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# Sequence Isomerism in [3]Rotaxanes

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***Abstract:*** We describe a strategy for assembling different macrocycles onto a nonsymmetrical rotaxane thread in a precise sequence. If the macrocycles are small and rigid enough so that they cannot pass each other then the sequence is maintained mechanically, affording stereoisomerism in a manner reminiscent of atropisomerism. The method is exemplified through the synthesis of a pair of [3]rotaxane diastereomers that are constitutionally identical other than for the sequence of the different macrocycles on the thread. The synthesis features the iterative binding of different palladium(II) pyridine-2,6-dicarboxamide complexes to a pyridine ligand on the thread followed by their macrocyclization by ring-closing olefin metathesis. Removal of the palladium(II) from the first rotaxane formed frees the pyridine site to coordinate to a second, different, palladium(II) pyridine-2,6-dicarboxamide unit which, following macrocyclization, provides a multiring rotaxane of predetermined macrocycle sequence.

## Introduction

Nature famously employs polymeric sequences of only four DNA bases to encode the genetic information that contains the instructions for the workings of an entire organism.[1] Such "sequence isomerism" of covalently connected building blocks—a form of constitutional isomerism[2]—is also intrinsic to RNA,[3] proteins,[4] and many oligosaccharides[5] and is fundamental to the transfer of information in biological systems. The order of the sequence is often crucial; even slightly different building block sequences can have very different meanings[6] and potentially disastrous consequences[7] for the cell. In fact, any polymer comprised of two or more monomer units can potentially exhibit sequence isomerism, and controlling the order of different covalently linked building blocks still poses a major, largely unmet, challenge in synthetic polymer chemistry.[8]

Perhaps less well appreciated is that mechanically linked molecular level structures,[9] such as multiring catenanes and rotaxanes that contain at least two different macrocycles, can also exhibit various forms of sequence isomerism, some types of which are closely analogous to that of covalently linked systems and some that are less so. Here we report on a strategy for assembling rotaxanes with constitutionally different macrocycles on a thread in a particular sequence. A pair of [3]rotaxanes is prepared which differ only in the relative order of the macrocycles on the rotaxane thread. The rings are sufficiently small and rigid that the sequence is maintained mechanically.

**Sequence Isomerism in Catenanes and Rotaxanes.** As there are few examples in the literature of even the simplest types of catenane and rotaxane sequence isomers, it is worth noting the different kinds of mechanical isomerism that can potentially arise (Figure 1). Linear "chain" catenanes[10] composed of at least two distinguishable rings (Figure 1a) can, in principle, exhibit connectivity sequential isomerism analogous to the ordering of different building blocks in covalently linked systems.[11] Somewhat surprisingly, of the chain [3]catenanes that feature two different interlocked rings that have been prepared to date, only a single isomer appears to have been made or isolated in each case.[10] Rotaxanes with multiple rings and "molecular necklace" catenanes (molecules in which several rings are threaded onto one ring[12]) can display a unique alternative form of sequence isomerism that arises from the order of the interlocked components around the cyclic or linear "backbone" component (the central ring in a catenane or the thread in a rotaxane). In these cases, purely mechanical,[13] not topological, sequence diastereoisomers can arise[14] (see Figure 1b−e) in which the isomers

(1) For the first time that DNA was implicated as the carrier of genetic information, see: Hershey, A. D.; Chase, M. *J. Gen. Physiol.* **1952**, *36*, 36.
(2) *Stereochemistry of Organic Compounds*; Eliel, E. L., Wilen, S. H., Mander, L. N., Eds.; John Wiley & Sons: New York, 1994.
(3) For some of the first studies that showed RNA synthesis is templated by DNA, see: (a) Geiduschek, E. P.; Nakamoto, T.; Weiss, S. B. *Proc. Natl. Acad. Sci. U.S.A.* **1961**, *47*, 1405. (b) Hayashi, M.; Hayashi, M. N.; Spiegelman, S. *Proc. Natl. Acad. Sci. U.S.A.* **1963**, *50*, 664. For the first deciphering of an RNA three letter codon specifying an amino acid, see: (c) Matthaei, J. H.; Nirenberg, M. W. *Proc. Natl. Acad. Sci. U.S.A.* **1961**, *47*, 1588. For an account of the role of ribosomal RNA in protein synthesis, see: (d) Dahlberg, A. E. *Cell* **1989**, *57*, 525.
(4) For pioneering work relating protein sequence to structure, see: Anfinsen, B. C. *Science* **1970**, *181*, 223.
(5) *Oligosaccharides: Their Synthesis and Biological Roles*; Osborn, H. M. I., Kahn, T. H., Eds.; OUP: New York, 2000.
(6) For example, the sequence of RNA nucleobases AUG is a start codon, whereas its sequence isomers UAG and UGA are stop codons, see: Caskey, C. T.; Tompkins, R.; Scolnick, E.; Caryk, T.; Nirenburg, M. *Science* **1968**, *162*, 135.
(7) For example, the single change of a valine to a glutamic acid residue in the amino acid sequence of the $\beta$-chain of hemoglobin can lead to sickle-cell anemia; see: Ingram, V. M. *Nature* **1957**, *180*, 326.
(8) (a) Badi, N.; Lutz, J.-F. *Chem. Soc. Rev.* **2009**, *38*, 3383. (b) Lutz, J.-F. *Polym. Chem.* **2010**, *1*, 55. (c) Lutz, J.-F. *Nature Chem.* **2010**, *2*, 84.
(9) *Molecular Catenanes, Rotaxanes, and Knots: A Journey through the World of Molecular Topology*; Sauvage, J.-P., Dietrich Buchecker,C., Eds.; Wiley-VCH: Weinheim, 1999.


**10.1021/ja1006838** 

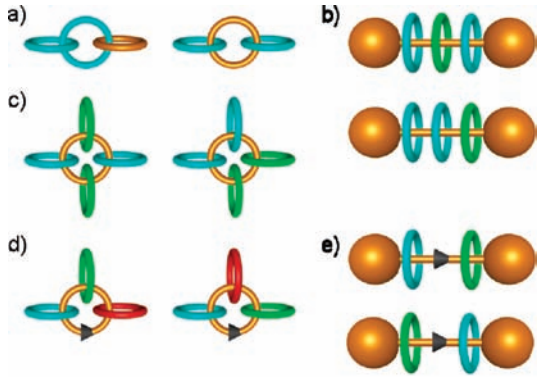



***Figure 1.*** Minimum structural requirements for catenane and rotaxane mechanical sequence diastereomers: (a) linear [3]catenanes consisting of two different ring types; (b) [4]rotaxane and (c) [5]catenane sequence isomers on a symmetrical thread/ring; (d) [4]catenane and (e) [3]rotaxane sequence isomers with an unsymmetrical central ring/thread. In b−e, a requirement for sequence diastereoisomerism is that each ring is unable to pass through the cavity of another.

differ only by the sequence of the different rings on the backbone component, provided their order is conserved (i.e., the rings are sufficiently small and/or rigid that they are prevented from slipping past each another).

If all the interlocked components of a rotaxane (Figure 1b) or molecular necklace catenane (Figure 1c) are symmetrical there need only be two distinct types of macrocycle (shown as blue and green) threaded onto the backbone component (orange) for sequence isomerism to arise. The fewest number of rings that must be linked onto the backbone is four (two of each type, blue and green) for a catenane[12] ([5]catenane, Figure 1c) and three for a rotaxane ([4]rotaxane, Figure 1b).[15] When directionality (one-dimensional asymmetry) is incorporated into the central component (Figure 1d and 1e), the number of threaded macrocycles needed to form mechanical sequence isomers decreases by one to three for a catenane and two for a rotaxane.[16] Interestingly, however, a diastereomeric pair of [4]catenane sequence isomers actually requires three constitutionally different macrocycles (green, blue and red, Figure 1d) locked onto the central ring,[17] one more than for the [5]catenane, Figure 1c, whereas a pair of [3]rotaxane sequence diastereoisomers can still be achieved with only two distinct macrocycles (green and blue, Figure 1e).[18]

Few examples of rotaxanes that contain constitutionally different macrocycles have been prepared to date.[19] A pseudo[3]rotaxane was prepared[19a] by adding differently sized macrocycles to a thread using different assembly routes, the smaller via a "threading" strategy and the larger using a

(10) (a) Hubbard, A. L.; Davidson, G. J. E.; Patel, R. H.; Wisner, J. A.; Loeb, S. J. *Chem. Commun.* **2004**, 138. (b) Leigh, D. A.; Wong, J. K. Y.; Dehez, F.; Zerbetto, F. *Nature* **2003**, *424*, 174. (c) Iwamoto, H.; Itoh, K.; Nagamiya, H.; Fukazawa, Y. *Tetrahedron Lett.* **2003**, *44*, 5773. (d) Gunter, M. J.; Farquhar, S. M.; Jeynes, T. P. *Org. Biomol. Chem.* **2003**, *1*, 4097. (e) Chiu, S. H.; Elizarov, A. M.; Glink, P. T.; Stoddart, J. F. *Org. Lett.* **2002**, *4*, 3561. (f) Hori, A.; Kumazawa, K.; Kusukawa, T.; Chand, D. K.; Fujita, M.; Sakamoto, S.; Yamaguchi, K. *Chem.—Eur. J.* **2001**, *7*, 4142. (g) Safarowsky, O.; Vogel, E.; Vögtle, F. *Eur. J. Org. Chem.* **2000**, 499. (h) Cabezon, B.; Cao, J. G.; Raymo, F. M.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Chem.—Eur. J.* **2000**, *6*, 2262. (i) Ashton, P. R.; Baldoni, V.; Balzani, V.; Claessens, C. G.; Credi, A.; Hoffmann, H. D. A.; Raymo, F. M.; Stoddart, J. F.; Venturi, M.; White, A. J. P.; Williams, D. J. *Eur. J. Org. Chem.* **2000**, 1121. (j) Amabilino, D. B.; Ashton, P. R.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Chem.—Eur. J.* **1998**, *4*, 460. (k) Amabilino, D. B.; Ashton, P. R.; Balzani, V.; Boyd, S. E.; Credi, A.; Lee, J. Y.; Menzer, S.; Stoddart, J. F.; Venturi, M.; Williams, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 4295. (l) Amabilino, D. B.; Ashton, P. R.; Boyd, S. E.; Lee, J. Y.; Menzer, S.; Stoddart, J. F.; Williams, D. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2070. (m) Kern, J. M.; Sauvage, J.-P.; Weidmann, J. L. *Tetrahedron* **1996**, *52*, 10921. (n) Amabilino, D. B.; et al. *J. Am. Chem. Soc.* **1995**, *117*, 1271. (o) Armaroli, N.; Balzani, V.; Barigelletti, F.; Decola, L.; Flamigni, L.; Sauvage, J.-P.; Hemmert, C. *J. Am. Chem. Soc.* **1994**, *116*, 5211. (p) Amabilino, D. B.; Ashton, P. R.; Reder, A. S.; Spencer, N.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1286. (q) Ashton, P. R.; Brown, C. L.; Chrystal, E. J. T.; Goodnow, T. T.; Kaifer, A. E.; Parry, K. P.; Slawin, A. M. Z.; Spencer, N.; Stoddart, J. F.; Williams, D. J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1039. (r) Dietrich-Buchecker, C. O.; Hemmert, C.; Khemiss, A. K.; Sauvage, J.-P. *J. Am. Chem. Soc.* **1990**, *112*, 8002. (s) Guilhem, J.; Pascard, C.; Sauvage, J.-P.; Weiss, J. *J. Am. Chem. Soc.* **1988**, *110*, 8711. (t) Dietrich-Buchecker, C. O.; Guilhem, J.; Khemiss, A. K.; Kintzinger, J. P.; Pascard, C.; Sauvage, J.-P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 661. (u) Sauvage, J.-P.; Weiss, J. *J. Am. Chem. Soc.* **1985**, *107*, 6108.

(11) These types of isomers are topologically nontrivial since the isomers are not interconvertible without changing the molecular graph.

(12) (a) Kim, K. *Chem. Soc. Rev* **2002**, *31*, 96. The molecular necklace [5]catenanes prepared to date all contain identical macrocycles surrounding the central component; see: (b) Park, K. M.; Kim, S. Y.; Heo, J.; Whang, D.; Sakamoto, S.; Yamaguchi, K.; Kim, K. *J. Am. Chem. Soc.* **2002**, *124*, 2140. (c) Roh, S. G.; Park, K. M.; Park, G. J.; Sakamoto, S.; Yamaguchi, K.; Kim, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 638. (d) Bitsch, F.; Dietrich-Buchecker, C. O.; Khemiss, A. K.; Sauvage, J. P.; Vandorsselaer, A. *J. Am. Chem. Soc.* **1991**, *113*, 4023.

(13) The sequence isomerism that arises through steric blocking in mechanically interlocked structures (e.g., Figure 1b−e), as opposed to sequence isomerism that arises through connectivity/topolological differences (e.g., Figure 1a), is conceptually similar to atropisomerism, which formally only refers to restricted rotation about single bonds.

(14) These types of isomers are topologically trivial since deformation of one or more of the rings would allow scrambling of the sequence without changing the molecular graph.

(15) The linear [4]rotaxanes prepared to date all incorporate only constitutionally identical rings: (a) Tuncel, D.; Steinke, J. H. G. *Chem. Commun.* **2002**, 496. (b) Parham, A. H.; Schmieder, R.; Vögtle, F. *Synlett* **1999**, 1887. (c) Asakawa, M.; Ashton, P. R.; Ballardini, R.; Balzani, V.; Bělohradský, M.; Gandolfi, M. T.; Kocian, O.; Prodi, L.; Raymo, F. M.; Stoddart, J. F.; Venturi, M. *J. Am. Chem. Soc.* **1997**, *119*, 302. (d) Ashton, P. R.; Ballardini, R.; Balzani, V.; Bělohradský, M.; Gandolfi, M. T.; Philp, D.; Prodi, L.; Raymo, F. M.; Reddington, M. V.; Spencer, N.; Stoddart, J. F.; Venturi, M.; Williams, D. J. *J. Am. Chem. Soc.* **1996**, *118*, 4931. (e) Amabilino, D. B.; Ashton, P. R.; Balzani, V.; Brown, C. L.; Credi, A.; Frechet, J. M. J.; Leon, J. W.; Raymo, F. M.; Spencer, N.; Stoddart, J. F.; Venturi, M. *J. Am. Chem. Soc.* **1996**, *118*, 12012.

(16) Interlocked structures that incorporate symmetrical central components and macrocycles that are constitutionally identical but have prochiral faces can also exhibit diastereoisomerism: (a) Chang, S. Y.; Jeong, K. S. *J. Org. Chem.* **2003**, *68*, 4014. (b) Schmieder, R.; Hubner, G.; Seel, C.; Vögtle, F. *Angew. Chem. Int. Ed.* **1999**, *38*, 3528. (c) Kishan, M. R.; Parham, A.; Schelhase, F.; Yoneva, A.; Silva, G.; Chen, X.; Okamoto, Y.; Vögtle, F. *Angew. Chem., Int. Ed.* **2006**, *45*, 7296. For a polyrotaxane incorporating two different types of macrocycles, see: (d) Ooya, T.; Inoue, D.; Choi, H. S.; Kobayashi, Y.; Loethen, S.; Thompson, D. H.; Ko, Y. H.; Kim, K.; Yui, N. *Org. Lett.* **2006**, *8*, 3159.

(17) There does not appear to be any examples of this type of structure in the literature.

(18) Since the two faces of a cyclodextrin molecule are different, rotaxanes and catenanes featuring two or more cyclodextrins threaded onto an axle or ring can exhibit diastereoisomerism, not as a consequence of the different sequence of the rings but rather through their differing relative orientations. (a) Cheetham, A. G.; Claridge, T. D. W.; Anderson, H. L. *Org. Biomol. Chem.* **2007**, *5*, 457. (b) Saudan, C.; Dunand, F. A.; Abou-Hamdan, A.; Bugnon, P.; Lye, P. G.; Lincoln, S. F.; Merbach, A. E. *J. Am. Chem. Soc.* **2001**, *123*, 10290. (c) Eliadou, K.; Yannakopoulou, K.; Rontoyianni, A.; Mavridis, I. M. *J. Org. Chem.* **1999**, *64*, 6217. (d) Qu, D. H.; Wang, Q. C.; Ma, X.; Tian, H. *Chem.—Eur. J.* **2005**, *11*, 5929. (e) Craig, M. R.; Claridge, T. D. W.; Hutchings, M. G.; Anderson, H. L. *Chem. Commun.* **1999**, 1537.

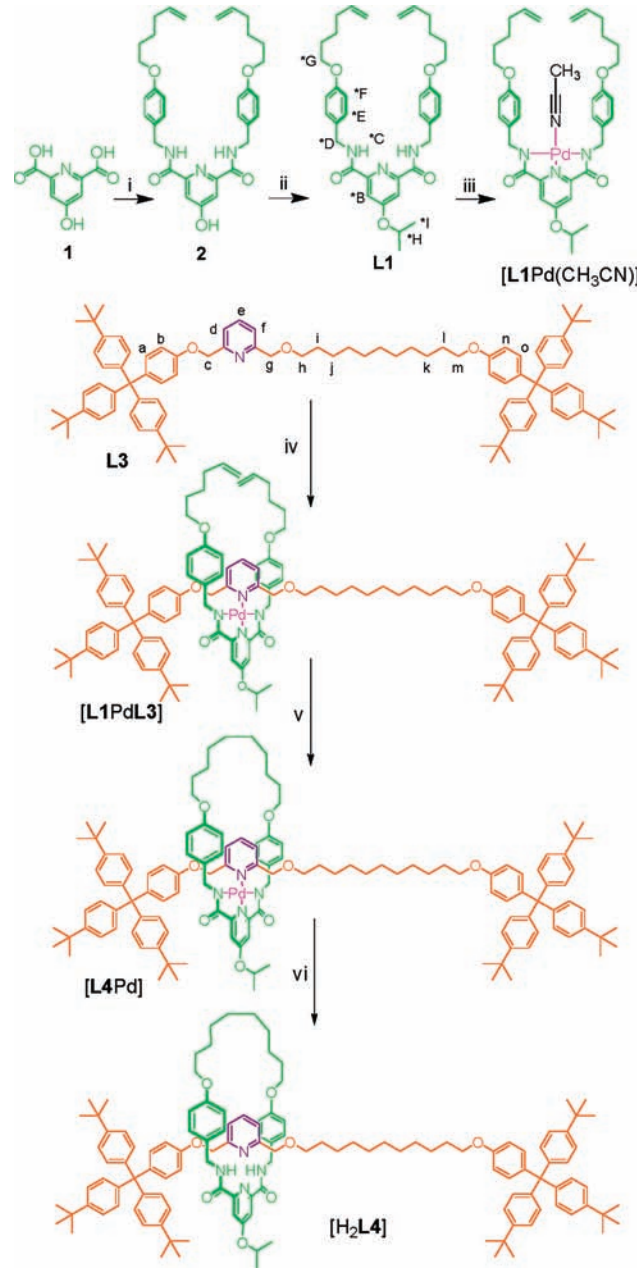
(19) (a) Amabilino, D. B.; Ashton, P. R.; Bělohradský, M.; Raymo, F. M.; Stoddart, J. F. *J. Chem. Soc., Chem. Commun.* **1995**, 747. (b) Jiang, W.; Winkler, H. D. F.; Schalley, C. A. *J. Am. Chem. Soc.* **2008**, *130*, 13852. (c) Chen, L.; Zhao, X.; Chen, Y.; Zhao, C. X.; Jiang, X. K.; Li, Z. T. *J. Org. Chem.* **2003**, *68*, 2704.

"slippage" strategy.[20] However, a symmetrical thread was employed, and consequently, the structure displays no isomerism. A pseudo[3]rotaxane with an unsymmetrical thread has been synthesized from two different crown ethers and a thread with ammonium groups of differing hydrogen-bond-donating ability.[19b] Two different template interactions have been used to assemble a [3]rotaxane with two constitutionally different rings.[19c] The thread incorporated a $\pi$-acceptor$-\pi$-donor site as well as a hydrogen-bonding template site, and as a result, two macrocycles, one specific for each site, were interlocked around the unsymmetrical thread in a spatial arrangement determined by the positions of the template sites. In general, however, having the order of macrocycles on a thread dependent on the template sequence on the thread is not conducive to the preparation of different mechanical sequence isomers since aligning the macrocycles in different orders would imply constitutionally different threads.

**[3]Rotaxane Sequence Isomers: Synthesis.** We were intrigued by the possibility of preparing sequence isomers by the iterative addition[21] of different macrocycles onto a single template site of a rotaxane thread. Our approach was to utilize a square-planar geometry Pd(II)-based "clipping" methodology that has been successfully used to make [2]catenanes and [2]-, [3]-, and [4]rotaxanes.[21–23] The metal ion is bound to a tridentate 2,6-pyridinedicarboxamide ligand (e.g., **L1** or **L2** in Schemes 1 and 2). Significantly, this involves deprotonation of the ligand amide groups. The resulting complex [**L1**/**L2**Pd($CH_3CN$)] is coordinated to a monodentate pyridine unit on a thread such that subsequent macrocyclization by ring-closing metathesis (RCM) occurs around the thread to generate an interlocked architecture. The key to extending this protocol so that further, different, ligands can be cyclized around the template after the first is decomplexed is that while complexes of the type [**L1**/**L2**Pd($CH_3CN$)] will readily exchange the labile coordinated acetonitrile molecule for a pyridine unit, they do not undergo tridentate ligand exchange with protonated (that is, metal-free) versions of the 2,6-pyridinedicarboxamide system. Thus, a pyridine group on a thread can repetitively be used to replace acetonitrile ligands of complexes of the type [**L1**/**L2**Pd($CH_3CN$)], with the resulting coordinated ligands being macrocyclized, providing the rings in a defined order on the thread.

In order to access a pair of [3]rotaxane sequence isomers, two constitutionally different macrocycles need to be used interchangeably in the synthesis. Building block [**L2**Pd($CH_3CN$)] has previously been used[21] to construct [2]rotaxane $H_2$**L5** (Scheme 2). Building block [**L1**Pd($CH_3CN$)], identical to [**L2**Pd($CH_3CN$)] other than having an isopropyl ether attached to the 4-position of the pyridine group, was chosen as a precursor to the other macrocycle. Complex [**L2**Pd($CH_3CN$)] was

***Scheme 1.*** Synthesis of Building Block [**L1**Pd($CH_3CN$)] and [2]Rotaxane $H_2$**L4**[a]




[a] Reagents and conditions: (i) (1) pentafluorophenol, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), $CH_2Cl_2$, 0 °C, (2) (4-(hex-5-enyloxy)phenyl)methamine, $CHCl_3$, 0 °C, 89% over two steps; (ii) $^i$PrI, $K_2CO_3$, butan-2-one, $\Delta$, 95%; (iii) $Pd(OAc)_2$, $CH_3CN$, 70%; (iv) [**L1**Pd($CH_3CN$)], $CH_2Cl_2$, 97%; (v) (1) PhCH═Ru($PCy_3$)$_2Cl_2$ (0.12 equiv), $CH_2Cl_2$, (2) 2-nitrobenzenesulfonyl hydrazide (NBSH),[24] $NEt_3$, $CH_2Cl_2$, 70% (over two steps); (vi) KCN, $CH_2Cl_2$/MeOH, 98%.

prepared in three steps from chelidamic acid **1** and elaborated into [2]rotaxane $H_2$**L4** as shown in Scheme 1. Amide bond formation via the pentafluorophenol ester of chelidamic acid afforded **2** which was *O*-alkylated (with no competing *N*-alkylation at the pyridine or amide nitrogen atoms) to give **L1** in 85% overall yield. Treatment of **L1** with $Pd(OAc)_2$ in acetonitrile gave the key building block [**L1**Pd($CH_3CN$)], which was combined with thread **L3** in dichloromethane to generate complex [**L1**Pd**L3**] as the only product formed (Scheme 1, iv). Subjecting [**L1**Pd**L3**] to ring closing metathesis with Grubbs' first generation olefin metathesis catalyst, followed by hydro-

(20) Structures formed by "slippage" are not formally rotaxanes; rather, they are pseudorotaxanes that are kinetically stable under some conditions. Rotaxanes are "molecules in which a ring encloses another, rod-like molecule having end groups too large to pass through the ring opening, and thus holds the rod-like molecule in position without covalent bonding": McNaught, A. D.; Wilkinson, A. *The IUPAC Compendium of Chemical Terminology*, 2nd ed.; Blackwell Science: London, 1997.

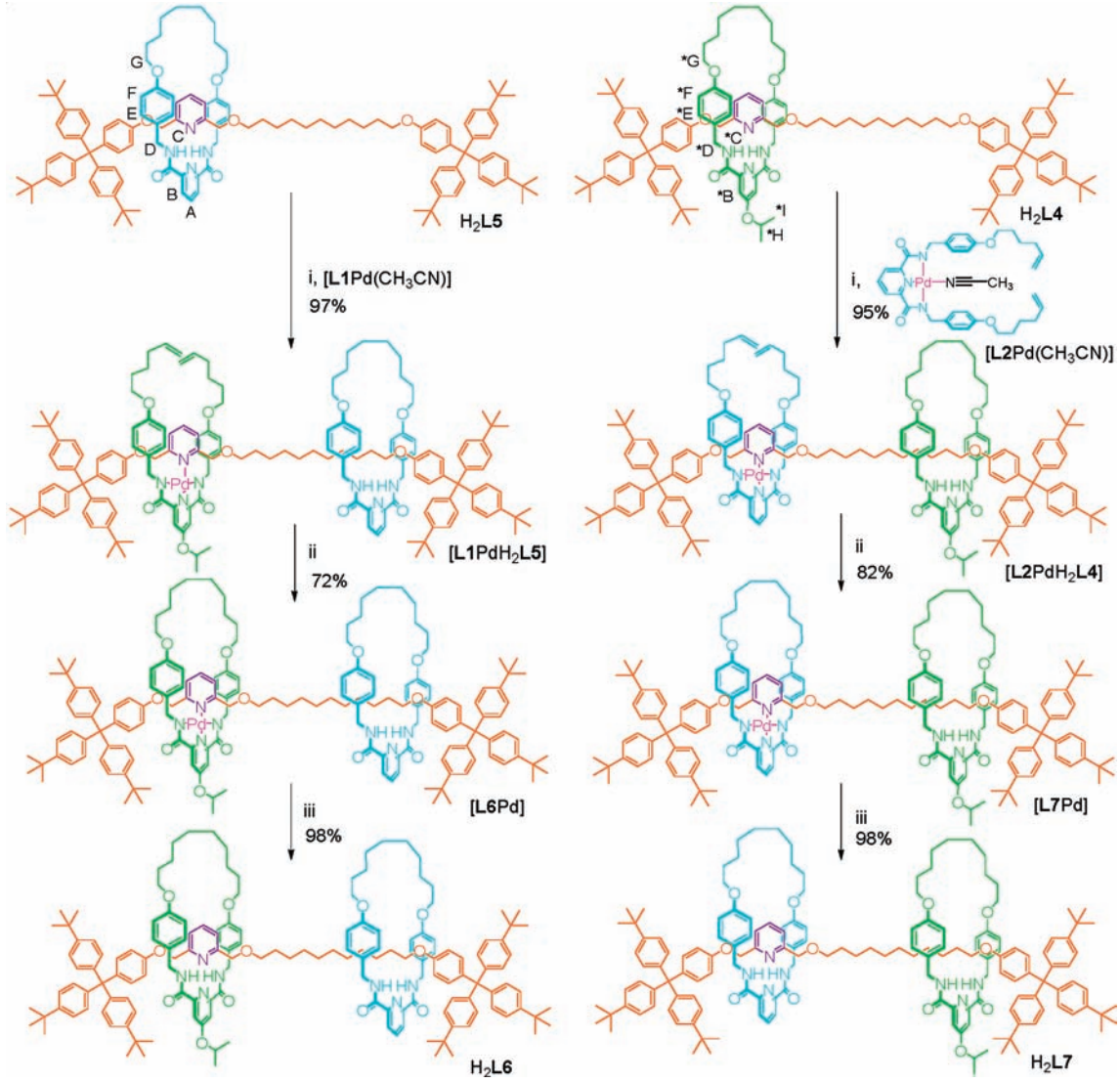
(21) Fuller, A. M. L.; Leigh, D. A.; Lusby, P. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 5015.

(22) Fuller, A. M.; Leigh, D. A.; Lusby, P. J.; Oswald, I. D. H.; Parsons, S.; Walker, D. B. *Angew. Chem., Int. Ed.* **2004**, *43*, 3914.

(23) Fuller, A. M. L.; Leigh, D. A.; Lusby, P. J.; Slawin, A. M. Z.; Walker, D. B. *J. Am. Chem. Soc.* **2005**, *127*, 12612.

(24) Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, *62*, 7507.

***Scheme 2.*** Parallel Syntheses of [3]Rotaxane Sequence Isomers $H_2$**L6** and $H_2$**L7**[a]




[a] Reagents and conditions (i) $CH_2Cl_2$; (ii) (a) $PhCH{=}Ru(PCy_3)_2Cl_2$ (0.12 equiv), $CH_2Cl_2$, (b) NBSH, $NEt_3$, $CH_2Cl_2$; (iii) KCN, $CH_2Cl_2$/MeOH.

genation[24] of the resulting internal double bond, afforded the palladium-complexed [2]rotaxane [**L4**Pd] in 70% yield over two steps.

The structures of [**L4**Pd] and the metal-free rotaxane, $H_2$**L4**, were confirmed by mass spectrometry and $^1$H NMR spectroscopy. Protons $H_c$ and $H_g$ protons of the thread (Figure 2a) exhibit characteristic changes in chemical shift in the rotaxanes (Figures 2b and 2c) caused by the ring currents of the aromatic rings of the macrocycle. The appearance of the benzylic protons ($H_{*D}$ and $H_{*D}'$) of the macrocycle in [**L4**Pd] as an AB system (Figure 2b), and the corresponding ABX system in $H_2$**L4** (Figure 2c), are a consequence of the two faces of the macrocycle experiencing different magnetic environments as a result of the threading with an unsymmetrical axle. The large downfield shift amide protons ($H_{*C}$) at 9.3 ppm in $H_2$**L4** are indicative of intercomponent hydrogen bonding between the macrocycle and the pyridine group of the thread.[25]

The two [2]rotaxanes $H_2$**L4** and $H_2$**L5** were elaborated into [3]rotaxanes possessing the same macrocycles in a different sequence by coordinating each [2]rotaxane with the complementary building block for the other macrocycle followed by the macrocyclization procedure (Scheme 2). Thus, $H_2$**L5** was treated with [**L1**Pd($CH_3CN$)] (Scheme 2, i), generating a single positional isomer [**L1**Pd$H_2$**L5**] with the macrocycle located on the alkyl chain of the thread since it is sterically unfavorable[17] for it to reside between the coordinated building block and the closest stopper. Ring-closing metathesis and hydrogenation (Scheme 2, ii) afforded the palladium-complexed [3]rotaxane [**L6**Pd] in 72% yield, which was demetalated with KCN to give the metal-free [3]rotaxane $H_2$**L6**. Following a complementary procedure, [2]rotaxane $H_2$**L4** was elaborated into [3]rotaxane $H_2$**L7** by coordination with building block [**L2**Pd($CH_3CN$)] (Scheme 2, i), macrocyclization, hydrogenation, and demetalation (Scheme 2, ii and iii).

**[3]Rotaxane Sequence Isomers: Characterization.** [3]Rotaxanes $H_2$**L6** and $H_2$**L7** gave very similar molecular ions of $m/z$ = 2372.49202 ($H_2$**L6**) and $m/z$ = 2372.49443 ($H_2$**L7**) by high-resolution mass spectrometry consistent with the anticipated molecular formulas (calculated $[MH]^+$ for $^{12}C_{156}{}^{13}CH_{196}N_7O_{12}$

(25) Bifurcated hydrogen bonding between the amides and the pyridine groups of interlocked molecules has previously been observed: (a) Leigh, D. A.; Lusby, P. J.; Slawin, A. M. Z.; Walker, D. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 4557. (b) Leigh, D. A.; Lusby, P. J.; Slawin, A. M. Z.; Walker, D. B. *Chem. Commun.* **2005**, 4919.

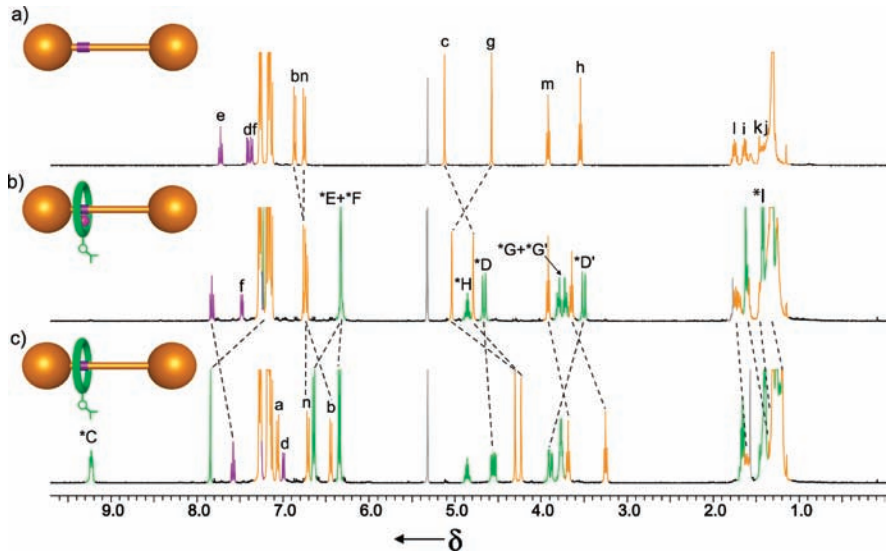



***Figure 2.*** $^1$H NMR spectra (400 MHz, $CD_2Cl_2$, 298 K) of (a) thread **L3**; (b) palladium-complexed [2]rotaxane [**L4**Pd]; and (c) metal-free [2]rotaxane $H_2$**L4**. The lettering refers to the assignments in Scheme 1.

= 2372.49756). Intriguingly, the sequence isomers $H_2$**L6** and $H_2$**L7** exhibit slightly different fast atom bombardment (FAB) mass spectrometry fragmentation patterns. Both sets of spectra show the daughter ion peaks ($m/z$ = 1800 and 1858) corresponding to the [2]rotaxanes $H_2$**L4** and $H_2$**L5**, respectively. However, for $H_2$**L7** the 1858 signal intensity is 40% greater than that of the 1800 peak, while the relative peak intensities are reversed for $H_2$**L6**: the signal intensity of the $m/z$ = 1800 ion is 73% greater than that of the $m/z$ = 1858 ion. This suggests that the macrocycle nearest to the stopper that bears the pyridine group is more likely to fragment and be lost under the FAB conditions. This "sequence fingerprint" by mass spectrometry is reminiscent of different amino acid arrangements showing different fragmentation patterns that can be diagnostic of a particular polypeptide sequence. The Pd(II) complexes of the two [3]rotaxane isomers, [**L6**Pd] and [**L7**Pd], have distinctive differences in their $^1$H NMR spectra above 7.5 ppm (i.e., protons $H_A$, $H_{*A}$, $H_B$ and $H_{*B}$) as a result of constitutionally different macrocycles being coordinated to the thread in each rotaxane (Figure 3a,d). For example, in [**L7**Pd] the (blue) macrocycle lacking the isopropyl ether is coordinated to palladium and its $H_B$ pyridine protons appear at 7.8 ppm, whereas in [**L6**Pd] (in

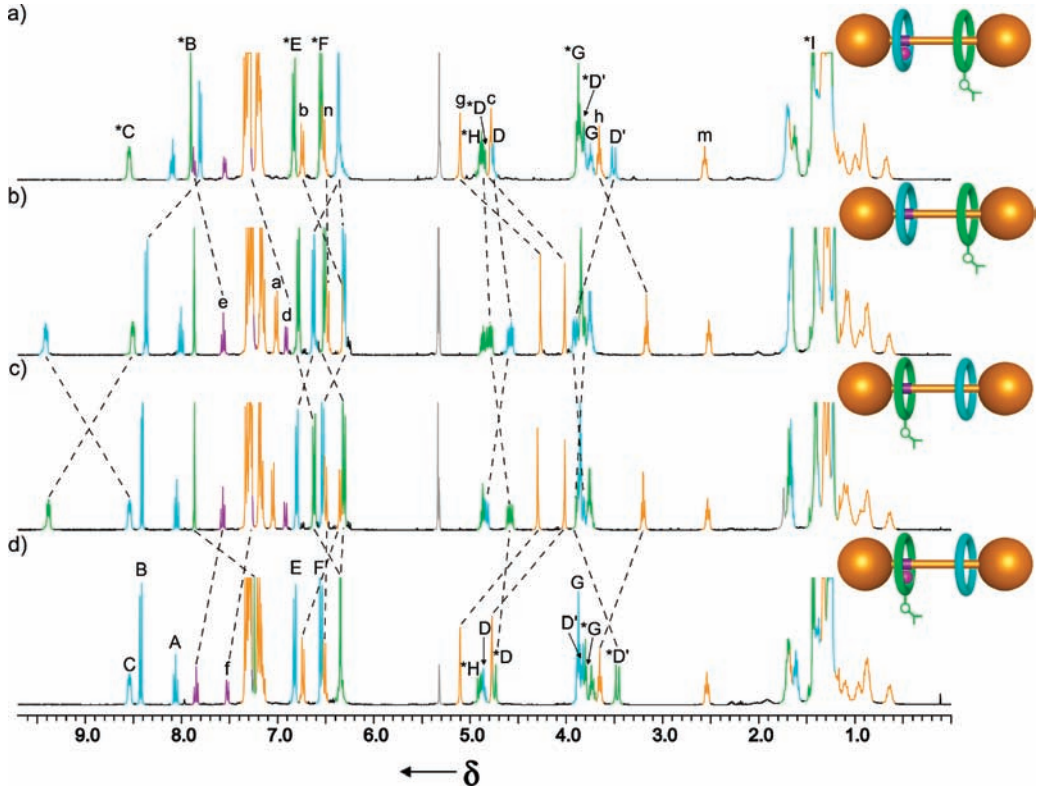



***Figure 3.*** $^1$H NMR Spectra (400 MHz, $CD_2Cl_2$, 298 K) of (a) palladium-complexed [3]rotaxane [**L7**Pd]; (b) metal-free [3]rotaxane $H_2$**L7**; (c) metal-free [3]rotaxane $H_2$**L6**; (d) palladium-complexed [3]rotaxane [**L6**Pd]. The lettering refers to the assignments in Schemes 1 and 2.

which the other macrocycle is the one coordinated to the metal) the equivalent protons resonate at 8.4 ppm. Conversely, the $H_{*B}$ protons of the noncomplexed isopropyl ether macrocycle (green) appear at 7.9 ppm in [**L7**Pd] but in [**L6**Pd] the protons are shifted upfield to 7.2 ppm as a result of the coordinated palladium. As expected, the resonances of the alkyl region of the thread in [**L6**Pd] and [**L7**Pd] show increased shielding due to the presence of metal-free macrocycle, and in particular, the aliphatic protons are significantly shifted nearly a whole ppm upfield compared to the analogous [2]rotaxanes (see Figure 2). Although the two metal-free rotaxane isomers have very similar $^1$H NMR spectra (Figure 3b,c), close inspection reveals very subtle differences in the shifts of certain protons. For example, the aromatic stopper protons ($H_b$) are shifted slightly downfield in $H_2$**L7** compared to $H_2$**L6**, and the benzylic resonances of both macrocycles appear at slightly different shifts in each isomer. After several months on the bench, there was no sign of any interconversion from one [3]rotaxane isomer to the other as evidenced by $^1$H NMR (no doubling of signals) and mass spectrometry (no change in the fragmentation pattern ratios).

## Conclusions

The challenge of precisely controlling the order and number of constitutionally different macrocycles in rotaxane syntheses has been addressed through the synthesis of a pair of [3]rotaxane sequence isomers. Successive ligand complexation, macrocyclization, and demetalation reactions were used to assemble different macrocycles onto an asymmetric thread in different orders. As far as we are aware, the resulting [3]rotaxane sequence isomers are the first pair of diastereoisomers to be prepared in which the distereomerism arises from mechanical sequence isomerism, a counterpart of atropisomerism in covalently bonded systems. The physical and spectroscopic characteristics of the [3]rotaxanes are very similar, although the palladium-complexed [3]rotaxanes show differences in the $^1$H NMR spectra characteristic of the order of the macrocycles on the thread. The synthetic strategy could potentially be extended to add multiple different rings to a rotaxane thread, in any desired order, thus enabling the synthesis of single isomer higher order rotaxanes with a defined macrocycle sequence.

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**Supporting Information Available:** Experimental procedures and spectral data for all compounds. Complete ref 10n. This material is available free of charge via the Internet at http://pubs.acs.org

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