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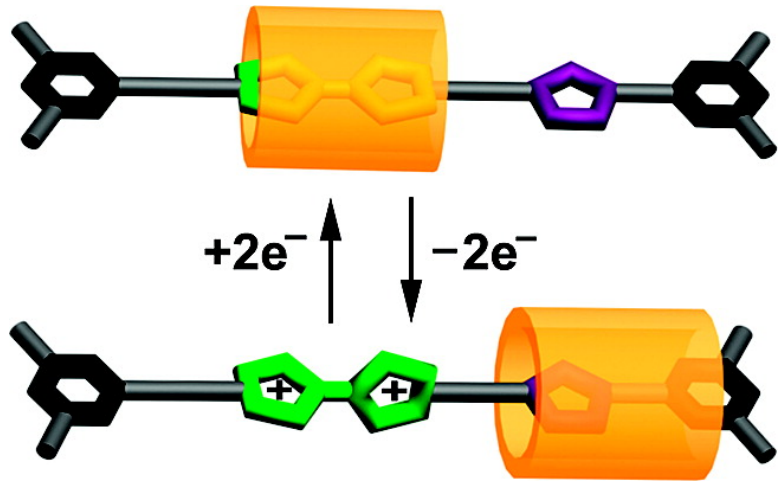

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A Redox-Switchable α-Cyclodextrin-Based [2]Rotaxane

Yan-Li Zhao,[†] William R. Dichtel,[†,§] Ali Trabolsi,[‡] Sourav Saha,[†] Ivan Aprahamian,[†] and J. Fraser Stoddart*[,†,‡]

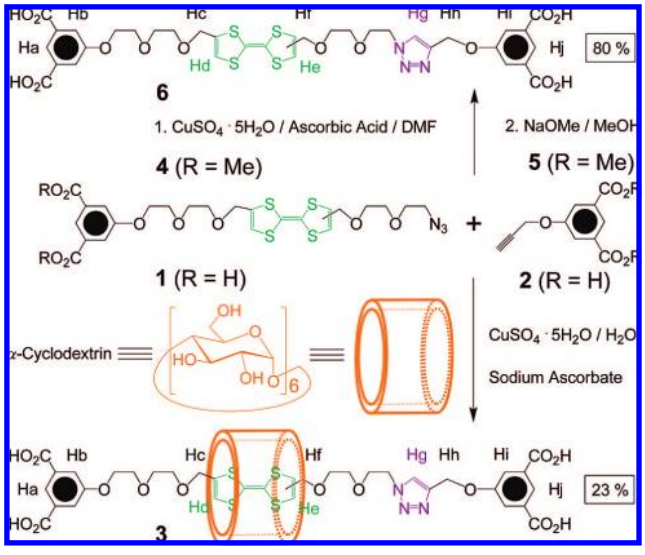
Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095, Department of Chemistry, Northwestern University, Evanston, Illinois 60208, and Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125

Received May 14, 2008; E-mail: stoddart@northwestern.edu

Switchable, mechanically interlocked molecules have attracted much interest[1,2] on account of their ability to alter the relative positions of their ring and dumbbell components in response to external stimuli, such as changes in pH, the absorption of light, and the consecutive addition or removal of electrons. This switching at a molecular level has been harnessed in a range of devices, including nanoelectromechanical ones,[3] surface-property controllers,[4] mesoporous nanoparticle-mounted nanovalves,[5] and molecular electronic devices.[6] Redox-responsive bistable [2]rotaxanes and [2]catenanes are of considerable interest because the redox-responsive switching process is usually rapid and precise and can be controlled within solid-state devices, as well as on surfaces.

Though cyclodextrins (CDs) have also been introduced[7,8] as the ring components into [2]rotaxanes because of (i) their ability to interact favorably with hydrophobic units and (ii) their biocompatibility, redox-responsive bistable [2]rotaxanes incorporating CD rings have yet to be investigated. Such systems might be able to interface with redox-active enzymes or even act as the switching components in implantable medical devices. Herein, we describe the template-directed synthesis[9] and switching behavior of a bistable [2]rotaxane **3**, wherein an α-CD ring can be induced to move on account of the redox properties of a tetrathiafulvalene (TTF) unit

Scheme 1. Syntheses of the [2]Rotaxane **3** and the Corresponding Dumbbell Compound **6**



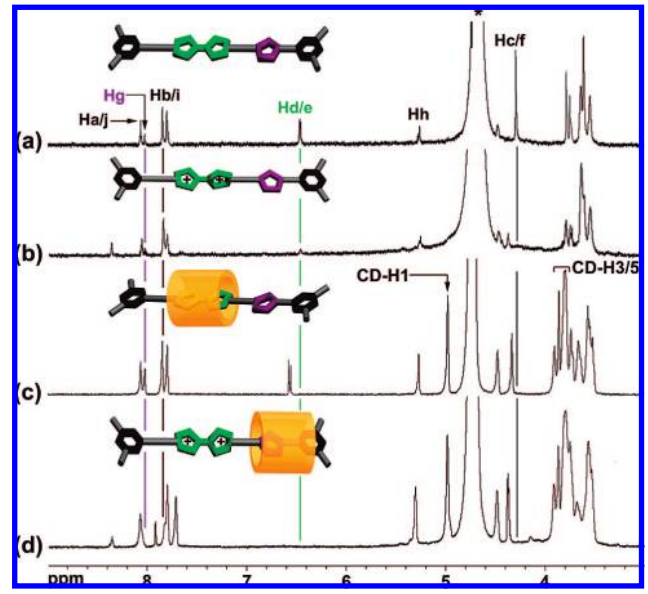


Figure 1. ^{1}H NMR spectra of (a) the dumbbell **6** (0.9 mM) in K_2CO_3 (4.0 mM)/D_2O solution, (b) the oxidized dumbbell **6** in the presence of 30% D_2O_2/D_2O solution ([D_2O_2] = 2.2 mM), (c) [2]rotaxane **3** (1.0 mM) in K_2CO_3 (4.0 mM)/D_2O solution, and (d) the oxidized [2]rotaxane **3** in the presence of 30% D_2O_2/D_2O solution ([D_2O_2] = 2.2 mM) at 25 °C.

located in the dumbbell component of **3** which was obtained[10] from aqueous solution (Scheme 1) employing a recently developed threading-followed-by-stoppering approach[11] which relies on the efficiency of the copper (I)-catalyzed azide−alkyne cycloaddition. The free dumbbell compound **6** was also made by a similar route [see the Supporting Information (SI) and Scheme 1], except that α-CD was omitted from the reaction mixture. ^{1}H NMR and UV−vis spectroscopies, together with cyclic voltammetry (CV) and induced circular dichroism (ICD) experiments, have been employed in conjunction with one another, to show that the 1,2,3-triazole ring, which is installed during the synthesis of **3**, serves as the second port of call for the α-CD ring where the TTF unit—the preferred resting place for the α-CD ring by far—is oxidized either to its radical cation or to its dication.

To characterize **3** and establish the nature of the coconformation adopted by the chiral α-CD on the achiral chromophoric dumbbell component, ICD experiments (see Figure S5 in the SI) were performed on both **3** and **6** at 25 °C in K_2CO_3/H_2O solution. As expected, no ICD signal was observed for **6**. The ICD spectrum of **3**, however, reveals a positive Cotton effect peak at 311 nm with a $\Delta\varepsilon$ value of 9.85 dm^{-3} mol^{-1} cm^{-1}. From previous investigations[12] carried out by Harata, Kajtár, and Nau on the ICD properties of CD complexes, we can deduce that the TTF unit in the dumbbell is encircled by the α-CD ring in the [2]rotaxane.[13] This deduction

[†] University of California, Los Angeles.
[§] California Institute of Technology.
[‡] Northwestern University.

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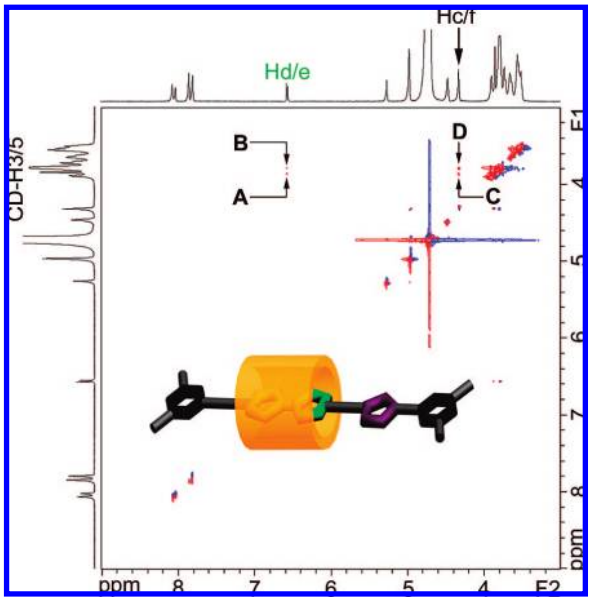

Figure 2. ^{1}H NOESY spectrum (600 MHz) of α-CD [2]rotaxane **3** (1.0 mM) in K_2CO_3 (4.0 mM)/D_2O solution at 25 °C with mixing time = 150 ms.

is confirmed by the fact that the chemical shifts of the TTF resonances for Hc/f and Hd/e shifted downfield by 0.09 and 0.12 ppm, respectively, relative (Figure 1 a,c) to those obtained for the analogous protons in **6**. In the ^{1}H NOESY spectrum[14] (Figure 2) of **3**, NOE crosspeaks (A−D) between the protons (Hc/f and Hd/e) of the TTF unit and the protons (H3 and H5) lining the inside of the α-CD are observed, supporting the conclusion that the neutral TTF unit is encircled by the α-CD ring in **3**.

The preferred encirclement of the TTF unit can also be monitored by UV−vis spectroscopy. The UV−vis spectra of **3** and **6**, recorded (see Figure S6 in the SI) in K_2CO_3/H_2O solution at 25 °C, show that the absorption peak at 432 nm for the TTF unit in the dumbbell compound **6** is decreased in intensity and red-shifted to 457 nm in the [2]rotaxane **3**. Also, the peak observed at 595 nm for the $TTF^{\bullet+}$ radical cation[15] after partial oxidation of **6** is attenuated relative to that in **3**, following its oxidation, showing that the encirclement by the α-CD ring prevents the oxidization of the TTF unit in the [2]rotaxane under these conditions. When the oxidization of **3** was monitored (Figure 3) by UV−vis spectroscopy, following the addition of $Fe(ClO_4)_3$ solutions, the peak for the TTF unit at 457 nm shifts back to one centered on 432 nm after the addition of 0.2

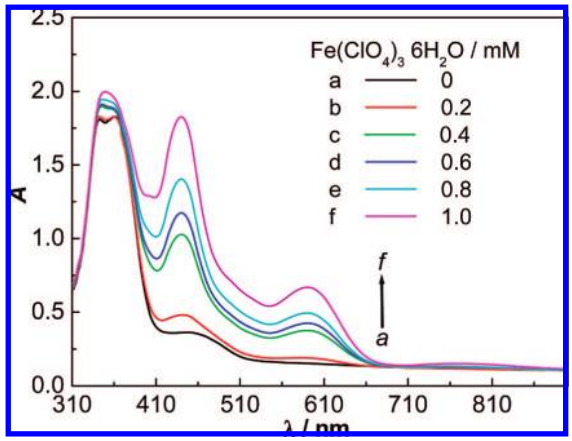

Figure 3. UV−vis spectral changes of [2]rotaxane **3** (1.1 mM) in 4.0 mM K_2CO_3/H_2O upon addition of $Fe(ClO_4)_3 \cdot 6H_2O$ (0∼1.0 mM from concentration a to f) aqueous solution at 25 °C.

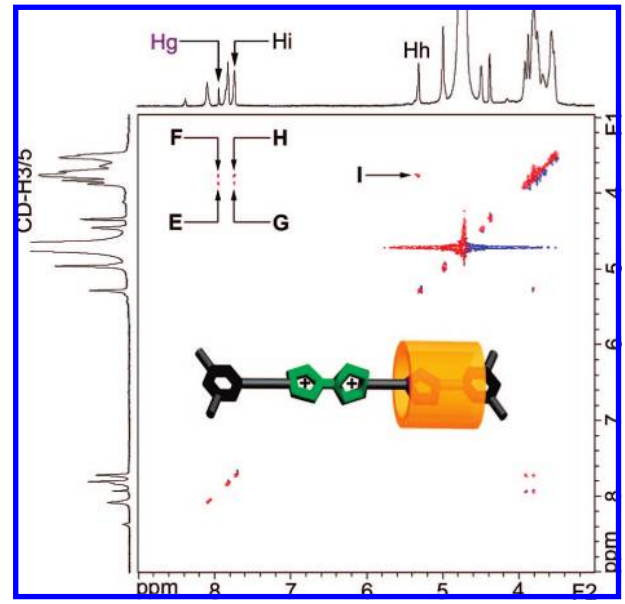

Figure 4. ^{1}H NOESY spectrum (600 MHz) of α-CD [2]rotaxane **3** (1.0 mM) in K_2CO_3 (4.0 mM)/D_2O solution after the addition of 30% D_2O_2/D_2O solution ($[D_2O_2]$ = 2.2 mM) at 25 °C with mixing time = 150 ms.

equiv of the oxidant, an observation which indicates that the α-CD ring moves away from the TTF unit immediately after oxidation. The peak at 595 nm, which corresponds to the presence[15] of the $TTF^{\bullet+}$ radical cation in the [2]rotaxane, emerges during the course of addition of 0.2−1.0 equiv of $Fe(ClO_4)_3$.

The location of the α-CD ring in the oxidized forms of **3** can also be deduced from ^{1}H NMR experiments (Figure 1c,d). The peaks for Hd/e, which resonate around 6.58 ppm when **3** is dissolved in K_2CO_3/D_2O solution at 25 °C, shift downfield to 8.36 ppm, corresponding to TTF^{2+}, after the addition of 30% D_2O_2/D_2O solution (2 equiv), while the peaks for Hi and Hg move upfield by 0.10 and 0.08 ppm, respectively and the peaks for Hh moves downfield by 0.02 ppm, suggesting that, on oxidation of the TTF unit, the α-CD ring moves to the triazole ring system. Since the oxidized form of **3** is stable in D_2O for several hours, we were able to perform ^{1}H NOESY NMR experiments on the oxidized rotaxane. They reveal (Figure 4) NOE crosspeaks between the H3/H5 protons on the inside of the α-CD ring and (i) Hg (crosspeaks E and F), (ii) Hi (crosspeaks G and H), and (iii) Hh (crosspeak I), indicating the relocation of the α-CD ring on the triazole unit.

CV experiments, carried out (Figure 5) on both **3** and **6**, demonstrate that, while the latter exhibits two one-electron reversible oxidation processes at +0.17 and +0.54 V (in the potential

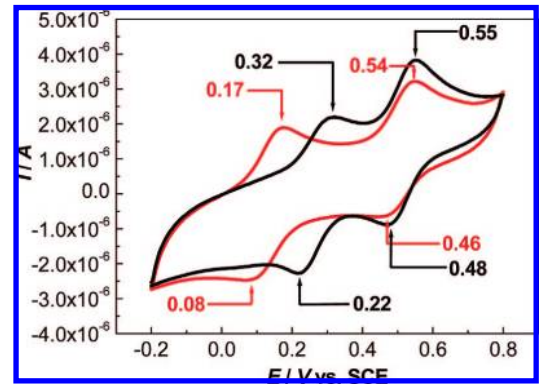

Figure 5. Cyclic voltammetry of [2]rotaxane **3** (black, 1.1 mM) and dumbbell **6** (red, 1.1 mM) in 0.1 M $LiClO_4/H_2O$ at scan rate = 100 mV s^{-1}.

range between −0.2 and +0.8 V at a scan rate of 100 mV s^{-1}) for the first and second oxidization peaks[16] of the TTF unit, the former reveals that the first oxidization peak for the [2]rotaxane shifts dramatically to +0.32 V, whereas the second oxidization peak at +0.55 V is very similar to that observed for the dumbbell. These observations support those obtained from UV−vis spectroscopy, that is, the α-CD ring moves away from the TTF unit in the [2]rotaxane just as soon as it is oxidized to the $TTF^{\bullet+}$ radical cation. In the reducing cycle, the first reduction peaks of the TTF^{2+} dication at +0.46 and +0.48 V for **3** and **6**, respectively, are almost identical. The fact that the separation between the second reduction peaks for **3** and **6** is 0.14 V seems to suggest that the α-CD ring is already close enough to the TTF unit in the [2]rotaxane to influence the reduction of the $TTF^{\bullet+}$ radical cation back its neutral form.[17] The α-CD ring might also be facilitating the desolvation of the $TTF^{\bullet+}$ radical cation in aqueous solution.[18]

In a nutshell, we have demonstrated the operation of a redox-switchable α-CD-based [2]rotaxane using both spectroscopic and electrochemical probes. The α-CD ring in the [2]rotaxane moves between a TTF unit, the more preferred[19] station, and a triazole ring system, the less preferred[19] station, under redox control. This dynamic property has consequences for the design, synthesis, and fabrication of nanoscale systems and devices. These findings have implications for the production of mechanized nanoparticles[5] that can be used for drug delivery where the stimulus is a unique redox state often present within diseased cells but not in healthy cells.

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Supporting Information Available: Experimental details and spectral characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Since the TTF unit has two cis−trans constitutional isomers and the α-CD ring has a primary and a secondary face, four isomeric [2]rotaxanes can be, in principle, formed as a consequence of the dumbbell being constitutionally unsymmetrical. We have employed an orange cylinder to represent the α-CD ring in the different isomeric forms of **3**, whether it be a structural formula or a graphical representation. On the basis of the ratio of two TTF methine proton peaks (Hd and He) in the ^{1}H NMR spectrum of the [2]rotaxane, we have calculated that the ratio of the cis and trans TTF units-based constitutional isomers in the [2]rotaxane is ca. 3:2.

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(12) Achiral entities located in chiral environments will produce ICD signal(s) in the corresponding transition band(s). An empirical rule for the ICD properties of the cyclodextrin complexes with achiral chromophoric guests has been proposed: if the transition moment of the guest chromophore is parallel to the axis of symmetry of cyclodextrin (that is, the principal C6 axis of α-CD), then the sign of the ICD signal for that transition will be positive, whereas, if the moment axis is aligned perpendicular to the principal axis, then the sign of ICD will be negative. See:(a) Harata, K.; Uedaira, H. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 375–378. (b) Kajtár, M.; Horvath-Toro, C.; Kuthi, E.; Szejtli, J. *Acta Chim. Acad. Sci. Hung.* **1982**, *110*, 327–355. (c) Zhang, X.; Nau, W. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 544–547.

(13) Since the ICD spectrum of **3** reveals a positive Cotton effect peak around the absorption band of the TTF unit, we can conclude that the TTF unit is included in the cavity of the α-CD ring, according to the empirical rule as outlined in ref 12.

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(18) With different scan rates (10−500 mV s^{-1}), **3** produces a new peak (see Figure S9 in the Supporting Information) around +0.44 V at a scan rate of 200 mV s^{-1}, indicating that the α-CD ring does not move away entirely from the $TTF^{\bullet+}$ radical cation at higher scan rates. See:(a) Zhao, S.; Luong, J. H. T. *Anal. Chim. Acta* **1993**, *282*, 319–327. (b) Schmidt, P. M.; Brown, R. S.; Luong, J. H. T. *Chem. Eng. Sci.* **1995**, *50*, 1867–1876. (c) Bergamini, J.-F.; Hapiot, P.; Lorcy, D. *J. Electroanal. Chem.* **2006**, *593*, 87–98.

(19) Microcalorimetric titrations have been performed (see the SI) at 298.15 K in buffer solutions (pH 10) on the mixing of α-CD to (i) a TTF diol and (ii) a triazole-containg stopper—both model complexes for the TTF and triazole recognition sites present in **3** and **6**—and yielded K_a values of 856 ± 47 and 92 ± 24 M^{-1}, respectively. The order of magnitude difference in these K_a values equates extremely well with the more stable co-conformation in **3** being the one where the TTF unit is encircled by the α-CD ring and with the less stable co-conformation being the one where the α-CD ring encircles the triazole unit.

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