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Directional Molecular Transportation Based on a Catalytic Stopper-Leaving Rotaxane System

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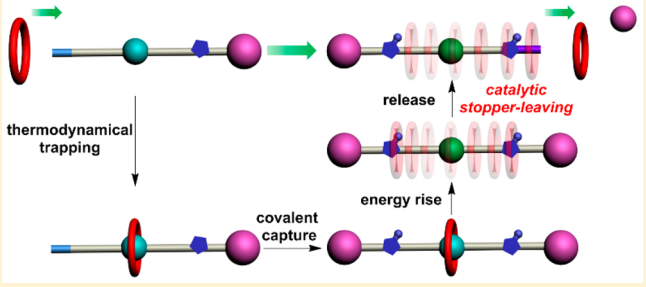
Supporting Information

ABSTRACT: Ratchet mechanism has proved to be a key principle in designing molecular motors and machines that exploit random thermal fluctuations for directional motion with energy input. To integrate ratchet mechanism into artificial systems, precise molecular design is a prerequisite to control the pathway of relative motion between their subcomponents, which is still a formidable challenge. Herein, we report a straightforward method to control the transportation barrier of a macrocycle by selectively detaching one of the two stoppers using a novel DBU-catalyzed *stopper-leaving* reaction in a rotaxane system. The macrocycle was first allowed to thread onto a semidumbbell axle from the open end and subsequently thermodynamically captured into a nonsymmetrical rotaxane. Then, it was driven energetically uphill until it reached a kinetically trapped state by destroying its interaction with ammonium site, and was finally quantitatively released from the other end when the corresponding stopper barrier was removed. Although the directional transportation at the present system was achieved by discrete chemical reactions for the sake of higher transportation efficiency, it represents a new molecular transportation model by the strategy of using stopper-leavable rotaxane.



INTRODUCTION

Biomolecular machines and motors[1] are ubiquitously used in cells to implement cargo delivery,[2] organelles' movement,[3] active transmembrane transport,[4] and proteins synthesis,[5] which are crucial to the metabolism process. A distinguishing feature of these tiny and exquisite machines is their ability to employ stochastic ratchet mechanisms[6] to rectify random thermal noise into unidirectional transportation and other useful work with defined energy input. Mechanically interlocked molecules (MIMs),[7] especially rotaxanes[8] and catenanes,[9] have proven to be promising candidates for the design of molecular switches and molecular machines[10] because of the controllability of noncovalent interactions between their subcomponents, which results in large amplitude relative motions. Not merely mimicking their programmed controlled motion, but to further evolve MIMs-based artificial molecular machines comparable to the natural analogues in functions, great efforts have been devoted by chemists to utilize ratchet mechanism in MIM system.[10b,11] Pioneering contributions made by Leigh, Stoddart and Credi, respectively, have rendered serials of clever performances realized in MIMs-based molecular machines, such as directional molecular motion,[12] sequence-specific peptide synthesis,[13] and active transport.[14] The ratchet mechanism, especially energy ratchet, raises stringent need on precise molecular design to control over kinetic barriers,[11b,14c,15] however, is still formidable challenge to integrate into artificial systems.

In this study, we have discovered a DBU-catalyzed stopper-leaving reaction within a rotaxane series, which executed highly regio- and chemoselective cleavage of the stopper when it was linked at the C-4 position of the electron deficient *N*-methyltriazolium (**MTA**) group through two carbon atoms, following a base-catalyzed β-elimination mechanism. This clean and efficient reaction was then harnessed to design a macrocycle transportation system where the dibenzo-24-crown-8 (DB24C8) was first allowed to thread onto a semidumbbell axle from its open end and subsequently covalently captured[16] by a nonsymmetrical rotaxane, then motivated to a metastable, kinetically trapped state by destroying its interaction with ammonium station, and finally quantitatively released from the other end by selectively detaching the corresponding phenol stopper. The present system provides a new directional molecular transportation model based on the energy of a ratchet mechanism.

RESULTS AND DISCUSSION

Discovery of the Stopper-Leaving Reaction. The **MTA** group, known for its relatively weak interaction with dibenzo-

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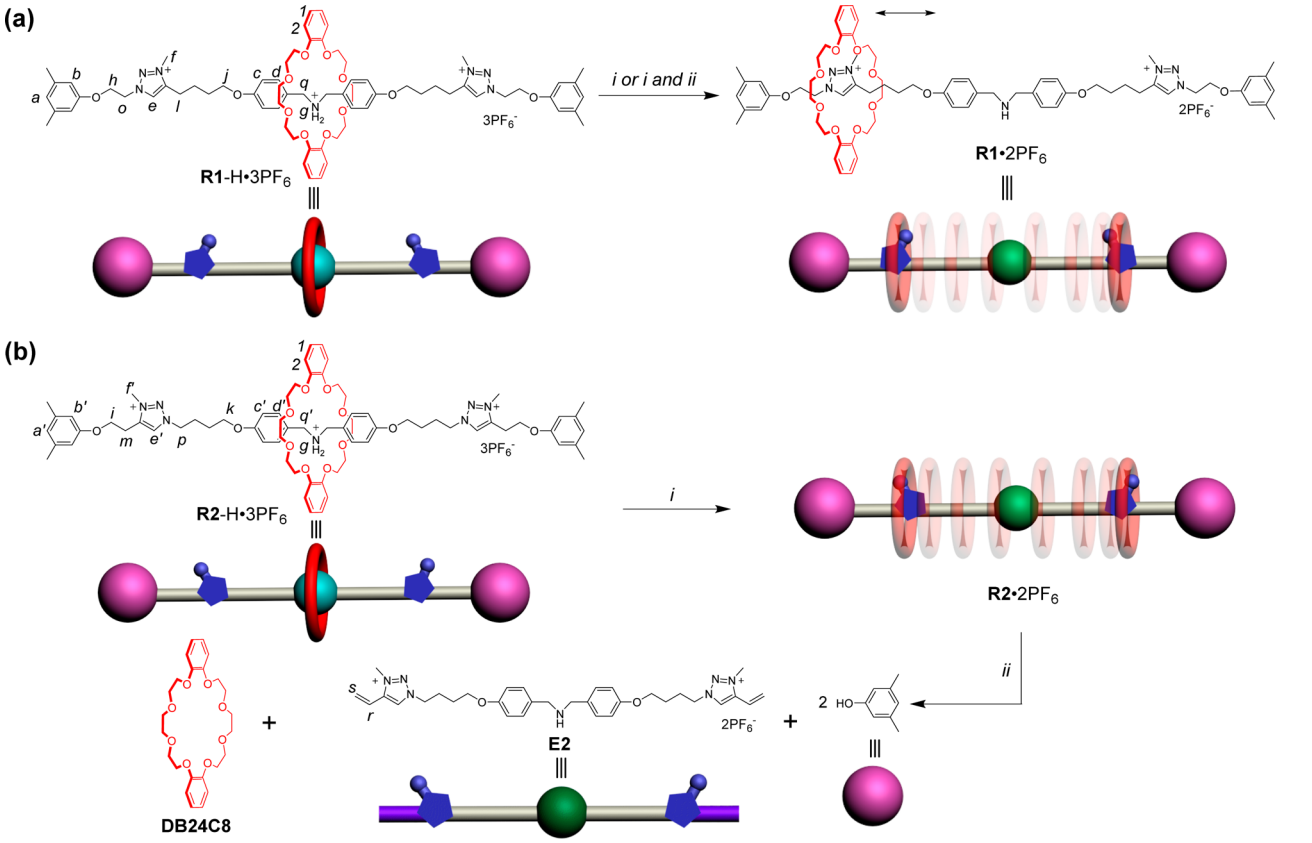

Figure 1. Comparison of the different outcomes of a pair of stereoisomeric rotaxanes with the addition of DBU. (a) Adding base DBU to **R1**-H·3PF$_6$ generates a degenerate [2]rotaxane **R1**·2PF$_6$. (b) The addition of DBU to **R2**-H·3PF$_6$ not only produces the degenerate [2]rotaxane **R2**·2PF$_6$, but also subsequently detaches its stoppers causing the DB24C8 ring to dethread from the axle molecule. Conditions: (i) 1.50 equiv of DBU, 298 K; (ii) heating at 348 K for 2.5 h.

24-crown-8 host compared with ammonium,[17] can serve as a very useful recognition site in building various MIMs based molecular switches.[17a,18] Because the N-3 position of the 1,2,3-triazole was methylated, the whole positively charged aromatic ring is electron-deficient. It is reasonable to recognize the **MTA** group as an electron-withdrawing group. Typical electron-withdrawing groups, such as ester, amide and cyano group, usually activate the C−H bond of their α position, making it vulnerable to base. Although we may envision its possible electronic effect, it is still not clear how and to what extent would the **MTA** group affect the reactivity of its two neighboring (N-1 and C-4 substituted) carbon atoms.

Our discovery of the stopper-leaving reaction originated from the study of the shuttling dynamic of a pair of stereoisomeric rotaxanes, **R1**-H·3PF$_6$ and **R2**-H·3PF$_6$ shown in Figure 1 (see Supporting Information for the details of synthetic procedures). The two **MTA** groups in each rotaxane were linked by the same spacers (butylene and ethylene chain, respectively) between the dibenzylammonium recognition site and the 3,5-dimethylphenol stopper. The only difference of the two rotaxanes is the connection mode of the **MTA** group. In **R1**-H·3PF$_6$, the **MTA** group is linked between the ammonium site and the stopper via C-4 and N-1 position, while the circumstance is reversed in **R2**-H·3PF$_6$. When 1.50 equiv of DBU was added to the acetonitrile solution of **R1**-H·3PF$_6$ in which the DB24C8 ring was located at the dibenzylammonium site (Figure 2a, Figure S3), a degenerate [2]rotaxane[19] **R1**·2PF$_6$ was formed with the DB24C8 ring rapidly oscillating between the two **MTA** groups (Figure 2b, Figures S6 and S7). With the increasing of the temperature, the oscillating frequency accelerated.

Unexpectedly, when the same amount of DBU was added to **R2**-H·3PF$_6$ (Figure 2c) under the same condition, the dethreading of DB24C8 ring slowly took place in the degenerate [2]rotaxane **R2**·2PF$_6$ (Figure 2d), giving a new set of DB24C8 signals that exactly consistent with its free form in the H ^{1}NMR spectra (Figures S16 and S20). When the solution was kept under 348 K for 2.5 h, total dethreading of DB24C8 was accomplished. ^{1}H NMR spectrum of resulted solution showed a new quartet at 6.77−6.68 ppm, and two double peak at 6.17 and 5.97 ppm, exhibiting the characteristics of terminal alkene signals, however with considerable downfield shifts (Figure 2e). Meanwhile, high resolution electrospray ionization mass spectrometry also gave a strong m/z peak at 278.6734 of a doubly positively charged species (Figure 2f), besides the m/z peaks corresponding to DB24C8. With these clues in hand, the structure of terminal alkene **E2** as drawn in Figure 1b was figured out, implying that the slippage of DB24C8 ring was caused by the leaving of the 3,5-dimethylphenol stopper through a β-elimination.

Mechanism Study. The distinct reactivity of isomeric rotaxanes highlighted the regio-selectivity of the stopper-leaving reaction which preferred to happen at the C-4 end of the **MTA** group. We further found that when the free axle component **L2** of **R2**·2PF$_6$ was treated with 1.50 equiv of DBU, the corresponding elimination reaction still happened, as proven by the ^{1}H NMR and HR-ESI-MS spectrum (Figures S28 and S29). This result indicated that the stopper-leaving reaction was

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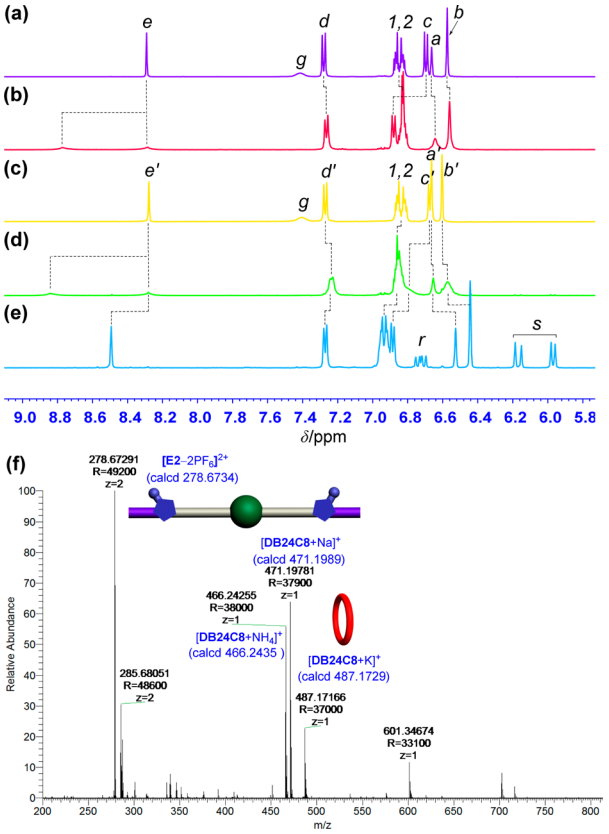

Figure 2. Partial ^{1}H NMR spectra (500 MHz, 298 K, c = 5.00 mM, CD_3CN, 298 K) of (a) **R1**-H·3PF$_6$; (b) the solution obtained after adding 1.50 equiv of DBU to (a) and then heating at 348 K for 2.5 h; (c) **R2**-H·3PF$_6$; (d) the solution obtained immediately after adding 1.50 equiv of DBU to (c); (e) the solution in (d) after heating at 348 K for 2.5 h. The proton assignments correspond to those shown in Figure 1. (f) HR-ESI-MS of the solution in (e). The corresponding calculated values, also shown in the spectra, were found to be consistent with the experimental values.

a general phenomenon for **MTA** group, whether the substrate is an interlocked architecture or not.

A detailed study on mechanism of the stopper-leaving reaction was then performed using **L2** as a substrate (Figure 3a), in which the amount of DBU used and the temperature were explored. When the concentration of the product 3,5-dimethylphenol was plotted versus time and the data points were fitted according to a model of a first-order kinetic, good agreement was obtained (Figure 3b, Figure S30). As equimolar amount of DBU was quickly (far less than 1 min at 298 K) neutralized by the ammonium group, the actual content of DBU in solution was only the excess part. Kinetic NMR experiments showed that only a 10% excess of DBU was able to lead a clear and quantitative transformation of **L2** to the terminal alkene **E2** and 3,5-dimethylphenol within 10 h at 348 K. However, when it was performed under insufficient DBU (such as 0.90 equiv), no corresponding product was detected even after a heating at that temperature for 1 day (Figure S32). With the increasing of concentrations of DBU, the reaction rate constants k' showed a perfect linear growth (Figure 3c). Further considering the stoichiometric ratio of **L2** and net DBU, it was deduced that the base DBU was a catalyst and the stopper-leaving reaction, in fact, should be characterized as a DBU-catalyzed pseudo-first-order reaction (Figure S31).[20] On the basis of the rate constants k' calculated at different

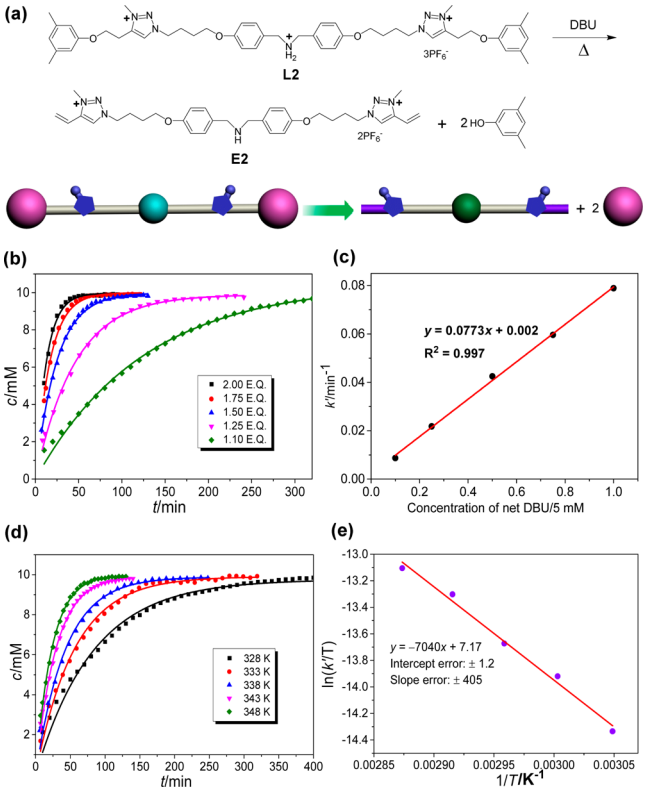

Figure 3. (a) The stopper-leaving reaction of ammonium **L2** in the presence of excess DBU and the corresponding graphical representation. (b) Concentrations of the detached stopper change with the time after the addition of 1.10–2.00 equiv of DBU to **L2** (c = 5.00 mM in CD_3CN) at 348 K. The x-axis denotes the concentration of DBU that was the excess part. Solid lines represent the data fitting according to a first-order kinetic model. The rate constants k' were obtained with deviations <2.5% for all circumstances. (c) The rate constants change with the concentration of net DBU. (d) Concentrations of the detached stopper change with the time after the addition of 1.50 equiv of DBU to **L2** (c = 5.00 mM in CD_3CN) at 328 to 348 K. Solid lines represents the data fitting according to a first-order kinetic model, giving the rate constants k' with deviations <3.5%. (e) The rate constants k' and temperature T were fitted according to the Eyring equation.

temperatures (Figure 3d), kinetic parameters of the stopper-leaving reaction were derived using the Eyring eq (Figure 3e, Figure S34), in which the activation enthalpy ($\Delta H^{\ddagger}$) and the activation entropy ($\Delta S^{\ddagger}$) are 14.0 kcal mol^{-1} and −32.9 cal K^{-1} mol^{-1}, respectively.

On the basis of these investigations on **L2**, a possible mechanism of stopper-leaving reaction was outlined in Figure 4.

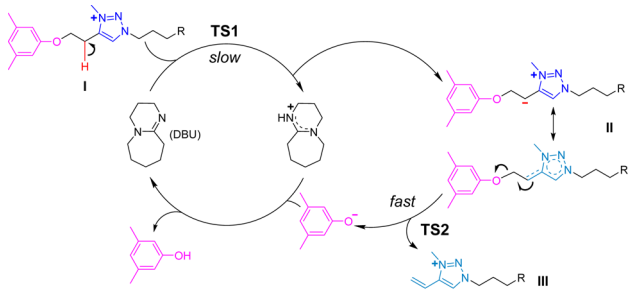

Figure 4. Mechanism of DBU-catalyzed stopper-leaving reaction.

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Due to electron withdrawing effect of the **MTA** group, the α-hydrogen of its C-4 position is easily attacked by the strong base DBU with its sp^2 N atom.[21] The generated deprotonated species **II** can stabilize the negative charge on the α-carbon through p$-\pi$ conjugation with electron deficient **MTA** group. DFT calculations (see Supporting Information for details) revealed that in active intermediate **II**, the C$-$O bond linking the phenol stopper and **MTA** group was notably lengthened to 1.5613 Å compared with 1.4598 Å in **I**. The intermediate then underdoes a unimolecular dissociation to give the terminal alkene **III** and 3,5-dimethylphenol anion. As the methyl-substituted phenol anion (pK_a > 27.5, Figure S35) is more basic than DBU (pK_a = 24.1) in acetonitrile,[22] the protonated DBU would be neutralized by the former, making the catalyst DBU recovered. Considering that the activation entropy ($\Delta S^{\ddagger}$) determined by experiments was reasonably negative, it is deduced that the attack of substrate **I** by DBU is the rate-determining step of this reaction.[23] The energy rise of the calculated transition state of this nucleophilic attack step[21a,24] corresponding to the substrates is 10.8 kcal mol^{-1}, much higher than that of the unimolecular splitting step (1.9 kcal mol^{-1}, see also the Supporting Information). It was also in accord with the fact that the rate constant of stopper-leaving reaction in rotaxane **R2**·2PF$_6$ (0.0259 min^{-1}) was smaller than that in free axle molecule **L2** (0.0425 min^{-1}), which may result from the hindrance effect of DB24C8.

As implied from the calculated results, the leaving of the phenol group and the subsequent generating of the conjugated olefin were likely the main driving force for this reaction. Consequently, another two rotaxanes, **R3**-H·3PF$_6$ and **R3**-H·3PF$_6$ as shown in Figure 5, which shared the same structure with **R2**-H·3PF$_6$ except that the former had 3,5-di*tert*-butylphenol stoppers and the latter had a C3 spacer between the stopper and the **MTA** group, were synthesized (see Supporting Information for their synthesis) for reactivity test. It was found that the stopper-leaving reaction happened for the former in the presence of DBU after heating (Figure 5a, Figure S21). However, under the same conditions, the latter only gave a degenerate rotaxane (Figure 5b, Figure S22).

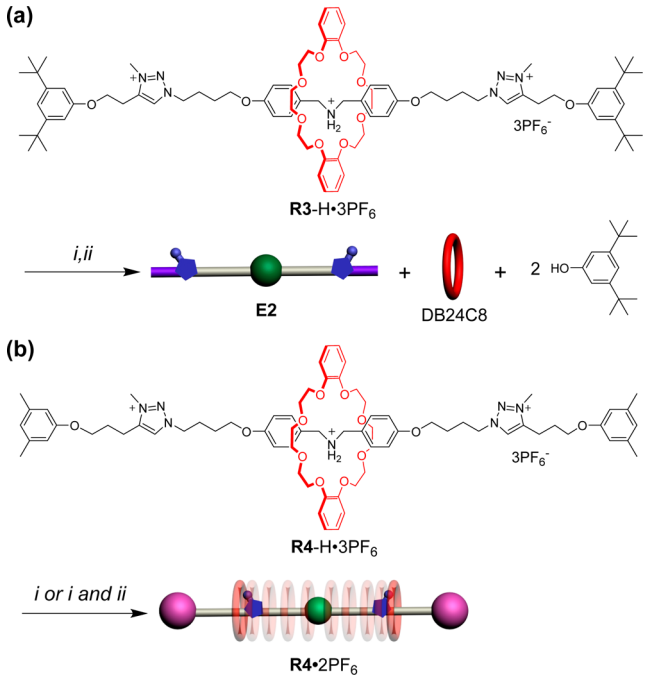

Figure 5. (a) The addition of excess DBU to **R3**-H·3PF$_6$ detaches its stoppers causing the DB24C8 ring to dethread from the axle. (b) Adding excess DBU to **R4**-H·3PF$_6$ only generated a degenerate [2]rotaxane **R4**·2PF$_6$. The conditions used are as demonstrated in Figure 1.

We also performed another five groups of control reactions on the axle **L2** and the rotaxane **R2**-H·3PF$_6$, respectively, with commonly used bases, including pyridine, 4-dimethylaminopyridine (DMAP), 1,4-diazabicyclo[2.2.2]octane (DABCO), triethylamine, and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), whose pK_a values cover from 12.3 to 26.0 in acetonitrile. The stopper-leaving phenomenon was not detected for pyridine, DMAP, DABCO and trimethylamine which are weaker bases compared with DBU (Figures S23 and S24). When TBD, a slightly stronger base than DBU, was used, faster rate of the stopper-leaving reaction was observed (Figures S25$-$S27). This was probably because a stronger base would promote the deprotonation of the α-hydrogen of **MTA** group which we recognized as the rate-determining step of the stopper-leaving reaction.

Unidirectional Molecular Transportation. The DBU has played a dual role in releasing the macrocycle of **R2**-H·3PF$_6$ and **R3**-H·3PF$_6$. It not only neutralized the ammonium, and thus raised the energy of DB24C8 by destroying its strong hydrogen bonding interaction with the ammonium site, but also catalyzed a β-elimination at the C-4 end of the **MTA** group, leading the macrocycle to release into solution after the stopper was detached. In an energy ratchet mechanism, the directed motion is driven by modulation both of the depths of energy wells and the heights of energy barriers.[15a] Undoubtedly, the catalytic stopper-leaving reaction provides us a method to control the direction of the macrocycle release by selectively detaching one of two stoppers in a rotaxane. We anticipated that unidirectional macrocycle transportation could be realized based on an energy ratchet mechanism if we could further control the threading path of the macrocycle in the same system.

To this end, the ammonium guest **A** was synthesized with one of its two terminals precapped with a 3,5-dimethylphenol stopper, which was linked by two carbon atoms at the C-4 position of the 1,2,3-triazole group (see Supporting Information for the synthetic details). Due to the semidumbbell-shaped structure of axle **A**, the macrocycle was only allowed to thread into the axle through the open terminal (the left side, see Figure 6a,b). The ^{1}H NMR spectra (Figure 7a$-$c) showed that in a 1:1 solution (c = 5.00 mM) of acetonitrile, the complexation between **A** and DB24C8 was a slow exchange process on NMR time scale. From the integral values, it was calculated that 45% of macrocycle was transferred to **A**, corresponding to an association constant of 298 M^{-1}. In a less polar solvent of dichloromethane that facilitates the non-covalent interactions, the ratio of macrocycle threaded is higher than 85% (K_a = 8.44 × 10^3, Figure S39). The complex **A**⊂DB24C8 was then covalently captured[16] by blocking the open end with another 3,5-dimethylphenol stopper using Huisgen alkyne$-$azide 1,3-dipolar cycloaddition in the **A**-DB24C8 (molar ratio 1:1.20) solution in CH_2Cl_2. Subsequent methylation of triazole group gave the rotaxane **R**-H·3PF$_6$ in an overall yield of 78% (The yield is based on the axle **A**, and see Supporting Information for synthetic details). **R**-H·3PF$_6$ has a nonsymmetrical structure with the two stoppers linked at the N-1 and C-4 position of the **MTA** group, respectively, and

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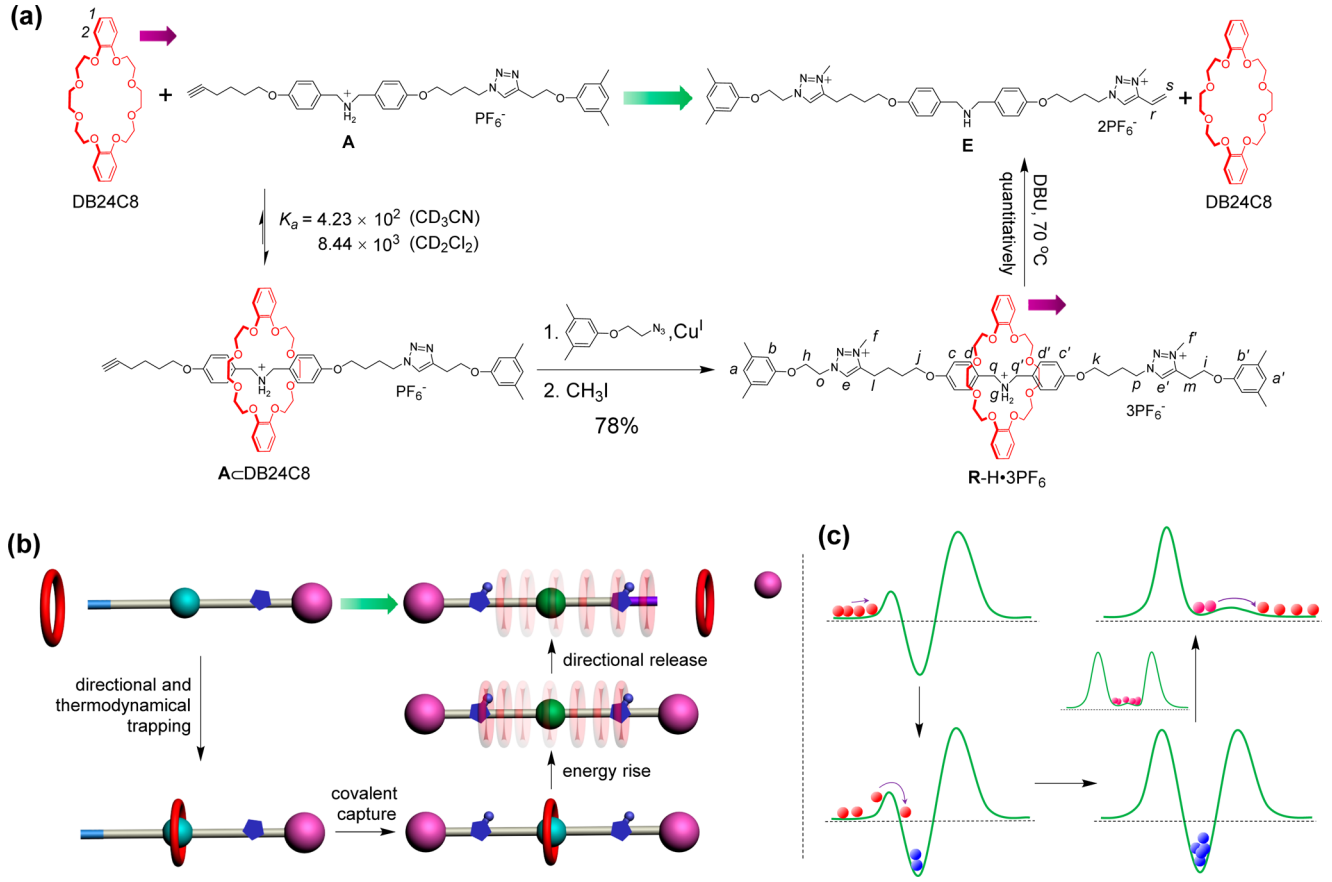

Figure 6. Unidirectional transportation of the DB24C8 macrocycle based on an energy ratchet mechanism driven by chemical energy. (a) Chemical drawings and (b) cartoon representations of the transportation, and (c) energy profiles representing the free energy of the system during the ring's movement from the left to the right side of the axle.

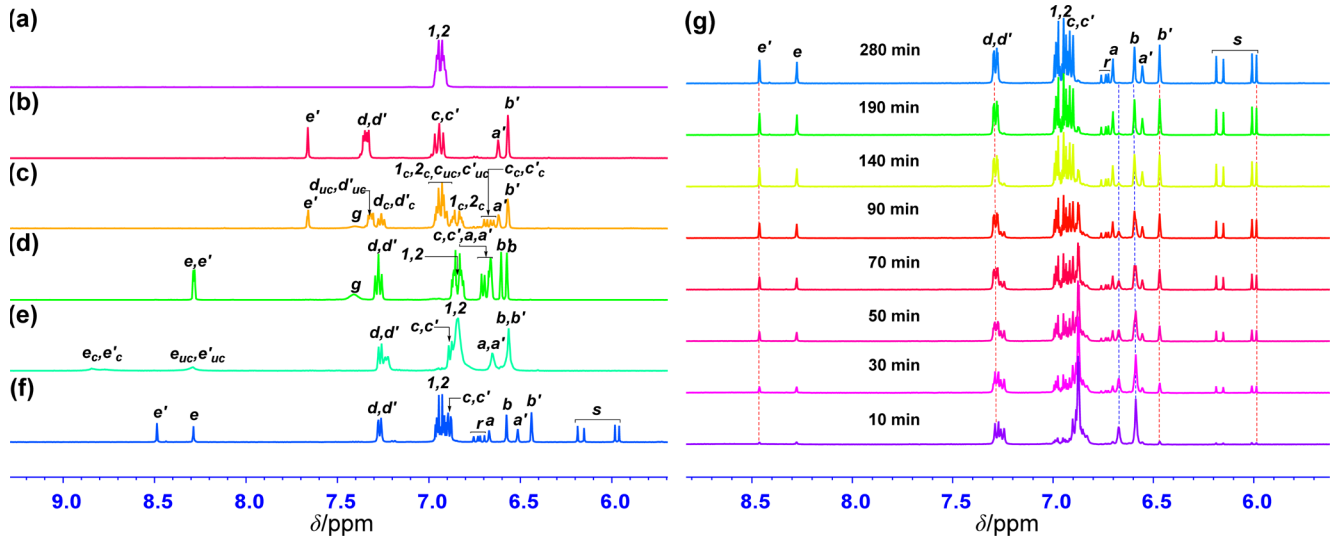

Figure 7. ^{1}H NMR spectra (500 MHz, c = 5.00 mM, CD$_3$CN) for characterizing the unidirectional transportation of the macrocycle. Partial ^{1}H NMR spectra of (a) DB24C8, (b) semidumbbell axle **A**, (c) 1:1 solution of DB24C8 and **A**, (d) rotaxane **R**-H·3PF$_6$, (e) rotaxane **R**-H·3PF$_6$ immediately after adding 1.50 equiv of DBU, (f) the solution in (e) after heating at 348 K for 5.0 h, and (g) rotaxane **R**-H·3PF$_6$ after adding 1.50 equiv of DBU and then kept at 348 K for 10−280 min. The proton assignments correspond to those shown in Figure 6a. The red and blue dotted lines marked part of the signals that grew or vanished with time, respectively. Spectra (a−f) were recorded at 298 K, and (g) was at 348 K.

macrocycle DB24C8 is thermodynamically trapped in the ammonium energy well (Figure 7d).

The addition of 1.50 equiv DBU to **R**-H·3PF$_6$ quickly generated a quasi-degenerate rotaxane **R**·2PF$_6$ (Figure 7e), in which the macrocycle was in a metastable state[25] and oscillating between the two **MTA** groups. The **MTA** moiety was so weak a molecular station for DB24C8 that there is in fact no complexation between their separated form in solution, because

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the enthalpic energy (directly related to the weak noncovalent interactions between DB24C8 and **MTA**) cannot compensate the energy loss caused by entropic increase.[17b,18a,26] The macrocycle in **R**·2PF$_6$ was thereby not in the stable state as in the bulk solution where the system had lower free energy, but kinetically trapped in the deprotonated axle due to the insurmountable stopper barriers (Figure 6c). The excess amount of DBU further catalyzed the stopper-leaving reaction at the C-4 side of the **MTA** group. On the basis of the selectivity of the stopper-leaving reaction demonstrated above, only the stopper on the right side would be detached, which was further proved by the ^{1}H NMR spectra (Figure 7f). Once the kinetic barrier on the right side was removed, the macrocycle spontaneously diffused to the solution from the same side. The rate constant of macrocycle release was 0.0134 min^{-1} at 348 K, slightly smaller ($\Delta k' = 1.3 \times 10^{-5}$ s^{-1}) than that of the stopper leaving (0.0142 min^{-1}), a sign that the oscillation rate of the macrocycle was much more rapid (k = 3.58 s^{-1} determined by 2D EXSY spectrum, see Figure S40) than the leaving of stopper. In terms of the power stroke, the catalytic stopper-leaving reaction is the decisive factor for the kinetic properties of the energy release process, while the friction from subcomponents of the MIM itself is negligible.[27] After the solution was kept at 348 K for 5 h, quantitate macrocycle releasing was achieved (Figure 7g). Taking the whole process into account, 65% ((78%/1.2) × 100%) of the macrocycles were transported from the initial DB24C8−**A** solution.

CONCLUSIONS

In summary, we have discovered a DBU-catalyzed stopper-leaving reaction within a rotaxane series. The reaction showed high regio- and chemoselectivity, and happened at the C-4 end of electron deficient **MTA** group only when the phenol stopper was linked at the C-4 position through two carbon atoms. Detailed kinetic NMR experiments and theoretical studies showed that the reaction followed a base-catalyzed β-elimination mechanism. On the basis of an energy ratchet mechanism, a unidirectional molecular transportation system was designed and constructed exploiting the stopper-leaving reaction, in which the macrocycle DB24C8 was first allowed to thread into a semidumbbell axle molecule from the open end and subsequently covalently captured by a nonsymmetrical rotaxane to form a thermodynamically trapped product. The macrocycle was then driven to a metastable, kinetically trapped state by destroying its interaction with ammonium, and finally directionally released from the other end by selectively detaching the stopper barrier.

The present system provides a new directional molecular transportation model by the strategy of using stopper-leavable rotaxane to implement the catalytic energy releasing process, circumventing the contingents in controlling local kinetic barriers. Besides its high efficiency, the rate of the stopper leaving can be also expediently tuned by varying the catalyst loading or temperature under relatively benign and succinct conditions, signifying the facility in controlling molecular release. It is anticipated that this new method would find its wide applications in designing other artificial molecular transportation system, and in constructing controlled release devices[28] by grafting MIMs onto nanoparticles or surfaces.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b01852.

Detailed synthesis, characterization data of all the new compounds, kinetic NMR experiments and details of theoretical calculations (PDF)

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Notes

The authors declare no competing financial interest.

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