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Sequential Formation of a Ternary Complex among Dihexylammonium, Cucurbit[6]uril, and Cyclodextrin with Positive Cooperativity

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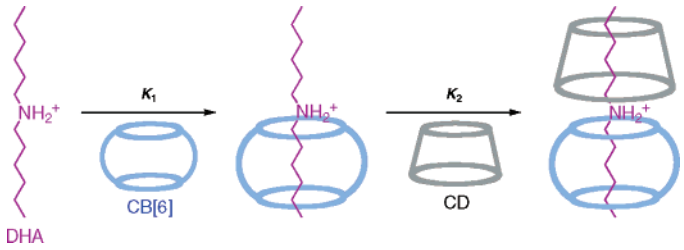
ABSTRACT



A unique ternary 1:1:1 cucurbit[6]uril (CB[6])–cyclodextrin (CD)–dihexylammonium (DHA) complex was designed and noncovalently synthesized in stepwise fashion: first, CB[6] interacts strongly with DHA to form a 1:1 complex; second, addition of CD into the solution of the 1:1 complex leads to the exclusive formation of the 1:1:1 ternary complex. The ternary complex was characterized by various experimental techniques including ITC, NMR, and ESI-MS.

One of the vital current tasks in supramolecular chemistry is to develop simple yet comprehensive and reliable methods to effectively hold together separate parts of complex architectures, exclusively through cooperative noncovalent interactions. For this purpose, it is beneficial to have a set of simple guest molecules which function as a molecular clip/nail/glue to keep different macrocycles together as one complex architecture. In reality, it becomes more difficult to find an appropriate glue ligand capable of holding the host components together, as each component differs in its physicochemical and binding properties. In this study, we selected native cyclodextrins (α-, *β*-, and *γ*-CD) and cucurbit[6]uril (CB[6]; see Figure 1)[1,2] as two types of macrocycles with contrasting physicochemical properties and guest se-

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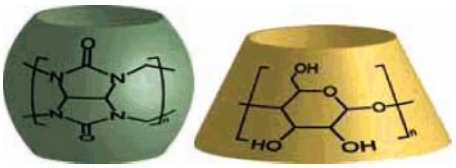

Figure 1. Cucurbit[n]uril and cyclodextrin macrocycles.

lectivities. Indeed, native CDs bind neutral hydrophobic guests very strongly, but cationic guests such as organic amines are bound only moderately, with dicationic guests not appreciably interacting with CDs.[3] In contrast, CB[6] exhibits much larger affinities toward cationic guests, such as aliphatic amines and in particular diamines, in comparison to the relevant neutral guests.[1] It was shown previously that CB[6] can form weak complexes with native CDs in pure water with an affinity less than 40 M^{-1}.[4] This poor complex stability does not allow significant solubilization of CB[6] (its solubility in water is less than 20 μM) in aqueous solutions of native CDs. To dissolve CB[6] in water in millimolar concentrations, one has to add alkaline or other metal salts into pure water.[1] Metal cations coordinate to both portals of CB[6], and an originally neutral CB[6] macrocycle becomes positively charged (for instance, forms [CB[6]·2Na]$^{2+}$; see Supporting Information). It should be noted that not only CB[6] but also other CB homologues tend to form complexes with dicationic guest molecules in aqueous solutions.[1b,1c,5,6]

As it is stated above, native CDs hardly make any complexes with dicationic guests/species and thus it becomes very challenging to hold CD and CB[6] in one supramolecular architecture in the aqueous solutions where CB[6] exists as a dicationic species. Employing these two different hosts, we now demonstrate that an unprecedented sequential association of these two macrocycles, of different binding properties, into a single supramolecular architecture can be achieved by sharing a small guest molecule as "molecular glue" in 0.05 M NaCl.

Taking into account the very similar geometrical dimensions of α-CD and CB[6] cavities that can include only small guest molecules possessing straight aliphatic chains,[1,3] we chose positively charged compounds with two separate aliphatic chains as guests most suitable for our purposes, e.g., dialkylamines. One aliphatic chain is likely to be inserted into the CB[6] cavity, which is greatly assisted not only by van der Waals interactions with CB[6]'s inside walls but also by the ion−dipole interactions of the cationic (ammonium) group with the carbonyl array of the CB[6] portal. The other aliphatic chain remains outside in the bulk solution (as the small CB[6] cavity cannot accommodate two aliphatic chains simultaneously) and may interact with α-CD. The optimal length of the aliphatic chains is another serious issue. CB[6] strongly interacts with aliphatic amines possessing a relatively short chain of 3−6 methylenes.[1a] In contrast, affinity to α-CD steadily increases with increasing alkyl chain length, thus giving binding constants (K) of 17, 99, and 389 M^{-1} for butyl-, pentyl-, and hexylamine, respectively.[7] These considerations led us to a conclusion that only hexyl can be exploited as a common residue which exhibits appreciably high affinities toward both CB[6] and α-CD. It should be emphasized however that a substantial difference in affinity, leading to stepwise complexation with the two hosts, is essential not only for unambiguously elucidating the binding behavior of CB[6] and α-CD discretely but also for stepwise supramolecular manufacturing.

Microcalorimetric titration experiments, using a VP−ITC instrument (Microcal), revealed that CB[6] strongly interacts with dihexylammonium (DHA) to give a very stable 1:1 complex with a K of 5.2×10^5 M^{-1}, which is driven both enthalpically and entropically (Table 1; see Figure 2 and Supporting Information for details of ITC experiments).

Table 1. Stability Constant (K), Standard Enthalpy ($\Delta H°$), and Entropy Changes ($T\Delta S°$) for Stepwise Complexation Reactions of Dihexylammonium (DHA) with Cucurbit[6]uril (CB[6]) and Then with α-, β-, and γ-Cyclodextrin (CD) in Aqueous NaCl Solution (0.05 M; pH 3) at 298.15 K[a]

complexation reaction	K/ M^{-1}	$\Delta H°$/ kJ mol^{-1}	$T\Delta S°$/ kJ mol^{-1}
$[CB[6]\cdot 2Na]^{2+} + DHA^+ = [CB[6]\cdot DHA\cdot Na]^{2+} + Na^+$	$(5.2 \pm 0.8) \times 10^5$	-24.9 ± 0.5	7.7 ± 0.6
$[CB[6]\cdot 2Na]^{2+} + HA^+ = [CB[6]\cdot HA\cdot Na]^{2+} + Na^+$	$(1.5 \pm 0.3) \times 10^5$	-24.9 ± 0.4	4.6 ± 0.5
$[CB[6]\cdot DHA\cdot Na]^{2+} + \alpha\text{-CD} = [CB[6]\cdot DHA\cdot \alpha\text{-CD}\cdot Na]^{2+}$	800 ± 30	-20.5 ± 0.3	-3.9 ± 0.3
$[CB[6]\cdot DHA\cdot Na]^{2+} + \beta\text{-CD} = [CB[6]\cdot DHA\cdot \beta\text{-CD}\cdot Na]^{2+}$	2150 ± 100	-15.5 ± 0.2	3.5 ± 0.2
$[CB[6]\cdot DHA\cdot Na]^{2+} + \gamma\text{-CD} = [CB[6]\cdot DHA\cdot \gamma\text{-CD}\cdot Na]^{2+}$	240 ± 40	-11.1 ± 0.5	2.5 ± 0.5
$HA^{1+} + \alpha\text{-CD} = [HA\cdot \alpha\text{-CD}]^{1+}$	389 ± 15	-17.5 ± 0.2	-2.8 ± 0.2
$HA^{1+} + \beta\text{-CD} = [HA\cdot \beta\text{-CD}]^{1+}$	65 ± 15	2.5 ± 0.4	12.9 ± 0.8

[a] K, $\Delta H°$, and $T\Delta S°$ values for reaction of n-hexylammonium, (HA) + CB[6], are given for comparison.

The experiments were carried out in 0.05 M NaCl solution, where CB[6] was solubilized by forming a dicationic complex $[CB[6]\cdot 2Na]^{2+}$. Interestingly, the 3.5 times higher affinity of DHA toward CB[6] than that of hexylammonium (HA), having only one alkyl chain, has an exclusively entropic origin (Table 1), which indicates that the second aliphatic chain of DHA stays outside the cavity rather than forming an inclusion complex with CB[6]. The complex

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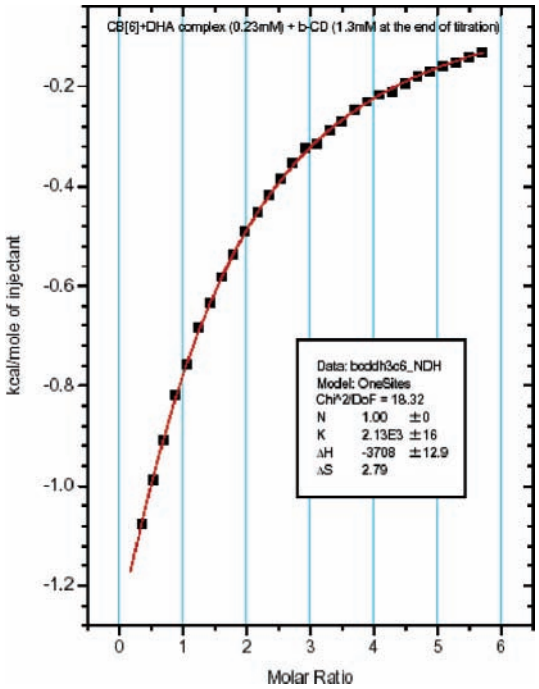

Figure 2. Results of the computer simulation of the ITC titration curve upon formation of the ternary [CB[6]·DHA·β-CD] complex.

structure with one alkyl chain of DHA included in the CB-[6] cavity and the other chain staying in solution is also supported by our NMR study (Supporting Information). It should be noted that the K value for the CB[6]/HA complexation determined in this work (Table 1) is about 2 orders of magnitude larger than that found by Mock[1a] which may be due to the difference in reaction medium (0.05 M NaCl solution (this work) and a 1:1 mixture of formic acid/water[1a]).

ITC experiments revealed no interaction between α-, β-, or γ-CD and $[CB[6]\cdot 2Na]^{2+}$ or $[CB[6]\cdot HA\cdot Na]^{2+}$. We also found no evidence for this type of complexation in our NMR or ESI-MS study. Nevertheless, microcalorimetric titration of a 1:1 mixture of DHA and CB[6] with an α-CD solution revealed moderately strong complexation, leading to a novel 1:1:1 DHA−CB−CD complex (Table 1) with $K = 800\ M^{-1}$, which is about 2 times higher than that for HA ($K = 389\ M^{-1}$; we compare CB[6]−DHA with HA because both have one hexyl chain accessible for CDs). The large negative enthalpy change for the ternary complex formation is readily accountable in terms of strong van der Waals interactions of the second alkyl chain of DHA with the α-CD cavity, leading to conformational restriction of the chain and, thereby, an associated negative entropy change (Table 1). Addition of β-CD into the same CB[6]−DHA mixture leads to formation of an even more stable complex with $K = 2150\ M^{-1}$, which is 33 times higher than that for HA ($K = 65\ M^{-1}$).[7] The $[CB[6]\cdot DHA\cdot\beta\text{-CD}\cdot Na]^{2+}$ complex was unambiguously detected by ESI-MS measurement (Supporting Information).

Because the affinity of straight-chain aliphatic compounds is generally larger for α-CD than for β-CD,[3] the opposite

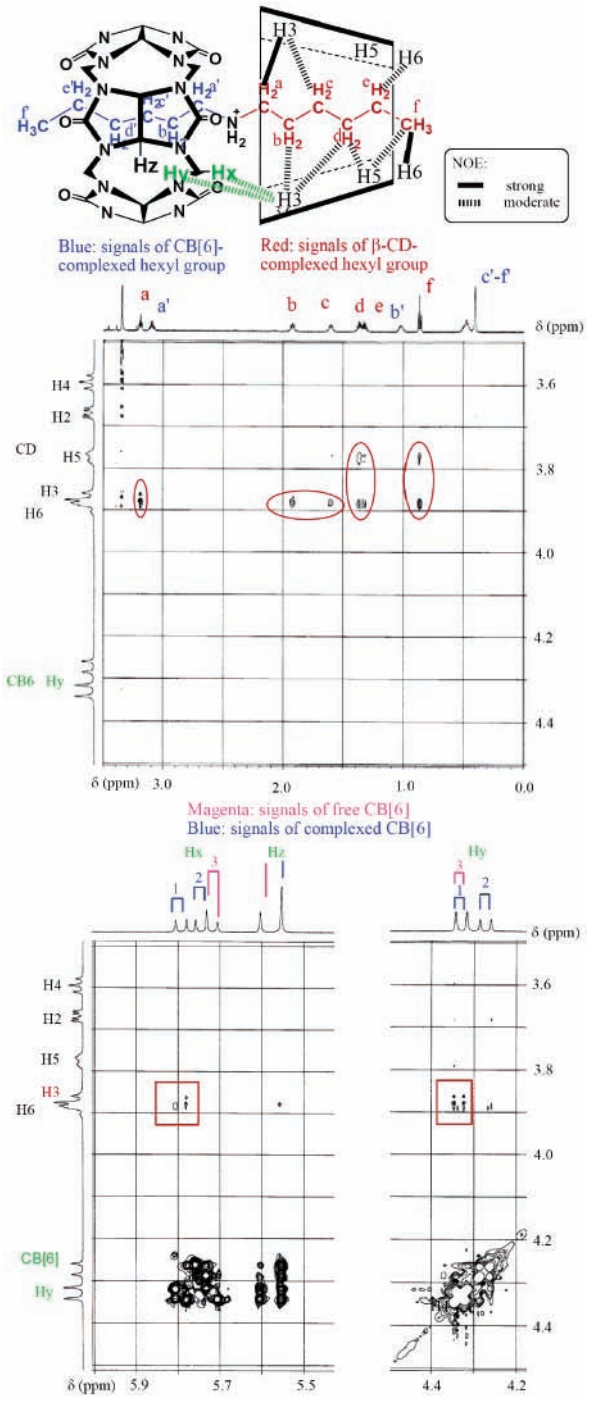

Figure 3. Plausible structure of the ternary [CB[6]·DHA·β-CD] complex (top) elucidated from the NMR study: direct NOE signals observed in ROESY spectra upon formation of the [CB[6]·DHA·β-CD] complex.

preference found in this study needs further rationalization, for which we employed 2D NMR spectroscopy. Upon addition of native α- or β-CD into a solution of $[CB[6]\cdot DHA\cdot Na]^{2+}$ complex, clear NOE cross-peaks were observed between the hexyl protons which originally stayed in the bulk solution and the CD's H3, H5, and H6 protons in the ROESY spectra, demonstrating the deep penetration of this hexyl

group into the CD cavity (Figure 3 and Supporting Information). Interestingly, for β-CD, clear cross-peaks were observed between the CD's H3 and CB[6]'s Hx and Hy protons in the ROESY spectra of the ternary [CB[6]·DHA·β-CD·Na]$^{2+}$ complex (Figure 3 and Supporting Information). The cross-peaks between CB[6]'s and β-CD's protons provide strong evidence for the two macrocycles being closely locating in the ternary complex and suggest multiple point interactions (most likely multiple hydrogen bonds between the OH groups of the CD and the carbonyl groups of CB[6]) leading to strong complexation (Table 1). In contrast, we could not find any cross-peaks between CB[6]'s and α- or γ-CD's protons in the ROESY spectra, which indicates larger CB[6]−CD distances and/or weaker interactions. Thus, the stability of the ternary complex is determined not only by the hexyl−CD interactions but also, and most importantly, by CB[6]−CD interactions, leading to the strongest complex with β-CD. A plausible structure of the ternary [CB[6]·DHA·β-CD] complex is shown in Figure 4.

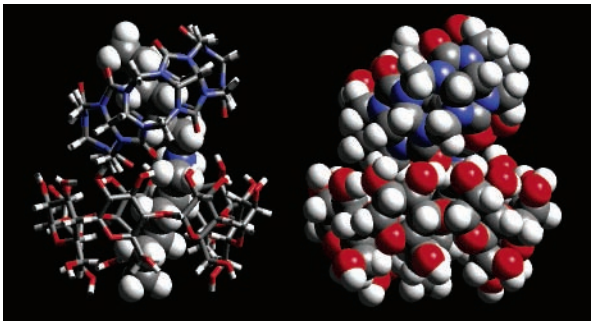

Figure 4. Plausible structure of the ternary [CB[6]·DHA·β-CD] complex constructed according to the NMR study, where DHA's hexyl chains penetrate through CB[6] (top) and β-CD (bottom). Upon complexation, direct NOE signals between H3 protons of β-CD and Hx/Hy protons of CB[6] were observed in ROESY spectra (Figure 3). This structure optimized by MM2 calculations suggests formation of multiple hydrogen bonds between β-CD and CB[6] upon ternary complexation.

The essential difference between the stepwise formation of ternary CB[6]·DHA·CD complexes reported here and the spontaneous formation of guest·2CD complexes should be discussed. It is often reported for some supramolecular systems that only a 1:2 guest−host complex is found in the solution, as exemplified by the solubilization of bicyclo[2.2.2]octane derivatives by α-CD in aqueous solution.[8] This phenomenon, arising from the much higher solubility of the 1:2 complex than that of the 1:1 complex, may apparently look similar to the present system. However, the conventional ternary system is hardly controllable and it is practically impossible to selectively prepare the 1:1 complex or to freely manipulate the concentrations of 1:1 vs 1:2 complexes at the desired levels. Technically, the thermodynamic parameter determination of the individual steps of guest·2CD complexation is extremely difficult.[9] Both of these drawbacks may have been preventing the potential use of the conventional ternary supramolecular systems in nanofabrication. The present ternary system is free from these disadvantages and is easily maneuverable. Nevertheless, it is clear that the present and the conventional ternary supramolecular systems, each possessing its own features, will jointly contribute to the construction of more sophisticated supramolecular architectures.

The facile synergetic formation of the ternary CB[6]−CD−DHA complex through a higher-order complexation of a host−guest complex by another host should be emphasized. This effect is particularly pronounced for the CB[6]·DHA·β-CD complex where the affinity of β-CD toward the single accessible hexyl chain of the CB[6]·DHA complex is 33 times higher than that for the same alkyl chain of HA. This originates from the *supramolecular positive cooperativity*, as the first complexation with a trigger ligand (CB[6]) greatly facilitates the second binding of the target ligand (CD). Previously, such supramolecular positive cooperativity has been recognized and described in detail predominantly in connection with metal ion coordination[10] and some organic systems,[11] whereas we have presented here a new example of the same effect operating in the fully organic ternary CB[6]·DHA·β-CD complex. This is a conceptual analogy of the allosteric effect, which is amply found in many biological systems. We also believe that the concept of supramolecular positive cooperativity is an important key to the construction of sophisticated supramolecular assemblies/architectures/materials of the next generation.

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Supporting Information Available: ESI-MS and 1D/2D NMR spectra of CB[6], CB[6]-DHA, and CB[6]-DHA-CD complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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