Communication

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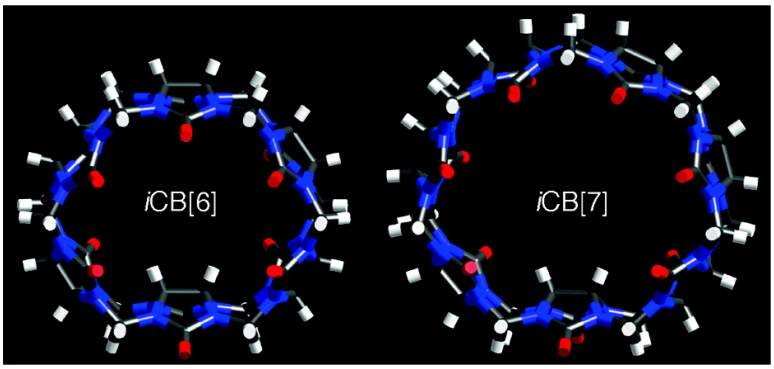

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The Inverted Cucurbit[*n*]uril Family

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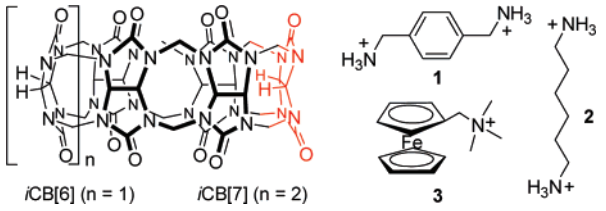
The supramolecular chemistry of the cucurbit[*n*]uril (CB[*n*]) family[1] of macrocycles expanded dramatically with the discovery of CB[*n*] homologues (CB[5], CB[7], CB[8], and CB[5]@CB[10]).[2] More recently, the disclosure of methods for the direct functionalization of CB[*n*][3] and building block strategies for the preparation of CB[*n*] derivatives[4] and analogues[5] providing CB[*n*] with solubility in both organic and aqueous solution has further expanded the range of applications to which CB[*n*] can be applied (e.g., cation transport, supramolecular vesicles, and fluorescence sensing). Previously, we have used S- and C-shaped diastereomeric methylene-bridged glycoluril dimers to probe fundamental steps in the mechanism of CB[*n*] formation, which suggested the presence of diastereomeric CB[*n*].[6] In this paper, we report the isolation, characterization, and recognition properties of inverted cucurbit[6]uril and inverted cucurbit[7]uril (*i*CB[6] and *i*CB[7]; Scheme 1), which contain a single glycoluril unit directed into the CB cavity.

Scheme 1



The new *i*CB[*n*] can be detected by ^{1}H NMR spectroscopy in CB[*n*] reaction mixtures[2] produced from the reaction between glycoluril and formaldehyde in acidic media. When *p*-xylylenediammonium ion (**1**) is added as a probe to a mixture of CB[*n*], each different CB[*n*]·**1** and *i*CB[*n*]·**1** exhibits a single diagnostic aromatic resonance (Figure 1a, 6.9−6.4 ppm). *i*CB[6] and *i*CB[7] were isolated in 2.0 and 0.4% yields, respectively, in pure form either by gel permeation chromatography (Superdex 30, 0.15 M $NH_4^+HCO_3^-$) or by fractional crystallization (18% aq. HCl) followed by selective complexation (*i*CB[6]: $^+H_3N(CH_2)_6NH_3^+$, **2**) to remove other CB[*n*]. The structures of *i*CB[6] and *i*CB[7] (Figure 1b and c) were unequivocally established by 2D NMR spectroscopy (Supporting Information). The methine resonances for the inverted subunit of *i*CB[6] appear as small but distinct signals at ∼5.05 and 62.8 ppm in open regions of the ^{1}H and ^{13}C NMR spectra (Figure S3), respectively, which are upfield-shifted compared with those of CB[6] (5.65 and 71.0 ppm, respectively). The inverted protons of *i*CB[6] and *i*CB[7] undergo remarkable upfield shifts (1.66 and 1.48 ppm, respectively) when complexed to **1** due to the anisotropic effect of the aromatic ring of **1** as well as its preferred alignment along the long axis of the *i*CB (Figures S6 and S16).

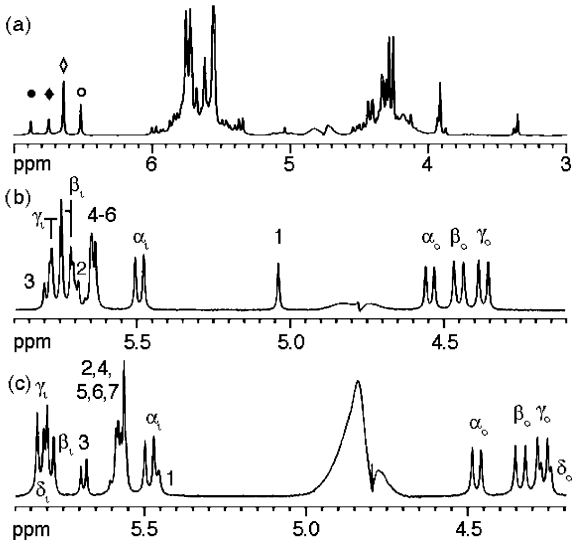


Figure 1. ^{1}H NMR spectra recorded (500 MHz, D_2O:NaCl, 298 K) with water presaturation for (a) a mixture of *i*CB[6]·**1** (●), *i*CB[7]·**1** (◆), CB[7]·**1** (◇), and CB[6]·**1** (○); (b) *i*CB[6]; (c) *i*CB[7].

Fortunately, we were able to obtain single crystals of *i*CB[6] and *i*CB[7] that were suitable for structure determination by X-ray diffraction. Figure 2 shows their X-ray crystal structures and electrostatic potential energy surfaces. The most striking feature is the inverted glycoluril unit, which places two methine protons *within the cavity*. This inverted glycoluril unit decreases the cavity volume of *i*CB[*n*] relative to their CB[*n*] counterparts, flattens the inner surface of the macrocycle, alters the electrostatic potential within the cavity, and displays two ureidyl−carbonyl groups outward, which gives the macrocycle a permanent dipole moment (AM1: μ = 10.63 and 9.77 D for *i*CB[6] and *i*CB[7], respectively).

Because of their smaller cavities and more open portals, *i*CB[6] and *i*CB[7] bind most guest molecules less tightly than their CB[*n*] counterparts do. For example, when a slight excess of **1** is added to a solution containing CB[6] and *i*CB[6] (1:1), almost all CB[6] forms a complex with the guest, but only a half of *i*CB[6] does so, as shown in Figure 3a. Alkylammonium ions, such as **2**, are known to bind tightly to CB[6] with values of K_d in the micromolar range.[7] In contrast, **2** binds less strongly to *i*CB[6] (*i*CB[6]·**2**: K_a= 460 ± 50 M^{-1} in 0.1 M Na_2SO_4). Similarly, *i*CB[7] retains the ability to bind to guests commonly bound to CB[7][1,8] (e.g., **1**, **2**, and (ferrocenemethyl)trimethylammonium ion (**3**)), but with lower affinity and higher kinetic lability.[10] The association constants (K_a)

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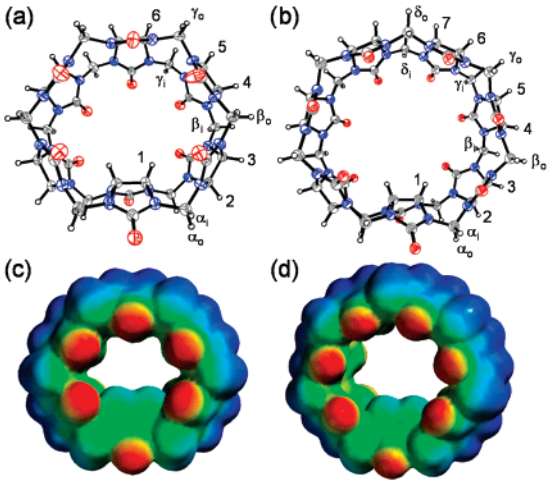

Figure 2. X-ray crystal structures of (a) *i*CB[6] and (b) *i*CB[7], and electrostatic potential energy surfaces for (c) *i*CB[6] and (d) *i*CB[7]. The red to blue color range spans −78 to 35 kcal mol^{-1}.

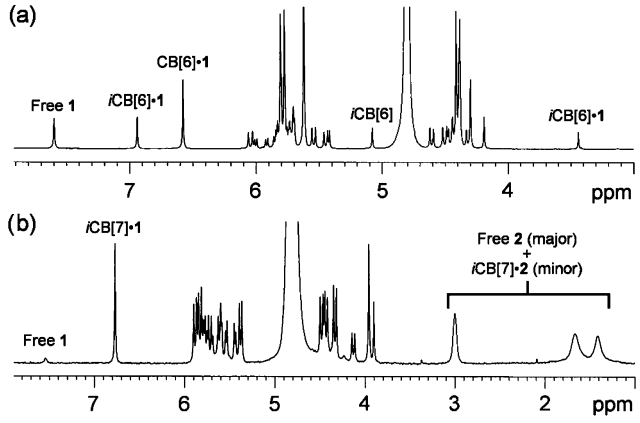

Figure 3. ^{1}H NMR spectra recorded (500 MHz, D_2O, RT) for (a) *i*CB[6], CB[6], and **1** in a ratio of 1:1:2 (0.5 M NaCl), and (b) *i*CB[7], **1**, and **2** in a ratio of 1:1:1.

for the guests **1**, **2**, and **3** with *i*CB[7] measured by isothermal titration calorimetry (ITC) are $(9 \pm 1) \times 10^6$, $(8.8 \pm 0.9) \times 10^5$, and $(2.2 \pm 0.1) \times 10^6$ M^{-1}, respectively, which are 2−6 orders of magnitude lower than those with CB[7].[8]

Interestingly, however, *i*CB[6] and *i*CB[7] show a distinct preference for guests with a flatter profile. For example, *i*CB[7] binds aromatic guest **1** more strongly than linear aliphatic guest **2**. In the presence of 1 equiv of **1** and **2**, the majority of *i*CB[7] forms a complex with **1**, while **2** exists mainly as a free guest, as seen in Figure 3b. Also, the K_a value of *i*CB[7] for **1** is higher than that for voluminous guest **3**, which is in sharp contrast to the behavior of CB[7], which displays much higher affinity for **3** than **1**.[8] The picture that emerges is that the inverted glycoluril unit modulates their guest binding affinity and rates of dissociation,[9] both of which are of critical importance in the creation of CB[*n*]-based molecular machines.[1]

To determine whether *i*CB[6] and *i*CB[7] are kinetic or thermodynamic products in CB[*n*] forming reactions, we performed product resubmission experiments. When purified *i*CB[6] was heated in concentrated DCl, it was transformed into a mixture of CB[5], CB[6], and CB[7] (24:13:1) in 87% combined isolated yield. When *i*CB[7] was treated similarly, a 4:1 mixture of CB[6] and CB[7] was obtained in 71% combined yield. These results allow us to add a new complexity to the currently accepted mechanism of CB[*n*] formation[2b,6a]—namely, that *i*CB[*n*] are viable intermediates.[11]

The implications of the new *i*CB[*n*] for the future of CB[*n*] research are manifold. First, the *i*CB[*n*] groups bridge and exceed the recognition properties of known CB[*n*] by displaying unprecedented size and shape selectivity. Second, although we have only isolated two members of the *i*CB[*n*] family in pure form, current and previous synthetic and mechanistic studies suggest that the preparation and isolation of *i*CB[*n*] with larger ring sizes (e.g., *i*CB[8]) and with larger numbers of inverted glycoluril units (e.g., *i*^{2}CB[7] with two inverted glycoluril units) is readily achievable.[2a,6a] Third, functional groups, such as OH[3a] or CO_2H,[5a] may be introduced to the inverted unit to directly interact with guests within their hydrophobic cavity. Last, the isolation of the *i*CB[*n*] enhances our understanding of the mechanism of CB[*n*] formation, which promises the tailor-made synthesis of CB[*n*] derivatives with exciting new applications.

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Supporting Information Available: Synthetic procedures and characterization data for *i*CB[6], *i*CB[7], and their complexes (.pdf), and details of the X-ray structure determination of *i*CB[6] and *i*CB[7] (.cif). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Host−guest complexes of *i*CB[*n*] are kinetically more labile than those of CB[*n*]. For example, the exchange of **2** in and out of the cavity of CB[7] is slow on the NMR time scale, whereas that of *i*CB[7] is fast (Figure S17).
(11) A preliminary ab initio calculation (using B3LYP, 3-21G basis set) suggests that there is little difference (∼1.5 kcal/mol) in energy between normal and inverted CB[*n*] ($n = 6$ and 7). A higher level calculation is in progress.

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