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Triggering a [2]rotaxane molecular shuttle through hydrogen sulfide

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A novel chemically-controlled [2]rotaxane molecular shuttle was successfully designed and synthesized. A H_2S-responsive bulk barrier was introduced between the two identical recognition stations of the [2]rotaxane to prevent dynamic shuttling of the macrocycle. Upon addition of H_2S, the complete intramolecular cascade reaction occurs in a controllable manner, resulting in removal of the bulk barrier and the shuttling motion of the macrocycle between the two stations recovers.

rotaxane, molecular shuttle, chemically-controlled, hydrogen sulfide, stimuli-responsive

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1 Introduction

Biomolecular machines have attracted increasing attention, because their linear or rotational motion could implement the various functions in biology [1]. Rotaxanes [2], catenanes [3], and motors [4] have been created and developed as artificial molecular machines to mimic the biological motors by synthetic chemists. Among these molecular machines, rotaxanes, known as a kind of mechanically interlocked molecules (MIMs) [5], in which macrocycle is encircled onto a dumbbell-shaped thread, have been proved to be versatile as molecular switches [6], molecular muscles [7], nano-pumps [8] and nano-valves [9]. These functional applications are mostly based on bistable rotaxane molecular shuttles, in which the macrocycles can be switched to move between different stations by chemical [10], electrochemical [8a] and photochemical inputs [11]. However, there are few reports on the molecular shuttles controlled by chemical small-molecules [12]. Recently, some novel strategies for chemically controlled rotaxanes have been reported, such as steric hindrance strategy [13] and varied identical station strategy [14]. These intelligent driving modes triggering the molecular shuttling motion can broaden the strategies for the construction of multi-level molecular machines and the application of molecular machines in biological systems. Nowadays, molecular machines are progressively applied in biology, employing the bioactive molecules as external triggers directly to stimulate molecular machines [15]. The advantage of this novel strategy is to prevent the biological damage from chemical reagents. However, it is still a tremendous challenge to build a biomimetic molecular machine which can sense the biomolecular signal.

Hydrogen sulfide (H_2S), which is considered to be a toxic gas in the atmosphere, is an important neuromodulator and cell signaling molecule. In cells, H_2S can be produced by decomposition of *L*-cysteine via cystathionine γ-lyase (CSE) mediated [16]. *O*-azido-methylbenzoate (AzMB), known as a sensitive self-cleavable precursor, can be reduced into benzylamine by H_2S, leading to the formation of indolin-1-one after a series of intramolecular cascade reactions [17]. Although AzMB has been widely developed for protection of

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the hydroxyl and amino in nucleosides [18], no effort was made for the construction of chemically-controlled rotaxanes. We foresee that the successful introduction of the bioactive group such as AzMB group would significantly develop and enrich the chemically controlled rotaxane systems.

Herein we report, for the first time, a successful triggering the shuttling motion of macrocycle in a degenerate [2]rotaxane via intramolecular cascade reaction induced by H_2S, as shown in Figure 1. In this design, the H_2S responsive group AzMB is introduced and covalent-bonded into the middle of two identical sites of dumbbell-shaped thread as a bulky barrier to limit the movement of macrocycle, indicating a "gated" state that the macrocycle is localized on the one of the stations. Upon addition of H_2S, complete cascade reaction occurs in a controllable method, leading to the removal of the bulky barrier, meaning an "open" state that the balanced shuttling motion of the macrocycle between two identical stations recovers.

2 Experimental

2.1 Materials and apparatus

2-(Chloromethyl) benzoic acid methyl ester **6** [18], 2-(azidomethyl) benzoic acid **5** [19] and the dumbbell-shaped thread **4** [11b] were prepared according to the previously reported procedure. All solvents were reagent grade, which were dried and distilled prior to use according to standard procedures. The molecular structures of the unknown compounds were confirmed via ^{1}H NMR, ^{13}C NMR and high resolution-electronic spray ionization mass spectroscopy (HR-ESI MS). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brücker AM400 spectrometer (Germany). The ESI MS were tested on a LCT Premier XE mass spectrometer (Wasters, USA).

2.2 Synthesis of compound 3

A stirred solution of the dumbbell-shaped thread **4** (1.0 g, 1.2 mmol), the 2-(chloromethyl) benzoic acid methyl ester **6** (637 mg, 3.6 mmol), and 4-dimethylaminopyridine (DMAP) (147 mg, 1.2 mmol) in dimethylformamide (DMF, 15 mL) was added EDCI (917 mg, 4.8 mmol) at 25 °C. After the solution was stirred at 25 °C for 12 h, the solution was diluted with water (250 mL), and filtered through a Buchner funnel. The filter cake was washed with dichloromethane (DCM), then dried in vacuum to give compound **3** (1.19 g, 1.2 mmol). ^{1}H NMR (DMSO-d_6, 400 MHz, 298 K), δ (ppm): 8.81 (d, J=8.0 Hz, 2H), 8.30 (t, J_1=4.0 Hz, J_2=8.0 Hz, 2H), 7.85 (d, J=8.0 Hz, 1H), 7.66 (t, J_1=J_2=8.0 Hz, 1H), 7.56 (d, J=8.0 Hz, 1H), 7.50 (t, J_1=J_2=8.0 Hz, 1H), 7.33–7.21 (m, 20H), 7.16 (d, J=8.0 Hz, 4H), 6.92 (d, J=12.0 Hz, 4H), 6.11 (d, J=8.0 Hz, 2H), 5.70–5.65 (m, 1H), 4.77 (s, 2H), 4.41–4.34 (m, 4H), 4.18 (d, J=8.0 Hz, 4H), 2.49 (t, J_1=J_2=8.0 Hz, 4H), 2.39 (t, J_1=J_2=8.0 Hz, 4H). ^{13}C NMR (DMSO-d_6, 100 MHz, 298 K), δ (ppm): 171.2, 170.7, 165.8, 157.0, 142.6, 136.2, 132.9, 132.2, 130.5, 129.1, 128.5, 128.2, 127.2, 126.8, 114.42, 71.2, 66.2, 55.8, 51.8, 41.4, 30.8. HRMS (ESI) (m/z): $[M+Na]^+$ calcd for $C_{59}H_{57}N_7O_8Na$, 1014.4166; found, 1014.4169. m.p. 175.8–177.9 °C.

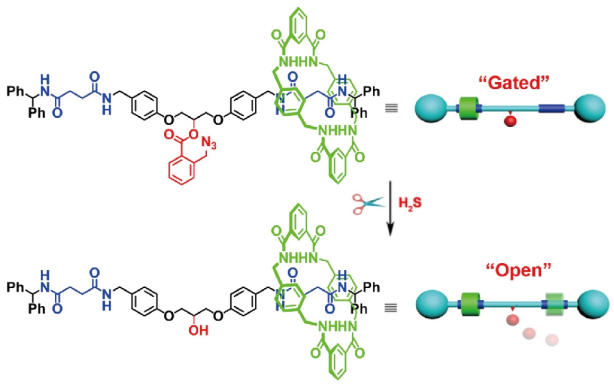


Figure 1 The schematic representation of the two modes of the [2]rotaxane before and after addition of H_2S (color online).

2.3 Synthesis of [2]rotaxane1

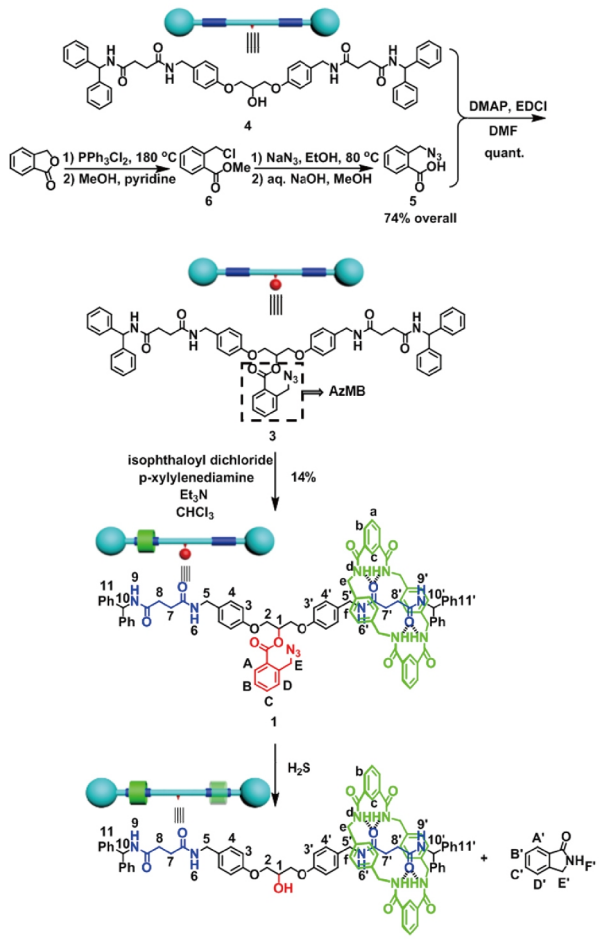
Compound **2** (200 mg, 0.202 mmol) and Et_3N (652 mg, 6.45 mmol) in anhydrous $CHCl_3$ (500 mL) were stirred vigorously whilst solutions of *p*-xylylenediamine (329 mg, 2.42 mmol) in anhydrous $CHCl_3$ (50 mL) and the corresponding isophthaloyl dichloride (491 mg, 2.42 mmol) in anhydrous $CHCl_3$ (50 mL) were simultaneously added over a period of 5 h using syringe pumps. After a further 4 h stirring, MeOH (10 mL) was added, the resulting suspension was filtered through a celite pad, and the filtrate was evaporated to dryness. The resulting solid was purified by preparative TLC (SiO_2, DCM:MeOH=20:1) to yield [2]rotaxane **1** (44 mg, 0.0283 mmol, 14%) as a yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz, 298K), δ (ppm): 8.94 (d, J=8.0 Hz, 1H), 8.81 (d, J=8.0 Hz, 1H), 8.41–8.37 (m, 6H), 8.29 (t, J_1=8.0 Hz, J_2=4.0 Hz, 1H), 8.14 (t, J_1=8.0 Hz, J_2=4.0 Hz, 1H), 8.02 (d, J=8.0 Hz, 4H), 7.83 (d, J=8.0 Hz, 1H), 7.65–7.59 (m, 3H), 7.53 (d, 8.0 Hz, 1H), 7.46 (t, J_1=4.0 Hz, J_2=8.0 Hz, 1H), 7.40–7.22 (m, 20H), 7.14 (d, J=8.0 Hz, 2H), 6.90 (s, 12H), 6.82 (d, J=8.0 Hz, 2H), 6.11 (d, J=8.0 Hz, 1H), 5.98 (d, J=8.0 Hz, 1H), 5.67–5.63 (m, 1H), 4.74 (s, 2H), 4.31 (t, J_1=12.0 Hz, J_2=4.0 Hz, 8H), 4.21 (t, J_1=4.0 Hz, J_2=12.0 Hz, 6H), 3.86 (d, J=4.0 Hz, 2H), 2.49 (t, J_1=4.0 Hz, J_2=8.0 Hz, 2H), 2.39 (t, J_1=4.0 Hz, J_2=8.0 Hz, 2H), 1.33 (t, J_1=J_2=8.0 Hz, 2H), 1.15 (t, J_1=J_2=8.0 Hz, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz, 298 K), δ (ppm): 177.4, 177.0, 176.4, 175.9, 171.1, 171.0, 162.3, 162.2, 147.89, 147.3, 142.4, 139.7, 135.9, 135.7, 134.0, 133.7, 133.6, 133.5, 132.6, 132.5, 132.0, 119.6, 76.4, 71.5, 61.0, 57.0, 48.3, 47.0, 46.6, 36.0. HRMS (ESI) (m/z):

$[M+Na]^+$ calcd for $C_{91}H_{85}N_{11}O_{12}Na$, 1546.6277; found, 1546.6285.

3 Results and discussion

3.1 Design of a H_2S-responsive [2]rotaxane 1

As shown in Scheme 1, we chose the benzylic amide macrocycle to investigate the shuttling motion and a H_2S-sensitive group (AzMB) **5** as a stopper to prevent the shuttling motion of the macrocycle. The thread component **3**, which contains a dumbbell-shaped thread **4** with two succinamide recognition sites and AzMB group, is designed and synthesized. Subsequently, three-component clipping reaction resulted in the formation of [2]rotaxane **1**. The structure of this target [2]rotaxane **1** was confirmed with ^{1}H NMR, ^{13}C NMR spectroscopies and the HR-ESI mass spectrometry. The mass spectrum showed a signal peak at *m*/*z* 1546.6285, corresponding to the specie $[M+Na]^+$, which is consistent with the calculated value of 1546.6277 for $[C_{91}H_{85}N_{11}O_{12}Na]$.



Scheme 1 Synthetic routes of the target [2]rotaxane **1**, the dumbbell-shaped thread compounds **3**, **4** and the H_2S-responsive reaction of [2]rotaxane **1** to yield degenerate [2]rotaxane **2** (color online).

In order to confirm the interlocked structure of the [2]rotaxane **1**, ^{1}H NMR experiments was investigated. The ^{1}H NMR spectra of dumbbell-shaped thread **3** and [2]rotaxane **1** were compared, as shown in Figure 2, respectively. The protons of [2]rotaxane **1** were rationally assigned, and the chemical shifts at δ=8.02, 7.62, 6.90, 8.39, and 4.31 ppm are attributed to the protons on benzene ($H_{a-c, f}$), amide (H_d), benzyl (H_e) of benzylic amide macrocycle, respectively. The signals of the protons on AzMB (H_{A-E}) and most peaks of protons on the thread **3** were split into two parts. Significantly, the signals of methylene protons H_7 and H_8 on the succinamide station of dumbbell-shaped thread **3** were split and shifted upfield ($\Delta\delta$=−1.24 ppm), due to the introduction of the macrocycle. Additionally, other similar shielding signals from H_{3-6}, H_{10} to proton $H_{3'-6'}$, $H_{10'}$ can be found in Figure 2(b), as well. However, the protons H_{11} on the phenyl stoppers and H_9 on the thread **3** shifted downfield ($\Delta\delta$=−0.09 ppm), attributing to the deshielding effects of the aromatic rings of macrocycle. In principle, [2]rotaxane **1** should exists four stereoisomers, however, we did not observed the signals of four stereoisomers according to the ^{1}H NMR, as shown in Figure 2(b), which is consistent with previously result [11b]. Moreover, a ^{1}H NOESY spectrum (DMSO-d_6, 400 MHz, 298 K) of [2]rotaxane **1** shown *n*Oe correlations between the amide protons (H_d), the methylene-group protons (H_e) of macrocycle and methylene-group protons (H_5, $H_{7'}$, and $H_{8'}$) of thread, confirming that the ring was interlocked mechanically in the thread (for details, see the Supporting Information online). Therefore, all these results proved that the interlocked structure of the target [2]rotaxane **1** has been successfully synthesized by three-component clipping reaction, in which the two recognition sites showed different chemical environments because of the encircling of the macrocycle into one of the two recognition site, indicating the gated state of rotaxane **1**.

3.2 Triggering the shuttling motion of H_2S-responsive [2]rotaxane 1

The H_2S-responsiveness of the [2]rotaxane **1** was detected by ^{1}H NMR spectrum, as shown in Figure 3. 2 eq. NaSH (a standard source for hydrogen sulfide) was added to the DMSO-d_6 of [2]rotaxane **1** and the reaction result was investigated by ^{1}H NMR spectroscopy after 20 min [20]. Obviously, after 20 min, the key signals at δ=7.46, 7.53, 7.61, and 4.74 ppm of H_{B-E} on the H_2S-responsive group AzMB in [2]rotaxane **1**, shifted to 7.14, 7.68, 7.48, and 4.38 ppm of $H_{B'-E'}$ in [2]rotaxane **1** correspondingly, and these chemical shifts of $H_{B'-E'}$ were similar to the protons on indolin-1-onedue due to the addition of NaSH, which indicates that the bulky group has been successfully cleaved upon the addition of NaSH. Significantly, the signals (δ=5.65 ppm) of the H_1 proton on the axel of [2]rotaxane **1** disappeared, and a new signals (δ = 4.06 ppm) simultaneously appeared, which can be explained

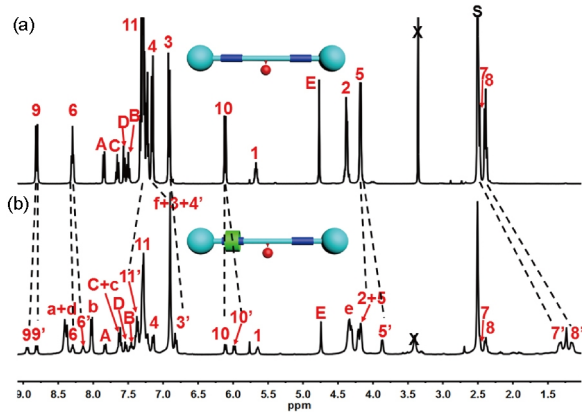


Figure 2 ^{1}H NMR spectra (400 MHz, DMSO-d_6, 298 K) of (a) dumbbell-shaped thread **3** and (b) [2]rotaxane **1**. See Scheme 1 for proton assignments (color online).

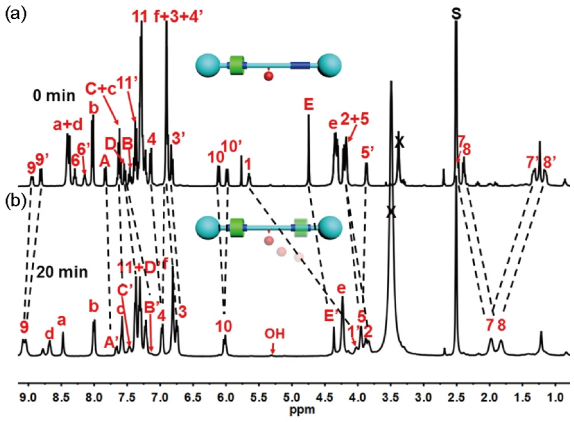


Figure 3 ^{1}H NMR spectra (400 MHz, DMSO-d_6, 298 K, 1.24×10^{-2} M) of (a) H_2S-responsive process of [2]rotaxane **1** at 0 min, and (b) [2]rotaxane **2** after 20 min (color online).

as the break of carbonic ester in [2]rotaxane **1** indicating formation of hydroxyl group in [2]rotaxane **2**. These observations directly show the efficient and complete H_2S-induced self-cleavable reaction of the AzMB group, releasing a hydroxyl group in the obtained [2]rotaxane **2** in a chemically-controlled mode, as shown in Scheme 1.

To further confirm the final product of H_2S-responsive cascade reaction of [2]rotaxane **1**, the "open" [2]rotaxane **2** was purified for further analysis and investigation. Compared with the ^{1}H NMR spectra of [2]rotaxane **1**, as shown in Figure 4(a), the chemical shift of the methyne protons (H_1) in [2]rotaxane **2** (Figure 4(b)) was shielded ($\Delta\delta$=−1.59 ppm), and a new peak at 5.41 ppm of H_{OH} was appeared, these changes were identical with the ^{1}H NMR spectra shown in Figure 3, which attributed to the fracture of AzMB. Furthermore, we found that the chemical shifts at δ=2.49, 2.39, 1.33, 1.15 ppm of H_7, $H_{7'}$, H_8, $H_{8'}$ on the [2]rotaxane **1** (Figure 4(a)) were shifted to δ=1.96, 1.81 ppm

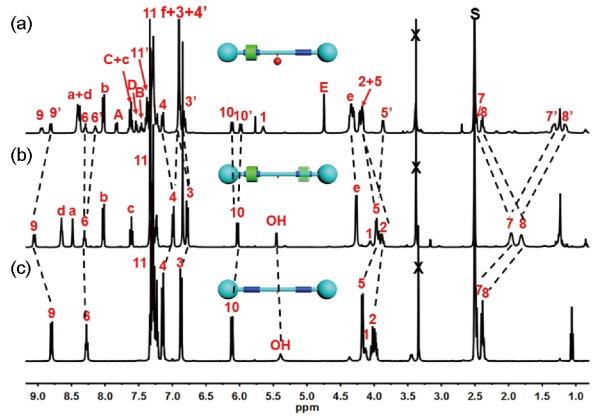


Figure 4 ^{1}H NMR spectra (400 MHz, DMSO-d_6, 298 K) of (a) [2]rotaxane **1**, (b) an "open" [2]rotaxane **2**, (c) dumbbell-shaped thread **4** (color online).

for H_7 and H_8 in rotaxane **2** in Figure 4(b), respectively, which proved that the chemical environments of the protons on two succinamide recognition sites were identical in [2]rotaxane **2** because of the fast shuttling dynamic motion induced by the removal of the bulky middle stopper. Additionally, the signals of $H_{3'}$, $H_{4'}$, $H_{5'}$, $H_{10'}$ in rotaxane **1** (Figure 4(a)) to H_3, H_4, H_5, H_{10} in rotaxane **2** (Figure 4(b)) can also be found as the same change tendency as well. These obvious changes of chemical shifts showed that the macrocycle was characterized by fast shuttling between the two stations along the thread in [2]rotaxane **2**, and the shuttling rate (k_s) and free energy of activation ($\Delta G^{\neq}$) are consistent with those in our previous result [11b]. Finally, in order to prove that a similar shuttling motion still occurs in the H_2S-triggered mode, the comparation between Figure 3(b) (mixture sample) and Figure 4(b) (pure sample) was investigated. We found that two ^{1}H NMR spectra were similar, which certified that the [2]rotaxane **2** was successfully formed after addition of H_2S, leading to the shuttling motion.

4 Conclusions

In conclusion, a novel [2]rotaxane in its gated state has been successfully synthesized and demonstrated via the introduction of H_2S-responsive group as a removable bulk barrier. The binding behavior and shuttling motion upon addition of NaSH have been investigated through ^{1}H NMR spectroscopy. The results showed that H_2S can motivate a controlled motion of the rotaxane by site-specific cleavage of the AzMB groups. This work could enrich the biochemistry-controlled modes for the motion of molecular shuttle. We envision that this novel H_2S-responsive strategy will afford an efficient method for construction of bioresponsive rotaxanes and advance the study artificial molecular machines.

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Conflict of interest The authors declare that they have no conflict of interest.

Supporting information The supporting information is available online at http://chem.scichina.com and http://link.springer.com/journal/11426. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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