Graftpolyrotaxane: Graft Polymer Possessing Movable Graft Chains on Cyclodextrins as The Polyrotaxane Wheels

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Abstract. Graftpolyrotaxanes having graft chains on the wheel components were prepared from main chain-type polyrotaxane having monofunctional cyclodextrin wheels and terminal end-reactive poly(ethylene glycol) (PEG). The well-defined polyrotaxane having mono(6-hydroxyl) permethyl-α-CD (monoOH-α-CD) as the wheel components and a polytetrahydrofuran (PTHF) axle with bulky end-capping groups was synthesized by the two pathways; (i) synthesis by solid-state end-capping of pseudopolyrotaxane consisting of monoOAc-α-CD and hydroxy-terminated PTHF and (ii) one-pot synthesis using monoOH-α-CD and amine-terminated PTHF in water. The grafting reaction on the wheel moieties of the resulting polyrotaxane was carried out by acylation reaction with PEG-mono-carboxylic acid derivatives in high conversion yields. To estimate the relative rotary movement of CDs and the axle polymer in the polyrotaxane and graftpolyrotaxane, the rotational correlation time ($\tau_c$) of polyrotaxanes was estimated from the longitudinal relaxation time ($T_1$) of $^{13}$C NMR. The results clearly indicate that the graftpolyrotaxane described here is a new type of graft polymer in terms of the special circumrotation behavior such as the independent rotary movement of CDs with the graft chain and the axle polymer.

1. Introduction
Supramolecules with interlocked structures have attracted great interests experimentally and theoretically [1]. One of the typical examples can be provided by cyclodextrin (CD)-containing main-chain type polyrotaxane, in which many cyclic molecules are threaded on a single polymer chain and are trapped by capping the chain end with bulky groups. Networked polymer of polyrotaxane obtained by cross-linking of wheel components on the main-chain type polyrotaxane has unique characteristics based on the interlocked structures of the cross-link points, such as highly swelling nature for several solvents, high elasticity, and high stress-releasing ability [2]. Graft polyrotaxane, a new type of polymer characterized by the movable (translative and circumrotative) graft chains, is an intriguing class of polyrotaxanes, which can be provided by a grafting protocol to wheel components of the main chain-type polyrotaxane (Figure 1). Although several studies of graftpolyrotaxane directed toward drug delivery systems using a biodegradable property [3] or high stress releasing materials exploiting the sliding property of wheel components [4] have been extensively studied, the dynamic characteristic of graftpolyrotaxane has never been studied owing to the high structural
disorderness of graftpolyrotaxane [5]. Namely, the grafting reaction onto CDs of polyrotaxane naturally involves non-regioselective functionalization, since CD has many free hydroxyl groups.

![Graft chains on polyrotaxane undergo both translative movement and circumrotative movement.](image)

**Figure 1.** Structure of graftpolyrotaxane.

Recognizing these issues, we planned the synthesis of structure-well-defined graftpolyrotaxane by exploiting monoOH-α-CD as a crucial component of main chain-type polyrotaxane. Herein, we wish to report the synthesis, characterization, and dynamic property of graftpolyrotaxane.

2. Experimental Section

2.1. Materials and Methods. MonoOH-α-CD 5 and polytetrahydrofuran bisamine terminated (PTHFBA, $M_n = 9400$, $M_w/M_n = 1.1$) were prepared according to the literature [6,7]. Dichloromethane was distilled from CaH$_2$ and stored over MS 4A. Commercially available dehydrated solvents, tetrahydrofuran (THF), and dimethylformamide (DMF) were used without further purification. All other reagents from commercial sources were used as obtained.

\[
\text{H NMR (270 MHz, acetone-d$_6$):} \delta = 3.5 \text{ Hz, 6H,} \\
\text{2.07 (s, CD})
\]

\[\text{3.16 (m,} \quad \text{87H,} \quad \text{2.07 (s,} \quad \text{CD})\]

\[\text{5.03 (brd, C(1)H of CD}}\]

\[\text{5.03 (brd, C(1)H of CD}}\]

Preparation of Mono(6-acetoxy)-permethyl-α-CD (monoOAc-α-CD, 1): To a solution of MonoOH-α-CD 5 (1.9 g, 1.6 mmol) in THF (10 mL) was added Ac$_2$O (605 µL, 6.4 mmol) and pyridine (516 µL, 6.4 mmol) at room temperature. The mixture was stirred for 12 h at the same temperature. The reaction was stopped by the addition of sat. aq. CuSO$_4$ (200 mL) and the layers were separated. The products were extracted with CHCl$_3$ (100 mL x 2). The combined organic layer was washed with brine, dried over MgSO$_4$, and concentrated in vacuo to give MonoOAc-α-CD 1 (1.7 g) in 85% yield: m.p. 240–247 °C, \[^1\text{H NMR (270 MHz, CDCl$_3$) } \delta 5.06 (d, J = 3.5 Hz, 6H), 3.90–3.16 (m, 87H), 2.07 (s, 3H), \]

**Synthesis of Polyrotaxane by Solid-State End-Capping Reaction:** MonoOAc-α-CD 1, 1.5 g, 1.2 mmol) and polytetrahydrofuran (PTHF) (M$_n$ 2000, 75 mg, 0.038 mmol) were suspended in water and sonicated for 1 h at room temperature and allowed to stand overnight at the same temperature. The resulting mixture was separated by centrifugation, washed with H$_2$O, and dried under vacuum to give pseudopolypyraxane 2 (726 mg, 100%, on the basis of PTHF). The crude material was used for next reaction without further purification: \[^1\text{H NMR (270 MHz, acetone-d$_6$) } \delta 5.03 \text{(brd, C(1)H of CD moieties), 3.86–3.03 (m, C(2–6)H and MeO of CD moieties, and PTHF), 2.18 (s, AcO), 1.61 (m, PTHF)}\]

A mixture of the crude pseudopolypyraxane 2 (600 mg, 0.019 mmol), tritylphenyl isocyanate (205 mg, 0.57 mmol) [8], and dibutylindilulate (DBTDL, 1.1 mL, 1.9 mmol) was well ground in an agate mortar at room temperature. After 30 min grinding, the resulting mixture was dissolved in CHCl$_3$ and
filtrated. The filtrate was precipitated into Et₂O to give a white solid which was dissolved in CHCl₃ and precipitated into MeOH to give the corresponding polyrotaxane as a white solid (3, 107 mg) in 43% yield. ¹H NMR (270 MHz, CDCl₃ in the presence of a catalytic amount of TFA) δ 7.37–7.06 (m, ArH of end-capping group), 5.01 (brd, C(1)H of CD moieties), 3.98–3.01 (m, C(2–6)H and MeO of CD moieties, and PTHF), 2.18 (s, AcO), 1.61 (brd, PTHF).

Synthesis of Reactive Polyrotaxane Consisting of MonoOH-α-CD (4): To a solution of the resulting polyrotaxane (3, 90 mg, 6.9 mmol) in CHCl₃ (2.0 mL) was added a solution of saturated K₂CO₃ in MeOH (2.0 mL) at room temperature. The mixture was warmed to 50 °C, stirred overnight, and concentrated in vacuo. The crude materials dissolved in CHCl₃ was filtrated through Celite® pad. The filtrate was concentrated in vacuo to give the reactive polyrotaxane with monoOH-α-CD (4, 88 mg) in a quantitative yield: ¹H NMR (270 MHz, CDCl₃ in the presence of a catalytic amount of TFA) δ 7.42–7.07 (m, ArH of end-capping group), 5.03 (brd, C(1)H of CD moieties), 3.87–2.94 (m, C(2–6)H and MeO of CD moieties, and PTHF), 1.60 (brd, PTHF).

Preparation of Reactive Polyrotaxane Consisting of MonoOH-α-CD (7) by One-pot Synthesis: MonoOH-α-CD (5, 1.2 g, 1.0 mmol) and PTHFBA (140 mg, 2.0 mmol) were suspended in water and sonicated for 30 min at room temperature. To the reacting mixture containing colorless precipitate was directly added 3.5-dimethylphenyl isocyanate (110 µl, 0.75 mmol), and the mixture was stirred for 1 h at room temperature. Colorless precipitate was separated by centrifugation and dried under vacuum. Crude product was purified by a gel permeation chromatography (GPC) and precipitation with Et₂O to yield pure polyrotaxane (7, 108 mg, M₅ = 28000, M₆/M₅ = 1.3). Coverage ratio of polyrotaxane was approximately 44% estimated by comparison of the integration of C(1)H of monoOH-α-CD and methylene proton of PTHFBA. ¹H NMR (400 MHz, CDCl₃, 298 K) δ 5.02 (brd, 6H, C(1)(H), 4.11–3.13 (m, 123H, C(2-6)H, O(2,3,6)CH₂, CH₂O of PTHF), 1.60 (m, 13H, CH₂ of PTHF) ppm. ¹³C NMR (100 MHz, CDCl₃, 298 K) δ 100.3 (C1), 100.0, 99.9, 99.7, 82.2, 81.9, 81.3 (C2), 71.3, 71.1, 70.5 (PTHF), 61.8, 58.9, 57.8, 57.7, 26.4 (PTHF) ppm, IR (KBr) 3482, 2931, 1459, 1356, 1302, 4037, 1039, 973, 857, 701, 559 cm⁻¹. Tₛδ = 55 °C, Tₛδ = 355 °C.

Preparation of polyethylene glycol mono oleylether mono carboxylic acid (OPEGCOOH, 8): To a solution of polyethylene glycol oleyl ether (OPEG, 3.5 g, 3.0 mmol) and tetramethylpiperidine N-oxide (TEMPO, 0.59 g, 3.8 mmol) in H₂O (20 mL) was added dropwise 5 w% aq. NaOCl (60 mL, 37 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 15 min. The mixture was diluted with CH₂Cl₂ and quenched by the addition of EtOH. The product was extracted with CH₂Cl₂ (x 3), and the combined organic extracts were washed with brine, dried over MgSO₄, and concentrated in vacuo. The crude materials were purified by repeated precipitation from hexane to give 8 (2.50 g, 72%, M₅ = 1200). ¹H NMR (400 MHz, CDCl₃, 298 K) δ 5.38–5.33 (m, 1H, CH=CH), 4.16 (s, 2H, OCH₂COO), 3.82–3.43 (m, 84H, OCH₂CH₂O), 2.02–1.99 (m, 4H, CH₂), 1.57 (t, J = 6.8 Hz, 2H, CH₂), 1.41–1.25 (m, 27H, CH₃), 0.88 (t, J = 6.6 Hz, 3H, CH₃) ppm, Tₛ = 22 °C.

Synthesis of graft polyrotaxane (10) utilizing OPEGCOOH (8): To a solution of polyrotaxane (7, 30 mg, 20 µmol on the basis of CD unit), 8 (220 mg, 200 µmol) and N,N-dimethylaminopyridine (DMAP, 25 mg, 200 µmol) in CH₂Cl₂ (1.0 mL) was added N-(3-dimethylaminopropyl)-N’-ethylcarbodiimide hydrochloride (EDC·HCl, 380 mg, 2.0 mmol) at room temperature. After stirring for 4 d at the same temperature, the mixture was quenched by the addition of H₂O. The product was extracted with CH₂Cl₂ (x 3), and the combined organic extracts were washed with brine, dried over MgSO₄, and concentrated in vacuo. The crude materials were purified by a gel permeation chromatography to give the graft polyrotaxane 10 (7.2 mg, 14%, M₅ = 16000). ¹H NMR (400 MHz, CDCl₃, 298 K) δ 5.38–5.33 (m, 1H, CH=CH), 5.02 (brd, 6H, C(1)H), 4.53 (s, 1H, C(5)H), 4.39 (brd, 1H, C(5)H), 4.12 (brd, 2H, CH₂COO), 4.11–3.13 (m, 123H, C(2-6)H, O(2,3,6)CH₂, CH₂O of PTHF), 2.02–1.99 (m, 4H, CH₂), 1.61 (brd, 2H, CH₂), 1.41–1.25 (m, 27H, CH₃), 0.88 (t, J = 6.6 Hz, 3H, CH₃) ppm, ¹³C NMR (100 MHz, CDCl₃, 298 K) δ 169.9, 129.8, 100.4 (C1), 100.0, 99.8, 82.4, 82.3, 82.1, 81.2 (C2), 71.5, 71.4, 71.2, 70.8, 70.5 (PTHF), 61.8, 59.0, 57.8, 31.8, 29.7, 29.6, 29.5, 29.3, 27.1, 26.4 (PTHF), 26.0, 22.6,
14.1 ppm, IR (KBr) 3512, 2926, 2861, 1759, 1655, 1560, 1459, 1370, 1301, 1252, 1111, 1041, 977, 954, 857, 703, 564 cm⁻¹, no Tₐ, Tₕ = 325 °C.

Longitudinal relaxation time measurements. $^{13}$C NMR measurements of 7 and 10 were performed to determine the longitudinal relaxation time ($T₁$) by using resonance frequencies for $^{13}$C at $\nu₁ = 75$ MHz and 100 MHz at 298 K via a conventional inversion recovery pulse sequence, $90° - \pi - 180°$, under the deuterium lock mode. The rotational correlation time ($\tau_r$) for each $^{13}$C nucleus in the polyrotaxanes was determined with the obtained $T₁$ values at different resonance frequencies according to eq. 1:

$$\frac{1}{NT₁} = \left( \frac{\mu_0}{4\pi} \right) \frac{γ^2 γ_c^2 h^2}{40π^2 r_{CH}^3} \left( \frac{τ_r}{1 + 9(ω_ττ_r)} \right) + \frac{3τ_r}{1 + (ω_ττ_r)^2} + \frac{6τ_r}{1 + 25(ω_ττ_r)^2}$$

where $N$, $μ₀$, $γ_H$, $γ_C$, $h$, and $r_{CH}$ are the number of $¹^H$ nuclei directly bound to $^{13}$C, permeability of free space ($4π \times 10^{-7}$ H·m⁻¹), gyromagnetic ratio of $H$ (2.675 x 10⁶ rad·T⁻¹·s⁻¹), gyromagnetic ratio of $^{13}$C (0.688 x 10⁶ rad·T⁻¹·s⁻¹), Planck’s constant (6.626 x 10⁻³⁴ J·s), and distance between $¹^H$ and $^{13}$C, respectively, 0.1091 nm for methylene protons of a PTHF and 0.1092 nm for C1-H and C2-H of the α-CDs. These distances were calculated by Jaguar 6.5 (Schrödinger, DFT, 6-31G**, B3LYP).

3. Results and Discussion

3.1. Synthesis of Main Chain-Type Polyrotaxane. Scheme 1 features the synthetic routes of structure-definite main chain-type polyrotaxanes via two pathways. One approach (top) involves the synthesis of polyrotaxane 4 by end-capping of the pseudopolyrotaxane 2 comprising of monoOAc-α-CD (1) and PTHF with electrophiles in the solid-state [9]. Protection of the wheel hydroxyl group by acetylation to 1 (85% yield) was followed by the complexation with PTHF ($M_n$ 2000) to produce pseudopolyrotaxane 2 (100% yield). After considerable experimental works for the end-capping reactions of 2, we turned out that the homogeneous systems in organic solvents such as DMAc were unfruitful, i.e., dethreading of the wheel components occurs at a rate much faster than the end-capping at the axle termini to afford the end-reacted PTHF without any CD moiety. We thereby subjected it to solid-state reaction. A mixture of 2, bulky isocyanate (R-NCO), and DBTDL was well ground in an agate mortar at room temperature. After 30 min grinding, polyrotaxane 3 was isolated in 43% yield as the E₂O- and MeOH-insoluble part. The $¹^H$ NMR spectrum of 3 suggests that the two terminal hydroxyl groups were completely converted to urethane groups and that the polymer had 8.2 wheels per axle on average (degree of coverage of the axle: $θ$ 56%). Although the grinding was prolonged to 90 min, neither $θ$ nor yield increased. The alkaline methanolation of 3 quantitatively yielded the structure-definite reactive polyrotaxane 4 with the hydroxyl-functionalized wheels.

The other synthetic of polyrotaxane (bottom) utilizes one-pot protocol exploiting our recent approach [10], in which monoOH-α-CD 5 and PTHFBA were used in H₂O. A mixture of 5 and PTHFBA ($M_n$ 9400, $M_w/M_n$ 1.1) in H₂O was subjected to the sonication for 30 min at room temperature to give pseudopolyrotaxane 6 as white precipitates, which was followed by the direct addition of 3,5-dimethylphenylisocyanate (5.0 equiv.) and stirring for 1 h at room temperature, yielding polyrotaxane 7 in 16% yield ($M_w$ 28000, $M_w/M_n$ 1.3, estimated by GPC based on polystyrene standards, $θ$ 44%). The structure was confirmed by $¹^H$ NMR spectrum.

3.2. Synthesis of Graft Polyrotaxane. Scheme 2 shows the synthesis of graft polyrotaxane 10. Several classical esterifications of 7 via graft-onto protocol were examined (Table 1). After many experiments, we found that this goal was achieved by exploiting OPEGCOOH 8 ($M_n$ 1300, $M_w/M_n$ 1.2) with excess amount of EDC-HCl as dehydrating agent in the presence of DMAP to allow the effective introduction of graft chains on the wheel (entry 1). The conversion yield of 10 was determined from the integral ratio of $¹^H$ NMR spectrum. When the grafting reaction was carried out at 40 °C (entry 2), the molecular weight distribution of 10 became broad probably owing to the occurrence of the partial cross-linking reaction at the olefin moieties. On the other hand, treatment of 7 bearing higher coverage ratio ($θ$ 72%) afforded the corresponding graftpolyrotaxane (10) in a low grafting conversion yield mostly due to the coverage of the reacting points (entry 3).
Solid-state Synthesis

One-pot Synthesis

Scheme 1. Two synthetic approaches to structure-definite polyrotaxanes (4 and 7).

Although OPEGCOCI 9 was also used to give 10 in a high conversion yield, the reaction needed higher temperature (40 °C) rather than the case of 8 (entry 5). The graft polyrotaxane 10 showed good solubility in various solvents such as THF, DMF, acetone, CHCl₃ and CH₂Cl₂ in contrast to polyrotaxane 7 which was soluble only in CHCl₃ and CH₂Cl₂.

Scheme 2. Synthesis of graftpolyrotaxane 10 according to the grafting-onto protocol.

| Entry | Graft Chain | Reagents | Temp. (°C) | Conversion (%) | Mₙ | Mₚ/Mₙ |
|-------|-------------|----------|------------|----------------|-----|--------|
| 1     | 8           | EDC·HCl  | RT         | 99             | 16000 | 1.9 |
| 2     | 8           | EDC·HCl  | 40         | 99             | 13000 | 6.5 |
| 3     | 8           | EDC·HCl  | RT         | 59             | 39600 | 1.8 |
| 4     | 9           | TMEDA    | RT         | 49             | 24000 | 3.4 |
| 5     | 9           | TMEDA    | 40         | 96             | 13000 | 1.9 |

a) The grafting reaction was carried out using 7 (Mₙ 19000, Mₚ/Mₙ 1.4, θ 72%).

3.3. Investigation of Rotational Behavior of the Components. Longitudinal relaxation times (T₁) measured by ¹³C NMR for 7 and 10 in CDCl₃ at 298 K provided the average time scale for molecular motions of α-CDs. In the observation of the motion of rotaxanes, it is necessary to distinguish the motion of axle polymer and α-CD components. We measured the T₁ for ¹³C of the 1 and 2-position in α-CDs and ¹³C of methylene moiety of PTHF axle by using 300 and 400 MHz NMR spectrometers. Table 2 shows the relationship between the obtained T₁ data and the resonance frequency for polyrotaxane. Curve fitting was performed on these plots by using eq. 1 to determine the rotational correlation time (τₑ) showing the molecular fluctuation. The relative movements between α-CDs and
axle polymer were estimated by $\Delta (1/\tau_c)$. The $\tau_c$ of the axle polymer was smaller than those of $\alpha$-CDs in each polyrotaxane, indicating that the relative circumrotation rates of axle polymer are faster than that of $\alpha$-CDs. Because the order of $\Delta (1/\tau_c)$ of $\alpha$-CDs and/or axle polymer in polyrotaxanes was almost same, it turned out that the wheel components on the graftpolyrotaxane maintained a rotatory capability without a lack of characteristic property of main chain-type polyrotaxane. The results revealed that the movement of the grafting polymer on the wheel components is also independent on the movement of the main chain, strongly suggesting a new type of graft polymer.

Table 2. Relative circumrotation of graftpolyrotaxane.

| Rotaxane     | $\tau_c \times 10^{11}$ (s) | $1/\tau_c$ (axle) – $1/\tau_c$ (C1) $\times 10^{10}$ (s$^{-1}$) |
|--------------|-------------------------------|---------------------------------------------------------------|
| Graftpolyrotaxane 10 | 3.40                          | 23.4, 43.0                                                   |
| Polyrotaxane 7    | 2.37                          | 41.2, 25.4                                                   |

4. Summary This paper has disclosed the synthesis, characterization, and dynamic property of graftpolyrotaxane. Grafting reaction based on the graft-onto protocol resulted in the efficient synthesis of graftpolyrotaxane from main chain-type reactive polyrotaxane possessing monofunctional wheels. The present study clearly suggested that the new type of graft polymer, graftpolyrotaxane, would enable the attachment of special characteristics to the graft polymer.

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