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Mediated Electrochemical Oxidation of a Fully Encapsulated Redox Active Center

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Electron transfer (ET) involving redox proteins is one of the most important processes in biological systems.[1] The ET rates depend on various factors including thermodynamic driving forces, reorganization energies, and the extent of electronic coupling between the reactants. The latter normally diminishes exponentially with the distance between the redox centers, a fact that is used in biological systems to attenuate ET rates.[2] In many redox proteins the active center is partially or completely buried in the polypeptide framework, in such a way that its accessibility to a redox partner may change drastically with orientation. In heterogeneous ET reactions, the prevalent orientation of the protein at the electrode surface controls the resulting rates, as evidenced by the well-known electrochemical behavior of cytochrome *c*.[3]

Dendrimers have been proposed as protein analogues, and when they contain a redox active core, their electrochemistry usually shows substantial kinetic attenuations with the growth of the dendritic mass surrounding the redox core.[4] Years ago we demonstrated with relatively small ferrocene-containing dendrimers that their electrochemical ET rates were strongly affected by their orientation at the electrode surface.[5] Recent advances in supramolecular chemistry also permit the noncovalent encapsulation of guest molecules, which opens up additional research avenues to investigate the electrochemistry of redox centers partially or completely insulated from the electrode surface.[6] A number of hydrophobic molecules can be included as guests in dimeric molecular capsules formed by the deep-cavity cavitand **1**[7] (see Figure 1 for structures) in buffered pH 10 aqueous solutions. We have recently demonstrated that the encapsulation of ferrocene inside this dimeric molecular capsules ($\mathbf{1}_2$) leads to a supramolecular assembly, Fc@$\mathbf{1}_2$, which is voltammetrically silent.[8] In contrast to this, simple *N,N'*-dialkyl-4,4′-bipyridinium (viologen) dications are strongly attracted to the outside of the $\mathbf{1}_2$ capsule due to the negative charge afforded by the 16 surface carboxylates.[8] Surface attachment to the large anionic capsules slows down the electrochemical kinetics of the viologens, but their heterogeneous ET reactions are still perfectly observable in voltammetric experiments, in stark contrast with encapsulated ferrocene. Here, we show that it is possible to use a cationic mediator to relay electrons from the encapsulated ferrocene center to the electrode surface. The system reported here is fully synthetic but has properties similar to those of much more complicated biological structures. Furthermore, mediated electron transfer leads to the formation of oxidized ferrocenium inside the capsule, which causes the disassembly of the supramolecular system, as ferrocenium is positively charged and insufficiently hydrophobic to keep the capsule components together.

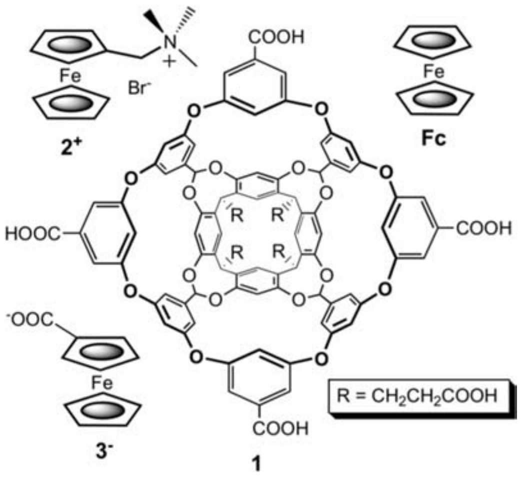

Figure 1. Structures of the deep-cavity cavitand **1** and the ferrocene derivatives used in this work.

The formation of dimeric cavitand capsules ($\mathbf{1}_2$) around Fc has been previously demonstrated.[8] Addition of 1.0 mM cationic ferrocene derivative $\mathbf{2}^+$ to a D_2O solution containing 1.0 mM Fc and 2.0 mM **1** does not change the pattern of NMR signals corresponding to the Fc@$\mathbf{1}_2$ assembly, but the resonance for the methyl protons of $\mathbf{2}^+$ shifts upfield by 0.1 ppm (Figure S1, Supporting Information). Diffusion coefficient (D_o) measurements using Pulse Gradient Stimulated Echo (PGSE) NMR techniques[9] yield a value of 1.7×10^{-6} cm^2 s^{-1} for $\mathbf{2}^+$ in this medium (Table S1), which is extremely close to the value 1.6×10^{-6} cm^2 s^{-1} measured for the Fc@$\mathbf{1}_2$ supramolecular assembly. These findings indicate that $\mathbf{2}^+$ is electrostatically attached to the outside of the capsular assembly. If we increase the concentration of $\mathbf{2}^+$ to 2.0 mM, its D_o value increases to 3.0×10^{-6} cm^2 s^{-1}, reflecting that only one $\mathbf{2}^+$ cation can experience tight association with the capsule's exterior. Similar D_o values were measured if Fc is replaced by (*E*)-stilbene, a hydrophobic guest that is well-known to drive the formation of $\mathbf{1}_2$ capsules.[10]

As expected, the voltammetric behavior of $\mathbf{2}^+$ is perfectly reversible, with the one-electron oxidation of the ferrocene residue at a half-wave potential ($E_{1/2}$) of 0.44 V vs Ag/AgCl. In the presence of 1.0 equiv of electroinactive stilbene and 2.0 equiv of cavitand **1**, the voltammetric current levels are depressed (Figure 2A) but the half-wave potential does not shift significantly. These findings are consistent with the anticipated external binding of $\mathbf{2}^+$ to the stilbene@$\mathbf{1}_2$ assembly. Replacement of stilbene by ferrocene leads to a number of interesting changes in the observed cyclic voltammetric behavior (Figure 2B). On the forward scan, no faradaic current is detected on the potential range where Fc would be directly oxidized, a finding consistent with the lack of voltammetric response already observed in the Fc@$\mathbf{1}_2$ system. At more positive potentials, the oxidation of $\mathbf{2}^+$ is clearly recorded, with current levels higher than expected for the capsule-attached cation. On the reverse scan, the reduction of $\mathbf{2}^{2+}$ back to $\mathbf{2}^+$ is observed, but the current level for this peak is clearly lower than its corresponding anodic peak. Finally, a second reduction peak is observed in the potential range

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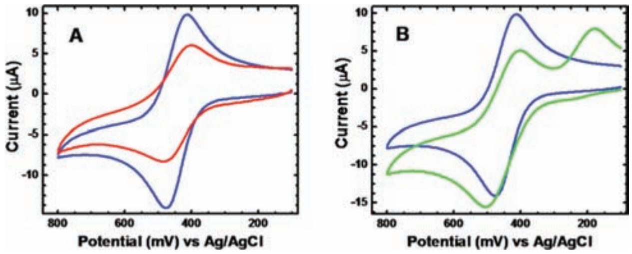
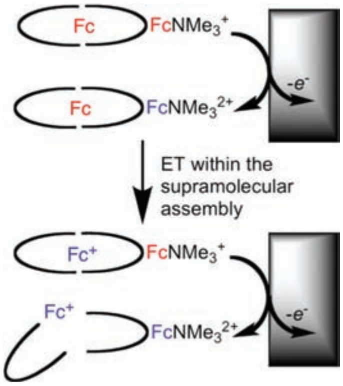


Figure 2. CV responses on glassy carbon (0.071 cm^2) of 50 mM NaCl aqueous solutions buffered at pH 9 with 10 mM sodium borate. (A) 1.0 mM $\mathbf{2}^+$ in the absence (blue) and in the presence (red) of 1.0 equiv of stilbene@$\mathbf{1}_2$. (B) 1.0 mM $\mathbf{2}^+$ in the absence (blue) and in the presence (green) of 1.0 equiv of Fc@$\mathbf{1}_2$. Scan rate: 0.1 V s^{-1}.

for reduction of free Fc^+ (ferrocenium). From the shape of this voltammogram, we conclude that oxidized $\mathbf{2}^{2+}$, on the outside of the Fc@$\mathbf{1}_2$ capsule, accepts an electron from encapsulated Fc in a homogeneous electron transfer process that regenerates $\mathbf{2}^+$ and yields Fc^+ inside the capsule[11] (Scheme 1). This homogeneous ET process is responsible for the 2-fold current increase observed for $\mathbf{2}^+$ oxidation, the relatively smaller current for $\mathbf{2}^{2+}$ reduction, and the observation of a reduction peak ascribed to ferrocenium (at ca. 0.2 V vs Ag/AgCl). The latter reveals that the capsule opens up after ferrocene oxidation, releasing the encapsulated Fc^+ species. However, if potential cycling is continued, the shape of the observed CV is identical to that observed in the first cycle, which suggests that reduction of ferrocenium to ferrocene regenerates the Fc@$\mathbf{1}_2$ assembly efficiently.

Scheme 1. Sequence of Oxidation Events As the Supramolecular Assembly Is Exposed to Increasingly Positive Potentials



We have also carried out control experiments with anionic ferrocenecarboxylate ($\mathbf{3}^-$) in the role of possible mediator for Fc@$\mathbf{1}_2$ oxidation. In this case the voltammetric behavior of $\mathbf{3}^-$ does not change in the presence of 1.0 equiv of stilbene@$\mathbf{1}_2$, which reflects the anticipated lack of interaction between anionic $\mathbf{3}^-$ and the anionic surface of the capsule. When stilbene is replaced by Fc, the type of voltammetric behavior recorded in Figure 2B is not observed (Figure S4), which clearly suggests that the homogeneous ET process from the encapsulated Fc to the outer (oxidized) **3** does not take place in this case. These results are consistent with the data obtained in NMR spectroscopic experiments (including D_o measurements, see Table S1). Finally, we also performed a series of experiments to investigate the mediated electrochemical oxidation of Fc@$\mathbf{1}_2$ by $\mathbf{2}^+$ in the presence of the cucurbit[7]uril (CB7) host. This host forms a highly stable inclusion complex with $\mathbf{2}^+$.[12] Electrochemical and NMR spectroscopic data are consistent with the formation of the CB7•$\mathbf{2}^+$ complex in the presence of the stilbene@$\mathbf{1}_2$ and Fc@$\mathbf{1}_2$ assemblies, but the CB7•$\mathbf{2}^+$ complex proved to be a poor mediator for the oxidation of Fc@$\mathbf{1}_2$ compared to uncomplexed $\mathbf{2}^+$ (see Figures S5 and S6). The obvious conclusion is that for homogeneous ET to take place at measurable rates in the CV experiments, strong attachment of the outside ferrocene-containing mediator to the outer surface of the capsule is necessary.[13]

The results of this work demonstrate that a fully synthetic supramolecular system exhibits suppressed direct ET between the encapsulated redox active center (Fc) and the electrode surface. Addition of suitable mediators that can engage in strong electrostatic interactions with the surface of the capsule leads to effective mediated ET and subsequent breakup of the supramolecular assembly (as long as the Fc center remains oxidized and thus positively charged). The analogies between this experimental behavior and that recorded with some redox proteins are remarkable. We are currently continuing our research in this area and plan to use similar systems in photoinduced ET reactions.

Acknowledgment. The authors are grateful to the National Science Foundation for the generous support of this research work (to A.E.K., CHE-0600795 and CHE-848637).

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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JA9045108