# DESIGNING ROTAXANES: FROM SELF-ASSEMBLY TO DYNAMIC FUNCTION

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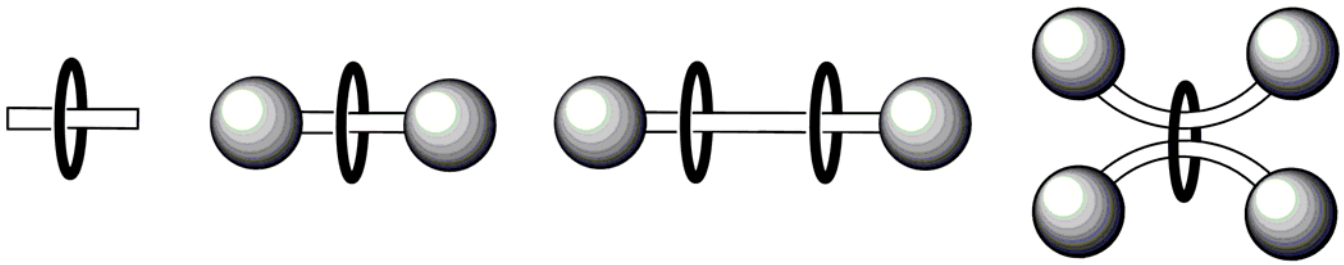
## INTRODUCTION

The structure-function relationship of molecules has been a long-standing concept in chemical synthesis. The ability to study the function of small molecules in many different contexts has relied on the diverse and rich chemistries afforded by organic synthesis to access a seemingly infinite number of compounds. Above and beyond traditional small molecule synthesis, versatile syntheses of mechanically-interlocked molecules have challenged organic chemists for decades.[1] Within the various classes of interlocked molecules, a considerable amount of effort has been applied to the synthesis of rotaxanes due to their potential use in nanoscale electronic devices, artificial muscles, drug-delivery, and memory storage.[2] Herein a discussion will be provided of the recent developments in rotaxane synthesis and the potential applications of these interlocked molecules.

## STRUCTURAL FEATURES

The architectural motif of rotaxanes consists of an acyclic component threaded through the cavity of a second macrocyclic component. A key distinction between rotaxanes and pseudorotaxanes is the presence of sterically hindering moieties, known as stoppers, on the termini of the 'thread' component in a rotaxane. These stoppers prevent the macrocycle from slipping off the thread. Therefore, the kinetic barrier to the disassembly of the components provided by the steric hindrance of the stoppers is the fundamental difference between a rotaxane and pseudorotaxane. The accepted nomenclature for this class of compounds utilizes brackets to denote the number of components that make up the system. Figure 1 shows a schematic representation of a [2]pseudorotaxane, [2]rotaxane, and two unique [3]rotaxanes.

**Figure 1. Representative Rotaxane Structures**

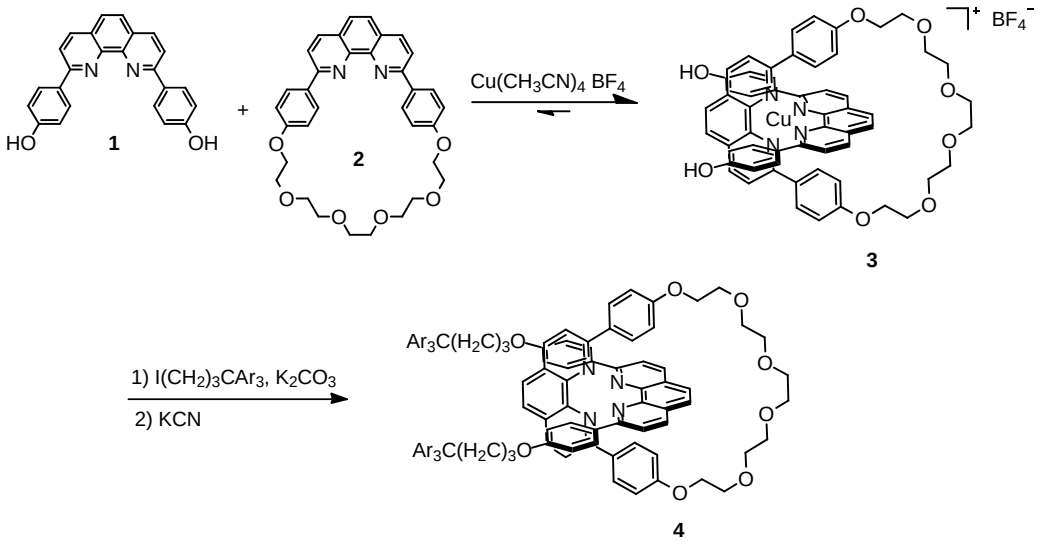


The mechanically-interlocked nature of the components imparts dynamic functional properties to the entire molecule. Coherent control of the translational movement of the macrocycle with respect to thread has been an enduring goal.[3] External stimuli, including changes in pH,[4] electrochemical,[5] photochemical,[6] thermal,[7] and ion coordination,[8] have been applied to these molecular systems to impart nanoscale control over this molecular motion. Furthermore, the macrocycle has been utilized as a molecular 'sheath' to afford increased chemical stability to the thread or 'dumbell' component.[9] Finally, these structural features have been incorporated into polymers and nanoparticles[4-6] in attempts to create materials with novel macroscopic properties.

## TRADITIONAL SYNTHETIC STRATEGIES

The first attempts to construct compounds with the rotaxane topology relied on the statistical possibility of an acyclic precursor to be alkylated on both termini while residing in the cavity of a second cyclic precursor.[10] This synthetic approach proved to have limited utility and produced poor yields of products. A key advance in the design and synthesis of interlocked molecules was reported by Sauvage in 1983.[11] Sauvage identified the need to provide a driving force to the precursors to self-assemble before attempting to mechanically interlock the components. Sauvage utilized a Cu(I)-template to coordinate two phenanthroline-based precursors to a Cu(I) metal to produce a stable pseudorotaxane Cu(I) complex. Subsequent macrocyclization led to the first template synthesis of an interlocked molecule, a [2]catenane. In 1991 Gibson and co-workers applied the use of Cu coordination towards the first template-directed synthesis of a [2]rotaxane (Scheme 1).[12] Diphenol **1** and macrocycle **2** were treated with a Cu(I) salt to produce the stable Cu(I) complex **3**. Pseudorotaxane **3** was treated with an alkyl halide in the presence of a base and demetallated with KCN to produce [2]rotaxane **4** in 42% yield.

**Scheme 1. Cu(I)-template strategy to produce a [2]rotaxane**



Also in 1991, Stoddart and coworkers employed a complimentary strategy to produce the first 'all-organic' rotaxane synthesized by a template process.[13] This strategy required the affinity of the π-electron deficient, cyclobis(paraquat-p-phenylene) ($CBPQT^{4+}$), and a π-electron-rich hydroquinol. The term 'molecular shuttle' was coined in this work because the macrocycle was observed to translate across thread in variable temperature NMR experiments. Furthermore, Stoddart and co-workers increased the functionality of these 'donor-acceptor' rotaxanes by introducing two different π-electron-rich moieties into the thread component. This allowed access to bistable rotaxanes wherein the translation of the macrocycle could be controlled upon addition of a stimulus (Scheme 2). Compared to the statistical approaches to rotaxane synthesis, these types of template-directed syntheses have improved access to rotaxane-based architectures and increased their functionality. However, only a narrow range of coordinating species was used, which limited the scope of rotaxane structures that were achieved. Strategies have recently been adopted that involve templating ions that both direct the self-assembly process and facilitate the formation of covalent bonds to interlock the reacting species.[14] This process has been named 'active-metal' template synthesis (Figure 2).

**Scheme 2. Redox-Controlled Shuttling of a Rotaxane**

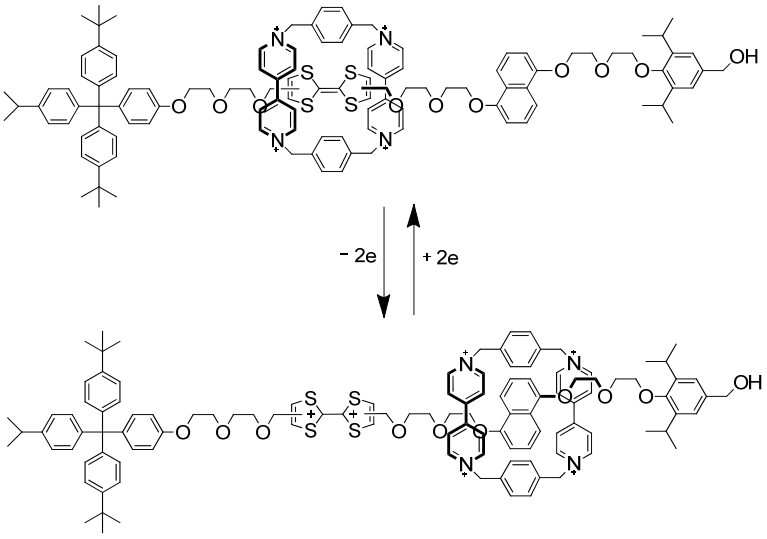
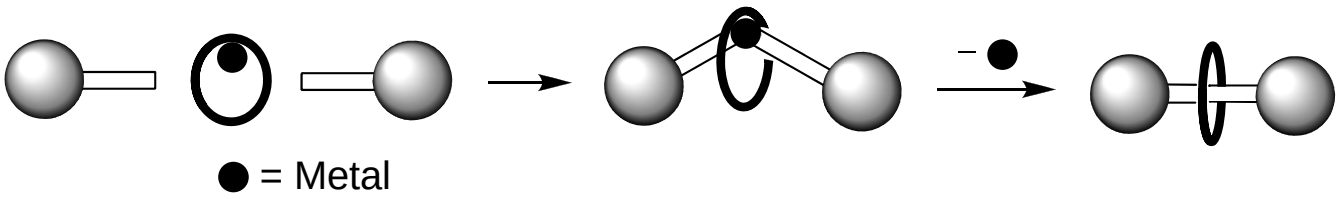



**Figure 2. Active-Metal Template Synthesis of a Rotaxane**



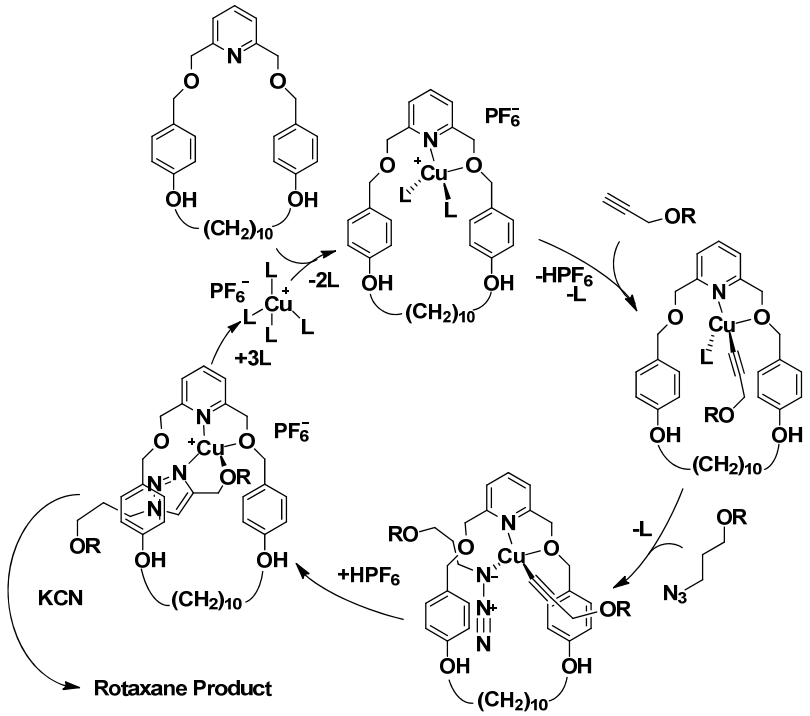

Furthermore, recent advances in the so-called 'stoppering' and 'clipping' reactions have broadened the range of accessible rotaxanes.[15,16] The purpose of adopting these new methodologies is to increase the diversity of structural features that can be incorporated into rotaxanes (e.g. rigid thread components, neutral macrocycles) and to increase the yields of rotaxane-forming reactions which have limited their practical applications.

## ADVANCES IN SYNTHESIS

### Cu(I)-Promoted and Cu(I)-Catalyzed Reactions

**Cu(I)-Catalyzed Huisgen 1,3-dipolar cycloaddition.** The Cu(I) Huisgen 1,3-dipolar cycloaddition between azides and terminal alkynes (the CuAAC "click" reaction) has found broad use in many areas of chemistry. The power of this reaction is owed to its broad functional group tolerance, mild reaction conditions, and reliability. Heath and co-workers have used this reaction to improve yields of donor-acceptor rotaxanes.[17] These donor-acceptor rotaxanes, based on $CBPQT^{4+}$ as the π-acceptor, were previously constrained to the clipping strategy due to the sensitivity of the $CBPQT^{4+}$ to various chemical reagents. This restriction required the $CBPQT^{4+}$ to be introduced in the last step of the synthetic sequence. The $CBPQT^{4+}$ was shown to be insensitive to reaction conditions of the CuAAC reaction which allowed the ring to be pre-formed and then threaded to produce a stable pseudorotaxane. Subsequent stoppering of the pseudorotaxane with the CuAAC reaction produced the [2]rotaxane in 82% yield. In addition, the utilization of the "click" reaction provided access to [3]- and [4]rotaxanes that were previously unattainable by clipping reactions. Furthermore, Sauvage and co-workers utilized this strategy to improve the overall yields of a Cu(I)-rotaxane complex.[18] The poor yields previously observed in the synthesis of this type of [2]rotaxane were due to the unstable pseudorotaxane Cu(I) complex that was subjected to a Williamson ether reaction to attach the stoppers. However, the CuAAC reaction afforded the [2]rotaxane Cu(I) complex in 62% yield. Leigh and co-workers have also begun to pioneer the approach they call the 'active-metal' template strategy[14] beginning with the Cu(I)-catalyzed azide-alkyne 1,3-cycloaddition (Scheme 3). This methodology relies on the metal to perform a dual function. First, it must template the reacting species towards interlocking through coordination and, second, it must catalyze the final covalent bond-forming reaction through

**Scheme 3. Proposed Catalytic Cycle of CuAAC Synthesis of [2]Rotaxanes**



the cavity of the macrocycle, which mechanically traps the components of product. There are several proposed advantages to the active-metal template methodology: 1) it alleviates the need for strong interactions between the macrocycle and thread component, 2) many known transition-metal-catalyzed reactions are potentially amenable to this strategy, 3) it could increase the structural diversity of rotaxanes alleviating the constraint of employing traditional template-directed previously discussed, and 4) substoichiometric quantities of the metal can be used. In the first example of this strategy by Leigh and co-workers, an equimolar mixture of pyridine macrocycle, alkyne, azide, and $Cu(CH_3CN)_4PF_6$ in $CH_2Cl_2$ was stirred overnight at room temp. to produce a mixture of [2]rotaxane (57% yield) and the non-interlocked product (41%).[19] When the amount of Cu(I) salt was lowered to only 20 mol % the yield of the [2]rotaxane reduced to 20%, suggesting that the rotaxane inhibited the catalyst. It was eventually found that addition of pyridine as a competing ligand allowed the catalyst to turn over, requiring only 20 mol % of the Cu(I) salt.

**Additional Cu-Mediated Reactions.** In 2006, Saito and co-workers published the first example of [2]rotaxanes that were constructed with oxidative alkyne homocoupling and C-S bond formation through the cavity of a macrocycle.[21] The reaction to form the [2]rotaxane by the Cu-catalyzed C-S bond formation produced the desired [2]rotaxane in 27% yield and the corresponding non-interlocked product in 81% yield. However, the [2]rotaxane constructed with Cu-catalyzed alkyne homocoupling produced the desired interlocked product in 72% yield and the non-interlocked product in 26% yield. Leigh and co-workers expanded on this idea in their report on the synthesis of unsymmetrical [2]rotaxanes using Cu(I)-mediated Cadiot-Chodkiecz heterocoupling of terminal alkynes and haloalkynes.[22] The advantage of this strategy is the incorporation of a relatively rigid linear thread that reduces folding of the rotaxane. Furthermore, this reaction can introduce two unsymmetrical units on the thread. Unsymmetrical units are favorable for a switchable rotaxane that binds to different 'stations' on thread.

**Pd-Catalyzed Cross-Coupling Reactions**

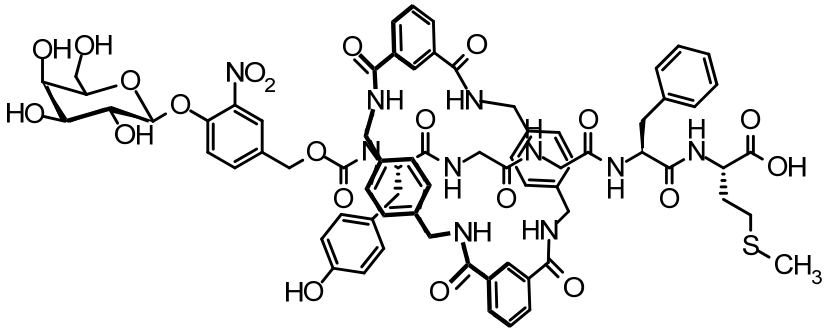
Pd-catalyzed cross-coupling reactions have provided access to a wealth of organic compounds through the construction of carbon-carbon bonds. These powerful transformations have also begun to be applied in the synthesis of rotaxanes. Anderson and co-workers employed sequential Suzuki-Miyauri cross-coupling reactions as the stoppering reactions to synthesize hetero-[3]rotaxanes.[23] These rotaxanes consisted of a stillbene moiety and cyanine dye encapsulated in a single cyclodextrin macrocycle. This report provided the first example of two different 'dumbells' mechanically interlocked in one

macrocycle. Expanding on the 'active-metal' template strategy, Leigh and co-workers reported Pd(II)-catalyzed oxidative Heck cross-couplings in the synthesis of [2]rotaxanes.[24].

**Hydrogen-Bonding Templates**

Attracted by the incredible topological complexity observed in biomolecules, Leigh and co-workers investigated the possibility of synthesizing peptide-based rotaxanes by a hydrogen-bond-directed assembly.[9a] In 1997 they reported the synthesis of glycyl-glycine derivative encapsulated by a benzylic amide macrocycle to form a [2]rotaxane via a 'clipping' strategy. The strategy was thought to be successful due to the hydrogen-bond-directed assembly of the benzylic amide macrocycle around the 1,3-diamide thread. The hydrogen bonding interactions between the macrocycle and the peptide thread that persist in the rotaxane product were investigated by $^{1}$H NMR spectroscopy and X-ray crystallography. In non-polar solvents and in the solid state, the macrocycle was confined to the 1,3-diamide portion of the thread. However, in polar solvent-water mixtures the macrocycle was observed to access the entire length of the peptide backbone. In 2009, Leigh and co-workers expanded this idea by synthesizing [2]rotaxane propeptide **5** (Figure 3) using an identical hydrogen-bond-directed template.[9c]

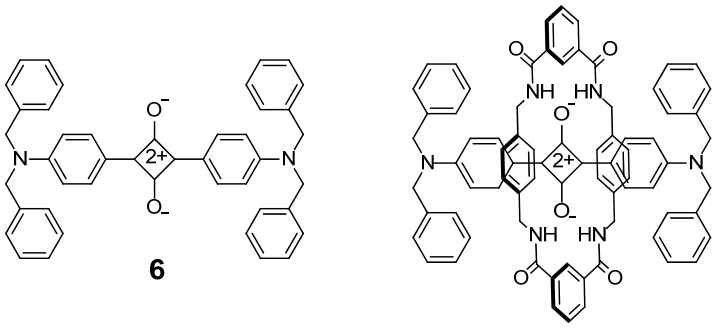
**Figure 3. [2]Rotaxane Propeptide 5**



**5**

The bioactive pentapeptide was incorporated into the thread component of the rotaxane and was shown to be protected from enzymatic degradation in the presence of a variety of peptidases. This increased chemical stability was attributed to the macrocycle being able to access the entire portion of the thread as previously noted. The authors also realized the limited utility of a bioactive peptide that is chemically inert and cannot be recognized to its receptor due to its incorporation into a rotaxane. Therefore, the rotaxane was synthesized with an enzyme-accessible monosaccharide on one of the stoppers. When treated with *E. coli* β-galactosidase, the macrocycle was unthreaded and the free bioactive peptide was released. Smith and co-workers have also been able to expand ideas pioneered by Anderson and co-workers to impart enhanced chemical stability to squaraine dyes (Figure 4).[9b]

**Figure 4. Squaraine Dye 6 and Squaraine Rotaxane 7**




**6** **7**

Encapsulation of the dianionic squaraine **6** is achieved by using a 'clipping' protocol. Reaction of the appropriate diacid chloride and *p*-xylenediamine in the presence of **6** afforded [2]rotaxane **7**. The chemical stability of **6** and **7** was compared by treatment with cysteine. **6** showed a half-life of 5 min in the presence of cysteine, while **7** was essentially inert. This result was directly attributed to the steric protection afforded by the macrocycle.

## APPLICATIONS OF SWITCHABLE ROTAXANE-BASED ARCHITECTURES

### 'Mechanized' Nanoparticles

The discovery and utilization of novel drug delivery methods is an extremely active area of research that spans many disciplines. Recently, rotaxanes have been used to control drug release. Mesoporous silica nanoparticles can be 'loaded' with a drug by simple diffusion, and the pores of the nanoparticle can be effectively 'capped' by tethering rotaxanes to the surface. The macrocycle functions as the 'cap' by inhibiting diffusion of the drug from the pores of the nanoparticle. The release of the drug can then be controlled by translation of the macrocycle along the thread by a variety of stimuli, including changes in pH,[4] electrochemical,[5a] and photochemical.[6] In an extensive study by Zink and co-workers, the optimal position to tether the rotaxanes within the pore and the optimal lengths of the rotaxanes were discovered. It was found that tethering the rotaxanes deeper inside the pore or shortening the length of the rotaxanes effectively prevented premature leakage of the probe molecules.[5]

### Synthetic Molecular Muscles

The stretching and contracting process of muscle filaments is a highly regulated process at the nanoscale. Rotaxane-based systems have been shown to reproduce this behavior. In 2000 Sauvage and co-workers utilized a rotaxane dimer with two unique coordination sites to extend and contract based on the addition of either Cu(I) or Zn(II).[8] $^1$H NMR spectroscopy was used to provide evidence of the

presence of both the contracted and extended states. A study by Huang and co-workers in 2009 demonstrated that surface-bound [3]rotaxanes cause a microcantilever to bend when electrochemically activated.[5b] The deflection of the microcantilever was determined by an atomic force microscope. This study proved that the molecular motion of the macrocycle could be controlled and transduced through the material to produce mechanical work.

## CONCLUSIONS AND FUTURE DIRECTIONS

The potential of the rotaxane topology to impart novel functional properties to molecular systems and materials will continue to motivate their syntheses. However, the structure-function relationship will always limit their tangible applications. Therefore, novel synthetic approaches to access rotaxanes are being conceived and executed to increase the structural diversity of both the building blocks and rotaxane products. These synthetic strategies will likely afford rotaxane architectures that have previously been inaccessible.

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