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One-pot Synthesis of Permethylated α-CD-based Rotaxanes Having Alkylene Chain Axles and Their Structural Characteristics

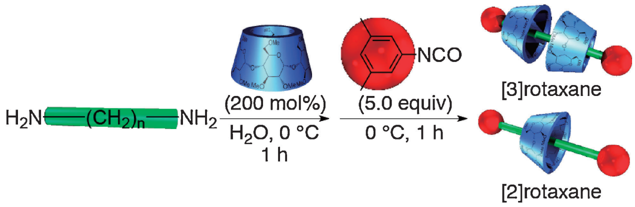
Yosuke Akae,[1] Takayuki Arai,[1,2] Yasuhito Koyama,[1] Hisashi Okamura,[1] Kohei Johmoto,[3]
Hidehiro Uekusa,[3] Shigeki Kuwata,[4] and Toshikazu Takata*[1]
[1]*Department of Organic and Polymeric Materials, Tokyo Institute of Technology,*
2-12-1 O-okayama, Meguro-ku, Tokyo 152-8552
[2]*Research Laboratory, LINTEC Corporation,*
5-14-42 Nishiki-cho, Warabi, Saitama 335-0005
[3]*Department of Chemistry and Materials Science, Tokyo Institute of Technology,*
2-12-1 O-okayama, Meguro-ku, Tokyo 152-8551
[4]*Department of Applied Chemistry, Tokyo Institute of Technology,*
2-12-1 O-okayama, Meguro-ku, Tokyo 152-8552

(Received May 21, 2012; CL-120436; E-mail: ttakata@polymer.titech.ac.jp)

Permethylated α-CD-based rotaxanes with short alkylene chains as an axle were synthesized through urea end-capping in one pot: Products were [2]rotaxane and [3]rotaxane. The head-to-head structure of [3]rotaxane obtained as a single isomer was confirmed by the characteristic ^{1}H NMR peak shifts and X-ray single-crystal structure analysis.

Since the discovery of cyclodextrin (CD)-containing polyrotaxane by Harada et al.,[1–3] many attractive concepts and materials based on their unique structures and functions have been hitherto reported, e.g., stimuli-responsive systems,[4] insulated molecular wires,[5] and polyrotaxane networks.[6] Miyake et al. have reported that about 80% α-CD in polyrotaxane takes a head-to-head conformation to face the secondary hydroxy groups of two CDs, as determined by STM measurements.[7] In addition, several reports including the X-ray crystal structure analysis of the inclusion complex of CD also support the probability of the favorable head-to-head formation.[8] The selective head-to-head formation strongly suggests the important contribution of "intermolecular" hydrogen-bondings between two CDs. The coupled CDs seem to act as one fragment during a threading process of polyrotaxane synthesis. The directional regularity of CDs on the polyrotaxane could affect densely to the polyrotaxane-specific sliding properties, because the dynamic behavior of each CD would be related to the interactions with the adjacent CDs. On the other hand, *O*-methylated α-CD derivatives such as permethylated α-CD (PMeCD) are frequently used to overcome the low solubility of the corresponding polyrotaxanes consisting of native α-CDs in organic solvents and to restrict the reacting points on the α-CD. However, the directional regularity of PMeCDs has not been unveiled yet, due to the synthetic challenges of the PMeCD-based simple model rotaxane to clarify the regularity. We have recently disclosed the one-pot high-yielding synthesis of α-CD-based polyrotaxane[9] and a simple alkylene axle-containing rotaxane[10] in water. We expected that this synthetic protocol would be applicable to the PMeCD-based simple rotaxane consisting of very weak interactions between the components.

Herein, we describe the synthesis of simple rotaxanes consisting of PMeCD as a wheel and a short alkylene chain as an axle component by urea end-capping in one pot and the structural characterization of the rotaxanes.[7] The structural analyses of the resulting [3]rotaxanes first revealed the unexpected characteristics of PMeCD to afford selectively a head-to-head conformation, the same as α-CD-based [3]rotaxane.[8]



Scheme 1. One-pot synthesis of rotaxanes.

Table 1. Synthesis of rotaxanes consisting of PMeCD via urea end-capping in water[a]

Entry	*n* of $(CH_2)_n$	Product	Yield[b]/%
1	10	[3]rotaxane **1**	trace
		[2]rotaxane **2**	trace
2	12	[3]rotaxane **3**	8
		[2]rotaxane **4**	15
3	18	[3]rotaxane **5**	16
		[2]rotaxane **6**	trace

[a]200 mol % of PMeCD per α,ω-diaminoalkane was used. [b]Isolated yield.

Scheme 1 shows the synthesis of PMeCD-based simple rotaxanes using several α,ω-diaminoalkanes as the axle component. The results are summarized in Table 1. The threading reaction of the axle into PMeCD was carried out in water at 0 °C on the basis of the lower critical solution temperature (LCST) of PMeCD in water. After stirring for 1 h, to the mixture was directly added 3,5-dimethylphenyl isocyanate as an end-capping agent. Standard workup gave corresponding rotaxanes. As a result, the use of 1,10-diaminodecane afforded a trace amount of [3]rotaxane **1** and [2]rotaxane **2** (Entry 1), which were detectable by the MALDI-TOFMS. Surprisingly, a combination of 1,12-diaminododecane with PMeCD yielded a single [3]rotaxane isomer **3** (8%) along with [2]rotaxane **4** (15%, Entry 2). Moreover, a combination of PMeCD with 1,18-diaminooctadecane also afforded the corresponding [3]rotaxane **5** in 16% yield as a single isomer together with a trace amount of

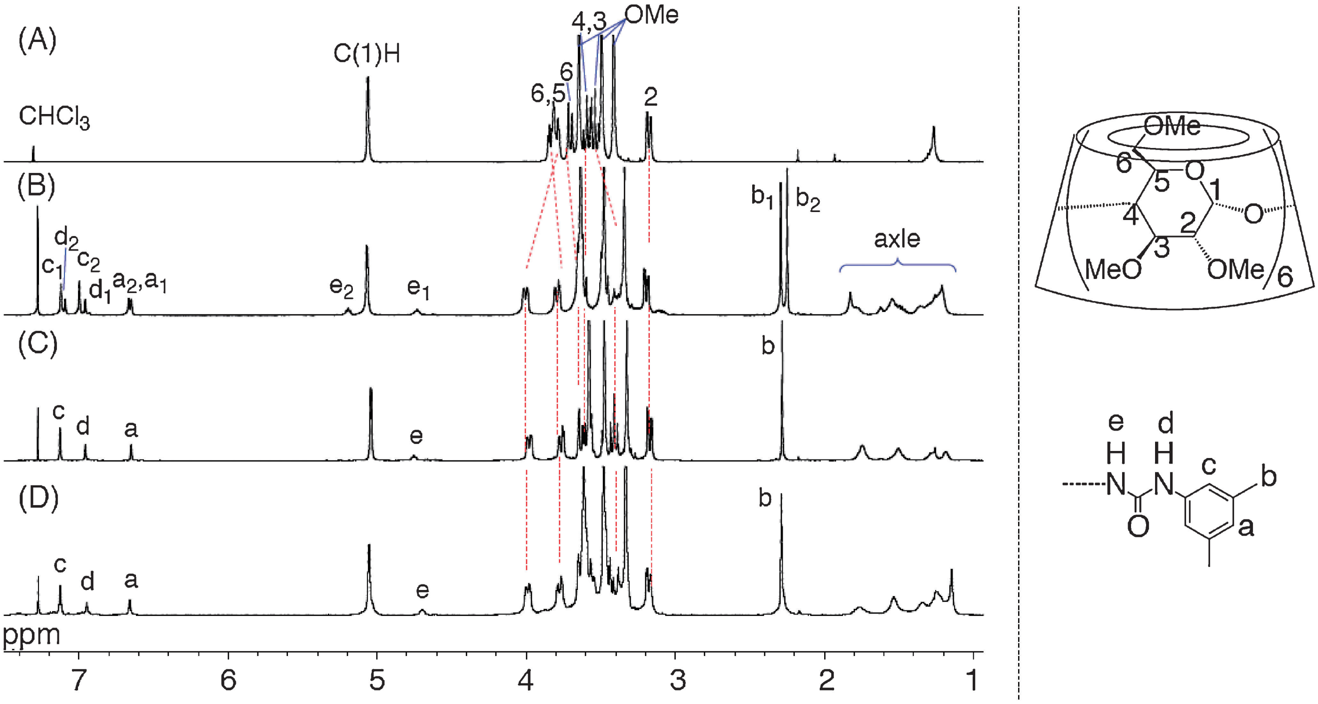


Figure 1. ^{1}H NMR spectra of (A) PMeCD, (B) **4**, (C) **3**, and (D) **5** (400 MHz, $CDCl_3$, 298 K).

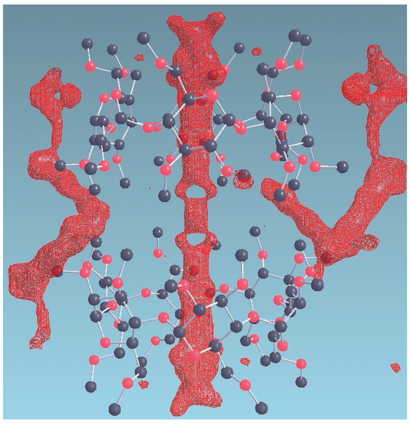


Figure 2. X-ray crystal structure of **3**.

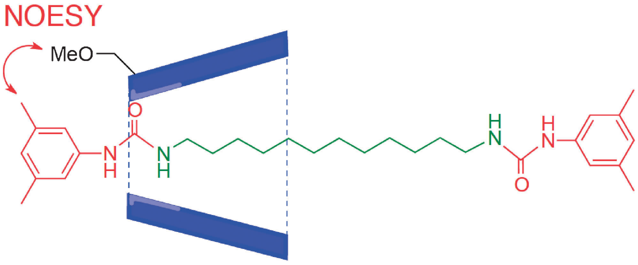


Figure 3. Proposed structure of [2]rotaxane **4** by NOESY correlation.

[2]rotaxane **6**. The evidence for the formation of single [3]rotaxane isomers **3** and **5** was obtained from the ^{1}H NMR peak shifts based on the conversion of PMeCD to [3]rotaxane.

In the ^{1}H NMR spectrum of **3** (Figure 1C), the signals of the two end-cap moieties appear as one set of the peaks to suggest either the head-to-head or the tail-to-tail conformation. The peak shifts based on the conversion of PMeCD to **3** originate from the shielding effects of the benzene moieties of the end-cap groups, which perfectly coincide with that of another reported CD-based [3]rotaxane with a head-to-head structure,[10] implying the PMeCD-directions of **3** with a head-to-head structure. Finally, the structure of **3** was determined by X-ray single-crystal structure analysis (Figure 2).

Figure 2 reveals that the coupled PMeCD took unambiguously a head-to-head structure.[11] It is very interesting that hydroxy group-free PMeCDs are regularly arranged to the head-to-head conformation, whereas the competitive formation of [2]rotaxane is characteristic of PMeCD, but not of native α-CD.[10] The axle moiety is disordered and presented as a vague rod-like electron density distribution in Figure 2, which was not modeled. The electron densities outside of the CD units would be due to the crystalline solvents. The disorder of the axle moiety is probably due to the delocalization of the axle component originating from the shuttling and/or rotational movement that blurred the electron density. However, the electron density distribution of the axle moiety supports certainly the included structure into the cavity of PMeCD.

Meanwhile, we noticed that the peak shifts of PMeCD signals of [2]rotaxane **4** were very similar to those of **3** (Figure 1B), indicating the similar chemical environment of PMeCD on **4** to **3**. The NOESY spectrum of **4** suggested the abnormal inclusion complex structure, in which the tail face of PMeCD covered the end-cap group, by the distinct NOE correlation between the methyl groups on the end-cap groups and the methoxy groups at the 6 position of PMeCD (Figure 3). The proposed inclusion complex with the tail face can be more stable than that with the head face, contrary to the inclusion behavior of native α-CD. Although the reason is not clear at present time, the complex formation probably comes from the flexible structure of PMeCD without any intramolecular hydrogen bonding that restricts the structure of α-CD. The methyl signal (b_1) included into the cavity of PMeCD on **4** (Figure 1B) is determined by HMQC and HMBC NMR spectra of **4**[12] and the chemical shift of b_1 is consistent with the peak (b) of **3** (Figure 1C). Therefore, it turned out that the chemical shift of b_1 is diagnostic to judge the inclusion structure with the tail face.

Moreover, it was revealed that the structure of **5** took also a head-to-head structure, which was determined by the characteristic ^{1}H NMR: (i) the simple spectrum based on the symmetric structure, (ii) the same peak shifts as **3**, and (iii) the same chemical shift of b as b_1 (Figure 1D). One of the plausible reasons for selectively taking a head-to-head conformation of [3]rotaxanes can be attributed to the nature of the tail face of PMeCD that favorably forms hydrogen bondings with the amine-termini to stabilize the inclusion structure of the pseudorotaxane intermediate.

In conclusion, the present study has provided several crucial insights and scientific bases for PMeCD-based rotaxane and polyrotaxane studies by the following: (i) complete structural characterization to elucidate the head-to-head regularity of PMeCD-type [3]rotaxanes; (ii) the first synthesis of simple [2]- and [3]rotaxanes consisting of PMeCD and short alkylene axles; and (iii) the evaluation of abnormal inclusion structure of PMeCD with the tail face in [2]rotaxane.

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11 Crystallographic data of **3**: $C_{138}H_{238}N_4O_{62}$, $M_r = 2945.32$, $I4_122$ (#98), $a = 17.9461(3)$ Å, $c = 55.1640(10)$ Å, $V = 17766.3(5)$ Å^3, $Z = 4$, $D_{calcd} = 1.101$ Mg m^{-3}, All 8154 unique reflections ($R_{int} = 0.0417$) were used for refinement, Final R indices $R_1 = 0.0765$ ($I > 2\sigma(I)$) and $wR_2 = 0.2712$ for all data. Details are deposited as a part of ESI. Crystallographic data reported in this manuscript have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-876327. Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, U.K.; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

12 Supporting Information is also available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.