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Reasons Why Aldehydes Do Not Generally Participate in Cucurbit[*n*]uril Forming Reactions

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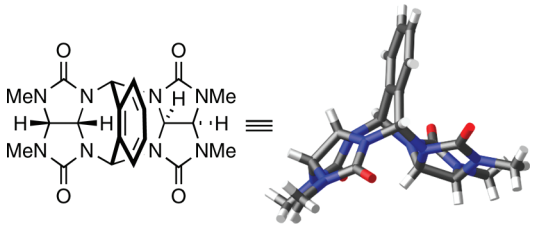

The reaction of substituted glycolurils or a glycoluril dimer with a dialdehyde (*o*-phthalaldehyde) delivers S-shaped dimers and an S-shaped tetramer selectively. A combination of X-ray crystallography, PM3 calculations, and product resubmission experiments establish that the S-shaped isomers are thermodynamically more stable than the C-shaped diastereomers which we attribute to the conformational preferences of the newly formed benzo bicyclo[3.3.2]decane ring system. The preferential formation of S-shaped subunits is one reason why *o*-phthalaldehyde and possibly other aldehydes do not usually participate in CB[*n*] forming reactions. We also present evidence that points toward an equilibrium between glycoluril monomer + phthalaldehyde and S-shaped dimer + water that responds to concentration over the 1−50 mM range. This result suggests a second reason, insufficient reactivity (e.g., low equilibrium constant), why *o*-phthalaldehyde and possibly other aldehydes do not participate in CB[*n*] forming reactions. Delineation of the reasons why some aldehydes fail in these reactions is the first step toward devising methods to overcome these limitations.

Introduction

In 1981 Mock and co-workers disclosed that the condensation reaction of glycoluril ($\mathbf{1}_H$) with formaldehyde under strongly acidic conditions delivers cucurbit[6]uril (CB[6]) in high yield (Scheme 1).[1] In a series of elegant papers throughout the 1980s, Mock established that CB[6] is a truly remarkable host with the ability to bind to alkaneammonium ions with high affinity and selectivity,[2] to act as a bead in a pH-switchable molecular shuttle,[3] and even to accelerate the click reaction between certain acetylenes and azides.[4] Around the turn of the millenium, the groups of Kim and Day reported that the condensation of glycoluril (1 equiv, generally >1 M) with formaldehyde (2 equiv) under milder conditions (e.g., conc HCl, 100 °C) results in the formation of a homologous series of cucurbit[*n*]uril (CB[*n*]; n = 5, 6, 7, 8, 10) hosts.[5,6] In the intervening years, the supramolecular chemistry of the larger CB[*n*] homologues (CB[7] and CB[8]) have been shown to be particularly exciting with applications ranging from molecular machines, chemical sensors, solid phases for sequestration and chromatography, and drug delivery vehicles.[7−9]

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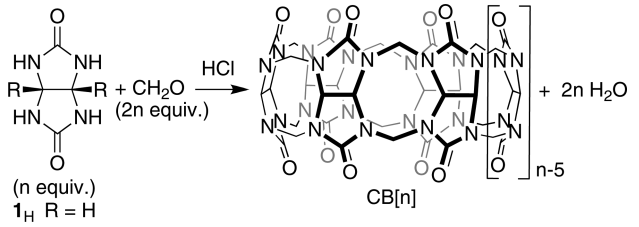
SCHEME 1. Synthesis of CB[*n*]



As a result of these exciting recognition properties, a number of groups have been interested in the synthesis of CB[*n*] derivatives with new structures and tailor-made properties (e.g., enhanced solubility). For this purpose, a number of synthetic strategies have been investigated (Scheme 2). For example, the condensation reaction between a few substituted glycolurils ($\mathbf{1}_R$) and formaldehyde was shown to give R_{10}CB[5] and R_{12}CB[6] compounds (Scheme 2a).[10,11] Cy_5CB[5] and Cy_6CB[6] have enhanced solubility in organic solvents and can be used in the formation of ion-selective electrodes.[11] Unfortunately, the self-condensation of a single glycoluril derivative (e.g., $\mathbf{1}_{Me}$) does not yield any substituted CB[7] or CB[8], presumably due to steric interactions between substituents that increase as the size of the ring increases.[12] To address this concern a number of researchers have performed the condensation between two different glycolurils and have been able to isolate partially substituted CB[*n*] (Scheme 2b).[12−15] For example, the condensation of $\mathbf{1}_H$ and $\mathbf{1}_{Ph}$ resulted in the formation of Ph_2CB[6].[14] Other research groups have developed building block strategies[16,17] based on condensation between glycoluril monomers and glycoluril oligomers.[13] For example, the group of Tao demonstrated that the condensation between glycoluril dimer **2C** and bis(cyclic ether) $\mathbf{1}_{Me}$BCE yields Me_4CB[6] (Scheme 2c).[13] Perhaps the most useful method for the synthesis of CB[*n*] derivatives involves the direct functionalization of preformed CB[*n*] ($n = 5, 6$). For example, Kim's group has described the perhydroxylation of CB[*n*] ($n = 5, 6$) to yield $(HO)_{2n}$CB[*n*] ($n = 5, 6$)[18] that is amenable to further functionalization reactions (Scheme 2d), which allows the properties of CB[6] derivatives to be tailored toward specific applications.[8]

All of the methods described above involve the use of glycoluril derivatives or the functionalization of the convex face of the glycoluril ring system. Is it possible to expand the scope of the CB[*n*] forming reaction beyond formaldehyde? Although this question has been posed and attempted experimentally by several researchers, the reasons behind the failure of such synthetic routes have remained unclear to date.[8] Here we address this question and delineate two of the reasons why aldehydes do not generally participate in CB[*n*] forming reactions.

Results and Discussion

This section is organized as follows. First, we present a summary of a portion of the mechanism of CB[*n*] formation proceeding *via* oligomers **2**−**6** that is relevant to the use of aldehydes in CB[*n*] forming reactions. Next, we present the unsuccessful attempts to react glycolurils with monoaldehydes followed by the successful synthesis of several S-shaped glycoluril dimers from glycolurils and *o*-phthalaldehyde. We use the results of these experiments along with product resubmission experiments to explain why aldehydes do not generally participate in CB[*n*] forming reactions.

Mechanism of CB[*n*] Formation. The Isaacs group has been heavily involved in the elucidation of the mechanism of CB[*n*] formation.[16,19−21] This section presents an overview of portions of the mechanism of CB[*n*] formation (Scheme 3) that are relevant to our discussion of the use of aldehydes in CB[*n*] forming reactions. Initially, glycoluril $\mathbf{1}_H$ undergoes condensation with formaldehyde to yield a mixture of C-shaped and S-shaped glycoluril dimers (**2C** and **2S**). Diastereomers **2C** and **2S** differ in the relative orientation of the pairs of methine H-atoms on the convex face of each equivalent of glycoluril. Previously, we studied the equilibrium between the C-shaped and S-shaped forms using end-capped derivatives of $\mathbf{1}_{COOEt}$ and established a large (>95:5) thermodynamic preference for the C-shaped form.[19] Subsequently, the **2C** may grow to yield trimer (**3**), tetramer (**4**), pentamer (**5**), hexamer (**6**), and higher oligomers by the stepwise addition of $\mathbf{1}_H$.[22] When the oligomer is long enough (e.g., **5** or **6**), addition of 1 equiv of formaldehyde yields *nor-seco*-CB[*n*],

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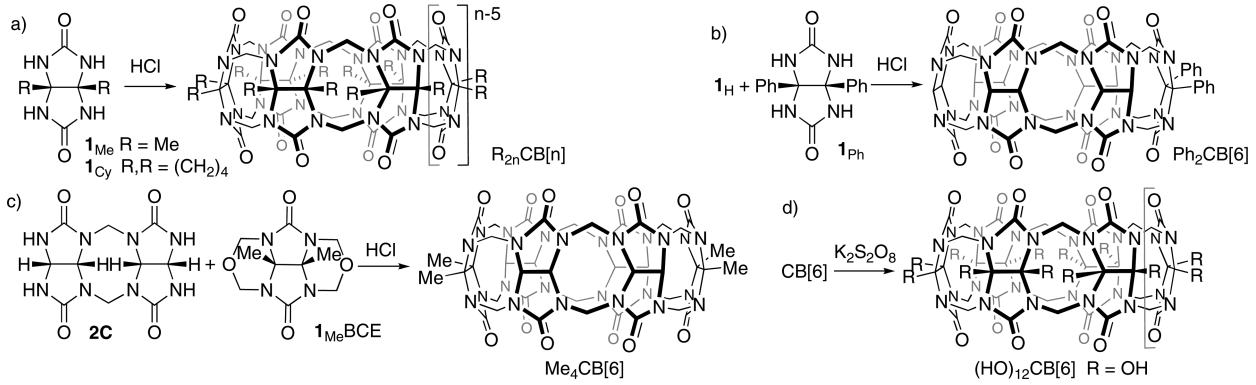
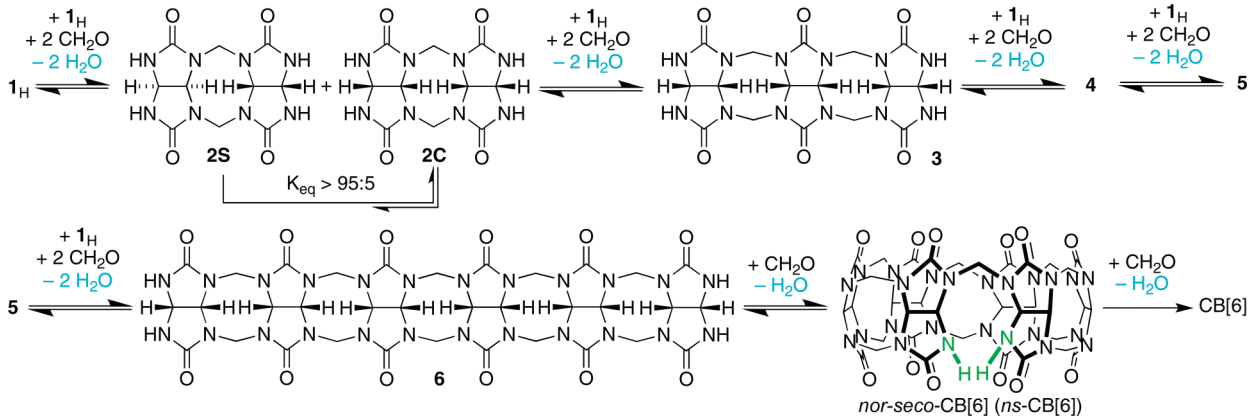
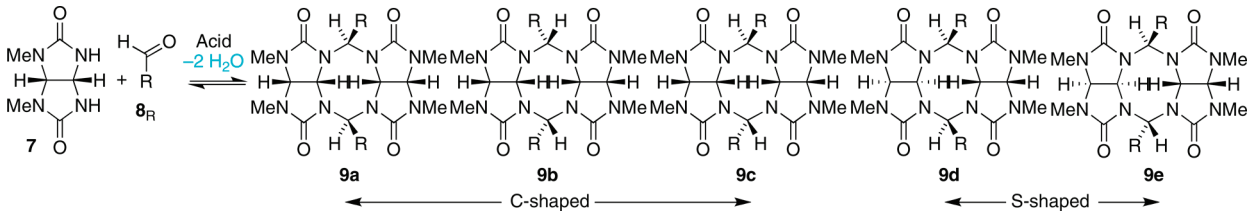
SCHEME 2. Synthesis of Substituted CB[6] Compounds



SCHEME 3. Portion of the Mechanism of CB[*n*] Formation



SCHEME 4. Possible Products from Condensation of 7 and an Aldehyde



which then goes on to yield CB[*n*] by addition of a final equivalent of formaldehyde. The Isaacs group has previously isolated *ns*-CB[6] and demonstrated its conversion to CB[6] by product resubmission experiments.[23] It is also possible for oligomers (e.g., **3** or **5**) to condense by a step-growth process (not shown) to yield *nor-seco*-CB[*n*] with double cavity (bis-*ns*-CB[10]) or even chiral ((±)-*ns*-CB[6]) structures.[24] Please note that in the depicted mechanism (Scheme 3) oligomers **2**−**6** are connected by equilibrium arrows that reflect the reversibility of these steps. At this time no quantitative information is available regarding the equilibrium constants for any of these steps. In contrast, Day has demonstrated by product resubmission experiments that the final conversion to CB[6] is an irreversible step and is indicted as such in Scheme 3.[5] Another fact worth noting is that CB[*n*] formation is a condensation reaction and that one molecule of H_2O is produced (highlighted in aqua) for each molecule of CH_2O that is consumed. Two factors that are critical in the successful formation of CB[6] from $\mathbf{1}_H$ and CH_2O are (1) that the equilibrium between $\mathbf{1}_H$ + CH_2O and **2S**/ **2C** + H_2O favors the dimers[25] and (2) that the equilibrium between S-shaped (e.g., **2S**) and C-shaped (e.g., 2C) diastereomers greatly favors the C-shaped forms.

Reactions between Capped Glycoluril 7 and Some Aldehydes Do Not Yield Dimeric Products. As described above it is critical that the equilibrium between $\mathbf{1}_H$ + formaldehyde and **2C**/**2S** + H_2O favors products for a successful CB[*n*] forming reaction. We wondered whether this fundamental

(22) At each step along the way (e.g., **3**−**6**) S-shaped diastereomers can be formed, but as demonstrated for **2C** and **2S** the equilibrium favors the all C-shaped form, which is conducive to macrocyclization.

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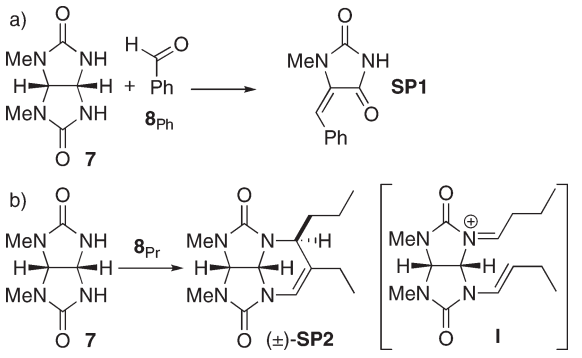
(25) By analogy it is important that the equilibrium also favors the formation of oligomers **3**− **6** from shorter oligomers.

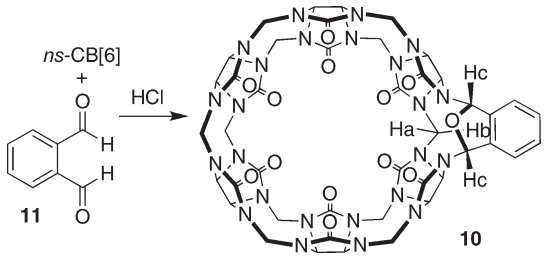
SCHEME 5. Reactions between 7 and (a) Benzaldehyde and (b) Butanal



step of the mechanism of CB[*n*] formation would still favor products when aldehydes are used instead of formaldehyde. To address this question we decided to use capped glycoluril derivative **7** in place of $\mathbf{1}_H$ to limit the complexity of the reaction to the formation of dimers.[26−28] Scheme 4 shows the theoretical reaction between **7** and an aldehyde to yield dimers comprising 2 equiv of **7** and 2 equiv of aldehyde. Similar to the condensation of $\mathbf{1}_H$ and formaldehyde described above (Scheme 3), there are two sets of diastereomers (C-shaped, **9a**−**9c** and S-shaped, **9d**− **9e**) that differ in the orientation of the H-atoms on the convex face of the glycoluril ring system. In addition, the use of an aldehyde generates two new stereogenic centers each of which could conceivably adopt two possible configurations. In total, five possible diastereomers could be formed (Scheme 4).

First, we investigated the reaction between **7** (100 mM) and benzaldehyde ($\mathbf{8}_{Ph}$, 100 mM) in conc DCl at 70 °C. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed consumption of starting materials **7** and $\mathbf{8}_{Ph}$, but resonances corresponding to the formation of **9** were not observed (Supporting Information, Figure S14). On the basis of this result we surmised that benzaldehyde and **7** are not sufficiently reactive (e.g., starting materials are favored under normal concentrations) and that eventually **7** and $\mathbf{8}_{Ph}$ undergo decomposition reactions instead. To be certain that this observation was not due to the particular experimental conditions, we conducted several additional sets of experiments. In one set of experiments we varied the concentrations of **7** and $\mathbf{8}_{Ph}$ (1 mM to 1 M) and still did not observe any dimer formation by ^{1}H NMR (Supporting Information, Figures S13−S16). In a second set of experiments we varied the temperature (70 °C, 50 °C, and room temperature) and followed the reaction by ^{1}H NMR (Supporting Information, Figures S13, S17, and S18). Once again we could not detect the formation of dimers. Given that the reaction between **7** and an aldehyde is a condensation reaction that leads to the formation of H_2O as byproduct we decided to conduct the reaction under anhydrous (CF_3CO_2H) rather than aqueous (conc HCl) conditions (Supporting Information, Figure S19). We hoped that the use of CF_3CO_2H as solvent

SCHEME 6. Synthesis of 10



would favor the formation of dimer as a consequence of Le Chatelier's principle. Unfortunately, similar to the reactions in HCl as solvent we did not observe the formation of any dimeric products. In many of the reactions between **7** and $\mathbf{8}_{Ph}$ we observed the formation of hydantoin side product **SP1** in low yield (Scheme 5a). This result is consistent with the known tendency of glycolurils to undergo transformation into hydantoins[26,29] followed by condensation with $\mathbf{8}_{Ph}$. Similar attempted dimerization reactions were conducted between **7** and acetaldehyde ($\mathbf{8}_{Me}$), pivaldehyde ($\mathbf{8}_{t\text{-}Bu}$), and acrolein ($\mathbf{8}_{CH=CH_2}$) (Supporting Information, Figures S20−S22). In these cases ^{1}H NMR showed the loss of the resonances due to the starting aldehyde, but no resonances that could be attributed to dimer **9** were observed.

We also conducted the reaction between **7** (1 M) and $\mathbf{8}_{Pr}$ (1 M) in TFA at 50 °C (Scheme 5b). Once again, we did not observe the formation of dimer, but in this case we were able to isolate (±)-**SP2** in 67% yield (Supporting Information, Figure S23).[30] Compound (±)-**SP2** is an *N*-acyl enamine that forms from 1 equiv of **7** and 2 equiv of $\mathbf{8}_{Pr}$. We believe that (±)-**SP2** probably forms results from intramolecular enamine-iminium ion condensation of intermediate **I**. The isolation of (±)-**SP2** provides strong evidence that aldehydes do react with glycoluril NH groups under acidic conditions but that other factors may divert the reaction away from the formation of methylene bridged glycoluril dimers that are required for CB[*n*] formation.

Reaction between ns-CB[6] and Phthaldehyde. Our lack of success in the reactions described in the previous section was somewhat surprising to us given that we previously reported that the reaction between *ns*-CB[6] and *o*-phthaldehyde (**11**) delivers CB[6] derivative **10** (Scheme 6).[23] Compound **10** is somewhat unusual in that it contains an N−C−O−C−N bridge rather than the standard N−C−N connection typical of CB[*n*] reactions. Despite this idiosyncrasy it was clear that **11**, probably facilitated by the entropic advantage provided by using a dialdehyde, was sufficiently reactive to participate in a CB[*n*] forming reaction. Accordingly, we wondered whether phthaldehyde **11** would be reactive toward glycolurils and glycoluril oligomers and provide a new route toward the formation of CB[*n*] derivatives.

Reaction between Glycolurils and Phthaldehyde 11. Given our interest in the development of building block strategies[16,31] for the construction of CB[*n*] derivatives and analogues, we wondered whether **11** would participate in such

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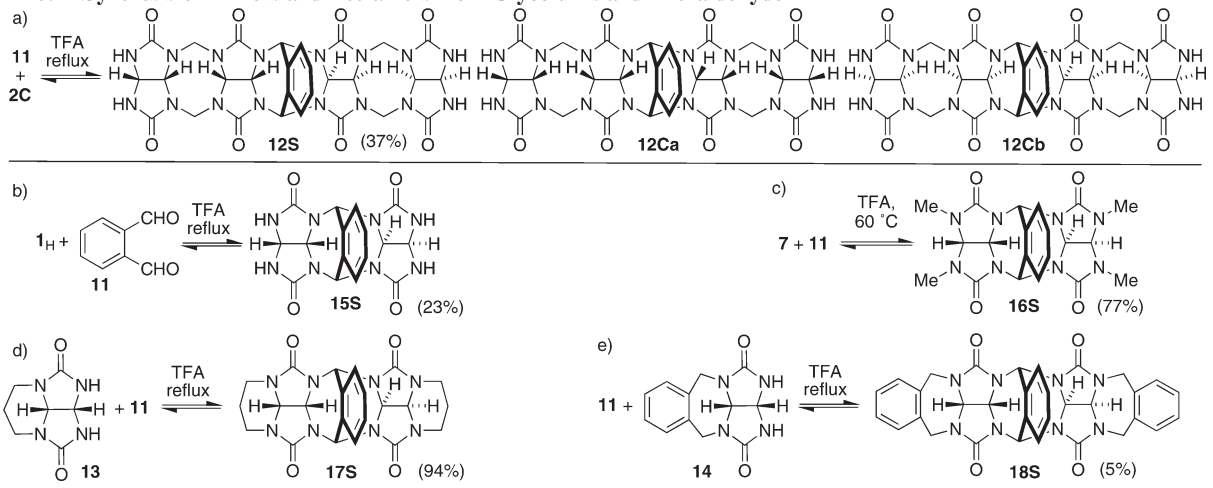
SCHEME 7. Synthesis of Dimers and Tetramers from Glycolurils and Phthaldehyde 11



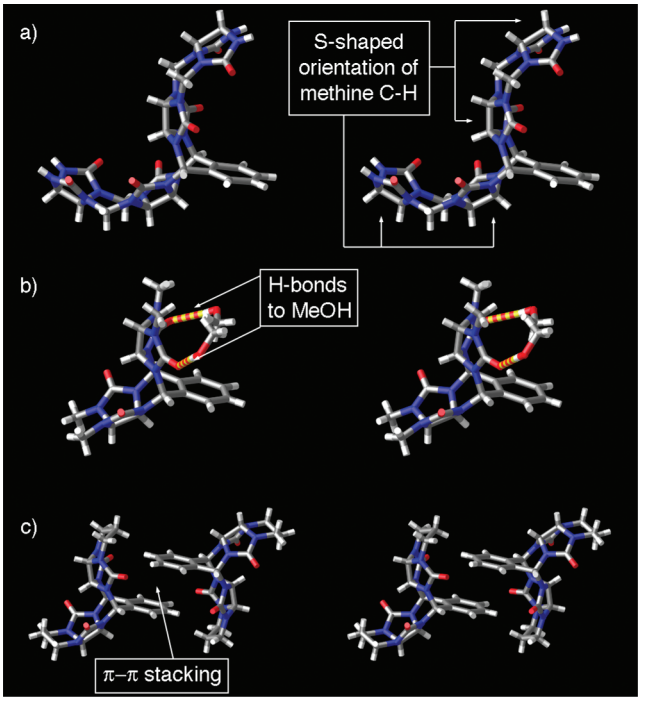


FIGURE 1. Stereoviews of the X-ray crystal structures of (a) **12S**, (b) **16S**, and (c) **17S** rendered with CrystalMaker. Color code: C, gray; H, white; N, blue; O, red; H-bonds, red-yellow striped.

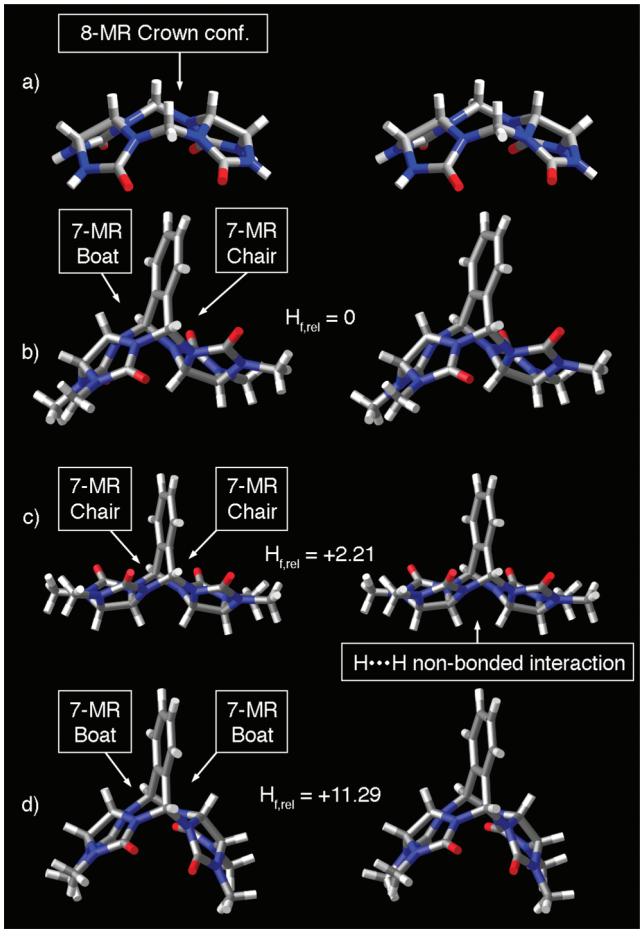


FIGURE 2. Stereoscopic representations of the X-ray crystal structure of (a) **2C** and the MMFF94s minimized geometries of (b) **16S**, (c) **16Cb**, and (d) **16Ca**. Color code: C, gray; H, white; N, blue; O, red. The quoted relative heats of formation (kcal mol^{-1}) were obtained from PM3 calculations.

reactions. First, we decided to conduct the reaction between glycoluril dimer **2C** (3 equiv) and **11** (3 equiv) in the hopes of creating a CB[6] derivative. This experiment was conducted in CF_3CO_2H rather than HCl because **2C** is nicely soluble in CF_3CO_2H. Contrary to expectation, we observed the formation of tetramer **12S** (Scheme 7a) whose structure was established by spectroscopic methods and also by X-ray crystallography (Figure 1a). Minor resonances were observed in the crude ^{1}H NMR that may correspond to diastereomers **12Ca** and **12Cb**.[32] The formation of **12S** was very interesting to us for a number of reasons. First, phthaldehyde **11** displayed a more normal reactivity in which the *o*-xylylene ring acts as bridge between the 1,5-positions of the newly formed eight-membered ring. Second, even though the condensation of two molecules of **2C** and one molecule of **11** could, in theory, yield three diastereomers (**12S**, **12Ca**, and

(32) The poor solubility of many glycoluril oligomers and their erratic chromatographic behavior prevented the isolation and structural elucidation of these minor products.

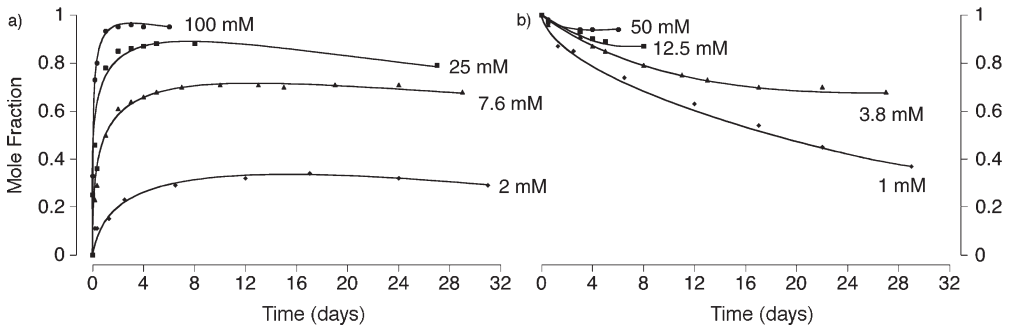


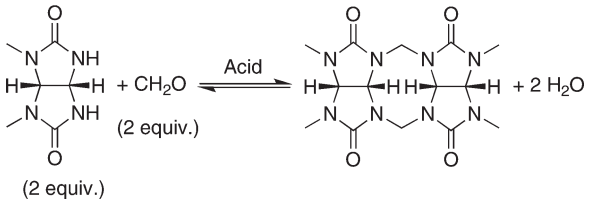
FIGURE 3. Plots of mole fraction of **16S** versus time for the (a) formation and (b) fragmentation of **16S**. Conditions: 5% DCl in D_2O, room temperature. The solid lines are intended merely as guides for the eye.

12Cb), we observe the dominant formation of **12S**. Next, we examined the reaction between phthaldehyde **11** and glycoluril $\mathbf{1}_H$ or capped glycolurils **7**, **13**, and **14**. In all cases, we observed the dominant formation of a single product (**15S**−18S) with an S-shaped geometry (Scheme 7b−e). We were fortunate to obtain single crystals of **12S**, **16S**, and **17S** and solve their structures (Figure 1). Figure 1a shows the X-ray crystal structure of **12S**, which illustrates the overall S-shape of the oligomer due to the relative orientation of the methine C−H groups on the convex face of 2 equiv of building block **2C** within **12S**. Figure 1b shows the X-ray crystal structure of **16S** which adopts a very similar geometry. In this case solvating MeOH molecules within the crystal form O−H···O=C H-bonds to the ureidyl carbonyls of **16S**. Compound **17S** also displays a similar overall geometry in the crystal (Figure 1c), but in this case the bridging *o*-xylylene rings of two adjacent molecules of **17S** in the crystal undergo $\pi-\pi$ stacking interactions.

The formation of the S-shaped diastereomers **12S** and **15S**−**18S** is of high relevance toward the use of **11** or aldehydes in CB[*n*] forming reactions. The formation of S-shaped subunits prevents the reactive NH tips of the oligomers from being close enough in space to undergo macrocyclization reactions. For this reason the use of **11** in CB[*n*] forming reactions is unlikely to be successful. We surmise that the reaction between *ns*-CB[6] and **11** is successful because *ns*-CB[6] is preorganized into the C-shape needed for macrocyclization before reaction with **11**.

Why Do the S-Shaped Diastereomers Predominate? The results described above and supported further below by product resubmission experiments establish that the S-shaped diastereomers **12S** and **15S**−**18S** are more stable than the corresponding C-shaped diastereomers. More importantly, why do the S-shaped forms predominate in this case? An examination of the X-ray crystal structure of **2C**[20] and the MMFF94s energy minimized structures of **16S**, **16Ca**, and **16Cb** (Figure 2) gives some insights. The central eight-membered ring of **2C** exists in the crown-conformation (Figure 2a).[33] Introduction of the bridging *o*-xylylene ring in **12** and **15**− **18** results in the formation of two new seven-membered rings (7-MR). It is well-known that 7-MR prefer the chair conformation over the boat conformation. In the case of **16S** one of the two 7-MR adopts the chair conformation whereas the other adopts the boat form. For **16Cb** both of these new 7-MR adopt the chair conformation, whereas for **16Ca** both adopt the boat conformation. This analysis predicts that **16Cb** should be the most stable diastereomer followed by **16S** and finally **16Ca**, which is contrary to the observed dominant formation of **16S**. Accordingly, we calculated the relative heats of formation of **16S**, **16Cb**, and **16Ca** of the MMFF94s minimized conformers using the PM3 method and found that theory predicts that **16S** is 2.21 kcal mol^{-1} more stable than **16Cb** (chair−chair) and 11.29 kcal mol^{-1} more stable than **16Ca** (boat−boat). We believe that unfavorable H···H nonbonded interactions (2.01 Å)[34] between H-atoms on adjacent glycoluril rings (Figure 2c) destabilize **16Cb**. On the basis of this analysis, it becomes clear that the conformational preferences of the newly forming 8-MR and 7-MR control the diastereomer (e.g., S-shaped or C-shaped) that is formed. For a CB[*n*] derivative forming reaction to proceed smoothly, it is critical that the equilibrium between S-shaped and C-shaped forms greatly favors the C-shaped form.

SCHEME 8. Formation of C-Shaped Glycoluril Dimer 19C



Product Resubmission Experiments. In combination, the synthetic and theoretical studies described above strongly suggested that the S-shaped diastereomers **12S** and **15S**−**18S** were thermodynamically more stable than the C-shaped diastereomers. In previous model system studies of the equilibrium between S-shaped and C-shaped methylene bridged glycoluril dimers we used product resubmission experiments to transform the S-shaped diastereomers into the C-shaped forms.[19] We decided to attempt similar experiments with **16S**. Accordingly, we monitored the composition of a solution of **16S** (12.5 mM) in 5% DCl at room temperature and observed a decrease in the concentration of **16S** over several days and somewhat surprisingly an increase in the concentration of glycoluril monomer **7** (Figure 3a).[35] No ^1H NMR resonances were detected that

(33) Isaacs, L; Anet, F. A. L.; Basus, V. J. *J. Am. Chem. Soc.* **1973**, *95*, 4424–4426. Dorofeeva, O. V.; Mastryukov, V. S.; Allinger, N. L.; Almenningen, A. *J. Phys. Chem.* **1985**, *89*, 252–257. Pakes, P. W.; Rounds, T. C.; Strauss, H. L. *J. Phys. Chem.* **1981**, *85*, 2469–2475. Calucci, L.; Zimmermann, H.; Poupko, R.; Luz, Z. *J. Phys. Chem.* **1995**, *99*, 14942–14948.

(34) Rowland, R. S.; Taylor, R. *J. Phys. Chem.* **1996**, *100*, 7384–7391.

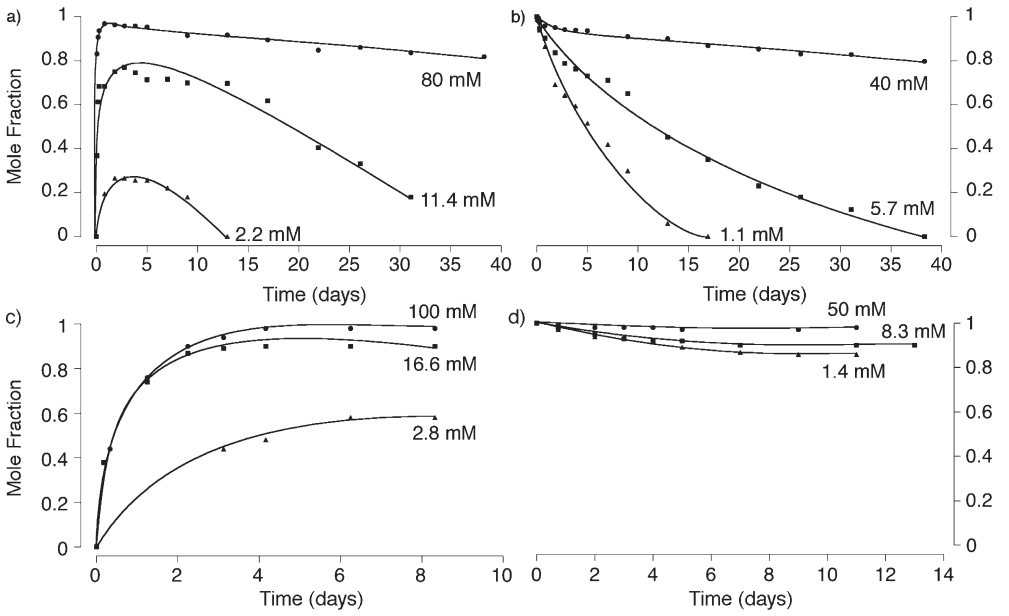


FIGURE 4. Plots of mole fraction of **19C** versus time for the (a) formation and (b) fragmentation of **19C** (5% DCl in D_2O, 70 °C) and (c) formation and (d) fragmentation of **19C** (5% DCl in D_2O, 50 °C). The solid lines are intended merely as guides for the eye.

would indicate the formation of C-shaped diastereomers **16Ca** or **16Cb**, which is in accord with the PM3 calculation described above. The observation of the mixture of S-shaped dimer **16S** and glycoluril monomer **7** suggested to us that the equilibrium constant for the conversion of **7** and **11** into **16S** and H_2O might be small due to the decreased reactivity of **11** relative to formaldehyde. To further verify this hypothesis, we dissolved **16S** in 5% DCl at room temperature at different concentrations (50, 12.5, 3.8, and 1 mM) and followed the decrease in the mole fraction of **16S** by ^{1}H NMR spectroscopy (Figure 3b). We also followed the formation of **16S** from equimolar mixtures of glycoluril monomer **7** and phthaldehyde **11** under identical conditions (Figure 3a). Figure 3 shows two important trends. First, both the formation and fragmentation of **16S** plateau at comparable mole fractions of **16S**.[36] Second, as the concentration increases from 1 to 50 mM we observe an increase in the mole fraction of **16S** at the plateau level. Both of these observations suggest that the conversion of **7** and **11** into **16S** and H_2O is an equilibrium process with a modest equilibrium constant. In sharp contrast to the reaction between glycolurils and formaldehyde which greatly favors products over starting materials over a range of conditions,[5] the use of less reactive phthalaldehyde **11** results in only partial dimerization in the 1−50 mM concentration regime. We infer that the lack of observed reactivity between **7** and benzaldehyde probably reflects an even lower equilibrium constant that cannot be accessed over the concentration range employed (up to 1 M).

Equilibrium and Reversibility of Formaldehyde Based Dimers. The previous section demonstrated that the formation of glycoluril dimer **16S** from **7** and phthaldehyde **11** is a reversible process with the mole fraction of **16S** experiencing large changes over the 1−100 mM range. As further evidence of the relevance of this behavior to CB[*n*] forming reactions similar experiments were performed on the transformation of **7** and formaldehyde into **19C** (Scheme 8) previously reported by the Sindelar group.[28] Given the higher reactivity of formaldehyde compared with that of aldehydes, we anticipated that we would need to resort to higher temperatures to entropically favor monomer **7**. Figure 4a shows a plot of mole fraction of **19C** versus time obtained during the formation of **19C** (5% DCl, 70 °C) at three different concentrations. In all three cases we observe an initial increase in the mole fraction of **19C** followed by a maximum and finally a decrease. At higher concentrations the mole fraction reaches a higher maximal value and decreases more slowly after this maximum is reached. As a complementary experiment we dissolved **19C** in 5% DCl at 70 °C and followed the fragmentation of **19C** by ^{1}H NMR as a function of time (Figure 4b). At higher concentrations of **19C** the mole fraction of **19C** decreases more slowly. We interpret this behavior as being indicative of two competing processes: (1) equilibrium between **7** and dimer **19C**, and (2) chemical decomposition of glycoluril monomer **7**.[37] We performed identical experiments at 50 °C in 5% DCl (Figure 4c and d) and observe clearer plateau regions, which indicates lower levels of side reactions (e.g., decomposition) relative to monomer−dimer equilibrium at this temperature.

Conclusions

We have shown that glycolurils react with a dialdehyde (*o*-phthaldehyde) to deliver S-shaped glycoluril dimers **15S**−**18S** and tetramer **12S**. We established that S-shaped compounds **12S** and **15S**−**18S** are thermodynamically preferred over the C-shaped diastereomers and trace this preference to the conformational biases of the newly formed benzo bicyclo[3.3.2]octane

(35) We did not observe ^{1}H NMR resonances for free phthaldehyde **11** under these conditions. We suspect that **11** undergoes oxidative decomposition.

(36) At higher temperatures or longer reaction times we observe the decomposition of **7**. This prevents us from measuring a value of K_{eq} for this reaction.

(37) We have confirmed that **7** undergoes decomposition when heated at 70 °C in 5% DCl.

ring system. The presence of S-shaped segments in glycoluril oligomers hinders macrocyclization to CB[*n*]-type compounds by holding the reactive NH groups far apart in space. Accordingly, the observation of the dominant formation of S-shaped dimers in the reaction between glycolurils and **11** provides one reason for the inability of *o*-phthalaldehyde and possibly other aldehydes to participate in CB[*n*] forming reactions. The side products observed in the reaction between **7** and aldehydes $\mathbf{8}_{Ph}$ and $\mathbf{8}_{Pr}$ illustrate two alternative reaction pathways (hydantoin formation and enamine-iminium ion cyclization) that become viable when less reactive aldehydes are used.

We used product resubmission experiments to provide evidence for an equilibrium between dimer **16S** and monomer **7** that responds to changes in concentration over the 1−50 mM range. This indicates that the equilibrium constant for dimer formation with *o*-phthalaldehyde is modest and that high concentrations of starting materials are needed to drive the reaction toward completion. In contrast to the results obtained with *o*-phthalaldehyde, we did not observe any reaction between benzaldehyde and glycoluril **7** under the range of concentrations (1 mM to 1 M) employed. We interpret this result as meaning that the reactivity of aldehydes toward glycolurils is even lower (lower equilibrium constant) than that of *o*-phthalaldehyde **11**. Given that concentrations of 50 mM are needed to drive the reaction with *o*-phthalaldehyde **11** to completion, perhaps it is not surprising that monoaldehydes do not react with glycolurils at concentrations up to 1 M. Accordingly, these results point toward poor reactivity (low equilibrium constant) as a second reason for the inability of aldehydes to participate in CB[*n*] forming reactions.

The delineation of two of the reasons why aldehydes do not generally participate in CB[*n*] forming reactions, i.e. the critical importance of the S- to C-shaped equilibrium and the magnitude of the equilibrium constant for chain growth, is important because it suggests methods to overcome these limitations in the future. When it is possible to introduce functionality onto the bridging CH_2 groups of CB[*n*], we expect that the range of applications (e.g., targeted drug delivery, affinity chromatography, and sensing arrays) to which CB[*n*] derivatives[8] can be applied will expand.

Experimental Section

General experimental details have been reported previously.[9,28] Starting materials were obtained from commercial suppliers and used without further purification. Compounds **2C**, **7**, **13**, and **14** were prepared by the literature procedures.[20,28] Compound **SP1** has been reported in the literature previously.[30]

Compound 12S. Compound **2C** (498 mg, 1.62 mmol) was dissolved in a mixture of TFA and water (19:1, v/v, 6 mL), and *o*-phthaldiadehyde (108 mg, 0.81 mmol) was added. The mixture was heated at 70 °C for 3 h. The solution was then poured into MeOH (150 mL). The precipitate was filtered to yield the crude product (580 mg). The crude solid was stirred in a mixture of formic acid and water (1:2, v:v, 120 mL) 30 min. The filtrate was concentrated under reduced pressure and then poured into MeOH (200 mL). After filtration and drying, the precipitate was further purified by recrystallization from TFA and water (4:1, v/v, 20 mL) to yield **12S** as a white solid (216 mg, 0.30 mmol, 37%). Mp 350 °C (dec). IR (ATR, cm^{-1}): 3450w, 1715s, 1445s, 1318 m, 1228s, 1185s. ^{1}H NMR (400 MHz, DMSO-d_6): 7.71 (s, 2H), 7.61 (s, 2H), 7.60−7.55 (m, 2H), 7.45−7.40 (m, 2H), 6.46 (s, 2H), 5.56 (d, J = 14.6 Hz, 2H), 5.54 (d, J = 6.8 Hz, 1H), 5.42 (d, J = 14.6 Hz, 2H), 5.41 (d, J = 8.6 Hz, 1H), 5.30 (d, J = 8.6 Hz, 1H), 5.23 (d, J = 8.6 Hz, 1H), 5.13 (d, J = 8.6 Hz, 1H), 5.10 (d, J = 8.6 Hz, 1H). 4.79 (d, J = 8.6 Hz, 1H), 4.16 (d, J = 14.6 Hz, 2H), 4.06 (d, J = 14.6 Hz, 2H). ^{13}C NMR (100 MHz, TFA, external DMSO reference): δ 158.6, 158.5, 154.5, 153.8, 130.1, 129.6, 127.8, 72.5, 72.3, 69.0, 68.5, 63.7, 61.7, 61.5, 61.3, 49.5, 49.1 (only 17 of the 18 expected resonances were observed). MS (ESI): m/z 715 ([M + H]$^+$). HR-MS (ESI$^+$): m/z 715.2220, calcd for $C_{28}H_{27}N_{16}O_8$ 715.2198. X-ray crystal structure.

Compound 16S. Compound **7** (300 mg, 1.76 mmol) was dissolved in TFA (7 mL), and *o*-phthaldialdehyde **11** (120 mg, 0.89 mmol) was added. The mixture was stirred and heated at 60 °C for 3 h. The solvent was removed under reduced pressure. The crude mixture was recrystallized from MeOH to yield **16S** as a white crystalline solid (300 mg, 0.68 mmol, 77%). Mp 322 °C (dec). TLC ($CHCl_3$/MeOH 6:1) R_f 0.28. IR (ATR, cm^{-1}): 3493w, 3003w, 2933w, 1692s, 1482s, 1405s, 1380s, 1203s, 1036s. ^{1}H NMR (400 MHz, $CDCl_3$): 7.50−7.45 (m, 2H), 7.40−7.35 (m, 2H), 6.59 (s, 2H), 5.34 (d, J = 7.9 Hz, 1H), 4.93 (d, J = 8.4 Hz, 1H), 4.85 (d, J = 7.9 Hz, 1H), 4.84 (d, J = 8.4 Hz, 1H), 3.01 (s, 6H), 2.84 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.2, 155.2, 134.2, 130.0, 129.2, 71.2, 71.1, 64.9, 64.3, 62.3, 30.2, 29.8. MS (ESI): m/z 439 ([M + H]$^+$). HR-MS (ESI$^+$): m/z 439.1818, calcd for $C_{20}H_{23}N_8O_4$ 439.1842. X-ray crystal structure.

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Supporting Information Available: Experimental procedures and characterization data for **SP1**, (±)-**SP2**, **15S**, **17S**, and **18S**; ^{1}H and ^{13}C NMR spectra for all new compounds and selected ^{1}H NMR spectra for crude reaction mixtures; crystallographic information files for **12S**, **16S**, and **17S** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.