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Tether-assisted Synthesis of [3]Rotaxane by Olefin Metathesis

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The tether-assisted synthesis of [3]rotaxane by olefin metathesis is described. The bis(crown ether)s, in which two crown ethers are connected by a linker, were converted to tethered rotaxanes, followed by removal of the linkers to produce [3]rotaxane. The biscrown structures promoted the formation of the tethered rotaxane, resulting in a notable improvement in the yield of the [3]rotaxane.

Topologically complex molecules, such as [*n*]rotaxanes and [*n*]catenanes, have received great interest in the field of supramolecular chemistry due to their unique molecular architectures, which suggest potential applications in molecular machines and switches.[1] The synthesis of their mechanically interlocked structures is enormously challenging. Many strategies have been developed, including clipping, capping, slipping, and entering.[2] A number of interesting rotaxane-based architectures have been reported.[3]

Olefin metathesis, which is commonly used in the synthesis of a number of organic molecules, has also been applied to the synthesis of topologically complex molecules, including rotaxanes[4] and catenanes,[5] showing remarkable efficiency in producing these products. In our previous work,[6] we demonstrated that the olefin metathesis reaction provides a powerful tool to prepare [3]catenanes. Based on that work, the metathesis reaction can be extended to the synthesis of [3]rotaxane **1·5·1** (Figure 1). The most straightforward synthetic method is to use pseudorotaxane **1·3**, which can be directly subjected to the metathesis reaction to produce **1·5·1**. However, this reaction process is sterically and entropically unfavorable. The encounter between the two macrocycles might create a serious steric interaction; one or both of the macrocycles can slip away from axle precursor **3** to form the simple axle and/or [2]rotaxane, reducing the production of [3]rotaxane.

The concept of preorganization is widely accepted in organic chemistry.[7] The covalent connection of two macrocycles with suitable linkages results in the formation of biscrown structures. When axle precursors **3** thread into biscrown structures, the terminal olefins are already preorganized for the next reaction. The final ester hydrolysis can give rise to the desired [3]rotaxane (Figure 1).

The synthesis of [3]rotaxane **1·5·1** was performed by using the bis(crown ether)s **2a**–**2c** and the axle precursor **3** under the following conditions:[8] A mixture of 25 mM of **2a**–**2c** and 50 mM of **3** in CH_2Cl_2 was treated with 10 mol % of 2nd generation Grubbs catalyst[9] at 50 °C in a sealed tube followed by methanolysis of tethered rotaxanes **4a**–**4c**[10] gave rise to the desired [3]rotaxane **1·5·1** with [2]rotaxane **1·5** as by-product.[11] These compounds were purified by column chromatography and GPC. The isolated yields of [3]rotaxane **1·5·1** and [2]rotaxane **1·5** are listed in Table 1. The metathesis reaction of axle precusor **3** in the presence of monocrown **1**[12] afforded the desired [3]rotaxane **1·5·1** in 40% yield and [2]rotaxane **1·5** in 23% yield. In contrast, for the metathesis reactions of **3** in the presence of **2a**–**2c**, the subsequent methanolysis resulted in a great improvement in the production of [3]rotaxane **1·5·1**,

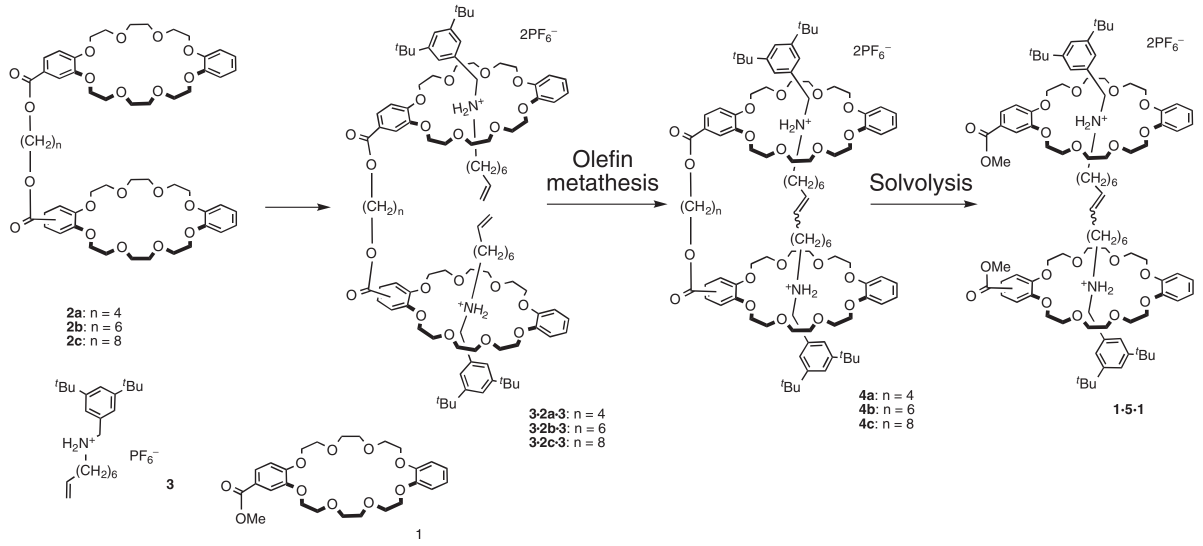

Figure 1. Schematic representation of [3]rotaxane synthesis by olefin metathesis using bis(crown ether)s.

Table 1. Yields of [3]rotaxane **1·5·1** and [2]rotaxane **1·5**

	2a	**2b**	**2c**	**1**
[3]rotaxane **1·5·1**	74%	84%	61%	40%
[2]rotaxane **1·5**	9%	8%	16%	23%

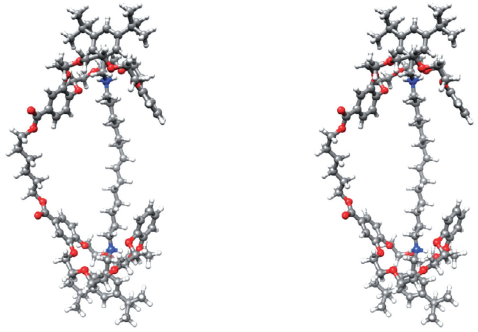

Figure 2. Stereoplot of the calculated structure for tethered rotaxane **4b**.

while the formation of [2]rotaxane diminished. It is particularly striking that an 84% yield of **1·5·1** was achieved when biscrowns **2b** and **3** were subjected to the reactions. The tethered biscrown structures obviously play a key role in the preorganization of reactive intermediates **3·2a**–**2c·3**.

The rate of cyclization may be interpreted in terms of the activation energy and the probability of end-to-end encounters. The activation energy is thought to reflect the strain energy of ring formation.[13] The probability of an end-to-end encounter generally decreases with increasing distance between the two reactive ends. The length of the linkers connecting the two crown ethers should affect the probabilities of the two terminal olefins of the complex coming close together. The more flexible the intermediate **3·2·3** becomes, the greater the entropic cost that must be paid. The most flexible intermediate, **3·2c·3**, must pay the largest entropic cost during cyclization; thus, its reaction showed the lowest yield of **1·5·1**. In contrast, **3·2a·3**, with a shorter linker, gave a lower yield of the tethered rotaxane than **3·2b·3**. Since the axle formed by coupling the two axle precursors is too long to fit nicely within the linked bis(crown ether), the cyclization process may result in an increase in the steric energy of **4a**. This may decrease the yield of the tethered rotaxane. A molecular modeling study of the tethered rotaxane supports this idea. In the calculated structure, the interaction between the crown ether and the ammonium salt works well, and alkyl chain of **4b** adopts an extended trans zigzag conformation without strain (Figure 2). This result indicates that the olefin metathesis reaction of pseudorotaxane **3·2b·3** proceeds more smoothly to produce tethered rotaxane **4b** than the reaction using **3·2a·3** or **3·2c·3**.

In conclusion, we examined the synthesis of [3]rotaxane using bis(crown ether)s under olefin metathesis conditions. The bis(crown ether)s formed tethered rotaxanes, and subsequent cleavage of the linker gave [3]rotaxane in excellent yield. This method should also be applicable to the synthesis of heteromeric [3]rotaxane derivatives.

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References and Notes

1 V. Balzani, M. Venturi, A. Credi, *Molecular Devices and Machines. Concepts and Perspectives for the Nanoworld*, Wiley-VCH, Weinheim, **2008**.

2 a) A. G. Kolchinski, R. A. Roesner, D. H. Busch, N. W. Alcock, *Chem. Commun.* **1998**, 1437. b) F. M. Raymo, K. N. Houk, J. F. Stoddart, *J. Am. Chem. Soc.* **1998**, *120*, 9318. c) S. J. Cantrill, S. J. Rowan, J. F. Stoddart, *Org. Lett.* **1999**, *1*, 1363. d) C. Heim, A. Affeld, M. Nieger, F. Vögtle, *Helv. Chim. Acta* **1999**, *82*, 746. e) S. J. Rowan, J. F. Stoddart, *Org. Lett.* **1999**, *1*, 1913. f) A. J. Baer, D. H. Macartney, *Inorg. Chem.* **2000**, *39*, 1410. g) K. Chichak, M. C. Walsh, N. R. Branda, *Chem. Commun.* **2000**, 847. h) Y. Furusho, T. Hasegawa, A. Tsuboi, N. Kihara, T. Takata, *Chem. Lett.* **2000**, 18. i) S.-Y. Chang, J. Choi, K.-S. Jeong, *Chem.—Eur. J.* **2001**, *7*, 2687. j) P. T. Glink, A. I. Oliva, J. F. Stoddart, A. J. P. White, D. J. Williams, *Angew. Chem., Int. Ed.* **2001**, *40*, 1870. k) M. J. Gunter, N. Bampos, K. D. Johnstone, J. K. M. Sanders, *New J. Chem.* **2001**, *25*, 166. l) C. A. Hunter, C. M. R. Low, M. J. Packer, S. E. Spey, J. G. Vinter, M. O. Vysotsky, C. Zonta, *Angew. Chem., Int. Ed.* **2001**, *40*, 2678.

3 a) D. B. Amabilino, J. F. Stoddart, *Chem. Rev.* **1995**, *95*, 2725. b) A. R. Pease, J. O. Jeppesen, J. F. Stoddart, Y. Luo, C. P. Collier, J. R. Heath, *Acc. Chem. Res.* **2001**, *34*, 433.

4 a) J. A. Wisner, P. D. Beer, M. G. B. Drew, M. R. Sambrook, *J. Am. Chem. Soc.* **2002**, *124*, 12469. b) R. G. E. Coumans, J. A. A. W. Elemans, P. Thordarson, R. J. M. Nolte, A. E. Rowan, *Angew. Chem., Int. Ed.* **2003**, *42*, 650. c) J. S. Hannam, T. J. Kidd, D. A. Leigh, A. J. Wilson, *Org. Lett.* **2003**, *5*, 1907. d) S. A. Vignon, T. Jarrosson, T. Iijima, H.-R. Tseng, J. K. M. Sanders, J. F. Stoddart, *J. Am. Chem. Soc.* **2004**, *126*, 9884.

5 a) B. Mohr, J.-P. Sauvage, R. H. Grubbs, M. Weck, *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1308. b) T. J. Kidd, D. A. Leigh, A. J. Wilson, *J. Am. Chem. Soc.* **1999**, *121*, 1599. c) M. Weck, B. Mohr, J.-P. Sauvage, R. H. Grubbs, *J. Org. Chem.* **1999**, *64*, 5463. d) L. Raehm, D. G. Hamilton, J. K. M. Sanders, *Synlett* **2002**, 1743. e) M. O. Vysotsky, M. Bolte, I. Thondorf, V. Böhmer, *Chem.—Eur. J.* **2003**, *9*, 3375. f) E. N. Guidry, S. J. Cantrill, J. F. Stoddart, R. H. Grubbs, *Org. Lett.* **2005**, *7*, 2129.

6 H. Iwamoto, K. Itoh, H. Nagamiya, Y. Fukazawa, *Tetrahedron Lett.* **2003**, *44*, 5773.

7 a) D. J. Cram, *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1009. b) N. Ghalit, D. T. S. Rijkers, J. Kemmink, C. Versluis, R. M. J. Liskamp, *Chem. Commun.* **2005**, 192.

8 General procedure for synthesis of [3]rotaxane: A solution of ammonium salt **3** (0.1 mmol), bis(crown ether) **2a**–**2c** (0.05 mmol) in dry CH_2Cl_2 (2 mL) was stirred for 30 min in a sealed tube. To the solution, 2nd generation Grubbs catalyst was added. After being stirred for 5 h at 50 °C, the reaction mixture was passed through silica gel pad (10% methanol in $CHCl_3$). Removal of the solvent, a brownish solid was obtained. The solid was treated with KOMe in dry methanol at 50 °C for 12 h. The reaction mixture was quenched with saturated aqueous NH_4Cl, and extracted with $CHCl_3$. The organic layer was dried over anhydrous Na_2SO_4. After removing Na_2SO_4 by filtration, the solvent was concentrated in vacuo. The crude product was purified by GPC ($CHCl_3$) to give [3]rotaxane **1·5·1** and [2]rotaxane. Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

9 T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18.

10 Isolated yields of tethered rotaxane **4a**–**4c** are 54%, 61%, and 47% yields, respectively (see the SI).

11 There is no evidence in terms of the olefin geometry formed by metathesis reaction.

12 An association constant of $5800 \pm 1200\,M^{-1}$ was determined by ^1H NMR titration in CD_2Cl_2 for the crown ether **1** and the axle precursor **3** (see the SI).

13 a) S. Usui, T. Haino, T. Hayashibara, Y. Hirai, Y. Fukazawa, M. Kodama, *Chem. Lett.* **1992**, 527. b) T. Takahashi, H. Yamada, T. Haino, Y. Kido, Y. Fukazawa, *Tetrahedron Lett.* **1992**, *33*, 7561.