Efficient Production of Polyrotaxanes from α-Cyclodextrin and Poly(ethylene glycol)

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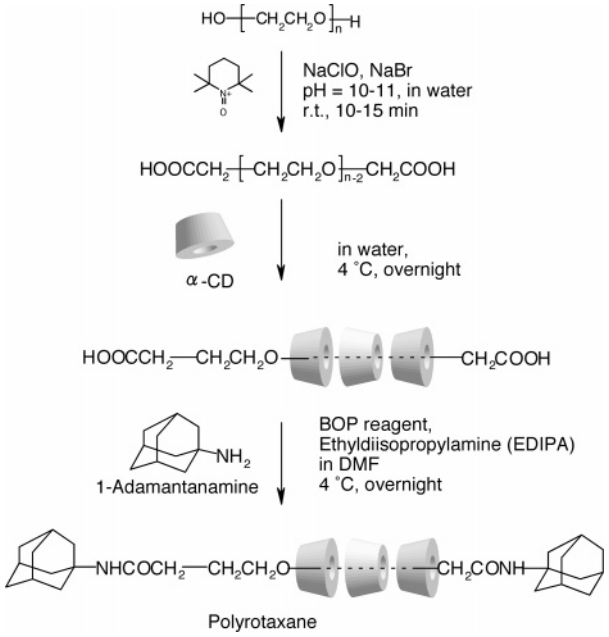
Introduction

Since their first discovery by Harada and coworkers,[1−5] followed by a series of intimate investigations by Wenz et al.,[6−8] pseudopolyrotaxane and polyrotaxane consisting of α-cyclodextrin (CD) and poly(ethylene glycol) (PEG) have been widely investigated by a number of research groups.[9−22] Many attractive concepts or materials have been reported, such as "molecular tubes" formed by cross-linking cyclodextrins in a single polyrotaxane and subsequent dissociation of included PEG,[9] drug delivery systems with hydrolyzable bulky ends,[10−12] construction of energy-transfer systems with modified CD,[13−16] "insulated molecular wires" incorporating conductive polymers,[17,18] and "topological gels" with novel sliding cross-linking points.[19] For the wider practical application of polyrotaxanes, a cost-effective method for their preparation needed to be developed.

Several preparation methods of polyrotaxanes have been reported to date, mainly distinguished by the nature of the bulky end groups and the manner of their binding. In addition to the first reported method of binding 2,4-dinitrofluorobenzene (DNFB) to the terminal amino groups of PEG,[3−5] the use of picrylsulfonic acid instead of DNFB,[15,20] the introduction of biodegradable bulky end groups containing amide or ester groups,[10−12] the use of isothiocyanate derivatives of fluorescent molecules,[21] the control of inclusion by photoisomerization of a terminal azobenzene moiety,[22] the binding of dansyl chloride to PEG-amine,[13] and the amidation of PEG-amine and adamantaneacetic acid mediated by (benzotriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate (BOP)[14] have been examined. Most of the methods stated above, however, depend on the use of PEG-bisamine (PEG-BA), which is difficult to prepare in high amine content (typically ∼80% of the termini[23]) and is expensive, especially for high-molecular-weight PEG. [Commercial PEG-BA with molecular weight of 20000 (Fluka) costs ca. $350/g, whereas PEG-BA with molecular weight of 3400 from the same supplier is sold for ca. $70/g.] Very recently, facile end-capping of terminal hydroxyl groups of pseudopolyrotaxane with bulky isocyanate at solid state was reported,[24] although the molecular weight of linear polymer is relatively low (MW = 1400) and the hydroxyl groups on CD have to be protected before capping.

Scheme 1. Preparation of Polyrotaxane from Poly(ethylene glycol)-Carboxylic Acid (PEG-COOH), α-Cyclodextrin, and 1-Adamantanamine



In the present study, we have developed an alternative synthetic route for polyrotaxanes from commercial dihydroxy-PEG (Scheme 1). This includes a novel synthesis of PEG-carboxylic acid (PEG-COOH), i.e., PEG with terminal carboxyl groups, by TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy radical)-mediated oxidation.[25,26] The terminal carboxyl groups of PEG were capped with adamantanamine via BOP-mediated amidation.[14] The polyrotaxanes thus prepared were characterized by ^{1}H NMR spectroscopy and gel permeation chromatography (GPC). The results were compared with those of polyrotaxanes prepared by a previously reported manner, i.e., binding of PEG diamino-terminated (PEG-DAT) to adamantaneacetic acid with BOP.

Experimental Section

Materials. α-Cyclodextrin (CD) was purchased from Nihon Shokuhin Kako Co. Ltd. (α-CD content > 99%); Poly(ethylene glycol) 35000 (PEG 35000), having a hydroxyl content of 7.00 × 10^{-5} mol/g, corresponding to number-average molecular weight of 28600 (determined by titration of phthalic anhydride bound to OH groups), was purchased from Fluka. The free-base form of 1-adamantanamine was from ICN Biomedicals Inc. (OH). 1,1′-Carbonyldiimidazole (CDI) was from Nacalai Tesque, Inc. (Kyoto, Japan). All dehydrated solvents (Wako Pure Chemical Industries, Ltd., water content < 50 ppm) were used as received. Other chemicals were purchased from Wako Pure Chemical Industries, Ltd. All reagents were of experimental grade and used without further purification.

Characterization. ^{1}H NMR spectroscopy in DMSO-d_6 was recorded at 400 MHz on a JEOL JNM-AL400 at ambient temperature. Chemical shifts were referenced by tetramethylsilane. GPC measurements were performed on a TOSOH SC-8010 chromatograph equipped with a Shodex K-800D and two Shodex K-805L columns, with $CHCl_3$ (for PEG, at 40 °C) or DMSO (for polyrotaxane, at 50 °C) as eluent at a flow rate of 0.4 mL/min using RI detection and PEG standards. The

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Table 1. Properties of Poly(ethylene glycol) (PEG), PEG Diamino-Terminated (PEG-DAT) and PEG-Carboxylic Acid (PEG-COOH)

PEG or PEG derivatives	molecular weight (M_w)	polydispersity (M_w/M_n)	terminal functional group content, mol/g PEG	terminal conversion ratio, %
unmodified PEG 35000 (Fluka)	33000	1.1	7.00×10^{-5}	
PEG-COOH	33300	1.1	6.88×10^{-5}	>98
PEG-DAT	33300	1.2	5.76×10^{-5}	82

elemental analysis of the polyrotaxane, which was performed with a Perkin-Elmer 2400 series II CHNS/O analyzer, typically showed a trace amount of sulfur (<0.8%). This sulfur seemed to come from remaining DMSO used in the preparation scheme because the polyrotaxanes are essentially sulfur-free. The results of elemental analysis were recalculated after the amounts of carbon, hydrogen, and sulfur corresponding to the estimated amount of remaining DMSO were subtracted.

Preparation of Polyrotaxane with PEG-Carboxylic Acid (PEG-COOH). Oxidation of terminal hydroxyl groups in PEG by 2,2,6,6-tetramethyl-1-piperidinyloxy radical (TEMPO) was performed under conditions similar to the method by Isogai et al.[26] with a few modifications. Ten grams of PEG were oxidized in water (100 mL) with TEMPO (100 mg, 6.40×10^{-4} mol), NaBr (100 mg, 9.72×10^{-4} mol), and 10 mL aqueous NaClO (available chlorine > 5.0%) at pH 10−11 at room temperature for 10−15 min. The oxidation was quenched by the addition of 10 mL of ethanol, followed by acidification with HCl to pH < 2 and three extractions with 100 mL aliquots of CH_2Cl_2. The combined CH_2Cl_2 layers were dried under reduced pressure and dissolved in 250 mL hot ethanol, followed by precipitation in a freezer overnight. Another recrystallization with ethanol and vacuum-drying gave PEG-COOH in >99% yield. The carboxyl content was determined to be 6.88×10^{-5} mol/g by titration with 0.01 N NaOH; that is, >98% of the hydroxyl groups of unoxidized PEG were converted to carboxylic acid groups.

The PEG-COOH thus obtained (3.0 g, 8.6×10^{-5} mol) and α-CD (12 g, 1.2×10^{-2} mol) were dissolved in water (100 mL) and kept in a refrigerator overnight, giving a white paste-like inclusion complex. The freeze-dried complex (14 g) was mixed with adamantanamine (0.16 g, 1.1×10^{-3} mol), (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent) (0.48 g, 1.1×10^{-3} mol), and ethyldiisopropylamine (EDIPA) (0.19 mL, 1.2×10^{-3} mol) dissolved in dehydrated DMF (100 mL). The slurrylike mixture was allowed to react at 4 °C overnight, followed by washing by centrifugation two times with DMF/methanol (1:1) and two times with methanol. Precipitation of the DMSO solution (80 mL) of the obtained solid into water (800 mL), repeated washing with water by centrifugation, and freeze-drying gave polyrotaxane as a white solid in 91−98% yield (9.55−10.3 g), based on PEG. ^{1}H NMR (DMSO-d_6) (400 MHz): δ 5.64 (O(2)H of CD), 5.46 (O(3)H of CD), 4.80 (C(1)H of CD), 4.44 (O(6)H of CD), 3.20−3.80 (C(2)H, C(3)H, C(5)H, and C(6)H of CD), 3.51 (CH_2 of PEG), 2.01, 1.94, 1.62 (adamantane). The number of CD molecules per chain calculated according to a previous study[19] was 90−100, corresponding to an inclusion ratio of ca. 22−25%. Anal. Calcd for $C_{4920}H_{8628}N_2O_{3651}(H_2O)_{250}$: C, 45.15; H, 7.04; N, 0.02. Found: C, 44.96; H, 7.17; N, 0.07. This molar ratio of water to polyrotaxan (250:1) corresponds to moisture content of 3.61%, whereas the measured value of moisture content ranges from 2.5 to 4.0%.

In several other batches, 1-adamantanamine hydrochloride was used instead of 1-adamantanamine, and other bases such as 2,4,6-trimethylpyridine (TMP), proton sponge (PS, *N,N,N′,N′*-tetramethyl-1,8-naphthalenediamine), or 4-(dimethylamino)-pyridine (DMAP) were used instead of EDIPA.

Preparation of Polyrotaxane with PEG Diamino-Terminated (PEG-DAT). PEG-DAT, i.e., PEG with terminal amino groups, was prepared by activation of PEG hydroxyl groups with CDI and subsequent binding of ethylenediamine in THF, similar to previous studies.[21,27] Briefly, CDI (1.0 g, 6.2×10^{-3} mol) and vacuum-dried PEG (50 g, 1.4×10^{-3} mol) dissolved in dehydrated THF (200 mL) were kept at 50 °C for 18 h, followed by addition of ethylenediamine (3.0 mL, 4.4×10^{-2} mol) and further reaction for 2 h at 50 °C. The modified PEG was precipitated by addition of ethanol (200 mL), standing in a freezer for 2 h, and washing with cold ethanol by suction to yield 47 g of PEG-DAT (94%). The amine content was determined to be 5.76×10^{-5} mol/g by titration with 0.1 N HCl; that is, 82% of the hydroxyl groups of the unmodified PEG were converted. The inclusion complex (14 g), prepared from PEG-DAT (3.0 g, 8.6×10^{-5} mol) and α-CD (12 g, 1.2×10^{-2} mol) in the manner described above, was mixed with adamantaneacetic acid (1.4 g, 7.2×10^{-3} mol), BOP reagent (3.0 g, 6.8×10^{-3} mol), 1-hydroxybenzotriazole (HOBt) (1.0 g, 7.4×10^{-3} mol), and EDIPA (1.3 mL, 7.6×10^{-3} mol) dissolved in dehydrated DMF (100 mL). The end-capping reaction with adamantaneacetic acid was carried out at 4 °C overnight, and the product was purified in the same manner as the polyrotaxane from PEG-COOH. The yield was 7.4 g (70%, based on the starting PEG), and the number of CD molecules in a single polyrotaxane chain calculated from the ^{1}H NMR spectrum[19] was 80−96. This corresponds to coverage of ca. 20−24% of the PEG chain with CD. Anal. Calcd for $C_{4786}H_{8406}N_4O_{3534}(H_2O)_{400}$: C, 44.30; H, 7.15; N, 0.04. Found: C, 44.41; H, 7.09; N, 0.04.

Results and Discussion

Modified PEGs, i.e., PEG-COOH and PEG-DAT, essential for the synthesis of polyrotaxanes, can be successfully prepared from commercially available PEG, as shown in Table 1. Molecular weights of PEG-COOH and PEG-DAT measured by GPC were identical to those of unmodified PEG, indicating that no cleavage occurred during the oxidation. PEG-DAT showed a lower level of modification (82%) compared with previous results,[27] probably due to the higher molecular weight of PEG used in the present study compared to that in ref 27 (MW = 2000). On the other hand, the carboxyl content of PEG-COOH, corresponding to >95% conversion of terminal hydroxyl groups, was considerably higher than that previously reported.[28−35] In other words, only TEMPO-mediated oxidation ensures both high yield and high conversion of terminal hydroxyls to carboxyls, as previously reported.[25] Other oxidation studies reported cleavage of PEG chains, as determined by viscometry.[28] Oxidation of PEG with a combination of MnO_2 and H_2O_2[29] requires lengthy two-step reactions and results in a low yield. Although carboxymethylation of PEG was reported to show a degree of modification of 105−110%,[30−32] the correct values correspond to 84−88% due to the presence of ∼25% of dihydroxy-PEG in commercially available monomethoxy-PEG.[33,34] Reaction of PEG with succinic anhydride also requires lengthy reaction conditions for a high degree of conversion.[35] Compared to the foregoing methods, the present TEMPO-mediated oxidation of PEG is a straightforward, facile, single-step method giving PEG-COOH of any molecular weight with a high degree of oxidation in high yields, within 10−15 min at room temperature.

The PEG-COOH and PEG-DAT prepared in the present study formed inclusion complexes with CD similar to ones from previous studies[2−19] and gave water-insoluble polyrotaxanes by subsequent BOP-

Table 2. Properties of Polyrotaxanes Prepared from PEG-DAT and PEG-COOH

entry	PEG derivatives	capping reagent (equiv relative to PEG terminal groups)	molecular weight (M_w)	polydispersity (M_w/M_n)	average number of included CDs	
					from NMR	from molecular weight
1	PEG-DAT	$C_{10}H_{15}$-CH_2COOH (80)	119000	1.3	80−96	86
2	PEG-COOH	$C_{10}H_{15}$-NH_2 (5)	118000	1.2	90−100	85

Table 3. Yields of Polyrotaxanes Prepared from 3 g of PEG Derivatives under Various Conditions

entry	PEG derivatives	capping reagent (equiv relative to PEG terminal)	tertiary base[a] (equiv)	other chemical[b] (equiv)	yield, g (PEG-based yield, %)
1	PEG-DAT	$C_{10}H_{15}$-CH_2COOH (80)	EDIPA (80)	HOBt (80)	6.0−9.0 (40−60)
2	PEG-COOH	$C_{10}H_{15}$-NH_2 (5)	EDIPA (5)	None	9.55−10.4 (91−98)
3	PEG-COOH	$C_{10}H_{15}$-NH_3Cl (5)	EDIPA (5)	None	2.29 (22)
4	PEG-COOH	$C_{10}H_{15}$-NH_3Cl (5)	EDIPA (20)	None	2.76 (26)
5	PEG-COOH	$C_{10}H_{15}$-NH_2 (5)	TMP (5)	None	10.2 (97)
6	PEG-COOH	$C_{10}H_{15}$-NH_2 (5)	PS (5)	None	10.0 (95)
7	PEG-COOH	$C_{10}H_{15}$-NH_2 (5)	DMAP (5)	None	10.1 (96)

[a] EDIPA: ethyldiisopropylamine; TMP: 2,4,6-trimethylpyridine; PS: Proton Sponge; DMAP: 4-(dimethylamino)pyridine. [b] HOBt: 1-hydroxybenzotriazole.

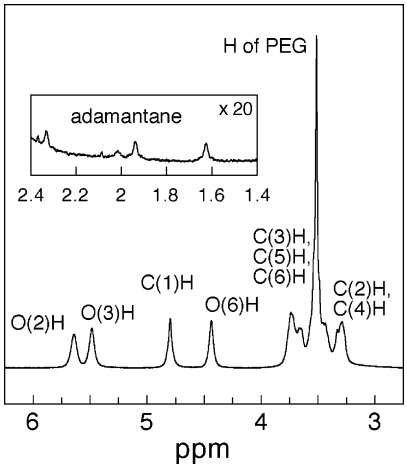

Figure 1. 400 MHz ^{1}H NMR spectra of the polyrotaxane prepared from PEG-COOH, α-CD, and adamantanamine, catalyzed by EDIPA (Entry 2 in Table 2) in DMSO-*d6*.

mediated coupling with adamantane derivatives. These results clearly show that the terminal functional groups in the modified PEGs did not affect the inclusion phenomenon. End-capping reactions of the inclusion complexes prepared from these two modified PEGs gave polyrotaxanes as white solids with almost the same properties as before, as shown in Table 2. The purified polyrotaxanes were soluble only in DMSO and 1 M NaOH, and insoluble in other solvents, similar to previously reported polyrotaxanes.[2−9] Molecular weights measured by GPC and the numbers of included CDs were similar for both polyrotaxanes. The ^{1}H NMR spectra of the present polyrotaxanes (Figure 1) were exactly identical to those of the previous samples. Starting from 3 g PEG, 9.55−10.3 g of polyrotaxane were obtained from PEG-COOH, whereas the yield from PEG-DAT was 6.0−9.0 g, as shown in Table 3. The former values correspond to 91−98% yield based on PEG, i.e., relative to the ideal weight of polyrotaxane (10.5 g) with M_w = 122840 g/mol (assuming 90 included CDs, estimated from ^{1}H NMR). The foremost reason for this difference is probably the high degree of modification for PEG-COOH (98%) compared to the value for PEG-DAT (82%). This contributed to the high degree of binding of the capping reagent (adamantanamine), resulting in low dissociation of the complex from mono-capped or uncapped PEG. The method in the present study showed the highest yield compared to other polyrotaxane studies. The numbers of the included CDs in the present polyrotaxane seem to be higher than those in the previously prepared polyrotaxane,[36] probably contributed by the larger molecular weight of the included PEG in the present study (= 35000).

The capping reaction in the present study is essentially a modification of the method by Tamura et al.,[14] i.e., binding of the adamantane moiety via BOP-mediated amidation. Ooya et al. also utilized BOP for capping pseudopolyrotaxanes with a hydrolyzable end-cap.[37] The BOP reagent is usually added in 1.5−2-fold molar excess relative to carboxyl groups.[38−41] In the methods reported by Tamura et al.[14] and our preparation from PEG-DAT, large excesses (40−80 molar excess vs PEG terminal hydroxyl groups) of amidation reagents such as BOP, HOBt, and EDIPA were added because a large excess of adamantaneacetic acid (capping reagent) was used. In contrast, the amounts of amidation reagents were drastically lowered to millimolar levels in the preparation from PEG-COOH because only a trace amount of carboxyl groups (7.0×10^{-5} mol) was present at the PEG termini. Additionally, HOBt was not essential for the synthesis of polyrotaxane and could therefore be eliminated because the main role of HOBt is suppression of racemization and has no effect on the synthesis of polyrotaxane. Similar to previous studies,[38−41] our experiments clearly showed that amidation proceeds without HOBt. Reduction or elimination of expensive reagents such as BOP, adamantanamine, EDIPA, and HOBt contributed to the synthesis of polyrotaxanes with considerably lowered total costs.

Although the complicated amidation mechanism reported for BOP is totally different from other amidation reactions,[38,39] the carboxyl-activating function of BOP implicitly suggests that the addition of excess amine to activated carboxyl groups would be advantageous, similar to other amidations such as the carbodiimide-mediated reaction. Therefore, addition of excess amine (i.e., adamantanamine) to carboxyls (of PEG-COOH) may have contributed to the higher yield that was attained compared to that of the procedure with adamantaneacetic acid and PEG-bisamine (or PEG-DAT).

The preparation of polyrotaxane from PEG-COOH was further investigated and yields of polyrotaxanes

prepared under various conditions are shown in Table 3. The use of TMP, PS, and DMAP, which were reported to be effective in other amidation systems,[42,43] gave high yields comparable to the yield obtained with EDIPA. All amines tested here acted as effective catalysts, and all polyrotaxanes showed the same range of the inclusion ratio (22−25% of the PEG chain). A considerable decrease in yield was observed, however, when adamantanamine hydrochloride was used instead of the free-base form of adamantanamine (entry 3 in Table 3). This situation is completely opposite to previously reported studies for BOP,[40,41] in which yields >80% were observed with the use of amine hydrochlorides. The dissociated hydrochloric acid from adamantanamine hydrochloride may suppress the reaction because the BOP-mediated amidation requires rather basic reaction conditions.[38] Three equivalents of tertiary amine are necessary to neutralize carboxyls, the amine salt, and acidic HOBt generated during reaction.[38] Increasing the amount of tertiary amine (EDIPA), however, did not improve reaction yield (entry 4 in Table 3). This drastic lowering in yield has not yet been elucidated, while it might be from detailed differences between the present methods and the previous, such as heterogeneous reaction conditions (reaction at insoluble solid surface) and/or selection of solvents.

In conclusion, the present method provides a route for polyrotaxane synthesis with a minimum of reagents, and an easy, one-step, high-yield preparation of PEG-COOH of any molecular weight and high degree of modification, via TEMPO-mediated oxidation. These novel improvements result in high-yield production of polyrotaxanes at low cost, with a potential for large-scale manufacture of polyrotaxanes leading to prospective applications.

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