Notes

Importance of Cavity Size of the Cucurbituril Homologues in Selective Synthesis of [2]- or [3]-Pseudorotaxanes with a *p*-Xylylenediammonium as the Guest

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Cucurbituril (or cucurbit[6]uril, CB[6]),[1] a macrocycle comprising six glycoluril units, has been employed in the construction of a wide variety of interlocked molecules,[2] and rotaxane-based molecular machines and switches.[3] The recent discovery of cucurbituril homologues[4] containing a different number of glycoluril units has further widened the scope of cucurbituril chemistry.[5,6] In terms of cavity size, CB[6], CB[7], and CB[8] are analogous to α-, β-, and γ-CD, respectively. CB homologues share characteristic features of CB[6], such as a hydrophobic cavity, and polar carbonyl groups surrounding the portals. Therefore their varying cavity and portal sizes lead to remarkable molecular recognition properties.[7]

CB[6] forms very stable complexes with protonated diaminoalkanes ($^+NH_3(CH_2)_nNH_3^+$, n = 4-7, $K > 10^5$ M^{-1}) and moderately stable complexes with protonated aromatic amines such as *p*-methylbenzylamine ($K \sim 3 \times 10^2$ M^{-1}). On the other hand, CB[7] forms complexes with larger guest molecules that are not included in CB[6]. For example, CB[7] forms a 1 : 1 complex with 2,6-bis(4,5-dihydro-1*H*-imidazol-2-yl)naphthalene (**BDIN**).[4] It binds protonated adamantylamine as well as the methyl viologen dication (*N*,*N*'-dimethyl-4,4'-bipyridinium, $\mathbf{MV^{2+}}$) in a 1 : 1 ratio.[5e,6a]

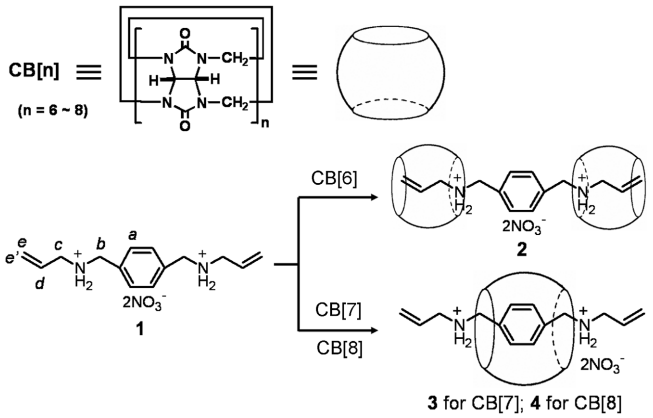

Figure 1. Structures of the ligand **1** and cucurbituril homologues and their selective binding interactions.

Neutral molecules such as ferrocene and carborane are easily encapsulated in CB[7] in aqueous solution.[6c,6e] The cavity of CB[8] is large enough to include two **BDIN** molecules to form a 1 : 2 complex, or another large macrocycle, such as cyclen and cyclam.[4,5b] During the course of these works, we noticed that the binding modes between the CB homologues and their guest molecules are differentiated according to the size of the hydrophobic part of the guest molecules. Herein we report the different binding interactions of CB homologues with a simple guest molecule, the 1,4-xylylenediammonium derivative **1**. Depending on the cavity size of the CB, complexation led to [2] or [3]pseudorotaxanes (Figure 1).

Experimental Section

***N*,*N*'-Diallyl-*p*-xylylenediammonium dinitrate 1:** A solution of terephthaldicarboxaldehyde (1.0 g, 7.46 mmol) in dichloromethane (30 mL) was treated with allylamine (1.23 mL, 16.41 mmol) and stirred for 6 h. The resulting solution was evaporated and redissolved in MeOH (30 mL). And sodium borohydride (1.2 g, 29.84 mmol) was added in ice bath and stirred for 6 hrs at room temperature. After general basic work up process, the resulting organic layer was dried over sodium sulfate. The solvent was evaporated and redissolved in ethanol. Then nitric acid was dropped in ice bath to give a nitrate salt of product (2.36 g, 93%). Mp 190-195 °C; ^{1}H NMR (500 MHz, D_2O) δ 3.73 (d, J = 6.6 Hz, 4 H), 4.29 (s, 4 H), 5.52-5.55 (m, 4 H), 5.94 (m, 2 H), 7.39 (s, 4 H); ^{13}C NMR (125 Hz, D_2O) δ 49.5, 50.2, 124.4, 127.6, 130.9, 132.6; MS (FAB): *m/z* 217 [M^+-HNO_3-NO_3^-]; Anal. calcd for $C_{14}H_{22}N_4O_6$: C, 49.12; H, 6.48; N, 16.37. Found C, 49.06; H, 6.65; N, 16.01.

[3]Pseudorotaxane 2: *N*,*N*'-Diallyl-*p*-xylylenediammonium dinitrate **1** (5.0 mg, 14.6 μmol) and CB[6] (30.0 mg, 2.0 equiv) were dissolved in distilled water (4.0 mL) and heated at 100 °C for 5 min. Slow cooling of the solution to room temperature produced colorless crystals of [3]pseudorotaxane **2** (32.0 mg, 94%). Mp > 210 °C dec; ^{1}H NMR (500

MHz, D_2O): δ3.13 (d, J = 7.1 Hz, 4 H), 4.34 (d, J = 15.6 Hz, 24 H), 4.52 (s, 4 H), 4.77-4.80 (m, 4 H), 5.00 (m, 2 H), 5.61 (s, 24 H), 5.78 (d, J = 15.6 Hz, 24 H), 7.94 (s, 4 H); ESI-MS: *m/z* 1105.2874 ($[M\text{-}2NO_3^-]^{2+}$, $C_{86}H_{94}N_{50}O_{24}$ requires 2210.7672). Anal. calcd for $C_{86}H_{94}N_{52}O_{30}\cdot 14H_2O$: C, 39.91; H, 4.75; N, 28.14. Found: C, 40.32; H, 4.65; N, 27.67.

[2]Pseudorotaxane 3: Ligand **1** (5.0 mg, 14.6 μmol) and CB[7] (17.0 mg, 1.0 equiv) were dissolved in distilled water (3.0 mL), sonicated, and the volume of the solution was reduced to about 0.5 mL by evaporation. Addition of EtOH (3 mL) to the solution precipitated and collected to afford [2]pseudorotaxane **3** (22.0 mg, 100%). Mp > 210 °C dec; ^{1}H NMR (500 MHz, D_2O): δ3.89 (d, J = 6.4 Hz, 4 H), 3.97 (s, 4 H), 4.27 (d, J = 15.5 Hz, 14 H), 5.38 (m, 2 H), 5.53-5.56 (m+s, 16 H), 5.77 (d, J = 15.5 Hz, 14 H), 5.98 (m, 2 H), 6.90 (s, 4 H); ESI-MS: *m/z* 690.2404 ($[M\text{-}2NO_3^-]^{2+}$, $C_{56}H_{64}N_{30}O_{14}$ requires 1380.5218). Anal. Calcd for $C_{56}H_{64}N_{32}O_{20}\cdot 8H_2O\cdot$ EtOH$\cdot$ $0.25H_2SO_4$: C, 40.05; H, 5.07; N, 26.01; S, 0.47. Found C, 40.65; H, 4.78; N, 25.52; S, 0.57.

[2]Pseudorotaxane 4: Ligand **1** (5.0 mg, 14.6 μmol) and CB[8] (24.6 mg, 1.0 equiv) were dissolved in distilled water (4.0 mL) and heated at 100 °C for 5 min. Slow cooling of the solution to room temperature produced colorless crystals of [2]pseudorotaxane **4** (23.3 mg, 95%). Mp > 210 °C dec; ^{1}H NMR (500 MHz, D_2O): δ3.43 (d, J = 6.8 Hz, 4 H), 4.04 (s, 4 H), 4.23 (d, J = 15.4 Hz, 16 H), 4.74-4.76 (m, 4 H), 5.25 (m, 2 H), 5.53 (s, 16 H), 5.79 (d, J = 15.4 Hz, 16 H), 6.74 (s, 4 H); ESI-MS: *m/z* 773.2435 ($[M\text{-}2NO_3^-]^{2+}$, $C_{62}H_{70}N_{34}O_{16}$ requires 1546.5709). Anal. Calcd for $C_{62}H_{70}N_{36}O_{22}\cdot 11H_2O$: C, 39.83; H, 4.96; N, 26.97. Found C, 40.04; H, 4.90; N, 26.56.

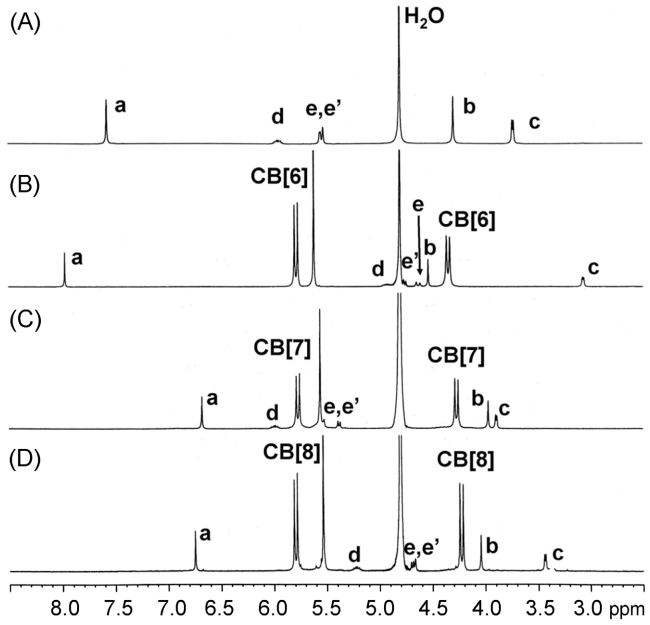

Figure 2. Comparison of ^{1}H NMR spectra in D_2O of ligand **1** (A), in the presence of 2 equiv of CB[6] (B), 1 equiv of CB[7] (C), and 1 equiv of CB[8] (D). ^{1}H NMR spectra were taken with 2.92 mM solutions.

Results and Discussion

The *N,N'*-diallyl-*p*-xylylenediammonium dinitrate **1** was synthesized *via* reductive amination between terephthaldicarboxaldehyde and allylamine. The binding interaction between CB homologues and ligand **1** is monitored by ^{1}H NMR spectroscopy. Threading of 2 equiv of CB[6] with ligand **1** gives [3]pseudorotaxane **2** in which each CB[6] bead resides exclusively at the outer two allylic units. Figure 2 shows the ^{1}H NMR spectra of ligand **1** in the absence (A) and in the presence (B) of CB[6]. The most noticeable changes observed in [3]psedorotaxane is the down-field shifts of the *a* and *b* peaks and the up-field displacements of the other peaks. In other words, the signals for the *a* and *b* protons, which are now located outside CB[6], shift downfield relative to those in the free guest whereas those for the *c*, *d*, *e*, and *e'* protons, which are located inside CB[6], shift upfield. The parent ion peak at 1105.3 in the ESI-MS spectrum suggests the formation of [3]pseudorotaxane between ligand **1** and CB[6]. Although we have been unable to obtain single crystals of **2** suitable for X-ray work, the energy-minimized structure (Figure 3A) of a [3]pseudorotaxane **2** obtained by molecular modeling (Cerius^2) is congruent with all of the NMR data described above. Owing to the small cavity size of CB[6], it forms a complex with the allylic units of the ligand **1**. Thus, the ^{1}H NMR spectroscopy, ESI-MS spectrometry, and the molecular mechanical

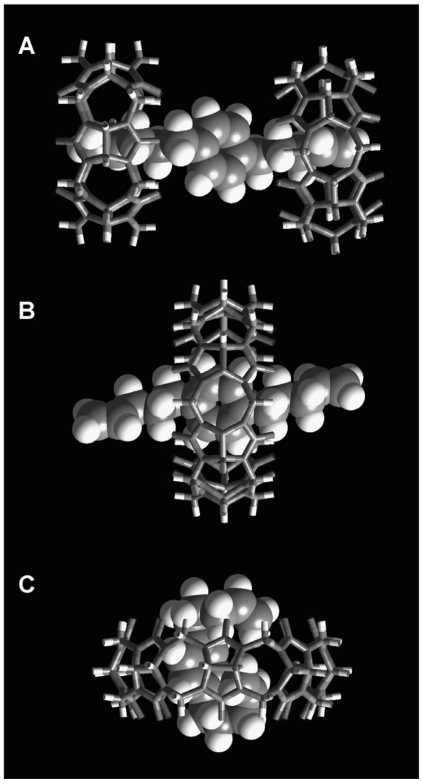

Figure 3. Energy-minimized structures of [3]pseudorotaxane **2** (A), [2]pseudorotaxane **3** (B), and [2]pseudorotaxane **4** (C) obtained by Cerius^2 calculations. CB[n] is represented with a stick model and the guest with a CPK model.

calculations confirm that the ligand **1** forms a dumbbell-shaped [3]pseudorotaxane with two CB[6] molecules.

Next, we investigated the binding behavior of ligand **1** and CB[7]. The ^{1}H NMR spectra of ligand **1** in the absence (A) and in the presence (C) of CB[7] are shown in Figure 2. The changes induced by CB[7] in the ^{1}H NMR spectrum of ligand **1** clearly depart from those observed with CB[6] and ligand **1**. CB[7] induces significant shifts in the aromatic and benzyl protons (*a* and *b*), while the other protons are displaced either slightly down field or not shifted at all. These complexation-induced shifts are similar to that observed in the methyl viologen dication-CB[7] complex previously reported by us.[5e] Thus, the inclusion complex of ligand **1** and CB[7] is formed with the CB[7] residing on the xylyl residue. The structure was further confirmed by the ESI-MS spectrometry. The molecular ion peak at 690.2 supports strongly the formation of [2]pseudorotaxane **3**. Figure 3B depicts the energy minimized structure of the inclusion complex **3** which is a [2]pseudorotaxane in accord with the expectation. The driving force for the stable [2]pseudorotaxane formation appears to be the charge-dipole interaction between the protonated amine of ligand **1** and portal oxygen atoms of CB[7] as well as the hydrophobic interaction between the aromatic moiety of ligand **1** and the inner cavity of CB[7].

Finally, we investigated the binding behavior of ligand **1** and CB[8]. The largest member of the cucurbituril family, CB[8], can accommodate two molecules of a naphthalene derivative (**BDIN**) to form a 1 : 2 host - guest complex.[4] So, we expected that CB[8] may form a 1 : 2 complex with ligand **1**. The addition of CB[8] causes all the proton peaks to shift to higher field (Figure 2D). This indicates that all the protons in the ligand molecule are encapsulated in the cavity of CB[8]. In order to be encapsulated in the cavity of CB[8] properly, the ligand molecule has to form a folded conformation. When CB[8] and the ligand **1** are mixed in a 1 : 2 stoichiometry, only the 1 : 1 host-guest complex is formed as evidence by NMR studies. The most convincing evidence for the 1 : 1 complex (**4**) formation is provided by ESI-mass spectrometry. Strong peaks at 773.2 corresponding to $[M\text{-}2NO_3^-]^{2+}$ is observed with an isotopic pattern nicely matching the calculated one. Energy-minimized structure of this complex **4** is shown in Figure 3C, which shows the folded conformation. It is also seen that one of the allyl moiety is located inside the cavity whereas the other one is on the carbonyl plane of CB[8]. NMR studies of **4** indicate that in solution state, these two allyl moieties may be fast exchanged.

In summary, we have demonstrated that the formation of inclusion complex between a *p*-xylylene diamine derivative and CB homologues results in a [3] or [2]pseudorotaxane depening on the cavity size of the CB. CB[6] forms [3]pseudorotaxane complex by residing on the allylic moiety because the aromatic moiety in ligand **1** is too big to be encapsulated in the cavity of CB[6]. CB[7] and CB[8] give rise to [2]pseudorotaxane complexes with ligand **1**. [2]Pseudorotaxane complexes derived from CB[7] and ligand **1** has free reactive allyl group at each end, therefore this complex could be useful as supramolecular synthon for creating elaborate supramolecular assemblies. In the [2]pseudorotaxane from the ligand **1** and the CB[8] the ligand remains in a folded conformation. This observation could provide an opportunity to study the complexation of CB[8] with the biological molecules known to undergo folding. We are currently working along this line.

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