Acyclic Cucurbit[n]urils Capped with Alkylene Linkers: Synthesis and Molecular Recognition Properties

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We report the synthesis and characterization of three new acyclic cucurbit[n]uril-type receptors that feature a covalent capping group in the form of an alkylene linker (**2a** – **2c**) that we hypothesized would have higher binding affinity toward alkylammonium ions in water. Hosts **2a** – **2c** have far lower aqueous solubility (≤ 2 mM) than the prototypical acyclic CB[n]-type host **1** (346 mM). Similar to **1**, new hosts **2a** – **2c** do not undergo significant intermolecular self-association over the experimentally accessible concentration range. In contrast, the results of ^{1}H NMR experiments shows that the alkylene linkers of **2b** and **2c** undergo self-inclusion in their own cavity and that this process is reversed upon addition of ammonium ions **6** – **10** as guests. The host•guest K_a values were determined for hosts **1** and **2a** – **2c** toward guests **6** – **10** by isothermal titration calorimetry. We find that **2a** – **2c** bind less strongly toward guests **6** – **10** than the prototypical host **1** due to the energetic penalty associated with expulsion of the alkylene linker from its own cavity.

Keywords: cucurbituril; host-guest chemistry; preorganization; cation receptors; ammonium ions

Introduction

The preparation of new macrocyclic compounds that function as hosts for complementary guest molecules in organic and aqueous remains a core activity of supramolecular chemistry.[1] The purpose of these studies is to discover new host systems and investigate their host•guest recognition properties as a means to improve our fundamental understanding of non-covalent interactions (e.g. H-bonds, electrostatic interactions, π–π interactions, hydrophobic effect) and enable new applications. Accordingly, much research has been directed toward a variety of macrocyclic host systems including cyclophanes, cyclodextrins, calixarenes, pillararenes, bambusurils, and self-assembled hosts[2] which can be used for a variety of applications including chemical sensors, supramolecular catalysis, supramolecular polymers, drug solubilization, gold sequestration, molecular machines, and the stabilization of reactive species.[3] We, and others, have been particularly interested in an alternative class of molecular containers known as cucurbit[n]urils (CB[n], Figure 1).[4] CB[n] are formed by the condensation of glycoluril with formaldehyde under strongly acidic conditions that generate a homologous series of compounds (n = 5, 6, 7, 8, 10, 13 – 15) whose recognition properties are defined by two symmetry equivalent ureidyl carbonyl portals and a central hydrophobic cavity.[5] For example, CB[n] compounds are well known to complex hydrophobic (di)cations with high affinity (K_a up to 10^{17} M^{-1}), high selectivity, and to respond to appropriate environmental stimuli (e.g. chemical, pH, electrochemical, photochemical).[4b,4d,6] Accordingly, CB[n] compounds have been used in a wide range of applications, including supramolecular materials for art conservation, drug delivery, sensing ensembles, drug reversal, molecular machines, and supramolecular organic frameworks.[7] Researchers have developed methods to prepare derivatives of macrocyclic CB[n][8] as a means to improve their aqueous solubility and enable their attachment by click chemistry to materials, polymers, assemblies, and even DNA as a route to new applications including materials for protein

purification, as supramolecular Velcro, to monitor vesicle fusion, (targeted) drug delivery, and for theranostic applications.[8b,9]

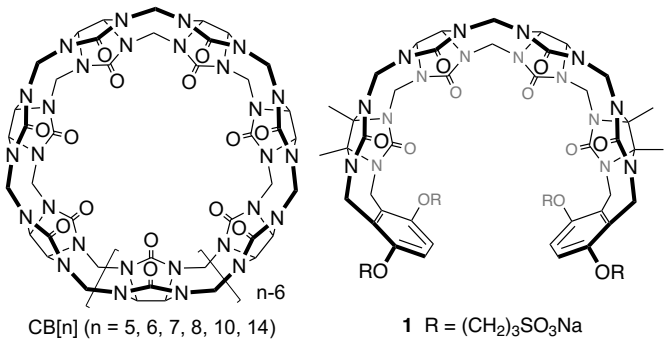
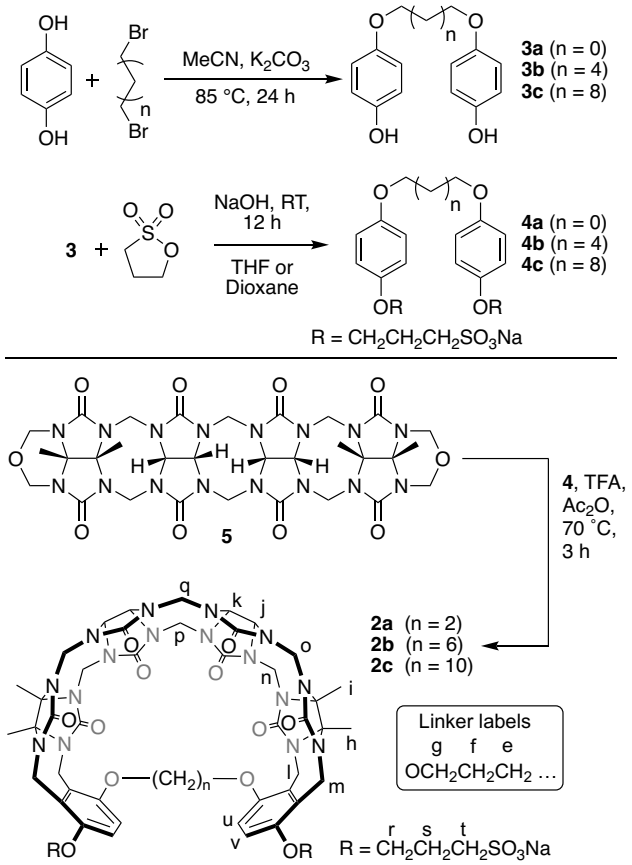


Figure 1. Chemical structures of cucurbit[n]urils (CB[n]) and acyclic CB[n]-type container **1**.

Previously, based on our synthetic and mechanistic knowledge of the CB[n] forming reaction, our group designed and synthesized acyclic CB[n]-type receptors (e.g. **1**, Figure 1) that are composed of a central glycoluril tetramer, two aromatic sidewalls, and four sulfonate solubilizing groups.[10] Despite its acyclic nature, host **1** is nicely preorganized into a C-shape by virtue of the supporting polycyclic ring system and therefore retains the essential molecular recognition properties of macrocyclic CB[n].[10d] Host **1** has high aqueous solubility (346 mM) and excellent biocompatibility. Accordingly, we investigated the use of **1** and analogues in biomedical applications including as a solubilizing excipient for insoluble drugs and as a reversal agent for neuromuscular blocking agents (NMBAs) and drugs of abuse (methamphetamine).[7d,10a,10d,11] Because **1** is prepared by a building block synthesis involving glycoluril oligomer and aromatic wall, we have conducted several structure-recognition property relationship studies. For example, the Isaacs and Sindelar groups have studied the influence of the nature of the solubilizing groups (e.g. SO_3^- vs NH_3^+ vs OH), aromatic walls, glycoluril oligomer length (e.g. monomer – tetramer), and length of the alkyl chain connecting (e.g. $(CH_2)_n$, n = 2, 3, 4) the solubilizing group to the aromatic wall on their molecular recognition properties.[10b,10c,12] From these studies, we found that hosts comprising

a longer glycoluril oligomer (e.g.: tetramer), larger aromatic walls (e.g.: substituted naphthalene), and negatively charged solubilizing groups (e.g.: sulfonate as compared to neutral or positive groups) lead to more potent molecular hosts with higher binding affinities towards guests such as hydrophobic diammonium cations. In this paper, we explore the recognition properties of a series of hosts (**2a – 2c**, Scheme 1) that are related to **1** but that feature a covalent alkylene linker (e.g. $(CH_2)_n$, n = 2, 4, 6) connection between adjacent sidewalls (e.g. a capping group). We hypothesized that such capped acyclic CB[n] would be more effectively preorganized, display higher affinity and selectivity toward its best guests, and therefore be better suited for application as a sequestration agent. Herein, we present the results of this study.

Results and Discussion. This results and discussion section is organized as follows. First, we describe the design and synthesis of hosts **2a** – **2c** (Scheme 1) as well as its aqueous solubility and self-association properties. Second, we gleen aspects of the conformational properties of uncomplexed **2** by ^{1}H NMR spectroscopy and report the results of qualitative host-guest binding studies. Third, we perform quantitative binding studies by isothermal titration calorimetry between hosts **2a – 2c** and guests **6** – **10** (Figure 2). Finally, we relate the trends in the ITC binding data to structural changes induced by the alkylene capping groups.



Scheme 1. Synthesis of hosts **2a** – **2c**.

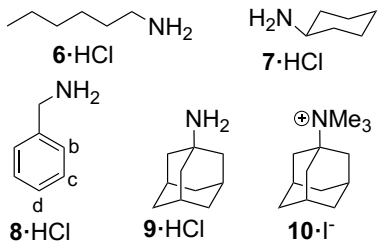


Figure 2. Chemical structures of guests used in this study.

Design and Synthesis of Hosts 2a– 2c.

We have previously reported that the synthesis of **1** proceeds by the double electrophilic aromatic substitution reaction between glycoluril tetramer bis(cyclic ether) building block (**5**) and the corresponding dialkoxybenzene sidewall in hot CF_3CO_2H.[10a] The high binding affinity of **1** toward various hydrophobic ammonium cations can be attributed to its electrostatically negative ureidyl carbonyl portals which engage in ion-dipole interactions,

its hydrophobic cavity which engages in π–π interactions and the hydrophobic effect, and its SO_3^- groups which impart high water solubility and engage in ion-ion interactions with its guests. In designing congeners of **1** we wanted to preserve the carbonyl portals, aromatic walls, and sulfonate solubilizing groups to maintain the recognition properties and aqueous solubility of **1**, while improving the preorganization of the cavity size of the acyclic host by locking the distance between sidewalls and providing additional binding surfaces to complement the guest. We hypothesized that the binding affinity of **1** toward hydrophobic cations could be increased by incorporation of a covalent alkylene capping group on one face of the host as manifested in **2a** – **2c** (Scheme 1).

The preparation of **2a** – **2c** required the synthesis of a new series of aromatic wall building blocks that feature covalent alkylene connections. For this purpose, we reacted hydroquinone with 1,*n*-dibromoalkanes under basic conditions (CH_3CN, K_2CO_3) to yield compounds **3a** – **3c** in modest yields (13%, 50%, and 33%, Scheme 1).[13] Subequently, **3a** – **3c** were separately alkylated with 1,3-propanesultone under basic conditions (NaOH) in aq. THF or dioxane to deliver the required covalently connected sidewalls **4a – 4c** in 87%, 77%, and 47% yields, respectively (Scheme 1). With the required aromatic wall building blocks in hand we proceeded to explore the double electrophilic aromatic substitution reaction with glycoluril tetramer **5**. When a mixture of tetramer **5** and aromatic wall **4** was heated in a 1:1 mixture of trifluoroacetic acid and acetic anhydride at 70 ˚C, we obtained the targeted alkylene capped containers **2a**, **2b**, and **2c** in 33%, 13%, and 26% yield, respectively. The purification of hosts **2a** – **2c** proceeded by ion exchange chromatography on Dowex® 1X2 (chloride form, 200-400 mesh ion exchange resin) which contains quaternary ammonium ion functional groups that electrostatically bind to the dianionic hosts. The new hosts were fully characterized by spectroscopic methods. For example, all three containers show ions in the high resolution negative ion mode electrospray ionization mass spectra that can be assigned

to the $[M - 2Na]^{2-}$ species. The ^{13}C NMR spectra display the number of resonances (**2a**: 26; **2b**: 28; **2c**: 30) expected given the top-bottom dissymmetry and overall C_s-symmetric nature of **2a** – **2c**. Similarly, the ^{1}H NMR spectra display resonances that can be attributed to the six chemically distinct CH_2-groups that connect two glycolurils and a glycoluril with a sidewall as expected for the top-bottom dissymmetric and overall C_s-symmetric structure of **2a** – **2c** (Supporting Information).

Solubility Properties of Hosts 2a– 2c

The use of molecular containers for biological applications such as drug reversal and drug solubilization requires good inherent solubility in water of the uncomplexed hosts and their host•guest complexes.[3c,7c,10d,14] Previously, we determined the inherent solubility of **1** as 346 mM in H_2O and 105 mM (D_2O, 20 mM sodium phosphate buffer, RT, pD 7.4) by ^{1}H NMR integration of host resonances versus resonances of an internal standard of known concentration.[10a] In analogous manner we determined the solubilities of **2a**, **2b**, and **2c** as 1.8 mM, 1.5 mM, and 1.7 mM respectively in 20 mM sodium phosphate buffered D_2O at pD 7.4 at room temperature. This large decrease in aqueous solubility was unexpected, but can be attributed to the loss of two solubilizing sulfonate groups per host and the addition of the hydrophobic alkylene ($(CH_2)_n$, n = 2, 6, 10) linkers into **2a** – **2c**. While this reduced aqueous solubility makes **2a** – **2c** less attractive for use in biological systems relative to **1**, we nevertheless decided to investigate the effect of the alkyl linker on the self-association properties and the molecular recognition properties of these hosts toward some common guests for CB[n].

Self-Association Properties of Hosts 2a– 2c

In order for molecular containers to function as good hosts in water they must not undergo strong self-association which would prevent host•guest binding. The self-association of **1** (K_s

= 47 M^{-1}) has been previously studied by dilution experiments monitored by ^1H NMR spectroscopy and fitted to a 2-fold self-association model.[10a] When acyclic CB[n]-type containers aggregate, typically the resonances for the aromatic rings shift upfield due to cavity inclusion. For **1** and analogues measured to date the K_s values are generally lower than 1000 M^{-1} which has been attributed to electrostatic repulsion between the tetraanionic molecules upon putative aggregation processes.[15] We performed analogous ^1H NMR dilution experiments over the accessible concentration range (1.0 – 0.1 mM) in 20 mM sodium phosphate buffered D_2O at pD 7.4 at room temperature (Supporting Information) for **2a** – **2c** we did not observe any significant changes in chemical shift that would be indicative of self-association. Accordingly, we conclude that **2a** – **2c** are monomeric over this concentration range as required for the detailed binding studies described below.

Although we conclude that the intermolecular association in **2a** – **2c** is low, we did note some concentration independent intramolecular features in the ^1H NMR spectra of our hosts which suggest the partial inclusion of the alkylene linker within the hydrophobic cavity of each host molecule. For example, Figure 3b shows the ^1H NMR spectrum of host **2b** in which the resonances of the methylene protons of the linker H_f, $H_{e'}$, and H_e are shifted upfield by 0.5 ppm relative to their resonances in **4b** (Supporting Information). This can be explained by the alkylene linker of **2b** being bound within the magnetic shielding environment inside the cavity of **2b** driven by the hydrophobic effect of the self-filling the cavity. The resonance for H_g is not significantly different between **2b** and **4b** indicating that its magnetic environment is unchanged and it does not enter the cavity of **2b**. A similar effect is observed for host **2c**, in which the resonances of all the methylene protons of the alkyl linker (except the ArO-CH_2 resonances) are upfield shifted by 0.2 - 0.6 ppm relative to their resonances in **4c** (Supporting Information). Figure 4 shows a stereoview of an MMFF minimized model of uncomplexed **2b**. Interestingly, **2b** assumes a splayed geometry in which one of the aromatic

rings is displaced downward and the other is displaced upward creating a helical twist. As a result, the hexylene linker of **2b** partially threads through the cavity; at the same time the downward displaced aromatic ring folds inwards to partially fill the cavity. As can be readily seen from Figure 4, the central protons of the hexylene linker are nearby the face of an aromatic sidewall.

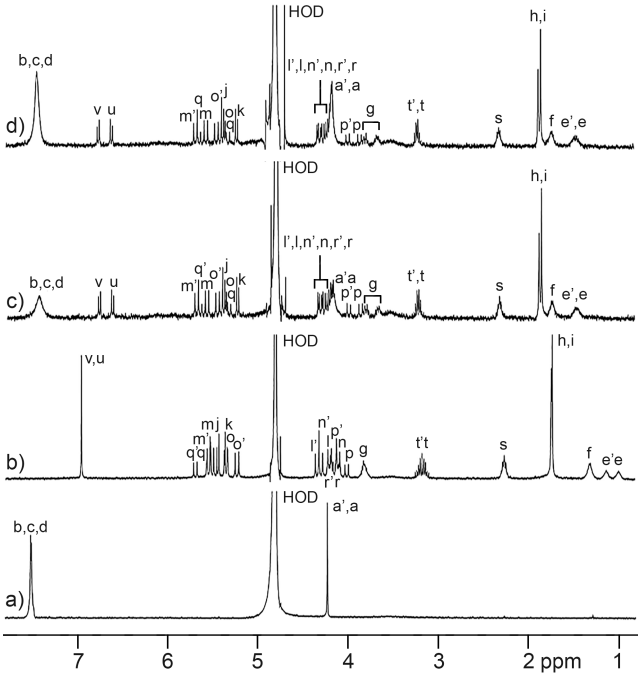


Figure 3. ^{1}H NMR spectra recorded (400 MHz, RT, 20 mM sodium phosphate buffered D_2O, pH 7.4) for: a) **8** (1 mM), b) **2b** (1 mM), c) a mixture of **2b** (0.5 mM) and **8** (0.5 mM), and d) **2b** (0.5 mM) and **8** (1.0 mM).

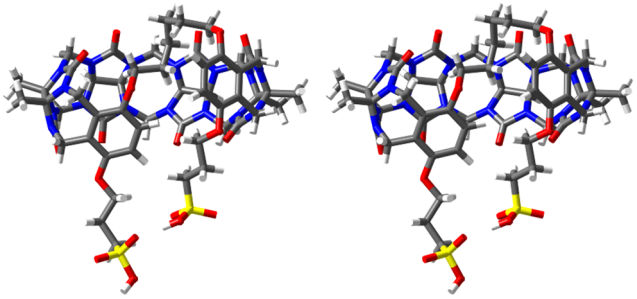


Figure 4. Cross-eyed stereoviews of an MMFF minimized molecular model of uncomplexed host **2b**. Color code: C, grey; H, white; N, blue; O, red; S, yellow.

Since the decyl linker is longer and has more degrees of freedom than the hexyl linker we observed a broadening of the ^{1}H NMR signals of the protons in the linker of **2c** as compared to the sharper resonances of those in **2b**. The decyl linker also penetrates more fully into its own cavity relative to the hexyl linker on account of its longer length, as is evidenced by the larger upfield shifts of its methylene protons at the mid-point of the linker. In case of host **2a**, the linker is shortest (ethyl group) and the methylene groups are both directly attached to the O-atoms on the aromatic walls of the host. Two well-resolved resonances are observed for the diasterotopic linker protons in **2a** at 4.47 ppm and 3.87 ppm respectively. The resonance at 3.87 ppm is shifted upfield by 0.5 ppm relative its position in the ^{1}H NMR spectrum of **4a** (Supporting Information) which indicates that this set of protons is experiencing a different magnetic environment, potentially from the anisotropic effect of the aromatic walls of the host. The other set of protons is probably downfield shifted due to their orientation with respect to the ureidyl C=O portals which constitute a deshielding region.[4a,16] This phenomenon of the alkylene linker of hosts **2a** – **2c** interacting with or being partially included within their cavities is expected to create an energetic penalty for guest molecules to be included within their cavities. In the following sections we investigate the binding properties of **2a** – **2c** toward a series of ammonium ion guests and qualtitatively assess the thermodynamic cost of this phenomenon.

^{1}H NMR Investigation of the Binding of 1 and 2a – 2c toward guests 6– 10.

Initially, we tried to investigate the ability of hosts **2a** – **2c** to bind typical dicationic guests known to bind to CB[n] such as 1,6-hexanediammonium ion, *trans*-1,4-cyclohexanediammonium, and *p*-xylene diammonium ion. We found that the complexes of these dicationic guests with our dianionic hosts **2a** – **2c** precipitated from aqueous solution

which precluded detailed ^{1}H NMR investigations. We rationalize this precipitation as a consequence of the formation of a zwitterionic host-guest complex which would have lower aqueous solubility. Therefore, we decided instead to study the water soluble complexes of monocationic guests **6** – **10** with hosts **1** and **2a** – **2c** by ^{1}H NMR spectroscopy. In each of these cases, upon host•guest complexation we observe upfield shifting of many guest resonances which indicates that these protons on the guest are located in the cavity of the host molecule.[4a,5a,16] The upfield shifting of guest resonances in the complexes with hosts containing alkyl linkers (**2a** – **2c**) was generally less than or equal to the upfield shifting of the same resonances in the complexes with host **1**. This preliminary observation suggests that in most cases the cavity of host **1** better accommodates or binds more strongly to guests **6** – **10** as compared to the cavities of **2a** – **2c**. All of the host•guest complexes display fast kinetics of exchange on the ^{1}H NMR timescale which suggests that these complexes would be of moderate stability in water. As additional evidence of cavity self-inclusion of the alkylene linkers, we observe that the binding of guests **6** – **10** to hosts **2a** – **2c** results in the downfield shifting of the resonances of the alkylene linker protons because cavity binding of the guest displaces the alkylene linkers from the cavity of the host. For example, the ^{1}H NMR spectrum of the **2b•8** complex is presented in Figure 3c. The resonances of the aromatic protons H_b, H_c, H_d of **8** undergo upfield shifting in its complex with **2b** as a result of the anisotropic environment of the aromatic walls of the host when the host and guest are combined in a 1:1 ratio. Upon adding excess guest (2:1 ratio) we observe that the peak corresponding to H_b, H_c, and H_d protons (Figure 3d) shifts to a position which is the average between the free (Figure 2a) and bound (Figure 3c) forms of the guest. This indicates a fast kinetics of exchange between free guest **8** and the **2a·8** complex relative to the ^{1}H NMR chemical shift time scale. The same trend is observed for the H_a methylene protons of **8** in free and bound form which experience the shielding effect of the cavity of the host when

bound to **2b**. The resonances of the aromatic protons of host **2b**, H_v and H_u also undergo upfield shifting in the **2b·8** complex. We believe that this change reflects the change in orientation of the two aromatic sidewalls with respect to one another as the cavity that was previously filled with the linker becomes filled with the guest; the presence of the aromatic ring of guest **8** may also play a role.[10b] Interestingly, H_v and H_u each appear as doublets (J = 9.0 Hz) in the **2b·8** complex. The other noteworthy change in the spectrum of **2b** occurs to the resonances of the H_f, $H_{e'}$, and H_e protons of the linker. In the spectrum of the **2b·8** complex these protons are shifted downfield by 0.5 ppm relative to their positions in free **2b**, at the same positions where they were observed in the spectrum of **4b** (Supporting Information). This downfield shift indicates that the presence of guest **8** in the cavity of host **2b** necessitates the displacement of the hexyl linker from the cavity of **2b**. Analogous phenomena were seen in the ^{1}H NMR spectra recorded for the remaining host-guest complexes.

One further aspect of the host•guest complexes between **2a** – **2c** and guests **6** – **10** deserve comment. Because both the host is top-bottom dissymmetric and the guests are monoammonium ions and therefore have two ends two different diastereomeric complexes are possible as indicated in Figure 5.[17] In one diastereomer, the ammonium ion resides at the portal containing the alkylene linker whereas in the other diastereomer the ammonium ion resides at the sulfonated portal and the hydrophobic residue points toward the alkylene linker at the other portal. We posit that the top diasteromer is preferred because it would benefit from sulfonate-ammonium electrostatic interactions and also van der Waals interactions between the guest hydrophobic residue and the alkylene linker. Unfortunately, because the ^{1}H NMR spectra indicate a fast exchange on the chemical shift timescale, we cannot differentiate between these different possibilities experimentally.

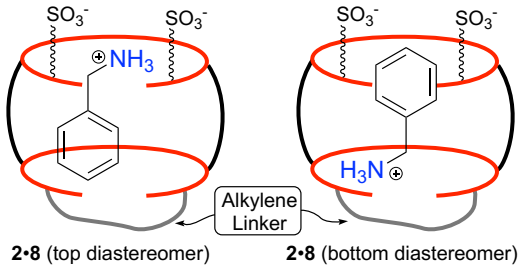


Figure 5. Cartoon representation of the top and bottom diastereomers of the **2•8** complex.

Measurement of Binding Affinities of Hosts 1 and 2a – 2c toward Guests 6 – 10 by Isothermal Calorimetry (ITC)

Given the high binding constants exhibited by CB[n]-type containers toward their guests, direct ^{1}H NMR titrations to determine K_a are not generally reliable.[5e,16] To avoid the need to perform competition experiments (e.g. ^{1}H NMR or UV/Vis) we decided to turn to ITC for direct measurements of the thermodynamic parameters of binding. For example, Figure 6 shows the thermogram recorded for the titration of **2b** (100 μM) in the cell with **8** (0 – 200 μM) which was fitted with the MicroCal PEAQ-ITC analysis software to deliver K_a = (1.6 ± 0.1) × 10^6 $M^{-1}$and ΔH = - 9.5 ± 0.1 kcal mol^{-1} for the **2b•8** complex. Table 1 presents the values of K_a and ΔH measured for the remaining complexes between hosts **1** and **2a** – **2c** and guests **6** – **10** that were determined analogously (Supporting Information).

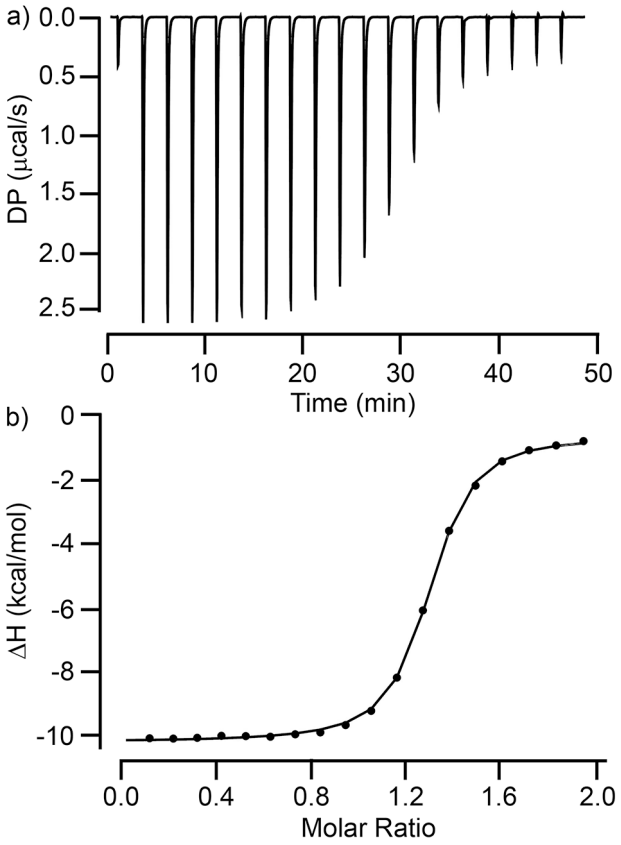


Figure 6. a) ITC thermogram recorded during the titration of **2b** (0.1 mM) in the cell with **8** (1.0 mM) in the syringe. d) Fitting of the data to a 1:1 binding model with $K_a = (1.6 \pm 0.1) \times 10^6\ M^{-1}$.

Table 2. Thermodynamic parameters determined by ITC for the interaction between molecular containers **1**, **2a** – **2c** and guests **6 – 10**.

	K_a (M^{-1}) and ΔH (kcal mol^{-1}) values			
	Hosts: 1	**2a**	**2b**	**2c**
Guests: 6	$(2.4 \pm 0.1) \times 10^6$ $- 8.7 \pm 0.1$	$(6.2 \pm 0.9) \times 10^3$ -3.9 ± 0.4	$(1.3 \pm 0.1) \times 10^5$ -5.5 ± 0.1	$(2.3 \pm 0.2) \times 10^4$ -5.0 ± 0.2
7	$(1.7 \pm 0.1) \times 10^6$ -8.2 ± 0.04	$(2.3 \pm 0.2) \times 10^4$ -8.7 ± 0.1	$(7.9 \pm 0.1) \times 10^5$ -8.6 ± 0.02	$(3.2 \pm 0.3) \times 10^4$ -6.0 ± 0.2
8	$(3.9 \pm 0.2) \times 10^6$ -10.5 ± 0.03	$(2.1 \pm 0.1) \times 10^4$ -11.3 ± 0.2	$(1.6 \pm 0.1) \times 10^6$ -9.5 ± 0.1	$(7.1 \pm 0.4) \times 10^4$ -8.5 ± 0.1
9	$(4.9 \pm 0.2) \times 10^5$ -7.1 ± 0.1	$(2.7 \pm 0.6) \times 10^4$ -4.5 ± 0.5	$(7.2 \pm 1.0) \times 10^5$ -3.9 ± 0.2	$(1.5 \pm 0.04) \times 10^4$ -6.5 ± 0.1
10	$(6.2 \pm 0.6) \times 10^6$ -9.0 ± 0.1	$(6.9 \pm 0.3) \times 10^4$ -6.9 ± 0.1	$(1.3 \pm 0.03) \times 10^6$ -9.6 ± 0.04	$(2.7 \pm 0.2) \times 10^5$ -5.7 ± 0.1

Discussion of the Thermodynamic Parameters.

A perusal of the binding constant and ΔH values collected in Table 1 reveal a number of trends that are worthy of comment. First, the K_a values measured for the various hosts and guests in this study ranged from 6.2×10^3 to 6.2×10^6 M^{-1}. Host **1** is the most potent host in this series (low μM to high nM affinity) and displays higher K_a values toward virtually all of the guests compared to the capped hosts **2a** – **2c**. Among the capped hosts, **2b** performs best and binds guests **6 – 8** and **10** only 2 – 18-fold weaker than **1**; **2b** even binds guest **9** 1.5-fold stronger than **1**. Toward this panel of guests, host **2c** with a decylene linker performs significantly worse than **1** with K_a differences in the 20- to 100-fold range. Finally, host **2a** with an ethylene linker is the least potent host with K_a values that are generally 2 orders of magnitude weaker than **1**. Clearly, the inferiority of **2a** – **2c** compared to **1** is caused by the introduction of the covalent alkylene caps. We suggest the reasons are multifaceted. First, hosts **2a – 2c** are dianionic whereas host **1** is tetranionic which decreases the electrostatic driving force for host•guest complexation with **2a** – **2c**. Second, as shown in Figure 4, the presence of the covalent capping group results in a helical twist to the acyclic CB[n]-type receptor that prompts the alkylene linker to thread through the cavity rather than acting as a true capping group. A related effect has been previously identified crystallographically for a naphthalene walled acyclic CB[n]-type receptor.[12b] This intramolecular self-inclusion of the linker for **2b** and **2c** is energetically favorable; the energetic cost of explusion of the linker from the cavity must therefore be paid during the host•guest complexation step. The 5 – 48 fold higher binding affinities of hexylene capped **2b** compared to **2c** most likely reflects the larger energetic penalty associated with expulsion of the longer more hydrophobic decylene linker. The very poor performance of **2a** probably reflects that the short ethylene linker deforms the cavity by sterically preventing ammonium complexation at one portal and splaying the ureidyl carbonyls at the other portal which would reduce the potent ion-dipole

driving force which is well known for CB[n] hosts.[4e,16]

Individually, these hosts do not display high selectivity toward this series of guests (**6** – **10**) with the spread of K_a values covering a relatively small range (Host **1**: 13 fold; **2a**: 11-fold; **2b**: 12-fold; **2c**: 18-fold). The high affinity, but low selectivity nature of host **1** was previously put to good use through the solubilization of water insoluble anticancer agents.[10b] We were somewhat surprised that we did not see a trends in binding affinity related to guest size across the series from narrow guest **6** to bulky guest **10** for **2a** – **2c** as is observed for macrocyclic CB[n] because we presumed that the covalent caps would hold the aromatic walls in a more well defined and preorganized geometry. Unfortunately, Nature had other ideas and the host assumed the self-included geometry shown in Figure 4. Despite the low selectivity of these hosts, several trends in binding affinity can still be gleaned. First, guests **10** and **8** are the tightest binders toward hosts **1** and **2a** – **2c**. This is perhaps unsurprising given the well known complementarity between the methylene bridged glycoluril oligomer backbone of CB[n] and the roughly spherical surface of adamantanes that leads to ultratight (up to 10^{15} M^{-1}) binding toward CB[7].[4d,6a] Compound **8** with its aromatic ring is a preferred guest presumably because it benefits from enthalpically favorable π–π in the host•guest complexes. This interpretation is reinforced by the observation of largest enthalpic driving forces for the host•**8** complexes (Table 1). A comparison of the binding affinity of guest **9** and **10** reveals that all four hosts prefer the quaternary guest **10** by factors ranging from 2- to 18-fold. Related differences have been observed in the binding behavior of CB[7] and have been interpreted to result from the ability of the quaternary ammonium to engage in more and better ion dipole interactions with the ureidyl C=O portals of the host.[6b,18] Finally, we note that all of the complexation events listed in Table 1 are enthalpically favorable. Enthalpically favorable complexation is typically seen with cyclophanes and with CB[n] where it is attributed to a non-classical hydrophobic effect involving the release of intracavity waters

that do not possess a full complement of H-bonds.[4e,8g,19] In the present case, given that the cavities of **2a – 2c** are partially filled with their alkylene linkers the enthalpic driving force also reflects the difference between the intramolecular host-host contacts and the intermolecular host-guest contacts in the complexes. Finally, the strain energy associated with the helical distortion of uncomplexed host will be gained upon complexation.

Conclusions

Three new hosts **2a** – **2c** were synthesized with alkylene linkers of different lengths (ethyl, hexyl, and decyl) that were designed to cap one portal of the acyclic CB[n]-type skeleton and thereby preorganize the system. These new hosts were less water soluble than **1** due to the loss of two sulfonate groups and did not undergo intermolecular self-association. However, the intramolecular self-inclusion of the alkyl linkers inside the cavity of these hosts thwarted our attempts at increased preorganization and instead led to decreased binding affinities toward guests relative to **1**. Future work will try to overcome these disadvantages in the solubility and molecular recognition properties of **2a** – **2c** by incorporating linkers with more rigidity and hydrophilic groups that do not undergo self-inclusion processes. Such linkers would lead to entropic gains from the improved preorganization of the acyclic CB[n] cavity and enthalpic gains from the favorable interactions between the capping linker and encapsulated guest; without the energetic penalty of self-inclusion or loss in aqueous solubility.

Experimental Section.

General Experimental Details. Starting materials were purchased from commercial suppliers and were used without further purification. Compound **1** and **5** were prepared according to literature procedures.[10a] The synthesis of **3a**, **3b**, and **3c** from dibromoalkanes

and hydroquinone were performed by procedures similar to those reported in the literature.[13] The characterization data matches the reported data. Melting points were measured on a Meltemp apparatus in open capillary tubes and are uncorrected. IR spectra were measured on a JASCO FT/IR 4100 spectrometer and are reported in cm^{-1}. NMR spectra were measured on Bruker spectrometers operating at 400 or 600 MHz for ^{1}H and 200 MHz for ^{13}C NMR. ITC data was collected on a Malvern Microcal PEAQ-ITC instrument. Mass spectrometry was performed using a JEOL AccuTOF electrospray instrument (ESI).

Synthetic Procedures and Characterization Data.

Compound 3a. A mixture of hydroquinone (17.55 g, 159 mmol) and potassium carbonate (44.00 g, 318 mmol) in acetonitrile (123 mL) was heated to 85 °C under N_2. 1,2-dibromoethane (3.0 g, 1.4 mL, 15.9 mmol) was added dropwise and the reaction was stirred for 12 h. The reaction mixture was cooled and filtered and the filtrate was evaporated under reduced pressure to obtain the crude solid product. This crude product was washed with water (375 mL) and recrystallized from ethanol (75 mL) to obtain **3a** as an off white solid (0.51 g, 2.1 mmol, 13%). M.p. = 212-214 °C. IR (ATR, cm^{-1}): 3365w(br), 2943 w, 1512s, 1452m, 1373w, 1268w, 1211s, 1109 m, 1081w, 1070m, 1011w, 954s, 943w, 831s, 813m, 756s. ^{1}H NMR (600 MHz, DMSO): 8.91 (s, 2H), 6.78 (d, J = 8.9, 4H), 6.67 (d, J = 8.9, 4H), 4.14 (s, 4H). ^{13}C NMR (150 MHz, DMSO, 1,4-dioxane as internal reference): δ 151.4, 151.2, 115.8, 115.5, 67.0. High-Res MS (ESI): *m/z* 245.0825 ($[M - H]^-$), calculated for $C_{14}H_{13}O_4^-$ 245.0814.

Compound 3b. A mixture of hydroquinone (27.10 g, 246 mmol) and potassium carbonate (68.00 g, 492 mmol) in acetonitrile (190 mL) was heated to 85 °C under N_2. 1,6-dibromohexane (6.0 g, 3.8 mL, 24.6 mmol) was added dropwise and the reaction was stirred for 12 h. The reaction mixture was cooled and filtered and the filtrate was evaporated under reduced pressure to obtain the crude solid product. This crude product was washed with water

(500 mL) and recrystallized from ethanol (100 mL) to obtain **3b** as an off white solid (3.66 g, 12.3 mmol, 50%). M.p. = 178-180 °C. IR (ATR, cm^{-1}): 3381w(br), 2944w, 2866w, 1506s, 1477m, 1452m, 1395w, 1374m, 1299m, 1221s, 1167m, 1104s, 1072w, 1022s, 826s, 806m, 763s, 732m. ^{1}H NMR (600 MHz, DMSO): 8.85 (s, 2H), 6.72 (d, *J* = 8.9, 4H), 6.65 (d, *J* = 8.9, 4H), 3.84 (t, *J* = 6.5, 4H), 1.72-1.63 (m, 4H), 1.48-1.38 (m, 4H). ^{13}C NMR (150 MHz, DMSO): δ 151.5, 151.1, 115.7, 115.3, 67.8, 28.8, 25.4. High-Res MS (ESI): *m/z* 301.1443 ($[M - H]^-$), calculated for $C_{18}H_{21}O_4^-$ 301.1440.

Compound 3c. A mixture of hydroquinone (11.00 g, 100 mmol) and potassium carbonate (27.64 g, 200 mmol) in acetonitrile (160 mL) was heated to 85 °C under N_2. 1,10-dibromodecane (3 g, 2.2 mL, 10 mmol) was added dropwise and the reaction was stirred for 12 h. The reaction mixture was cooled and filtered and the filtrate was evaporated under reduced pressure to obtain the crude solid product. This crude product was washed with water (500 mL) and recrystallized from ethanol (75 mL) to obtain **3c** as an off white solid (1.18 g, 3.3 mmol, 33%). M.p. = 146-148 °C. IR (ATR, cm^{-1}): 3420w(br), 2931w, 2917w, 2852w, 1509m, 1473w, 1451w, 1395w, 1371w, 1299w, 1227s, 1168w, 1104w, 1048w, 822s, 767s. ^{1}H NMR (600 MHz, DMSO): 8.84 (s, 2H), 6.72 (d, *J* = 8.9, 4H), 6.65 (d, *J* = 8.9, 4H), 3.82 (t, *J* = 6.5, 4H), 1.64 (p, *J* = 7.0, 4H), 1.41-1.34 (m, 4H), 1.34-1.22 (m, 8H). ^{13}C NMR (150 MHz, DMSO, 1, 4-dioxane as internal reference): δ 151.5, 151.0, 115.6, 115.3, 67.8, 28.9, 28.8, 28.7, 25.5. High-Res MS (ESI): *m/z* 357.2080 ($[M - H]^+$), calculated for $C_{22}H_{29}O_4^-$ 357.2066.

Compound 4a. A solution of 1,3-propanesultone (1.34 g, 11 mmol) in 1,4-dioxane (11 mL) was added to a solution of **3a** (1.2 g, 4.1 mmol) in aqueous sodium hydroxide solution (10 wt%, 9 mL). This mixture was stirred at RT for 12 h and then filtered to collect the crude solid. The crude product was washed with acetone (30 mL). The filtered solid was dissolved

in hot water (15 mL) and precipitated with ethanol (30 mL) to obtain the off white solid **4a** (1.91 g, 3.6 mmol, 87%). M.p. > 300 °C. IR (ATR, cm^{-1}): 3422w(br), 2942w, 2520w, 1512s, 1450w, 1285w, 1201s, 1053s, 943m, 758m, 734m. ^{1}H NMR (600 MHz, D_2O): 7.06-7.04 (m, 4H), 7.04-7.02 (m, 4H), 4.37 (s, 4H), 4.18 (t, *J* = 6.3, 4H), 3.13-3.09 (m, 4H), 2.25-2.18 (m, 4H). ^{13}C NMR (150 MHz, D_2O, 1, 4-dioxane as internal reference): δ 152.3, 151.9, 115.9, 115.8, 67.0, 66.7, 47.3, 23.8. High-Res MS (ESI): *m/z* 489.0882 ($[M - 2Na + H]^-$), calculated for $C_{20}H_{25}O_{10}S_2^-$ 489.0889.

Compound 4b. A solution of 1,3-propanesultone (7.7 g, 63 mmol) in tetrahydrofuran (152 mL) was added to a solution of **3b** (7.6 g, 25.2 mmol) in aqueous sodium hydroxide solution (10 wt%, 76 mL). This mixture was stirred at RT for 12 h and then filtered to collect the crude solid. The crude product was washed with acetone (200 mL). The filtered solid was dissolved in hot water (100 mL) and precipitated with ethanol (200 mL) to obtain the off white solid **4b** (11.5 g, 9.4 mmol, 77%). M.p. > 300 °C. IR (ATR, cm^{-1}): 2941w, 2905w, 2870w, 1508s, 1475m, 1399w, 1289w, 1220s, 1188s, 1170s, 1115m, 1050s, 1031s, 830s, 805m, 767s, 755m, 734m. ^{1}H NMR (600 MHz, D_2O): 7.03-7.00 (m, 4H), 7.00-6.98 (m, 4H), 4.16 (t, *J* = 6.3, 4H), 4.07 (t, *J* = 6.5, 4H), 3.13-3.07 (m, 4H), 2.24-2.16 (m, 4H), 1.82-1.75 (m, 4H), 1.54-1.50 (m, 4H). ^{13}C NMR (150 MHz, DMSO, 1,4-dioxane as internal reference): δ 152.6, 115.3, 115.3, 67.8, 67.1, 48.0, 28.8, 25.4. High-Res MS (ESI): m/z 545.1519 ($[M - 2Na + H]^-$), calculated for $C_{24}H_{33}O_{10}S_2^-$ 545.1515.

Compound 4c. A solution of 1,3-propanesultone (1.00 g, 8.25 mmol) in tetrahydrofuran (20 mL) was added to a solution of **3c** (1.2 g, 3.3 mmol) in aqueous sodium hydroxide solution (10 wt%, 10 mL). This mixture was stirred at RT for 12 h and then filtered to collect the crude solid. The crude product was washed with acetone (30 mL). The filtered solid was dissolved in hot water (15 mL) and precipitated with ethanol (30 mL) to obtain the off white

solid **4c** (1.0 g, 1.6 mmol, 47%). M.p. > 300 °C. IR (ATR, cm^{-1}): 2935w, 2924w, 2853w, 1508s, 1475m, 1396w, 1289w, 1217s, 1115w, 1046s, 1029s, 827s, 768m, 731m. ^{1}H NMR (600 MHz, DMSO, 1, 4-dioxane as internal reference): 7.02-7.00 (m, 4H), 7.00-6.98(m, 4H), 4.14 (t, *J* = 6.3, 4H), 4.05 (t, *J* = 6.5 4H), 3.11-3.07 (m, 4H), 2.23-2.16 (m, 4H), 1.74 (p, *J* = 6.9, 4H), 1.44 (p *J* = 7.3, 4H), 1.39-1.30 (m, 8H). ^{13}C NMR (150 MHz, DMSO, 1, 4-dioxane as internal reference): δ 152.6, 152.6, 115.3, 115.2, 67.8, 67.1, 48.0, 29.0, 28.9, 28.8, 25.5, 25.4. High-Res MS (ESI): m/z 601.2131 ($[M - 2Na + H]^-$), calculated for $C_{28}H_{40}NaO_{10}S_2^-$ 601.2141.

Compound 2a. Compound **4a** (1.8 g, 3.4 mmol) was added to a solution of **5** (1.3 g, 1.7 mmol) in a mixture of trifluoroacetic acid (130 mL) and acetic anhydride (130 mL). This solution was stirred and heated at 70 °C for 3 h. The reaction mixture was cooled to room temperature, treated with methanol (130 mL), and the solvent was removed under reduced pressure to obtain the crude product. The crude product was washed three times with a mixture of water (50 mL) and acetone (100 mL). The dark orange colored solid obtained was loaded onto a Dowex® 1X2 chloride form, 200-400 mesh ion exchange resin (50 g). The column was eluted with increasing concentrations of hydrochloric acid (HCl) starting from plain water (750 mL) to 6M HCl (750 mL) to 12 M HCl (300 mL). The eluted fractions were analyzed by ^{1}H NMR and the almost pure compound **2a** was obtained in the fractions eluted with 12 M HCl. This fraction was dried under reduced pressure and washed with a mixture of water and methanol (1:1, v/v, 100 mL). Finally, the solid obtained was dissolved in water and the pH of the solution was adjusted to 7 using aqueous sodium hydroxide (1M). The solvent was removed under reduced pressure and the solid was further dried under high vacuum to obtain pure **2a** as a light orange solid (0.72 g, 0.56 mmol, 33%). M.p. > 300 °C. IR (ATR, cm^{-1}): 3447w (br), 1712s, 1466s, 1422m, 1377m, 1317s, 1228s, 1182s, 1084m, 1036s, 974m, 926w, 794s, 760s, 731m. ^{1}H NMR (600 MHz, D_2O): 7.17 (d, *J* = 9.0, 2H), 7.05 (d, *J* = 9.0,

2H), 5.63 (d, *J* = 15.5, 2H), 5.54 (d, *J* = 15.5, 2H), 5.50 - 5.42 (m, 8H), 5.26 (d, *J* = 16.4, 2H), 4.47 (d of d, *J* = 5.4, 2H), 4.33 (d, *J* = 16.4, 2H), 4.31 (d, *J* = 15.7, 2H), 4.27 – 4.24 (m, 4H), 4.19 – 4.14 (m, 6H), 3.87 (d of d, *J* = 5.4, 2H), 3.29-3.13 (m, 4H), 2.30 (p, *J* = 7.2, 4H), 1.76 (s, 6H), 1.75 (s, 6H). ^{13}C NMR (125 MHz, D_2O, 1, 4-dioxane as internal reference): δ 157.3, 156.2, 155.9, 154.5, 151.2, 149.0, 127.8, 127.7, 117.9, 113.9, 81.4, 78.9, 77.4, 71.1, 70.8, 70.6, 68.0, 51.8, 47.9, 47.7, 47.5, 35.4, 33.7, 24.2, 14.5, 13.7. High-Res MS (ESI): m/z 616.1650 ([M - 2Na]$^{2-}$), calculated for $C_{50}H_{56}N_{16}O_{18}S_2^{2-}$ 616.1700.

Compound 2b. Compound **4b** (2.0 g, 3.4 mmol) was added to a solution of **5** (1.3 g, 1.7 mmol) in a mixture of trifluoroacetic acid (130 mL) and acetic anhydride (130 mL). This solution was stirred and heated at 70 °C for 3 h. The reaction mixture was cooled to room temperature, treated with methanol (130 mL), and the solvent was removed under reduced pressure to obtain the crude product. The crude product was washed three times with a mixture of water (50 mL) and acetone (100 mL). The dark orange colored solid obtained was loaded onto a Dowex® 1X2 chloride form, 200-400 mesh ion exchange resin (50 g). The column was eluted with increasing concentrations of hydrochloric acid (HCl) starting from plain water (750 mL) to 6M HCl (750 mL) to 12 M HCl (300 mL). The eluted fractions were analyzed by ^{1}H NMR and the almost pure compound **2b** was obtained in the fractions eluted with 12 M HCl. This fraction was dried under reduced pressure and washed with a mixture of water and methanol (1:1, v/v, 100 mL). Finally, the solid obtained was dissolved in water and the pH of the solution was adjusted to 7 using aqueous sodium hydroxide (1M). The solvent was removed under reduced pressure and the solid was further dried under high vacuum to obtain pure **2b** as a light yellow solid (0.30 g, 0.56 mmol, 13%). M.p. > 300 °C. IR (ATR, cm^{-1}): 3449w (br), 2939w, 1719s, 1464m, 1425w, 1378w, 1314m, 1230m, 1181m, 1084m, 1036s, 972m, 924w, 797s, 758m, 730w. ^{1}H NMR (600 MHz, D_2O): 7.01-6.96 (m, 4H), 5.72 (d, *J* = 15.4, 1H), 5.57 (d, *J* = 15.4, 1H), 5.56 (d, *J* = 15.7, 2H), 5.53 (d, *J* = 15.7, 2H), 5.46

(d, *J* = 9.0, 2H), 5.38 (d, *J* = 16.4, 2H), 5.37 (d, *J* = 9.1, 4H), 5.25 (d, *J* = 16.4, 2H), 4.36 (d, *J* = 15.7, 2H), 4.32 (d, *J* = 16.4, 2H), 4.24 – 4.12 (m, 4H), 4.22 (d, *J* = 15.7, 2H), 4.16 (d, *J* = 15.4, 1H), 4.13 (d, *J* = 16.4, 2H), 4.03 (d, *J* = 15.4, 1H), 3.90-3.76 (m, 4H), 3.127-3.11 (m, 4H), 2.34-2.23 (m, 4H), 1.76 (s, 6H), 1.75 (s, 6H), 1.39-1.26 (m, 4H), 1.18-1.09 (m, 2H), 1.05-0.95 (m, 2H). ^{13}C NMR (150 MHz, DMSO, 1, 4-dioxane as internal reference): δ 156.0, 155.2, 154.8, 154.1, 150.2, 150.0, 127.8, 126.6, 113.9, 113.5, 77.3, 76.9, 70.5, 70.2, 69.5, 68.5, 64.6, 59.2, 48.5, 48.3, 48.0, 35.7, 34.4, 28.0, 25.6, 24.0, 16.8, 15.0. High-Res MS (ESI): m/z 644.2016 ([M - 2Na]$^{2-}$), calculated for $C_{54}H_{64}N_{16}O_{18}S_2^{2-}$ 644.2013.

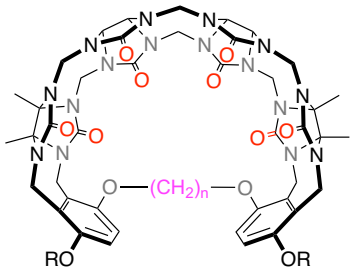
Compound 2c. Compound **4c** (1.7 g, 2.6 mmol) was added to a solution of **5** (1.0 g, 1.3 mmol) in a mixture of trifluoroacetic acid (100 mL) and acetic anhydride (100 mL). This solution was stirred and heated at 70 °C for 3 h. The reaction mixture was cooled to room temperature, treated with methanol (100 mL), and the solvent was removed under reduced pressure to obtain the crude product. The crude product was washed three times with a mixture of water (50 mL) and acetone (100 mL). The dark orange colored solid obtained was loaded onto a Dowex® 1X2 chloride form, 200-400 mesh ion exchange resin (50 g). The column was eluted with increasing concentrations of hydrochloric acid (HCl) starting from plain water (750 mL) to 6M HCl (750 mL) to 12 M HCl (300 mL). The eluted fractions were analyzed by ^{1}H NMR and the almost pure compound **2c** was obtained in the fractions eluted with 12 M HCl. This fraction was dried under reduced pressure and washed with a mixture of water and methanol (1:1, v/v, 100 mL). Finally, the solid obtained was dissolved in water and the pH of the solution was adjusted to 7 using aqueous sodium hydroxide (1M). The solvent was removed under reduced pressure and the solid was further dried under high vacuum to obtain pure **2c** as an off white solid (0.47 g, 0.34 mmol, 26%). M.p. > 300 °C. IR (ATR, cm^{-1}): 3435w (br), 2930w, 1721s, 1463s, 1425m, 1378m, 1313m, 1230s, 1181s, 1085m, 1037s, 972m, 924w, 823m, 797s, 757m, 731m. ^{1}H NMR (600 MHz, D_2O): 7.10-6.98 (m, 4H), 5.72

(d, *J* = 15.2, 1H), 5.64 (d, *J* = 15.2, 1H), 5.59 (d, *J* = 15.7, 2H), 5.56 (d, *J* = 15.7, 2H),5.45 (d, *J* = 9.0, 2H), 5.45 (d, *J* = 16.5, 2H), 5.40 (d, *J* = 9.0, 2H), 5.31 (d, *J* = 16.5, 2H), 4.31 (d, *J* = 15.7, 2H), 4.23 (d, *J* = 15.7, 2H), 4.20 – 4.08 (m, 11H), 4.06 (d, J = 15.2, 1H), 4.01-3.93 (m, 2H), 3.28-3.09 (m, 4H), 2.35-2.22 (m, 4H), 1.78 (s, 6H), 1.74 (s, 6H), 1.58-1.46 (m, 2H), 1.40-1.27 (m, 2H), 1.12-0.93 (m, 4H), 0.91-0.75 (m, 6H), 0.75-0.65 (m, 2H). ^{13}C NMR (150 MHz, DMSO, 1, 4-dioxane as internal reference): δ 156.1, 155.2, 154.6, 154.0, 150.2, 150.1, 128.1, 114.0, 113.6, 113.5, 77.5, 76.4, 70.7, 70.4, 69.8, 68.6, 64.6, 59.2, 48.4, 48.3, 48.2, 34.7, 34.5, 28.5, 27.2, 27.1, 25.6, 24.2, 16.6, 15.7.High-Res MS (ESI): m/z 672.2341 ([M - 2Na]$^{2-}$), calculated for $C_{58}H_{72}N_{16}O_{18}S_2^{2-}$ 672.2326.

Disclosure statement. L.I. holds an equity stake in Calabash Bioscience which aims to develop acyclic cucurbiturils for biomedical applications.

Acknowledgement. We thank the National Science Foundation (CHE-1404911 and CHE-1807486 to L.I.) and the University of Maryland (Graduate Deans Dissertation Fellowship to S. G.).

Table of Contents Graphic.



2 (n = 2, 6, 10), R = $(CH_2)_3SO_3Na$

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