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Cucurbit[*n*]uril Analogues

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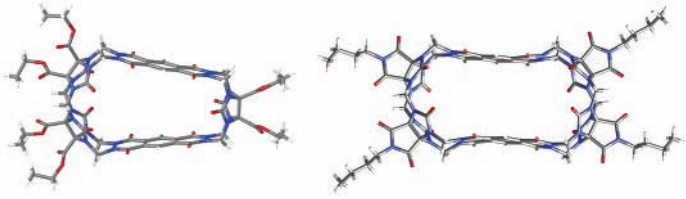
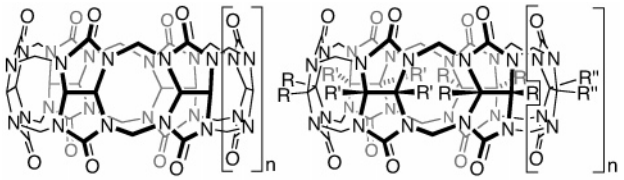
ABSTRACT



Cucurbits come in a variety of sizes, shapes, and colors. We present a building block approach that allows the tailor-made synthesis of CB[5], CB[6], and CB[7] analogues whose sizes, shapes, and colors differ from those of the known CB[*n*].

Members of the plant family Cucurbitaceae come in a variety of sizes, shapes, and colors. Prime examples include pumpkins, squash, zucchini, cucumbers, cantaloupe, and gourds. The similarity between the molecular shape of cyclic hexameric **CB**[6] and the shape of a pumpkin led Mock and co-workers to name this molecule cucurbituril.[1] Through their pioneering work, the groups of Mock[2] and Kim[3] have defined the molecular recognition properties of **CB**[6] and demonstrated its application in self-assembly studies. The cucurbituril family recently gained four new members—**CB**[5], **CB**[7], **CB**[8], and **CB**[5]@**CB**[10]—that differ in molecular size from **CB**[6].[4,5] The molecular recognition properties of this extended cucurbit[*n*]uril family exceed those of **CB**[6] itself and demonstrate their broad utility in molecular recognition and self-assembly studies.[6] The further development of **CB**[*n*] supramolecular chemistry requires tailor-made synthetic approaches that yield control over size, functionalization pattern, and solubility characteristics of the formed **CB**[*n*] derivatives. In this paper, we describe a building block approach toward **CB**[5], **CB**[6], and **CB**[7] analogues that differ in molecular size, shape, and color from the parent **CB**[*n*] macrocycles.[7]



The preparation of cucurbituril derivatives by the use of functionalized glycoluril monomers in **CB**[*n*]-forming reactions began shortly after Mock's report and has resulted in the synthesis of Me_{10}**CB**[5], Cy_5**CB**[5], Cy_6**CB**[6], Ph_2**CB**[1,5], and Me_6**CB**[3,3].[6,8] Despite these successes, no general approach to the synthesis of **CB**[*n*] derivatives with control over size and functionalization pattern has been reported. On the basis of mechanistic studies of **CB**[*n*] formation, we[9] and others[8e] hypothesized that combinations of glycoluril building blocks containing free ureidyl NH groups (e.g., **1**) and cyclic ethers (e.g., **2**) should undergo selective hetero-

(1) Freeman, W. A.; Mock, W. L.; Shih, N. Y. *J. Am. Chem. Soc.* **1981**, *103*, 7367−7368.
(2) Mock, W. L. *Top. Curr. Chem.* **1995**, *175*, 1−24.
(3) Kim, K. *Chem. Soc. Rev.* **2002**, *31*, 96−107.
(4) Kim, J.; Jung, I.-S.; Kim, S.-Y.; Lee, E.; Kang, J.-K.; Sakamoto, S.; Yamaguchi, K.; Kim, K. *J. Am. Chem. Soc.* **2000**, *122*, 540−541.
(5) (a) Day, A.; Arnold, A. P.; Blanch, R. J.; Snushall, B. *J. Org. Chem.* **2001**, *66*, 8094−8100. (b) Day, A. I.; Blanch, R. J.; Arnold, A. P.; Lorenzo, S.; Lewis, G. R.; Dance, I. *Angew. Chem., Int. Ed.* **2002**, *41*, 275−277.
(6) For a review of cucurbit[*n*]uril homologues and derivatives: Lee, W.; Samal, S.; Selvapalam, N.; Kim, H.-J.; Kim, K. *Acc. Chem. Res.* **2003**, *36*, 621−630.
(7) For other glycoluril-based macrocycles, see: (a) Smeets, J. W. M.; Sijbesma, R. P.; Niele, F. G. M.; Spek, A. L.; Smeets, W. J. J.; Nolte, R. J. M. *J. Am. Chem. Soc.* **1987**, *109*, 928−929. (b) Murray, B. A.; Whelan, G. S. *Pure Appl. Chem.* **1996**, *68*, 1561−1567.

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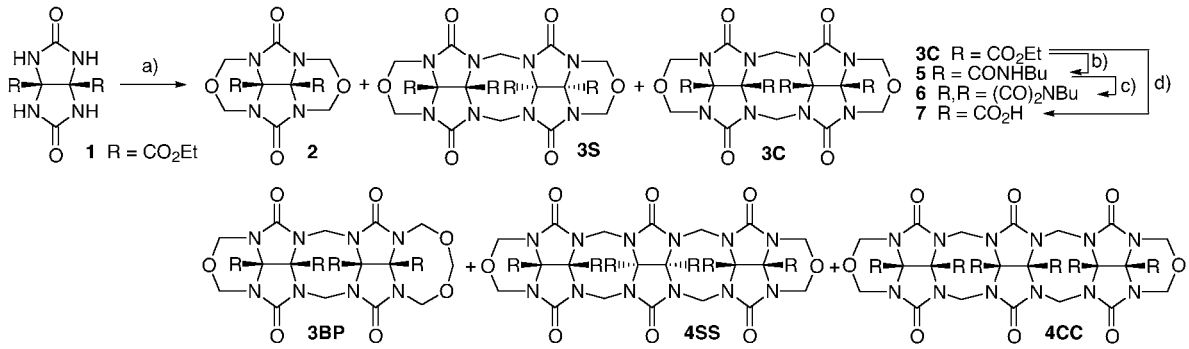
Scheme 1. Controlled Oligomerization of **1**[a]



[a] Conditions: (a) $ClCH_2CH_2Cl$, PTSA, reflux; (b) $CH_3(CH_2)_3NH_2$, 75 °C, 68%; (c) $ClCH_2CH_2Cl$, PTSA, reflux, 39%; (d) LiOH, H_2O, CH_3OH, 89%.

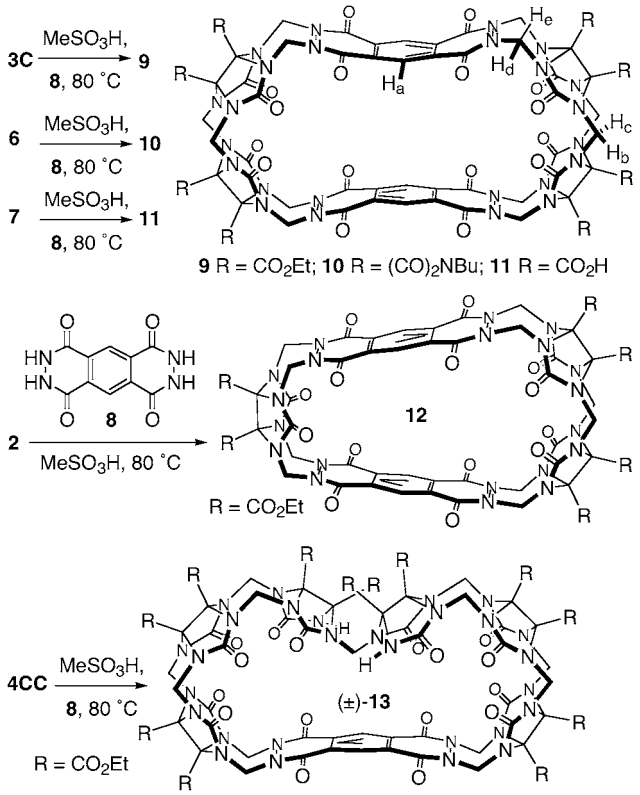
meric cyclization reactions that would yield control over the pattern of functional groups in **CB**[*n*]-forming reactions.

To access a series of glycoluril bis(cyclic ether) building blocks needed to test this mechanistically guided hypothesis, we performed the controlled oligomerization of **1** which yielded **2**, **3S**, **3C**, **3BP**, **4SS**, **4CC**, and higher oligomers (Scheme 1). Through a combination of selective dissolution and chromatographic separations, we were able to obtain multigram quantities of **2** and **3C** and lesser amounts of **4CC**. The transformation of the ethyl ester groups of **3C** into amide (**5**), imide (**6**), and carboxylic acid (**7**) functional groups proceeded smoothly by established procedures.[10]

We discovered that phthalhydrazides are potent nucleophiles in condensation reactions with glycoluril cyclic ethers (e.g., **2**). We hypothesized, therefore, that bis(phthalhydrazide) **8** would function as a surrogate for glycoluril building blocks containing free ureidyl NH groups (e.g., **1**) in the synthesis of cucurbit[*n*]uril analogues. After some experimentation, we found that **3C** and **8** undergo a smooth reaction in hot anhydrous CH_3SO_3H yielding **CB**[6] analogue **9** in 78% yield (Scheme 2). Similarly, **6** and **7** bearing imide and carboxylic acid substituents yield **10** and **11** in 70% and 65% yield, respectively. We next investigated the reaction of monomeric building block **2** with **8** which yields **CB**[5] analogue **12** in 6% isolated yield.[11] Last, we investigated the reaction of trimeric building block **4CC** with **8** which yields **CB**[7] analogue (±)-**13** in high yield (67%). Compound (±)-**13** possesses several unusual structural features: (1) it is chiral and racemic due to its C_2-symmetry, (2) it contains a single methylene bridge between the 2 equiv of **4CC**, and (3) this methylene group is directed into the cavity of (±)-**13**. Compounds **9**, **10**, **12**, and (±)-**13** are soluble in polar organic solvents ($CHCl_3$/MeOH, CH_3CN, and DMSO), whereas **10** has excellent aqueous solubility. In contrast to all previously reported **CB**[*n*] derivatives, **12** and (±)-**13** are amenable to purification by simple silica gel column chromatography.[12]

Figure 1 shows the X-ray crystal structure of **10**. Unlike the known pumpkin-shaped **CB**[*n*], **10** assumes the shape of a cucumber with cavity dimensions of 5.90 × 11.15 × 6.92 Å. In the absence of structural information from X-ray diffraction studies, we performed AM1 calculations on **12**

Scheme 2. Cucurbit[*n*]uril Analogues



(8) (a) Flinn, A.; Hough, G. C.; Stoddart, J. F.; Williams, D. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1475−1477. (b) Zhao, J.; Kim, H.-J.; Oh, J.; Kim, S.-Y.; Lee, J.-W.; Sakamoto, S.; Yamaguchi, K.; Kim, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 4233−4235. (c) Isobe, H.; Sato, S.; Nakamura, E. *Org. Lett.* **2002**, *4*, 1287−1289. (d) Miyahara, Y,; Abe, K.; Inazu, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 3020−3023. (e) Day, A. I.; Arnold, A. P.; Blanch, R. J. *Molecules* **2003**, *8*, 74−84.

(9) (a) Chakraborty, A.; Wu, A.; Witt, D.; Lagona, J.; Fettinger, J. C.; Isaacs, L. *J. Am. Chem. Soc.* **2002**, *124*, 8297−8306. (b) Wu, A.; Chakraborty, A.; Witt, D.; Lagona, J.; Damkaci, F.; Ofori, M.; Chiles, J. K.; Fettinger, J. C.; Isaacs, L. *J. Org. Chem.* **2002**, *67*, 5817−5830.

(10) Burnett, C. A.; Lagona, J.; Wu, A.; Shaw, J. A.; Coady, D.; Fettinger, J. C.; Day, A. I.; Isaacs, L. *Tetrahedron* **2003**, *59*, 1961−1970.

(11) The crude reaction mixture contains approximately 30% **12**.

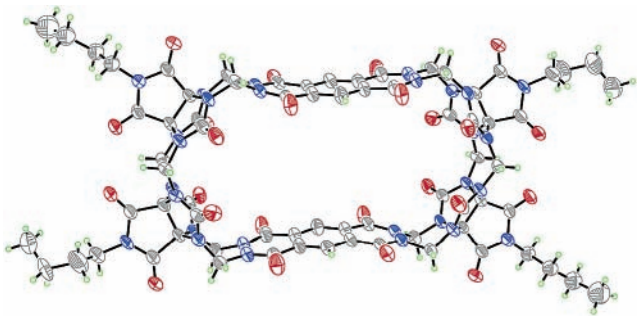


Figure 1. ORTEP plot of the crystal structure of **10**. The solvating CH_3CN molecules have been removed for clarity.

and (±)-**13**. The cavity of **12** is shaped like a butternut squash with dimensions of 5.58 Å × 9.75 Å × 6.22 Å. Last, the asymmetric cavity of (±)-**13** resembles two **CB**[5] molecules fused together and has dimensions of 5.71 Å × 11.34 Å × 4.28 Å. As a result of their bis(phthalhydrazide) walls, **9**−**13** differ not only in size and shape, but also in color from the known **CB**[*n*]. Accordingly, the UV/vis spectra recorded for **9**, **12**, and (±)-**13** in CH_3CN show a broad absorption with λ_{max} = 342 nm (Figure 2).[13]

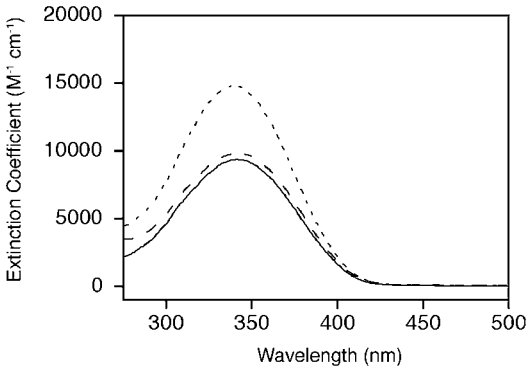


Figure 2. UV/vis spectra (CH_3CN, 298 K) recorded for **9** (- - -), **12** (− − −), and (±)-**13** (—).

The structural relationship between **CB**[*n*] and **9**−**13** suggests that the **CB**[*n*] analogues should possess similar recognition properties. Similar to **CB**[8], the cavities of **9**−**13** are spacious and possess two binding sites which potentially allows for termolecular complex formation. Parts a and b of Figure 3 show the ^{1}H NMR spectra of **11** and *p*-xylylene diamine (**14**) recorded separately. The ^{1}H NMR spectrum of a 1:1 mixture of **11** and **14** (Figure 3c) shows significant upfield shifts for the aromatic (H_f) and methylene (H_g) protons of **14** in accord with their proximity to the shielding

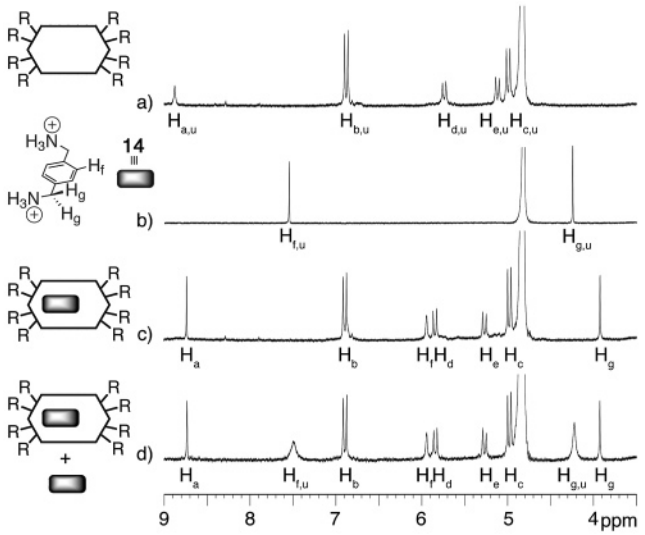


Figure 3. ^{1}H NMR spectra (50 mM acetate buffered D_2O, pD 4.9, 298 K, 400 MHz) for (a) **11** (1.2 mM), (b) **14** (1.2 mM), (c) **11** (1.2 mM) and **14** (1.2 mM), and (d) **11** (1.2 mM) and **14** (4.8 mM). Protons attached to uncomplexed host and guest are indicated with a subscript (u).

region defined by the bis(phthalhydrazide) walls of **11**. Figure 3d shows the ^{1}H NMR spectrum recorded for a 1:4 mixture of **11** and **14** which demonstrates that chemical exchange between free and bound guest is slow on the chemical shift time scale. Integration of the resonances for host versus bound guest allows us to establish the 1:1 stoichiometry of the **11**·**14** complex.

In summary, we have described a building block approach to the synthesis of **CB**[5], **CB**[6], and **CB**[7] analogues based on the condensation of nucleophilic glycoluril surrogate **8** with glycoluril bis(cyclic ethers) bearing ester, imide, and carboxylic acid functional groups. Although we have used bis(phthalhydrazide) **8** exclusively in this paper, the use of longer, nonplanar, and functionalized bis(phthalhydrazides) in **CB**[*n*] analogue forming reactions promises to deliver further control over the size, shape, and recognition properties of **CB**[*n*] analogues. Ongoing studies are directed toward delineating the recognition properties of the **CB**[5]−**CB**[7] analogues in both aqueous and organic solution, the formation of ter- and higher molecularity complexes, and the opportunity for diastereoselective recognition processes with the cavities of (±)-**13**. We anticipate that the recognition properties of **CB**[*n*] analogues will complement those of the parent **CB**[*n*] and their derivatives, thereby expanding the range of applications available to the **CB**[*n*] family.

Acknowledgment. We thank the University of Maryland and the NIH (GM61854) for partial support of this work. L.I. is a Cottrell Scholar of Research Corporation.

Supporting Information Available: Experimental procedures and characterization data for all new compounds and crystallographic information file for **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Although (±)-**13** was easily chromatographed with high recovery, losses during chromatographic purification of **12** on SiO_2 were significant.

(13) We also expect these **CB**[*n*] analogues to be fluorescent and electrochemically active. (a) Drew, H. D. K.; Pearman, F. H. *J. Chem. Soc.* **1937**, 586−592. (b) Viehbeck, A.; Goldberg, M. J.; Kovac, C. A. *J. Electrochem. Soc.* **1990**, *137*, 1460−1466.