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Detection of Isomeric Microscopic Host–Guest Complexes. A Time-Evolving Cucurbit[7]uril Complex

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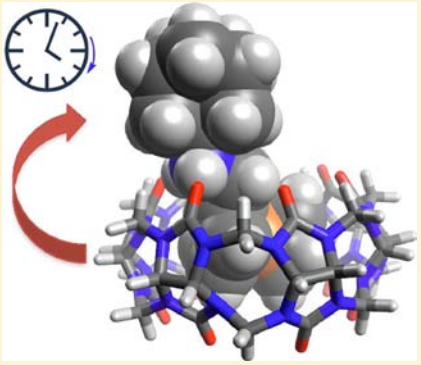
Supporting Information

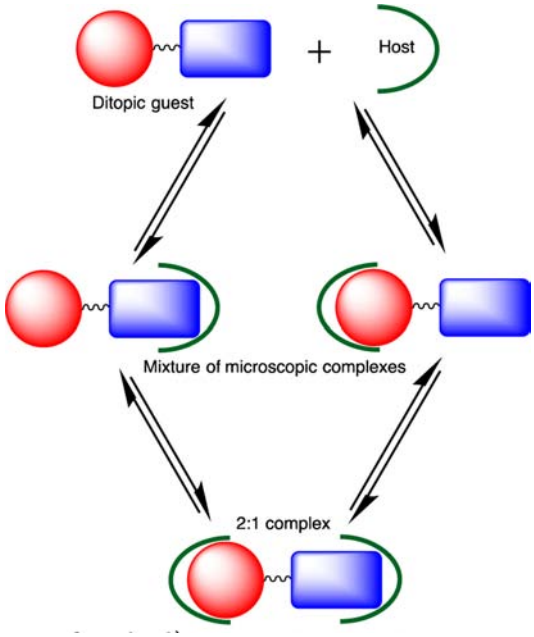
ABSTRACT: The formation of inclusion complexes between the cucurbit[7]uril host and a cationic guest containing ferrocenylmethyl and adamantyl residues connected to an ammonium nitrogen initially leads to an ~1:1 mixture of two isomeric microscopic complexes, which evolves as a function of time toward the thermodynamically stable mixture, dominated by the adamantyl-included complex.



INTRODUCTION

The binding interactions between a ditopic substrate (a molecular guest containing two binding sites) and a receptor or host having a single binding site (see Scheme 1) were addressed in detail by Connors and Pendergast[1] using 1,4-disubstituted benzenes, as ditopic guests, and α-cyclodextrin (αCD) as the host. In general terms, the cyclodextrins form relatively labile complexes, which makes difficult the detection of the resulting microscopic inclusion complexes, although fast time scale techniques, such as electron paramagnetic resonance (EPR), have allowed some success in this regard.[2,3] Increasing the degree of structural complexity of guests and hosts may also facilitate the detection of microscopic complexes.[4] A completely different approach may take advantage of the higher kinetic stability of inclusion complexes formed by cucurbit[n]uril hosts, as the slower exchange of the host between two or more binding sites may facilitate the individual detection of each of the microscopic complexes using techniques with relatively slow time scales, such as NMR.

Scheme 1. Binding Interactions between a Ditopic Guest and a Host with a Single Binding Site



The cucurbit[n]uril (CBn) host family has attracted considerable attention after Kim and co-workers first showed, about 12 years ago, that is possible to isolate higher cucurbiturils ($n > 6$) from the mixtures obtained in the acidic condensation of glycoluril with formaldehyde.[5] These rigid molecular container hosts[6−11] have a hydrophobic cavity with a well-defined barrel shape and two identical cavity portals lined by n carbonyl oxygens. Thus, the CBn hosts are ideally suited to form inclusion complexes with hydrophobic cationic guests in aqueous media, taking advantage simultaneously of hydrophobic and ion–dipole interactions.[12] The release of high-energy water molecules from the host cavities has recently been identified as an essential driving force for the formation of CBn inclusion complexes,[13] which can be extremely stable, and equilibrium association constants (K) as high as 10^{15} M^{-1} ($\Delta G^{\circ} = -86$ kJ mol^{-1}) have been reported.[14] This is an important

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finding because the binding affinity is equivalent to that measured with the well-known avidin–biotin host–guest pair.[15]

Inclusion complexes with such a high level of thermodynamic stability are of substantial interest, among other reasons because they lead to supramolecular species of considerable kinetic stability, with very long lifetimes. A simple calculation reveals that a bimolecular complex with $K = 10^{15}$ M^{-1} and a kinetic association rate constant close to diffusion control ($k_{ON} \sim 10^9$ M^{-1} s^{-1}) has a lifetime of more than 11 days! Of course, if the kinetic association processes take place at rates slower than those expected for diffusion control, the complex lifetimes also decrease in proportion. Nonetheless, we were intrigued by the formation of inclusion complexes between relatively simple guests and hosts that exhibit such long lifetimes and decided to investigate guests containing two molecular residues that can individually form highly stable inclusion complexes with the heptameric cucurbit[7]uril (CB7) host. We selected a compound (**1**, see Figure 1 for structures), available in our group from previous work,[16,17] which contains ferrocenylmethyl and adamantyl (Ad) units. Both of these residues are known to form extremely stable inclusion complexes with CB7.[18]

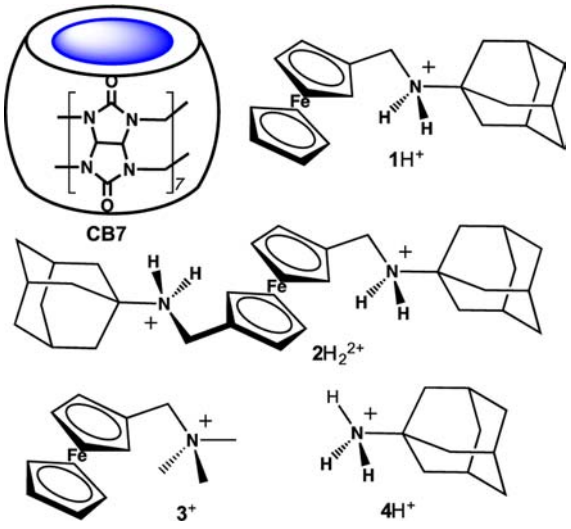

Figure 1. Structures of the guests and the CB7 host used in this work.

RESULTS AND DISCUSSION

Our initial investigation of the supramolecular complex formed between the protonated form of compound **1** (**1**H$^+$) and the CB7 host was carried out using ^{1}H NMR spectroscopy. Obviously, this technique is particularly useful for elucidating the main binding site for the interaction between a guest compound and an including host, such as CB7. It is well established that the signals of protons located on a residue that is included inside the CB*n* cavity will experience considerable upfield shifts.[6−11] Conversely, generally smaller downfield shifts are observed for protons that are close to the cavity portal in the CB7 complex, but fail to be included. The ^{1}H NMR spectra obtained upon mixing of compound **1**H$^+$ with 1.0 equiv of CB7 in D_2O solution are shown in Figure 2. The series of spectra in the figure show signal patterns that vary as a function of time. Clearly, the peaks corresponding to the protons of the included ferrocenyl (Fc) residue, at ca. 3.5 ppm, decrease in intensity as time elapses. Conversely, the resonances associated with the included adamantyl unit, around 1.0 ppm, become more

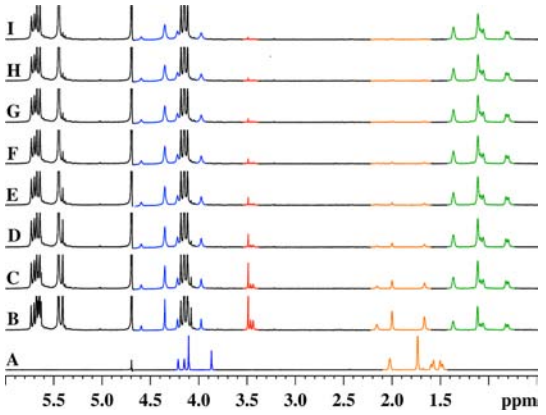

Figure 2. ^{1}H NMR spectra (500 MHz, 50 mM NaCl in D_2O) of (A) guest **1**H$^+$ and equimolar mixture of **1**H$^+$ and CB7 (B) upon mixing, (C) 90 min, (D) 180 min, (E) 270 min, (F) 360 min, (G) 450 min, (H) 540 min, and (I) 615 min after mixing. Color coding: Blue for signals corresponding to unbound ferrocenyl protons, red for CB7-bound ferrocenyl protons, orange for unbound adamantyl protons, and green for CB7-bound adamantyl protons.

intense as a function of time. These findings are consistent with the initial formation of a mixture of two microscopically different complexes, probably those formed by the CB7 inclusion of either the ferrocenyl residue or the adamantyl unit. As time elapses, the relative concentration of the adamantyl-included complex gradually increases at the expense of the concentration of the ferrocenyl-included complex.

While the data in Figure 2 should allow kinetic investigations of the conversion process between the two complexes, we quickly found a more convenient way to monitor the kinetics using voltammetric measurements. The anodic electrochemical behavior of compound **1**H$^+$ is dominated by the reversible one-electron oxidation of the ferrocenyl residue.[19] Figure 3 shows

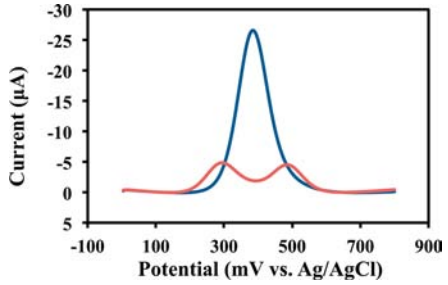

Figure 3. SWV behavior on glassy carbon (0.07 cm^2) of 0.5 mM **1**H$^+$ in aqueous solution also containing 50 mM NaCl in the absence (blue line) and immediately after addition (red line) of 1.0 equiv of CB7.

the square wave voltammetric (SWV) behavior of **1**H$^+$ in which a single wave is observed at a half-wave potential of +0.38 V vs Ag/AgCl. Upon addition of 1.0 equiv of CB7, two waves are observed, at +0.29 and +0.49 V vs Ag/AgCl, respectively. The wave at +0.49 V is assigned to the oxidation of the complex in which the ferrocenyl residue is bound inside the host cavity. We have previously shown that inclusion of (ferrocenylmethyl)-ammonium groups in the cavity of CB7 leads to a considerable displacement of the ferrocene oxidation half-wave potential to more positive values.[20,21] This anodic potential shift results from the poorer solvation experienced by the positively charged, oxidized ferrocenium form inside the host's hydrophobic cavity. The second wave in this voltammogram (Figure

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3) corresponds to the complex in which the adamantyl group is included inside CB7. The reason for the observed shift to more negative potentials, compared to the half-wave potential for unbound $1H^+$, is probably related to solvation changes associated with the proximity of the CB7 cavity portal to the redox active ferrocenyl residue.[22] Notice also that the sum of the peak currents for the two SWV peaks recorded for the CB7 complex is lower than the single peak current observed for free $1H^+$. This is the result of the reduced diffusivity of the CB7 complex relative to the unbound guest compound. Similar reductions of the effective diffusion coefficient upon CB7 complexation have been observed with other electroactive guests.[21]

Although the initial experiments in this work were conducted in 50 mM NaCl aqueous solution, binding of guests to cucurbiturils is known to be quite sensitive to medium composition, and thus, we decided to use a different medium for the remaining, more quantitative kinetic experiments. We selected aqueous 50 mM sodium acetate (NaAc), buffered at pH 4, because of the large number of equilibrium association constants reported by Isaacs and co-workers in this medium,[18] which has become the best choice for research with the cucurbituril host family.

In analogy to the NMR spectroscopic data, the voltammetric data were also found to be time-dependent. Figure 4 clearly

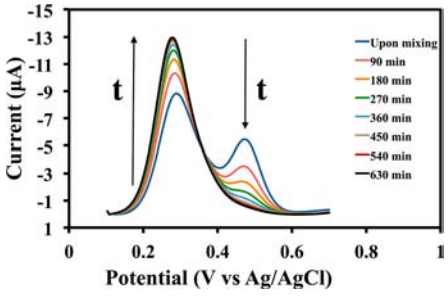
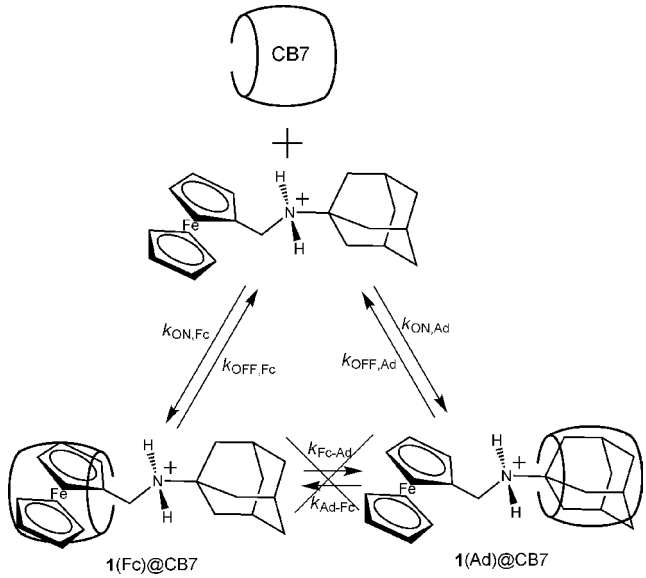


Figure 4. Time dependent SWV behavior on glassy carbon (0.07 cm^2) of 0.5 mM $1H^+$ + 0.5 mM CB7 in aqueous solution also containing 50 mM NaAc (pH = 4) as the supporting electrolyte.

shows that the current level associated with the peak at +0.49 V decreases as a function of time while, concurrently, the peak at 0.29 V grows. This is in full agreement with the NMR spectroscopic data (Figure 2) and shows that two different microscopic complexes coexist at the beginning of the experiment. As time elapses, the concentration of the complex in which CB7 encircles the ferrocenyl unit, which we will denote as **1**(Fc)@CB7, gradually decreases, while the concentration of the adamantyl-included complex, **1**(Ad)@CB7, increases. Clearly, the mixture of isomeric microscopic complexes observed initially is not thermodynamically stable and the system evolves over time to reach a mixture that is considerably richer in the adamantyl-included complex.

Notice that zero time in our experiments does not correspond exactly to the time at which guest $1H^+$ and CB7 are mixed. No matter how fast we try to carry out our experiments, a few minutes elapse between mixing and the recording of the first measurement. Therefore, the starting mixture in our experiments is always close to a 60/40 molar ratio ([**1**(Ad)@CB7]/[**1**(Fc)@CB7]). The formation of this mixture can be understood in the following terms. As mentioned before, CB7 forms highly stable inclusion complexes with both ends of guest $1H^+$ (ferrocene and adamantane). The observed ratio of these two complexes must correspond to the ratio between the two kinetic association rate constants ($k_{ON,Fc}$ and $k_{ON,Ad}$). Clearly, the high thermodynamic stability of these two complexes translates into very slow dissociation rate constants ($k_{OFF,Fc}$ and $k_{OFF,Ad}$), which exert control over the time evolution of the "kinetic" mixture of complexes to the final mixture of complexes (Scheme 2). The composition of the final

Scheme 2. Association and Dissociation Processes Involving the Two Forms of the Complex between $1H^+$ and CB7



mixture reflects the relative thermodynamic stabilities of the two isomeric, microscopic complexes. Clearly, inclusion of the adamantyl unit by CB7 is strongly preferred to the inclusion of the ferrocenyl unit.

We used the electrochemical data to follow the disappearance of the CB7-ferrocenyl complex using the time-dependent decrease of the corresponding voltammetric peak current for the wave at +0.49 V. We also monitored the increase in the concentration of the CB7-adamantyl complex by measuring the increasing peak current of the voltammetric wave at +0.29 V. These measurements were done at several concentrations of CB7, including an identical concentration (1.0 equiv) to that of the guest $1H^+$ and various moderate excess ratios of the CB7 host. Figure 5 shows the time-dependent variation of the peak current for both complexes measured under two different experimental conditions: (a) in the presence of exactly 1.0 equiv of CB7 and (b) in the presence of a 40% excess of CB7 (1.4 equiv). It is clearly evident that the rate of conversion between the two complexes increases substantially in the presence of excess CB7. We actually measured the rate of disappearance of the ferrocenyl-included complex at various concentrations of CB7 and confirmed that the effective rate increases linearly with the host concentration (see Table 1 and the Supporting Information). This finding is not consistent with the proposed reaction mechanism (Scheme 2). According to the scheme, we can propose that the conversion of the ferrocenyl-included complex to the adamantyl-included complex takes place by direct "sliding" of the host from one residue to the other, which will require the rigid CB7 host to slip over the positively charged nitrogen. This process should be hampered by the lack of linear alignment between the two

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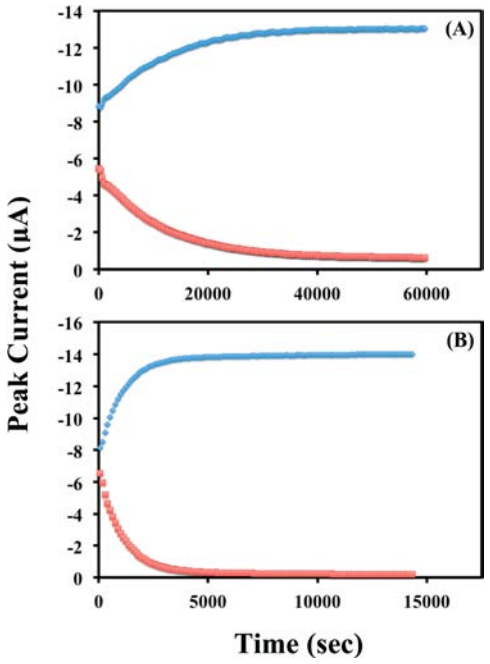


Figure 5. Time dependence of the SWV peak currents corresponding to the adamantyl-included (blue diamonds) and ferrocenyl-included (red squares) complexes. Data obtained with a solution containing 0.5 mM $1H^+$ and 50 mM NaAc (pH = 4) and (A) 1.0 equiv of CB7 and (B) 1.40 equiv of CB7.

Table 1. Apparent Rate Constants (k) for the Disappearance of 1(Fc)@CB7[a] as a Function of the CB7 Concentration at 25°C

CB7/mM	0.5	0.55	0.60	0.65	0.70	0.75
k ($\times 10^3$)/s^{-1}	0.07	0.10	0.24	0.48	0.82	1.09

[a]The concentration of $1H^+$ was 0.5 mM in all experiments. The medium composition was 50 mM NaAc (pH = 4).

rather bulky guest subunits and, more importantly, by the presumably high energy content of an intermediate in which the ammonium nitrogen would have to undergo desolvation (or deprotonation) to pass through the CB7 cavity.[23] We have also investigated the CB7 binding of guest **2** (Figure S1), which has two terminal adamantyl units and a central ferrocenyl unit flanked by two positive charges. While the central ferrocenyl unit in compound **2** is similar to those known to give rise to extremely stable complexes with CB7,[14] we only observed CB7 inclusion of the terminal adamantyl residues (see NMR spectroscopic data in Figure S1). This experimental finding supports our arguments for the intrinsic difficulties associated with the direct sliding of CB7 over the ammonium nitrogen in these guest compounds. In other words, the rate constants $k_{Fc\text{-}Ad}$ and $k_{Ad\text{-}Fc}$ in Scheme 2 must be both exceedingly small.

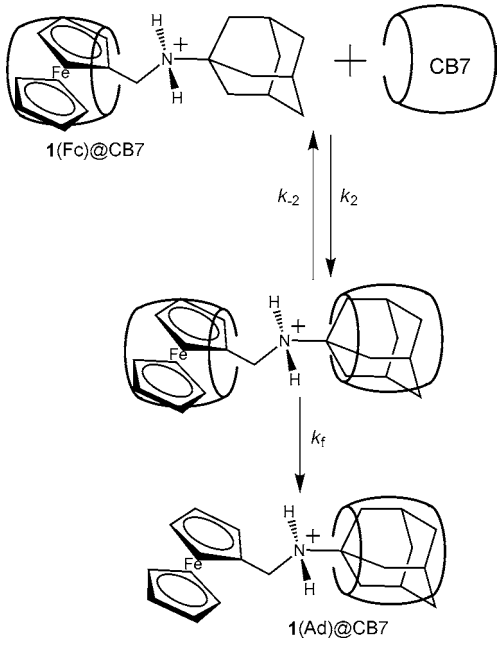
After discarding a direct sliding mechanism, we turned our attention to the possibility that the conversion may take place via a dissociation-association mechanism, that is, dissociation of the ferrocenyl-included complex followed by CB7 inclusion of the adamantyl residue. Under conditions far from equilibrium, the first process would be much slower than the second process, that is, the dissociation of the **1**(Fc)@CB7 complex would become the rate-determining step of the overall conversion and the rate of disappearance of the **1**(Fc)@CB7 complex (or the rate of formation of the **1**(Ad)@CB7 complex) would be determined by $k_{OFF,Fc}$ (Scheme 2). However, because dissociation of **1**(Fc)@CB7 is inherently a unimolecular, first order process, the overall rate would be independent from the concentration of CB7, which is at variance with our experimental data. Therefore, we must conclude that neither one of these two mechanisms (direct sliding or sequential dissociation-association) is consistent with the experimental results in the presence of excess CB7 host.

The formation of a stable ternary complex of guest $1H^+$ with two hosts, in which CB7 would include (fully or partially) both terminal residues is not observed experimentally, by either NMR spectroscopy or mass spectrometry. Such a ternary complex (2:1 complex in Scheme 1) would not be very stable due to the electrostatic repulsions between two CB7 hosts, since the host cavity portals are lined up by carbonyl oxygens and simultaneous binding of the two terminal residues would place the cavity portals in very close proximity around the ammonium nitrogen. However, even if such a ternary complex is not thermodynamically stable, we can still assume that a closely related structure may form as a reaction intermediate. It is thus possible to postulate a mechanism based on the formation of an intermediate in which guest $1H^+$ interacts simultaneously with two host molecules. Applying the steady state approximation to this intermediate, we obtain the following expression for the rate of disappearance of the ferrocenyl-included complex,

$$r = \frac{k_f \cdot k_2}{k_f + k_{-2}}[1(\mathrm{Fc})@\mathrm{CB7}][\mathrm{CB7}] \quad (1)$$

which shows the observed linear dependence (Figure S3) between the apparent kinetic rate and the concentration of excess CB7 added to the medium. The individual rate constants in eq 1 are defined in Scheme 3, which shows the formation of the intermediate containing two CB7 molecules interacting with the guest.

Scheme 3. Kinetic Scheme for the Conversion between the Two Microscopic Isomeric Complexes in the Presence of Excess CB7 Host



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Therefore, we can conclude that the formation of the complexes **1**(Fc)@CB7 and **1**(Ad)@CB7 is relatively fast and leads to a mixture of the two isomeric, microscopic complexes, quickly after exposure of the guest to the host in aqueous solution. While both microscopic complexes are initially formed in relatively similar amounts, indicating the similar values of both association rate constants, $k_{ON,Fc}$ and $k_{ON,Ad}$, the adamantyl-included complex is more stable and the system evolves to produce eventually a mixture of microscopic complexes in which only a very small fraction is present as the ferrocenyl-included complex. In the absence of excess CB7, the measured rate constant (7×10^{-5} s^{-1}, see Table 1) for the disappearance of **1**(Fc)@CB7 corresponds to the unimolecular rate of dissociation of this complex, which should be essentially identical to the rate of dissociation of **3**@CB7. Our value is close to that determined by Isaacs and co-workers for the dissociation of an adamantyl-CB7 complex.[24] We can also use the reported equilibrium association constant value for **3**@CB7[18] ($K_3 = 3.31 \times 10^{11}$ M^{-1}) to estimate the association rate constant for this complex as $k_{ON} = K_3 k_{OFF} = (3.31 \times 10^{11}$ $M^{-1})(7 \times 10^{-5}$ $s^{-1}) = 2 \times 10^7$ M^{-1} s^{-1}, which indicates that the formation of this host–guest complex is fast, although still 2 orders of magnitude under the diffusion limit. These calculations are obviously made possible by the consistent use of the same medium composition in all the experiments.

We were intrigued by the apparently more pronounced adamantyl versus ferrocenyl selectivity observed in the ditopic guest **1**H$^+$, which is at variance with the reported binding affinities for CB7 complexes of guests containing single ferrocenyl or adamantyl epitopes.[18] Therefore, we investigated equilibrium mixtures containing identical concentrations (0.5 mM) of monotopic guests **3**$^+$ and **4**H$^+$ (see structures in Figure 1) and a single equivalent of CB7. ^{1}H NMR spectroscopy of these mixtures clearly shows that the signals corresponding to the CB7-bound ferrocenyl protons are relatively more intense than those observed in an equilibrium mixture of **1**H$^+$ and 1.0 equiv of CB7 (Figures S2 and S3). A simple equilibrium analysis reveals that the observed behavior with the ditopic and monotopic guests is not unexpected. Let us consider the equilibrium equations for the exchange between the two microscopic complexes formed between CB7 and **1**H$^+$.

$$\mathbf{1}(\mathrm{Fc})@\mathrm{CB7} \rightleftarrows \mathbf{1}(\mathrm{Ad})@\mathrm{CB7} \tag{2}$$

$$K_1 = \frac{[1(\mathrm{Ad})@\mathrm{CB7}]}{[1(\mathrm{Fc})@\mathrm{CB7}]} \tag{3}$$

Similar exchange equilibrium for the intermolecular system composed by **3**$^+$, **4**H$^+$, and CB7

$$\mathbf{3}@\mathrm{CB7} + \mathbf{4} \rightleftarrows \mathbf{3} + \mathbf{4}@\mathrm{CB7} \tag{4}$$

$$K_2 = \frac{[\mathbf{4}@\mathrm{CB7}][\mathbf{3}]}{[\mathbf{3}@\mathrm{CB7}][\mathbf{4}]} = \left(\frac{[\mathbf{4}@\mathrm{CB7}]}{[\mathbf{3}@\mathrm{CB7}]}\right)^2 \tag{5}$$

Based on these equations, the [**4**@CB7]/[**3**@CB7] ratio is expected to be smaller ($\sqrt{K_2}$) than the [**1**(Ad)@CB7]/[**1**(Fc)@CB7] ratio (K_1), since it is reasonable to assume that both equilibrium constants, K_2 and K_1, are similar. (See the Supporting Information for details on the derivation of eq 5.) This is consistent with the experimental observations.

CONCLUSIONS

Binding between CB7 and ditopic guest **1**H$^+$ is an excellent example of the complexation of a substrate having two binding epitopes by a host with a single binding site. A similar case was investigated by Connors and Pendergast in 1984 using α-cyclodextrin as the host and 1,4-disubstituted benzenes as guests.[1] In pronounced contrast to that case, our work provides a rare example for the clear detection of the two isomeric microscopic complexes, as kinetic products, during the formation of a thermodynamically stable supramolecular complex. Under conditions in which the concentration of free CB7 is negligible, the kinetic evolution of the initial mixture of complexes to the final product mixture, dominated by the adamantyl-included complex, can be described by Scheme 2, with the two kinetic constants associated with host sliding over the ammonium nitrogen ($k_{Fc\text{-}Ad}$ or $k_{Ad\text{-}Fc}$) being negligible. However, when excess CB7 is present, a different kinetic scheme needs to be considered (Scheme 3) in which the conversion between the two CB7 complexes takes place via formation of an intermediate with two CB7 hosts interacting with the hydrophobic residues on the guest. This intermediate has a catalytic effect on the overall reaction rate, which increases linearly with the concentration of excess CB7. The catalytic nature of the intermediate may be due to electrostatic repulsion between the two CB7 hosts, which facilitates dissociation. On the other hand, loss of one of the two CB7 hosts from the intermediate leads naturally to the **1**(Ad)@CB7 product or back to the **1**(Fc)@CB7 starting complex, with the former being favored owing to its higher stability.

Isaacs and co-workers reported a related system in which two guests, with one of them having two different binding epitopes, engage in binding interactions with CB6 and CB7.[24] This host–guest recognition system also leads to the initial detection of a kinetically self-sorted mixture of complexes, which evolves to a more stable, thermodynamically self-sorted mixture as a function of time. Since these authors use an interesting systems chemistry approach, the observation of the initial kinetic state is based on the competition between two guests and two hosts (CB6 and CB7). In contrast to their system, the work presented here relies on a single guest with two binding epitopes (**1**H$^+$) and a single host (CB7). We are currently investigating in further detail the kinetics[25] and thermodynamics[18] of this system and their potential applications, including those that would take advantage of systems chemistry approaches.

An interesting result from this work is the clear detection of two isomeric microscopic host–guest complexes formed between guest **1**H$^+$ and the CB7 receptor. The equilibrium mixture containing these two complexes is considerably richer in the most stable complex (**1**(Ad)@CB7) than predicted from the thermodynamic stabilities of the two individual complexes **3**$^+$@CB7 and **4**H$^+$@CB7. This result was rationalized by analysis of the equilibria involved (eqs 1–5) and is related to the impossibility of forming a stable 2:1 complex, which enhances the relative stability of one of the microscopic complexes (**1**(Ad)@CB7) in relation to the other one (**1**(Fc)@CB7). We are currently exploring ways in which these intramolecular effects may be used to advantage in the design of chemical systems based on the CB7 receptor.

EXPERIMENTAL SECTION

Compounds **1** and **2** were available in our group from previous work.[16,17] Compounds **3** and **4** were commercially available. CB7 was

prepared and isolated as reported before.[26] Its purity was determined as previously reported by our group.[27] Square wave voltammetry (SWV) was carried out using a BAS 100B/W electrochemical workstation. The key parameters for the SWV experiments were as follows: Step potential = 4 mV; square wave amplitude = 25 mV; frequency = 15 Hz. All SWV measurements were done in a single compartment cell fitted with a glassy carbon working electrode (0.07 cm^2), a Pt auxiliary electrode, and a Ag/AgCl reference electrode. The supporting electrolyte was 50 mM NaAc (pH 4). To simplify the comparison between electrochemical and NMR spectroscopic measurements, NMR samples of compounds $\mathbf{1}H^+$, $\mathbf{3}^+$, and $\mathbf{4}H^+$ also contain 50 mM deuterated NaAc (pH 4). Mass spectra were obtained with a high resolution, ESI time-of-flight mass spectrometer. ^{1}H NMR spectra were recorded on a 500 MHz instrument. For all kinetic studies, two solutions of cucurbit[7]uril and $\mathbf{1}H^+$ were made separately and the pH was set to ~4. Measurements were made right after mixing the two solutions in the desired proportions. In the case of $\mathbf{2}H_2^{2+}$, the solution pD was set to ~3.5. The computational structures shown were minimized with the Gaussian software using PM6 semiempirical methods.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Additional NMR data, kinetic data, mass spectrometric data, and energy minimized structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Connors, K. A.; Pendergast, D. D. *J. Am. Chem. Soc.* **1984**, *106*, 7607.
(2) Kotake, Y.; Janzen, E. G. *Chem. Phys. Lett.* **1988**, *150*, 199.
(3) Kotake, Y.; Janzen, E. G. *J. Am. Chem. Soc.* **1988**, *110*, 3699.
(4) Park, J. W.; Lee, S. Y. *J. Inclusion Phenom.* **2003**, *47*, 143.
(5) 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.
(6) Lee, J. W.; Samal, S.; Selvapalam, N.; Kim, H.-J.; Kim, K. *Acc. Chem. Res.* **2003**, *36*, 621.
(7) Lagona, J.; Mukhopadhyay, P.; Chakrabarti, S.; Isaacs, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4844.
(8) Masson, E.; Ling, X.; Joseph, R.; Kyeremeh-Mensah, L.; Lu, X. *RSC Adv.* **2012**, *2*, 1213.
(9) Ko, Y. H.; Kim, E.; Hwang, I.; Kim, K. *Chem. Commun.* **2007**, 1305.
(10) Kim, K.; Selvapalam, N.; Ko, Y. H.; Park, K. M.; Kim, D.; Kim, J. *Chem. Soc. Rev.* **2007**, *36*, 267.
(11) Isaacs, L. *Chem. Commun.* **2009**, 619.
(12) Kaifer, A. E.; Li, W.; Yi, S. *Isr. J. Chem.* **2011**, *51*, 496.
(13) Biedermann, F.; Uzunova, V. D.; Scherman, O. A.; Nau, W. M.; De Simone, A. *J. Am. Chem. Soc.* **2012**, *134*, 15318.
(14) Rekharsky, M. V.; Mori, T.; Yang, C.; Ko, Y. H.; Selvapalam, N.; Kim, H.; Sobransingh, D.; Kaifer, A. E.; Liu, S.; Isaacs, L.; Chen, W.; Moghaddam, S.; Gilson, M. K.; Kim, K.; Inoue, Y. *Proc. Nat.. Acad. Sci. U.S.A.* **2007**, *104*, 20737.
(15) Green, N. M. *Biochem. J.* **1966**, *101*, 774.
(16) Qiu, Y.; Yi, S.; Kaifer, A. E. *Org. Lett.* **2011**, *13*, 1770.
(17) Qiu, Y. H.; Yi, S.; Kaifer, A. E. *J. Org. Chem.* **2012**, *77*, 4622.
(18) Liu, S.; Ruspic, C.; Mukhopadhyay, P.; Chakrabarti, S.; Zavalij, P. Y.; Isaacs, L. *J. Am. Chem. Soc.* **2005**, *127*, 15959.
(19) Connelly, N. G.; Geiger, W. E. *Chem. Rev.* **1996**, *96*, 877.
(20) Jeon, W. S.; Moon, K.; Park, S. H.; Chun, H.; Ko, Y. H.; Lee, J. Y.; Lee, E. S.; Samal, S.; Selvapalam, N.; Rekharsky, M. V.; Sindelar, V.; Sobransingh, D.; Inoue, Y.; Kaifer, A. E.; Kim, K. *J. Am. Chem. Soc.* **2005**, *127*, 12984.
(21) Cui, L.; Gadde, S.; Li, W.; Kaifer, A. E. *Langmuir* **2009**, *25*, 13763.
(22) Yi, S.; Captain, B.; Ottaviani, M. F.; Kaifer, A. E. *Langmuir* **2011**, *27*, 5624.
(23) Ling, X. X.; Samuel, E. L.; Patchell, D. L.; Masson, E. *Org. Lett.* **2010**, *12*, 2730.
(24) Mukhopadhyay, P.; Zavalij, P. Y.; Isaacs, L. *J. Am. Chem. Soc.* **2006**, *128*, 14093.
(25) Tang, H.; Fuentealba, D.; Ko, Y. H.; Selvapalam, N.; Kim, K.; Bohne, C. *J. Am. Chem. Soc.* **2011**, *133*, 20623.
(26) Day, A.; Arnold, A. P.; Blanch, R. J.; Snushall, B. *J. Org. Chem.* **2001**, *66*, 8094.
(27) Yi, S.; Kaifer, A. E. *J. Org. Chem.* **2011**, *76*, 10275.