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Daisy Chain Assembly Formed from a Cucurbit[6]uril Derivative

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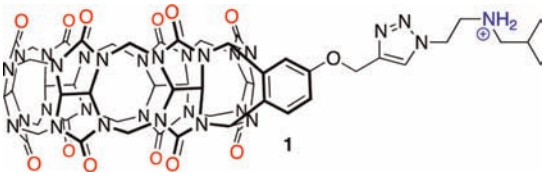
ABSTRACT



The building block synthesis of a derivative of CB[6] that bears a reactive propargyloxy group and its functionalization by click chemistry to yield 1 which contains a covalently attached isobutylammonium group is presented. Compound 1 undergoes self-assembly to yield a cyclic [c2] daisy chain assembly (1_2) in water. The behavior of 1_2 in response to various stimuli (e.g., guests and CB[*n*] receptors) is described.

The synthesis of cucurbit[*n*]uril (CB[*n*]) molecular containers proceeds by the condensation of glycoluril with formaldehyde in hot concentrated acidic conditions.[1] Contemporary interest in the supramolecular chemistry of CB[*n*] molecular containers[2] has been fueled by the commercial availability of a homologous series of hosts (CB[*n*], $n = 5, 6, 7, 8, 10$) that display exceptionally high affinity and selectivity toward their guests in aqueous solution.[3] These high affinity and high selectivity CB[*n*]•guest interactions have been used to create a number of functional CB[*n*] systems including molecular machines,[4] biomimetic systems,[5] sensing ensembles,[6] stimuli responsive polymers,[7] gas sequestration and purification,[8] and drug delivery systems.[9] In order to further extend the supramolecular chemistry of CB[*n*] it is necessary to develop efficient synthetic methods to prepare functionalized CB[*n*] derivatives. A major step in this direction was accomplished by the Kim group who

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performed the direct perhydroxylation of CB[*n*] using $K_2S_2O_8$ as an oxidant to yield $(HO)_{2n}$CB[*n*].[10] The multiply functionalized CB[*n*] derivatives prepared in this manner have been used in numerous application areas including ion channels, membrane protein fishing, and nanocapsules.[11] Despite the demonstrated utility of these (per)functionalized CB[*n*] derivatives, it would be useful to develop clickable monofunctionalized CB[*n*] to ensure chemical homogeneity of compounds and materials derived therefrom. Scherman's group recently tamed the persulfate oxidation of CB[6] which allowed the isolation of $(HO)_1$CB[6] (Figure 1) in 12% yield after chromatography on a reversed-phase macroporous resin.[12] They transformed $(HO)_1$CB[6] into propargyloxyCB-[6] which undergoes azide−acetylene click reaction to generate a self-complexing CB[6] derivative.

Our group has been using our knowledge of the mechanism of CB[*n*] formation[13,14] to develop robust, scalable procedures for the synthesis of monofunctionalized CB[*n*] derivatives that bear reactive functional groups. Recently, we reported the gram scale templated synthesis of methylene bridged glycoluril hexamer **2** and its conversion into monofunctionalized CB[6] derivatives by the reaction with substituted phthalaldehydes.[14] In this paper we report the synthesis of phenol substituted CB[6] (**3**), its transformation into propargyloxy compound (**4**), and finally triazole **1**. We describe the self-assembly properties of **1** in water and its response to various forms of chemical stimuli.

Scheme 1 shows the synthesis of compound **1**. First, we react hexamer **2** with 4-hydroxyphthalaldehyde (**5**,[15] Supporting Information) to give CB[6] derivative **3** in 52% yield on the gram scale. Next, we reacted **3** with propargyl bromide in *N*-methylpyrrolidinone (NMP) as solvent with anhydrous K_2CO_3 as the base to yield CB[6] derivative **4** in 97% yield which contains a reactive propargyloxy substituent. Finally, we reacted **4** with azido amine **6** (Supporting Information) in the presence of Pericàs' catalyst **7**[16] to give compound **1** in 75% yield.

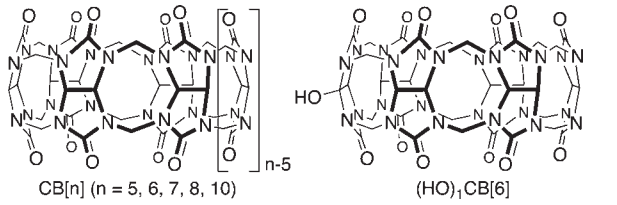

Figure 1. Chemical structures of CB[*n*] and $(HO)_1$CB[6].

The chemical structure of **1** features a CB[6] sized cavity covalently connected to an isobutylammonium group that we anticipated would act as a guest for the substituted CB[6] group. Accordingly, we measured the ^{1}H NMR spectrum of **1** in D_2O (Figure 2a) in the presence of spermine (**8**) as a tight binding guest to eliminate the self-assembly of **1**. The ^{1}H NMR spectrum is fully consistent with the C_s-symmetric structure of **1**•**8**. Of particular note are the two nonequivalent CH groups (H_k and H_l) of **1** which resonate at 6.66 and 6.65 ppm, the triazole proton (H_f) at 8.21 ppm, the glycoluril methine protons (H_m and H_n) which are upfield shifted by the adjacent *o*-xylylene ring, and the free nonbinding isobutylammonium group ($H_a - H_c$).

A priori, compound **1** could be expected to undergo intramolecular self-complexation, form cyclic assemblies (e.g., dimer, trimer, tetramer), or undergo supramolecular polymerization. Based on the design of **1** we expected that intramolecular self-complexation[12] would be sterically unfavorable. Furthermore, we did not expect the relatively weak binding constant for the complexation with isobutylammonium groups (3.0×10^4 M^{-1})[14] to support supramolecular polymerization over the experimentally accessible concentration regime.[17]

Figure 2b shows the ^{1}H NMR spectrum recorded for **1** on its own. Quite interestingly, we observe four resonances in the 8.7−8.4 ppm region of the spectrum, two of which are of equal intensity, which corresponds to the triazole CH protons (H_f). In order to obtain information about the constitution of the mixture of assemblies present in solution we performed diffusion ordered spectroscopy (DOSY) on the mixture.[18] The diffusion coefficient measured for each of the four peaks was in the range of $(2.25-2.60) \times 10^{-10}$ m^2 s^{-1} whereas the value for a monomeric analogue was 3.16×10^{-10} m^2 s^{-1} (Supporting Information). The ~18−29%

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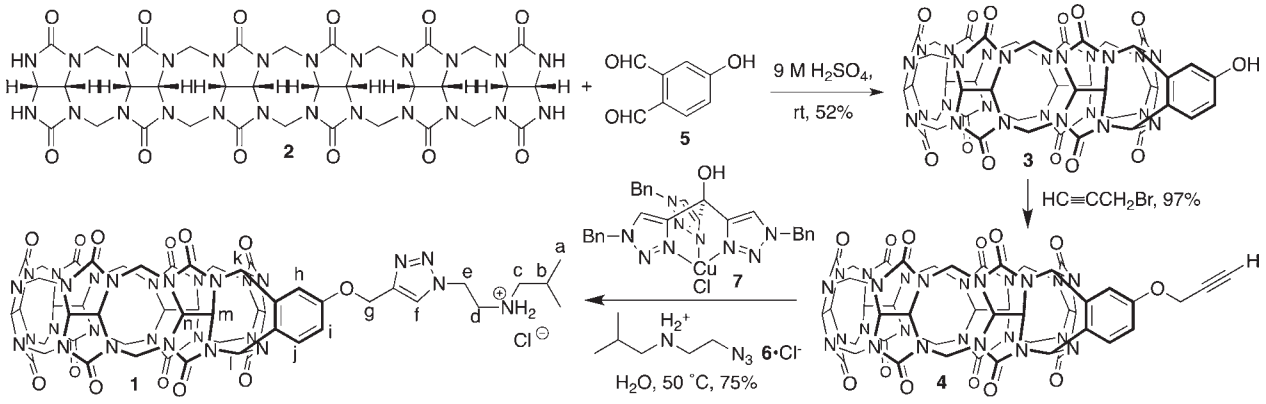
Scheme 1. Synthesis of Compound **1**



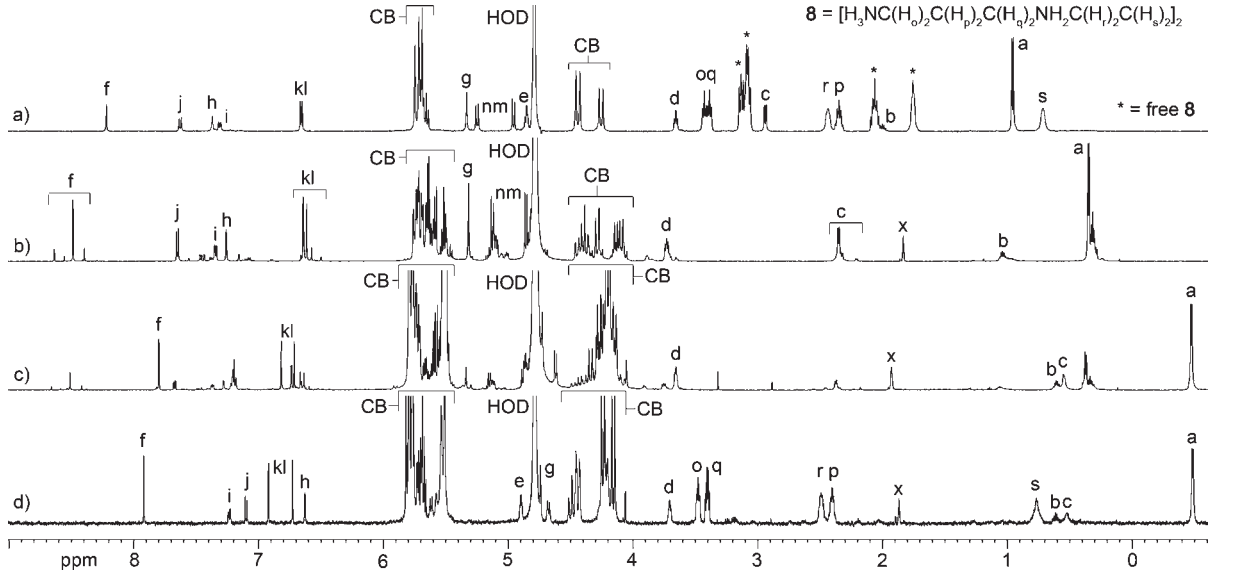
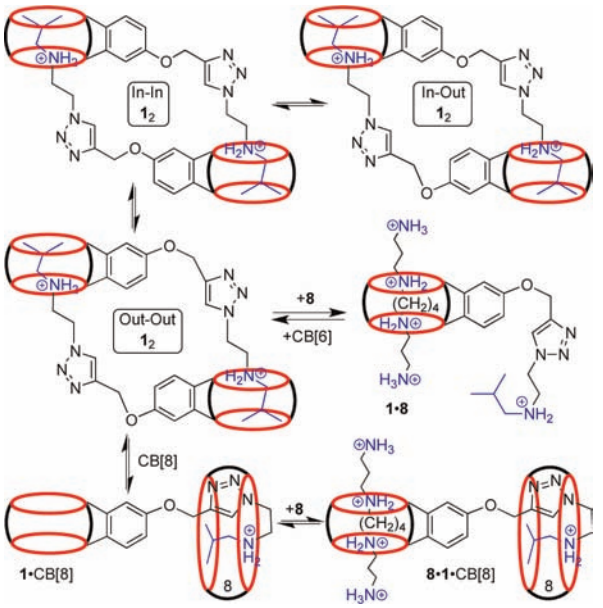


Figure 2. ^{1}H NMR spectra recorded for (a) **1•8** (1 mM) and excess **8** (1 mM) in D_2O (500 MHz, rt), and (b) $\mathbf{1}_2$ (1 mM), (c) a mixture of **1** (0.45 mM) and CB[8] (0.675 mM), and (d) a mixture of **1** (0.4 mM), **8** (0.48 mM), and CB[8] (0.48 mM) in 50 mM NaO_2CCD_3 buffer (pD 4.74, 600 MHz, rt). x = acetate buffer; CB = resonances from CB[6] group.

decrease in diffusion coefficient is consistent with the formulation of all three assemblies as dimers. Furthermore, we performed ESI-MS experiments and observed sizable ions corresponding to $(\mathbf{1}_2)^{3+}$ and $(\mathbf{1}_2)^{2+}$ (Supporting Information). The symmetry properties of monomeric **1** allow us to rationalize the formation of a mixture of cyclic dimers ($\mathbf{1}_2$). Because of the position of attachment of the O-atom on the aromatic ring of **1**, the two ureidyl carbonyl portals are nonequivalent. Therefore, when an alkylammonium ion binds to **1** it can do so in two isomeric orientations. Scheme 2 shows the three isomers of the cyclic dimer daisy chain assembly $\mathbf{1}_2$ (in−in, in−out, and out−out). Symmetry considerations dictate that the in−out isomer should display two singlets of equal intensity for the symmetry nonequivalent triazole protons (H_f and $H_{f'}$) whereas the out−out and in−in isomers should each display one singlet for the symmetry equivalent H_f protons. On the basis of the diffusion measurements and molecular models (Supporting Information) we believe that in−in $\mathbf{1}_2$ is the predominant isomer.

To try to bias the self-assembly of **1** toward larger cyclic oligomers we studied the response toward changes in concentration, temperature, and metal ion concentration. Variable temperature ^{1}H NMR experiments over the 277−333 K range do not show any changes indicative of changes in oligomerization state (Supporting Information). Similarly, the ^{1}H NMR spectra recorded for $\mathbf{1}_2$ do not change over the experimentally accessible range of concentration ([**1**] = 0.15 to 1.25 mM) and in the presence of different metal ions (Na^+, K^+, Cs^+, Mg^{2+}, Cu^{2+}) which suggests that the cyclic [c2] daisy chain assembly $\mathbf{1}_2$ is of high thermodynamic stability. In order to gauge the

Scheme 2. Depiction of the Three Isomers of $\mathbf{1}_2$ and Their Response to Addition of **8**, CB[8], and CB[6]



increase in affinity for the formation of cyclic dimer $\mathbf{1}_2$ relative to monomeric models[14] we added 1 equiv of guests of increasing affinity toward the CB[6] derivative (butanediammonium (**9**), $K_a = 4.9 \times 10^5\ M^{-1}$; pentanediammonium (**10**), $K_a = 5.7 \times 10^6\ M^{-1}$; hexanediammonium (**11**), $K_a = 1.4 \times 10^7\ M^{-1}$).[14] We found that 1 equiv of **10** and **11**, which bind 190−466-fold tighter than isobutylammonium, cause significant dissociation (75−81%) of $\mathbf{1}_2$ to give **1•10** and **1•11** which reflects the thermodynamic advantage for cyclic dimer versus 1:1 complex formation.

We also probed the response of [c2] daisy chain $\mathbf{1}_2$ toward chemical stimuli in the form of added molecular containers (CB[6], CB[7], CB[8], and HP-β-CD). We hoped that the added molecular containers, in particular HP-β-CD and CB[8], would bind to the substituted *o*-xylylene and triazole rings of **1** and thereby rigidify the linking group between the cavity and the isobutylammonium ion arm which might result in a preference for different sized cyclic daisy chains. In practice, the addition of CB[6], CB[7], and HP-β-CD did not result in a significant dissociation of $\mathbf{1}_2$ (Supporting Information). In contrast, however, the addition of 1.5 equiv of CB[8] resulted in a significant dissociation of $\mathbf{1}_2$ with concomitant formation of a new complex **1**•CB[8] (Figure 2c and Scheme 2). Addition of **8** as a guest for the CB[6] sized cavity of **1** yields **8•1**•CB[8] which simplifies the ^{1}H NMR spectrum as shown in Figure 2d. Complexation induced chemical shifts that provide evidence for the geometry of **1**•CB[8] and **8•1**•CB[8] include the upfield shift observed for triazole H_f and isobutylammonium H_a resonances. Based on this evidence, we formulate the geometry of **1**•CB[8] and **8•1**•CB[8] as the backfolded form[13g,19] depicted in Scheme 2. As described above, we found that **8** causes dissociation of $\mathbf{1}_2$ to yield **1•8**. Interestingly, we found that addition of CB[6] to a solution of **1•8** results in the formation of CB[6]•**8** and the reformation of $\mathbf{1}_2$ (Scheme 2). We believe this process is driven by the higher affinity of **8** toward CB[6] than **1**.

In conclusion, we have reported the synthesis of monofunctionalized CB[6] derivative **4** which contains a propargyloxy substitutent which undergoes a click reaction to yield **1**. Compound **1** undergoes self-assembly in water to give the cyclic [c2] daisy chain $\mathbf{1}_2$. Assembly $\mathbf{1}_2$ is responsive to chemical stimuli in the form of competing guests and competing hosts. For example, the addition of **8** opens up dimer $\mathbf{1}_2$ to give **1•8**; subsequent addition of CB[6] reverses this process to deliver cyclic [c2] daisy chain $\mathbf{1}_2$. The most significant aspect of the work, however, is the gram scale synthesis of monofunctionalized CB[6] derivative **3** and its high yield transformation into **4** which contains a clickable propargyloxy group. Accordingly, it is straightforward to imagine merging the recognition properties of CB[6] with other functional supramolecular and biomolecular systems by simple click chemistry.

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Supporting Information Available. Details of the synthesis and characterization of **1** and **3**−**6**, and results of variable temperature, dilution experiments, diffusion ordered spectroscopy, chemical stimuli experiments, and molecular modeling performed with $\mathbf{1}_2$. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.