Organic LETTERS

Letter

pubs.acs.org/OrgLett

Synthesis and Recognition Properties of Cucurbit[8]uril Derivatives

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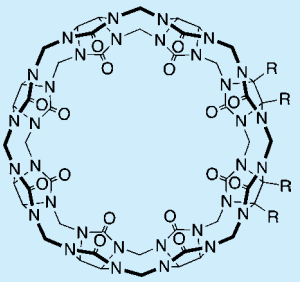
Supporting Information

ABSTRACT: A building block approach to the synthesis of Me_4CB[8] and Cy_2CB[8] by condensation of glycoluril hexamer **1** with bis(cyclic ethers) **2** is reported. X-ray crystallography demonstrates that the equatorial substitution results in an ellipsoidal cavity. Me_4CB[8] and Cy_2CB[8] display enhanced aqueous solubility and retain the ability to bind to guests (**3**–**9**) typical of unsubstituted CB[8]. The higher inherent solubility of Me_4CB[8] allowed it to be used as a solubilizing excipient for insoluble drugs.



The condensation reaction of glycoluril with sources of formaldehyde under strongly acidic conditions gives cucurbit[*n*]uril (CB[*n*], *n* = 5, 6, 7, 8, 10, 14) homologues as the major products in high yield.[1] CB[*n*] containers are highly symmetric (D_{nh}) and feature a hydrophobic cavity defined by the glycoluril rings and two hydrophilic C═O portals.[2] CB[*n*] compounds have been the subject of intense investigation over the past 15 years because of their ability to bind strongly (K_a commonly 10^9 M^{-1}) and selectively to hydrophobic cations in aqueous solution.[2b,3] The high selectivity displayed by unfunctionalized CB[*n*] translates into highly stimuli responsive (e.g., pH, electrochemistry, photochemistry, chemical) host–guest complexation phenomena.[4] Accordingly, CB[*n*] compounds have been used to construct a variety of functional supramolecular systems including chemical sensors, polymeric systems for triggered drug delivery, molecular machines, and supramolecular catalysts.[4a,b,5] Unfortunately, CB[*n*] compounds have some undesirable characteristics including the poor aqueous solubility of CB[6] and CB[8] and the lack of reactive functional groups. Therefore, an important goal in the field has been the development of methods for the preparation of CB[*n*] derivatives and related CB[*n*]-type molecular containers including hemicucurbiturils, bambusurils, biotinurils, multifarenes, and acyclic CB[*n*].[6] In one approach, unfunctionalized CB[*n*] compounds are subjected to oxidation with persulfate to deliver perhydroxylated CB[*n*] (e.g., $(HO)_{2n}$CB[*n*]) or monohydroxylated derivatives $(HO)_1$CB[*n*].[7] In a second approach combinations of glycoluril or glycoluril surrogate building blocks undergo macrocyclization reactions to deliver CB[*n*] derivatives and CB[*n*] analogues.[8] Recently, the Isaacs group prepared glycoluril hexamer **1** by template synthesis and transformed **1** into monofunctionalized CB[6] and CB[7] derivatives.[9] In this paper we further develop this building block methodology to allow for the synthesis of derivatives of CB[8].

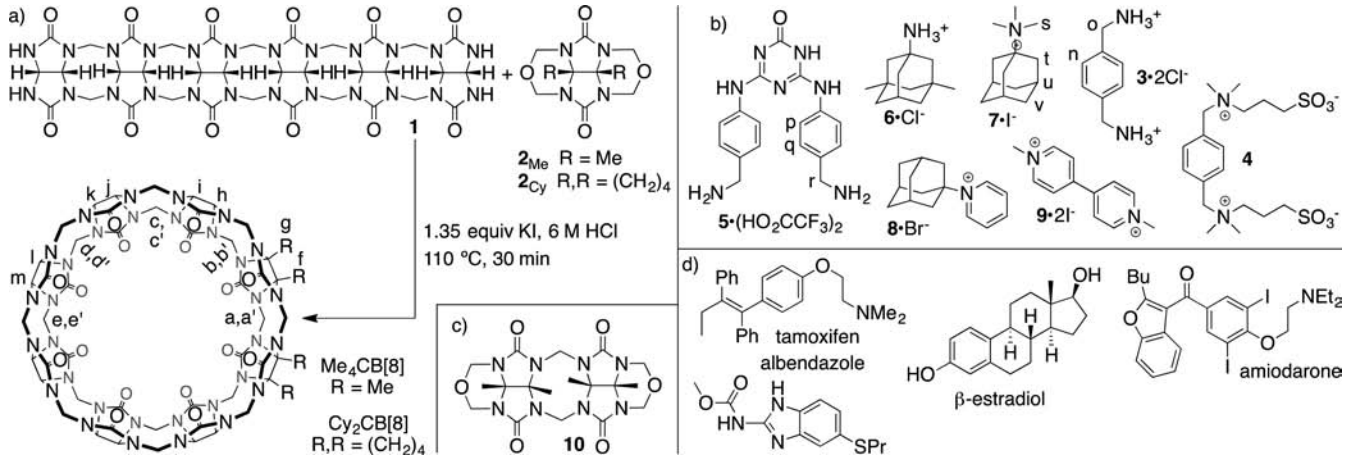
The successful synthesis of monofunctionalized CB[7] derivatives by reaction of **1** with glycoluril bis(cyclic ethers) $\mathbf{2}_{Me}$ and $\mathbf{2}_{Cy}$ encouraged us to adapt this chemistry toward CB[8]. Accordingly, we performed the reaction between **1** and $\mathbf{2}_{Me}$ (2.5 equiv) in the presence of KI in 6 M HCl at 110 °C for 30 min (Scheme 1). The crude reaction mixture was analyzed by ^{1}H NMR using *p*-xylylenediammonium ion (**3**) as a probe[9b] which revealed the presence of CB[6], Me_2CB[7], and Me_4CB[8] in a 5:32:52 ratio. The purification was challenging. Initially, the crude reaction mixture was treated with disulfonated guest **4** to form the tight and very slowly dissociating Me_2CB[7]·**4** complex. This mixture was loaded onto a Dowex 50WX2-400 ion exchange column that was eluted with formic acid/HCl mixtures. Complex Me_2CB[7]·**4** which is a neutral zwitterion but which bears two external SO_3^- groups elutes rapidly from the sulfonated Dowex resin followed by an admixture of CB[6] and Me_4CB[8]. To further enrich the Me_4CB[8] content of the refined solid, the solid was washed with a mixture of formic acid, acetic acid, and acetone. The refined solid was subsequently treated with activated carbon and heated at reflux to yield Me_4CB[8] in a pure form (320 mg, 11% yield). Me_4CB[8] was fully characterized by the standard methods which are fully in accord with the depicted structure. For example, the electrospray ionization spectrum established the molecular formula $C_{60}H_{70}N_{34}O_{16}$ corresponding to $[Me_4CB[8]\cdot\mathbf{3}]^{2+}$ (Supporting Information (SI)). Figure 1a and b shows the ^{1}H NMR spectrum recorded for Me_4CB[8] on its own and as the Me_4CB[8]·$\mathbf{3}_2$ complex. The observation of two Me resonances (f and g) and five doublets (H_a – H_e; 1:2:2:2:1 intensity ratio) in the 4–5 ppm region for the diastereotopic CH_2 groups is consistent with the depicted structure of Me_4CB[8] as is the observation of four C═O resonances in the ^{13}C NMR spectrum (Figure S10).

Cy_2CB[8] was prepared and purified in an analogous manner and was fully characterized (SI). Both CB[8] derivatives possess enhanced solubility in pure water relative to CB[8] itself (Me_4CB[8] = 3.1 mM, Cy_2CB[8] = 0.9 mM, CB[8] < 10

Received: September 8, 2015
Published: September 25, 2015

DOI: 10.1021/acs.orglett.5b02558
Org. Lett. 2015, 17, 5068–5071

Scheme 1. (a) Synthesis of $Me_4CB[8]$ and $Cy_2CB[8]$; (b) Guests 3–9; (c) Building Block 10; (d) Insoluble Drugs



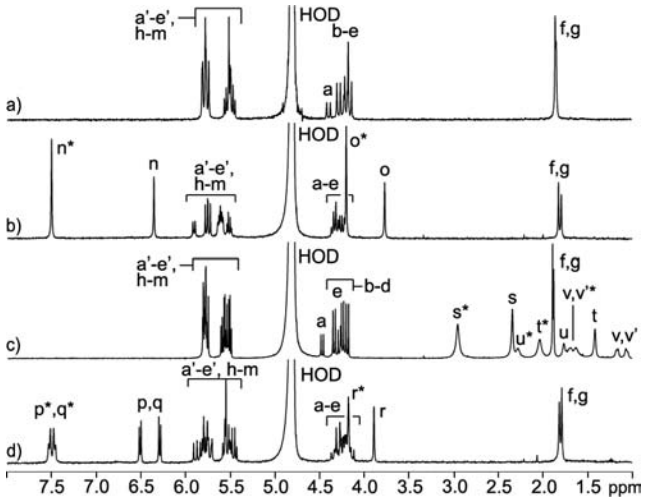


Figure 1. ^1H NMR spectra (D_2O, 600 MHz, rt) of (a) $Me_4CB[8]$, (b) $Me_4CB[8]{\cdot}\mathbf{3}_2$ and excess **3**, (c) $Me_4CB[8]{\cdot}\mathbf{7}$ and excess **7**, and (d) $Me_4CB[8]{\cdot}\mathbf{5}$ and excess **5**. Resonances marked with asterisks (*) arise from unbound guest.

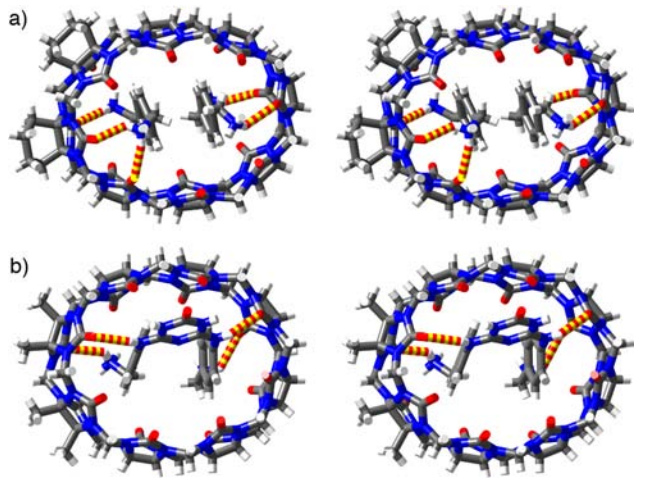


Figure 2. Stereoviews of the X-ray crystal structures of (a) $Cy_2CB[8]{\cdot}\mathbf{3}_2$ and (b) $Me_4CB[8]{\cdot}\mathbf{5}$. Color code: C, gray; H, white; N, blue; O, red; H-bonds, red-yellow striped.

μM).[10] In an effort to better understand the $Me_4CB[8]$ forming reaction and thereby improve the scope and yield of this reaction, we performed some control experiments. A priori, one can postulate two pathways (SI): (1) 2 equiv of $\mathbf{2}_{Me}$ undergo dimerization to yield tetramethyl glycoluril dimer **10** which then reacts with **1** to give $Me_4CB[8]$, or (2) the two pairs of NH groups of **1** react with 2 equiv of $\mathbf{2}_{Me}$ to give a linear glycoluril octamer bis(cyclic ether) which then undergoes unimolecular cyclization to give $Me_4CB[8]$. Experimentally, we reacted **1** with **10** (Scheme 1c)[11] under our standard reaction conditions and observed mainly CB[6], traces of $Me_2CB[7]$, but no $Me_4CB[8]$. Accordingly, we believe that $Me_4CB[8]$ formation predominately follows pathway 2.

We were fortunate to obtain single crystals of $Me_4CB[8]{\cdot}\mathbf{3}_2$, $Cy_2CB[8]{\cdot}\mathbf{3}_2$, and $Me_4CB[8]{\cdot}\mathbf{5}$ and determine their structures by X-ray crystallography (Figure 2, SI) which corroborates the structural assignments made by NMR spectroscopy and symmetry arguments. There are several noteworthy aspects of the crystal structures. For example, the complexes exhibit substantial ellipsoidal deformations as measured between opposing CH_2 groups ($Cy_2CB[8]{\cdot}\mathbf{3}_2$: long axis = 14.00 Å and short axis = 10.95 Å; $Me_4CB[8]{\cdot}\mathbf{5}$: long axis = 14.37 Å and short axis = 11.21 Å) which can be attributed in part to the steric demands of the substituted glycolurils and in part to the shape of the guests; related deformations have previously been noted for $Me_4CB[6]$ and its complexes.[8c] The cyclohexyl rings of $Cy_2CB[8]$ exist in the boat conformation because of the conformational restraints of the bicyclic glycoluril framework enforcing a syn-periplanar dihedral angle (0.51° in the crystal). The two aromatic rings of guest **3** in the $Cy_2CB[8]{\cdot}\mathbf{3}_2$ complex are arranged in an offset geometry with a mean interplanar separation of 3.71 Å which is slightly longer than that typically ascribed to π–π interactions (3.4–3.6 Å).[12] In the structure of $Me_4CB[8]{\cdot}\mathbf{5}$, guest **5** adopts a U-shaped conformation as previously observed for $CB[8]{\cdot}\mathbf{5}$.[3b] The three-dimensional packing of the complexes in the crystal feature the I^- counterions in the interstitial sites between complexes presumably benefiting from glycoluril CH···I^- interactions on the convex face of the CB[8] derivatives.[13]

After having firmly established the structures of $Me_4CB[8]$ and $Cy_2CB[8]$ along with their enhanced aqueous solubility we turned to an investigation of their host–guest recognition properties toward **3**–**9**. Figure 1b shows the ^1H NMR spectra recorded for a mixture of $Me_4CB[8]$ and excess **3** which gives a mixture of $Me_4CB[8]{\cdot}\mathbf{3}_2$ and free **3**. Exchange processes are slow on the ^1H NMR chemical shift time scale, and distinct

DOI: 10.1021/acs.orglett.5b02558
Org. Lett. 2015, 17, 5068–5071

upfield shifted resonances are observed for H_n and H_o. Similarly, Figure 1d shows the ^{1}H NMR spectrum recorded for a mixture of Me_4CB[8] and **5** (2 equiv) which shows resonances for free **5** and the Me_4CB[8]·**5** complex. The observation of two upfield shifted doublets for H_p and H_q indicate that **5** adopts a U-shaped conformation in the Me_4CB[8]·**5** complex in solution similar to what is observed in the solid state (Figure 2b). Lastly, Figure 1c shows the ^{1}H NMR spectrum recorded for a mixture of Me_4CB[8] and **7** (2 equiv) which shows resonances for free **7** and separate upfield shifted resonances for the Me_4CB[8]·**7**. The expected five resonances in a 1:2:2:2:1 ratio for $H_a - H_e$ are observed in the 4.2−4.5 ppm region. We also investigated the complexes of Me_4CB[8] with guests **6**−**9** and Cy_2CB[8] with guests **3**−**9** (SI). Overall, we find that Me_4CB[8] and Cy_2CB[8] form host−guest complexes with guests previously known to bind with CB[8].[3b]

After having qualitatively determined that the CB[8] derivatives share the recognition abilities of unsubstituted CB[8] we decided to compare the binding constants of Me_4CB[8] with those of CB[8] in a quantitative manner. We hypothesized that the ellipsoidal deformation observed in the X-ray crystal structure of Me_4CB[8]·**5** might translate into a higher affinity of Me_4CB[8] toward ellipsoidal guests compared to unsubstituted CB[8]. For this purpose, we allowed Me_4CB[8] and CB[8] to compete for a limited quantity of guest according to eqs 1 and 2.[14] We identify resonances for Me_4CB[8]·guest and CB[8]·guest that can be separately integrated which allows a determination of the relative concentrations of Me_4CB[8]·guest and CB[8]·guest, and by use of mass balance expressions we can determine the concentrations of free Me_4CB[8] and CB[8] (SI). For example, Figure 3 shows the ^{1}H NMR spectra recorded at 800 MHz for a

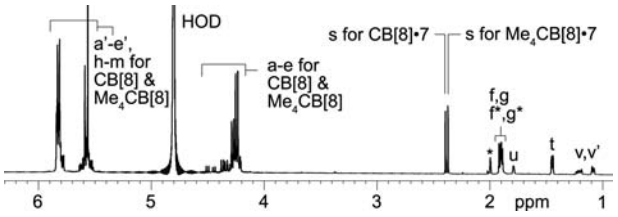


Figure 3. ^{1}H NMR spectra (50 mM NaO_2CCD_3 buffered D_2O, pH 4.74, 800 MHz, rt) for an equimolar (50 μM) mixture of Me_4CB[8], CB[8], and **7**.

1:1:1 mixture of CB[8], Me_4CB[8], and **7**. We use the ^{1}H NMR resonances for H_s in the CB[8]·**7** and Me_4CB[8]·**7** complexes which appear at 2.39 and 2.37 ppm respectively to determine the complex concentrations. Substitutions of the concentration values into eq 2 allows us to determine K_{rel}; eq 3 is then used to determine K_a for Me_4CB[8] using the known values toward unsubstituted CB[8].[3b] In this manner, we determined that Me_4CB[8] binds tighter to guests **5** (2.52-fold, $K_a = 1.45 \times 10^{11}$ M^{-1}), **7** (1.16-fold, $K_a = 1.12 \times 10^{11}$ M^{-1}), and **8** (2.43-fold, $K_a = 4.87 \times 10^9$ M^{-1}) than CB[8] does; in contrast Me_4CB[8] binds more weakly than CB[8] to **6** (K_{rel} = 0.26, $K_a = 1.13 \times 10^{11}$ M^{-1}). Unfortunately, the trends in K_{rel} values are not sufficiently clear to allow us to make any conclusions regarding the influence of host ellipsoidal deformation on K_{rel}.

$$\begin{array}{ccc} \text{CB[8]}\cdot\mathbf{G} & & \text{Me}_4\text{CB[8]}\cdot\mathbf{G} \\ + & \overset{K_{rel}}{\rightleftharpoons} & + \\ \text{Me}_4\text{CB[8]} & & \text{CB[8]} \end{array} \quad (1)$$

$$K_{rel} = \frac{[\text{Me}_4\text{CB[8]}\cdot\mathbf{G}][\text{CB[8]}]}{[\text{CB[8]}\cdot\mathbf{G}][\text{Me}_4\text{CB[8]}]} \quad (2)$$

$$K_{a,\text{Me}_4\text{CB[8]}} = K_{rel}\cdot K_{a,\text{CB[8]}} \quad (3)$$

Finally, we sought to take advantage of the higher solubility of Me_4CB[8] compared to CB[8] in a relevant application area. Accordingly, we decided to investigate the ability of Me_4CB[8] to act as a solubilizing agent for four insoluble drugs (amiodarone, estradiol, tamoxifen, albendazole).[15] Experimentally, we stir a solution of a known concentration of Me_4CB[8] (or CB[8]) with an excess of insoluble drug until equilibrium is reached, filter off the insoluble material, and then measure the concentration of drug in solution by ^{1}H NMR integration of drug resonances relative to an internal standard of known concentration. Multiple measurements at different host concentrations are then used to construct a phase solubility diagram. Figure 4 shows the phase solubility diagrams (PSDs)

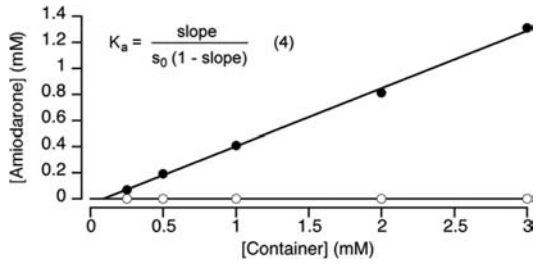


Figure 4. Phase solubility diagrams constructed for amiodarone with Me_4CB[8] (●) and CB[8] (○). Conditions: 20 mM sodium phosphate buffered D_2O (pH = 7.4, rt).

constructed for Me_4CB[8] or CB[8] with amiodarone. Linear PSDs are generally indicative of the formation of soluble well-defined 1:1 host−guest complexes.[15] The slope of linear phase solubility diagrams (PSD) is related to the inherent solubility of the drug (s_0) and the binding constant (K_a, M^{-1}) for the host−drug complex according to eq 4. The slope of the PSD for Me_4CB[8] with amiodarone is 0.44 (K_a = 12 100 M^{-1}) whereas the slope is too small to measure for CB[8]. Given that the K_a values for Me_4CB[8] and CB[8] complexes are very similar for soluble guests as shown above, it is somewhat counterintuitive that Me_4CB[8] is the superior solubilizing agent. In this case, the CB[8]·amiodarone complex is formed but is insoluble, hence it is the enhanced solubility of Me_4CB[8] and its Me_4CB[8]·drug complexes relative to CB[8] that is crucial for its function as a solubilizing agent. Similar PSD measurements were done with tamoxifen, albendazole, and estradiol (Table S1). In all cases, Me_4CB[8] was a good solubilizing agent with slope values in the 0.08−0.44 range.

In summary, we have demonstrated that Me_4CB[8] and Cy_2CB[8] can be formed by the condensation of glycoluril hexamer **1** with bis(cyclic ethers) **2** under well-defined conditions. The CB[8] derivatives maintain the essential binding features of unfunctionalized CB[8] in that they also bind to guests **3**−**9** and display comparable complexation induced changes in chemical shift. ^{1}H NMR competition experiments between Me_4CB[8] and CB[8] for a limited

DOI: 10.1021/acs.orglett.5b02558
Org. Lett. 2015, 17, 5068−5071

quantity of guest established that $Me_4CB[8]$ displays quite similar binding constants (K_a) compared to CB[8]. Finally, $Me_4CB[8]$ is a better solubilizing agent than CB[8] for four insoluble drugs which can be traced to the enhanced solubility of the $Me_4CB[8]$·drug complexes. In conclusion, we present the first building block strategy that allows the synthesis of CB[8] derivatives. The work, especially in light of the recent report of $(HO)_1CB[8]$,[7d] suggests a bright future for CB[8] derivatives in the basic science of CB[*n*] chemistry and advanced applications.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02558.

Experimental procedures, characterization data, ^1H and ^{13}C NMR spectra for new compounds; ^1H NMR spectra for host·guest complexes; data from NMR competition experiments; data from phase solubility measurements (PDF)

Crystallographic information for $Me_4CB[8]\cdot\mathbf{3}_2$ (CIF)

Crystallographic information for $Cy_2CB[8]\cdot\mathbf{3}_2$ (CIF)

Crystallographic information for $Me_4CB[8]\cdot\mathbf{5}$ (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

B.V. thanks the University of Maryland for a Millard and Lee Alexander Fellowship. We thank the National Science Foundation (CHE-1404911 to L.I.) for partial financial support.

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Org. Lett. 2015, 17, 5068−5071