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Communication

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A Water Soluble pH-Triggered Molecular Switch

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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 ^{1}H 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 molecules[1] (MIMs), which embrace a large family of bistable catenanes[2] and rotaxanes[3], have been identified as prototypes for the construction of artificial molecular switches[4] (AMSs) and machines[5] on account of our ability to exhibit control over the relative intramolecular movements of their mechanically interlocked components. This attribute has rendered bistable MIMs indispensible 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 towards 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 examples[13] 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 ($BIPY^{2+}$) and a diazapyrenium (DAP^{2+}) unit. The system, however, relies on a reversible coordination process which attenuates the electron deficiency of the DAP^{2+} unit to induce the pirouetting motion. In order to develop AMSs which operate in water, it is desirable to create MIMs that can be switched between two states by varying the pH of the aqueous solution[14] 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 $\mathbf{1}^{4+}$ state and the protonated **1**-H_2^{6+} state.

The bistable [2]catenane consists of two mechanically interlocked rings, one, an electron-deficient tetracationic cyclophane, cyclobis(paraquat-*p*-phenylene)[15] (**CBPQT**$^{4+}$) and the other a crown ether containing a hydroquinone

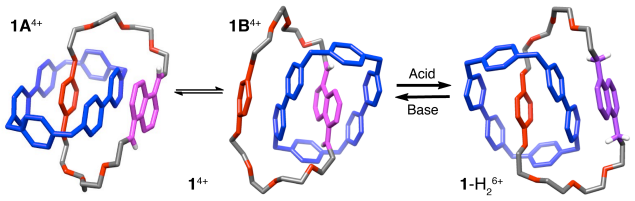
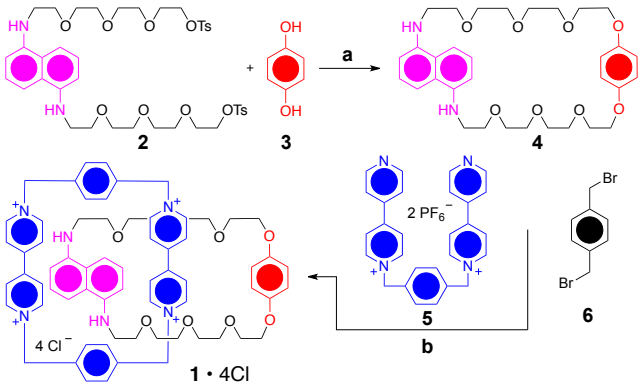


Figure 1. The translational isomerism between $\mathbf{1A}^{4+}$ and $\mathbf{1B}^{4+}$ and the pH-triggered switching of the bistable [2]catenane $\mathbf{1}^{4+}$ which exists both in solution (78:22) and in the solid state (32:68) as a mixture of $\mathbf{1A}^{4+}$ and $\mathbf{1B}^{4+}$, respectively. Acid converts $\mathbf{1}^{4+}$ into **1**-H_2^{6+} (protonation of the DAN nitrogen atoms) and base **1**-H_2^{6+} into $\mathbf{1}^{4+}$. 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.



Scheme 1. The synthesis of **1**·4Cl. Conditions and reagents: a) $CsCO_3$, DMF, 80° C, 35%; b) (i) DMF, RT, 4d, (ii) MeCN, TBACl, RT, 48%.

(HQ) unit and a 1,5-diaminonaphthalene (DAN) unit, both competing[16] to reside inside the cavity of the $CBPQT^{4+}$ ring in aqueous solution. The [2]catenane $\mathbf{1}^{4+}$ exists as two translational isomers $\mathbf{1A}^{4+}$ (DAN inside $\mathbf{CBPQT}^{4+}$) and $\mathbf{1B}^{4+}$ (HQ inside $\mathbf{CBPQT}^{4+}$) in the ground state. Circumrotation of the crown ether with respect to the $CBPQT^{4+}$ 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 guests and $\mathbf{CBPQT}^{4+}$ as the host. Because the electron-rich guests are not soluble in water before complexation, the comparative binding study was conducted with $\mathbf{CBPQT}^{4+}\cdot 4PF_6$ in MeCN. The formation of the charge-transfer (CT) complexes $\mathbf{CBPQT}^{4+}\subset$**HQ-gly** and $\mathbf{CBPQT}^{4+}\subset$**DAN-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

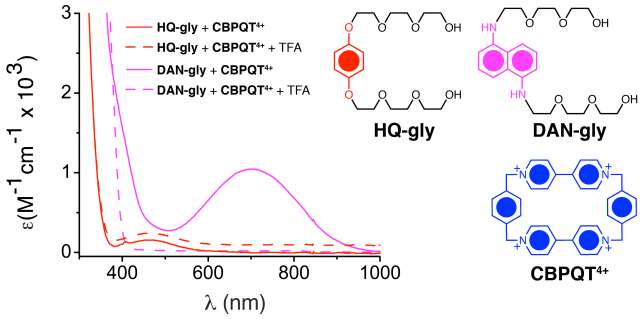


Figure 2. Partial absorption spectra of the pseudorotaxanes formed between the guests **HQ–gly** (red) and **DAN–gly** (magenta) before (solid) and after (dashed) addition of excess of TFA. In both cases, the major absorption band corresponds to the CT interaction between the guest and the host. On addition 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.

acid (TFA), the UV/Vis spectrum of the **CBPQT^{4+}⊂HQ-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 work-up, as **1**·4PF$_6$ from the template-directed reaction[17] between the template **4** and **5**·2PF$_6$ and **6** in MeCN. In order to render the bistable [2]catenane soluble in water, the PF$_6^-$ anions in **1**·4PF$_6$ were exchanged with Cl$^-$ anions using tetrabutylammonium chloride (TBACl) to afford **1**·4Cl after purification by HPLC (See Supplementary Information (SI)). Analysis (Figure 3a) of **1**·4Cl by ^{1}H NMR spectroscopy in D$_2$O at room temperature revealed the presence of two translational isomers, a major (78%) one **1A**$^{4+}$, where the DAN unit is located inside the cavity of the CBPQT^{4+} ring, and a minor (22%) one **1B**$^{4+}$, where the HQ unit resides inside the cavity. By utilizing ^{1}H NMR correlation spectroscopy (COSY), heteronuclear multiple bond correlation (HMBC), and heteronuclear single-quantum correlation (HSQC) experiments, all the ^{1}H signals for the two translational isomers, **1A**$^{4+}$ and **1B**$^{4+}$, could be assigned: see Figure 3b and Figures S1–S4 in the SI. The resonances for **1A**$^{4+}$ at 8.96/8.80, 7.23/7.20 and 8.03/7.99 ppm are assigned to $H_{\alpha 1}/H_{\alpha 2}$, $H_{\beta 1}/H_{\beta 2}$ and H_a/H_b on the CBPQT^{4+} ring, respectively, while the signals for the DAN unit, located inside the CBPQT^{4+} 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 CBPQT^{4+} ring at 6.13 (H_{HQ}) ppm. The two heterotopic sets ($H_{\alpha 1}/H_{\alpha 2}$) of eight α protons and the two heterotopic sets ($H_{\beta 1}/H_{\beta 2}$) of eight β protons on the two bipyridinium (BIPY^{2+}) units, as well as the two heterotopic sets (H_a/H_b) for the eight paraxylene protons are a consequence of the DAN unit imposing its local C_{2h} symmetry on the BIPY^{2+} units which are rendered equivalent as a result of rapid pirouetting of the HQ unit around the CBPQT^{4+} ring on the ^{1}H NMR time scale at room temperature. In the case of **1B**$^{4+}$, all eight of the α protons (H'_α) and all eight of the alpha 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.

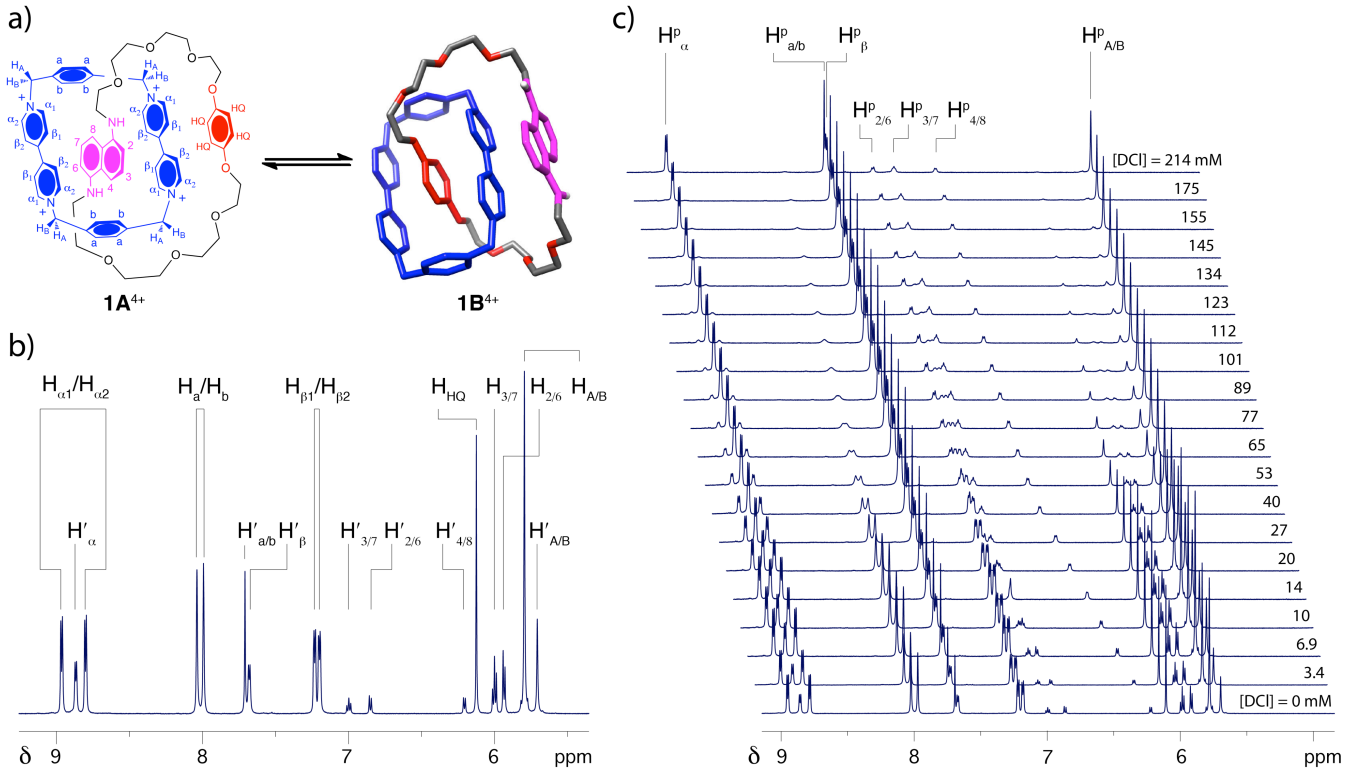


Figure 3. (a) The equilibrium in D$_2$O between **1A**$^{4+}$ (structural formula showing the proton assignments) and **1B**$^{4+}$ (solid-state structure) of **1**·4Cl. (b) Partial ^{1}H NMR (600 MHz, D$_2$O, 298 K) spectrum of the equilibrium mixture of the major (**1A**$^{4+}$) and minor (**1B**$^{4+}$) isomers. The peaks labeled with primes correspond to **1B**$^{4+}$. From integration, the ratio of **1A**$^{4+}$ to **1B**$^{4+}$ was found to be 78:22. (c) ^{1}H NMR titration with DCl in D$_2$O. Increasing the [DCl] to 214 mM results in complete protonation of the DAN unit and the conversion of the **1A**$^{4+}$ / **1B**$^{4+}$ isomeric mixture to **1**–H$_2^{6+}$.

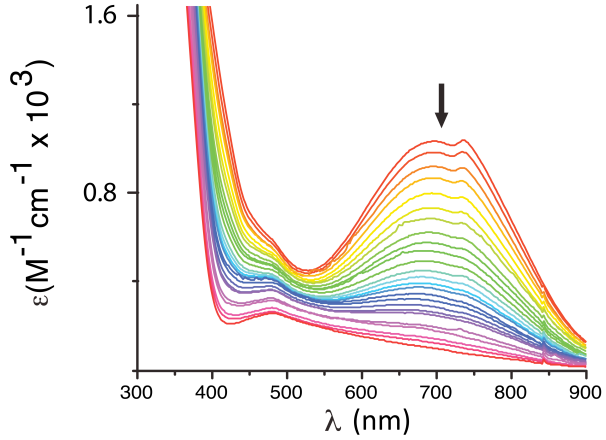


Figure 4. UV/Vis Titration of **1**·4Cl in H_2O (5 x 10^{-4} M). Addition of 0.6 M aqueous HCl (in 0.5 μL aliquots) leads to protonation of the DAN unit which is obliged to leave the cavity of the $CBPQT^{4+}$ ring, resulting in a decrease in the CT band at ca. 720 nm. During the addition of the HCl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

The eight paraxyxylene protons $H'_{a/b}$ 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 ($H'_{3/7}$), 6.85 ($H'_{2/6}$) and 6.21 ($H'_{4/8}$) ppm.

Single crystals of the [2]catenane were obtained by slow diffusion of Me_2CO into an aqueous solution of **1**·4Cl. X-Ray analysis[18] 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 [π···π] stacking mode. Red single crystals of **1**-D_2·6Cl were obtained by cooling a D_2O solution of the [2]catenane containing DCl down to 277 K. As expected, X-ray analysis[18] revealed[21] (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 [π···π] 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 spectroscopy. A neutral 0.5 mM solution of **1**·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 pHs. 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 **1**-H_2·6Cl.

^{1}H 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 **1**·4Cl in D_2O and ^{1}H 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 ($H^P_{2/6}$, $H^P_{3/7}$, $H^P_{4/8}$) 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 (**1**-D_2^{6+}, Figure 1) were confirmed in the COSY ^{1}H NMR spectra (Figure S8 in the SI). Back titrating **1**-D_2•6Cl 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 ^{1}H NMR spectroscopy (Figure S11).

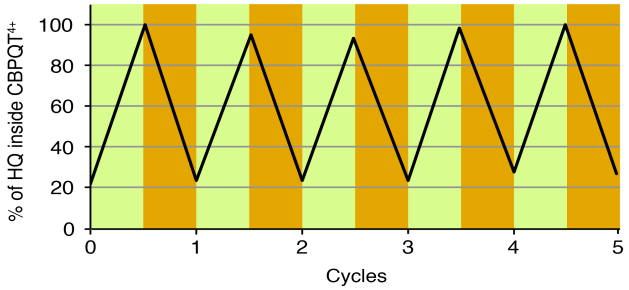


Figure 5. Acid/base switching of the [2]catenane **1**·4Cl monitored by ^{1}H NMR spectroscopy. Addition of 1.15 M DCl in D_2O leads to protonation of the DAN unit and build-up (pale green stripe) of the HQ unit inside the $CBPQT^{4+}$ ring. This process can be reversed on addition of 1.15 M DABCO in D_2O. Repeating this procedure of acid/base addition leads to a reversible interconversion between $\mathbf{1}^{4+}$ and **1**-H_2^{6+}, 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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(16) Typically, the equilibrium (Figure 1) between the two translational isomers – $\mathbf{1A}^{4+}$ and $\mathbf{1B}^{4+}$ – of $\mathbf{1}^{4+}$ depends on a combination of [π···π] and [C–H···O] interactions. The former are enhanced in aqueous solution on account of hydrophobic forces, whereas the [C–H···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 $\mathbf{1A}^{4+}$ 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 $\mathbf{1B}^{4+}$and $\mathbf{1A'}^{4+}$ 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 inversed in solution and the solid state is currently unknown. The crystal packing of $\mathbf{1B}^{4+}/\mathbf{1A}^{4+}$ is random. Crystal parameters for $\mathbf{1B}^{4+}/\mathbf{1A'}^{4+}$: $C_{68}H_{76}Cl_4N_6O_8$, M_r = 1247.15, yellow plates, crystal size 0. 33 x 0.31 x 0.01 mm, orthorhombic, space group *Pccn*, a = 29.0878(6), b = 10.0431(2), c = 26.8906(5) Å, α= 90.00 °, V = 7855.6(3) Å^3, Z = 4, ρ_{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_2O into a MeCN solution of **1**·$4PF_6$ produced brown single crystals suitable for X-ray analysis. Crystal parameters for **1** • $4PF_6$: $C_{80}H_{94}F_{24}N_{12}O_8P_4$, M_r = 1931.55, brown plates, crystal size 0.21 x 0.19 x 0.02 mm, Triclinic, space group *P-1*, a = 13.34(4), b = 13.59(3), c = 25.053(4) Å, α= 86.557(8) β = 81.545(10)° γ = 76.912(9), V = 4374.1(19) Å^3, Z = 2, ρ_{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$_2$**$^{6+}$•6Cl: $C_{68}H_{78}Cl_4N_6O_{16}$, M_r = 1377.16, Red plates, crystal size 0.45 x 0.39 x 0.02 mm, monoclinic, space group *P2(1)/c*, a = 29.60(4), b = 9.899(14), c = 28.00(4) Å, α= 90.00 β = 102.00(3)°, V = 8025(20) Å^3, Z = 4, ρ_{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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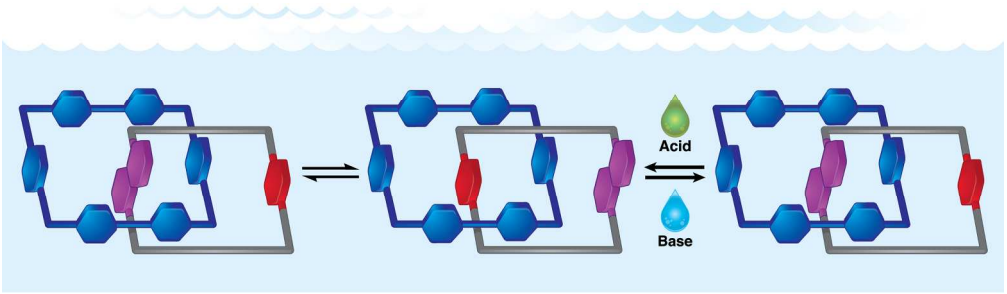

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