Reactive Pseudorotaxanes: Inclusion Complexation of Reduced Viologens by the Hosts β-Cyclodextrin and Heptakis(2,6-di-O-methyl)-β-Cyclodextrin

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Abstract: The complexation of three guests containing 4,4′-bipyridinium redox-active residues by β-cyclodextrin (β-CD) and its heptakis-(2,6-*O*-dimethyl) analogue (DM-β-CD) was investigated by means of voltammetric techniques. The three 4,4′-bipyridinium (viologen) derivatives used as guests were designed to be water-soluble in all three accessible oxidation states. The *N*-substituents chosen to enhance aqueous solubility were: 2-(2-(2-ethoxy)ethoxy)ethanol (guest $\mathbf{1}^{2+}$), 6-hexanoate (guest **2**), and 3-propanesulfonate (guest **3**). Detailed analysis of the voltammetric results by digital simulation techniques revealed that the oxidized forms of the guests did not interact appreciably with either CD host; the two-electron reduced guests formed extremely stable inclusion complexes, with association constants in the range $10^3-10^4\,M^{-1}$, while the cation radical forms exhibited intermediate binding affinities ($\approx 10^2\,M^{-1}$). In all cases, DM-β-CD was found to form more stable complexes than unmodified β-CD.

Keywords
cyclic voltammetry · cyclodextrins · host–guest chemistry · pseudorotaxanes · viologens

Introduction

The viologens[1] constitute an interesting class of compounds with well-established herbicidal properties which result from their ability to disrupt biological electron transfer processes. The 4,4′-bipyridinium nucleus of the viologens is dicationic in nature (V^{2+}) and undergoes two consecutive monoelectronic reductions, according to Equations (1) and (2). The first reduction is typically very fast and gives rise to an intense blue cation radical (V^+). Since viologen dications are often colorless, the color development associated with this electron transfer process is responsible for many of the proposed applications of viologens in electrochromic systems.[1] The second reduction is somewhat slower and yields a neutral species (V^0) of pale color.

$$V^{2+} + e \rightleftharpoons V^+ \quad (1)$$

$$V^+ + e \rightleftharpoons V \quad (2)$$

This simple electrochemistry is usually complicated in aqueous media by precipitation of the cation radical and/or the neutral viologen forms, as well as by the dimerization of the cation radical. Viologen precipitation arises because the reduced forms (V^+ and V^0) are less charged and, thus, more hydrophobic than the original dicationic form. The problem is more or less severe depending on factors such as the detailed structure of the viologen and medium composition. In addition to this, the cation radical has a marked tendency to dimerize according to Equation (3).[2] Cation radical dimerization and precipitation of the reduced forms have seriously limited the practical application of viologen electrochromic properties. Inclusion complexation by β-cyclodextrin (β-CDs) has been proposed as a possible mechanism to minimize these problems.[3] The water-soluble CD host[4] would solubilize the reduced form of the viologens while depressing the dimerization equilibrium constant by imposing a physical barrier to close encounters between cation radicals. About a decade ago, the fully reduced, uncharged form of methylviologen was shown to be bound by the host β-CD.[5] However, the V^{2+} and V^+ forms did not interact appreciably with this host. Our group has demonstrated that amphiphilic viologen dications interact with both α-CD and β-CD,[6] but the main binding site in these cases is the aliphatic chain on the viologen substituent. Several other studies have been published exploring CD–viologen interactions,[7–11] but very often the determination of quantitative results, such as thermodynamic or kinetic constants for the viologen–CD binding processes, has been prevented by the ubiquitous precipitation of the reduced viologen species.

$$2V^+ \rightleftharpoons V_2^{2+} \quad (3)$$

We decided to investigate viologen–CD binding interactions in a more quantitative fashion. To avoid the usual precipitation problems, we elected to use a series of three viologens ($\mathbf{1}^{2+}$, **2**, and **3**) that exhibit reasonable aqueous solubility in all

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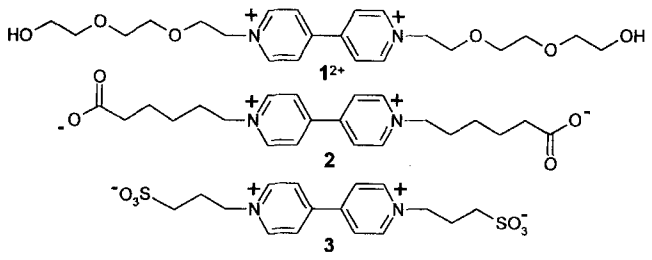
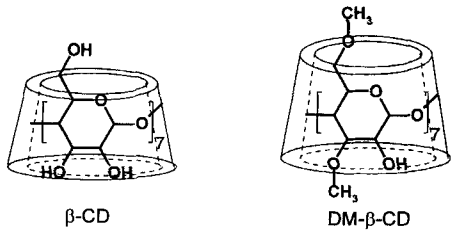


their oxidation states. The solubility of these viologens was obviously enhanced by the appropriate selection of their *N*-substituents. We chose ethyleneglycol (guest $\mathbf{1}^{2+}$), hexanoate (guest **2**), and propylenesulfonate (guest **3**) groups for reasons of synthetic accessibility. As hosts we decided to survey β-CD and its heptakis-(2,6-*O*-dimethyl) analogue (DM-β-CD) because we anticipated that they would present the best size match to the binding sites offered by the selected guests. This prediction was verified by voltammetric experiments with α-CD and γ-CD hosts, in which these two receptors proved to have only minor effects on the electrochemical behavior of the viologen guests.



The complexation between the viologen guests and the β-CD receptors was monitored by following the voltammetric behavior of the guest in the presence of variable concentrations of the CDs. The results were quantitatively interpreted by means of digital simulation techniques.

Experimental Section

Materials: β-Cyclodextrin (Amaizo, 99+ %) and DM-β-CD (Aldrich) were used without further purification. The latter material contains $\approx$30% heptakis-(2,6-*O*-dimethyl)-β-CD; the remaining material is higher and lower *O*-methylated homologues. 4,4′-Bipyridinium-*N*,*N*′-di-(propylsulfonate) (viologen guest **3**) was obtained from Sigma and used as received. 4,4′-Bipyridyl was purchased from Fluka; 2-(2-(2-chloroethoxy)ethoxy)ethanol and 6-bromohexanoic acid were supplied by Aldrich. Acetonitrile (Aldrich, 99.9+ %, HPLC grade) was dried by refluxing over CaH_2 and distilled under a nitrogen atmosphere. Deionized water was further purified by passage through a pressurized, 4-cartridge Barnstead Nanopure system until a final resistivity of 18 MΩcm was attained.

Synthesis of 4,4′-bipyridinium-N,N′-di-(2-(2-(2-ethoxy)ethoxy)ethanol) dichloride ($\mathbf{1}\cdot Cl_2$): 4,4′-Bipyridyl (0.5 g, 3.2 mmol) and 2-(2-(2-chloroethoxy)ethoxy)ethanol (4.0 g, 24 mmol) were stirred at 70 °C. NaI (50 mg) was also added as a catalyst. After 48 h, 30 mL of acetonitrile was added and the mixture was stirred for another 48 h. The resulting precipitate was filtered off, recrystallized from hot ethanol, and dried in vacuo to yield 0.60 g (38% yield) of very deliquescent dark yellow crystals. ^{1}H NMR (400 MHz, D_2O): δ = 3.46 (4H, t), 3.55 (8H, m), 3.61 (4H, t), 4.00 (4H, t), 4.83 (4H, t), 8.40 (4H, d), 9.00 (4H, d). Anal. calcd. for $C_{22}H_{34}N_2O_6Cl_2$: C, 53.55%; H, 6.95%; N, 5.68%. Found: C, 53.47%; H, 6.99%; N, 5.75%.

Synthesis of 4,4′-bipyridinium-N,N′-di-(carboxyhexane) dihexafluorophosphate ($\mathbf{2}\cdot(PF_6)_2$): 4,4′-Bipyridyl (1.0 g, 6.4 mmol) and 6-bromohexanoic acid (5.0 g, 25 mmol) were dissolved in 20 mL of acetonitrile and stirred at 70 °C for 24 h. A copious yellow precipitate was formed. After the solution was cooled to room temperature, the precipitate was filtered off and dried. The bromide viologen salt was then dissolved in the minimum possible volume of hot water and precipitated as the hexafluorophosphate salt by dropwise addition of a concentrated solution of NH_4PF_6. The resulting white precipitate was filtered off, recrystallized from hot water, and dried under vacuum to yield 4.1 g (93% yield) of pure hexafluorophosphate salt. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.44 (4H, m), 1.64 (4H, m), 2.03 (4H, m), 2.31 (4H, t), 4.61 (4H, t), 8.37 (4H, d), 8.90 (4H, d). Anal. calcd. for $C_{22}H_{30}N_2O_4P_2F_{12}$: C, 39.06%; H, 4.47%. Found: C, 39.18%; H, 4.35%.

Electrochemical Experiments: The electrochemical experiments were performed with a BAS 100 B/W electrochemical analyzer (Bioanalytical Systems, West Lafayette, IN). A glassy carbon working electrode (0.08 cm^2), a Pt counter electrode, and a home-made sodium chloride saturated calomel electrode (SSCE) were utilized in a single-compartment cell. The working electrode was polished with 0.05 μm alumina on a felt surface and rinsed with abundant water immediately prior to electrochemical experimentation. The experiments were conducted in 0.1 M phosphate buffer solutions (pH = 7) prepared with purified water. All solutions were deoxygenated by purging with nitrogen gas and maintained under an inert atmosphere during the electrochemical experiments. The viologen concentration was typically in the 0.3–1.0 mM range. The CD hosts were added to the solution in the electrochemical cell to yield the required concentrations. Aliquots from a concentrated CD stock solution were added to yield host concentrations lower or equal to that of the viologen guest. Weighted amounts of solid CD were added to reach higher host concentrations. The voltammetric data were analyzed by using digital simulations carried out with the Digi-Sim version 2.1 software package[12] (Bioanalytical Systems, West Lafayette, IN).

Results and Discussion

While guest $\mathbf{1}^{2+}$ is a dication, the other two surveyed viologens are zwitterionic at neutral pH due to the ionization of their terminal carboxylate and sulfonate functional groups. Thus, these two guests are better represented as **2** and **3** in their fully oxidized states. Under neutral pH, the voltammetric behavior of all three viologen derivatives is characterized by two consecutive, reversible monoelectronic reduction processes. Figure 1 shows a typical voltammogram obtained with guest **3** in 0.1 M phosphate buffer (pH = 7) solution. Similarly shaped voltammograms were recorded with the other two viologen compounds. The corresponding half-wave potentials ($E_{1/2}$) and the diffusion coefficients (D_{free}) measured for the three viologen guests are given in Table 1. Clearly, the nature of the sub-

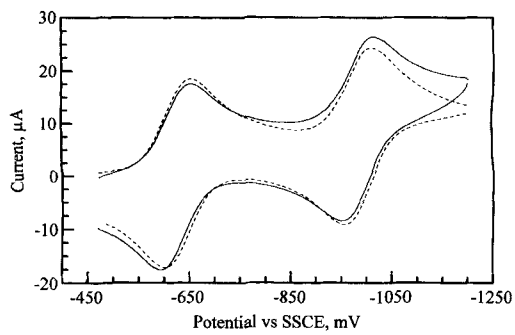


Figure 1. Cyclic voltammogram (0.1 Vs^{-1}) of a 0.5 mM solution of viologen **3** in a pH 7, 0.1 M phosphate buffer (solid line). The dotted line represents the simulated voltammogram. Lower values for $k_s/(D_{free})^{1/2}$ are equal to 64 s$^{-1/2}$ and 32 s$^{-1/2}$ for the first and second reductions, respectively. The half-wave potentials were taken as −0.634 and −0.998 V vs. SSCE.

Table 1. Voltammetric parameters for the surveyed viologen guests in 0.1 M phosphate buffer (pH = 7) solution at 25 °C.

Viologen	$E^1_{1/2}$ (ΔE_p) [a]	$E^2_{1/2}$ (ΔE_p) [b]	D_{free} ($cm^2 s^{-1}$) [c]
1^{2+}	−0.624 (63)	−0.980 (62)	8.0×10^{-6}
2	−0.695 (58)	−1.048 (71)	7.6×10^{-6}
3	−0.634 (55)	−0.998 (60)	1.0×10^{-5}

[a] Half-wave potential for the first reduction process expressed in Volts vs. SSCE. The value in parenthesis represents the potential difference in mV between the cathodic and anodic peak potentials measured at 0.1 Vs^{-1}. [b] Same as [a] for the second reduction process. [c] Diffusion coefficients determined from chronocoulometric experiments.

stituents on these viologens is sufficiently hydrophilic to impart aqueous solubility to all three oxidation states, thus, yielding perfectly reversible, diffusion controlled voltammetric behavior.

Figure 1 also shows a digitally simulated voltammogram for guest **3**. Obtaining a good fit between the experimental and simulated voltammogram is trivial in this case, and the pertinent simulation parameters are given in the figure caption. However, the simulation is explicitly plotted to show that, even in a case as simple as this one, the agreement between the experimental and simulated currents is rather poor in the potential region negative from −1.0 V. This is expected as the experimental currents in this potential range contain a contribution from solvent reduction ($2H^+ + 2e \rightarrow H_2$) which is not taken into account by the simulations.

The addition of either β-CD or DM-β-CD to the solution has a pronounced effect on the voltammetric behavior of all three viologen guests (see Figure 2 for a representative example). The first reduction wave is only slightly affected, exhibiting small positive shifts in the apparent half-wave potential

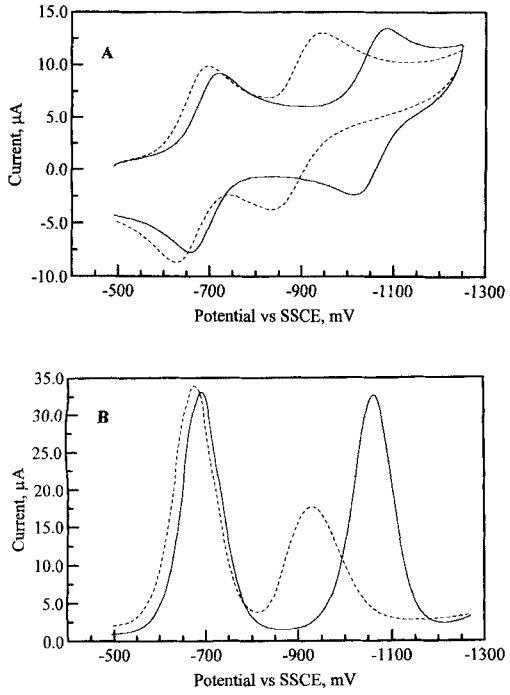


Figure 2. A: Cyclic voltammograms (0.1 Vs^{-1}) of a 0.5 mM solution of **2** in the absence (solid line) and in the presence (dotted) of 0.0125 M DM-β-CD in a pH 7, 0.1 M phosphate buffer. B: Osteryoung square-wave voltammograms of the same system recorded with a potential step of 4 mV, pulse amplitude of 25 mV, and frequency of 15 Hz.

($\Delta E^1_{1/2} < 15$ mV). The second reduction wave is much more strongly affected by the presence of CD and undergoes larger positive shifts in the $E_{1/2}$ value ($\Delta E^2_{1/2}$ as large as 160 mV). Interestingly, the presence of CD at moderate concentration levels (< 3 equiv) does not result in significant changes in the observed voltammetric current levels, although larger CD concentrations depress the currents associated with the second reduction process. The association of electroactive guests with CD hosts typically results in a significant current decrease. This has been previously observed with ferrocene derivatives and used to determine the corresponding binding constants.[13, 14] The magnitude of the voltammetric currents observed with Nernstian redox couples is generally determined by the diffusion coefficient of the initial form of the electroactive species, that is, the form present in solution at the beginning of the voltammetric scan. In the reported work with ferrocene derivatives,[13, 14] the initial form is strongly bound by β-CD, which causes a substantial reduction in the effective diffusion coefficient and a marked decrease in the current levels in the presence of moderate host concentrations. By contrast, the relative insensitivity of the voltammetric currents to the presence of CD hosts that we observe in this work (especially true for the first reduction process) indicates that the initial (fully oxidized) form of all three guests does not interact appreciably with the CD hosts. This conclusion is reinforced by ^1H NMR spectroscopic experiments showing that the chemical shifts of the viologen proton resonances are unchanged by the addition of 2 to 3 equiv of either CD (data not shown). Therefore, none of the three guests are bound to a detectable extent by either CD receptor before reduction of the viologen nucleus.

Uptake of electrons by the 4,4′-bipyridinium residue is anticipated to enhance its interaction with CD hosts. As positive charge is removed from the bipyridinium residue, its hydrophobic character and the stability of its CD inclusion complexes should increase. Therefore, the neutral, two-electron reduced viologen form should be a better guest for β-CD than the cation radical form, which in turn should be better than the essentially noninteracting dication form. These predictions are in agreement with the voltammetric results in the presence of either CD. The small positive shifts in the $E_{1/2}$ value of the first reduction process (V^{2+}/V^+) observed upon CD addition reveal that the product of this reduction (the cation radical form) interacts with the CD more strongly than the initial, dicationic form. Similarly, the much larger, CD-induced positive shifts observed in the half-wave potentials for the second reduction process (V^+/V^0) indicate that the fully reduced, neutral species is complexed much more strongly by either CD than the cation radical form. Figure 2 (top) shows typical cyclic voltammetric (CV) results obtained with guest **2** and DM-β-CD. Figure 2 (bottom) shows the CD-induced effects on the square-wave voltammograms (SWV) of the same guest. Qualitatively similar results were obtained with all other host–guest combinations. Although both CV and SWV can be used to investigate the binding interactions between the viologen guests and the CD hosts, we selected CV because of the capabilities and limitations of the simulation software used.

These systems afford an excellent example of *redox control on the strength of host–guest interactions*.[15] A pictorial representation of the relationship between the oxidation state of the

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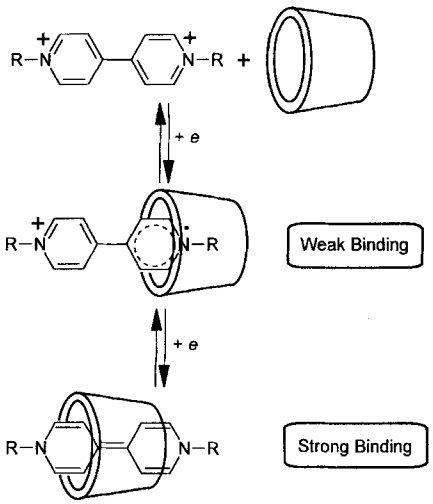
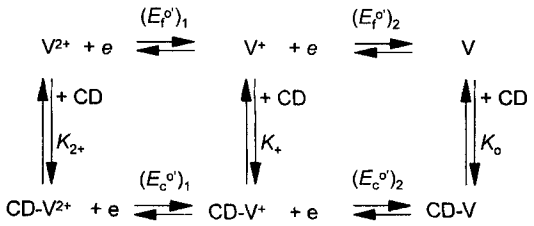
viologen guest and its binding affinity to the β-CD hosts is given in Scheme 1. The morphology of the viologen guests leads (upon two-electron reduction) to the formation of inclusion complexes in which the CD host is "threaded" by the guest. These inclusion



Scheme 1. Redox control on the CD binding of viologen guests.

complexes have been termed *pseudorotaxanes*[16] since they can be considered as precursors of rotaxanes. Reaction of the terminal functional groups on the guest with bulky "stopper" molecules should lead to the trapping of the threaded CD, yielding the corresponding rotaxane.[16] A unique characteristic of the viologen–CD pseudorotaxanes investigated here is that the complexed subunit (V^0) is highly reduced, and, thus, extremely reactive. If rotaxanes can be assembled around these reactive residues, their chemical reactivity is likely to be affected by strong and still largely unexplored supramolecular effects.

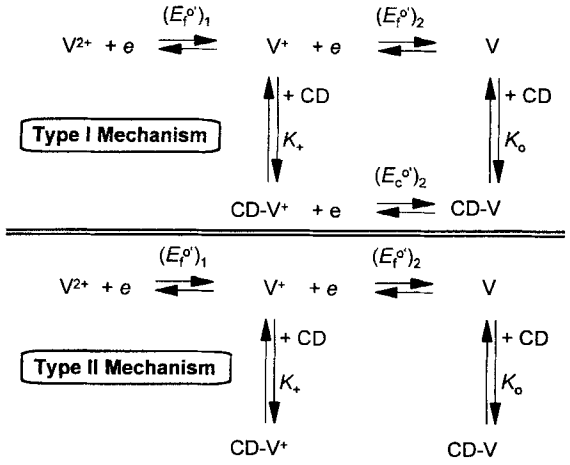
In order to interpret the voltammetric data in a quantitative fashion and extract thermodynamic parameters for the corresponding binding equilibria it is necessary to postulate a detailed mechanism for the electrochemical and chemical processes involved. An acceptable mechanism should provide simulated voltammograms that closely approach the experimental voltammograms. Furthermore, when such a mechanism is identified, the optimization of the fit between the simulated and experimental voltammetric data will allow the estimation of the thermodynamic parameters for the complexation equilibria involving the three oxidation states of the viologen guests and the CD hosts. Scheme 2 shows all the electrochemical and chemical equilibria relevant to the interpretation of the voltammetric data. This mechanism can be readily simplified by considering



Scheme 2. Electrochemical and chemical equilibria involved in the reduction of viologen guests in the presence of CD hosts.

that the interaction between the fully oxidized viologen form (V^{2+}) and the CD is too weak to be observed experimentally, and therefore, the corresponding association constant K_{2+} can be safely assumed to be negligible. Therefore, we conclude that the complex CD–V^{2+} does not reach appreciable concentrations during our electrochemical experiments and can be disregarded.

Our voltammetric results indicate that the association constants of the CD hosts with the cation radical and fully reduced viologen forms (K_+ and K_o, respectively) are both significant. The only unresolved mechanistic issue is whether the corresponding complexed viologen forms (CD–V^+ and CD–V) can exchange electrons directly or not. In other words, is the electrochemical equation at the bottom right of Scheme 2 truly necessary to describe the electrochemical behavior of the viologen guests in the presence of CD hosts? An affirmative answer would imply that encapsulation by the CD hosts does not preclude the viologen guests from engaging directly in electron transfer reactions. Alternatively, CD encapsulation may hinder electron transfer to the point that it only takes place after dissociation of the inclusion complex. The mechanisms that result from each one of these alternatives are represented in Scheme 3



Scheme 3. Type I and Type II mechanisms.

and arbitrarily labeled Type I (allowing direct electron transfer to and from inclusion complexes) and Type II (forbidding electron transfer to and from inclusion complexes). Several years ago, Evans and co-workers investigated the voltammetric behavior of ferrocenecarboxylate in the presence of β-CD.[13] They concluded that the CD–ferrocenecarboxylate inclusion complex does not undergo oxidation directly; *electrochemical oxidation takes place only after dissociation of the complex*. We have reached similar conclusions in an investigation of CD complexation of a series of water-soluble, positively charged ferrocene derivatives.[14] Furthermore, the rate of electron transfer reactions of fully encapsulated redox centers is also the subject of current investigations in our group.[17]

What key experiments can be performed to decide which one of these two possible mechanisms better describe the voltammetric data? Following the lead of Evans and co-workers,[13] we decided to investigate the voltammetric behavior of viologen–CD solutions at fast scan rates. By increasing the scan rate, the

time scale of the voltammetric experiments is shortened to the point that it approaches the lifetime of the inclusion complexes. Therefore, if the inclusion complexes are capable of direct electron transfer, the voltammetric behavior should not be affected much. On the other hand, if complex dissociation must precede the electron transfer, one would expect to see substantial current reductions as the availability of the electroactive material at the electrode surface is limited by the kinetics of the dissociation reaction.

Figure 3 shows the voltammetric response recorded (at a scan rate of 3.0 Vs^{-1}) with guest **2** in the presence of 30 equiv of DM-β-CD (solid line). The most interesting feature of this

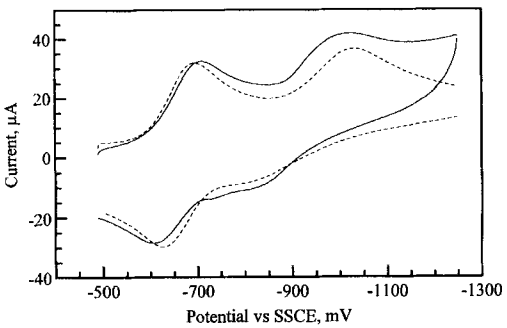


Figure 3. CV (3 Vs^{-1}) of a 0.5 mM solution of viologen **2** after addition of 0.015 M DM-β-CD (solid line) in pH 7, 0.1 M phosphate buffer and simulated voltammogram (dotted) at the same scan rate. Lower values for $k_s/(D_{free})^{1/2}$ are equal to 72 $s^{-1/2}$ and 36 $s^{-1/2}$ for the first and second reductions, respectively. $K_+ = 1 \times 10^2\,M^{-1}$. $K_o = 7 \times 10^4\,M^{-1}$. The association rate constants for both complexation reactions were taken as $k_a = 8 \times 10^8\,M^{-1}s^{-1}$. $D_{complex}/D_{free} = 0.46$.

voltammogram is the almost complete disappearance of the anodic peak corresponding to the oxidation from the fully reduced form to the cation radical ($V^0 \rightarrow V^+$). Considering that the fully reduced form of the viologen guest is the most strongly bound by the CD host, the substantial flattening of its oxidation peak at fast scan rates is strong evidence for the prevalence of a Type II mechanism.

Further support for this hypothesis is provided by the simulated voltammograms (at 3.0 Vs^{-1}) shown in Figure 4. The dotted line voltammogram corresponds to the behavior expected if the inclusion complexes do not engage directly in electrochemical processes, while the continuous line voltammogram would be obtained if the inclusion complexes reacted directly at the

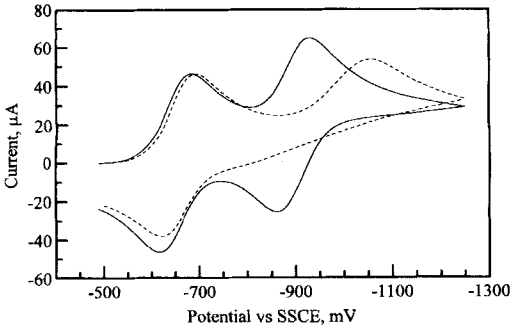


Figure 4. Simulated voltammograms calculated with Type I mechanism (solid line) and Type II mechanism (dotted) at 3 Vs^{-1} for a 0.5 mM solution of **2** in the presence of a 50-fold excess of cyclodextrin. Parameters used in the simulations are similar to those given in Figure 3.

electrode surface. As previously shown in Figure 3, the voltammetric behavior observed in our fast scan rate experiments is very close to that represented by the dotted line simulation, thus supporting a Type II mechanism. We thus conclude that *the surveyed viologen guests do not engage directly in heterogeneous electron transfer reactions when included by either β-CD or DM-β-CD hosts*. In particular, the fully reduced form of these viologen guests, which is strongly bound by either host, is not electrochemically oxidized when it is encapsulated inside the CD. Our data suggest that dissociation of the host–guest complex must precede the oxidation to the cation radical form.

At slower scan rates (<1 Vs^{-1}), the two mechanisms afford similar simulations, which reproduce satisfactorily the observed voltammetric behavior when appropriate values for the binding constants K_+ and K_o (see Scheme 2 and 3 for definitions) are used. For instance, Figure 5 shows the response obtained (at

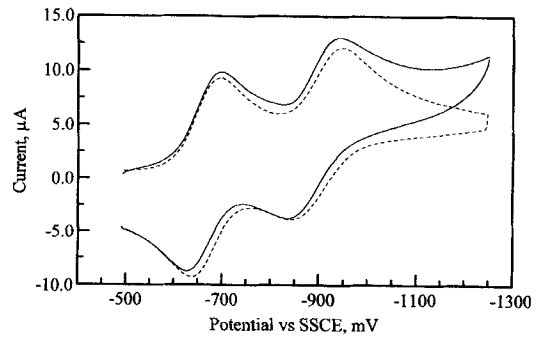


Figure 5. CV (0.1 Vs^{-1}) of a 0.5 mM solution of viologen **2** after addition of 0.0125 M of DM-β-CD (solid line) in pH 7, 0.1 M phosphate buffer. The dotted line is a simulated voltammogram obtained by using parameters similar to those given in Figure 3.

0.1 Vs^{-1}) with viologen guest **2** in the presence of 25 equiv of DM-β-CD and the corresponding simulation (Type II mechanism). Notice that the simulation reproduces the experimentally observed increase in ΔE_p values for the V^+/V^0 redox couple, which is caused by the CD complexation reactions, not by slower rates of heterogeneous electron transfer. The simulation obtained using a Type I mechanism (not shown) is equally acceptable in this case.

As discussed before, by optimizing the fit between simulated voltammograms generated with the Type II mechanism and the experimental voltammograms we can determine the binding constants K_+ and K_o. This approach yields the thermodynamic values given in Table 2. The quality of the reported binding constant values can be assessed by checking the fit between

Table 2. Association constants (M^{-1}) between the viologen guests and the CD hosts measured at 25 °C in 0.1 M phosphate buffer.

Guest	Constant	Host	
		β-CD	DM-β-CD
1^+	K_+	5×10^1	5×10^1
1	K_o	6×10^3	2×10^4
2^-	K_+	9×10^1	1×10^2
2^{2-}	K_o	2×10^4	7×10^4
3^-	K_+	5×10^1	7×10^1
3^{2-}	K_o	7×10^3	1×10^4

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simulated and experimental voltammetric data as a function of CD concentration. Acceptable values for the two constants relevant to a given host–guest combination should provide consistently good fits throughout the entire range of CD concentrations surveyed in the experiments. A convenient and simple way to test the fit is to compare the apparent half-wave potentials for the second reduction process (V^+/V^0), as this potential is much more strongly affected by the presence of the CD hosts than the V^{2+}/V^+ process. Figure 6 shows the experimentally determined

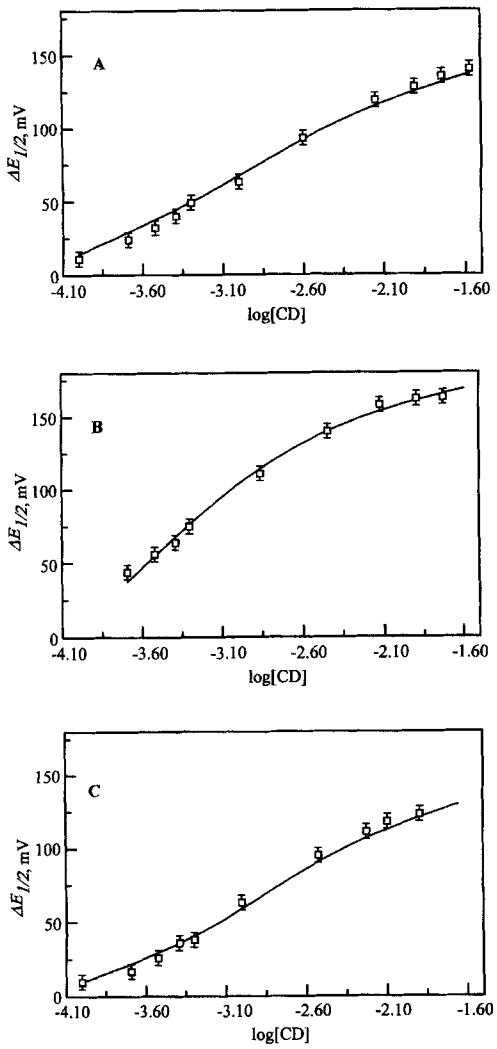

Figure 6. Plots of the CD-induced half-wave potential shifts ($\Delta E_{1/2}$) for the second reduction of viologens $\mathbf{1}^{2+}$, **2**, and **3** (graphs A, B, and C, respectively) as a function of concentration of added DM-β-CD. Simulated values, continuous line; □, experimental results with 10 mV error bars. Experimental conditions are similar to those given in previous figures. Values of diffusion coefficients for each viologen are taken from Table 1 and the lower values for the heterogeneous rate constants k_s are equal to 0.2 and 0.1 cm s^{-1} for the first and second reduction processes, respectively. K_+ and K_o values are those given in Table 2. All other parameters for the simulations were similar to those used in Figure 3.

shifts in the $E^2_{1/2}$ values for each one of the viologen guests in the presence of variable DM-β-CD concentrations. In each plot, the continuous lines were drawn by using the corresponding potential values obtained from simulations based on the K_+ and K_o values reported in Table 2. As can be seen, the simulations reproduce within the error margins the experimental $E_{1/2}$ values throughout the entire range of host concentrations. Similar results (data not shown) were obtained for the three viologen guests and the host β-CD. In the case of DM-β-CD, its higher aqueous solubility (compared to β-CD) permits the investigation of a wider concentration range. In all cases, the agreement between the simulated and experimental $E^2_{1/2}$ values is very good. On these grounds, the quality of the binding constant values reported in Table 2 seems to be satisfactory and comparable to that of values determined by more traditional procedures. We estimate the error margin of these binding constants to be smaller than 20%.

The predominance of the Type II mechanism means that, at fast scan rates, the voltammetric data contain information on the kinetics of the association and dissociation steps involving the CD hosts and the two-electron reduced forms of the viologen guests. The best fit to fast scan rate voltammograms, such as that shown in Figure 3, were obtained by using association rate constants (k_a) of around 8×10^8 M^{-1} s^{-1}. Therefore, the dissociation rate constants are in the order of 10^4 s^{-1}, which are perfectly comparable to other values previously reported for CD inclusion complexes.[13] The charged groups at the ends of guests **2** and **3** do not seem to slow down significantly the association/dissociation kinetics of the β-CD inclusion complexes.

Inspection of the values in Table 2 reveals several interesting trends. First, the K_o values are substantially higher than the K_+ values. Indeed, this was anticipated from the charges associated with each one of the viologen oxidation states. The inclusion complexes of the fully reduced forms are expected to be substantially more stable than those of the cation radicals. In addition the electron density and polarizability of the former are also higher, thus, favoring the induced dipole–dipole interactions, which are at the core of the stabilization of CD inclusion complexes. Second, every oxidation state of the viologen guests exhibits a higher binding affinity with DM-β-CD than with β-CD. This binding selectivity was also anticipated owing to the linear character of these viologen guests and the well-known preference of biphenyl-type guests for the deeper cavity of DM-β-CD.[18] Finally, it is also instructive to compare the relative stabilities of the three most stable complexes formed in our experiments, that is, those between the fully reduced viologens ($\mathbf{1}$, $\mathbf{2}^{2-}$, and $\mathbf{3}^{2-}$) and DM-β-CD. As represented in Scheme 1, in all these inclusion complexes the cavity of the CD host is threaded by the viologen guest, yielding pseudorotaxane structures. The K_o values for **1** and $\mathbf{3}^{2-}$ are rather similar and certainly lower than that for guest $\mathbf{2}^{2-}$. The structure of $\mathbf{2}^{2-}$ optimizes the stability of the complex as it affords a very well defined binding site (the two-electron reduced bipyridinium residue) which extends itself along the two covalently attached aliphatic chains. In the inclusion complex, the solvation of the terminal carboxylate groups is essentially unaffected by the threaded CD. This is probably not the case in the inclusion complex formed between DM-β-CD and $\mathbf{3}^{2-}$, in which the solvation of the terminal sulfonate groups may be somewhat disrupted by the threaded CD host, since the sulfonate groups are closer to the bipyridinium nucleus. Guest **1** probably represents an intermediate situation. In any instance, the binding constant values between the fully reduced guests and DM-β-CD are remarkably large.

Conclusions

We have demonstrated that β-CD and DM-β-CD hosts form extremely stable inclusion complexes (pseudorotaxanes) with two-electron reduced viologen derivatives. The viologen guests were designed to enhance the water-solubility of all their oxidation forms and prevent the usual precipitation of reduced viologen species, which has plagued most previous studies of viologen–CD interactions. The appropriate substituent functionalization of the viologen guests permitted the full characterization of their interactions with CD hosts by voltammetric techniques. The pseudorotaxane structures and high binding constants of the inclusion complexes formed between the CD receptors and the fully reduced viologens make them ideal candidates for the preparation of novel rotaxanes containing highly reactive, encapsulated residues.

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