J|A|C|S COMMUNICATIONS

Published on Web 02/24/2010

Actuator Prototype: Capture and Release of a Self-Entangled [1]Rotaxane

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Pseudo[1]rotaxanes are a conformationally dynamic unimolecular (hence [1]) species comprised of a macrocycle with an appended tail-like chain. The pseudo prefix denotes the ability of these species to establish an equilibrium between disentangled conformations and self-entangled conformations, wherein the macrocycle is threaded by its own tail. When such a molecule takes on a tail-threaded conformation, it is a pseudo[1]rotaxane.[1] In the presence of sufficient barriers within disentanglement pathways, a given species will be trapped in a self-entangled state; such a species is a [1]rotaxane.[2]

An accurate understanding of how ring-threading events can occur is of fundamental importance[3] as they relate to the transport of biopolymers across membranes[4] as well as to the fabrication of molecular textiles[5] and to the engineering of synthetic nanomechanical devices.[6] In connection to the latter endeavor, the reversible unthreading behavior of a pseudo[1]rotaxane is of technological interest because this motion is essentially that of a nanomechanical actuator[7,8] and thus may be exploited in certain settings. For example, three-dimensional networks or gels, a portion of which is depicted in Scheme 1, which include hypothetical randomly oriented pseudorotaxane actuators as part of the backbone scaffold of the network, could exhibit a macroscopic breathing-like motion (swelling) in response to stimuli which induce reversible threading (entanglement/contraction) and unthreading (disentanglement/extension) at the molecular level. Thus, and within a broader study,[9] we questioned how to engineer useful, mechanistically unambiguous, reversible pathways between threaded and unthreaded conformations and, further, how to control the populations of these mutually exclusive states.

There are several distinct mechanisms by which a disentangled pseudo[1]rotaxane may self-entangle. A mechanism of self-threading that can be envisioned, perhaps most readily, is one in which the terminus of the tail-like chain is seen to approach, fill, and pass through the cavity of the macrocycle, i.e., by an unassisted, end-in, threading mechanism. However, as it is, this mechanism of entanglement would not be useful for actuation, at least as depicted in Scheme 1, since the chain, as shown, is part of the network and has no well-defined local terminus.

A less obvious but potentiality more useful entanglement pathway that we pursued stemmed from the observation that many known cyclophanes feature aryl groups, as part of a macrocyclic ring, that are capable of facile rotation;[10] this structural feature may be likened to a stochastic bidirectional turnstile. The result of incorporating such a rotatable group, along a segment of a macrocycle, and further equipping the rotatable group with a tail-like chain would be the inception of an "easy-thread" macrocycle. A macrocycle so functionalized gains an additional mechanism by which it may self-entangle. Since no free chain end is required for this mode of threading, this mechanism could be useful for actuation as shown in Scheme 1.

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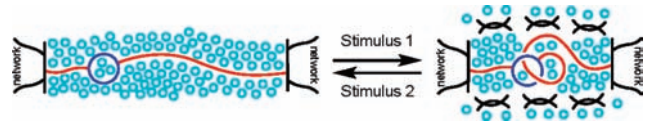
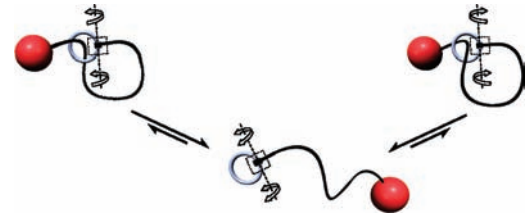
Scheme 1. Reversible Stimulated Network Contraction/Extension



Scheme 2. Self-Entanglement/Disentanglement Equilibria



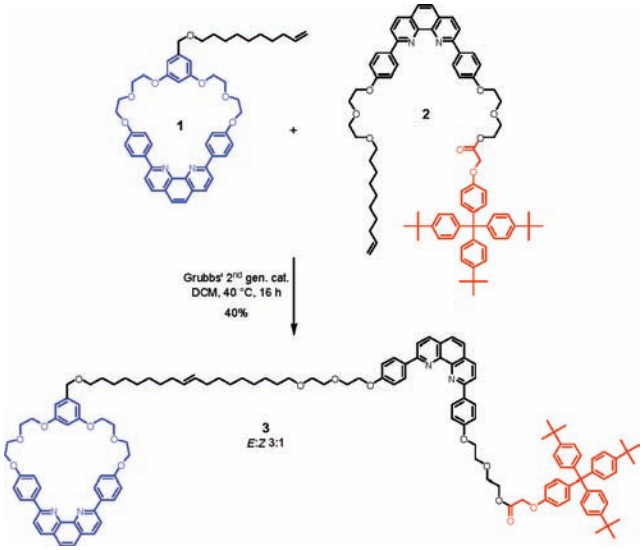
To test the validity of this concept and realize such a system with near certainty of mechanism and unfettered operation, a somewhat exacting model was designed. The model (Scheme 2, center) consists of a chain that is functionalized, on one end, with a macrocycle and, on the other end, with a moiety that is large enough, relative to the macrocycle cavity, that passage of this end through the macrocycle (threading/unthreading) is essentially impossible. This arrangement precludes unwanted competitive threading events, i.e., both unassisted, end-in, intramolecular threading and also unassisted intermolecular threading. Of course, enabling to the design is that the site of attachment, of the tail-like chain to the macrocycle, must be able to rotate through the interior of the macrocycle to carry the appended chain through and achieve threading.

Of further importance to this actuator design is that, even when the macrocycle is equipped with a turnstile-like feature to guide threading, the self-entangled state should not be favored at equilibrium, though for utility, as in Scheme 1, it must be trappable by some means. The turnstile-like feature should merely allow the species to readily sample conformations of both the entangled and the disentangled types. Indeed, in the absence of a stabilizing force to maintain the entangled state or in the absence of a barrier to disentanglement, the disentangled state should generally be favored.[7b] In a good chain-solvating environment, the driving force for disentanglement stems from a gain in conformational entropy, as in a macrocyclic ring-opening reaction. This bias in the equilibrium is key since favorable disentanglement would provide the driving force for restoring the extended state of Scheme 1.

Herein we report the preparation of a compound that dynamically samples both self-entangled and disentangled conformations, yet favors disentangled conformations. We also report the independent synthesis of a metal complex of the same compound, trapped, exclusively, in a self-entangled state. Lastly, we demonstrate chemically stimulated switching, i.e., capture and release, between the primarily disentangled (yet conformationally dynamic) state and the exclusively entangled state.

10.1021/ja9077655

Scheme 3. Synthesis of Disentangled Pseudo[1]rotaxane **3**

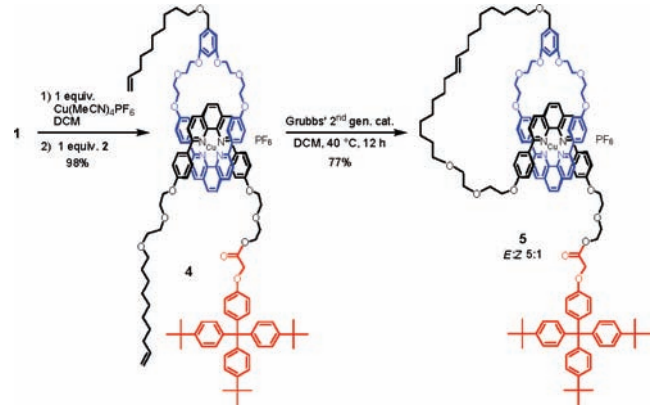


A model compound (**3**) that embodies the characteristics of the model actuator of Scheme 2 was synthesized and isolated in 40% yield via olefin hetero-cross-metathesis from macrocycle **1** and chain **2**, Scheme 3.[11] Model **3** features a Sauvage-type[12] 31-membered ring on one end and a bulky tris(*p-tert*-butylphenyl) methyl group[13] on the other end. Model **3** goes beyond the design of the actuator of Scheme 2, however, in that **3** has an added feature; i.e., it possesses an inwardly directed 1,10-phenanthroline ligand within the macrocycle to trap, upon self-entanglement in the presence of Cu(I), another phenanthroline ligand that makes up a portion of the mainly flexible chain between the macrocycle and the bulky chain terminus. The particular bulky chain end group selected for use here has been previously employed in numerous studies and has been demonstrated to be unable to pass through the specific 31-membered macrocycle[8e,f] of compound **3**. Additionally, the macrocycle features a 1,3,5-trisubstituted aromatic moiety that was incorporated with the intent to allow rotation of this moiety through large angles in excess of 360° as a result of the appropriate spaciousness of the cavity of the macrocycle, the presence of the two flexible σ-bond-rich polyether linkers, and also the 1,3,5-substitution pattern itself[14] of the aromatic moiety.

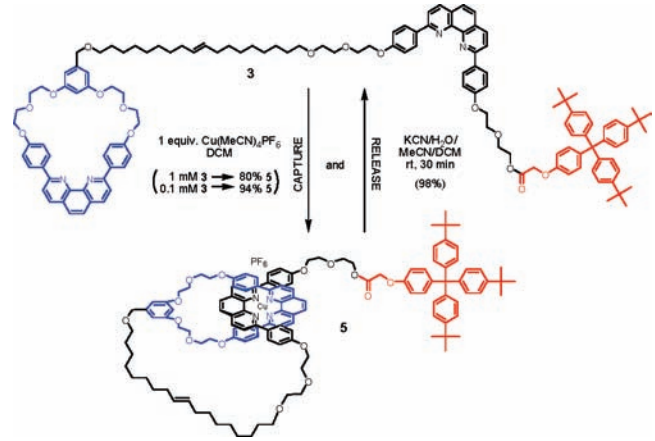
Model **3** bears a strong resemblance to the prototype in Scheme 2 in that it was specifically designed to reversibly self-entangle but not to be biased toward the entangled state.[15] Indeed, the dynamics of **3** appear to favor the entangled state no more than macrocycle **1** itself favors a self-entangled, tail-threaded conformation, as demonstrated by ^{1}H NMR spectroscopic data which show that the spectrum of **3**, except for the signals due to the olefin, is a superposition of the spectra of pure and separate **1** and **2**. The spectrum of **3** does not show any characteristic signal broadening or shifts as would be anticipated to accompany a significant increase in the population that exists in an entangled conformation, at any rate of exchange.

An independent preparation of **3**, albeit as a Cu(I) complex, trapped exclusively in a self-entangled conformation, by strong chelation of the two phenanthroline ligands to the Cu(I) center, was performed as shown in Scheme 4. In this route, macrocycle **1** was first treated with 1 equiv of Cu(I). Two molecules of **1** are incapable of forming a bis-phenanthroline copper complex due to the prohibitive strain that would result from one macrocycle threading the other. Without isolation of an intermediate, the mixture was further treated with 1 equiv of **2**. The resulting bis-phenanthroline copper complex **4** was found to be very stable; it was purified by column chromatography and isolated in 98% yield. A 2.5 mM solution of **4** was subjected to 10 mol % Grubbs' second generation catalyst to effect a ring-closing metathesis and ultimately afford **5** (50-membered ring including copper) in 77% isolated yield.

Scheme 4. Synthesis of [1]Rotaxane **5**



Scheme 5. Capture and Release



As shown in Scheme 2, for suitably engineered structures, threading and unthreading are expected to be reversible. Likewise, **3** was designed to rapidly and reversibly sample accessible conformations of both the self-entangled and the disentangled types. To indirectly test for this behavior, the capture of **3**, in an exclusively entangled conformation, was attempted by treatment of **3** with 1 equiv of Cu(I) under dilute conditions, Scheme 5. Dilute conditions were used to minimize competitive bimolecular chain−chain complexation. Indeed, upon treatment of 1 mM **3** with Cu(I), self-entangled [1]rotaxane **5** was isolated in 80% yield. Beginning with 100 μM **3**, [1]rotaxane **5** was isolated in 94% yield. Compound **5** (from **3**) and **5** (from **4**) provided identical characterization data, barring a slight difference in the *E*/*Z* ratio.[11]

Regarding the mechanism of synthesis of entangled **5** from disentangled **3**, introduction of Cu(I) is unlikely to be the direct cause of self-entanglement. Instead, it is more likely that an initially formed, labile, monophenanthroline (either site) Cu(I) complex possesses an ability to sample both self-entangled and disentangled states, as described for **3**. If so, formation of the highly stable bis-phenanthroline Cu(I) complex (**5**), which must derive from a monophenanthroline Cu(I) complex residing in a self-entangled conformation, thus traps self-entangled conformations. Consequentially, dethreadable conformations would be removed from the overall population, disturbing the dynamic balance and pulling further members into a self-entangled conformation for eventual

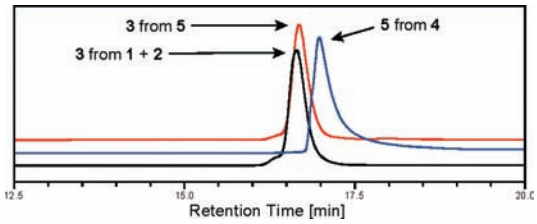


Figure 1. SEC chromatograms of **3** (black trace), **5** (blue), and **3** (red).

capture. Separately, because **5** cannot be obtained from **3** via a slippage-type mechanism[16] wherein the bulky end group passes through the macrocycle, this experiment of Scheme 5 corroborates the original supposition that the 1,3,5-trisubstituted aryl group of **3** can function as a rotatable turnstile-like carrier of a tethered chain through the macrocycle.

In this particular model system, removal of the Cu(I) ion, which maintains association of the two phenanthroline moieties of **5**, should release the captive self-entangled species and allow the population to re-equilibrate. In an effort to test this idea and attempt removal of the Cu(I) linchpin that retains the threaded state, a solution of [1]rotaxane **5** was treated with an excess of KCN, Scheme 5. As a result, the characteristic dark red color of the Cu(I)bis-phenanthroline complex faded over 30 min, thus providing a near colorless solution. From the crude product, compound **3** was isolated in 98% yield. Due to the efficiency of the templated cross-metathesis, the three-step 74% overall yield of **3** (from **5** from **4** from **1** and **2**) significantly contrasts with the 40% yield of **3** directly from **1** and **2**. The characterization data for **3** (from **5**) exactly matched the characterization data for **3** (from **1** and **2**). Hence **3** (from **5**) and **3** (from **1** and **2**) were proved to be the same, again barring a slight difference in the *E*/*Z* ratio.[11] Since the bulky end group of **5** was too large to pass through the interior cavity of the macrocycle, upon removal of the copper ion, it is likely that reversibility and disentanglement were accomplished via passage of the aliphatic chain through the macrocycle followed by rotation of the aromatic moiety.

In an initial effort to investigate practical differences that arise specifically from entanglement, we examined molecular size. Molecular modeling suggested end-to-end distances of 6.39 nm for **3** (in a highly extended disentangled form) and of 4.12 nm for **5**, i.e., a 35% contraction in length upon self-entanglement.[11] Analytical size exclusion chromatography (SEC) was employed to experimentally probe this difference,[17] Figure 1. Cross metathesis product **3**, prepared as shown in Scheme 3, produced a single sharp peak with a retention time of 16.6 ± 0.1 min. In contrast [1]rotaxane **5**, prepared as shown in Scheme 4, reproducibly exhibited a broad peak with tailing. Nevertheless, a longer retention time, with a maximum at 17.0 ± 0.1 min, was consistently observed for **5**.[18] The product of demetalation of [1]rotaxane **5**, i.e., **3**, likewise displayed a peak at 16.6 ± 0.1 min. Despite the fact that **5** is 12% greater in mass (due to $CuPF_6$) than **3**, **3** behaved as if it were larger than **5**. To rationalize the differences in retention times, we conclude that **5** exists exclusively in a contracted entangled state while **3** exists as a dynamic ensemble of conformations that includes a significant population of extended disentangled conformations.

In summary, conformationally dynamic **3** and exclusively self-entangled **5** were separately prepared and characterized. They were shown to controllably interconvert under appropriate chemically stimulated conditions. The change in size upon reversible capture and release of self-entangled [1]rotaxane **5** thus provides motivation for development of related network-incorporable structures that could respond to various stimuli at various rates.

Acknowledgment. This research was supported by the Robert A. Welch Foundation (D-1635) and by the Texas Advanced Research Program (003644-0060-2007). We thank Mr. George Tamas for the molecular modeling of **3** and **5**.

Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA9077655