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Kinetic vs Thermodynamic Self-Sorting of Cucurbit[6]uril, Cucurbit[7]uril, and a Spermine Derivative

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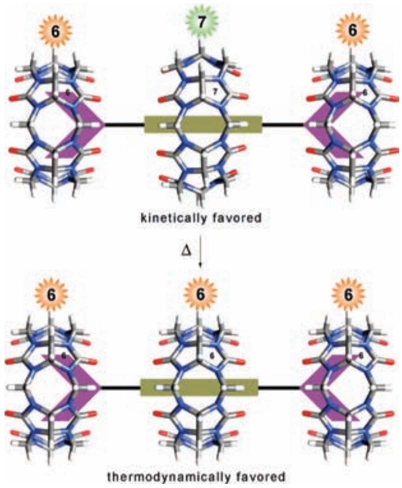
ABSTRACT



Cucurbit[6]-, cucurbit[7]-, and cucurbit[6]uril cavitands can be aligned along a spermine derivative axle in a well-defined, kinetically favored sequence at room temperature, and can undergo a reorganization toward a more stable [4]pseudorotaxane bearing three cucurbit[6]uril units upon thermally induced scrambling.

Living organisms owe their phenotypes, their functionalities, and their survival to the intricate interplay between myriad molecular machines in which self-assembly and self-sorting between various chemical entities (nucleic acids, proteins, etc.) play a crucial and fascinating role.[1] In an ongoing effort toward mimicking natural systems with synthetic structures, chemists have managed to design, synthesize, and evaluate increasingly complex supramolecular assemblies with high-fidelity recognition properties. Recognition has been mainly achieved through selective metal−ligand interactions,[2] hydrogen bonding,[3] hydrophilic and hydrophobic effects,[4] $\pi-\pi$ stacking,[5] and site-selective reversible linkage.[6]

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High-fidelity recognition implies effective discrimination between a set of guests and a set of hosts. Recently, a mixture of eight well-characterized aggregates were found to undergo perfect pairing, with no trace of pair mismatch.[7] Such a remarkable achievement becomes more challenging when targets bearing common properties (such as the shape, the charge distribution, and the hydrophilicity) are deliberately chosen. For example, Schalley et al. managed to build a self-sorting [3]pseudorotaxane incorporating two highly similar crown ethers in a well-defined sequence.[8]

The recognition between molecular units depends on thermodynamic and kinetic parameters.[7,9] In this study, we present the kinetic self-sorting of two similar cavitands, cucurbit[6]- and cucurbit[7]uril (CB[6] and CB[7]), in the presence of a spermine derivative bearing multiple binding sites and its reorganization upon thermal activation toward a different thermodynamically driven self-sorted assembly. While the kinetic vs thermodynamic self-sorting between a pair of cucurbiturils and a pair of guests (i.e., CB[6]•guest 1 and CB[7]•guest 2 vs CB[6]•guest 2 and CB[7]•guest 1 adducts) has been reported in detail by Isaacs et al.,[10] the self-sorting system described herein possesses only one guest, to which CB units bind according to two different well-defined sequences.

Cucurbit[*n*]urils[11] (CB[*n*]) are pumpkin-shaped cavitands obtained from the condensation of *n* glycoluril units and formaldehyde. CB[6] and CB[7] have a common 9.1 Å depth and possess a hydrophobic cavity (5.8 and 7.3 Å, respectively) and two hydrophilic portals which are approximately 2 Å narrower than the cavity.[12] CB[*n*]s incorporate hydrophobic moieties into their cavity; the binding affinity is particularly high (up to 3 × 10^{15} M^{-1}!)[12b] when the hydrophobic unit is connected to a positively charged group, such as an ammonium or a pyridinium, which interacts with the hydrophilic portal through ion−dipole stabilization and hydrogen bonding. Affinities are at their highest when the guest fits tightly into the CB[*n*] cavity.[12c]

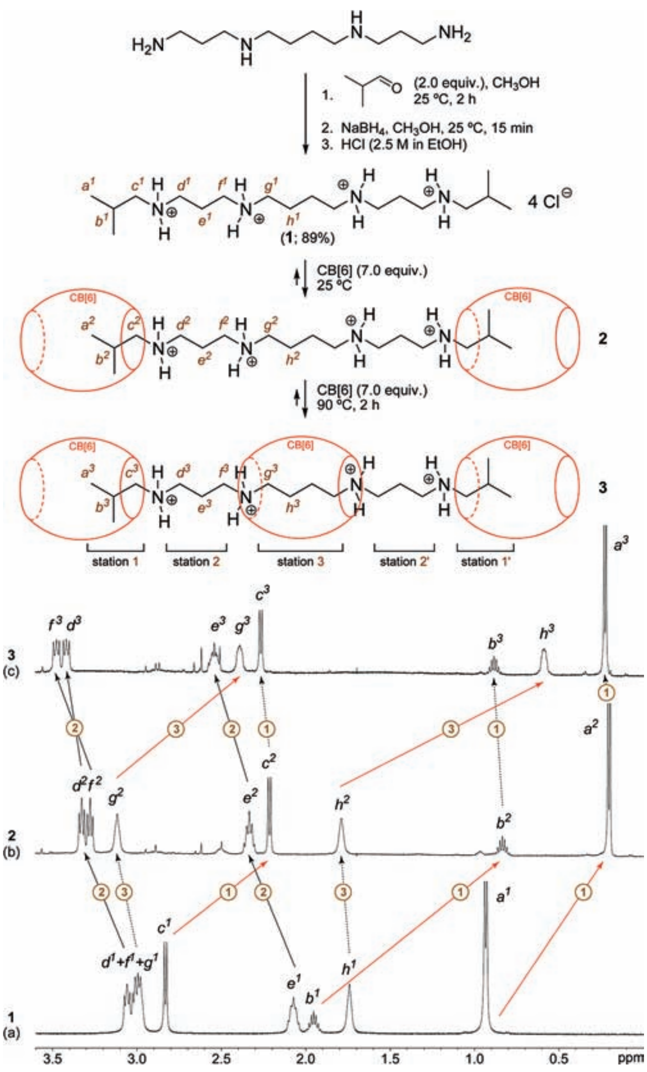

Figure 1. Preparation of spermine derivative **1** and the formation of [3]pseudorotaxane **2** and [4]pseudorotaxane **3** in the presence of CB[6]. ^{1}H NMR spectra of (a) spermine derivative **1**, (b) a mixture of spermine derivative **1** and 7.0 equiv of CB[6] at 25 °C ([3]pseudorotaxane **2** is formed quantitatively), and (c) a mixture of spermine derivative **1** and 7.0 equiv of CB[6] after subsequent heating to 90 °C for 2 h ([4]pseudorotaxane **3** is formed quantitatively). Red arrows emphasize the strong upfield shift caused by the complexation of CB[6] with stations 1, 1′, and 3. Circled numbers in brown indicate the station to which hydrogen atoms at positions *a*−*h* belong. Doublets a^1−a^3 are half-truncated. All measurements were performed in a buffered D_2O solution (pD 8.65), with the residual signal of HDO as the reference signal (δ = 4.70 ppm).

Like various alkylammonium cations,[13] we have found that the isobutylammonium cation binds strongly to CB[6] with

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a slow exchange rate on the nuclear magnetic resonance time scale. Also, its particular shape led us to think that its threading through the CB[6] portal would be particularly energy costly, both in terms of enthalpy and entropy. On the contrary, the threading of isobutylammonium through the larger CB[7] is expected to be a rapid process. Such a plausible selective “filtration” of CB[6] and CB[7] prompted us to design a guest bearing multiple stations for CB[6] and CB[7] and to study its potent self-sorting properties toward these two cavitands.

Commercially available spermine is an ideal polyaminated scaffold that can be further functionalized. Polyammonium salt **1** was readily obtained upon treatment of spermine with 2 equiv of isobutyraldehyde, subsequent reduction with sodium borohydride, and protonation with ethanolic hydrogen chloride (see Figure 1).

In the presence of an excess of CB[6] at 25 °C, spermine derivative **1** interacted with 2 CB[6] units to form [3]pseudorotaxane **2**. The structure of such an assembly can be easily identified by ^{1}H NMR spectroscopy[12a] (see Figure 1, spectra a and b), since (1) hydrogen atoms residing at the core of the CB[*n*] cavitand undergo a strong upfield shift (up to 1.6 ppm);[14a] (2) hydrogen atoms closer to the portal but still inside the cavity of CB are moderately shifted upfield (0.1−0.8 ppm),[14b] and (3) hydrogens outside the cavity undergo a moderate downfield shift (up to 0.7 ppm) that weakens as the distance between the hydrogen and the portal increases.[14c]

Hydrogen atoms at positions *a*, *b*, and *c* undergo the characteristic strong upfield shift upon binding with CB[6] (0.73, 1.12, and 0.62 ppm, respectively), while hydrogens outside the cavitand are shifted downfield moderately (positions *d*, *e*, and *f*; approximately 0.3 ppm). Hydrogen atoms at positions *g* and *h*, albeit remote, are slightly affected by the entering CB[6] units (downfield shifts of approximately 0.1 ppm, see Figure 1, spectra a and b).

Upon thermal activation at 90 °C during 2 h, a CB[6] unit underwent translation to the central butane-1,4-diammonium station (station 3, see Figure 1) and an additional CB[6] encapsulated the terminal isobutyl group (station 1) to form the more stable [4]pseudorotaxane **3**.

Hydrogen atoms at positions *a*, *b*, and *c* are barely affected by the incoming CB[6] unit (downfield shifts of less than 0.05 ppm), while hydrogens at positions *d*, *e*, and *f*, now surrounded by two CB[6] units, undergo a moderate downfield shift (0.10, 0.21, and 0.20 ppm, respectively). Hydrogens at positions *g* and *h* are encapsulated into CB[6] and are strongly shifted upfield (0.72 and 1.20 ppm, see Figure 1, spectrum c).

The two propane-1,3-diammonium sections of spermine derivative **1** (sections 2 and 2′, see Figure 1) could also arguably act as stations for CB[6], although the affinity of 1,3-propanediammonium has been shown to be almost 10^5 times weaker than the affinity of 1,4-butanediammonium toward CB[6] (K_a = 3.3×10^2 and 2.0×10^7 M^{-1}, respectively).[13] If CB[6] happened to be bound to section 2, it would be adjacent to the neighboring CB[6] which encapsulates the isobutyl substituent and would interact with the same NH_2^+ group. Until now, we have not encountered a single case where such an arrangement

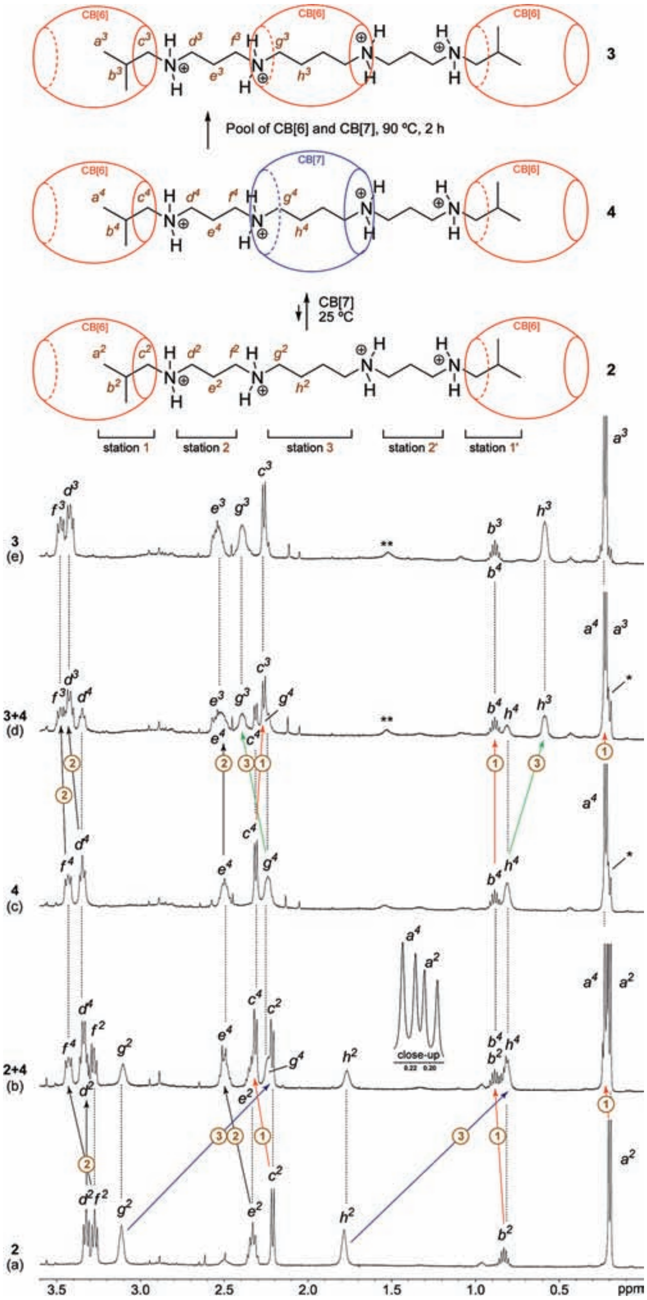

Figure 2. ^{1}H NMR spectra of (a) [3]pseudorotaxane **2** in the presence of 7.0 equiv of CB[6], (b) a 2:3 mixture of [3]pseudorotaxane **2** and [4]pseudorotaxane **4** upon addition of 1.5 equiv of CB[7], (c) [4]pseudorotaxane **4** upon addition of 10 equiv of CB[7], (d) a 1:3 mixture of [4]pseudorotaxanes **4** and **3** upon heating to 90 °C for 15 min, and (e) [4]pseudorotaxane **3** upon heating to 90 °C for 2 h. All measurements performed at 25 °C. Blue arrows emphasize the strong upfield shift caused by the complexation of CB[7] with station 3; red arrows outline the repositioning of CB[6] at stations 1 and 1′ upon encapsulation of station 3 with CB[7] or CB[6]; green arrows indicate the chemical shifts of hydrogens at positions *g* and *h* when the surrounding CB[7] is replaced by CB[6]. Doublets a^2−a^4 are half-truncated. *[4]Pseudorotaxane **4** is contaminated with residual amounts of [3]pseudorotaxane **2** (less than 5%). **For reasons yet to be determined, a broad signal at 1.5 ppm appears when the turbidity of the reaction mixture increases.

occurs. For example, we found that diisobutylammonium chloride binds to one CB[6] unit only, even in the presence of a large excess of CB[6].

The relative affinity of CB[7] compared to CB[6] toward the 1,4-butanediammonium cation was evaluated in a competition experiment and estimated to be at least 10^3 times weaker (no detectable amount of CB[6] could be displaced upon addition of a 10-fold excess of CB[7] to a CB[6]/1,4-butanediammonium complex). A similar result was obtained when comparing the affinity of the isobutylammonium cation with CB[6] and CB[7]. We attribute this relative lack of affinity to the size of CB[7], in which both guests fit loosely.

The self-sorting properties of spermine derivative **1** in the presence of a pool of CB[6] and CB[7] was subsequently studied. Since the affinity of isobutylammonium toward CB[6] is much stronger than toward CB[7], two CB[6] units are expected to bind to the two terminal isobutyl substituents (stations 1 and 1′, see Figure 2). Also, complexation of CB[7] with the butane-1,4-diammonium station 3 is thermodynamically favorable, albeit weakly.

At 25 °C, the terminal isobutyl groups are not bulky enough to prevent CB[7] from slipping toward station 3. Upon consecutive additions of CB[7] to a mixture of spermine derivative **1** and an excess of CB[6], [4]pseudorotaxane **4** was formed at the expense of [3]pseudorotaxane **2** (see Figure 2, spectra a−c). The two terminal CB[6] units thus act as rapidly oscillating valves which allow CB[7] to reach station 3.

^{1}H NMR spectra 2a−c display some remarkable differences upon reorganization from [3]pseudorotaxane **2** to [4]pseudorotaxane **4**. Hydrogens at positions *a*, *b*, and *c* undergo a moderate downfield shift (0.02, 0.06, and 0.10 ppm, respectively), indicating a minor repositioning of CB[6] at stations 1 and 1′. Similarly to [4]pseudorotaxane **3**, hydrogens at positions *d*, *e*, and *f* are now surrounded by two CB units and thus undergo a moderate downfield shift (0.03, 0.17, and 0.16 ppm, respectively), while hydrogen atoms at positions *g* and *h* are strongly shifted upfield (0.87 and 0.98 ppm), due to encapsulation by CB[7]. A 2:3 mixture of pseudorotaxanes **2** and **4** (Figure 2, spectrum b) shows that all equilibria involved in the reorganization process are slow on the NMR time scale. This is consistent with the preliminary observation that the interaction between CB[6] and isobutylammonium is a slow exchange process: in [4]pseudorotaxane **4**, the motion of CB[7] is subjected to the behavior of the two CB[6] valves, and therefore, it must exchange slowly. The reaction mixture containing the kinetically self-sorted [4]pseudorotaxane **4** and the pool of CB[6] and CB[7] was subsequently heated to 90 °C, thus making the terminal isobutyl groups permeable to both CB[6] and CB[7]. Cavitands can therefore rearrange freely along the spermine derivative axle, and the most stable interlocked structure is formed. Since the affinity of butane-1,4-diammonium toward CB[6][13] is at least 10^3 times higher than toward CB[7], [4]pseudorotaxane **4** is converted quantitatively into [4]pseudorotaxane **3** after 2 h at 90 °C (see Figure 2, spectrum e).

Hydrogens at positions *a*−*f* are barely affected by the reorganization from [4]pseudorotaxanes **4** to **3** (shifts between −0.05 and +0.07 ppm, see Figure 2, spectra c−e), while hydrogens at positions *g* and *h* are sensitive to the nature of the surrounding cavitand (+0.15 and −0.22 ppm shifts, respectively, when CB[7] is replaced by CB[6]). It is however difficult to rationalize the downfield shift of hydrogens at position *g* and the upfield shift of the hydrogen atoms at position *h*.

Even such a simple system, bearing two distinctive stations (stations 1 and 3) which can both be targeted by two guests (CB[6] and CB[7]), can adopt up to 18 different equilibrating configurations upon interaction with the guests (i.e., configurations ---, --6, -6-, -66, 6-6, 666, --7, -7-, -77, 7-7, 777, -76, 7-6, 776, -67, 767, 766, and 676, if the occupancy of stations 1, 3, and 1′ is listed consecutively, where - represents a free station and $n = 6$ or 7 a station complexed by CB[*n*]). We showed that when ad hoc stations are chosen, and upon careful optimization of experimental conditions (such as buffer composition, concentration of hosts and guests, temperature, etc.), the intricate interplay between multiple equilibria and complexation rates can be controlled, and a short set of configurations (“676” and “666” in this case) can be obtained selectively.

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Supporting Information Available: Preparation and characterization of spermine derivative **1** and pseudorotaxanes **2**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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