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Modes of Binding Interaction between Viologen Guests and the Cucurbit[7]uril Host

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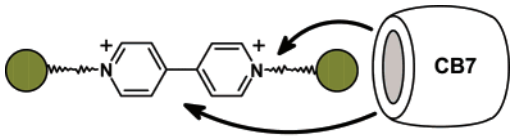
ABSTRACT



Host–guest interactions between cucurbit[7]uril (CB7) and a series of dialkyl-4,4′-bipyridinium (viologen) dicationic guests were investigated by NMR spectroscopy. CB7 includes the aromatic nucleus of short chain viologens, but the mode of interaction is different with longer chain viologens due to the favorable hydrophobic interactions between the terminal alkyl substituents and the inner cavity of the host. A new pseudorotaxane was designed and synthesized on the basis of viologen–CB7 binding interactions.

Cucurbit[7]uril (**CB7**) was first synthesized by Kim and coworkers a few years ago.[1] Structurally similar to the better known cucurbit[6]uril[2] (**CB6**), both compounds share a well-defined, hollow barrel shape with two identical cavity openings lined with carbonyl groups. **CB6** has long been known to bind aliphatic diamines in acidic medium, but its application as a molecular receptor is limited because the only guests that fit inside its relatively narrow cavity are those having the cross-section of an aliphatic chain.[2] The synthesis and isolation of **CB7** led to new possible guests, since its cavity diameter is larger. Our group[3] and Kim's[4] reported simultaneously that methyl viologen ($\mathbf{MV^{2+}}$) forms a very stable inclusion complex with the host **CB7**. In this complex, the aromatic bipyridinium unit of the guest fits tightly inside the host cavity, and each of the two positively charged nitrogen atoms on the guest is encircled by a rim of carbonyl oxygens. The $\mathbf{CB7{\cdot}MV^{2+}}$ inclusion complex is an excellent example of Fisher's key-and-lock molecular recognition principle, as the host and the guest bestow an almost ideal combination of complementary structural features.

In our initial report[3] of the inclusion complexation of methyl viologen by **CB7**, we also investigated a second viologen guest in which the terminal methyl groups were replaced by $-CH_2CH_2CH_2OH$ substituents. We have also reported the complexation by **CB7** of dendrimers containing a single viologen group.[5] The fact that all these viologen derivatives form highly stable inclusion complexes with **CB7** ($K \sim 10^5$ L/mol)[3−5] led us to believe that many other viologen derivatives would form similar inclusion complexes with this host. In this work, we carry out a systematic investigation with a series of symmetric viologens having aliphatic substituents of variable length. Our data reveal that, although all the viologen guests are bound by **CB7**, the actual binding site depends strongly on the length of the aliphatic substituents on the bipyridinium nucleus. These findings were exploited for the design and preparation of a new pseudorotaxane.

The series of viologen guests selected for this study is shown in Figure 1. As is clearly evident from their structures, our key objective was to assess the effect of the length of

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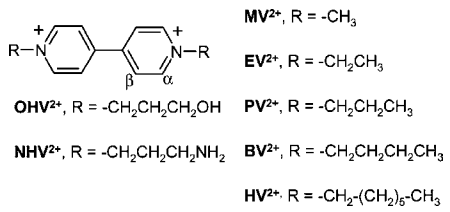


Figure 1. Structures of the viologen guests used in this work.

the aliphatic substituent on the binding interactions with the host **CB7**. With the exception of methyl viologen, which is commercially available, all other guests were straightforwardly prepared by the treatment of 4,4′-bipyridine with excess of the corresponding bromo derivative (see the Supporting Information).

The binding interactions between each of the viologen guests and **CB7** can be conveniently monitored by ^{1}H NMR spectroscopy. Figure 2 shows the ^{1}H NMR spectra of $\mathbf{EV}^{2+}$

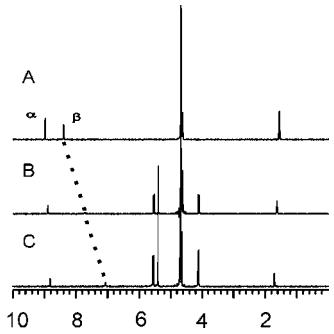


Figure 2. ^{1}H NMR spectra (500 MHz, 0.2 M NaCl−D_2O) of $\mathbf{EV}^{2+}$ in the absence (top) and in the presence of 0.5 equiv (middle) and 1.1 equiv of **CB7** (bottom).

in 0.2 M NaCl/D_2O recorded in the absence (top) and in the presence of 0.5 (middle) and 1.1 (bottom) equiv of host. The most noticeable effect observed upon **CB7** addition is the upfield displacement and broadening of the β aromatic protons of the guest. Upon addition of 1.1 equiv of host, this resonance shows a chemical shift of 7.1 ppm, compared to its original chemical shift of 8.6 ppm in the absence of host. This sizable complexation-induced shift ($\Delta\delta = -1.5$ ppm) is similar to that observed in the $\mathbf{CB7}\cdot\mathbf{MV}^{2+}$ inclusion complex, as previously reported by us.[3] Other complexation-induced shifts observed with this guest are also similar to those reported with $\mathbf{MV}^{2+}$ and include small ($|\Delta\delta| \sim 0.1$ ppm) upfield and downfield shifts for the α aromatic protons and the terminal CH_3 protons, respectively. Due to the similar **CB7** complexation effects observed with guests $\mathbf{MV}^{2+}$ and $\mathbf{EV}^{2+}$, both guests must present a similar mode of binding interactions with **CB7**. In other words, inclusion complexation takes place with these two viologen guests in such a way that the host is fully threaded by the guest and the main binding site for the host is the aromatic viologen residue. These inclusion complexes can be considered to have pseudorotaxane structures.

We attempted to measure the binding constant between $\mathbf{EV}^{2+}$ and **CB7** by electronic absorption spectroscopic measurements, using the same methodology previously employed by us with $\mathbf{MV}^{2+}$. In contrast to $\mathbf{MV}^{2+}$, the main parameters (λ_{max} and ϵ) of the UV absorption band of $\mathbf{EV}^{2+}$ were unchanged by the presence of **CB7**. The origin of this difference in spectral behavior between the guests $\mathbf{EV}^{2+}$ and $\mathbf{MV}^{2+}$ is not understood at this time. We also measured the apparent diffusion coefficients of $\mathbf{EV}^{2+}$ in D_2O solutions containing 0.2 M NaCl and variable concentrations of **CB7** using pulse gradient stimulated echo (PGSE) NMR techniques.[6] The diffusion coefficient of $\mathbf{EV}^{2+}$ decreases linearly with increasing concentration of host, until the total concentration of **CB7** reaches 1 equiv, at which point the diffusion coefficient attains a constant value. These data (see the Supporting Information) show clearly that this technique cannot afford an accurate value for the corresponding equilibrium association constant. The binding saturation behavior observed only allows us to provide a minimum value for the corresponding binding constant between $\mathbf{EV}^{2+}$ and **CB7** ($K > 10^4$ L/mol).

The changes induced by **CB7** in the ^{1}H NMR spectrum of $\mathbf{BV}^{2+}$ clearly depart from those observed with $\mathbf{MV}^{2+}$ and $\mathbf{EV}^{2+}$. Figure 3 shows the corresponding spectra. Notice that

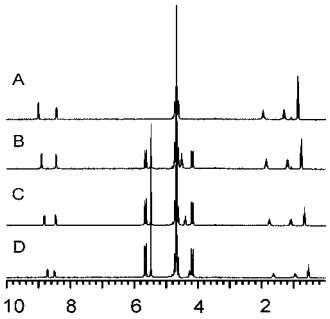


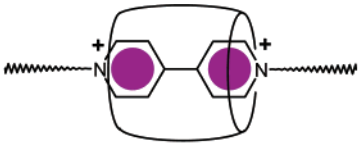
Figure 3. ^{1}H NMR spectra (300 MHz, 0.2 M NaCl−D_2O) of $\mathbf{BV}^{2+}$ in the absence (A) and in the presence of 0.35 equiv (B), 0.7 equiv (C), and 1.1 equiv of **CB7** (D).

the host does not induce any significant shifts in the β aromatic protons, while the α aromatic protons are displaced upfield by ~0.2 ppm. At the same time the three resonances corresponding to the terminal $-CH_2CH_2CH_3$ protons on the aliphatic butyl chains undergo upfield shifts. This pattern of complexation-induced shifts can be clearly ascribed to **CB7** binding to one of the positively charged nitrogens while including the butyl chain inside its cavity. This point was corroborated with a series of experiments with host **CB6**, which has a cavity too small to include the aromatic viologen group, and is thus necessarily limited to interact with one of

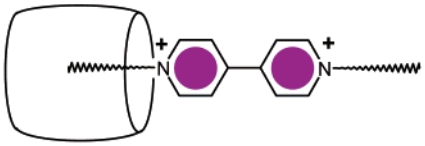
(6) Braun, S.; Kalinowski, H.-O.; Berger, S. *150 and More Basic NMR Experiments*; VCH: Weinheim, 1998; pp 442−444.

the two outside (nonaromatic) binding sites offered by $\mathbf{BV}^{2+}$. The pattern of changes induced by **CB6** in the ^{1}H NMR spectrum of $\mathbf{BV}^{2+}$ is identical to that induced by **CB7**. Clearly, both hosts act in a similar fashion and bind to the "outside" aliphatic docking sites instead of reaching the central viologen nucleus (Scheme 1). Our NMR data in D_2O solution indicate that any viologen derivative having identical aliphatic substituents with chains longer that four carbon atoms will undergo binding interactions with the **CB7** host similar to those observed with $\mathbf{BV}^{2+}$.

Scheme 1. Two Modes of Binding Interaction between Viologen Guests and the CB7 Host



Pseudorotaxane inclusion complex: **CB7** on the viologen nucleus



External complex: **CB7** 'docked' on the aliphatic substituent

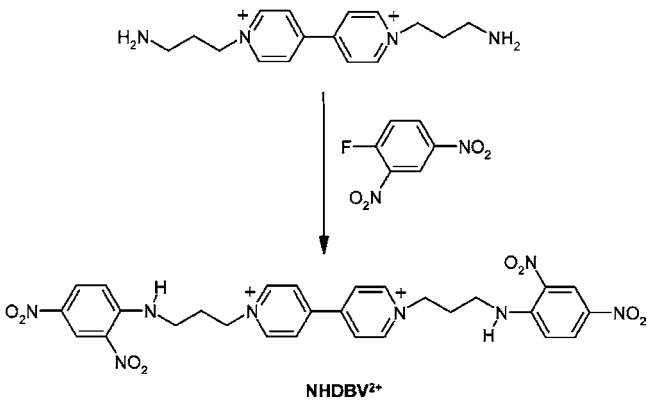
The binding interactions between $\mathbf{PV}^{2+}$ and **CB7** are different from those observed between this host and either $\mathbf{MV}^{2+}$ or $\mathbf{BV}^{2+}$. Most notably, the addition of the host causes a modest upfield shift of the resonance for the β aromatic protons, while the peak corresponding to the α aromatic protons undergoes a larger upfield displacement and both the terminal methylene and methyl peaks are shifted slightly upfield (see the Supporting Information). This spectral pattern suggests that $\mathbf{PV}^{2+}$ behaves as an intermediate case. In other words, this guest represents the transition point from the binding behavior of the short chain viologens ($\mathbf{MV}^{2+}$and $\mathbf{EV}^{2+}$) to that of the longer chain viologens.

The remarkable transition from **CB7** inclusion of the viologen nucleus to its binding of the external aliphatic sites defied detection in our group for some time because the structures of the two initially surveyed viologen guests [$\mathbf{MV}^{2+}$and $\mathbf{OHV}^{2+}$] favor binding on the viologen nucleus, that is, the resulting inclusion complexes have well-defined pseudorotaxane structures.[3] While the case of $\mathbf{MV}^{2+}$ is clear-cut, the case of $\mathbf{OHV}^{2+}$ deserves additional discussion. Here, we have shown that **CB7** does not form pseudorotaxane inclusion complexes with $\mathbf{PV}^{2+}$ and $\mathbf{BV}^{2+}$. Why is it then that the presence of terminal OH groups on the two propyl groups of $\mathbf{OHV}^{2+}$ allows the **CB7** to reach the viologen nucleus? The answer to this question lies on the disruption of the hydrophobic interactions between the aliphatic chain and the inner cavity of **CB7**, which is brought about by the two terminal OH groups. Clearly, the presence of the polar OH termini destabilizes the binding of **CB7** on the two external docking sites and directs the host to continue its threading motion to include the viologen nucleus. In the case of $\mathbf{BV}^{2+}$ ($\mathbf{PV}^{2+}$ is a borderline case) the butyl chains stabilize the **CB7** host when bound to the external sites and their hydrophobic character will destabilize the complex if the **CB7** host were to slide on to include the viologen nucleus. Therefore, the overall hydrophilic/hydrophobic balance of the terminal viologen substituents plays a crucial role in defining the structure and stability of the resulting inclusion complexes. We also investigated the binding interactions between the amino terminated viologen guest $\mathbf{NHV}^{2+}$ and **CB7**, and as would be anticipated from the results obtained with $\mathbf{OHV}^{2+}$ and the arguments described above, the NMR spectroscopic data clearly supported inclusion of the viologen nucleus (pseudorotaxane structure).

The importance of the hydrophobic interactions between the aliphatic chains of the viologen substituents and the inner cavity of **CB7** was further emphasized by our binding investigation of the guest $\mathbf{HV}^{2+}$ and this host in DMSO solution. Although **CB7** is not soluble in DMSO, its solubility is indeed enhanced by the presence of $\mathbf{HV}^{2+}$, a strong indication of the binding affinity between these two compounds. In fact, ^{1}H NMR spectroscopic data obtained in deuterated DMSO solution (see the Supporting Information) reveal that **CB7** reaches the viologen nucleus and forms pseudorotaxane inclusion complexes. The key experimental finding supporting this conclusion is the pronounced complexation-induced upfield shift ($\Delta\delta \sim -1.6$ ppm) observed for the β aromatic protons of the guest. DMSO is considerably less polar than water and solvophobic interactions are less important in DMSO solution than in aqueous medium.[7] As a result, the interaction between the heptyl chains and the cavity of the host is less relevant, leading to the formation of the pseudorotaxane complex. Therefore, we must conclude that any polar functional groups or solvent effects that interfere with the development of hydrophobic interactions between the viologen's *N*-substituents and the **CB7** cavity direct the host to bind on the viologen nucleus and form symmetric pseudorotaxane inclusion complexes.

The results from these experiments led us to design a more kinetically stable pseudorotaxane based on **CB7**−viologen host−guest interactions. We prepared a synthetically modi-

Scheme 2. Preparation of Dumbbell Viologen Guest NHDBV^{2+}



NHDBV^{2+}

fied version of $\mathbf{NHV}^{2+}$ by reacting its amine termini with fluorodinitrobenzene. The resulting dumbbell viologen, compound $\mathbf{NHDBV}^{2+}$ (structure given in Scheme 2), can then be exposed to **CB7** in aqueous solution. As anticipated from CPK molecular models (Figure 4), the **CB7** host can

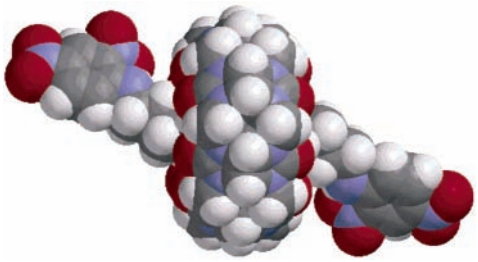


Figure 4. CPK model of the pseudorotaxane formed between **CB7** and $\mathbf{NHDBV}^{2+}$.

slip through the dinitrobenzene stopper groups[8] of the dumbbell and slide onto the central viologen residue, as evidenced by the corresponding ^{1}H NMR spectra (see the Supporting Information). As expected from the cross-section of the dinitrobenzene group, the rate of complex dissociation is now slower, which permits the simultaneous observation of the resonances for the bound and unbound guests, when [**CB7**] < [viologen guest]. The corresponding binding constant was readily determined from UV−vis spectroscopic measurements, as **CB7** complexation of $\mathbf{NHDBV}^{2+}$ depresses the molar absorptivity coefficient of the viologen UV absorption band. Analysis of the data leads to a K value equal to 3.2×10^5 L/mol in 0.1 M NaCl, which is comparable to the K values obtained for the $\mathbf{CB7{\cdot}MV}^{2+}$ complex.[3,4]

In conclusion, we have demonstrated that the binding interactions between viologen guests and the **CB7** host may lead to two different types of complexes.[9] $\mathbf{MV}^{2+}$ and $\mathbf{EV}^{2+}$ give rise to pseudorotaxane complexes because the *N*-substituents are too short and cannot develop significant hydrophobic interactions with **CB7**. $\mathbf{BV}^{2+}$ (and other viologens with longer aliphatic *N*-substituents) form external complexes in which the viologen nucleus is not engulfed by the host. $\mathbf{PV}^{2+}$ appears to be the transitional guest that shows mixed behavior (**CB7** binding at both the viologen nucleus and the external docking points). Guests $\mathbf{OHV}^{2+}$ and $\mathbf{NHV}^{2+}$ have terminal polar groups, which interfere with the hydrophobic docking of **CB7** and favor the formation of pseudorotaxane inclusion complexes.

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Supporting Information Available: Synthetic details and spectroscopic characterization data for noncommercially available viologen guests and additional ^{1}H NMR spectroscopic 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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(9) For a related case, see: Lee, J. W.; Kim, K. *Top. Curr. Chem.* **2003**, *228*, 111.