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Ferrocene Derivatives Included in a Water-Soluble Cavitand: Are They Electroinactive?

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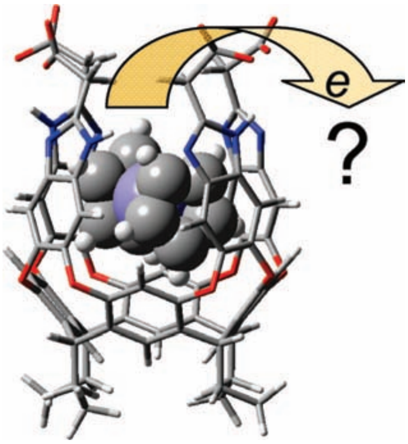
ABSTRACT



The formation in aqueous solution of kinetically stable inclusion complexes between a deep-cavity cavitand and several redox active ferrocene derivatives was demonstrated using ^{1}H NMR spectroscopy. The electrochemical kinetics of the inclusion complexes was strongly attenuated as compared to that observed with the free guests.

Hydrophobic interactions play a crucial role in the formation and stability of host−guest complexes in aqueous media.[1,2] The development of synthetic water-soluble hosts with hydrophobic cavities allows the investigation of the properties of included guests, which can be considered excellent models for enzyme-bound substrates.[3] In the past, we have investigated the electrochemical behavior of ferrocene[4] and cobaltocenium[5] derivatives inside molecular capsules or included by water-soluble guests, such as cyclodextrins[6] and cucurbit[*n*]urils.[7,8] Here, we investigate the formation of inclusion complexes between a series of ferrocene derivatives

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and a water-soluble, deep-cavity cavitand (host **1**, see Figure 1 for structures) which was previously reported by some of us.[9] The results indicate the formation of kinetically stable inclusion complexes in which the rates of heterogeneous electron transfer experience a pronounced decrease from those observed for the free guests.

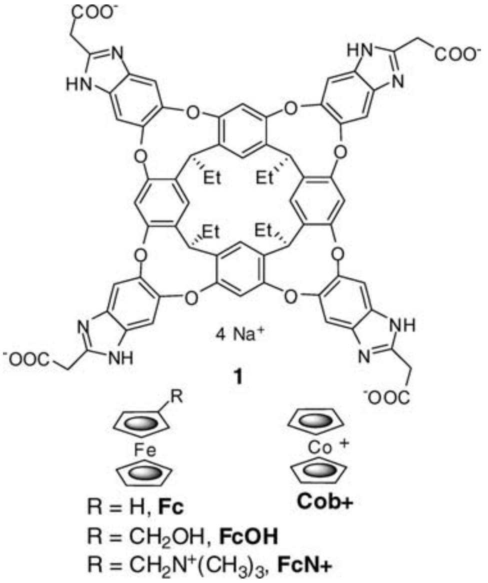

Figure 1. Structures of host **1** and guests used in this work.

The synthesis of host **1** has been reported already.[9a] The guests are either commercially available (**Fc**, **FcOH**, **Cob+**) or readily prepared as described before[6] (**FcN+**). We elected to carry out electrochemical experiments in aqueous solution containing 50 mM NaCl. This salt (supporting electrolyte) concentration was also added to D_2O in the NMR spectroscopic experiments in order to keep the ionic strength constant throughout this work.

The complexation of the ferrocenyl guests was first investigated using ^1H NMR spectroscopy. **Fc** is quite hydrophobic and exhibits poor solubility in aqueous solution. Its solubility has been reported as ca. 50 μM in 0.1 M NaCl at 25 °C.[10] However, the presence of host **1** in the solution enhances the solubility of **Fc** to the point that it is possible to dissolve **Fc** at the 1.0 mM level if the D_2O solution also contains 1.0 mM **1**. This finding strongly suggests that **Fc** is bound by the cavitand host. Figure 2 shows the corresponding ^1H NMR spectrum, from which we conclude that ferrocene is fully included in the aromatic cavity of the host, as evidenced by the considerable complexation-induced shift of its proton signal, which was recorded at 0.81 ppm. The pronounced high field shift of the ferrocene protons reflects their exposure to the ring currents of the aromatic groups on the walls of the host cavity. The pattern of aromatic resonances in the region between 7.3 and 8.1 ppm is also consistent with the inclusion complexation of the ferrocene guest. Thus, NMR spectroscopy reveals the quantitative formation of the **1·Fc** complex at 1.0 mM concentrations of host and guest. If we assume that a maximum of 10% of the ferrocene may be uncomplexed (and undetected by NMR spectroscopy), a minimum value for the equilibrium association constant (K) can be estimated as 9×10^4 M^{-1}.

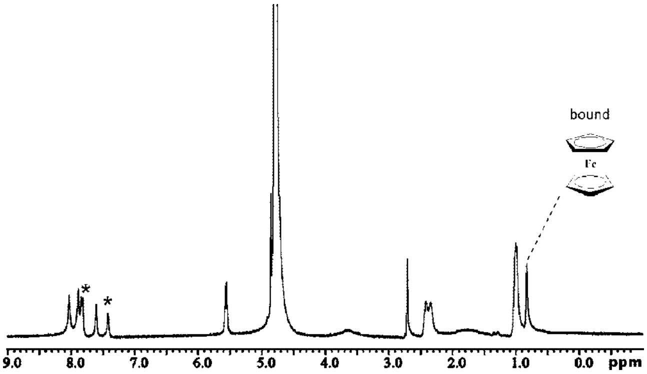

Figure 2. ^1H NMR spectrum (400 MHz, D_2O/0.050 M NaCl) of 1.0 mM **Fc** + 1.0 mM host **1**. New complexation-induced aromatic peaks are labeled with a $*$ symbol.

The much higher aqueous solubility of the guest ferrocenemethanol (**FcOH**) allows experiments in concentration ratios that are impossible with **Fc**. Figure 3 summarizes some of these spectroscopic data and shows conclusively that the exchange between the free and complexed guest is slow on

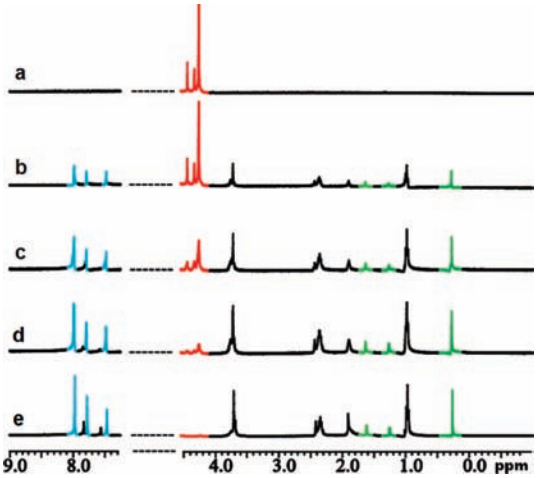

Figure 3. ^1H NMR spectra (400 MHz, D_2O/0.050 M NaCl) of 1.0 mM **FcOH** in the presence of (a) 0 mM **1**, (b) 0.3 mM **1**, (c) 0.7 mM **1**, (d) 1.0 mM **1**, and (e) 1.3 mM **1**. The blue peaks correspond to bound host protons, the red peaks to free guest protons, and the green peaks to bound guest protons.

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the NMR time scale of these experiments, as the peaks corresponding to the guest's unsubstituted cyclopentadienyl protons are simultaneously observed at 4.26 ppm (free **FcOH**) and 0.26 ppm (bound **FcOH**) for host concentrations under 1.3 equiv. The relative integration of these peaks allows us to calculate the equilibrium concentrations of free and bound guests at each concentration of added host. From these data we can determine the equilibrium association constant for the **1·FcOH** complex as $K = 4800\ (\pm 300)\ M^{-1}$. Similar behavior was observed in ^1H NMR spectroscopic experiments with the cationic guest **FcN+**, and a K value of 1300 (±100) M^{-1} was measured for this guest using the same method (see the Supporting Information). All of the NMR spectroscopic data indicate that the interaction of the guest **FCOH** and **FCN+** with host **1** takes place by insertion of the ferrocene residue in the cavity of the host, with the polar residues still exposed to the solvent molecules. Although host **1** has been found to dimerize in the absence of suitable guests,[9e] it forms a velcrand-type dimer which does not have any internal cavity space. All of our data are consistent with the formation of 1:1 complexes, in very good agreement with the body of existing data on inclusion complexes formed by this host.[9]

Cobaltocenium (**Cob+**) is very similar in size and has the same charge as ferrocenium, the one-electron oxidized form of **Fc**. Therefore, we have often used **Cob+** as a diamagnetic model for the paramagnetic ferrocenium ion.[11,12] Our NMR spectroscopic data shows that **Cob+** is also complexed by host **1** (see the Supporting Information), although the dissociation rate of this complex appears to be faster than those observed with the ferrocene derivatives. This is clearly evidenced by the fast exchange between the free and bound forms of the guest, which leads to the observation of a single, weighted-averaged peak for the **Cob+** protons.

The electrochemical behavior of the guests in the presence of variable concentrations of **1** was investigated using cyclic voltammetry (CV). As in the NMR experiments, the low solubility of **Fc** precluded us from recording its voltammetric response at 1.0 mM concentration in 50 mM NaCl. However, a solution containing 1.0 mM **Fc** and 1.0 mM **1** in the same electrolyte medium is perfectly clear. Its cyclic voltammetric response is shown in Figure 4. Quite remarkably, no significant faradaic currents associated with the reversible one-electron oxidation of ferrocene were observed in the surveyed potential window. In fact, the voltammogram was essentially flat and showed only background current levels associated with charging of the working electrode double layer. Excess concentration of host **1** has little effect on the observed voltammetric response. In contrast to this, addition of excess **Fc** (over 1.0 equiv) leads to turbid solutions, as some of the hydrophobic guest is not solubilized by complexation. Under these conditions, the observation of a set of waves for the reversible one-electron oxidation of **Fc**, unequivocally demonstrates that (i) the electrode is not passivated by the presence of host **1** in the solution and (ii) the **1·Fc** complex *is not electroactive* under the conditions of these experiments (or its electrochemical kinetics is too slow to yield measurable currents under our experimental conditions).[13]

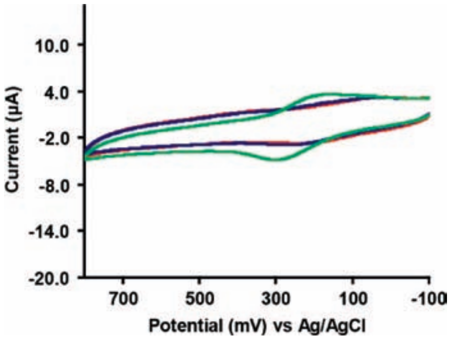

Figure 4. Cyclic voltammetric response on glassy carbon (0.071 cm^2) of a solution containing 1.0 mM **1** and 50 mM NaCl in the presence of 0.5 mM (red line), 1.0 mM (blue line), and 2.0 mM **Fc** (green line). Scan rate: 0.10 V s^{-1}.

Similar experiments with the cationic **FcN+** guest yield similar results. In this case, we can, of course, record without any solubility problems the well-known, reversible voltammetric behavior of this cationic ferrocene derivative.[6,8] The half-wave potential ($E_{1/2}$), measured as the average of the anodic and cathodic peak potentials, was found to be +0.44 V vs Ag/AgCl. As we add host **1**, the set of reversible waves losses intensity and eventually disappears at a concentration of host **1** between 1 and 2 equiv. This is consistent with the results obtained with **Fc**. The current levels of the set of waves centered at 0.44 V decrease with increasing host concentration because the inclusion complex is not electroactive. Thus, as the concentration of **1** increases, the original set of waves exhibits gradually lower currents, reflecting the decreasing concentration of free guest. Eventually, when all the **FcN+** has been complexed, no significant faradaic currents are observed in the surveyed potential range. As is the case in the NMR experiments, we must add an excess of host **1** to complete the conversion from free **FcN+** into its complex, **1·FcN+**, which is perfectly consistent with the corresponding K values measured in the NMR experiments. Similar CV data were recorded with the other water-soluble ferrocene guest (**FcOH**, see the Supporting Information).

Our electrochemical data do not provide any indication that the electrochemical oxidation of the guest may lead to complex dissociation, which is perfectly consistent with the observed complexation of the positively charged **Cob+** guest inside the cavity of host **1** (see the Supporting Information)

The lack of voltammetric response observed in this work with the inclusion complexes formed between host **1** and all three ferrocene-containing guests (**Fc**, **FcOH**, and **FCN+**) is a very intriguing finding. A few years ago, we investigated the voltammetric behavior of **Fc** trapped inside a hemicar-

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(13) The observed current depression in the CV response can be rationalized by a decrease of at least 1000-fold in the standard constant for the heterogeneous electron transfer process.

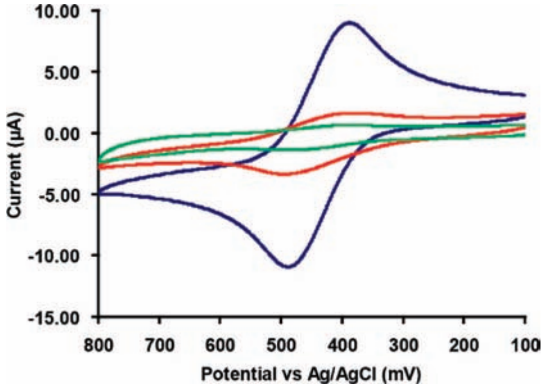

Figure 5. Cyclic voltammetric response on glassy carbon (0.071 cm^2) of a solution containing 1.0 mM **FcN+** and 50 mM NaCl in the absence (blue line) and in the presence of 1.0 mM (red line) and 2.0 mM (green line) host **1**. Scan rate: 0.10 Vs^{-1}.

cerand and showed that the electrochemical kinetics upon encapsulation was slower than that of free **Fc**.[4] More recently, we have investigated the voltammetric response of **Cob+** inside hexameric resorcinarene molecular capsules[5] and demonstrated that encapsulated **Cob+** is voltammetrically silent. These two cases correspond to kinetically stable complexes, which are only soluble in nonpolar solvents, such as CH_2Cl_2. In both cases, the relative attenuation of the electrochemical kinetics was rationalized by the increased distance between the encapsulated redox center and the electrode surface at the time of the heterogeneous electron-transfer event (closest approach to the electrode surface). Very recently, Sarmentero and Ballester[14] have reported the electrochemical behavior in MeOH and acetone of the guest **Cob+** included in a hybrid cavitand−resorcin[4]arene structurally related to host **1**. In this case, the inclusion complex shows a reversible set of waves at more negative half-wave potential than the free guest.

In aqueous solution, very recent work by our group has shown that **Fc** trapped inside a dimeric molecular capsule (formed reversibly by two deep-cavity, octaacid cavitands) is also voltammetrically silent,[15] implying a very pronounced decrease of the heterogeneous electron transfer rate upon encapsulation. However, the molecular weight of this dimeric capsule is 3456 Da (2 × 1728), while the single cavitand investigated in this work has a smaller molecular weight of 1289 Da (formulated as an acid). Nonetheless, the effect of encapsulation appears to be very similar in both cases, leading to voltammetrically silent inclusion complexes. It must be noted however that, in aqueous solution, not all kinetically stable inclusion complexes of ferrocene derivatives are voltammetrically silent. Relevant examples are the inclusion complexes formed by the host cucurbit[7]uril (MW: 1163 Da), which exhibit essentially reversible voltammetric behavior under similar conditions.[7,8] Obviously, other factors beyond molecular weight of the host (or associated size/distance effects), must be at play here (see the Supporting Information for models of both types of complexes). The collection of voltammetric data accummulated so far is not well understood at this point, which highlights the need for continued research work on these fascinating supramolecular systems and their electrochemical behavior.

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Supporting Information Available: Additional NMR spectroscopic and voltammetric data as mentioned in the text This material is available free of charge via the Internet at http://pubs.acs.org.

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