Bimodal Cyclodextrin Complexation of Ferrocene Derivatives Containing *n*-Alkyl Chains of Varying Length

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Received April 4, 1990

The complexation of alkyldimethyl(ferrocenylmethyl)ammonium salts, where the alkyl group is methyl ($FC_1^+PF_6^-$), heptyl ($FC_7^+Br^-$), or hexadecyl ($FC_{16}^+Br^-$), by α-, β-, and γ-cyclodextrin was studied by electrochemical methods and high-field ^1H NMR spectroscopy. The apparent diffusion coefficients of all the ferrocene derivatives were found to decrease upon addition of any cyclodextrin (CD). The oxidation potential of the ferrocene derivatives was substantially shifted to more positive values in the presence of β-CD; however, α-CD and γ-CD only caused slight shifts. FC_1^+ and FC_7^+ form 1:1 complexes with α-CD, β-CD, and γ-CD, respectively. FC_{16}^+ forms a 1:2 complex with α-CD and 1:1 complexes with β-CD and γ-CD. Binding constants between FC_1^+, FC_7^+, and all three cyclodextrins were determined from the variation of the diffusion coefficient as a function of CD concentration. These results suggest that α-CD interacts with the aliphatic region of the derivatives, while β-CD and γ-CD interact with the ferrocene subunit. The dual mode of CD binding to these derivatives was used to build small supramolecular aggregates in which a ferrocene derivative directs several CD hosts to bind at different molecular regions. This was exemplified by the isolation of a quaternary complex between FC_{16}^+, α-CD, and β-CD, which exhibited the stoichiometric ratio (1:2:1) predicted in terms of the individual interactions of this ferrocene derivative with α-CD and β-CD, respectively.

Introduction

Cyclodextrins[1,2] are macrocyclic glucopyranose oligomers having at least 6 units linked together by α-(1,4) linkages. The three unmodified cyclodextrins (CD's) are α-cyclodextrin (α-CD, 6 glucopyranose units), β-cyclodextrin (β-CD, 7 glucopyranose units), and γ-cyclodextrin (γ-CD, 8 glucopyranose units). Their most prominent structural feature is the rigid, well-defined cavity that gives CD's the appearance of molecular buckets. The secondary 2- and 3-hydroxyl groups are located around the wider opening of the cavity while the primary 6-hydroxyl groups are situated on the narrower opening. Both sets of hydroxyl groups are responsible for the solubility of CD's in aqueous media.[2,3] The hydrophobic inner surface of the cavity is formed by the oxygen atoms of the glucopyranosidic linkages and the hydrogen atoms at the 3- and 5- positions. The hydrophobic nature of the cavity is usually invoked to explain the promiscuous binding properties of CD's in aqueous media. CD's act as molecular hosts to a wide variety of guest species, from certain polar compounds to small inorganic ions to nonpolar compounds. In all cases, the guest is at least partially included in the CD cavity, that is, the complexes are of the inclusion type.

CD's have been frequently used as enzyme models presumably because their hydrophobic and well-defined cavities resemble enzyme binding sites. In this context, the research efforts of Breslow[4-7] and Tabushi[8-11] deserve mention because of their extensive and elegant utilization of modified and unmodified CD hosts for the modeling of enzyme action. These studies and others have shown that CD's act as rather indiscriminate hosts in aqueous solutions although the rigidity of the cavity greatly influences complexation and introduces a certain degree of size selectivity in the binding process.

Although the literature on CD's is very extensive, not many reports can be found on the interactions of CD's and surfactant molecules. The available reports focus primarily on the interactions between CD's and single-chain surfactants.[12-20] Initially, the experimental data were interpreted by assuming the formation of 1:1 inclusion complexes between the lipophilic (alkyl) tail of the surfactant and the CD host. In the last three or four years evidence is mounting to support the idea that more than one CD receptor may bind to a lipophilic hydrocarbon chain of sufficient length.[18-20]

Our group's interest lies in the study of the effects of cyclodextrin complexation on the properties of surfactants containing a covalently attached electroactive group. Previously, we have reported the effect of α-CD and β-CD on the aggregation behavior and electrochemical properties of two asymmetric viologen compounds.[21,22] In this paper, we report on the interactions of several ferrocene derivatives and unmodified CD's. Ferrocene was selected as the electroactive subunit due to its simple oxidative electrochemistry. Furthermore, ferrocene is a well known CD substrate. Harada and Takahashi[23,24] reported that β-CD and γ-CD form 1:1 stoichiometric inclusion compounds with ferrocene and its derivatives, while α-CD forms 2:1

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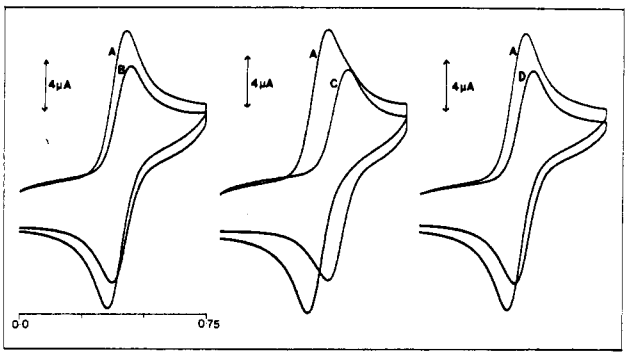
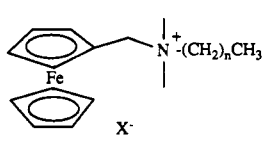


Figure 1. Cyclic voltammograms obtained on a GC electrode immersed in a 50 mM NaCl solution also containing (A) 1.0 mM $FC_7^+Br^-$, (B) 1.0 mM $FC_7^+Br^-$ + 18 mM α-CD, (C) 1.0 mM $FC_7^+Br^-$ + 12 mM β-CD, (D) 1.0 mM $FC_7^+Br^-$ + 18 mM γ-CD. Scan rate = 50 mV/s.

complexes with ferrocene and its monosubstituted derivatives. Electrochemical studies on the interactions of ferrocene carboxylic acid (FCAH) with β-CD, performed by Evans et al.,[25,26] showed that this CD forms inclusion complexes with the FCA^- anion although no evidence was found for CD complexation of its oxidized form. Other reports on the binding of ferrocene derivatives by β-CD are also available.[27-31] Molecular mechanics calculations on the docking interactions between ferrocene and several cyclodextrins have also been published recently.[32,33]

The structures of the ferrocene derivatives used here display hydrocarbon chains of varying length. Thus, these derivatives may be considered as potential multisite substrates for CD complexation since they have two regions of marked hydrophobic character: the ferrocene moiety and the hydrocarbon chain.



n=0, $FC_1^+X^-$ (X^- = PF_6^-)

n=6, $FC_7^+X^-$ (X^- = Br^-)

n=15, $FC_{16}^+X^-$ (X^- = Br^-)

Besides varying the length of the alkyl chains in the ferrocene derivatives, we were also quite interested in addressing the effects of the size of the CD cavities on the binding interactions. Therefore, all three unmodified CD's were used to assess the preference of binding sites and the stability of the complexes as a function of cavity size. In this study, we utilized a rather infrequent combination of techniques: 400 MHz ^1H NMR spectroscopy and voltammetry, which allowed us to determine effectively the predominant binding sites for each ferrocene–CD pair.

Results and Discussion

Voltammetric Characterization of CD Complexation. The voltammetric behavior of both FC_1^+ and FC_7^+ is characterized by the reversible oxidation of the ferrocene group. Figure 1A shows the cyclic voltammogram of a 1.0 mM $FC_7^+Br^-$ solution also containing 50 mM NaCl as the supporting electrolyte. The observed voltammetric behavior clearly corresponds to that expected from a compound containing the ferrocene moiety. Figure 1 also demonstrates the effects of α-CD, β-CD, and γ-CD on the electrochemical behavior of the FC_7^+ cation. All cyclodextrins cause the peak currents to decrease indicating that a fraction of the ferrocene-based cation FC_7^+ exists as the more slowly diffusing inclusion complex. Reduction in peak currents could also result from an increase of solution viscosity with a corresponding decrease in the diffusion coefficients. However, we verified that the viscosity changes are negligible and cannot account for the observed decrease in the diffusion coefficient values. Figure 1 also shows that the reversible shape of the voltammograms is retained in all cases.

The oxidation and reduction peak potentials of FC_7^+ are shifted substantially to more positive values by the addition of 12.0 mM β-CD (see Figure 1C) while addition of 18 mM α-CD (Figure 1B) or γ-CD (Figure 1D) caused only a small shift in the same direction. The voltammetric changes observed with $FC_1^+PF_6^-$ and $FC_{16}^+Br^-$ in the presence of the three unmodified CD's are similar to those depicted in Figure 1, i.e., β-CD substantially shifts the half-wave potential for the oxidation of the ferrocene derivatives while the other two CD's only cause small shifts. The presence of CD decreases the apparent diffusion coefficient of the ferrocene derivative for all ferrocene–CD pairs, suggesting that complexation takes place in all cases. In the instance of FC_{16}^+, the voltammetric behavior in CD-free solution is not diffusion-controlled due to adsorption and micellization of this hydrophobic cation.[34] However, in the presence of a 4-fold excess of any CD, the voltammetric behavior exhibits all the characteristics of diffusion control, reflecting the diminished hydrophobic character of the CD complexes as compared to the free cation. We have reported similar CD-induced solubilization effects with amphiphilic viologens.[21,22]

The observed potential difference between the oxidation and the reduction peaks for all ferrocene derivatives in the presence of excess β-CD is about 70 mV at moderate scan rates (20–100 mV/s) whereas the expected value for a reversible electrochemical process in which none of the redox species is involved in chemical reactions is 57 mV. This same behavior was observed by Evans et al. in voltammetric studies of FCA^- in the presence of β-CD.[25] These authors conclusively demonstrated that the larger peak-to-peak splitting is due to the prevalence of a CE mechanism (a chemical step followed by an electrochemical step), i.e., the electrochemical oxidation of the ferrocene derivative occurs only after the dissociation of the CD-inclusion complex. Thus, the inclusion complex hinders the electron-transfer process, suggesting that the β-CD cavity engulfs the electroactive ferrocene subunit. Since our electrochemical results in the presence of β-CD parallel those reported by Evans and co-workers for the FCA^-/β-CD system, we conclude that the same mechanism prevails for the oxidation of our ferrocene derivatives in the presence of β-CD.

Cyclic voltammetry of all three ferrocene derivatives in the presence of α-CD shows no evidence for chemical reactions coupled to the electron transfer process. Thus, in contrast to β-CD, the potential difference between the oxidation and reduction peaks remains essentially constant at 60 mV throughout the 1–18 mM α-CD concentration

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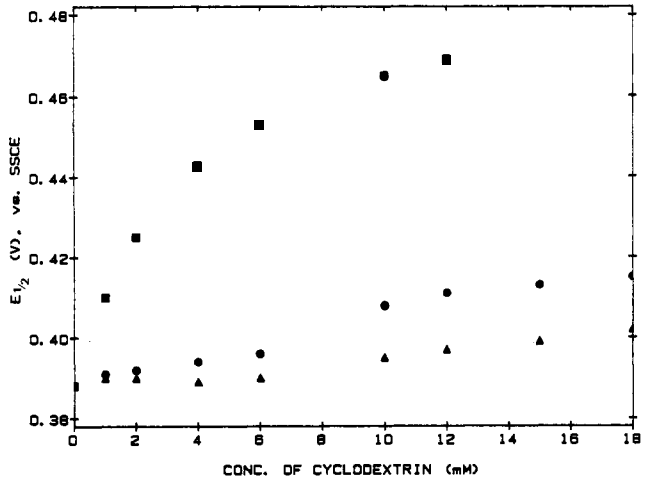

Figure 2. Dependence of the half-wave potential for the oxidation of FC_7^+ on the concentration of cyclodextrins. (▲) α-CD. (■) β-CD. (●) γ-CD.

range. Similarly, the presence of γ-CD did not alter the observed peak potential difference in the voltammetric experiments. Two interpretations are consistent with these results: (i) The interaction between these CD's and the ferrocene derivatives takes place in a molecular region removed from the electroactive ferrocene subunit so that the electron-transfer process remains unaffected, of (ii) the kinetics of the complexation and decomplexation processes are very fast so that no effects are observed on the voltammetric behavior at the rather slow scan rates used in this study.

In order to assess the variation of the half-wave potential as a function of α-CD, β-CD, or γ-CD concentration we recorded cyclic voltammograms at slow scan rates in order to maintain equilibrium conditions as the potential was gradually changed. Apparent half-wave potentials were determined from the mean of the anodic and cathodic peak potentials. Figure 2 shows that, even at the lowest concentration of β-CD (1.0 mM), there is a considerable shift in half-wave potential, while addition of an 18-fold excess of α-CD or γ-CD causes a much smaller shift. These findings also support the interaction of β-CD with the electroactive ferrocene subunit resulting in strong effects on the half-wave potential. In the cases of α-CD and γ-CD, either the interactions are weaker or take place without disrupting the heterogeneous electron transfer process, i.e., the binding occurs in a molecular region removed from the ferrocene subunit.

Determination of FC–CD Binding Constants. The diffusion coefficients of the complexes were determined using rotating disk voltammetry (RDV) measurements. Plots of anodic current in the limiting region (at a potential positive from the half-wave value for the ferrocinium/ferrocene couple) vs the square root of angular velocity were linear (see Figure 3), as expected for a diffusion-controlled process. Indeed, the diffusion coefficient can be calculated from the slope of these plots. The variations in the apparent diffusion coefficient as a function of cyclodextrin concentration permit the determination of the binding constants for the inclusion complexes as discussed in the Experimental Section. Figure 4 shows the experimental D_{app} vs CD concentration data points obtained for the FC_1^+ and FC_7^+ systems. The solid lines were calculated with the K and D_c values given in Table I, which were those affording the best fits to the experimental points. Binding constants for FC_{16}^+–CD complexes could not be obtained by this method because the complicated voltammetric behavior of this hydrophobic cation precluded the

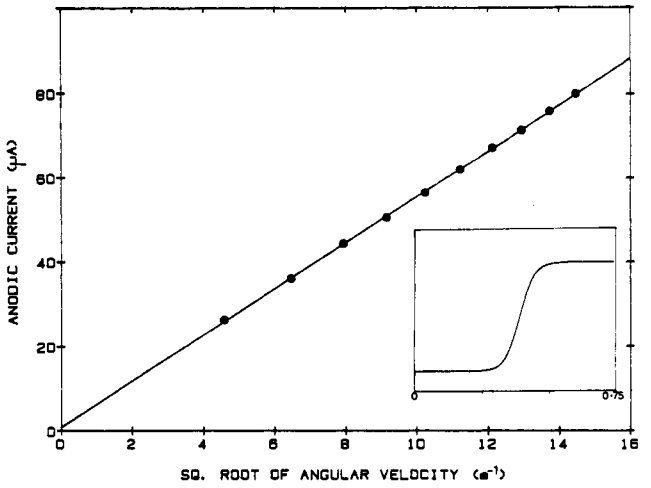

Figure 3. Levich plot obtained on a GC electrode immersed in a 50 mM NaCl solution also containing 1.0 mM $FC_7^+Br^-$ and 4.0 mM γ-CD. Inset: RDV voltammogram obtained in the same solution. Scan rate = 50 mV/s. Rotation rate = 2000 rpm.

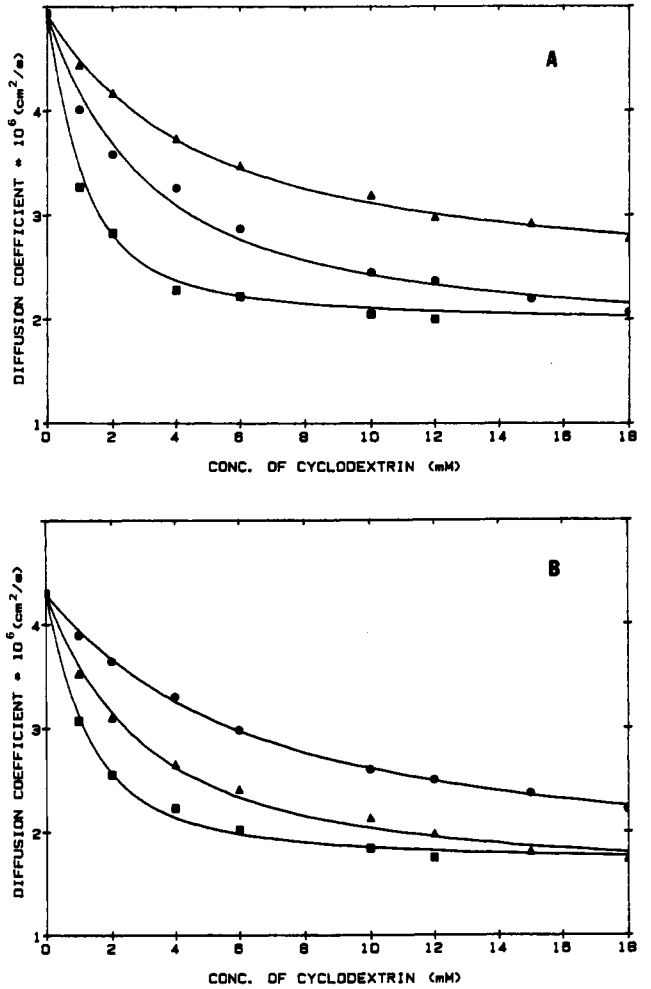

Figure 4. Apparent diffusion coefficient of (A) FC_1^+ and (B) FC_7^+ as a function of CD concentration. (▲) α-CD. (■) β-CD. (●) γ-CD. The solid lines were obtained with the values given in Table I.

determination of the diffusion coefficient in the absnece of CD hosts. The diffusion coefficients obtained for free and uncomplexed FC_1^+ and FC_7^+ are close to those reported before for structurally similar compounds or complexes.[25] The apparent diffusion coefficients of FC_1^+ and FC_7^+ drop quite rapidly with the initial β-CD additions (Figure 4), indicating that the complexes are more stable than those formed by α-CD and γ-CD. This is indeed

Table I. Association Constants, Stoichiometries, and Diffusion Coefficients of CD Complexes of Ferrocene Derivatives

derivative	D_f, cm²/s	CD	D_c, cm²/s	K, M⁻¹	(FC:CD)
		α	2.3×10^{-6}	240 ● 15	1:1[a]
FC_1^+	4.9×10^{-6}	β	1.9×10^{-6}	1900 ± 180	1:1[a]
		γ	1.8×10^{-6}	400 ± 25	1:1[a]
		α	1.5×10^{-6}	420 ± 30	1:1[a]
FC_7^+	4.3×10^{-6}	β	1.7×10^{-6}	1400 ± 130	1:1[a]
		γ	1.6×10^{-6}	170 ± 10	1:1[a]
		α			1:2[b]
FC_{16}^+		β			1:1[b]
		γ			1:1[b]

[a] Stoichiometry obtained from diffusion coefficient measurements. [b] Stoichiometry obtained by NMR analysis of precipitated complex.

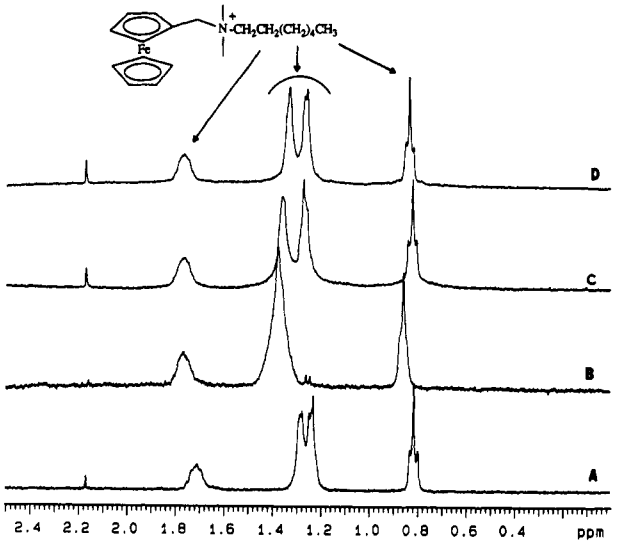

Figure 5. Aliphatic region of the 400-MHz ^1H NMR spectrum of (A) 1.0 mM $FC_7^+Br^-$ in D_2O, (B) same + 10 mM α-CD, (C) same + 10 mM β-CD, (D) same + 10 mM γ-CD.

reflected in the data of Table I since β-CD complexes with FC_1^+ and FC_7^+ exhibit the highest association constant values. The data the Table I also suggest that the association constant of α-CD complexes increases as the length of the alkyl chain in the ferrocene derivative increases while the opposite trend is observed for β-CD and γ-CD complexes.

Characterization of the FC–CD Interactions by High-Field ^1H NMR. The most direct evidence for the interaction sites of the ferrocene derivatives with the different cyclodextrins was obtained using 400-MHz ^1H NMR spectroscopy. Figure 5 shows the aliphatic region of the FC_7^+ NMR spectrum in the absence and in the presence of 10-fold excesses of α-CD, β-CD, and γ-CD, respectively. In the alkyl region of the spectrum of the uncomplexed compound (see Figure 5A), the peaks at 0.82 (triplet), 1.26, and 1.72 ppm correspond to the terminal methyl protons, the next four methylenes, and the fifth methylene, respectively, in the pendant heptyl chain. Addition of 10 mM α-CD to the $FC_7^+Br^-$ solution (1.0 mM in D_2O) broadens and shifts downfield the absorption peaks of the terminal methyl group and the four adjacent methylene groups. We have recently reported similar spectral changes for the interaction between *N*-ethyl-*N'*-hexadecyl viologen and α-CD.[35] In the presence of a 10-fold excess of either β-CD or γ-CD, only minor changes

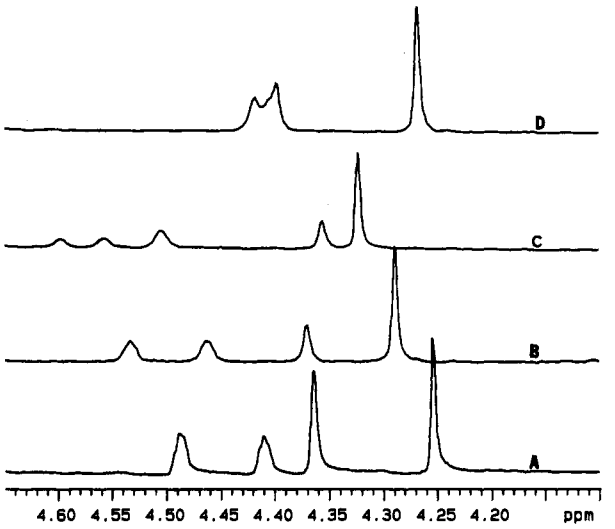

Figure 6. Expansion of the 400-MHz ^1H NMR spectrum of (A) 1.0 mM $FC_1^+PF_6^-$ in D_2O, (B) same + 10 mM α-CD, (C) same + 10 mM β-CD, (D) same + 10 mM γ-CD showing the resonances of the ferrocene subunit.

are detected in this spectral region, indicating that these two CD's interact much less effectively than α-CD with the aliphatic heptyl chain.

Figure 6 shows the absorption peaks of FC_1^+ corresponding to protons in the ferrocene subunit. The resonance at 4.25 ppm corresponds to the unsubstituted cyclopentadienyl ring, the peak at 4.36 ppm belongs to the anchoring methylene group, and the two triplets at 4.41 and 4.49 ppm result from the four protons in the substituted cyclopentadienyl ring. Although the presence of all three cyclodextrins causes shifts in this spectral region, the strongest interaction is with β-CD, as demonstrated by the peak corresponding to the unsubstituted cyclopentadienyl ring (4.25 ppm) which splits into two peaks (see Figure 6C). Furthermore, the other three peaks are substantially shifted downfield. The relative integrated intensities of these resonances maintain the expected 2:2:2:5 ratio which verifies the above assignments in the presence of β-CD. Interaction of γ-CD with the ferrocene moiety is not strong enough to cause the peak at 4.25 ppm to split, but the spectral pattern exhibited by the substituted cyclopentadienyl ring hydrogens suggests that the inclusion configuration of the ferrocene subunit into the CD cavity could be different from that prevalent in the case of β-CD. α-CD only causes small shifts of all the resonances in this spectral region.

The NMR spectra of FC_7^+ in the presence of α-CD, β-CD, and γ-CD show the same changes of Figure 6 in the spectral region corresponding to the ferrocene moiety. An interesting situation develops in the case of the FC_{16}^+ cation because its CD complexes precipitate slowly from a solution containing 50 mM NaCl. The precipitates were collected, dried, dissolved in DMSO-d_6, and submitted to NMR analysis. As expected, all the absorption peaks due to the CD host and the ferrocene derivative are present. The integrated intensities of the doublet at 5.4–5.6 ppm (OH's on C-2 and C-3 of α-CD)[36] and the broad singlet at 1.25 ppm (13 CH_2's in the hexadecyl chain of FC_{16}^+) afford a simple way to determine the stoichiometry of the complex. The results indicate that FC_{16}^+ forms 1:2 complexes with α-CD and 1:1 complexes with β-CD and γ-CD, respectively.

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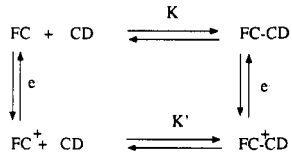
Scheme I



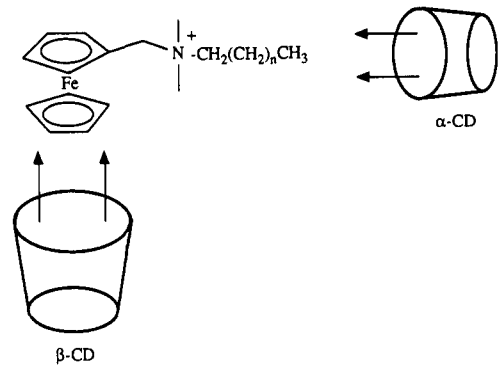
The Bimodal Nature of the CD Complexation of FC_1^+, FC_7^+, and FC_{16}^+. The combination of electrochemical and high-field NMR data presented here clearly indicates that the three ferrocene derivatives surveyed in this work possess two molecular regions susceptible to binding by unmodified CD hosts. The first of these regions, the ferrocene subunit, is poorly bound by α-CD as evidenced by the small shifts in the half-wave potential observed with all three ferrocene compounds in the presence of this CD. ^1H NMR spectra unequivocally reveal, however, that α-CD strongly binds the heptyl chin of FC_7^+. This is also in excellent agreement with the potential separation (60 mV) observed between the voltammetric peaks of the ferrocene derivatives in the presence of α-CD. Thus, inclusion of the alkyl chain by this CD does not interfere with the electron-transfer reaction between the ferrocene subunit and the electrode surface.

In contrast, β-CD seems to possess the ideal cavity diameter for binding to the ferrocene group. This is certainly confirmed by the substantial β-CD-induced shift observed in the half-wave potential for the voltammetric oxidation of all three ferrocene derivatives and by the NMR data as well. The data for γ-CD indicate binding of the ferrocene subunit but the resulting complexes are much weaker than those formed by β-CD probably reflecting the imperfect "fit" of the ferrocene group inside the large γ-CD cavity.

The chemical and electrochemical equilibria in which the ferrocene derivative and the CD host are involved are represented in Scheme I. Evans et al. have thoroughly discussed this scheme for the case of FCA^- complexation by β-CD.[25] Based on Scheme I oxidation of the ferrocene derivative to the corrsponding ferrocinium compound can occur via three pathways: (i) direct electron transfer between the inclusion complex and the electrode surface, (ii) dissociation of the complex followed by electron transfer between the free ferrocene derivative and the electrode surface (a chemical–electrochemical mechanism, CE), and (iii) electron transfer between the partially dissociated inclusion complex and the electrode surface. The first pathway is possible only if the interaction between the ferrocene derivative and the CD host does not interfere with the electron transfer. This is the case in the α-CD complexes of our ferrocene derivatives, particularly for FC_7^+ and FC_{16}^+, where the small CD interacts with an alkyl chain sufficiently long to generate strong van der Waals interactions with the hydrophobic cavity. In fact, the complex between FC_{16}^+ and α-CD exhibits 1:2 stoichiometry indicating that the hexadecyl chain is long enough to sustain complexation by 2 α-CD molecules.

The oxidation of β-CD complexes follows a completely different mechanism as evidenced by the larger potential separation observed between the voltammetric peaks. Evans et al. clearly demonstrated that this behavior results from the prevalence of a CE mechanism.[25,26] Thus, oxidation of the ferrocene group takes place only after dissociation of the inclusion complex. Furthermore, this means that the oxidized form of the ferrocene derivative is not complexed by β-CD, i.e., the interaction is disrupted by the oxidation of the ferrocene derivative. In terms of the parameters represented in Scheme I, this case corresponds to a K' value nearly equal to zero and to nonexistent electron transfer between the included species (elimination of the right lateral process in the square scheme).

Scheme II



Complexation by γ-CD represents a more difficult case because it shows no electrochemical evidence for a CE oxidation mechanism while the NMR data indicate that the interaction takes place at the ferrocene subunit. The larger size of the cavity of this CD host probably plays a crucial role in understanding these findings. Binding constant values for the γ-CD complexes (Table I) show that they are substantially weaker than the corresponding β-CD complexes, reflecting the looser fit of the ferrocene group inside the larger cavity adn the correspondingly faster decomplexation rates. Therefore, a CE mechanism may also operate in this case but, owing to much faster decomplexation kinetics, no effects were detected in our voltammetric experiments.

The ferrocene derivatives surveyed exhibit two distinctly different modes of interaction with α-CD and β-CD, respectively. *This duality in the interactions of the ferrocene derivatives with simple unmodified CD's ensues from the limited binding selectivity which is imparted by the varying sizes of the CD cavities.* The internal diameters of α-, β-, and γ-CD are 4.5, 7.0, and 8.5 Å, respectively.[37] An aliphatic chain has a cross-section diameter of 5 Å in an all-gauche conformation. CPK models indicate that the ferrocene moiety has a thickness of 7 Å. Thus, based on the optimization of size matching between the interacting hydrophobic moieties, α-CD is expected to bind strongly to the aliphatic chain while β-CD should engulf tightly the ferrocene subunit. Furthermore, the binding of a hydrocarbon chain by β- and γ-CD should be weaker due to the looser fit of the chain inside these larger cavities. γ-CD can bind to ferrocene but the fit is not optimum as it seems to be in the case of β-CD. α-CD is too small to include the ferrocene group and can only interact partially with it.

Ternary and Quaternary Complexes. In a way, these ferrocene derivatives act as templates in their interactions with CD's, directing them to specific molecular regions in order to maximize the stability of the resulting complexes. This idea is represented in Scheme II. It can be used to build small supramolecular aggregates in which several CD's group together around a central molecule in an arrangement predetermined by the structure of the central (template) molecule. This is exemplified by the formation of a ternary complex of FC_7^+ with α-CD and β-CD which is characterized by the following experimental observations. If 4.0 mM α-CD is added to a 1 mM solution of

(37) James, W. J.; French, D.; Fundle, R. E. *Acta Crystallogr.* **1959**, *12*, 385.

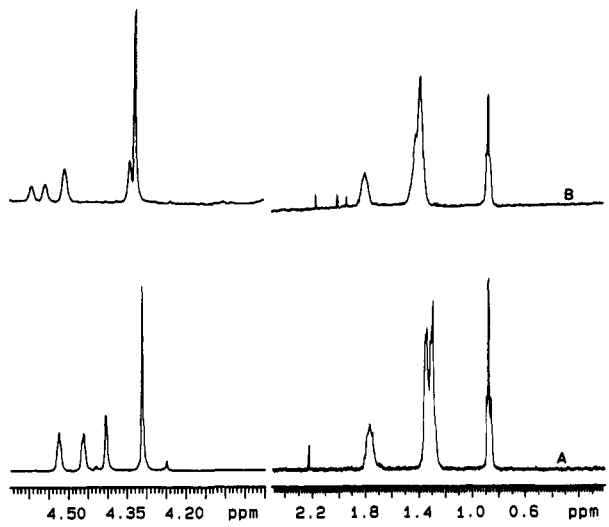


Figure 7. The aliphatic and ferrocene regions of the 400-MHz ^{1}H NMR spectrum of (A) 1.0 mM $FC_7^+Br^-$ in D_2O and (B) same + 4.0 mM α-CD + 4.0 mM β-CD. The spectral changes indicate that β-CD binds to the ferrocene group while α-CD includes the aliphatic chain.

$FC_7^+Br^-$ the half-wave potential for the oxidation of the ferrocene subunit does not change but the voltammetric peak currents decrease indicating the formation of a complex in which α-CD embodies the heptyl chain of the FC_7^+ cation. Subsequently, 4.0 mM β-CD is added to this solution, and the voltammetric peak currents decrease more while the half-wave potential shifts to the same value that it has in the presence of 4.0 mM β-CD with no α-CD in the medium. These findings indicate the formation of a ternary complex in which FC_7^+ is bound by both CD's, with α-CD interacting with the heptyl chain and β-CD engulfing the ferrocene group. The proposed structure for this complex was further verified by ^{1}H NMR spectroscopy. Figure 7B shows the aliphatic and ferrocene regions of the spectrum of the ternary complex which are clearly identical to those observed for the FC_7^+–α-CD (in the case of the aliphatic region) and the FC_7^+–β-CD (for the ferrocene region) binary complexes, respectively. This small aggregate or ternary complex has a molecular weight of more than 2000 Da and constitutes the simplest example of a series of CD-wrapped structures that can be built around ferrocene derivatives having pendant alkyl chains.

In principle, the binding constants in this ternary complex could be determined using the same voltammetric method utilized with the binary complexes. In the case of the ternary complex, on can define four binding constants corresponding to the following interactions: FC_7^+ + α-CD, FC_7^+ + β-CD, FC_7^+·α-CD + β-CD, and FC_7^+·β-CD + α-CD. The first two are already known from the binary complexation studies. The last two might be accessible by monitoring the changes in the apparent diffusion coefficient of the ferrocene derivative in solutions containing a large excess of one CD while the concentration of the other CD is gradually varied. However, the need to add a large excess of one CD to guarantee full initial complexation of the FC_7^+ cation introduces complications. For instance, to determine the binding constant between FC_7^+·β-CD and α-CD, one needs to measure the apparent diffusion coefficient of FC_7^+ in the presence of a large excess of β-CD as a function of smaller concentrations of α-CD. Under these conditions β-CD may compete effectively (due to its larger concentration) with α-CD in binding the heptyl chain of FC_7^+. Because of these problems we have not attempted to determine these binding constants.

A more compelling example of these CD-wrapped complexes was isolated (see the Experimental Section) using FC_{16}^+, α-CD, and β-CD as the building blocks. The 400-MHz ^{1}H NMR spectrum of this material shows two doublets corresponding to the OH's on C-2 and C-3 of α-CD (5.4–5.6 ppm) and β-CD (5.6–5.8 ppm). This fortuitous circumstance permits the easy determination of the stoichiometric ratio of FC_{16}^+, α-CD, and β-CD in the complex from the integrated intensities under these two doublets and the broad singlet at 1.25 ppm which corresponds to 13 CH_2's in the hexadecyl chain of FC_{16}^+. Our integration data for complexes isolated after precipitation from solutions containing either 2 mM FC_{16}^+ + 6 mM α-CD + 12 mM β-CD or 2 mM FC_{16}^+ + 12 mM α-CD + 12 mM β-CD yield stoichiometries of 1:2.0:1.16 and 1:1.96:1.0 (FC_{16}^+:α-CD:β-CD), respectively, which are both very close to the ratio (1:2:1) that would be predicted from the individual interactions of the hexadecyl ferrocene derivative with both CD hosts. Furthermore, the fact that the observed stoichiometry of the quaternary complex does not depend on the concentration ratios of the initial solution rules out co-precipitation as a factor to explain the composition of these precipitates. Thus, this quaternary complex (molecular weight >3000 Da) seems to be formed by the ferrocene derivative wrapped by one molecule of β-CD engulfing the ferrocene group and two molecules of α-CD entrapping the hexadecyl chain.

An important characteristic of these aggregates is that, while the number of bound α-CD hosts should be determined by the total length of the hydrocarbon chains,[35] the binding of β-CD's can be controlled by the oxidation state of the ferrocene groups since β-CD does not seem to interact with the oxidized (ferrocinium) form. We are currently studying these aggregates in molecules having a ferrocene subunit attached to two or more long hydrocarbon tails.

Experimental Section

Materials. α-CD and β-CD were obtained from Fluka and used without further purification. γ-CD was a gift of Professor Fujio Toda from the Tokyo Institute of Technology. $FC_7^+Br^-$ and $FC_{16}^+Br^-$ were synthesized according to published procedures[38] by stirring in a benzene/ether mixture equimolar amounts of ((dimethylamino)methyl)ferrocene [Aldrich] with bromoheptane and bromohexadecane, respectively. The precipitated reaction products were isolated by filtration and recrystallized from acetone/ether. FC_1^+ was synthesized as the iodide salt using methyliodide as the alkylating agent.[38] $FC_1^+PF_6^-$ was prepared by treatment of an aqueous solution of $FC_1^+I^-$ with a saturated solution of NH_4PF_6. The PF_6^- salt of FC_1^+ was used to avoid potential complications due to iodide oxidation or adsorption on the electrode surface. The structure and purity of the ferrocene derivatives were verified by ^{1}H NMR and elemental analysis. Calculated for $C_{20}H_{32}NFeBr$ ($FC_7^+Br^-$): C, 56.89; H, 7.64; N, 3.32. Found: C, 56.79; H, 7.65; N, 3.32. Calculated for $C_{29}H_{50}NFeBr$ ($FC_{16}^+Br^-$): C, 63.51; H, 9.19; N, 2.55. Found: C, 63.39; H, 9.21; N, 2.51.

The quaternary complex FC_{16}^+·(2 α-CD)·β-CD was isolated by preparing a solution containing 2 mM FC_{16}^+ + 12 mM (or 6 mM in a different experiment) α-CD + 12 mM β-CD in 50 mM NaCl. Precipitation of the complex was induced by addition of a few drops of satuated aqueous NaCl and cooling. The precipitate was separated by centrifugation and dried under vacuum at 60 °C for 24 h and dissolved in DMSO-d_6 for NMR analysis.

All solutions were freshly prepared using distilled water that had been further purified by passage through a Barnstead Nanopure system. D_2O (99.96 atom % D) and DMSO-d_6 (99.9 atom % D) were purchased from Aldrich and used for the preparation of NMR samples.

(38) Lombardo, A.; Bieber, T. I. *J. Chem. Ed.* **1983**, *60*, 1080.

Equipment. The electrochemical instrumentation has already been described.[21] A Pine Model ASR Analytical Rotator Assembly was used for the diffusion coefficient measurements. For cyclic voltammetry GC disk electrodes (0.080 cm^2) were obtained from Bioanalytical Systems. A GC electrode of larger surface area (0.196 cm^2), purchased from Pine, was used for rotating disk electrode measurements.

Methods. Electrode surfaces were polished with 0.05 μm alumina, sonicated in water, and air-dried immediatly before use. All potentials were measured against a sodium saturated calomel electrode (SSCE) at room temperature. The supporting electrolyte was 50 mM NaCl.

Voltammetric studies of the complexation phenomena were started by recording the voltammetric behavior of a 1.0 mM solution of the ferrocene derivative in pure supporting electrolyte solution. Variable amounts of carefully weighed solid CD were then added to adjust its concentration to the desired levels. After each CD addition, the voltammetric behavior was recorded. α-CD and γ-CD were added to give concentrations within the 1–18 mM range. β-CD was added to give concentrations in the narrower 1–12 mM range due to its lower solubility in water. The electrochemical behavior of free FC_{16}^+ is very intricate due to micellization and adsorption of this amphiphilic derivative. In the presence of at least 4 mM α-CD, β-CD, or γ-CD, reversible, diffusion-controlled voltammetric behavior was observed in all cases. However, the determination of quantitative voltammetric data for this system was also impaired because the supporting electrolyte (50 mM NaCl) seems to slowly induce the precipitation of CD complexes of FC_{16}+. This was utilized to isolate the complexes that were subsequently analyzed by NMR spectroscopy to determine their stoichiometries.

Rotating disk electrode voltammetry (RDV) was used to determine diffusion coefficients because it provided data of better quality and reproducibility than cyclic voltammetry. The diffusion coefficients were determined from the slopes of Levich plots (limiting current vs square root of rotation rate). The kinematic viscosity of the solution was always taken as 0.010 cm^2/s since our measurements demonstrated that the addition of CD's in the 1–20 mM concentration range caused negligible changes in the viscosity and density of the solutions. For each ferrocene–CD pair, binding constants were obtained from the variation of the measured diffusion coefficient as a function of the CD concentration. Assuming that (i) the complex has a 1:1 stoichiometry and that (ii) the complexation equilibrium is fast in the voltammetric timescale,[39] the measured diffusion coefficient D_{app} can be expressed as

$$D_{app} = X_f D_f + X_c D_c \quad (1)$$

where D_f and D_c refer to the diffusion coefficients of the free and complexed ferrocene substrate, and X_f and X_c are the corresponding molar fractions. The complexation equilibrium is given by

$$FC + CD \rightleftharpoons FC\text{–}CD \quad (2)$$

and the binding constant K is defined as

$$K = [FC\text{–}CD]/[FC][CD] \quad (3)$$

where [FC–CD], [FC], and [CD] stand for the equilibrium concentrations of the complex, free ferrocene derivative, and free cyclodextrin, respectively. Then, assuming values for the association constant K and the complex diffusion coefficient D_c, one can calculate X_f, X_c, and D_{app} for a given combination of FC and CD concentrations. The binding constant was determined using a simple iterative algorithm, written in BASIC, to calculate the values of the parameters K and D_c yielding the best least-squares fit to the experimental data points. A minimum of seven experimental D_{app} vs CD concentration data points were used for each FC–CD pair. The reproducibility of our D_{app} measurements was found to be better than 6%. The 1:1 complexation stoichiometry assumed in our model was verified in several instances by doubling the concentration of the ferrocene substrate, obtaining new D_{app} vs CD concentration data points, using the computer algorithm to determine new K and D_c values, and comparing them to those obtained previously. Constancy (within 10%) of both the binding constant and the complex diffusion coefficient was always observed indicating the validity of the assumed 1:1 stoichiometry. We estimate that the error margin of the reported binding constants is less than 10%.

Presaturation was used in the NMR experiments to remove the residual HDO peak and facilitate the observation of the solute resonances. Chemical shifts were calculated using residual amounts of acetone as an internal reference (2.17 ppm).

Acknowledgment. R.I. gratefully acknowledges the Malaysian Petroleum Company (PETRONAS) for a graduate fellowship. We warmly thank Prof. Fujio Toda for the gift of a generous sample of γ-CD, the NIH for providing funds to purchase the NMR spectrometer, and Orlando Garcia for performing some preliminary experiments. Financial support by the University of Miami Research Council is also acknowledged.

Registry No. $FC_1^+PF_6^-$·α-CD, 130096-43-4; $FC_1^+PF_6^-$·β-CD, 130096-44-5; $FC_1^+PF_6^-$·γ-CD, 130096-45-6; $FC_7^+Br^-$·α-CD, 130096-46-7; $FC_7^+Br^-$·β-CD, 130096-47-8; $FC_7^+Br^-$·γ-CD, 130096-48-9; $FC_{16}^+Br^-$·α-CD, 130096-49-0; $FC_{16}^+Br^-$·β-CD, 130096-50-3; $FC_{16}^+Br^-$·γ-CD, 130096-51-4; $FC_1^+PF_6^-$, 75592-18-6; $FC_7^+Br^-$, 119638-20-9; $FC_{16}^+Br^-$, 114188-47-5; $FC_{16}^+Br^-$·2(α-CD)·β-CD, 130096-52-5.

(39) Evans, D. H. *J. Electroanal. Chem.* **1989**, *258*, 451.