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Highly Selective and High-Yielding Rotaxane Synthesis via Aminolysis of Prerotaxanes Consisting of a Ring Component and a Stopper Unit

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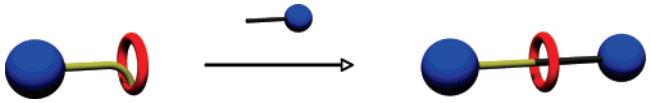
ABSTRACT



A highly rotaxane-selective synthesis via aminolysis of prerotaxanes, which were composed of a phenolic pseudo-crown ether as a ring component and a bulky stopper unit, was developed. The best result was obtained in the case of aminolysis of 3b with 3,5-dimethylbenzylamine which proceeded quantitatively with ca. 100% rotaxane selectivity forming the corresponding rotaxane 5b. The rotaxanes were formed by kinetically controlled attack of the amine from the backside of the ring component of the prerotaxanes.

Several synthetic methods for the preparation of interlocked molecules have been reported. A pioneering work for preparing rotaxanes via covalently bonded intermediates was reported by Schill during the 1960s.[1] However, covalent methods were not thought to be versatile because the synthetic process is complicated and requires many reaction steps resulting in very low yields of interlocked molecules. Recently, high-yielding syntheses of interlocked molecules by a stepwise covalent method were reported[2] including Kawai's rotaxane synthesis using dynamic covalent bonds between the axle and ring components. Among the stepwise covalent methods, Hiratani reported a unique method based on simultaneous cleavage of an ester linkage and formation of an amide linkage via aminolysis of prerotaxanes having ester linkages composed of ring and axle components.[3] This was not only useful because of an experimentally simple method but also a milestone which might guide us to realize a perfect rotaxane synthesis.

Here, we developed a highly rotaxane-selective synthetic method via aminolysis of prerotaxanes, which were composed of a phenolic pseudo-crown ether as a ring component and a bulky benzoyl group as a stopper unit. The rotaxane selectivity is defined here as a ratio of rotaxane produced over all products by an aminolysis, namely, rotaxane over the sum of a rotaxane and a dumbbell. Scheme 1illustrates our method for preparing rotaxanes. If the aminolysis proceeds via the nucleophilic attack of amine **4** from the backside of the crown ether ring of prerotaxanes **3a**−**e**, as shown in Scheme 1, the corresponding rotaxanes **5a**−**f** would be obtained. To study the scope and limitation of this method, six prerotaxanes **3a**−**f** having either different ring sizes or different substituents on the ring components and/or the stopper group were synthesized and aminolyses with 3,5-dimethylbenzylamine were investigated. This versatile method is convincingly simple, consisting of two steps: first, esterification of a phenolic crown ether with an acid chloride; second, aminolysis with an amine compound having a bulky

(1) Schill, G.; Zollenkopf, H. *Liebigs Ann. Chem.* **1969**, *721*, 53−74.
(2) For rotaxane synthesis, see: (a) Kawai, H.; Umehara, T.; Fujiwara, K.; Tsuji, T.; Suzuki, T. *Angew. Chem., Int. Ed. Engl.* **2006**, *45*, 4281−4286. (b) Hiratani, K.; Kaneyama, M.; Nagawa, Y.; Koyama, E.; Kanesato, M. *J. Am. Chem. Soc.* **2004**, *126*, 13568−13569. (c) Kameta, N.; Hiratani, K.; Nagawa, Y. *Chem. Commun.* **2004**, 466−467. For catenane syntheses, see: (d) Godt, A. *Eur. J. Org. Chem.* **2004**, 1639−1654.
(3) Hiratani, K.; Suga, J.; Nagawa, Y.; Houjou, H.; Tokuhisa, H.; Numata, M.; Watanabe, K. *Tetrahedron Lett.* **2002**, *43*, 5747−5750.

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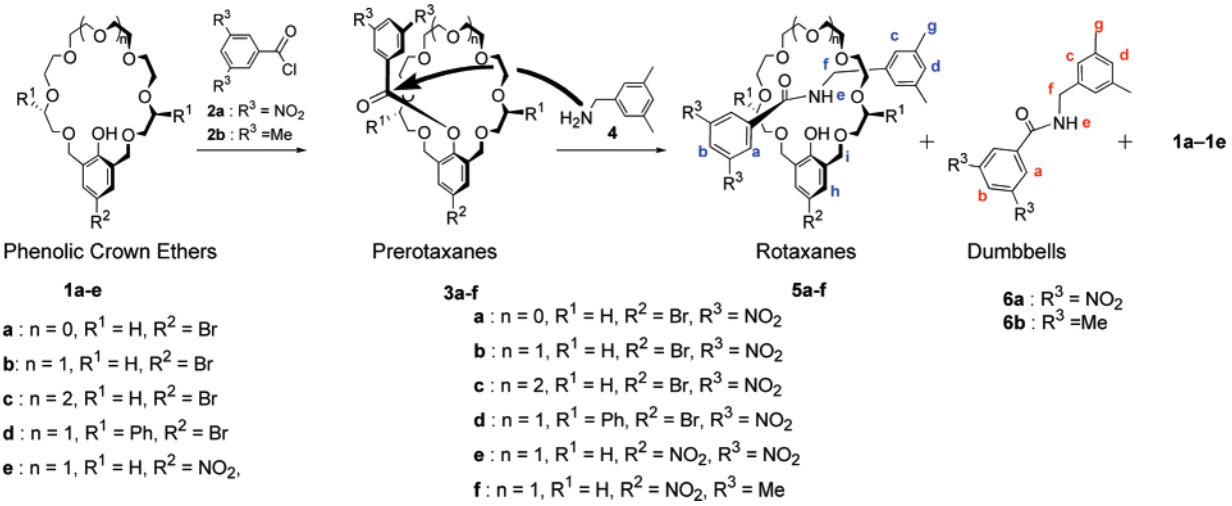
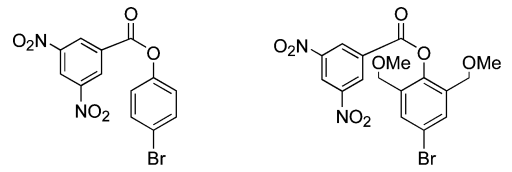
Scheme 1. Preparation and Aminolysis of Prerotaxanes **3a**−**f**



group. Several rotaxanes were readily synthesized in moderate to good yields by this method.

Prerotaxanes **3a**−**f** were prepared by acylation of crown ethers **1a**−**e**[4] with benzoyl chloride **2a** or **2b** in the presence of KO^{t}Bu in THF. As reference compounds, acyclic esters **7** and **8** were also prepared (Figure 1).



7 **8**

Figure 1. Reference compounds **7** and **8**.

The reaction procedure from prerotaxanes **3a**−**f** to the corresponding rotaxanes **5a**−**f** was very simple.[5] A mixture of a prerotaxane and amine **4** in an appropriate solvent was stirred at room temperature. The residue after removal of the solvent was subjected to column chromatography on silica gel to give the rotaxane, the dumbbell compound, and the crown ether.

In the aminolyses of **3a** and **3c** having pseudo-21-crown-7 and pseudo-27-crown-9 substructures, respectively, no rotaxane was isolated because the size of the rings was not suited (either too small or too large) for rotaxane formation. Only the corresponding dumbbell compound **6a** and crown ether **1a** or **1c** were formed. On the contrary, the reactions of **3b** and **3d**−**f** having a pseudo-24-crown-8 structure with amine **4** proceeded to give the corresponding rotaxanes in good selectivities. The ^{1}H NMR signals of the prerotaxane, rotaxane, and dumbbell at low magnetic fields are simple and are conclusively assigned. Therefore, the efficiency of the reaction was easily monitored by ^{1}H NMR measurement of the reaction mixture. In Figure 2, ^{1}H NMR monitoring spectra of a reaction mixture of aminolysis of **3b** in different solvents are shown as examples. In polar solvent DMF-d_7, the signals due to rotaxane **5b** (blue) and dumbbell **6a** (red) are clearly observed in a 3:2 ratio. In less polar solvents, however, the dumbbell signals are greatly diminished to negligible extent especially in C_6D_6, indicating a remarkable effect of solvent on the rotaxane selectivity. No product other than rotaxane **5b**, dumbbell **6a**, and crown ether **1b** was detected; the aminolyses took place quantitatively in C_6D_6. Indeed, **5b** was isolated in high yield (82%). The selectivities and isolated yields of the rotaxanes are summarized in Table 1.

The structures of rotaxanes **5b** and **5d**−**f** were characterized by spectral data. For example, ^{1}H NMR spectra of rotaxane **5b** and the corresponding dumbbell **6a** are shown in Figure 3with assignments. A significant downfield shift of the signal due to the amide proton H_e of the axle in

(4) Compounds **1a**−**f** were synthesized according to the same procedures reported in the following literature. Spectral data are found in the Supporting Information. (a) Hirose, K.; Fujiwara, A.; Matsunaga, K.; Aoki, N.; Tobe, Y. *Tetrahedron Lett.* **2002**, *43*, 8539−8542. (b) Hirose, K.; Fujiwara, A.; Matsunaga, K.; Aoki, N.; Tobe, Y. *Tetrahedron: Asymmetry* **2003**, *14*, 555−566.

(5) Representative procedure of aminolysis: Into a solution of **3b** (52.9 mg, 78.7 μmol) in dry C_6H_6 (5 mL) was added amine **4** (13.1 mg, 97.0 μmol) in dry C_6H_6 (2 mL). After stirring for 3 days at room temperature, the solvent was removed under reduced pressure. The residue was purified by chromatography on SiO_2 (ethyl acetate) to afford **5b** (51.9 mg, 82% yield) as a pale brown solid. Recrystallization from hexane−$CHCl_3$ gave colorless plates (mp 131.0−132.0 °C): ^{1}H NMR (270 MHz, $CDCl_3$, 30 °C) δ 2.31 (s, 6H), 2.56−2.63 (m, 2H), 2.99−3.05 (m, 2H), 3.09−3.15 (m, 2H), 3.20−3.27 (m, 2H), 3.33−3.42 (m, 4H), 3.44−3.78 (m, 12H), 4.10 (d, J = 10.7 Hz, 2H), 4.56 (d, J = 5.5 Hz, 2H), 4.59 (d, J = 10.7 Hz, 2H), 6.87 (s, 1H), 6.88 (s, 2H), 7.06 (s, 2H), 8.25 (t, J = 5.5 Hz, 1H), 8.79 (t, J = 2.0 Hz, 1H), 9.28 (d, J = 2.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 30 °C) δ 21.3 (p), 44.6 (s), 68.4 (s), 70.2 (s), 70.3 (s), 70.3 (s), 70.5 (s), 70.6 (s), 70.7 (s), 112.3 (q), 119.2 (t), 126.9 (t), 128.5 (t), 128.6 (q), 131.2 (t), 131.3 (t), 137.3 (q), 138.0 (q), 138.5 (q), 146.9 (q), 152.4 (q), 164.3 (q). IR (KBr, cm^{-1}) 3324, 3087, 2902, 2875, 1646, 1538, 1465, 1343, 1247, 1215, 1107, 953, 846, 731; MS (FAB) m/z 808 (M + H)$^+$, HRMS (FAB) calcd for $C_{36}H_{47}O_{13}N_3Br$ (M + H)$^+$ 808.2292; found, 808.2280.

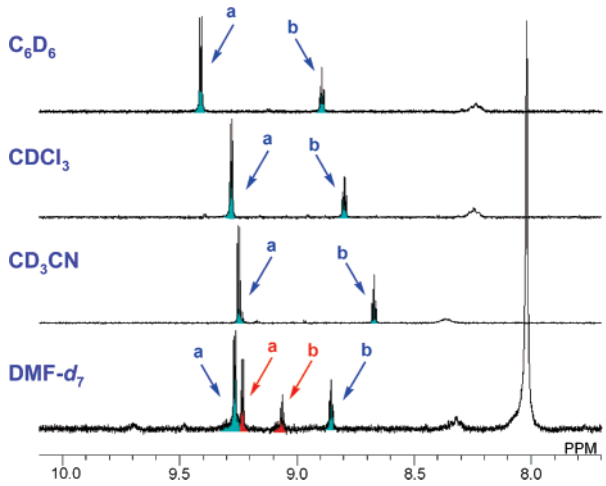


Figure 2. Partial ^{1}H NMR (270 MHz, $CDCl_3$) spectra of the reaction mixture of aminolysis of **3b** with **4** in (a) C_6D_6 ([**3b**] = 7.1 μmol, [**4**] = 10.3 mmol), (b) $CDCl_3$ ([**3b**] = 6.8 μmol, [**4**] = 9.6 mmol), (c) CD_3CN ([**3b**] = 6.9 μmol, [**4**] = 10.4 mmol), and (d) DMF-d_7 ([**3b**] = 6.8 μmol, [**4**] = 10.5 mmol).

Table 1. Selectivities and Yields of Rotaxanes in the Reaction of Prerotaxanes **3a**−**f** with Amine **4** at 30 °C

prerotaxane (10^{-3} M)	amine **4** (10^{-3} M)	solvent	time (h)	yield[a] (%)	selectivity[c] (%)
3a (4.9)	(10.0)	$CDCl_3$	36	0	0[d]
3b (7.1)	(10.3)	C_6D_6	28	82	100
3b (6.8)	(9.6)	$CDCl_3$	244	—[b]	96
3b (6.9)	(10.4)	CD_3CN	24	—[b]	95
3b (6.8)	(10.5)	DMF-d_7	36	—[b]	67
3c (4.9)	(10.0)	$CDCl_3$	37	0	0[d]
3d (4.9)	(9.9)	C_6D_6	36	81	94
3e (5.0)	(9.9)	C_6D_6	0.70	81	89
3e (4.9)	(10.0)	$CDCl_3$	2	—[b]	85
3f (4.9)	(10.0)	C_6D_6	60	—[b]	40
3f (4.9)	(10.0)	$CDCl_3$	160	—[b]	12
3f (4.9)	(9.9)	C_6H_{12}	240	52	68[e]

[a] Isolated yield. [b] Not isolated. [c] Selectivity of rotaxane (=rotaxane/(rotaxane + dumbbell)) determined by ^{1}H NMR. [d] Only the dumbbell and crown ether were formed. [e] Selectivity of rotaxane determined by HPLC.

rotaxane **5b** was observed relative to the corresponding signal of dumbbell **6a** (δ 6.50−8.30), indicating the formation of hydrogen bonding between the amide hydrogen and the oxygen atoms of the crown ether of **5b**. The aromatic protons H_a of one of the stopper units shifted downfield from 8.9 to 9.4, implying that the aromatic group of the ring component is closely located to H_a. On the other hand, the corresponding aromatic protons H_c of the other stopper unit did not shift, suggesting that this unit is located away from the phenol ring. In addition to the ^{1}H NMR spectrum, X-ray crystallographic structure analysis of rotaxane **5b** revealed the spatial arrangement of the ring and axle units as shown in Figure 4.[6,7] The distance between the nitrogen atom of the amide group and the oxygen atom of the crown ether ring is 3.02 Å, and the distance between the OH oxygen and the

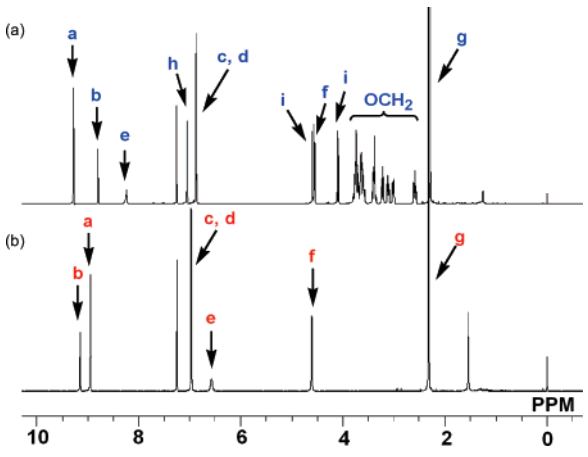


Figure 3. ^{1}HNMR (270 MHz, $CDCl_3$) spectra of (a) rotaxane **5b** and (b) dumbbell **6a**. The descriptors refer to the signals representing rotaxane and dumbbell protons shown in Scheme 1.

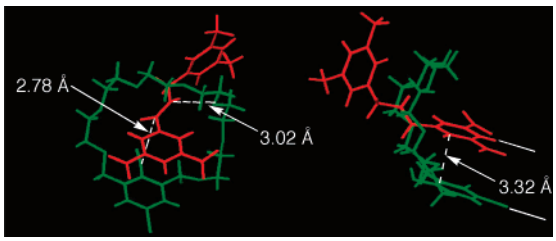


Figure 4. Views of the rotaxane **5b**. Broken lines represent intramolecular hydrogen bonds and $\pi-\pi$ stacking.

carbonyl oxygen is 2.78 Å, in accord with the presence of hydrogen bonding. The 3,5-dimethylphenyl group is located away from the phenol moiety of the ring component, whereas the 3,5-dinitrophenyl group is located above the phenolic moiety of the ring component with an interring distace of 3.32 Å.

To confirm the absence of a slippage mechanism[8] for the formation of rotaxanes **5b** and **5d**−**f**, a solution of **5b** in $CDCl_3$ was held at 30 °C for 10 days. No dumbbell was detected. In addition, the mixture of **1b** and **6a** was held at 30 °C for 10 days. No rotaxane was detected.

(6) Mercury: visualization and analysis of crystal structures. Macrae, C. F.; Edgington, P. R.; McCabe, P.; Pidcock, E.; Shields, G. P.; Taylor, R.; Towler, M.; van de Streek, J. *J. Appl. Crystallogr.* **2006**, *39*, 453−457.

(7) Crystallographic data for **5b**: $C_{36}H_{46}BrN_3O_{13}$, M_r = 808.68, triclinic, space group *P*-1, a = 11.553(3), b = 13.301(3), c = 14.853(4) Å, α = 65.085(10), β = 71.700(10), γ = 66.440(7)°, V = 1868.1(8) Å^3, Z = 2, ρ_{calcd} = 1.438 g/cm^{-3}, μ(Mo Kα) = 11.73 cm^{-1}, T = 173.2 K, colorless prism, 0.80 × 0.50 × 0.50 mm, R1 = 0.0501 [$I > 2\sigma(I)$], wR2 = 0.1185 (all data), GOF = 1.108.

(8) (a) Ashton, P. R.; Belohradsky, M.; Philp, D.; Stoddart, J. F. *Chem. Commun.* **1993**, 1269−1274. (b) Ashton, P. R.; Ballardini, R.; Balzani, V.; Belohradsky, 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*, 4931−4951. (c) Asakawa, M.; Ashton, P. R.; Ballardini, R.; Balzani, V.; Belohradsky, M.; Gandolfi, M. T.; Kocian, O.; Prodi, L.; Raymo, F. M.; Stoddart, J. F.; Venturi, M. *J. Am. Chem. Soc.* **1997**, *119*, 302−310.

Because no deslippage of axle **6a** out of the ring **1b** and no slippage of **6a** into **1b** was detected, the above possibility was ruled out. Hence the formation of rotaxanes **5b** and **5d**−**f** should result from the attack of stopper amine **4** from the backside of the benzoyl group of prerotaxanes **3b** and **3d**−**f** through the crown ether ring.

To study the effect of the crown ether ring on reaction rates of the aminolysis, the rate constants were determined by following the consumption of **3a**−**c**, **7**, and **8** by ^{1}H NMR at 30 °C in $CDCl_3$. The rate constants of the aminolyses of prerotaxanes **3a**−**c** were determined to be 1.7×10^{-3}, 3.2×10^{-3}, and 2.8×10^{-3} M^{-1} s^{-1}, respectively, whereas both of those of **7** and **8** were too small to be determined precisely at this temperature ($<3 \times 10^{-5}$ M^{-1} s^{-1}). These results clearly indicate that the presence of the crown ether ring significantly accelerates the aminolysis, presumably because it stabilizes the tetrahedral intermediates by hydrogen bonding.[9] On the other hand, the size of the crown ether ring exerts little effect on the rates of consumption of **3a**−**c**, even though the products were different (dumbbell **6a** from **3a** and **3c**, rotaxane **5b** from **3b**), indicating that both rotaxane and dumbbell formation takes place through similar transition states. Consequently, it is deduced that the high rotaxane selectivity of this method results from the acceleration of aminolysis from the backside through the ring component by participation of the crown ether ring.[10]

(9) (a) Hogan, J. C.; Gandour, R. D. *J. Org. Chem.* **1992**, *57*, 55−61. (b) Basilio, N.; García-Río, L.; Mejuto, J. C.; Pérez-Lorenzo, M. *J. Org. Chem.* **2006**, *71*, 4280−4285.

(10) To elucidate the effect of the crown ring, the substituents, and solvents on the selective formation of the rotaxanes, a detailed kinetic study on the aminolysis is underway.

Regarding the effect of substituents on the rotaxane selectivities, the selectivities of **3b** and **3e** were similar (100% and 89%) in C_6D_6, as were those for **3b** and **3d** (100% and 94%). Therefore, the effects of both substituents at the different positions on the ring component are minor. However, in the case of aminolysis of prerotaxane **3f** having the 3,5-dimethylbenzoyl group as a stopper unit, the rotaxane selectivity dropped significantly to 12% in $CDCl_3$ and to 40% in C_6D_6 (cf. 85% and 89%, respectively, for **3e**). In less polar C_6H_{12}, the rotaxane selectivity of **3f** recovered up to 68%. It turned out that the substituents on the axle unit of the prerotaxanes exerted a significant effect on the rotaxane selectivity.

In conclusion, we developed an efficient method of rotaxane synthesis based on the aminolysis of prerotaxanes which proceeded with moderate to excellent selectivities and yields. We also found that the rotaxane selectivity was significantly influenced by the substituents on the stopper units and the solvents of the reactions.

Acknowledgment. This work was partially supported by the SUNBOR foundation from the Suntory Institute for Bioorganic Research.

Supporting Information Available: Crystallographic data of rotaxane **5b** and experimental procedures for the preparation of **3a**−**f**, reference compound **8**, rotaxanes **5d**−**f**, and dumbbells **6a** and **6b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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