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Binding Selectivity of Cucurbit[7]uril: Bis(pyridinium)-1,4-xylylene versus 4,4′-Bipyridinium Guest Sites

Vladimir Sindelar, Kwangyul Moon, and Angel E. Kaifer*

Center for Supramolecular Science and Department of Chemistry, University of Miami, Coral Gables, Florida 33124-0431

akaifer@miami.edu

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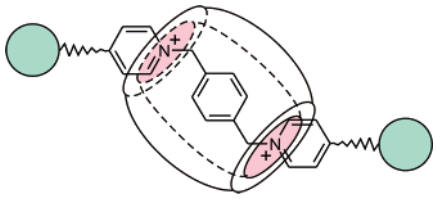
ABSTRACT



The binding interactions between the host cucurbit[7]uril (CB7) and a series of linear guests containing bis(pyridinium)-1,4-xylylene and/or 4,4′-bipyridinium residues were investigated by ^{1}H NMR spectroscopy. CB7 was found to exhibit considerable binding selectivity for bis(pyridinium)-1,4-xylylene over 4,4′-bipyridinium sites. New pseudo-rotaxane and rotaxane compounds were synthesized utilizing the host–guest interactions between CB7 and the surveyed guests.

The cucurbiturils (**CB**) constitute a group of macrocyclic hosts that bind guest molecules through ion dipole as well as hydrogen bonding and hydrophobic interactions.[1] Cucurbit[6]uril[2] (**CB6**) was the first compound synthesized in the family, which later expanded to include other cucurbit[*n*]urils (**CBn**) (where $n = 5$ and $7-10$).[3] In the past two years, our group has investigated the host−guest complexation between **CB7** and 4,4′-bipyridinium (viologen) derivatives.[4] Specifically, **CB7** forms a highly stable inclusion complex with dimethyl viologen in aqueous solution. We have also reported the formation of an inclusion complex between **CB7** and viologen units covalently attached to Newkome-type dendrons.[5]

Very recently, we studied the binding interactions between **CB7** and a series of symmetric viologens having aliphatic substituents of variable length.[6] We have shown that the predominant binding site for **CB7** inclusion depends strongly on the length of the aliphatic substituents of the bipyridinium nucleus. While **CB7** engulfs the viologen residue, forming a pseudo-rotaxane inclusion complex with diethyl viologen, in the case of viologen derivatives substituted with butyl and longer aliphatic substituents, external complexation takes place, with **CB7** docked to one of the aliphatic chains.

Here, as a natural continuation of our previous work, we investigate host−guest interactions between **CB7** and a series of linear guests that contain viologen and/or bis(pyridinium)-1,4-xylylene subunits (see Figure 1 for guest structures). As the inclusion complexes formed by some of the investigated guests and **CB7** are highly stable, their binding constants were estimated using guest competition experiments.[7]

We started our investigation with dibenzyl viologen ($\mathbf{1}^{2+}$). ^{1}H NMR spectra of $\mathbf{1}^{2+}$ in 0.2 M NaCl/D_2O were recorded in the absence (top) and presence of 0.5 (middle) and 1.2 (bottom) equiv of **CB7** (Figure 2). After addition of 1.2 equiv

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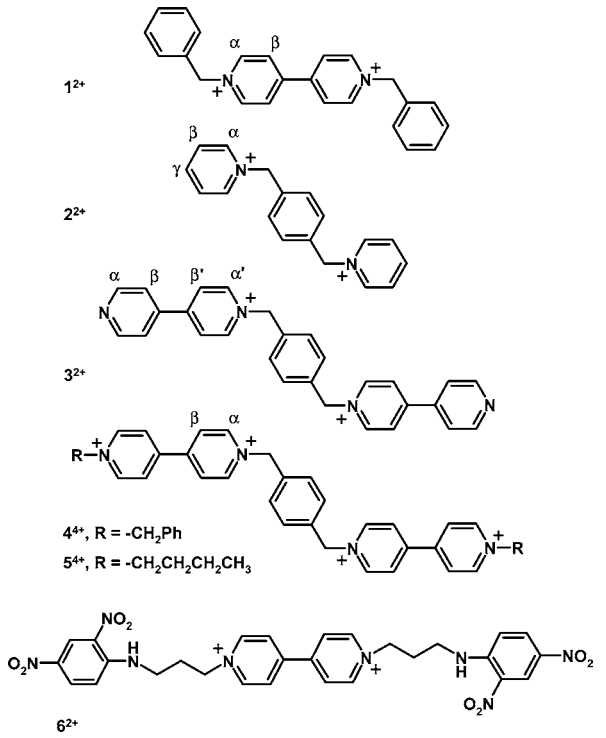


Figure 1. Structures of the guests used in this work.

of the host, the singlet corresponding to the aromatic protons of the benzyl unit broadened, split into three separated peaks, and experienced an upfield shift of ca. 0.4 ppm. The α- and *β*-aromatic protons of the viologen unit shifted to chemical shift values closer to each other, with the α-protons moving ∼0.2 ppm upfield and the *β*-protons shifting ∼0.2 ppm downfield. The complexation-induced shift pattern of the α- and *β*-viologen protons, together with the broadening and significant upfield displacement of the benzyl protons, is consistent with **CB7** including the benzyl unit inside its cavity while the positively charged nitrogen interacts with the carbonyl oxygens on the host's portal. This mode of

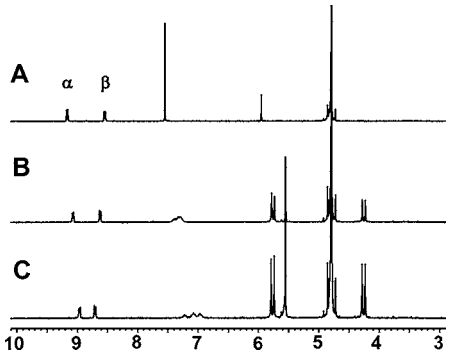


Figure 2. ^{1}H NMR spectra (400 MHz, 0.2 M NaCl−D_2O) of $\mathbf{1}^{2+}$ in the absence (A) and in the presence of 0.5 equiv (B) and 1.2 equiv of **CB7** (C).

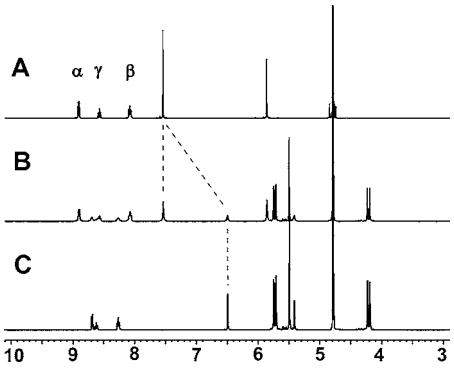


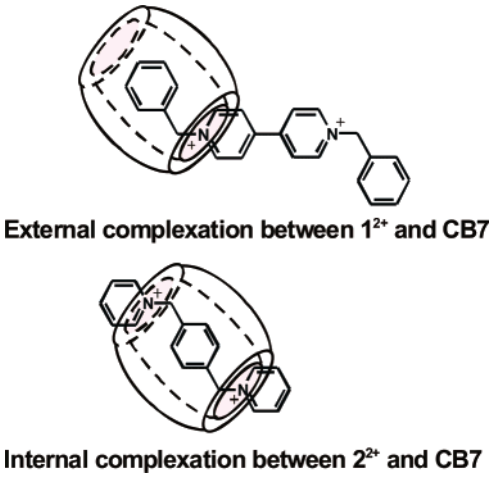
Figure 3. ^{1}H NMR spectra (400 MHz, 0.2 M NaCl−D_2O) of $\mathbf{2}^{2+}$ in the absence (A) and in the presence of 0.4 equiv (B) and 1.2 equiv of **CB7** (C).

"external" complexation is similar to that previously described for **CB7** and the guest dibutyl viologen.[6]

Initially, we assumed that steric hindrance could play a key role determining the main binding site for **CB7**. In other words, the shape of the $\mathbf{1}^{2+}$ dication, with two pronounced methylene bending points, could play an important role in the binding process. To address this issue we prepared compound $\mathbf{2}^{2+}$, in which two pyridinium units are attached to a central phenylene unit via methylene linkers. We reasoned that as **CB7** slides along the structure of this dication, it should find a similar level of steric hindrance to reach the central binding site of $\mathbf{2}^{2+}$ as that experienced in $\mathbf{1}^{2+}$ (see Supporting Information for molecular models of both guests). Upon addition of 1.2 equiv of **CB7** to a solution of $\mathbf{2}^{2+}$ in 0.2 M NaCl/D_2O, the signal corresponding to the aromatic protons of the phenylene unit exhibits a pronounced upfield shift of ca. 1.1 ppm (Figure 3), while the CH_2 protons shift upfield by 0.4 ppm. At the same time, the α- and *β*-protons of the pyridinium groups shift ca. 0.2 ppm upfield and downfield, respectively. No change was observed for the *γ*-protons. The significant upfield shift of the phenylene and methylene protons reveals that **CB7** engulfs the central 1,4-xylylene unit, forming an internal inclusion complex with $\mathbf{2}^{2+}$. The different locations of the main **CB7** binding sites for guests $\mathbf{1}^{2+}$ and $\mathbf{2}^{2+}$ suggest that factors other than simple steric considerations are responsible for the binding positions of **CB7** on these two guests. Furthermore, the driving force for internal inclusion complexation between **CB7** and $\mathbf{2}^{2+}$ is the strong binding of the bis(pyridinium)-1,4-xylylene unit inside the hydrophobic cavity of the host. The resulting pseudo-rotaxane is stabilized by the interaction between the positively charged pyridinium nitrogens and the carbonyl portals on both openings of the host (Scheme 1).

The exchange between free and **CB7**-bound $\mathbf{2}^{2+}$ is slow on the NMR time scale. As can be seen in Figure 3B, in the presence of 0.4 equiv of host, signals corresponding to both the bound and free phenylene protons of the guest are clearly evident. The signals for the free guest disappear upon the addition of more than 1.0 equiv of **CB7**. Thus, the equilibrium association constant is clearly above the range acces-

Scheme 1. Two Different Modes of Binding Interaction between the Investigated Guests and the **CB7** Host



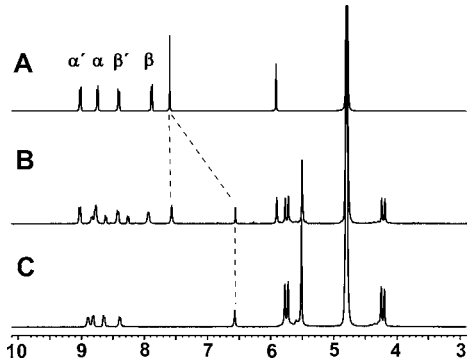


Figure 4. ^{1}H NMR spectra (400 MHz, 0.2 M NaCl-D_2O) of $\mathbf{3}^{2+}$ in the absence (A) and in the presence of 0.5 equiv (B) and 1.2 equiv of **CB7** (C).

sible through NMR data at mM host/guest concentrations. We monitored the **CB7** complexation between an excess of guest $\mathbf{6}^{2+}$ and $\mathbf{2}^{2+}$ for the determination of the binding constants from these competition experiments.[7] Guest $\mathbf{6}^{2+}$ was selected as a reference guest because its binding constant with **CB7** had been previously determined by our group.[6] Unfortunately, a 2- or 3-fold excess of $\mathbf{6}^{2+}$ failed to draw any **CB7** away from $\mathbf{2}^{2+}$, which prevented us from obtaining an accurate value for the binding constant with the latter guest. At this point, we can only state with certainty that the **CB7**·$\mathbf{2}^{2+}$ complex has a stability constant larger than 1.0×10^6 L/mol.

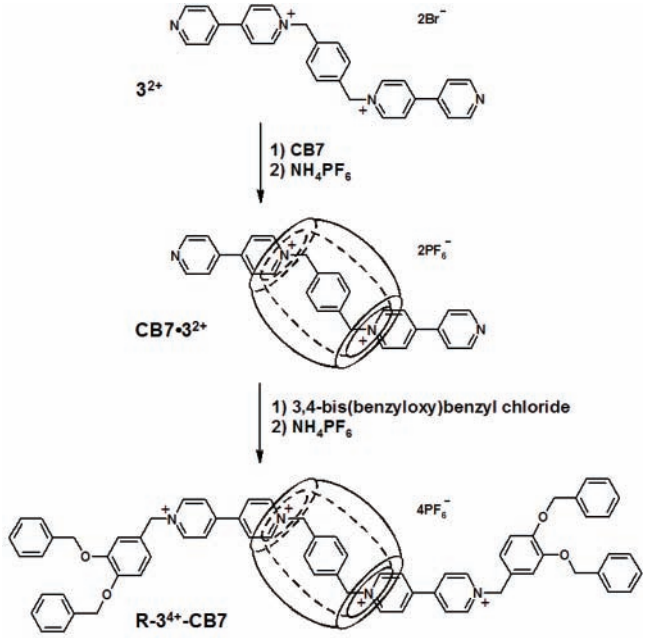
The strong inclusion complexation between **CB7** and $\mathbf{2}^{2+}$ led us to believe that other derivatives of $\mathbf{2}^{2+}$ would show similar binding properties with **CB7**. We prepared compound $\mathbf{3}^{2+}$, which contains two 4-pyridyl-pyridinium units connected to a central phenylene unit via methylene linkers. The changes induced by **CB7** in the ^{1}H NMR spectrum of $\mathbf{3}^{2+}$ (Figure 4) are similar to those observed with $\mathbf{2}^{2+}$. Upon addition of 1.2 equiv of the host, substantial upfield shifts of the methylene (~0.4 ppm) and phenylene (~1.0 ppm) protons of $\mathbf{3}^{2+}$ were observed. The signals for the α- and α′-protons (for proton identification, see Figure 1) shift upfield no more than 0.2 ppm, while those for the β- and β'-protons exhibit downfield shifts of 0.65 and 0.1 ppm, respectively. The NMR spectroscopic results show that internal complexation [at the central bis(pyridinium)-1,4-xylylene unit] takes place between $\mathbf{3}^{2+}$ and **CB7**. The binding of **CB7** to the central unit of the guest reflects the thermodynamic preference of the **CB7** host for the dicationic xylylene residue over the singly charged 4-pyridyl-pyridinium unit.

The guests $\mathbf{5}^{4+}$ and $\mathbf{4}^{4+}$ contain three possible binding sites for the **CB7** host. The first possible binding site is external, around the butyl or benzyl groups, respectively. This binding site has been previously described as the predominant one for **CB7** binding of dibutyl viologen[6] and $\mathbf{1}^{2+}$, respectively. The other possible binding sites are the internal viologen and xylylene moieties. Notice that while the external and viologen sites are present twice, the central xylylene site is present only once in each guest. Quite remarkably, ^{1}H NMR experiments reveal that both viologen-containing guests ($\mathbf{5}^{4+}$ and $\mathbf{4}^{4+}$) behave similarly to $\mathbf{3}^{2+}$, forming internal pseudorotaxane inclusion complexes, in which **CB7** engulfs the central xylylene unit (see Supporting Information). Once again, competition experiments with reference guest $\mathbf{6}^{2+}$ failed to produce accurate K values, since the host heavily favors complexation of the guests containing the dicationic 1,4-xylylene residue. The binding constant of host **CB7** with guests $\mathbf{5}^{4+}$ and $\mathbf{4}^{4+}$ must exceed 1.0×10^6 L/mol, in analogy to our findings with guest $\mathbf{2}^{2+}$.

We took advantage of the high stability of these inclusion complexes to isolate the complex between **CB7** and $\mathbf{3}^{2+}$ (**CB7**·$\mathbf{3}^{2+}$). Mixing $\mathbf{3}^{2+}$ (as its bromide salt) and a slight excess of **CB7** in aqueous solution leads to the formation of the inclusion complex, which can be isolated by treatment with a concentrated aqueous solution of NH_4PF_6. The resulting precipitate was collected as a white solid (92% yield), and the structure of the complex was confirmed by ^{1}H NMR spectroscopy and by MALDI-TOF MS, with the observation of a clear peak corresponding to the m/z ratio 1578 consistent with $\mathbf{[CB7{\cdot}3-2PF_6]^+}$. The solid complex exhibits good solubility in organic solvents (acetonitrile, DMSO) and two terminal nitrogen atoms that are suitable for quaternization in Menschutkin reactions. Therefore, this complex is an excellent precursor for the preparation of **CB7**-based rotaxanes, polyrotaxanes, and catenanes. To demonstrate this application, we prepared rotaxane $\boldsymbol{R}$-$\mathbf{3}^{4+}$−**CB7** using 3,4-bis(benzyloxy)benzyl chloride as a stopper group (Scheme 2). The unchanged position of the phenylene protons in the ^{1}H NMR spectrum confirms that, after the quaternization reaction of the two terminal nitrogens, **CB7** remains on the same position as in the complex with $\mathbf{3}^{2+}$ (see Supporting Information). A space-filling molecular model of this rotaxane is shown in Figure 5, as obtained after energy minimization using the AM1 force field.

Our data shows unequivocally that, as it slides along the linear guests represented in Figure 1, host **CB7** displays a pronounced selectivity for the dicationic bis(pyridinium)-

Scheme 2. Preparation of the Rotaxane ***R*-3^{4+}−CB7**



1,4-xylylene residues in preference to the dicationic 4,4′-bipyridinium sites or monocationic 4-pyridyl-pyridinium, alkylpyridinium, or benzylpyridinium sites. What are the reasons for this selectivity? In particular, why does **CB7** prefer bis(pyridinium)-1,4-xylylene versus the equally charged (2+) and more rigid viologen sites? Two main reasons can be advanced at this stage. First, the distance between the two positively charged nitrogens in 4,4′-bipyridinium residues is fixed and approximately equal to 7 Å, while the corresponding value in bis(pyridinium)-1,4-xylylene groups is not completely fixed, thus permitting a better induced fit. This relative flexibility may allow a more pronounced optimization of the ion−dipole interactions with the carbonyl rims on the host. A second factor may be that the shape of the xylylene residue fits better the internal barrel shape of the **CB7** cavity.

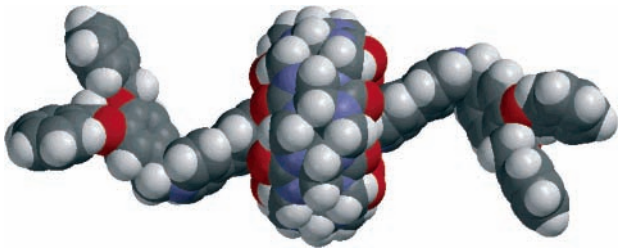


Figure 5. CPK model of rotaxane ***R*-3^{4+}−CB7**.

In conclusion, we have shown that **CB7** binds **1**$^{2+}$ externally, while the remaining guests **2**$^{2+}$, **3**$^{2+}$, **4**$^{4+}$, and **5**$^{4+}$ give rise to pseudo-rotaxane complexes, with the **CB7** host occupying the central residue. Internal inclusion complexation results from the strong and selective binding of **CB7** around the bis(pyridinium)-1,4-xylylene unit. The potential of the pseudo-rotaxane **CB7·3**$^{2+}$ as a precursor for the preparation of more complex topological molecules was demonstrated by the synthesis of rotaxane ***R*-3^{4+}−CB7**. Preparation of polyrotaxanes and catenanes based on the pseudo-rotaxane **CB7·3**$^{2+}$ is presently in progress.

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Supporting Information Available: Synthetic and characterization details and additional NMR spectroscopic and modeling data, as mentioned in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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