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Synthesis of rotaxanes consisting of crown ether wheel and *sec*-ammonium axle under basic condition

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Abstract—A novel synthetic method of [2]rotaxane by end capping of pseudorotaxane via conjugate addition of thiol to N-substituted maleimide C=C bond under basic condition was developed. Several [2]rotaxanes were obtained in good yields.

Two motifs of crown ether wheel and *sec*-ammonium axle are the most versatile combination for synthesis of rotaxanes characterized by excellent applicability among several kinds of rotaxanes. A variety of end capping approaches as the straightforward ones for the synthesis of rotaxanes have been proposed so far.[1–3] Since the hydrogen bonding interaction between *sec*-ammonium ion and crown ether (e.g., dibenzo-24-crown-8 ether, DB24C8) stabilizes the intermediate pseudorotaxane formed initially via threading, generally the end capping reaction should be carried out under neutral or acidic conditions.[1–3] Under this limitation, a lot of end cappings have been hitherto developed: amide formation,[2a,b] ester formation,[2c,3e] 1,3-dipolar cycloaddition,[2d] Wittig reaction,[2e] disulfide formation by oxidation of thiol,[2f] urea formation,[2g,h] cross metathesis,[2j,k] acetylene–$Co_2(CO)_6$ complexation,[2k] and so on.[1,2] Although many synthetic methods by end capping have been reported as mentioned above, further synthetic methods should be developed to obtain rotaxanes with functions for sophisticated application. We have studied the development of new synthetic method for rotaxane by end capping on focusing the utilization of thiol function from viewpoint of its versatile and high reactivity:[3] addition to olefin[3a] and nucleophilic reaction with trityl salt[3f] and so on under neutral condition.[3] In our continuing research works, it has been concluded that rotaxane may be prepared by the end capping of pseudorotaxane under basic condition,[4,5] if the end-capping reaction is fast enough to take place before the decomposition of pseudorotaxane by base takes place. Actually, we have succeeded in preparing rotaxane by the end capping via the addition of thiol to olefin under basic condition. This result is described in the present Letter.

Terminal thiol-containing *sec*-ammonium salt **1** was synthesized with referring to our previous report.[3f,6] *N*-(1-Naphthyl)maleimide **2a** chosen as an electrophile was obtained from 1-naphthylamine and maleic anhydride.[7] Chloroform was selected as solvent because non- or less polar solvent is favorable to achieve sufficiently high degree of pseudorotaxane formation under the equilibrium between **1** and DB24C8, although addition of thiol to N-substituted maleimide proceeds without any accelerator in polar solvent at room temperature.[8]

To a mixture of **1** and DB24C8 (1.2 equiv) in chloroform were added **2a** (3.0 equiv) and pyridine (100 mol %). The resulting mixture was stirred for 24 h at room temperature. The product isolated by preparative HPLC was the corresponding [2]rotaxane **3a** (51% yield) (Table 1, entry 2; Scheme 1). The result clearly indicated the efficient formation of *sec*-ammonium-crown ether-based rotaxane in the end-capping reaction of pseudorotaxane even under basic condition. In the absence of base, **3a** was also formed in a low yield, probably via a radical process, although there was no clear evidence (Table 1, entry 1). We examined the reaction conditions in detail to search the optimum condition. The selected results are summarized in Table 1.

The yield of **3a** increased to 62% (entry 3) with 50 mol % of 4-dimethylaminopyridine (DMAP) and to 71% with

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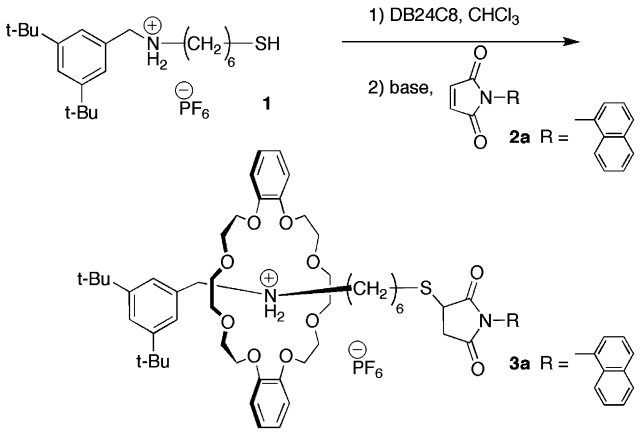
Table 1. Synthesis of [2]rotaxane **3a** under basic condition[a]

Entry	Base	pK_{aH}[b]	Amount (mol %)	Temp (°C)	Reaction time (h)	Yield (%)[c]
1	None	—	—	rt	48	21
2	Pyridine	5.2	100	0	24	51
3	DMAP	9.6	50	0	24	62
4	DMAP		100	0	24	71
5	DMAP		150	0	24	56
6	DBU	>13	30	0	24	66
7	DMAP	9.6	100	rt	24	61
8[d]	DMAP		100	rt	24	44
9[e]	DMAP		100	rt	24	Trace

[a] Reaction conditions: **1**, 0.05 mmol; DB24C8, 0.06 mmol; **2a**, 0.15 mmol; 4-dimethylaminopyridine (DMAP), 0.05 mmol; solvent: $CHCl_3$, 1 mL; temperature, 0 °C.
[b] pK_{aH} value was obtained from Ref. 10.
[c] Isolated yield.
[d] Solvent, toluene.
[e] Solvent, DMF.



Scheme 1.

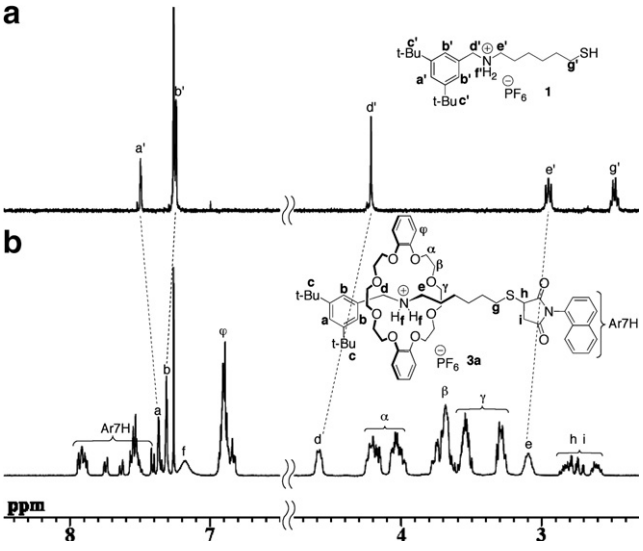


Figure 1. Partial ^{1}H NMR spectra of **1** and **3a** ($CDCl_3$, 400 MHz, 298 K): (a) thiol **1** and (b) [2]rotaxane **3a**.

100 mol % DMAP (entry 4),[9] although excess use of DMAP caused the yield decrease (entry 5). A catalytic amount of 8-diazabicyclo[5.4.0]undec-7-ene (DBU) was also effective (entry 6), although higher concentration resulted in the decrease in yield. At higher temperature (room temperature, entries 7–9), the yield of **3a** decreased probably because the in situ formation of pseudorotaxane in equilibrium was somewhat suppressed. Other solvents such as toluene (entry 8), dichloromethane, etc. could be used. Since polar solvent prevents the pseudorotaxane formation in the initial stage use of DMF hardly yielded the product **3a** (entry 9).

The structure of **3a** was determined from its spectroscopic and analytical data. Especially, ^{1}H NMR spectrum of **3a** unambiguously suggested the structure of **3a** as shown in Figure 1. The most characteristic evidence for the formation of rotaxane structure was the large downfield shift of the benzyl proton signals (H_d; δ 4.6 ppm, H_e; δ 3.1 ppm), which well coincided with that of the reported downfield for the *sec*-ammonium-DB24C8 complex in comparison with that of **1**.[2] This obvious change suggests that the DB24C8 stays on the *sec*-ammonium moiety of **3a** in chloroform. The peak broadening of H_d and H_e was similar to that of the reported ones.[2] As seen in Figure 1, all ^{1}H NMR signals were fully assignable for the structure of **3a**, along with the crown ether methylene signals as split due to the lost planar symmetry of DB24C8.

To establish the present synthetic method of conjugate addition of thiol under basic conditions, a few structure-different N-substituted maleimides **2b–d** (Table 2) were employed in the reaction under the following conditions: 0 °C, $CHCl_3$, DB24C8 (1.2 equiv), N-substituted maleimide (3.0 equiv) and 100 mol % of DMAP. The results are summarized in Table 2. Using *N*-(1-pyrenyl) and 4-(tritylphenyl) maleimides, the corresponding [2]rotaxanes were obtained in good yields. Lower yield (35%) with use of *N*-(*tert*-butyl)maleimide can be attributed to the non-aromatic substituent (*t*-Bu), which does not participate in the whole conjugation of the molecules.

Table 2. Synthesis of a few [2]rotaxanes[a]

Entry	Maleimide		Rotaxane	Yield of **3** (%)
1	**2a**	*N*-(1-Naphthyl)maleimide	**3a**	71
2	**2b**	*N*-(1-Pyrenyl)maleimide	**3b**	62
3	**2c**	*N*-(4-Tritylphenyl)maleimide	**3c**	61
4	**2d**	*N*-(*tert*-Butyl)maleimide	**3d**	35

[a] Reaction condition: **1**, 0.05 mmol; DB24C8, 0.06 mmol; **2**, 0.15 mmol; 4-dimethylaminopyridine (DMAP), 0.05 mmol; solvent, $CHCl_3$, 1 mL; temperature, 0 °C.

A facile synthesis of [2]rotaxane by utilizing the conjugate addition of thiol to N-substituted maleimide under basic conditions has been demonstrated in this work. Because many N-substituted maleimides are commercially available or can be rapidly synthesized, the present synthetic method of rotaxane will be applied to the synthesis of a variety of functionalized rotaxanes. Furthermore, the efficient end capping under basic condition is expected to expand the possibility of rotaxane synthesis along with the utility of rotaxane, because there are many known useful reactions under basic condition applicable to the rotaxane synthesis.

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9. To a solution of *sec*-ammonium salt-thiol **1** (24 mg, 0.05 mmol) in $CHCl_3$ (1 mL) was added DB24C8 (27 mg, 0.06 mmol) at 0 °C. After allowing the mixture to stand for 10 min at 0 °C, *N*-(1-naphthyl)maleimide **2a** (34 mg, 0.15 mmol) and 4-dimethylaminopyridine (DMAP, 3 mg, 0.05 mmol) were added. The mixture was stirred for 24 h at 0 °C, the solvent was removed, and the residue was subjected to the purification with preparative HPLC (solvent: $CHCl_3$). Yield of **3a** in 41 mg (71%); pale yellow amorphous solid; mp 90–91 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94–7.88 (m, 2H), 7.74 (d, $J = 7.1$ Hz, 0.5H), 7.63 (d, $J = 8.3$ Hz, 0.5H), 7.57–7.48 (m, 3H), 7.41 (d, $J = 7.1$ Hz, 0.5H), 7.37–7.34 (m, 1.5H), 7.32–7.31 (m, 2H), 7.17 (br, 2H), 6.94–6.82 (m, 9H), 4.60–4.57 (m, 2H), 4.24–4.15 (m, 4H), 4.07–3.97 (m, 4H), 3.78–3.62 (m, 8H), 3.60–3.50 (m, 4H), 3.32–3.26 (m, 4H), 3.10 (br, 2H), 2.87–2.70 (m, 2H), 2.64–2.57 (m, 1H), 1.49–1.42 (m, 2H), 1.37–1.24 (m, 2H), 1.21 (s, 18H), 1.13–1.01 (m, 2H), 1.00–0.93 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 176.1, 174.6, 151.3, 147.5, 134.3, 131.7, 129.9, 129.8, 129.7, 129.5, 128.5, 128.39, 128.35, 127.5, 127.2, 126.71, 126.67, 126.5, 126.1, 125.5, 125.2, 124.3, 123.2, 122.4, 121.9, 112.8, 77.2, 70.5, 70.0, 68.3, 68.2, 52.8, 49.1, 39.5, 39.3, 36.7, 36.6, 34.8, 31.9, 31.4, 28.5, 28.4, 27.8, 26.1, 25.7, 25.6 ppm. IR (KBr) 1718, 1507, 1459, 1252, 1187, 1124, 1107, 1056, 842, 746, 557 cm^{-1}.
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