ORGANIC LETTERS

2011
Vol. 13, No. 15
4112–4115

Recognition Properties of Acyclic Glycoluril Oligomers

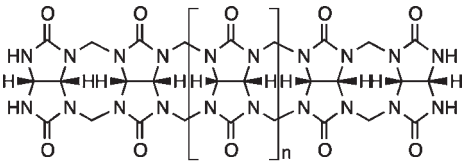
Derick Lucas and Lyle Isaacs*

Department of Chemistry and Biochemistry, University of Maryland, College Park, Maryland 20742, United States

LIsaacs@umd.edu

Received June 17, 2011

ABSTRACT



The fragmentation reaction of bis-nor-seco-CB[10] with 3,5-dimethylphenol (3) delivers methylene bridged glycoluril pentamer 5 in 81% yield. The host–guest recognition properties of the previously known tetramer 4 and those of pentamer 5 and hexamer 6 toward cationic guests in water are used to delineate some important features of the binding of acyclic CB[*n*]-type receptors.

Cucurbit[*n*]uril molecular containers are prepared by the condensation of glycoluril (**1**) with formaldehyde (**2**) under acidic conditions.[1] Interest in the cucurbit[*n*]uril (CB[*n*]) family of molecular containers[2] has surged in recent years due to the availability of a homologous series (n = 5, 6, 7, 8, 10) of hosts that display high affinity and high selectivity toward cationic 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] supramolecular catalysts,[6] sensing ensembles,[7] stimuli responsive polymers,[8] and drug delivery systems.[9] Our research group has developed an in-depth knowledge of the mechanism of CB[*n*] formation[10] and used these insights to prepare macrocyclic CB[*n*] type receptors lacking one or more bridging CH_2-groups known as nor-seco-CB[*n*]

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10.1021/ol201636q
Published on Web 07/08/2011

which display interesting recognition properties such as size dependent homotropic allostery, chiral recognition, and control over guest folding.[11] In this paper we continue this line of inquiry by comparing and contrasting the recognition properties of acyclic glycoluril oligomers **4**–**6** (Figure 1) with those of their macrocyclic counterparts CB[6] and CB[7]. We delineate some key factors governing the recognition properties of CB[*n*]-type receptors (e.g., preorganization and macrocyclic effect).

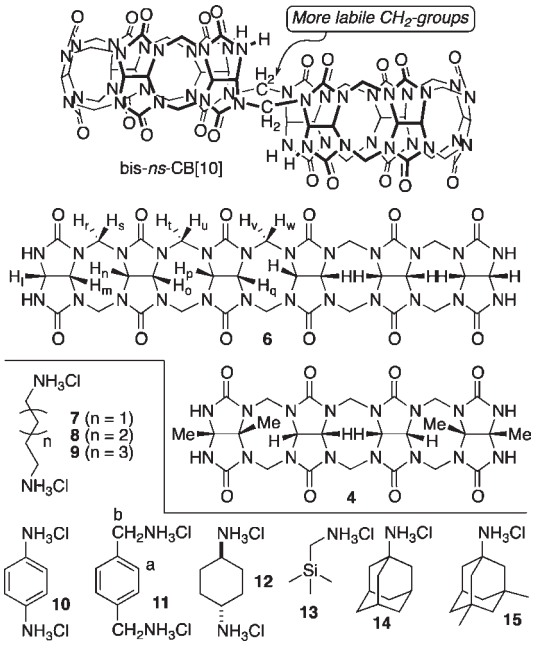
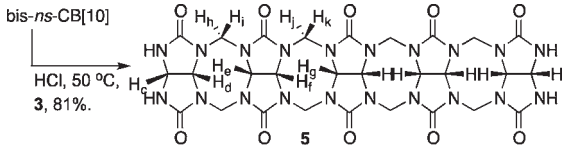


Figure 1. Hosts and guests used in this study.

We have previously reported the synthesis of methylene bridged glycoluril pentamer **5** and hexamer **6** and their purification by time-consuming DOWEX ion-exchange chromatography.[10d] In order to streamline the synthesis and purification of **5** we considered the use of bis-*ns*-CB[10] as a readily available starting material (Figure 1).[11a] Bis-*ns*-CB[10] is a macrocycle composed of 10 glycoluril rings and 18 CH_2-bridges whose connectivity features two glycoluril pentamer fragments connected by a single CH_2-bridge. We envisioned that these single CH_2-bridges would be more susceptible to cleavage than the remaining double CH_2-bridges. In practice, we found that heating bis-*ns*-CB[10] with 3,5-dimethylphenol (**3**) as a formaldehyde scavenger at 50 °C in HCl delivers **5** in 81% yield (Scheme 1). Next, we decided to investigate the recognition properties of **5** and **6** toward cationic guests in aqueous solution.

Scheme 1. Synthesis of Glycoluril Pentamer **5**



Before studying the recognition properties of any new host it is wise to perform dilution experiments to determine whether the host undergoes self-association. We performed ^{1}H NMR dilution experiments for **5** (maximum solubility = 1 to 0.1 mM) and **6** (maximum solubility = 2.57 to 0.1 mM) and did not observe any changes in chemical shift that would be indicative of self-association (Supporting Information). Therefore, we decided to investigate the binding of **5** and **6** toward guests **7**–**15** which are typical guests for CB[*n*]-type receptors by ^{1}H NMR spectroscopy (Supporting Information). All guests show upfield shifts in their NMR spectra upon binding which indicates guest binding within the cavity of hosts **5** and **6** as expected. In contrast to what is commonly observed with CB[*n*] hosts, only a few of the guests investigated displayed slow kinetics of guest exchange (Host **5**: **11**; Host **6**: **11**, **9**, **12**) on the chemical shift time scale.[3a,b] For illustration, Figure 2 shows the ^{1}H NMR spectra recorded for mixtures of host **5**

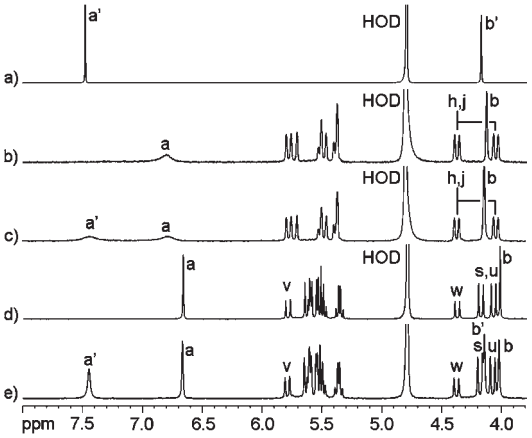


Figure 2. ^{1}H NMR spectra recorded (D_2O, 400 MHz, RT) for (a) **11** (1 mM), (b) a mixture of **5** (1 mM) and **11** (1 mM), (c) a mixture of **5** (1 mM) and **11** (2 mM), (d) a mixture of **6** (1 mM) and **11** (1 mM), and (e) a mixture of **6** (1 mM) and **11** (2 mM).

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Table 1. Binding Constants (K_a, M^{-1}) Measured for Host•Guest Complexes between Hosts **3**–**6**, CB[6], and CB[7] and Guests **7**–**15**

guest	host **4**[a]	host **5**	host **6**	CB[6]	CB[7]
7	–	$(4.7 \pm 0.5) \times 10^4$	$(5.0 \pm 0.3) \times 10^4$	$(2.0 \pm 0.2) \times 10^7$ [c]	–
8	–	$(1.4 \pm 0.1) \times 10^5$	$(1.6 \pm 0.3) \times 10^6$	$(1.5 \pm 0.1) \times 10^8$ [c]	–
9	$(5.6 \pm 0.4) \times 10^3$	$(1.0 \pm 0.2) \times 10^6$	$(2.2 \pm 0.4) \times 10^6$	$(4.5 \pm 0.8) \times 10^8$ [b] $(2.9 \pm 0.2) \times 10^8$ [c]	$(9.0 \pm 1.4) \times 10^7$ [b]
10	–	$(1.0 \pm 0.1) \times 10^4$	$(4.9 \pm 0.6) \times 10^4$	$(1.9 \pm 0.1) \times 10^3$ [b]	$(2.1 \pm 0.3) \times 10^6$ [b]
11	$(1.5 \pm 0.1) \times 10^4$	$(1.2 \pm 0.1) \times 10^6$	$(2.2 \pm 0.4) \times 10^7$	550 ± 30 [b]	$(1.8 \pm 0.3) \times 10^9$ [b]
12	–	$(2.7 \pm 0.4) \times 10^4$	$(6.8 \pm 1.4) \times 10^5$	1.4×10^6 [d]	$(2.3 \pm 0.4) \times 10^7$ [b]
13	–	nb[e]	$(2.6 \pm 0.3) \times 10^4$	nb	$(8.9 \pm 1.4) \times 10^8$ [b]
14	–	$(1.1 \pm 0.2) \times 10^6$	$(1.8 \pm 0.4) \times 10^7$	–	$(4.2 \pm 1.0) \times 10^{12}$ [b]
15	–	$(6.1 \pm 0.9) \times 10^5$	$(6.0 \pm 1.3) \times 10^6$	–	$(2.5 \pm 0.4) \times 10^4$ [b]

[a] K_a values taken from ref 13a. [b] K_a values taken from ref 3b. [c] K_a values taken from ref 3d. [d] K_a values taken from ref 12b. [e] nb = no binding.

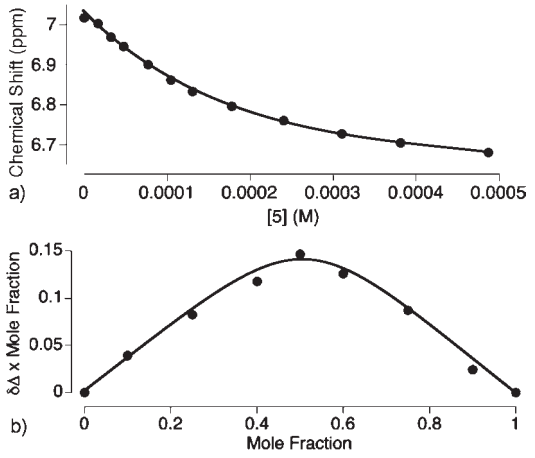

Figure 3. (a) A plot of chemical shift of **10** obtained in the direct NMR titration (298 K, 20 mM NaO_2CCD_3, pD 4.74) with **5** (0–487 μM) and (b) Job plot for **5•10** ([**5**] + [**10**] = 0.5 mM).

or host **6** in the presence of 1 or 2 equiv of guest **11**. Overall, these studies suggest that **5** and **6** retain the essential binding features typical of the CB[*n*] family but do so with faster kinetics of exchange. Because **5** and **6** are acyclic they should not display the constrictive binding generally observed for CB[*n*] hosts[12] which decreases the association and dissociation rate constants due to steric effects in the transition state. This is an essential difference between the recognition behavior of **5** and **6** relative to CB[*n*].

We next decided to measure the binding constants for **5** and **6** toward guests **7**–**15**. For this purpose we first performed the direct ^{1}H NMR titration of *p*-phenylenediammonium ion **10** with **5** and of trimethylsilylmethylammonium ion **13** with **6** (Table 1; Supporting Information). For example, Figure 3a shows a plot of chemical shift of H_a of guest **10** as a function of [**5**] and the best fit of the data to a 1:1 binding model with $K_a = (1.0 \pm 0.1) \times 10^4$ M^{-1}. Figure 3b shows a Job plot prepared for mixtures of **5** and **10** ([**5**] + [**10**] = 0.5 mM) which confirms the 1:1 nature of the **5•10** complex. Next, we performed ^{1}H NMR competition experiments between **5•10** and guests **7**, **8**, and **12** and between **6•13** and guests **7** and **10** by monitoring the chemical shift of guests **10** (for **5•10**) and **13** (for **6•13**) which undergo fast exchange on the chemical shift time scale and fit the data to a standard competitive binding model (Supporting Information) to determine K_a values (Table 1). To determine the remaining values of K_a we performed ^{1}H NMR competition experiments between **5•11** (or **6•11**) and guests by monitoring the integrals for the free and binding guest **11** which exhibits slow exchange on the chemical shift time scale (Table 1). Table 1 also presents the K_a values measured previously for hosts **4**, CB[6], and CB[7] for purposes of comparison.

The binding constant data presented in Table 1 allows us to tease out some features of the recognition behavior across the series of glycoluril oligomers to macrocyclic CB[*n*]. First, consider the binding constants of guests **9** and **11** toward oligomers **4**–**6** of increasing length. Progression from **4** to **5** results in an ~100-fold increase in K_a whereas the lengthening to **6** results in more modest increases (2–18-fold) in K_a. We believe these differences reflect the fact that tetramer **4** is a clip-like receptor whereas **5** and **6**, by virtue of the additional glycolurils, possess a more well-defined hydrophobic cavity. The smaller increases in K_a from **5** to **6** reflect the increase in the hydrophobic surface area and volume of the cavity of the oligomer and also the more fully formed electrostatically negative ureidyl C=O portals which may provide increased ion–dipole interaction driving force for complexation. Second, we can compare the binding constants of **6** and its macrocyclic counterpart CB[6] to gauge the influence of cyclization on binding strength and selectivity. For example, **9** binds to **6** 205-fold less tightly than to CB[6]; similar trends hold for **8** (94-fold) and **7** (400-fold). For guests that do not exceed the capacity of CB[6] (e.g., **7**–**9**) macrocyclization of **6** results in an ~100-fold increase in affinity probably due to increased preorganization, higher energy solvating H_2O molecules inside CB[6], and increased negative electrostatic potential at the C=O portals. For guests like **11** (**10**) that are slightly too large to fit

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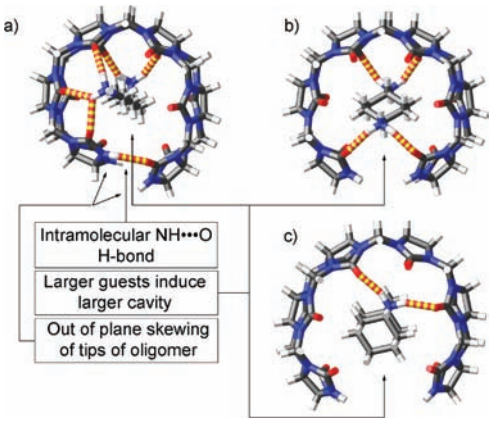

Figure 4. MMFF94s minimized models of (a) **6•9**, (b) **6•12**, and (c) **6•14**. Color code: C, gray; H, white; N, blue; O, red; H-bonds, red-yellow striped.

comfortably inside CB[6], a 40 000-fold (26-fold) decrease in K_a is observed. For even larger guests **12**–**14** the more appropriate comparison is between hosts **6** and CB[7]. In these cases the CB[7]•guest complexes are more stable by 34-fold to 3.4×10^5-fold which reflects both the presence of an additional glycoluril unit and macrocyclization. The high selectivity[3a,b] observed for macrocyclic CB[*n*] is due in part to the relative rigidity of the host which disfavors inappropriately sized or shaped guests. Third, for both **5** and **6**, adamantane derivatives **14** and **15** are among the guests with the highest K_a values. This is surprising for two main reasons: (a) guests **14** and **15** are too large to form inclusion complexes with CB[5] or CB[6], and (b) guests **14** and **15** are monoammonium ions whereas the tightest binding guest for **5** and **6** is **11** which is a diammonium ion. It is known from CB[*n*] binding studies that an additional NH_3^+ group increases the binding affinity by factors of 10^1–10^5.[2c] Figure 4 shows MMFF minimized models of **6•9**, **6•12**, and **6•14**. As the guest gets larger the glycoluril oligomer backbones of **5** and **6** are able to undergo conformational changes (e.g., flex like a hand) to accommodate larger guests (e.g., **14** and **15**).[13] The fact that guest **15**, which is slightly too large for CB[7], binds better to **6** suggests that **6** is able to expand its cavity size beyond that of CB[7] toward CB[8]. We believe that the excellent size and shape match of hydrophobic adamantane derivatives documented for CB[7] plays an important role in the strong binding affinity of **14** and **15** toward **5** and **6**.[2c,3b,14]

In summary, we have reported a directed synthesis of glycoluril pentamer **5** by the fragmentation reaction of bis-*ns*-CB[10] under acidic conditions in the presence of **3** as a formaldehyde scavenging reagent. The recognition properties of pentamer **5** and hexamer **6** toward a series of ammonium ions (**7**–**15**) in water were investigated. Acyclic glycoluril oligomers **5** and **6** preserve the ability of the CB[*n*] family to bind to cationic species in water but do so with lower affinity, lower selectivity, and faster kinetics of exchange than their macrocyclic counterparts. Particularly interesting trends in binding affinity are seen: (a) across the tetramer **4**–hexamer **6** series where an increasing number of glycolurils increases binding affinity by $\sim 10^3$ overall; (b) between K_a values of hexamer **6** or CB[6] toward a common guest (e.g., **7**–**9**) where macrocyclization increases affinity by ~100-fold; and (c) for K_a values of adamantane derivatives **14** and **15** toward **5** or **6** where high affinity is observed and attributed to the hydrophobicity of the adamantane group and the good shape match with the cavity of **5** and **6**. We believe the work described here has broader significance. Because **5** and **6** are acyclic, are structurally responsive to guest size, and preserve many of the binding properties of CB[*n*] but do so with faster kinetics of exchange, they may be particularly well suited for certain classes of applications. For example, we envision that acyclic CB[*n*]-type hosts would be useful for the preparation of stimuli responsive molecular machines with fast response times, for the derivatization of polymeric materials by direct clipping onto linear polymer backbones, and as a component of sensor arrays with broad analyte affinity for chemically and biologically important amines. As such we believe that acyclic glycoluril oligomers promise to enrich the scope of CB[*n*] supramolecular chemistry.

Acknowledgment. We thank the National Science Foundation (CHE-0615049 and CHE-1110911 to L.I.) for financial support. D.L. thanks the Department of Education for a GAANN Fellowship (P200A090105).

Supporting Information Available. Synthesis of **5**, ^{1}H NMR for host•guest complexes, and binding constant determination. This material is available free of charge via the Internet at http://pubs.acs.org.

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