Host Properties of α-Cyclodextrin and a Water-Soluble Calix[6]arene Probed with Dimeric Bipyridinium Guests

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The complexation properties of two complementary hosts, α-cyclodextrin and a water-soluble sulfonated calixarene, with dimeric viologen guests, in which the viologen units are linked by an undecyl chain, have been investigated. While the complexation behavior of the cyclodextrin host is driven by hydrophobic interactions, that of the calixarene is largely electrostatic in nature. Both hosts show high affinity for the viologen guests, but for completely different reasons. ^{1}H NMR spectroscopic evidence demonstrates the inclusion complexation of the alkyl chain connecting the two viologen subunits by the hydrophobic cyclodextrin cavity. This interaction is strongly pH dependent, and the complexation can be switched by protonating the two unquaternized nitrogen atoms of the guest, thereby making it more hydrophilic and resulting in partial unthreading of the cyclodextrin host. Calorimetric data shows the association constant to be quite high and the complexation to be enthalpically driven, in accord with nonclassical hydrophobic interactions. Cyclic voltammetric experiments demonstrate the solubilization of the reduced viologen form by the cyclodextrin, lessening its deposition on the electrode surface. The strong electrostatically driven association between the cationic viologen guests and the hexaanionic calixarene host was also examined. The binding constants determined from NMR data were on the order of 10^3 M^{-1}. The data suggest that these complexes are also of the inclusion type. Unlike α-CD, calixarene complexation makes the guests more prone to deposit on the electrode surface during voltammetric experiments.

Introduction

Compounds with long aliphatic chains are excellent substrates for binding by cyclodextrin (CD) receptors. Numerous reports have described the binding interactions between CDs and a variety of surfactants.[1] Among the three unmodified CDs (α, *β*, and *γ*), binding to α-CD is optimum because the excellent fit between an extended alkyl chain and the cavity of this CD receptor leads to the formation of inclusion complexes in which the CD is threaded by the chain. These interactions have been used to prepare α-CD based rotaxanes by our group and others.[2] Similar interactions between α-CD and poly(ethylene glycol) chains have been exploited by Harada and co-workers to prepare polyrotaxanes and CD-based polytubules.[3] These and many other reports establish the CDs as important building blocks for the construction of supramolecular structures.[4] In addition to the CDs, calixarenes constitute another very important class of host.[5] Although water-soluble calixarenes are indeed known, their host properties have not been thoroughly explored. Our group has reported on the complexation of simple ferrocene and viologen (4,4′-bipyridinium) guests by the calix[6]arene hexasulfonate host $\mathbf{1}^{8-}$.[6] In this work, we compare the host properties of the highly related calix[6]arene host $\mathbf{2}^{6-}$ (see structures below) to those of α-CD. The comparison is interesting because of the many contrasting and complementary features exhibited by the two hosts. For instance, α-CD has a rigid cavity while $\mathbf{2}^{6-}$, as most calix[6]arenes, is conformationally very flexible. The hydrophobic cavity of the cyclodextrin is lined by the CH and O linkages of the glucopyranose units, but the hydrophobicity of the calixarene cavity is not so well established, perhaps because the cavity itself is not so clearly defined. Furthermore, the hexaanionic nature of the calixarene also clearly contrasts with the neutral character of the cyclodextrin.

These studies are of considerable fundamental interest to support and sustain the progress in the design and synthesis of elaborate CD- or calixarene-containing supramolecular assemblies. Also, methods to modulate and/or alter on demand the binding strength of host−

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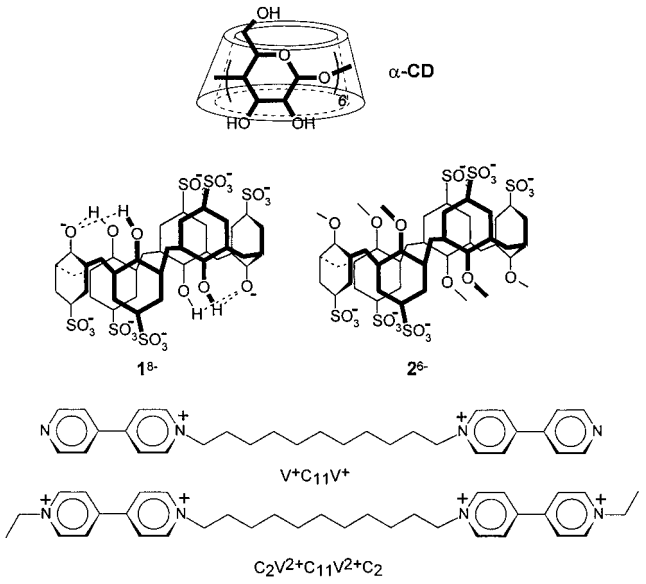
Chart 1



guest complexes are extremely relevant to the development of responsive or switchable molecular systems.[7]

In this report, we describe calorimetric, electrochemical, and spectroscopic studies on the binding interactions between the hosts $\mathbf{2}^{6-}$ and α-CD and dimeric viologen derivatives, whose structures are given in Chart 1.

Experimental Section

Materials. 4,4′-Bipyridine, KH_2PO_4, and Na_2HPO_4 were purchased from Fluka. D_2O was supplied by Isotec. α-CD was obtained as a gift from the American-Maize Products Company (Hammond, IN). The calixarene host $\mathbf{2}^{6-}$ was synthesized by the method of Shinkai and co-workers.[8] All other chemicals were obtained from Aldrich. All solutions were freshly prepared with distilled water further purified by passage through a four-cartridge Barnstead Nanopure system (ρ > 18MΩ•cm).

Synthesis of $\mathbf{V^+C_{11}V^+\cdot 2Br^-}$. This compound was prepared according to a literature procedure.[2b] The purity of the isolated material was found to be satisfactory by ^{1}H NMR and elemental analysis.

Synthesis of $\mathbf{C_2V^{2+}C_{11}V^{2+}C_2\cdot 4Br^-}$. 1-Ethyl-4-(4′-pyridyl)-pyridinium bromide[9] (5.5 g, 20.7 mmol) and 1,11-dibromoundecane (3.15 g, 10 mmol) were refluxed in CH_3CN (75 mL) for 48 h. A yellow precipitate developed during the reaction. Upon cooling, the precipitate was collected by filtration and recrystallized from methanol/ether several times to yield the tetrabromide salt as a yellow powder (3.5 g, 41%), mp > 250 °C. ^{1}H NMR (400 MHz, D_2O) δ 9.12 (m, 8H), 8.57 (d, 8H), 4.75 (m, 8H), 2.10 (m, 4H), 1.72 (t, 6H), 1.25−1.45 (m, 14H). Anal. Calcd for $C_{35}H_{48}N_4Br_4\cdot H_2O$: C, 48.74%; H, 5.84%. Found: C, 48.99%; H, 5.85%.

Equipment. ^{1}H-NMR spectra were recorded on a Varian VXR400 spectrometer. All combustion analyses were performed by Atlantic Microlab (Atlanta, GA). Cyclic voltammetric experiments were carried out with a Princeton Applied Research (PAR) Model 175 universal programmer, a Model 173 potentiostat, and a Model 179 digital coulometer equipped with positive feedback circuitry for IR compensation. Voltammograms were recorded on a Soltec VP-6423S X-Y recorder. The calorimetric measurements were performed with a LKB 2107 flow microreaction calorimeter immersed in a water bath at 298 K.

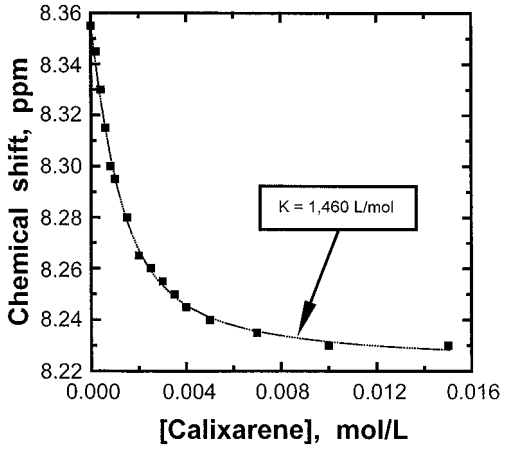


Figure 1. ^{1}H NMR chemical shift of the upfield aromatic signals of $C_2V^{2+}C_{11}V^{2+}C_2$ (squares) plotted as a function of added host $\mathbf{2}^{6-}$. The line represents the best fit to a 1:1 complexation model and was calculated using K = 1464 M^{-1} and $\delta_{complex}$ = 8.222 ppm. The reported binding constants are the average of the constants obtained by identical treatment of the aromatic resonances for each guest.

Procedures. ^{1}H NMR spectroscopy was used for qualitative and quantitative binding studies. A 0.7-mL sample of a 2 mM solution of the bipyridinium compound in I = 0.1 M (pH = 7) deuterated phosphate buffer (in D_2O, CH_3CN or acetone as internal reference) was titrated with aliquots from a stock 70 mM α-CD solution prepared in the same solvent system. Aliquot additions were sequentially performed until a total of 10 equiv of α-CD had been added. The ^{1}H NMR spectrum was recorded after each addition. The acid/base behavior of $V^+C_{11}V^+$ was investigated using a 0.7 mL sample of a solution containing 2 mM of this compound and 2 mM α-CD in the buffer medium. The pH of the medium was altered by the stepwise addition of (i) 10 μL concd DCl (37% w/w) and (ii) 25 μL concd ND_4OD (26% w/w) to the sample. The ^{1}H NMR spectrum was recorded after each addition. The qualitative calixarene NMR experiments were done similarly. The calixarene association constants were obtained by measuring the change in chemical shift of the guest protons *vs* the concentration of added host in 0.2 M NaCl and fitting the data to a 1:1 binding model with a regression least-squares algorithm. A typical plot of the NMR data along with the least squares fit is shown in Figure 1.

Cyclic voltammetric experiments were performed in a single-compartment, 10-mL cell fitted with a glassy carbon or gold disk working electrode (0.031 cm^2), a platinum wire auxiliary electrode, and a sodium chloride saturated calomel electrode (SSCE) or Ag/AgCl electrode as the reference for potential measurements. The working electrode was polished with a 0.05-μm alumina/water slurry on a felt surface at the beginning of the experiment and immediately before recording each voltammogram. All the solutions were prepared by using a I = 0.1 M (pH = 7) phosphate buffer or 0.2 M NaCl as the solvent/supporting electrolyte system. The solution was carefully deoxygenated by purging with nitrogen at the beginning of the experiment and after each host addition.

The calorimetric measurements were carried out by mixing in a flow calorimeter a 2 mM solution of α-CD with several solutions having varying concentrations of the bipyridinium guest in the range 0.6 to 6 mM. A phosphate buffer solution (pH = 7, I = 0.1) was used as the solvent medium for complexation studies at neutral pH. A pH = 1 HCl solution was the solvent medium of choice for the calorimetric titration of $V^+C_{11}V^+$ with α-CD under acidic conditions. Additional details on the instrumentation as well as the treatment of the calorimetric data have been recently reported elsewhere.[10]

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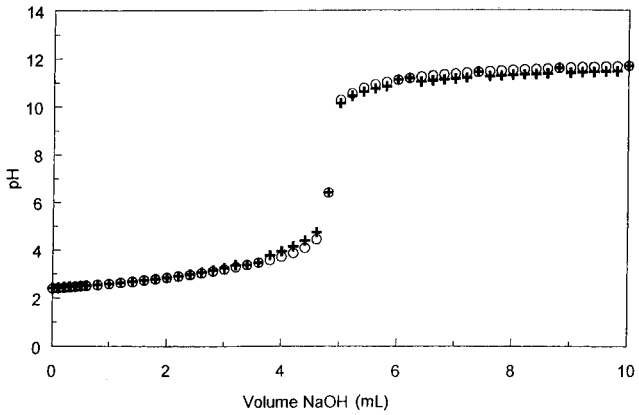

Figure 2. Experimental (○) and simulated (+) values for the potentiometric titration of 0.025 g of $V^+C_{11}V^+ \cdot 2Br^-$ + 0.14 mL of 1.0 M HCl in 0.1 M NaCl with 0.029 M NaOH. The resulting pK_a values of the two viologen units are 2.63 and 3.96.

Table 1. Thermodynamic Parameters (kcal/mol) for α-CD Binding of $V^+C_{11}V^+$ and $C_2V^{2+}C_{11}V^{2+}C_2$ in Aqueous Media at 25 °C

guest	medium	$\Delta G°$ (K, M^{-1})	$\Delta H°$	$T\Delta S°$
$HV^{2+}C_{11}V^{2+}H$	pH = 1	−3.8 ± 0.1 (580)	−7.8 ± 0.4	−4.0
$V^+C_{11}V^+$	pH = 7	−4.9 ± 0.1 (4050)	−7.0 ± 0.1	−2.1
$C_2V^{2+}C_{11}V^{2+}C_2$	pH = 7	−3.2 ± 0.1 (230)	−8.4 ± 0.6	−5.2

Results and Discussion

α-Cyclodextrin Host. The two guests consist of a central aliphatic chain and two terminal bipyridinium groups. The guest $C_2V^{2+}C_{11}V^{2+}C_2$ is a tetracation and does not exhibit pH dependent behavior since all the nitrogen atoms are quaternized. In contrast, guest $V^+C_{11}V^+$ has two basic nitrogens. The pK_a values of this compound were verified to lie in the expected 3−5 range by analysis of its pH titration curves, Figure 2.[11] Therefore, $V^+C_{11}V^+$ is a dication in neutral media (pH = 7) and a tetracation in strongly acidic media (pH = 1). The thermodynamic parameters for the complexation of the bipyridinium derivatives by α-CD were obtained by calorimetric titrations. The results are given in Table 1.

These results indicate that $V^+C_{11}V^+$ (at pH = 7) forms the more stable complex with α-CD. The thermodynamic parameters reported here are in reasonable agreement with those previously reported by Wylie and Macartney for the binding of $V^+C_{11}V^+$ by α-CD in unbuffered neutral media.[2b] The thermodynamic data show that the complexation is enthalpically driven with a high degree of enthalpy/entropy compensation. This is in accordance with the nonclassical hydrophobic effect known to be operational in CD complexation.[12] From the data in Table I, it is clear that the stability of this complex decreases substantially in acidic medium (pH = 1) where its thermodynamic parameters approach those found for the tetracationic guest $C_2V^{2+}C_{11}V^{2+}C_2$. This is consistent with the fact that guest $V^+C_{11}V^+$ becomes a tetracation at pH = 1 due to the protonation of the terminal bipyridinium nitrogens. The complexation of the guests by the CD host can be controlled by changing the pH and is therefore switchable as shown in Scheme 1.

The complexation of the $C_2V^{2+}C_{11}V^{2+}C_2$ guest is not affected by the pH of the medium. In fact the thermodynamic values for the interaction of this guest with α-CD in acidic medium (pH = 1) are identical within experimental error to the values determined in neutral medium. This finding strongly suggests that general medium effects have little to do with the observed pH-induced changes in the thermodynamic parameters describing binding of $V^+C_{11}V^+$ by α-CD. It is reasonable to conclude that the protonation of the terminal nitrogens of this guest is indeed responsible for the decreased binding affinity to α-CD. Note that the diminished stability of the α-CD−$V^+C_{11}V^+$ complex under acidic conditions has essentially an entropic origin, *i.e.*, in going from pH = 7 to pH = 1 the $\Delta H°$ value actually becomes more negative (by −0.8 kcal/mol) but the formation of the complex becomes entropically more unfavorable (a decrease of 1.9 kcal/mol is observed in the $T\Delta S°$ value).

Why the tetracationic guest has such a decreased affinity for α-CD, however, is less obvious. While the extra positive charges in the viologen units would certainly make it more difficult for the CD host to thread onto the alkyl chain due to the larger solvation cage around the viologen, the height of this barrier is a kinetic obstacle to complexation. In principle, the CD would gain the same stabilization upon threading no matter how hard it was to get to the binding site. The Gibbs free energy is a state function and is therefore concerned only with initial and final states so the height of the barrier that the CD has to overcome is of no direct consequence. However, increasing the overall thickness of this barrier may have an indirect effect on the potential well between the two viologen units as shown in Figure 3.

As the solvation sphere of the viologen units increases, so does the height *and the thickness* of the barrier. As the two barriers become thicker with a constant distance between them, the well becomes more shallow and less stabilizing. Taking this argument to the limit, if the barriers were thick enough, they would merge and there would be no well! A smaller effective alkyl chain between the two viologen units is then available for stabilization by complexation because of the necessary extra solvation needed by the now more highly charged viologen groups. This would lead to a reduced entropy complex since the guest and the CD fit more tightly. In essence, the situation reduces to having less hydrophobic aliphatic "grease" available for complexation by the CD, as if we were removing part of the chain. This reduced affinity of CDs for shorter aliphatic chains is a well known phenomenon.[1] Interestingly, the binding constant with α-CD for a compound very similar to $V^+C_{11}V^+$ but with an alkyl chain of only nine methylene groups under similar conditions to ours (0.1 M NaCl, 25 °C) has been previously determined to be K = 440 ± 30 M^{-1}.[2b] This value is very close to our values for the two tetracationic guests (580 and 230 M^{-1}) and suggests that protonation of $V^+C_{11}V^+$ affords a guest with two less methylene groups effectively available for complexation by α-CD, supporting this explanation of the differences in association constants. Other interactions may also contribute to the thermodynamic parameters given in Table 1. For instance, the terminal, uncharged pyridine rings in guest $V^+C_{11}V^+$ may exhibit weak interactions with the CD hosts which, although minor, may be responsible for the tighter binding to $V^+C_{11}V^+$ as compared to its diprotonated form or the $C_2V^{2+}C_{11}V^{2+}C_2$ guest.

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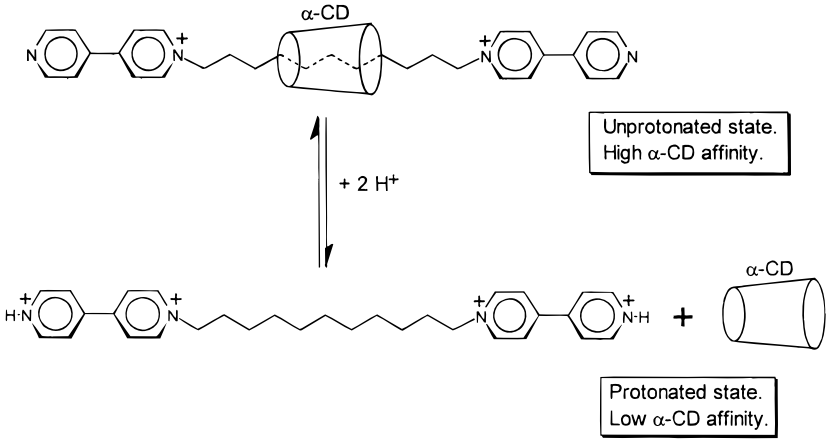
Scheme 1



Analysis of the ^{1}H NMR spectra of these guests in the absence and presence of α−CD and under pH control provides a powerful tool to follow the binding interactions at the molecular level. Figure 4 shows the aromatic region of the ^{1}H NMR spectra of the two viologen guests with and without α-CD at different pH values. The spectrum of $V^+C_{11}V^+$ (Figure 4a) consists of four signals for the two equivalent viologen units while that of $C_2V^{2+}C_{11}V^{2+}C_2$ (Figure 4b) has the eight protons meta to the nitrogens chemically equivalent and the protons ortho to the N attached to the ethyl groups almost equivalent to the protons ortho to the N attached to the undecenyl group. Addition of 1 equiv of α-CD to the $V^+C_{11}V^+$ solution (Figure 4c) causes the appearance of a separate set of signals of about equal intensity for both viologen guests corresponding to the threaded CD complex in addition to the signals for the free viologens, similar to what Macartney has shown.[2b] This suggests that we are operating in the slow exchange timescale and that the binding constant is not extremely large, otherwise all of the viologen would be complexed. Note that the protons whose chemical shifts change the most on the diquaternized guest upon adding the CD host are the "interior" ones corresponding to the quaternized pyridinium rings attached to the long alkyl chain not the neutral rings, suggesting complexation of the linking chain and not simple end-on interaction or complexation of the viologen unit itself. Upon protonating the neutral nitrogen atoms of $V^+C_{11}V^+$ with DCl (pH < 2), the spectrum (see Figure

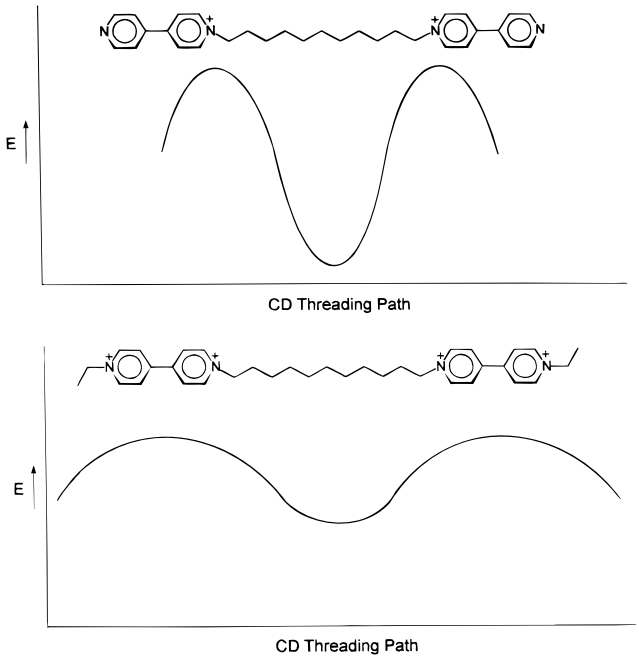


Figure 3. Qualitative depiction of the potential energy profile experienced by α-cyclodextrin as it threads along the viologen guests.

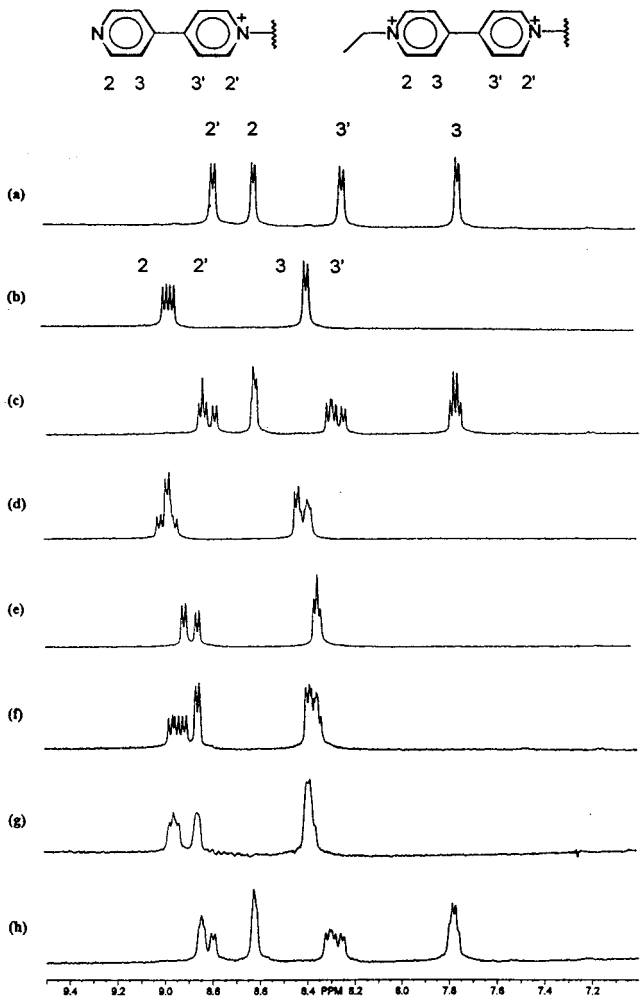


Figure 4. ^{1}H NMR spectra in D_2O of (a) $V^+C_{11}V^+$, (b) C_2V^{2+}-$C_{11}V^{2+}C_2$, (c) $V^+C_{11}V^+$ + 1 equiv of α-CD, (d) $C_2V^{2+}C_{11}V^{2+}C_2$ + 1 equiv of α-CD, (e) $V^+C_{11}V^+$ + 10 μL of DCl (concd), (f) $V^+C_{11}V^+$ + 10 μL DCl (concd) + 1 equiv of α-CD, (g) $V^+C_{11}V^+$ + 10 μL of DCl (concd) + 50 equiv of α-CD, (h) $V^+C_{11}V^+$ + 10 μL of DCl (concd) + 1 equiv of α-CD + 25 μL of ND_4OD (concd).

4e) closely resembles that of $C_2V^{2+}C_{11}V^{2+}C_2$. The aromatic protons on either side of the bipy units are not as equivalent, however, due to the fact that having a proton attached to the terminal nitrogen atom makes the viologen unit more asymmetric than if a carbon atom were attached to the nitrogen and also due to the dynamic nature of the quaternization when a proton is involved. Addition of α-CD (1 equiv) to the protonated $V^+C_{11}V^+$ (Figure 4f) produces a spectrum very similar to the spectrum of $C_2V^{2+}C_{11}V^{2+}C_2$ with α-CD. The spectra of the complexed protonated viologen then reverts essentially to that of the unprotonated complexed form upon addition of excess base, thus proving the switchable nature of this system as suggested by the calorimetric data.

Close inspection of the three complexed spectra (Figure 4c,d,f) shows that there are more signals than can be accounted for if it is assumed that the two viologen units of the guests are equivalent upon complexation (even assuming fast exchange). For example, Figure 4c shows six signals if we subtract the uncomplexed spectrum 4a: a pseudo triplet (two partially superimposed doublets) at 8.83 ppm, an unresolved multiplet at 8.60 ppm, a doublet of doublets at 8.30 ppm, and another doublet at 7.79 ppm. Figures 4d and 4f also show extra signals. The only way that so many signals can be generated upon complexation (assuming no intramolecular or intermolecular aggregation, or large conformational change which might be disrupted, all of which are valid assumptions due to the highly charged and mutually repulsive nature of the guests) is if the two viologen units become unequivalent upon complexation, the exchange being slow on the NMR timescale. Static complexation of only one viologen unit (although extremely unlikely due to the fact that the CD complexes the chain, not the viologen) without internal exchange leaving the other unchanged would render the signals of the uncomplexed viologen essentially equal to the completely free guest's signals leaving extra signals still unaccounted for. Other explanations involving higher order assemblies can be dismissed by noting that the aliphatic chain is not long enough to complex more than one CD at a time (CPK models) and that the CDs strongly prefer complexation of the chains over the charged and therefore highly hydrophilic viologen units. Local stereodifferentiation of the viologen protons (for example the four ortho protons on one viologen unit) caused by internal asymmetry due to the inherently chiral CD could be a possibility but this could be easily averaged out simply by rotation of the CD around its axis. The extra signals then are most likely caused by the two different and unequivalent openings of the CD positioned between the two viologen units.[13] This type of situation has been noted by us before upon the isolation of two isomeric α-CD rotaxanes differing only in the orientation of the threaded α-CD unit.[2a] While the inclusion of aliphatic chains by α-CD has been proven many times (especially by the isolation of rotaxanes), the observation of an extra set of signals in the ^{1}H NMR spectra for the *undecenyl aliphatic protons* of the guests upon the addition of the CD host also lays additional support for our claim of inclusion complexation.

The electrochemical behavior of the two viologen guests in water is dominated by the deposition of their reduced neutral forms (and even the partially reduced form of the tetracationic viologen) on the electrode surface producing tell-tale spikes in the cyclic voltammograms.[14] Addition of α-CD to the solution tends to reduce the peak currents due to complexation and thus slows diffusion of the now bulkier molecule. The potentials, however, are not affected much because α-CD does not interact effectively with the aromatic residues. Even though it will thread around the viologens to get to the alkyl chains, the fit around the viologens is too tight for it to stay on even when the viologen is reduced and substantially more hydrophobic. Complexation by the CD host also reduces the size of the current spikes by helping to solubilize the reduced forms of the viologen guests, thus lessening deposition on the electrode surface. Figure 5 shows the effect of added α-CD on the cyclic voltammetric wave corresponding to the first reduction of $C_2V^{2+}C_{11}V^{2+}C_2$.

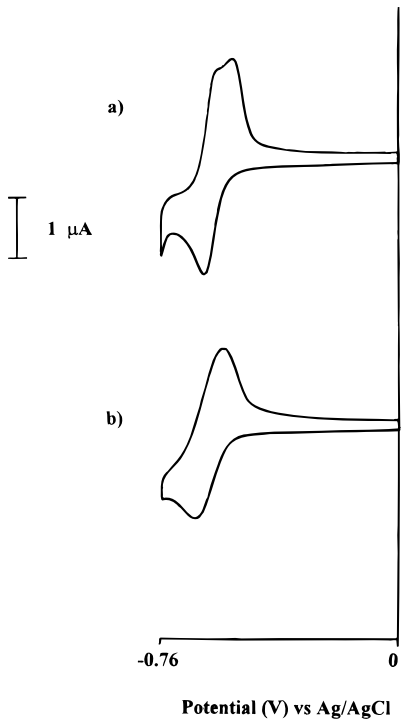


Figure 5. Cyclic voltammetric response of $C_2V^{2+}C_{11}V^{2+}C_2$ (1 mM in 0.1 M NaCl) on a Au working electrode, $\nu = 100$ mV/s, (a) in the absence and (b) in the presence of 5 equiv of α-CD.

Calixarene Host. While the complexation of the viologen guests with the CD host is driven by hydrophobic and Van der Waals forces, the calixarene host $\mathbf{2}^{6-}$ should operate mainly under the control of electrostatic interactions.[15] Flow calorimetric experiments were not carried out with this host due to the technique's requirement for large amounts of compounds. ^{1}H NMR binding studies in 0.2 M NaCl (aq) revealed strong association between the two viologen guests and the anionic host. In sharp contrast to the CD receptor, the complexation here is in the fast exchange regime, and a smooth shift in the proton signals corresponding to a weighted average of the complexed and free guests is observed as the calixarene host is added. Figure 6 shows the effect of added calixarene host on the aromatic region of one of the

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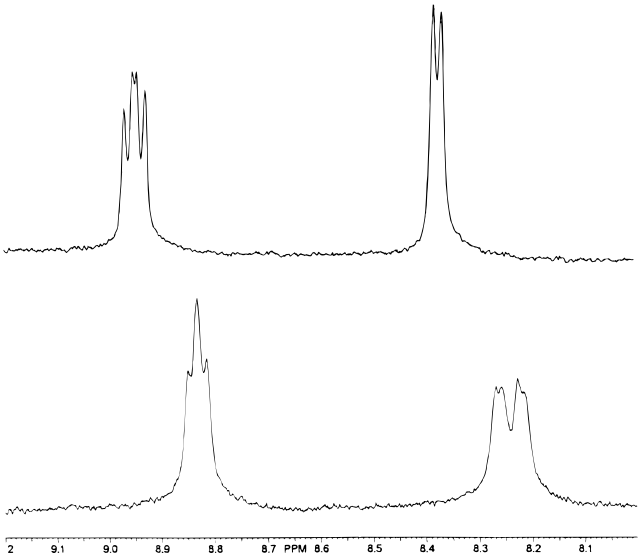
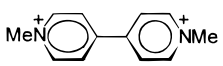


Figure 6. ^{1}H NMR spectra in D_2O of $C_2V^{2+}C_{11}V^{2+}C_2$ showing the aromatic region in the absence of (top) and in the presence of 10 equiv of $\mathbf{2}^{6-}$ (bottom).

viologen guests. Note that complexation again induces asymmetry in the guest, and the previously chemically equivalent upfield aromatic signals are now split.

Fitting the NMR data to a 1:1 complexation model gave an association constant $K = 1900 \pm 200$ M^{-1} for the dicationic $V^+C_{11}V^+$ guest while the more highly charged guest $C_2V^{2+}C_{11}V^{2+}C_2$ only showed a $K = 1600 \pm 200$ M^{-1} at 25 °C. While these two values are within experimental error, it is very surprising that the guest with twice the positive charge is about equally attracted to the anionic host. In an effort to further understand this phenomenon, we determined the association constant of a "model" compound, methylviologen (paraquat), with $\mathbf{2}^{6-}$ under the same conditions using the same NMR method.



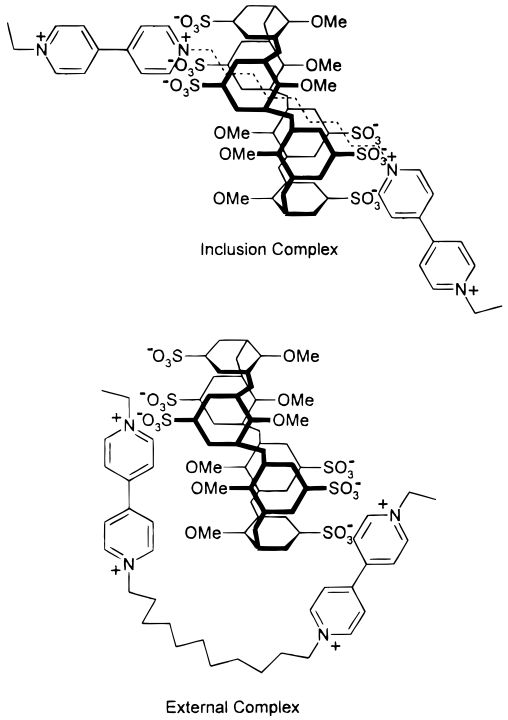
Methylviologen

The binding constant between methylviologen and $\mathbf{2}^{6-}$ was determined to be $K = 220 \pm 10$ M^{-1}. This value suggests that, for the dimeric viologen guests, the complexes with $\mathbf{2}^{6-}$ derive stability from interactions between the host and the *two* positively charged ends of the guest since their association constants are an order of magnitude higher than that measured with methylviologen. The involvement of this "chelate" effect might be the reason for the two dimeric guests having similar association constants with the calixarene host.

Methylviologen is actually much more charge dense than $V^+C_{11}V^+$ since it has the same two positive charges in a much smaller molecular area and should be expected to exhibit an association constant with the calixarene about equal to or larger than that for $V^+C_{11}V^+$. Indeed, we found that methylviologen binds more weakly to $\mathbf{2}^{6-}$ than both dimeric guests, which suggests that, for the calixarene host, multiple points of interaction are more important than greater charge density at a certain point. The similar association constant of the two dimeric viologen guests then is a manifestation of the multisite association being a crucial factor in these host−guest phenomena.

Before addressing in more detail the structure of the complexes of $\mathbf{2}^{6-}$ with the dimeric viologen guests, it is

Scheme 2



imperative to ascertain the conformation of the calixarene host itself in aqueous solution. The X-ray crystal structure of $\mathbf{1}^{8-}$ has been determined by Atwood and coworkers.[16] This host exhibits a partial cone conformation with three adjacent sulfonate groups pointing to one side of the cavity and the remaining three sulfonates pointing to the opposite end. At neutral pH two of the phenolic groups of this host are ionized, resulting in hydrogen bonds between each one of the phenolate oxygens and the two neighboring phenolic hydrogens.[16] These hydrogen bonds help rigidify the host structure, which is similar to that shown in Chart 1. We have recently determined the X-ray crystal structure of $\mathbf{2}^{6-}$ [with Co(III)sepulchrate as the counterion[17]] and found that, although the network of phenolic hydrogen bonds is obviously missing, the conformation of the host resembles the partial cone found with $\mathbf{1}^{8-}$. In the case of $\mathbf{2}^{6-}$ the sulfonates tend to fan away from one another more than in the unmethylated analog, but there are still three adjacent sulfonate groups pointing to one end of the molecule and the remaining three pointing to the other opening of the calixarene cavity.[17] It is then reasonable to assume that the partial cone conformation shown in Chart 1 for $\mathbf{2}^{6-}$ prevails in aqueous solution.

How do the dimeric viologen guests interact with the calixarene host? Two structures can be reasonably proposed for these complexes. Scheme 2 shows the two postulated structures for the tetracationic guest ($C_2V^{2+}C_{11}V^{2+}C_2$), but similar structures can be proposed for the dicationic guest ($V^+C_{11}V^+$). The first possibility (top of the scheme) is a true inclusion complex in which the host cavity is threaded by the long guest in such a way that the positive charges at the two ends of the guest structure are perfectly positioned to interact with the negative charges in each of the sides of the calixarene

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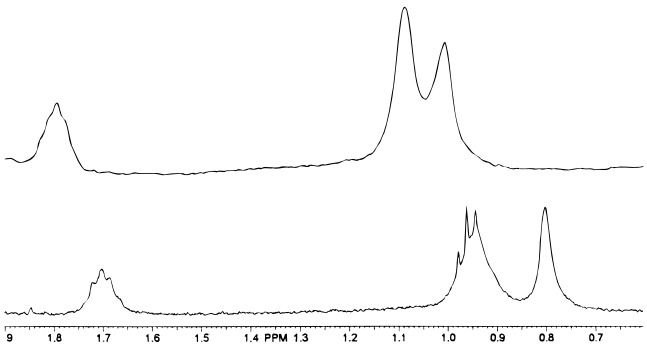

Figure 7. Aliphatic region of the ^{1}H NMR spectra of guest $V^+C_{11}V^+$ in the absence (top) and in the presence (bottom) of 5 equiv of $\mathbf{2}^{6-}$. The triplet superimposed on the peak at 0.95 ppm in the bottom spectrum is due to residual ethanol.

cavity. CPK models indicate that the size match is perfect, that is, the distance between the inner positive charges of the dimeric tetracationic guest (which is the same as the distance between the two positive charges in the dicationic guest) is very close to the distance between the two regions of negative charge in the partial cone conformation of $\mathbf{2}^{6-}$. This type of inclusion structure clearly affords a cogent explanation for the finding that the two dimeric guests exhibit similar binding constants with the calixarene host in spite of the obvious difference in their charges. Essentially, the two outside charges on the tetracationic guest are positioned two far away from the sulfonate negative charges on the host to provide any additional stabilization.

The second postulated structure in Scheme 2 is an external type of complex in which the guest wraps around the host in an attempt to optimize the electrostatic interactions between the two species. While this type of structure appears less likely for a number of reasons, it cannot be discarded without reservation. The key differences between the two types of postulated complex structures revolve around the placement of the undecyl chain connecting the two viologen subunits of the guest. Therefore, a close look at the complexation-induced changes observed in the aliphatic region of the ^{1}H NMR spectrum of the guest may yield important clues regarding the relative importance of the two postulated structures. Figure 7 shows the corresponding spectral changes for the dicationic guest. It is evident that complexation by $\mathbf{2}^{6-}$ causes shifts to higher field for all the aliphatic proton resonances of the guest. Although the magnitude of the complexation-induced shifts is moderate, the direction of the shift is certainly consistent with the undecyl chain being inserted in a cavity lined by the aromatic rings of the calixarene. The well known flexibility of the calix[6]arene cavity is probably responsible for the modest size of the observed shifts.

While NOESY and ROESY experiments could be extremely valuable to verify the inclusion nature of these complexes, they are made very difficult by the molecular weight of the complexes (NOESY) and by their tendency to precipitate at high concentrations (NOESY and ROESY). The dynamic and highly flexible nature of the calix[6]arene in water and its effects on complexation also exacerbates the situation. On the basis of the combination of all our binding data and the complexation-induced NMR spectral changes observed in the aliphatic chain connecting the two viologen subunits in the guests, we conclude that an inclusion structure best describes the

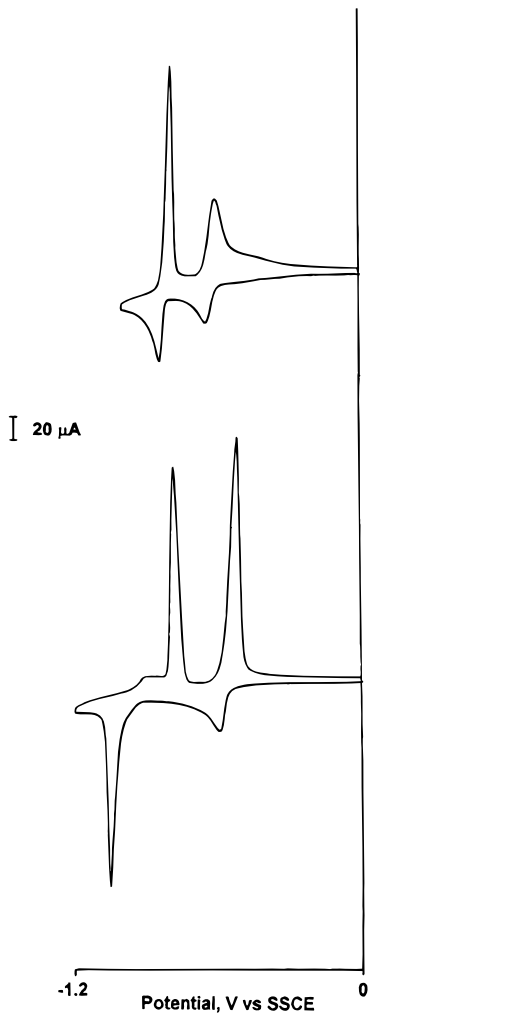

Figure 8. Cyclic voltammetric response of $C_2V^{2+}C_{11}V^{2+}C_2$ (1 mM in 0.2 M NaCl) on a glassy carbon working electrode, ν = 200 mV/s, in the absence of (top) and in the presence of 5 equiv of $\mathbf{2}^{6-}$ (bottom).

complexes $\mathbf{2}^{6-}$– $C_2V^{2+}C_{11}V^{2+}C_2$ and $\mathbf{2}^{6-}$– $V^+C_{11}V^+$. We are currently attempting to verify this hypothesis by preparing calixarene-based rotaxanes inspired by these novel inclusion complexes.

Continuing to examine the complementarity of the two hosts used in this study, we next tried to mimic with the calixarene host the pH switching situation found with the CD host. In this case, the calixarene should have a greater affinity for charged substrates over neutral ones. We chose 4,4′-bipyridine as the guest to maintain as much similarity as possible with the other guests used in this study. ^{1}H NMR spectra were taken of bipyridine in 0.2 M NaCl (aq) in the presence and absence of host $\mathbf{2}^{6-}$ under pH control. A situation very similar to that found with the CD host was seen. The calixarene shows some affinity for the neutral bipyridine as evidenced by upfield shifts of the bipyridine resonances ($\Delta\delta = -0.04$ ppm), possibly due to weak hydrophobic interactions in the cavity of the flexible host. Larger upfield shifts for the bipyridine resonances ($\Delta\delta = -0.08$) are seen, however, upon adding the host in the presence of enough DCl to protonate the nitrogens. These changes are reversible upon adding base. While the changes are not dramatic, more of a change should not be expected since the association constant for the permanently quaternized methyl viologen is only 220 M^{-1} with a complexation-

induced shift in the viologen proton resonances of only about −0.3 ppm. The protonated bipyridine in this case is in equilibrium with its neutral form thereby lessening the overall binding strength.

The cyclic voltammetry of the two dimeric viologen guests in the presence of $\mathbf{2}^{6-}$ showed similar electrode deposition spikes as for the CD experiments. Electrode deposition makes the interpretation of cyclic voltammograms risky at best, but one interesting feature of the electrochemistry of the guests in the presence of $\mathbf{2}^{6-}$ is that the deposition spikes actually increase as the calixarene is added. The complex of the viologens with the calixarene is much less soluble than either compound alone and will actually precipitate if the concentration is too high. This will increase the tendency for the complex to precipitate on the electrode surface as shown in Figure 8.

Conclusions

We have shown that two hosts, α-CD and a water soluble calix[6]arene, display distinctly complementary behavior toward several bipyridinium-based guests. The cyclodextrin threads past the bipyridinium units of the guests and strongly complexes the bridging alkyl chain of the dimeric guest $V^+C_{11}V^+$. This interaction can be substantially decreased by increasing the solvation of the viologen moieties with protonation. Spectroscopic and thermodynamic calorimetric data support these findings. The complexation properties of the calixarene host $\mathbf{2}^{6-}$, on the other hand, are dominated by electrostatic forces. This host also strongly associates with the dimeric viologen guests, but the attraction is electrostatic in nature, although the resulting complexes appear to be also of the inclusion type.

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