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Electron Transfer and Molecular Recognition in Metallocene-Containing Dendrimers

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Dedicated to the late Professor Moisés Morán

Keywords: Metallocenes / Dendrimers / Electrochemistry / Molecular recognition / Supramolecular chemistry

This manuscript provides a summary of the relatively large body of research on the preparation and characterization of dendrimers containing (1) multiple copies of metallocene residues on their surfaces or (2) a single metallocene residue at their core. Special emphasis is placed on dendrimers functionalized with either ferrocene or cobaltocenium groups, because their reversible electrochemistry makes them particularly attractive to the author's group. Dendrimers containing multiple, peripheral metallocene residues are of interest to develop multivalent interactions with suitable receptors or receptor assemblies. With dendrimers containing a single metallocene at their cores, the key questions relate to the effects of the dendritic mass on their properties and degree of encapsulation or site isolation. We focused our work on the electrochemical properties of these dendrimers as well as on their use as guests in molecular recognition processes with freely diffusing hosts.

Introduction

Dendrimers[1] are highly branched macromolecules spanning from a central core and containing a series of layers, structurally and synthetically distinct, which are usually referred to as "generations". Whereas the initial interest in dendrimers was basically related to the synthetic and structural characterization challenges that they pose, their fractal geometries, high molecular weights, and nanometer-range sizes, a little more than a decade ago many groups started to focus on their functionalization. In very simplistic terms, one can look at a functionalized dendrimer as one or more functional residues attached to a large dendritic mass that defines the shape, size, and other properties of the macromolecule. In some cases, the dendritic mass also has a pronounced influence on the chemical or physical properties of the functional residue. There are two general ways to approach dendrimer functionalization. First, one can attach many copies of a functional residue on the surface of the dendrimer (peripheral functionalization). Second, one can grow dendritic mass branching out from a functional residue (core functionalization). Both styles of functionalization (see Figure 1 for schematic drawings) have different advantages and target various purposes. Peripheral functionalization is advantageous to develop multivalent interactions with dendrimers or to achieve chemical amplification. Core functionalization is more suitable when the main interest revolves around site isolation of the residue and/or the concomitant alteration of its properties.

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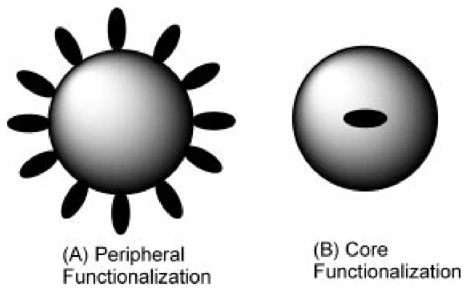

Figure 1. Main approaches to dendrimer functionalization.

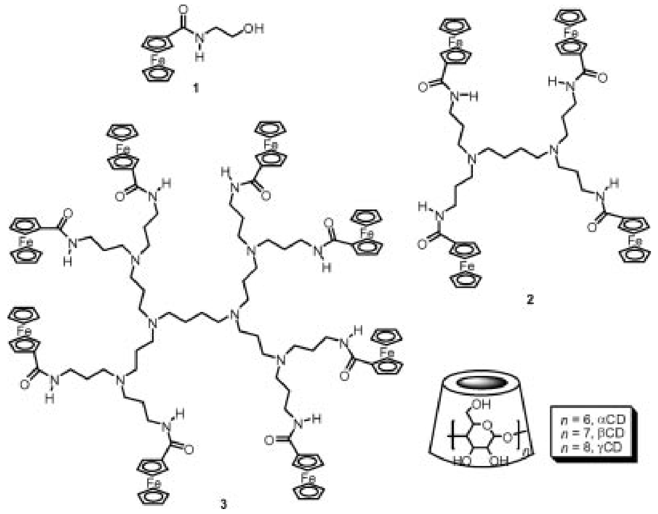

Figure 2. Structures of model compound **1**, dendrimers **2** and **3**, and the cyclodextrin hosts.

In this manuscript, research work on dendrimers functionalized with metallocene residues is described, placing significant emphasis on the work done by my research group, without relegating the very important work done by other groups, from which we have gained inspiration and a healthy measure of competition. From the standpoint of my own group, reversible electrochemical properties are quite desirable, and, thus, we have mostly focused our efforts on dendrimers functionalized with either ferrocene [bis(cyclopentadienyl)iron(II)] or cobaltocenium [bis(cyclopentadienyl)cobalt(III)] centers. Both metallocene residues are stable, 18-electron systems, which differ on the charge of their most accessible oxidation states: zero for ferrocene and +1 for cobaltocenium. Ferrocene undergoes fast one-electron oxidation to the positively charged ferrocenium form, whereas cobaltocenium exhibits fast one-electron reduction to produce the neutral cobaltocene. Both electrochemical processes take place at accessible potentials and usually maintain fast kinetics (*reversibility* in electrochemical jargon) in ferrocene- and cobaltocenium-containing compounds.

Dendrimers Containing Multiple Peripheral Metallocene Residues

Our initial interest in this type of system was sparked by the elegant work of Cuadrado and Morán, at Universidad Autónoma de Madrid, who were among the pioneering groups reporting the preparation of dendrimers with multiple, peripheral metallocene centers.[2] Our long-standing interest on the binding interactions between water-soluble ferrocene derivatives (see compound **1** as an example) and cyclodextrins, naturally led to the investigation of the supramolecular interactions between dendrimers **2** and **3** with cyclodextrin hosts[3] (see Figure 2).

The binding interactions between **1** and β-cyclodextrin (βCD) were studied by using ^{1}H NMR spectroscopy in 0.1 M NaCl/D$_2$O. An equilibrium association constant (K) of 1230 M^{-1} was measured by using this technique.[4] The formation of inclusion complex **1**·βCD was also evident from cyclic voltammetric data. The binding interactions between dendrimers **2** and **3**, as guests, and the βCD host were harder to study, as these dendrimers are quite insoluble in aqueous media. We observed, however, that the solubility of the dendrimers in aqueous solution containing 6.0 mM βCD was substantially higher.[4] In fact, our solubility measurements suggested that a minimum number of ferrocene residues per dendrimer must be CD bound for solubilization to take place. Competition experiments with a second guest (2-naphthalenesulfonate) and voltammetric experiments revealed that all the ferrocene residues in dendrimers **2** and **3** are accessible to βCD for formation of the inclusion complexes. On the other hand, a larger dendrimer (compound **4**, structure not shown) containing 16 ferrocenyl groups on its surface, shows signs of steric peripheral congestion, as not all the ferrocene groups are accessible for βCD complexation under our experimental conditions.

Conceptually, these dendrimers serve as three-dimensional templates for the organization of the CD receptors on their peripheries, giving rise to large supramolecular assemblies. For instance, the molecular weight of the octameric inclusion complex formed by the interaction of dendrimer **3** and excess βCD exceeds 11 kDa.[4] In addition to this, the one-electron oxidation of the ferrocene derivatives provides a reversible mechanism to release the CD receptors from these supramolecular complexes, as it is well known that the binding affinity of a ferrocene–βCD inclusion complex decreases by approximately two orders of magnitude upon oxidation of the ferrocene guest, effectively going from a K value in the range 1×10^3 to 5×10^3 M^{-1} to less than 50 M^{-1}.[5]

Our joint work with the Madrid group quickly moved to the exploration of the binding interactions between a similar series of dendrimers containing multiple cobaltocenium units on their surfaces and cyclodextrin hosts.[6] The simplest structures (dendrimers **5** and **6**) within this dendrimer series are shown in Figure 3. Unlike their ferrocene counterparts, these dendrimers have excellent aqueous solubility due to their polycationic character. Previous work from my group on the binding interactions between βCD and simple cobaltocenium revealed that the positively charged, oxidized form does not interact significantly with the CD host.[7] However, one-electron reduction leads to the formation of a stable inclusion complex between the neutral cobaltocene form and βCD. These binding interactions have a strong effect on the shape of the current–potential voltammetric curves for cobaltocenium. In the absence of βCD, one-electron reduction gives rise to extensive precipitation on the electrode surface of the neutral, hydrophobic cobaltocene, which results in a distorted, very sharp peak for its reoxidation process back to cobaltocenium.[7] The sharpness of this peak is strongly related to the stripping nature of the electrochemical process, as material deposited onto the electrode surface is redissolved back into the solution as a result of the electron-transfer reaction. Not surprisingly, similar cyclic voltammograms were observed with dendrimers **5** and **6** (Figure 4), strongly suggesting that the same βCD binding mechanism operates on them as it does on simple cobaltocenium derivatives. The lack of binding interactions between βCD and the fully oxidized, cationic forms of the dendrimers was verified by ^{1}H NMR spectroscopic data.[6] When comparing the behavior of ferrocene- and cobaltocenium-containing dendrimers, it is clear that dendrimers **5** and **6** interact with the cyclodextrin host only after one-electron reduction of the cobaltocenium units, whereas in the case of the ferrocene dendrimers (**2** and **3**, for instance) the binding interactions are disrupted by one-electron oxidation of the electroactive peripheral units. Whereas the behavior is similar in the sense that the neutral metallocene forms are complexed by βCD and the cationic forms are not, we must recognize that the ferrocene dendrimers are bound in their most stable and accessible oxidation state, and the cobaltocenium dendrimers are only bound after electrochemical stimulation. Therefore, electrochemical stimulation has opposite effects on these two types of dendrimers; it leads to the disassembly of the supramolecular complexes in the case of the ferrocene dendrimers and to supramolecular association for the cobaltocenium dendrimers.

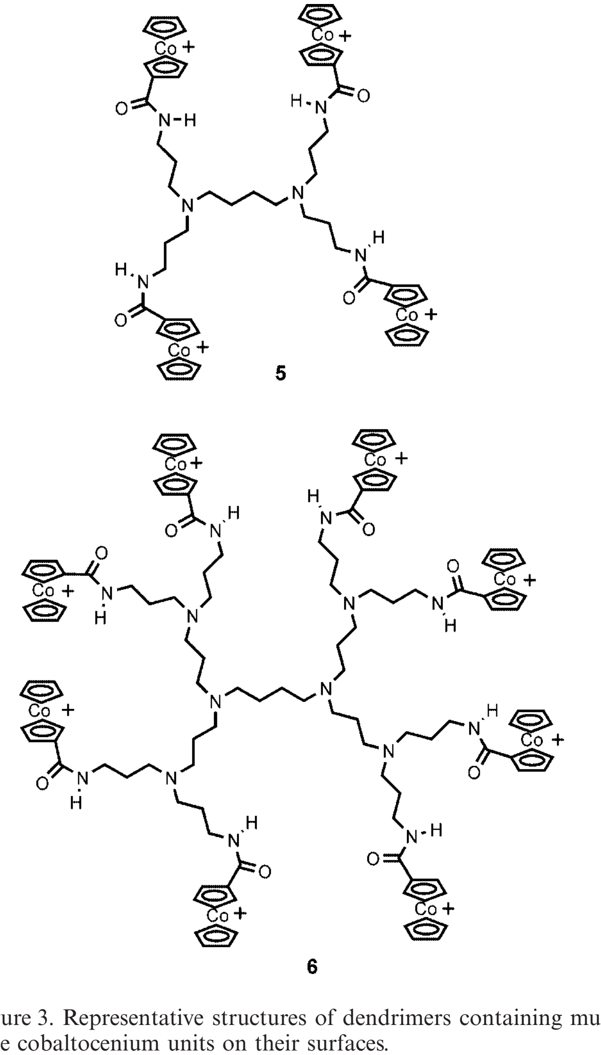

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Figure 3. Representative structures of dendrimers containing multiple cobaltocenium units on their surfaces.

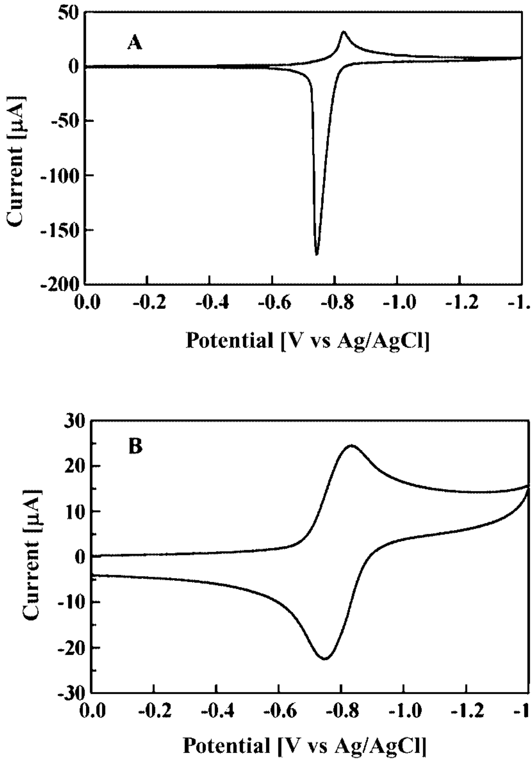

Figure 4. Cyclic voltammetric behavior on glassy carbon (0.08 cm^2) of a solution containing **5** (0.5 mM) and NaCl (0.1 M) (A) in the absence and (B) in the presence of βCD (7.0 mM).

We noted early that dendrimers with multiple copies of a metallocene unit on their surfaces could be interesting to express chemical amplification and or multivalency properties.[4] However, we did not explore this kind of phenomena. Reinhoudt and coworkers started to investigate the interactions between dendrimers containing multiple peripheral copies of adamantyl units with βCD and were able – by decreasing substantially the pH of the solution – to solubilize these dendrimers in aqueous media and investigate their CD binding interactions in more detail.[8] Whereas we observed limitations on the number of βCD hosts that can interact with dendrimers containing 16 peripheral ferrocene groups or more, their experimental conditions led to more open dendrimer structures that can interact easily with larger number of cyclodextrin hosts, even if considerable steric crowding is expected on the dendrimer surface. This group moved on to perform a series of elegant studies on the interaction between dendrimers containing multiple surface guest units, such as adamantyl or ferrocenyl, and gold surfaces covered with self-assembled monolayers prepared with complementary host (βCD) monomers.[9] These are multivalent interactions involving several guest units from an individual dendrimer that interact simultaneously with several binding cavities in the cyclodextrin monolayer. The multivalent aspect of the interaction adds considerable thermodynamic stability to the assembly, leading to the robust immobilization of the dendrimers on the monolayer-covered surfaces. These multivalent dendrimer–monolayer interactions constitute the supramolecular basis for the development of a new class of soft nanolithographic patterning methods.

The βCD binding properties of cobaltocenium and ferrocene units were combined in a single compound (**7**), which exhibits three oxidation states that we can represent as Fc^+–Cob^+, Fc–Cob^+ and Fc–Cob (see Figure 5).[10] The first form (Fc^+–Cob^+) does not interact with βCD, the second forms a 1:1 inclusion complex (Fc included, Cob^+ not bound), and the third oxidation state interacts with two βCD hosts (both Fc and Cob units are bound). The group of Cuadrado and Morán has also prepared dendrimers containing multiple ferrocene and cobaltocenium residues,[11] but their binding interactions with βCD were not investigated.

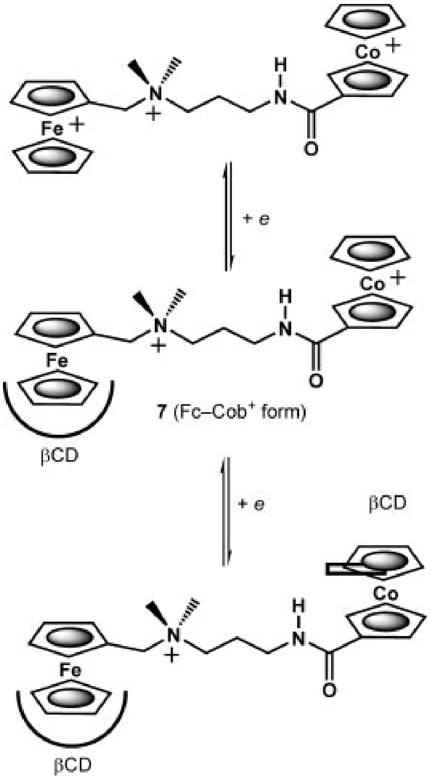

Figure 5. The three oxidation states of compound **7** and their respective binding sites for βCD.

The group of Astruc has pioneered a large amount of work with dendrimers having multiple ferrocenyl and other organometallic residues on their surfaces. Among many other goals, this group has emphasized the possible use of these systems in anion binding/sensing applications.[12] Furthermore, they have also utilized gold nanoparticles as the scaffold to assemble a multiple set of peripheral metallocene subunits for anion recognition.[13] Inspired by this work, we decided to modify the structure of our ferrocene dendrimers, such as **2** and **3**, to enhance the binding of biologically relevant anions, of which phosphate is one of the most significant examples. The preparation of **2** and **3** relies on the reaction of commercially available amine-terminated, poly(propylene imine) (PPI) dendrimers with chlorocarbonylferrocene (**8**).[2b] The final dendrimer products have multiple ferrocenyl centers covalently attached to the dendrimer through amide functional groups. Whereas amides are known to hydrogen bond to anions, ureido groups are typically more effective for this purpose. Therefore, we treated the amine-terminated PPI dendrimers with isocyanatoferrocene, which was prepared from **8** via formation of the acyl azide derivative as an intermediate.[14] We obtained a series of novel dendrimers terminated in 4, 8, 16 or 32 ferrocenyl–ureido termini (see Figure 6 for an example). These dendrimers exhibit a voltammetric behavior in DMSO solution that is quite sensitive to the presence of hydrogenphosphate anions. The addition of hydrogenphosphate (1 equiv.) shifts the observed half-wave potential for ferrocene oxidation 112 mV to less positive values, whereas hydrogensulfate and chloride cause much smaller potential shifts (40 and 16 mV, respectively). Furthermore, the selectivity of the ferrocenyl–urea dendrimers for hydrogenphosphate was excellent as judged by the potential shifts observed in the presence of anion mixtures.[14] A particularly interesting aspect of this work is that the anion binding interactions and their voltammetric sensing were performed in a relatively polar solvent (DMSO), affording a reasonable measure of optimism for the development of structur-

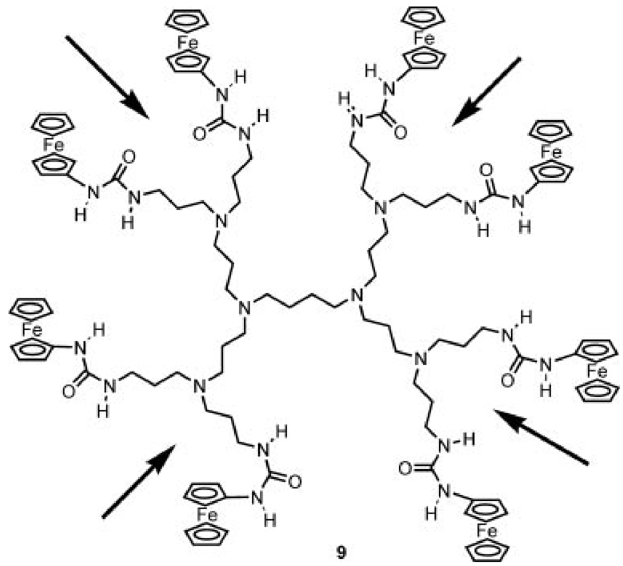

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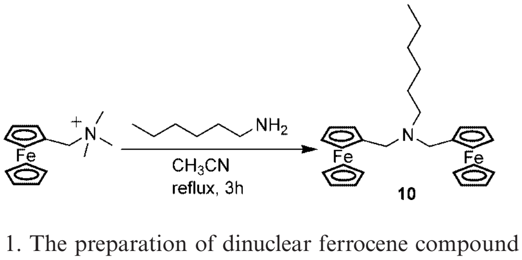
Figure 6. Representative structure of the series of anion-binding dendrimers with ferrocenyl–ureido termini. The arrows represent the four possible binding sites for hydrogenphosphate anions.

ally related systems that might have similar operational characteristics in aqueous environments.

When discussing the electrochemistry of dendrimers such as **2**, **3**, **5**, **6**, **9**, and related compounds having an even larger number of metallocene units on their surfaces, it is important to clearly point out that their electrochemical behavior is characterized by a single voltammetric wave (anodic in the case of ferrocene systems and cathodic for cobaltocenium dendrimers). This wave may be distorted due to precipitation effects, because these dendrimers suffer a large change in their hydrophilic/hydrophobic nature as a result of electron-transfer reactions. However, the individual oxidation of all the ferrocene centers (or reduction of all the cobaltocenium units) takes place at rather similar potentials. In other words, all metallocene units undergo electron transfer independently and no significant degree of electronic coupling among them can be discerned. This is so in spite of the spatial proximity between adjacent metallocenes forced by the crowding on the dendrimer surface. Even dendrimer systems with 64 peripheral ferrocenes, thus located very close to one another, exhibit a single, albeit relatively broad, oxidation wave.[15] In other words, the electrochemical behavior of these dendrimers clearly suggests that through space communication between adjacent metallocenes does not seem to be very effective in these systems.

A few years ago we prepared a new class of dinuclear ferrocene compounds containing a $-CH_2-N(R)-CH_2-$ bridge between the two ferrocenyl residues.[16] These compounds could be readily synthesized by thermal decomposition in polar solvents of (ferrocenylmethyl)trimethylammonium in the presence of a primary amine (Scheme 1). Interestingly, we observed that the level of electronic coupling between the two ferrocenyl residues was dependent on the state of protonation of the central nitrogen atom in the bridge. For instance, unprotonated amine **10** showed a modest level of electronic coupling between the ferrocene centers, as reflected by the measurable difference between the two half-wave potentials ($\Delta E_{1/2}$ = 82 mV), but the protonated compound exhibited a $\Delta E_{1/2}$ value of 46 mV, which was barely above that expected for fully independent redox centers. Alkylation of the bridge nitrogen atom had an effect similar to protonation on the level of communication between the two ferrocene centers.[16]



Scheme 1. The preparation of dinuclear ferrocene compound **10**.

Intrigued by these observations, we decided to express this dinuclear ferrocene motif on dendritic surfaces. By allowing the thermal decomposition of ferrocenyltrimethylammonium in the presence of amine-terminated PPI dendrimers, we successfully prepared a series of small dendrimers shown in Figure 7.[17] Unfortunately, the modest level of electronic communication existing in simple ferrocene dinuclear compounds bridged by $-CH_2-N(R)-CH_2-$ linkages is not observable on the surface of these dendrimers. However, their voltammetric behavior was interesting in a different way. For simplicity, let us discuss first the behavior of compound **13**. Our experiments were recorded in an 80:20 v/v mixture of CH_2Cl_2/CH_3CN, in order to minimize precipitation problems associated with the electron transfer reactions. In this solvent system the electrochemical behavior of **13** is characterized by a single reversible oxidation at a half-wave potential of 0.45 V vs. Ag/AgCl. However, the addition of HCl leads to the observation of two distinct oxidation waves at 0.45 and 0.61 V vs. Ag/AgCl. The addition of an excess amount of acid eliminates the first redox couple at 0.45 V and develops the second wave (at 0.61 V) to maximum current levels.[17] Clearly, protonation of one of the two tertiary nitrogen atoms of the compound shifts the half-wave potential of the two attached ferrocene centers to more positive values, and thus, the voltammetric behavior reveals the presence of protonated and unprotonated nitrogen centers on the periphery of the compound. This was further verified by partial methylation of one of the peripheral tertiary nitrogen atoms, leading to compound **14**, which we also prepared and characterized. The voltammetric behavior of **14** shows two oxidation processes at 0.48 and 0.67 V vs. Ag/AgCl. Protonation of **14** eliminates the redox couple at 0.48 V and leads to a single oxidation wave at the higher half-wave potential. These experiments suggest that the protonation (or methylation) of each of the peripheral nitrogen atoms leads to an anodic shift of the half-wave potential corresponding to the oxidation of the two ferrocenyl units covalently attached to it. One would expect, therefore, that the behavior of larger dendrimer **11**, containing four pairs of ferrocenyl units on its surface, would be similar. In fact, this expectation was fully realized. The voltammetric response of **11** in the absence of acid shows a single redox couple at 0.50 V vs. Ag/AgCl, which corresponds to the oxidation of eight ferrocene centers. The addition of HCl gives rise to a new redox wave at 0.61 V, which grows at the expense of the original wave as more acid is added to the solution. Eventually, upon addition of ca. 10 equiv. of HCl, the first wave disappears and the second wave at 0.61 V reaches full development.[17] This behavior reveals that it is possible to control − by the addition of suitable concentrations of acid − the relative population of the two types of ferrocene centers attached to protonated or unprotonated nitrogen atoms, which are characterized by different half-wave potentials. It is interesting to point out that compound **12** was isolated during the preparation of **11**. This defective compound (missing one ferrocenyl group in comparison to **11**) affords an interesting example on the poor diagnostic power of elemental analysis with some types of dendrimers. Both **11** and **12** gave experimental elemental compositions (C, H) that agree with the calculated compositions of both **11** and **12** within accepted error margins. This highlights the importance of mass spectrometry for the unequivocal confirmation of dendritic structures.

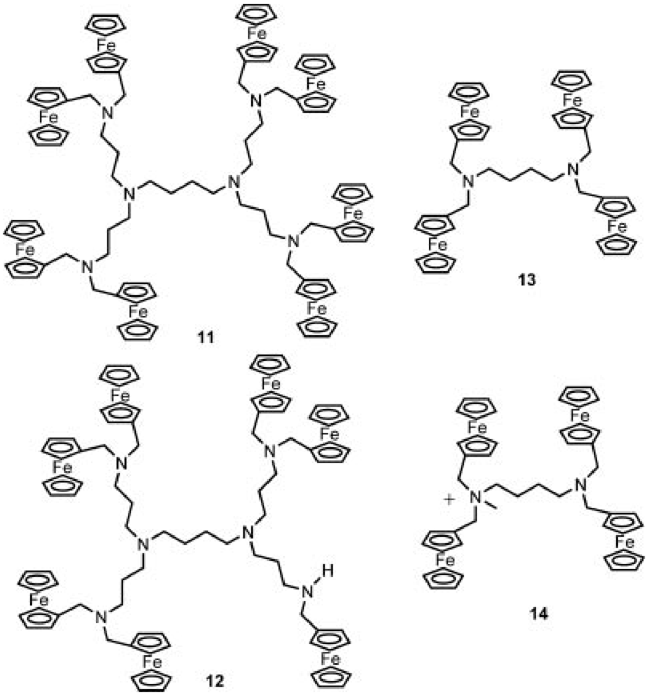


Figure 7. Small dendrimers containing Fc–CH_2–N(R)–CH_2–Fc units on their surfaces.

Dendrimers with multiple metallocene centers on their surfaces are interesting systems from the standpoint of their electrochemical properties and their possible use as guests in multivalent interactions, either in new nanolithographic surface patterning methods or in their potential applications as anion sensors.

Dendrimers with a Single Metallocene Unit at Their Focal Positions

As discussed in the Introduction, dendrimer functionalization can take many forms. Whereas we first became interested in dendrimers with multiple metallocene units on their surfaces, our interests evolved and eventually focused on the properties of metallocene core dendrimers, that is, dendrimers containing a single metallocene residue covalently attached to one or more dendrons. Dendron growth may give rise to site isolation, that is, the partial or complete encapsulation of the metallocene unit by dendrimer mass. These dendritic systems are interesting for a number of reasons. Primarily, site isolation leads to new and intriguing properties for the dendrimer-surrounded metallocene residue, which may exhibit very different electrochemical and optical properties relative to those of the free metallocene. This has some biological overtones because in redox proteins the electrochemical reactivity of the prosthetic redox active group is often modulated by its partial encapsulation in the polypeptide framework. Therefore, we decided to start a research program to prepare and characterize dendronized metallocenes, that is, dendrimers containing a single metallocene unit attached to their focal points.

Our molecular design relies on the use of three dendrimer building blocks based on the branching architecture of a triester amine (Behera's amine, compound **15** in Figure 8) first reported by Newkome and coworkers.[18] We modified slightly the synthetic procedures published by this group and prepared Behera's amine, as well as its second and third generation analogs[19] (Figure 8). Once these amine dendrons are available, we can easily tap into the reactivity of the focal amine groups to covalently attach a variety of electroactive and fluorescent groups to the dendrons. Our group has taken advantage of this chemistry to prepare dendrimers with ferrocene,[19,20] dansyl,[21] pyrene,[22] viologen,[23] cobaltocenium,[24] and hydrogen-bonding ureidopyrimidine[25] groups attached to the focal position of the dendron. In this review, we will obviously focus our attention on the properties of dendronized ferrocene and cobaltocenium compounds, but will use some of the data obtained with other functional groups to support specific conclusions along the way.

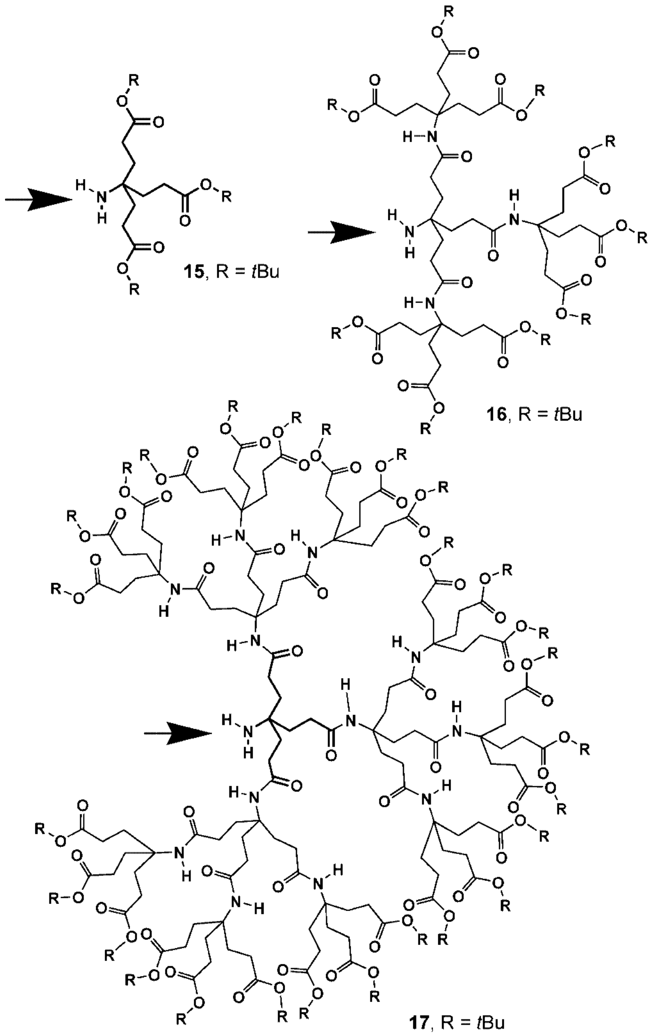


Figure 8. Structures of the Newkome dendrons used in this work. The arrows point to the focal sites used in functionalization reactions.

Dendronized Ferrocenes: Electrochemistry

These compounds were readily prepared by reaction of the amine dendrimer building blocks (compounds **15**, **16**, and **17**) with chlorocarbonylferrocene.[19] The amidation reaction worked well and led to the dendronized ferrocenes in reasonable yields (31–49%). These dendrimers (Figure 9), having 3, 9 and 27 *tert*-butyl esters on their surfaces, were characterized by ^1H and ^{13}C NMR spectroscopy, MALDI-TOF mass spectrometry, UV/Vis and IR spectroscopy, and electrochemical data.

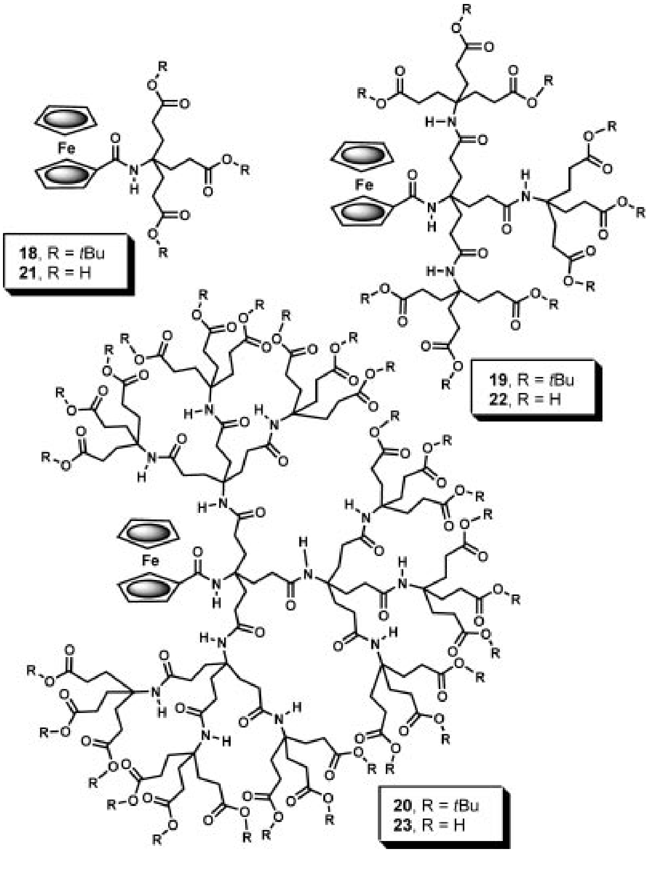


Figure 9. Hydrophobic (**18**, **19**, and **20**) and hydrophilic (**21**, **22**, and **23**) series of dendronized ferrocenes.

The anodic voltammetric behavior in dichloromethane solution is characterized by the one-electron oxidation of the ferrocenyl group. Table 1 gives the relevant electrochemical parameters obtained in voltammetric experiments. Generally, ferrocene derivatives exhibit fast (reversible) electrochemical kinetics in their one-electron oxidation processes. In agreement with this expectation, the first generation ferrocene dendrimer (compound **18**) shows reversible electrochemical behavior, characterized by a reasonably fast heterogeneous electron transfer rate constant ($k°$). However, the $k°$ values decrease quickly as the size of the attached dendron increases,[19] which is consistent with the findings of other groups who have investigated electrochemical kinetics with core dendrimers.[26] These results are understood as a straightforward effect of molecular size. As the dendrimer grows, its diffusion coefficient decreases, which leads to lower current levels due to slower mass transport of electroactive molecules to the electrode surface. However, the decrease in the $k°$ value represents an intrinsic slowdown of the electrochemical kinetics and is thought to be associated with the distance between the redox center and electrode surface when the interfacial electron transfer takes place. As electroactive molecules move towards the electrode surface, they reach a point of maximum approach, which is defined by the so-called outer Helmholtz plane (OHP). The larger the molecule, the further away from the electrode the OHP will be located. Therefore, if one considers all possible rotational orientations for the dendrimer, it is clear that the average distance between the ferrocene center and the electrode surface should increase with the molecular size. The electron transfer rate is well known to decrease exponentially with distance,[27] thus explaining the general trend observed with most core dendrimers and the $k°$ values reported in Table 1.

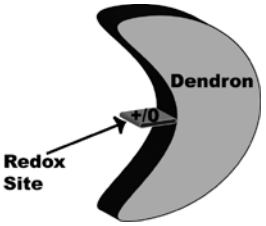
Table 1. Molecular weights and electrochemical parameters (0.2 M $TBA^+PF_6^-$ in CH_2Cl_2 at 25 °C) for the dendronized ferrocenes.

Dendrimer	MW[a] [amu]	$E_{1/2}$ [V vs. Ag/AgCl]	D_o[b] [$10^6 \times cm^2 s^{-1}$]	$k°$[b] [$10^3 \times cm s^{-1}$]
18	627.6	0.63	9.5 ± 1.0	80 ± 20
19	1652.0	0.60	4.0 ± 0.5	17 ± 3
20	4725.0	0.54	2.3 ± 0.3	5 ± 1

[a] Calculated and verified by MALDI-TOF mass spectrometry. [b] Determined from digital simulations of the voltammetric data obtained on glassy carbon electrodes (0.078 cm^2).

The data in Table 1 also shows a very interesting trend in the variation of the half-wave potentials for ferrocene oxidation, which tend to decrease with increasing size of the attached dendron. When we first reported this data, a similar trend had been reported by Diederich and coworkers for porphyrin-core dendrimers.[28] Our data clearly indicate that, in dichloromethane solution, Newkome dendrimer growth differentially stabilizes the positively charged, oxidized ferrocenium form. Although Smith and coworkers demonstrated a different trend in half-wave potentials for dendronized ferrocenes with unrelated architecture,[29] we investigated the half-wave potentials of dendrimers of the same architecture containing a single, electroactive 4,4′-bipyridinium (viologen) residue at their apical positions.[23] These dendronized viologens have more favorable solubility properties, allowing the exploration of their electrochemistry in a variety of solvents, with a large range of polarities. The results provide a very clear picture in which the variation of the half-wave potential as a function of dendron size can be rationalized by the balance of polarities between the bulk solution and the inner phase of the dendrimer. Basically, as the dendron grows, it starts to affect the microenvironment of the redox center attached to the apical position (Scheme 2). If the inner phase of the dendrimer is more polar than the bulk solution, dendrimer growth is expected to differentially stabilize the more highly charged form of the redox couple. This is why the positively charged ferrocenium form is differentially stabilized versus neutral ferrocene by the growth of the attached Newkome dendron –

containing polar amide groups – in a low polarity solvent, such as dichloromethane. Therefore, the half-wave potential decreases as the dendrimer size increases, as seen in Table 1.

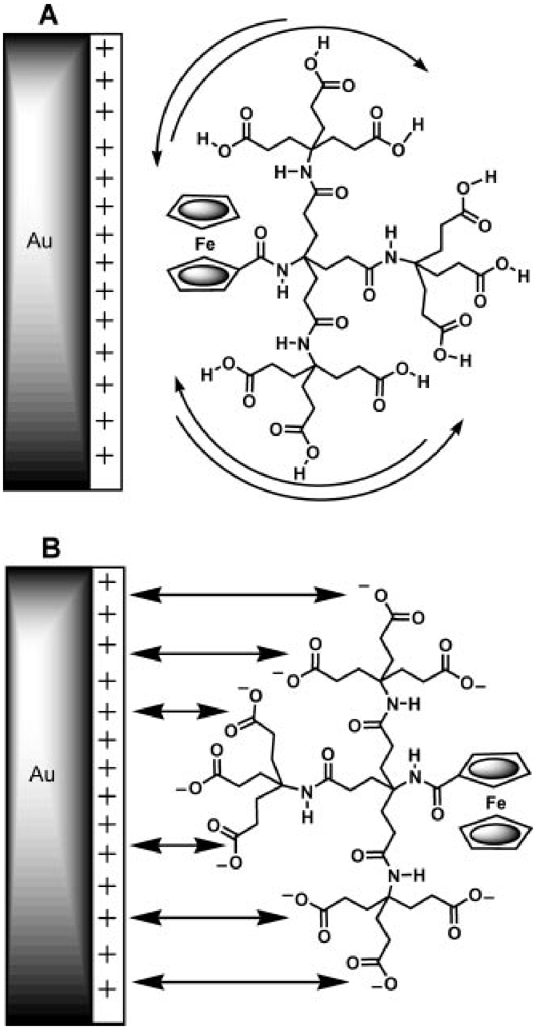


Scheme 2. Cartoon representation of the effect of dendron growth on the microenvironment of the apical redox center.

One of the advantages of our dendrimer architecture is that the set of peripheral *tert*-butyl esters can be easily hydrolyzed to yield dendrimers with multiple carboxylic acid groups on their surfaces.[19b] In fact, hydrolysis transforms a series of hydrophobic dendrimers (**18**–**20**), soluble in low polarity solvents, such as chloroform and dichloromethane, into a series of hydrophilic dendrimers (**21**–**23**, see structures in Figure 9) with moderate solubility in aqueous solution. The presence of multiple carboxylic acids on the surface immediately suggests the possibility of endowing these dendrimers with considerable negative charge (up to a maximum of 27 negative charges in the case of **23**). Charge development on these dendrimers was of interest to us because we assumed that the negative charges could favor specific dendrimer orientations at the electrode solution interface. Titration experiments with these dendrimers revealed that their pK_a values are in the range 4.5–6.[20] Therefore, we started to focus our attention on a comparison of properties between solutions in the pH range 3–4, where the dendrimers are protonated and uncharged, and solutions in the pH range 7–8, in which the dendrimers are extensively deprotonated and negatively charged. Electrochemical experiments on bare gold electrodes did not show any significant differences on the electrochemical parameters measured for ferrocene oxidation in the 3–8 pH range. Faced with these initial results, we hypothesized that the surface density of positive charge on the electrode surface was probably not high enough to enforce specific dendrimer orientations at the interface. Therefore, we decided to derivatize the gold electrode surface by preparing a self-assembled monolayer (SAM) with a protonated amine in order to increase the positive charge surface density on the electrode. For simplicity, we selected cystamine as the monomer for SAM formation, as it is known that it stays protonated in the pH range 3–7, and it forms a relatively disorganized, albeit thin SAM, which is suitable for our purposes.

On gold electrodes covered with cystamine SAMs, the voltammetric behavior of the second generation dendrimer **22** was found to be extremely pH dependent.[20] At low pH (3–4) the reversible, one-electron oxidation of the ferrocene group was clearly detected, whereas at high pH (7–8) the oxidation wave basically disappeared. Similarly pronounced pH-induced changes in the voltammetric response were observed with the third generation dendrimer **23**. However, the first generation dendrimer **21** (a much smaller molecule) showed only small changes in its voltammetric response as the solution pH was changed from 3 to 8. The square wave voltammograms recorded in all these cases could be fitted to digital simulations in which the variable degree of voltammetric response could be rationalized by dramatic changes in the heterogeneous electron transfer rate constants. For instance, the $k°$ values for dendrimer **22** on cystamine-covered gold electrodes were found to decrease from $(8 \pm 1)\times 10^{-3}\,\mathrm{cm\,s^{-1}}$ at pH 4 to $(1.5 \pm 0.1)\times 10^{-5}\,\mathrm{cm\,s^{-1}}$ at pH 7.[20] This considerable decrease is completely gradual and reversible, as the measured $k°$ values oscillate between quasireversible to irreversible electrochemical behavior as the pH of the solution is titrated back and forth. What could be responsible for the pronounced change in electrochemical kinetics as the pH of the solution oscillates between these two extremes? Our interpretation of the data relies on the presence of a large negative charge on the dendrimer surface. The anionic form of the dendrimer, present at high pH, experiences strong electrostatic forces with the positively charged electrode surface, enforcing orientations in which the ferrocene group faces away from the electrode surface. Conversely, at low pH, the uncharged form of the dendrimer is free from these electrostatic forces and no specific interfacial orientations are favored, thus allowing free rotation of the dendrimer. These two extreme situations are represented in Scheme 3. When the dendrimer reaches the OHP and becomes ready for electron transfer, the average distance between the electrode surface and the ferrocene residue is larger at high pH than at low pH. Thus the electrochemical kinetics is considerably faster in the latter situation, as free rotation allows the electrode surface to sample dendrimers in which the ferrocene residue is facing it. As the pH increases, negative charge develops on the dendrimer, restricting free rotation and forcing the electrode surface to sample dendrimers in which the redox active center is facing towards the bulk solution. Therefore, dendrimers **22** and **23** are synthetic macromolecular compounds exhibiting strong pH-induced, orientational effects on their interfacial electron transfer reactions. In this sense, both dendrimers show similar electrochemical behavior to that exhibited by a number of redox proteins, providing an interesting kind of validation for our molecular design.

An aspect of these experiments that should not go unnoticed is the possible effect that surface ionization may have on the solution conformation of the dendrimers. In the polyelectrolyte field, it is well known that charge development in a polymer chain usually leads to remarkable conformational changes, as the polymer goes from a random coil arrangement to a fully extended chain, in which the charges are well solvated and separated from one another. Similarly, we could anticipate that surface ionization of the dendrimer should lead to a more expanded conformation, particularly in comparison with the more collapsed structure expected for the neutral, uncharged macromolecule. Quite recently, we looked at this issue by doing careful diffusion coefficient measurements on these dendrimers[30] with the use of pulse gradient stimulated echo (PGSE)



Scheme 3. Interfacial orientation of dendrimer **22** as it approaches the OHP next to a gold electrode covered by a positively charged SAM of cystamine in aqueous solution at (A) pH 3–4 and (B) pH 7–8.

NMR techniques. The data (Table 2) shows that the diffusion coefficient of any of these dendrimers is always smaller in pH 7 solution than in pH 2, which is consistent with the electrostatically expanded conformation anticipated for the ionized dendrimer. However, we must point out that these conformational changes by themselves cannot be responsible for the observed changes in electrochemical kinetics, as shown by the essentially pH independent electrochemical behavior obtained on bare gold electrodes.

Table 2. Approximate radii and diffusion coefficients at 25 °C for water-soluble dendronized ferrocenes.

Dendrimer	Radius[a] [Å]	D_o at pH 2 [cm^2 s^{-1}]	D_o at pH 7 [cm^2 s^{-1}]
21	3.5–8	4.8×10^{-6}	4.2×10^{-6}
22	3.5–12	3.0×10^{-6}	2.5×10^{-6}
23	3.5–18	1.9×10^{-6}	1.5×10^{-6}

[a] Radius range as estimated from molecular modeling.

Dendronized Cobaltocenium Derivatives: Electrochemistry

The attachment of cobaltocenium units to the Newkome dendrons shown in Figure 8, can be readily accomplished by reaction of their apical amine groups with cobaltocenium carboxylic acid (as its chloride salt) in dry DMF by using *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (*n*-HATU) to promote amide coupling.[24] As it is the case with the ferrocene derivatives, the dendrimers are initially prepared with *tert*-butyl ester peripheries (hydrophobic series, **24**–**26**) but hydrolysis with formic acid led to their water-soluble forms (hydrophilic series, **27**–**29**, see Figure 10 for structures). As expected, the cathodic electrochemical behavior of the dendrimers is dominated by the reversible one-electron reduction of cobaltocenium. The corresponding electrochemical parameters obtained in voltammetric experiments and the diffusion coefficients measured in PGSE NMR experiments are given in Table 3.

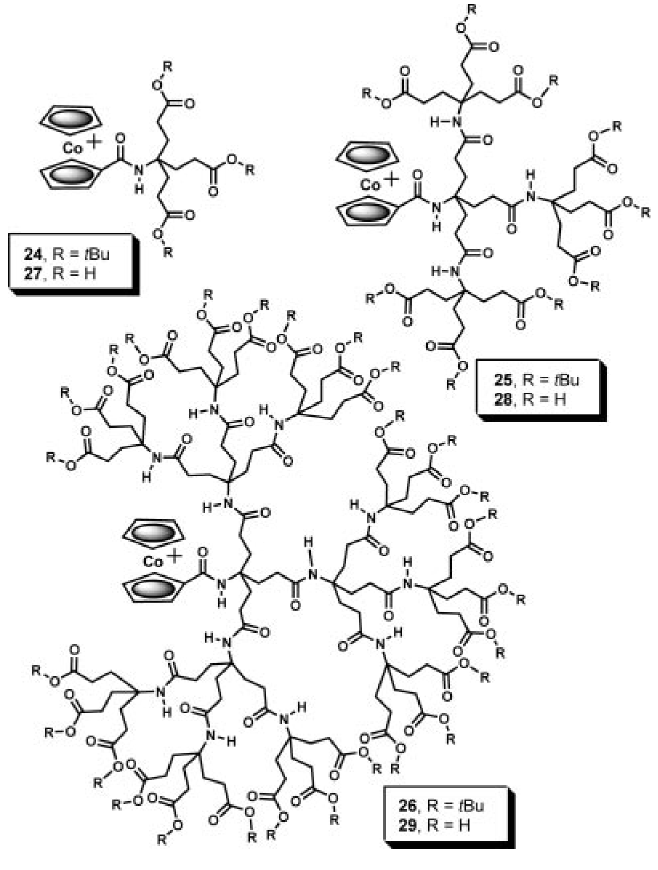


Figure 10. Hydrophobic (**24**, **25**, **26**) and hydrophilic (**27**, **28**, **29**) series of cobaltocenium-containing dendrimers.

The data in Table 3 generally follow the trends discussed before with dendronized ferrocenes. For instance, within the hydrophobic series of dendrimers (**24**–**26** surveyed in dichloromethane solution), *k*° values and diffusion coefficients decrease with dendrimer size, as expected. The half-

Table 3. Electrochemical parameters and diffusion coefficients for the cobaltocenium-containing dendrimers.

Dendrimer	$E_{1/2}$ [V vs. Ag/AgCl]	$k°$ [cm s^{-1}]	$10^6 \times D_o$ [cm^2 s^{-1}]
24	–0.66[a]	reversible[a]	9.6[c]
25	–0.70[a]	3.2×10^{-2}[a]	6.8[c]
26	–0.75[a]	3.0×10^{-3}[a]	5.1[c]
27	–0.91[b]	1.4×10^{-2}[b]	4.1[d]
28	–0.92[b]	8.0×10^{-3}[b]	3.2[d]
29	–0.95[b]	6.0×10^{-3}[b]	2.1[d]

[a] Measured in CH_2Cl_2 with 0.1 M $TBAPF_6$. [b] Measured in pH 7 phosphate buffer. [c] Measured in CD_2Cl_2 at 25 °C. [d] Measured in D_2O buffered at pH 7 (phosphate) at 25 °C.

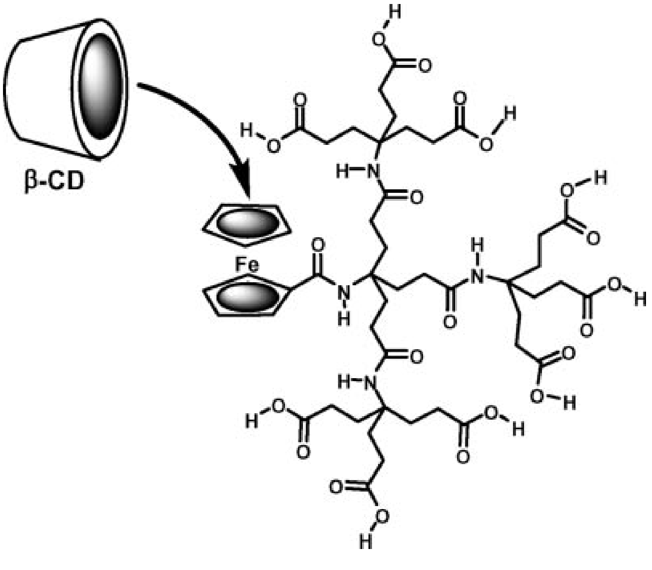
wave potential for the one-electron reduction of cobaltocenium shifts to more negative values as the dendron grows. This potential variation is consistent with the differential stabilization of the charged member of the redox couple (the positively charged cobaltocenium) by the inner phase of the dendrimer. The hydrophilic dendrimers were investigated in aqueous solution buffered at pH 7. The *k°* values and diffusion coefficients again decrease as the size of the dendrimer grows. The half-wave potentials for cobaltocenium reduction show minor changes as the dendron size increases. However, for the third generation dendrimer (**29**) the $E_{1/2}$ value is about 30 mV more negative than in the first generation dendrimer (**27**). Because these experiments were run in a very polar, aqueous solution, we cannot attribute this small potential variation to the inner phase of the dendrimer having greater polarity than the bulk solution. We believe that this unusual potential trend may be associated to electrostatic interactions between the cobaltocenium unit and some of the carboxylate groups on the surface of the dendrimer.

Guest Behavior of Dendronized Metallocenes

One of the most interesting aspects of these metallocene dendrimers is that their structures are “unsymmetric” in the sense that they offer two very different directions of approach for a species capable of reacting with the metallocene unit. Of course, this unsymmetric character was used to advantage in our demonstration of strong pH-induced, orientation effects on the electron transfer reactions between the dendronized ferrocene residue and a properly derivatized electrode surface.[20] Because of our long-standing interest in host–guest interactions, we decided to investigate the guest properties of dendronized metallocenes with freely diffusing hosts. These macromolecules can be used as guests because the metallocene unit is accessible to a free host that approaches the dendrimer near the apical site, where the metallocene is located. Basically, the driving force for this research work is to understand the effects of dendron size on the thermodynamic binding affinity between the partially buried, dendronized guest and the free host. We recently published a review of our research work on dendrimers as guests in molecular recognition phenomena.[31] Thus, we will limit ourselves here to provide a brief account of some of the most recent data involving dendronized metallocenes.

We started this research by investigating the binding interactions between the βCD host and dendronized ferrocenes **21**, **22**, and **23** in aqueous solution (0.1 M NaCl) buffered at pH 7 with 0.05 M tris.[19b] The complexation phenomena was monitored by using cyclic voltammetric experiments, as our group has considerable experience analyzing voltammetric data to extract information on chemical reactions, such as complexation by βCD, involving electroactive species, such as ferrocene derivatives. Fitting of the experimental current–potential curves by using digital simulation techniques is a powerful methodology to extract thermodynamic and/or kinetic parameters for the host–guest reactions coupled to the electron transfer processes. The addition of βCD to a solution containing any of the dendronized ferrocenes has two major effects on the voltammetric response: (1) the apparent half-wave potential for the one-electron oxidation of the ferrocene center shifts to more positive values and (2) the overall current levels of the voltammetric peaks decrease. The CD-induced, anodic potential shift reflects the differential stabilization of ferrocene relative to ferrocenium. This is consistent with the strong thermodynamic preference for the neutral ferrocene versus the positively charged ferrocenium of the host, which reflects the well-known selectivity of CD hosts for hydrophobic guests.[3] The CD-induced current decrease is readily explained by the lower diffusion coefficient of the ferrocene derivative due to its binding interactions with the bulky CD host. By optimizing the fitting of digitally simulated voltammograms to the experimental ones at variable βCD concentrations, we obtained 950, 250, and 50 M^{-1} as the *K* values for the βCD association with **21**, **22**, and **23**, respectively. The binding constant between the first generation dendrimer (**21**) with βCD is at the lower end of the usual range (1000–5000 M^{-1}) for binding of this host with small, water-soluble ferrocene derivatives. However, the binding constant comes down quite rapidly as the dendron size increases. By the third generation dendrimer, the host–guest binding interaction is almost completely quenched by the presence of the dendron.

What causes such a rapid decrease in the *K* values as the dendron grows from first to third generation? Clearly, the larger dendron hinders the host approach towards the unsubstituted cyclopentadienyl ring of the ferrocene group, which is the main βCD binding site (Scheme 4). We also know that dendron growth leads to changes in the microenvironment around the ferrocene residue. In aqueous solution, dendrimer growth should decrease the polarity of the environment, which is expected to decrease the strength of the βCD–ferrocene binding interaction. In any instance, the effect of dendron growth on the stability of the inclusion complex formed between βCD and the dendronized ferrocenes is quite pronounced. The key question that must be asked upon examination of these data concerns the possible extrapolation of these effects to other host–guest systems.



Scheme 4. Complexation of dendrimer **22** by the βCD host.

The cucurbit[*n*]urils[32] are a family of molecular receptors that can be prepared by the acid-catalyzed condensation of glycoluril with formaldehyde. Recent work on expanded cucurbiturils ($n \geq 6$) was sprung by their first isolation, reported by Kim and coworkers.[33] Whereas the cavity size of cucurbit[6]uril (CB6) is similar to αCD, cucurbit[7]uril (CB7) resembles βCD, and the similarities between these two host families are more superficial than real.[34] CB hosts are known to be much more sensitive to guest charge, charge distribution, and shape than CD hosts. Therefore, the CBs are capable of achieving higher levels of binding selectivity. In optimal cases, CB hosts reach extremely high levels of binding affinities ($K > 10^{10}\,\text{M}^{-1}$), which are completely unimaginable with unmodified cyclodextrins. The binding interactions between the simple ferrocene derivatives (**30**, **31**, and **32**) with βCD and CB7 provide an excellent illustration of these differences. All these ferrocene derivatives, regardless of their charge, form stable inclusion complexes with βCD, with *K* values in the range 1–$5 \times 10^{3}\,\text{M}^{-1}$, as mentioned before. In contrast to this, CB7 forms a very stable complex with **30** ($K = 3 \times 10^{9}\,\text{M}^{-1}$) and even more so with **31** ($K = 2 \times 10^{12}\,\text{M}^{-1}$), but does not bind anionic **32** at all.[34] The complete lack of binding between **32** and CB7 is understood to result from the electrostatic repulsion between the carboxylate group of the guest and the negative charge density accumulated on the carbonyl oxygen-laced portals of the host (Figure 11).

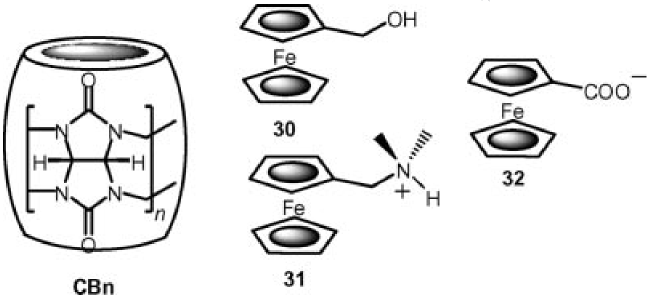


Figure 11. Structures of the cucurbituril hosts (CBn) and ferrocene derivatives **30**–**32**.

As a result of our interest in cucurbit[*n*]uril chemistry, we decided to investigate the interactions between CB7 and dendrimers **21**–**23**. In this case the binding constants are readily obtained in ^{1}H NMR spectroscopic experiments in which the dendronized ferrocene and a reference guest compete for a limited amount of the CB7 host.[30] The corresponding binding constants are given in Table 4. Measurements were made at two solution pH values (2 and 7) to ascertain the magnitude of the electrostatic effects between the anionic carboxylate charges on the dendrimer surface and the negatively charged portal openings on the host. These electrostatic effects are clearly evidenced by the lack of binding observed between ionized **21** (at pH 7) and CB7, in analogy with the absence of binding interactions between **32** and this host.[34] However, dendrimer growth decreases the intensity of the electrostatic repulsions opposing host–guest association, as evidenced by the measured binding constants at pH 7 with the dendronized guests **22** and **23**. In these larger macromolecules, the average distance between the peripheral carboxylates and the ferrocene site is sufficiently long for binding to take place. At pH 2, the binding constant between neutral **21** and CB7 is moderately high. Similarly the *K* value measured for neutral **22** is larger than that determined for anionic **22** (at pH 7) due to the lack of coulombic repulsion in the former case. In general terms, however, the trends observed in the *K* values with CB7 are quite different from what was observed with βCD, as dendrimer growth does not decrease the binding affinity in the quick and pronounced way that was observed with the latter host.

Table 4. Equilibrium association constants (*K*) at 25 °C measured in aqueous media between dendronized metallocenes and the CB7 host.

Dendrimer	*K* [L mol^{-1}] at pH 2	*K* [L mol^{-1}] at pH 7
21	3.9×10^{4}	n.b.[a]
22	4.2×10^{6}	3.8×10^{5}
23	Insol.[b]	7.7×10^{5}
27	3.2×10^{5}	1.0×10^{4}
28	1.1×10^{7}	3.4×10^{6}
29	4.0×10^{5}	4.0×10^{5}

[a] No binding detected. [b] Insoluble under these conditions.

We also investigated the binding interactions between CB7 and cobaltocenium-containing dendrimers[24] **27**–**29** (Table 4). The *K* values offer many similarities to those obtained with the dendronized ferrocenes. Perhaps the key difference between the two data sets is that the first generation dendrimer **27**, in its ionized form at pH 7, does form a stable complex with CB7. This is in clear contrast with unprotonated **21**. Clearly, the positive charge on the metallocene nucleus plays an important role in neutralizing the coulombic repulsions between the CB7 portal and the peripheral carboxylates on the dendrimer. In general terms, the *K* values with the cobaltocenium systems are slightly larger than the corresponding values with the dendronized ferrocenes, probably a reflection of the positive charge on the cobaltocenium residue.

The differences observed in the host–guest binding interactions between our dendronized metallocenes and the hosts βCD and CB7 are part of a growing body of data,[31] which will eventually allow us to rationalize the effect of dendron size on the thermodynamic binding affinity. So far, the observed effects have proven to be very specific to the particular host–guest system under examination, and extended generalizations cannot be made at this time.

Hybrid Dendrimers Containing Newkome and Fréchet Dendrons

Whereas all the work discussed so far on single metallocene dendrimers used Newkome-type dendrons, we recently reported a new class of dendrimers containing a single ferrocene group and two different dendrons (Newkome and Fréchet) covalently attached to a triazine nucleus.[35] Some examples are shown in Figure 12.

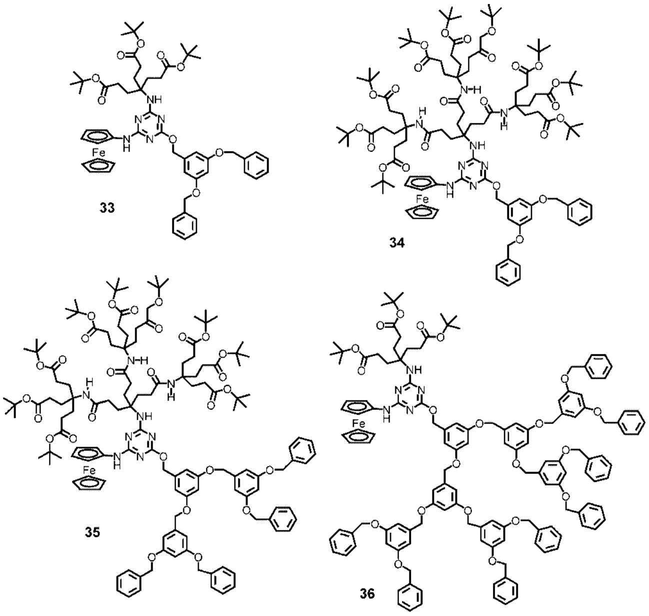


Figure 12. Hybrid dendrimers containing a ferrocene unit and Newkome and Fréchet dendrons attached to a central triazine nucleus.

This new series of dendrimers offers the possibility of comparing on the same molecule the relative effects of two different types of dendritic architectures. Because of their synthetic availability and widespread use by various research groups, we decided to use AB_3 Newkome-type, ester-terminated dendrons[18] and AB_2 Fréchet-type, aromatic ether dendrons.[36] Initially, we focused our attention on comparative dendron effects on the electrochemical parameters of the ferrocene residue and on the diffusion coefficients of the macromolecules.[35] Our preliminary data suggest that the Fréchet dendrons expand as wedges away from the core, whereas the Newkome dendrons are more effective at changing the polarity of the microenvironment around the ferrocene residue. This is probably a reflection of the more highly branched AB_3 architecture of the Newkome dendrons and their greater flexibility.

Conclusions

This manuscript has addressed many aspects of the research work done by the authors' group on metallocene dendrimers. Whereas most of our work has focused on electrochemical processes and host–guest interactions in which the dendrimers act as mono- or multivalent guests, these systems also have tremendous potential as nanoscale objects for surface patterning, sensors, and other interesting applications. Furthermore, it is important to realize that the synthetic degree of sophistication of these systems is still in its infancy. Most of the synthetic work described here is based on the straightforward functionalization of existing dendritic architectures with metallocene units. More elaborate synthetic schemes, such as those leading to hybrid dendrimers **33**–**36**, may yield macromolecules with more complex structures and yet unexplored and, hopefully, exciting properties. The exploration of these novel structures and their properties is one of the major goals of our continuous research work in this field.

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