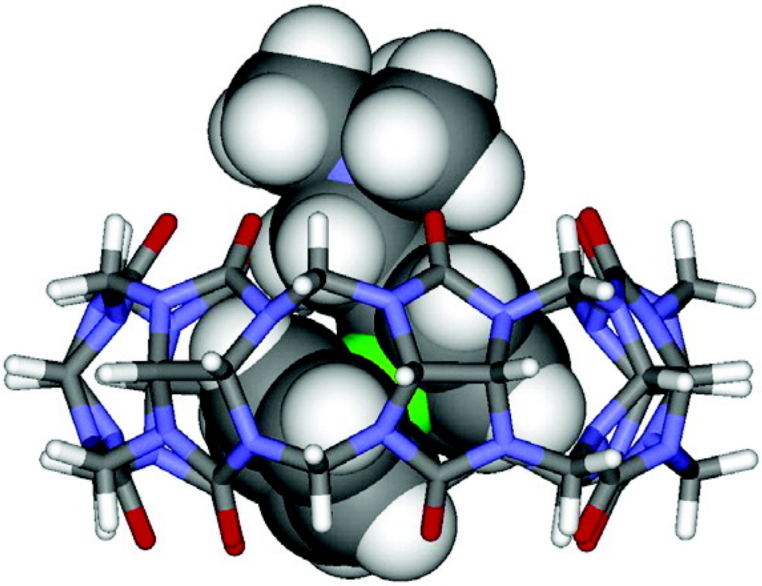
JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Article

Complexation of Ferrocene Derivatives by the Cucurbit[7]uril Host: A Comparative Study of the Cucurbituril and Cyclodextrin Host Families

Woo Sung Jeon, Kwangyul Moon, Sang Hyun Park, Hyungpil Chun, Young Ho Ko, Jin Yong Lee, Eun Sung Lee, S. Samal, N. Selvapalam, Mikhail V. Rekharsky, Vladimir Sindelar, David Sobransingh, Yoshihisa Inoue, Angel E. Kaifer, and Kimoon Kim

J. Am. Chem. Soc., **2005**, 127 (37), 12984-12989• DOI: 10.1021/ja052912c • Publication Date (Web): 23 August 2005



Journal of the American Chemical Society is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

J|A|C|S

ARTICLES

Complexation of Ferrocene Derivatives by the Cucurbit[7]uril Host: A Comparative Study of the Cucurbituril and Cyclodextrin Host Families

Woo Sung Jeon,[†] Kwangyul Moon,[‡] Sang Hyun Park,[†] Hyungpil Chun,[†]
Young Ho Ko,[†] Jin Yong Lee,[§] Eun Sung Lee,[†] S. Samal,[†] N. Selvapalam,[†]
Mikhail V. Rekharsky,[⊥] Vladimir Sindelar,[‡] David Sobransingh,[‡] Yoshihisa Inoue,*[,⊥]
Angel E. Kaifer,*[,‡] and Kimoon Kim*[,†]

Contribution from the Center for Supramolecular Science and Department of Chemistry, University of Miami, Coral Gables, Florida 33124-0431, National Creative Research Initiative Center for Smart Supramolecules and Department of Chemistry, Division of Molecular and Life Sciences, Pohang University of Science and Technology, San 31 Hyojadong, Pohang 790-784, Republic of Korea, Entropy Control Project, ICORP, JST, 4-6-3 Kamishinden, Toyonaka 560-0085, Japan, and Department of Chemistry, Chonnam National University, Gwangju 500-757, Republic of Korea

Received May 19, 2005; E-mail: akaifer@miami.edu; inoue@chem.eng.osaka-u.ac.jp; kkim@postech.ac.kr.

Abstract: The formation of inclusion complexes between cucurbit[7]uril (CB[7]) and ferrocene and its derivatives has been investigated. The X-ray crystal structure of the 1:1 inclusion complex between ferrocene and CB[7] revealed that the guest molecule resides in the host cavity with two different orientations. Inclusion of a set of five water-soluble ferrocene derivatives in CB[7] was investigated by ^{1}H NMR spectroscopy and calorimetric and voltammetric techniques. Our data indicate that all neutral and cationic guests form highly stable inclusion complexes with CB[7], with binding constants in the 10^9-10^{10} M^{-1} and $10^{12}-10^{13}$ M^{-1} ranges, respectively. However, the anionic ferrocenecarboxylate, the only negatively charged guest among those surveyed, was not bound by CB[7] at all. These results are in sharp contrast to the known binding behavior of the same guests to β-cyclodextrin (β-CD), since all the guests form stable inclusion complexes with β-CD, with binding constants in the range 10^3-10^4 M^{-1}. The electrostatic surface potentials of CB[6], CB[7], and CB[8] and their size-equivalent CDs were calculated and compared. The CD portals and cavities exhibit low surface potential values, whereas the regions around the carbonyl oxygens in CBs are significantly negative, which explains the strong affinity of CBs for positively charged guests and also provides a rationalization for the rejection of anionic guests. Taken together, our data suggest that cucurbiturils may form very stable complexes. However, the host−guest interactions are very sensitive to some structural features, such as a negatively charged carboxylate group attached to the ferrocene residue, which may completely disrupt the stability of the complexes.

Introduction

The family of cucurbituril hosts has been recently expanded.[1] While cucurbit[6]uril (CB[6])[2] is a molecular receptor with well-established host properties,[3,4] the larger-cavity homologues cucurbit[7]uril and cucurbit[8]uril (CB[7] and CB[8], respectively) have been recently isolated and quickly attracted considerable attention as hosts for inclusion complexation.[5−7] Cucurbiturils have often elicited comparisons with cyclodextrins (CDs).[8] The cavity sizes of CB[6], CB[7], and CB[8] are similar to those of α-CD, β-CD, and γ-CD, respectively.[5] However, these size similarities should not be confused with similarities in composition and binding properties. CDs are natural products resulting from the action of the enzyme cyclodextrinase on starch.[8] They are composed of chiral glucopyranose subunits

---

[†] Pohang University of Science and Technology.

[‡] University of Miami.

[§] Chonnam National University.

[⊥] Entropy Control Project.

(1) (a) Kim, J.; Jung, I.-S.; Kim, S.-Y.; Lee, E.; Kang, J.-K.; Sakamoto, S.; Yamaguchi, K.; Kim, K. *J. Am. Chem. Soc.* **2000**, *122*, 540. (b) Day, A. I.; Arnold, A. P.; Blanch, R. J.; Snushall, B. *J. Org. Chem.* **2001**, *66*, 8094.

(2) Freeman, W. A.; Mock, W. L.; Shih, N.-Y. *J. Am. Chem. Soc.* **1981**, *103*, 7367.

(3) For reviews, see: (a) Mock, W. L. In *Comprehensive Supramolecular Chemistry*; Vögtle, Ed.; Pergamon: Oxford, 1996; Vol. 2, p 447. (c) Cintas, P. *J. Incl. Phenom.* **1994**, *17*, 205.

(4) (a) Mock, W. L.; Shih, N.-Y. *J. Org. Chem.* **1986**, *51*, 4440. (b) Mock, W. L.; Shih, N.-Y. *J. Am. Chem. Soc.* **1988**, *110*, 4706. (c) Mock, W. L.; Shih, N.-Y. *J. Am. Chem. Soc.* **1989**, *111*, 2697. (d) Hoffmann, R.; Knoche, W.; Fenn, C.; Buschmann, H.-J. *J. Chem. Soc., Faraday Trans.* **1994**, *90*, 1507. (e) Jeon, Y.-M.; Kim, J.; Whang, D.; Kim, K. *J. Am. Chem. Soc.* **1996**, *118*, 9790. (f) Whang, D.; Heo, J.; Park, J. H.; Kim, K. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 78. (g) Haouaj, M. E.; Luhmer, M.; Ko, Y. H.; Kim, K.; Bartik, K. *J. Chem. Soc., Perkin Trans. 2* **2001**, 804. (h) Haouaj, M. E.; Ko, Y. H.; Luhmer, M.; Kim, K.; Bartik, K. *J. Chem. Soc., Perkin Trans. 2* **2001**, 2104. (i) Meschke, C.; Buschmann, H. J.; Schollmeyer, E. *Thermochim. Acta* **1997**, *297*, 43. (j) Buschmann, H. J.; Jansen, K.; Schollmeyer, E. *Thermochim. Acta* **2000**, *346*, 33. (k) Buschmann, H.-J.; Jansen, K.; Schollmeyer, E. *J. Incl. Phenom.* **2000**, *37*, 231. (l) Buschmann, H. J.; Cleve, E.; Jansen, K.; Wego, A.; Schollmeyer, E. *J. Incl. Phenom. Macrocyclic Chem.* **2001**, *40*, 117. (m) Marquez, C.; Nau, W. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3155. (n) Marquez, C.; Hudgins, R. R.; Nau, W. M. *J. Am. Chem. Soc.* **2004**, *126*, 5806.

10.1021/ja052912c CCC: $30.25

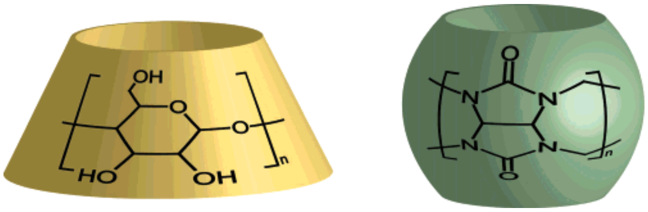
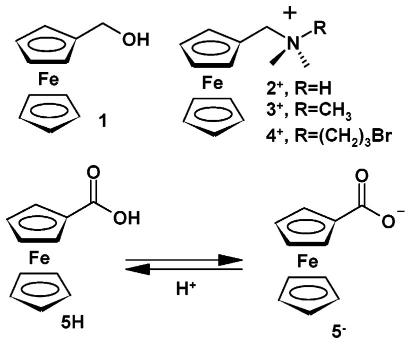


Figure 1. Schematic comparison of the structures of cyclodextrins (left) and cucurbiturils (right).

and, thus, are chiral molecular receptors. CBs are prepared synthetically by the acid-catalyzed condensation of symmetric glycoluril repeating units with formaldehyde; they are achiral compounds that exhibit an equatorial symmetry plane, which does not exist in the CDs. A consequence of this symmetry is that both cavity openings in CBs are identical. In contrast to this, the two cavity openings of the CDs differ both in size and chemical nature, with the smaller opening lined by primary hydroxyl groups and the larger opening lined by twice as many secondary hydroxyl groups (see Figure 1).

Not surprisingly, the main intermolecular interactions between molecular guests and these two classes of hosts are different. A considerable body of evidence suggests that hydrophobic interactions are primarily responsible for the stabilization of the inclusion complexes formed between CDs and most organic and organometallic guests.[8,9] The hydroxyl groups lining the CD cavity openings do not appear to engage in strong interactions with most included guests. In stark contrast to this, the interactions between CBs and included guests result from a combination of two types of intermolecular forces: (1) ion−dipole interactions between positive charges on the guest and carbonyl oxygens lining both CB cavity openings and (2) hydrophobic interactions between the guest and the inner surface of the CB host cavity.[3,5] The carbonyl oxygens on the CB portals are also known to interact strongly with metal ions.[4e,f,10] In a number of ways, the methyl viologen dication (MV^{2+}) is the prototypical guest for CB[7] and CB[8], giving rise to very stable inclusion complexes ($K \approx 10^5$ L/mol) in aqueous environments.[6c,d,7h] Interestingly, the methyl viologen dication does not form stable inclusion complexes with β-CD, although its reduced forms (MV^+ and MV) do, with the 2-electron reduced, neutral species (MV) forming the most stable complex ($K \approx 10^4$ L/mol) among the three possible oxidation states of this guest.[11]

Chart 1. Structures of the Ferrocene Derivatives Surveyed in This Work



Intrigued by some of these host−guest complexation differences, our groups developed strong interest on the possible binding interactions between CB[7] and ferrocene and its derivatives. Previous work has shown that ferrocenium, the one-electron oxidized form of ferrocene, is an excellent guest for CB[7].[12] In the course of that investigation the formation of a stable host−guest complex between ferrocene and CB[7] was also demonstrated experimentally. Since ferrocene and its derivatives are well-known guests for inclusion complexation by CDs,[13] we decided to start a detailed investigation of the binding interactions between the CB[7] host and ferrocene and some of its simplest water-soluble derivatives. We report here the results of this work, which provide interesting and unexpected insights into the properties of CBs as molecular hosts.

In addition to ferrocene (Fc) the guests selected for this study (Chart 1) were the neutral derivative hydroxymethylferrocene (**1**), the positively charged derivatives of (ferrocenylmethyl)dimethylamine ($\mathbf{2}^+$−$\mathbf{4}^+$) and ferrocenecarboxylic acid (**5H**). While **1** and **5H** are uncharged, the latter may be ionized in neutral or basic medium to produce a negatively charged carboxylate form

---

(5) For reviews, see: (a) Lee, J. W.; Samal, S.; Selvapalam, N.; Kim, H.-J.; Kim, K. *Acc. Chem. Res.* **2003**, *36*, 621. (b) Kim, K.; Kim, H.-J. In *Encyclopedia of Supramolecular Chemistry*; Atwood, S., Ed.; Marcel Dekker Inc.: New York, 2004; p 390. (c) Kim, K.; Selvapalam, N.; Oh, D.-H. *J. Incl. Phenom.* **2004**, *50*, 31.

(6) CB[7] inclusion complexes: (a) Marquez, C.; Nau, W. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 4387. (b) Blanch, R. J.; Sleeman, A. J.; White, T. J.; Arnold, A. P.; Day, A. I. *Nano Lett.* **2002**, *2*, 147. (c) Kim, H.-J.; Jeon, W. S.; Ko, Y. H.; Kim, K. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 5007. (d) Ong, W.; Gomez-Kaifer, M.; Kaifer, A. E. *Org. Lett.* **2002**, *4*, 1791. (e) Moon, K.; Kaifer, A. E. *Org. Lett.* **2004**, *6*, 185. (f) Ong, W.; Kaifer, A. E. *J. Org. Chem.* **2004**, *69*, 1383. (g) Wheate, N. J.; Day, A. I.; Blanch, R. J.; Arnold, A. P.; Cullinane, C.; Collins, J. G. *Chem. Commun.* **2004**, 1424. (h) Jeon, Y. J.; Kim, S.-Y.; Ko, Y. H.; Sakamoto, S.; Yamaguchi, K.; Kim K. *Org. Biomol. Chem.* **2005**, *3*, 2122. (i) Marquez, C.; Pischel, U.; Nau, W. M. *Org. Lett* **2003**, *5*, 3911. (j) Wagner, B. D.; Stojanovic, N.; Day, A. I.; Blanch, R. J. *J. Phys. Chem. B* **2003**, *107*, 10741.

(7) CB[8] inclusion complexes: (a) Kim, H.-J.; Heo, J.; Jeon, W. S.; Lee, E.; Kim, J.; Sakamoto, S.; Yamaguchi, K.; Kim, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 1526. (b) Kim, S.-Y.; Jung, I.-S.; Lee, E.; Kim, J.; Sakamoto, S.; Yamaguchi, K.; Kim, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 2119. (c) Jon, S. Y.; Ko, Y. H.; Park, S.-H.; Kim, H.-J.; Kim, K. *Chem. Commun.* **2001**, 1938. (d) Lee, J. W.; Kim, K. P.; Choi, S. W.; Ko, Y. H.; Sakamoto, S.; Yamaguchi, K.; Kim, K. *Chem. Commun.* **2002**, 2692. (e) Choi, S.; Park, S. H.; Ziganshina, A. Y.; Ko, Y. H.; Lee, J. W.; Kim, K. *Chem. Commun.* **2003**, 2176. (f) Ziganshina, A. Y.; Ko, Y. H.; Jeon, W. S.; Kim, K. *Chem. Commun.* **2004**, 806. (g) Jeon, Y. J.; Bharadwaj, P. K.; Choi, S. W.; Lee, J. W.; Kim, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 4474. (h) Jeon, W. S.; Kim, H.-J.; Lee, C.; Kim, K. *Chem. Commun.* **2002**, 1828. (i) Chubarova, E. V.; Samsonenko, D. G.; Sokolov, M. N.; Gerasko, O. A.; Fedin, V. P.; Platas, J. G. *J. Incl. Phenom.* **2004**, *48*, 31. (j) Wu, A.; Isaacs, L. *J. Am. Chem. Soc.* **2003**, *125*, 4831. (k) Moon, K.; Grindstaff, J.; Sobransingh, D.; Kaifer, A. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 5496. (l) Mukhopadhyay, P.; Wu, A.; Isaacs, L. *J. Org. Chem.* **2004**, *69*, 6157. (m) Pattabiraman, M.; Natarajan, A.; Kaanumalle, L. S.; Ramamurthy, V. *Org. Lett.* **2005**, *7*, 529.

(8) (a) Wenz, G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 803. (b) Connors, K. A. *Chem. Rev.* **1997**, *97*, 1325. (c) Rekharsky, M. V.; Inoue, Y. *Chem. Rev.* **1998**, *98*, 1875. (d) Szejtli, J. *Chem. Rev.* **1998**, *98*, 1743.

(9) (a) Inoue, Y.; Hakushi, T.; Liu, Y.; Tong, L.-H.; Shen, B.-J.; Jin, D.-S. *J. Am. Chem. Soc.* **1993**, *115*, 475. (b) Inoue, Y.; Liu, Y.; Tong, L.-H.; Shen, B.-J.; Jin, D.-S. *J. Am. Chem. Soc.* **1993**, *115*, 10637.

(10) (a) Buschmann, H.-J.; Cleve, E.; Schollmeyer, E. *Inorg. Chim. Acta* **1992**, *193*, 93. (b) Zhang, X. X.; Krakowiak, K. E.; Xue, G.; Bradshaw, J. S.; Izatt, R. M. *Ind. Eng. Chem. Res.* **2000**, *39*, 3516. (c) Heo, J.; Kim, J.; Whang, D.; Kim, K. *Inorg. Chim. Acta* **2000**, *279*, 307. (d) Sokolov, M. N.; Virovets, A. V.; Dybtsev, D. N.; Gerasko, O. A.; Fedin, V. P.; Hernandez-Molina, R.; Clegg, W.; Sykes, A. G. *Angew. Chem., Int. Ed.* **2000**, *39*, 1659.

(11) Mirzoian, A.; Kaifer, A. E. *Chem. Eur. J.* **1997**, *3*, 1052.

(12) Ong, W.; Kaifer, A. E. *Organometallics* **2003**, *22*, 4181.

(13) (a) Harada, A.; Takahashi, S. *J. Chem. Soc., Chem. Commun.* **1984**, 645. (b) Menger, F. M.; Sherrod, M. J. *J. Am. Chem. Soc.* **1988**, *110*, 8606. (c) Thiem, H.-J.; Brandl, M.; Breslow, R. *J. Am. Chem. Soc.* **1988**, *110*, 8612. (d) Breslow, R.; Czarniecki, M. F.; Emert, J.; Hamaguchi, H. *J. Am. Chem. Soc.* **1980**, *102*, 762. (e) Sigel, B.; Breslow, R. *J. Am. Chem. Soc.* **1975**, *97*, 6869. (f) Matsue, T.; Evans, D. H.; Osa, T.; Kobayashi, N. *J. Am. Chem. Soc.* **1985**, *107*, 3411. (g) Isnin, R.; Salam, C.; Kaifer, A. E. *J. Org. Chem.* **1991**, *56*, 35. (h) Godínez, L. A.; Patel, S.; Criss, C. M.; Kaifer, A. E. *J. Phys. Chem.* **1995**, *99*, 17449. (i) Coutouli-Argyropoulou, E.; Kelaidopoulou, A.; Sideris, C.; Kokkinidis, G. *J. Electroanal. Chem.* **1999**, *477*, 130. (j) Osella, D.; Carretta, A.; Nervi, C.; Ravera, M.; Gobetto, R. *Organometallics* **2000**, *19*, 2791.

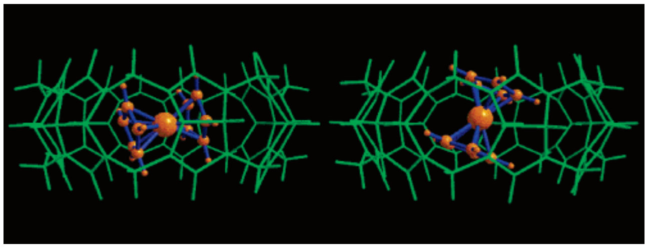


Figure 2. X-ray crystal structure of the complex between ferrocene and CB[7].

($\mathbf{5}^-$). Two of the remaining ferrocene derivatives ($\mathbf{3}^+$ and $\mathbf{4}^+$) are cationic regardless of pH conditions, but $\mathbf{2}^+$ requires acidic conditions to be positively charged.

Results and Discussion

The formation of a highly stable inclusion complex between the ferrocenium cation and the CB[7] host has been previously demonstrated.[12] Attempts to determine the corresponding association equilibrium constant (K) using electronic absorption spectroscopy failed to yield a defined value, due to the high stability of the complex. A limit of $K > 10^6$ L/mol was estimated from the UV−vis data. Cyclic voltammetric data strongly suggested that ferrocene also forms a stable inclusion complex with CB[7].[12] The formation of a Fc@CB[7] inclusion complex is also suggested by experimental observations on the enhanced solubility of Fc in aqueous media containing CB[7]. Careful crystallization from these solutions yielded single crystals suitable for X-ray diffraction analysis.

The resulting crystal structure shows two crystallographically independent Fc@CB[7] molecules that differ on the ferrocene orientation inside the host cavity (see Figure 2). In both molecules the cyclopentadienyl (Cp) rings of ferrocene are nearly eclipsed, and the average Fe−C bond distances, 2.008(7) for one and 1.989(9) Å for the other, are similar or slightly shorter than the known values for unbound ferrocene residues adopting the same eclipsed conformation. The iron atom is located very close to the geometric center of the host in both molecules (at distances of 0.29 and 0.07 Å, respectively). The most important difference between the two molecules is the angle formed by the main ferrocene axis (intersecting the centers of the two Cp rings) and the main CB[7] axis (intersecting the centers of the two cavity portals). These angles are 22° and 79°, respectively.

The crystallographic data reveal that ferrocene enjoys a reasonable degree of rotational freedom inside the cavity of the macrocyclic host. The two ferrocene alignments observed in the crystal structure may result from an accumulation of subtle nonbonded contacts between the peripheral hydrogens on the ferrocene Cp rings and internal cavity atoms (C, N) in CB[7]. It is also clear that any substituents covalently attached to one of the ferrocene's Cp rings may exert a considerable influence on the host−guest interactions.

The covalent attachment of polar functional groups to one of the Cp rings of ferrocene increases the aqueous solubility of the resulting ferrocene derivatives and facilitates the investigation of their binding interactions with CB[7] using NMR spectroscopy.[13g] For instance, the ^{1}H NMR spectrum of $\mathbf{3}^+$ undergoes considerable changes upon addition of 1 equiv of CB[7]. All the ferrocene protons experience a considerable upfield shift, while the methyl protons undergo a smaller downfield shift (Figure 3). This CB[7]-induced shift pattern suggests that the ferrocene residue is included inside the host cavity while the guest's positively charged nitrogen interacts with the carbonyl oxygens on the host portal. When an excess amount of the guest is present, the signals of the free and bound guests were simultaneously observed, revealing that the rate of exchange between these species is slow in the NMR time scale. The kinetic stability of this complex was also verified by 2D EXSY experiments (Supporting Information). Another interesting feature in the ^{1}H NMR spectrum of the CB[7]$\cdot\mathbf{3}^+$ complex is that the doublets corresponding to the host's methylene protons split into two sets, reflecting the differences between the two portals created by the interaction of the positively charged nitrogen on the guest with one of the carbonyl portals.

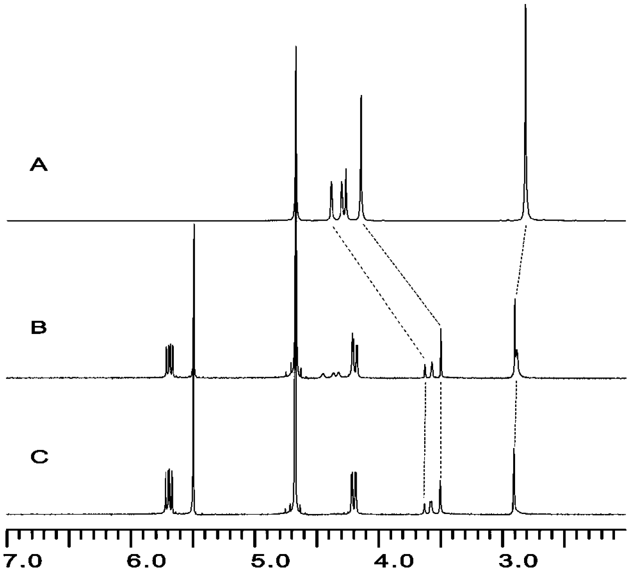


Figure 3. ^{1}H NMR spectra (500 MHz, D_2O) of $\mathbf{3}^+$ (A) in the absence, and in the presence of (B) 0.5 equiv and (C) 1.1 equiv of CB[7].

Similar NMR data were obtained with the other cationic guests $\mathbf{2}^+$ and $\mathbf{4}^+$, as well as with the neutral guests **1** and **5H**. In contrast to these findings, deprotonation of **5H** leads to an anionic guest $\mathbf{5}^-$, which does not show any signs of binding with CB[7] by NMR spectroscopy (Supporting Information). This is a very surprising result, especially because all of these ferrocene-containing guests form stable inclusion complexes with β-CD regardless of their charge.[13] Specifically, the binding constant between $\mathbf{5}^-$ and β-CD was determined by Evans and co-workers[13f] to be 2100 M^{-1}. However, development of negative charge nullifies the affinity of the ferrocene derivative $\mathbf{5}^-$ for CB[7], probably because of the intense charge repulsion between the guest's carboxylate and the carbonyl oxygens on the host portals.

The equilibrium constants (K) and the relevant thermodynamic parameters for association of the ferrocene derivatives with CB[7] were measured by isothermal titration calorimetry (ITC), and the results are given in Table 1. The K values determined for the ferrocene derivatives, particularly cationic $\mathbf{2}^+$ and $\mathbf{3}^+$, are extremely high for synthetic host−guest systems, exceeding the stability of typical antibody−antigen complexes. From the $\Delta H°$ and $\Delta S°$ values in the table, it is clear that the formation of all the inclusion complexes is enthalpically driven. Although we also verified by NMR spectroscopy that **5H** is bound by CB[7] (Supporting Information), we could not

Table 1. Thermodynamic Parameters for the Equilibrium between Ferrocene-Containing Guests and the Host CB[7]

guest	K^a (M^{-1})	$\Delta H°$ (kcal mol^{-1})	$T\Delta S°$ (kJ mol^{-1})
1	$(3.0 \pm 0.5) \times 10^9$	-88 ± 3	-34 ± 3
$\mathbf{2}^+$	$(2 \pm 1) \times 10^{12}$	-88 ± 3	-18 ± 3
$\mathbf{3}^+$	$(4 \pm 1) \times 10^{12}$	-89 ± 3	-17 ± 3

[a] Obtained from ITC in pure water[14] at 298.15 K.

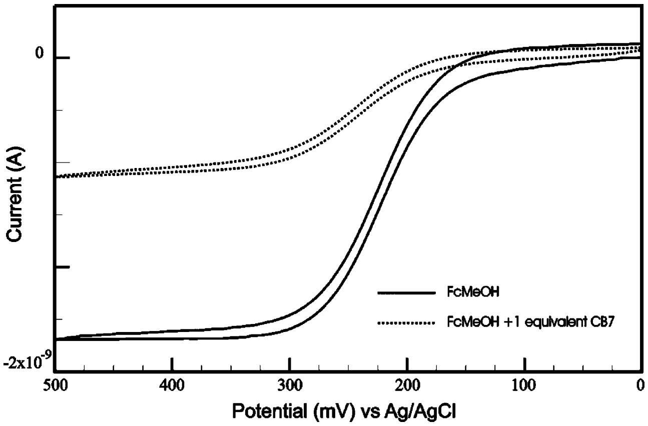


Figure 4. Steady-state voltammograms of 1.0 mM **1** in 0.1 M aqueous NaCl in the absence (solid line) and in the presence (dotted line) of 1.0 equiv of CB[7] recorded using a 5-μm radius glassy carbon ultramicroelectrode at a scan rate of 10 mV/s.

determine the corresponding binding constant due to the very limited solubility of this acid in aqueous solution.

The K values for the complexation of the ferrocenyl guests with CB[7] are much higher than those measured for the same guests with β-cyclodextrin ($\sim 10^3$ M^{-1}).[13] This huge binding enhancement is most probably due to the contribution of ion−dipole interactions, which are not important in the β-CD complexes.

The reversible electrochemical oxidation of ferrocene derivatives affords an additional opportunity to examine the host−guest interactions in these systems. More specifically, voltammetric techniques can be used to explore not only the interactions between CB[7] and the ferrocene-containing guests but also those between CB[7] and the oxidized, ferrocenium forms of the guests.[15] For instance, Figure 4 shows the steady-state voltammetric behavior of **1** in the absence and in the presence of CB[7]. Clearly, the host does not alter significantly the Nernstian (reversible) character of the current−potential curve obtained under these conditions (using a 5-μm ultramicroelectrode). However, the overall level of current is diminished, due to the association between the guest and the host, which decreases the effective diffusion coefficient of the electroactive species. Upon CB[7] addition, the half-wave potential ($E_{1/2}$) associated with the one-electron oxidation of the ferrocene nucleus increases by ca. 10 mV, suggesting that the reduced (ferrocene) form is slightly more stabilized by CB[7] than the oxidized (ferrocenium) form. Similar results were obtained using cyclic voltammetry (CV).

The effect of CB[7] on the cyclic voltammetric behavior of guest $\mathbf{3}^+$ is recorded in Figure 5. Clearly, the presence of 1 equiv of CB[7] results in a pronounced anodic shift (~110 mV) in the position of the corresponding $E_{1/2}$ value for oxidation of the ferrocene residue, as well as the expected current level decrease caused by the host−guest association. The anodic shift reveals that the ferrocene form of the guest is considerably more stabilized by CB[7] complexation than the oxidized form. In other words, oxidation of the ferrocene residue weakens considerably the stability of the inclusion complex. This is in strong contrast to the observed behavior with neutral hydroxymethylferrocene (**1**), in which the shift in the $E_{1/2}$ value was found to be much smaller (~10 mV), revealing only minor differences in the stabilities of the complexes formed by both oxidation states.

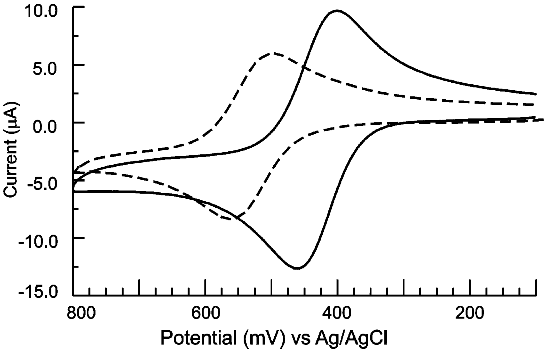


Figure 5. Cyclic voltammetric response on a glassy carbon electrode (0.071 cm^2) of a 1.0 mM $\mathbf{3}^+$ aqueous solution in the absence (continuous line) and in the presence (discontinuous line) of 1.1 mM CB[7]. The supporting electrolyte is 0.1 M NaCl, and the scan rate is 0.1 V/s.

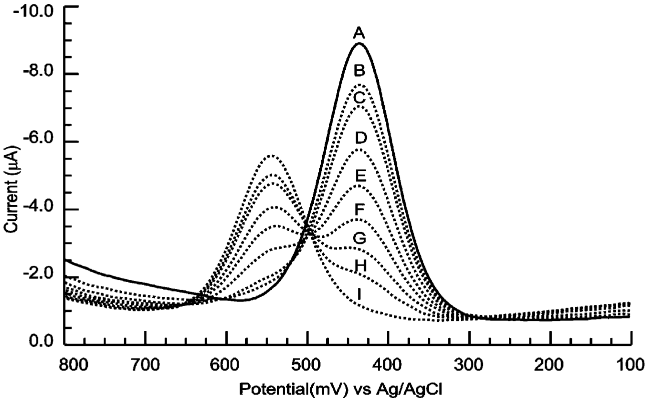


Figure 6. SWV response of guest $\mathbf{3}^+$ (0.2 mM) on a glassy carbon electrode (0.071 cm^2) in 0.1 M NaCl solution in the absence (A) and in the presence of varying concentrations of CB[7] (0.13, 0.26, 0.40, 0.53, 0.67, 0.80, 0.92, and 1.07 equiv, curves B−I). Scan rate: 0.10 $V \cdot s^{-1}$.

The high binding constant between guest $\mathbf{3}^+$ and the large complexation-induced shift in the $E_{1/2}$ value suggest that it should be possible to observe simultaneously the redox couples for free and bound guests[15] when the host concentration is less than 1 equiv. This is indeed observed in CV and square wave voltammetry (SWV) experiments. The greater sensitivity of the latter technique allows experiments with submillimolar concentrations of guest. For instance, Figure 6 displays SWV data corresponding to guest $\mathbf{3}^+$, showing the gradual conversion from the redox couple of the free guest to that of the CB[7]-bound guest, as the host concentration increases. The fact that the complexation is clearly detected at submillimolar concentrations supports the high thermodynamic stability of these complexes.

In strong contrast to the results recorded with **1**, $\mathbf{2}^+$−$\mathbf{4}^+$, and **5H**, *the presence of CB[7] has no effect on the voltammetric*

---

(14) The ionic composition of the medium is very important in binding studies involving CB[7]. See, for instance: Ong, W.; Kaifer, A. E. *J. Org. Chem.* **2004**, *69*, 1383.

(15) Kaifer, A. E.; Gómez-Kaifer, M. *Supramolecular Electrochemistry*; Wiley-VCH: Weinheim, 1999; Chapter 9.

response of the anionic derivative $\mathbf{5}^-$, in excellent agreement with the NMR results (vide supra). Both electrochemical and NMR spectroscopic data support clearly the total lack of host−guest interactions between CB[7] and $\mathbf{5}^-$, which we ascribe to the strong electrostatic repulsions between the guest's carboxylate and the carbonyl oxygens on the host portals. This result clearly demonstrates that the stability of the inclusion complexes between CB[7] and ferrocene derivatives depends strongly on the type of functional group attached to the ferrocene residue. In contrast to this, β-CD forms similarly stable inclusion complexes with all the ferrocene derivatives in Chart 1.

Another important difference between β-CD and CB[7] as hosts for ferrocene derivatives can be derived from the electrochemical results reported here. While β-CD complexation uniformly leads to a positive shift in the observed half-wave potential for the oxidation of the guest's ferrocene residue, the effect of CB[7] on the $E_{1/2}$ values is more complex and depends on the guest structure. For instance, addition of 1 equiv of CB[7] leads to positive shifts larger than 100 mV in the $E_{1/2}$ values for guests $\mathbf{2}^+-\mathbf{4}^+$. However, the effect of CB[7] on the $E_{1/2}$ value for **1** is just a small shift of ca. 10 mV in the positive direction. While the latter potential shift suggests a slight destabilization of the complex upon guest oxidation, the electrochemical data with the positively charged guests $\mathbf{2}^+-\mathbf{4}^+$ clearly indicate that the oxidized (+2) species is considerably less stable inside the cavity than the reduced (+1) ferrocene form. This is perhaps related to the greater hydrophilicity of the oxidized forms in these guests, or to the inability of the host to adapt to the spatial locations of the two charges in these ferrocenium-containing guests.

One final aspect of the electrochemical data must also be highlighted. The electrochemical behavior of the CB[7] complexes is fast and reversible in the range of scan rates investigated (up to 1 $\mathrm{V \cdot s^{-1}}$). This reveals that electron transfer to and from the inclusion complex is possible, and this constitutes another difference with the β-CD inclusion complexes, in which the electrochemical oxidation follows a so-called CE mechanism, that is, the electron transfer only takes place to and from the unbound ferrocene guest after dissociation of the complex.[13f,g] A complete rationalization of these differences in electrochemical behavior will require further electrochemical investigations of CB[7] complexes but could be related to their slower kinetic rates of dissociation compared to the more labile β-CD complexes.

To understand the intriguing host−guest behavior better we calculated the electrostatic surface potentials (ESP) of three cucurbituril hosts, CB[6], CB[7], and CB[8], and their size-equivalent CDs (see Figure 7). Our results with the CD hosts parallel previous reports by several groups. The rim of the CD's wider opening exhibits relatively hydrophilic character with low surface potential values. Inclusion complexation is driven by the affinity of the hydrophobic inner CD surface for the hydrophobic surface of the guest. On the other hand, cucurbiturils are an entirely different case. The regions around the carbonyl oxygens are found to be significantly negative, as expected. Interestingly, the inner cavity surface is also somewhat negatively charged. Clearly, this explains the affinity of CBs for positively charged guests. This also provides a rationalization for the rejection of an anionic guest, such as $\mathbf{5}^-$, by CB[7]. In the case of CDs, guest hydrophobicity and size are the key determining factors for binding.[8,9] With CBs, however, a more delicate match between the hydrophobicity, charge, and size of the guest to those of the host is necessary. When these factors combine in favor of the inclusion complex, its stability is considerably higher than those attainable with CDs. On the negative side, structural variations that are tolerated by CD complexes may lead to a complete loss of stability in CB complexes.

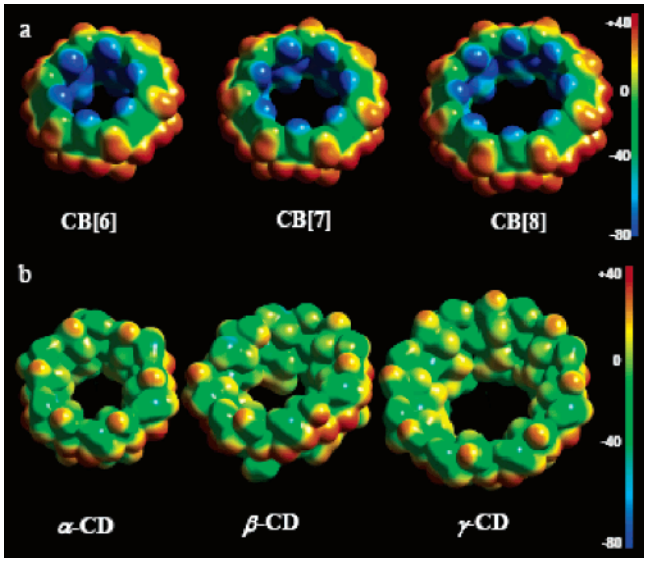


Figure 7. Electrostatic surface potentials calculated for (a) CB and (b) CD hosts.

Conclusions

The NMR spectroscopic, calorimetric, and electrochemical data presented here reveal that the surveyed ferrocene derivatives can form very stable inclusion complexes with the CB[7] host. While these complexes show thermodynamic association constants in the 10^9-10^{13} $\mathrm{M^{-1}}$ range, the same ferrocene derivatives exhibit K values in the 10^3-10^4 $\mathrm{M^{-1}}$ with β-CD. It would be tempting to conclude that CB[7] is a better host for these guests than β-CD, but this generalization would be misleading, as one of the surveyed guests ($\mathbf{5}^-$) illustrates very clearly. This anionic guest is bound by the CD host, while it is not bound at all by CB[7]. In general terms, we can conclude that the stability of CB[7] complexes is generally higher than those formed by β-CD, but it also seems to be considerably more sensitive to the nature of the substituent on the Cp ring. While the inclusion complexation of the surveyed guests inside β-CD seems to be controlled mainly by the hydrophobic character of the ferrocene residue, their interactions with CB[7] are more complicated. Further work is necessary to understand the sophisticated guest inclusion behavior of the cucurbituril family.

Experimental Section

Materials. Ferrocene (Fc), (ferrocenemethyl)dimethylamine (**2**), hydroxymethylferrocene (**1**) and ferrocenecarboxylic acid (**5H**) were purchased from Aldrich and (ferrocenemethyl)dimethyl(bromopropyl)ammonium bromide (**4**) was prepared according to literature methods.[13g] CB[7] was prepared according to our previous report.[1] The corresponding inclusion complexes were prepared by stirring a 1:1 mixture of CB[7] and ferrocene derivatives in water. The concentrations of ferrocene in solution were calculated from UV−visible absorption data using the molar absorption coefficient at 262 nm (ϵ = 21 000 $\mathrm{M^{-1}\ cm^{-1}}$).

NMR Spectroscopy. Samples for NMR spectroscopy were prepared with D_2O (99.99%D) purchased from Cambridge Isotope Laboratories. The sample solutions also contained 0.1−0.2 M NaCl to create experimental conditions similar to those employed in electrochemical experiments.

Isothermal Titration Calorimetry (ITC). The formation constants and thermodynamic parameters for the inclusion of ferrocene derivatives in CB[7] were determined by titration calorimetry using a VP-ITC instrument from MicroCal. All solutions were prepared in purified water (Milli-Q, Millipore). A solution (0.05−0.2 mM) of CB[7] was placed in the sample cell. As 1−5 mM solution of ferrocene derivatives was added in a series of 25−30 injections (10 μL), the heat evolved was recorded at 25 °C. The heat of dilution was corrected by injecting the ferrocene derivative solution into deionized water and subtracting these data from those of the host−guest titration. Since the formation constants are very large, ITC experiments were performed using the one- or two-step competition method with 1,6-diaminohexane ($K = 2.1 \times 10^9$ M^{-1}) and/or L-phenylalanine ($K = 1.78 \times 10^6$ M^{-1}) as competitors, as it is exemplified by a typical ITC thermogram given in the Supporting Information. The data were analyzed and fitted by the Origin software (MicroCal).

Electrochemical Experiments. The electrochemical experiments were performed with a Princeton Applied Research model 273 multipurpose instrument interfaced to a personal computer. A glassy carbon working electrode (0.071 cm^2), a Pt counter electrode, and a saturated calomel electrode (SCE) as a reference electrode separated with a fine glass frit were utilized in a single-compartment cell. The surface of the working electrode was polished with 0.05 μm alumina/water slurry on a felt surface and rinsed with purified water prior to electrochemical experiments. The experiments were conducted in 0.075 M phosphate buffer solutions (pH = 7.0) prepared with purified water (Milli-Q, Millipore). All solutions were deoxygenated by purging with nitrogen gas. An inert atmosphere was maintained during electrochemical experiments. The voltammetric data were analyzed by digital simulations carried out with the Digi-Sim version 2.1 software package (Bioanalytical Systems, West Lafayette, IN).

The electrochemical experiments in Miami were performed with a BAS 100B/W workstation from Bioanalytical Systems. The single-compartment electrochemical cell was fitted with a glassy carbon working electrode (0.07 cm^2), platinum flag counterelectrode, and Ag/AgCl reference electrode. The solution contained ca. 1 mM of the guest and variable concentrations of CB[7] plus 0.1 M NaCl as supporting electrolyte. Steady-state voltammograms were recorded with a 5-μm radius carbon ultramicroelectrode. Electrode polishing, solution deoxygenation, and data treatment procedures were otherwise identical to those used by the Pohang group.

Computations. The geometries of CB[n] (n = 6−8) were first optimized with the Hartree−Fock (HF) method using 3-21G* basis sets. The geometry of CB[7] was further optimized using density functional theory (DFT) at the B3LYP/6-31G* level. All the calculations were performed using a suite of Gaussian 98 program.[16] At the optimized geometries, the electrostatic potential surface (ESP) profiles were obtained using the AM1 method of the MOPAC 6.0 package. Since the electrostatic nature does not depend much either on the level of calculations or on the basis sets used, the ESP profiles for CB[n] (n = 6−8) are not expected to be changed much by higher level of calculations. The relative potential values were projected in color-coded form onto the isodensity surfaces by using the Cerius2 3.8 modeling package.

X-ray Crystal Structure Determination of Ferrocene·CB[7]. Slow evaporation of an aqueous solution (10 mL) containing CB[7] (10 mg, 9 μmol) and ferrocene (5 mg, 27 μmol) gave orange-colored platelets (8 mg). A single crystal ($0.5 \times 0.3 \times 0.1$ mm^3) was picked up with paraton oil and mounted on a Siemens SMART CCD diffractometer equipped with a graphite-monochromated Mo Kα ($\lambda = 0.71073$ Å) radiation source and a nitrogen cold stream (−40 °C). The data were corrected for Lorentz and polarization effects (SAINT), and semiempirical absorption corrections based on equivalent reflections were applied (SADABS). The structure was solved by Patterson methods and refined by full-matrix least-squares on F^2 (SHELXTL). The crystallographic asymmetric unit contains two ferrocene-CB[7] complexes and about 30 water molecules. The contributions of the mostly disordered solvent molecules were removed from the diffraction data using the SQUEEZE routine of PLATON software (c.a. 1200 e/u.c.), and then final refinements were carried out. The relatively large thermal parameters for the carbon atoms of ferrocene are probably due to librational motion and were not treated as a disorder. All the non-hydrogen atoms were refined anisotropically, and hydrogen atoms were added to their geometrically ideal positions. Ferrocene·CB[7]: $C_{52}H_{52}N_{28}O_{14}Fe$, fw = 1349.07, monoclinic, $P2_1/c$ (No. 14), a = 25.7295(3) Å, b = 13.5967(2) Å, c = 45.4640(3) Å, β = 102.600(1)°, V = 15521.9(3) Å^3; Z = 8, T = 233 K, d_{calc} = 1.15 g/cm^3; R_1 ($I > 2\sigma(I)$) = 0.081, wR_2 (all data) = 0.234, GOF = 1.047.

Acknowledgment. We are grateful to the NSF (to A.E.K., Grant CHE-0240295), Creative Research Initiative Program and the International R&D Cooperation Program of the Korean Ministry of Science and Technology (K.K.), the BK 21 Program of the Korean Ministry of Education (K.K.), and the Japan Science and Technology Agency (Y.I.). We thank Professor Lyle Isaacs for sharing with us unpublished results, which led us to determine the equilibrium association constants in Table 1 (by ITC competition methods).

Note Added after ASAP Publication. After this article was published ASAP on August 23, 2005, the Supporting Information file was updated. The new Supporting Information was posted on August 24, 2005.

Supporting Information Available: Complete ref 16, additional NMR spectroscopic data, ITC data set sample; X-ray crystallographic file for Fc@CB[7] in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

JA052912C

---

(16) Frish, M. J.; et al. *Gaussian 98*, Revision A6; Gaussian Inc.: Pittsburgh, PA, 1999.