Solvent-Tunable Binding of Hydrophilic and Hydrophobic Guests by Amphiphilic Molecular Baskets

Yan Zhao* and Eui-Hyun Ryu

Department of Chemistry, Iowa State University, Ames, Iowa 50011-3111

zhaoy@iastate.edu

Received June 3, 2005

Responsive amphiphilic molecular baskets were obtained by attaching four facially amphiphilic cholate groups to a tetraaminocalixarene scaffold. Their binding properties can be switched by solvent changes. In nonpolar solvents, the molecules utilize the hydrophilic faces of the cholates to bind hydrophilic molecules such as glucose derivatives. In polar solvents, the molecules employ the hydrophobic faces of the cholates to bind hydrophobic guests. A water-soluble basket can bind polycyclic aromatic hydrocarbons including anthracene, pyrene, and perylene. The binding free energy ($\Delta G$) ranges from 5 to 8 kcal/mol and is directly proportional to the surface area of the aromatic hosts. Binding of both hydrophilic and hydrophobic guests is driven by solvophobic interactions.

Introduction

Rigid supramolecular hosts with minimal conformational flexibility have traditionally been favored by chemists because of their perceived benefits in binding affinities. Most biomolecules, on the other hand, can respond to environmental stimuli by changing their conformations. As suggested by the induced-fit model, the substrate of an enzyme can cause necessary conformational change of the active site (to bring the catalytic groups into proper alignment), but nonsubstrates cannot. Allosteric proteins change their conformations, and in turn their binding or catalytic functions, upon binding with effectors or inhibitors. Conformational responses may result from changes of general environmental properties as well. Proteins may denature, or undergo drastic unfolding of the peptide chains, when pH, ionic strength, temperature, or other environmental properties are altered.

In addition, solvent polarity also has profound influence on the conformations of biomolecules, as hydrophobic interaction is a major driving force for the folding of polypeptide chains. One class of biomolecules that adopts dramatically different conformations with the change of environmental polarity is $\alpha$-helical antimicrobial peptides. These peptides tend to assume random conformations in water but change to amphipathic $\alpha$-helical structures when they come in contact with bacterial membranes.
much less polar environment. In fact, polarity-induced conformational change is important to many biological processes including the translocation of proteins across membranes.5

Design of synthetic molecules with controllable conformations has received much attention in recent years and is highlighted in foldamer research.6 Foldamers are synthetic oligomers with biomolecule-like, ordered conformations. Because their conformational flexibility allows their folding and unfolding (and in turn their properties) to be controlled by physical or chemical stimuli, they are very attractive as responsive materials. However, using weak, noncovalent forces to stabilize desired conformations in foldamers (and in synthetic molecules in general) remains as difficult challenges.6

We previously reported an amphiphilic molecular basket 1a constructed from cholic acid.7 Cholic acid8 is an example of facial amphiphiles.9 The cone-shaped aminocalix[4]arene is used as a scaffold to promote intramolecular aggregation among the cholates. In polar solvents, the hydrophilic (α) faces of the cholates point outward and the molecule resembles a unimolecular micelle. In nonpolar solvents, the hydrophobic (β) faces turn outward, giving a reversed-micelle-like conformation.10,11 We hypothesize that the internal cavity of 1a is sufficiently large to bind guest molecules and that its conformational flexibility will allow it to bind either hydrophilic or hydrophobic guests in a solvent-dependent fashion. In this paper, we report the dual binding properties of 1 in different solvents. We also find that a water-soluble version of 1 indeed acts as a unimolecular micelle to solubilize hydrophobic molecules in aqueous solutions.

Results and Discussion

Binding Properties of the Reversed-Micelle-like Conformer in Nonpolar Solvents. Similar to surfactant reversed micelles,12 the reversed-micelle-like conformer of 1a requires a small amount of a polar solvent for stability. A typical solvent mixture is carbon tetrachloride/methanol (90/10). Carbon tetrachloride is a better solvent than chloroform for the reversed-micelle-like conformer, which has a nonpolar exterior. In the reversed-micelle-like conformer, all the hydroxyl groups turn inward to create a binding pocket, which should be mostly filled with the polar solvent. We expect that 1a should bind a hydrophilic guest of appropriate size. Because cholate groups are totally aliphatic, we choose hydrophilic guests with an aromatic substituent, hoping to monitor the binding event by complexation-induced 1H NMR chemical shifts. Also, during NMR titrations, both the host and the guest need to be sufficiently soluble in the solvents; a totally hydrophilic guest may not have good enough solubility for the titration experiments.

Indeed, when 1a is mixed with phenyl β-D-glucopyranoside in carbon tetrachloride/methanol (90/10), the proton signals on the phenyl of the guest shift upfield.13 The binding stoichiometry was studied by the Job plots (Figure 1). Even though a few data points (at 0.1 and 0.9) are missing because of signal overlap, the maximum at 0.5 molar fraction clearly indicates a 1:1 binding stoichiometry. The changes in chemical shifts are most significant for the para protons, followed by the meta and the ortho protons. It seems that the guest resides in the binding site with its phenyl pointing down to the calixarene, possibly as a result of favorable π−π interaction between the phenyl and the calixarene and solvophobic interaction between the sugar unit and the cholate groups.


Solvent-Tunable Binding by Amphiphilic Molecular Baskets

TABLE 1. Association Constants ($K_a$) between 1 and Several Hydrophilic Guests at 20 °C

<table>
<thead>
<tr>
<th>entry</th>
<th>guest</th>
<th>host</th>
<th>solvent mixture</th>
<th>$K_a$ (M$^{-1}$)</th>
<th>$-\Delta G$ (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>phenyl $\beta$-D-glucopyranoside</td>
<td>1a</td>
<td>CCl$_4$/CD$_3$OD = 95/5</td>
<td>330 ± 180$^a$</td>
<td>3.4</td>
</tr>
<tr>
<td>2</td>
<td>phenyl $\beta$-D-glucopyranoside</td>
<td>1a</td>
<td>CCl$_4$/CD$_3$OD = 90/10</td>
<td>290 ± 60</td>
<td>3.3</td>
</tr>
<tr>
<td>3</td>
<td>phenyl $\beta$-D-glucopyranoside</td>
<td>1a</td>
<td>CCl$_4$/CD$_3$OD = 85/15</td>
<td>70 ± 10</td>
<td>2.5</td>
</tr>
<tr>
<td>4</td>
<td>phenyl $\beta$-D-glucopyranoside</td>
<td>1a</td>
<td>CCl$_4$/CD$_3$OD = 80/20</td>
<td>340 ± 60</td>
<td>3.4</td>
</tr>
<tr>
<td>5</td>
<td>phenyl $\beta$-D-glucopyranoside</td>
<td>1b</td>
<td>CCl$_4$/CD$_3$OD = 95/5</td>
<td>340 ± 60</td>
<td>3.4</td>
</tr>
<tr>
<td>6</td>
<td>phenyl $\beta$-D-glucopyranoside</td>
<td>1b</td>
<td>CCl$_4$/DMSO = 90/10</td>
<td>140 ± 30</td>
<td>2.9</td>
</tr>
</tbody>
</table>

$^a$ The error is larger than usual because of low solubility of 1a in the solvent mixture. $^b$ Nearly no change in chemical shifts occurred during NMR titration, suggesting negligible binding.

Aggregation of the host is negligible under the binding conditions because the $^1$H NMR spectrum of 1a or 1b is essentially the same when its concentration is varied from 0.2 to 15 mM. The binding constants are obtained by nonlinear least-squares fitting and are summarized in Table 1. According to the binding data, host–guest interaction between 1a and phenyl $\beta$-D-glucopyranoside becomes weaker as the percentage of methanol increases in the solvent mixture: $-\Delta G = 3.4$, 3.3, and 2.5 kcal/mol in 5, 10, and 15% methanol, respectively (entries 1–3 of Table 1). In 20% methanol, no binding can be detected by $^1$H NMR titration (entry 4). Binding properties of 1a and the more soluble 1b are quite similar in the reversed-micelle-like conformation ($K_a$ = 330 M$^{-1}$ (entry 1) with 1a and 340 M$^{-1}$ with 1b (entry 5) for the binding of phenyl $\beta$-D-glucopyranoside in 5% methanol.

These data rule out the $\pi$–$\pi$ interaction between the calixarene and the phenyl group of the guest as the major driving force for the binding. Instead, solvophobic interaction plays decisive roles. This is because $\pi$–$\pi$ interaction is expected to decrease in a solvent with higher polarizability. Thus, a $\pi$–$\pi$-based binding should increase in strength when methanol (a less polarizable solvent) increases and carbon tetrachloride (a more polarizable solvent) decreases in the solvent mixture. We also performed a similar titration of phenol in CCl$_4$/CD$_3$OD (90/10) and found no shifts in the proton signals of either the guest or the host. This result again suggests that the contribution of $\pi$–$\pi$ interaction to the overall binding energy is minor at most.

Interestingly, the initial 5% increase in methanol reduces the binding affinity only slightly (~0.1 kcal/mol), but a further increase by the same magnitude (i.e., from 10 to 15%) causes a much larger reduction (~0.8 kcal/mol). Such a solvent response is different from what have been observed in conventional solvophobically driven associations in rigid supramolecular hosts. For example, Schneider and co-workers found that, in several solvophobically driven host–guest complexations, the binding free energies correlate linearly with the solvophobicity parameters of the solvents. Because solvophobicity parameters of binary mixtures are almost linearly related to the volume percentages, binding energies ($-\Delta G$) found to vary linearly as a function of solvent volume.

host. Strong binding, however, requires more than a
if one assumes that a more stable conformer is a better
We then realized that weak binding is only unexpected
DMSO (90/10) and is almost undetectable by NMR
ranoside is extremely weak in carbon tetrachloride/
 solvent mixture for reversed-micelle-like conformer.
protons also happens with
ortho to the amido group show distinct changes according
to solvent composition, as a single peak at an intermediate
ratio (90% DMSO in this case) but as two peaks above
or below this ratio. Such nonequivalence of the aromatic
protons has also been attributed to the formation of ordered (micelle- or reversed-
micelle-like) conformations.7 Unlike 1a, however, the
reversed-micelle-like conformer of 1b gives rather sharp
proton signals, especially in solvents with less than 20%
DMSO. Also, the splitting between the two peaks for 1b
in carbon tetrachloride/DMSO is consistently larger than
those for 1a in carbon tetrachloride/methanol. Previously,
the splitting between the two peaks was found to be a
good indicator for the stability of a particular (micelle-
like or reversed-micelle-like) conformer.7 Therefore, DMSO
in carbon tetrachloride seems to be an especially good
solvent mixture for reversed-micelle-like conformer.

However, binding between 1b and phenyl \( \beta \)-D-glucopy-
ranoside is extremely weak in carbon tetrachloride/
DMSO (90/10) and is almost undetectable by NMR
titration. This result was quite a surprise to us initially.
We then realized that weak binding is only unexpected
if one assumes that a more stable conformer is a better
host. Strong binding, however, requires more than a
suitable host structure. This is because the polar solvents
entrapped by the host need to be displaced by the guest
during binding. It is more difficult to displace strongly
solvating solvent molecules than weakly solvating ones.
Therefore, the same interaction that stabilizes the re-
versed-micelle-like conformer, that is, preferential sol-
vation of the hydrophilic \( \alpha \) faces of cholates by DMSO or
methanol, actually works against the host in the guest
binding. Apparently, selection of solvents in solvophobi-
cally driven molecular recognition is even more important
in conformationally mobile systems than in rigid ones.
The amphiphilic baskets described in this paper in fact
only has limited conformational mobility, which mostly
comes from the few bonds between the fused steroidal
rings and the calixarene. Even for such a molecule, a
small change in solvent composition has a very large
effect on its conformational and binding properties.

Host 1a also can bind the \( \alpha \)-anomer of phenyl glucopy-
ranoside, albeit with a reduced association constant of
140 M\(^{-1}\) (entry 7 of Table 1) in carbon tetrachloride/
methanol (90/10). This moderate selectivity is probably
due to the shape of the binding pocket, which prefers the
straighter \( \beta \)-anomer because of the upright arrangement
of the cholate units.

**Binding Properties of the Micellelike Conformer**

**in Polar Solvents.** In a polar environment, 1a is
expected to bind hydrophobic guests by its micellelike
conformer. We use a mixture of deuterated methanol/
water (80/20) as the solvent, in which 1a has solubility
in the millimolar range. Addition of pyrene causes upfield
changes of the methyl protons on the hydrophobic \( \beta \) face
of the cholates. Hence, the guest is bound through
favorable hydrophobic contact with the host. Accurate
determination of the association constant is difficult
because neither the host nor the guest has good solubility
in the solvent. We then performed \( ^{1} \)H NMR titration with
1-aminopyrene, which is more soluble than pyrene in
aqueous methanol. The binding constant was about 10
M\(^{-1}\) (entry 1 of Table 2).
Such a low binding affinity (\(\Delta G = 1.3 \text{ kcal/mol}\)) is entirely unsatisfactory. Weak binding may have resulted from tight intramolecular aggregation among the cholate units of 1a. This is quite possible because the cholate groups are very close from one another. Intramolecular aggregation, nevertheless, does not seem to cause any problems in the reversed-micelle-like conformer, as the hydrophilic guests are bound with reasonable strength. This contrast is likely due to the curvature of the cholate backbone, which is bent toward the hydrophilic \(\alpha\) face and is expected to prevent tight aggregation of the \(\alpha\) faces in the reversed-micelle-like conformer.

When the solvent is changed from methanol/water (80/20) to pure methanol, the methyl proton signals on the cholates no longer experience any shifts with the addition of 1-aminopyrene, suggesting negligible binding (entry 2 of Table 2). Hence, solvophobic interaction is also the main driving force in this conformer. Encouraged by this fact, we decided to prepare a water-soluble version of the aromatic compounds by basket 2 in hand, we performed solubilization of anthracene and perylene, in addition to pyrene. These polycyclic aromatic hydrocarbons have extremely low solubility in water; thus, their binding can be monitored by enhanced solubilization. The experiment is similar to the dye-solubilization test used in the characterization of the critical micelle concentration (CMC) of surfactants. In these experiments, a hydrophobic dye, which has nearly zero solubility in water below the CMC, is solubilized by surfactant micelles above the CMC. When the concentration of the solubilized dye is plotted against the concentration of the surfactant, a kinked curve is therefore obtained, with the inflection point corresponding to the CMC. In fact, pyrene has been frequently used to determine the CMC of surfactants because of its low water solubility and fluorescence (which allows for its sensitive detection). Solubilization of the aromatic compounds by basket 2 does not follow the pattern of typical surfactants. Instead of a kinked curve, the concentration of the solubilized polycyclic aromatics is linearly related to the concentration of 2 (Figure 4). The absence of concentration dependence in the solubilizing power suggests that aggregation is not necessary for 2 to solubilize hydrophobic guests. In other words, 2 does not have a CMC and is truly qualified as a unimolecular micelle. Our experiments indicate that basket 2 is most efficient at solubilizing pyrene, followed by anthracene and perylene. More efficient solubilization, nonetheless, does not mean

```
<table>
<thead>
<tr>
<th>entry</th>
<th>guest</th>
<th>host solvent mixture</th>
<th>(K_a ) (M(^{-1}))</th>
<th>(\Delta G) (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-aminopyrene (^a)</td>
<td>1a CD, OD, DOD, 80/20</td>
<td>3.0 ± 5.3</td>
<td>1.3</td>
</tr>
<tr>
<td>2</td>
<td>1-aminopyrene (^b)</td>
<td>1a CD, OD</td>
<td>7.8 x 10^3</td>
<td>5.3</td>
</tr>
<tr>
<td>3</td>
<td>anthracene (^b)</td>
<td>2 water</td>
<td>5.0 x 10^4</td>
<td>6.4</td>
</tr>
<tr>
<td>4</td>
<td>pyrene (^b)</td>
<td>2 water</td>
<td>6.8 x 10^5</td>
<td>8.0</td>
</tr>
</tbody>
</table>

\(^a\) Determined by \(^1\)H NMR titration. \(^b\) Determined by a dye solubilization method with linear fitting of the experimental data (see text).
```

See the Supporting Information for experimental details.
FIGURE 4. Solubilization of anthracene (●), pyrene (●), and perylene (■) in water by 2. Theoretical lines are line fitting of the experimental data.

stronger binding, because the amount of the solubilized guest also depends on the solubility of the guest by itself. For 1:1 complexations, the binding constant can be calculated from these dye-solubilization experiments according to the following equation:\(^{24}\)

\[
s = s_0 + \left(\frac{K_a s_0}{1 + K_a s_0}\right) \text{[host]}
\]

in which \(s_0\) is the solubility of the guest in the absence of any host, \(s\) is the solubility of the guest at a given host concentration [host], and \(K_a\) is the binding constant. Because \(s_0\) has an extremely large effect on the calculation of \(K_a\) but cannot be determined accurately as the intercept, we used the literature values instead (\(s_0 = 0.45, 0.67,\) and \(0.0016 \mu\text{M}\) for anthracene, pyrene, and perylene, respectively).\(^{25}\) The binding constants (\(K_a\)) obtained for three aromatic compounds are extremely large: 7.8 \(\times\) \(10^3\), 5.0 \(\times\) \(10^4\), and 6.8 \(\times\) \(10^5\) \text{M}^{-1} for anthracene, pyrene, and perylene (entries 3, 4, and 5 of Table 2). Strong binding is probably a result of much higher solvophobic driving force in water as compared to aqueous methanol. It may also be due to poor intramolecular aggregation among the cholates, which are now positively charged. These binding constants correspond to \(-\Delta G\) of 5.3, 6.4, and 8.0 kcal/mol, respectively. Therefore, the binding affinity increases linearly with the size of the aromatic guests. Such a trend is consistent with the solvophobic binding mechanism because the strength of solvophobic interaction is directly proportional to the area of solvophobic surface removed from solvent contact during complexation.\(^3\)

Conclusions

In summary, we have shown that judicious introduction of conformational flexibility converts an otherwise simple host into a novel environmentally responsive molecule. The binding properties respond to solvent changes as the host undergoes conformational changes. The reversed-micelle-like conformer prefers hydrophilic guests in solvent mixtures consisting of mostly a nonpolar solvent with a small amount of a polar solvent. Preferential solvation of the hydrophilic faces of the cholate groups by the polar solvent is important to the stability of the reversed-micelle-like conformer. Too strong solvation, however, leads to weak binding because the polar solvent molecules entrapped by the host cannot be easily displaced by the guest. The micelle-like conformer binds hydrophobic guests in polar solvents. Binding is weak for 1-aminopyrene (\(-\Delta G < 1.5\) kcal/mol) in a methanol/water (80/20) mixture. In pure water, however, very strong binding (\(-\Delta G = 5–8\) kcal/mol) is observed for anthracene, pyrene, and perylene.

Experimental Section

General Method. See the Supporting Information.

Compound 1a. See the Supporting Information.

Compound 1b. See the Supporting Information.

Compound 4. See the Supporting Information.

Compound 5. Compound 4 (2.194 g, 2.21 mmol) was dissolved in anhydrous THF (20 mL). Lithium aluminum hydride (1.0 M in ether, 11.2 mL, 11.2 mmol) was added via a syringe. The mixture was stirred at room temperature under \(N_2\) for 1.5 h. The reaction was quenched by slow addition of EtOAc (5 mL) followed by 6 N HCl (20 mL) and brine (20 mL). The aqueous layer was extracted with ether (40 mL). The combined organic phase was dried (MgSO\(_4\)), concentrated in vacuo, and pumped dry at 70 °C. The alcohol intermediate (1.765 g) was combined with \(\text{MgO} (\text{CH}_2\text{CH}_2\text{O})_2\)-CH\(_2\) (5.400 g, 22.3 mmol) and Bu\(_4\)NI (0.077 g, 0.21 mmol) in anhydrous THF (50 mL). NaH (60%, 0.912 g, 22.8 mmol) was added in one portion. The mixture was heated to reflux under \(N_2\) for 2.5 h. Another batch of the mesylate (1.07 g, 2.42 mmol) and NaH (0.205 g, 5.13 mmol) was added. After another 4.5 h, the reaction was cooled to room temperature and was quenched by careful addition of water (10 mL). The mixture was extracted with ether (40 mL). The combined organic phase was dried (MgSO\(_4\)) and concentrated in vacuo. The residual oil was dissolved in CH\(_2\)Cl\(_2\)/H\(_2\)O (20 mL/20 mL) and was cooled to 0 °C. Nitric acid (98%, 10 mL) was added slowly. The solution was stirred at room temperature for 3 h and was diluted with chloroform (30 mL) and water (60 mL). The organic phase was evaporated in vacuo. The residue was purified by column chromatography over silica gel using chloroform/acetone (1/1) as the eluents to give an orange oil.

\(^1\)H NMR (400 MHz, CDCl\(_3\), δ): 7.42 (s, 8H), 4.57 (d, 4H, \(J = 14.0\) Hz), 4.16 (br, 8H), 3.72 (br, 8H), 3.55–3.40 (m, 48H), 3.30 (d, 4H, \(J = 14.0\) Hz), 3.24 (s, 12H). \(^13\)C NMR (100 MHz, CDCl\(_3\), δ): 162.0, 142.9, 135.9, 124.0, 77.7, 74.6, 72.0, 72.7, 70.6, 70.5, 59.1, 31.2. ESI-MS (m/z): [M + K + H\(^+\)]\(^+\) calcd for C\(_{64}\)H\(_{100}\)N\(_4\)K\(_4\)O\(_{20}\), 702.5; found, 702.0.

Compound 6. A solution of compound 5 (412 mg, 0.302 mmol) and SnCl\(_2\)-2H\(_2\)O (857 mg, 2.80 mmol) in MeOH (15 mL) was heated to reflux for 24 h. Na\(_2\)O (2 N, 30 mL) was added. The aqueous layer was extracted with chloroform (3 × 40 mL). The combined organic phase was washed with brine (20 mL), dried (MgSO\(_4\)), filtered, and concentrated in vacuo to give a brown oil (337 mg, 90% yield). \(^1\)H NMR (400 MHz, CDCl\(_3\), δ): 5.97 (s, 8H), 4.23 (d, 4H, \(J = 13.2\) Hz), 3.90 (t, 8H, \(J = 5.6\) Hz), 3.75 (t, 8H, \(J = 5.6\) Hz), 3.65–3.46 (m, 48H), 3.30 (s, 12H), 2.82 (d, 4H, \(J = 13.2\) Hz). \(^13\)C NMR (100 MHz, CDCl\(_3\), δ): 149.7, 140.8, 135.6, 115.8, 73.0, 72.1, 70.8, 70.7, 70.5, 59.2, 31.3. ESI-MS (m/z): [M + H\(^+\)]\(^+\) calcd for C\(_{64}\)H\(_{100}\)N\(_4\)K\(_4\)O\(_{20}\), 1245.5; found, 1246.0; [M + 4K\(^+\)]\(^+\) calcd for C\(_{64}\)H\(_{100}\)N\(_4\)K\(_4\)O\(_{20}\), 350.3; found, 350.0.

---

(23) We were not able to obtain Job plots for complexation between 1a and 1-aminopyrene because of the low binding affinity. A 1:1 binding stoichiometry was assumed for all three aromatic guests because 1a and phenyl-\(\beta\)-\(\beta\)-glucopyranoside (which is similar to anthracene in size and smaller than pyrene and perylene) formed a 1:1 complex.


Compound 7. See the Supporting Information.

Compound 2. Compound 7 (110.3 mg, 0.254 mmol), compound 6 (63.3 mg, 0.0508 mmol), and O-benzotriazol-1-yl-N,N,N',N'-tetramethyleuronium hexafluorophosphate (HBTU, 97.6 mg, 0.257 mmol) were dissolved in anhydrous THF (3 mL). Diisopropylethylamine (91.6 mg, 0.709 mmol) was added. The mixture was heated to reflux under N₂ for 24 h. Solvent was evaporated in vacuo. The residue was purified by column chromatography over silica gel and preparative TLC using chloroform/methanol (15/1) as the eluents to afford a brown glass. The tetraazide intermediate and triphenylphosphine (41.0 mg, 0.156 mmol) was dissolved in THF/water (80/20, 2 mL). Another batch of triphenylphosphine (39.5 mg) was added. The reaction was continued for another 6 h. Solvent was removed in vacuo. The residue was purified by preparative TLC using chloroform/methanol/ammonium hydroxide (5/3/1) as the developing solvents to afford a light brown glass (24.3 mg, 19%).

Job Plot. Stock solutions (1.43 mM) of 1a and phenyl-β-D-glucopyranoside in carbon tetrachloride/deuterated methanol (90/10 = v/v) were prepared. In 11 separate NMR tubes, portions of the two solutions were added such that their ratios changed from 0 to 1 while maintaining a total volume of 0.6 mL. 1H NMR spectrum was taken for each sample and the chemical shifts of phenyl protons of guest were monitored. Maximum at 0.5 molar fraction indicated a 1:1 binding stoichiometry.

Acknowledgment is made to the donors of Petroleum Research Fund, administered by the American Chemical Society, and to Iowa State University for support of this research.

Supporting Information Available: The general method of the experiments, synthetic procedures (for 1a, 1b, 4, and 7), and NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.