

## The Dendritic Effect in Molecular Recognition: Ferrocene Dendrimers and Their Use as Supramolecular Redox Sensors for the Recognition of Small Inorganic Anions

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Dendrimers<sup>1–6</sup> could serve as supramolecular exoreceptors for molecular recognition,<sup>4</sup> viewing the fractality of their surface which resembles that of viruses, cancer cells, and biomolecules.<sup>2</sup> Other supramolecular aspects of dendrimers such as transport<sup>5</sup> and self-assembly<sup>6</sup> have been exemplified, but molecular recognition using specific sensors based on dendrimers is not known. Various sensors have been reported with endoreceptors<sup>4,7,8</sup> *inter alia* for the recognition of anions,<sup>7–9</sup> in particular redox sensors with macrocycles and tripods.<sup>8</sup> A few cores with ferrocene and other redox active units are known.<sup>8,10–12</sup> We report here the synthesis of amido-ferrocene dendrimers (FcDs) and the remarkable dendritic effect found in the recognition of small anions (Figure 1).

The orange-red powdery polyamidoferrocene dendrimers 9-Fc and 18-Fc (Chart 1) were synthesized by reaction of 9- and 18-amine dendrimers<sup>13</sup> with FcCOCl (Fc = ferrocenyl) at 20 °C:<sup>14</sup>



Reactions of the 36- and 72-amine with FcCOCl gave materials which were insoluble in all solvents, indicating that,

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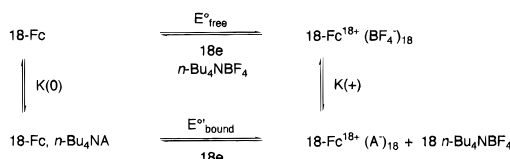
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(13) The new 9-amine dendrimer was synthesized by FeCp<sup>+</sup> induced nonaallylation of mesitylene, removal of FeCp<sup>+</sup> by visible photolysis, hydroboration followed by oxidation to the nonol, Michael addition of acrylonitrile, and reduction of the nonanitrile to the nonaamine using BH<sub>3</sub>-Me<sub>2</sub>S. The 18-amine dendrimer was made from the above nonaamine using a variation of Vögtle's strategy,<sup>1</sup> Michael addition of two acrylonitrile units per branch, and reduction of the 18-nitrile using BH<sub>3</sub>-Me<sub>2</sub>S.

### Scheme 1



**Table 1.** Titration of the FcDs by Various *n*-Bu<sub>4</sub>N<sup>+</sup> Salts Monitored by the Variation  $\Delta E^\circ$  (mV for 1 Equivalent of Anion per Branch) of the Standard Redox Potential  $E^\circ$  of the Redox Couple in Cyclic Voltammetry<sup>a</sup>

	1-Fc	3-Fc	9-Fc	18-Fc
H <sub>2</sub> PO <sub>4</sub> <sup>-</sup>	45	110	220	315
HSO <sub>4</sub> <sup>-</sup>	ε	30	65	130
Cl <sup>-</sup>	ε	ε	20	45
NO <sub>3</sub> <sup>-</sup>	ε	ε	ε	30

<sup>a</sup> In the case of HSO<sub>4</sub><sup>-</sup>, the variation  $\Delta E^\circ$  along the titration is represented in Figure 1 for the various dendrimers. The uncertainties of the  $\Delta E^\circ$  values are estimated to be 20 mV. Thus, lower shifts are indicated by ε.

as well-known in dendrimer chemistry,<sup>1</sup> surface steric saturation was reached between the 18-Fc and 36-Fc.

Titrations of the FcDs were effected by *n*-Bu<sub>4</sub>N<sup>+</sup> salts of H<sub>2</sub>PO<sub>4</sub><sup>-</sup>, HSO<sub>4</sub><sup>-</sup>, Cl<sup>-</sup>, Br<sup>-</sup>, and NO<sub>3</sub><sup>-</sup> and monitored by cyclic voltammetry (CV) and <sup>1</sup>H NMR (200 MHz) which are complementary techniques.

The CV of all the ferrocene dendrimers show a single anodic reversible wave at  $E^\circ = 0.69$  V vs SCE indicating that all the Fe<sup>II</sup>/Fe<sup>III</sup> redox centers are independent and equivalent. Titration by *n*-Bu<sub>4</sub>NH<sub>2</sub>PO<sub>4</sub> provokes the progressive appearance of a new wave at a less positive potential and the progressive disappearance of the initial wave. The replacement of the initial wave by the new one is complete after addition of 1 equiv of *n*-Bu<sub>4</sub>NH<sub>2</sub>PO<sub>4</sub>. This is rationalized by Scheme 1 where  $K(+)$  is several orders of magnitude larger than  $K(0)$  because of the electrostatic interaction between the cationic ferricinium branch and the H<sub>2</sub>PO<sub>4</sub><sup>-</sup> anion. Equation 1 applies,  $K(+)$  and  $K(0)$  being the apparent association constants of the anion with the ferricinium- and ferrocene dendrimers, respectively:<sup>15</sup>

$$E^\circ_{\text{free}} - E^\circ_{\text{bound}} = \Delta E^\circ(\text{V}) = 0.059 \log(K(+)/K(0)) \quad \text{at } 25^\circ\text{C} \quad (1)$$

Measurement of the  $\Delta E^\circ$  values (Table 1 and Figure 1) leads to  $K(+)/K(0)$ , and eventually to  $K(+)$  if  $K(0)$  is accessible by <sup>1</sup>H NMR,<sup>16,17</sup> *vide infra*.

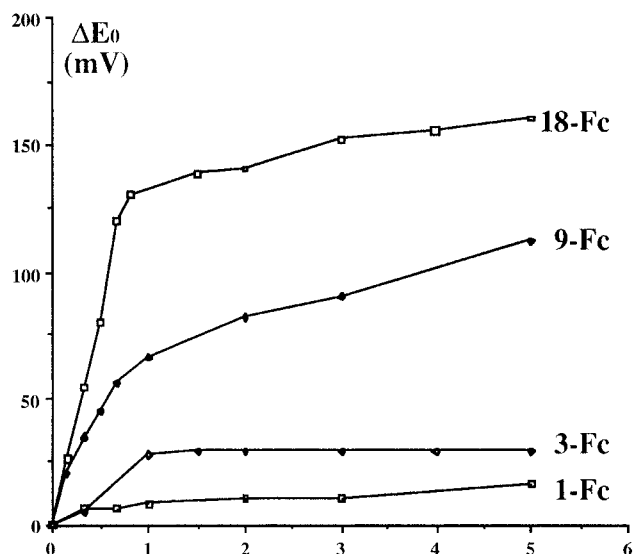
Titration of the ferrocene dendrimers by HSO<sub>4</sub><sup>-</sup>, Cl<sup>-</sup>, and NO<sub>3</sub><sup>-</sup> salts did not give rise to a new wave but only to a progressive cathodic shift of the initial wave. This means that  $K(0)$  is small (<1), and eq 2 allows the calculation of  $K(+)$

(14) A mixture of NEt<sub>3</sub> (1.1 mL, 8 mmol), FcCOCl (0.4 g, 1.62 mmol) in 5 mL CH<sub>2</sub>Cl<sub>2</sub>, and the 9-amine (0.15 g, 0.13 mmol), resp. 18-amine (0.10 g, 0.047 mmol) was stirred at room temperature for a day; then the medium became clear and orange-red. After removing the solvent under vacuum, 50 mL of CH<sub>2</sub>Cl<sub>2</sub> was added, the organic layer was washed with water (4 × 50 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>, and the solvent was removed under vacuum. The orange-red oily residue was washed with 6 × 30 mL ether and dried under vacuum, which gave 9-Fc (0.32 g, 80% yield), resp. 18-Fc (0.19 g, 68% yield) of orange-red powders. Anal. for 9-Fc: Calc. C, 62.15; H, 6.50; N, 4.00. Found: C, 61.92; H, 6.99; N, 3.58. MALDI TOF: *m/z*: 3066 (MH<sup>+</sup>). Anal. for 18-Fc: Calc. C, 55.21; H, 5.97; N, 5.52. Found: C, 54.95; H, 6.38; N, 5.00. MALDI TOF: *m/z*: 6024 (MNa<sup>+</sup>); NMR, IR and other mass spectral data: see Supporting Information.

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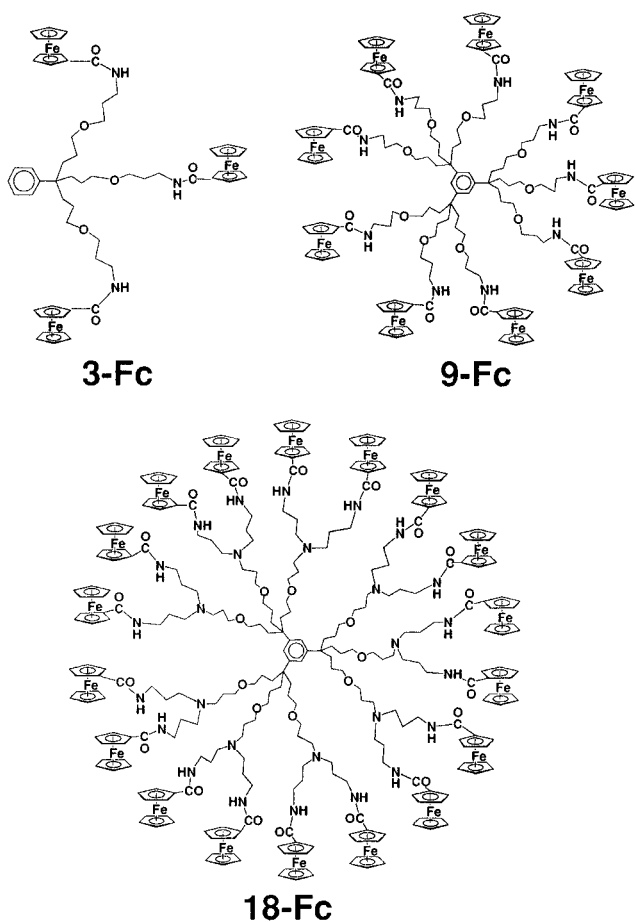
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**Figure 1.** Number of equiv of  $n\text{-Bu}_4\text{N}^+\text{HSO}_4^-$  added per branch. Titration of 1-Fc (1-Fc =  $[\text{Fe}(\text{C}_5\text{H}_5)(\text{C}_3\text{H}_4\text{CONHCH}_2\text{CH}_2\text{OPh})]$ ), 3-Fc, 9-Fc, and 18-Fc (see Chart 1) by  $n\text{-Bu}_4\text{N}^+\text{HSO}_4^-$  monitored by CV. Concentrations in FcDs were 0.001 M,  $\text{CH}_2\text{Cl}_2$ ,  $n\text{-Bu}_4\text{N}^+\text{BF}_4^-$  (0.1 M), 20 °C, reference electrode: SCE, auxiliary and working electrodes: Pt, scan rate:  $100\text{ mV}\cdot\text{s}^{-1}$ .

**Chart 1**



(Table 2). The equivalence point of the titration always corresponds to 1 equiv anion per branch.

$$\Delta E^\circ (\text{V}) = 0.059 \log[cK(+)] \quad \text{at } 25^\circ\text{C}, c = [\text{added anion}] \quad (2)$$

Interestingly, in all cases,  $\Delta E^\circ$  considerably increases as the number of dendritic branches increases in the series  $1 \rightarrow 3 \rightarrow$

**Table 2.** Apparent Association Constants  $K(+)$  Determined in  $\text{CH}_2\text{Cl}_2$  by CV for the FcD Series from the Shift of the CV Wave Using Eqs 1 and 2

	1-Fc	9-Fc	18-Fc
$\text{H}_2\text{PO}_4^-$	9390	216900 <sup>a</sup>	<i>b</i>
$\text{HSO}_4^-$	544	8530	61400
$\text{Cl}^-$	<i>c</i>	917	2120
$\text{NO}_3^-$	<i>c</i>	<i>c</i>	403

<sup>a</sup>  $K(+)$  determined for the 9-Fc dendrimer from the combination of  $K(0)$  determined by  $^1\text{H}$  NMR in  $\text{CD}_2\text{Cl}_2$  and the  $K(+)/K(0)$  ratio determined by CV in  $\text{CH}_2\text{Cl}_2$  using eq 1. <sup>b</sup> For 18-Fc, the  $K(+)/K(0)$  ratio was found to be 219 000. The uncertainties on  $K$  values are estimated to 10%. <sup>c</sup> Since the  $\Delta E^\circ$  values are much smaller than the uncertainties (Table 1), calculation of the small  $K$  values would be meaningless.

$9 \rightarrow 18$ -amido ferrocene (Table 1 and Figure 1), which shows the dendritic effect. The order of  $\Delta E^\circ$  values for either dendrimer is  $\text{H}_2\text{PO}_4^- > \text{HSO}_4^- > \text{Cl}^- > \text{NO}_3^-$ . Finally, the waves are still electrochemically reversible during and after the titrations indicating that the binding process is fast and reversible on the electrochemical time scale.

Monitoring the titration of the ferrocene dendrimer by  $^1\text{H}$  NMR ( $\delta_{\text{NH}}$ ) is not as useful as monitoring by cyclic voltammetry, because the ferrocene dendrimers are not charged. Their interaction with anions in the absence of electrostatic contribution is considerably weaker than that of ferricinium dendrimers. Thus, the equivalence point is reached for an amount of equiv anion which considerably differs from unity and varies with the nature of the anion and the dendritic generation.<sup>17</sup> Only in the case of 9-Fc and  $\text{H}_2\text{PO}_4^-$  is the equivalence point reached with 1 equiv of  $\text{H}_2\text{PO}_4^-$  per branch ( $\delta_{\text{NH free}} = 6.82$  ppm;  $\delta_{\text{NH bound}} = 6.65$  ppm,  $\text{CD}_2\text{Cl}_2$ ). This gives access to  $K(0)$  and  $K(+)$  (Table 2).

The starting point for the rationalization of all the data is the synergy between the electrostatic interaction (involving the ferricinium cation and the anion) and the H-bonding of the amide H atom with the anion.<sup>8</sup> The NMR data show that, with the H-bonding alone (18-electron ferrocene state), the interaction is usually weak. However, even when the two conditions for the synergy are fulfilled, the  $\Delta E^\circ$  value obtained is small when the ferrocene compounds is monometallic (1-Fc) or trimetallic (3-Fc). Thus, the shape selectivity designed in the dendrimer is also an essential factor and delineates the dendritic effect. The dendritic effect is clear from Table 1 and Figure 1. It can be defined as the ability for a dendrimer to achieve a better sensing and recognition of anions by cyclic voltammetry as the dendritic generation increases (i.e.,  $3 \rightarrow 9 \rightarrow 18$ ). The dendritic effect is maximum for the generation (18-Fc) preceding steric surface saturation (36-Fc). Since the amide H atom is located on the branch behind the ferrocene block, the anion has to penetrate the surface cavity defined by these large ferrocene termini. As the dendritic generation becomes higher, the smaller the surface hole for the penetration of the anion is, since the ferrocene termini of the different dendritic branches become closer to one another (as shown by molecular models). Since the anions are small, it is not surprising that the greatest effect and selectivity is found for the highest soluble generation because it forms the best open cavities. In comparison, endoreceptors also favor anion inclusion with open cavities where size compatibility plays a role.<sup>4,7</sup>

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**Supporting Information Available:** NMR, IR, details of the mass spectra for 9-Fc and 18 Fc, and cyclic voltammograms (4 pages). See any current masthead page for ordering and Internet access instructions.

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