A Novel Crown Ether Stopping Group for Side Chain Polyrotaxane. Preparation of Side Chain Polybenzimidazole Rotaxane Containing Alkyl Side Chain Ended by Crown Ether−ONa Group

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ABSTRACT: NaH promoted deprotonation of the NH group in poly(*p*-phenylenebenzimidazole) (**1**) followed by treatment with $Br(CH_2)_{12}OH$ causes substitution of the NH hydrogen of **1** to give N-alkylated polymer (**2**) having a $-CH_2ONa$ group at the end of the side chain. The ^1H NMR spectrum of **2** indicates that 90% of the imidazole rings are N-alkylated. Stirring a DMF solution of **2** with α-cyclodextrin (α-CD) leads to inclusion of α-CD onto the N-alkyl side chain, and subsequent addition of 15-crown 5-ether (15C5) causes complex formation of the −ONa group with 15C5. Because of the formation of the bulky 15C5−ONa end group, dethreading of α-CD from the side chain is prevented. The ^1H NMR spectrum of the side chain polyrotaxane (**4**) reveals that α-CD is incorporated in 57% of the side chain and that all the ONa groups form the complex with 15C5. GPC and DSC profiles of **4** support formation of the side chain polyrotaxane. Treatment of **4** with H_2O causes detaching of 15C5 and dethreading of α-CD from the side chain.

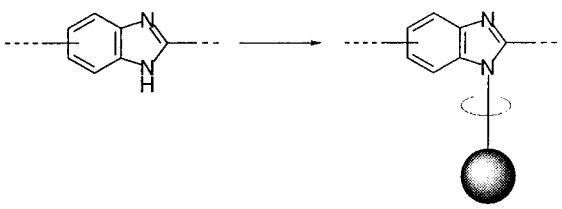
Introduction

Polyrotaxanes, which are comprised of macrocycles threaded by a linear polymer molecule, have attracted growing attention from both their unique structure and properties.[1] However, reports on side chain polyrotaxanes have been limited, compared with a large number of studies on main chain polyrotaxanes.[3−5]

Most of the already reported side chain polyrotaxanes were prepared by side chain reactions. As depicted in Scheme 1, the side chain rotaxane group was usually constructed according to method (a) which involves the side chain reaction in the presence of macrocyclic species such as cyclodextrins.[6] Recently radical polymerization of vinyl compounds having the side chain rotaxane group has also been reported (method (b) in Scheme 1).[7]

The percent content of the macrocyclic species attained in method (a) as well as physical properties of the side chain polyrotaxane depends on the structure of the polymer backbone. It has been reported that the polymers with a rigid main chain give a higher content of macrocyclic species than those with a flexible main chain.[6a,b] The macrocyclic species seem to have a stronger affinity with the side chain when the side chain is attached to the rigid main chain.

Polybenzimidazoles have a rigid main chain structure and exhibit high thermal and chemical stabilities. Their having reactive NH groups makes it possible to introduce various side chains to the polymer. On this basis, we have recently reported preparation of the side chain polybenzimidazole rotaxanes containing permethyl-*β*-cyclodextrin(s) as the host component.[8]



As an extension of this research, we have attempted a novel preparation method (method (c) in Scheme 1) of side chain polyrotaxanes. This method involves the synthesis of a graft copolymer that contains a guest group at the end of the side chain (step i in method (c)), threading of the macrocyclic species (step ii), and construction of the stopping group by a host−guest reaction (step iii). We have synthesized such N-alkylated polybenzimidazole rotaxanes by choosing α-cyclodextrin (α-CD) as the macrocyclic species and a reaction between an −ONa group and a crown ether as the host−guest reaction. Herein we report results of the synthesis.

Experimental Section

General Considerations, Materials, and Measurements. All chemicals were obtained from commercial suppliers. Poly(*p*-phenylenebenzimidazole) was purchased from Aldrich Co. Ltd. Solvents were dried over CaH_2 and distilled under reduced pressure before use. IR and NMR spectra were recorded on a JASCO-IR 810 spectrophotometer and a JEOL EX-400 spectrometer, respectively. GPC analyses were carried out by a Toso HPLC 8120 equipped with polystyrene gel columns (TSK gel G2500, G4000, and G5000), using a DMF solution of LiBr (0.006 M) as the eluent with a flow rate of 1.0 mL min^{-1}. RI and UV detectors were used. DSC analyses were performed on a Shimadzu DSC-50 thermal analyzer. Elemental analyses were carried out on a Yanaco MT-5 CHN autocorder.

Synthesis of N-Alkylated Poly(*p*-phenylenebenzimidazole), 2. A DMSO (5 mL) solution of NaH (100 mg, 4.3 mmol) was stirred at 40 °C for 30 min and at 75 °C for 1 h. To the solution was added a DMSO (10 mL) solution of poly(*p*-phenylenebenzimidazole) (**1**) (310 mg, 1.0 mmol) to give a deep red solution. After stirring for 24 h at 40 °C, $Br(CH_2)_{12}OH$ (670 mg, 2.5 mmol) was added in one portion to the reaction mixture. Stirring the mixture at 30 °C for 22 h gave a dark red precipitate, which was collected by filtration to give a brown solid. The solid was dissolved in DMSO (3 mL), and the solution was poured into methanol (300 mL) to give N-alkylated polymer **2** as brown precipitate, which was collected by filtration and dried in vacuo (0.62 g, 91%). IR (KBr, cm^{-1}): 2926 (m), 2852 (m), 1652 (w), 1460 (m), 1143 (s), 1052 (m), 798 (m), 698 (w). The absorption around 3400 cm^{-1} may

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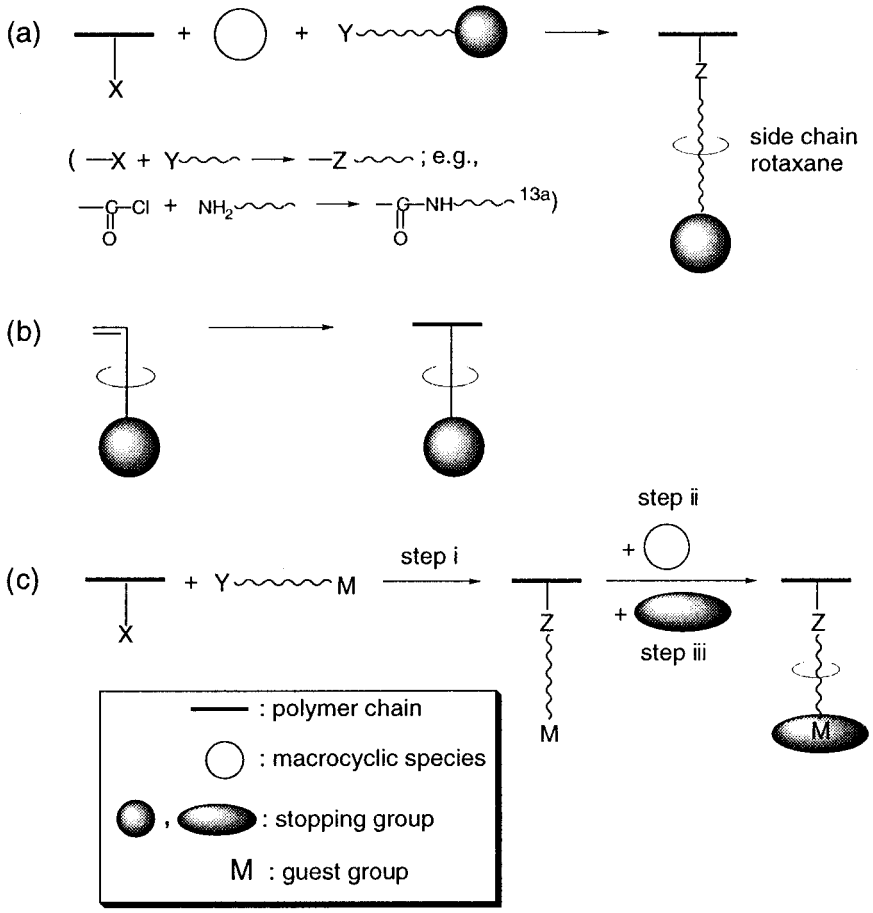
Scheme 1. Approaches for Preparation of Side Chain Polyrotaxanes[a]



[a] (a) Grafting in the presence of macrocyclic species. (b) Recently reported radical polymerization. (c) Threading of grafted polymer and capping the end group.

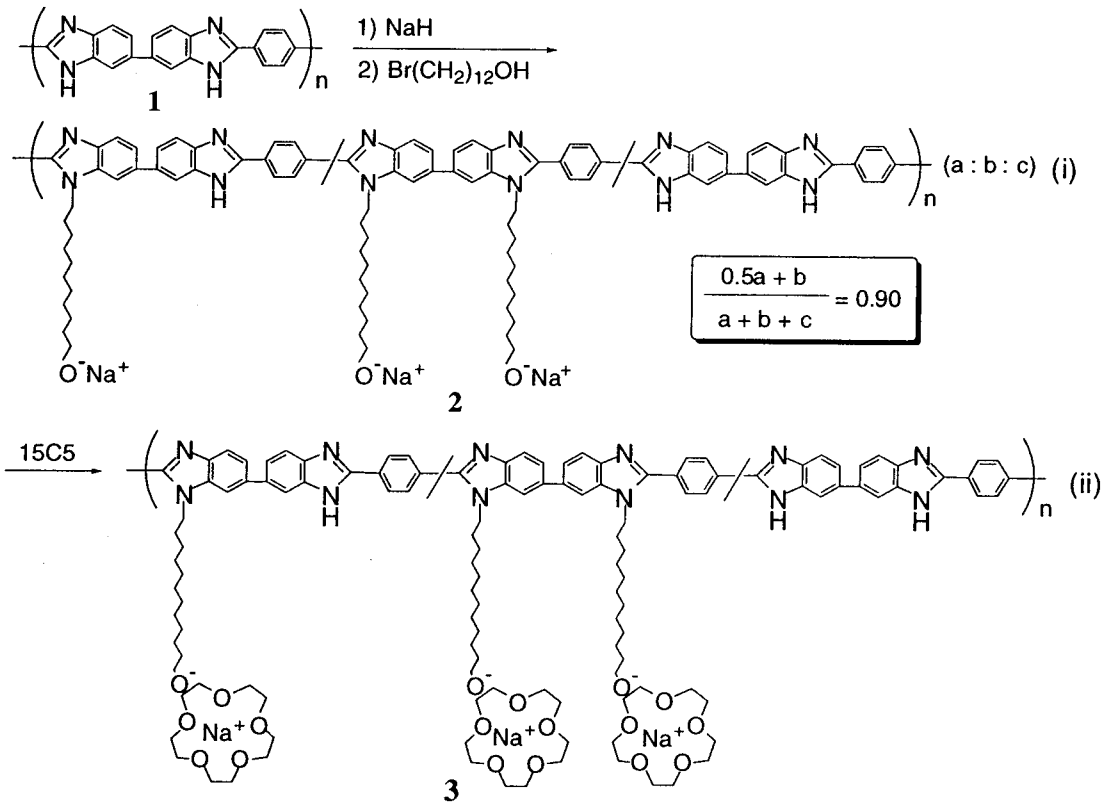
be due to ν(O−H) of H_2O contaminated in KBr or absorbed by the polymer during the preparation of the pallet. ^{1}H NMR (400 MHz in DMF-d_7): δ, 8.4−7.6 (m, 10H, aromatic hydrogens), 4.59 (br, 3.6 H, CH_2N), 3.48 (br, 3.6H, CH_2ONa), 1.85, 1.42, and 1.20 (m, 36H, $(CH_2)_{10}$). ^{13}C{^{1}H} NMR (100 MHz in DMF-d_7): δ, 153.8 (C=N), 114.7, 143.3, 137.6, 137.5, 137.4, 136.9, 136.3, 132.4, 131.0, 130.8, 130.0, 123.3, 122.7, 120.3, 111.8, 110.1 (aromatic carbons), 62.0 (CH_2ONa), 49.5 (CH_2N), 41.2, 33.7, 29.5, 26.6 ($(CH_2)_{10}$). Anal. Calcd for $(C_{44}H_{58}N_4Na_2O_2)_{0.90}$-$(C_{20}H_{12}N_4)_{0.10}$: C, 73.51%; H, 7.92%; N, 8.24%; Na, 6.09%. Found: C, 74.64%; H, 8.98%; N, 7.70%; Na, 6.35%. $M_n = 3.7 \times 10^4$, $M_w = 1.9 \times 10^5$ (by GPC, polystyrene standards).

Synthesis of a Host−Guest Adduct between Polymer 2 and Crown Ether. After stirring DMSO (5 mL) solution of **2** (66 mg, 0.10 mmol) at 25 °C for 30 min, 15C5 (60 μL, 0.25 mmol) was added to the solution. After the reaction mixture was stirred at 25 °C for 24 h, the solvent was removed by evaporation under high vacuum. The resulting brown solid was washed with MeOH (50 mL) and dried under vacuum to give a model polymer **3** as a light yellow solid (81 mg, 81%). IR (KBr, cm^{-1}): 2922 (s), 2850 (m), 1635 (w), 1457 (m), 1354 (w), 1117 (s), 943 (w), 854 (w), 805 (m), 709 (w). The absorption around 3400 cm^{-1} may be due to ν(O−H) of H_2O contaminated in KBr or absorbed by the polymer during the preparation of the pallet. ^{1}H NMR (400 MHz in DMSO-d_6): δ, 8.5−7.9 (m, 10H, aromatic hydrogens), 4.41 (br, 3.6H, CH_2N), 3.56 (s, 36H, CH_2 of 15C5), 3.05 (br, 3.6H, CH_2ONa), 1.95, 1.48, and 1.22 (m, 36H, $(CH_2)_{10}$). Anal. Calcd for $(C_{64}H_{98}N_4Na_2O_{12})_{0.90}$-$(C_{20}H_{12}N_4)_{0.10}$: C, 66.52%; H, 8.37%; N, 5.21%. Found: C, 68.19%; H, 8.08%; N, 5.22%.

Synthesis of Polyrotaxane 4. After stirring a DMSO (5 mL) solution of **2** (66 mg, 0.10 mmol) at 25 °C for 30 min, α-CD (240 mg, 0.25 mmol) was added to the solution. After the reaction mixture was stirred at 25 °C for 24 h, 15C5 (40 μL, 0.20 mmol) was added to the mixture and stirred for 24 h. The solvent was removed under high vacuum, and the resulting light brown solid was washed with MeOH/water (v/v = 9:1, 50 mL) and dried under vacuum to give polyrotaxane **4** as a light yellow solid (0.13 g, 65%). IR (KBr, cm^{-1}): 3246 (s), 2924 (s), 2850 (m), 1653 (m), 1458 (m), 1328 (w), 1151 (w), 1029 (s), 856 (w), 799 (m), 703 (w). ^{1}H NMR (400 MHz in DMF-d_7): δ, 8.4−7.8 (m, 10H, aromatic hydrogens), 5.65 (d, 6.8H, OH of α-CD, J = 7 Hz), 5.58 (s, 6.8H, CH of α-CD), 4.90 (d, 6.8H, OH of α-CD, J = 3 Hz), 4.62 (t, 6.8H, OH of α-CD, J = 5 Hz), 4.40 (br, 3.6H, CH_2N), 3.78 (s, 6.8H, CH of α-CD), 3.75 (s, 6.8H, CH of α-CD), 3.41−3.55 (m, 66.8H, CH_2 of 15C5, CH_2-ONa, and CH and CH_2 of α-CD), 1.89, 1.41, and 1.17 (s, 36H, $(CH_2)_{10}$). Anal. Calcd for $(C_{140}H_{218}N_4O_{72}Na_2)_{0.57}(C_{68}H_{98}N_4O_{12}$-$Na_2)_{0.33}(C_{20}H_{12}N_4)_{0.10}$: C, 56.18%; H, 7.14%; N, 2.51%; O, 32.11%. Found: C, 56.10%; H, 7.19%; N, 3.08%; O, 32.84%.

Synthesis of 1-(12-Sodium oxydodecyl)-2-phenylbenzimidazole. A DMSO (5 mL) solution of NaH (66 mg, 2.8 mmol) was stirred at 40 °C for 30 min and at 75 °C for 1 h. 2-Phenylbenzimidazole (389 mg, 2.0 mmol) was then added to the solution at 40 °C. The resulting dark red solution was stirred for 23 h at 40 °C. $Br(CH_2)_{12}OH$ (538 mg, 2.0 mmol) was added in one portion to the reaction mixture. After the mixture was stirred at 30 °C for 24 h, the solvent was removed under high vacuum. The light yellow residue was washed with water and purified by alumina column chromatography (eluent: acetone) to give 1-(12-sodium oxydodecyl)-2-phenylbenzimidazole (0.57 g, 71%). IR (KBr, cm^{-1}): 3436 (w), 3300 (w), 2994 (s), 2912 (s), 2354 (w), 2092 (w), 2002 (w), 1646 (m), 1599 (m), 1435 (s), 1408 (s), 1309 (s), 1275 (s), 1141 (m), 1141 (s), 952 (s), 931 (s), 895 (m), 856 (m), 741 (m), 696 (s), 666 (m). ^{1}H NMR (400 MHz in DMSO-d_6): δ, 8.2−7.2 (m, 9H, aromatic hydrogens), 4.24 (s, 2H, CH_2N), 3.64 (s, 2H, CH_2ONa), 1.59, 1.18, and 1.02 (s, 20H, $(CH_2)_{10}$). Anal. Calcd for $C_{25}H_{33}N_2$-

Scheme 2. Preparation of Polymers 2 and 3



NaO: C, 74.97%; H, 8.30%; N, 6.99%. Found: C, 75.36%; H, 8.01%; N, 6.77%.

Host−Guest Reaction between 15C5 on 1-(12-Sodium oxydodecyl)-2-phenylbenzimidazole. To a DMF (1 mL) solution of 1-(12-sodium oxydodecyl)-2-phenylbenzimidazole (80 mg, 0.20 mmol) was added 15C5 (39 mg, 0.20 mmol). The reaction mixture was stirred at 20 °C for 24 h, and the solvent was removed by evaporation under reduced pressure at 100 °C to give a model compound as a light yellow solid (0.11 g, 89%). ^{1}H NMR (400 MHz in DMSO-d_6): δ, 8.2−7.2 (m, 9H, aromatic hydrogens), 4.24 (s, 2H, CH_2N), 3.64 (s, 2H, CH_2-ONa), 3.52 (s, 20H, CH_2 of 15C5), 1.59, 1.18, and 1.02 (s, 20H, $(CH_2)_{10}$). Anal. Calcd for $C_{35}H_{53}N_2NaO_6$: C, 67.72%; H, 8.60%; N, 4.51%. Found: C, 67.40%; H, 8.51%; N, 4.37%. FAB-MS (m/z): 621 [M + H$^+$].

Treatment of Polyrotaxane with Water. A DMF solution (2 mL) of **4** (140 mg) was poured into H_2O (20 mL). The resulting precipitate was collected by filtration and dried in vacuo to give a product (**5**) (63 mg, 95%). ^{1}H NMR (400 MHz in DMSO-d_6): δ, 8.4−7.8 (m, 10H, aromatic hydrogens), 5.65 (d, 1.2H, OH of α-CD, J = 7 Hz), 5.58 (s, 1.2H, CH of α-CD), 4.90 (d, 1.2H, OH of α-CD, J = 3 Hz), 4.62 (t, 1.2H, OH of α-CD, J = 5 Hz), 4.40 (br, 3.6H, CH_2N), 3.78 (s, 1.2H, CH of α-CD), 3.75 (s, 1.2H, CH of α-CD), 3.41−3.55 (m, 44.4H, CH_2 of 15C5, CH_2ONa, and CH and CH_2 of α-CD), 1.89, 1.41, and 1.17 (s, 36H, $(CH_2)_{10}$).

Results and Discussion

N-Alkylation of Poly(*p*-phenylenebenzimidazole), 1. Reaction of poly(*p*-phenylenebenzimidazole) (**1**) and sodium hydride in DMSO caused deprotonation of NH group of the imidazole rings to give a polyanion. Subsequent treatment of the polyanion with 12-bromo-1-dodecanol gave N-alkylated polybenzimidazole (**2**). The OH groups in the polymer were converted into ONa groups as depicted in Scheme 2i.

The IR spectrum of **2** (Figure 1a) shows peaks due to ν(C−H) of the side chain at 2852 and 2926 cm^{-1}. The ^{1}H NMR spectrum of **3** shows new peaks due to the

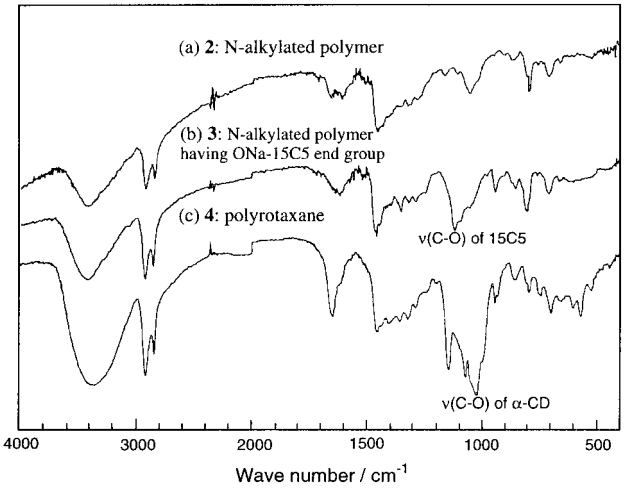
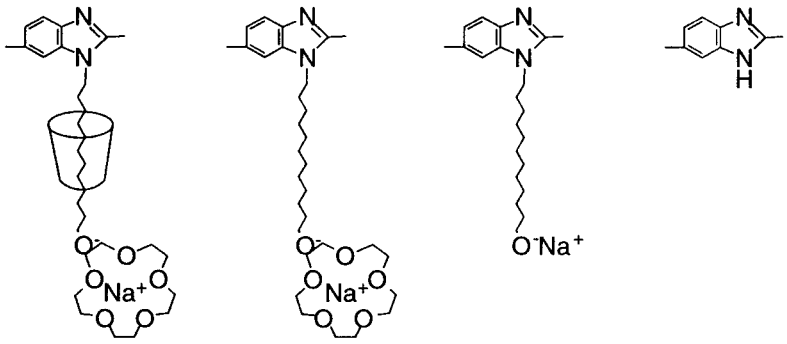


Figure 1. IR spectra of (a) **2**, (b) **3**, and (c) **4**: polyrotaxane in KBr disks.

NCH_2 and CH_2ONa hydrogens at δ 4.59 and 3.48, respectively (Figure 2a). Peaks due to the OH group were not observed. These spectroscopic data as well as analytical data indicate the N-alkylation and conversion of the OH into the ONa group. The degree of the N-alkylation, $(0.5a + b)/(a + b + c)$, was calculated as 90% from the peaks integral ratio between the NCH_2 and aromatic hydrogens.

Synthesis of Complex of Polymer 2 with 15C5 and a Model Compound. Reaction of **2** and 15-crown 5-ether (15C5) formed an complex at the end of the side chain to give the polymer **3** shown in Scheme 2ii. The ^{1}H NMR spectrum of **3** depicted in Figure 2a shows a peak due to CH_2 hydrogens of 15C5 at a position essentially agreeing with that of naked 15C5 (δ 3.56). The peak area ratio between NCH_2 (δ 4.41) and OCH_2

Chart 1. Benzimidazole Units in Polyrotaxanes 4 and 5



A		B		C		D	
57	:	33	:	0	:	10	(4)
10	:	0	:	80	:	10	(5)

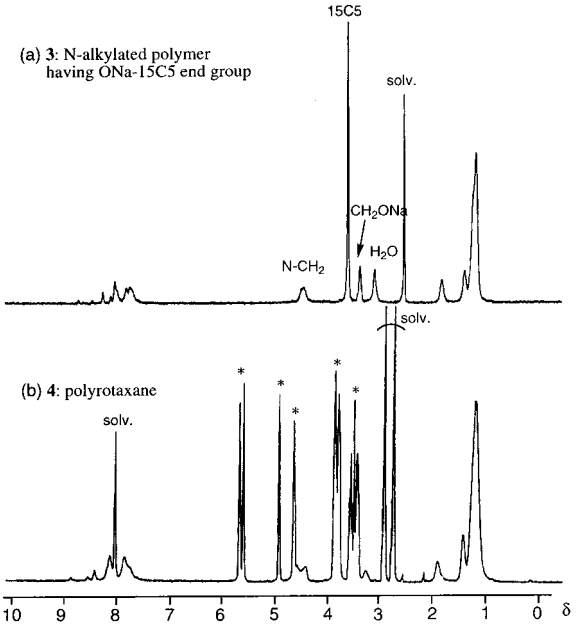
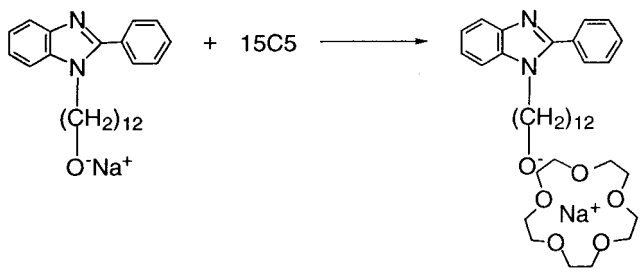


Figure 2. ^{1}H NMR spectra of **3** in DMSO-d_6 (a) and **4** in DMF-d_7 (b). Peaks with an asterisk are due to α-CD.

reveals that all the ONa groups are included by 15C5. The IR spectrum of **3** shows an absorption peak due to the ν(C−O) vibration of the 15C5 unit at 1117 cm^{-1} (Figure 1b).

To confirm the formation of the complex, a model reaction of 1-(12-sodium oxydodecyl)-2-phenylbenzimidazole with 15C5 was carried out (cf. Experimental Section).



The ^{1}H NMR spectrum of the product shows peaks due to NCH_2 and CH_2ONa hydrogens at δ 4.24 and 3.64, respectively. The FAB-MS spectrum of the product shows a peak at m/z of 621 due to [M + H$^+$], supporting the formation of the stable complex unequivocally.

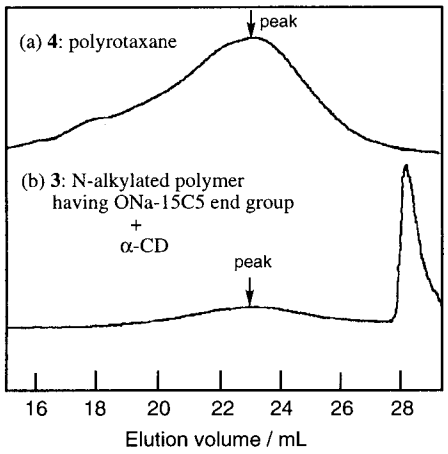


Figure 3. GPC curves of (a) **4** and (b) a 1:1 mixture of **3** and α-CD. Elution was carried out by using a DMF solution of LiBr (0.006 M) with a flow rate of 1.0 mL min^{-1}. An RI detector was used.

Synthesis of Side Chain Polyrotaxane 4. Stirring of a DMF solution of **2** and α-cyclodextrin (α-CD) for 24 h at room temperature caused inclusion of α-CD onto the side chain and following introduction of 15C5 to the ONa group to give the polyrotaxane (**4**) in 65% yield (Chart 1). 15C5 has a molecular size of ca. 5.5 Å diameter to prevent slipping off of the α-CD.[9] The starting polymer **1** is soluble in DMSO and NMP above 80 °C, whereas polymers with N-alkyl side chain **2**−**4** are soluble in the solvents at room temperature.

The ^{1}H NMR spectrum of **4** depicted in Figure 2b shows a peak due to NCH_2 at δ 4.40. The peak due to 15C5 was overlapped with peaks of α-CD. Similar to polyrotaxanes of poly(ethylene oxide) and cyclodextrins,[3] the peaks due to α-CD appear at the same position as those of free α-CD. Peak integrals of the ^{1}H NMR spectrum indicate that all the Na$^+$ ion were included by 15C5 and that a molar ratio of α-CD to polymer main chain benzimidazole unit is 57% (Chart 1).

To confirm formation of rotaxane structure of **4**, GPC measurement was carried out. Figure 3 compares GPC traces of **4** and a mixture of **3** and α-CD. The elution peak pattern of **4** indicates that all the α-CD is incorporated onto the side chain. The polymer **4** gives somewhat higher M_n (3.8×10^4) and M_w (9.0×10^4) than those ($M_n = 3.0 \times 10^4$, $M_w = 8.8 \times 10^4$) of the polymer **3** in GPC analysis using polystyrene standards.

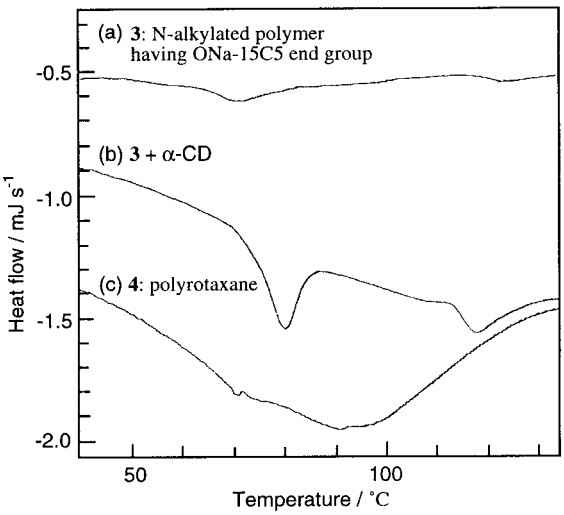


Figure 4. DSC traces of (a) **3**, (b) a physical mixture of **3** and α-CD, and (c) **4**. Temperature was increased from −100 °C at 10 °C min^{-1}. Second scans are shown.

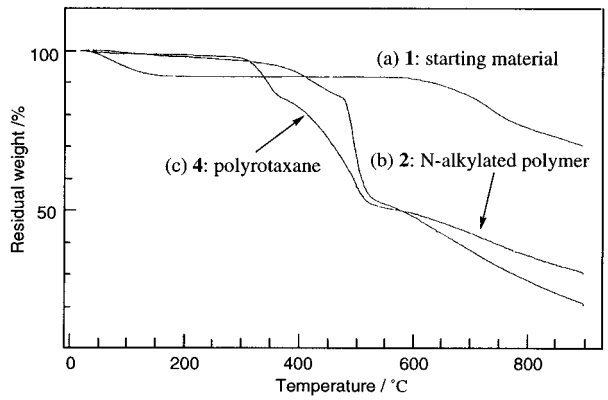


Figure 5. TG curves of (a) **1**, (b) **2**, and (c) **4** at a heating rate of 10 °C min^{-1} under nitrogen.

It has been reported that the host−guest complex of alkaline metal with crown ether is dissociated in H_2O.[10] Treatment of **4** with H_2O caused detaching of 15C5 and dethreading of α-CD to give product (**5**). The ^1H NMR spectrum shows that **5** is constituted of units A−D in a molar ratio of 10:0:80:10 as exhibited in Chart 1. This result also support that the host−guest complex prevents α-CD from dethreading from the side chain. The continuance of a part of the unit A after treatment of H_2O suggests the presence of a certain stabilization effect of α-CD on the complex formation between −ONa and the crown ether.

Thermal Properties of Polymers. Figure 4 depicts DSC traces of **3**, **4**, and a physical mixture of **3** and α-CD. The mixture shows endothermic peaks at 80 and 118 °C, whereas **4** shows a large endothermic peak at 95 °C with a shoulder peak at 70 °C. The data indicate that **4** is different from the mixture of model polymer and α-CD. Figure 5 shows TG curves of **1**, **2**, and **4**. Gradual thermal decomposition of **2** and **4** begins at much lower temperature than **1**. **4** shows an initial weight loss due to decomposition of α-CD at 300 °C.

Conclusion and Scope

The present study has revealed that host−guest adduct of crown ether is useful as the flexible stopping group for the side chain polyrotaxane. The stopping group can be detached by treatment with H_2O, and control of threading and dethreading of macrocyclic species from the side chain becomes possible. The introduction of the new stopping group will be applicable to the preparation of various side chain polyrotaxanes. Development of this kind of side chain polyrotaxanes with threading cyclodextrin bearing drug units may be useful for future design of a drug delivery material.

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