# Trapping of Bulky Guests inside Dimeric Molecular Capsules Formed by a Deep-Cavity Cavitand

Yanhua Qiu, Song Yi, and Angel E. Kaifer*

Center for Supramolecular Science and Department of Chemistry, University of Miami, Coral Gables, Florida 33124, United States

ⓢ *Supporting Information*

ABSTRACT: The inclusion of three bulky guests, adamantyl(ferrocenylmethyl)amine (**2**), adamantylferrocenecarboxylamide (**3**), and 1,1′-bis(adamantylaminomethyl)ferrocene (**4**), inside dimeric molecular capsules formed by an octaacid deep-cavity cavitand (**1**) was investigated using ^{1}H NMR spectroscopy and voltammetric techniques. Guests **2** and **3** were encapsulated inside 1_2 assemblies, as evidenced by ^{1}H NMR spectroscopic data. Although both guests are electroactive, the supramolecular complexes $2@1_2$ and $3@1_2$ showed no voltammetric current responses in the potential window corresponding to the electrochemical oxidation of their ferrocenyl groups. In contrast, each of the adamantyl ends of compound **4** is bound by the cavitand **1**, but the central ferrocene residue was not fully encapsulated in this supramolecular assembly and the voltammetric behavior of $4·1_2$ was clearly detected. In marked contrast with the experimental results obtained with guests **2** and **3**, we could not obtain any evidence for the simultaneous encapsulation of free ferrocene and adamantane inside the 1_2 capsular assembly.
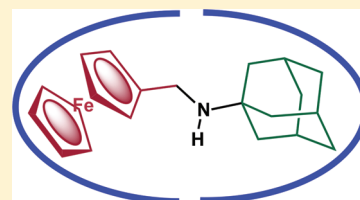
INTRODUCTION

Gibb's octaacid[1−3] (compound **1**) is a bowl-shaped, deep-cavity cavitand that has attracted attention[3−12] among compounds that can self-assemble to form molecular capsules in aqueous media. It is now well understood that, in the presence of suitable hydrophobic guests, two molecules of **1** come together in aqueous solution to form a dimeric molecular capsule, 1_2. Because each octaacid cavitand has a container shape and its internal cavity is hydrophobic, an external guest may be partially included by one cavitand, assisting in the development of suitable van der Waals contacts between two cavitands, as they come together to form a capsule around the guest. Guest encapsulation by the 1_2 assembly has been demonstrated with a variety of hydrophobic guests, including adamantane derivatives.[13,14]

Our own group has focused its attention on the encapsulation of redox-active guests, such as ferrocene[15] (Fc) and tetrathiafulvalene[16] (TTF). We have shown that encapsulation leads to the complete loss of electroactivity for $Fc@1_2$ and $TTF@1_2$ under normal voltammetric conditions. The presence of 16 negatively charged carboxylate groups (8 from each cavitand) on the outer surface of the 1_2 capsule leads to strong electrostatic interactions with positively charged compounds. Therefore, we have shown that dicationic 4,4′-bipyridinium derivatives (viologens) interact—via strong Coulombic interactions—with the outer surface of guest@1_2 capsular assemblies.[15] We have taken advantage of this property to attach a positively charged ferrocene derivative (ferrocenylmethyltrimethylammonium) to the anionic surface of $Fc@1_2$ capsules and use it as an electron transfer mediator between the capsule-included ferrocene and the electrode surface in voltammetric experiments.[17]

Adamantane (Ad) and ferrocene are two hydrophobic groups with pronounced differences from a chemical standpoint but very similar sizes. Both adamantane and ferrocene individually serve as hydrophobic guests to drive the formation of 1_2 capsules. Ramamurthy and co-workers have reported the entrapment of two adamantane molecules inside 1_2 assemblies under certain experimental conditions.[13,14] Given the availability in our group of compounds containing both units (see compounds **2−4** in Figure 1), we decided to investigate the possible encapsulation of these compounds inside 1_2 dimeric capsules.

RESULTS AND DISCUSSION

In analogy with ferrocene, adamantane acts as an ideal hydrophobic guest, leading to its encapsulation inside dimeric capsules of cavitand **1**. However, according to Ramamurthy and co-workers, adamantane can also form 2:2 complexes with **1**; that is, when excess guest is present, two adamantane molecules are included inside the 1_2 assembly.[13,14] In our investigation of ferrocene inclusion by 1_2 capsules we never found clear evidence for a similar 2:2 complex, in which two ferrocenes would share the inner space of the molecular capsule. Therefore, before starting any work with guests **2−4**, we attempted the simultaneous encapsulation of ferrocene and adamantane inside 1_2. Unfortunately, our efforts were in vain and we could not collect any evidence for such supramolecular species. When an aqueous solution containing **1** is exposed to an equimolar mixture of ferrocene and adamantane, the resulting NMR spectrum (Figure 2) shows signals corresponding to both encapsulated guests. However, the signals for the
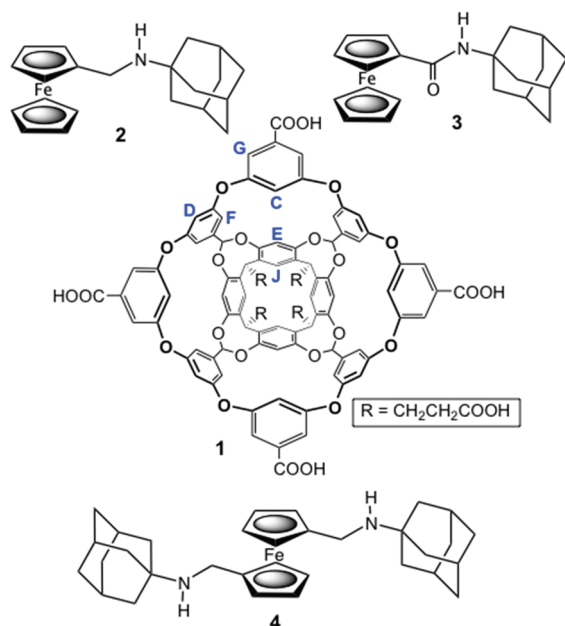
Figure 1. Structures of the octaacid cavitand **1** and the guests (**2**–**4**) used in this work.

host protons do not show any evidence for the reduced symmetry of the **1**$_2$ capsule that would be expected if two different bulky guests were included. Further analysis of this NMR spectrum using 2D NOESY techniques (Figure S2, Supporting Information) reveals the spatial proximity of the encapsulated guest protons to some of the host protons, but no cross peaks between ferrocene and adamantane protons. All these data suggest the formation of Ad@**1**$_2$ and Fc@**1**$_2$, but no evidence for capsules containing both guests. Similarly, if we add excess adamantane to a solution already containing the Fc@**1**$_2$ complex, the final result is a solution containing the two 1:2 inclusion complexes. Under our experimental conditions, we could not obtain evidence for the formation of any of the possible species containing more than one guest: that is, (Ad)$_2$@**1**$_2$, (Fc)$_2$@**1**$_2$, or (Ad-Fc)@**1**$_2$. We must note that these experiments are complicated by the poor solubility of both guests in aqueous solution, a factor that also hinders the accurate quantitative determination of the adamantane/ferrocene selectivity exhibited by the **1**$_2$ assembly. In general terms, these negative experimental results highlight the inherent entropic decrease associated with the assembly of four individual molecules (two guests and two hosts) to form a 2:2 supramolecular complex.

Guests **2** and **3** have similar structures. Both contain ferrocenyl and adamantyl residues, and their differences relate to the functional groups connecting them. Guest **2** is an amine, in which the central nitrogen is connected to ferrocenylmethyl and adamantyl groups, while guest **3** is a ferrocenecarboxylamide in which the adamantyl group is connected to the amide's nitrogen. Guest **2** can be protonated under acidic conditions. Following well-established methodology with cavitand **1**, we carried out all our experiments in mildly basic aqueous solution (pH 8.9). On the basis of voltammetric titration data (Figure S1, Supporting Information) the pK_a of this compound was measured to be around 8.6; thus, guest **2** exists in our solutions as a mixture of protonated (**2H**$^+$) and unprotonated (**2**) species. However, given the hydrophobic character of the inner cavity of **1**$_2$, it is reasonable to assume that only the basic species **2** is encapsulated inside the **1**$_2$ capsular assembly. Similar arguments would apply to the bis-amine guest **4**.

Guest **2** appears to be readily included inside **1**$_2$, as suggested by NMR spectroscopic data. Figure 3 shows the NMR spectrum of guest **2** in the absence and in the presence of 2.0 equiv of cavitand **1**. Clearly, in the presence of **1**, both the ferrocenyl and adamantyl protons are strongly shifted upfield, as expected due to their encapsulation inside the aromatic walls of cavitand **1**. In addition to this, the signals corresponding to the cavitand protons are split into two sets (with the exception of the L and M protons, which are in the cavitand "feet", too far removed from the supramolecular action). This signal splitting of the host protons is in excellent agreement with the breakup of the equatorial symmetry of the **1**$_2$ capsule, due to the inclusion of an asymmetric guest with two different ends (ferrocene and adamantane), which should lead to different chemical shifts for equivalent protons on the two cavitands forming the molecular capsule.

Figure 4 shows partial ^{1}H NMR spectra of cavitand **1** in the presence of increasing amounts of guest **2**. Addition of the guest to the solution containing cavitand **1** leads to the evolution of a new set of split peaks for the host protons. When guest **2** reaches about 0.5 equiv, only the proton signals corresponding to the **2**@**1**$_2$ assembly are visible, and further addition of guest **2** does not result in any change for the proton signals of **1**.

Two-dimensional DOSY NMR experiments are useful to determine diffusion coefficients (D_0) of molecules in the solution phase.[18] The corresponding 2D spectra (Figure S4, Supporting Information) show that all guest signals have D_0 values identical with those corresponding to the host signals except peaks that are close to the water peak, an artifact that results from the irradiation of the water peak for suppression
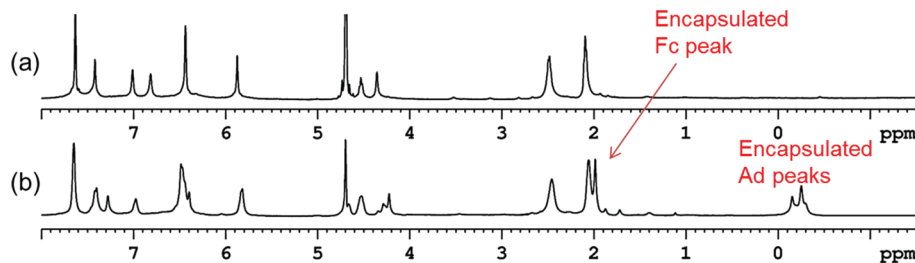

Figure 2. ^{1}H NMR spectra (500 MHz, 10 mM borate buffer pH 8.9 in D$_2$O) of host **1** (1.0 mM) (a) in the absence and (b) in the presence of Fc (0.5 mM) + Ad (0.5 mM).
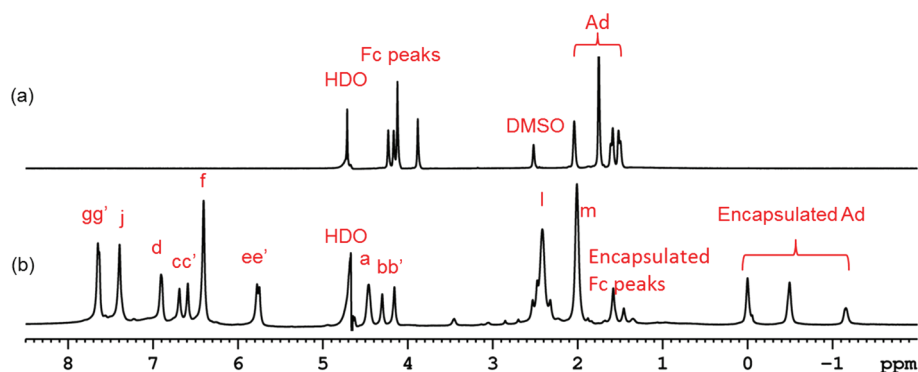
Figure 3. ^{1}H NMR spectra (500 MHz, 10 mM borate buffer pH 8.9 in D_2O) of guest **2** (0.5 mM) (a) in the absence and (b) in the presence of 2.0 equiv of **1**.
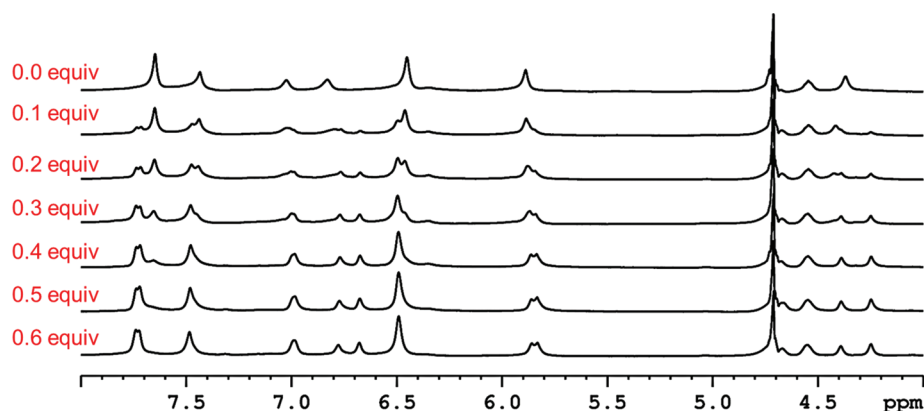

Figure 4. Aromatic section of the ^{1}H NMR spectra (500 MHz, 10 mM borate buffer pH 8.9 in D_2O) of host **1** (1 mM) in the presence of increasing concentrations of guest **2**.

purposes. The measured diffusion coefficient of 1.45×10^{-6} cm^2/s is consistent with other D_0 values previously reported for guest@1_2 species,[16] further confirming the formation of the **2@1_2** complex in aqueous solution.

Given our interest in the electrochemical behavior of encapsulated redox centers, we carried out cyclic voltammetric experiments with solutions containing variable concentrations of cavitand **1** and guest **2**, which contains a redox-active ferrocenyl residue in its structure. Our voltammetric data (Figure 5) clearly show that the current levels corresponding to the reversible one-electron oxidation of the ferrocenyl residue
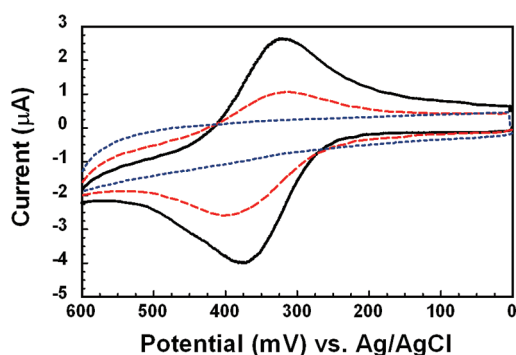

Figure 5. Cyclic voltammetric response on glassy carbon (0.07 cm^2) of 0.5 mM guest **2** in 10 mM borate buffer (pH 8.9) also containing 50 mM NaCl in the absence (black solid line), in the presence of 1.0 equiv (red dashed line), and in the presence of 2.0 equiv (blue dotted line) of host **1**. Scan rate: 0.1 V s^{-1}.

are gradually attenuated in the potential window from 0 to 600 mV, as the host/guest molar ratio increases. When 2.0 equiv of cavitand **1** is added to the solution, the cyclic voltammograms recorded for guest **2** are basically flat and no measurable Faradaic currents associated with the oxidation of the ferrocenyl unit are detected in the potential range where its electrochemical oxidation is clearly observed in the absence of **1**. These experimental results are very similar to those recorded with Fc@1_2 and suggest that the encapsulation of guest **2** leads to a considerable attenuation of the electrochemical kinetics for the oxidation of the ferrocenyl residue.[15,17]

Guest **3** is basically insoluble in water, due to its considerable hydrophobic character. When solid **3** was added to a solution containing cavitand **1**, we did not observe any dissolution of the guest immediately after its addition. However, after heating at 60 °C and 2 h of sonication, guest **3** was gradually dissolved into the cavitand-containing solution. The appearance of signals corresponding to the included guest and the splitting of host peaks in the ^{1}H NMR spectra clearly demonstrated the formation of the **3@1_2** complex (see Figure 6). Due to the extremely low solubility of guest **3** in aqueous solution, no faradaic currents could be recorded when running cyclic voltammetry with the free (undissolved) guest. However, in analogy to the **2@1_2** complex, **3@1_2** showed flat cyclic voltammograms in the potential window for ferrocene oxidation (Figure S2, Supporting Information).

Noticeably, guests **2** and **3** have similar sizes and both fill ca. 61% of the available space within the cavity of capsule 1_2, suggesting that these guests are not too far from optimal
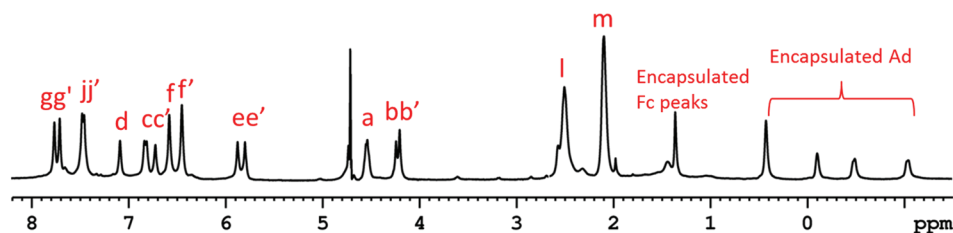
Figure 6. ^{1}H NMR spectrum (500 MHz, 10 mM borate buffer pH 8.9 in D$_2$O) of guest **3** (0.5 mM) in the presence of 2.0 equiv of **1**.
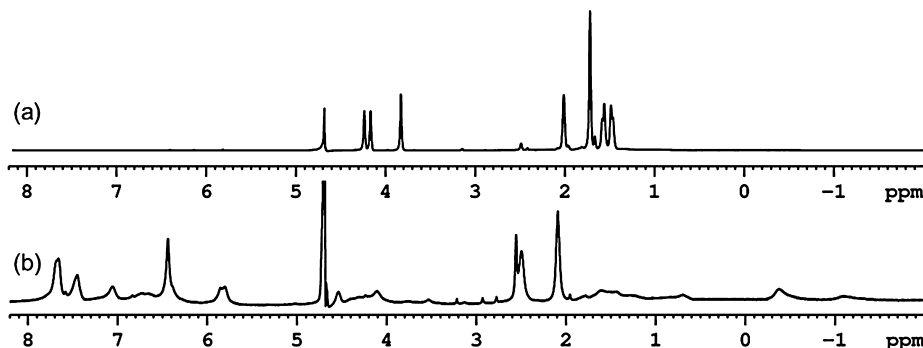

Figure 7. ^{1}H NMR spectra (500 MHz, 10 mM borate buffer pH 8.9 in D$_2$O) of guest **4** (0.5 mM) (a) in the absence and (b) in the presence of 2.0 equiv of **1**.

according to Rebek's rule,[19] which establishes 55% occupation as ideal in host−guest inclusion phenomena. However, the level of occupation of the cavity suggests a tight fit of either guest inside the dimeric molecular capsule.

In contrast to guests **2** and **3**, guest **4** contains two adamantyl units connected to the central ferrocenyl unit. When 2.0 equiv of cavitand **1** was added, the inclusion of the terminal adamantyl units of guest **4** within the host was evident from the upfield shift of the adamantyl hydrogen signals (Figure 7). The extensive broadening of guest and host signals observed in the ^{1}H NMR experiments is probably due to chemical exchange among bound and unbound states involving guest **4** and cavitand **1**. This is related to the flexibility of guest **4** and the relatively dynamic binding between the adamantyl groups and the cavitand hosts, which results in a more flexible and labile supramolecular assembly.

Square wave voltammetry (SWV) was also used to investigate the interactions between guest **4** and cavitand **1**. When 2.0 equiv of **1** was added to a solution containing 0.5 mM guest **4**, the current for the oxidation of the ferrocene subunit was reduced, owing to the slow diffusional motion of the complex (Figure 8), but was not completely depressed, suggesting that the electroactive ferrocenyl unit in guest **4** was still "exposed" to the electrode. The half-wave potential ($E_{1/2}$) for the oxidation of the ferrocene subunit also shifted positively, in comparison to the value for the free guest, presumably indicating that the ferrocene subunit surrounded by two bulky cavitands, though not completely sealed inside the capsule, still experiences a relatively hydrophobic microenvironment, which would stabilize the reduced form of the central ferrocenyl unit and hinder the solvation of the oxidized ferrocenium residue by water molecules. A second possibility to explain the voltammetric response of this supramolecular species would rely on the fast dissociation of one cavitand, which will leave compound **4** bound to a single cavitand, with its ferrocenyl unit more exposed. Dissociation of one cavitand in **4@1₂** is conceivably faster than in **2@1₂** or **3@1₂** because there are
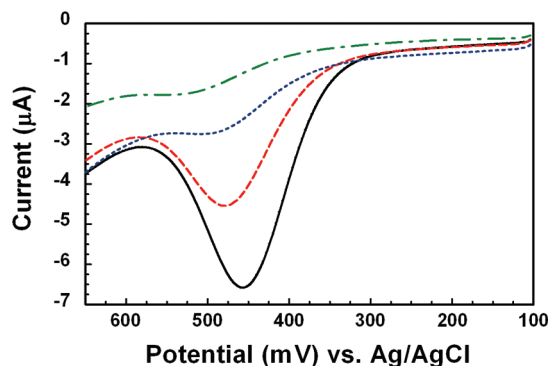

Figure 8. Square wave voltammetric response on glassy carbon (0.07 cm^2) of 0.5 mM guest **4** in 10 mM borate buffer (pH 8.9) also containing 50 mM NaCl in the absence (black solid line), in the presence of 1.0 equiv (blue dashed line), in the presence of 2.0 equiv (red dotted line) and in the presence of 3.0 equiv (green dash-dotted line) of host **1**. Scan rate: 0.1 V s^{-1}.

no direct contacts or "clamping" interactions between the two cavitands that would contribute to keep them together.

Due to the large size of guest **4**, formation of a snugly closed capsule around this guest is sterically impossible. From these experimental results, we postulate a pseudocapsular structure for the complex in which each of the adamantyl units of guest **4** is included by cavitand **1**, leaving the connecting ferrocenyl unit of the guest still exposed to the solution, through the cleft formed between the two capping cavitands (Figure 9). Rebek and co-workers have reported a similar pseudocapsular assembly.[20]

In conclusion, we have presented data showing very clearly that cavitand **1** forms dimeric capsules around the bulky guests **2** and **3** in aqueous solution. Notably, we have not been able to obtain experimental evidence for the simultaneous encapsulation of freely diffusing adamatane and ferrocene. Both NMR spectroscopic and voltammetric data are consistent with the
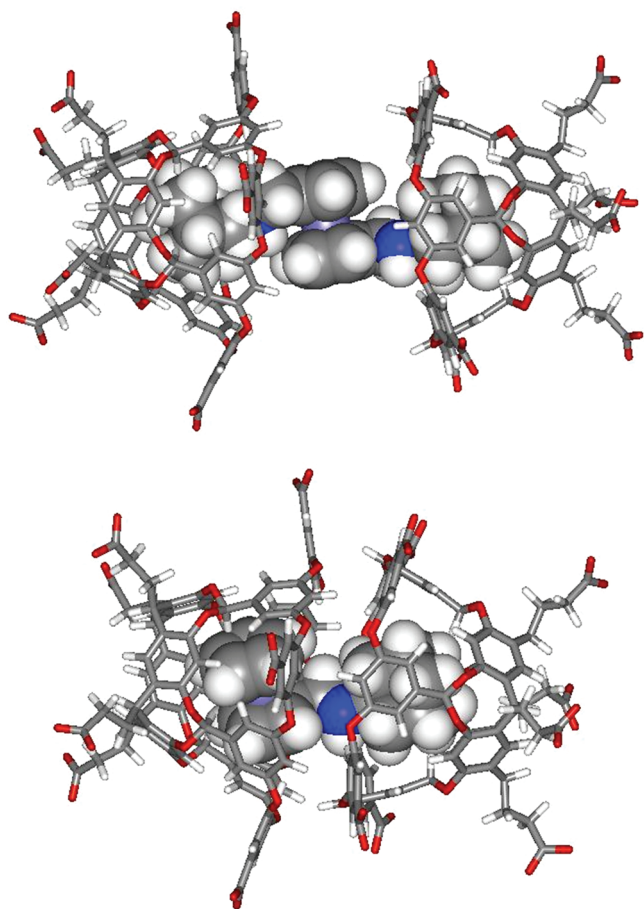
Figure 9. Energy minimized structures (PM3) of the supramolecular assemblies formed by interaction of two molecules of cavitand **1** with guest **4** (top) and with guest **2** (bottom).

complete encapsulation of **2** and **3** inside **1**$_2$ capsules. In contrast to this, guest **4** leads to a 1:2 complex with two molecules of cavitand **1** bound to the terminal adamantyl residues. This complex is not, however, a "sealed" molecular capsule, and the middle ferrocenyl residue does not appear to be included inside the supramolecular assembly, as evidenced by the measurable voltammetric response recorded for the electrochemical oxidation of the ferrocenyl unit.

■ EXPERIMENTAL SECTION

Materials. The cavitand host (compound **1**) was prepared as reported by Gibb and co-workers.[1,3] All other chemicals were of the highest purity available and were purchased from commercial suppliers.

Synthesis of Adamantyl(ferrocenylmethyl)amine (2). To an absolute methanol solution (50 mL) of ferrocenecarboxaldehyde (200 mg, 0.93 mmol) and 1-adamantylamine (948 mg, 6.3 mmol) also containing activated 4A type molecular sieves was added 5 M HCl in methanol to adjust the pH of the solution to ca. 7. After the reaction mixture was stirred for 1 h at room temperature under N$_2$, NaBH$_3$CN (352 mg, 5.6 mmol) was added, and this mixture was then heated and stirred at 60 °C for 2 days. The resulting mixture was filtered through Celite 545 and then concentrated in vacuo to give a red solid, which was purified by column chromatography on Al$_2$O$_3$ (neutral) using chloroform/ethyl acetate (5/1) as the eluent. The yellow solid product was obtained after solvent evaporation and recrystallization from methanol (130 mg, yield 36.1%). Mp: 202 °C dec. ^{1}H NMR (500 MHz, D$_2$O): 1.54 (ds, 3H), 1.62 (ds, 3H), 1.78 (s, 6H), 2.07 (s, 3H), 3.92 (s, 2H), 4.16 (s, 5H), 4.20 (s, 2H), 4.27 (s, 2H). ^{13}C NMR (125

MHz, D$_2$O): 28.8, 34.9, 37.9, 39.4, 57.5, 68.9, 69.6, 69.9, 76.7. HRMS (ESI-TOF): m/z calcd for C$_{21}$H$_{28}$NFe 350.1571, found 350.1579.

Synthesis of Adamantylferrocenecarboxylamide (3). Ferrocenecarboxaldehyde (200 mg, 0.87 mmol) was mixed with 1-adamantylamine (158 mg, 1.04 mmol) in 200 mL of anhydrous dichloromethane. To this solution were added n-HATU (397 mg, 1.04 mmol) and Proton Sponge (224 mg, 1.04 mmol). The reaction mixture was stirred under N$_2$ at room temperature for 1 day and then concentrated in vacuo to give a red solid, which was purified by column chromatography (SiO$_2$) using hexane/chloroform/ethyl acetate (2/2/1) as the eluent. The final product was obtained (200.8 mg, yield 63.6%) after solvent evaporation and recrystallization from CH$_3$CN/CHCl$_3$ (1/1). Mp: 212 °C dec. ^{1}H NMR (500 MHz, d_6-DMSO): 1.63 (s, 6H), 2.02 (s, 9H), 4.11 (s, 5H), 4.27 (t, 2H), 4.80 (t, 2H), 6.72 (s, 1H). ^{13}C NMR (125 MHz, d_6-DMSO): 29.4, 36.6, 41.7, 50.7, 68.8, 69.83, 70.2, 78.0, 168.6. HRMS (ESI-TOF): m/z calcd for C$_{21}$H$_{26}$NOFe 364.1364, found 364.1351.

1,1′-Bis(adamantylaminomethyl)ferrocene (4). To an absolute methanol solution (60 mL) of 1,1′-ferrocenedicarboxaldehyde (200 mg, 0.83 mmol) and 1-adamantylamine (998 mg, 6.6 mmol) also containing 4A type molecular sieves was added 5 M HCl in methanol to adjust the pH of the solution to ca. 7. After the reaction mixture was stirred for 1 h at room temperature under N$_2$, NaBH$_3$CN (415 mg, 6.6 mmol) was added, and this mixture was then refluxed for 2 days. The resulting mixture was filtered through Celite 545 and then concentrated to give a red residue, which was purified by column chromatography on Al$_2$O$_3$ (neutral) using CHCl$_3$/EtOAc/MeOH (20/4/1) as the eluent. The yellow solid product was obtained after the solvent was evaporated and recrystallized from hot methanol (90.5 mg, yield 21.4%). Mp: 201−202 °C. ^{1}H NMR (500 MHz, D$_2$O): 1.50 (ds, 6H), 1.59 (ds, 6H), 1.74 (s, 12H), 2.04 (s, 6H), 3.86 (s, 4H), 4.20 (s, 4H), 4.26 (s, 4H). ^{13}C NMR (125 MHz, d_6-DMSO): 28.9, 35.7, 38.1, 39.1, 57.0, 70.5, 72.0, 79.0. HRMS (ESI-TOF) m/z calcd for C$_{32}$H$_{45}$N$_2$Fe 513.2932, found 513.2940.

Electrochemistry. The voltammetric experiments were recorded using a single-compartment cell fitted with a glassy-carbon working electrode (0.071 cm^2), a platinum auxiliary electrode, and a Ag/AgCl reference electrode. The working electrode was polished immediately before the experiments using a water/alumina (0.05 μm) slurry on a felt surface. The solution was thoroughly deoxygenated by purging with high-purity nitrogen gas and maintained under a nitrogen atmosphere during the experiments.

Computational Studies. Energy minimization of supramolecular structures (see Figure 9) was carried out using the PM3 semiempirical method as implemented in the Gaussian software package. Guest molecular volumes were calculated with YASARA after energy minimization using DFT methods. The van der Waals volumes of compounds **2** and **3** were measured as 380.8 and 379.7 Å^3. The **1**$_2$ dimeric molecular capsule was energy minimized using molecular mechanics and its cavity volume computed using the SPDB viewer (version 4.04); a value of 630 Å^3 was obtained.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

Figures giving additional electrochemical and NMR spectroscopic data mentioned in the paper. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: akaifer@miami.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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