

Calixarenes as Hosts in Aqueous Media: Inclusion Complexation of Ferrocene Derivatives by a Water-soluble Calix[6]arene

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The complexation of trimethyl(ferrocenylmethyl)ammonium hexafluorophosphate **1**·(BF₆), heptyldimethyl(ferrocenylmethyl)ammonium bromide **2**·(Br) and ferrocenylmethanol **3** by a sulfonated calix[6]arene host was investigated in aqueous media using electrochemical and ¹H NMR spectroscopic techniques; the binding interactions between the calixarene host and the surveyed guests are similar to those operating in the complexation of organic compounds by cyclodextrin or cyclophane hosts in aqueous media.

The calixarenes¹ are a class of versatile synthetic hosts with growing applications in the fields of molecular recognition and supramolecular chemistry. In spite of the diversity of calixarene structures available, the literature contains only a limited number of reports describing well-characterized complexation by calixarene hosts in the solution phase.² In this communication we report electrochemical and spectroscopic data that demonstrate the inclusion complexation of three ferrocene derivatives, compounds **1**·PF₆, **2**·Br and **3**, by the water-soluble calix[6]arene host Na₈**4** in neutral aqueous media. Two of the ferrocene-based guests are cationic but have aliphatic chains of different length, thus altering their relative hydrophobic character. The third guest is neutral. The calixarene host has been reported to be an octaanion in neutral aqueous media due to the deprotonation of two phenol groups.³

The anodic electrochemistry of all three guests is characterized by the reversible monoelectronic oxidation of the ferrocene moiety. Addition of 1–4 equiv. of calixarene host has two effects: (i) it induces a sizable negative shift in the half-wave potential for the oxidation process; and (ii) it brings about a substantial decrease of the peak currents in all cases. Fig. 1 shows typical voltammetric curves obtained with guest **3**. Electrochemical potential data for the interaction of the calixarene host with each one of the guests are given in Table 1.

The cationic guests **1**⁺ and **2**⁺ exhibit larger potential shifts than the uncharged guest **3**. This reflects the electrostatic component of the overall binding interaction which is indeed expected from a host having such a large negative charge. The direction of the potential shift indicates that the oxidized form (ferrocenium, subunit charge = +1) of the guest is more strongly bound than the reduced form (ferrocene, subunit charge = 0). Again, this reveals the importance of electro-

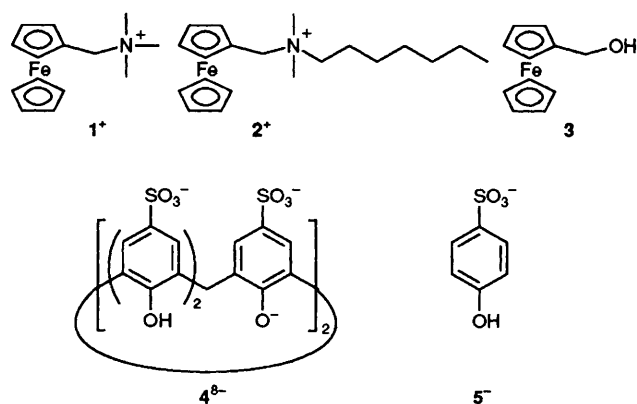


Table 1 Electrochemical potential data at 25 °C for ferrocene-based guests in the absence and in the presence of the calixarene host

[Calixarene]/ [Guest]	1 ⁺		2 ⁺		3	
	$E_{1/2}^a/V$	$\Delta E_p^b/mV$	$E_{1/2}^a/V$	$\Delta E_p^b/mV$	$E_{1/2}^a/V$	$\Delta E_p^b/mV$
0:1	0.400	60	0.400	60	0.180	60
1:1	0.295	90	0.290	100	0.130	110
2:1	0.280	80	0.270	80	0.110	90
4:1	0.280	80	0.270	80	0.90	80

^a Vs. sodium chloride saturated calomel electrode. Determined in 50 mmol dm⁻³ NaCl with a glassy carbon working electrode.
^b Potential difference between the cathodic and anodic peaks determined at 100 mV s⁻¹

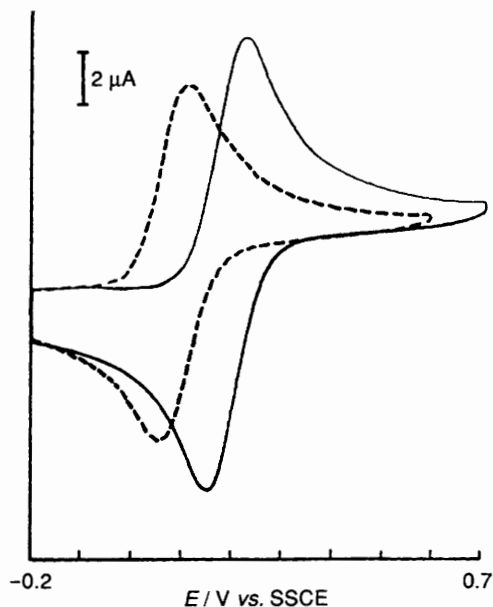


Fig. 1 Cyclic voltammetric response on glassy carbon (0.08 cm²) of a 1.0 mmol dm⁻³ solution of **3** in 50 mmol dm⁻³ NaCl in the absence of host **4**⁸⁻ (—) and in the presence of 4.0 mmol dm⁻³ host (---). Scan rate = 100 mV s⁻¹

static interactions in the complexation. However, the calixarene-induced current decrease which is observed in all cases indicates that the anionic calixarene host binds all three guests prior to oxidation. Calixarene complexation decreases the apparent diffusion coefficient of the ferrocene derivatives because the complexes are much bulkier than the corresponding free guests. The dependence of the apparent diffusion coefficient on calixarene concentration can be utilized to determine the equilibrium binding constants between **4**⁸⁻ and all three guests using our previously reported procedure.⁴ The values obtained are: 10930 ± 960 dm³ mol⁻¹ for **1**⁺, 7610 ± 680 dm³ mol⁻¹ for **2**⁺ and 3650 ± 360 dm³ mol⁻¹ for **3**.

¹H NMR spectroscopy was also employed to study these host-guest interactions. Relevant values are summarized in Fig. 2. Substantial shifts of the ferrocene protons are observed upon addition of an equimolar amount of host **4**⁸⁻ to a D₂O solution of **1**⁺. Even larger changes are observed for the resonances of the methyl and methylene protons adjacent to the charged quaternary nitrogen. Similar results are observed with **2**⁺, *i.e.*, large shifts for the ferrocene protons as well as for the protons on the methyl and methylene groups adjacent to the positively charged nitrogen atom. Only minor changes ($\Delta\delta < 0.05$) were observed for the proton resonances assigned to the terminal methyl and the adjacent 4 methylenes at the end of the heptyl chain. Addition of an equimolar amount of **4**⁸⁻ to a D₂O solution of the uncharged substrate **3** also results in substantive changes in its spectrum but the magnitude of the $\Delta\delta$ values parallels the lower binding constant found for the **3**·**4**⁸⁻ complex.

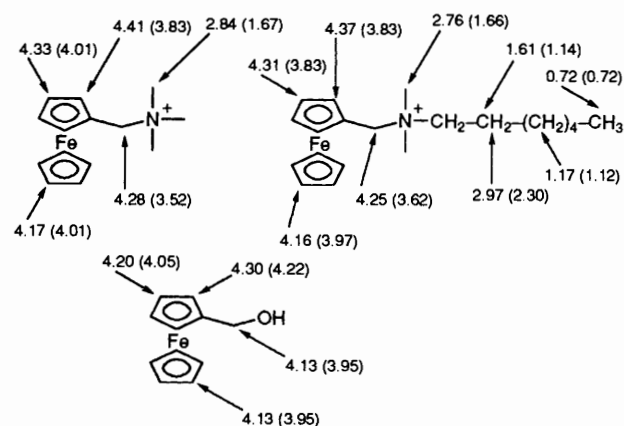


Fig. 2 400 MHz ¹H NMR chemical shifts (δ) for the guests in D₂O solution. Values in parenthesis were recorded after addition of 1 equiv. of calixarene host.

4-Hydroxybenzenesulfonate, **5**⁻, can be considered as a monomeric analogue of the calixarene host. We performed voltammetric and spectroscopic measurements for all three guests in the presence of Na·**5** as control experiments. No significant changes were detected in the voltammetric behaviour or in the ¹H NMR spectra of **1**–**3** upon addition of large excesses of **5**⁻. Therefore, our electrochemical and spectroscopic data reveal that rather strong binding interactions take place between all three guests and the calixarene host. This is consistent with the formation of inclusion complexes in all cases.

From our results we conclude that electrostatic interactions between the positively charged guest and the anionic host play an important role in the complexation. However, the binding constant value measured with the neutral guest **3** is only a factor of 2–3 lower than the values obtained with the positively charged guests **1**⁺ and **2**⁺. This means that a large fraction of the free energy change in the complexation process is due to nonelectrostatic interactions. We postulate that the binding interactions found here constitute an example of apolar inclusion complexation, using terms recently introduced by Diederich.⁵ This means that the process is similar to the inclusion complexation of organic compounds by cyclodextrins or cyclophanes in aqueous media. Therefore, the steric fit of the guest inside the host's cavity is of paramount importance. Our NMR and voltammetric data suggest that the guest's ferrocene subunit is engulfed inside the calixarene cavity and the interactions resulting from ferrocene inclusion provide most of the stabilization necessary for complex formation. Favourable electrostatic interactions add stability to the complex but are of secondary importance as indicated by the large binding constant measured for the calixarene complexation of the neutral guest **3**.

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