

A Water-Soluble pH-Triggered Molecular Switch

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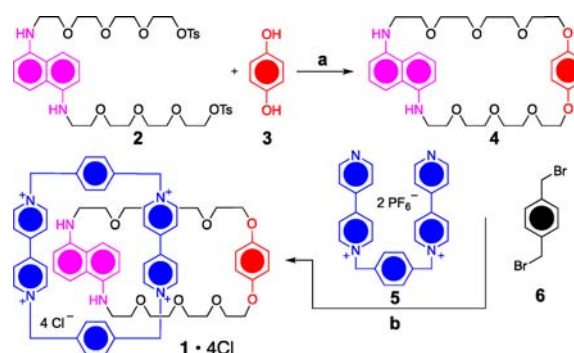
S Supporting Information

ABSTRACT: A bistable donor–acceptor [2]catenane, which is composed of a crown ether containing a hydroquinone unit and a 1,5-diaminonaphthalene unit, interlocked mechanically by cyclobis(paraquat-*p*-phenylene) as its tetrachloride, exists as a mixture of translational isomers, both in the solid state and in aqueous solution. UV/vis and ¹H NMR spectroscopies demonstrate that this isomeric mixture can be switched in water in the presence of hydrochloric acid to afford a single diprotonated derivative in which only the hydroquinone unit resides inside the cavity of the tetracationic cyclophane. Treatment with 1,4-diazabicyclo[2.2.2]octane resets the molecular switch.

Mechanically interlocked molecules¹ (MIMs), which embrace a large family of bistable catenanes² and rotaxanes,³ have been identified as prototypes for the construction of artificial molecular switches⁴ (AMs) and machines⁵ on account of our ability to exhibit control over the relative intramolecular movements of their mechanically interlocked components. This attribute has rendered bistable MIMs indispensable compounds for incorporation into integrated systems such as molecular actuators,⁶ molecular electronic devices,⁷ and drug delivery vehicles.⁸

In the search for more application-driven devices derived from MIMs, we are looking currently toward their operation in aqueous solutions where most biological processes based on motor proteins express their functions, e.g., myosin,⁹ kinesin,¹⁰ ATP-ase,¹¹ and bacterial flagella.¹² Only a relatively few examples¹³ of MIMs that can be switched in water have been reported. For example, MIMs based on π -electron-rich tetrathiafulvalene (TTF) units can be switched between two states chemically in water by utilizing an amine as the trigger^{13b} to induce pirouetting of a tetracationic cyclophane containing two different π -electron-deficient recognition units, e.g., a bipyridinium (BIPY²⁺) and a diazapyrenium (DAP²⁺) unit. The system, however, relies on a reversible coordination process which attenuates the electron deficiency of the DAP²⁺ unit to induce the pirouetting motion. In order to develop AMs which operate in water, it is desirable to create MIMs that can be switched between two states by varying the pH of the aqueous solution¹⁴ as opposed to relying upon a coordination event. Herein, we present an acid–base switchable [2]catenane **1**·4Cl (Scheme 1) which can undergo (Figure 1) mechanically induced motion in water, simply by altering the pH of its aqueous solution, between the **1**⁴⁺ state and the protonated **1**-H₂⁶⁺ state.

Scheme 1. Synthesis of **1**·4Cl^a



^aConditions and reagents: (a) Cs₂CO₃, DMF, 80° C, 35%; (b) (i) DMF, RT, 4d, (ii) MeCN, TBACl, rt, 48%.

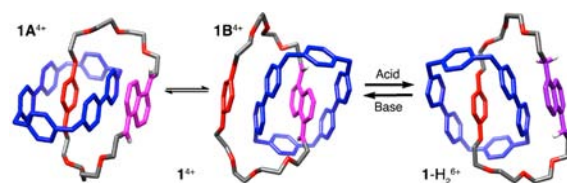


Figure 1. Translational isomerism between **1A**⁴⁺ and **1B**⁴⁺ and pH-triggered switching of the bistable [2]catenane **1**⁴⁺ which exists both in solution (78:22) and in the solid state (32:68) as a mixture of **1A**⁴⁺ and **1B**⁴⁺, respectively. Acid converts **1**⁴⁺ into **1**-H₂⁶⁺ (protonation of the DAN nitrogen atoms) and base **1**-H₂⁶⁺ into **1**⁴⁺. These three compounds are illustrated as X-ray crystal structures in their tubular representations. In addition to disordered Cl[−] counterions, solvent molecules and hydrogen atoms are omitted for the most part for the sake of clarity.

The bistable [2]catenane consists of two mechanically interlocked rings, one, an electron-deficient tetracationic cyclophane, cyclobis(paraquat-*p*-phenylene)¹⁵ (CBPQT⁴⁺), and the other, a crown ether containing a hydroquinone (HQ) unit and a 1,5-diaminonaphthalene (DAN) unit, both competing¹⁶ to reside inside the cavity of the CBPQT⁴⁺ ring in aqueous solution. The [2]catenane **1**⁴⁺ exists as two translational isomers **1A**⁴⁺ (DAN inside CBPQT⁴⁺) and **1B**⁴⁺ (HQ inside CBPQT⁴⁺) in the ground state. Circumrotation of the crown ether with respect to the CBPQT⁴⁺ ring is induced (Figure 1) by protonation of the nitrogen atoms on the DAN unit. In order to probe the extent of the Coulombic effect upon the circumrotation process (Figure 1), UV/vis spectroscopy was performed (Figure 2) on pseudorotaxanes consisting of HQ-gly and DAN-gly as the

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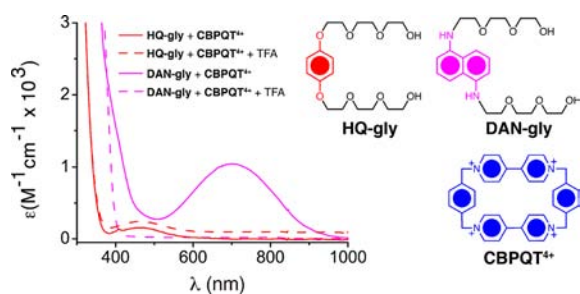


Figure 2. Partial absorption spectra of the pseudorotaxanes formed between the guests HQ-gly (red) and DAN-gly (magenta) before (solid) and after (dashed) addition of excess of TFA. In both cases, the major absorption band corresponds to the CT interaction between the guest and the host. On addition of TFA, the CT band complex for the DAN-gly complex disappears on account of the protonation of the secondary amino groups, a reaction that leads to the dissociation of the pseudorotaxanes. No change is observed in the case of the HQ-gly complex since it does not become protonated under the conditions of the experiment.

guests and CBPQT⁴⁺ as the host. Because the electron-rich guests are not soluble in water before complexation, the comparative binding study was conducted with CBPQT⁴⁺. 4PF₆ in MeCN. The formation of the charge-transfer (CT) complexes CBPQT⁴⁺CHQ-gly and CBPQT⁴⁺CDAN-gly in MeCN results in characteristic CT absorption bands (solid lines in Figure 2) at ca. 476 and ca. 720 nm, respectively. Upon addition of an excess of trifluoroacetic acid (TFA), the UV/vis spectrum of the CBPQT⁴⁺CHQ-gly complex at ca. 720 nm disappeared entirely, indicating dissociation of the donor-acceptor (DA) complex. The disruption of the DA complex in MeCN suggests that an analogous Coulombic interaction between the DAN unit and the CBPQT⁴⁺ ring in the bistable

[2]catenane 1·4Cl will occur in water, thus inducing the circumrotation process (Figure 1) to occur on the addition of acid.

The bistable [2]catenane was obtained (Scheme 1), after workup, as 1·4PF₆ from the template-directed reaction¹⁷ between the template 4 and 5·2PF₆ and 6 in MeCN. In order to render the bistable [2]catenane soluble in water, the PF₆⁻ anions in 1·4PF₆ were exchanged with Cl⁻ anions using tetrabutylammonium chloride (TBACl) to afford 1·4Cl after purification by HPLC (See Supporting Information (SI)). Analysis (Figure 3a) of 1·4Cl by ¹H NMR spectroscopy in D₂O at room temperature revealed the presence of two translational isomers, a major (78%) one 1A⁴⁺, where the DAN unit is located inside the cavity of the CBPQT⁴⁺ ring, and a minor (22%) one 1B⁴⁺, where the HQ unit resides inside the cavity. By utilizing ¹H NMR correlation spectroscopy (COSY), heteronuclear multiple bond correlation (HMBC), and heteronuclear single-quantum correlation (HSQC) experiments, all the ¹H signals for the two translational isomers, 1A⁴⁺ and 1B⁴⁺, could be assigned: see Figure 3b and Figures S1–S4 in the SI. The resonances for 1A⁴⁺ at 8.96/8.80, 7.23/7.20, and 8.03/7.99 ppm are assigned to H_{α1}/H_{α2}, H_{β1}/H_{β2}, and H₃/H_b on the CBPQT⁴⁺ ring, respectively, while the signals for the DAN unit, located inside the CBPQT⁴⁺ ring, appear at 6.00 (H_{3/7}), 5.94 (H_{2/6}), and 1.40 (H_{4/8}) ppm, and for the HQ unit alongside the CBPQT⁴⁺ ring at 6.13 (H_{HQ}) ppm. The two heterotopic sets (H_{α1}/H_{α2}) of eight α protons and the two heterotopic sets (H_{β1}/H_{β2}) of eight β protons on the two bipyridinium (BIPY²⁺) units, as well as the two heterotopic sets (H_a/H_b) for the eight paraxylylene protons, are a consequence of the DAN unit imposing its local C_{2h} symmetry on the BIPY²⁺ units which are rendered equivalent as a result of rapid pirouetting of the HQ unit around the CBPQT⁴⁺ ring on the ¹H NMR time scale at room temperature. In the case

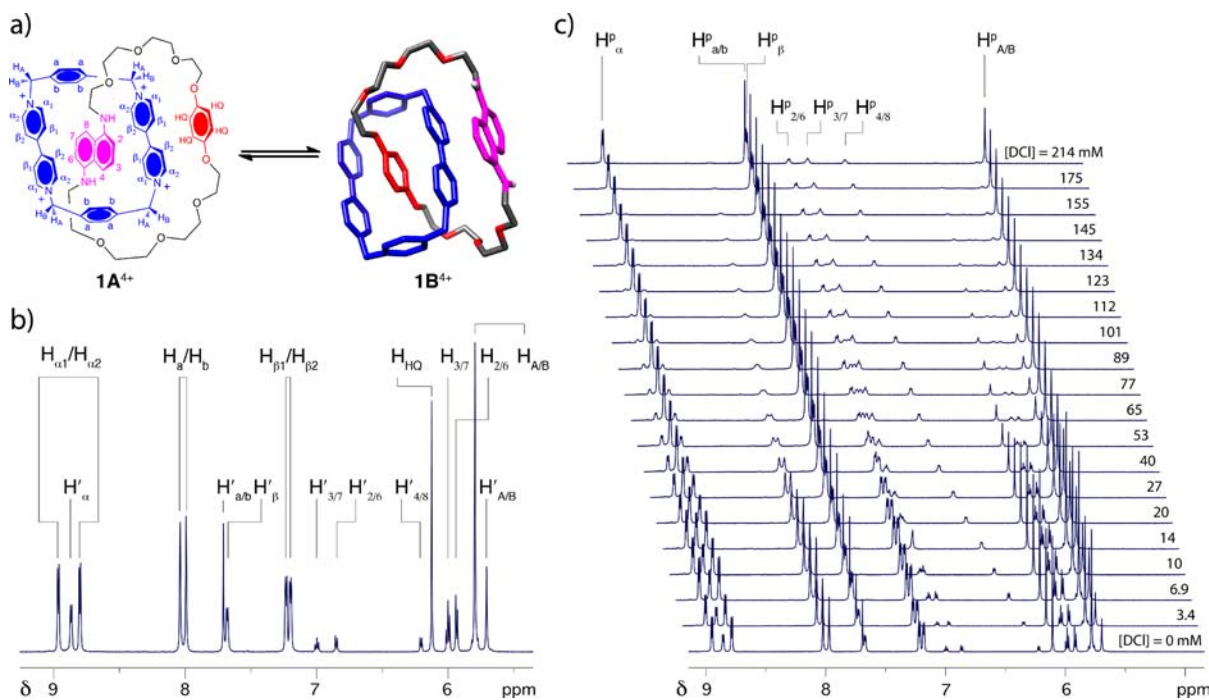


Figure 3. (a) Equilibrium in D₂O between 1A⁴⁺ (structural formula showing the proton assignments) and 1B⁴⁺ (solid-state structure) of 1·4Cl. (b) Partial ¹H NMR (600 MHz, D₂O, 298 K) spectrum of the equilibrium mixture of the major (1A⁴⁺) and minor (1B⁴⁺) isomers. The peaks labeled with primes correspond to 1B⁴⁺. From integration, the ratio of 1A⁴⁺ to 1B⁴⁺ was found to be 78:22. (c) ¹H NMR titration with DCl in D₂O. Increasing the [DCl] to 214 mM results in complete protonation of the DAN unit and the conversion of the 1A⁴⁺/1B⁴⁺ isomeric mixture to 1·D₂⁶⁺.

of $\mathbf{1B}^{4+}$, all eight of the α protons (H'_{α}) and all eight of the β protons (H'_{β}) on the two equivalent BIPY $^{2+}$ units are homotopic and so only two resonances are observed at 8.86 and 7.68 ppm, respectively. The eight paraxylylene protons $\text{H}'_{a/b}$ are all homotopic and resonate at 7.71 ppm, as are the eight CH_2 protons which resonate at 5.71 ppm. The signal for the HQ unit appears at 3.35 ppm, while those for the alongside DAN unit resonate at 7.00 ($\text{H}'_{3/7}$), 6.85 ($\text{H}'_{2/6}$), and 6.21 ($\text{H}'_{4/8}$) ppm.

Single crystals of the [2]catenane were obtained by slow diffusion of Me_2CO into an aqueous solution of $\mathbf{1}\cdot\mathbf{4Cl}$. X-ray analysis¹⁸ revealed^{19,20} the presence (Figure 1) of $\mathbf{1A}^{4+}$ and $\mathbf{1B}^{4+}$ in the same crystal in a ratio of 32:68, respectively, with the two translational isomers packed randomly in a $[\pi\cdots\pi]$ stacking mode. Red single crystals of $\mathbf{1}\cdot\text{D}_2\text{-}^6\text{Cl}$ were obtained by cooling a D_2O solution of the [2]catenane containing DCl down to 277 K. As expected, X-ray analysis¹⁸ revealed²¹ (Figure 1) that the HQ unit resides inside the CBPQT $^{4+}$ ring. Somewhat surprisingly, however, the crystal packing (Figure S15) in the SI is governed by $[\pi\cdots\pi]$ stacking of the tetradeuterated DAN $^{2+}$ units located intra- and intermolecularly between two BIPY $^{2+}$ with a plane-to-centroid distance of only 3.22 Å in the latter case.

In order to probe the switching of the [2]catenane in H_2O using acid/base triggers, titration experiments employing HCl and DABCO (1,4-diazabicyclo[2.2.2]octane) have been monitored (Figure 4 and Figures S12 and S13 in the SI) by UV/vis

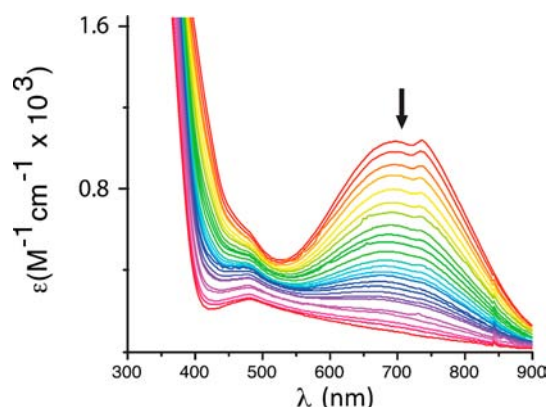


Figure 4. UV/vis titration of $\mathbf{1}\cdot\mathbf{4Cl}$ in H_2O (5×10^{-4} M). Addition of 0.6 M aqueous HCl (in 0.5 μL aliquots) leads to protonation of the DAN unit which is obliged to leave the cavity of the CBPQT $^{4+}$ ring, resulting in a decrease in the CT band at ca. 720 nm. During the addition of the HCl a CT band appears at ca. 476 nm, indicating that the HQ unit is now occupying the cavity of the CBPQT $^{4+}$ ring.

spectroscopy. A neutral 0.5 mM solution of $\mathbf{1}\cdot\mathbf{4Cl}$ displays a green color, arising from an absorption band at ~ 720 nm, which can be attributed to a DAN·CBPQT $^{4+}$ charge transfer (CT) interaction. Upon the stepwise addition of 0.6 M HCl, this CT band starts to disappear gradually as a new band emerges at ~ 476 nm producing a red color that can be associated with an HQ·CBPQT $^{4+}$ CT interaction. The evolution of both CT bands supports the argument that the CBPQT $^{4+}$ ring is encircling the DAN unit at neutral pH and the HQ unit at acidic pH's. The switching which occurs by circumrotation of the crown ether through the CBPQT $^{4+}$ ring can be reversed by the stepwise addition of 0.6 M DABCO to a red solution of $\mathbf{1}\cdot\text{H}_2\text{-}^6\text{Cl}$.

^1H NMR titration experiments were also performed on the [2]catenane in D_2O using DCl and DABCO as the acid/base triggers. A 1.15 M DCl/ D_2O solution was added in 1.5 μL aliquots to a 3.5 mM solution of $\mathbf{1}\cdot\mathbf{4Cl}$ in D_2O , and ^1H NMR

spectra (Figure 3c) were recorded at room temperature after equilibration. Initially, only 22% ($\mathbf{1B}^{4+}$) of the HQ units reside inside the CBPQT $^{4+}$ ring. Upon deuteration (protonation) of the nitrogen atoms, the resonances ($\text{H}^{\text{P}}_{2/6}$, $\text{H}^{\text{P}}_{3/7}$, $\text{H}^{\text{P}}_{4/8}$) shift downfield as Coulombic repulsion in $\mathbf{1A}^{4+}$ induces the crown ether to circumrotate through the CBPQT $^{4+}$ ring until 100% of the HQ units reside inside it. All the resonances for this translational isomer ($\mathbf{1}\cdot\text{D}_2\text{-}^6\text{Cl}$, Figure 1) were confirmed in the COSY ^1H NMR spectra (Figure S8 in the SI). Back titrating $\mathbf{1}\cdot\text{D}_2\text{-}^6\text{Cl}$ with a 1.15 M solution of DABCO restored the distribution of $\mathbf{1A}^{4+}$ to $\mathbf{1B}^{4+}$ to that of a 78:22 ratio. The reproducibility and stability of this acid–base switch was established by performing (Figure 5) five complete cycles, monitored by ^1H NMR spectroscopy (Figure S11).

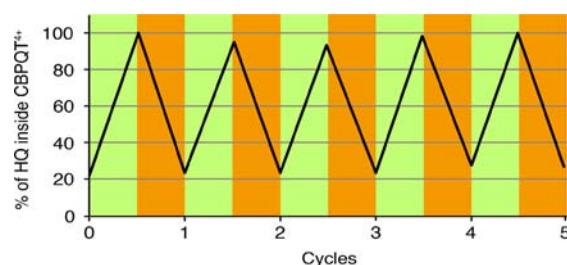


Figure 5. Acid/base switching of the [2]catenane $\mathbf{1}\cdot\mathbf{4Cl}$ monitored by ^1H NMR spectroscopy. Addition of 1.15 M DCl in D_2O leads to protonation of the DAN unit and buildup (pale green stripe) of the HQ unit inside the CBPQT $^{4+}$ ring. This process can be reversed on addition of 1.15 M DABCO in D_2O . Repeating this procedure of acid/base addition leads to a reversible interconversion between $\mathbf{1}^{4+}$ and $\mathbf{1}\cdot\text{D}_2\text{-}^6\text{Cl}$, which has been driven through five complete cycles without any visible signs of decomposition.

The fact that a bistable [2]catenane can be induced to undergo large amplitude, relative motions, while being switched between two different states by changing the pH of an aqueous solution, raises the possibility of developing integrated nanobiomechanical systems at a level commensurate with molecular prosthetics.²²

■ ASSOCIATED CONTENT

📄 Supporting Information

Synthesis and characterization of all compounds and additional experimental results. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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- (16) Typically, the equilibrium (Figure 1) between the two translational isomers, $1A^{4+}$ and $1B^{4+}$, of 1^{4+} depends on a combination of $[\pi \cdots \pi]$ and $[C-H \cdots O]$ interactions. The former are enhanced in aqueous solution on account of hydrophobic forces, whereas the $[C-H \cdots O]$ interactions become stifled in water. DAN is a stronger electron donor than HQ, leading to DAN being sited preferably inside the CBPQT $^{4+}$ acceptor, resulting in $1A^{4+}$ being the favored translational isomer in the ground state. See: (a) Oslovsky, G. V.; Reinhoudt, D. N.; Verboom, W. *Angew. Chem., Int. Ed.* **2007**, 46, 2366–2393. (b) Martinez, C. R.; Iverson, B. L. *Chem. Sci.* **2012**, 3, 2191–2201.
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- (18) Crystallographic data for 1-4Cl, 1-4PF $_6$, and 1-D $_2$ -6Cl have been deposited with the Cambridge Crystallographic Data Center under supplementary publication nos. CCDC-956146, 956144, and 956145, respectively.
- (19) Both translational isomers $1B^{4+}$ and $1A^{4+}$ were obtained from one crystal in a 68:32 ratio of HQ-inside:DAN-inside the CBPQT $^{4+}$ ring. Their crystal structures are shown in Figure 1. The observation that the ratio of the two translational isomers is inverted in solution and the solid state is currently unknown. The crystal packing of $1B^{4+}/1A^{4+}$ is random. Crystal parameters for $1B^{4+}/1A^{4+}$: C $_{68}$ H $_{76}$ Cl $_4$ N $_6$ O $_8$, $M_r = 1247.15$, yellow plates, crystal size 0.33 × 0.31 × 0.01 mm 3 , orthorhombic, space group *Pccn*, $a = 29.0878(6)$, $b = 10.0431(2)$, $c = 26.8906(5)$ Å, $\alpha = 90.00^\circ$, $V = 7855.6(3)$ Å 3 , $Z = 4$, $\rho_{\text{calc}} = 1.055$, $T = 100(2)$ K, $R_1(F^2 > 2\sigma F^2) = 0.1293$, $wR_2 = 0.3903$.
- (20) Slow diffusion of *i*-Pr $_2$ O into a MeCN solution of 1-4PF $_6$ produced brown single crystals suitable for X-ray analysis. Crystal parameters for 1-4PF $_6$: C $_{80}$ H $_{94}$ F $_{24}$ N $_{12}$ O $_8$ P $_4$, $M_r = 1931.55$, brown plates, crystal size 0.21 × 0.19 × 0.02 mm 3 , triclinic, space group *P* $\bar{1}$, $a = 13.34(4)$, $b = 13.59(3)$, $c = 25.053(4)$ Å, $\alpha = 86.557(8)^\circ$, $\beta = 81.545(10)^\circ$, $\gamma = 76.912(9)^\circ$, $V = 4374.1(19)$ Å 3 , $Z = 2$, $\rho_{\text{calc}} = 1.467$, $T = 100(2)$ K, $R_1(F^2 > 2\sigma F^2) = 0.0431$, $wR_2 = 0.1201$.
- (21) Crystal parameters for 1-D $_2$ -6Cl: C $_{68}$ H $_{78}$ Cl $_4$ N $_6$ O $_{16}$, $M_r = 1377.16$, red plates, crystal size 0.45 × 0.39 × 0.02 mm 3 , monoclinic, space group *P2(1)/c*, $a = 29.60(4)$, $b = 9.899(14)$, $c = 28.00(4)$ Å, $\alpha = 90.00^\circ$, $\beta = 102.00(3)^\circ$, $V = 8025(20)$ Å 3 , $Z = 4$, $\rho_{\text{calc}} = 1.140$, $T = 100(2)$ K, $R_1(F^2 > 2\sigma F^2) = 0.1285$, $wR_2 = 0.3748$.
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