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Binding Modes of Cucurbit[6]uril and Cucurbit[7]uril with a Tetracationic Bis(viologen) Guest

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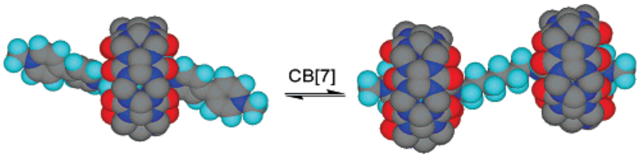

Binding behaviors of two cucurbit[*n*]urils (CB[*n*]) hosts with the $[CH_3bpy(CH_2)_6bpyCH_3]^{4+}$ (bpy = 4,4′-bipyridinium) guest were investigated by ^{1}H NMR and MALDI-TOF-MS experiments. While the CB[6] and CB[7] form [2]pseudorotaxanes with the host located over the hexamethylene chain of the guest, only the CB[7] forms a [3]pseudorotaxane with both host molecules residing over the bipyridinium groups. The initial CB[7] host vacates the inclusion of the hexamethylene chain as a result of the electrostatic and steric repulsions that would arise in simultaneous binding of adjacent aliphatic and aromatic portions of the guest.

Cucurbit[*n*]urils (CB[*n*]) are a family of cyclic oligmers of *n* glycoluril units bridged by two methylene groups per glycoluril.[1−4] The most common member of this host family is cucurbit[6]uril (CB[6]), which was first synthesized in 1905[5] but not fully characterized as to its chemical structure until the work of Mock and Freeman.[6,7] More recently, improvements to the syntheses of the other cucurbit[*n*]urils,[8] particularly the more water-soluble CB[7], has led to a surge of research interest in these host molecules.[4] The hydrophobic cavities of the cucurbituril hosts have portals rimmed with ureido carbonyl oxygens making them excellent binders of cationic organic[9−13] and organometallic guests.[14,15] A combination of hydrophobic interactions with the interior of the cavity and hydrogen-bonding and/or electrostatic ion−dipole interactions with the carbonyl groups lining the portals facilitates very strong binding.[4] Recents reports of the guest−host chemistry of CB[7] provide examples of certain amines and ferrocenes with binding constants ($K_{CB[7]} \geq 10^{11}$ M^{-1})[10,14,15] that approach the highest binding constants observed in biological systems.

Among the guest molecules that have demonstrated specific molecular recognition in their binding modes with the CB[6], CB[7], and CB[8] hosts, the N-alkylated viologen cations have perhaps received the most attention.[16−25] Polypseudorotaxanes have been formed using polyviologens with decamethylene spacers between the viologen groups.[17] The ^{1}H NMR spectra indicated that the CB[6] reside on the decamethylene chains, rather than the viologen units. While the parent methyl viologen dication has been shown to form a very stable guest−host complex with CB[7] ($K_{CB[7]} = 10^5$ M^{-1}),[16] it is much weaker with the smaller CB[6] host ($K_{CB[6]} = 21$ M^{-1}). Other N-alkylated viologen derivatives have binding affinities for both the CB[6] and CB[8] hosts through different binding motifs.[18,20] The CB[6] resides on the aliphatic chains, whereas viologen dications will bind tightly to CB[7] in aqueous solution with CB[7] including the aromatic portion.[2] Kaifer and co-workers have reported that the $\{RVR{\cdot}CB[7]\}^{2+}$ binding mode changes with the length of the aliphatic chains (R) on the viologen (V).[19] The CB[7] includes the aromatic part of viologens with short chains; however, for viologens with the aliphatic chain which is longer than three carbons, the CB[7] resides on the aliphatic chain due to the favorable hydrophobic interactions between CB[7] inner cavity and the terminal aliphatic chain. This binding behavior has been used to construct a simple pH controlled molecular shuttle in which the alkyl substituents (penta- and

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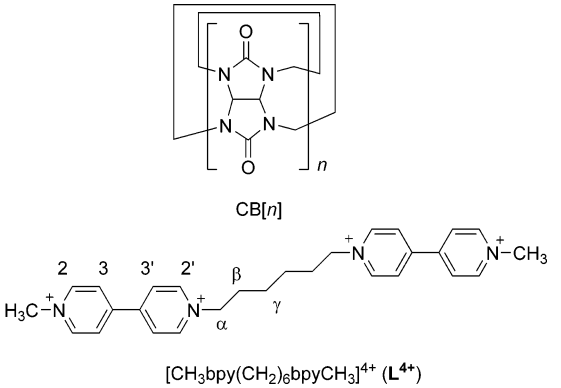
CHART 1. Structures of the Cucurbit[*n*]uril Hosts (*n* = 6 or 7) and the $[CH_3bpy(CH_2)_6bpyCH_3]^{4+}$ (L^{4+}) Guest



hexamethylene) of the thread are terminated by carboxylic acid groups.[22] At low pH with the carboxylate groups protonated the CB[7] bead resides over the alkyl groups, while deprotonation of the carboxylate groups causes the CB[7] to switch to residing over the bipyridinium core. Tuncel and co-workers[24] have recently reported on pH controlled molecular switches based on a CB[6]rotaxane where the binding modes are dictated by acid−base chemistry or heat stimuli. Liu and co-workers have recently shown that CB[7] resides on one of the octyl chains on *N*,*N*′-dioctyl-4,4′-bipyridinium, but it can be moved to the bipyridinium moiety by addition of α-cyclodextrin.[25]

Kuz'mina et al.[26] have reported that the larger CB[8] host binds the tetracationic 1-(3-ammoniopropyl)-4-(*E*)-2-[1-(3-ammoniopropyl)-4-quinolininiumyl]-1-ethenyl quinolium guest in 1:1 ($K_{CB[8]} = 4 \times 10^4$ M^{-1}, fast exchange), 1:2 ($K_{CB[8]} = 1 \times 10^3$ M^{-1}, slow exchange), and 2:1 ($K_{CB[8]} = 2.5 \times 10^3$ M^{-1}, fast exchange) stoichiometries. In the present study we have investigated the binding motifs of CB[6] and CB[7] with a tetracationic bis(viologen) guest, $[CH_3bpy(CH_2)_6bpyCH_3]^{4+}$ ($\mathbf{L}^{4+}$),[20,27] in which a hexamethylene chain is terminated by methyl viologen units (Chart 1).

Kim and co-workers[20] have shown that a 1:1 complex of $\mathbf{L}^{4+}$ with CB[8] will reversibly form a 2:1 complex upon the one-electron reduction of the guest, as a result of the formation of a stable methylviologen radical cation dimer in the host cavity. There had been, however, no study of the binding of this guest with either CB[6] or CB[7]; however, Buschmann and co-workers have reported inclusion complexes for related bis(viologen) dications $[bpy(CH_2)_nbpy]^{2+}$ ($n = 5-7$).[28]

The binding modes of the $[CH_3bpy(CH_2)_6bpyCH_3]^{4+}$ guest with CB[6] and CB[7] were investigated by ^{1}H NMR spectroscopy as a function of the CB[*n*] to guest ratio. The CB[*n*]/guest stoichiometry has a significant effect on the binding mode of CB[7], whereas no effect on the binding mode of CB[6] was observed. The ^{1}H NMR spectra of $[CH_3bpy(CH_2)_6bpyCH_3]^{4+}$ in the absence and in the presence of 0.6, 1.1, and 1.9 equiv of CB[6] in 0.10 M NaCl/D_2O were recorded after 24 h incubation in a 50 °C water bath, as shown in Figure 1.

After the addition of 1.1 equiv of CB[6], the Hα, Hβ, and Hγ methylene protons are shifted upfield by 0.16, 0.83, and 0.87 ppm, respectively, from the resonances of the free guest. Upfield complexation-induced chemical shifts are observed for guest protons which are located in the interior cavity of cucurbiturils, while downfield shifts are associated with guest protons located near the carbonyl oxygens on the portals of the host.[1,9,19] For the aromatic protons, the H2′ and H3′ resonances experience downfield shifts of 0.53 and 0.05 ppm, while the H2 and H3 resonances (and the methyl resonance) remain essentially unchanged. This behavior indicates the formation of a [2]pseudorotaxane with the CB[6] residing on the central hexamethylene chain, with two positively charged nitrogen atoms interacting with the carbonyl oxygen atoms of the CB-[6] portals. Kaifer[16b] has reported previously that the binding constant for the methylviologen cation with CB[6] is very small ($K_{CB[6]} = 21 \pm 2$ M^{-1}) so it would not be expected to reside over the viologen portion of the guest. The exchange between free and bound guests is relatively slow on the NMR time scale, as indicated by the separate resonances corresponding to respective protons of the free and bound guest. Even with a host/guest ratio higher than two, only the [2]pseudorotaxane of CB[6] with the guest was formed. The formation of the 1:1 complex is supported by the MALDI-TOF mass spectrum with peaks at $m/z = 355$ for $[\mathbf{L}+CB[6]]^{4+}$, 474 for $[\mathbf{L}+CB[6]H^+]^{3+}$, 711 for $[\mathbf{L}+CB[6]\text{-}2H^+]^{2+}$, and 774 for $[\mathbf{L}+CB[6]+I^-\text{-}H^+]^{2+}$. The stability constant for the formation of the [2]pseudorotaxane has been determined by a ^{1}H NMR titration to be $K_{CB[6]} = (8 \pm 2) \times 10^3$ M^{-1}. This value is in good agreement with the value of 2.5×10^4 M^{-1} reported by Buschmann and co-workers for the 1:1 complex between $[bpy(CH_3)_6bpy]^{2+}$ and CB[6].[28]

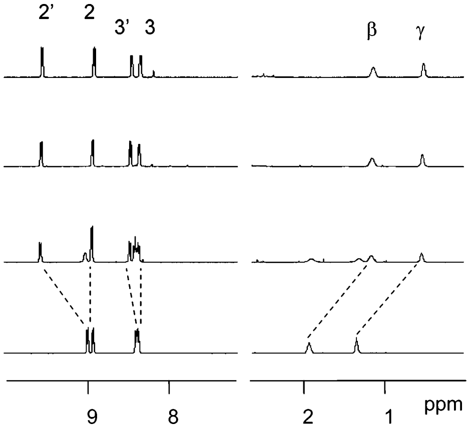


FIGURE 1. ^{1}H NMR spectra of $[CH_3bpy(CH_2)_6bpyCH_3]^{4+}$ in the absence and in the presence of 0.6, 1.1, and 1.9 equiv (from bottom to top) of CB[6] at 25 °C in D_2O/0.1 M NaCl.

With the larger CB[7] host, a titration of the $[CH_3bpy(CH_2)_6bpyCH_3]^{4+}$ guest, monitored by ^{1}H NMR spectroscopy (0.1 M NaCl/D_2O), reveals two different binding behaviors (Figure 2). As the ratio of CB[7] to the guest increases up to 1.1, the resonances of aliphatic Hβ and Hγ resonances move upfield by 0.75 ppm while the aromatic proton H2′ shifts upfield by 0.18 ppm. The H2, H3, and H3′ aromatic protons are slightly downfield shifted, while the methyl protons remain unchanged. As observed for CB[6], this may be explained by the formation of a 1:1 [2]pseudorotaxane of CB[7] with the host including the hexamethylene chain of the guest.

While the exchanges between free and bound [2]pseudorotaxane states are slow on the NMR time scale for both CB[6] and CB[7], the upfield shift of the 2′ proton in the presence of

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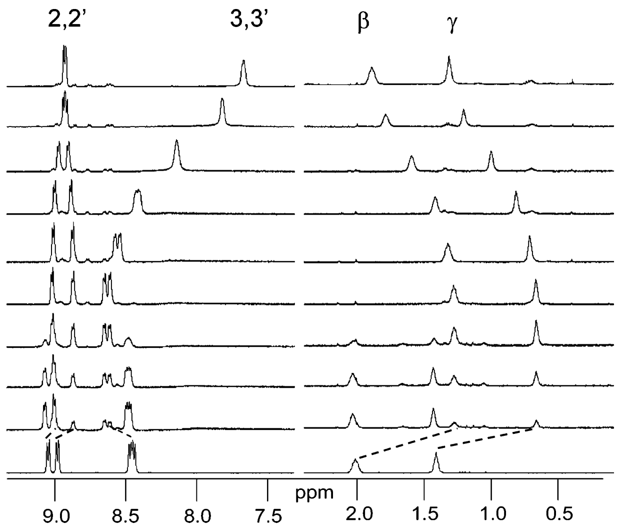

FIGURE 2. ^{1}H NMR spectra of $[CH_3bpy(CH_2)_6bpyCH_3]^{4+}$ (1 mM) in the presence of (from bottom to top) 0.0, 0.3, 0.6, 0.9, 1.1, 1.4, 1.6, 1.8, 2.1, and 2.5 equiv of CB[7] at 25 °C in 0.1 M NaCl/D_2O.

CB[7] suggests that the larger bound host has a greater range of motion along the chain than that in the case of CB[6], where a downfield shift in proton H2′ is observed. Kaifer and co-workers[19b] observed similar behavior with CB[7] using a guest with a 1,4-xylene spacer between two viologen groups. In their [2]pseudorotaxane, the preference of the CB[7] for the dicationic xylyl group over the dicationic viologen group was related to the greater flexibility in the former group in optimizing the positions of the positive charges relative to carbonyl oxygens on the host portals. With the hexamethylene spacer in this study, this flexibility would be even more advantageous in maximizing these noncovalent ion−dipole interactions.

The formation of this 1:1 complex can be confirmed by mass spectra, with peaks at m/z 397 for $[\mathbf{L}+CB[7]]^{4+}$ and 857 for $[\mathbf{L}+CB[7]\text{-}H^+]^{2+}$. As the ratio of CB[7] to the guest is increased beyond one, the changes in the ^{1}H NMR spectra suggest that the [2]pseudorotaxane is converted into a [3]pseudorotaxane by the inclusion of the tetracationic thread by a second CB[7] host. The chemical shifts of the guest protons at higher host/guest ratios are now an average of the shifts associated with the [2]- and [3]pseudorotaxanes as the exchange between these two species is rapid on the NMR time scale. The changes in the ^{1}H NMR spectra (Figures 2 and 3) with higher host/guest ratios are indicative of the two host molecules now residing over the viologen end units.

The resonances of aromatic H3 and H3′ protons undergo a substantial upfield shift from 8.6 ppm for the [2]pseudorotaxane to a limiting shift of 7.1 ppm for the [3]pseudorotaxane (Figure 3). Similar chemical shifts are observed for these protons are seen in CB[7] complexes of other symmetrical RVR^{2+} viologens.[19] At the higher host/guest ratios, the resonances of the aliphatic Hβ and Hγ protons move downfield toward the original chemical shifts observed in the free guest. This suggests that, in the presence of a second CB[7] molecule, the original host molecule is forced to abandon its inclusion of the hexamethylene chain in favor of the unoccupied viologen group. The simultaneous inclusion of the hexamethylene chain and an adjacent viologen group is less stable because of electrostatic and steric interactions between the hosts in these locations. The polar carbonyl-rimmed portals would result in significant repulsive dipole−dipole electrostatic interactions between two CB[7] hosts when placed over neighboring regions of the guest. With the two CB[7] encapsulating the two viologen groups, each portal of the host is adjacent to its own site of positive change, maximizing the number of ion−dipole interactions between the guest and hosts. In addition, because of the bend in the long axis of the guest between the viologen and hexamethylene sections of the guest, there would be some unfavorable steric interactions between two hosts on adjacent sections of the guest.

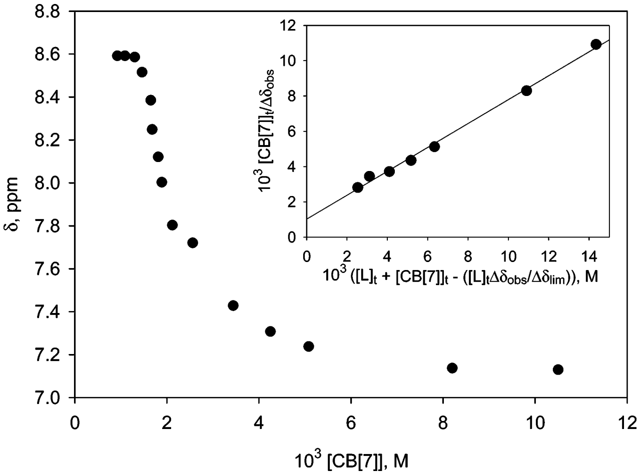

FIGURE 3. Chemical shift change of H3/H3′ protons of the $[CH_3bpy(CH_2)_6bpyCH_3]^{4+}$ guest upon addition of CB[7]. Inset: a plot of $[CB[7]]/\Delta\delta$ against $[\mathbf{L}]_t + [CB[7]]_t + ([\mathbf{L}]_t\Delta\delta_{obs}/\Delta\delta_{lim})$ from which the value of $K_{2CB[7]}$ was determined.

In the mass spectrum of $\mathbf{L}^{4+}$ in the presence of an excess of CB[7], the peak at $m/z = 688$ for $[\mathbf{L}+2CB[7]]^{4+}$ further confirms the formation of 2:1 complex of CB[7] with the $\mathbf{L}^{4+}$ guest. The binding constant for the [2]pseudorotaxane, $K_{CB[7]}$, was determined at 25 °C to be $(6 \pm 2) \times 10^3$ M^{-1} $(-\Delta G° = 5.3$ kcal mol$^{-1})$ from the integrations of the free and bound guest species at low host/guest ratios. The equilibrium constant for the binding of a second CB[7] host molecule, $K_{2CB[7]}$, was determined using the ^{1}H NMR chemical shift changes of the H3 and H3′ resonances at host/guest ratios above two (Figure 3).[29] From the ratio of the slope to the intercept of the linear regression of the data in the inset to Figure 3, a value of $K_{2CB[7]} = (6.8 \pm 0.5) \times 10^2$ M^{-1} s^{-1} $(-\Delta G° = 3.9$ kcal mol$^{-1})$ was calculated (see the Supporting Information). This value is significantly smaller than the 1:1 stability constants reported for the inclusion of dialkylviologen dications with CB[7], $K_{CB[7]} = 10^4-10^6$ M^{-1}.[19] This suggests that the extra process of shifting the original CB[7] bound to the hexamethylene chain over to the viologen unit reduces the favorability of adding the second CB[7]. The overall favorability of including two viologens units $(2\Delta G° = -7.8$ kcal mol$^{-1})$, as opposed to having a free CB[7] and one hexamethylene chain $(\Delta G° = -5.2$ kcal mol$^{-1})$ included, provides the driving force for the formation of the [3]pseudorotaxane observed.

There is considerable interest in the use of cucurbituril and cyclodextrin host molecules in the construction of molecular shuttles and switches with viologen guests.[22−25] This study demonstrates that the movement of CB[7] between different moieties on extended viologen guest molecules can be effected

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by changes in the host−guest stoichiometry, as the result of steric and electrostatic interactions between the host units. We are currently investigating the kinetics and thermodynamics of the formations and dissociations of other CB[6] and CB[7] pseudorotaxanes and rotaxanes employing $[RVR]^{2+}$ and $[R'(CH_2)_nR']^{2+}$ type threads in which R′ is a substituted pyridine, 4,4′-bipyidine, or pyrazine group.

Experimental Section

The cucurbit[6]uril was synthesized by the method developed by Mock and co-workers[6] and characterized by ^{1}H NMR spectroscopy and mass spectrometry. Cucurbit[7]uril was used as received (Aldrich). The bis(viologen) ligand $[CH_3bpy(CH_2)_6bpyCH_3]I_4$ was prepared by adapting a literature procedure.[27] To a solution of 4,4′-bipyridine (8 mmol) in 3 mL of DMF was added 1,6-diiodohexane (2 mmol) in 15 mL of DMF dropwise over a period of 26 h while the temperature of reaction mixture was maintained at 70 °C. After cooling, diethyl ether was added to produce a yellow precipitate of $[bpy(CH_2)_6bpy]I_2$. This compound was subsequently treated with 3 equiv of iodomethane in 5 mL of DMF and heated at 90 °C for 10 h. The resulting red precipitate was filtered and dried under vacuum to give $[CH_3bpy(CH_2)_6bpyCH_3]I_4$. Yield 70%. mp 244−246 °C (decomposed). ^{1}H NMR (DMSO-d_6) δ 9.42 (d, J = 6.4 Hz, 4H), 9.29 (d, J = 6.8 Hz, 4H), 8.81 (d, J = 6.4 Hz, 4H), 8.77 (d, J = 6.8 Hz, 4H), 4.71 (t, J = 7.4 Hz, 4H), 4.44 (s, 6H), 2.00 (m, 4H), and 1.40 (m, 4H) ppm. ^{13}C NMR (DMSO-d_6) δ 148.5, 148.0, 146.6, 145.7, 126.5, 126.1, 60.6, 48.1, 30.4, 24.9 ppm. HRMS (TOF-MS) m/z 806.99456 ($[M - I]^+$); calculated 806.9917.

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Supporting Information Available: The ^{1}H and ^{13}C NMR spectra of $[CH_3bpy(CH_2)_6bpyCH_3]I_4$ and experimental details on the calculations of the stability constants. This material is available free of charge via the Internet at http://pubs.acs.org.

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