Binding interactions between the host cucurbit[7]uril and dendrimer guests containing a single ferrocenyl residue†

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The stability of the inclusion complexes formed between the host cucurbit[7]uril and dendrimers containing a single ferrocene residue is strongly affected by the solution pH and the growth of the dendrimer, reaching its highest values on the second and third generation dendrimers, whereas no complex is formed with the first generation compound.

In the last five years the binding properties of cucurbit[*n*]uril hosts[1] have received considerable attention resulting from Kim's initial report[2] on the isolation of cucurbit[7]uril and cucurbit[8]uril (**CB7** and **CB8**, respectively). In particular, **CB7** forms a stable inclusion complex with both oxidation states of ferrocene,[3] although the oxidized, ferrocenium form is more strongly bound than the neutral ferrocene form. Whereas hydrophobic interactions play an important role on the stability of these complexes, the binding selectivity for ferrocenium is consistent with the negatively charged character of the inner cavity surface of **CB** hosts, as revealed by electrostatic surface potential mapping calculations.[1] Conversely, the negative charge that resides on the carbonyl oxygens at the cavity portals of **CB7** has been identified as the most likely factor destabilizing the complex between this host and the anionic guest ferrocenecarboxylate.[4]

We have recently investigated the formation of inclusion complexes between **CB7** (or **CB8**) and Newkome-type dendrimers containing a single 4,4′-bipyridinium (viologen) residue at their apical positions.[5,6] Given this background and our general interest in the host–guest binding interactions between molecular receptors and dendrimers containing accessible guest residues,[7] we decided to investigate the complexation by host **CB7** of Newkome-type dendrimers containing a single ferrocene residue. The preliminary results of this work are presented here.

The synthesis, characterization and electrochemical properties of the ferrocene-containing dendrimers used in this work (see Fig. 1) have been previously reported.[8] Previous studies in our group demonstrate that the carboxylic acid groups on the hydrophilic periphery of these dendrimers have an average pK_a value of *ca.* 4.5.[9] Therefore, the dendrimers are protonated and essentially uncharged in solutions with pH $\leqslant$ 2, while they are anionic in solutions with pH $\geqslant$ 7. **CB7** was prepared and isolated as reported in the literature.[2]

Ferrocenecarboxylic acid (**FG0**) was used as a simple model compound for the dendrimers in this work. As mentioned before, ferrocenecarboxylate is not complexed at all by **CB7**. ^{1}H NMR spectroscopic studies in pH 7 solutions show no **CB7**-induced changes in the chemical shifts of the ferrocenyl proton resonances. Similarly, the half-wave potential ($E_{1/2}$) and current levels associated to the oxidation of the ferrocenyl residue of **FG0** are not altered by the presence of **CB7** in pH 7 solutions. The lack of interaction is very likely due to the electrostatic repulsion between the negative charge on the carboxylate group and the negative ends of the carbonyl dipoles on the two **CB7** portals.[4] This electrostatic force predominates over any stabilization that the hydrophobic cavity of **CB7** may provide to the ferrocenyl residue, thus preventing the formation of the inclusion complex.

At pH 7, the first generation dendrimer **FG1** is also deprotonated and presents three negative charges on its periphery. ^{1}H NMR spectroscopic and electrochemical studies demonstrate the complete lack of binding interactions between **CB7** and **FG1**. Molecular modelling shows that the carboxylate negative charges are in close proximity to the ferrocene core of the dendrimer, a situation that would give rise to intense electrostatic repulsion between the three carboxylates and the electron-rich portal of **CB7** in the hypothetical inclusion complex.

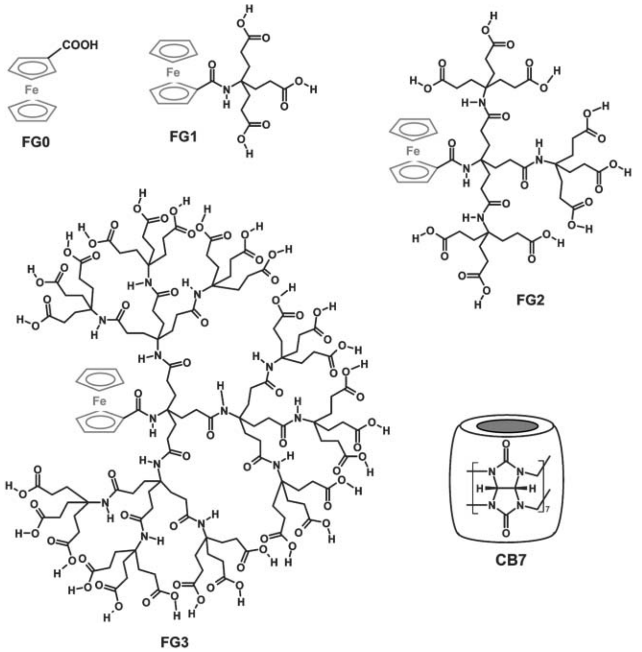

Fig. 1 Structures of **CB7** host and the ferrocene guests used in this work.

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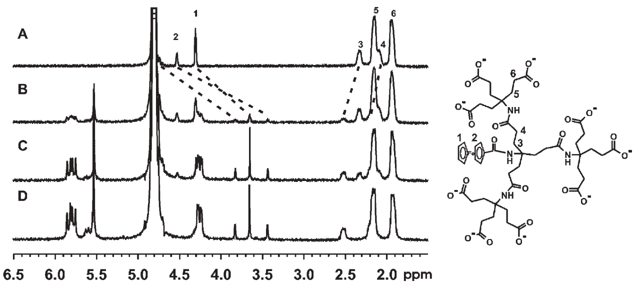

Fig. 2 ^{1}H NMR spectra (400 MHz) of **FG2** at pD 7, 0.1 M phosphate buffer, 0.1 M NaCl in the presence of (A) 0 equiv. of **CB7**, (B) 0.5 equiv. of **CB7**, (C) 1.0 equiv. of **CB7**, and (D) 1.5 equiv. of **CB7**. Similar spectra were observed in all cases where complexation occurred.

In contrast to these findings, ^{1}H NMR spectroscopic experiments provide clear evidence for complex formation in pH 7 solutions between **CB7** and the guests **FG2** and **FG3**, as shown by the host-induced, upfield shifts of the ferrocenyl proton resonances and downfield shifts of the resonances of the 12 protons (labelled 3 and 4 in Fig. 2) on the inner dendritic branches. The rate of exchange is slow in the NMR timescale, so two sets of peaks (for bound and unbound dendrimers) are observed in the presence of 0.5 equivalents of host. Dendrimers **FG1–FG3** are unsymmetric and, upon binding to **CB7**, the equatorial plane of symmetry in the host is lost. This lack of symmetry is clearly displayed in the ^{1}H NMR spectra, where there is an obvious signal splitting of the upper and lower methylene protons of **CB7**. The protons on the outer dendritic branches hardly interact with the core and their resonances are not shifted by **CB7** binding. The fact that these outer proton resonances are not shifted suggests that the dendrimer's anionic periphery is sufficiently far away from the electron-dense portals of the host to decrease any repulsive forces in the inclusion complex to low levels, making its formation possible.

As dendritic growth continues, going from guest **FG2** to **FG3**, the number of negatively charged carboxylate groups in the periphery (at pH 7) quickly increases. However, dendritic growth also ensures that the greater negative charge on the periphery has less influence on the ferrocene core due to the increased distance between them (Fig. 3). This effect is clearly evidenced by the increasing stability constants measured for the **CB7** inclusion complexes in going from **FG1** to **FG3** at pH 7 (see data in Table 1). From steric considerations only, increasing the dendron size should lead to a decrease in binding affinity.[7] Therefore, this finding highlights the importance of electrostatic forces in binding interactions involving **CB7**.

The complexation of **FG2** by **CB7** was also verified by cyclic voltammetric experiments. The half-wave potential for the oxidation of the ferrocene residue in **FG2** undergoes a cathodic shift of *ca.* 18 mV upon the addition of 1.5 equiv. of **CB7**. This **CB7**-induced $E_{1/2}$ shift results from the additional stability provided to the oxidized (+1) ferrocenium form by the electron-rich cavity of **CB7**. The voltammetric behavior of the dendrimer exhibits quasi reversible character in the presence of the host. This trend is more pronounced in dendrimer **FG3**, which exhibits completely irreversible voltammetric behavior in the presence of **CB7**. Clearly, the formation of an inclusion complex between **CB7** and the dendrimer's ferrocenyl residue gives rise to slower electrochemical kinetics, as the ferrocene center is encapsulated by the simultaneous effect of the dendritic mass and the including host, both combining to decrease the access and hinder the approach of the redox core to the electrode surface.[10] As anticipated from the relative dendritic masses, this effect is more pronounced with **FG3** than with **FG2**.

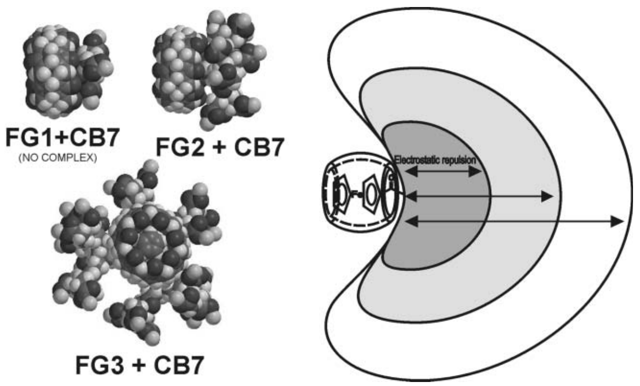

Fig. 3 Structures of the **CB7** complexes as obtained by molecular modelling (AM1). Note that the **CB7·FG1** complex is computationally unstable as represented here and would undergo dissociation upon energy minimization. The stability of the complexes with the two larger dendrimers is rationalized by the longer distance between the peripheral carboxylates and the **CB7** portals.

The formation of a stable complex between the **FG2** dendrimer and **CB7** was further verified by the observation of an intense peak corresponding to the complex [**CB7·FG2**]$^+$ at *m*/*z* 2310 in MALDI-TOF mass spectrometric experiments.

At pH 2, however, the periphery of the **FG1** ferrocene dendrimer is protonated and neutral, which removes any possibility of electrostatic repulsions between the dendrimer periphery and the **CB7** portal. The ferrocene core is now free to occupy the hydrophobic cavity of **CB7** and binding was demonstrated by ^{1}H NMR spectroscopic experiments. Key observations are the **CB7**-induced upfield shifts of the ferrocenyl proton resonances and the simultaneous downfield shifts of the resonances corresponding to the protons on the dendrimer branches. Cyclic voltammetric experiments with solutions containing **FG1** also provide evidence for complexation. The presence of 1.5 equiv. **CB7** leads to a cathodic shift of 26 mV in the half-wave

Table 1 Diffusion coefficients (D_0), equilibrium association constants (K) and half-wave potential shifts ($\Delta E_{1/2}$) measured with compounds **FG0–FG3** interacting with the host **CB7**

	pH 7			pH 2		
Guest	$10^6 D_0{}^a$/ cm^2 s^{-1}	K^c/ L mol^{-1}	$\Delta E_{1/2}{}^e$/ mV	$10^6 D_0$/ cm^2 s^{-1}	K^c/ L mol^{-1}	$\Delta E_{1/2}{}^e$/ mV
FG0	nm[b]	nb[d]	0	Insol.[g]	n/a	n/a
FG1	4.2	nb[d]	0	4.8	3.9×10^4	−26
FG2	2.5	3.8×10^5	−18	3.0	4.2×10^6	−41
FG3	1.5	7.7×10^5	Irrev.[f]	1.9	Insol.[g]	Insol.[g]

[a] The diffusion coefficients were measured by PGSE NMR techniques. [b] Not measured. [c] Measured by NMR spectroscopy using competition experiments between the ferrocene-containing guest and dimethyldiazapyrenium as a reference guest (see ESI). [d] No binding observed. [e] Observed half-wave potential shift upon addition of 1.5 equiv. of host. [f] Irreversible voltammetric behaviour [g] Insoluble.

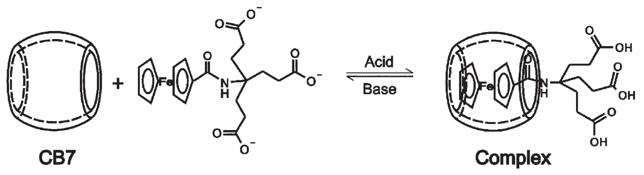

Fig. 4 The complexation of **FG1** by host **CB7** can be switched 'on–off' through peripheral protonation/deprotonation.

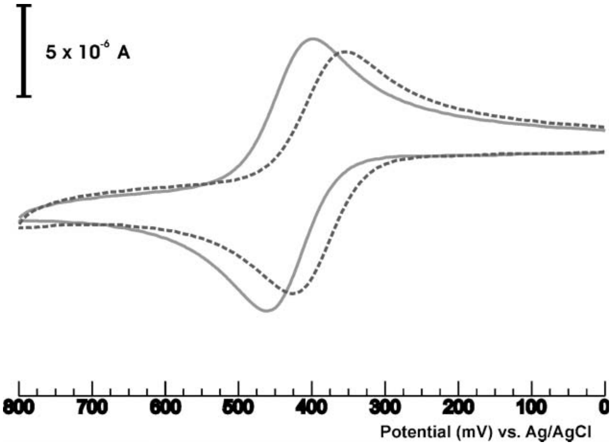

Fig. 5 Cyclic voltammetric response on glassy carbon (0.071 cm^2) of (1.0 mM) in pH 2 phosphate buffer, 0.1 M NaCl, in the absence (solid line) and presence of 1.5 equivalents (dotted line) of **CB7** at a scan rate of 0.1 V s^{-1}.

potential associated to the one-electron oxidation of the ferrocenyl residue of **FG1**. Again, **CB7** provides increased stability to the positively charged oxidized species, as expected from the electron-rich character of the inner cavity of this host. The presence of a complex at pH 2 was also confirmed by MALDI-TOF mass spectroscopic experiments, which showed an intense peak for [**CB7·FG1**]$^+$ at *m*/*z* 1621. A stability constant of 3.9×10^4 L mol^{-1} was measured for this complex. This is an interesting result since it demonstrates pH-switchable binding with **CB7** and the importance of electrostatic forces in **CB7** binding (Fig. 4).

In pH 2 solutions the guests **FG2** and **FG3** also form complexes with **CB7**. ^{1}H NMR and MALDI-TOF mass spectroscopic data verify the complexation of **FG2**. For instance, a peak for [**CB7·FG2**]$^+$ at *m*/*z* 2,310 was observed in MALDI-TOF mass spectrometry and a stability constant of 4.2×10^6 L mol^{-1} was determined. Cyclic voltammetry shows a significant half wave potential cathodic shift of 41 mV upon addition of **CB7** and some degree of quasi reversibility, which results from the overall encapsulation of the ferrocenyl center (Fig. 5). The **CB7·FG3** complex, however, precipitates immediately upon addition of **CB7** to acidic solutions containing **FG3**. Thus, NMR spectroscopic and electrochemical experiments were not possible. In spite of this precipitation, however, MALDI-TOF mass spectrometric experiments were still possible, yielding a clear indication of complex formation, due to the observation of peak for [**CB7·FG3**]$^+$ at *m*/*z* 4372.

Table 1 summarizes the diffusion coefficients, equilibrium binding constants with **CB7**, and electrochemical data of interest for these dendrimers in acidic (pH 2) and neutral (pH 7) solutions. The diffusion coefficients of the dendrimers were obtained by PGSE NMR techniques[11] and correlated very well with the limiting currents obtained in voltammetric experiments performed with ultramicroelectrodes. The diffusion coefficients are smaller in the pH 7 solutions, which is consistent with larger hydrodynamic radii in this medium. According to previous results on similar dendrimers,[12] their structure in acidic solution is relatively collapsed, while the presence of negative charges in neutral solution leads to expanded conformations that minimize the electrostatic repulsions among the peripheral carboxylate groups. In spite of the more open and expanded dendrimer conformation in neutral solutions, the second generation compound **FG2** is more strongly bound by **CB7** in pH 2 solutions, a finding that must reflect the lack of negative charges on the dendrimer at that pH.

Our group has investigated extensively the binding interactions between well-known molecular hosts and dendrimers containing guest residues located on the same position as that of the ferrocenyl moiety in **FG1–FG3**. This body of work has been the subject of a recent review.[7] Generally, the equilibrium association constants tend to decrease with dendrimer growth, although the incremental decrease from generation to generation does not follow a simple pattern. For instance, the stability of the complexes formed by dendrimers **FG1–FG3** with the host β-cyclodextrin decreases quickly from the first to the third generation dendrimer, which is bound very weakly by β-cyclodextrin. In this work, we demonstrate exactly the opposite trend, that is, increasing the size of the dendritic component leads to increasing thermodynamic stability of the **CB7** inclusion complex. This is a unique finding that underlines the importance of electrostatic factors in host–guest binding interactions involving **CB7**. It is likely that other cucurbit[*n*]uril hosts will be subject to similar electrostatic effects and this is the subject of current research work in our group.

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