

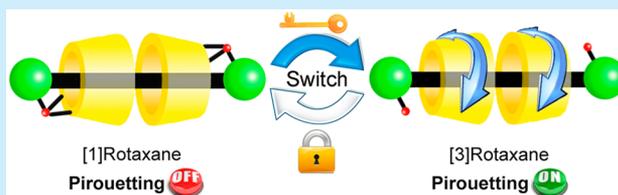
Cyclodextrin Rotaxane with Switchable Pirouetting

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Supporting Information

ABSTRACT: A [1]rotaxane with two threaded α -cyclodextrin (α -CD) wheels was synthesized in 92% yield using a one-pot process at room temperature that employed spontaneous α -CD threading onto a 12-carbon alkyl chain in water followed by an oxime condensation reaction that attached two boronic acid-containing stopper groups. Rapid pirouetting of the threaded α -CD wheels around the encapsulated dumbbell was switched “ON” or “OFF” by the presence of chemical additives that controlled boronate ester bond formation between the interlocked components.



Molecular motors are ubiquitous in biology and can be classified into two distinct types: linear motors, such as the myosin–actin complex, which is a central feature in muscles and kinesin-containing systems,¹ and rotary motors, such as the F_0F_1 -ATP synthase, which manufactures ATP from ADP and P_i and undergoes a spinning action.² To mimic these natural molecular motors, supramolecular chemists have developed various molecular machine prototypes that exhibit controllable linear or rotary motion. Among the various classes of synthetic machines, mechanically interlocked rotaxanes are popular choices because they have inherently dynamic structures. The surrounding macrocyclic wheel can translocate along the encapsulated dumbbell (shuttling), or alternatively, the wheel can rotate around the dumbbell (pirouetting).³ To date, a wide variety of switchable molecular shuttles have been shown to respond to external stimuli, such as electrochemical,⁴ pH,⁵ light,⁶ and other factors.⁷ In contrast, only a few rotaxanes have been reported with controllable pirouetting, including stepwise rotation controlled by a change in metal cation coordination⁸ and adjustable pirouetting dynamics using hydrogen bonding, steric hindrance, or other non-covalent effects.⁹ However, to our knowledge there is no example of a rotaxane whose pirouetting behavior can be completely switched off. Here we describe a new type of cyclodextrin-based rotaxane. The pirouetting motion of this rotaxane can be switched “ON” or “OFF” by the presence of chemical additives that control the formation of boronate ester bonds between the interlocked components. The boronate bonds act as a brake that prevents pirouetting of the wheels relative to the dumbbell stopper groups.

Cyclodextrins (CDs) are macrocycles composed of six (α -CD), seven, eight, or more glucopyranosyl units, and they are used widely in supramolecular chemistry because of their biocompatibility and versatile ability to bind guest molecules in water.¹⁰ CD-based rotaxanes are normally obtained by a two-step process of CD threading followed by in situ stoppering in water. The initial CD threading process is driven by the

hydrophobic effect and is disfavored by high temperature. Thus, the in situ stoppering reaction must be efficient in water under mild conditions. We were drawn to oxime formation as the stoppering reaction because of its high yields, chemoselectivity, and water compatibility.¹¹ A review of the literature suggested that 1,12-bis(oxyamino)dodecane (**3**) would be a good choice as an axle that could accommodate two threaded α -CDs and form a head-to-head [3]pseudorotaxane in water.¹² As summarized in Figure 1, rotaxane **6** was obtained in high yield (92%) simply by mixing **3** with 2 equiv of α -CD in water to create an insoluble pseudorotaxane (Figure S1 in the Supporting Information (SI)) and then adding 2-formylphenylboronic acid (2FPBA) with additional stirring for 1 h at room temperature. The very high yield and mild aqueous conditions are quite remarkable for a chemical reaction that assembles five building blocks in a single step. No rotaxane product was obtained when the same reaction was conducted using the *meta* or *para* isomer of 2FPBA or if the α -CD was replaced with permethyl- α -CD. It appears that the *ortho* relationship between the aldehyde and boronic acid in 2FPBA promotes two important effects: accelerated oxime formation¹³ and stabilizing boronate ester bonds between the interlocked components.¹⁴

Figure 2 shows a comparison of the ^1H NMR spectra for rotaxane **6**, free dumbbell **5**, and a binary admixture of free **5** and α -CD. Peak integration indicated that the rotaxane consisted of two α -CDs threaded onto the dumbbell. Classic CD-based [3]rotaxanes exhibit simple glucopyranosyl spectral patterns as a result of rapid pirouetting of the CD wheels. In stark contrast, the spectrum of rotaxane **6** (Figure 2a) shows a complex pattern for the α -CD protons, indicating loss of the sixfold symmetry. Furthermore, only four of the primary hydroxyl protons of α -CD (^6OH) are present, in a 1:1:1:1 ratio (the middle two are partially overlapped), implying loss of two

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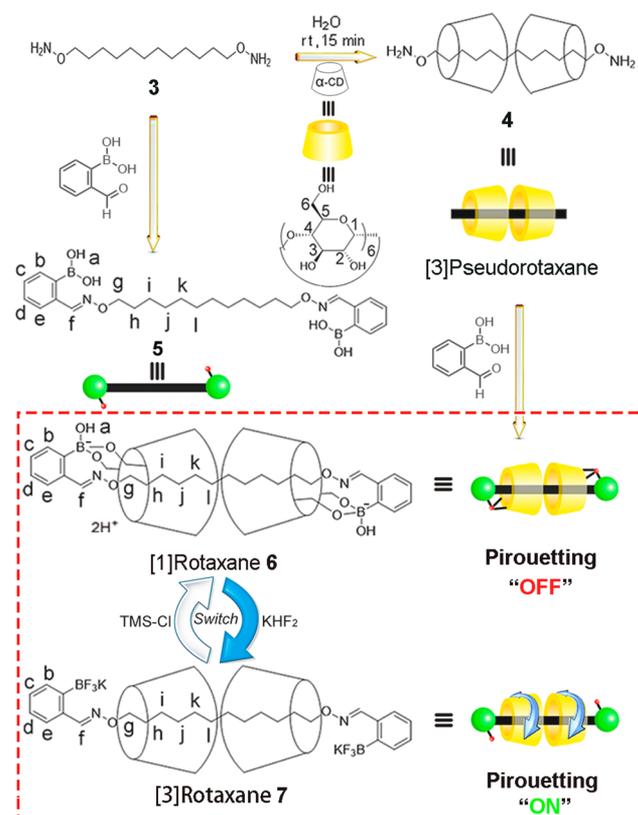


Figure 1. Schematic diagram of the preparation of dumbbell **5** and [1]rotaxane **6** and switching between **6** and [3]rotaxane **7**.

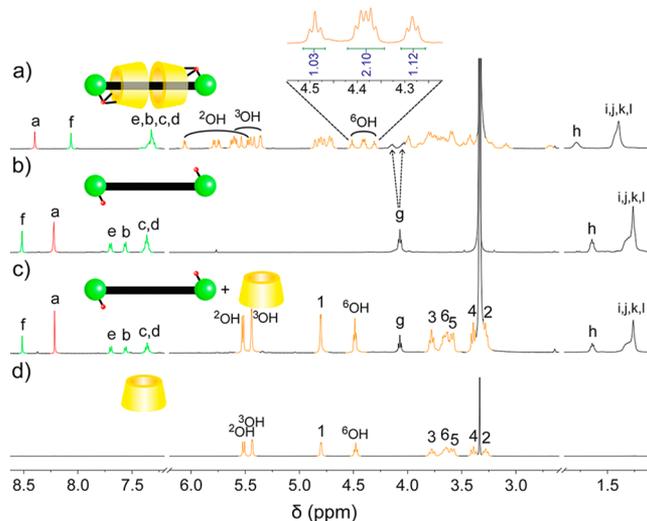


Figure 2. ^1H NMR spectra (500 MHz, $\text{DMSO}-d_6$, 298 K) of (a) [1]rotaxane **6**, (b) free dumbbell **5**, (c) a binary admixture of **5** and $\alpha\text{-CD}$, and (d) free $\alpha\text{-CD}$. See [Figure 1](#) for atom labels.

^6OH protons. Also missing in rotaxane **6** is one of the two BOH protons from each boronic acid. These results indicate the formation of a tetrahedral boronate ester with two ^6OH residues from the primary rim of $\alpha\text{-CD}$ ([Figure 1](#)).¹⁵ The structure of rotaxane **6** was completely assigned by analyzing homonuclear (DQF-COSY, TOCSY, and ROESY) and heteronuclear ($^1\text{H}-^{13}\text{C}$ HSQC, HSQC-TOCSY, and HMBC) spectra acquired using a very high field (800 MHz) NMR spectrometer. The DQF-COSY and TOCSY spectra provided

information about the proton connectivities, and the HSQC spectra furnished the $^1\text{J}_{\text{H}-^{13}\text{C}}$ correlations. Analysis of the HMBC and HSQC-TOCSY spectra enabled assignments of the quaternary carbon resonances (for an extended discussion, see the [SI](#) and [Figures S2–S7](#)). The HMBC analysis also proved that the boron atom at each end of the dumbbell is covalently bonded to oxymethylene groups ($^6\text{CH}_2\text{O}$) on two adjacent glucopyranosyl units (labeled **A** and **B** in [Figure 3](#)). Thus,

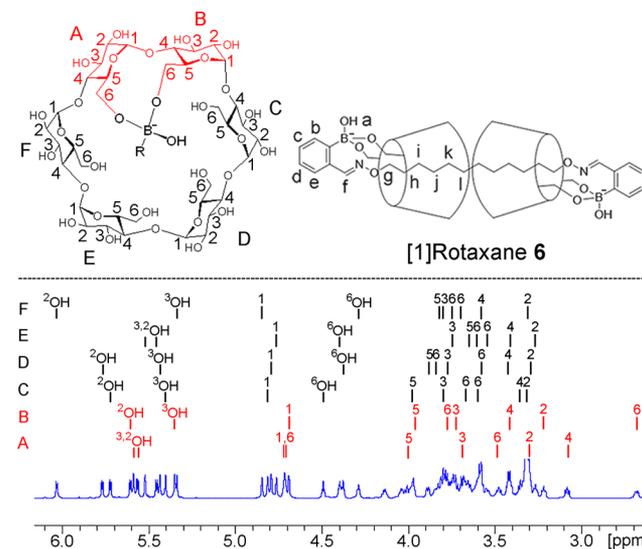


Figure 3. Resonance assignments for the cyclodextrin protons of [1]rotaxane **6**, as determined by analysis of homonuclear (DQF-COSY, TOCSY, and ROESY) and heteronuclear ($^1\text{H}-^{13}\text{C}$ HSQC, HSQC-TOCSY, and HMBC) spectra (800 MHz, $\text{DMSO}-d_6$, 298 K).

rotaxane **6** is actually a [1]rotaxane, in which the two threaded $\alpha\text{-CD}$ wheels are covalently connected to the encapsulated dumbbell (one at each end) by boronate ester bonds (see [Figure S8](#) for a molecular model). Individual assignments of the cyclodextrin protons are presented in [Figure 3](#), and the complete ^1H and ^{13}C resonance assignments for rotaxane **6** are given in [Table S1](#). Independent support for the structure of [1]rotaxane **6** was gained by ESI-MS analysis ([Figure S9](#)). The observed base peak at 1201.4459 uniquely corresponds to the molecular ion $[\mathbf{6} - 2\text{H}]^{2-}$, and there is an unambiguous match of the measured and calculated isotopic cluster patterns.

Close inspection of the 1D and 2D NMR spectra for [1]rotaxane **6**, especially the $^1\text{H}-^{13}\text{C}$ HSQC connectivities, revealed two interesting features that indicate a constrained structure. One is the distinct chemical shifts for the diastereotopic dumbbell methylene protons **g** (4.139 ppm) and **g'** (4.039 ppm) ([Figure 4](#)). This large difference in chemical shift contrasts with the single resonance observed for the two **g** protons in free dumbbell **5** ([Figure 2b](#)). Also, literature reports of analogous axle methylene protons in CD-based [3]rotaxanes with freely rotating wheels do not see a large difference in chemical shift.¹² A second informative spectral feature with [1]rotaxane **6** is the difference in signal dispersion for the six chemically different C6 methylene groups ($^6\text{CH}_2$) on the primary rim of the surrounding $\alpha\text{-CD}$ wheels. Only two of these six diastereotopic methylene groups exhibit a large difference in chemical shift for their two constituent protons, i.e., $^6\text{CH}_2(\text{A})$ (4.714 and 3.489 ppm) and $^6\text{CH}_2(\text{B})$ (3.784 and 2.683 ppm) ([Figure 4](#)). The highly anisotropic shielding for these two specific methylenes arises because they

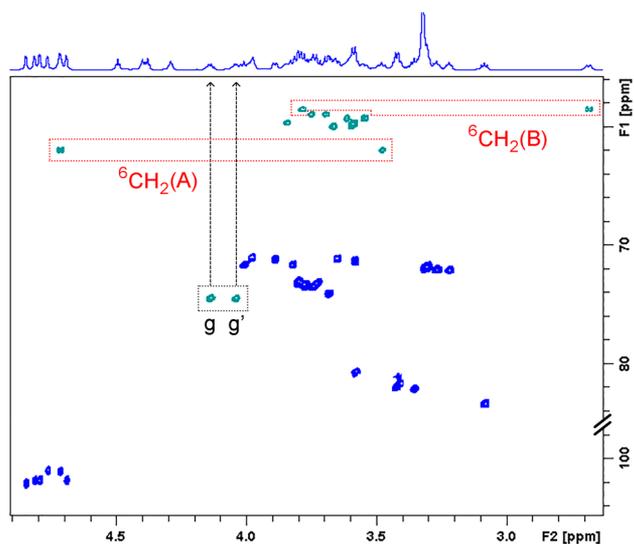


Figure 4. Partial ^1H - ^{13}C HSQC spectrum (800 MHz, $\text{DMSO-}d_6$, 298 K) of [1]rotaxane **6** (blue spots for $-\text{CH}-$ and green spots for $-\text{CH}_2-$).

are part of a conformationally constrained cyclic boronate ester that is created when the adjacent $^6\text{CH}_2\text{OH}$ residues on the A and B glucopyranosyl rings of each α -CD form B–O bonds with the proximal boron on the dumbbell. This can only occur if the two surrounding α -CDs in [1]rotaxane **6** are in a head-to-head orientation with primary hydroxyl groups on the smaller rim of the α -CD bonded to the dumbbell boronic acid groups, as presented in Figure 3. It is worth noting that the interaction of boronic acids with CD hydroxyls has been inferred in several literature studies, but without extensive experimental support.¹⁴ The formation of the 11-membered cyclic boronate esters in [1]rotaxane **6** is favored because the reacting boron and $^6\text{CH}_2\text{OH}$ groups are forced by the threaded architecture to be proximal with a high “effective concentration”.

Additional support for the threaded structure and head-to-head orientation of α -CD wheels in [1]rotaxane **6** was provided by the 2D ROESY spectrum (Figure 5). First, cross-peaks were

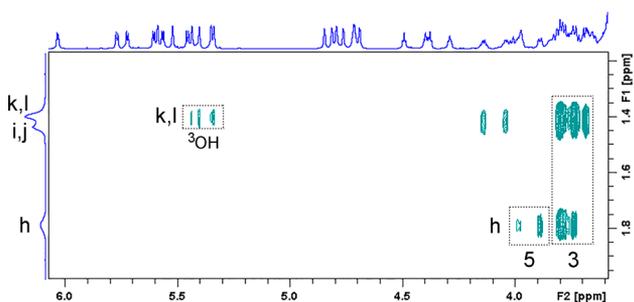


Figure 5. Partial 2D ROESY NMR spectrum (800 MHz, $\text{DMSO-}d_6$, 298 K) of [1]rotaxane **6**.

observed between internal protons of α -CD (^3H , ^5H) and the dumbbell axle protons g – l . In comparison, there were no cross-peaks between these internal α -CD protons and the dumbbell stopper group aryl protons (b – e). This shows clearly that the two α -CDs in [1]rotaxane **6** surround the dumbbell alkyl chain rather than the aryl stopper groups. Second, the head-to-head orientation of α -CDs in [1]rotaxane **6** agrees with the observation of cross-peaks between the internal α -CD proton

^5H (close to the primary rim of α -CD) and dumbbell protons h (near the ends of the dumbbell) and no cross-peaks between proton ^5H and methylene protons k and l (in the middle of the dumbbell). In addition, cross-peaks between α -CD protons ^3OH and methylene protons k and l indicate that the secondary rim of α -CD surrounds the middle of the dumbbell. Taken together, these independent observations strongly support the head-to-head orientation of the two threaded α -CDs in [1]rotaxane **6** and are in accordance with the structures of analogous α -CD rotaxanes.¹²

We hypothesized that if boronate formation was the reason for the blocked pirouetting in [1]rotaxane **6**, then well-known boronate chemistry could be used to make the process reversible. That is, pirouetting could be switched “ON” or “OFF” by chemical conditions that favor or disfavor boronate ester bonds between the two interlocked components. After some experimentation, we found that an effective way to switch the pirouetting “ON” was to treat [1]rotaxane **6** with potassium hydrogen fluoride (KHF_2)¹⁶ which converted the boronate ester bonds on each end of the threaded dumbbell into stable trifluoroborate groups and created [3]rotaxane **7** in 95% yield (Figure 1). The ^1H NMR spectrum of [3]rotaxane **7** (Figure 6b) is substantially simpler than the spectrum of [1]rotaxane **6**

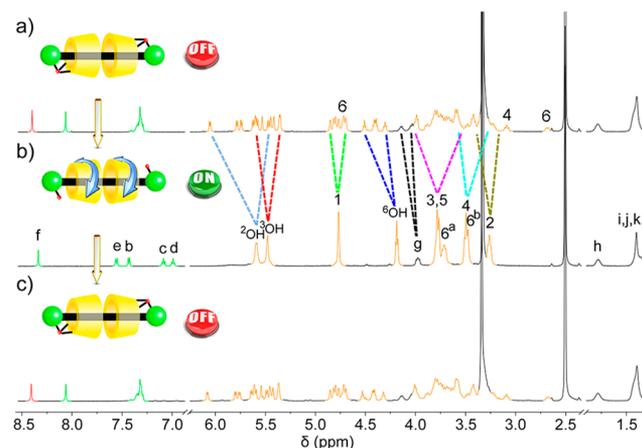


Figure 6. ^1H NMR spectra (500 MHz, $\text{DMSO-}d_6$, 298 K) of (a) [1]rotaxane **6**, (b) [3]rotaxane **7**, and (c) [1]rotaxane **6** recovered from **7** by reaction with TMSCl . (For clarity, there are no dashed lines indicating changes in signals for the $^6\text{CH}_2$ protons).

(Figure 6a). Rapid pirouetting of the two α -CD wheels around the dumbbell in [3]rotaxane **7** explains why the six glucopyranosyl units are chemically equivalent and the encapsulated dumbbell methylene protons g and g' have the same chemical shift. Chemical shift assignments for [3]rotaxane **7** were readily achieved by analyzing a combination of 2D HSQC and HMBC spectra (Figures S10 and S11), and the integrity of the rotaxane mechanical bond was confirmed by a 2D ROESY spectrum showing cross-peaks between the dumbbell methylene protons (g – l) and internal α -CD protons ^3H and ^5H (Figure S12). In addition, a unique molecular ion of [3]rotaxane **7** ($[\text{M} - 2\text{K}]^{2-}$) was clearly observed by ESI-MS (Figure S13). The next step in the switching cycle was to recover pirouetting “OFF”, and this was readily achieved by treating [3]rotaxane **7** with the fluoride scavenger trimethylsilyl chloride (TMSCl) in methanol, which regenerated [1]rotaxane **6** in 90% yield (Figure 6c).¹⁵

In conclusion, we have prepared a new α -CD-based rotaxane in very high yield (92%) at room temperature using an oxime reaction to attach boronic acid-containing stopper groups to each end of a threaded α -CD complex in water. The unique reactivity of 2FPBA, with its aldehyde and boronic acid groups in an *ortho* relationship, is crucial for synthetic success, as it undergoes very rapid oxime formation at neutral pH and permits boronate stabilization of the rotaxane product. Pirouetting of the permanently threaded α -CD wheels relative to the dumbbell stopper groups is prevented by boronate ester bonds between the interlocked components. The boronate ester bonds can be conveniently broken or reformed by treatment with KHF_2 or TMSCl , respectively. Thus, pirouetting is switched “ON” or “OFF” as the mechanically interlocked molecule is interconverted between [1]rotaxane and [3]-rotaxane structures. Not only is this discovery a new strategy for controlling the rate of pirouetting within CD-based rotaxanes, but it may also be possible to incorporate reversible boronate formation as a switchable feature in other classes of dynamic interlocked molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00655.

Experimental procedures, compound characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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