

Probing the tolerance of cucurbit[7]uril inclusion complexes to small structural changes in the guest†

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The binding properties of the cucurbit[7]uril host with three structurally related ferrocene-containing guests, ferrocenyltrimethylammonium, ferrocenylmethyltrimethylammonium and ferrocenylethyltrimethylammonium, have been investigated using ¹H NMR spectroscopy, mass spectrometry, voltammetry and computational methods. The experimental and computational data indicate that the stability of the cucurbit[7]uril inclusion complexes is relatively insensitive to the number of methylenes connecting the trimethylammonium and the ferrocenyl groups, although some of their properties are affected in significant ways.

Introduction

The cucurbit[*n*]uril^{1–5} (CB_{*n*}) hosts are attracting increasing attention because, among other reasons, they can reach extremely high binding affinities with suitable guests. An excellent example is the inclusion complex formed between cucurbit[7]uril (CB7) and the dicationic guest 1,1'-bis(trimethylammonio-methyl)ferrocene (Fc²⁺), whose association equilibrium constant (*K*) is $3 \times 10^{15} \text{ M}^{-1}$ in pure water at 25 °C,⁶ a value similar to that measured with the well-known avidin–biotin pair. The CB7·Fc²⁺ complex is predominantly stabilized by two noncovalent interactions: (1) ion–dipole forces between each of the trimethylammonium groups on the guest and the carbonyl-lined portals on the host, and (2) hydrophobic forces between the included ferrocenyl group and the inner surface of the CB7 cavity. Furthermore, detailed thermodynamic analysis reveals that the rather surprising lack of entropic penalty accompanying the host–guest association process is a very important factor behind the high stability of the CB7·Fc²⁺ complex.⁶ In general terms, high stability CB_{*n*} inclusion complexes appear to assemble with relatively small entropic changes, taking these complexes out of the commonly observed enthalpy–entropy compensation relations that prevail in other supramolecular host families.^{7–10}

While the dicationic CB7·Fc²⁺ inclusion complex exhibits extraordinarily high thermodynamic stability, CB7 complexes of monocationic ferrocenyl guests are also very stable. For instance, we have investigated in some detail the properties of the CB7 complex formed by the ferrocenylmethyltrimethylammonium guest (Fc¹⁺), which shows a *K* value of $4 \times 10^{12} \text{ M}^{-1}$ in pure water at 25 °C.¹¹ This complex is also stabilized by the same combination of ion–dipole interactions and hydrophobic forces. In this work, we compare the properties of the CB7·Fc¹⁺ complex with those of the CB7 complexes formed by two highly related ferrocenyl guests: ferrocenyltrimethylammonium (Fc⁰⁺) and ferrocenylethyltrimethylammonium (Fc²⁺). The structures of the guests and the CB7 host are shown in Fig. 1. Clearly, the only structural difference among the three guests investigated here is the number of methylenes on the

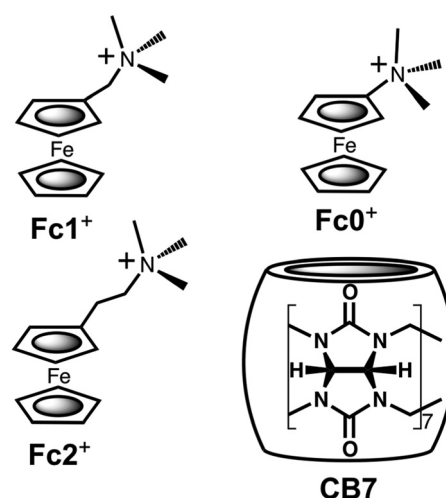


Fig. 1 Structures of the host and guests used in this work.

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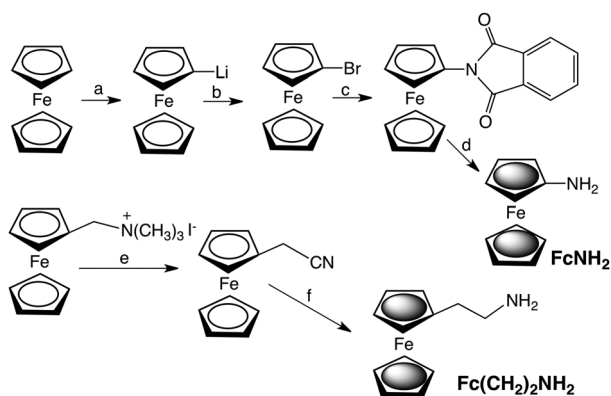
linker between the ferrocenyl and the trimethylammonium groups. We are interested in understanding the effects that this rather minor structural variation on the guest could have on the stability and properties of the corresponding CB7 inclusion complexes. We describe here the results of this investigation.

Experimental section

Synthesis

The preparation of Fc^+ and CB7 has been reported before. Ferrocenylamine [FcNH_2 , $\text{Fc} = (\text{C}_5\text{H}_5)_2\text{Fe}(\eta^5\text{-C}_5\text{H}_4)$] was prepared in several reaction steps by adapting literature procedures,^{12,13} starting with the selective monometalation of ferrocene with *t*-BuLi. Subsequently, bromoferrocene (prepared by reaction of lithioferrocene and bromine¹²), was converted into the key intermediate *N*-ferrocenylphthalimide, by treatment with phthalimide and cuprous oxide, under Gabriel synthesis conditions. Hydrazinolysis of this intermediate with hydrazine hydrate in ethanol, gives pure aminoferrocene FcNH_2 , which was isolated as a yellow solid in 82% yield. 2-(Ferrocenyl)ethylamine ($\text{Fc}(\text{CH}_2)_2\text{NH}_2$), was prepared in two steps from *N,N,N*-trimethylferrocenylmethylammonium iodide as a commercial starting material, by adapting literature procedures.^{14,15} First, $\text{FcCH}_2\text{N}(\text{CH}_3)_3\text{I}$ was reacted with potassium cyanide, resulting in 1-cyanomethylferrocene, which was isolated as a yellow crystalline solid in 63% yield. Cyanomethylferrocene was then converted into 2-(ferrocenyl)ethylamine by reduction with LiAlH_4 followed by treatment with aqueous sodium hydroxide. After aqueous workup and distillation *in vacuo*, the primary amine $\text{Fc}(\text{CH}_2)_2\text{NH}_2$ was obtained as an amber-brown oil, in 66% yield (Scheme 1).

Both amine compounds were exhaustively methylated with iodomethane in chloroform-methanol (1:3 v/v) to yield FcO^+ and $\text{Fc}2^+$, respectively as their iodide salts, which were recrystallized from methanol-chloroform-diethyl ether (1:1:20 v/v/v). Exposure of an aqueous solution of either salt to an Amberlite anion exchange resin in its chloride form led to the



Scheme 1 Synthesis of the ferrocenyl amines. Conditions: (a) *t*-BuLi, -10°C , THF/*n*-hexane, (b) Br_2 , -80°C , THF, (c) $\text{HN}(\text{CO})_2\text{C}_6\text{H}_4$, Cu_2O , Py, reflux, (d) $\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}$, EtOH, reflux, (e) KCN, H_2O , reflux, (f) LiAlH_4 , Et_2O , reflux.

corresponding chloride salts, which were used in the electrochemical experiments. The structure of the resulting ferrocenyl-containing cations was confirmed using ^1H and ^{13}C NMR spectroscopies and high resolution ESI-TOF mass spectrometry.

Equipment

Voltammetric experiments were recorded with a Bioanalytical Systems BAS-100W electrochemical workstation. A single-compartment electrochemical glass cell was fitted with a glassy carbon working electrode (0.07 cm^2), platinum auxiliary and Ag/AgCl reference electrodes. The solution was thoroughly purged with high-purity nitrogen before the experiments and maintained under an inert nitrogen atmosphere during the voltammetric scans. The working electrode was polished with $0.050\ \mu\text{m}$ alumina powder on a felt surface using pure water as the lubricant.

Computations

All energy minimizations were done using DFT methods (B3LYP/3-21G*).¹⁶ The complexes were initially assembled using the reported crystal structure of CB7¹⁷ and the previously minimized structure of the guest. The guest was always placed partially included inside the host before energy-minimization of the host-guest complex was allowed to proceed. The inclusion complex converged to the same energy-minimized structure, regardless of the initial relative positions of host and guest.

Results

The initial assessment of the binding interactions between any of the cationic ferrocenyl guests and the CB7 host is best carried out with ^1H NMR spectroscopy. For instance, Fig. 2 shows the spectra for guest FcO^+ in D_2O solution in the absence and in the presence of 0.5 and 1.0 equiv. of the CB7 host. Clearly all the protons on the guest experience

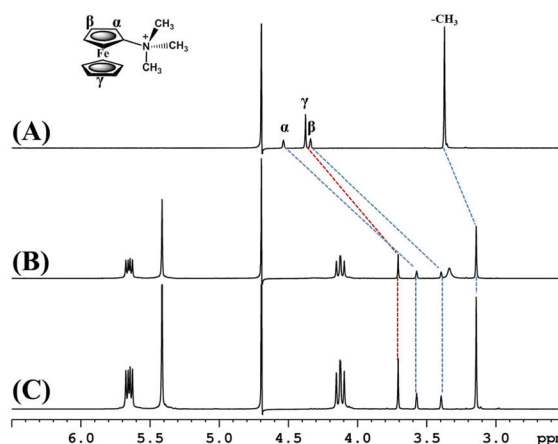


Fig. 2 ^1H NMR spectra (500 MHz, D_2O) of 1.0 mM FcO^+ in (A) the absence and the presence of (B) 0.5 equiv. and (C) 1.0 equiv. of CB7.

significant upfield shifts upon complexation with CB7, which is consistent with guest inclusion in the host cavity. Notice that in the presence of 0.5 equiv. of CB7 the ferrocenyl protons of free Fc0^+ are not observed, but the methyl protons of the free guest show a broad resonance at 3.4 ppm in slow exchange with that corresponding to the CB7-bound guest. Once 1.0 equiv. of host is added, the proton resonances of the free guest completely disappear and only the proton resonances for the CB7-bound Fc0^+ are observed. Further additions of CB7 do not result in any further spectroscopic changes. The quantitative formation of the $\text{CB7}\cdot\text{Fc0}^+$ complex at the millimolar concentrations of host and guest used in these experiments suggest that the association equilibrium constant for this complex is high. Notice also that the CB7 protons at 5.65 ppm, corresponding to the methylene protons facing the inside of the CB7 cavity show a more complex pattern than the doublet expected in free CB7. The splitting of this resonance in two doublets reflects the loss of the equatorial symmetry on the host, a result of the inclusion of a guest that renders both cavity portals different, since only one of them can interact directly with the trimethylammonium group.

The same kind of data set obtained with Fc2^+ shows relatively similar results regarding the quantitative formation of the $\text{CB7}\cdot\text{Fc2}^+$ complex (Fig. S1†). However, the methyl protons now experience a downfield shift upon addition of CB7, while the two different methylene signals show upfield shifts of variable magnitude. Of course, the NMR spectroscopic data for the formation of $\text{CB7}\cdot\text{Fc1}^+$ have been previously reported by us.^{11,18} Table 1 collects relevant spectroscopic data contrasting the binding behavior of the three guests with CB7.

In all three guests the ferrocene protons show negative complexation-induced shifts. This finding clearly indicates that the ferrocene residue is positioned inside the cavity of the CB7 host in all three complexes. In contrast to this, the measured $\Delta\delta$ values for the methyl protons go from negative in Fc0^+ to positive in Fc2^+ , which suggests that, as the distance between the trimethylammonium and ferrocene groups increases, the three equivalent methyl groups on the positively charged nitrogen move away from the CB7 cavity.

In order to estimate the association equilibrium constants between CB7 and the guests Fc0^+ and Fc2^+ , we carried out binding competition experiments¹⁹ for a limited amount of the host between each of these guests and a reference guest (*N*-adamantyl-pyridinium, Ad-Py^+). After allowing the system to reach equilibrium, NMR spectroscopy was used to calculate

Table 1 Selected ^1H NMR complexation-induced shifts (in ppm) corresponding to the interaction of CB7 with guests Fc0^+ – Fc2^+ in D_2O at 25 °C

Guest	$\Delta\delta(\alpha)^a$	$\Delta\delta(\beta)^a$	$\Delta\delta(\gamma)^a$	$\Delta\delta(\text{CH}_3)$
Fc0^+	−0.96	−0.94	−0.67	−0.23
Fc1^+	−0.86	−0.82	−0.72	0.02
Fc2^+	−0.74	−0.93	−0.72	0.13

^a The $\Delta\delta$ values were calculated as $\delta_{\text{complex}} - \delta_{\text{free guest}}$. The symbols α , β and γ correspond to the three different types of ferrocene protons as labelled in the figure.

the relative amounts (molar fractions) of CB7-bound and unbound Ad-Py^+ , which led to the determination of the corresponding molar fractions for the ferrocenyl guest. From these values, the corresponding equilibrium concentrations were computed and the K value for CB7 complexation of the ferrocenyl guest was extracted from the already reported K value for complexation of Ad-Py^+ .¹⁹ Using this procedure we extracted K values of $3.6 \times 10^{10} \text{ M}^{-1}$ and $7.3 \times 10^{10} \text{ M}^{-1}$ for Fc0^+ and Fc2^+ , respectively, in 50 mM sodium acetate pH 4.5 solution. The corresponding value for Fc1^+ was previously reported as $3.3 \times 10^{11} \text{ M}^{-1}$ in the same aqueous medium.¹⁹ These K values indicate that the structure of Fc1^+ is optimal for inclusion complexation with CB7. Obviously, removal of the single methylene connecting the ferrocenyl and trimethylammonium groups leads to a 10-fold decrease in the K value for complexation of Fc0^+ . Similarly, the addition of an extra methylene to the linker (guest Fc2^+) also causes a small decrease in the stability of the complex.

Highly stable inclusion complexes in aqueous solution are often detected in the gas phase using mass spectrometric techniques,^{20,21} which are thus extremely useful to confirm the formation of supramolecular complexes and to verify their stoichiometries. We used high-resolution mass spectrometry [electrospray (ESI) ionization with time-of-flight (TOF) mass analysis/detection] to confirm the formation of complexes between CB7 and all three guests. Fig. 3 shows the ESI mass spectrum obtained with an aqueous solution containing equal concentrations of Fc0^+ and CB7. The main peak in the spectrum, at m/z ratio of 714.7081, corresponds to the doubly charged species $\text{Na}^+\cdot\text{CB7}\cdot\text{Fc0}^+$. The formation of this species suggests that inclusion complexation between Fc0^+ and CB7 leaves one of the host portals free to interact with a sodium ion. A similar result was obtained with guest Fc1^+ leading to the observation of the doubly charged species $\text{Na}^+\cdot\text{CB7}\cdot\text{Fc1}^+$ at an m/z value of 721.7164 (Fig. S2†). In marked contrast to these results, mass spectrometric experiments with Fc2^+ led to

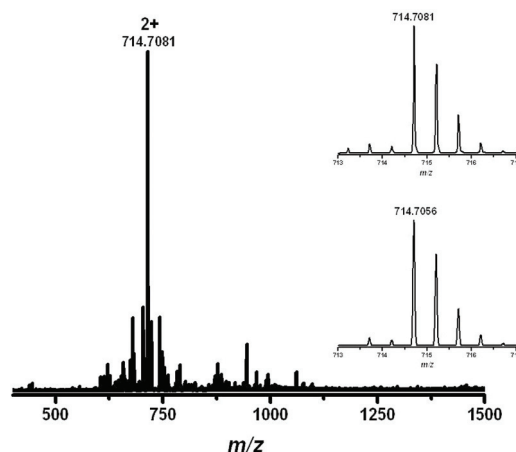


Fig. 3 High-resolution ESI-TOF mass spectrum obtained with an aqueous solution containing equal concentrations of Fc0^+ and CB7. The insert shows the experimental (top) and calculated (bottom) isotopic distributions corresponding to the main peak.

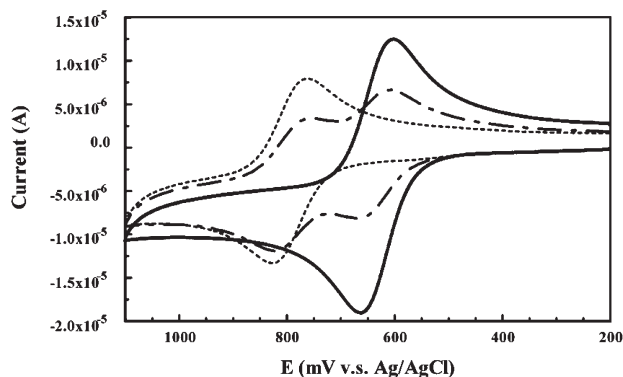


Fig. 4 Cyclic voltammetric behavior on glassy carbon (0.07 cm^2) of a 1.0 mM solution of $\text{Fc}^{\text{0}+}$ also containing 0.1 M NaCl in the absence (continuous line) and in the presence of 0.5 equiv. (discontinuous) and 1.0 equiv. (dotted) of CB7. Scan rate: 0.1 V s^{-1} .

the clear observation of the doubly charged species $\text{CB7}\cdot\text{Fc}^{\text{2}+}$ ($m/z = 717.2293$, Fig. S3[†]), which lacks the sodium ion attached to one of the host portals. In this species the second positive charge must be centered on the ferrocene group, reflecting the relative ease of oxidation of this ferrocenyl derivative (*vide infra*).

Ferrocene derivatives exhibit very fast and reversible one-electron oxidation.²² Therefore, the anodic electrochemical behavior of the guests $\text{Fc}^{\text{0}+}$ – $\text{Fc}^{\text{2}+}$ and their CB7 complexes is dominated by the presence of the reversible wave corresponding to the ferrocenium/ferrocene redox couple. For instance, Fig. 4 shows the cyclic voltammetric behavior recorded with $\text{Fc}^{\text{0}+}$, which shows a set of waves corresponding to the $\text{Fc}^{\text{0}2+}/\text{Fc}^{\text{0}+}$ redox couple centered at a half-wave potential ($E_{1/2}$) of 0.632 V vs. Ag/AgCl. Upon addition of 0.5 equiv. of CB7, a new set of waves is observed at a $E_{1/2}$ value of 0.797 V vs. Ag/AgCl. The new set of waves is assigned to the one-electron oxidation of the $\text{CB7}\cdot\text{Fc}^{\text{0}+}$ complex. Once the added concentration of CB7 reaches a full equivalent, the original set of waves disappears and the second set of waves reaches full development, consistent with the quantitative conversion of the free guest to its CB7 complex. The considerable shift of the $E_{1/2}$ value caused by the complexation with CB7 is consistent with the encapsulation of the ferrocenyl residue inside the CB7 cavity, which hampers the solvation of the oxidized and positively charged form of the ferrocenyl residue owing to the hydrophobic character of the host cavity. This electrochemical behavior is similar to that previously reported for $\text{Fc}^{\text{1}+}$,^{11,18} although the CB7-induced shift of the half-wave potential is larger with $\text{Fc}^{\text{0}+}$.

However, the anodic electrochemical behavior of $\text{Fc}^{\text{2}+}$ (Fig. 5) offers contrasting features. First, the half-wave potential for the one-electron oxidation of the free guest is 0.259 V vs. Ag/AgCl, and the oxidation of the ferrocenyl residue in this compound is thermodynamically easier than in $\text{Fc}^{\text{0}+}$. The reason for this difference relates to the presence in $\text{Fc}^{\text{2}+}$ of two methylenes, connecting the electron withdrawing trimethylammonium group and the ferrocene center. In $\text{Fc}^{\text{0}+}$ the direct

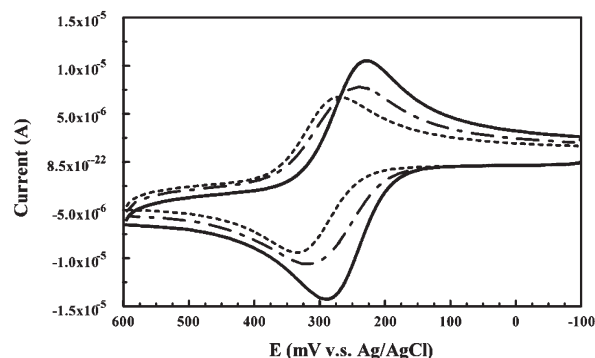


Fig. 5 Cyclic voltammetric behavior on glassy carbon (0.07 cm^2) of a 1.0 mM solution of $\text{Fc}^{\text{2}+}$ also containing 0.1 M NaCl in the absence (continuous line) and in the presence of 0.5 equiv. (discontinuous) and 1.0 equiv. (dotted) of CB7. Scan rate: 0.1 V s^{-1} .

attachment of the trimethylammonium group diminishes the electronic density in the ferrocene center, making its one-electron oxidation thermodynamically harder. Addition of 0.5 equiv. of CB7 to the $\text{Fc}^{\text{2}+}$ solution does not lead to the observation of a new set of waves, but simply to a shift of the original redox couple to more positive values (Fig. 5). This shift continues as more CB7 is added, until it reaches saturation when 1.0 equiv. of host is present in the solution. Clearly, the K value for the formation of the $\text{CB7}\cdot\text{Fc}^{\text{2}+}$ complex is high enough to allow for quantitative formation of the complex at the millimolar concentrations of host and guest used in these experiments. However, the observation of a single, shifting set of waves in this case, instead of the two sets of waves observed with $\text{Fc}^{\text{0}+}$ or $\text{Fc}^{\text{1}+}$ in the presence of less than 1.0 equiv. of host, is due to the smaller difference between the $E_{1/2}$ values for oxidation of the complex and the free guest.²³ The proximity (small potential difference) of the two sets of waves makes its voltammetric resolution impossible and is the key reason behind the observation of a single redox couple.

Table 2 summarizes the parameters obtained from the voltammetric experiments for all three guests and their CB7 inclusion complexes. Several trends are clear from the data in Table 2. First, the diffusion coefficient of each CB7 complex is lower than that for the free guest. This finding is an expected result of the larger effective volume of the complexes relative

Table 2 Electrochemical parameters obtained from the voltammetric experiments in 0.1 M NaCl solution at 25 °C

Compound	D_0^a ($\text{cm}^2 \text{ s}^{-1}$)	$E_{1/2}^b$ (V)	k^{oc} (cm s^{-1})
$\text{Fc}^{\text{0}+}$	6.9×10^{-6}	0.632	Fast
$\text{CB7}\cdot\text{Fc}^{\text{0}+}$	3.6×10^{-6}	0.797	0.011 ± 0.003
$\text{Fc}^{\text{1}+}$	5.2×10^{-6}	0.423	Fast
$\text{CB7}\cdot\text{Fc}^{\text{1}+}$	2.6×10^{-6}	0.541	0.019 ± 0.003
$\text{Fc}^{\text{2}+}$	5.3×10^{-6}	0.259	Fast
$\text{CB7}\cdot\text{Fc}^{\text{2}+}$	2.9×10^{-6}	0.303	0.022 ± 0.008

^a Diffusion coefficients measured using a disk ultramicroelectrode. Error margin <5%. ^b Half-wave potentials measured against Ag/AgCl reference. Error margin: $\pm 0.004 \text{ V}$. ^c Heterogeneous rates of electron transfer determined using Nicholson's method.²⁴

to the free ferrocene derivatives. The thermodynamic ease of oxidation of the free guests decreases in the order $\text{Fc}2^+ > \text{Fc}1^+ > \text{Fc}0^+$, due to the decreasing attenuation of the electron withdrawal effect exerted by the trimethylammonium group as methylenes are removed from the tether. The same order is maintained with the inclusion complexes. The CB7-induced shift in the half-wave potential ($\Delta E_{1/2} = E_{1/2,\text{complex}} - E_{1/2,\text{free}}$) follows the opposite trend and is largest for $\text{Fc}0^+$ (165 mV) and lowest for $\text{Fc}2^+$ (44 mV). Finally, the voltammetric behavior of the complexes was found to be in the quasi-reversible regime, while that of the free guests is fully reversible (fast electron transfer). The standard rate constants (k^0) for heterogeneous electron transfer for the latter were thus too fast to measure in these cyclic voltammetric experiments. However, the k^0 values were measurable for the complexes and show a slight increasing trend in going from the $\text{CB7}\cdot\text{Fc}0^+$ to the $\text{CB7}\cdot\text{Fc}2^+$ complex.

Our attempts to crystallize these complexes failed to produce single crystals suitable for X-ray diffraction analysis. This problem was not unexpected given the usual difficulties involved in obtaining single crystals of CB7 complexes.²⁵ (Typically, CB6 and/or CB8 complexes are much easier to crystallize.) In order to gain some information on the structures of the complexes, we resorted to DFT computational methods. In our experience, computational methods tend to produce very reliable structures for cucurbituril complexes. In those cases in which we have obtained both the X-ray crystal structure and the energy-minimized computational structure, both sets of data have shown very good agreement.^{6,26,27} Therefore, we run energy minimizations for the three CB7 complexes surveyed here. The resulting structures are shown in Fig. 6.

Inspection of these structures reveals that as the number of methylenes in the tether between the trimethylammonium group and the ferrocene center increases the complex becomes less compact, with larger fractional volumes of the guest protruding out of the cavity through both host portals. The effect of a single methylene addition is relatively subtle, but the structural differences between the two extreme cases, $\text{CB7}\cdot\text{Fc}0^+$ and $\text{CB7}\cdot\text{Fc}2^+$, are clear. A noticeable result from guest elongation is that the ferrocenyl group is not completely encapsulated in the CB7 cavity and is partially exposed to the solution in the $\text{CB7}\cdot\text{Fc}2^+$ complex.

Discussion

The high stability of the $\text{CB7}\cdot\text{Fc}1^+$ complex results from a combination of hydrophobic and ion-dipole interactions. However,

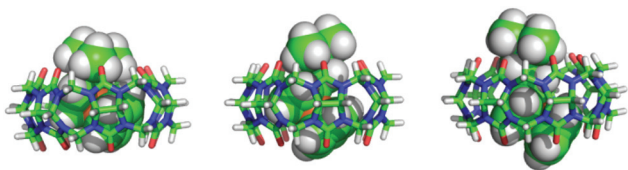


Fig. 6 Energy-minimized structures (B3LYP/3-21G*) computed for the $\text{CB7}\cdot\text{Fc}0^+$, $\text{CB7}\cdot\text{Fc}1^+$ and $\text{CB7}\cdot\text{Fc}2^+$ complexes (from left to right).

thermodynamic measurements with several ferrocene derivatives suggest that hydrophobic interactions between the ferrocenyl residue and the inner cavity of CB7 are more important than ion-dipole interactions between the tetramethylammonium group and the carbonyl oxygens on the host portal.^{6,10} A key motivation behind this work was to test this hypothesis by varying the distance between the tetramethylammonium and ferrocene residues on the guest and forcing the complex to favor one of the two interactions, presumably the strongest one. We should note here that the factors affecting the thermodynamic stability of the inclusion complexes formed between alkylammonium ions and the smaller CB6 host were investigated by Mock and Shih more than two decades ago.²⁸

The equilibrium association constants determined here suggest that the presence of a single methylene between the tetramethylammonium and ferrocenyl groups leads to the optimum development of attractive interactions in the inclusion complex. As a result the measured K values are in the order $\text{CB7}\cdot\text{Fc}1^+ > \text{CB7}\cdot\text{Fc}2^+ > \text{CB7}\cdot\text{Fc}0^+$. Nonetheless, the overall variation of the K values is moderate, suggesting that the complex can adjust without pronounced stability losses to small variations in the distance between the trimethylammonium and ferrocene residues. The NMR spectroscopic data (Table 1) show a very interesting trend in these complexes. The complexation-induced shift of the guest methyl protons goes from -0.23 ppm (CB7 induces an upfield shift) in $\text{Fc}0^+$ to $+0.13$ ppm in $\text{Fc}2^+$. The upfield (negative) shift in the former case indicates that the trimethylammonium group is very close to the plane defined by the carbonyl oxygens on the host portal, whereas the positive value in the latter case reveals that the trimethylammonium group is further removed from the portal entrance. Guest $\text{Fc}1^+$ represents a compromise between both extremes and the trimethylammonium group adopts an intermediate position. This finding is in excellent agreement with the energy-minimized structures obtained computationally (Fig. 6).

The mass spectrometric data also show an important difference for the $\text{CB7}\cdot\text{Fc}2^+$ complex. The $\text{CB7}\cdot\text{Fc}0^+$ and $\text{CB7}\cdot\text{Fc}1^+$ complexes are clearly detected as Na^+ adducts, with a total +2 charge. This finding indicates that both complexes possess a region that can easily interact with Na^+ . Based on the known affinity of CBn carbonyl rims with metal cations,^{29,30} we postulate that the binding site for Na^+ in both complexes is the cavity portal not occupied by the trimethylammonium group. In marked contrast to this, $\text{CB7}\cdot\text{Fc}2^+$ does not form a Na^+ adduct under our MS conditions, but acquires a second charge through oxidation. As indicated before, this is far from surprising because $\text{CB7}\cdot\text{Fc}2^+$ has the lowest half-wave potential (Table 2) for one-electron oxidation among the three complexes. The presence of a positive charge on the ferrocenyl center is thus expected to prevent the binding of any cations to the cavity portal in the immediate vicinity. Alternatively, another factor that may influence the lack of bound Na^+ ion to the second host portal in this complex, is the fact that the ferrocenyl group partially protrudes through

the portal (see Fig. 6), thus hindering the possible binding of the sodium ion.

The electrochemical behavior of the complexes is also very instructive. The most interesting parameter is the already defined CB7-induced shift of the half-wave potential, which decreases steadily from CB7·Fc0⁺ to CB7·Fc2⁺. These values can be interpreted as a measure of the increased thermodynamic hindrance for the one-electron oxidation of the ferrocenyl residue due to its encapsulation inside the host. While both CB7·Fc0⁺ and CB7·Fc1⁺ show values that are within the range expected for ferrocenyl groups deeply inserted in the CB7 cavity ($\Delta E_{1/2} > 100$ mV), the $\Delta E_{1/2}$ value measured for CB7·Fc2⁺ is clearly smaller (44 mV). This reflects that the microenvironment of the ferrocenyl residue in this complex is much closer to that experienced by the unbound guest as compared to the other two complexes. Therefore, we conclude that the ferrocenyl center is partially exposed to the surrounding aqueous solution, which is in excellent agreement with the computational results (Fig. 6). Overall, the measured CB7-induced $\Delta E_{1/2}$ values in these complexes are extremely sensitive to the location of the ferrocenyl residue within the CB7 cavity and its relative exposure to water molecules. This finding illustrates very nicely that electrochemical techniques can be very useful to detect small structural variations.

The standard rate constants for heterogeneous electron transfer measured here seem to be in agreement with these conclusions, as they show a slight trend to increase according to the order CB7·Fc0⁺ < CB7·Fc1⁺ < CB7·Fc2⁺. This trend is in agreement with expectations based on the relative level of shielding and insulation from the electrode surface³¹ that is imposed on the ferrocenyl groups by their various levels of encapsulation inside the CB7 host.

It is instructive to analyze the DFT computational data in further detail. We measured the distance between the positively charged ammonium nitrogen and the plane defined by the carbonyl oxygen on the nearest host portal in the structures of the energy-minimized complexes (Fig. S4†). The measured values are 0.39, 0.73 and 0.85 Å for CB7·Fc0⁺, CB7·Fc1⁺ and CB7·Fc2⁺, respectively. We also measured the corresponding distances between the iron(II) ion in the ferrocene moiety and the carbonyl oxygen plane on the opposite portal, finding values of 3.17, 2.33 and 1.22 Å, in the same order as before. Clearly, both the trimethylammonium and the ferrocene group experience displacements from their ideal positions, defined by those observed in the most stable complex (CB7·Fc1⁺). However, the displacements observed with the ferrocene group are of larger magnitude than those experienced by the trimethylammonium group. This is slightly counterintuitive since hydrophobic forces are believed to predominate in these complexes. On the other hand, the larger displacements of the ferrocene group may also reflect the fact that the hydrophobic contact surface in the host cavity is relatively large and permits larger shifts on the position of the ferrocene residue without significant losses in the stability of the complex.

Conclusions

Overall, the experimental and computational data obtained in this work show that small variations on the length of the tether (0–2 methylenes) connecting the trimethylammonium and ferrocenyl groups in these guests lead to subtle, but well defined changes in the structures of the CB7 complexes, which translate into significant differences in their voltammetric behavior. The overall thermodynamic stability of the three CB7 complexes studied here is however relatively resilient to the number of methylenes in the linker.

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Notes and references

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