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Cucurbituril Slippage: Translation is a Complex Motion

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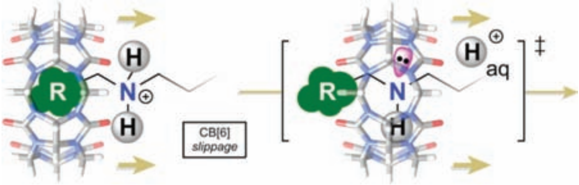
ABSTRACT



The kinetics of cucurbit[6]uril slippage along a polyaminated axle are highly dependent on even minor sterical alterations of the guest. According to in silico experiments, a plausible threading mechanism includes the deprotonation of the ammoniums prior to slippage, their tunneling through the cavitand as neutral amines, and their reprotonation upon exiting cucurbit[6]uril.

Interlocked molecular assemblies are fascinating structures that have generated a great number of theoretical studies and elegant applications in nanoscience. Upon application of an external stimulus, they can undergo specific structural modifications, from the simple translation of a cyclic molecular bead along a linear chain to many more sophisticated motions.[1] Cucurbit[*n*]urils[2] (CB[*n*]) are cavitands bearing a pumpkin-like shape, which can form interlocked structures with adequate guests. All members of the family (i.e., CB[5], [6], [7], [8], and [10]) have a common 9.1 Å depth and possess a hydrophobic, 4.4−13 Å wide cavity, as well as two hydrophilic portals, approximately 2 Å narrower than the cavity.[3] CB[6] (**1**; see Figure 1) can be readily obtained from glycoluril and formaldehyde and can also be functionalized,[4] making it a particularly attractive building block for rotaxane synthesis, since it displays strong affinities toward protonated alkylamines (binding constants up to 3 × 10^9 M^{-1}).[5]

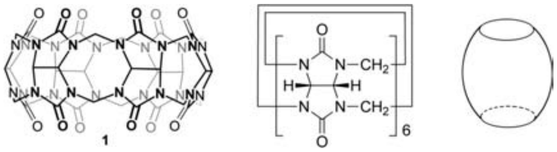


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Figure 1. Structure of CB[6] (**1**). The barrel-like cartoon will be used as a simplified depiction of CB[6] in the next schemes.

A few years ago, Nau et al. reported the mechanism of CB[6] complexation with various alkylammonium salts, involving first an association complex between the ammonium and the carbonylated portal, with the alkyl chain still dangling in the aqueous phase, followed by a “flip-flop”

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(1) For a few recent examples, see: (a) Balzani, V.; Credi, A.; Venturi, M. *Chem. Soc. Rev.* **2009**, *38*, 1542. (b) Lee, C. F.; Leigh, D. A.; Pritchard, R. G.; Schultz, D.; Teat, S. J.; Timco, G. A.; Winpenny, R. E. P. *Nature* **2009**, *458*, 314. (c) Serreli, V.; Lee, C. F.; Kay, E. R.; Leigh, D. A. *Nature* **2007**, *445*, 523. (d) Browne, W. R.; Feringa, B. L. *Nature Nanotechnol.* **2006**, *1*, 25.

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mechanism of the alkyl unit into the CB[6] cavity, using the ion−dipole interaction between the ammonium and the cavitand rim as an anchor.[6] In this study, we decipher the mechanism of the CB[6] translation along a polyaminated axle, which involves the threading of ammonium groups or their corresponding neutral amines through the CB[6] cavity. Although this process has been frequently exploited to design molecular shuttles and other CB-interlocked systems,[7] its mechanism has never been unveiled.

We first prepared a series of N^1,N^6-disubstituted hexane-1,6-diammonium salts **2a−d** and then determined the effect of the N^1-substituents on the slippage rate of CB[6] along this axle. The 3,5-dimethoxybenzyl N^6-substituent acts as a stopper, which forces CB[6] to slip through the N^1-substituent R (see Figure 2).

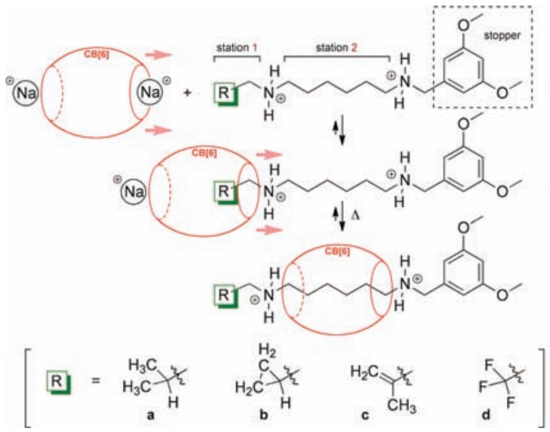

Figure 2. CB[6] slippage through N^1,N^6-disubstituted hexane-1,6-diammonium salts **2** to afford rotaxanes **4**, via pseudorotaxanes **3**.

Since CB[6] displays good affinity toward primary alkyl ammonium cations ($K_a = 10^5 - 10^6$ M^{-1}, see Table 2), the first intermediates in the slippage mechanism are pseudorotaxanes **3a−d**, which undergo subsequent translation to rotaxanes **4a−d** upon thermal activation (see Figure 2). Sodium cations present in the reaction mixture are consecutively ejected from the CB[6] portal, as reported in previous studies.[3a,5a] The slippage process was found to follow first-order kinetics, since (1) the fast equilibrium between CB[6], diammonium salts **2**, and pseudorotaxanes **3** is totally shifted toward the interlocked structures ($K_a > 10^5$ M^{-1}) and (2) the reverse reaction from rotaxanes **4** to intermediates **3** is negligible; this approximation is valid since the affinity of CB[6] toward station 2 (see Figure 2) was found to be at least 10^2 times greater than toward station 1 (the affinity of CB[6] for hexane-1,6-diammonium is 2.9 × 10^8 M^{-1}, compared to 10^5−10^6 M^{-1} for primary alkylammonium cations R-$CH_2NH_3^+$).[5a] CB[6] slippage was carried out in the presence of sodium cations (50 mM) under various pD conditions using adequate buffers (pD 0−12), and the reaction rates were found not to depend on pD values, suggesting that the same mechanism takes place regardless of the acidity of the solution. Interestingly, the various counteranions associated with the different buffer compositions did not affect the slippage rates significantly.

While the structure of reactants **3** and products **4** can be readily determined by ^{1}H NMR spectroscopy,[7] the nature of the slippage transition state(s) remains unclear. Although the threading of the protonated ammonium guest through CB[6] (see pathway 1, Figure 3) first comes to mind, we also consider an alternate process, involving (1) the “intrarotaxanic” deprotonation of the ammonium cation by the carbonyl portal of CB[6], followed by acid−base equilibrium with the aqueous medium, (2) the slippage of the neutral amine through the CB[6] cavity, and (3) the fast protonation of the opposite CB[6] carbonyl followed by the reprotonation of the amine guest (see pathway 2, Figure 3). As reported previously,[7b−d] CB[6] *can* readily shuttle over neutral amines under basic conditions; however, it remains unknown whether the amine *must* be neutral in order to allow slippage, regardless of pH conditions. Also, in both protonated and neutral processes, water molecules may be incorporated into CB[6] during slippage, or the cavitand may shield the axle from external aqueous solvation completely. This solvation issue is of tremendous importance when discriminating between a threading process along a neutral or a positive axle, since the solvation of a dialkylammonium cation amounts to 60 kcal/mol, and only to 4 kcal/mol when it is deprotonated, a 56 kcal/mol difference![8]

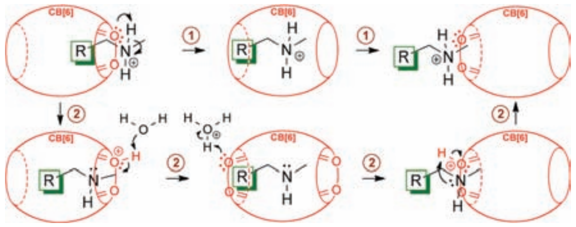

Figure 3. Two slippage pathways: (1) threading along an ammonium cation; (2) deprotonation of the ammonium, threading along the neutral amine, and subsequent reprotonation.

Experimental evidence for either one of these mechanistic pathways is unfortunately not available, especially since neither dialkylammonium cations nor neutral dialkylamines have ever been found to undergo encapsulation by CB[6], contrary to some tetraalkylammonium cations which interact with CB[7],[9a] as well as cyclen and cyclam tetrahydrochloride which can be encapsulated by CB[8].[9b] In order to discriminate between pathways 1 and 2, we designed in silico mimetics of both transition states by forcing CB[6] to encapsulate (1) a dialkylammonium cation (assembly **5a**, see Figure 4), (2) the same cation in the presence of *n* water

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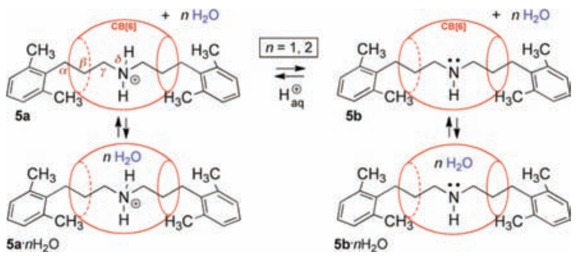

Figure 4. Mimetic structures of plausible transient complexes along the slippage pathway.

molecules (rotaxane **5a**·nH_2O), (3) the corresponding neutral amine **5b**, and (4) the neutral amine and n water molecules (assembly **5b**·nH_2O), and we determined the relative stabilities $\Delta\Delta G_r$ of these interlocked systems relative to rotaxane **5a** (see Table 1, entry δ) using the B3LYP density functional method with the 6-31G(d) basis set, as recently applied to CB[n]-interlocked structures.[10]

Table 1. Stabilities $\Delta\Delta G_r^0$ of Assemblies **5a**·H_2O, **5a**·$2H_2O$,**5b**,**5b**·H_2O, and **5b**·$2H_2O$, Relative to Rotaxane **5a**[a]

amine position[b]	**5a**·$2H_2O$[c]	**5a**·H_2O[c]	**5a**	**5b**	**5b**·H_2O[c]	**5b**·$2H_2O$[c]
β			0	+22[d]		
γ	–[e]	+21	0	−0.5	+19	–[e]
δ	+36[f]	+14	0	−7.2	+9.4	+39
δ,noCB			0	−40		

[a] In kcal/mol; a negative value indicates a more stable assembly than rotaxane **5a**. [b] See Figure 4. [c] Water molecules are encapsulated into CB[6] together with the organic guest. [d] An even higher value is probable, since the NH_2^+ unit of assembly **5a** sits at the CB[6] periphery and may be stabilized by solvent contact. [e] Calculation did not converge or water molecules were expelled from the cavity. [f] Only one water molecule interacts with the ammonium unit.

Terminal m-xylenes are used as stoppers to prevent the dislocation of the unfavorable complexes, and do not exert any particular sterical pressure on CB[6]. The amine function at position δ (see Figure 4) was subsequently switched with neighboring carbon atoms (positions β and γ), and the stabilities of the solvated and unsolvated amines and ammonium salts were determined again. Relative stabilities $\Delta\Delta G_r^\circ$ of assemblies **5** relative to rotaxane **5a** were determined using the standard Gibbs free energy of these systems in the gas phase, the free energy of the proton (−6.3 kcal/mol),[11a] its solvation energy (−266.1 kcal/mol),[11b] and the free energy of water in water calculated using the SMD solvation model.[11c] We used gas-phase energies of assemblies **5** with no additional correction for solvation, since CB[6] is expected to shield its guests from the solvent regardless of the nature of the guests: the solvation energies of all assemblies **5** are thus considered to be equal, and therefore cancel each other.

Although one should consider values obtained in silico with utmost care, especially for such large supramolecular assemblies, the results in Table 1 suggest that (1) CB[6] provides its guests with some solvation. Indeed, the energy cost for the heterolytic NH cleavage of a secondary ammonium salt in aqueous medium amounts to approximately +15 kcal/mol (since the pK_a of a dialkylammonium salt is approximately 11);[8] if the proton were solvated, but both the neutral amine and its protonated form were totally shielded from the solvent, the energy balance would be reversed to −41 kcal/mol,[8] and the neutral species would be greatly favored (in perfect accordance with calculations; see entry "δ, no CB" in Table 2: the nonsolvated neutral dialkylamine is favored by 40 kcal/mol over its protonated counterpart). However, the neutral rotaxane **5b** and its solvated proton are not favored by more than 7.2 kcal/mol, indicating some solvation from CB[6], or some adverse sterical or electronic interactions when CB[6] encapsulates the neutral amine. (2) Incorporating water molecules into the CB[6] cavity in an attempt to better solvate the ammonium salt or the amine is unfavorable and leads to significant distortion of the cavitand, regardless of the position of the amine along the axle and the number of water molecules added. (3) The axle is protonated when the amine function sits at the CB[6] portal (when the nitrogen atom is located at the β position, the positive form is at least 22 kcal/mol more stable than its neutral counterpart), due to favorable ion-dipole interactions. (4) The ammonium group undergoes deprotonation when it enters the CB[6] cavity, since the neutral rotaxane **5b** becomes gradually more favorable when the nitrogen atom moves toward the core of the cavitand (from −0.5 down to −7.2 kcal/mol). These results support pathway 2 (see Figure 3) as the valid slippage mechanism and are corroborated by the observation of a constant slippage rate between pD 0 and 12 (an encapsulated neutral amine favored by 7.2 kcal/mol corresponds to a pK_a of −5.3 for the virtual encapsulated ammonium!) The mechanism is therefore not supposed to change when the pH of the solution is much greater than −5.3 but lower than the pK_a of pseudorotaxanes **3**, which have been found to be greater than 13 (i.e., between 1 and 2 pK_a units higher than free ammoniums **2**, due to the stabilization of the protonated species by the CB[6] carbonylated portal).[6a,12]

The effect of the N^1-substituent on the slippage process was subsequently assessed by ^1H NMR (see Figures 5a−c). The translation rates were determined at various temperatures

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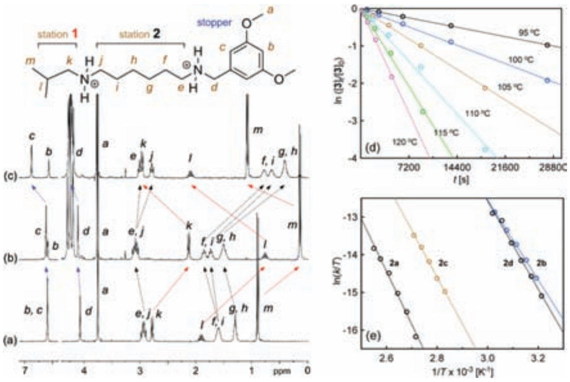

Figure 5. ^{1}H NMR spectra of (a) guest **2a**, (b) pseudorotaxane **3a**, and (c) rotaxane **4a**. (d) Linear regressions confirming a first-order mechanism. (e) Eyring plot describing the threading of CB[6] along axles **2a−d**.

and the activation enthalpy $\Delta H^{\ddagger}$, entropy $\Delta S^{\ddagger}$, and Gibbs energy $\Delta G^{\ddagger}$ were calculated using the Eyring equation by plotting $\ln(k/T)$ versus $1/T$, where k is the translation rate constant at temperature T (Figure 5d,e). $\Delta H^{\ddagger}$ can be obtained from the slope of the best straight line, and $\Delta S^{\ddagger}$ from its intersection with the y-axis. This method has been used successfully in previous studies dealing with the kinetics of rotaxanic motions.[13]

Interestingly, approximately isosteric N^1-substituents were found to affect the translation rate of CB[6] along the diammonium axle very differently. The half-life of pseudorotaxanes **3** (CB[6] at station 1) at 100 °C varies between a few seconds, when CB[6] has to slip over a cyclopropyl group, to more than 3 h when isopropyl is the substituent (see Table 2). Changes in slippage enthalpies were found to mirror variations in Gibbs free energies for all substituents. Slippage enthalpies are usually correlated with the size of the threading substituent,[13a,b] and this study is no exception. Since numerical data describing the size of all substituents **a−d** (such as *A* values or Taft steric parameters E_s) are not available, we computed them using the B3LYP/6-31G(d) method and an isovalue of 0.002 (i.e., electrons are found inside the volume boundaries with a 99.8% probability, see Table 2).

Table 2. Thermodynamic and Kinetic Parameters of the CB[6] Slippage Process along Axles **2a−d**^{a}

R	$K_a{}^b$	V^c	$t_{1/2}{}^d$	$\Delta G^{\ddagger e}$	$\Delta H^{\ddagger f}$	$\Delta S^{\ddagger g}$
a	5.4×10^5	70	3.2 h	28.9 ± 1.6	27.9 ± 1.3	-3 ± 3
b	1.1×10^6	63	2.4 s	23.7 ± 0.5	21.1 ± 0.4	-9 ± 1
c	1.8×10^5	66	4.0 min	26.8 ± 0.9	24.7 ± 0.7	-7 ± 2
d	1.1×10^5	47	19 s	24.0 ± 1.4	23.2 ± 1.1	-3 ± 3

[a] Determined in the presence of sodium chloride (50 mM). [b] Binding affinity of ammonium cations R-CH$_2$NH$_3^+$ toward CB[6] (M^{-1}). [c] Volume of hydrocarbon R-H (Å^3), calculated at the 6-31G(d) level with an isovalue of 0.002. [d] Half-life of pseudorotaxanes **3** at 100 °C. [e] Gibbs free activation energy of the slippage process (kcal/mol). [f] Activation enthalpy (kcal/mol). [g] Activation entropy (cal/mol·K).

Smaller groups lead to lower activation enthalpies, with the exception of the trifluoromethyl substituent **d**, which causes an unusually high slippage barrier; this anomaly is attributed to the repulsion between the lone pairs of the three fluorine atoms and of the CB[6] carbonyl oxygens at the cavitand rim. We conclude that the rate of CB[6] slippage is exceptionally sensitive to minor sterical variations between substituents, which not only can affect their ability to cross the CB[6] portal but also may induce a repositioning of the nitrogen atom threading through the opposite carbonylated rim. Such a readjustment could significantly alter the energy of the transition states and the slippage rates.

Rationalizing the variations in slippage entropy is more difficult, and extra caution should be applied because of the error associated with this parameter when determined on an inevitably narrow temperature range. All entropies were found to be consistently negative, although the displacement of the coordinating sodium cation from the CB[6] portal of pseudorotaxanes **3**, and the ejection of solvent molecules from the cavitand, are expected to be entropically favorable processes.[5a] The slippage of substituents **a−d** through the CB[6] portal and the incorportion of the amine into its cavity should constrain rotational freedom, distort CB[6], and induce a decrease in activation entropy, which is significant enough to counterbalance all entropic gains.

In addition to unveiling the complexity of a seemingly elementary translational motion, we hope that this study can inspire the design of new CB[n]-containing time-dependent molecular machines for controlled release applications.

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Supporting Information Available: Preparation and characterization of axles **2**, pseudorotaxanes **3**, and rotaxanes **4**; kinetic procedures; coordinates and thermodynamic parameters of rotaxanes obtained in silico. This material is available free of charge via the Internet at http://pubs.acs.org.

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