ORGANIC LETTERS

2003
Vol. 5, No. 11
1907−1910

"Magic Rod" Rotaxanes: The Hydrogen Bond-Directed Synthesis of Molecular Shuttles under Thermodynamic Control

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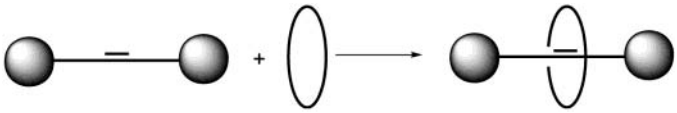
Received March 21, 2003

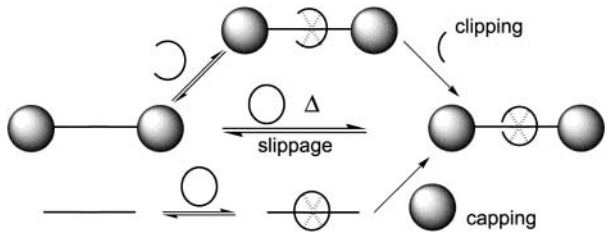
ABSTRACT



Peptide [2]- and [3]rotaxanes are assembled in high yields under thermodynamic control using hydrogen bonding interactions and reversible cross olefin metathesis.

While the use of noncovalent interactions to direct the synthesis of rotaxanes[1] often leads to greatly improved yields over statistical methods, the final step in the rotaxane-forming reaction ("clipping" or "capping", Scheme 1) is generally under kinetic control. Consequently, noninterlocked byproducts formed during the reaction cannot be recycled even if the rotaxane is the most energetically favored structure because of the built in favorable noncovalent interactions between the components. So-called "slippage" strategies[2] *are* under thermodynamic control,[3] but the necessary elevated temperatures reduce the strength of noncovalent interactions and therefore also the efficiency of rotaxane formation. Accordingly, novel approaches to the efficient synthesis of rotaxanes are still desirable.

Scheme 1. Common Noncovalent Bond-Directed Strategies for Rotaxane Synthesis[a]



[a] Clipping and capping steps are usually irreversible, so "errors" in the synthesis (i.e., noninterlocked byproducts) cannot be corrected.

Thermodynamic control over mechanical bond formation is particularly amenable to the principles of dynamic combinatorial chemistry (DCC).[4] The kinetic lability of metal−ligand coordination bonds and disulfide exchange reactions have both been employed to shift equilibria between interlocked and non-interlocked products.[5−7] Imine exchange, together with post-assembly covalent modification,[3] allows the high-yielding synthesis of rotaxanes by both clipping and

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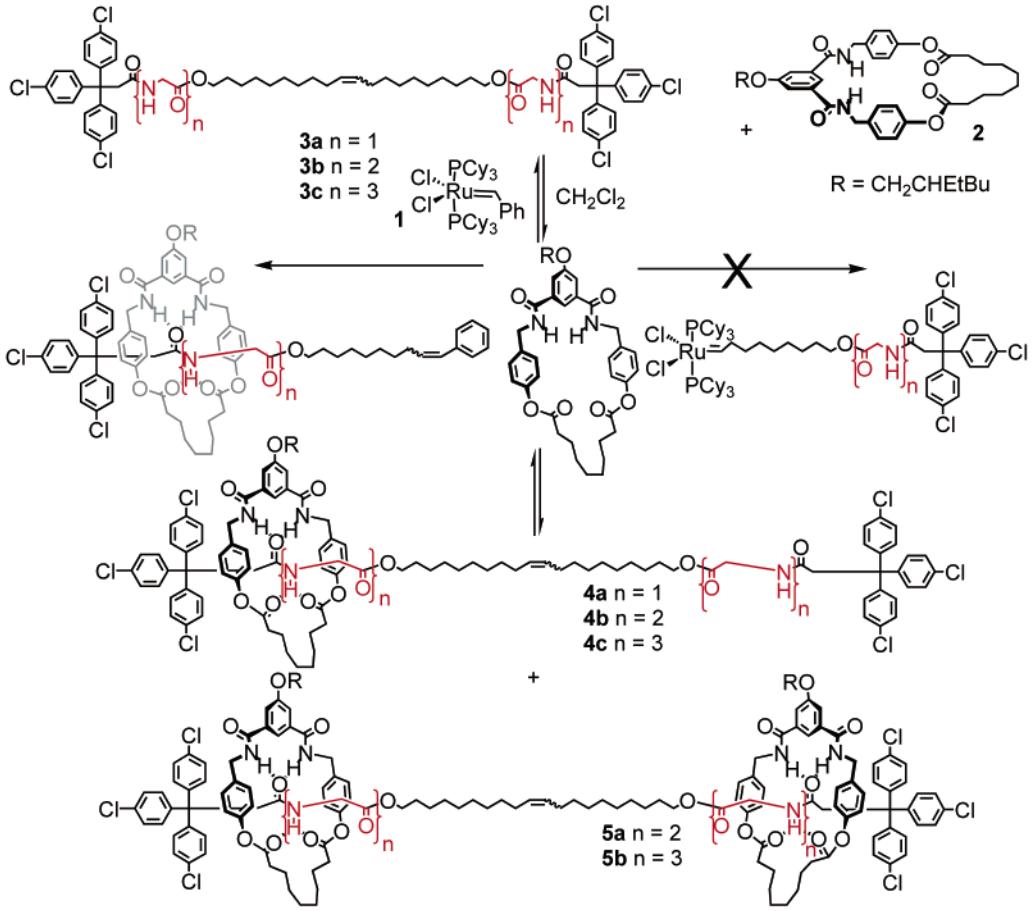
10.1021/ol0344927 CCC: $25.00
Published on Web 04/30/2003

Scheme 2. Synthesis of [2]- and [3]Rotaxanes **4a**−**c** and **5a**−**b** under Thermodynamic Control Using a Reversible Threading Strategy Facilitated by Olefin Metathesis



capping[8] and has also been used to achieve catenane synthesis under thermodynamic control.[9] Of the remaining synthetic transformations previously used in DCC, olefin metathesis is advantageous because removal of a reaction-specific catalyst (e.g., **1**) is all that is required to "lock" the product distribution. Indeed, olefin metathesis has been used to synthesize catenanes,[9,10] rotaxanes[11] and knots[12] under kinetic control and cantenanes and catenates under thermodynamic[9,13] control. In our own laboratories, reversible ring-opening metathesis combined with the hydrogen bond-directed assembly of self-complementary macrocycles allowed the synthesis of kinetically robust catenanes in near quantitative yields.[14] Here we report the extension of this concept to the synthesis of hydrogen bond-assembled rotaxanes under thermodynamic control.

Schematically, when benzylic amide macrocycle **2** and a rod **3a**−**c** containing two bulky stoppers, peptide-based template sites, and a "magic"[14] olefin are exposed to Grubbs first-generation metathesis catalyst **1**, the rod is opened and the macrocycle binds to the template through four-point hydrogen bonding. Upon reformation of the carbon−carbon double bond, the macrocycle is trapped on the thread producing a [2]rotaxane (**4a**−**c**, Scheme 2). The [2]rotaxane

(6) For capping, see: (a) Chichak, K.; Walsh, M. C.; Branda, N. R. *Chem. Commun.* **2000**, 847−848. (b) Baer, A. J.; Macartney, D. H. *Inorg. Chem.* **2000**, *39*, 1410−1417. (c) Gunter, M. J.; Bampos, N.; Johnstone, K. D.; Sanders, J. K. M. *New J. Chem.* **2001**, *25*, 166−173. For clipping, see: (d) Hunter, C. A.; Low, C. M. R.; Packer, M. J.; Spey, S. E.; Vinter, J. G.; Vysotsky, M. O.; Zonta, C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2678−2682. (e) Chang, S.-Y.; Choi, J. S.; Jeong, K.-S. *Chem. Eur. J.* **2001**, *7*, 2687−2697.

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(13) Hamilton, D. G.; Feeder, N.; Teat, S. J.; Sanders, J. K. M. *New J. Chem.* **1998**, 1019−1021.

(14) For organic "magic" rings−macrocycles that interlock without any final net change to their covalent structure, see: Kidd, T. J.; Leigh, D. A.; Wilson, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 1599−1600. For the original magic rings based on coordination chemistry, see ref 5a.

Table 1. Yields of Magic Rod Rotaxanes **4a**−**c** and **5a**−**b** from Olefin Metathesis of Magic Rods **3a**−**c**

reactants	concn	[2]rotaxane **4a**−**c**	[3]rotaxane **5a**−**b**	interlocked products
1 equiv of **2** and **3a**	0.2 M	15%	0%	15%
1 equiv of **2** and **3b**	0.2 M	36%	20%	56%
1 equiv of **2** and **3c**	0.2 M	34%	24%	58%
5 equiv of **2** and **3b**	0.2 M	52%	43%	95%
1 equiv of **2** and **3b**	0.05 M	29%	11%	40%
5a	0.05 M	29%	11%	40%
1 equiv of **2** and **3b**	0.0002 M	1%	0%	1%

can subsequently become a [3]rotaxane (**5a**, **5b**) through another round of metathesis (models show that the ruthenium carbene acts as a stopper in the first round preventing direct assembly of the [3]rotaxane).

The synthesis of macrocycle **2** has previously been reported,[14] while the syntheses of threads **3a**−**c** were carried out in four steps using simple amide and ester bond-forming reactions and cross olefin metathesis in the final step. The long C_{20} threads were used because we found shorter chains (C_{10}) to react poorly, either because of steric hindrance or the formation of metal chelates with the Grubbs catalyst as proposed in the literature[15]. A triphenylmethine stopper was used as smaller groups allowed the macrocycle to dethread.[16,17] Metathesis experiments were carried out in CH_2Cl_2 (the noncompeting solvent maximizes the strength of the intercomponent hydrogen bonding) using Grubbs catalyst **1**.[18] As the metathesis reaction is reversible (although care needs to be taken to ensure this[14]), the product distribution is determined only by the relative stabilities of the products; at high concentrations, predominantly threaded species are obtained that can, if desired, be converted back to the uninterlocked components by simply diluting the reaction mixture (but *only* in the presence of active catalyst). The rather spectacular results (overall yields of interlocked products ranging from 1 to 95% merely by changing the concentration) of the metathesis reactions of "magic rods" **3a**−**c** at different concentrations are shown in Table 1. Decomposition of the catalyst (for example, by adding *n*-propylamine) or simply sequestering it from the reaction mixture with poly(divinylbenzene) fixes the product distribution unless, and until, additional catalyst is added. Trifluoroacetylation ($(CF_3CO)_2O$) of the amide groups of the rotaxane removes the intramolecular hydrogen bonding interactions and allows disassembly of the rotaxane into its components at any concentration (but *only* in the presence of **1**).[14]

The yields imply that at least two amides are necessary in each template for rotaxane assembly to be effective. However, this is probably because the N-terminal amide is sterically hindered by the stopper and therefore cannot bind efficiently to the macrocycle. The reactions were shown to be under true thermodynamic control by the identical product distributions obtained from the metathesis of different starting materials containing the same overall proportions of thread and macrocycle (for example [3]rotaxane **4b** and a 1:2 mixture of thread **3b** and macrocycle **2**).

Representative ^{1}H NMR spectra of the glycylglycine magic rod rotaxanes **4b**, **5a**, and thread **3b** in $CDCl_3$ at 50 °C are shown in Figure 1. The resonances of the thread H_e and H_g protons appear at the normal chemical shifts for glycine residues (Figure 1a). The same signals in the [2]rotaxane **4b** (Figure 1b), however, display the characteristic upfield shifts[19] of a threaded species as a result of shielding by the aromatic rings of the macrocycle (note, each peptide station is only occupied at most 50% of the time in the [2]rotaxane). The amide protons, H_D, of the macrocycle appear downfield due to hydrogen bonding. Only one thread amide (H_f) undergoes an appreciable change in chemical shift and is shifted upfield, suggesting that the effects of hydrogen bonding are mostly offset by the shielding effect of the macrocycle and/or the thread amide groups intramolecularly hydrogen bonding in **3b**. Only one set of signals is seen for each glycylglycine station, indicating that shuttling of the macrocycle along the axis of the thread is fast on the NMR time scale. The [3]rotaxane (Figure 1c) experiences changes in chemical shift similar to the [2]rotaxane, although these are somewhat more pronounced (because each peptide station is occupied nearly 100% of the time in the [3]rotaxane). Finally, in the case of the [3]rotaxane, an ABX system is observed for the H_E protons of macrocycle **2**. This arises because the faces of the macrocycle experience different environments in the [3]rotaxane (one points toward the other macrocycle, the other toward the nearest stopper), while in the analogous [2]rotaxane, the two faces of the fast-shuttling macrocycle effectively experience identical environments.

In a manner similar to previously described peptide-based molecular shuttles,[19] this class of rotaxanes exhibit solvent-dependent translational isomerism; that is, in d_6-DMSO, the hydrogen bonding between the thread and the macrocycle is disrupted and the macrocycle(s) sit(s) predominantly on the alkyl chain of the thread shielding it from the polar solvent.

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(16) Experiments (Supporting Information) reveal that macrocycle **2** and glycylglycine threads bearing diphenyl stoppers form complexes (pseudorotaxanes, $K_a = 300\ M^{-1}$) only slowly at room temperature. This could be considered "slow slippage" rotaxane formation.

(17) The trischlorophenyl derivative was readily available in larger and cheaper quantities than other alternatives.

(18) For a detailed description of the experimental procedure, see Supporting Information.

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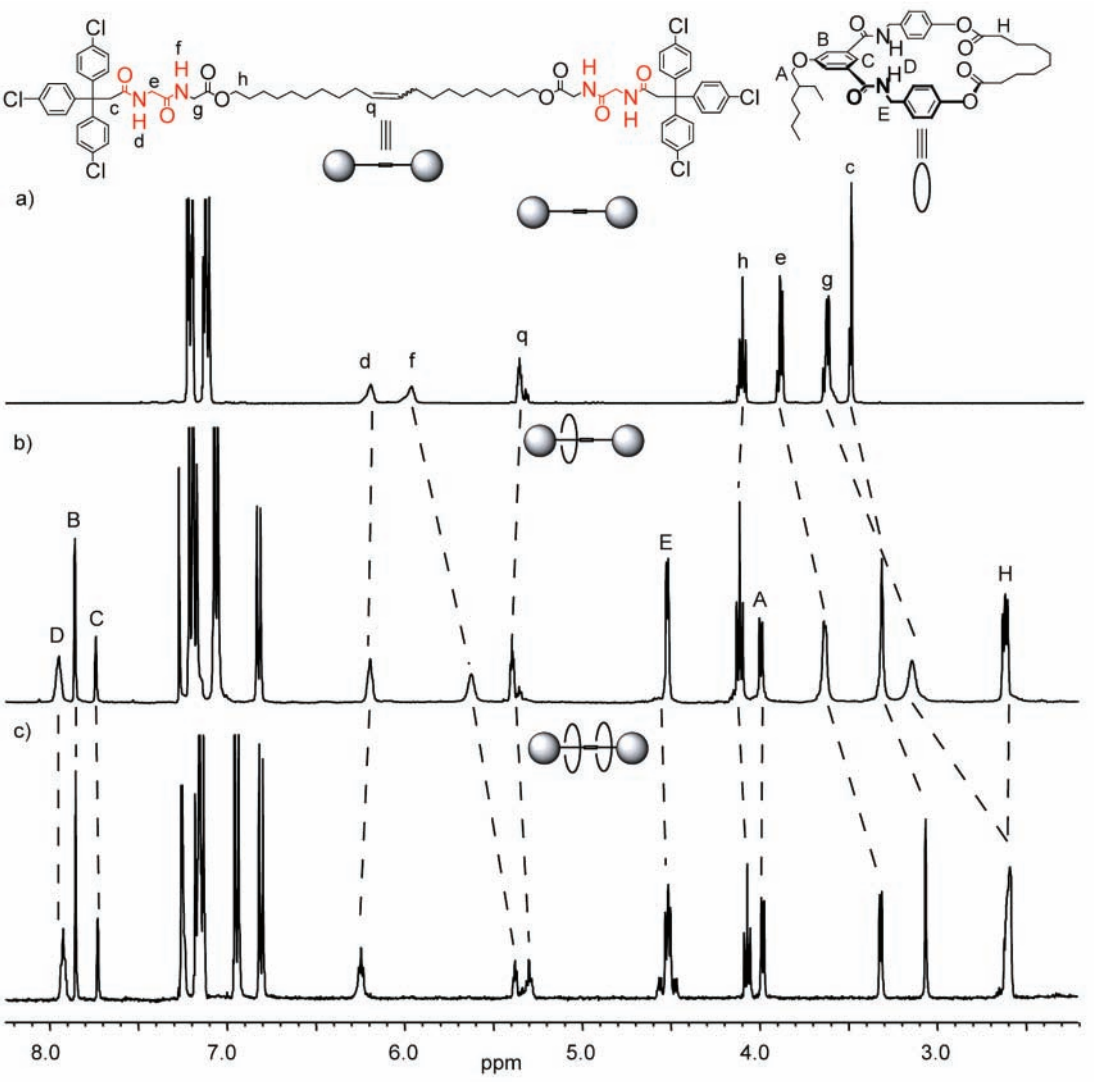

Figure 1. ^{1}H NMR spectra in $CDCl_3$ at 50 °C of (a) bis-glycylglycine thread **3b**, (b) [2]rotaxane **4b**, and (c) [3]rotaxane **5a**.

In conclusion, the combination of directed hydrogen bonding and cross olefin metathesis provides a powerful tool for the assembly (or disassembly) of rotaxanes through built in recycling of nonpreferred byproducts; a useful quality in developing "engineering up" approaches to large functional supermolecules. Significantly, since the reversible reaction involves breaking a strong C═C bond and only occurs in the presence of a specific catalyst, molecules assembled in this way are not inherently labile. Furthermore, this technique can be carried out at room temperature and below, so the programmed noncovalent interactions can be maximized. The result is the best possible kind of synthetic strategy: a thermodynamically controlled, noncovalent bond-directed assembly of a kinetically robust final superstructure.

Acknowledgment. The authors would like to thank the EPSRC and the TMR initiative of the European Union through Contracts FMRX-CT96-0059 and FMRX-CT97-0097 for support of this research. D.A.L. is an EPSRC Advanced Research Fellow.

Supporting Information Available: Full experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0344927