

Synthesis of Sulfuric Macrocycles and a Rotaxane through Thiol-yne Click and Dithiol Coupling Reactions

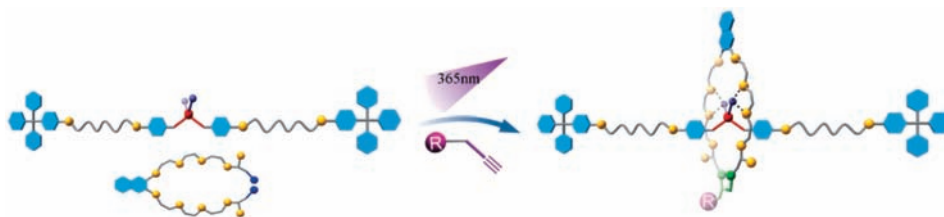
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ABSTRACT



A macrocycle and a rotaxane were constructed by virtue of the thiol-yne click reaction under the irradiation of light in high yield, which can proceed at ambient temperature and humidity under an air atmosphere. Two disulfide macrocycles were synthesized through a simple dithiol coupling reaction, which exhibited high stability and a weak assembly interaction with a dialkylammonium ion.

Biological molecular machines, such as the supramolecular system in photosynthesis, which are able to transform chemical energy into mechanical motion, have been well studied during the past few years. To simulate these biological machines with synthetic systems, many simple prototypes of artificial molecular motors, consisting of a few components capable of moving in a controllable way, have been proposed in recent years.¹ Mechanically interlocked molecules, such as catenanes and rotaxanes, have become typical candidates in the design of artificial molecular machines because some of their components have the ability of reversibly moving among two or more stations on application of external stimuli.¹ “Threading followed by stopping” and “clipping” are two efficient strategies for the construction of rotaxanes.² As for the clipping method, several reactions have been employed for pseudorotaxanes to form rotaxanes, such as olefin metathe-

ses³ and imine formation.⁴ However, in practice, the use of metal catalysts or reducing agent limits their application. Therefore, the development of mild and high yielding reactions suitable for the construction of² rotaxanes is still important for scientists in this field.

The thiol-yne reaction involves addition of a thiol to an alkyne followed by addition of another thiol to the resulting alkene, giving a fully saturated specie.^{5–7} Although the thiol-yne reactions were reported more than 50 years ago to be facile processes,^{5–7} there has been little effort to capitalize on what could be an exceptional opportunity for materials fabrication. Recently, it had new life for materials synthesis

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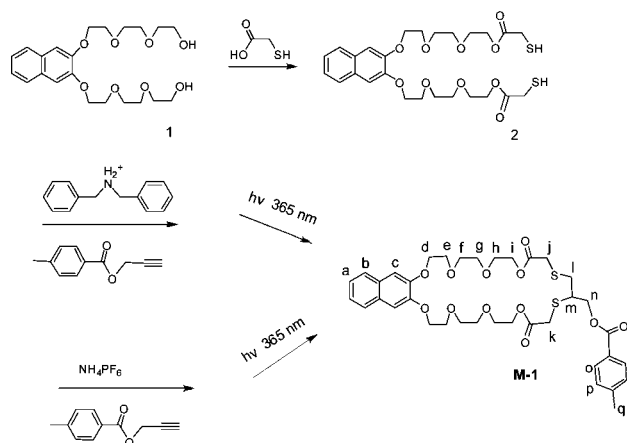
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from the recognition by Bowman,⁸ Lowe and Hoyle,⁹ Perrier,¹⁰ Stenzel,¹¹ etc. that the reaction possessed exceptional qualities including rapid, high-yield reactions that proceeded under ambient conditions. These conditions for the thiol-yne radical reaction purport to be a facile method for the rapid fabrication of macrocycles and interlocked molecules. To date, thiol-yne reactions have not been used for making macrocycles, though this reaction has recently attracted significant attention in the materials area^{8–11} because it displays many attributes of click chemistry. The reaction proceeds by reacting 2 equiv of thiol with the alkyne, via a two-step process. Therefore, after the reaction, each alkyne functional group will be combined with two thiols, which is very attractive and advantageous in the synthesis of macrocycle and rotaxane through the “clipping” method.

We proposed herein a new method to construct a macrocycle and an interlocked molecule via a thiol-yne reaction based on templates of secondary dialkylammonium ions. The template-induced clipping reaction was conducted under the irradiation of UV light in apolar solvent with high yield. The reaction could proceed at high rate under ambient humidity and atmospheric oxygen conditions to high conversion, thereby providing an extremely efficient methodology for fabricating macrocycles and interlocked molecules. In addition, we also synthesized two other disulfide macrocycles through a simple method—a thiol coupling reaction—in high yield, which exhibit higher stability compared with linear disulfide compounds.

The thiol-yne addition based sulfuric macrocycle was designed and synthesized as outlined in Scheme 1. The

Scheme 1. Synthetic Route Toward Macrocycle **M-1**



esterification of **1** with thioglycolic acid in the presence of 4-methylbenzenesulfonic acid gave dithiol **2**. **2** was as-

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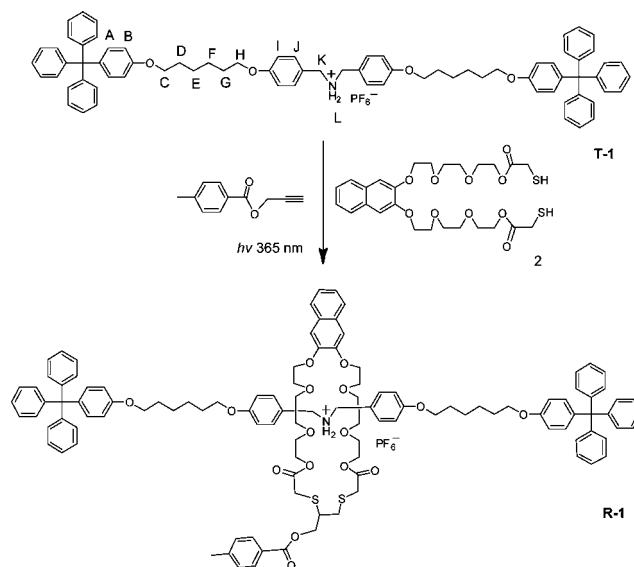
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sembled with secondary dialkylammonium ions in CH₂Cl₂/THF (1/1, v/v) with high concentration. After the addition of prop-2-ynyl benzoate, the mixture was irradiated with UV light for 15 min in the presence of 2 × 10⁻³ M 2,2-dimethoxy-2-phenylacetophenone (DMPA) as the initiator, giving the target macrocycle in a yield of 80%. Reducing the concentration of dithiol **2** did not enhance the yield significantly but depressed the rate and enlarged the reaction time, which can be attributed to the radical mechanism of thiol-yne reaction. In this reaction, one intermediate thiyl radical must collide with another thiol molecule to abstract a hydrogen atom and induce another thiyl radical in a chain transfer reaction. When we reduced the quantity of initiator DMPA to 1% of compound **2**, the reaction still reached 70% conversion within 5 min and was complete after 20 min. The NH₄PF₆ could also function as the effective template with the yield of 75% in the same condition as the template of secondary dialkylammonium ions, which indicated the effective hydrogen bonding between the -(OCH₂CH₂)- unit and the -NH⁺- core (Scheme 1).

When a dumbbell-shaped thread containing a secondary dialkylammonium ion was utilized as a template, interlocked molecule **R-1** was obtained in high yield (75%) as shown in Scheme 2. Since

Scheme 2. Synthetic Route Towards Rotaxane **R-1**



the xylylene parts of the macrocycle shields encapsulated regions of the thread, the position of the macrocycle could

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be determined by comparing the chemical shift of the protons in the rotaxane with those of the corresponding thread. The ^1H NMR spectra (Figure 1) of thread **T-1** and

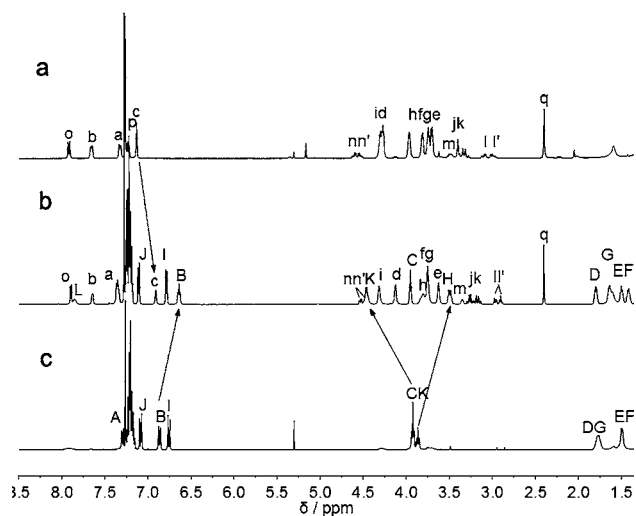
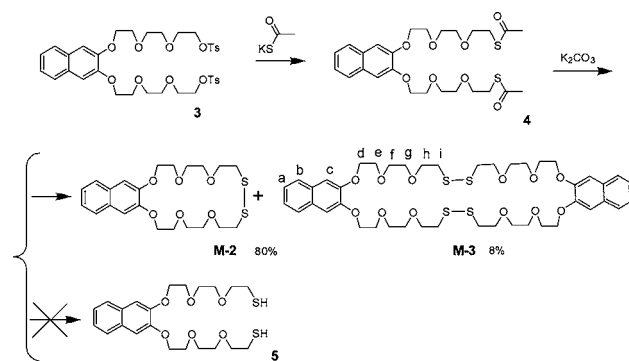


Figure 1. Partial ^1H NMR spectra (600 MHz, 298 K, CDCl_3 , 1×10^{-3} M) of (a) **M-1**, (b) **R-1**, and (c) **T-1**.

macrocycle **M-1** confirm the interlocked nature of **R-1** and show that in the form of **R-1** the macrocycle is largely localized on the dialkylammonium ion region of the thread (Scheme 2). The upfield shifts of the methylene resonances of the dialkylammonium ion station (H_H 0.36, H_G 0.11) in **R-1** are characteristics of aromatic shielding by the encapsulating macrocycle. The thread dialkylammonium ion resonance, H_K , is shifted downfield by 0.55 ppm in the rotaxane as a result of the hydrogen bonds between the macrocycle and corresponding protons.¹² All these features confirm the interlocked nature of **R-1**, which indicates the synthetic approach presented here is a rapid and effective approach for interlocked molecules containing sulfur.

When we tried to synthesize the dithiol **5**, a precursor for a smaller macrocycle **M-2**, according to the synthetic strategy in Scheme 3, surprisingly, we obtained disulfide macrocycles **M-2** and **M-3** directly. This phenomenon tells us that dithiol **5** was very difficult to isolate because of its oxidative macrocyclization reaction to either **M-2** or **M-3**. Compound **4** was obtained from the nucleophilic substitution reaction between potassium ethanethioate and compound **3** in THF/EtOH (1/1) at 70 °C. The hydrolysis of compound **4** in the presence of K_2CO_3 resulted in the formation of disulfide macrocycle **M-2** and **M-3** directly in yields of 80 and 8%, respectively. Interestingly, this high yield of **M-2** (80%) was

Scheme 3. Synthetic Route Toward Macrocycles **M-2** and **M-3**



obtained from a highly concentrated solution (shown in Supporting Information). Obviously, the potential polymerization has been prevented by the templating effect of K^+ , which facilitates the formation of crown ether macrocycles **M-2** and **M-3**.

It has been reported that disulfide bonds can be cleaved by various stimulation,¹³ i.e., nucleophile, photoirradiation, and heating. Takata has reported a method for the preparation of dynamic controlled [2]rotaxane and [3]rotaxane by utilizing the reversible dithiol–disulfide interchange reaction.¹⁴ It gave us inspiration that we might be able to utilize this dithiol–disulfide interchange reaction of disulfide macrocycles **M-2** and **M-3** for the construction of a [2]rotaxane, using a so-called thermodynamic-control method. Unfortunately, we did not find any significant change of **M-2** and **M-3** under the initiator of benzenethiol and template of dialkylammonium ion for 14 days. In addition, when macrocycles **M-2** and **M-3** were irradiated by UV light (365 nm) for 30 min with DMPA as the initiator and prop-2-ynyl benzoate as the capturing reagent, no new product could be detected, and all reactants did not exhibit any reduction. All of these phenomena indicated the high stability of the disulfide macrocycles **M-2** and **M-3**.

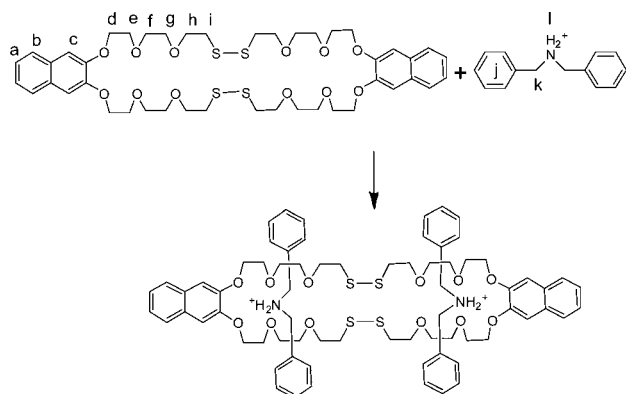
The binding affinities between disulfide macrocycles (**M-2**, **M-3**) and ammonium ion have been recorded. The results show that, compared to the 24-crown-8, two disulfide macrocycles exhibit much lower binding affinities toward the ammonium ion. Mixing disulfide macrocycle **M-2** and dialkylammonium ion in $\text{CDCl}_3/\text{CD}_3\text{CN}$ (1/1, v/v), no significant change in the ^1H NMR spectra was detected (shown in Supporting Information), which indicated that there was no interaction between the disulfide macrocycle and $-\text{NH}_2^+$ in this condition. Mixing disulfide **M-3** and dialkylammonium ion in $\text{CDCl}_3/\text{CD}_3\text{CN}$ (1/1, v/v) (Scheme 4), slight changes in the ^1H NMR spectra

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Scheme 4. Interaction between Macrocycle **M-3** and Dialkylammonium Ion



were observed (Figure 2), which indicated that there was weak interaction between disulfide macrocycle **M-3** and

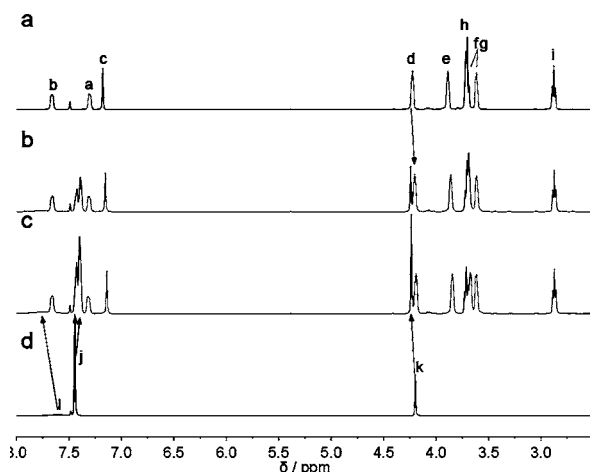


Figure 2. Partial ^1H NMR spectra (400 MHz, 298 K, $\text{CDCl}_3/\text{CD}_3\text{CN}$ (1/1, v/v), 1×10^{-3} M) of (a) **M-3**, (b) **M-3** + 1 equiv of dialkylammonium ion, (c) **M-3** + 2 equiv of dialkylammonium ion, and (d) dialkylammonium ion.

$-\text{NH}_2^+$ in this condition. Both phenomena indicated that the macrocycle **M-2** is spatially small compared with the

phenyl unit, which increases the bulky effect and prevents the threading process for the dialkylammonium ion. Huang et al. have reported that the phenyl group is big enough to work as a stopper for 21-crown-7 derivatives.¹⁵ It is surprising that the addition of one disulfide bond did not cause conspicuous cavity increase of the macrocycle compared with 21-crown-7. As for the weak interaction between **M-3** and $-\text{NH}_2^+$, this phenomenon can be attributed to the incorporation of the disulfide bond owning less hydrogen bonding ability. Previously, Shinkai had researched the coordination ability of the similar macrocycle toward alkali metal ions compared with 21-crown-7.¹⁶ They also found obvious negative results for binding of alkali metal ions, meaning that introduction of the long noncoordinative unit is very unfavorable to ion binding.

In conclusion, we exploited a novel synthesis method for the construction of a macrocycle and interlocked rotaxane to take advantage of the thiol-yne click reaction in high yield, which can proceed under facile conditions (at ambient temperature and humidity under an air atmosphere). The mild condition of this reaction provides extensive opportunity for the construction of [2]rotaxane. In addition, two disulfide macrocycles were synthesized through a simple method, which exhibit weak assembly interaction with dialkylammonium ion and high stability under the irradiation of the UV light or benzenethiol.

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Supporting Information Available: Full experimental details pertaining to the preparation and characterization of **R-1**, **M-1**, **M-2**, and **M-3**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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