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Jonathan J. Danon, David A. Leigh, Paul R. McGonigal, John W. Ward, and Jhenyi Wu

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Jonathan J. Danon,[†] David A. Leigh,[†,‡,*] Paul R. McGonigal,[‡] John W. Ward[†] and Jhenyi Wu[‡]

[†] School of Chemistry, University of Manchester, Oxford Road, Manchester, M13 9PL, United Kingdom

[‡] School of Chemistry, University of Edinburgh, The King's Buildings, West Mains Road, Edinburgh, EH9 3JJ, United Kingdom

ABSTRACT: [4]Rotaxanes featuring three axles threaded through a single ring have been prepared through active metal template synthesis. Nickel-catalyzed sp^3-sp^3 homocouplings of alkyl bromide 'half threads' through 37- and 38-membered 2,2':6',2"-terpyridyl macrocycles generates triply-threaded [4]rotaxanes in up to 11 % yield. An analogous 39-membered macrocycle produced no rotaxane products under similar conditions. The constitutions of the [4]rotaxanes were determined by NMR spectroscopy and mass spectrometry. Doubly-threaded [3]rotaxanes were also obtained from the reactions but no [2]rotaxanes were isolated, suggesting that upon demetallation the axle of a singly-threaded rotaxane can slip through a macrocycle that is sufficiently large to accommodate three threads.

INTRODUCTION

Although there are many examples of rotaxanes consisting of several macrocycles threaded onto a single molecular strand,[1] rotaxanes with more than one axle passing through a ring remain rare.[2,3] Doubly-threaded [3]rotaxanes have been prepared[3] by active metal template synthesis,[4] exploiting the ability of the metal atom bound by the macrocycle to turn over and catalyze formation of a second axle through the ring. However, to date no rotaxanes have been reported with more than two strands threaded through a macrocycle. This is likely due to a 'Goldilocks requirement' of the macrocycle needing to be large enough to accommodate three (or more) molecular chains threaded through its cavity whilst also having to be sufficiently small to prevent the ring slipping over the stoppers of an individual axle.

We previously described the synthesis of doubly-threaded [3]rotaxanes using the one-pot nickel-catalyzed sp^3-sp^3 reductive homocoupling of alkyl bromides[3a] through a 2,2':6',2"-terypyridyl macrocycle. In that system the macrocycle-nickel complex is able to turn over, allowing covalent capture of a second thread through a 35-membered ring. Here we report that modestly increasing the size of the macrocycle to a 37- or 38-membered ring enables a third axle to be assembled through the cavity, generating the first examples of triply-threaded rotaxanes.

One might expect that a modest increase in the size of stoppers that are sufficiently bulky to form a [2]rotaxane should enable multiply-threaded rotaxanes to be formed with a large macrocycle *via* successive covalent bond-forming reactions directed through the cavity. However, experiments[5] and molecular modeling both show that even small increases in macrocycle cavity size require very significant expansion of the stoppers to prevent dethreading of singly-threaded [2]rotaxanes, which in many cases are necessary intermediates *en route* to multiply threaded structures. Furthermore, once one axle has formed in the cavity the increased steric bulk around the catalytic site may hinder subsequent thread-forming reactions. To try to address both of these issues we investigated the efficacy of a slightly larger (37-membered ring) macrocycle, **1a**, than we utilized previously, with axle-forming components of different lengths (**2a-c**) in the rotaxane-forming active template nickel-catalyzed homocoupling reaction (Scheme 1, full synthetic procedures and characterization data are provided in the Supporting Information).

RESULTS AND DISCUSSION

A catalytically active macrocycle-Ni(0) complex of **1a** was generated by the *in situ* reduction of a Ni(II) salt in *N*-methyl-2-pyrrolidone (NMP), to which was added 20 equivalents of **2a** in tetrahydrofuran (THF). The reaction mixture was heated at 60 °C for 18 hours before washing with ammoniacal ethylenediaminetetraacetic acid disodium salt solution (Na$_2$EDTA-NH$_3$ (aq)) to remove the metal ions (Scheme 1). Purification of the crude organic products by size-exclusion chromatography (SEC) led to the recovery of unreacted macrocycle **1a** (44 %) and the isolation[6] of three products, identified by ^{1}H NMR (e.g. relative integration of axle-to-ring protons) and mass spectrometry (e.g. mass of molecular ion) as the non-interlocked thread **3a**, doubly-threaded [3]rotaxane **4a** (19 %) and triply-threaded [4]rotaxane **5a** (11 %).

Scheme 1. Active Template Synthesis of [3]- and [4]Rotaxanes through Nickel-Catalyzed sp³-sp³ Homocoupling Reactions.[a]
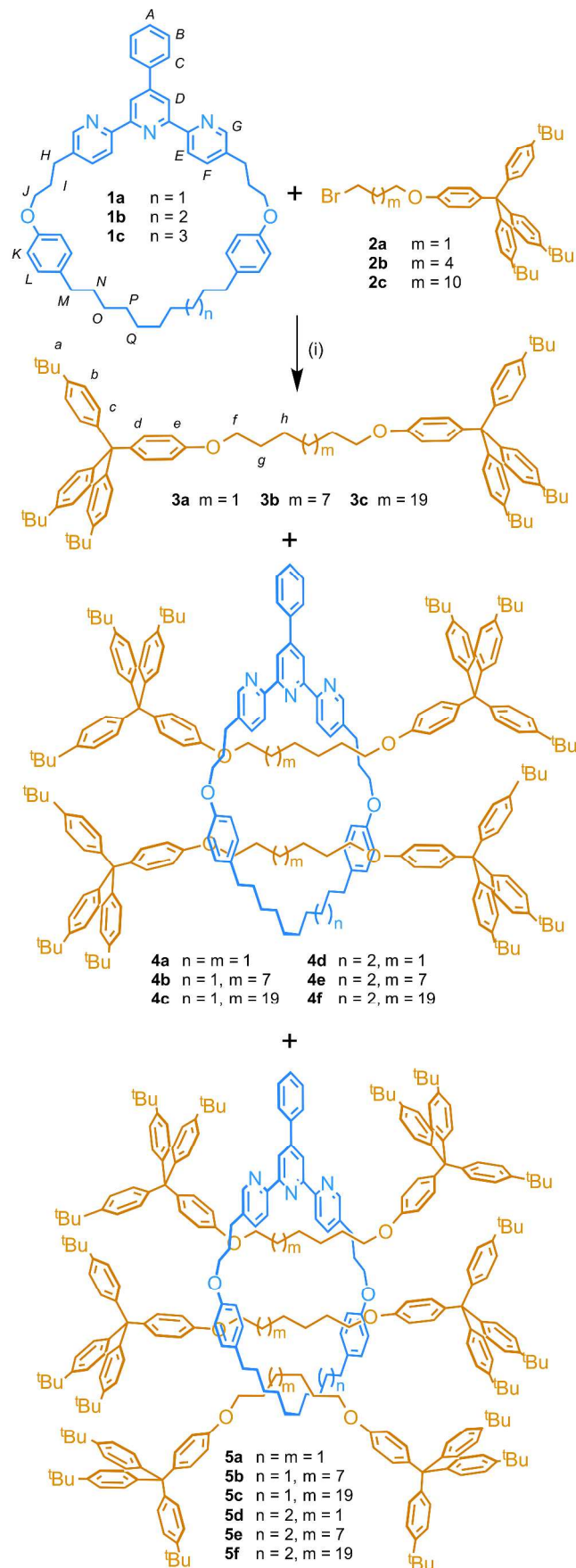
The absence of any singly-threaded [2]rotaxane among the rotaxane products isolated from the active template reaction was initially surprising, but CPK models show that tris(^{t}Bu-phenyl)methine stoppers can slip through the cavity of metal-free **1a**. However, a singly-threaded species must be an intermediate in the assembly of the more highly threaded structures, **4a** and **5a**. This is possible because the cavity of the nickel-coordinated macrocycle is considerably smaller than that of the metal-free ring. It appears that the nickel-complexed singly-threaded [2]rotaxane intermediate is sufficiently long-lived to react with two more alkyl bromide molecules and catalyze the formation of a second axle to form the doubly-threaded [3]rotaxane **4a** before dethreading, either directly or through transient loss of the metal center (Figure 1). The [3]rotaxane is kinetically stable and can, in turn, promote a third active template nickel-catalyzed homocoupling of thread-forming components **2a** to form the triply-threaded [4]rotaxane, **5a** (Table 1, entry 1). The kinetic stability of nickel-coordinated **2a** is also consistent with the recovery of significant quantities of macrocycle **1a** after the reaction is worked up, despite the use of a large excess (20 equivalents) of the thread-forming component. Much of the recovered macrocycle likely results from decomposition of the nickel-coordinated [2]rotaxane during the workup procedure, as <30% macrocycle was recovered in the previously reported active template reactions that use slightly smaller macrocycles and generate stable [2]rotaxanes.[3a]
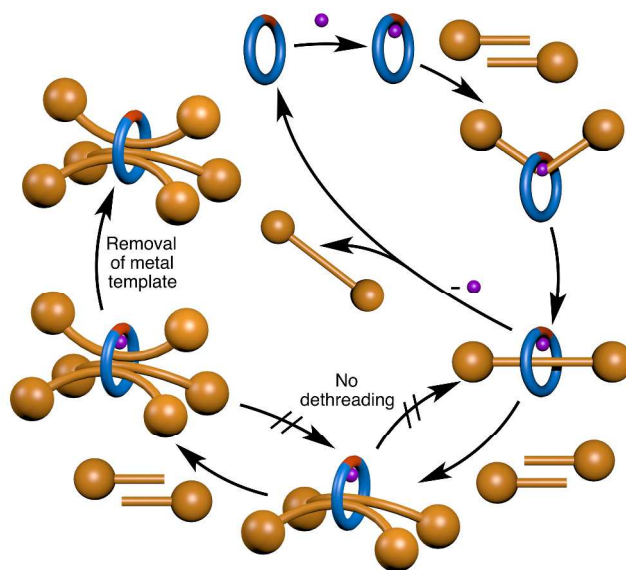
Figure 1. Proposed pathway for one-pot active template synthesis of triply-threaded [4]rotaxanes, **5a-f**. A Ni(0) center

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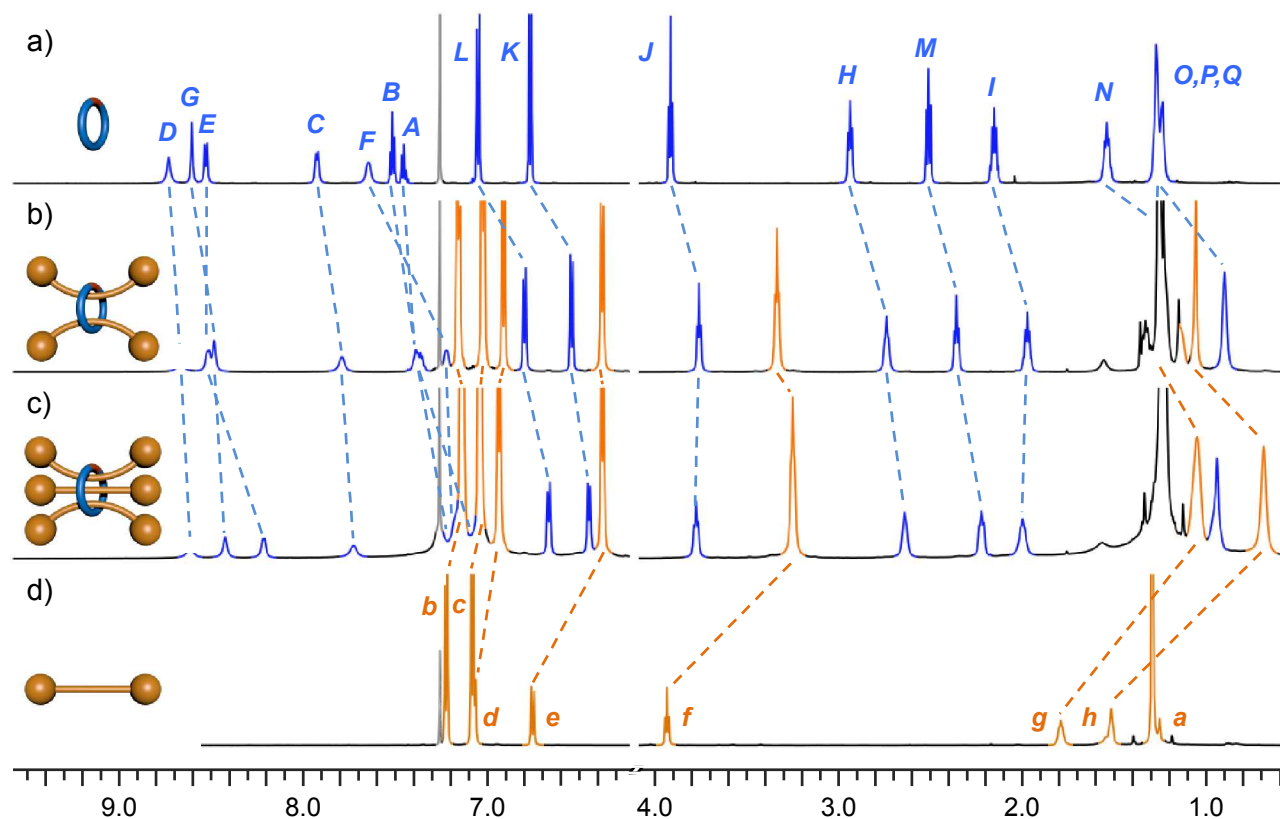
Figure 2. ^{1}H NMR spectra (600 MHz, CDCl$_3$, 298 K) of a) macrocycle **1a**, b) [3]rotaxane **4a**, c) [4]rotaxane **5a** and d) free thread **3a**. Assignments correspond to labeling in Scheme 1.

(purple) bound to the endotopic terpyridyl coordination site (red) of a macrocycle (blue) catalyzes the sp^3-sp^3 homocoupling reaction of two alkyl bromide building blocks through the cavity. The thread and macrocycle can dissociate, either by transient demetallation forming a larger cavity or through a slow dethreading process, or the coordinated Ni(0) can catalyze a second carbon-carbon bond forming reaction between two more building blocks, to give a doubly-threaded [3]rotaxane. The presence of a second thread prevents any further dethreading. A further Ni(0)-catalyzed homocoupling of thread building blocks generates the triply-threaded [4]rotaxane **5a-f**.

The ^{1}H NMR spectra of rotaxanes **4a** and **5a** (Figure 2b and c) show several upfield chemical shifts with respect to that of their non-interlocked components, **1a** and **3a** (Figure 2a and d), consistent with face-on interactions of regions of one component with the aromatic rings of another. The shifts are generally more pronounced for the [4]rotaxane (Figure 2c), a consequence of the tight packing of the axles in the cavity resulting in them spending more time close to one another and to the macrocycle aromatic rings. A further indication of the increased steric crowding in the triply-threaded [4]rotaxane is the broadening of a number of signals (e.g. H$_{H,M,I}$), likely due to restricted movement of the components relative to each other on the ^{1}H NMR timescale.

The structure of the triply-threaded [4]rotaxane **5a** was modeled with Spartan'14.[7] The semi-empirical PM6 geometry minimized structure shows the terpyridyl group tilted almost orthogonally to the plane of the macrocycle, which maximizes the size of the cavity to accommodate the three threaded chains (Figure 3). In adopting this co-conformation, the stopper groups of the three chains are brought in close proximity to each other at both ends of the rotaxane. The protruding phenyl ring of the macrocycle is directed towards the aromatic rings of one of the stoppers, consistent with the upfield shifts of protons H$_A$ and H$_B$ after the third threading event (Figures 2b and c).
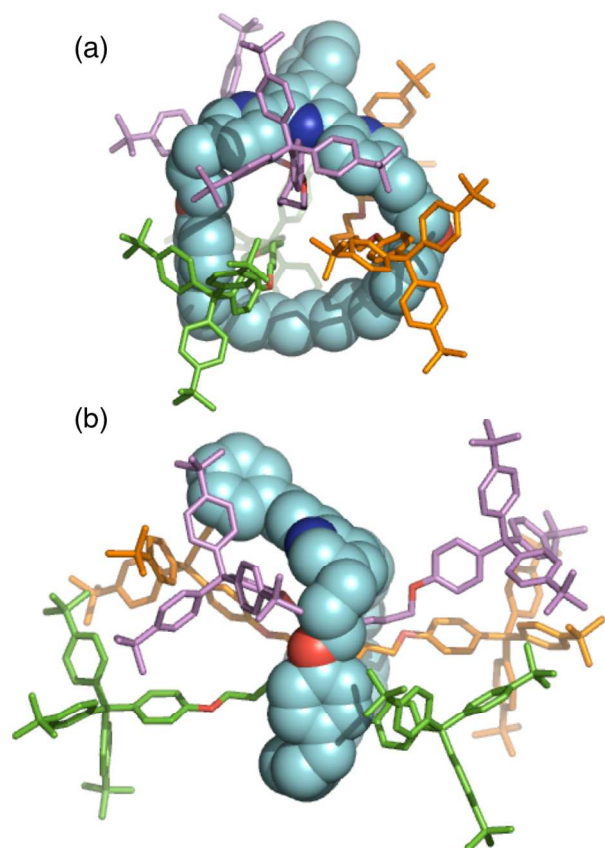
Figure 3. Spartan'14 semi-empirical PM6 geometry-minimized structure of [4]rotaxane **5a**.[7] Hydrogen atoms not shown for clarity. (a) Viewed through the macrocycle cavity and (b) side-on.

To probe the multiple threading process further, we investigated the influence of changes in both the axle length and macrocycle size on the active template rotaxane-forming reaction (Table 1). Increasing the distance between the bromine atom and the stopper of the axle-forming alkyl bromides from a three-carbon chain in **2a** to six and twelve carbons in **2b** and **2c**, respectively, had little effect on the yields of the corresponding [3]- (**4b** and **4c**) and [4]rotaxanes (**5b** and **5c**) (Table 1, entries 2 and 3). A comparison of the ^{1}H NMR spectra of [4]rotaxanes **5a-c** shows less shielding with increasing chain length (Supporting Information, Figure S2), indicating that the longer threads can position themselves to minimize unfavorable steric interactions between the bulky stoppers and the macrocycle. Nevertheless, the greater steric congestion from threaded chains close to the metal binding site in the synthesis of **5a** does not significantly affect the ability of the nickel to catalyze the active template reaction.

Macrocycles **1b** and **1c**, containing one and two extra methylene groups in the southern hemisphere, respectively, were prepared to investigate the effect of a modest increase in cavity size on the ability to trap multiply-threaded rotaxanes. Using the 38-membered ring macro-

cycle **1b**, [3]rotaxanes (**4d-f**) and [4]rotaxanes (**5d-f**) were obtained in similar yields to those obtained using macro-cycle **1a** (Table 1, entries 4-6). The ^{1}H NMR spectra of [4]rotaxanes **5a** and **5d** are very similar to each other (Supporting Information, Figure S3), although the down-field chemical shift of proton H_E ($\Delta\delta$ = +0.09 ppm with the wider cavity) provides some indication that the 38-membered ring somewhat alleviates the close packing of the threads.

When macrocycle **1c** was employed in the analogous active template reactions, however, no rotaxane products could be isolated. Apparently the cavity of the 39-membered ring is too large to be prevented from slipping over the tris(^{t}Bu-phenyl)methine stoppers of a single threaded axle, even when the macrocycle is coordinated to a Ni(0) center.

Table 1. Yields of [3]- and [4]Rotaxane Formation Reactions

Entry	Thread building block **2**[a]	[3]Rotaxane **4** (% yield)[b]	[4]Rotaxane **5** (% yield)[b]
1[c]	**2a**	**4a** (19)	**5a** (11)
2[c]	**2b**	**4b** (22)	**5b** (7)
3[c]	**2c**	**4c** (21)	**5c** (7)
4[d]	**2a**	**4d** (19)	**5d** (4)
5[d]	**2b**	**4e** (20)	**5e** (7)
6[d]	**2c**	**4f** (17)	**5f** (3)

[a] 20 equivalents. [b] Isolated yields with respect to amount of macrocycle employed.[6] [c] Performed with macrocycle **1a**. [d] Performed with macrocycle **1b**. Reactions carried out under the conditions shown in Scheme 1. >95 % conversion to homocoupled products was observed in each case.

CONCLUSIONS

Rotaxanes with multiple axles threaded through the same ring are challenging to access, requiring a delicate balance of macrocycle cavity size and conformation to stopper size, and a threading reaction that can tolerate increasing steric bulk at the site where the chains are joined through the ring. The one-pot active metal template nickel-catalyzed homocoupling of stoppered alkyl bromides of various lengths through 37 or 38-membered 2,2':6',2"-terpyridyl macrocycles affords the first examples of triply-threaded [4]rotaxanes, together with doubly-threaded [3]rotaxanes and the non-interlocked thread. Although the cavities of the macrocycles utilized are too large for [2]rotaxanes to be isolated using the stoppers employed, the nickel-coordinated macrocycles are small enough to form [2]rotaxaxane intermediates that can re-

act further to form kinetically stable, multiply threaded, [3]- and [4]rotaxanes. We anticipate that this approach will be useful for the synthesis of rotaxanes featuring even more chains threaded though a single ring, by judicious choice of template, coupling reaction, macrocycle size and conformation, and stopper size and shape.

EXPERIMENTAL SECTION

General Experimental Procedure for the Active Metal Template Synthesis of [3]- and [4]Rotaxanes

To a solution of the terpyridine macrocycle (**1a** or **1b**, 1 equiv.) and NiCl$_2$·6H$_2$O (1 eq.) in NMP (2.5 mL) under an inert atmosphere of nitrogen was added activated Zn powder (20 equiv.) and the resulting suspension stirred vigorously for 1 hour, resulting in a color change from greenish yellow to deep purple. A solution of the stoppered bromide (**2a**, **2b** or **2c**, 20 equiv.) in THF (2.5 mL) was added and the resulting mixture stirred at 60 °C for 18 h. The reaction mixture was diluted with EtOAc (200 mL) and washed with a 17.5 % aqueous solution of ammonia saturated with Na$_2$EDTA (2 × 50 mL), H$_2$O (3 × 50 mL) and brine (50 mL). The organic layer was dried over MgSO$_4$, the solvent removed under reduced pressure and the resulting residue purified by size exclusion chromatography (CH$_2$Cl$_2$ as eluent, see Supporting Information Figure S1) to yield the corresponding [3]- and [4]rotaxanes (**4a-f** and **5a-f**, respectively) as colorless powders or clear films.

ASSOCIATED CONTENT

Supporting Information.

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

AUTHOR INFORMATION

Corresponding Author

* David.Leigh@manchester.ac.uk.

Notes

The authors declare no competing financial interest.

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(6) The rotaxane yields reported are with respect to the macrocycle, the limiting reactant employed. The reactions typically proceeded with >95% conversion of the alkyl bromide building blocks, used in excess, to the combined homocoupled axle products (non-interlocked thread and [3]- and [4]-rotaxanes).

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