New Cucurbituril Homologues: Syntheses, Isolation, Characterization, and X-ray Crystal Structures of Cucurbit[*n*]uril (*n* = 5, 7, and 8)

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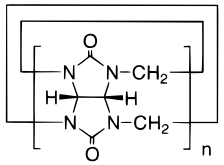
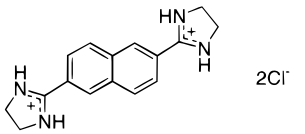
Cucurbituril (CB[6]) is a hexameric macropolycyclic compound self-assembled from an acid-catalyzed condensation reaction of glycoluril and formaldehyde.[1,2] Its easy synthesis and rigid structure with a hollow core make CB[6] one of the attractive synthetic receptors. Its inclusion properties have been investigated extensively by Mock and co-workers.[3] Enzyme-like behavior of CB[6] effecting a large rate acceleration in a cycloaddition reaction has also been observed.[4] Its ability to bind alkali metal ions at the portals of the cavity allowed us to study molecular container systems capable of reversible encapsulation and release of guest molecules.[5] We also have demonstrated that CB[6] can be used as a molecular "bead" in self-assembly of interlocked structures such as polyrotaxanes and molecular necklaces.[6] CB[6] is also known to be effective for removal of dyes from waste waters.[7]

Although several homologues are available in calixarenes, which are obtained from a base-catalyzed condensation of phenol and formaldehyde, cucurbituril homologues with greater or fewer glycoluril units have not been reported.[8] Here we report the new family of cucurbituril, cucurbit[*n*]uril (CB[*n*]) (*n* = 5, 7, and 8) containing five, seven, and eight glycoluril units, respectively.

Reaction of glycoluril with formaldehyde in 9 M sulfuric acid at ∼75 °C for 24 h and then at ∼100 °C for 12 h yielded a mixture of CB[*n*] (*n* = 5−11) as evidenced by electrospray ionization mass spectrometry.[9] Although its contents vary from batch to batch, the mixture typically contains ∼60% of CB[6], ∼10% of CB[5], ∼20% of CB[7], and ∼10% of other higher CB homologues. Apparently, the reaction of glycoluril and formaldehyde first generates linear oligomeric products which then cyclize to produce a library of cucurbituril. The cyclization at the lower temperature compared to that employed in the conventional synthesis[2] of CB[6] allows formation of significant amounts of other CB homologues besides CB[6]. The major product CB[6] was separated from the mixture by fractional dissolution of other CB homologues with acetone/water. From the acetone/water soluble portion, CB[5] and CB[7] were isolated by fractional crystallization/precipitation.[9]



CB[n]



1•2HCl

The homologue CB[8] was isolated from a CB[*n*] mixture that had been prepared by a modified procedure. Reaction of glycoluril and formaldehyde in the presence of HCl in a high-pressure reactor at 115 °C for 24 h produced a white powder which, when treated with dilute sulfuric acid in a way similar to the one described above, yielded a mixture of CB[*n*] having a similar composition with slightly higher CB[7] and CB[8] contents. Upon standing, crystals of CB[8] were produced from a solution of the CB[*n*] mixture in 6 M sulfuric acid.[9]

The new CB homologues CB[5], CB[7], and CB[8] have been characterized by various spectroscopic methods and X-ray crystallography. In the ^{1}H NMR spectra, CB homologues show the same peak pattern as that of CB[6], but their chemical shift values are slightly and yet distinctively different from each other. Electrospray ionization mass spectral data support the pentameric, heptameric, and octameric nature of CB[5], CB[7], and CB[8], respectively. Their structures have been confirmed by X-ray crystallography (Figure 1).[10] Table 1 compares some structural parameters of the CB homologues. As we go from CB[5] to CB[8], the mean diameter of the internal cavity increases progressively from ∼4.4 to ∼8.8 Å. Likewise, the oxygen-bounded portal increases its mean diameter from ∼2.4 to ∼6.9 Å.

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(9) A mixture of glycoluril (5.68 g, 40.0 mmol), formaldehyde (37% in water, 7.0 mL, 91 mmol), and 9 M sulfuric acid (20 mL) was heated at 75 °C for 24 h and then at 100 °C for 12 h. After the reaction mixture was poured into water (200 mL), acetone (1.0 L) was added to produce precipitate. The precipitate was separated by decantation, washed with water/acetone (1:4), and filtered. The major product CB[6] was separated from the mixture by fractional dissolution of other CB homologues with acetone/water (1:2). From the acetone/water soluble portion, CB[5] and CB[7] were isolated by fractional crystallization/precipitation and further purified by recrystallization: CB[5], 220 mg (2.2%); CB[7], 245 mg (2.8%). For CB[8], glycoluril (2.79 g, 19.6 mmol), formaldehyde (6.0 mL, 78 mmol), and 12 N HCl (0.5 mL) were reacted in a high-pressure reactor at 115 °C for 24 h to produce a white powder that was then treated with 7.5 M sulfuric acid in a way similar to the one described above to yield a mixture of CB[*n*]. Crystals of CB[8] were produced when a solution of the CB[*n*] mixture in 6 M sulfuric acid was allowed to stand (120 mg, 2.9%). See Supporting Information for details. CB[5]: ^{1}H NMR(500 MHz, $D_2O/CF_3CO_2D/D_2SO_4$ (1:1:0.15)): δ 4.43 (d, 10H, J = 15.5 Hz), 5.65 (s, 10H), 5.85 (d, 10H, J = 15.5 Hz), ^{13}C NMR (125 MHz) δ 54.0, 72.9, 160.0. ESI-MS: m/z 963.19 (CB[5] + Cs)$^+$. CB[7]: ^{1}H NMR(500 MHz, $D_2O/CF_3CO_2D/D_2SO_4$ (1:1:0.15)): δ 4.29 (d, 14H, J = 15.5 Hz), 5.60 (s, 14H), 5.91 (d, 14H, J = 15.5 Hz), ^{13}C NMR (125 MHz) δ 56.5, 75.2, 160.2. ESI-MS: m/z 1295.19 (CB[7] + Cs)$^+$. CB[8]: ^{1}H NMR(500 MHz, $D_2O/CF_3CO_2D/D_2SO_4$ (1:1:0.15)): δ 4.28 (d, 16H, J = 15.5 Hz), 5.60 (s, 16H), 5.93 (d, 16H, J = 15.5 Hz), ^{13}C NMR (125 MHz) δ 57.6, 75.9, 160.5. ESI-MS: m/z 1461.31 (CB[8] + Cs)$^+$. Satisfactory elemental analyses were obtained for all the new compounds.

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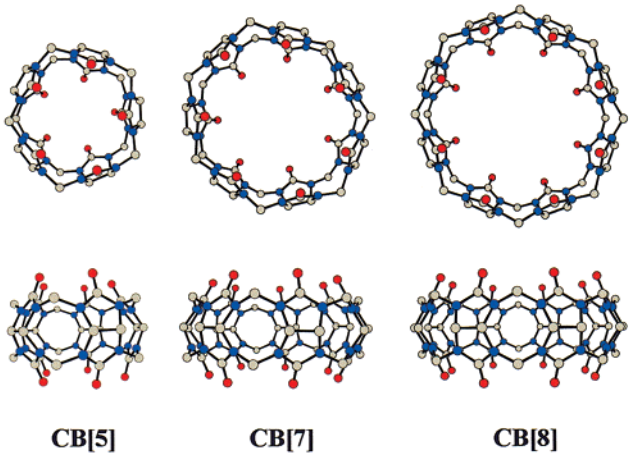

Figure 1. X-ray crystal structures of CB[5], CB[7], and CB[8]. Guest molecule(s) encapsulated in the cavities[10] are omitted for clarity. Color codes: carbon, gray; nitrogen, blue; oxygen, red.

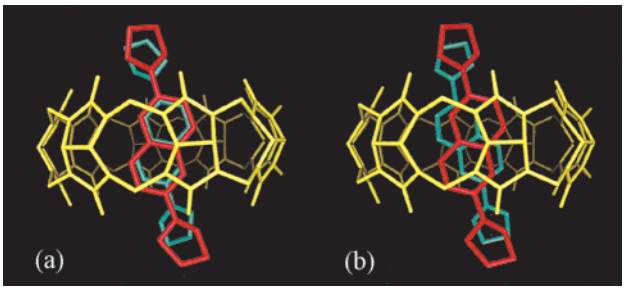

Figure 2. X-ray crystal structure of **2**. An inversion center is located at the center of the host. Each guest molecule is disordered over two sites. The two naphthalene rings in **2** are in either "*syn*" (meso form) (a) or "*anti*" (*dl*-form) (b) orientation.

Table 1. Structural Parameters for Cucurbit[*n*]uril ($n = 5-8$)

	CB[5][a]	CB[6][b]	CB[7][a]	CB[8][a]
portal diameter (Å)	2.4	3.9	5.4	6.9
cavity diameter (Å)[c]	4.4	5.8	7.3	8.8
cavity volume (Å^3)	82	164	279	479
outer diameter (Å)[c]	13.1	14.4	16.0	17.5
height (Å)	9.1	9.1	9.1	9.1

[a] Based on X-ray crystal structures determined in this work. [b] Based on X-ray crystal structures taken from ref 5a. [c] Values measured at the "equator" of the receptors.

The much larger cavities of CB[7] and CB[8] compared to that of CB[6] prompted us to study inclusion properties of the new receptors. A molecular mechanical calculation suggested that protonated 2,6-bis(4,5-dihydro-1*H*-imidazol-2-yl)naphthalene (**1**)[11] would be too large to form a host−guest complex with CB[6], but would form a 1:1 complex with CB[7] and a 1:2 complex with CB[8]. This conjecture has been confirmed by ^{1}H NMR spectroscopy and mass spectrometry (see Supporting Information). Interestingly, when CB[8] and the guest are mixed in a 1:1 stoichiometry, only the 1:2 host−guest complex is observed by NMR spectroscopy. The structure of the 1:2 host−guest complex (**2**) has been determined by X-ray crystallography (Figure 2).[12] As expected, the naphthalene moieties are located inside the cavity while the protonated dihydroimidazole rings reside outside the portal to form hydrogen bonds with the oxygen atoms of the receptor. The two guest molecules, each of which is disordered over two sites, are related to each other by an inversion center located at the center of the host. The inversion symmetry and 2-fold disorder allow two possible relative orientations of the naphthalene rings in **2**: they are either in "*syn*" orientation (meso form) with full overlap (Figure 2a) or "*anti*" orientation (*dl*-form) with partial overlap (Figure 2b).[13] In both cases, the two aromatic rings are parallel with a mean separation of ~3.4 Å, indicating the presence of $\pi-\pi$ stacking interactions between them. However, only one set of ^{1}H NMR signals for **1** encapsulated in the host indicates that **2** exists as either the meso form or the *dl*-form, but not a combination of the two. The relative orientation of the two guest molecules in **2** still remains to be established. Encapsulation of other guest molecules in CB[7] and CB[8] is being studied.

In summary, the new family of cucurbituril, CB[*n*] ($n = 5-11$), have been discovered, among which CB[5], CB[7], and CB[8] have been successfully isolated and fully characterized. We are currently trying to isolate other CB homologues and optimize the separation and purification processes. The discovery and isolation of the cucurbituril homologues provides new opportunities in molecular recognition, separation, catalysis, and many other applications. We are actively working along this line.

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Supporting Information Available: Synthetic procedures of CB[5], CB[7], CB[8], and **1** and X-ray crystallographic information on CB[5], CB[7], CB[8], and **2** including ORTEP diagrams (PDF). An X-ray crystallographic file (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Crystal data for CB[5]: $(C_{30}H_{30}N_{20}O_{10})\cdot 4H_2O$, fw = 902.80, orthorhombic, *Pnma* (No. 62), $a = 13.2314(8)$ Å, $b = 18.8133(12)$ Å, $c = 14.0361(9)$ Å, $V = 3494.0(4)$ Å^3, $Z = 4$, $T = 188$ K, $R_1(I > 2\sigma(I)) = 0.054$, wR_2(all data) = 0.130, GOF = 1.110. Crystal data for CB[7]: $(C_{42}H_{42}N_{28}O_{14})\cdot(C_4H_8O)\cdot 4(H_2SO_4)\cdot 19H_2O$, fw = 2097.99, monoclinic, $P2_1/n$ (No.14), $a = 12.8547(2)$ Å, $b = 20.1325(2)$ Å, $c = 31.6616(1)$ Å, $\beta = 92.588(1)°$, $V = 8185.6(2)$ Å^3, $Z = 4$, $T = 188$ K, $R_1(I > 2\sigma(I)) = 0.112$, wR_2(all data) = 0.323, GOF = 1.076. Crystal data for CB[8]: $(C_{48}H_{48}N_{32}O_{16})\cdot 2(H_2SO_4)\cdot 30H_2O$, fw = 2065.82, tetragonal, $I4_1/a$ (No. 88), $a = 28.3805(4)$ Å, $c = 22.0986(2)$ Å, $V = 17799.4(4)$ Å^3, $Z = 8$, $T = 188$ K, $R_1(I > 2\sigma(I)) = 0.100$, wR_2(all data) = 0.290, GOF = 1.042. In the crystal structure of CB[5], two water molecules are encapsulated in the cavity of the receptor. A disordered THF molecule is found inside the cavity of CB[7] and disordered water molecules and/or hydronium ions in the cavity of CB[8]. A detailed description of the structures will be published elsewhere.

(11) The hydrochloride salt of 2,6-bis(4,5-dihydro-1*H*-imidazol-2-yl)-naphthalene (**1**) was synthesized from 2,6-dicarboxynaphthalene and ethylenediamine according to a literature method (Kraft, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 705).

(12) Crystal data for **2**: $(C_{48}H_{48}N_{32}O_{16})\cdot 2(C_{16}H_{16}N_4)\cdot 2(HCl)\cdot(H_2SO_4)\cdot 30H_2O$, fw = 2569.31, monoclinic, $P2_1/c$ (No. 14), $a = 13.8327(3)$ Å, $b = 18.5925(2)$ Å, $c = 22.4398(6)$ Å, $\beta = 98.962(1)$ Å, $V = 5700.7(2)$ Å^3, $Z = 2$, $T = 213$ K, $R_1(I > 2\sigma(I)) = 0.102$, wR_2(all data) = 0.311, GOF = 1.019.

(13) The 1:2 inclusion complex **2** presents a new type of stereoisomerism.