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Cucurbituril Slippage: Cations as Supramolecular Lubricants

Xiaoxi Ling and Eric Masson*

Department of Chemistry and Biochemistry, Ohio University, Athens, Ohio 45701, United States

masson@ohio.edu

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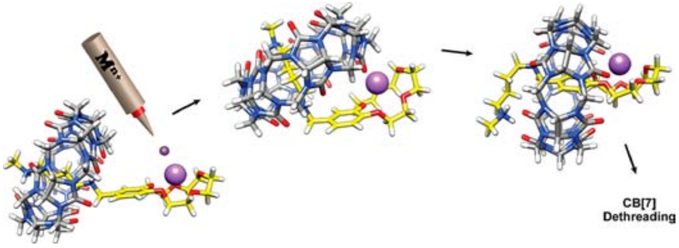
ABSTRACT



The dethreading rate of a polyaminated axle flanked by two benzo-15-crown-5 stoppers from the cavity of Cucurbit[7]uril (CB[7]) was enhanced by up to 500 times in the presence of aqueous metallic and organic cations. Cations likely stabilize the highest energy transition state of the dethreading process by interacting with both crown ether and CB[7] units.

Lubricants are used on mechanical devices to reduce friction between moving parts, to protect the devices and to increase energy efficiency. While nanoscale devices capable of performing molecular motions have been generating tremendous interest for the past two decades,[1] little attention has been paid to the alteration of the rates of these motions with additives that would interact with the different parts of the devices. At a molecular level, Shimizu and co-workers showed very recently that the rotation along the $C_{aryl}-N$ bond of an *N*-(quinolin-8-yl) imide rotor could be enhanced 10^7-fold upon application of a “proton grease”, i.e. upon protonation of the quinoline unit.[2] In this study, we define as “supramolecular lubricants” species that promote the threading or the dethreading of organic axles through cyclic units, and show that metallic and organic cations (the lubricants) can enhance the dethreading rate of a polyaminated axle flanked by two crown ether units through the cavity of Cucurbit[7]uril (CB[7]).[3] The mechanism is reminiscent of the easier removal of a stuck ring once soap has been applied to the finger knuckle.

Axle **1** (see Figure 1) was prepared by reductive amination of 1,4-butanediamine and 4′-formylbenzo-15-crown-5 and could slip through CB[7] to form [2]pseudorotaxane **1**•CB[7] in an aqueous medium. A few years ago, Fedorova and Isaacs had shown that an axle bearing 15-crown-5 stoppers could thread CB[7];[4] therefore it was no surprise that CB[7] could reach the central station of guest **1**. The rationale behind the design of this axle was the likely affinity between its crown ether stoppers and various alkali and alkali-earth cations that may affect dethreading rates through CB[7].

Due to the simplicity of its ^{1}H NMR signal and its very high affinity toward CB[7], we opted for *p*-xylylene diammonium dichloride (**2**) as the competing guest to extract CB[7] out of axle **1**. Dethreading was readily monitored by following the ^{1}H NMR signals of the central 1,4-butane station, whose hydrogen nuclei undergo strong downfield

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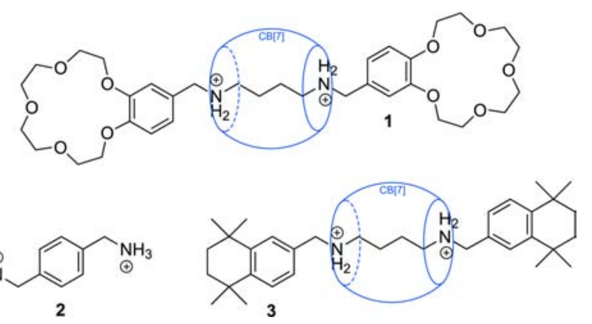

Figure 1. Structure of [2]pseudorotaxanes **1**•CB[7] and **3**•CB[7]; competitive guest **2**.

shifts upon CB[7] release (0.73 and 0.84 ppm). As expected, dethreading of [2]pseudorotaxane **1**•CB[7] followed pseudo-first-order kinetics, since the ingression of competitive guest **2** into CB[7] is much faster than the egression of axle **1**. Although the dethreading and guest exchange processes are under thermodynamic control, the difference in CB[7] affinity between *N*-substituted 1,4-butane and *p*-xylylene diammonium derivatives is so large (approximately 10^3-10^4 M^{-1})[5] that dethreading can be safely considered as irreversible. However, pseudo-first-order kinetics do not imply that the formation of free CB[7] and free axle **1** (or exclusion complexes between both units) is a single-step mechanism; in fact, we propose the existence of at least one intermediate, when CB[7] is sitting between the crown ether stopper and its neighboring ammonium unit (see assembly **1**•CB[7]^{crown} in Figure 2). We will show later that the highest energy transition state of the dethreading process is likely the one leading to the formation of intermediate **1**•CB[7]^{crown}. Half-lives of assembly **1**•CB[7] ranged from 4.3 h at 80 °C to 65 h at 50 °C (corresponding to dethreading rates of 4.5×10^{-5} and 3.0×10^{-6} s^{-1}, respectively). As shown on previous occasions by our group[6a] and others,[6b,c] the enthalpy and entropy of activation of the dethreading process could be obtained by using the Eyring equation and by plotting $\ln(k/T)$ versus $1/T$, where k is the dethreading rate constant at temperature T (see Figure 2a). An activation enthalpy of 19.5 (±0.1) kcal/mol was obtained from the slope of the regression line, and a very negative activation entropy of −23.4 (±0.2) cal/mol·K was calculated from its intersection with the y-axis, thereby affording a 26.5 (±0.1) kcal/mol free energy of activation for the dethreading process at 25 °C. The negative activation entropy is likely caused by significant rotational and confirmational constraints of the crown ether stopper upon entering the cavity of CB[7].

The kinetics of the dethreading process were then monitored in the presence of alkali and alkali-earth cations (0.10 M) as well as cadmium and ammonium (0.10 M) and in a 0.10 M solution of deuterium chloride. Unexpectedly, the dethreading rate of [2]pseudorotaxane **1**•CB[7] was *enhanced* by 500 times in the presence of Ba^{2+} and 90 times with K^+ (see Table 1 and Figure 2b)! A 260-fold rate increase was also observed in "saline" solution (2.1×10^{-4} s^{-1}), compared to deionized D_2O at body temperature (37 °C; 7.8×10^{-7} s^{-1}, rate extrapolated using the Eyring equation; see Figure 2a).

Table 1. Rates of [2]Pseudorotaxane **1**•CB[7] Dethreading Triggered by Competitive Guest **2**[a]

M^{n+}	r [Å] [b]	k [s^{-1}]	M^{n+}	r [Å] [b]	k [s^{-1}]
Li^+	0.78	2.93 (± 0.08) × 10^{-5}	– [c]		2.97 (± 0.28) × 10^{-6}
Na^+	0.98	2.69 (± 0.07) × 10^{-4}	Mg^{2+}	0.78	1.00 (± 0.10) × 10^{-4}
K^+	1.33	2.88 (± 0.11) × 10^{-4}	Ca^{2+}	1.06	1.49 (± 0.05) × 10^{-3}
Rb^+	1.49	1.09 (± 0.01) × 10^{-4}	Sr^{2+}	1.27	9.11 (± 0.14) × 10^{-4}
Cs^+	1.65	1.42 (± 0.05) × 10^{-4}	Ba^{2+}	1.43	1.48 (± 0.10) × 10^{-3}
Cd^{2+}	1.09	1.96 (± 0.06) × 10^{-5}	D^+		1.06 (± 0.03) × 10^{-5}
NH_4^+	1.61 [d]	4.77 (± 0.08) × 10^{-5}	Na^+ [e]	0.98	2.26 (± 0.09) × 10^{-4}

[a] Dethreading experiments carried out in the presence of MCl_n (0.10 M), [2]pseudorotaxane **1**•CB[7] (1.0 mM), and competitive guest **2** (1.0 mM) in D_2O at 50 °C, unless specified otherwise. [b] Cation radii from ref 7, unless noted otherwise. [c] In pure D_2O. [d] Ill-defined radius, based on ref 8 and an average coordination number of 6. [e] In "saline" solution (9.0 g/L NaCl ≈ 0.15 M in D_2O) at 37 °C.

To confirm the importance of the benzo-15-crown-5 stoppers in the cation-promoted rate enhancements, we prepared control [2]pseudorotaxane **3**•CB[7], whose stoppers (1) do not bear polyethylene glycol substituents or heteroatoms and are thus unlikely to interact with metallic cations albeit perhaps via cation−π interactions, (2) are bulky enough to allow the slow ejection of CB[7] in the presence of competitive guest **2**, and (3) do not significantly complicate ^1H NMR spectra used in kinetic studies. Dethreading experiments were carried out at 135 °C in the absence and presence of sodium chloride (0.10 M), and similar exchange rates were obtained in both cases (3.0×10^{-6} vs 3.6×10^{-6} s^{-1}, respectively). We can thus conclude that (1) cation−π interactions do not play a significant role in rate enhancements observed with assembly **1**•CB[7] and (2) the crown ether stoppers are key units in the cation-promoted dethreading process.

Four observations can be readily made when deciphering a plot of the dethreading rate constants vs the ionic radii of the cations (see Figure 2b): (1) at similar ionic radii, divalent ions display stronger rate enhancing effects than monovalent cations (an approximately 3−5-fold difference); (2) at least in the case of alkali and ammonium cations, a bell-shaped trend is observed, with optimal radii ranging from 1.0 − 1.3 Å; small cations such as Li^+ or the bulkier ammonium are much less efficient at promoting dethreading; (3) the soft Lewis acid Cd^{2+}, albeit doubly charged with an optimal radius similar to Ca^{2+}, causes a much milder enhancing effect compared to all other hard Lewis acid cations; (4) contrary to other cations, D^+ has a minimal impact on the dethreading rate of complex

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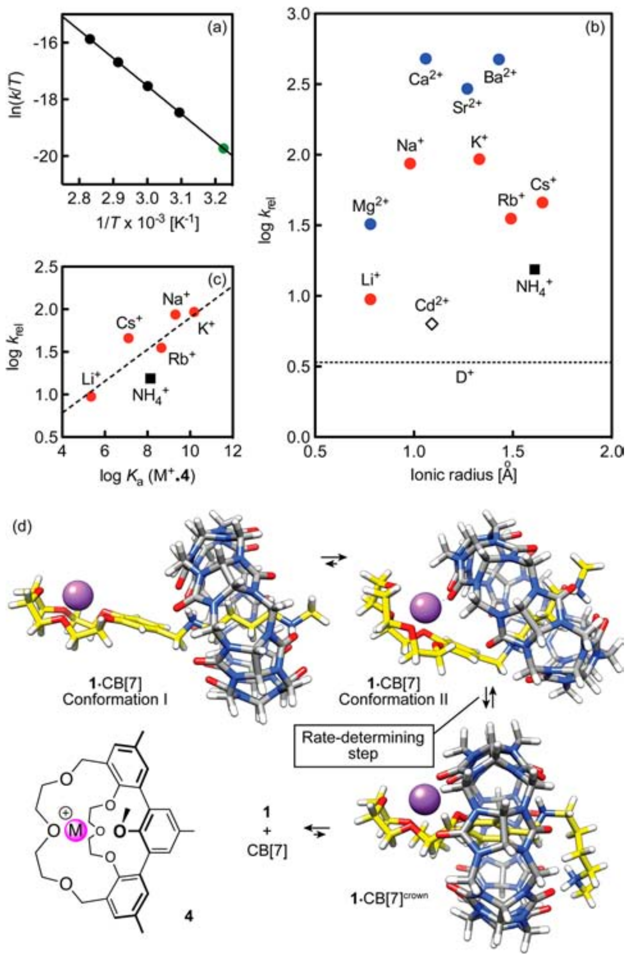

Figure 2. (a) Eyring plot describing the dethreading of axle **1** from [2]pseudorotaxane **1**•CB[7] at 50, 60, 70, and 80 °C (black dots); extrapolation to 37 °C (green dot). (b) Logarithmic plot of the dethreading rate constants k_{rel} as a function of the radius of the added cations; rates relative to the dethreading in the absence of cations. (c) Correlation between dethreading rate constants k_{rel} and the binding affinities of hemispherand **4** toward various cations in D_2O-saturated chloroform-*d*. (d) A plausible "lubricated" dethreading pathway: cations (Na^+, for example; violet sphere) stabilize intermediate **1**•CB[7]$^{\mathrm{crown}}$ and the transition state leading to its formation, to a greater extent than [2]pseudorotaxane **1**•CB[7] (conformation II, and a fortiori, conformation I), thereby favoring CB[7] egression. CB[7] carbon atoms in gray, axle carbons in yellow. Structures optimized at the B97-D/SVP level; the second, likely inert benzo-15-crown-5 stopper of axle **1** has been replaced by a hydrogen atom, to limit the total number of conformations, and to shorten optimization time; solvent molecules omitted.

1•CB[7] (a 3.3-fold acceleration compared to a neutral medium; see Figure 2b).

In order to rationalize this "lubricating" effect of cations, one should assess their stabilizing impact on complex **1**•CB[7] during the translation of the macrocycle. Alkali cations display a weak affinity toward benzo-15-crown-5 in an aqueous medium (approximately 2.4 M^{-1}, with insignificant differences between the cations);[9] thermodynamic data for alkali-earth cations are only available in the case of Ba^{2+}, with a binding affinity of 9.1 M^{-1}.[10] Therefore, only a fraction of [2]pseudorotaxane **1**•CB[7] is expected to interact with the metallic cations (approximately 19%), if CB[7] does not affect alkali recognition, and the affinity of these cations toward complex **1**•CB[7] is comparable to their affinity for benzo-15-crown-5[11] (see conformation I in Figure 2d; second, likely inert benzo-15-crown-5 stopper omitted). However, CB[7] could also interact with the cations via a fraction of its carbonyl oxygens and impose a significant distortion to axle **1** (see conformation II, Figure 2d). This structure is likely, especially since most metallic cations do not actually sit above the center of CB[*n*] portals when interacting with these macrocycles.[12] Although in silico stabilities should be considered with utmost care, especially with such large assemblies, conformation II may be more stable than conformation I in the presence of Na^+ by up to 16 kcal/mol in an aqueous medium (structure optimizations were carried out with the B97D functional and SVP basis sets, single-point energy calculations with TZVPP basis sets,[13] and vibrational and solvation analysis at the B3LYP/6-31G(d) level using the SMD[14] solvation model). Also, Fedorova and Isaacs recently reported the formation of a ternary complex between Hg^{2+}, CB[7], and a dithia-dioxa-monoaza-15-crown-5 macrocycle, whose likely structure bears a striking resemblance to conformation II. The authors showed that CB[7] cooperated to enhance Hg^{2+}-binding to the macrocycle by 25-fold.[15] Regardless of the exact structure of [2]pseudorotaxane **1**•CB[7], the crown ether and CB[7] units in intermediate **1**•CB[7]$^{\mathrm{crown}}$ should form tighter complexes with cations, since both units are well positioned to participate in their stabilization (see Figure 2d); it is thus very likely that this improved cooperativity from CB[7] also stabilizes the high-energy transition state leading to the formation of intermediate **1**•CB[7]$^{\mathrm{crown}}$.

The rate enhancement of the CB[7] translation is then directly linked to the difference in cation affinity between

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assembly **1**•CB[7] (conformation II) and the transition state resembling and preceding intermediate **1**•CB[7]^{crown}. Interactions between cations and assembly **1**•CB[7] were too weak to be measured by NMR spectroscopy or isothermal titration calorimetry; moreover, the high concentrations of salts (up to 1.0 M) used in titrations triggered dethreading and prevented us from determining any relevant binding affinities. For lack of a quantitative assessment, we will neglect cation interactions with assembly **1**•CB[7] and assume that dethreading rate enhancements are mostly due to the stabilization of the transition state resembling intermediate **1**•CB[7]^{crown}. We propose that in the presence of large cations (Rb^+, Cs^+, $NH_4{}^+$), which are perched above the crown ether ring,[16] optimal CB[7] cooperativity in the stabilization of the 15-crown-5/metal adduct takes place before the key transition state of the dethreading process (i.e., when CB[7] is closer to the 1,4-butane diammonium central station); in the presence of Na^+ and K^+, CB[7] cooperativity is optimal at the transition state, and with small cations such as D^+, Li^+, which nest inside the crown ether unit,[16] optimal, yet weak CB[7] stabilization occurs after the transition state. These considerations are consistent with the observed bell-shaped trend between dethreading rates and the ionic radii of alkali metals (see Figure 2b). This trend is also reminiscent of a similar sequence observed with binding affinities of alkali metals toward hemispherand **4**[17] that resembles intermediate **1**•CB[7]^{crown} (see Figure 2; the crown ether-like unit and the overlooking *p*-methyl anisole in host **4** mimic the benzo-15-crown-5 stopper and one glycoluril section of CB[7] in intermediate **1**•CB[7]^{crown}, respectively). In fact, a logarithmic plot of dethreading rate constants from [2]pseudorotaxane **1**•CB[7] vs the binding affinities of macrocycle **4** toward ammonium and alkali cations (in chloroform-*d* saturated with D_2O) shows a significant level of linearity (see Figure 2c). A major structural difference between both systems is of course the movability of CB[7] along its axle to better adapt to the cations, compared to the steadier *p*-methyl anisole unit in host **4**.

As shown in Figure 2b, dethreading is faster in the presence of alkali-earth cations compared to alkali metals; this effect is likely due to (1) stronger Coulombic interactions with both crown ether and CB[7] units and (2) a higher entropy gain associated with the desolvation of the cations upon binding.[7]

Coordination of the metallic cations may also affect the dethreading rate of [2]pseudorotaxane **1**•CB[7]: a horizontal view of Figure 2b shows (1) poor rate enhancements with Li^+, whose coordination number is often four,[18a] and with $NH_4{}^+$, which is commonly surrounded by an ill-defined coordination shell of 4 to 11 ligands;[8,18b] (2) intermediate rates for the remaining alkali metals and Mg^{2+}, which are prone to hexacoordination;[7] and (3) fast rates with Ca^{2+}, Sr^{2+}, and Ba^{2+}, which often interact with eight ligands.[7,18c] In the latter case, CB[7] would provide the metallic cation with up to three coordination sites in addition to the benzo-15-crown-5 stopper and, hence, further stabilize the key transition state of the dethreading process.

Finally, despite a doubly positive charge and a radius similar to that of Ca^{2+}, Cd^{2+} has only a minor enhancing effect on dethreading rates (6.3-fold compared to a cation-free environment, 74 times weaker than Ca^{2+}). Contrary to alkali and alkali-earth metals, Cd^{2+} is a soft Lewis acid; it is thus expected to interact weakly with the hard oxygen ligands of the benzo-15-crown-5 and CB[7] units.[19] Furthermore, at a concentration of 0.10 M, cadmium is present as a mixture of Cd^{2+}, $CdCl^+$, $CdCl_2$, and possibly $CdCl_3{}^-$;[20] the low concentration of Cd^{2+}, and possible repulsion between the carbonyl portal of CB[7] and the chloride ligand of crown ether-bound $CdCl^+$, may also contribute to the slow dethreading process.

In conclusion, we found that metallic and organic cations can be applied as "supramolecular lubricants" to facilitate the translation of macrocycles along organic axles, as long as the cations stabilize the highest energy transition state of the dethreading process better than the stable interlocked assemblies. Key factors include the radius, valence, coordination number, and hardness of the cations, as well as the exact location of the transition state along the dethreading pathway. To the best of our knowledge, this study constitutes the first case of a mechanical motion between two interlocked structures facilitated on-demand by a third molecular partner.

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Supporting Information Available. Preparation and characterization of axles **1** and **3**, and their CB[7]-interlocked assemblies; kinetic and computational procedures; coordinates of assemblies shown in Figure 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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