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En Route to a Molecular Sheaf: Active Metal Template Synthesis of a [3]Rotaxane with Two Axles Threaded through One Ring

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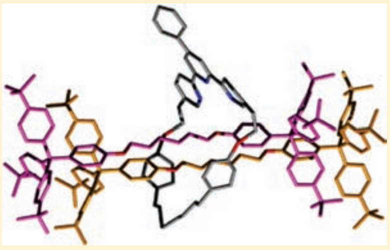
S *Supporting Information*



ABSTRACT: We report that a 2,2′:6′,2″-terpyridylmacrocycle−Ni complex can efficiently mediate the threading of two alkyl chains with bulky end groups in an active metal template sp^3-carbon-to-sp^3-carbon homocoupling reaction, resulting in a rare example of a doubly threaded [3]rotaxane in up to 51% yield. The unusual architecture is confirmed by X-ray crystallography (the first time that a one-ring-two-thread [3]rotaxane has been characterized in the solid state) and is found to be stable with respect to dethreading despite the large ring size of the macrocycle. Through such active template reactions, in principle, a macrocycle should be able to assemble as many axles in its cavity as the size of the ring and the stoppers will allow. A general method for threading multiple axles through a macrocycle adds significantly to the tools available for the synthesis of different types of rotaxane architectures.

INTRODUCTION

Rapid advances in many aspects of template synthesis, ligand design, and methods for covalent capture are allowing access to increasingly complex mechanically interlocked architectures.[1] However, while there are numerous examples of rotaxanes consisting of several rings threaded onto a single axle,[2,3] rotaxanes featuring multiple axles passing through a single ring remain rare.[4−6] This disparity is accounted for by the relative structural demands on the cyclic component(s) and thread(s). The structural elements used for the synthesis of a [2]rotaxane can, in principle, be extrapolated to multiring rotaxanes with relative ease by simply employing an elongated axle with several template sites without changing the size and nature of the macrocycle or stoppers.[2] The synthesis of multithread rotaxanes is more challenging: The ring may require more than one template site to assemble multiple threads (using traditional template methods), and must be considerably larger than required for a [2]rotaxane in order to accommodate more than one axle, an issue that is further complicated by the sheer size of the stoppers required to prevent dethreading of large macrocycles.[4b,c,e,7] Furthermore, the macrocycle−thread interactions that direct the assembly of the interlocked components must overcome the sometimes severe steric clashes that can occur between crowded thread units.

Active metal template synthesis[8] is a strategy for the construction of mechanically interlocked architectures in which a macrocycle-bound transition metal ion acts as both the template to entwine or thread the components and as a catalyst to promote the covalent bond forming reaction that captures the interlocked structure. Unlike traditional 'passive' metal template approaches to the synthesis of rotaxanes,[9] a permanent metal binding site is only required on the macrocycle—the thread component may have little[8a−e,g,k,m] or no[8n] binding affinity for the transition metal ion after rotaxane formation. Thus, the metal ion may be able to turn over during the reaction, a corollary being that in some cases only a substoichiometric amount of the metal is required to achieve the transformation.[8a,c−e,k] Here, we report on a further consequence of employing such a catalytic template system: a single active template site in a suitably large macrocycle is able to mediate the sequential formation of two threads through one ring, giving rise to a doubly threaded [3]rotaxane. To do so the cavity of the macrocycle must be large enough to accommodate two axles yet still small enough to prevent dethreading. A 35-membered ring with an endotopic 2,2′:6′,2″-terpyridine (terpy) binding site successfully promotes one-ring-two-threads [3]rotaxane formation via an active template Ni-catalyzed homocoupling of alkyl bromides terminated with tris(*t*-butylphenyl)methyl groups in up to 51% yield in a simple one-pot reaction.

RESULTS AND DISCUSSION

We recently reported the discovery of a Ni-catalyzed sp^3-carbon-to-sp^3-carbon alkyl bromide homocoupling reaction and its application to the active metal template synthesis of [2]rotaxanes.[8n] An essential feature of the reaction is the use of a tridentate nitrogen-donor-atom ligand to inhibit competing β-hydride elimination of alkyl-Ni intermediates during the Ni-catalyzed reductive dimerization. [2]Rotaxane formation was demonstrated using a macrocyclic pyridine-2,6-bisoxazoline ligand. However, the bisoxazoline macrocycle and rotaxane were

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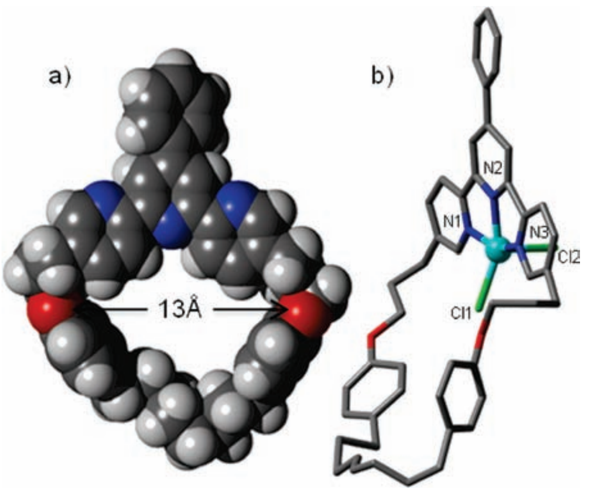


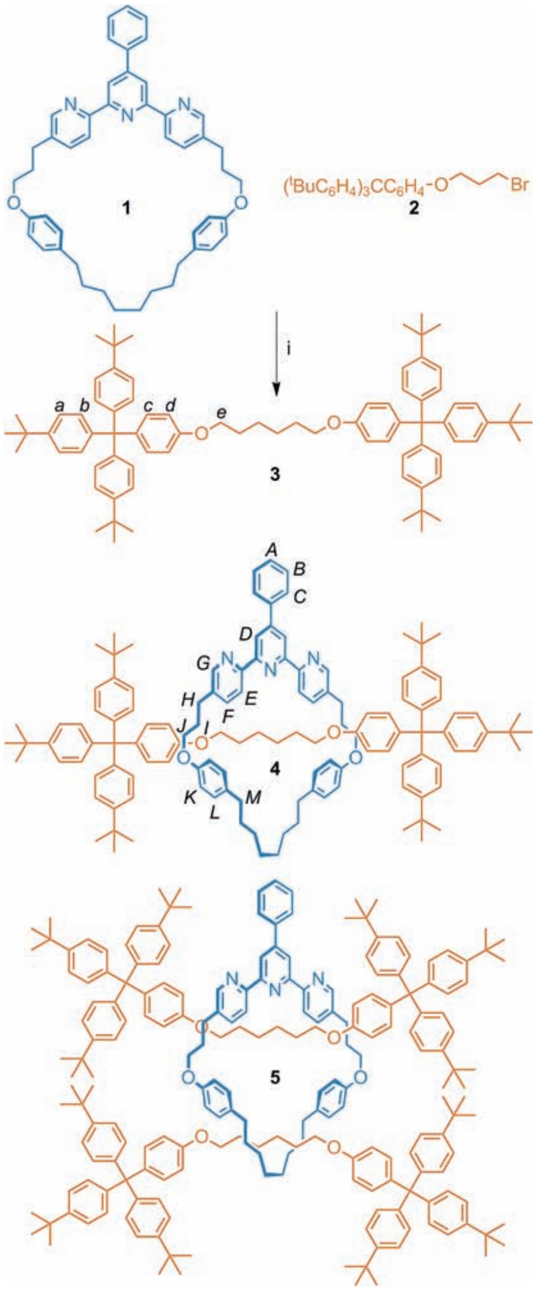
Figure 1. X-ray crystal structure of (a) macrocycle **1**, from a single crystal obtained by vapor diffusion of diethyl ether into a chloroform solution, space filling representation, and (b) complex **1**·$NiCl_2$, from a single crystal obtained by slow diffusion of methanol into a chloroform solution, stick representation. Solvent molecules and hydrogen atoms of **1**·$NiCl_2$ are omitted for clarity. Nitrogen atoms are shown in blue, oxygen atoms red, chlorine atoms green, nickel atoms cyan (ball), hydrogen atoms white, and carbon atoms gray. Selected bond lengths [Å] and angles [°]: N1−Ni 2.11, N2−Ni 1.97, N3−Ni 2.12, Cl1−Ni 2.27, Cl2−Ni 2.30, N1−Ni−N2 77.1, N1−Ni−N3 153.5, N2−Ni−Cl1 154.0, Cl1−Ni−Cl2 108.0, N2−Ni−Cl2 98.0.

prone to decomposition, limiting the scope of the reaction. Optimization of the Ni-catalyzed dimerization protocol with commercially available substrates revealed that terpy groups are also suitable catalyst ligands for this transformation and are much more stable than oxazoline units.[8n,10] It appeared that integration of the robust terpy binding motif into a macrocycle might overcome the rotaxane stability issue, enabling the Ni-catalyzed alkyl bromide homocoupling reaction to be rather more synthetically useful.

Macrocycle **1** was synthesized from commercially available 2,5-dibromopyridine and 4-(4-methoxyphenyl)-butyl bromide in 24% overall yield, with 8 steps in the longest linear sequence (for details of the synthesis, see the Supporting Information). Substitution at the 5- and 5″- position of the terpy ring system allows rotation of the pyridyl rings relative to one another[11] upon chelation of Ni^{II} and the 120° turn angle of the rigid aromatic framework induces cavity dimensions appropriate for use in rotaxane-forming reactions. Single crystals of both macrocycle **1** and the corresponding complex **1**·$NiCl_2$ were obtained by slow vapor diffusion of diethyl ether or methanol into chloroform solutions and the solid state structures determined by X-ray crystallography (Figure 1). The crystal structure of **1** shows that the rigid terpy portion of the macrocycle generates an aperture with a cavity width of up to 13 Å (Figure 1a). The terpyridyl ring system switches to a cis−cis geometry upon coordination to Ni^{II} (Figure 1b), holding the metal center endotopically as required for a rotaxane-forming active template mechanism.

The catalytically active macrocycle−Ni^0 complex was formed *in situ* by stirring **1** with $NiCl_2 \cdot 6H_2O$ in *N*-methyl-2-pyrrolidone (NMP) followed by reduction with Zn powder. After addition of a solution of the 'stoppered' alkyl bromide **2** in tetrahydrofuran (THF), the reaction mixture was heated at 60 °C for 18 h (Scheme 1 and Table 1), then demetalated with a basic ethylenediaminetetraacetic acid disodium salt−ammonia (Na_2EDTA-NH_3) solution.[12] Pleasingly, a stoichiometric amount of stoppered bromide **2** led to complete conversion to homocoupled products and formation of the desired [2]rotaxane **4** as observed by analysis of the crude reaction mixture by ^{1}H NMR spectroscopy and mass spectrometry. Purification of the crude reaction mixture by size-exclusion chromatography revealed only a modest 14% yield of [2]rotaxane **4** (Table 1, entry 1). However, as the catalytic Ni complex can turn over during the reaction, the yield of [2]rotaxane could be increased to 48% by employing a

Scheme 1. Synthesis of [2]- and [3]Rotaxanes via a Nickel-Catalyzed Active Template Reductive Homocoupling Reaction[a]



[a] Reagents and conditions: (i) 1. $NiCl_2 \cdot 6H_2O$, Zn, NMP-THF (1:1), 60 °C, 18 h. 2. $Na_2EDTA\text{-}NH_{3(aq)}$.

Table 1. Conversion of Macrocycle 1 to [2]Rotaxane 4 and [3]Rotaxane 5 (Scheme 1)

entry	equiv **2**	[2]rotaxane **4** yield[a]	[3]rotaxane **5** yield[a]
1[b]	2.0	14%	4%
2[b]	5.0	48%	9%
3[b]	10.0	29%	30%
4[c]	20.0	20%	51%

[a] Isolated yields based on macrocycle **1**. [b] Ten equivalents of Zn. [c] Fifteen equivalents of Zn. In all cases, ≥95% conversion to homocoupled products was determined by ^{1}H NMR analysis of the crude reaction mixture.[12]

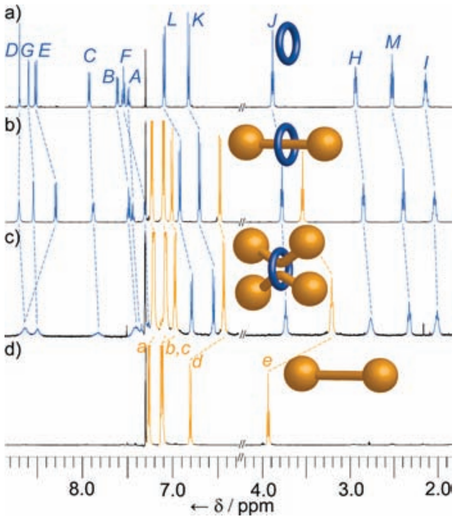


Figure 2. Partial ^{1}H NMR spectra (500 MHz, CDCl$_3$, 298 K) of (a) macrocycle **1**, (b) [2]rotaxane **4**, (c) [3]rotaxane **5**, and (d) non-interlocked thread **3**. The lettering corresponds to that shown in Scheme 1.

2.5-fold excess of bromide **2** (Table 1, entry 2). To our surprise, when a 5-fold excess of bromide **2** was used in an attempt to further increase the amount of **4** formed, the isolated yield of [2]rotaxane fell to 29% (Table 1, entry 3). The reason behind this unexpected drop in yield of **4** became apparent during the size-exclusion purification procedure: a substantial amount of material eluted before the [2]rotaxane indicating another product with a larger hydrodynamic volume. ^{1}H NMR spectroscopy and mass spectrometry revealed that the second product was the one-ring-two-thread [3]rotaxane **5** (Scheme 1).[13] Repetition of the reaction protocol using less equivalents of **2** (Table 1, entries 1 and 2) confirmed small amounts (<10%) of **5** are also formed under those conditions. The [3]rotaxane proved to be the major product when using a 10-fold excess of bromide **2**, producing a total of 71% interlocked products of which 51% was [3]rotaxane **5** (Table 1, entry 4). As complete conversion of **2** occurred and unconsumed macrocycle **1** could be recovered, the yield of interlocked products reflects the proportion of intermediate dialkyl-Ni species that react with the axle precursors protruding from opposite faces of the macrocycle (leading to rotaxane **4** or **5**) or from the same face (leading to the non-interlocked axle **3**). Unlike the bisoxazoline-macrocycle rotaxanes previously prepared using the Ni-catalyzed active metal template sp^3-carbon-to-sp^3-carbon homocoupling reaction,[8n] the terpy-macrocycle-based [2]rotaxane **4** and [3]rotaxane **5** proved completely stable (no degradation observed over several months, vide infra).

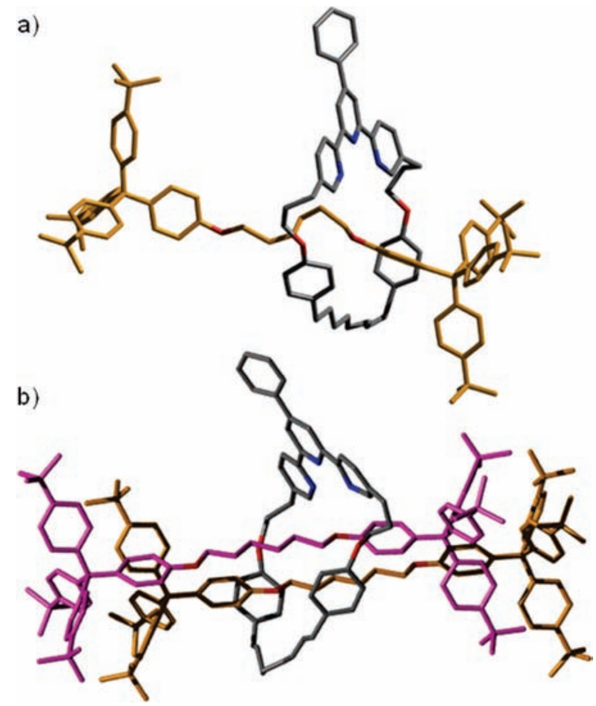


Figure 3. X-ray crystal structures of (a) [2]rotaxane **4**, and (b) [3]rotaxane **5**, from single crystals obtained by slow diffusion of methanol into deuterochloroform solutions. Hydrogen atoms and solvent molecules are omitted for clarity. Nitrogen atoms are shown in blue; oxygen atoms red; and the carbon atoms of the different components in gray, gold, and pink.

Comparison of the ^{1}H NMR spectrum (500 MHz, CDCl$_3$, 298 K) of the [2]rotaxane **4** (Figure 2b) with those of its non-interlocked components (macrocycle **1** and thread **3**; Figure 2, panels a and d, respectively) shows upfield shifts of protons from the thread and macrocycle typical of regions of mechanically interlocked structures that spend some time face-on to aromatic rings. The uniform distribution of the modest shielding effects suggest that no particular co-conformation is stabilized—the macrocycle and thread can undergo relatively unrestricted motion relative to one another, as would be expected in a system with no strong intercomponent interactions. However, threading of a second alkyl chain axle through the ring ([3]rotaxane **5**, Figure 2c) results in increased shielding of most of the thread protons as they are forced to spend more time closer to the aromatic rings of the macrocycle. Several of the macrocycle resonances (H_{A-H}) are broadened, possibly as a consequence of the steric congestion between the chains causing some co-conformational exchange processes, such as macrocycle pirouetting, to slow to rates close to the ^{1}H NMR time scale.

Single crystals of **4** and **5** suitable for X-ray diffraction were grown by slow diffusion of methanol into solutions of each rotaxane in deuterated chloroform. The crystal structures (Figure 3) confirm the constitution of both rotaxanes and the doubly threaded nature of [3]rotaxane **5**—the first time a one-ring-two-thread [3]rotaxane structure has been determined in the solid state. In the solid state, the alkyl chain of the thread of [2]rotaxane **4** (Figure 3a) adopts a folded conformation where it passes through the ring (C−C−C−C dihedral angles 50° ≤ ϕ ≤ 160°), apparently to occupy as much of the space within the macrocyclic cavity as possible, driven by crystal packing forces. In

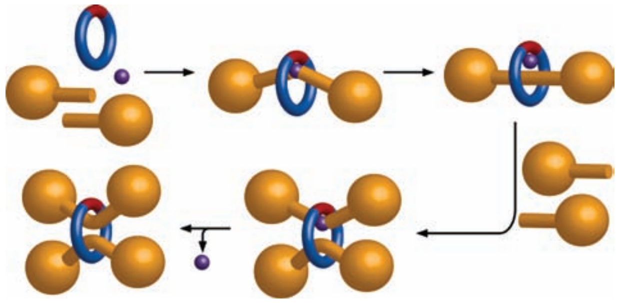


Figure 4. Active metal template synthesis of [3]rotaxanes. A macrocyclic ligand (blue) with an endotopic binding site (red) coordinates to a metal ion (purple). The metal can mediate the construction of interlocked products by promoting the formation of covalent bonds through the cavity. If the ring is large enough to accommodate two threads and the catalytic metal center can turn over, a doubly threaded [3]rotaxane can be assembled in a simple one-pot procedure.

contrast, both alkyl chains of [3]rotaxane **5** adopt fully extended zigzag conformations (C−C−C−C dihedral angles $\phi \approx 180°$)—there is comparatively little unfilled space remaining in the cavity of the doubly threaded macrocycle—and are offset from one another by approximately 4.5 Å along the vector of the thread which minimizes steric clashes between the bulky trityl stoppers. Avoiding stopper−stopper repulsion, perhaps through the use of longer threads, may be an important factor for extrapolating this methodology to the preparation of rotaxanes in which more than two axles are threaded through a single ring, particularly as the stopper size required to prevent dethreading increases dramatically with only small increases in macrocycle size.[4b,c,e,7]

The formation of [3]rotaxane **5** likely proceeds in a stepwise manner via a [2]rotaxane intermediate as depicted schematically in Figure 4. After active template assembly of the first axle (to give [2]rotaxane **4**), the catalytically active metal center is regenerated and can then gather another pair of building blocks and mediate the formation of a second covalent bond, furnishing the [3]rotaxane. Other active template reactions may also have the potential to form multiply threaded rotaxanes. However, the macrocycles used in previous studies have not possessed a cavity of a size capable of accommodating more than one thread and a metal ion simultaneously.[8]

The paucity of doubly threaded rotaxanes in the literature[4] stems from the delicate balance that must be struck between the relative dimensions of the components in order to successfully entrap two axles in one ring—the macrocycle must possess a cavity large enough to accommodate both threads but should not be so large as to be able to slip over the stoppering groups. Indeed, in previously reported syntheses of doubly threaded [3]rotaxanes around an octahedral metal template[4c] or using DNA building blocks,[4e] removal of the template interaction results in metastable structures that dethread over several hours or days at ambient temperature, illustrating the general tradeoff between synthetic accessibility and stability for such structures. Neither [2]rotaxane **4** nor [3]rotaxane **5** showed any signs of dethreading over several months at ambient temperature or upon heating for several hours at 60 °C (see the Supporting Information). As [2]rotaxane **4** is stable, isolable, and can be obtained in good yield (up to 48%; Table 1, entry 2), it may be useful as an intermediate for the synthesis of [3]rotaxanes with two constitutionally different threads,[4a,e] ring-in-ring complexes[14] and for the stepwise assembly of more complex interlocked architectures, such as heterocircuit Borromean rings.

CONCLUSIONS

2,2′:6′,2″-Terpyridyl macrocycle **1** is a highly effective ligand for the Ni-catalyzed active template sp^3-carbon-to-sp^3-carbon homocoupling of alkyl bromides to form chemically robust and kinetically stable rotaxanes. The axles of the rotaxanes are simple alkyl chains (terminated with suitably bulky groups to prevent dethreading) rendering the synthesis effectively traceless in terms of the structure of the threads. The cavity of the 35-membered ring of **1** is sufficiently small that tris(*t*-butylphenyl)-methyl groups can act as the stoppers, but large enough that two alkyl chain threads can be accommodated within the cavity. A one-ring-two-thread [3]rotaxane **5** was isolated in up to 51% yield in a simple one-pot procedure from a five component reaction that features two mechanical bond-forming steps. A small increase in macrocycle size may enable higher order multiply threaded rotaxanes to be synthesized, for example, a ring clasping three threads in its cavity, a type of molecular architecture for which no examples exist to date. Ways of using this, presently unique, synthetic tool for assembling sheaves[15] of molecular chains with no recognition elements[6] are currently being investigated in our laboratory.

ASSOCIATED CONTENT

Ⓢ **Supporting Information.** Experimental procedures and spectral data for all compounds and the details of the X-ray analyses of **1**, $\mathbf{1}\cdot NiCl_2$, **4**, and **5** including cif files. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) In general, free 2,2′:6′,2″-terpyridine ligands preferentially adopt a trans—trans geometry. When acting as a tridentate ligand, rotation around the 2,2′- and 6′,2″ bonds occurs to give the coordinating cis—cis geometry, see: Bazzicalupi, C.; Bencini, A.; Bianchi, A.; Danesi, A.; Faggi, E.; Giorgi, C.; Santarelli, S.; Valtancoli, B. *Coord. Chem. Rev.* **2008**, *252*, 1052–1068.

(12) An optimized 46% yield of [2]rotaxane was reported in ref 8n using the bisoxazoline macrocycle and 2.2 equiv of alkyl bromide at room temperature in DMF. In the present study with the terpyridyl—macrocycle (**1**), the use of a 1:1 mixture of THF—NMP enabled all of

the reactants to be in solution at the start of the reaction. Heating to 60 °C was necessary to allow reactions with >5 equiv of **2** to reach completion within 18 h. The proportion of interlocked and non-interlocked products was unchanged when the reactions were carried out with DMF as solvent and/or at room temperature (other conditions as for Table 1, entry 2).

(13) Two-ring-one-thread [3]rotaxanes have previously been observed as byproducts in Cu-catalyzed azide-alkyne cycloaddition (CuAAC) active metal template reactions, see ref 8d.

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(15) A “sheaf” (plural: sheaves) is a bundle of objects held together by a band or other mechanical binder. Familiar examples include the way that wheat, rye, and other cereals are traditionally bound with straw or twine after reaping.