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Inclusion Complexes of Ferrocenes and *β*-Cyclodextrins. Critical Appraisal of the Electrochemical Evaluation of Formation Constants

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We report the results of a systematic electrochemical study of the host−guest supramolecular adducts between ferrocene (Fc), ferrocenium cation (Fc^+), and other mono- and disubstituted ferrocene derivatives with different *β*-cyclodextrins (CD) in mixed organic−aqueous media. The influence on the formation constants (K_f) of the organic cosolvent, the different substituents on Fc, and the type of CDs are evaluated. NMR and conductometry responses of ferrocenium cation solutions in the presence of CD confirm the weak propensity of Fc^+ to enter into the cyclodextrin cavity. The K_f value generally decreases as the steric bulk and the rigidity of Fc substituents increases, consistent with an inclusion model in which the Fc fits into the CD cavity in an axial mode while the substituent protrudes out. Interestingly, the addition of sulfated *β*-CD shifts the redox Fc/Fc^+ couple toward cathodic values, indicating that the oxidized, cationic form Fc^+ is more strongly bound to the sulfated cyclodextrin than neutral Fc, probably by means of electrostatic interaction with the external $-SO_3^-$ functionalities.

Introduction

In an inclusion reaction, a host molecule traps a guest molecule to form a complex held together by a combination of hydrogen bonding, hydrophobic forces, and dipole interactions. The guest encapsulated in the host cavity generally exhibits significantly modified properties and reactivity compared to the free guest. Cyclodextrins (CD) are cyclic oligosaccharides containing six, seven, and eight glucose units and are commonly called α-, *β*-, and *γ*-cyclodextrins, respectively.[1−4] The toroidal structure of CDs has a hydrophilic surface resulting from the 2-, 3-, and 6-position hydroxyls, and the cavity is composed of glucoside oxygens and methylene hydrogens, giving it a hydrophobic character. As a consequence, CDs can include apolar molecules of appropriate dimensions inside their cavity, making them more water-soluble. Formation of inclusion complexes of organic and organometallic molecules with cyclodextrins is important for their pharmaceutical[5] and technological applications.[6] In particular, cyclodextrins are an ideal matrix for spectroscopic studies of supramolecular complexes, as they are transparent throughout the visible and near-UV range. Finally, the mobility of organometallic compounds in CD cavities is surprisingly high.[7]

The effect of CDs on the electrochemical properties of various electroactive species included in the cavity has been reported.[8] Different voltammetric/polarographic techniques were employed in the determination of formation constants (K_f) between host and guest. Despite a wealth of information on the CD complexes of organic compounds, less is known about inclusion of transition-metal complexes.[9] Among the metal complexes investigated are ferrocene (Fc) and its substituted derivatives, since they are suitable guests for the hydrophobic cavities of cyclodextrins (especially *β*-CD) and exhibit simple electrochemical behavior which is favorable to this study.[10−13] Furthermore, the effects of CDs on the electrochemical properties of ferrocenes are well-known, since the ferrocene/ferrocenium redox couple is a suitable redox system for testing biomimetic models, which involve a one-electron-transfer step.[14] For these

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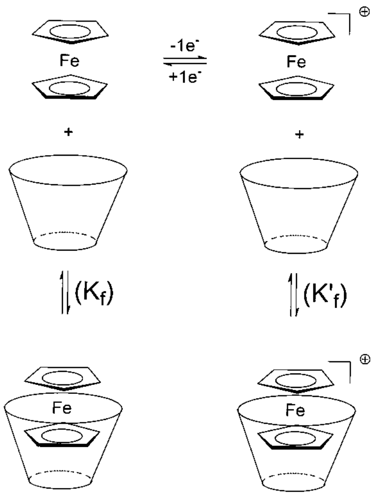
Scheme 1



reasons there is a plethora of formation constant values of inclusion complexes between CDs and ferrocenes bearing hydrophilic groups, mainly obtained by means of electrochemical investigations.[10,15-21] However, the study of the voltammetric behavior of nonpolar ferrocenes is complicated by the insolubility of their neutral forms in water; also, the solubility of CDs in nonaqueous solvents and water/organic solvent mixtures is less than in aqueous solutions. When the amount of organic component in water is increased, a decrease in the K_f value is expected, since the hydrophobic driving forces pivoting the inclusion complex formation are markedly reduced.[22] Therefore, K_f values obtained under different conditions are hard to compare, since the kind and amount of organic cosolvent are often different.

A 1:1 stoichiometry for both the [Fc(β-CD)] and [Fc^+(β-CD)] complexes was always suggested,[13,15] as shown in Scheme 1.

Several authors have proposed that the oxidized form of Fc, i.e. the ferrocenium cation Fc^+, forms inclusion complexes with CDs (if any) less stable than the neutral counterparts (i.e. $K_f' \ll K_f$ in Scheme 1).[18,21] This hypothesis simplifies the calculation of the formation constants from electrochemical data (CE mechanism: i.e. a shift toward anodic potentials and current drop as CD is added to the solution), but it has been recently criticized on the basis of bioelectrochemical experiments.[14] In this paper we offer experimental evidence of the poor complexation undergone by Fc^+ cation by means of NMR and conductivity measurements.

The present work deals with the inclusion complexes of Fc and Fc derivatives with β-cyclodextrin (β-CD) in aqueous solutions containing a small amount of organic cosolvent. Modified cyclodextrins, namely heptakis(2,6-di-*O*-methyl)-β-cyclodextrin (dm-CD), heptakis(2,4,6-tri-*O*-methyl)-β-cyclodextrin (tm-CD), hydroxypropyl-β-cyclodextrin (pr-CD), and sulfated-β-cyclodextrin (sulf-CD), have also been utilized. The chemically modified cyclodextrins represent “second generation” reagents and open new and unexpected applications.[23] For instance, the solubility of pr-CD is at least 50 times higher than that of β-CD itself, allowing the use of elevated concentrations. This is advantageous in the electrochemical approach, since a large molar ratio of host to guest is required in order to obtain meaningful results.[24]

Experimental Section

Materials. Ferrocenes were purchased from Aldrich and Strem and used without further purification. (Ferrocenylmethyl)trimethylammonium hexafluorophosphate ([TMA^+Fc][PF_6^-]) was obtained from [TMA^+Fc][I^-] by displacement of the iodide anion according to the literature procedure.[21] [TMA^+-Fc^+] ion was obtained in water from [TMA^+Fc][I^-] by using $AgPF_6$ in a 1:2 stoichiometric amount. The precipitate of AgI was filtered off and the solution directly tested by electrochemical techniques.

The employed CDs were ion-free, since their solutions and purified water had the same conductivity. Purified water was prepared by passing through several exchange columns and had a residual conductivity of 2×10^{-6} S cm^{-1}. ^1H NMR spectra were collected on a JEOL EX-400 spectrometer, and the chemical shifts were reported positive downfield with respect to TMS.

Conductivity measurements were determined with an AMEL Model 160 digital conductivity meter in a water bath thermostated at 25 ± 0.1 °C. Small aliquots of solid CD were added to $FcPF_6$ or KPF_6 water solutions at known concentration.

The electrochemical measurements were performed with an EG&G PAR Model 263 potentiostat. A three-component electrochemical cell was used with a glassy-carbon electrode as the working electrode, a platinum wire as the counter electrode, and a saturated calomel electrode (SCE) as the reference electrode. The surface of the working electrode was polished with a 0.05 μm alumina/water slurry on a felt surface and rinsed with purified water before each cyclic voltammetric run. The solutions for the electrochemical experiments were purged with nitrogen and kept under an inert atmosphere throughout the measurements. The cyclic voltammograms were collected with a scan rate of 0.1 V s^{-1}. The peak potentials reported were referenced to SCE. Typically, the right amount of ferrocenes, enough to set the final concentration to about 0.8 mM, was dissolved in a small amount of organic solvent and then the aqueous supporting electrolyte was added. After the organic solution was mixed with the aqueous one, the resulting suspension was filtered off, yielding a saturated solution of ferrocenes suitable for electrochemical measurements. The concentrations of CDs in the solution were adjusted to the desired level (within the 1−18 mM range) by adding carefully weighed amounts of solid CD.

Results and Discussions

Conductivity Measurements. If the complexation of ferrocenium (Fc^+) by means of β-CD takes place extensively, a solution of Fc^+ salt should have noticeably decreased conductivity by adding solid β-CD. The effect

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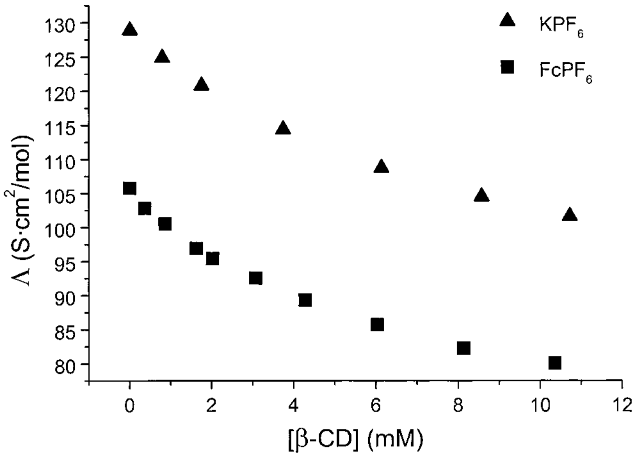

Figure 1. Equivalent conductivity, Λ, of solutions of KPF_6 (2.15 mM, top) and $FcPF_6$ (2.04 mM, bottom) in H_2O at different β-CD concentrations.

is related to the smaller diffusion coefficient of the complex $[Fc(\beta\text{-CD})]^+$ with respect to that of free Fc^+ (see below). However, the complexation of the counteranion PF_6^- must be also considered. For this purposes, a parallel conductance experiment using the salt KPF_6 has been performed (see Figure 1), in which the cation K^+ is practically not complexed by CDs.[25] Figure 1 shows that the conductivity of $FcPF_6$ mimics that of KPF_6, but the guest molecule Fc^+ has an affinity for the hydrophobic cavity of β-CD higher than that of the cation K^+.

Although the KPF_6 salt is not completely dissociated,[26] the thermodynamic equilibrium constant for the association process is quite low ($K_a = 1.78$) and, for our purposes, can be neglected, since we operate at low concentrations (ca. 2 mM). In fact, the plot of Λ vs $[\beta\text{-CD}]^{1/2}$ for KPF_6 under our experimental conditions is almost linear. The value of the molar conductivity at infinite dilution previously reported ($\Lambda_0 = 132.70$ S cm^2 mol^{-1})[27] is in agreement with the Λ_0 value found here by simple linear regression (133.62). It is generally accepted that the role of anions is predominant in the interactions between CDs and inorganic salts; hence, the reaction between β-CD and KPF_6 could be assigned mainly to the complexation of the anion.[25]

The conductivity could also be affected if the addition of β-CD would cause an increase of the solution viscosity. However, it was reported that no change in solution viscosity was detected in the range 0−10 mM.[15]

If only the complexation of the anion PF_6^- is assumed, the formation constant of $[PF_6^-(\beta\text{-CD})]$, K_f'', can be calculated by using the equation[28]

$$\frac{\Lambda_0 - \Lambda}{[\beta\text{-CD}]} = K_f''\Lambda - K_f''\Lambda_{[PF_6(\beta-CD)]K} \quad (1)$$

where Λ_0 is the equivalent conductance of KPF_6 (measured in the absence of β-CD) and Λ is the analogous value in the presence of β-CD, while $\Lambda_{[PF_6(\beta-CD)]K}$ is the equivalent conductance of the complex $[PF_6(\beta\text{-CD})]K$. From the slope of the plot of $(\Lambda_0 - \Lambda)/[\beta\text{-CD}]$ vs Λ, the value of K_f'' can be readily obtained ($K_f'' = 110$ M^{-1}) (Figure 2). If both ions are complexed, $(\Lambda_0 - \Lambda)/[\beta\text{-CD}]$ is a more complex function of Λ and [β-CD]. However, if K_f' and K_f'' are small enough, the plot of $(\Lambda_0 - \Lambda)/[\beta\text{-CD}]$ vs Λ is linear and the slope is approximately $K_f' + K_f''$. This is the case for $FcPF_6$ (Figure 2), with a slope of 175 M^{-1}. It follows that the formation constant of $[Fc(\beta\text{-CD})]^+$ is about 65 M^{-1} and is thus negligible with respect to that of $[Fc(\beta\text{-CD})]$ (ca. 4100 M^{-1}, see below).

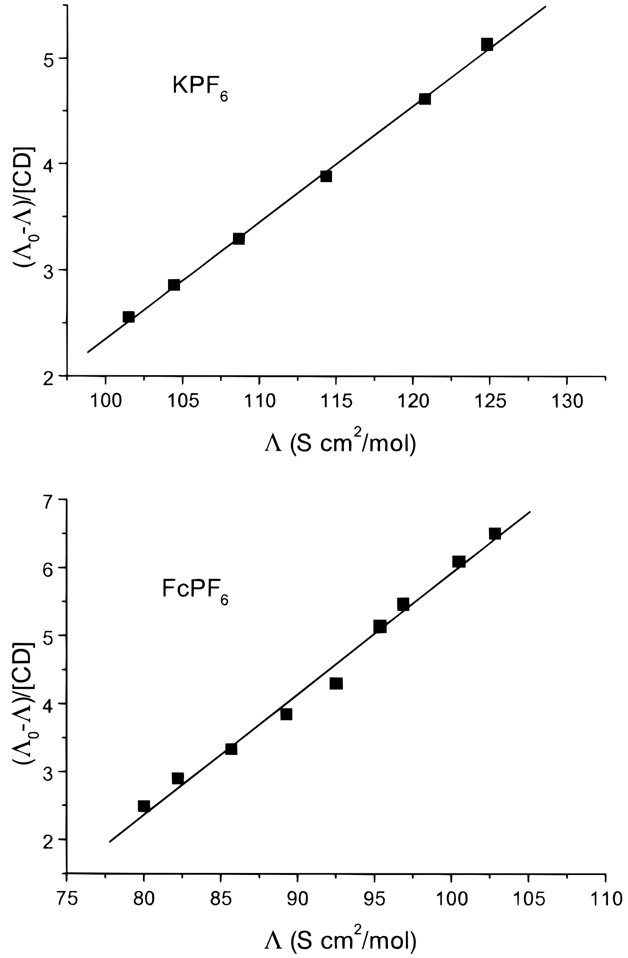

Figure 2. Conductometric determinations of K_f'' (KPF_6, top) and $K_f' + K_f''$ ($FcPF_6$, bottom) in H_2O.

NMR Measurements. NMR spectroscopy has been extensively used to establish inclusion modes, stoichiometries, and association constants of host−guest complexes with CD.[29] In particular, NMR shift titration appears as an appropriate method for an independent evaluation of association constants. Equation 2 gives

$$\frac{1}{\Delta} = \frac{1}{\Delta_0} + \frac{1}{K_f'\Delta_0}\frac{1}{[\beta\text{-CD}]} \quad (2)$$

the relationship of the fast exchange averaged chemical shift of the Fc^+ protons as a function of the β-CD concentration,[30] where Δ_0 is the difference in the chemi-

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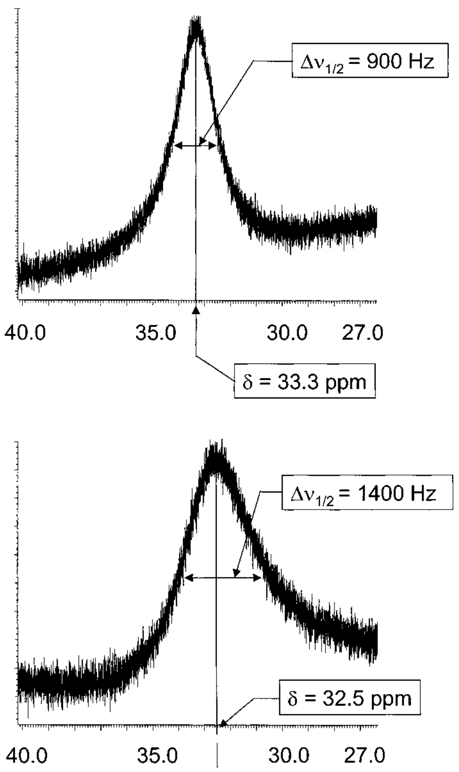

Figure 3. NMR spectra of Fc^+ (1 mM) in D_2O in the absence (top) and in the presence (bottom) of β-CD (18 mM), in the cyclopentadienyl resonance region.

cal shift of the complexed Fc^+ protons with respect to free Fc^+ ($\delta_{[Fc(\beta-CD)]^+} - \delta_{[Fc]^+}$) and Δ is the difference in the chemical shift of the Fc^+ protons measured during the addition of CD ($\delta_{[Fc]^+ + \beta-CD} - \delta_{[Fc]^+}$, where $\delta_{[Fc]^+}$ is 33.3 ppm). The measured Δ values are used to obtain the least-squares fit to eq 2, from which K_f' may be obtained. The presence of an unpaired electron spin in the ferrocenium ion influences the observed line shape and the line position of the ring protons.[31,32] Addition of β-CD to a D_2O solution of $FcPF_6$ (Figure 3) leads to small changes in the chemical shifts of the ferrocenium protons ($\Delta_0 \approx -0.8$ ppm), which, after linearization, give a K_f' value of 36 M^{-1}. The conductivity and NMR experiments are of the same order of magnitude and reveal that only the neutral form of Fc is significantly bound to the β-CD host. It is important to note that the scheme of complexation (Scheme 1) is validated here by two techniques other than electrochemistry.

Electrochemistry. The main goal of the present study is the evaluation of equilibrium constants K_f of ferrocenes with CDs by using cyclic voltammetry (CV) at a glassy-carbon (GC) working electrode.

Determinations in Pure Water. The electrochemical measurements in H_2O are complicated by the very low solubility of Fc itself. We successfully overcame this problem by studying the reduction of the water-soluble ferrocenium (Fc^+) ion, following a similar procedure employed by Kaifer et al.[33] for $[CoCp_2]^+$. A solution of $FcPF_6$ in pure H_2O containing $LiClO_4$ (0.1 M)[43] shows an *electrochemically* and *chemically reversible* 1e reduction process with $E^{\circ\prime} = +0.214$ V vs SCE. This redox process is complicated by deposition of insoluble Fc at the electrode surface electrogenerated in the reduction scan; the shape and size of the anodic peak in the reverse (reoxidation) scan clearly indicate the process. As a consequence of the gradual addition of β-CD in solution, the formal electrode potential $E^{\circ\prime}$ of ferrocenium ($E^{\circ\prime} = (E_p{}^a + E_p{}^c)/2$) is shifted to more positive potentials (EC process for $Fc^+ + 1e^- \rightarrow Fc$) but the peak currents do not markedly diminish. This constancy in peak currents upon addition of β-CD indicates that complexation has occurred for the reduced Fc only.

A similar electrochemical behavior was observed for $[TMA^+Fc^+]$: in this case the reduced form $[TMA^+Fc]$ is soluble in water, so that nondistorted voltammograms are obtained in the reverse scan. The resulting K_f value, 4800 M^{-1}, was confirmed by digital simulation:[34] the best fitting of simulated and experimental voltammograms gave a K_f value of 4830 M^{-1} and a K_f' value of 70 M^{-1}. Once again, the experimental indications are consistent with the proposed mechanism.

The formation constants K_f were determined using the shift of potential $\Delta E^{\circ\prime} = E^{\circ\prime}{}_{[Fc(\beta-CD)]} - E^{\circ\prime}{}_{[Fc]}$ according to the treatment proposed by Van Leeuwen et al.[24] Assuming a 1:1 stoichiometry for $[Fc(\beta\text{-CD})]$, a fast complexation–decomplexation equilibrium,[35] and the concentration relationship $[\beta\text{-CD}] \gg [Fc^+]$, the equation ($t = 25$ °C)

$$\Delta E^{\circ\prime} = 59.15 \log \sqrt{(1 + K_f[\beta\text{-CD}])(1 + rK_f[\beta\text{-CD}])} \quad (3)$$

can be obtained, where $r = D_{[Fc(\beta-CD)]}/D_{Fc}$.

If the concentration of β-CD is much larger than the total concentration of Fc so that $K_f\,[\beta\text{-CD}] \gg 1$, a further simplification to eq 3 holds:

$$\Delta E^{\circ\prime} = 59.15\,(\log\,[\beta\text{-CD}] + \log K_f\sqrt{r}) \qquad (4)$$

By plotting $\Delta E^{\circ\prime}$ vs log $[\beta\text{-CD}]$, the intercept $K_f\sqrt{r}$ can be obtained. The experimentally found 57 mV slope confirms the 1:1 stoichiometry for the complex. Interestingly, in eq 4 the concentration of Fc does not appear, as a consequence of the high $[\beta\text{-CD}]/[Fc]$ ratio (see above).

The value of r is readily achieved by means of the *apparent* diffusion coefficient, D_{app}, an average of the diffusion coefficients of the two species, weighted by their relative concentrations in solution. Since peak currents i_p are proportional to $D^{1/2}$, D_{app} can be obtained from the peak heights of ferrocene dissolved in a water/acetonitrile mixture (95/5) (see below) recorded at increasing concentrations of β-CD, $(i_p)_{app}$. In this case, being a CE process for $Fc \rightarrow Fc^+ + 1e^-$, the oxidation current noticeably decreases when solid β-CD is added to the solution.

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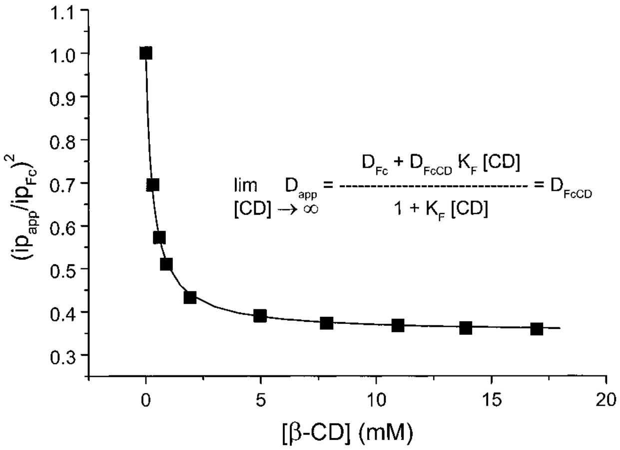

Figure 4. Plot of $[(i_p)_{app}/(i_p)_{Fc}]^2$ vs [β-CD] from the anodic peak dependence of ferrocene dissolved in a water–acetonitrile mixture (95/5): (■) experimental data; (—) nonlinear regression using D_{app}/D_{Fc}.

Since

$$\frac{(i_p)_{app}}{(i_p)_{Fc}} \propto \sqrt{\frac{D_{app}}{D_{Fc}}}$$

when $(i_p)_{app}/(i_p)_{Fc}$ is plotted vs [β-CD] the ratio

$$r = \frac{D_{[Fc(\beta-CD)]}}{D_{Fc}} \cong \lim_{[\beta\text{-CD}]\to\infty} \frac{D_{app}}{D_{Fc}}$$

can be evaluated as a limit value for [β-CD]→∞ (Figure 4).

The value of $r = 0.35$ is in line with those previously reported (ranging from 0.25 to 0.55 for different substituted water-soluble ferrocenes[15,17,18,21]).

When this value is used, $K_f = 4100 \pm 197\ M^{-1}$ is obtained for the ferrocene in pure water.

Determinations in Mixed Water–Organic Solvent. The low Fc solubility in water (ca. 1.7×10^{-5} M, determined by atomic absorption spectroscopy) causes very weak peak currents in CV. Furthermore, the complexation with CDs gives rise to a substantial decrease in the diffusion coefficient. Therefore, the evaluation of both peak potentials and currents is difficult. To obtain K_f values directly from neutral ferrocenes is necessary to increase the Fc solubility and, consequently, the electrochemical response by adding small amounts of organic cosolvent. In this case, an anodic shift of $E^{\circ\prime}$ has been observed in the CV responses of water–organic solutions of Fc in the presence of β-CD, as expected (CE process for $Fc \to Fc^+ + 1e^-$) (Figure 5).

To seek the best cosolvent, we examined the trend of K_f of Fc in different water–organic mixtures (Figure 6). When the cosolvent percentage is increased, K_f values dramatically decrease, in particular in the case of low-polarity tetrahydrofuran (THF). The water–acetonitrile mixture (95/5 v/v) was the best compromise between low volatility (it is vital to avoid solvent evaporation during standard degassing procedures) and polarity. In these conditions the K_f value of Fc decreases ca. 15% with respect to the value in pure water. In addition, the β-CD solubility in such a solution is still good (maximum [β-CD] ≈ 18–20 mM) and the concentration of ferrocenes rises up to around 0.8 mM. Molecules of organic solvents can also be complexed by β-CD, but the formation constant for the adduct CH_3CN–(β-CD) has been reported to be 6.0 M^{-1} and is therefore negligible.[36]

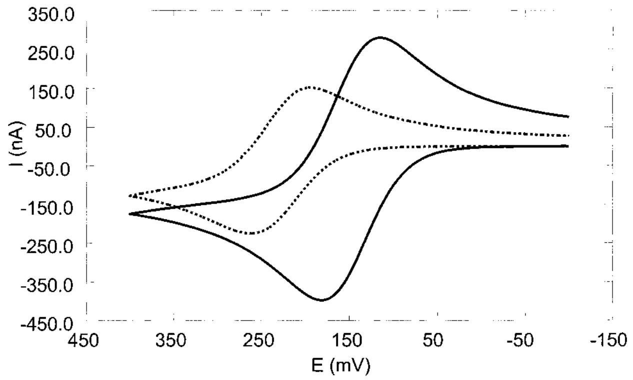

Figure 5. Cyclic voltammograms of saturated solutions of Fc (water–acetonitrile (95/5), 0.1 M $LiClO_4$) in the absence (solid line) and the presence (dotted line) of β-CD (15 mM).

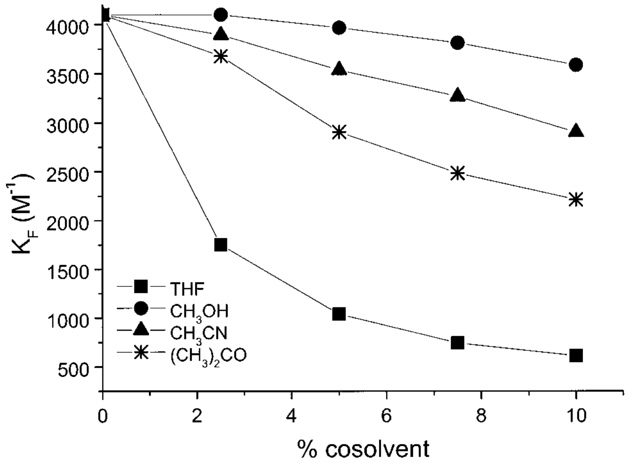

Figure 6. K_f values at different cosolvent amounts.

To estimate the value of the formation constant K_f for the different substituted ferrocenes, we performed a series of experiments with various concentrations of β-CD in the bulk (ca. 1–18 mM), evaluating corresponding $\Delta E^{\circ\prime}$ values (see Experimental Section). Since the decrease of diffusion coefficient for [Fc(β-CD)] is thought to be mainly due to the β-CD, we maintained the 0.35 $D_{[Fc(\beta-CD)]}/D_{Fc}$ ratio thoroughly for all ferrocenes (Table 1). All measurements were performed three times, and we estimated the average standard deviations of K_f values ranging from 10 to 15%.

Because of its high hydrophobicity, decamethylferrocene needs a higher amount of CH_3CN (25%). This could underestimate the true K_f value, but it is certainly very low (if any).

To a first approximation, the magnitude of binding constants correlates with the fit for the guest in the cavity. The interaction of β-CD and monosubstituted ferrocenes has been reported as a 1:1 complex with the substituent groups protruding out into bulk solution.[37] As expected, the presence of a substituent on the

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Table 1. Formal Electrode Potentials ($E^{\circ\prime}$) of Ferrocenes in the Absence of β-CD and Formation Constants (K_f) of the Related Inclusion Compounds with β-CD

compd	$E^{\circ\prime}$ (V vs SCE)^a	K_f (M^{-1})^b	lit. K_f (M^{-1})
decamethylferrocene	−0.205^c	∼0^c	
1,1′-diacetylferrocene	+0.742^d	250 (±40)	
ferrocenylboronic acid (pH 4)	+0.235	780 (±100)	
ethynylferrocene	+0.324	830 (±140)	
ferrocenecarboxaldehyde	+0.494^d	1130 (±160)	
acetylferrocene	+0.458	1240 (±220)	
(hydroxymethyl)ferrocene	+0.189	2120 (±170)	
1,1′-dimethylferrocene	+0.051	2470 (±300)	
tert-butylferrocene	+0.140	3060 (±370)	
vinylferrocene	+0.124	3140 (±390)	
ethylferrocene	+0.138	3180 (±330)	
ferrocene	+0.149	3530 (±350)	3626 (EtOH 5%/H_2O, 0.1 M $LiClO_4$)[17]
(ferrocenylmethyl)trimethylammonium ion (TMA^+Fc)	+0.390	4210 (±130)^e 4170 (±120)^f	1900 ± 180 (0.05 M NaCl)[18] 4500 (0.2 M Na_2HPO_4)[42] 4700 ± 300 (0.1 M phosphate buffer)[16] 4900 ± 600 (0.1 M $NaBF_4$)[21] 4810 ± 600 (D_2O, 0.025 M phosphate buffer)^{g,20}

^{a} Evaluated as $(E_p{}^a + E_p{}^c)/2$ at 0.1 V s^{-1} if not otherwise stated. ^{b} Data are means ± s.d. calculated from three replicated measurements in CH_3CN-H_2O (5/95 v/v) if not stated otherwise. ^{c} Evaluated in CH_3CN-H_2O (25/75 v/v). ^{d} The electrochemical process is chemically quasi-reversible; therefore, the $E^{\circ\prime}$ values have been evaluated at 0.40 V s^{-1}. ^{e} K_f was evaluated by oxidation of [TMA^+Fc]. ^{f} K_f was evaluated by reduction of [TMA^+Fc^+]. ^{g} NMR shift titration.

Table 2. Formation Constant (K_f) between Fc and Modified Cyclodextrins

cyclodextrin	K_f (M^{-1})^a	cyclodextrin	K_f (M^{-1})^a
β-CD	3530 (±350)	tm-CD	1900 (±150)
dm-CD	4430 (±540)	pr-CD	2130 (±260)

^{a} Data are means ± s.d. from three replicated measurements.

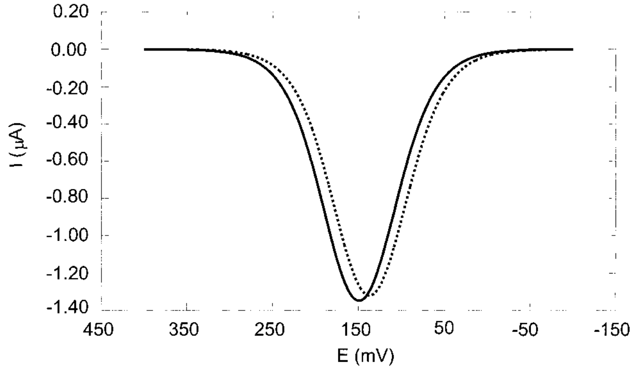

Figure 7. SWV of Fc in the absence (solid line) and in the presence (dotted line) of sulf-CD. Data were recorded using a potential step of 2 mV, a pulse amplitude of 25 mV, and a frequency of 15 Hz.

cyclopentadienyl ring decreases the value of K_f. Apolar groups, even if bulky like t-Bu, seems to cause less detriment on K_f values with respect to polar ones. However, TMA^+Fc is better included than ferrocene itself, possibly because of favorable electrostatic interactions: for instance, the positive charge on the substituent interacting with OH groups near the cavity. A negative charge on the external substituent has been reported to reduce the complexation: the K_f value for $FcCOO^-$ is around 2100 M^{-1}.[15,19] Interestingly, a positive charge on the metal inside the hydrophobic cavity (in Fc^+) hampers the complexation, while a positive charge on the substituents outside the cavity (in TMA^+Fc) increases it. This is in line with the behavior showed by other redox-active guests, such as viologen[38] and cobaltocenium[33] derivatives, whose neutral forms are strongly bound to the CD host while charged units of similar size are not. Moreover, the rigidity of the substituents plays a role in the encapsulation because by passing from sp^3 (ethylferrocene) and sp^2 (vinylferrocene) to sp carbons (ethynylferrocene), K_f values deeply decrease.

Disubstituted ferrocenes show measurable K_f values. Indeed, complexes of β-CD and disubstituted ferrocenes have been synthesized.[12,13] Decamethylferrocene is not able to form an inclusion complex at all because the diameter of the pentamethylcyclopentadiene ring is approximately 7−8 Å and is thus much larger than the cavity of β-CD.

We tried to find a relationship between K_f and Hammett substituents constants as a rough indication of the overall polarity of the ferrocenes. Good correlations of the oxidation potentials for ferrocenes with Hammett σ_m and σ_p have been previously reported[32] and are in agreement with our results.[39] However, similar correlations with K_f data were not obtained.

K_f values for the Fc complexation with different CDs are reported in Table 2. The partial substitution of −OH groups for methyls in dm-CD increases K_f. This stabilizing effect is attenuated by the steric hindrance of the 21 methyl groups in tm-CD and possibly by the 7 hydroxypropyl groups in pr-CD.

A quite different behavior is observed for sulf-CD. The square-wave voltammogram (SWV) in Figure 7 shows that the presence of sulf-CD does not change significantly the summit current. Surprisingly, E_{su} slightly shifts toward more negative potentials (ΔE_{su} = 12 mV when sulf-CD concentration passes from 0 to 8.5 mM), indicating that the oxidized form (ferrocenium) of the guest is now more strongly bound than the reduced form (ferrocene). Certainly, the electrostatic interactions between $-SO_3^-$ groups and Fc^+ is responsible for this (EC mechanism); this behavior resembles that of sulfated calix[6]arene with several Fc derivatives.[40] The actual

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supramolecular compound is better considered as an *association complex* instead of a classical *inclusion complex*.[41]

Conclusions

(i) The ferrocenium cation is not significantly included in the β-CD cavity; for that reason the assumption of an EC mechanism is correct.

(ii) The average standard deviations for electrochemical measurements employing the same experimental conditions range from 10 to 15%. Therefore, only general comparisons can be made. Moreover, the use of different organic cosolvents causes an enormous spread of results.

(iii) The presence of a substituent on the cyclopentadienyl ring decreases the value of K_f, except in the case of (ferrocenylmethyl)trimethylammonium ion, [TMA$^+$Fc], which is more readily included than ferrocene itself. Moreover, the rigidity of the substituents of the β-CD plays a role.

(iv) The use of the "second generation" alkylated cyclodextrins (namely dm-CD, tm-CD, and pr-CD) in lieu of β-CD allows the formation of inclusion complexes with Fc as well, indicating that the dimensions of hydrophobic cavities are similar. The highly polar sulf-CD does not form any measurable inclusion complex with neutral Fc; on the contrary, it forms an association complex with the electrogenerated Fc$^+$ cation.

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