Unusual Electrochemical Properties of the Inclusion Complexes of Ferrocenium and Cobaltocenium with Cucurbit[7]uril

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Received April 25, 2003

Summary: Ferrocenium and cobaltocenium form highly stable 1:1 inclusion complexes with the host cucurbit[7]uril. From electronic absorption spectroscopic data the association equilibrium constants for both complexes were found to be larger than 10^6 L/mol. The electrochemical reduction of either guest leads to a modest loss in binding affinity.

The use of redox chemistry to control the stability of noncovalent inclusion complexes has been the subject of recent reviews.[1] In simple host−guest complexes, electron transfer (et) reactions on either partner strongly perturb the intermolecular forces between the host and the guest, leading to drastic changes in the overall binding affinity.[1a,c,d] For interlocked or topological molecules, such as rotaxanes and catenanes, the translocation of the macrocyclic components can be regulated by the selection of their oxidation states.[1b]

In contrast to the pronounced effects that et reactions exert on the stability of many host−guest complexes, our group[2] and Kim's[3] independently reported a novel type of inclusion complex whose stability is little affected by the one-electron reduction of the guest. In these complexes, formed by the cucurbit[7]uril[4] (CB7) host and simple viologen (V^{2+}) guests, one-electron reduction of their dicationic forms to their monocationic analogues ($CB7{\cdot}V^{2+} + e \rightarrow CB7{\cdot}V^{\bullet+}$) gives rise to a very modest drop in their relative complex stabilities ($\Delta\Delta G \approx 0.4$ kcal/mol). Furthermore, the mechanism of heterogeneous et for the same reduction process departed[2] from the conventional chemical−electrochemical (CE) mechanism[5] that is usually observed with encapsulated, electroactive guests. These unusual thermodynamic and electrochemical results prompted us to investigate the CB7 complexes of other electroactive guests, to further explore the effects of this new host on the electrochemical properties of its inclusion complexes. In this communication, we report the formation and the spectroscopic and electrochemical characterization of the highly stable inclusion complexes between the CB7 host and the monocationic ferrocenium (Fc^+) and cobaltocenium (Cob^+) guests (Scheme 1).

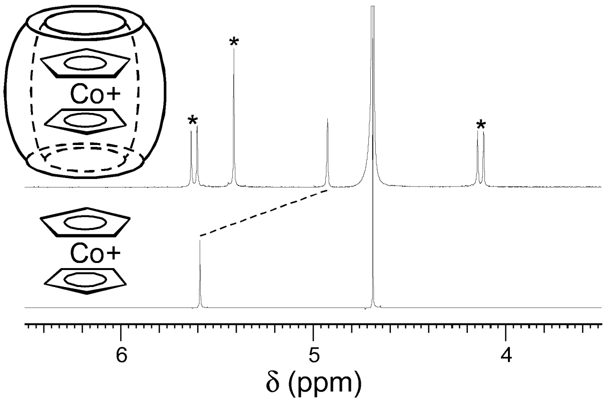
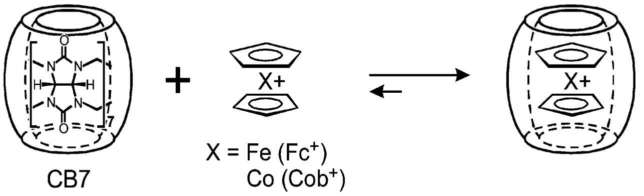


Figure 1. ^1H NMR spectra (500 MHz, 0.1 M NaCl/D_2O) of Cob^+ in the absence (bottom) and in the presence (top) of 1 equiv of CB7. Resonances labeled with an asterisk correspond to the CB7 host.

Scheme 1. Formation of Highly Stable Inclusion Complexes between CB7 and the Guests Fc^+ and Cob^+



The encapsulation of Cob^+ inside the cavity of CB7 was clearly evident in the ^1H NMR spectrum of its inclusion complex (Figure 1). In the presence of increasing concentrations of the CB7 host, the resonances of the cyclopentadienyl ring protons of Cob^+, introduced as its hexafluorophosphate salt, progressively shifted upfield (up to a maximum complexation-induced shift of ∼0.7 ppm, which is reached upon binding saturation with 1.0 equiv of CB7). The rate of exchange between the free and complexed Cob^+ was also fast in the ^1H NMR time scale, although molecular modeling predicted a relatively tight fit for the inclusion complex. Similar experiments with ferrocenium were impossible due to its paramagnetic nature, which hindered the observation of its proton NMR resonances.

The molar absorptivity coefficient of Cob^+ at 261 nm (ϵ_{261nm}) is depressed upon encapsulation by CB7 (see Figure 3). Therefore, the stoichiometry of the $CB7{\cdot}Cob^+$

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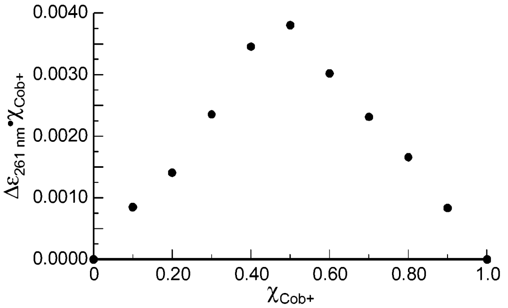

Figure 2. Job plot for the CB7·Cob$^+$ complex ([CB7]+[Cob$^+$] = 23 μM) in 0.03 M TRIS buffer (pH 7.3) also containing 0.1 M NaCl.

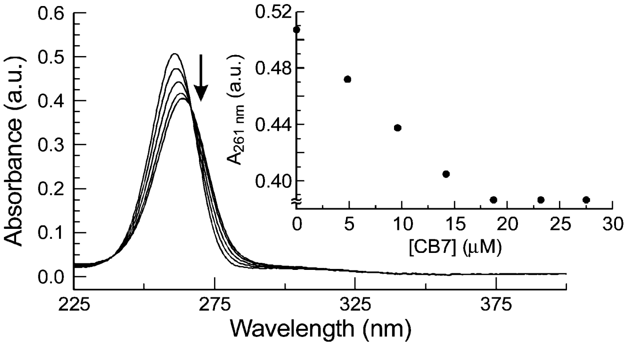

Figure 3. Electronic absorption spectra of Cob$^+$ (14.8 μM in 0.03 M TRIS buffer (pH 7.3) + 0.1 M NaCl) in the presence of various CB7 concentrations (0−27.5 μM, in the direction of the arrow). The inset shows the binding isotherm recorded at 261 nm.

inclusion complex was established by the continuous variation method[6] (Job plot) using UV−vis spectroscopy and the resulting plot is shown in Figure 2. The plot revealed a maximum at $\chi_{Cob^+} \approx 0.5$, clearly indicating a 1:1 binding stoichiometry between the host and the guest. We also attempted to determine the equilibrium constant for the formation of the binary inclusion complex via titration[6] of Cob$^+$ with CB7 (Figure 3). However, despite the use of micromolar concentration levels of Cob$^+$ for the UV−vis titrations, complete binding saturation was immediately reached after the addition of 1.0 equiv of CB7. From this saturation behavior, it can be estimated that the association constant (K) value for the CB7·Cob$^+$ inclusion complex ($\epsilon_{261nm} = 2.55 \times 10^4$ M^{-1} cm^{-1}) must be at least 10^6 M^{-1} (see Table 1). A similar titration experiment with Fc$^+$, also introduced as its hexafluorophosphate salt, yielded the same result (complexation-induced depression of the ϵ_{251nm} value and binding saturation at 1.0 equiv of CB7) on the binding isotherm of its CB7 complex ($\epsilon_{251nm} = 1.04 \times 10^4$ M^{-1} cm^{-1}). This result is a clear indication that Fc$^+$, being almost identical in molecular size to Cob$^+$, also forms a highly stable inclusion complex with CB7.

Table 1. Thermodynamic, Electrochemical, and Spectroscopic Parameters for the Inclusion Complexes between Host CB7 and the Guests Cob$^+$ and Fc$^+$

complex	thermodynamic params				other params			
	oxidized form[a]		reduced form[b]		free guest[c]		complex[c]	
	K	ΔG	K'	$\Delta G'$	$E_{1/2(f)}$	$10^{-4}\epsilon_f$	$E_{1/2(c)}$	$10^{-4}\epsilon_c$
CB7·Fc$^+$	$\geq 10^6$	≤ -8.2	$\geq 4 \times 10^5$	≤ -7.6	0.191	1.30	0.169	1.04
CB7·Cob$^+$	$\geq 10^6$	≤ -8.2	$\geq 3 \times 10^4$	≤ -6.1	−1.15	3.42	−1.24	2.55

[a] Binding constant (K) in L/mol and free energy of complexation (ΔG) in kcal/mol. [b] Same values after one-electron reduction of the guest. [c] Half-wave potentials ($E_{1/2}$) in V vs Ag/AgCl and molar absorptivity coefficients (ϵ) in M^{-1} cm^{-1} (measured at 251 and 261 nm, for Fc$^+$ and Cob$^+$ species, respectively).

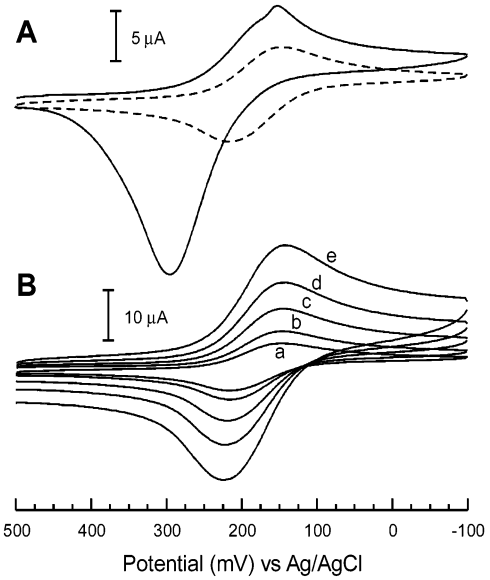

Figure 4. (A) CV responses of 0.82 mM Fc$^+$ in 0.1 M NaCl recorded on a glassy-carbon electrode (0.071 cm^2) in the absence (—) and in the presence (- - -) of 0.87 mM CB7 at a scan rate of 0.1 V/s. (B) CV responses of the CB7·Fc$^+$ complex in A at scan rates of (a) 0.1, (b) 0.2, (c) 0.5, (d) 1, and (e) 2 V/s.

We used cyclic voltammetry (CV) to investigate the aqueous electrochemistry of Fc$^+$ in the absence and in the presence of the CB7 host. Representative CVs are depicted in Figure 4A. In the absence of CB7, the CV of free Fc$^+$ was dominated by precipitation effects due to the insoluble nature of its reduced form (Fc) in aqueous media. In the presence of 1 equiv of CB7, precipitation was completely eliminated. Further additions of host did not result in any detectable effects (decrease in peak currents and/or half-wave potential shifts) on the recorded voltammetric behavior. This binding saturation, reached at 1 equiv of CB7, is consistent with the experimental observations in the UV−vis titrations.

The complete solubilization of the electrogenerated Fc in the presence of CB7 suggests that the host *also* encapsulates the neutral guest. The half-wave potential ($E_{1/2}$) value for the free Fc$^+$/Fc redox couple, obtained using normal pulse voltammetry (NPV),[7] shifted by 22 mV to more cathodic potential values upon binding saturation with CB7 (Table 1). This cathodic shift corresponds to a stability drop ($\Delta\Delta G$) of only 0.5 kcal/mol upon reduction of the monocationic complex (CB7·Fc$^+$) into its neutral form (CB7·Fc). As with the CB7·V^{2+} → CB7·V$^{\bullet+}$ reduction process previously reported by us,[2] this drop is very modest, considering that the stability of many inclusion complexes is strongly altered by redox conversions on either the host or the guest.[1]

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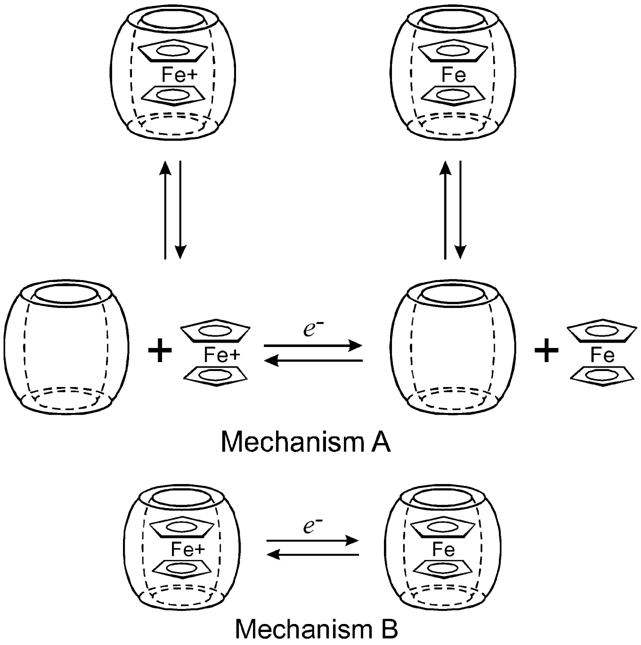
(7) The limiting currents in the NPV measurements of both Fc$^+$ and Cob$^+$ significantly decreased in the presence of CB7. This observation is consistent with the concomitant decrease of their diffusion coefficients upon encapsulation.

Scheme 2. Two Possible Mechanisms for the Heterogeneous Fc$^+$/Fc Electron Transfer Reaction in the Presence of the CB7 Host



The association constant (K') for the neutral CB7·Fc complex can be determined using eq 1, where $\Delta E^{\circ\prime}$ is

$$K'/K = \exp(F\Delta E^{\circ\prime}/RT) \qquad (1)$$

the shift in the $E_{1/2}$ value for free Fc$^+$ upon binding with CB7 (i.e., −22 mV). We obtained a K'/K ratio of 0.4, and this translates to a K' value of at least 4×10^5 M^{-1} (Table 1). To the best of our knowledge, this is by far the largest[8] reported association constant value for *neutral* binary complexes of CB7.

We further examined the mechanism of et for the CB7·Fc$^+$ + e → CB7·Fc reduction process by conducting CV experiments at shorter time scales, i.e., at faster scan rates (Figure 4B). Typically, heterogeneous et reactions of electroactive guests in inclusion complexes are preceded by a complex dissociation process[9] (mechanism A in Scheme 2). At shorter time scales, the complex cannot dissociate fast enough to produce enough free guests for electrochemical conversion and the resulting voltammograms are distorted. However, for the CB7·Fc$^+$ complex, the CVs remained undistorted and fully reversible at scan rates as fast as 2 V/s. This means that, up to the shortest time scale accessible in our voltammetric experiments, the et process for the reduction of Fc$^+$ uncharacteristically proceeded in its encapsulated form (mechanism B in Scheme 2). The reversible shape of all the CVs in Figure 4B also means that the rate constant for the heterogeneous electron-transfer process ($k°$) for the Fc$^+$/Fc redox couple remained fast even after encapsulation by the CB7 host. This observation is also uncommon, because molecular encapsulation normally attenuates the $k°$ value of redox active guests.[1a,c]

The shape of the CVs for the CB7·Cob$^+$ complex remained similar at variable scan rates (0.1−2 V/s), indicating that the pathway for et was also via mechanism B (data not shown). However, at all of the surveyed scan rates, the CVs still showed slight precipitation on both cathodic and anodic scans. Most noticeably from the data in Table 1, the $\Delta\Delta G$ value for the one-electron reduction of the CB7·Cob$^+$ complex was significantly larger than that for CB7·Fc$^+$. Although this value is relatively larger for the CB7 complex of Cob$^+$, the absolute stability of its reduced form (CB7·Cob) is still large ($K' > 3 \times 10^4$ M^{-1}, $\Delta G' < -6.1$ kcal/mol) for such a simple host−guest system.

The large K' values might probably explain the observed et route, i.e., via mechanism B. The fact that K' remains large ($>4 \times 10^5$ M^{-1} and $>3 \times 10^4$ M^{-1} for CB7·Fc and CB7·Cob, respectively) may suggest that dissociation of the complex into their free components is not necessary, since the reduced guests (Cob and Fc) are still strongly bound to the CB7 host. This case is completely different from inclusion complexes that undergo et via the CE mechanism (mechanism A in Scheme 2), where the redox-converted forms of the host or guest are weakly bound to each other ($K < 100$ M^{-1}).[1a,c,9]

Mapping of the electrostatic potential surface[10] (data not shown) of CB hosts revealed an electron-rich center, suggesting that Fc$^+$ and Cob$^+$ may fit very well in the inner cavity of CB7 both from steric and electrostatic standpoints. Thus, their tight binding is most likely a simultaneous combination of hydrophobic interactions with the inner cavity of CB7 as well as ion−dipole interactions with the two oligourea rims and its inner cavity. Subsequent reduction of both guests probably removes some of the electrostatic components in the stabilization of these complexes, with the effect being larger for CB7·Cob than CB7·Fc, as indicated by the corresponding $\Delta\Delta G$ values. The observed differences between the Cob$^+$/Cob and Fc$^+$/Fc couples as guests for CB7 underscore the presence of electronic effects on the host−guest interactions. In any instance, the CB7·Fc$^+$ and CB7·Cob$^+$ pairs are the first examples of CB7 complexes containing a guest with a centered positive charge. To date, the only other similar reported CB complexes are Kim's dolls,[11] where complexed Cu^{2+} and Zn^{2+} ions are docked at the center of the CB8 cavity.

In conclusion, we have shown that the Cob$^+$ and Fc$^+$ guests form highly stable inclusion complexes with the CB7 host. The electrochemical properties of these complexes are very unusual and interesting and provide additional examples of redox behavior similar to that previously observed with the CB7·V^{2+} complexes.[2,3]

Acknowledgment. We are grateful to the National Science Foundation for the generous support of this work (to A.E.K., Grant No. CHE-0204295).

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