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Cucurbit[*n*]uril Formation Proceeds by Step-Growth Cyclo-oligomerization

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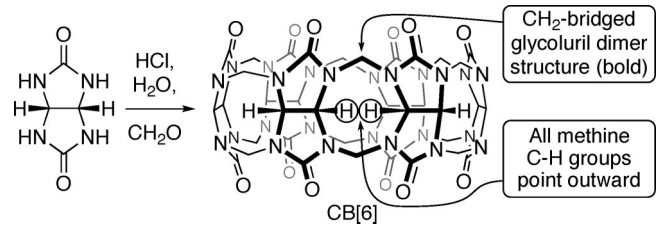
Abstract: In contrast to the high yield formation of cucurbit[*n*]uril (CB[*n*]) from a 1:2 ratio of glycoluril to formaldehyde, the condensation of glycoluril with less than 2 equiv of formaldehyde delivers a reaction mixture that contains glycoluril oligomers (**2**−**6**) and CB[*n*] compounds that lack one or more methylene bridges known as nor-seco-cucurbit[*n*]urils (*ns*-CB[*n*]). In this paper we report the chromatographic purification of C-shaped glycoluril oligomers (dimer−hexamer), their characterization in solution, and their X-ray crystal structures. Quite interestingly, despite being acyclic glycoluril pentamer **5** and hexamer **6** retain the ability to bind to guests typical of CB[6] but are also able to expand their cavity to accommodate larger guests like cationic adamantane derivatives. We performed product resubmission experiments with glycoluril oligomers **2**−**6** and found preferences for the formation of specific ring sizes during CB[*n*] formation. A comprehensive mechanistic scheme is proposed that accounts for the observed formation of **2**−**6** and *ns*-CB[*n*]. Overall, the experiments establish that a step-growth cyclo-oligomerization process operates during CB[*n*] formation.

Introduction

In 1981 Mock reported that the condensation of glycoluril and formaldehyde delivers the cyclic hexameric macrocycle cucurbit[6]uril (CB[6]).[1] This remarkable reaction (Scheme 1) results in the formation of 24 new C−N bonds and six eight-membered rings all with complete control over the relative orientation of the glycoluril C−H atoms which point out of the cavity. During the 1980s Mock extensively studied the host−guest recognition behavior of CB[6] and found that CB[6] exhibits remarkably tight (K_a up to 10^8 M^{-1}) and selective binding toward organic ammonium ions in water.[2,3] Subsequent work by Mock showed that these binding characteristics could be used to catalyze a dipolar cycloaddition (click-chemistry) and to create one of the first examples of a molecular shuttle.[4,5] As supramolecular chemists, we were inspired by the outstanding recognition properties of CB[6] and hypothesized that if we could tailor the recognition properties of CB[6] by synthetic chemistry (e.g., the creation of cucurbit[*n*]uril homologues (CB[*n*]),[6–8] analogues, derivatives, or congeners) that we might be in the position to create contemporary molecular devices like chemical sensors, supramolecular catalysts, ion and molecular channels, and molecular machines (e.g., molecular shuttles). As physical organic chemists, we decided to target a thorough understanding of the mechanism of CB[*n*] formation with the expectation that such knowledge would enable the tailor-made synthesis of CB[*n*]-type receptors with new geometrical features and recognition properties.

Scheme 1. Synthesis of CB[6]



Since we began our work on the mechanism of CB[*n*] formation upon arriving at the University of Maryland in 1998 there have been a number of developments in the CB[*n*] area that post facto validate our plan to enhance the range of applications to which the CB[*n*] family[6,7] can be applied by the creation of new CB[*n*]-type receptors. For example, the isolation of the cucurbit[*n*]uril homologues ($n = 5, 6, 7, 8$) by the groups of Kim and Day provided a series of macrocycles

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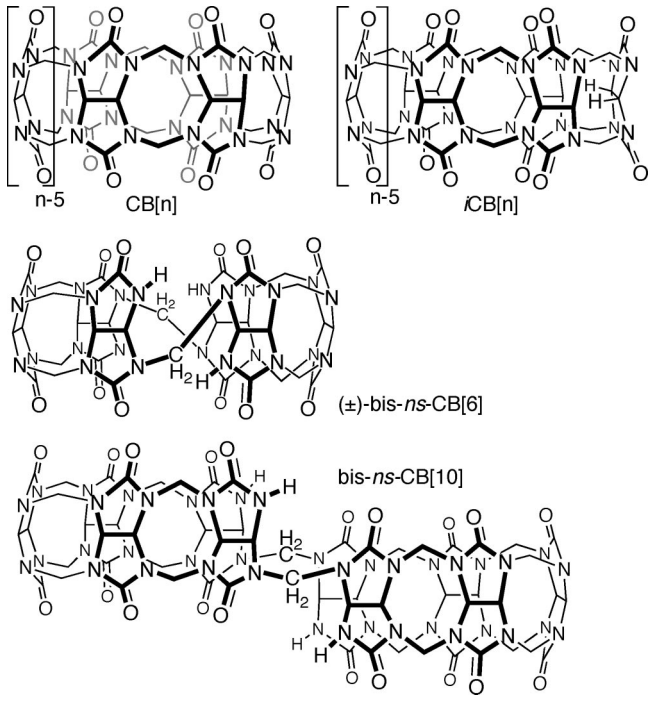
10.1021/ja8013693 CCC: $40.75

Chart 1. Chemical Structures of CB[*n*], *i*CB[*n*], bis-*ns*-CB[10], and (±)-bis-*ns*-CB[6]



whose sizes (82, 164, 279, 479 Å^3) parallel those of α-, β-, and γ-cyclodextrins (Chart 1).[9,10] These new macrocycles, therefore, participate in a variety of interesting applications including supramolecular dye lasers,[11] novel drug delivery vehicles,[12] as a mediator of organic reactions,[5,13] peptide recognition,[14] chemical sensors,[15,16] as components of complex self-sorting systems,[3,17] and in the development of molecular machines.[18] More recently, our group has reported the isolation of free CB[10] from its CB[10]·CB[5] complex and the ability of its 870 Å^3 cavity to promote folding, forced unfolding, and refolding of non-natural oligomers in water and as a host for metalloporphyrins.[19] Most recently, in collaboration with Kimoon Kim's group, we have reported the isolation and recognition properties of diastereomeric CB[*n*] known as inverted-CB[*n*] (*i*-CB[*n*]) in which a single pair of methine C−H groups point into the central cavity.[20,21] The formation of these new CB[*n*] under milder kinetically controlled conditions provide an existence proof for intermediates in the mechanism of CB[*n*] formation and have helped guide our mechanistic studies over the years.[20–25]

In this paper we explore the consequences of our realization that the cyclo-oligomerization reaction between glycoluril and formaldehyde—tetrafunctional and difunctional monomers, respectively—is in many ways related to a classical polymerization reaction. For example, classical polymerization reactions between two different multifunctional monomers only proceed to give high molecular weight material when there is a stoichiometric balance between the reactive groups of the two monomers.[26] When there is an excess of one of the monomers, it acts as an end-capping group and shorter oligomers are obtained. Realizing that cyclic oligomeric CB[*n*] can be viewed as infinitely long oligomers raised the question in our mind of what would happen if we starved the CB[*n*] forming reaction of formaldehyde. Would new mechanistic intermediates in the formation of CB[*n*] be delivered as kinetically stable isolable materials? Our previous reports on the isolation, structural characterization, and recognition properties of bis-nor-seco-CB[10][27] and (±)-bis-nor-seco-CB[6] provide an answer in the affirmative and we describe our complete mechanistic study in detail here.

Results and Discussion

We begin this results and discussion section with a brief review of the state-of-the-art concerning the mechanism of

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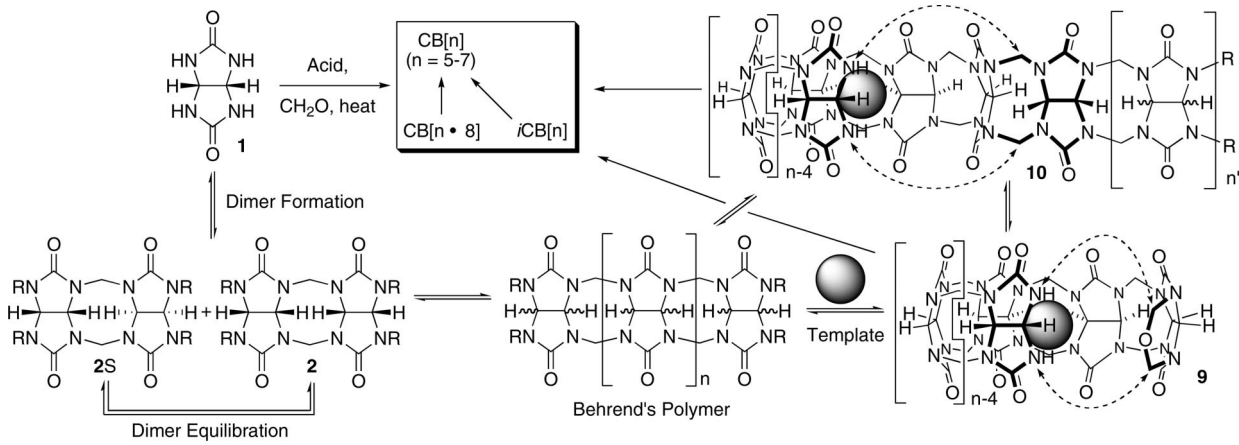
Scheme 2. Proposed Mechanism of CB[*n*] Formation



CB[*n*] formation that sets the stage for a discussion of the results reported in this paper.

Previous Mechanistic Studies. Scheme 2 shows the fundamental steps of the mechanism of CB[*n*] formation that were previously presented by the groups of Isaacs and Day.[10,23] First, glycoluril **1** reacts with 2 equiv of formaldehyde to potentially deliver a mixture of diastereomers (**2** and **2***S*) that differ in the relative orientation of the pairs of methine C−H groups. It was further hypothesized that these dimers undergo further oligomerization via **3**−**8** to ultimately yield a substance known as Behrend's polymer.[28] The length of the polymer chain and diastereomeric orientation of methine C−H groups in Behrend's polymer was ill-defined. At this stage, Behrends polymer must undergo an isomerization reaction that converts its S-shaped to C-shaped subunits—potentially aided by templating groups[29]—to create an oligomer (e.g., **9** or **10**) that is poised to undergo macrocyclization to enter the CB[*n*] family manifold by either end-to-end cyclization or back-biting mechanisms.

Our group and the group of Anthony Day have been heavily involved in elucidating the mechanistic details of the CB[*n*] forming reaction.[10,23,25,29] Day's group has focused on the final steps of the mechanism of CB[*n*] formation and have examined the influence of numerous potential templating agents on the distribution of CB[*n*] obtained (e.g., ammonium ions and alkali metal ions).[30] Further transformations can occur inside the manifold of CB[*n*]-type receptors. For example, Day showed that heating CB[8] under the reaction conditions, where CB[5], CB[6], and CB[7] are stable, results in a partial ring contraction to deliver the smaller CB[*n*] homologues.[10] Similarly, we recently reported product resubmission experiments that show that *i*-CB[6] and *i*-CB[7] are converted into CB[*n*] which establishes that these diastereomeric CB[*n*] are kinetically controlled intermediates in the mechanism of CB[*n*] formation.[21]

Based on our realization that the methylene-bridged glycoluril dimer substructure (bold in Chart 1) constituted the fundamental building block of the CB[*n*] family of macrocycles we initially studied derivatives of **2** and **2***S* that contained solubilizing CO_2Et groups on their convex face and capping *o*-xylylene groups.[22,23] These model studies of the earliest steps of the mechanism of CB[*n*] formation (e.g., dimer formation and interconversion) allowed us to establish the high thermodynamic preference for the C-shaped forms ($\Delta\Delta G$ > 2 kcal mol^{-1}), elucidate the intramolecular nature of the S-shaped to C-shaped interconversion, and to propose and validate the great potential of building block strategies in the formation of CB[*n*]-type receptors.[22–25,31] In combination, the results described above shed significant light on the earliest and latest steps of the mechanism of CB[*n*] formation. What was lacking was information about what goes on in the middle.

Reaction Mixtures Deficient in Formaldehyde Deliver Glycoluril Oligomers 2−6 as Isolable Species. On the basis of the connections described above between a classical copolymerization between multifunctional monomers and CB[*n*] formation we decided to conduct the condensation of glycoluril (**1**) with less than 2 equiv of formaldehyde under aqueous acidic conditions (Scheme 3). From these reaction mixtures, we were able to isolate the series of glycoluril oligomers **2**−**6** by a combination of Dowex ion-exchange chromatography and recrystallization.[32] We were able to establish the constitution of glycoluril oligomers **2**−**6** by mass spectrometry. Given the large number of potential diastereomers of these oligomers **2** (2), **3** (3), **4** (6), **5** (10), **6** (21), structural elucidation by ^{1}H NMR spectroscopy alone is challenging (Figure 1). Compounds **2**−**6** with all methine C−H groups on a single side of the molecule are C-shaped and C_{2v}-symmetric. Symmetry considerations dictate that dimer **2** show two doublets for the methine C−H groups (H_a and H_b) and two doublets for the diastereotopic CH_2-groups (H_c and H_d) as is observed experimentally. The ^{1}H NMR spectrum for trimer **3** consists of two doublets and one singlet for the glycoluril methine C−H groups (H_a, H_b, H_c) in

(28) Previous reports have referred to the product of the initial stage of Behrend's synthesis of CB[*n*] (aq. HCl, 100 °C, 3 equiv of formaldehyde) as "Behrend's polymer". The results reported in this paper suggest that this substance may, in fact, consist of a mixture of glycoluril oligomers, nor-seco-CB[*n*], and other kinetically controlled intermediates in the mechanism of CB[*n*] formation.

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(30) The influence of glycoluril concentration, acid identity and concentration and temperature have also been studied by Day and co-workers. The point in the mechanistic pathway where these variable exert their influence remains unclear.

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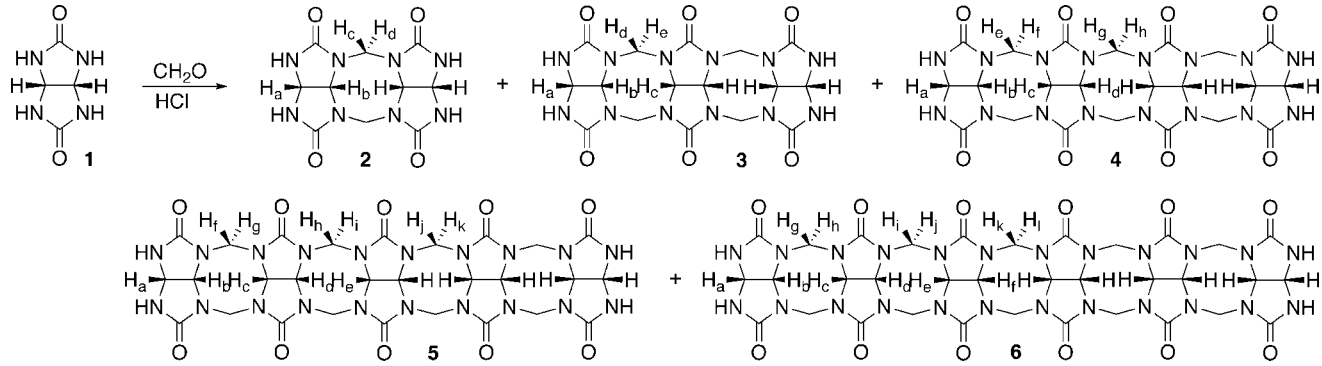
(32) In addition to oligomers **2**−**6**, bis-*ns*-CB[10], (±)-bis-*ns*-CB[6], and *ns*-CB[6] the crude reaction mixtures typically contain some CB[6] and CB[7]. We have been unsuccessful in developing an HPLC method to more precisely quantify the components of the reaction mixture for several reasons including (1) incompatibility of silica gel with the aq acid required for solubility, (2) irreversible adsorption during Dowex ion-exchange chromatography, and (3) lack of a convenient chromophore for detection.

Scheme 3. Synthesis of C-Shaped **2**−**6**



addition to two doublets for the diastereotopic CH_2-groups. The ^{1}H NMR spectra for **4**−**6** are complicated by spectral overlap in the methine CH region, although the number and relative intensity of the resonances for the diastereotopic CH_2-groups are in accord with symmetry considerations, and complete assignment was not possible on the basis of mass spectrometry and ^{1}H NMR spectroscopy alone.

X-ray Crystal Structures of 2−**6.** Although we were quite confident in our assignment of the structures of the oligomers **2**−**6** based on spectroscopic techniques and previous model studies which indicated a significant thermodynamic preference for the C-shaped diastereomers we wanted to obtain final structural proof in the form of X-ray crystal structures. With some effort we were able to obtain single crystals of **2**, **3**, **4**, **5**, and **6** (Figure 2). The structures of **2**−**6** are striking for several reasons: (1) the anticipated C-shaped geometries are observed in all cases, (2) the curvature of **2**−**5** is mainly restricted to a single plane (e.g., out of plane twisting is not significant), and (3) the degree of curvature maps well onto that of CB[6] which is in accord with theoretical calculations which show that CB[6] is the least strained and thermodynamically most stable CB[*n*] on a per glycoluril basis.[7] To quantify the degree of curvature of **2**−**6** relative to CB[5]−CB[8] we measured the angles between the adjacent glycoluril rings (θ, Figure 2) through their

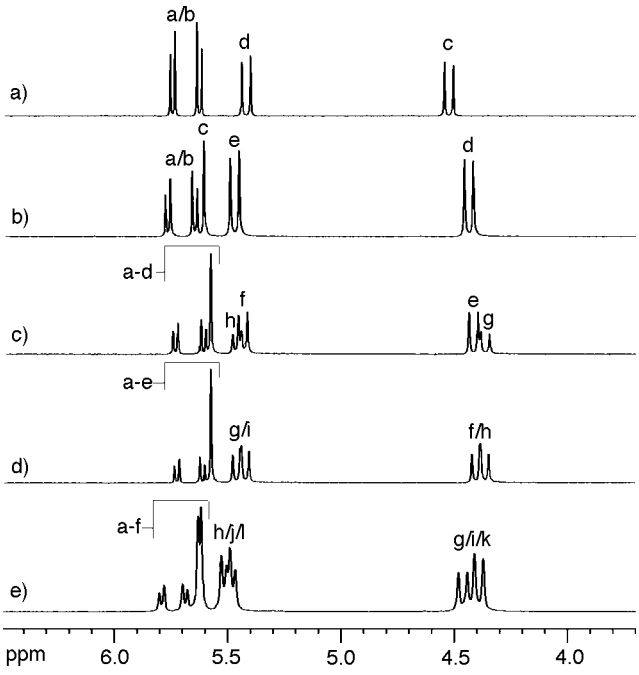


Figure 1. ^{1}H NMR spectra (400 MHz, 35% DCl, room temp) for (a) **2**, (b) **3**, (c) **4**, (d) **5**, and (e) **6**.

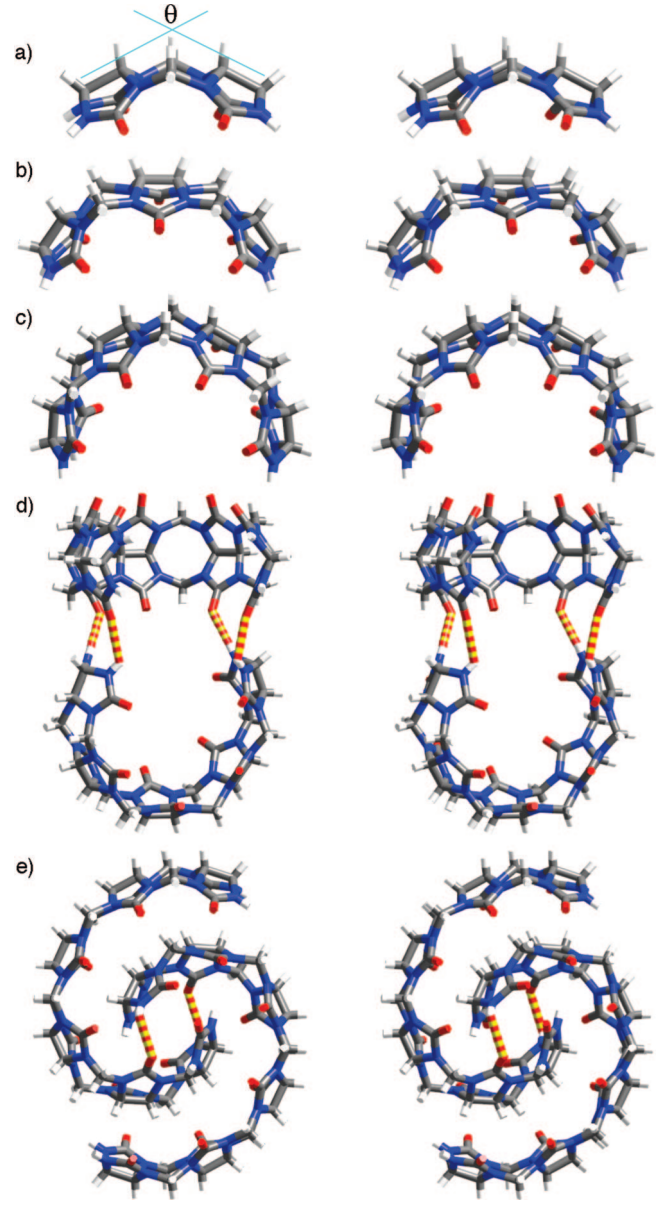


Figure 2. Cross-eyed stereoviews of the crystal structures of (a) **2**, (b) **3**, (c) **4**, (d) **5**, and (e) **6**. Solvating CF_3CO_2H and H_2O molecules have been removed for clarity. Color code: C, gray; H, white; N, blue; O, red; H-bonds, red-yellow striped.

Table 1. Values of θ Measured from the X-ray Structures of **2**−**6** and CB[5]−CB[8][1,9]

compound	θ	average θ
2	123.5	123.5
3	123.6, 123.6	123.6
4	124.2, 120.0, 124.2	122.8
5	124.8, 123.6, 123.6, 124.8	124.2
6	132.9, 143.6, 130.5, 116.3, 117.9	128.2
CB[5]	103.4, 109.7, 109.7, 103.3, 113.8	108.0
CB[6]	118.7, 116.6, 124.5, 118.7, 116.7, 124.4	119.9
CB[7]	124.4, 130.4, 129.5, 129.6, 123.3, 133.8, 128.4	128.5
CB[8]	135.4, 135.9, 139.5, 129.2, 135.4, 135.8, 139.5, 129.2	135.0

equatorial methine C-atoms (Table 1). An examination of Table 1 shows that oligomers **2**−**5** have an average curvature (θ) that is intermediate between that of CB[6] and CB[7]. Hexamer **6**, in contrast, has a wider spread of values of θ and an average θ that is close to that of CB[7] which indicates the inherent flexibility of longer glycoluril oligomers.

Beyond the connectivity of the molecular structures of **2**−**6** and their curvature there are intriguing aspects of the solvation and packing of **2**−**6** in the crystal (Supporting Information). For example, compound **2** crystallizes (Figure 2a) as the CF_3CO_2H (TFA) solvate which segregates the molecules of **2** from one another by forming H-bonds to the ureidyl groups of **2**. Trimer **3** also crystallizes (Figure 2b) as the TFA solvate by H-bonding interactions with the ureidyl groups of **3**. In this case, however, multiple molecules of **3** segregate themselves into slabs in the ab-plane that are separated by solvating slabs of TFA molecules along the *c*-axis. The packing of tetramer **4** (Figure 2c) in the crystal is facilitated by the interaction of the center two ureidyl C═O groups of 2 equiv of **4** forming a head-to-tail dimeric entity by ion−dipole interactions with Na^+. Interestingly, these dimers of **4** are further organized by NH···O═C H-bonds between the tips of **4** and the C═O rim of another molecule of **4** to form a complex network motif (Supporting Information). The packing of pentamer **5** which begins to look like CB[5] is even more interesting. Each molecule of pentamer **5** contains one solvating molecule of TFA *within its cavity*. Furthermore, these molecules of **5** organize themselves into infinite 1-dimensional tapes along the *a*-axis by *four* H-bonds between the N−H tips of **5** with the ureidyl C═O of the adjacent equivalents of **5** (Supporting Information). Most interesting and relevant toward the mechanism of CB[*n*] formation is the packing observed in the crystal structure of **6**. Individual molecules of **6** are distorted from a symmetric CB[6]-like shape and exhibit an out-of-plane twist toward the tips of the molecule. Both features speak to the inherent flexibility of the growing glycoluril oligomer chains which is less apparent by examination of the macrocyclic CB[*n*]. Furthermore, two molecules of **6** dimerize in the crystal driven by NH···O H-bonds. Although glycoluril derived supramolecular structures[33] are well-known to undergo self-association in organic and aqueous solution by H-bonds or π-π interactions this is the first example that we are aware of that implicates self-association of water soluble CB[*n*] fragments.[34] The implication is that (self)-association of glycoluril oligomers may be considered as a relevant side pathway during the CB[*n*] forming reaction.

Table 2. The Molar Ratio of Glycoluril and Formaldehyde Units Needed to Construct CB[*n*], *i*-CB[*n*], *ns*-CB[*n*], and Oligomers **2**−**6**

compound	glycoluril	formaldehyde
CB[*n*]	1	2
i-CB[*n*]	1	2
ns-CB[6]	1	1.84
bis-*ns*-CB[10]	1	1.80
(±)-bis-*ns*-CB[6]	1	1.67
6	1	1.67
5	1	1.60
4	1	1.50
3	1	1.33
2	1	1

Reaction Mixtures Deficient in Formaldehyde Also Deliver nor-seco-CB[*n*] as Isolable Species. From similar reaction mixtures we have previously isolated bis-*ns*-CB[10], (±)-bis-*ns*-CB[6], and *ns*-CB[6].[27,35,36] Although the quantitation of the amounts of each oligomer and nor-seco-CB[*n*] in a given reaction mixture has proved challenging because of extensive peak overlap in the ^{1}H NMR spectrum and losses that occur during Dowex ion exchange we have developed a guiding principle to maximize the yield of a given compound from condensations of glycoluril and formaldehyde that contain a deficiency of formaldehyde.[32]This guideline is based on the theoretical ratio of glycoluril to formaldehyde in a given oligomer or *ns*-CB[*n*] (Table 2) and can be considered a consequence of Le Chatelier's principle. For example, dimer **2** is composed of 2 equiv of glycoluril and 2 equiv of formaldehyde and is best targeted with reaction mixtures containing a 1:1 ratio of the two starting materials. Similarly, the recently described *ns*-CB[*n*] (*ns*-CB[6], bis-*ns*-CB[10], and (±)-bis-*ns*-CB[6]) can be efficiently isolated from reaction mixtures comprising a 1:1.5−1:1.67 molar ratio of glycoluril/formaldehyde.[37] This ratio is slightly lower than the calculated ratio since entry into the CB[*n*] manifold is an irreversible process that reduces overall yield and complicates product isolation. Lastly, the synthesis of CB[*n*] is known to be most efficient at a stoichiometric ratio of 1:2.[10]

Implications of the Isolation of 2−6, Bis-ns-CB[10], (±)-Bis-ns-CB[6], and ns-CB[6] Toward the Mechanism of CB[*n*] Formation. The isolation of glycoluril oligomers **2**−**6** and nor-seco-CB[*n*] allows us to add levels of detail to the mechanism of CB[*n*] formation that was not previously possible. Scheme 4 illustrates in detail our current level of understanding of the CB[*n*] formation process. The isolation of oligomers **2**−**6** from reaction mixtures comprising glycoluril and a deficiency of formaldehyde provides an existence proof for these structures as kinetically controlled intermediates in the formation of CB[*n*]. Accordingly, Scheme 4 shows the stepwise interconversion of glycoluril **1** into hexamer **6** by stepwise addition of monomer

(33) (a) Rebek, J. J. *Acc. Chem. Res.* **1999**, *32*, 278–286. (b) Rowan, A. E.; Elemans, J. A. A. W.; Nolte, R. J. M. *Acc. Chem. Res.* **1999**, *32*, 995–1006. (c) Wu, A.; Chakraborty, A.; Fettinger, J. C.; Flowers, R. A., II.; Isaacs, L. *Angew. Chem., Int. Ed.* **2002**, *41*, 4028–4031. (d) Isaacs, L.; Witt, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1905–1907.

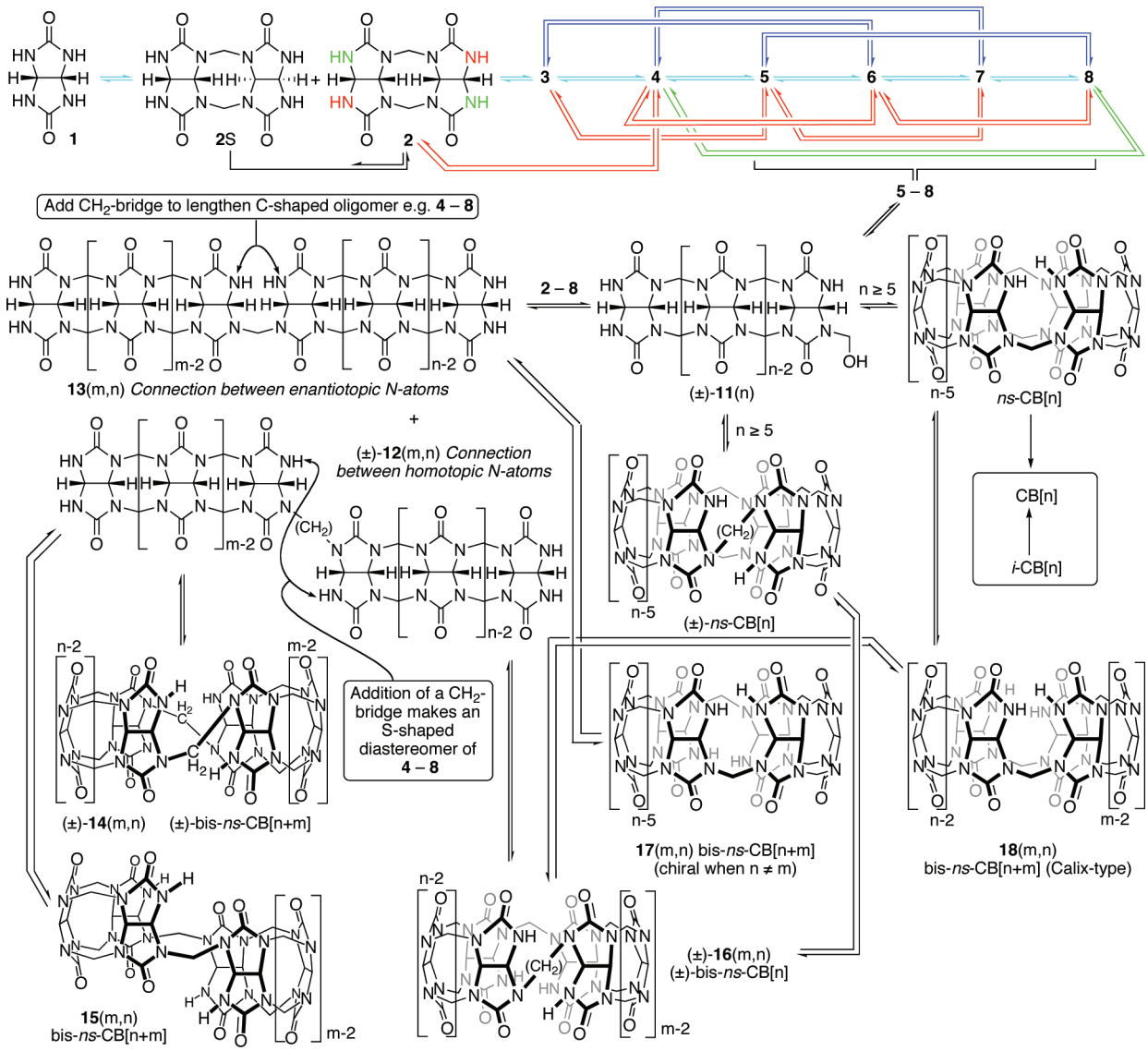
(34) The formation of CB[10]·CB[5] and the gelation of purified CB[7] provide evidence for the (self)-association of CB[*n*] in aqueous solution. Although the presented x-ray structure is a solid state structure we find it highly likely that glycoluril oligomers will also undergo (self)-association in aqueous solution.

(35) Huang, W.-H.; Zavalij, P. Y.; Isaacs, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 7425–7427.

(36) Huang, W.-H.; Zavalij, P. Y.; Isaacs, L. *Org. Lett.* **2008**, *10*, 2577–2580.

(37) The isolation of **2**−**6**, bis-*ns*-CB[10], (±)-bis-*ns*-CB[6], and *ns*-CB[6] from reaction mixtures containing a deficiency of formaldehyde was possible because this stoichiometric imbalance slows down their transformation to the thermodynamically more stable CB[*n*]. In particular, the precipitation of certain compounds (e.g. bis-*ns*-CB[10]) from the reaction mixture can result in significant kinetic stability.

Scheme 4. Comprehensive Mechanistic Scheme for the Formation of CB[*n*][a]



[a] Color coding: chain growth, aqua arrows; step growth; red arrows (addition of **2**), blue arrows (addition of **3**); green arrows (addition of **4**).

1 (aqua arrows). Such a process where monomer is added stepwise is known in polymer chemistry as chain growth polymerization.[26] Although we have not isolated glycoluril heptamer or octamer (**7** and **8**) we depict them as highly likely mechanistic intermediates. As the oligomer lengthens from **1** to **8** the formation of undesired S-shaped diastereomers is likely. As depicted for **2***S* and **2**—and studied in detail in model systems by us[22,23]—an equilibration occurs that dramatically favors the C-shaped forms **3**−**8**. Once these oligomer chains have grown long enough (**5**−**8**) they may undergo direct *intramolecular* end-to-end cyclization by way of chiral hydroxymethylated intermediate (±)-**11**(*n*) then *ns*-CB[*n*], and finally enter into the CB[*n*] manifold by addition of the final CH_2-group. This portion of Scheme 4 is in essence an enhanced version of Scheme 2 which accounts in detail for the presence of oligomers **3**−**6** and also takes into account the intermediacy of *ns*-CB[6].

The isolation of bis-*ns*-CB[10] and (±)-bis-*ns*-CB[6], comprising two oligomer chains (e.g., **5** and **3**, respectively) linked by two CH_2-groups, alerted us to the potential operation of a second type of mechanistic pathway known as a *step-growth* process. In a step-growth process, the reaction between two oligomer chains is also possible. Consider, for example, intermediate (±)-**11**(*n*) ($n \leq 4$) which is too short to undergo direct *intramolecular* end-to-end cyclization. Intermediate (±)-**11**(*n*) is, therefore, forced to undergo intermolecular reaction with an oligomer of identical or different length. The sets of colored equilibrium arrows in Scheme 4 indicate the step-growth occurring by the addition of dimer **2** (blue arrows), trimer **3** (red arrows), and tetramer **4** (green arrows) and 2 equiv of formaldehyde to give longer C-shaped oligomers. Analysis of the intermediate stage of the addition of 1 equiv of formaldehyde is instructive. Despite the fact that **1**−**8** are achiral, their ureidyl NH groups are prochiral and pairs of NH groups are either homotopic (pairs of red or pairs of green NH groups in structure of **2**) or enantiotopic (pairs of red and green NH groups in structure of **2**). Connection of a pair of homotopic groups between two oligomers results in intermediate (±)-**12**(*m*,*n*) whereas connection of a pair of enantiotopic NH groups by means of a CH_2-bridge results in the formation of **13**(*m*,*n*).[38] Intermediates **13**(*m*,*n*) and (±)-**12**(*m*,*n*) may add a second CH_2-

(38) Compounds **13**(*m*,*n*) and **17**(*m*,*n*) are chiral when $m \neq n$.

group in the middle of the molecule to form longer C-shaped oligomers **4**−**8** or diasteromeric oligomers with one S-shaped subunit, respectively. Alternatively, if intermediates (±)-**12**(*m*,*n*) and **13**(*m*,*n*) are long enough ($m + n \geq 5$) they may make a new N−CH_2−N bridge between the ends of the oligomer chain to deliver macrocyclic compounds. In this manner, (±)-**12**(*m*,*n*) leads to (±)-**14**(*m*,*n*) and **15**(*m*,*n*) by connection of homotopic NH groups. The previously isolated (±)-bis-*ns*-CB[6] and bis-*ns*-CB[10] serve as examples of these types of macrocycles and provide strong evidence for the depicted mechanistic pathway. To provide even stronger evidence for this mechanistic scheme we performed product resubmission experiments with trimer **3** and pentamer **5**. When trimer **3** was treated with 1 equiv of formaldehyde in HCl we observed the formation of (±)-bis-*ns*-CB[6] by ^{1}H NMR at partial conversion.[35,39] When **5** was treated similarly, we observed and quantified the formation of CB[6] and bis-*ns*-CB[10] (0.39:1 ratio) by ^{1}H NMR spectroscopy of the crude reaction mixture. In combination, these results provide strong evidence for the operation of a step-growth cyclo-oligomerization reaction in the mechanism of CB[*n*] formation.

This mechanistic analysis that can be used to rationalize the formation of **2**− **8**, *ns*-CB[6], (±)-bis-*ns*-CB[6], and bis-*ns*-CB[10] can also be used to predict the structures of *ns*-CB[*n*] that have not yet been isolated.[40] For example, although (±)-**11**(*n*) may cyclize to yield *ns*-CB[*n*] by connection between enantiotopic NH groups it may also react to form (±)-*ns*-CB[*n*] by connection between homotopic NH groups. Similarly, either **13**(*m*,*n*) or (±)-**12**(*m*,*n*) may be transformed into (±)-**16**(*m*,*n*) by the addition of an appropriate bridging group. Two additional bis-*ns*-CB[*n*] can be conceived by addition of a CH_2-bridge between enantiotopic NH groups of **13**(*m*,*n*) which delivers **17**(*m*,*n*) and **18**(*m*,*n*).[38] We are particularly intrigued by the geometrical features of **18**(*m*,*n*) which is reminiscent of the calixarenes with bridging at the lower rim and flexibility at the upper rim. We predict that **18**(*m*,*n*) will display quite interesting hybrid recognition and dynamic behavior.

Oligomer Resubmission Experiments. Although we viewed the evidence for the mechanistic scheme presented above as strong given the isolation of **2**−**6**, bis-*ns*-CB[10], (±)-bis-*ns*-CB[6], and *ns*-CB[6] and previous mechanistic studies by us[21–25,27,35] and others[10,29,41] we wanted to obtain further evidence that applies directly to CB[*n*] formation rather than relying on evidence from *ns*-CB[*n*] formation. For this purpose we decided to perform product resubmission experiments between formaldehyde (2 equiv) and oligomers **2**−**6** alone and in binary mixtures. We assess the outcome of these reactions by ^{1}H NMR spectroscopy of the crude reaction mixtures in 20% DCl in which CB[5], CB[6], CB[7], and CB[8] display separate easily integrated resonances (Table 3).[42]

Reactions Conducted Between Formaldehyde and 1−6. Initially, we conducted the separate reaction between formaldehyde (2 equiv) and **1**−**6** (Table 3). The reaction of monomer alone (Table 3, entry 1), which serves as our point of reference for the results described below, delivers a reaction mixture that contains mainly CB[5] (15%), CB[6] (53%), and CB[7] (30%); CB[8] content is low (2%). In contrast, use of dimer **2** and trimer **3** lead to reaction mixtures that contain higher percentages of CB[6] and diminished amounts of CB[5] and CB[7] (Table 3, entries 2 and 3). This result is in accord with the portion of our mechanistic scheme which is based on step-growth polymerization in that **2** would be expected to give enhanced yields of CB[*n*] where *n* is an even number (e.g., a multiple of 2) and **3** would be expected to give enhanced yields of CB[*n*] where *n* is a multiple of 3. As anticipated based on the step-growth cyclo-oligomerization model for CB[*n*] formation, the reaction of tetramer **4** was found to give a high yield of CB[8] (40%) and lesser amounts of CB[6] and CB[7] (Table 3, entry 4). The reactions of pentamer **5** and hexamer **6**—the first oligomers capable of direct unimolecular macrocyclization—were particularly interesting (Table 3, entries 5 and 6). Pentamer **5** delivers mainly CB[5] (84%) and **6** delivers only CB[6] (100%) which indicates that these oligomers are preorganized to undergo macrocyclization in preference to further oligomerization. In these reactions conducted under aqueous acidic conditions, with the use of purified oligomeric building blocks **2**−**6**, the operation of step-growth processes is *not exclusive* as can be seen for example in the reaction of **3** (Table 3, entry 3) which gives CB[5] and CB[7] as side products. This indicates that the under the reaction conditions a given oligomer can undergo fragmentation processes (e.g., tetramer fragments to two dimers or to a trimer and monomer) to yield shorter oligomers which can then recombine to also give longer oligomers.[10] We have indicated this reversibility explicitly in Scheme 4.

Table 3. The Distribution of CB[*n*] Obtained from Reaction of **1**−**6** with Formaldehyde (2 equiv) Alone and in Combination

entry	reactant(s)	CB[5]	CB[6]	CB[7]	CB[8]
1	**1**	15%	53%	30%	2%
2	**2**	12%	68%	17%	3%
3	**3**	8%	75%	17%	0%
4	**4**	5%	22%	33%	40%
5	**5**	84%	10%	6%	0%
6	**6**	0%	100%	0%	0%
7	**1** + **2**	14%	52%	31%	3%
8[a]	**1** + **3**	20%	43%	33%	4%
9	**1** + **4**	35%	44%	18%	3%
10	**1** + **5**	27%	67%	6%	0%
11	**1** + **6**	3%	90%	7%	0%
12	**2** + **3**	26%	41%	30%	3%
13	**2** + **4**	10%	53%	17%	7%
14	**2** + **5**	41%	24%	35%	0%
15	**3** + **4**	11%	42%	42%	5%
16	**3** + **5**	48%	36%	13%	3%
17	**4** + **5**	57%	21%	15%	7%

[a] A small amount (4%) of *i*-CB[6] was also detected in this reaction mixture.

Reactions Conducted Between Formaldehyde and Binary Combinations of Building Blocks 1−6. Although a complete analysis of the reactions conducted between formaldehyde (2 equiv with respect to total building block concentration) and binary mixtures of building blocks **1**−**6** is not possible given the mixtures that are generally obtained from CB[*n*] forming reactions it is possible to tease out some information that we believe is significant (Table 3, entries 7−17). For example, combinations of oligomers **2**−**4** with monomer **1** increases the proportion of the first oligomer capable of macrocyclization, CB[5], which is consistent with the increased importance of a chain-growth process when the amount of monomer is

(39) If the reaction is run to completion we observe a more complex mixture whose analysis by ^{1}H NMR spectroscopy is challenging.

(40) This analysis is theoretically based and ignores the potential influence of strain and intramolecular NH···O H-bonds that are known to impact the stability and geometry of CB[*n*] and (±)-bis-ns-CB[6].

(41) Blanch, R. J.; Sleeman, A. J.; White, T. J.; Arnold, A. P.; Day, A. I. *Nano Lett.* **2002**, *2*, 147–149.

(42) In none of these reactions did we observe the formation of CB[10]·CB[5] which suggests that the formation of this aggregate is probably more complex than the reaction of two molecules of **5** to give CB[10] followed by stabilization with CB[5].

significant.[10,43] The results obtained with combinations of building blocks intended to lead to CB[7] (**1** + **6**, **2** + **5**, and **3** + **4**; Table 3, entries 11, 14, 15) are interesting. Of these combinations, **1** + **6** delivers mainly CB[6], **2** + **5** delivers a significant portion of CB[5] due to competing cyclization of **5** along with CB[7] (35%), and **3** + **4** delivers a substantial amount of CB[6] presumably due to competing formation of CB[6] formed from two molecules of **3** along with CB[7] (42%). In combination, these reactions shed light on one of the reasons why CB[6] is the dominant CB[*n*] formed under a variety of conditions. Although there are a variety of pathways that lead to CB[6] in high relative yield (e.g., **6**, **1** + **5**, **2** + **4**, **3** + **3**) there are fewer pathways that lead to CB[7] (e.g., **2** + **5** and **3** + **4**) or CB[8] (only **4** + **4**) and those do so only in modest yield due to competing dimerization, cyclization, or fragmentation (e.g., tetramer to trimer and monomer) pathways. In this regard, the quantitative cyclization of **6** suggests that this cyclization (Table 3, compare entries **5** and **6**) may be particularly favorable from a kinetic standpoint.

Is CB[*n*] Formation Under Kinetic or Thermodynamic Control? Previous experimental work from Day's group[10] has clearly demonstrated by product resubmission experiments that CB[8] undergoes ring contraction to yield a mixture of CB[5], CB[6], and CB[7]. This result strongly suggests that CB[5], CB[6], and CB[7] are thermodynamically more stable than CB[8]. This conclusion is backed up by the theoretical calculations at various levels of theory.[7,44] Day also reported that similar product resubmission experiments with purified individual samples of CB[5], CB[6], and CB[7] do not deliver mixtures of CB[*n*] homologues. This result suggests that CB[5], CB[6], and CB[7] are thermodynamically sufficiently stable such that their formation is *irreversible under the reaction conditions* (conc. HCl, 100 °C). Accordingly we have indicated the entry into the CB[*n*] (n = 5, 6, 7) manifold (Scheme 4) as an irreversible step.[45] Conversely, the isolation of **2**−**6**, *i*-CB[*n*], and various *ns*-CB[*n*] demonstrates that kinetic products do accumulate during CB[*n*] synthesis under milder conditions. Perhaps most informative are the product resubmission experiments performed with **2**−**6** (*vide supra*) that demonstrate that both kinetic and thermodynamic considerations are relevant under the standard reaction conditions. Although CB[5], CB[6], and CB[7] may be the ultimate thermodynamically controlled products of CB[*n*] forming reactions, the operation of a step-growth cyclo-oligomerization process during the reaction suggests routes to the tailor-made synthesis of new CB[*n*]-type receptors (e.g., *i*-CB[*n*] and nor-seco-CB[*n*]) that are kinetically stable and display exciting recognition properties (e.g., chiral recognition and homotropic allostery).[20,21,27,35,36]

Glycoluril Oligomers 5 and 6 Retain the Ability to Bind Ammonium Ions. Previously, Day's group has extensively studied the ability of organic and alkali metal cations to act as templates for a specific CB[*n*] during the CB[*n*] forming reaction from **1** and formaldehyde (2 equiv).[29] The influence of such guests as templates on the ratio of CB[*n*] formed is generally modest. Day hypothesizes that cationic templates exert their influence

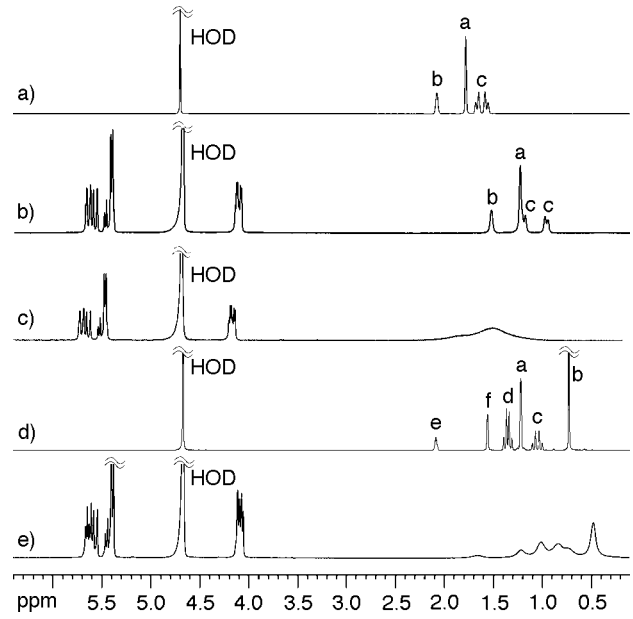


Figure 3. ^{1}H NMR spectra (400 MHz, D_2O, room temp) for (a) **23**, (b) **6**·**23**, (c) a mixture of **6**·**23** and excess **23**, (d) **24**, and (e) **6**·**24**.

by forming oligomer·guest complexes that either promote or disfavor certain cyclization reactions although the precise kinetic or thermodynamic factors influencing such templated reactions remain unclear. Given access to oligomers **2**−**6** we decided to test their ability to form complexes with representative guests. We did not observe any evidence of binding between **2**−**4** and **19** or **20** in water. This observation is not particularly surprising given that ion−dipole interactions between guest and *fully formed* ureidyl C═O portals of CB[*n*] provide substantial driving force in the formation of CB[*n*]·guest complexes.[7,16,35,46] In contrast, we find that pentamer **5** and hexamer **6** begin to exhibit recognition properties characteristic of CB[*n*]. For example, **5** forms a complex with **19** that displays slow exchange on the chemical shift time scale. Slow exchange kinetics on the chemical shift time scale are commonly observed for CB[*n*] host−guest complexes but are less common for other molecular containers like cyclodextrins and calixarenes. Evidence of binding between **5** and other guests (**21**−**24**) is apparent based on induced upfield shifts in the ^{1}H NMR spectrum although exchange is faster than the ^{1}H NMR chemical shift time scale (Supporting Information). The recognition behavior of **6** is equally interesting (Figure 3). For example, hexamer **6** retains the ability to bind with common guests for CB[6] (e.g., **19**−**21** and **25**) and does so with slow exchange on the chemical shift time scale which is noteworthy given the acyclic nature of **6**. Other guests that are too large for CB[6] (e.g., **23**, **24**, and **26**) are readily complexed by **6**. The ability to bind these guests, which are good guests for CB[7] (**23** and **26**) or even CB[8] (**24**), indicates that hexamer **6** is quite flexible in solution and is able to expand its cavity and wrap itself around larger guests (e.g., **24**) to form complexes (Figure 4). One particularly interesting aspect shown in Figure 4 is that the NH tips of **6** are held apart from one another in a way that would disfavor direct cyclization to CB[6]. Overall, these results show that glycoluril oligomers **5** and **6** and by extension **7** and **8** are capable of binding guests typical of the CB[*n*] family. This suggests that the use of suitable templating groups that either

(43) Day has previously shown that CB[*n*] forming reactions when conducted at high dilution lead mainly to CB[5]. At high dilution intermolecular reactions are slowed and chain-growth rather than step-growth processes tend to dominate.

(44) (a) Oh, K. S.; Yoon, J.; Kim, K. S. *J. Phys. Chem. B* **2001**, *105*, 9726–9731. (b) Maslii, A. N.; Grishaeva, T. N.; Kuznetsov, A. M.; Bakovets, V. V. *J. Struct. Chem.* **2007**, *48*, 552–557.

(45) The reaction of ns-CB[8] to CB[8] is reversible as established by Day's product resubmission experiments.

(46) Ong, W.; Kaifer, A. E. *Organometallics* **2003**, *22*, 4181–4183.

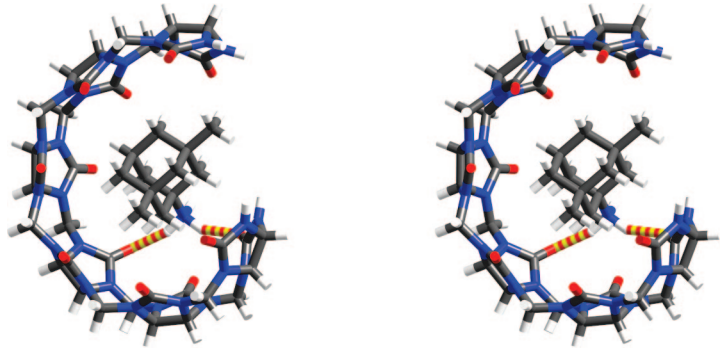
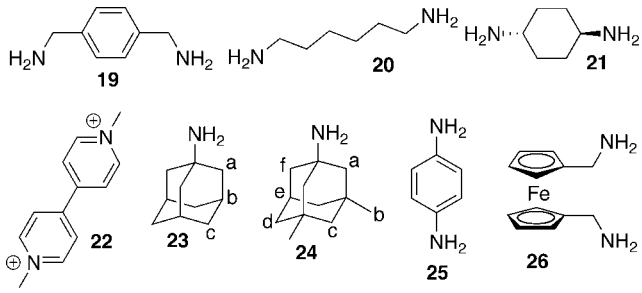


Figure 4. Cross-eyed stereoview of the MMFF minimized geometry of the **6**·**24** complex. Color code: C, gray; H, white; N, blue; O, red; H-bonds, red-yellow striped.

Chart 2. Guests for **5** and **6**



promote or disfavor cyclization of a particular oligomer may be useful in directing the CB[*n*] forming reaction toward an enhanced yield of a single CB[*n*] compound.

Conclusions

In summary, we have described the synthesis, purification, and solution and solid state characterization of methylene-bridged glycoluril oligomers **2**−**6**. As expected based on previous model studies, glycoluril oligomers **2**−**6** possess the energetically favored all C-shaped geometry. The curvature of **2**−**5** maps well onto that exhibited by CB[6] which is calculated to be the least strained member of the CB[*n*] family. The packing of oligomers **4**−**6** in the crystal is dominated by C=O···Na···O=C and NH···O=C interactions. Most interesting is the dimeric geometry of **6** in the crystal which demonstrates the inherent flexibility of the methylene-bridged glycoluril oligomer chain and suggests that self-association should be considered as a side pathway in the mechanism of CB[*n*] formation. On the basis of the isolation of **2**−**6** and the previously isolated bis-*ns*-CB[10], (±)-bis-*ns*-CB[6], and *ns*-CB[6], we were able to formulate a detailed picture of the mechanism of CB[*n*] formation based on a step-growth cyclo-oligomerization process. To further support the step-growth mechanism we performed product resubmission experiments between formaldehyde (2 equiv) and oligomers **1**−**6** and binary combinations thereof and observed the effect on the ratio of CB[5]−CB[8] formed. Finally, we find that pentamer **5** and hexamer **6**, but not **2**−**4**, retain the ability to bind organic ammonium ions (e.g., **19**−**26**) in water.

In conclusion, this study has painted a much more detailed picture of the mechanism of CB[*n*] formation, based on step-growth cyclo-oligomerization, than was previously possible. For example, this study allows us to rationalize the preferred formation of CB[6] in CB[*n*] forming reactions as a consequence of the multiplicity of pathways that leads to CB[6] relative to CB[7] or CB[8] and the pronounced kinetic tendency of **6** to undergo cyclization to CB[6] rather than oligomerization or fragmentation. The formulation of the mechanism of CB[*n*] formation as a step growth cyclo-oligomerization pathway also allows us to predict the structures of different-sized relatives of the previously isolated bis-*ns*-CB[10], (±)-bis-*ns*-CB[6], and *ns*-CB[6] and formulate the structures of classes of nor-seco-CB[*n*] that have not yet been isolated including (±)-*ns*-CB[6] and **17**(*m*,*n*) and **18**(*m*,*n*). We predict that **18**(*m*,*n*) will show particularly interesting recognition properties that blend the advantages of the CB[*n*] family of macrocycles with those of the calixarenes.

Of particular interest is the observation that **5** and **6** are capable of binding CB[6] sized guests (e.g., **19** and **20**) and can even expand their cavities to associate with larger guests (e.g., **23** and **24**) typically bound within CB[7] or CB[8]. This result establishes a high level of flexibility of the growing methylene-bridged glycoluril oligomer chain that suggests that the presence of suitable templating guests in the CB[*n*] forming reaction may be able to direct the reaction toward enhanced yield of a single sized CB[*n*]. This result also raises the prospect of using suitable guests to template the formation of larger *ns*-CB[*n*] ($n \geq 10$), *ns*-CB[*n*] containing multiple cavities and lacking more than two CH_2-groups,[27] and even the enantioselective synthesis of chiral *ns*-CB[*n*] (e.g., (±)-**14**(*m*,*n*), bis-*ns*-CB[$n + m$]). Given the wide range of applications to which CB[*n*] (e.g., sensing, molecular machines, drug delivery)[6] and its derivatives can be applied (e.g., polymer nanocapsules, affinity chromatography, and artificial ion-channels)[7,8] we expect that the ability to target tailor-made CB[*n*], CB[*n*] derivatives, and *ns*-CB[*n*] which is enabled by the mechanistic insights described herein will lead to new application areas that currently benefit from calixarene or cyclodextrin molecular containers.

Acknowledgment. We thank the National Science Foundation (Grant CHE-0615049) and the University of Maryland (Ann Wylie Dissertation Fellowship to W.-H. H.) for financial support of this work. We thank the reviewers for their thoughtful comments that helped improve the manuscript.

Supporting Information Available: Experimental procedures and characterization data, crystallographic information files for **2**, **4**, **5**, and **6** (cif), and selected NMR spectra for host−guest complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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