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Size Selective Supramolecular Cages from Aryl-Bisimidazolium Derivatives and Cucurbit[8]uril

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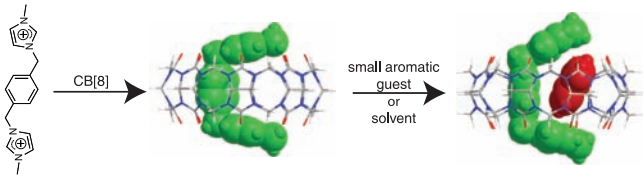
ABSTRACT



A series of bisimidazolium salts were synthesized as novel guests for the macrocyclic host molecule cucurbit[8]uril (CB[8]). These bisimidazolium-CB[8] binary complexes exhibited a unique cage structure with the imidazolium rings acting as lids, leading to a size-dependent binding selectivity by altering the hydrophobic linker between the two imidazolium moieties. This new class of CB[8] complexes was also capable of binding small solvent molecules, including acetone, acetonitrile, diethyl ether, and tetrahydrofuran (THF) in an aqueous environment.

Cucurbit[*n*]utrils (CB[*n*]) are a family of macrocyclic host molecules, which have been demonstrated to encapsulate various cationic and neutral guests in an aqueous environment.[1−3] Host−guest binding complexes with CB[*n*] arise from both portal binding (ion−dipole interactions) and hydrophobic cavity binding, leading to a wide range of binding constants, with binding affinities as high as 10^{16} M^{-1}.[4,5] Recently, imidazolium salts have been increasingly studied as guests for CB[*n*] hosts (primarily CB[6] and CB[7]), with studies focused on producing binding models, obtaining binding association constants, measuring counterion effects and solution properties on the imidazolium-CB[*n*] complexes.[6−9] The utility of the complexation between imidazolium salts and CB[*n*] have also been demonstrated in the isolation of CB[7] from a mixture of CB[*n*] homologues to achieve a "green" isolation and purification route.[10]

To extend the scope of imidazolium salts in CB[*n*] supramolecular chemistry, we present a series of bisimidazolium salts **1**, **2**, and **3** (in Figure 1a), as environmentally friendly, optically transparent, and thermally stable guests for a larger cucurbit[*n*]uril homologue host, CB[8]. Macartney et al. previously reported that CB[7] can form an inclusion complex with **1**, resulting in inhibition of H/D exchange of the acidic NCHN proton on an imidazolium ring (**1**).[11] As shown in Figure 1a, bisimidazolium species **2** and **3** also form 1:1 complexes with CB[7]; however, a reduction in the binding constant was observed (Supporting Information) upon increasing the distance between the two imidazolium moieties.

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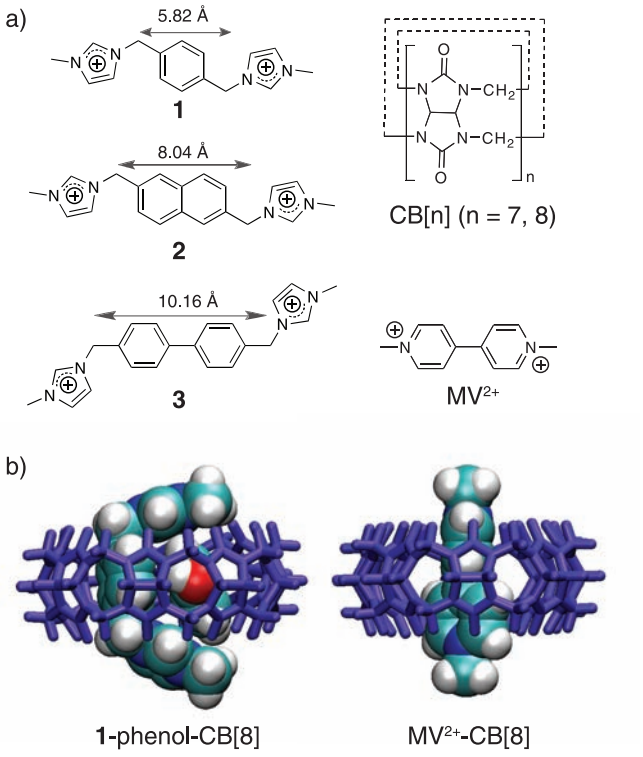

Figure 1. (a) Chemical structures of aryl-bisimidazolium salts (**1**, **2**, and **3**), methyl viologen (MV^{2+}), and CB[8] (see Supporting Information for synthetic procedures); (b) computational models calculated at the HF/3-21G level of theory for phenol-**1**-CB[8] (1:1:1) and MV^{2+}-CB[8] (1:1).

For the larger homologue CB[8], these bisimidazolium salts can also form 1:1 complexes, which are able to encapsulate a second guest in a 1:1:1 binding stoichiometry. In comparison with methyl viologen (an ubiquitous guest for both CB[7] and CB[8]),[12−15] these bisimidazolium guest molecules cannot access a fully planar structure. The cationic imidazolium rings can rotate and act as caps or lids for the carbonyl portals (Figure 1b), providing strong ion−dipole interactions through the formation of a unique binding structure. As shown in Figure 1b, computational modeling (HF/3-21G) of these bisimidazolium salts predicts a unique cage-like supramolecular complex through the strong portal binding effect. Additionally, it was found that the binding selectivity of second guests for a 1:1 bisimidazolium-CB[8] complex vary dramatically as the distance between the two charged imidazolium moieties is changed.

Solution binding affinities (K_a) between the bisimidazolium salts (**1**, **2**, and **3**) and CB[8] were measured by isothermal titration calorimetry (ITC) in water (Supporting Information). The obtained K_a values of **1**-CB[8]

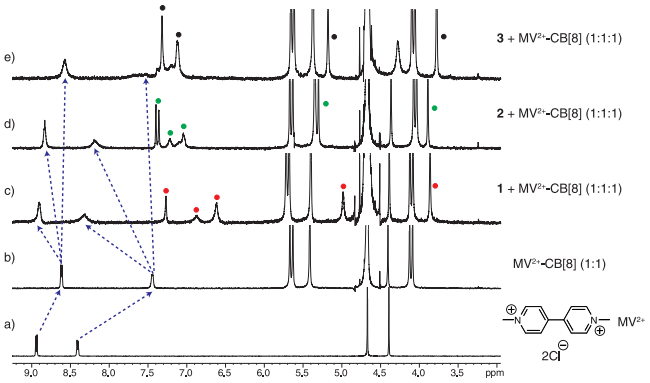

Figure 2. ^{1}H NMR spectra of competition studies in D_2O: (a) methyl viologen(MV^{2+}); (b) 1:1 complex of MV^{2+}-CB[8]; addition of 1 equiv of **1** (c), **2** (d), and **3** (e) into 1:1 MV^{2+}-CB[8] complex solution.

((1.9 ± 0.2) × 10^6 M^{-1}) and **2**-CB[8] ((3.6 ± 0.7) × 10^6 M^{-1}) are slightly greater than that for MV^{2+}-CB[8],[14] which was also confirmed by ^{1}H NMR (D_2O) competition experiments shown in Figure 2. Upon addition of 1 equiv of either guest **1** or **2** into a solution of the 1:1 MV^{2+}-CB[8] complex, guest exchange readily occurred as the viologen peaks experienced an upfield shift toward an 'unbound' position as displayed in Figure 2b−d. Consequently, by increasing the distance between the two imidazolium moieties, the K_a value of **3**-CB[8] was reduced to (2.0 ± 0.4) × 10^5 M^{-1}, which was incapable of displacing viologen from the MV^{2+}-CB[8] complex. Based on a previous gas phase K_a measurement study by mass spectrometry (MS),[16] the binding equilibria of these bisimidazolium-CB[8] complexes with MV^{2+} in the gas phase were also investigated and their relative binding affinities followed the series measured in solution (Supporting Information).

As illustrated in Figure 3a−b, upon addition of 1 equiv of CB[8] to an aqueous solution of imidazolium salt **1** (1 mM), protons *e* (aromatic) and *d* (methylene) shifted upfield by a remarkable amount. Simultaneously, proton *a* (methyl) was slightly shifted downfield. These ^{1}H NMR studies together with computational modeling (Figure 1b) clearly describe the complexation of CB[8] and bisimidazolium **1**. The aromatic core and methylene linkers are encapsulated by the CB[8] cavity, while the cationic imidazolium groups remain at the CB[8] portal areas,[17] which serves to retard the rate of H/D exchange of the NCHN proton as reported by Macartney et al. in the case of **1**-CB[7] complexation.[11] The CB[8] cavity is larger than that of CB[7] and as such bisimidazolium guest molecules do not fit as tightly inside the larger CB[8] cavity; thus the complex **1**-CB[8] has a much lower K_a value than **1**-CB[7][11] and exhibited fast exchange in the ^{1}H NMR spectrum.

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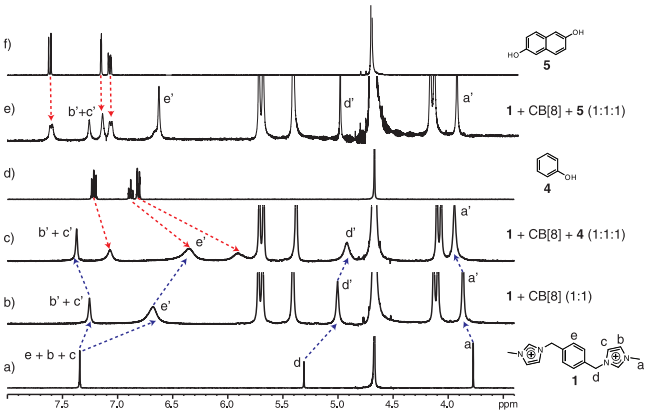

Figure 3. ^{1}H NMR spectra in D_2O: (a) bisimidazolium **1**; (b) 1:1 complex of **1**-CB[8]; (c) 1:1:1 complex of **1**-**4**-CB[8]; (d) phenol **4**; (e) 1:1:1 complex of **1**-**5**-CB[8]; (f) 2,6-dihydroxynaphthalene.

Upon the formation of 1:1 bisimidazolium-CB[8] "caged" complexes, the ability to bind a second guest inside the CB[8] cavity is highly dependent on the size of the aromatic core between the two imidazolium rings. For example, phenol **4**, which has a similar structure and size to the bound aromatic ring of **1**, is clearly encapsulated in the **1**-CB[8] complex leading to a 1:1:1 ternary complex, while the larger guest 2,6-dihydroxynaphthalene (**5**) is not bound (Figure 3e–f). In Figure 3c–d, when 1 equiv of **1**-CB[8] was added into an aqueous solution of phenol, the phenol proton peaks experienced broadening and significantly shifted upfield, which indicated the formation of a **4**-**1**-CB[8] ternary complex with a second guest K_a value of $(2.0 \pm 0.9) \times 10^3$ M^{-1}. Interestingly, when either of the larger bisimidazolium first guests **2** or **3** are employed, both **4** and **5** are capable of entering the CB[8] cavity as a good second guest, as shown by ^{1}H NMR, ITC, ESI-MS, and UV/vis (Supporting Information).

Upon formation of a 1:1 host–guest complex, the UV/vis absorption spectra of the bisimidazolium salts were altered (all UV/vis absorption spectra are shown in the Supporting Information). When the **2**-CB[8] complex was titrated with **5** (0.1 mM), an increased absorption between 240 and 300 nm and a decreased absorption at 340 nm were observed with an isosbestic point at 320 nm (Figure 4a). These observations further indicate that a simple equilibrium exists between the **2**-CB[8] binary complex and the **5**-**2**-CB[8] ternary complex in solution.[18] Moreover, the binding constant between **3**-CB[8] and a second guest (**5**) was measured by ITC to be $(2.1 \pm 0.6) \times 10^4$ M^{-1} (Figure 4b). The K_a values of the other ternary complexes formed from bisimidazolium-CB[8] with second guests (**4** and **5**) are listed in Table 1 (ITC measurements shown in the Supporting Information).

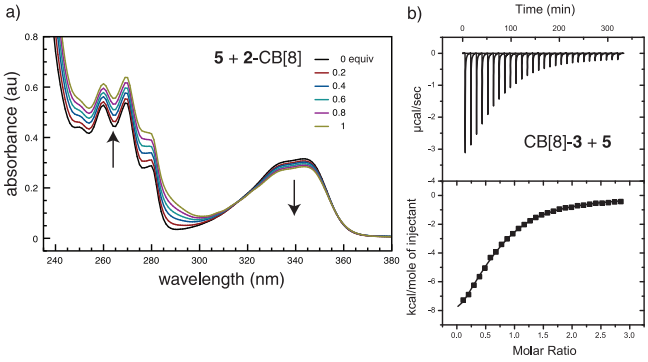

Figure 4. (a) UV/vis absorption spectra of **5** (0.1 mM) upon addition of a preformed 1:1 **2**-CB[8] complex. (b) ITC titration of **3**-CB[5] complexes with **5**.

Table 1. Binding Constants (M^{-1}) of Bisimidazolium with CB[8][a]

	1-CB[8]	**2**-CB[8]	**3**-CB[8]
4	$(2.0 \pm 0.9) \times 10^3$	$(3.1 \pm 0.2) \times 10^4$	$(9.2 \pm 0.4) \times 10^3$
5	–[b]	$(1.2 \pm 0.1) \times 10^3$	$(2.1 \pm 0.6) \times 10^4$
acetone	$(1.0 \pm 0.1) \times 10^3$	$(3.9 \pm 0.2) \times 10^3$	$(5.3 \pm 0.4) \times 10^3$
acetonitrile	<1000	–[c]	–[c]
diethyl ether	$(6.0 \pm 0.1) \times 10^3$	$(4.0 \pm 0.4) \times 10^3$	$(7.3 \pm 1.1) \times 10^3$
THF	$(1.1 \pm 0.4) \times 10^4$	$(1.3 \pm 0.1) \times 10^4$	$(1.1 \pm 0.1) \times 10^4$

[a] All data measured by ITC in water, errors estimated at 15%. [b] No binding was observed. [c] The binding constant was too weak to be measured.

While small neutral organic guest molecules have indeed been encapsulated inside CB[7] and reported by Macartney et al.,[19] encapsulation of such guests in CB[8] alone is not possible on account of the extremely low solubility of CB[8] in neutral water.[3] The bisimidazolium first guests dramatically increase CB[8] solubility and control the remaining cavity size of CB[8] available for second guests; small molecules such as solvents acetone, acetonitrile, diethyl ether, and THF were also found to be encapsulated inside these supramolecular cages, which could be readily visualized by ^{1}H NMR spectra (Supporting Information). In Figure 5a, the solvent molecules' proton peaks experienced an upfield shift, clearly indicating binding between solvent molecules and bisimidazolium **3**-CB[8] complexes. Intermolecular proton–proton interactions were observed between the first guest and solvent molecules inside the CB[8] cavity and resulted in perturbation of the aromatic proton peaks of **3**. As these solvent molecules are not aromatic, driving forces for ternary complex formation other than previously reported charge transfer and π–π stacking must be relevant, such as the hydrophobic encapsulation effect, resulting in the binding affinities of $\sim 10^3$ M^{-1} (Table 1). In contrast, ^{1}H NMR experiments of MV^{2+}-CB[8] complexes with the same solvent molecules clearly indicated that no ternary inclusion complexes

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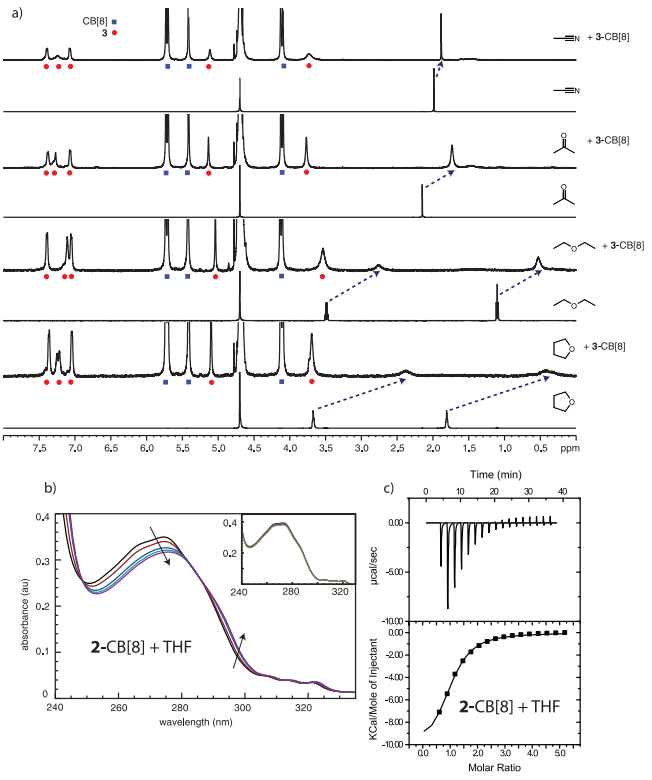

Figure 5. (a) ^{1}H NMR spectra of **3**-CB[8] binary complexes with addition of different solvent molecules, including acetonitrile, acetone, diethyl ether, and THF (top to bottom). (b) UV/vis absorbance titration of 0, 0.3, 0.7, 1, and 1.5 equiv of THF (2 mM) into **2**-CB[8] (0.1 mM) solution; inset spectra show the same titrations in the absence of CB[8]. (c) ITC measurements of **2**-CB[8] complexes with THF.

formed (Supporting Information). These observations further demonstrated that 1:1 complexation between the bisimidazolium salts and CB[8] led to unique structures with the imidazolium rings acting as lids.

UV/vis studies of solvent encapsulation by bisimidazolium (**1**, **2**, and **3**) and CB[8] were carried out (Supporting Information). As a representative example, increasing the amount of THF added to a solution of **2**-CB[8] led to a decrease in the absorption band between 260 and 280 nm and a red shift with an isosbestic point at 285 nm (Figure 5b). Figure 5b (inset) showed that no change in the UV/vis spectrum was observed in the absence of CB[8]. The corresponding ITC titration (Figure 5c) of **2**-CB[8] with THF depicted a typical isotherm for a weak binding interaction ($K_a = (7.3 \pm 1.1) \times 10^3$ M^{-1}). Both UV/vis absorption and ITC measurements suggested a 1:1:1 THF- **2**-CB[8] ternary complex formed in aqueous solution and are in agreement with the observations and data obtained from ^{1}H NMR studies as previously depicted.

In summary, we have presented a series of bisimidazolium salts capable of binding to the supramolecular host CB[8] in aqueous solution with a high binding affinity in a 1:1 stoichiometry. Unlike previously reported 1:1:1 ternary complexes of CB[8] with viologen and an electron-rich second guest, the 1:1 complexes of CB[8] with these bisimidazolium salts form unique supramolecular cages with the two imidazolium groups acting as lids. This feature allows for subsequent binding of not only aromatic guests but also small molecules and solvents inside the cavity. Furthermore, size selectivity of the second guest can be tuned by altering the distance between the two imidazolium moieties. These supramolecular caged complexes represent an important addition to understanding the binding selectivity of CB[*n*] hosts, leading to further opportunities in designing variable supramolecular systems.

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Supporting Information Available. ^{1}H NMR titration, UV/vis absorption spectra, ESI mass spectra, and ITC measurements can be found in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.