyclohexane, and methylcyclohexane served as good guests (Figure 3). In the case of cyclooctane and cyclohexane, the presence of one major peak is indicative of rapid guest tumbling on the NMR time scale. Methylcyclohexane also appears to tumble rapidly because of the close grouping of peaks around −2.5 ppm.[14] The addition of a heteroatom stops the tumbling of these guests on the NMR time scale, presumably through interaction with the rim or perhaps repulsion from the electron-rich aromatic walls of the cavity. This is clearly illustrated in the second row of Figure 3; selected ^{1}H signals for the aliphatic amines are assigned and their spread of chemical shifts gives support for slowed rotation as well as reveals the orientation of the guest. The magnetic anisotropy of the cavitand has the effect of providing the most shielding for species located near the resorcinarene: 4-methylpiperidine clearly places its methyl group deep into this cavity (δ −4.2 ppm, Me_C). Cyclooctylamine and cyclohexylamine behave similarly, burying the methylene furthest from the point of amine attachment deep in the cavity. Competitive binding experiments between the alkanes and their amine-substituted analogues revealed that nitrogen had a remarkable effect. In all instances the nitrogen-substituted alkanes were the only bound species observable with greater than 99:1 selectivity. There appeared to be little or no selectivity between cyclohexylamine and cyclooctylamine. When adamantylamine was compared with either cyclooctylamine or cyclohexylamine there also was no clear preference (not shown).

1.3. Binding Functionalized Anchors. The experiments thus far revealed that a combination of an appropriately sized and shaped hydrocarbon anchor in conjunction with a heteroatom substituent was most beneficial for cavitand binding and good selectivity could be obtained between qualitatively similar guests for **1** in micelles. This selectivity is not dependent on the substituent residing *outside* the cavity (in previous cavitand studies finite guest lengths were uncovered, above which binding did not readily occur).[14] We prepared several guests with a small variety of anchors to which we attached additional functionality that would reside outside the binding pocket of the cavitand. Dansyl-appended adamantylamine **2** (Figure 4) was shown to bind under the standard conditions, affording a fluorescently labeled guest. In addition, adamantyl-Gly-Gly-OH **3** and adamantyl maleimide bind strongly, demonstrating that the complex between **1** and micelles can act as a host for a variety of species functionalized with suitable binding anchors. The lack of selectivity of cavitand **1** for unfunctionalized adamantylamine vs cyclooctylamine encouraged us to explore the cyclooctyl analogue of **3**, cyclooctyldansylsulfonylamide; this compound showed no uptake in micelle bound **1**, revealing one example of a limitation on this strategy. The successful functionalized



2 3

Figure 4. Adamantane "anchor" with attached functionality.

adamantyl anchors employed here by no means define the limits of this approach; rather they set the stage for further exploration.

1.4. Cavitand Variation. The short ethyl "feet" and unfunctionalized benzimidazole wall afforded a cavitand that was soluble, folded, and well-behaved as a small molecule host while immersed in DPC micelles. Were these properties unique to cavitand **1** or could others be found? In an effort to answer this question we screened a variety of cavitands through varying both cavitand foot (R′) and rim (R) substitution (Figure 5). We decided to test several variables to get a better understanding of the properties of our prototypical cavitand **1**. Having a variety of functionality to choose from at both locations, we limited the functionalization of the feet to either the short ethyl group or the long $C_{11}H_{23}$ chain. At the rim of the cavitand we decided to explore a wider range of groups including an alkyl chain, alkyl esters, substituted aromatics, and an octaamide cavitand that differs in composition from the benzimidazole scaffold on which the others are based. We found that a number of these features were amenable to extraction into the micelle. The NMR spectra of the complexes of cavitands **4**−**9** in micelles are located in the Supporting Information.

The presence of ethyl esters at the rim with either ethyl (**4**) or C_{11} feet (**5**) gave results similar to **1** under the experimental conditions. The binding of adamantylamine was obvious in the upfield region of the NMR, and upon addition of base enhanced binding was observed. The incorporation of ester groups at the rim and the C_{11} chains at the feet (**5**) gave NMR spectra with broader signals. Longer alkyl chain surfactants could allow for better exploration of cavitand functionality, and we employed hexadecylphosphocholine (HPC). Cavitands **1**, **4**, and **5** were well-behaved in HPC when compared to DPC, and a slight increase in peak sharpness for the longer **5** was noted. Perhaps HPC allows a greater range of cavitands to be bound, purely due to its increased dimensions. With aromatic functionalized rims we found that **7** behaved as a weak host for adamantylamine, even in the presence of base. It is unclear at this time whether this is purely an issue of cavitand solubility in HPC micelles or if other factors are at work. Cavitand **8** with *p*-nitrophenyl groups served as a good host. Cavitand **6**, which was functionalized with *n*-octyl chains at the rim, resisted micelle uptake, presumably because of poor solubility. The protrusion of the octyl rim into the bulk solution may be the cause.

The benzimidazole functionality is not an essential feature for cavitand uptake and function; octamide **9** was also a successful host for adamantylamine in HPC micelles. In this case added NaOH has no effect on binding. This result is not surprising, as the walls of **9** lack the acidic benzimidazole functionality of the other cavitands. These results illustrate that a variety of substitution patterns of resorcinarene-based cavitands are well-tolerated for micelle localization and guest recognition. Variation at both the feet and the rim is possible, as well as in the composition of the walls, which are built up from a common resorcinarene scaffold. The breadth of tolerated substitution patterns in conjunction with the relative ease of cavitand preparation bode well for future exploration toward more complex membrane mimics.

2. Solution Studies of 1. While the cavitands could be extracted into solution by the micelles, and in several cases exhibit guest recognition, the broadest activity as a host was observed in the presence of added base, either NaOH or organic amine. In order to determine the reason for this, the host−guest properties of **1** were studied in the absence of micelles. In either DMSO-d_6 (Figure 6A) or 2:1 THF-d_8:D_2O (Figure 7A) cavitand **1** was soluble and existed in the folded C_{4v} conformation. In 2:1 THF-d_8:D_2O the spectrum was much sharper, attributed to THF's well-established ability to serve as a guest for systems like this.[32] Efforts to find suitable guests for **1** in THF:D_2O were hindered by an inability to displace THF from the cavitand interior. DMSO, on the other hand, only poorly occupies the cavity and led to a less kinetically stable receptor system, but one that proved more amenable to the binding of added guests.

2.1. Guest Binding in DMSO. The addition of adamantylamine to a DMSO-d_6:D_2O solution of **1** failed to yield evidence of guest binding or host solubility, contrary to what was observed in aqueous micelles. However, treatment of this solution with NaOH resulted in concomitant host solubilization and guest uptake, so an increase in binding affinity for the host:guest complex occurred. Adamantylacetic acid proved to be a very poor guest at neutral pH, and in this case the addition of NaOH resulted in a disappearance of all host and guest signals in the ^{1}H NMR spectrum. We also explored using tetramethylammonium bromide as a host for cavitand **1** in solution. The assignment of the (time-averaged) C_{4v} conformation of **1** in DMSO is shown Figure 6A. Upon addition of excess teatramethylammonium bromide a very small signal in the upfield region is observed, indicative of weak guest binding. Treatment of the sample with NaOH results in enhanced binding as a 1:1 host guest complex is now observed (Figure 6B vs C). The binding properties of tetraalkylammonium salts and other organics in related cavitands is well-known, so we decided to examine the role of base more closely.

2.2. The Role of Base. Why does the conformational stability and binding activity of the cavitand increase in the presence of base? The cavitand is held in the vase conformation by four water molecules that provide eight hydrogen bonds to the benzimidazole groups at the cavitand rim. Only four of the eight hydrogens from the water molecules are involved in hydrogen bonding; the remaining four are mere spectators. If NaOH (or, to a lesser extent, an organic amine base) is added, some of the hydrogens at the rim (either from the N−H or from H_2O) can be removed, increasing the electron density along the hydrogen-bonding network. Presumably, this could strengthen the weak forces holding the cavitand together. While a solvent mixture of THF:D_2O was incompatible with host−guest studies, the sharpness of the aromatic cavitand peaks in the ^{1}H NMR spectra

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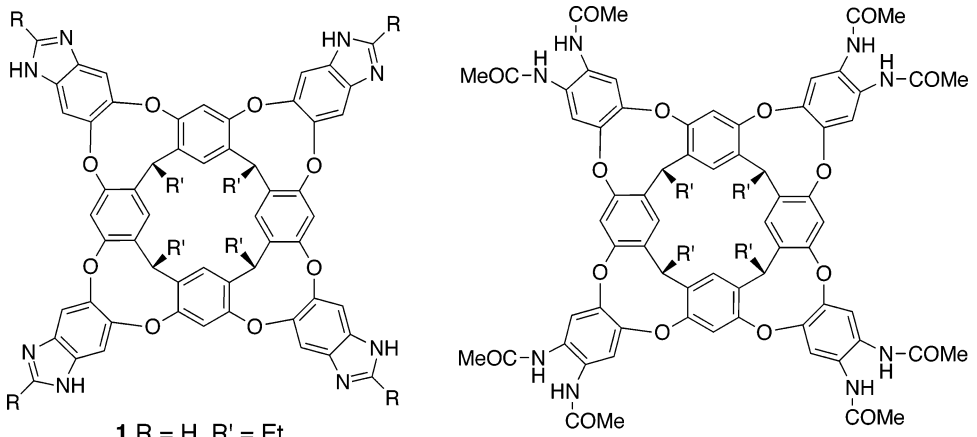

Figure 5. Benzimidazole (**1**, **4**−**8**) and octamide (**9**) cavitands studied as hosts in DPC and HPC micelles.

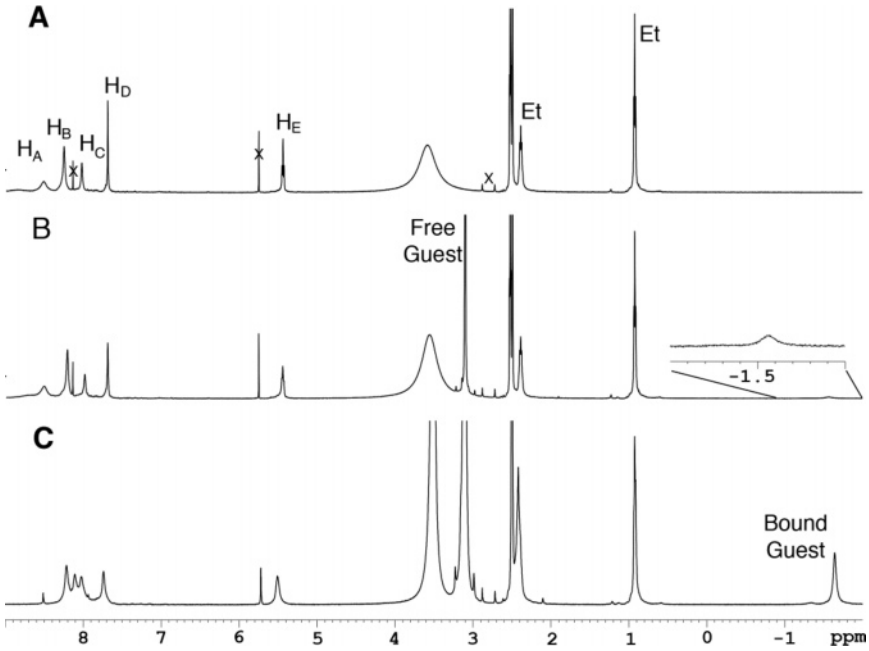

Figure 6. 600 MHz ^{1}H NMR of 19 mM cavitand **1** in 600 μL DMSO-d_6 (A), after addition of 65 mM tetramethylammonium bromide (B); subsequent addition of 20 μL of 3% NaOH results in 1:1 stoichiometric encapsulation (C). Trace solvents DMF and DCM indicated by X.

presented us with the opportunity to explore the role of pH more carefully. The downfield region of cavitand **1** shows sharp peaks for all unique protons (Figure 7A), the farthest downfield being the highest up on the cavitand wall, namely the C−H of the imidazole at 8.5 ppm (labeled H_A in Figure 1). The peak at 7.4 ppm corresponds to the aromatic proton H_D at the base of the cavitand. When HCl was titrated, cavitand peaks migrated downfield (Supporting Information), confirming an earlier account of the analogous C_{11} benzimidazole cavitand upon treatment of TFA in $CDCl_3$.[25]

When a solution of NaOH was titrated into a 1.4 mM solution of **1,** large upfield shifts occurred for the protons on the cavitand wall (Figure 7). Upon addition of 4 equiv of NaOH, H_A had shifted 0.6 ppm upfield. The remaining peaks of the cavitand wall also experienced significant changes, while the methine at the base of the resorcinarene ring remained relatively unchanged (see data for H_E in Figure 7B), indicating that the vase conformation remained intact. Protons H_A and H_B show the largest shift upon deprotonation in the H-bonding network, because they are sited in rings that are in direct conjugation with the benzimidazoles, whereas H_C and H_D reside in the resorcinarene and do not experience the electronic changes as strongly.

It is not completely clear from where the protons are removed in the hydrogen-bonded network; either deprotonation of one or more of the imidazole NHs or the removal of the spectator hydrogen on a bridging water molecule is plausible. In any case, the rapid exchange of these hydrogens renders the point moot. Modified Job's plot analysis was conducted[33] in THF:D_2O by titration of **1** with NaOH to discern the number of acidic protons

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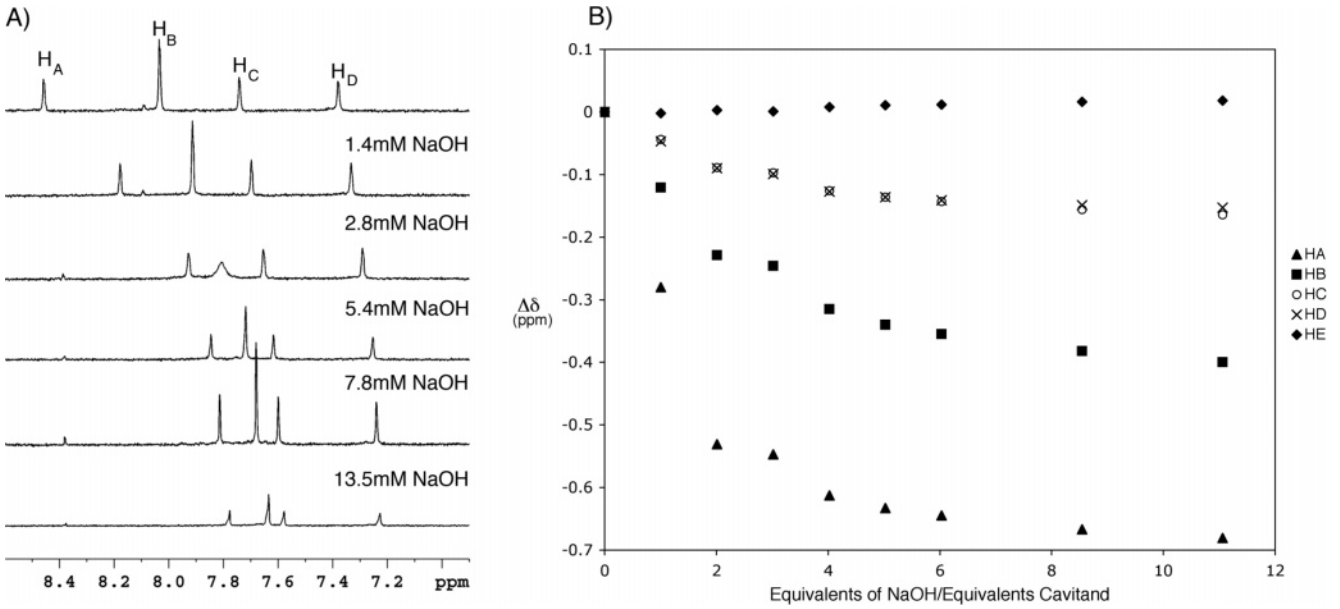

Figure 7. 600 MHz downfield ^{1}H NMR of 1.4 mM **1** (initial concentration) in 2:1 THF-d_8:D_2O with the addition of 0, 1, 2, 4, 6, and 11 equiv of NaOH (A) and graphical response in $\Delta\partial$ ($\partial_{final} - \partial_{initial}$) (B).

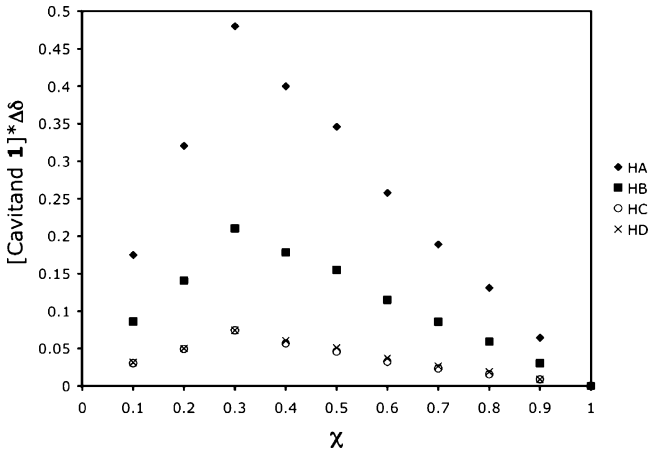

Figure 8. Modified Job's plot analysis of **1** with NaOH. α = 2 mM (constant) = $[cavitand]_0 + [base]_0$, $\chi = [cavitand]_0/([cavitand]_0 + [base]_0$; all measurements performed at 300 K using 600 MHz ^{1}H NMR, 2:1 THF-d_8:D_2O.

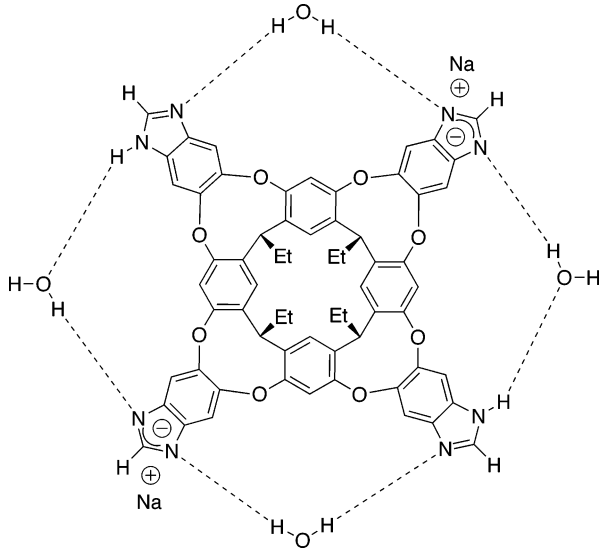

Figure 9. Hydrogen-bonding model of **1** after removal of two protons from the H-bonding network.

removed by added base (Figure 8). The intersection of lines revealed a maximum at [cavitand **1**] × $\Delta\delta$ = 0.48. This maximum occurs when χ = 0.3 (where $\chi = [cavitand]_0/([cavitand]_0 + [base]_0)$. To a first approximation this gives a 2.33:1 base:cavitand relationship. Both solubility issues at high base:cavitand ratios and acid−base equilibration are believed to result in this noninteger relationship. Nevertheless, this result in conjunction with dilution studies that show no change in $\Delta\delta$ as a function of concentration supports the hypothesis that deprotonation is responsible for the observed changes in chemical shift. We illustrate these effects with a model of the hydrogen-bonding seam that is supported by the experimental evidence (Figure 9).[26] The addition of base has a remarkable effect on the electronic environment of the capsule, resulting in buildup of negative charge, that in turn affects the binding ability of the host toward guests. This can be explained in one of two ways. With **1**, it is clear that a variety of conformations are adopted in response to environmental conditions (e.g., solvent, presence of guest, presence of micelles). Upon deprotonation the hydrogen-bonding network could be strengthened, resulting in a more kinetically stable conformation where the walls are more tightly held together and less likely to flex or "breathe." Deprotonation contracts the cavitand's time-averaged structure and increases its shape complementarity to suitable guests. Alternatively, the increase in electron density allows greater London dispersion forces to occur between the electron rich cavitand and the thin layer of positive charge displayed by the hydrocarbon guests. This latter explanation seems less likely to play as significant a role as an increase in the kinetic stability of the cavitand host would, yet at this time it cannot be discounted. It may even complement the effects of enhanced kinetic stability of guest binding as a result of changing the electronic nature of the hydrogen-bonding seam.

Conclusion and Outlook

In conclusion we report that deep, self-folding benzimidazole cavitands such as **1** are incorporated in aqueous phosphocholine

(PC) micelles and fold into the C_{4v} vase conformation, serving as small molecule hosts while residing in lipid micelles. As a micelle-bound host, **1** has the ability to sequester hydrophobic guests into its interior even though both host and guest are submersed in a formidable sea of competing alkyl side chains. The cavitands exhibit guest selectivity, which allowed us through the use of a hydrophobic anchor to localize both a fluorophore (**2**) and a dipeptide (**3**) within the micelle-bound receptor. Subsequent exploration of other cavitand substitution patterns reveals some flexibility and tolerance in both substitution at the feet and rim toward micelle localization. These variables should afford future opportunities in both the types of hosts and their respective guests that are amenable to migration into a variety of both synthetic and natural membranes. Additionally, the ability to incorporate aromatic groups at the cavitand rim should allow us to fluorescently label the host and perhaps further expand upon the types of suitable handles we can employ.

The transport of sensitive small molecules across biological membranes has been a long-standing goal of medicinal chemistry. Conceptually, several researchers have envisioned encapsulating drugs in larger chemical frameworks or capsules to effect targeted transport to a specific location.[34,35] These small molecule cavitand hosts are themselves guests within the hydrophobic interior of the micelle and are simple biomimetic receptors. The next steps of this research program will be to transport fluorophores and drug-like molecules into more complicated vesicular and lipid-bilayer systems.

Experimental Section

1. General Information. ^{1}H and DOSY[30] NMR spectra were recorded on a Bruker DRX-600 spectrometer with a 5 mm QNP probe. Proton chemical shifts are reported in parts per million (δ) with respect to tetramethylsilane (TMS, $\delta = 0$) and referenced internally with respect to the protio solvent impurity. The DOSY spectra were acquired using an LED pulse sequence with bipolar gradient pulses and two spoil gradients, as supplied with the Bruker software.[36] Sine-shaped pulsed gradients were incremented from 2.7 to 51.4 G cm^{-1} with an Acustar gradient system in 32 steps, with each step consisting of 256 scans. The raw data was processed using the MestreC program (Mestrelab Research, Santiago de Compostela). Deuterated NMR solvents were obtained from Cambridge Isotope Laboratories, Inc., Andover, MA, and used without further purification. Anhydrous solvents and reagents were obtained from Aldrich Chemical Co., St. Louis, MO, and were used as received. Cavitands **4**,[32] **6**,[37] **7**,[5] and **9**[6] were synthesized according to reported procedures. All micelle experiments were conducted by sonication of the indicated amounts of host, guest, and PC in D_2O for 10 min prior to NMR acquisition.

2. Synthesis of New Compounds. Procedure for the Synthesis of Cavitand 1. Ethyl-footed cavitand **1** was prepared following related reports for the synthesis of the C_{11}-footed cavitand.[24,25] Ethyl-footed octanitro cavitand[38] (300 mg, 0.24 mmol) was dissolved in DMF (12 mL) under N_2. $SnCl_2{\cdot}2H_2O$ (1.5 g, 6.6 mmol) was added followed by concentrated hydrochloric acid (6 mL). The reaction was heated to 105 °C for 16 h, cooled, and poured into iced water (75 mL). The slurry was centrifuged, and the supernatant was decanted. The solid was taken up in a minimal amount of methanol:CH_2Cl_2 and then concentrated to remove excess water and DMF. The solid was treated with 50 mL of dichloromethane, sonicated, filtered, and dried under vacuum to give **1** as a pale yellow powder (175 mg, 69%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 0.93 (t, $J = 7.2$ Hz, 12H); 2.39 (qn, $J = 7.2$ Hz, 8 H); 5.44 (t, $J = 7.8$ Hz, 4H); 7.69 (s, 4H); 8.02 (s, 4H); 8.25 (s, 8H); 8.51 (br s, 4H), ESIHRMS *m*/*z*: calcd for $C_{64}H_{49}N_8O_8$ (M + H) 1057.3668; found 1057.3658.

Representative Procedure for the Synthesis of Cavitands 5 and 8. C_{11} Ester Cavitand 5. To an oven-dried, 25 mL round-bottomed flask equipped with a magnetic stirrer and water-cooled condenser were added $C_{11}H_{23}$-footed octaamine cavitand, HCl salt[24] (100 mg, 0.060 mmol), ethyl 3-ethoxy-3-iminopropanoate hydrochloride[39] (0.36 mmol, 70 mg), and anhydrous ethanol (10 mL). The mixture was placed under argon and heated to reflux for 14 h. The solvent was removed by rotary evaporation, and the resulting solid was suspended in dry MeOH (25 mL). The suspension was filtered and washed with dry MeOH (3 × 20 mL) and then dried under high vacuum to yield cavitand **1a** (60 mg, 57%) as an off-white solid. ^{1}H NMR (600 MHz, $CDCl_3/D_2O$): δ 0.90 (t, $J = 6.6$ Hz, 12H); 1.2 − 1.4 (m, 16H); 1.31 (t, $J = 6.6$ Hz, 12H); 1.43 (qn, $J = 6.6$ Hz, 8H); 2.25 (q, $J = 7.8$ Hz, 8H); 4.26 (q, $J = 7.2$ Hz, 8H); 4.30 (s, 8H); 5.73 (t, $J = 7.8$ Hz, 4H); 7.25 (s, 4H); 7.44 (s, 4H); 8.01 (s, 8H); ESIHRMS *m*/*z*: calcd for $C_{116}H_{145}N_8O_{16}$ (M + H^+) 1906.0773; found 1906.0739.

C_{11} *p*-Nitrobenzylcavitand 8. Cavitand **8** was synthesized on a 0.06 mmol scale according to the procedure used for **5**, employing ethyl 2-(4-nitrophenyl)acetimidate hydrochloride **S1** (Supporting Information), giving an off-white solid (109 mg, 86%). ^{1}H NMR (600 MHz, THF-d_8/D_2O 4:1): δ 0.84 (t, $J = 7.2$ Hz, 12H); 1.2 − 1.4 (m, 16H); 1.41 (qn, $J = 7.2$ Hz, 8H); 2.23 (q, $J = 7.2$ Hz, 8H); 4.11 (s, 8H); 5.73 (t, $J = 7.2$ Hz, 4H); 7.29 (s, 4H); 7.48 (d, $J = 7.8$ Hz, 8H); 7.71 (s, 4H); 7.87 (s, 8H); 8.05 (d, $J = 7.8$ Hz, 8H); ESIHRMS *m*/z: calcd for $C_{128}H_{141}N_{12}O_{16}$ (M + H^+) 2102.0582; found 2102.0565.

Acknowledgment. We are grateful to the Skaggs Institute and the National Institutes of Health (GM 50174) for financial support. M.P.S. and R.J.H. are Skaggs Postdoctoral fellows. We wish to thank Dr. Enrique Mann for compound **3**.

Supporting Information Available: ^{1}H NMR spectra for all new cavitands. All spectra for encapsulation results that were discussed but not illustrated in the text. DOSY results for **1** with adamantylamine in DPC micelles showing one assembly along with DCl titration data of **1** in THF:D_2O. This material is available free of charge via the Internet at http://pubs.acs.org.

JA0723378

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