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Synthesis and Recognition Properties of Enantiomerically Pure Acyclic Cucurbit[*n*]uril-Type Molecular Containers

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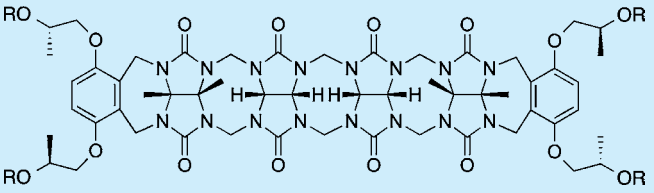
Supporting Information

ABSTRACT: Enantiomerically pure acyclic cucurbit[*n*]uril containers **1** and **2** were synthesized by the condensation of enantiomerically pure aromatic sidewalls **3b** and **4b** with glycoluril tetramer **5**. Containers **1** and **2** are C_2-symmetric, feature four arms of the same handedness, and bind to a variety of guests (**6**–**15**) in aqueous solution including aliphatic and aromatic ammonium ions, amino acids, dyes, and viologens. The binding constants of hosts $\mathbf{1}_{Ac}$ and $\mathbf{1}_{OH}$ toward selected chiral ammonium ions were measured by ^{1}H NMR and UV/vis spectroscopy.



Cucurbit[*n*]urils (CB[*n*], Figure 1) are a family[1] of highly symmetric (D_{nh}) molecular container compounds that

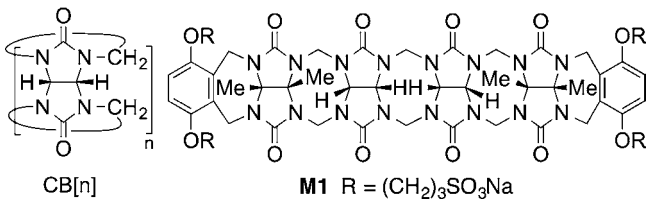


Figure 1. Cucurbit[*n*]uril and acyclic CB[*n*]-type containers.

feature a hydrodrophobic cavity that is guarded by two symmetry equivalent ureidyl carbonyl portals of highly negative electrostatic potential.[2] CB[*n*] compounds exhibit remarkable recognition properties toward hydrophobic cations (e.g., alkyl ammonium ions) in water with K_a values readily exceeding 10^9 M^{-1} and also exhibit high levels of selectivity toward structurally similar guests.[3] CB[*n*] complexes are chemically, electrochemically, and photochemically responsive and have been used therefore as the basis of advanced supramolecular systems including molecular machines, supramolecular materials, chemical sensors, drug delivery, gas purification, and (affinity) separations materials.[4] However, because unfunctionalized CB[*n*] compounds are achiral they are incapable of performing chiral recognition of guest compounds on their own.[5] This is unfortunate, because the high levels of affinity and selectivity exhibited by CB[*n*] compounds would be expected to translate into high levels of enantioselectivity which could be used to create enantioselective catalysts, sensors, and separations materials. This current limitation of CB[*n*] synthetic and supramolecular chemistry lead us to ponder how CB[*n*]-type receptors could be augmented to create enantioselective analogues.

Beyond unfunctionalized macrocyclic CB[*n*], researchers in the field have been synthesizing a variety of CB[*n*]-type receptors including CB[*n*] derivatives,[6] hemicucurbit[*n*]urils,[7] bambus[*n*]urils,[8] biotin[*n*]urils,[9] nor-seco-CB[*n*],[10] and acyclic CB[*n*].[11] Macrocyclic CB[*n*] derivatives are poorly suited for chiral recognition since any substituents are by necessity remote from the binding site. As anion binders, enantiomerically pure hemicucurbit[*n*]urils, bambus[*n*]urils, and biotin[*n*]urils show potential for the recognition of chiral organic acids. Specifically, enantiomerically pure cyclohexylhemicucurbit[6]uril has already been shown to bind more strongly to (*R*)-methoxyphenyl acetic acid (27 M^{-1} versus 20 M^{-1} for *S*) in $CDCl_3$.[7b] Previously, we have shown that (±)-bis-*ns*-CB[6] forms complexes with amino acids in water with up to 7:1 diastereoselectivity and affinity up to 10^5 M^{-1}.[10b] In recent years, we have been investigating the preparation of acyclic CB[*n*] (e.g., **M1** and derivatives, Figure 1), their molecular recognition properties in water, and their use as solubilizing agents for insoluble drugs and as agents to reverse neuromuscular block in vivo.[11c,d,g] Container **M1** and its derivatives consist of a central glycoluril tetramer to impart a C-shape, aromatic sidewalls to allow it to engage in π–π interactions with guests, and sulfonate-terminated arms to enhance aqueous solubility. In this paper, we explore the synthesis and molecular recognition properties of enantiomerically pure acyclic CB[*n*] containers **1** and **2**.

For the preparation of enantiomerically pure acyclic CB[*n*]-type containers, we decided to utilize aromatic sidewalls containing enantiomerically pure arms. Scheme 1 shows the synthesis of **3b** and **4b**. Alkylation of hydroquinone or 1,4-dihydroxynaphthalene with enantiomerically pure epichlorohydrin yields **3a** and **4a** in moderate yields, respectively. Subsequently, reduction of **3a** and **4a** with $LiAlH_4$ delivers sidewalls **3b** and **4b** in high yield.

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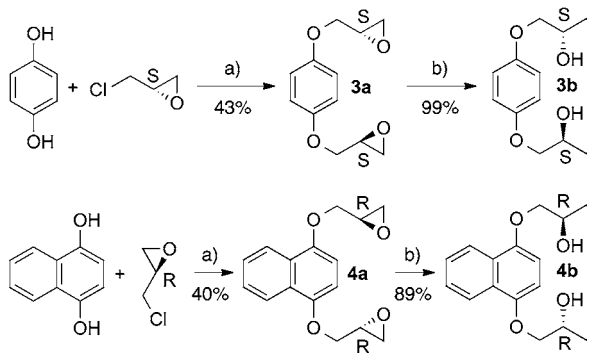
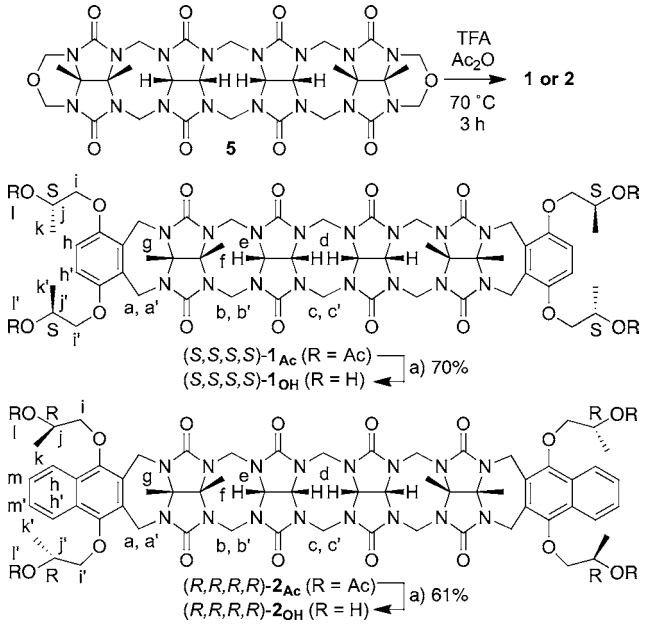
Scheme 1. Synthesis of Sidewalls 3 and 4[a]



[a]Conditions: (a) K_2CO_3, CH_3CN, reflux, 48 h; (b) $LiAlH_4$, THF, 1 h, 0–25 °C.

Next, we reacted enantiomerically pure sidewalls **3b** and **4b** with glycoluril tetramer **5** by double-electrophilic aromatic substitution reactions in TFA/Ac_2O as solvent to deliver enantiomerically pure tetraacetate acyclic CB[*n*]-type containers (*S*,*S*,*S*,*S*)-$\mathbf{1}_{Ac}$ and (*R*,*R*,*R*,*R*)-$\mathbf{2}_{Ac}$ in high yields (Scheme 2).

Scheme 2. Synthesis of Enantiomerically Pure Acyclic CB[*n*] Containers 1 and 2[a]



[a]Conditions: (a) 2 M LiOH, MeOH, 50 °C (70% for $\mathbf{1}_{OH}$, 61% for $\mathbf{2}_{OH}$).

Containers (*S*,*S*,*S*,*S*)-$\mathbf{1}_{Ac}$ and (*R*,*R*,*R*,*R*)-$\mathbf{2}_{Ac}$ could be hydrolyzed to the corresponding tetra-alcohols (*S*,*S*,*S*,*S*)-$\mathbf{1}_{OH}$ and (*R*,*R*,*R*,*R*)-$\mathbf{2}_{OH}$ by treatment with 2 M LiOH in MeOH at 50 °C in good yields. The structures of compounds **1** and **2** were fully characterized by FTIR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopy (Supporting Information). Compounds (*S*,*S*,*S*,*S*)-**1** and (*R*,*R*,*R*,*R*)-**2** do not possess mirror planes or inversion centers and are chiral and C_2-symmetric. The C_2-symmetry of (*S*,*S*,*S*,*S*)-$\mathbf{1}_{OH}$ and (*R*,*R*,*R*,*R*)-$\mathbf{2}_{OH}$ are reflected in their ^{1}H and ^{13}C NMR spectra. For example, (*R*,*R*,*R*,*R*)-$\mathbf{2}_{OH}$ shows two doublets at 1.25 and 1.21 ppm (coupling constant J = 6.4 and 6.2 Hz, respectively) for the two nonequivalent CH_3-groups (k and k′) located at the chiral center (Figure 2). The chirality of (*R*,*R*,*R*,*R*)-$\mathbf{2}_{OH}$ is also seen in the resonances for the aromatic

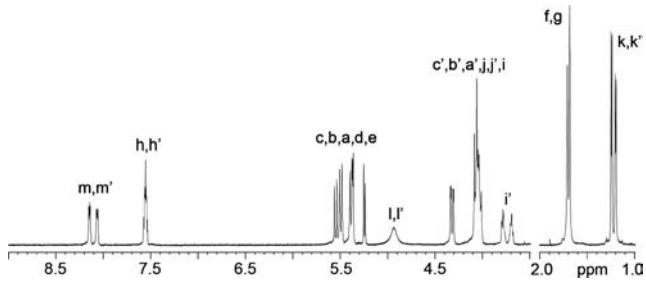


Figure 2. ^{1}H NMR spectra (DMSO-d_6, 600 MHz) of chiral acyclic CB[*n*]-type molecular container (*R*,*R*,*R*,*R*)-$\mathbf{2}_{OH}$.

naphthalene sidewalls where two sets of multiplets appear at 8.15–8.06 and 7.55 ppm which correspond to the nonequivalent protons m, m′ and h, h′. Similarly, the C_2-symmetric structure of compound $\mathbf{1}_{Ac}$ and $\mathbf{2}_{Ac}$ was evident on the basis of the four different ureidyl C=O ^{13}C NMR resonances (155.5, 155.4, 154.0, 153.8 ppm) of the central glycoluril tetramer unit (only two signals were observed for achiral C_{2v}-symmetric **M1** previously).

After having firmly established the structures of enantiomerically pure hosts (*S*,*S*,*S*,*S*)-**1** and (*R*,*R*,*R*,*R*)-**2**, we decided to explore their molecular recognition properties toward guests **6**–**15** (Figure 3). Initially, we measured the ^{1}H NMR spectra

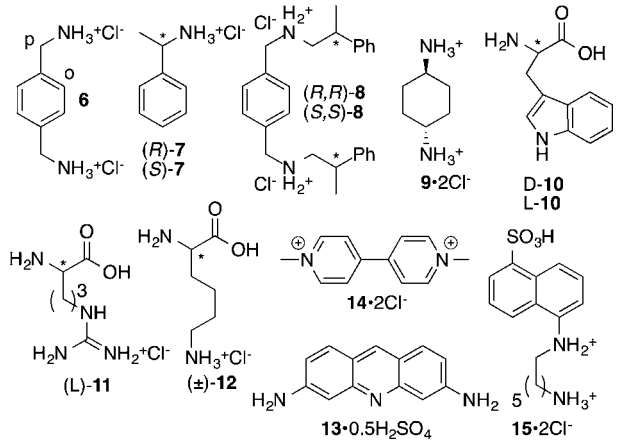


Figure 3. Structures of guests **6**–**15** used in this study.

for the complexes of hosts (*S*,*S*,*S*,*S*)-$\mathbf{1}_{Ac}$ and (*S*,*S*,*S*,*S*)-$\mathbf{1}_{OH}$, which are slightly soluble in water (~1 mM), toward *p*-xylylenediammonium ion **6** as shown in Figure 4. Parts b and d of Figure 4 display distinct resonances for free **6** and the (*S*,*S*,*S*,*S*)-$\mathbf{1}_{Ac}$·**6** and (*S*,*S*,*S*,*S*)-$\mathbf{1}_{OH}$·**6** complexes, which establishes that guest **6** undergoes slow exchange on the ^{1}H NMR time scale. Slow guest exchange on the NMR time scale would be advantageous for determination of the degree of chiral recognition of (*S*,*S*,*S*,*S*)-$\mathbf{1}_{Ac}$, for example, because when a chiral but racemic guest is used the ratio of the two competing diastereomeric complexes can be measured quite accurately by integration of the ^{1}H NMR spectrum. Accordingly, we proceeded to measure the ^{1}H NMR spectrum for the host·guest complexes formed between hosts (*S*,*S*,*S*,*S*)-$\mathbf{1}_{Ac}$ and (*S*,*S*,*S*,*S*)-$\mathbf{1}_{OH}$ and guests (*R*,*R*)-**8** and (*S*,*S*)-**8** (Supporting Information). Unfortunately, these ^{1}H NMR spectra are

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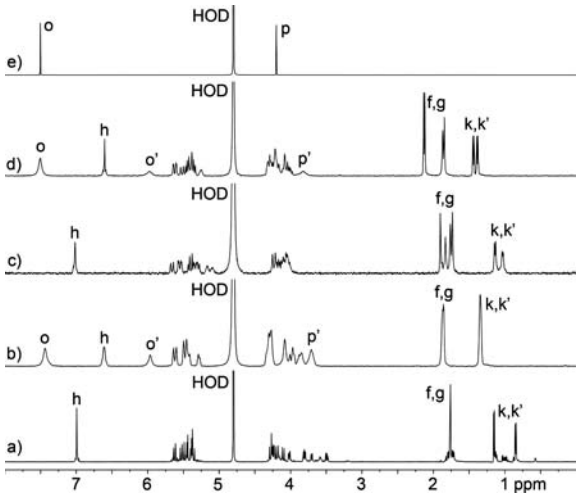

Figure 4. ^{1}H NMR spectra recorded (D_2O, 400 MHz, rt) for (a) host (*S,S,S,S*)-$\mathbf{1}_{OH}$ (0.5 mM); (b) a mixture of (*S,S,S,S*)-$\mathbf{1}_{OH}$ (0.5 mM) and guest **6** (1 mM); (c) host (*S,S,S,S*)-$\mathbf{1}_{Ac}$ (0.5 mM); (d) a mixture of (*S,S,S,S*)-$\mathbf{1}_{Ac}$ (0.5 mM) and guest **6** (1 mM); (e) guest **6** (1 mM).

broadened and do not exhibit slow exchange in the NMR time scale, which precludes the planned chiral recognition determination by ^{1}H NMR integration. Broadened spectra were also observed for the complexes formed between (*S,S,S,S*)-$\mathbf{1}_{OH}$ and guest **7** and amino acids **10**−**12**. In addition, we could not perform ^{1}H NMR competition experiments involving (*S,S,S,S*)-$\mathbf{1}_{Ac}$ or (*S,S,S,S*)-$\mathbf{1}_{OH}$, **6**, and chiral guests because the broadness of the ^{1}H NMR resonances for Ho and Ho′ for (*S,S,S,S*)-$\mathbf{1}_{Ac}$·**6** or (*S,S,S,S*)-$\mathbf{1}_{OH}$·**6** preclude accurate integration.

From our previous work, we know that acyclic CB[n] compounds with naphthalene sidewalls display higher affinity toward their guests and do so more frequently with slow exchange on the ^{1}H NMR time scale.[11c,d,g] Accordingly, we synthesized (*R,R,R,R*)-$\mathbf{2}_{Ac}$ and (*R,R,R,R*)-$\mathbf{2}_{OH}$ as described above in hopes of achieving the slow exchange kinetics needed for accurate relative binding constant measurement by ^{1}H NMR spectroscopic integration. Unfortunately, compounds (*R,R,R,R*)-$\mathbf{2}_{Ac}$ and (*R,R,R,R*)-$\mathbf{2}_{OH}$, which have larger and more hydrophobic naphthalene sidewalls, are nearly insoluble in water. Treatment of solid (*R,R,R,R*)-$\mathbf{2}_{Ac}$ and (*R,R,R,R*)-$\mathbf{2}_{OH}$ with solutions of guest **6** result in the formation of soluble (*R,R,R,R*)-$\mathbf{2}_{Ac}$·**6** and (*R,R,R,R*)-$\mathbf{2}_{OH}$·**6** complexes, with slow exchange on the ^{1}H NMR time scale (Supporting Information). Unfortunately, complexes between (*R,R,R,R*)-$\mathbf{2}_{OH}$ and chiral guests (*R,R*)-**8** and (*S,S*)-**8** once again display sufficiently broadened ^{1}H NMR spectra that determination of the degree of chiral recognition by ^{1}H NMR was not possible.

As described above, it was not possible to determine the degree of chiral recognition exhibited by **1** and **2** by ^{1}H NMR because the exchange rates were not appropriate. Accordingly, we decided to measure the binding constants of (*S,S,S,S*)-$\mathbf{1}_{Ac}$ and (*S,S,S,S*)-$\mathbf{1}_{OH}$ toward chiral guests **7** and **8**[10a] by UV/vis spectroscopy. Because guests **7** and **8** do not possess a chromophore that undergoes substantial UV/vis changes upon formation of the host·guest complexes, we decided to employ an indicator displacement assay. We selected **15** as indicator and measured the K_a values for the (*S,S,S,S*)-$\mathbf{1}_{Ac}$·**15** complex (K_a = 6.6 (±0.8) × 10^4 M^{-1}) and (*S,S,S,S*)-$\mathbf{1}_{OH}$·**15** complex (K_a = 2.4 (±0.1) × 10^3 M^{-1}) by direct UV/vis and ^{1}H NMR titration, respectively (Supporting Information). These measurements were performed in 50 mM NaOAc buffered H_2O at pH 5.5 to maximize the change in UV/vis absorbance upon complex formation. Subsequently, we performed the UV/vis indicator displacement assays. Figure 5 shows the UV/vis

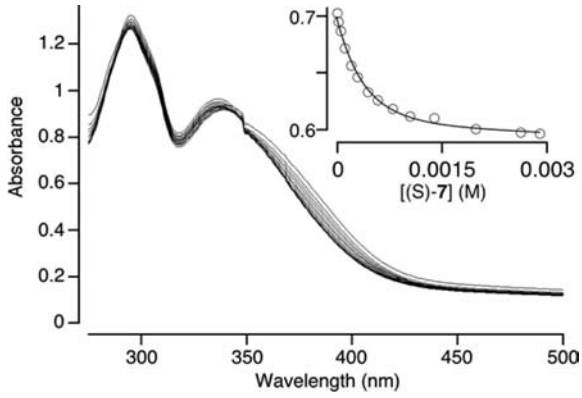

Figure 5. Representative UV/vis spectra for the titration of guest (*S*)-**7** toward host (*S,S,S,S*)-$\mathbf{1}_{OH}$ containing dye **15**. Conditions: 50 mM NaOAc buffered H_2O (pH = 5.5), 25 °C. [(*S,S,S,S*)-$\mathbf{1}_{OH}$] = 0.2 mM; [**15**] = 0.2 mM.

spectra recorded when a solution containing (*S,S,S,S*)-$\mathbf{1}_{OH}$ (0.2 mM), and **15** (0.2 mM) was titrated with a solution containing (*S*)-**7**. The inset to Figure 5 shows a plot of UV/vis absorbance versus [**15**]. We fitted this plot of absorbance at 370 nm versus [**15**] using a competitive binding model implemented in Scientist (Supporting Information) to determine K_a for the (*S,S,S,S*)-$\mathbf{1}_{OH}$·(*S*)-**7** complex (K_a = 9.3 (±1.0) × 10^3 M^{-1}). Binding constants for chiral guests (*R*)-**7**, (*S*)-**7**, (*R,R*)-**8**, and (*S,S*)-**8** toward host (*S,S,S,S*)-$\mathbf{1}_{Ac}$ (or (*S,S,S,S*)-$\mathbf{1}_{OH}$) were determined in an analogous manner and are given in Table 1.

Table 1. Binding Constants Measured from the UV/vis Titration for Host (*S,S,S,S*)-$\mathbf{1}_{Ac}$ and (*S,S,S,S*)-$\mathbf{1}_{OH}$ toward Selected Chiral Guests

	K_a (M^{-1})	
guest	(*S,S,S,S*)-$\mathbf{1}_{Ac}$	(*S,S,S,S*)-$\mathbf{1}_{OH}$
(*R*)-**7**	2.9 (±0.2) × 10^5	1.3 (±0.3) × 10^4
(*S*)-**7**	3.9 (±0.5) × 10^5	9.3 (±1.0) × 10^3
(*R,R*)-**8**	1.3 (±0.2) × 10^6	1.9 (±0.4) × 10^5
(*S,S*)-**8**	1.1 (±0.3) × 10^6	1.7 (±0.2) × 10^5
15	6.6 (±0.8) × 10^4	2.4 (±0.1) × 10^3

Quite disappointingly, the ratio of the binding constants for (*R*)-**7** and (*S*)-**7** toward hosts (*S,S,S,S*)-$\mathbf{1}_{Ac}$ and (*S,S,S,S*)-$\mathbf{1}_{OH}$ is only 0.74 and 1.4, respectively. In the case of (*R,R*)-**8** and (*S,S*)-**8**, the ratio is about 1.2 and 1.1 toward host (*S,S,S,S*)-$\mathbf{1}_{Ac}$ and (*S,S,S,S*)-$\mathbf{1}_{OH}$, respectively. We conclude that hosts (*S,S,S,S*)-$\mathbf{1}_{Ac}$ and (*S,S,S,S*)-$\mathbf{1}_{OH}$ do not display useful levels of chiral recognition toward guests **7** and **8**.

We were fortunate to obtain the X-ray crystal structure of (*S,S,S,S*)-$\mathbf{1}_{OH}$ as its acetone solvate (Figure 6). Compound (*S,S,S,S*)-$\mathbf{1}_{OH}$ packs in the crystal in dimeric units linked together by bridging K^+ ions via the C═O portals, which then further pack into tapes along the *c*-axis by π−π interactions between the substituted *o*-xylylene sidewalls. The individual molecules of (*S,S,S,S*)-$\mathbf{1}_{OH}$ exhibit a small helical twist, but both senses of helicity are observed in the crystal. In the design of (*S,S,S,S*)-$\mathbf{1}_{OH}$, we hoped that the OH groups would H-bond to

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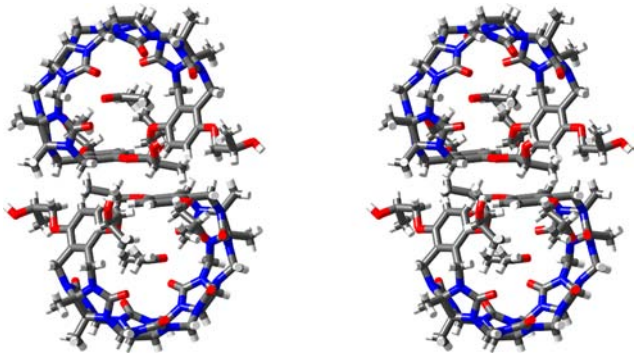

Figure 6. Stereoview of the X-ray crystal structure of (*S*,*S*,*S*,*S*)-$\mathbf{1}_{OH}$ as its acetone solvate. Color code: C, gray; H, white; N, blue; O, red.

the ureidyl C═O portals to rigidify the arms and therefore sculpt a chiral cavity. Figure 6 shows that the chiral arms are remote from and do not H-bond to the C═O portals. The lack of these structural features provides a rationale for the observed low levels of chiral recognition of hosts (*S*,*S*,*S*,*S*)-$\mathbf{1}_{Ac}$ and (*S*,*S*,*S*,*S*)-$\mathbf{1}_{OH}$.

In summary, we presented the synthesis of a series of enantiomerically pure CB[*n*]-type containers (*S*,*S*,*S*,*S*)-$\mathbf{1}_{Ac}$, (*S*,*S*,*S*,*S*)-$\mathbf{1}_{OH}$, (*R*,*R*,*R*,*R*)-$\mathbf{2}_{Ac}$, and (*R*,*R*,*R*,*R*)-$\mathbf{2}_{OH}$ that are C_2-symmetric, chiral, and enantiomerically pure by virtue of the arms attached to their aromatic sidewalls. Compounds (*S*,*S*,*S*,*S*)-$\mathbf{1}_{Ac}$, (*S*,*S*,*S*,*S*)-$\mathbf{1}_{OH}$, (*R*,*R*,*R*,*R*)-$\mathbf{2}_{Ac}$, and (*R*,*R*,*R*,*R*)-$\mathbf{2}_{OH}$ bind to a variety of cationic species in water but exhibit intermediate kinetics of exchange on the ^{1}H NMR time scale. The binding affinities of (*S*,*S*,*S*,*S*)-$\mathbf{1}_{Ac}$ and (*S*,*S*,*S*,*S*)-$\mathbf{1}_{OH}$ toward two pairs of enantiomers ((*R*)-**7** and (*S*)-**7**; (*R*,*R*)-**8** and (S,S)-**8**)) were therefore determined by UV/vis competition experiments and were found to be comparable. We conclude that (*S*,*S*,*S*,*S*)-$\mathbf{1}_{Ac}$ and (*S*,*S*,*S*,*S*)-$\mathbf{1}_{OH}$ display poor levels of enantioselectivity in their complexation behavior. We speculate that the remote location of the chiral centers on the side arm does not render the cavity itself, where binding occurs, significantly asymmetric. In ongoing work, we aim to introduce inherently chiral aromatic sidewall surfaces to enhance cavity asymmetry and enantioselectivity and enable the use of acyclic CB[*n*]-type containers in a variety of applications including chiral separations, enantioselective catalysis, and chiral recognition and sensing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01948.

Experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra for new compounds; ^{1}H NMR spectra for host·guest complexes; data from UV/vis and NMR titration experiments (PDF)

Crystallographic data for (*S*,*S*,*S*,*S*)-$\mathbf{1}_{OH}$ (CIF)

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Notes

The authors declare no competing financial interest.

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