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Precise rate control of pseudo-rotaxane dethreading by pH-responsive selectively functionalized cyclodextrins

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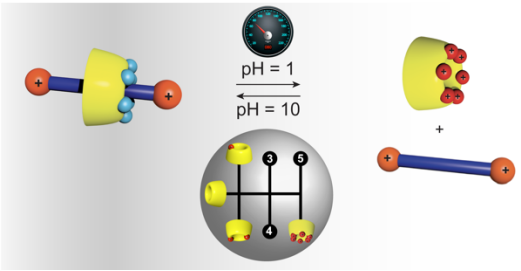
Supporting Information Placeholder



ABSTRACT: A family of cyclodextrins functionalized with zero, one, two or six amines was shown to control the rate of their threading and dethreading on a molecular axle depending on the pH and their substitution pattern. The originality of this system lies in the rate control of the switch by operating the stimulus directly on the macrocycle.

The ability to control motion at the molecular scale is key to build Feynman's famous "tiny machines with movable parts".[1] An essential element for the development of these molecular machines is the relative speed of movement between these movable parts. Interlocked architectures such as rotaxanes or catenanes have been used to control the relative motion of their subcomponents to develop molecular switches, shuttles or even motors.[2] While rotaxanes are composed of a macrocycle threaded onto an axle terminated with bulky stoppers that prevent its dissociation, pseudo-rotaxanes contain smaller stoppers that enable slow threading and dethreading reactions.[3] These architectures are thus valuable models to access and precisely tune the kinetics of such processes for the development of sophisticated multicomponent molecular machines. So far, most of the studies have been focused on the variation of the threading/dethreading kinetics by modifying the stoppers playing on their steric hindrance[4] or electrostatic repulsion[5] with some examples of stimuli responsive stoppers that can change their shape upon light irradiation[6] or pH modification. Due to synthetic challenges, the modulation on the macrocycle is much less explored. While syntheses of rotaxanes exploited modulation of the size of the macrocycle induced by metal coordination[7] or a chemical reaction[8] in a "threading-followed-by-shrinking" approach, control of the kinetics of threading/dethreading has been developed by Stoddart using redox-responsive macrocycles[9] which led to the elaboration of molecular pumps.[10]

Here, we wish to exploit the potential of selectively functionalized cyclodextrins (CD)[11] to modulate the kinetics of motion via the functionalization pattern on the CD and by applying a stimulus directly on this macrocycle. Despite extensive use in polyrotaxane[12] or slide-ring materials[13] CDs remain relatively underexploited as ring in rotaxane-based[14] molecular machines.[15] Indeed, most of the reported examples of stimuli responsive rotaxanes with CD use native CDs and a stimulus applied to the axle.[16] An example of mono-functionalized CD[17] and of a cone-shaped naphthotube[18] pH responsive switches have been described. However, to the best of our knowledge, no precise rate control of the threading/dethreading processes by playing on the functionalisation pattern of the macrocycle has been reported.

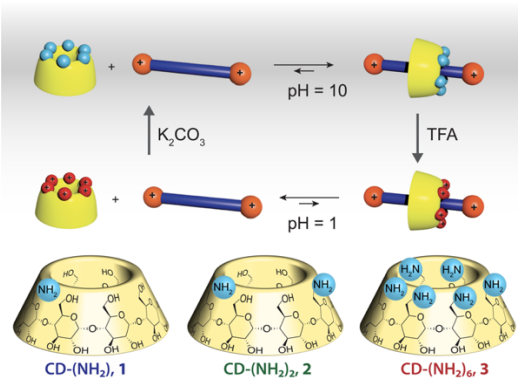
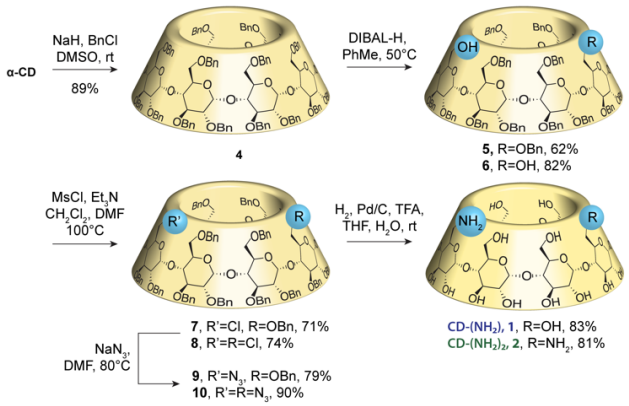


Figure 1. Principle of pH-controlled threading of functionalized CDs.

We have thus designed a pH-controlled molecular switch based on a pseudo[2]rotaxane architecture. The system is composed of a molecular axle terminated by two ammonium moieties acting as pseudo-stoppers, and α-CDs functionalized by one (CD-(NH_2), **1**), two (CD-(NH_2)$_2$, **2**) or six (CD-(NH_2)$_6$, **3**) amino groups as pH-responsive ring components. We anticipated a threading of the CD on the axle under basic conditions when the CD is neutral and a dissociation of the inclusion complex upon protonation due electrostatic repulsion from the cationic axle (Figure 1). The synthesis of the family of selectively functionalized CDs and the detailed thermodynamic and kinetic studies on the influence of the degree of functionalization on the switching mechanism are reported.

Amine-functionalized CDs were synthesized using two specific routes. Hexa-functionalized CD-(NH_2)$_6$ **3** was obtained in three steps by a direct per-functionalization of the primary rim adapted from the literature (see Scheme S2).[19] Mono and di-substituted CDs **1** and **2** were obtained via a five-step reaction sequence using a key regioselective debenzylation reaction with DIBAL-H.[20] After perbenzylation of native α-CD, **4** was subjected to the action of DIBAL-H. Depending on the reaction conditions, monol-CD **5** or A,D-diol-CD **6** were selectively obtained in 62 and 82 % yields respectively.[21] The hydroxyl groups were converted into chlorides with mesylchloride to give **7** and **8**, which was followed by a nucleophilic substitution with sodium azide[22] to afford **9** and **10**. Finally, catalytic hydrogenation on Pd/C cleaved the benzyl groups and reduced the azide moieties into amines to afford CD-(NH_2) **1** and CD-(NH_2)$_2$ **2** in 26% and 39% overall yield respectively. (Scheme 1)

Scheme 1. Synthesis of functionalized CD-(NH_2) 1 and CD-(NH_2)$_2$ 2



The threading of the CDs on cationic axle **11** was monitored by ^{1}H-NMR to access the thermodynamic and kinetic parameters. Methylammonium pseudo-stoppers were chosen to ensure water solubility of the axle and to slow down the threading process.[23] Threading of native α-CD was first evaluated in a 1:1 mixture with axle **11** at 2.8 mM in D_2O at pH = 10 using K_2CO_3. The NMR spectra showed progressive disappearance of the signals of free CD and axle and the appearance of a new series of signals corresponding to a pseudo[2]rotaxane **11**⊂ α-CD in slow exchange (Figure 2). The axle **11** signals at 3.15 ppm and around 1.5-1.6 ppm corresponding to the methyl groups and alkyl chain are split due to the dissymmetry induced by the cone-shaped CD. The anomeric protons of the CD also present a new signal for the threaded CD at 5.13 ppm. Native CD reached equilibrium fairly quickly in about 3.5 h, with a threading of 86% revealing its good affinity for the axis.

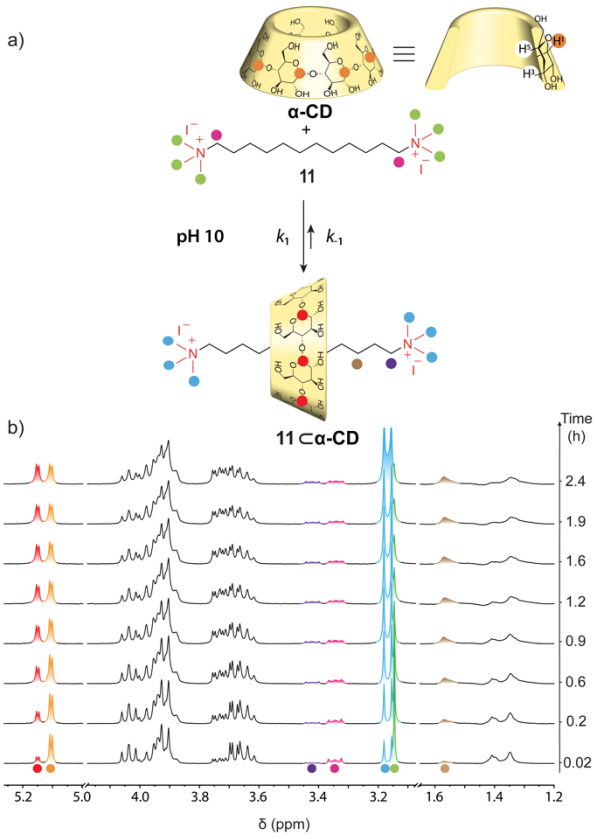


Figure 2. ^{1}H-NMR (600 MHz, 300K) monitoring of the threading of α-CD on axle **11**.

Similarly, functionalized CDs **1-3** presented a slow threading at basic pH with splitting of the axle protons and a new set of signals corresponding to threaded CD (see Figures S1-S3). For all CDs, the pseudo[2]rotaxanes were further characterized by DOSY ^{1}H NMR (see Figures S5-S6). The same value of diffusion coefficient for protons of the axle and threaded CD was observed indicating the formation of the inclusion complex. TROESY (Transverse Rotating-frame Overhauser Enhancement Spectroscopy) experiments (see Figures S8-S9) presented cross-correlation peaks between H^5 and H^3 protons located inside the CD cavity and protons in the middle of alkane chain confirming the inclusion of the axis into the CD cavity and no specific interaction between the CD and the ammonium pseudo-stoppers. Thermodynamic (log K) and kinetic (k_1, k_{-1}, k_2, k_{-2}, $t_{1/2}$) values were obtained from the NMR monitoring by non-linear fitting of the data with an equilibrium model using DynaFit[24] (See SI and Table 1). At pH 10, all the CDs present similar binding constants with log K between 3.3 and 4.3, native **α-CD** displaying the best affinity for axle **11**. The threading rates are in the same order of magnitude for all CDs with $t_{1/2}$ between 11 and 39 min at this pH. Functionalized CDs **1-3** thread slightly faster than native CD (k_1 in same order), CD-(NH_2)$_6$ **3** exhibiting the fastest threading rate with a half-life of 11 min and a k_1 10 times that of α-CD. Since the rate determining step is related to the crossing of the CD over the ammonium pseudo-stopper, this trend could be rationalized by the rigidity of the CD. The hydrogen bonding network on the primary rim of the CD makes

Table 1. Association constant and kinetics parameters for CD threading and dethreading.

	pH = 10				*pH =1*			
	log *K*	$t_{1/2}$ *(min)*	k_1 $(M^{-1}.h^{-1})$	k_{-1} (h^{-1})	log *K*	$t_{1/2}$ *(min)*	k_2 (h^{-1})	k_{-2} $(M^{-1}.h^{-1})$
α-CD	*4.3 ± 0.1*	*39 ± 0.7*	*174 ± 3*	*0.076 ± 0.004*	*4.3± 0.1*	*No dethreading observed*		
CD-(NH_2), **1**	*3.3 ± 0.1*	*20 ± 0.4*	*644 ± 9*	*0.28 ± 0.01*	*1.6 ± 0.1*	*240 ± 5*	*0.129 ± 0.002*	*4.9 ± 0.4*
CD-$(NH_2)_2$, **2**	*3.3 ± 0.1*	*25 ± 0.5*	*333 ± 12*	*0.12 ± 0.02*	*1.4 ± 0.1*	*190 ± 4*	*0.165 ± 0.002*	*4.5 ± 0.2*
CD-$(NH_2)_6$, **3**	*3.7 ± 0.1*	*11 ± 0.2*	*1370 ± 34*	*0.27 ± 0.02*	-	*15 ± 0.5*	*2.75 ± 0.03*	-

native CD quite rigid. Functionalization on the primary rim might destabilize the hydrogen bond network rendering these CDs more flexible thus lowering the threading energy barrier and increasing the rate.

Since amino groups are Bronsted bases, the effect of protonation on the stability of the pseudo[2]rotaxanes was investigated. Upon addition of trifluoroacetic acid (TFA) to a solution of pseudo-rotaxane with CD-$(NH_2)_6$ **3**, to obtain a solution at pH 1, a fast dethreading was observed by ^{1}H NMR (Figure 3). The signals of the rotaxane gradually disappeared while signals corresponding to free axle and protonated CD appeared. A total dethreading was reached after ~ 2 h (with $t_{1/2}$ = 15 min and k_2 2.75 h^{-1}) and confirmed by DOSY NMR (see Figure S7) showing two different diffusion coefficients corresponding to free CD-$(NH_3^+)_6$ (2.68 x 10^{-10} $m^2.s^{-1}$) and the free axle (4.28 x 10^{-10} $m^2.s^{-1}$). A dethreading in acidic media was also observed for CD-(NH_2) **1** and CD-$(NH_2)_2$ **2** (see Figures S11-S12) albeit with a much slower rate ($t_{1/2}$ =190, and 240 min and k_2 = 0.13, and 0.17 h^{-1} respectively) and the presence of a residual level of pseudorotaxane (of 6 and 14 % respectively) at equilibrium. As expected, for native α-CD, no change was observed on the NMR spectra in acidic medium even after 20 h indicating no dethreading (see Figure S10). These observations suggest that the dethreading is due to the protonation of the amino groups on the functionalized CDs **1-3**. Such change in the CD affinity might be interpreted by the destabilization of the inclusion complex in acidic medium due to electrostatic repulsion between the protonated amines and the cationic pseudo-stoppers. The kinetics data presented in Figure 4 clearly show that the increase of charges on the CD leads to a faster dissociation of the inclusion complex. This is in line with an increasing destabilization of the threaded state, which decreases the activation energy for the dethreading of CD as the number of positive charges increases. Such control of CD dethreading rate by playing on its degree of substitution is quite remarkable since the stimulus causing dissociation is applied directly to the CD and not on the axle as it was the case for systems previously described in the literature.

The reversibility of threading/dethreading was further investigated with CD-$(NH_2)_6$ **3** by sequential addition of potassium carbonate and TFA. Four successive cycles were performed and revealed a relative fatigue of the system with maximum threading gradually decreasing from 75% to 22% (See Figure S14). While the threading rate was little affected, the dethreading rate significantly decreased with the number of cycles. This fatigue could be rationalized by the accumulation of salts and the increase in ionic strength upon addition of acid and base, which leads to a stabilization of the ammonium solvation sphere and a rise of the hydrophobic effect.[25] This should increase the energy barrier of the passage of the CD through the pseudo-stopper and thus result in a decrease of the dethreading rate.

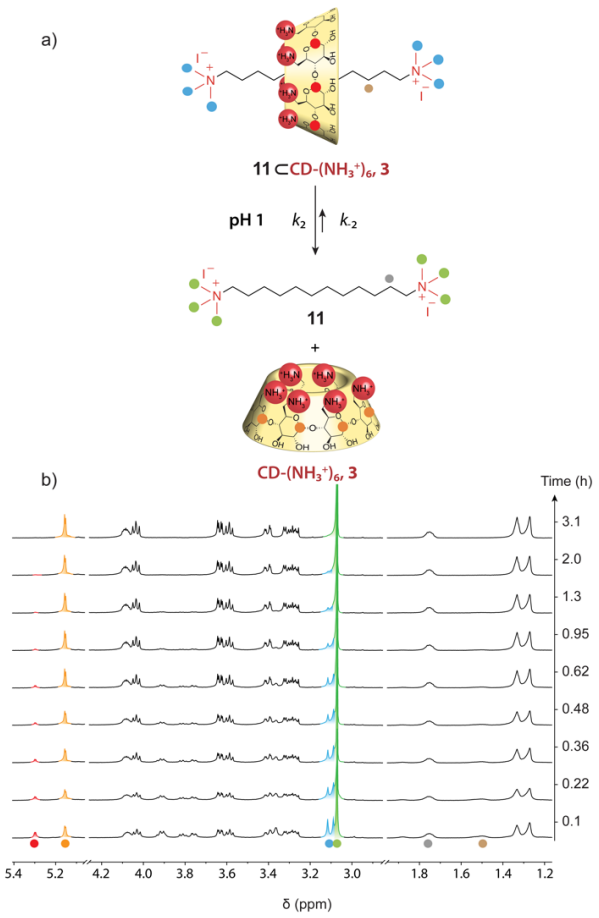


Figure 3. ^{1}H-NMR (600 MHz, 300K) monitoring of the dethreading of CD-$(NH_3^+)_6$ **3** and axle **11**.

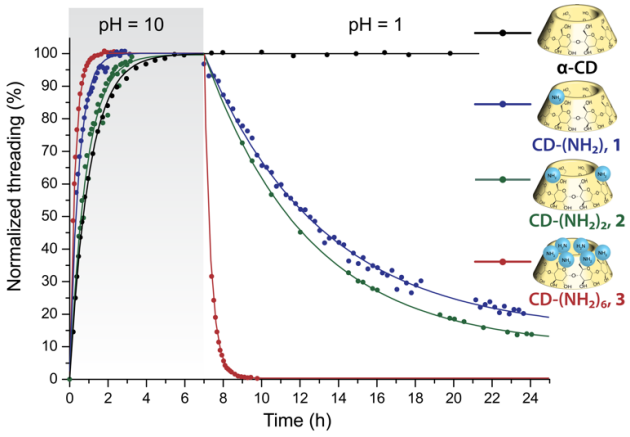


Figure 4. Kinetic profile of the threading at pH 10 and dethreading at pH 1 of α-CD and amino-CDs **1-3** on axle **11**.

In summary, a family of amine functionalized CDs was developed to control their threading and dethreading on a molecular axle depending on the pH. The originality of this system lies in the precise control of the dethreading rate through the degree of functionalization on the CD. Such stimuli-responsive CDs are attractive components for active transport mechanism in complex molecular machines.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization of products, and NMR spectra of threading/dethreading monitoring. (PDF)

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Notes

No competing financial interests have been declared..

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