

Multisite Inclusion Complexation of Redox Active Dendrimer Guests

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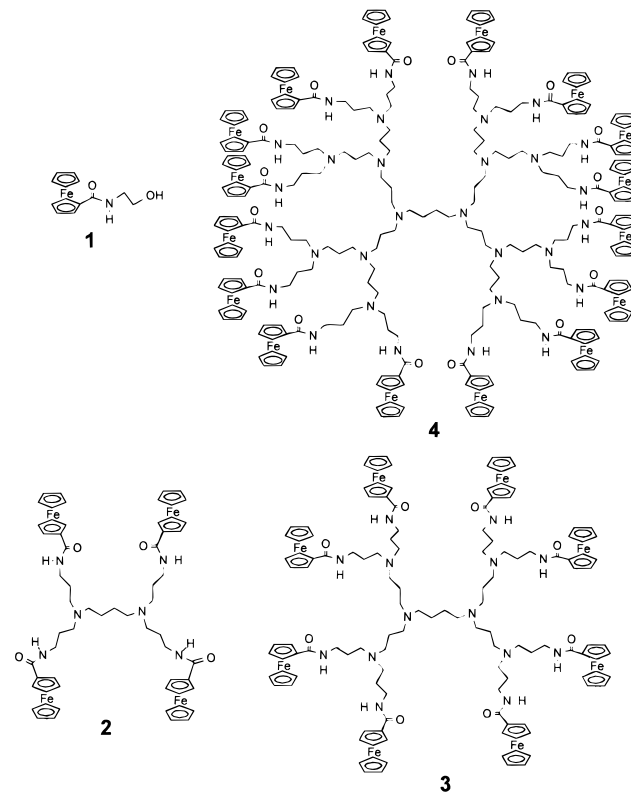
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Rapid advances in the chemistry of dendrimers^{1–6} are leading to their proposed use in a range of applications, some of them involving interactions with biological molecules.⁷ The structure of dendrimers allows the regular placement of repeating residues on their surfaces. Therefore, one may think of dendrimers as multisite guests for chemical interactions/reactions of any nature, an idea that conveys their potential use for chemical amplification. In this paper, we describe the first use of dendritic terminal groups for inclusion complexation by well-known molecular hosts,⁸ specifically the cyclodextrins (CDs). Our data indicate that dendrimers of moderate size act as effective guests leading to the formation of very large supramolecular complexes.

Some of us have recently reported a new class of organometallic dendrimers which contain up to 64 equivalent ferrocene centers on their surfaces.^{9–12} Therefore, we focus our attention on dendrimers **2–4**, whose synthesis has been described elsewhere.¹² Compound **1** was also prepared for comparison purposes. Ferrocene is indeed an excellent substrate for inclusion complexation by β -CD.^{13–17} According to this, we verified that β -CD binds the simple ferrocene derivative **1** in 0.1 M NaCl/D₂O. Using ¹H NMR spectroscopy, we measured a binding constant of 1230 M⁻¹ for the β -CD·**1** complex. The formation of the inclusion complexes β -CD·**1** and DM- β -CD·**1** (DM = dimethyl) was also clearly evidenced by the voltammetric data presented in Table 1. In contrast, the ferrocene electronic absorption band centered around 438 nm is not significantly affected by CD complexation.

Table 1. Electrochemical and Spectroscopic Parameters for Ferrocene Derivative **1** in the Presence and in the Absence of β -CD and DM- β -CD Measured in 0.1 M NaCl at 25 °C

	medium		
	0.1 M NaCl (no CD)	0.1 M NaCl + 5.0 mM β -CD	0.1 M NaCl + 5.0 mM DM- β -CD
$E_{1/2}$ (V vs SCE)	0.39	0.45	0.45
D_0 (cm ² /s)	5.7×10^{-6}	2.1×10^{-6}	2.5×10^{-6}
λ_{\max} (nm)	438	437	437
ϵ (M ⁻¹ cm ⁻¹)	365	365	365



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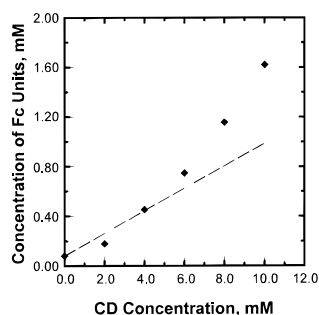
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While millimolar aqueous solutions of **1** can be easily prepared, the more hydrophobic compounds **2–4** exhibit very low solubilities in aqueous media (see Table 2). The aqueous solubility values were measured after prolonged mixing of dichloromethane solutions of the dendrimers with 0.1 M NaCl aqueous solutions (see Supporting Information for details). The data in Table 2 clearly show that the aqueous solubility of dendrimers **2–4** is greatly enhanced by the presence of either CD, a finding which can only be rationalized by the formation of inclusion CD·ferrocene complexes on the surface of the dendritic structures. Interestingly, the solubility measured in the presence of either CD host decreases markedly with increasing dendrimer generation. Thus, **4** shows the lowest solubility values among the three surveyed dendrimers. This effect is probably related to the steric hindrance associated with the complexation by CD hosts due to the increased proximity of the ferrocene subunits in **4** (as compared to **2** and **3**).

To address in more detail the complexation phenomena in these systems, we determined the solubility of compound **3** in a series of aqueous solutions containing varying concentrations of β -CD. Figure 1 shows the solubility values (\blacklozenge) measured as a function of the concentration of the β -CD host in the medium. As expected, the solubility values (expressed in millimoles of ferrocene units per liter of solution) rapidly increase with the CD concentration. However, the results deviate from those expected for the inclusion complexation of individual hydrophobic molecules. The dotted line in the figure represents the total concentration of solubilized ferrocene

Table 2. Solubilities (expressed as mmol of ferrocene/L) of Dendrimers 2–4 in 0.1 M NaCl Aqueous Media at 25 °C

dendrimer	medium		
	no CD	6 mM β -CD	6 mM DM- β -CD
2	0.013	1.0	1.7
3	0.081	0.71	0.80
4	0.028	0.17	0.12

**Figure 1.** Concentration of solubilized ferrocene subunits as a function of the concentration of β -CD in the aqueous phase (0.1 M NaCl). The data were obtained with dendrimer 3 and the ferrocene concentrations (\blacklozenge) were determined spectrophotometrically. The dotted line represents the calculated ferrocene solubilities assuming that single-ferrocene molecules are solubilized by complexation to a host that exhibits $K = 1230 \text{ M}^{-1}$ as the equilibrium association constant for ferrocene binding.

calculated for a simple 1:1 association equilibrium, according to the equation

$$[\text{Fc}]_{\text{T}} = \frac{K[\text{Fc}]_{\text{F}}[\text{CD}]_{\text{T}}}{1 + K[\text{Fc}]_{\text{F}}} + [\text{Fc}]_{\text{F}} \quad (1)$$

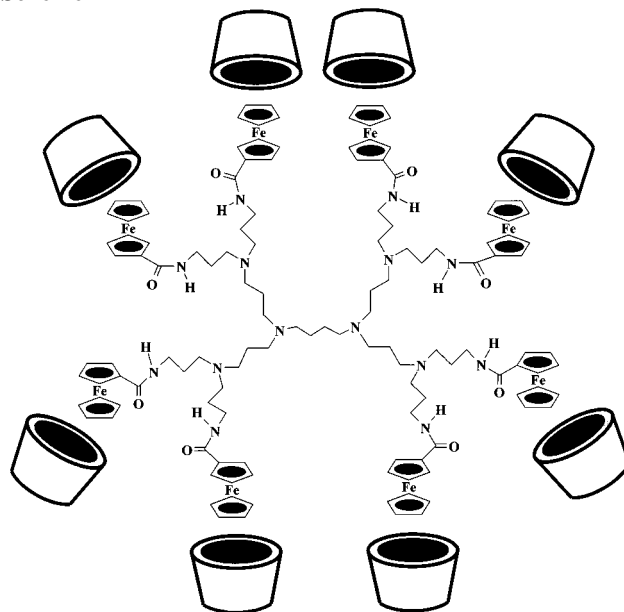
where $[\text{Fc}]_{\text{T}}$ is the total concentration of solubilized ferrocene, $[\text{Fc}]_{\text{F}}$ is the free ferrocene concentration (0.081 mM for compound 3 as taken from Table 2), $[\text{CD}]_{\text{T}}$ is the total concentration of β -CD host, and K is the binding constant value determined for the complexation of 1 with β -CD. The experimentally determined solubilities are smaller than those predicted by the line from eq 1 at low CD concentrations and larger at high CD concentrations. This finding suggests that solubilization of a dendrimer requires the complexation of a minimum number of ferrocene subunits. Therefore, at low CD concentration solubilization lags behind complexation, while the reverse is true at higher CD concentrations.

The addition of small aliquots of a concentrated solution of sodium 2-naphthalenesulfonate to a solution containing dendrimer 3 solubilized by β -CD resulted in the immediate formation of a light brown precipitate. The filtrate solution shows a perfectly flat spectral base line in the region around 438 nm (see Supporting Information), indicating the absence of solubilized ferrocene. The precipitate was found ($^1\text{H NMR}$) to be composed essentially of dendrimer 3 (with residual amounts of CD and sodium 2-naphthalenesulfonate). Clearly, the 2-naphthalenesulfonate anion, an excellent substrate for inclusion complexation by β -CD,¹⁸ displaces the ferrocene subunits from the CD cavities and causes the precipitation of the hydrophobic dendrimer.¹⁹ These results strongly support the formation of inclusion complexes of the dendrimer's peripheral ferrocene residues by the CD hosts in the solution.

The electrochemical behavior of the solutions containing dendrimers solubilized by the presence of either CD is dominated by the reversible oxidation of the ferrocene residues. For instance, the cyclic voltammogram (see Supporting Information)

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(19) The ionic nature of the competing guest 2-naphthalenesulfonate prompted us to verify that the observed precipitation was not due to nonspecific "salting out" effects. Similar concentrations of added NaCl failed to precipitate the dendrimer from these solutions.

Scheme 1

recorded with a solution of dendrimer 3 solubilized by β -CD exhibits only one voltammetric wave ($E_{1/2} = 0.51 \text{ V}$). Additions of β -CD to this solution left the voltammogram essentially unchanged. These results indicate that all the dendrimer's ferrocene residues are equivalent and undergo independent monoelectronic oxidation.¹² The invariance of the voltammogram to further CD additions clearly suggests that all ferrocene residues are complexed by the CD hosts under the initial conditions. In contrast to these results, the electrochemical behavior of dendrimer 4 solubilized by β -CD exhibits two different voltammetric waves (see Supporting Information). The wave at less-positive potentials ($E_{1/2} = 0.38 \text{ V}$ vs SCE) corresponds to uncomplexed ferrocene residues while the second, more anodic wave ($E_{1/2} = 0.51 \text{ V}$ vs SCE) results from the oxidation of complexed ferrocene subunits. Again, further additions of the CD host to the solution leave the voltammetric behavior unchanged, strongly suggesting that the uncomplexed ferrocene residues are not accessible to the CD hosts in the solution. These findings provide additional evidence for substantial steric congestion on the surface of dendrimer 4, which limits the number of ferrocene residues that can be included by the bulky CD hosts. This is in excellent agreement with the previously noted lower solubility of dendrimer 4 (compared to 2 and 3) in CD-containing solutions.

Although the complexation equilibria in these systems are very complicated, our electrochemical and spectroscopic results indicate that all the ferrocene residues in dendrimers 2 and 3 are accessible for inclusion complexation by the CD hosts. From a conceptual standpoint, the dendrimer serves as a three-dimensional template to organize the CD receptors in the periphery of the dendrimer structure, giving rise to large supramolecular assemblies (see Scheme 1). For instance, the molecular weight of the octameric inclusion complex pictorially represented in Scheme 1 is more than 11 kDa. Furthermore, a reversible electrochemical mechanism to break up these supramolecular species is available as the binding affinity of the CD-ferrocene complex is strongly diminished by ferrocene oxidation.^{13,15,16}

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Supporting Information Available: Experimental details and spectral data (4 pages). See any current masthead page for ordering and Internet access instructions.

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