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A new synthetic method for rotaxanes via tandem Claisen rearrangement, diesterification, and aminolysis

Kazuhisa Hiratani,[a,b,*] Jun-ichi Suga,[c] Yoshinobu Nagawa,[b] Hirohiko Houjou,[b] Hideo Tokuhisa,[b] Munenori Numata[b] and Kunihiro Watanabe[c]

[a]*Department of Applied Chemistry, Utsunomiya University, 7-1-2 Youtou, Utsunomiya 321-8585, Japan*
[b]*Nanoarchitectonics Research Center, National Institute of Advanced Industrial Science and Technology, Tsukuba Central 4, 1-1-1 Higashi, Tsukuba 305-8562, Japan*
[c]*Department of Industrial Chemistry, Tokyo University of Science, Noda, Chiba 278-8510, Japan*

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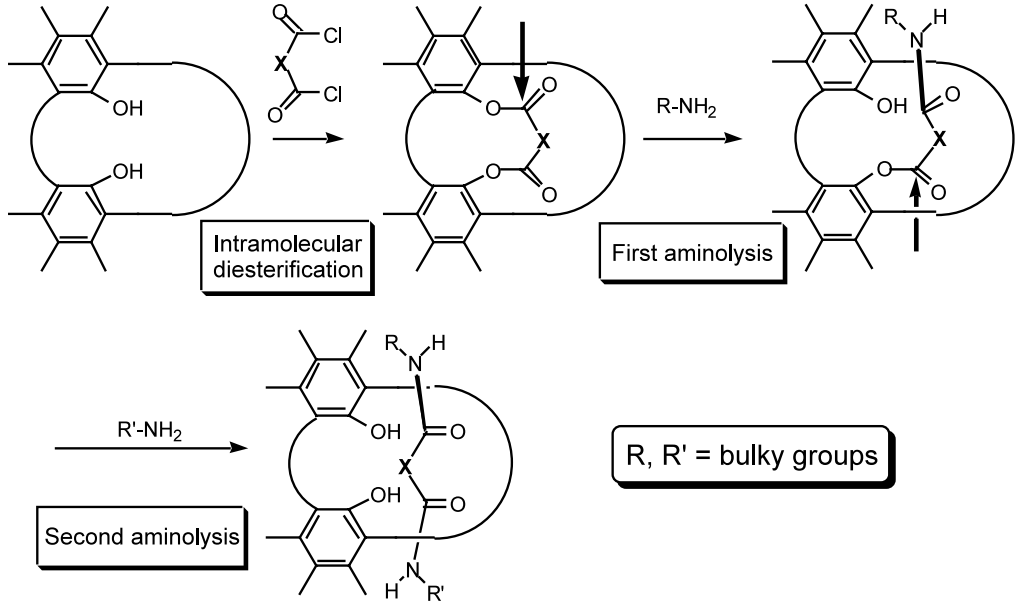
Abstract—A novel methodology to make rotaxanes via covalent bond formation has been developed. Rotaxanes composed of crownophanes having two phenolic hydroxy groups as a molecular rotor and an axle having diamide moieties were synthesized in moderate yields via three step processes: tandem Claisen rearrangement, intramolecular diesterification, and aminolysis.

In the last two decades much attention has been paid to supramolecular systems[1] such as interlocked molecules[2]—knots, catenanes, and rotaxanes—which have topologically interesting structures, that provide a wealth of potential abilities.[3] They could work as switching devices, memory devices, molecular machines such as a molecular motor, and so on.[4] Several synthetic methods for the preparation of such interlocked molecules have been reported so far, for example, the pioneering work via covalent bond formation of Schill,



Scheme 1. Synthetic strategy to construct rotaxanes.

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* Corresponding author. Fax: +81-(0)28-689-6146; e-mail: hiratani@cc.utsunomiya-u.ac.jp

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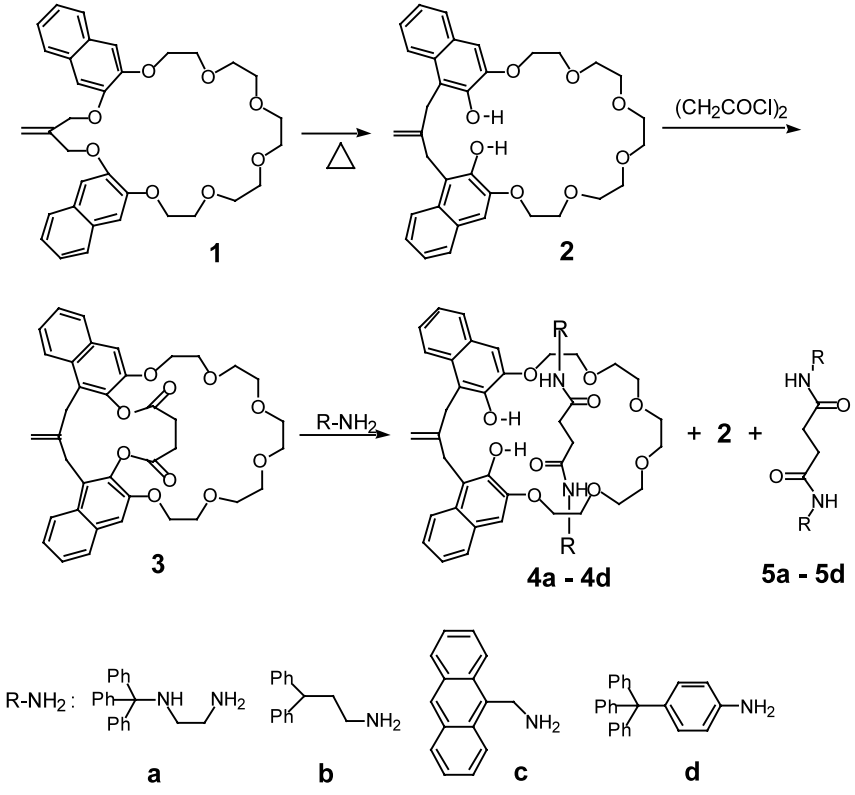
Harrison, and Wassermann,[5] Sauvage's method via formation of coordinated structure,[6] Stoddart's method utilizing charge transfer interaction and/or π–π stacking interaction between aromatic rings,[7] and a method utilizing hydrogen bond formation between molecules developed by Vögtle,[8] Hunter,[9] and Leigh[10] as representative methodologies, which are available and synthetically excellent. More recently self-assembled formation of rotaxanes using either the combination of cyclodextrin and polymeric linear molecules,[11] or transition metal complexation with acyclic aromatics containing N atoms[12] has been reported. In the 1960s, one sophisticated methodology for preparing rotaxanes via covalent bonding was proposed by Schill.[13] However, this method was not versatile because the synthetic process is complicated and requires many reaction steps resulting in a very low yield of the target interlocked molecules.

In this paper, the authors report a novel methodology to make rotaxanes including the process of covalent bond formation. This versatile method is a convincingly simpler candidate for the synthesis of rotaxanes. Scheme 1 illustrates our strategy for preparing rotaxanes; step 1: synthesis of crownophanes having two phenolic hydroxy groups from the corresponding macrocyclic polyethers via tandem Claisen rearrangement,[14] step 2: intramolecular diesterification of the crownophanes with diacid chloride, and step 3: aminolysis with amine compounds having a bulky group. To realize this concept, three important factors should be pointed out as follows: (1) diacid chloride used should selectively give rise to intramolecular esterification, (2) the ring size of macrocycles used should be appropriate for the diester moiety to be located inside the cavity, and (3) the bulky group of amines as a stopper of axles does not slip out through the ring. We have already reported a tandem Claisen rearrangement to synthesize novel macrocycles having plural phenolic hydroxy groups from the corresponding macrocyclic polyethers directly by either thermal or Lewis acid-assisted reaction.[15]

Consideration of the CPK model of crownophane **2**, which could satisfy conditions (1) and (2), made it our choice to make rotaxanes. The corresponding rotaxanes were prepared as shown in Scheme 2. As reported, the thermal reaction of macrocyclic polyether **1**, which can be prepared by the reaction of 2-[2-(3-hydroxynaphthyl-2-oxy)methyl]allyloxy-3-naphthol with pentaethylene glycol ditosylate in the presence of base in DMF, gave rise to crownophane **2** in good isolated yield.[16] The reaction of **2** with an equimolar succinic acid dichloride in THF at 50°C overnight gave intramolecularly cyclized diester **3**.[17] When malonic acid dichloride was used instead of succinic acid chloride, we did not succeed in obtaining a diester, but recovered crownophane **2**.

As shown in Scheme 2, the reaction procedure from **3** to **4** is very simple. The mixture of the diester and excess of amine in a small amount of DMF or without solvent is stirred at room temperature or 50°C overnight. The residue after removal of solvent if necessary is subjected to the preparative gel permeation



Scheme 2. Synthetic route of rotaxanes via covalent bond formation from a macrocyclic polyether.

Table 1. Yields of rotaxanes by the reaction of **3** with amines

Amine	Conditions[a]	Rotaxane (**4**)	**2**	Only axle (**5**)
a	1	42	44	27
b	1	13	85	71
b	2	26	69	74
c	1	56	28	34
d	1	0	–	–
d	3	0	–	–

[a] *Reaction conditions*: (1) 27 equimolar of amine in DMF, 50°C, 14 h, then 100°C, 2. (2) 27 equimolar of amine without solvent, rt, 14 h, then 100°C, 2 h. (3) 27 equimolar of amine in DMF, 100°C, 40 h, then 100°C, 2 h.

chromatography (GPC) with chloroform as an eluent to give rotaxane (**4**),[18] crownophane (**2**), and diamide (**5**), which can be isolated completely. In Table 1, the yields of rotaxane formation are summarized. As axles, we used 2-triphenylmethylaminoethyl amine (**a**), 3-diphenylpropyl amine (**b**), 9-(aminomethyl)anthracene (**c**), and 4-triphenylmethylaniline (**d**). As shown in Table 1, the reactions of **3** with amines (**a**–**c**) proceeded under mild conditions to give moderate yields of the rotaxanes, which are surprisingly high compared with the results via covalent bond formation reported so far.[13] Only aniline derivative (**d**) did not react with **3** even under the more severe conditions. The best yield of rotaxane reached 56% in the reaction of **3** with 9-(aminomethyl)anathracenne (**c**). In the formation of the rotaxane **4a**, crownophane **2** and 1,2-bis[2-(*N*,*N*′-triphenylmethylamino)-ethylaminocabonyl)ethane **5a** were obtained in 28% and 34%, respectively. As expected, the formation of rotaxanes **4** would result from two amines attacking from opposite sides of the macrocyclic ring. On the other hand, in the formation of **2** and **5** it can be considered that the second amine attacked the remaining ester group from the same side as the first aminolysis. Using amine **b**, which has a relatively small stopper (diphenylmethyl group), the yield of the rotaxane (**4b**) decreased. The reason might come from the second attack of amine **b** occurring more easily from the same side as the first attack than in the case of other amines having a bulkier stopper. It

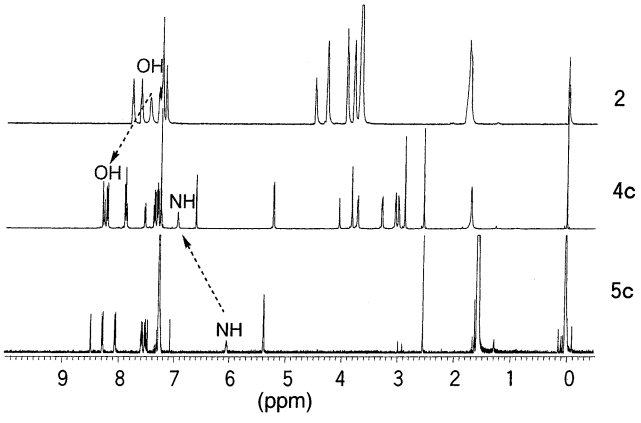


Figure 1. ^{1}H NMR spectra of crownophane **2**, axle **5c**, and rotaxane **4c** in $CDCl_3$.

was confirmed that the slippage of **5b** out of the rotor (**2**) did not occur at all after the heating of rotaxane **4b** in DMF at 100°C, 2 h. The reaction mechanism of the rotaxane formation indicates that we could make new types of rotaxanes having asymmetric axles.

In Fig. 1, ^{1}H NMR spectra of **2**, **5c**, and **4c** are shown. The amide protons of the axle **5c** in the rotaxane (**4c**) are drastically shifted downfield (from 6.03 to 6.93 ppm) compared to those of **5c** only. Ethyleneoxy protons are shifted upfield which imply that anthracenyl group of the axle is located near these protons, while OH protons are extremely shifted downfield (from 7.38 to 8.29 ppm) by the formation of hydrogen bonding with amide oxygens of the axle.[19] The ESI mass spectrum of rotaxane **4c** after the purification by preparative GPC supports the formation of rotaxane **4c**. At the same time, we can observe peaks due to **2** as a rotor and **5** as an axle, too, which might be separated by slippage.

Thus, we successfully demonstrated the synthesis of novel rotaxanes by using the method of intramolecular diester formation proposed in this paper. This method could potentially be a candidate for the synthesis of a series of supramolecular systems such as rotaxanes, as well as catenanes and others. We will now pursue this research in due course.

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17. *Synthesis of macrocyclic diester (**3**)*: To 100 ml of THF solution of crownophane **2** (1.15 g, 2.0 mmol), potassium *t*-butoxide (0.51 g, 4.5 mmol) was added and stirred for 5 h at room temperature. The solution became turbid gradually. After 250 ml of THF were added to it, succinyl dichloride (0.31 g, 2.0 mmol) was then added to make the mixture clear at once. The solution was stirred overnight at room temperature. After the solvent was removed by evaporation, the residue was extracted with chloroform and the chloroform layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed and the residue was subjected to a preparative GPC with chloroform as eluent to give 0.80 g of macrocyclic diester **3** as a main product together with the reactant (**2**) and dimeric succinate ester. Diester **3** was identified by NMR, IR, and mass spectroscopic methods. Without further purification, **3** was used in the reaction with amines. Compound **3**: yield 62.0%; mp 164°C; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) 3.16 (m, 2H, C(=O)-CH_2), 3.29 (m, 2H, C(=O)CH_2), 3.67–3.77 (m, 14H, Ar-CH_2(2H), OCH_2(12H)), 3.88 (m, 4H, OCH_2), 3.94–4.03 (m, 2H, Ar-CH_2), 4.24 (m, 4H, OCH_2), 4.35 (s, 2H, H_2C=C), 7.15 (s, 2H, Ar-H), 7.42 (m, 4H, Ar-H), 7.73 (m, 2H, Ar-H), 8.01 (m, 2H, Ar-H); IR (KBr, cm^{-1}) 1759 (ester); ESI mass, calcd for $C_{38}H_{40}O_{10}$ 656.26, found 679.0 (+Na^+).
18. *General procedure for rotaxane synthesis via intramolecular diester of crownophane*: To 5 ml of DMF, 110 mg (0.18 mmol) of **3** and then 27 equiv. of amine were added and stirred at 50°C (or 100°C in the case of amine **d**) for 14 h. Then DMF was evaporated under vacuum by Kugelrohr apparatus, and the residue was heated at 100°C for 2 h. The residue was directly subjected to a preparative GPC with chloroform as eluent to give **2**, **4**, and **5** as main products. The yields of each component are shown in Table 1. Compound **4a**: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) 2.10 (m, 4H, N-CH_2), 2.41 (s, 4H, C(=O)-CH_2), 3.19 (m, 4H, N-CH_2), 3.39 (s, 4H, OCH_2), 3.45 (m, 4H, OCH_2), 3.52 (m, 4H, OCH_2), 3.74 (m, 4H, OCH_2), 3.90 (s, 4H, Ar-CH_2), 4.09 (m, 4H, OCH_2), 4.20 (s, 2H, H_2C=C), 6.50 (broad, 2H, C(=O)-NH), 6.89 (s, 2H, Ar-H), 7.05 (m, 20H, Ar-H), 7.33 (m, 14H, Ar-H), 7.4 (broad, 2H, C-NH), 7.60 (m, 2H, Ar-H), 7.93 (m, 2H, Ar-H); IR (KBr, cm^{-1}) 1639 (amide); ESI mass, calcd for $C_{80}H_{84}N_4O_{10}$ 1260.62, found 1283.2 (+Na^+). Compound **4b**: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) 1.99 (m, 4H, CH-C$\underline{H}_2$-CH_2-N), 2.47 (s, 4H, C(=O)-CH_2), 2.97 (m, 4H, CH_2-N), 3.54 (m, 8H, OCH_2), 3.59 (m, 4H, OCH_2), 3.71 (m, 6H, OCH_2(4H), C-CH(2H)), 3.92 (s, 4H, Ar-CH_2), 4.01 (m, 4H, OCH_2), 4.34 (s, 2H, H_2C=C), 6.65 (broad, 2H, C(=O)-NH), 6.86 (s, 2H, Ar-H), 6.97 (m, 8H, Ar-H), 7.07–7.30 (m, 14H, Ar-H), 7.67 (m, 2H, Ar-H), 7.62 (m, 2H, Ar-H), 8.18 (m, 2H, Ar-H), 8.19 (broad, 2H, Ar-OH); IR (KBr, cm^{-1}) 1654 (amide); ESI mass, calcd for $C_{68}H_{74}N_2O_{10}$ 1078.54, found 1099.2 (+Na^+). Compound **4c**: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) 2.52 (s, 4H, C(=O)-CH_2), 2.88 (s, 4H, OCH_2), 2.99 (m, 4H, OCH_2), 3.04 (m, 8H, OCH_2), 3.27 (m, 4H, OCH_2), 3.70 (m, 4H, OCH_2), 3.83 (s, 4H, Ar-CH_2), 4.06 (s, 2H, H_2C=C), 5.22 (s, 4H, CH_2-anthryl), 6.60 (s, 2H, Ar-H), 6.93 (broad, 2H, C(=O)-NH), 7.26 (m, 2H, Ar-H), 7.33 (m, 6H, Ar-H), 7.39 (m, 4H, Ar-H), 7.54 (m, 2H, Ar-H), 7.88 (m, 2H, Ar-H), 7.92 (m, 4H, Ar-H), 8.21 (m, 4H, Ar-H), 8.29 (s, 2H, Ar-OH), 8.30 (s, 2H, Ar-H); IR (KBr, cm^{-1}) 1647 (amide); ESI mass, calcd for $C_{68}H_{66}N_2O_{10}$ 1070.48, found 1093.3 (+Na^+).
19. In the NOESY spectrum of **4c** at 298 K in $CDCl_3$, significant NOE cross peaks were observed between the anthryl protons and oxyethylene protons. This indicates that the anthracene ring of the axle (**5c**) exists in close proximity to the macrocyclic ring of the rotor (**2**).