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The Complexation of Ferrocene Derivatives by a Water-Soluble Calix[6]arene*

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Abstract. The complexation of several ferrocene derivatives by the water-soluble host *p*-sulfonato-calix[6]arene was investigated using electrochemical and ^{1}H-NMR spectroscopic techniques. The electrochemical results indicate that both oxidation states of the guests are bound to the calixarene host, although the oxidized (ferrocenium) forms are complexed more strongly than the reduced (ferrocene) species. ^{1}H-NMR spectroscopic data indicate that the complexation phenomena involves the inclusion of the guest's ferrocene moiety into the flexible calixarene cavity.

Key words: Inclusion complexation, sulfonated calixarenes, redox-active guests, voltammetry, apolar binding.

1. Introduction

The calixarenes [1–3] constitute a class of host compounds that is attracting substantial attention in the field of supramolecular chemistry. Calixarenes are macrocyclic oligomers formed by the condensation of a *p*-alkylphenol and formaldehyde. Cyclic tetramers, hexamers, and octamers are readily produced in these reactions, serving as the core nuclei for further synthetic elaboration. While the seminal work of Gutsche and coworkers on calixarenes [4] was published more than ten years ago, the literature does not contain many examples of well-characterized solution complexes of calixarenes [5–12]. In this regard, Shinkai's method for the preparation of sulfonated calixarenes [5] opened the possibility of studying calixarenes as hosts for complexation in aqueous media. Sulfonated calixarenes have become one of the most promising type of molecular hosts, since they can be viewed as conformationally flexible cyclodextrin analogs.

Our continuous interest in molecular recognition phenomena involving redox-active hosts or guests led us to explore the binding of ferrocene derivatives by sulfonated calixarenes in aqueous media. Therefore, we have investigated the binding of a series of ferrocene-containing guests (see Chart 1) by the water-soluble

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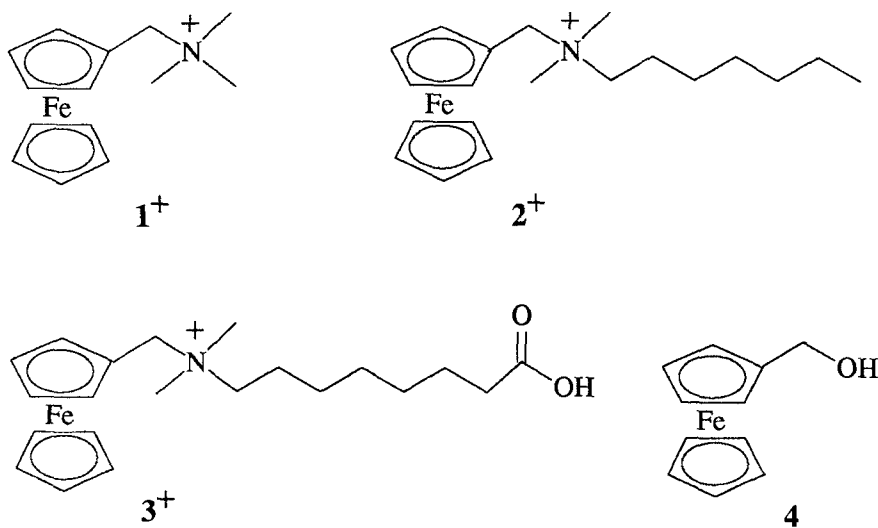** Author for correspondence.

Chart 1.

host p-sulfonatocalix[6]arene. We describe here the results of this investigation. A preliminary report has been published elsewhere [13].

2. Experimental

2.1. MATERIALS AND REAGENTS

Guest 4 was purchased from Aldrich and recrystallized from ethanol before use. The cationic guests 1^+ and 2^+ were prepared as described previously [14]. Guests 1^+ and 2^+ were used as their hexafluorophosphate and bromide salts, respectively. The bromide salt of guest 3^+ was synthesized by a similar procedure involving the quarternization of ((dimethylamino)methyl)ferrocene (Aldrich) with 8-bromooctanoic acid (Aldrich). The yellow product was first recrystallized from acetone/ether and then washed with CH_2Cl_2 to remove impurities. The remaining solid was filtered off and dried under vacuum at $60°C$ to yield pure 3·Br. Aqueous titration of 3·Br with a solution of NaOH yields a pK_a value of 4.44 and a neutralization equivalent of 452.3 (calculated value: 466.2, 3% error). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 4.50 (s, 2H) 4.38 (d, 4H), 4.25 (s, 5H), 3.10 (br, 2H), 2.83 (s, 6H), 2.20 (t, 2H), 1.70 (br, 2H), 1.5 (t, unresolved, 2H), 1.3 (br, 6H). DCI-MS (NH₃ as carrier gas): [M$^+$ = 386]. *Anal. Calcd.* for $C_{21}H_{32}O_2NFeBr$: C, 53.96%; H, 6.87%. *Found*: C, 54.10%; H, 6.92%.

The sodium salt of the anionic host p-sulfonatocalix[6]arene (Na₈·5) was synthesized by the procedure of Shinkai and coworkers [5]. All other reagents and solvents were of the best commercial quality available. D_2O was purchased from

Aldrich. Distilled water was further purified by passage through a four-cartridge Barnstead Nanopure water purification system.

2.2. EQUIPMENT

^{1}H-NMR spectra were recorded on a Varian VXR-400-S spectrometer operating at a frequency of 399.99 MHz. Mass spectra were obtained in VG-trio-2 spectrometer. The electrochemical instrumentation has been described elsewhere [15].

2.3. PROCEDURES

The voltammetric experiments were conducted in a single-cell compartment. The working electrodes were either a Bioanalytical Systems glassy carbon disk (0.080 cm^2) for cyclic voltammetry or a Pine Instruments glassy carbon disk of larger area (0.196 cm^2) for rotating disk electrode voltammetry. The auxiliary (Pt flag) and reference (sodium chloride saturated calomel) electrodes were home-made. Typically, the voltammetric behavior of a 1.0 mM solution of the ferrocene derivative in 50 mM NaCl was recorded at the beginning of each experiment. Immediately afterwards, aliquots from a stock solution containing 10 mM 5^{8-}, 1.0 mM ferrocene derivative, and 50 mM NaCl were added to adjust the concentration of the host in the test solution without diluting the redox-active guest or the supporting electrolyte. No effort was made to keep the test solutions oxygen-free as control experiments demonstrated that the presence of oxygen did not affect the voltammetric results.

Rotating disk electrode voltammetry was used to determine the apparent diffusion coefficients (D_{app}) of the ferrocene derivatives. The D_{app} values depend on the added concentration of host and reflect the position of the host–guest association equilibrium because the inclusion complexes diffuse substantially more slowly than the corresponding free guests. We utilized this concentration dependence to determine the equilibrium constants for the formation of each of the host–guest complexes surveyed here. The details of this method have been already published by us [14].

3. Results and Discussion

3.1. VOLTAMMETRIC STUDIES

As is widely known, the ferrocene subunit undergoes rapid monoelectronic oxidation to yield the corresponding cationic ferrocenium species. Thus, the ferrocenium/ferrocene redox couple is electrochemically reversible and provides a convenient handle to study the complexation of the ferrocene-containing guests 1^+–4^+ by the anionic calixarene host. Our experiments clearly indicate that all guests are strongly complexed by the calixarene host. For instance, Figure 1 shows the anodic voltammetric behavior of **4** in the absence and in the presence of host
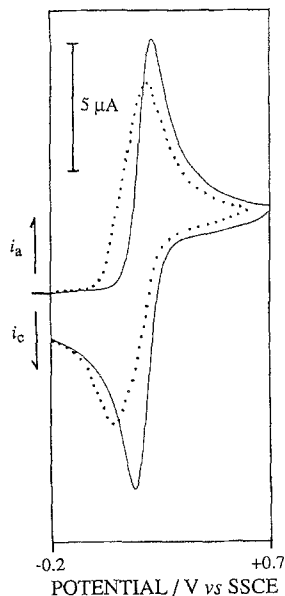
Fig. 1.   Voltammetric response (100 mV s^{-1}) on glassy carbon of a 0.5 mmol dm^{-3} solution of **4** in 50 mmol dm^{-3} NaCl in the absence (continuous line) and in the presence (dotted line) of 1.0 equiv. of host **5**$^{-8}$.

5^{8-}. It is clearly evident that the voltammetric response is strongly affected by the presence of the calixarene host as evidenced by the shift of the voltammetric waves to less positive potentials and the marked decrease in the current levels. The electrochemical conversions taking place at the electrode surface are represented by the following equation:
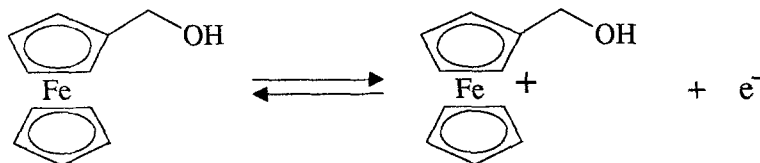
Complexation of **4** in either or both oxidation states is expected to shift the couple's half-wave potential ($E_{1/2}$). As seen in Figure 1, the $E_{1/2}$ value undergoes a substantial displacement in the negative direction, revealing that the oxidation process takes place more easily in the presence of the calixarene. This observation, in turn, reveals the stabilization of the ferrocenium form by complexation with the anionic host. However, the decreased current levels observed throughout the voltammogram indicate that the reduced form of **4** is also complexed by **5**$^{8-}$. Similar voltammetric results were obtained with all the remaining guests. It is interesting to compare these data with those previously reported by us for the complexation of guests **1**$^{+}$ and **2**$^{+}$ by β-CD [14]. In contrast to the anionic calixarene host, the

TABLE I. Voltammetric data at 25° C for the oxidation of ferrocene-based guests as a function of the concentration of added calixarene host. Medium: 50 mmol dm^{-3} NaCl.

Guest	[Calix.]/[Guest]	$E_{1/2}/V^a$	$\Delta E_p/mV^b$	K/M^{-1c}
	0:1	0.400	60	
1^+	1:1	0.295	90	10,900
	2:1	0.280	80	
	3:1	0.280	80	
	0:1	0.400	60	
2^+	1:1	0.290	100	7,600
	2:1	0.270	80	
	4:1	0.270	80	
	0:1	0.180	60	
4	1:1	0.130	110	3,700
	2:1	0.110	90	
	4:1	0.090	80	

^{a}Measured against a sodium chloride saturated calomel electrode.
^{b}Potential difference between the cathodic and anodic peaks determined at 100 mV/s.
^{c}Binding constants measured using the method given in reference[14]. See text for details.

presence of β-CD shifts the half-wave potential for the oxidation of either guest to more positive values, reflecting the preferential complexation of the reduced form of the guest. In fact, in our voltammetric studies with β-CD [14], we did not detect any complexation of the oxidized (ferrocenium) form of the guests. Thus, the anionic nature of the calixarene host investigated in this work substantially alters the complexation processes of these guests as compared to those observed with the uncharged cyclodextrin receptor. While both types of hosts interact with the reduced guests, only the calixarene seems capable of strongly complexing the oxidized species, a finding which can be easily rationalized by taking into account the electrostatic attraction between the positively charged (oxidized) guest and the negatively charged host.

A summary of relevant voltammetric data with guests 1^+, 2^+, and 4 is provided in Table I. The binding constant values correspond to the association equilibria between the reduced guest and the calixarene host 5^{8-} and were obtained from the concentration dependence of the calixarene-induced decrease in the apparent diffusion coefficients as measured by rotating disk electrode voltammetry (see Experimental Section). Interestingly, all three guests exhibit binding constants in the range 10^3–10^4 M^{-1}. The cationic guests 1^+ and 2^+ show larger values than the neutral guest 4. This is probably due to the favorable electrostatic interactions

TABLE II. Calixarene-induced effects on the half-wave potential[a] of guest 3^+ at 25°C as a function of medium pH. $[3]^+ = 1.0$ mmol dm^{-3}.

pH	$E_{1/2}$ at [Calix] = 0	$E_{1/2}$ at [Calix] = 2.0 mmol dm^{-3}
2	0.360	0.360
4	0.380	0.290
8	0.360	0.250

[a] Volts vs. SSCE.

between the cationic guests and the anionic calixarene. However, the binding constant measured with **4** is only a factor of 2–3 lower than those measured with the cationic guests, suggesting that the electrostatic component in the binding interactions is not the predominant binding force, i.e., a large fraction of the free energy released in the complexation processes is due to nonelectrostatic interactions. This point will be revisited later.

As discussed before, the negative direction of the calixarene-induced shift in the half-wave potentials leads to the conclusion that the *oxidized (ferrocenium) form of the guests is more strongly bound than the reduced (ferrocene) form.* This is true for all three guests in Table I, regardless of their cationic or neutral nature before electrochemical oxidation. Another important observation can be made from the voltammetric data: The peak-to-peak potential splittings (ΔE_p values) of the voltammetric set of waves are strongly affected by the presence of the calixarene host. This is also observed for all three guests. This finding clearly suggests that the complexation reactions interfere with the electrochemical conversions of the ferrocene subunit. In our studies with β-CD [14], we noted that the electrochemical oxidation of 1^+ (or 2^+) only occurs after dissociation of the corresponding cyclodextrin complex. The voltammetric data obtained with β-CD indicated that the oxidized guest is never included by the cyclodextrin host. In this work, the situation is more complex since both oxidation states of the ferrocene guests are included by the anionic calixarene host. Further electrochemical studies are necessary to obtain a detailed mechanistic picture of the oxidation of the calixarene complexes surveyed in this work.

The aliphatic chain of guest 3^+ ends up in an ionizable carboxylic acid group. This guest was included in this work with the idea of studying its binding to the calixarene host as a function of pH, because the overall charge of the reduced guest may be altered by appropriate pH changes in the reaction medium. However, the host is also pH-sensitive, which complicates considerably the interpretation of the results. Table II provides some preliminary data on the pH dependence of the interactions of this guest with the anionic calixarene host. Upon the addition of 2 equiv. of host, the largest change in the half-wave potential of 3^+ takes place at pH 8. A slightly lower change takes place at pH 4, and no significant shift is observed at pH 2. As reported in the Experimental Section, the pK_a of the carboxylic acid

group of 3^+ is 4.44 so that, at pH 2, this group is fully protonated (uncharged) and, at pH 8, is fully ionized (negatively charged). The fact that the largest $E_{1/2}$ shift is observed at the highest pH is probably the result of changes in the structure of the calixarene. At pH 8, the calixarene is present in aqueous solution as an octaanion. According to Atwood and coworkers [16], this octaanion has a solution structure that can be described as a double partial cone, with four negative charges (one phenolate and three sulfonate groups) pointing to each opening of the cavity. As the pH of the medium decreases, it is anticipated that the phenolate groups will undergo protonation [16], thus losing their negative charges and reducing the overall anionic character of the calixarene framework. These protonation-driven changes in the number and distribution of the negative charges of the host may affect its predominant solution conformation, perhaps, leading to less organized conformers which may not exhibit a clearly defined cavity for molecular complexation. Increased conformational flexibility associated to removal of negative charge might be responsible for the results that we obtained at pH 2, where no evidence for complexation was detected using electrochemical techniques.

3.2. ^{1}H-NMR SPECTROSCOPIC STUDIES

Although the substantial calixarene-induced shifts observed in the half-wave potential for the oxidation of all the guests strongly suggest that their main site of interaction with the host is the ferrocene subunit, such detailed information cannot be obtained only from electrochemical data. As we have done before [14, 15], we decided to obtain ^{1}H-NMR spectroscopic data to address this point in more detail. The results are compiled in Table III.

In general, the NMR data are in excellent agreement with the electrochemical results. The proton spectra of all three ferrocene-based guests are strongly affected by the addition of 1 equiv. of host 5^{8-}. The resonances for all guest protons shift upfield, which is consistent with guest inclusion in a cavity formed by aromatic rings. The magnitude of this displacement is largest for the aromatic protons on the ferrocene subunit or for neighboring protons. For instance, for guest 1^+ all proton resonances undergo substantial upfield shifts upon addition of 1 equiv. of calixarene. In contrast, under identical conditions, the protons labeled 3–7 on guest 2^+, do not exhibit appreciable shifts, while all the protons in the vicinity of the ferrocene moiety (as well as the ferrocene protons) experience upfield shifts of magnitude similar to those observed with guest 1^+. These observations clearly indicate that *the calixarene host interacts with the ferrocene residue of the guests.* No significant interaction is observed between the calixarene and the pendant heptyl chain of 2^+. The binding constant between 5^{8-} and 2^+ is lower than the corresponding K value between 5^{8-} and 1^+ (see Table I). This difference might be due to steric hindrance imposed on the complexation process by the heptyl chain of 2^+.

TABLE III. 400 MHz ^{1}H-NMR chemical shifts (δ) for guests $\mathbf{1^+}$, $\mathbf{2^+}$, and $\mathbf{4}$ in D_2O solution. Values for the corresponding complexes were recorded after addition of 1 equiv. of $\mathbf{5^{8-}}$.

Position	δ (free guest)	δ (complex)
α'	4.17	4.01
α	4.41	3.83
β	4.33	4.01
$1'$	4.28	3.52
1	2.84	1.67
α'	4.16	3.97
α	4.37	3.83
β	4.31	3.83
$1'$	4.25	3.62
$1''$	2.76	1.66
1	2.97	2.30
2	1.61	1.14
$3/6$	1.17	1.12
7	0.72	0.72
α'	4.13	3.95
α	4.30	4.22
β	4.20	4.05
1	4.13	3.95

4. Conclusions

We have clearly demonstrated the complexation in aqueous media of several ferrocene-based guests by the anionic calixarene host $\mathbf{5^{8-}}$. Control experiments with a monomeric 'analog' of the host, 4-hydroxybenzenesulfonate, showed no effect on the electrochemical or spectroscopic parameters of the guests, even after addition of large excesses of this anion. Therefore, our data indicate that *the anionic calixarene host forms inclusion complexes with all the guests surveyed.* The binding constants measured for the association of $\mathbf{5^{8-}}$ with guest $\mathbf{1^+}$, $\mathbf{2^+}$, and $\mathbf{4}$ are all in the range 10^3–10^4 M^{-1}. However, the voltammetric data reveal that in all cases the oxidized forms of the guests are more tightly bound than the reduced forms. This is probably a reflection of the stronger electrostatic attraction between the host and the oxidized guests.

Although attractive host–guest coulombic forces play an important role in the binding of these guests to the anionic calixarene, other interactions must be respon-

sible for most of the binding free energy as evidenced by the strong binding of neutral **4**. At this point, it seems reasonable to view these host–guest interactions as another example of *apolar binding*, as defined by Diederich and coworkers [17]. We are currently setting up calorimetric measurements to determine the relative enthalpic and entropic contributions to the free energy of complexation in these systems.

Since host 5^{8-} seems capable of apolar binding in aqueous media, it is of some interest to compare briefly its binding properties with those of cyclodextrin hosts. Host 5^{8-} exhibits a cavity, capable of molecular inclusion, which is similarly sized to that of β-CD. Although both 5^{8-} and β-CD exhibit roughly similar binding affinities for ferrocene-containing guests, the calixarene shows an even higher affinity for the oxidized (ferrocenium) guests, while the cyclodextrin does not bind the oxidized forms at all. This is probably due to the dissimilar charges on these receptors, i.e., the anionic nature of the calixarene and the cyclodextrin's lack of charge. Furthermore, while the cyclodextrin has a fairly rigid structure and maintains its well-defined cavity and binding properties throughout the pH 2–10 range, the same is not true for the calixarene. Our data suggest that, as the pH is lowered, a combination of negative charge removal (by protonation) and molecular flexibility tends to decrease the binding properties of the calixarene host. Thus, the anionic calixarene surveyed here shows some similarities in its host properties to β-CD, but its pH-dependent charge and its inherent conformational flexibility give rise to binding properties differing from those found in the substantially more rigid cyclodextrins.

Acknowledgments

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