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COMMUNICATION

A multiple-responsive water-soluble [3]pseudorotaxane constructed by pillar[5]arene-based molecular recognition and disulfide bond connection

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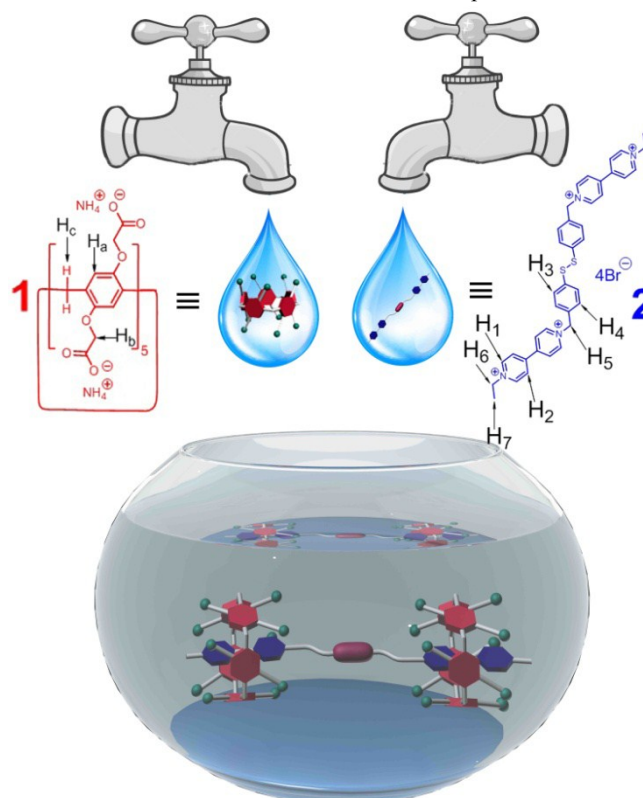
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A multiple-responsive water-soluble [3]pseudorotaxane was constructed by water-soluble pillar[5]arene-based molecular recognition and disulfide bond connection, showing multiple-responsive properties coming from non-covalent interactions and disulfide bond.

Pseudorotaxanes,¹ one of the typical representatives of interpenetrating structure molecules,² have attracted much attention owing to their unique topologies. They are constructed from linear and cyclic components through a variety of noncovalent forces, such as hydrogen bonding,^{3a} π - π stacking interactions,^{3b} hydrophobic interactions,^{3c} and host-guest interactions.^{3d,3e} On the basis of the dynamic property of the association and dissociation, pseudorotaxanes can be endowed with the functions of control/release and lock/key. It allows them to be applied in the construction of various molecular devices such as switches,^{4a} sensors,^{4b} logic gates,^{4c} and nanovalves.^{4d} The conversion between association and dissociation under external stimuli is considered as responsiveness.⁵ There are a wide variety of available stimuli, including chemical stimuli,^{6a} photochemical stimuli,^{6b} redox stimuli,^{6c} or other control elements.^{6d,6e} The introduction of more stimuli-responsiveness into pseudorotaxanes will endow pseudorotaxanes with more functions and make them more adaptive to the environment. In view of the advantages of stimuli-responsiveness, many stimuli-responsive materials have been widely used in many fields, such as the construction of intelligent materials, preparation of biological materials, and drug delivery.⁵ However, most reported pseudorotaxanes are prepared in organic solvents and only a relatively few examples of pseudorotaxanes that can be switched in water have been reported.^{7f-h} In order to expand more applications derived from pseudorotaxanes, we are looking currently toward their operation in aqueous solution where most biological processes based on motor proteins express their functions, for example, myosin,^{7a} ATP-ase,^{7b} kinesin,^{7c} and bacterial flagella.^{7d,7e}

Pillararenes, mainly including pillar[5]arenes⁸ and pillar[6]arenes,⁹ are a new generation of macrocyclic hosts for supramolecular chemistry. Their repeating units are connected by

45 methylene bridges at the *para*-positions, forming a special rigid pillar-like architecture. Pillararenes have been endowed with outstanding abilities to selectively bind different kinds of guests and used to construct various interesting supramolecular systems, including cyclic dimers,^{10a} chemosensors,^{10b,10f,10n} transmembrane channels,^{10c} supramolecular polymers,^{8b,10d} MOFs,^{10g} electrochemistry,^{10h,10i} battery,^{10j} antibacterial,^{10k} drug delivery,^{10l,10m} material science^{10o,10p} and liquid crystals^{10e} for their unique structures and easy functionalization since their first synthesis in 2008.⁸ⁱ Especially, it has been demonstrated that 55 water-soluble pillar[5]arenes^{8a,f,9c} are excellent hosts for molecules of various sizes and shapes in water.



Scheme 1. Chemical structures of **1** and **2**, and the illustration of the formation of the [3]pseudorotaxane in water.

Moreover, pillar[5]arene-based molecular recognition has been utilized to construct many pH-responsive supramolecular materials in water^{8a,f,9c,d,e} for the reason that the pillar[5]arene-based host-guest complexes can be disassembled by adding acid into water. The disulfide bond, a kind of the dynamic covalent bond with dynamic and reversible properties, can be broken and reformed quickly. On account of its redox and photo responsiveness in nature, it can be applied for fabricating various stimuli-responsive or self-healing materials.^{11,12} Therefore, a multiple-responsive water-soluble [3]pseudorotaxane was prepared in water, whose responsiveness were from pillar[5]arene-based host-guest interactions and the disulfide bond.

As shown in Scheme 1, **1** is a water-soluble pillar[5]arene and **2** is a paraquat derivative containing disulfide bond. It is well-known that a pillar[5]arene and paraquat can self-assemble into a 1 : 1 complex. Therefore, **2** can associate with two **1** to form a [3]pseudorotaxane in water. The [3]pseudorotaxane has pH responsiveness coming from the pillar[5]arene-based host-guest interactions. Moreover, the [3]pseudorotaxane can be endowed with redox and photo responsiveness^{11,12} by the disulfide bond. Therefore, the [3]pseudorotaxane has multiple responsivenesses in water.

The complexation between **1** and **2** was first studied by ¹H NMR spectroscopy experiment, which gave direct evidence for the complexation of **1** and **2**. As shown in Figure 1, when two equivalents of **1** (5.00 mM) was added into a D₂O solution of **2** (2.50 mM), the signals related to the protons on **2**, such as H₁, H₂, and H₃, shifted upfield significantly. The reason is that these protons located within the cavity of **1** and they were shielded by the electron-rich cyclic structure upon forming a threaded structure between **1** and **2**. On the other hand, H_a and H_b on the host **1** shifted downfield significantly and H_c on the host **1** shifted upfield due to the interactions between **1** and **2**.

Apart from proton NMR, NOESY NMR examination is a useful tool to study the relative positions of building components in host-guest inclusion complexes. From the 2D NOESY spectrum (Fig. 2) of a mixture of 30.0 mM **1** and 15.0 mM **2** in D₂O, correlations were observed between protons H₁–H₅ of **2** and protons H_a on **1**, suggesting that paraquat groups were threaded into the cavity of **1**. Therefore, it was confirmed that when **2** was mixed with **1**, the paraquat parts of **2** penetrated through the cavity of **1**. The formation of the complex between **1** and **2** was mainly driven by multiple electrostatic interactions between the carboxylate anionic groups on **1** and the cationic pyridinium units of **2**, hydrophobic interactions, and π - π stacking interactions between the benzene rings on the host **1** and the pyridinium rings on guest **2** in water.

Further evidence for the formation of a stable host-guest complex **1**⊃**2** was obtained from fluorescence titration experiments and electrospray ionization mass spectrum of **1**⊃**2** in H₂O (Figure S5, ESI[†]). As shown in Fig. 3, the quenching of fluorescence intensity was found to be significant upon gradual addition of **2**. A mole ratio plot based on the fluorescence titration experiments demonstrated that the complex between **1** and **2** had a 2:1 stoichiometry (Figure

S6, ESI[†]).

Therefore, according to the above experiment results, we can know that when **2** and **1** were mixed in water, a [3]pseudorotaxane of **1**⊃**2** formed.

It was envisioned that the assembly and disassembly between **1** and **2** can be reversibly controlled by sequential addition of DCI and NaOD aqueous solutions for the reason that anionic carboxylate groups and neutral carboxylic groups can be interconverted by changing the solution pH. In order to testify this reversible process, ¹H NMR spectroscopy experiment was conducted (Fig. S7, ESI[†]). When an aqueous DCI solution was added into a solution containing **1** and **2**, H₁–H₅ of **2** shifted downfield and became sharp. Simultaneously, H_a on **1** disappeared. This was because when the aqueous DCI solution was added into a solution containing **1** and **2**, the carboxylate groups on **1** changed into carboxylic acid groups, resulting in the precipitation of water-insoluble protonated **1** and decomplexation between **1** and **2**. Then when we continued to add NaOD to the solution, H₁–H₅ of **2** shifted upfield and became broad, H_a on **1** appeared again. The reason is the deprotonation of carboxylate groups on both rims of **1**. These phenomena indicated the reformation of the complex between **1** and **2**. Therefore, through the ¹H NMR spectra (Fig. S7, ESI[†]), it was confirmed that the [3]pseudorotaxane is pH-responsive.

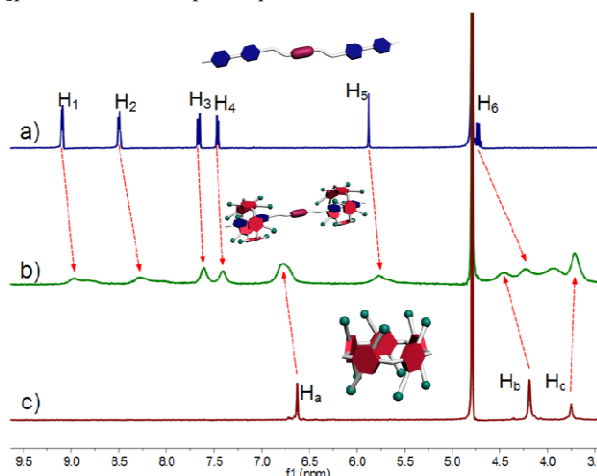


Fig. 1 Partial ¹H NMR spectra (400 MHz, D₂O, 298K): a) **2**; (b) 5.00 mM **1** and 2.50 mM **2**; (c) **1**.

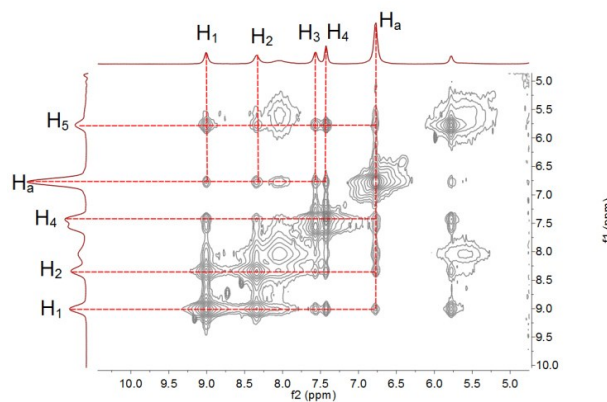


Fig. 2 Partial NOESY NMR spectrum (500 MHz, D₂O, 298 K) of 30.0 mM **1** and 15.0 mM **2**.

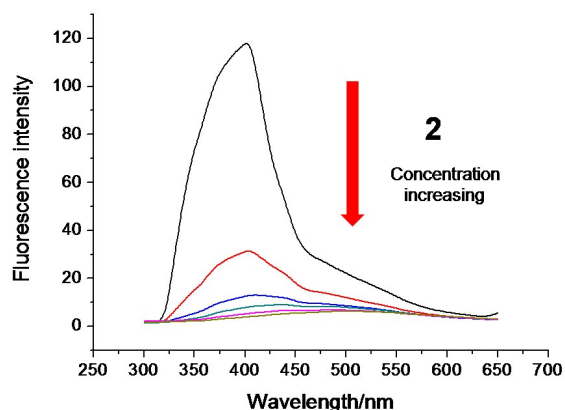


Fig. 3 Fluorescence spectra of **1** (1.00×10^{-6} M) in water at room temperature with different concentrations of **2**: 0, 0.450, 0.980, 2.10, 2.93, and 4.15×10^{-6} M. Excitation wavelength $\lambda = 280$ nm and the solution pH value is 7.

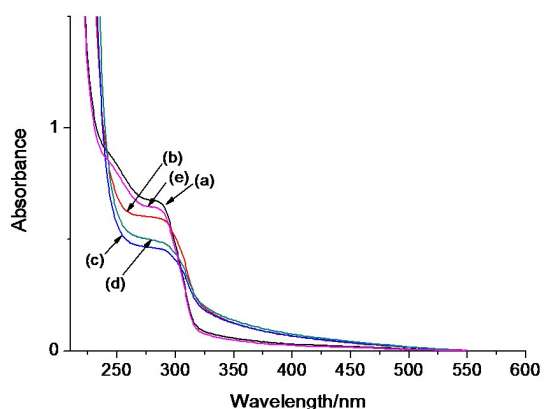


Fig. 4 UV-vis spectra of (a) the solution containing 0.200 mM **1** and 0.100 mM **2**; (b) after addition of 0.308 mg (1 equiv.) of GSH to (a); (c) after addition of 0.308 mg (1 equiv.) of GSH to (b); (d) after addition of 0.100 μ L (1 equiv.) of H₂O₂ to (c); (e) after addition of 0.100 μ L of H₂O₂ to (d).

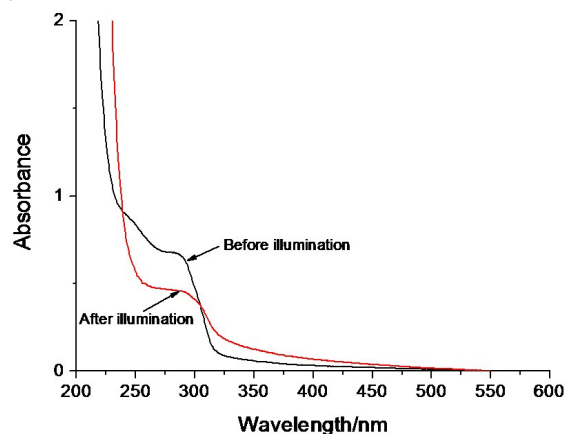


Fig. 5 UV-vis spectra of the solution containing 0.200 mM **1** and 0.100 mM **2** before and after illumination for 10 h.

Among various dynamic covalent bonds, disulfide bond is very attractive owing to its rich responsivenesses.^{11,12} Accordingly, disulfide bonds can be applied to prepare various stimuli-responsive materials. The breaking and formation of disulfide bonds can be regulated by redox, which means disulfide bonds

have redox-responsiveness. Here, L-glutathione (GSH) as a reductant was applied to destroy the disulfide bonds in the [3]pseudorotaxane.¹¹ Correspondingly, H₂O₂ as an oxidant was applied to oxidize the disulfide bonds.¹¹ An ultraviolet experiment (Fig. 4) and ¹H NMR spectroscopy experiment (Fig. S8, ESI[†]) were conducted to validate this reversible process. As shown in Fig. 4, after GSH was gradually added to the solution containing 0.200 mM **1** and 0.100 mM **2**, the UV absorbance at 285 nm decreased obviously, indicating the breakdown of the disulfide bond in **2**. Then, the UV absorbance at 285 nm increased again after continuously adding H₂O₂ to the solution, indicating the formation of the disulfide bond. Moreover, according to the ¹H NMR experiments (Fig. S8, ESI[†]), when GSH was added into the solution containing 5.00 mM **1** and 2.50 mM **2**, the signals of H₁, H₃ and H₄ split obviously. Simultaneously, H₃ and H₄ shifted upfield. This phenomenon illustrated the cleavage of disulfide bond in **2**. After that, H₂O₂ was added into the solution, the signals of H₁, H₃ and H₄ got back to the original states, indicating the formation of the disulfide bond. According to the above results, the introduction of disulfide bonds endowed the [3]pseudorotaxane with redox responsiveness.

In addition, disulfide bond is known to be labile upon UV irradiation treatment, which could make the disulfide bond damaged.¹² For this reason, the [3]pseudorotaxane containing disulfide bond could be damaged by UV at 265 nm, which could be monitored by UV-vis spectra. As shown in Fig. 5, when the mixture of 0.200 mM **1** and 0.100 mM **2** was irradiated by UV at 265 nm for 10 h, the UV absorbance at 285 nm decreased obviously, indicating the breakdown of the disulfide bond in **2**. Similarly, this process could be monitored by ¹H NMR (Fig. S9, ESI). After the solution of 5.00 mM **1** and 2.50 mM **2** was irradiated by UV at 265 nm for 10 h, the signals of H₃ and H₄ shifted upfield, indicating that the disulfide bond was fractured. Therefore, the disulfide bond endowed the [3]pseudorotaxane with photo responsiveness. The cartoon schematic of the expected effect of breaking and forming the disulfide bond on guest **2** in pseudorotaxane formation was shown in Fig. S15.

In summary, we have prepared a multiple-responsive water-soluble [3]pseudorotaxane constructed by the self-assembly of water-soluble pillar[5]arene **1** and bisparaquat salt **2** containing disulfide bond, which possessed multiple-responsive properties coming from non-covalent interactions and the disulfide bond. Through the characterizations of NMR spectroscopy, NOESY and fluorescence titration spectroscopy, we confirmed that **1** and **2** formed a stable 2:1 inclusion complex in water. More interestingly, due to pH-responsiveness of the pillar[5]arene-based host-guest interactions, the interactions between **2** and **1** could be reversibly controlled by adjusting the pH of the solution. Moreover, on account of the dynamic nature of the disulfide bond, the [3]pseudorotaxane is endowed with redox and photo responsivenesses. Therefore, the [3]pseudorotaxane possesses multiple responsivenesses. These responsivenesses can be controlled in water and afford us a better chance to imitate natural catalysts and motor molecules with artificial molecular switches/machines. This demonstration opens up opportunities for developing integrated nano biomechanical systems in the direction of applications such as molecular prosthetics.¹³

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Notes and references

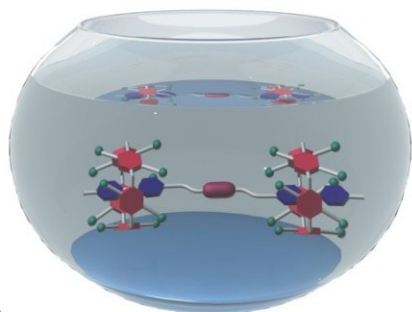
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Text:

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