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High-Yield One-Pot Synthesis of Permethylated α-Cyclodextrin-based Polyrotaxane in Hydrocarbon Solvent through an Efficient Heterogeneous Reaction

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ABSTRACT: We achieved a highly efficient one-pot synthesis of permethylated α-cyclodextrin(CD)-based polyrotaxane via an initial complexation to the inclusion complex with amine-terminated polytetrahydrofuran followed by end-capping with a bulky isocyanate *in hydrocarbon solvent under heterogeneous conditions*. Among various organic solvents tested, isooctane was the best solvent, while cyclohexane yielded no polyrotaxane. Effects of the reaction temperature, the molecular weight of the axle polymer, the structures of the wheel and axle components on the yield and coverage ratio of the polyrotaxane were studied in detail. Under the optimum conditions, we obtained a 71% yield of polyrotaxane with a 67% coverage ratio when amine-terminated poly(tetrahydrofuran) (M_n 8700) reacted with permethylated α-cyclodextrin at 50 °C in isooctane. We discuss the reason for and the mechanism of the efficient reaction that occurred in the heterogeneous system from the viewpoint of the role of the solvent and the results of the solvent-free synthesis previously reported. By a similar one-pot reaction, polyrotaxane consisting of permethylated α-cyclodextrin and poly(ethylene glycol) was first synthesized. Neither native α-CD nor permethylated *β*-CD gave any polyrotaxanes when amine-terminated poly(tetrahydrofuran) was used as an axle polymer.

Introduction

A variety of main chain-type polyrotaxanes[1] consisting of cyclodextrines (CDs)[2] and linear polymers has been synthesized and applied to unique polymer materials such as stress relaxation gels,[3] gene delivery systems,[4] and many others.[5] *O*-Methylated and functionalized CDs are used to overcome the low solubility of the corresponding polyrotaxanes with native CDs in water and organic solvents and to utilize the functional groups on the CDs. On the other hand, the polyrotaxanes having functionalized CDs often suffer from remarkably low synthetic yields in the end-capping step because of instabilities of the inclusion complexes, lowered association constants of the CDs with axle polymers because of their bulkiness, and decreased hydrophilicities of the CDs.[6] However, functionality and solubility are necessary properties in material design and synthesis, convenient and efficient syntheses of polyrotaxanes with functionalized CDs have long been desired. Actually, for example, a polyrotaxane consisting of permethylated α-CD (PMαCD) as a commercially available CD and poly(tetrahydrofuran) as a typical linear polymer had never been prepared until we recently achieved its solid-phase synthesis[7] and one-pot synthesis in water.[8] From the viewpoint of the advantage and significance of such polyrotaxanes as well as the improvement in efficiency of the solid-phase synthesis, we have further studied the high-yield syntheses of polyrotaxanes consisting of PMαCD. The polyrotaxane synthesis is desired to proceed using a least amount of the CDs required, since selective functionalization and modification of CDs are generally difficult or time-consuming. In addition, organic solvent system can expand the applicability of a variety of end-capping agents in comparison with aqueous system. Recently the inclusion phenomena of modified cyclodextrine in nonpolar solvents have been reported.[9] In particular, the inclusion of arenes with *β*-cyclodextrin derivatives suggests the possibility of the synthesis of polyrotaxane in an organic solvent.[9a] Although the host behavior of PMαCD in nonpolar solvent have never been reported, we expected the synthesis of polyrotaxane on the basis of such a weak dipole−dipole interaction between PMαCD and a linear polymer. In fact, we have recently succeeded in obtaining PMαCD-based polyrotaxane in organic solvent systems. This paper describes the unprecedented synthetic protocol of a PMαCD-based polyrotaxane involving a high-yield one-pot reaction via an initial threading reaction to a pseudopolyrotaxane, and subsequent end-capping reaction in a hydrocarbon solvent under heterogeneous conditions.

Experimental Section

Materials. α-CD and PMαCD were obtained from Nacalai Tesque Inc. and used after drying at 100 °C under vacuum. Amine-terminated poly(tetrahydrofuran) (PTHFBA, M_n 1100, 6700, and 8700) and amine-terminated poly(ethylene glycol) (PEGBA, M_n 1500) were prepared according to our previous report.[8] 3,5-Dimethylphenylisocyanate was obtained from Aldrich and used without further purification. The extra pure grade reaction solvents were used as received without further purification.

Characterization. ^{1}H NMR spectra were recorded with a JEOL JNM-AL-400/WB spectrometer using either $CDCl_3$ or DMSO-d_6 as the solvent with tetramethylsilane as the internal standard. We performed analytical size exclusion chromatography with a JASCO HSS-1500 system equipped with a

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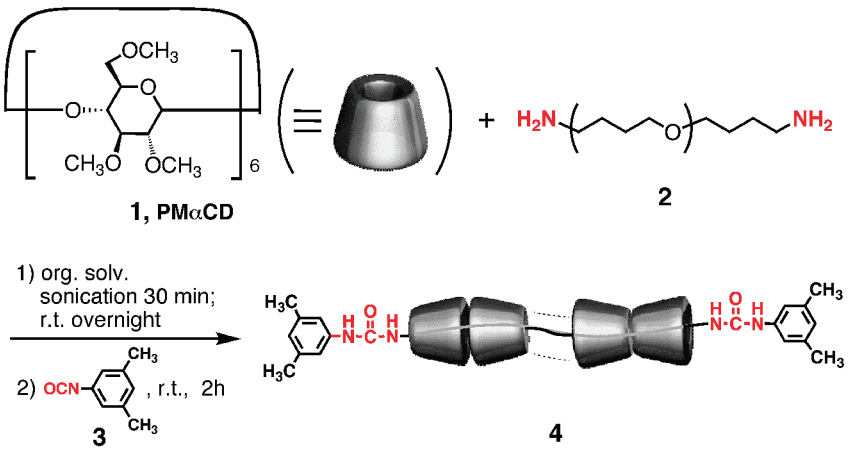
Scheme 1. One-Pot Synthesis of Polyrotaxane in an Organic Solvent System



TOHSO TSK gel G5000HXL and a TSK GMHXL eluted with chloroform at a flow rate of 0.85 mL/min, calibrated using polystyrene standards. Preparative HPLC was performed using a JAI HPLC LC-918 (columns = JASCO Megapack-Gel 201C, Megapack-Gel 201 CP, and JAI JAIGEL-1H; eluent = chloroform; flow rate = 3.5 mL/min).

Preparation of PMαCD, 1[10]**.** A solution of dried α-CD (4.9 g, 5.0 mmol) in dry DMF (80 mL) was added to a suspension of NaH (11 g, 60% in oil) in dry DMF and stirred the mixture for 2 h. A large excess of iodomethane (37 mL, 600 mmol) was added dropwise at 0 °C and then slowly warmed to ambient temperature. After stirring overnight, the reaction mixture was quenched with methanol (10 mL). The resulting mixture was extracted with toluene three times, and the combined organic layer was washed with aqueous $Na_2S_2O_3$ and brine. The organic layer was dried over $MgSO_4$, and concentrated in vacuo. The residual crude product was purified by silica gel column chromatography (hexane:acetone = 2:1; R_f = 0.18) followed by recrystallization with a hexane−acetone mixed solvent. PMαCD, **1** was obtained as a colorless powder (54%, 3.3 g, 2.7 mmol). Mp: 204−208 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 5.05 (d, 3.2 Hz, 6H, C(1)H), 3.84−3.16 (m, 123H, C(2−6)H, O(2,3,6)-CH_3) ppm.

One-Pot Synthesis of Polyrotaxanes from PMαCD and PTHFBA (Urea End-Capping Method). General Procedure. Dry PMαCD (**1**, 0.61 g, 0.50 mmol) and PTHBA (**2a**, 72 mg, 1.0 mmol (THF unit) were dissolved (suspended)) in solvent (2 mL) and the mixture was stirred for 1 day. The mixture was sonicated for 30 min at room temperature. 3,5-Dimethylphenylisocyanate (0.19 mL, 1.3 mmol) was added to the resulting mixture and stirred for 2 h at room temperature under an Ar atmosphere. The resulting mixture was quenched with methanol (1 mL) and poured into a large excess of ether; the precipitate was collected by centrifuge separation. The solid product was purified with preparative gel permeation column chromatography. Polyrotaxane **4a** was obtained as a pale yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 5.02 (br, C(1)H), 4.11−3.13 (m, C(2−6)H, O(2,3,6)CH_3, CH_2O of PTHF), 1.60 (m, CH_2 of PTHF) ppm.[8]

Synthesis of Polyrotaxane 4d from PMαCD and PTHF (Urethane End-Capping Method). General Procedure. PTHF M_n 1400 (**1d**, 72 mg, 1.0 mmol (THF unit)) instead of PTHFBA **2** was used in the presence of DBTDL (77 μL. 0.13 mmol). Other procedures were the same as those for the urea end-capping method mentioned above.

Synthesis of Polyrotaxane 4e from PMαCD and PEGBA (Urea End-Capping Method). General Procedure. PEGBA M_n1500 (**2e**, 72 mg, 1.6 mmol (ethylene glycol unit)) instead of PTHFBA **2a** was used. Other procedures were the same as those in the urea end-capping method mentioned above.

Synthesis of Polyrotaxane with PMβCD and PTHFBA. A suspension of PMβCD (0.72 g, 0.50 mmol) and PTHFBA (72 mg, 1.0 mmol (THF unit)) in isooctane (2 mL) was stirred vigorously at room temperature overnight. The mixture was subjected to sonication for 30 min and then allowed to stand overnight. To the mixture, we added tris(*p*-*tert*-butylphenyl)-methylphenyl isocyanate[11] (0.66 g, 1.33 mmol) and isooctane (2.0 mL) and stirred the resulting mixture for 2 h. The reaction mixture was quenched with methanol (1 mL), the solvent was removed under reduced pressure, and the residue purified by precipitation from diethyl ether. We did not obtain any polyrotaxane.

Results and Discussion

One-pot Synthesis of Polyrotaxane and the Effects of Organic Solvent. The one-pot synthesis of PMαCD-containing polyrotaxane in an organic solvent was performed according to Scheme 1. PMαCD, **1** and amine-terminated poly(tetrahydrofuran) **2a** (PTHFBA, M_n 1100) were prepared according to the literature methods.[8,10] Since one PMαCD molecule covers two THF units of PTHF judging from the calculated value of completely covered polyrotaxane, the stoichiometric ratio of PMαCD to PTHFBA is 1 to 2. A homogeneous or heterogeneous mixture of **1** and **2a** in an organic solvent was sonicated for 30 min after stirring it for a day at room temperature, and then allowed it to stand overnight. To the colorless mixture was added an excess amount (10 equiv) of 3,5-dimethyphenylisocyanate **3**, and the resulting mixture was stirred for 2 h. The product polyrotaxane **4a** was actually obtained, which was formed via the present urea end-capping protocol in organic solvent. This is well consistent with our previous report[8] that the combination of the primary amino groups at the axle terminal of pseudopolyrotaxane and the bulky isocyanate that provides effective end-capping in water and that results in a high yield of polyrotaxane even in a heterogeneous system.

The structure of **4a** was confirmed with spectroscopic analyses. Figure 1 shows the ^{1}H NMR spectrum of **4a** obtained in hexane (Table 1, run 6). Although the signals broadened, the spectrum mostly corresponded to the structure of **4a** as previously reported.[7,8] The large multiplet at 3−4 ppm included signals corresponding to most of the PMαCD protons and the methylene protons Ha of PTHF. Furthermore, the C(1) protons of PMαCD appeared as a broad singlet signal at 5.0 ppm. This signal was used to determine the coverage ratio of the axle of **4a** by comparing it to the integral ratio of the PTHF signal at 1.6 ppm. (The water signal was shifted from 1.6 ppm because of the addition of trifluoroacetic acid.)

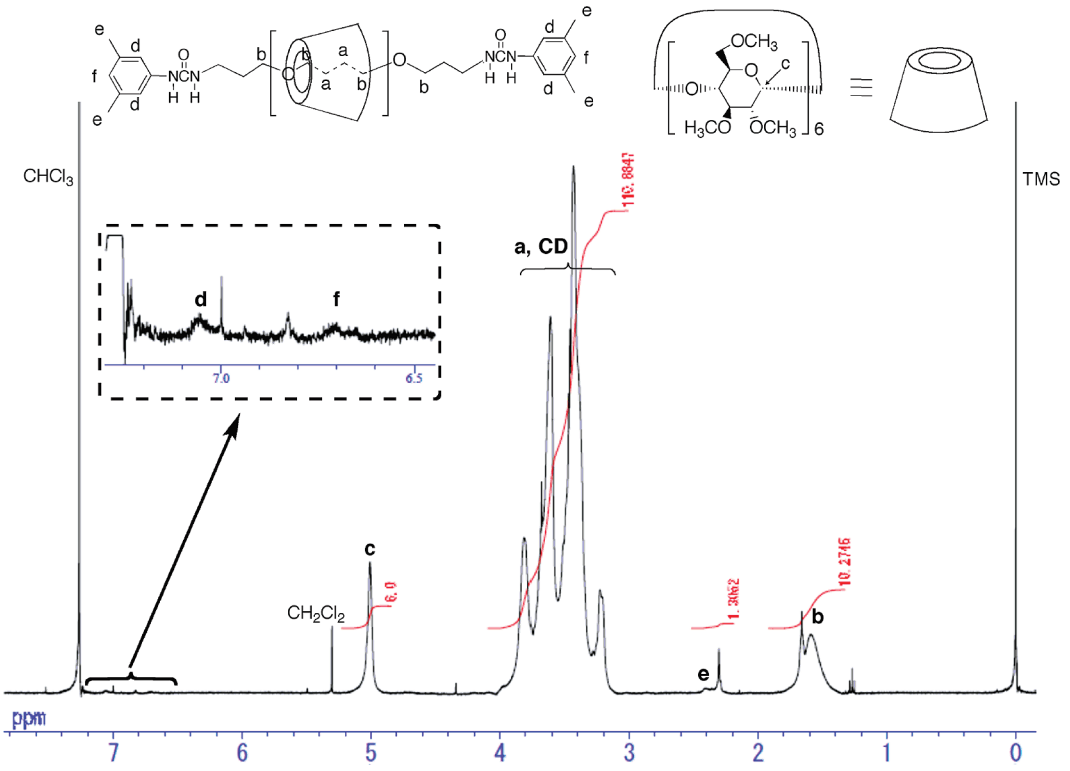


Figure 1. ^{1}H NMR spectrum of polyrotaxane **4a** (Table 1, run 6) ($CDCl_3$, 400 MHz, 298 K, in the presence of a small amount of trifluoroacetic acid). The spectrum was consistent with that of **4a** obtained from a one-pot synthesis in water.[8]

Table 1. Effect of the Solvent on the Synthesis of Polyrotaxane 4a[a]

				yield of 4a			
run	solvent	ε[b]	N_D[b]	(mg)	(%)[c] (axle)	(%)[d] (wheel)	coverage ratio (%)[e]
1	DMF	37	27	8	2	1	65
2	diethyl ether	4.2	19	14	3	2	77
3	acetonitrile	36	14	21	4	3	70
4	DMSO	46	30	31	6	4	74
5	methanol	33	19	42	11	6	51
6	hexane	1.9		132	23	19	82
7	water	79	18	105	17	15	90

[a] Substrates, reagents, and conditions: PMαCD (**1**) (0.5 mmol, 0.61 g), PTHFBA **2a** (M_n 1100, 1.0 mmol/THF unit, 72 mg), solvent (2 mL), and 3,5-dimethylphenylisocyanate **3** (1.3 mmol, 0.19 mL), room temperature, 2 h. [b] ε is the relative dielectric constant, while N_D is the donor number of solvent. [c] Yield calculated on the basis of the weight of axle component used. [d] Yield based on the amount of PMαCD incorporated in **4a**. [e] Determined by ^{1}H NMR. Coverage ratio: percent ratio of covered length of axle polymer chain on the basis of the complexation ratio (2 PTHF repeating units per PMαCD).

The signals of the end-cap group clearly had a reasonable ratio to the methylene signal of PTHF at 6.7 and 7.1 ppm. As the NMR spectra confirmed the purity of **4a**, the possible contamination of pseudopolyrotaxane can be ruled out to indicate its successful removal by the reprecipitation and preparative GPC. In addition to the ^{1}H NMR results, the GPC results also supported the proposed polyrotaxane structure of **4a** as discussed below.

Table 1 summarizes the effects of the organic solvent on the yield and the coverage ratio of **4a** as well as the solvent parameters. We obtained polyrotaxane **4a** with a similar treatment in 2−23% yields (on the basis of PTHFBA) that clearly depended on the type of solvent employed. The yield on the basis of PMαCD was also listed in Tables for easy understanding. Although the yields were not high, **4a** was actually obtained from a complete heterogeneous system in various organic solvents. That is, not only the threading of the axle PTHFBA to PMαCD to pseudopolyrotaxane but also its end-capping with a bulky isocyanate proceeded with high efficiency. As a result hexane, a nonpolar solvent, was the best solvent among those tested (23%, Table 1). This value was higher than that in water (17%).[8] The coverage ratio was in a range of 51−90% as calculated by the integral ratio of C(1)H of PMαCD (5.0 ppm) and CH_2 of PTHF (1.59 ppm) from the ^{1}H NMR spectrum of **4a** (Figure 1), suggesting that the different solvents directly affected the yields. For DMF, diethyl ether, DMSO, methanol, and water, all of which were capable of dissolving the starting materials to some extent, the yields and coverage ratios were lower than those of hexane. Acetone, nitromethane, ethyl acetate, and dichloromethane, which are not listed in Table 1, yielded no polyrotaxane. These results indicated that neither protic nor aprotic polar solvents were effective—in contrast to the results previously reported for the aqueous synthesis of polyrotaxane.[12−14] Neither the dielectric constant nor the donor number were indicative of the yield of **4a**. Because no clear solvation of the starting materials such as PMαCD and PTHF occurs in hexane (a nearly completely heterogeneous system), the weak interaction and aggregation force between PMαCD and PTHF seems to play an important role.

Table 2. Effects of Hydrocarbon Solvents on the Synthesis of 4a[a]

		yield of 4a			
run	solvent	(mg)	(%) (axle)[b]	(%) (wheel)[c]	coverage ratio (%)[d]
1	cyclohexane	0	0		
2	2,2-dimethylbutane	67	13	9	70
3	hexane	132	23	19	82
4	2-methylpentane	140	25	20	79
5	isooctane	157	29	23	78
6	wet isooctane (1 wt %)	110	26	15	58

[a] Substrates, reagents, and conditions: **1** (0.5 mmol, 0.61 g), **2a** (M_n 1100, 1.0 mmol/THF unit), 72 mg), solvent (2 mL), and **3** (1.3 mmol, 0.19 mL), room temperature, 2 h. [b] Yield calculated on the basis of the weight of axle component used. [c] Yield based on the amount of PMαCD incorporated in **4a**. [d] Determined by ^{1}H NMR. Coverage ratio: percent ratio of covered length of axle polymer chain on the basis of the complexation ratio (2 PTHF repeating units per PMαCD).

The dispersion force might have been another reason for this response in comparison with those of the solid-phase system.[7] However, the exact reason was not clear.

Effects of Hydrocarbon Solvents. Because of the favorable result from the use of hexane as a solvent, a similar one-pot synthesis was performed using several saturated hydrocarbon solvents. All the reaction systems seemed completely heterogeneous, judging from the formation of white slurry during the initial pseudorotaxanation after mixing **1** and **2a** as well as the fact that none of the hydrocarbon solvents were polar enough to dissolve either **1** or **2a**. Furthermore, the initial heterogeneous system was not altered by the addition of the end-capping agent **3**. Table 2 summarizes the results of the syntheses of **4a** with several different hydrocarbon solvents, including cyclic and branched hydrocarbons, as typical hydrocarbon solvents.

Polyrotaxane **4a** was obtained in good yield in every case except when we used cyclohexane as the solvent, in which it yielded no product. That was considered isooctane provided the highest yield of **4a**, up to 29%, which was 1.7 times more than that obtained in an aqueous system.[8] Although the coverage ratio did not depend on the solvent structure, the yields moderately tended to increase as the branching of the hydrocarbon solvents increased.

The present specific effectiveness of the hydrocarbon solvents could not be simply accounted for, i.e., by the simple solvent effect. What was the driving force for the efficient penetration between PMαCD and the axel polymer even in a heterogeneous system? As mentioned above, effective solvation of such polar substrates with hydrocarbon solvents seemed impossible because the system was heterogeneous; we might explain the present phenomena by assuming a similar mechanism to that of the solid-state synthesis of polyrotaxanes reported recently.[7] That is, the solid-state reaction proceeds by the press-grinding of a mixture of PMαCD and a poly(tetrahydrofuran) like **2**, wherein the crystalline state is destroyed by press-grinding to make the solid−solid reaction possible. In the present heterogeneous system, hydrocarbon solvent as a poor solvent could have promoted the aggregation of the substrate mixture due to its weak solvation power, and it could also have assisted the likelihood and progress of the reaction by destroying the crystal structure on the solid surface. Unlike the homogeneous system, the threading of the axle polymer to PMαCD would not achieve an equilibrium; therefore, we obtained the product pseudopolyrotaxane in a high yield. The large entropy loss resulting from the complexation could have been supplied by thermodynamic stabilization. On the other hand, solvation stabilizes each molecule in a homogeneous system. Therefore, the aggregation force was extremely weak. If PMαCD statistically penetrates, the penetrated complex is not stable enough to keep its structure because of the absence of thermodynamic stabilization. Because cyclohexane is likely to be encapsulated into PMαCD according to the CPK model study, cyclohexane might strongly block the penetration of PTHFBA **2** to eventually prevent the formation of pseudopolyrotaxane.

To examine the effects of moisture and water, we added 1 wt % of H_2O to the isooctane system. The results showed a coverage ratio (58%) lower than that of the dry condition (78%), but the yield (26%) was almost the same as that of the dry condition (29%) (Table 2, runs 5 and 6). Although the difference in the axle-based yields seems small at a glance, the yields calculated on the basis of the amount of wheel PMαCD incorporated in **4a** suggest the significant yield decrease (23% to 15%). In comparison to the results of the synthesis in water (Table 1, run 7), the yield was high, but the coverage ratio was fairly low. Thus, we conclude that a small amount of water did not affect the formation of the inclusion complex. However, the end-capping agent was not very stable in the presence of water; therefore, the decreased concentration of the end-capping agent seemed to be the main reason for the low coverage ratio. From another point of view, this result suggested that we might control the coverage ratio without seriously decreasing the yield by controlling the moisture concentration in the system.

Effects of Temperature and Molecular Weight of the Axle Polymer. We investigated the optimum conditions using isooctane, which gave the best results among the hydrocarbon solvents tested, as well as the effects of the molecular weight of the axle polymer **2**. Table 3 summarizes the results.

The effects of temperature were quite significant. The yield of **4a** gradually increased with increasing temperature and reached 65% at 90 °C in a heated heterogeneous mixture of PMαCD, **1**, and PTHFBAs (**2a**, M_n 1100) (runs 1−4). (Some yellow coloring was observed at 90 °C.) We did not confirm any effects at lower temperatures (run 2). Meanwhile, the effects of molecular weight of he axle polymers were examined with two higher molecular weight PTHFBAs. The yields of **4b** and **4c** increased up to 54% (**2b**, M_n 6700) and 60% (**2c**, M_n 8700), respectively, even at room temperature (Table 3, runs 4 and 5). The enhanced yields with the use of a higher molecular weight axle polymer (runs 6−8) was consistent with previously reported results.[8,15] Furthermore, we discovered that the yield increased unusually (up to 71%) with a higher molecular weight of the axle polymer **2c** and higher temperature (50 °C) (run 8). However, the reaction at 90 °C did not afford such a high yield of **4c** (M_n 8700). This could be attributed to the increased aggregation of the axle polymer due to the low-solvation power of isooctane. Both the yield and coverage ratio of **4** increased well at higher temperatures in every case in Table 3. It is well-known that a shorter axle polymer (e.g., **2a**) yields a higher coverage ratio in comparison with a longer axle polymer (e.g., **2c**) because the center portion of the longer axle cannot be covered with the CD wheel.

Table 3. Effects of Temperature and M_n of PTHFBA on the Synthesis of 4 in Isooctane[a]

			yield of 4				
run	PTHFBA, M_n[b]	temp (°C)[c]	**4**	(mg)	(%) (axle)[d]	(%) (wheel)[e]	coverage ratio (%)[f]
1	**2a**, 1100	room temp	**4a**	139 (±18)[g]	28 (±1)[g]	20 (±3)[g]	70 (±8)[g]
2	**2a**, 1100	−10	**4a**	134 (±22)[g]	29 (±3)[g]	19 (±1)[g]	65 (±4)[g]
3	**2a**, 1100	50	**4a**	352	55	51	93
4	**2a**, 1100	90	**4a**	415	65	60	93
5[h]	**2a**, 1100	room temp	**4a**	51[h]	50[h]	36	72[h]
6	**2b**, 6700	room temp	**4b**	262	54	32	60
7	**2c**, 8700	room temp	**4c**	264	60	37	61
8	**2c**, 8700	50	**4c**	341	71	48	67

[a] Substrates, reagents, and conditions: **1** (0.5 mmol, 0.61 g), **2** (1.0 mmol/THF unit, 72 mg), solvent (2.0 mL), and **3** (1.3 mmol, 0.19 mL), 2 h. [b] M_n of **2**. [c] Reaction temperature during the end-capping process. [d] Yield calculated on the basis of the weight of axle component used. [e] Yield based on the amount of PMαCD incorporated in **4a**. [f] Determined by ^{1}H NMR. Coverage ratio: percent ratio of covered length of axle polymer chain on the basis of the complexation ratio (2 PTHF repeating units per PMαCD). [g] Average value. [h] Excess wheel condition: **1** (0.5 mmol, 0.61 g), **2** (0.2 mmol/14 mg), solvent (2 mL), and **3** (1.3 mmol, 0.19 mL), 2 h.

Table 4. Effects of the Structures of the Axle Polymer and the CD Wheel on the Synthesis of Polyrotaxane in Isooctane[a]

					product and yield				
run	wheel	axle polymer	M_n	temp[b]	**4**	(mg)	(%) (axle)[c]	(%) (wheel)[d]	coverage ratio (%)[e]
1	PMαCD , **1**	PTHFBA, **2a**	1100	room temp	**4a**	139[f]	28[f]	20[f]	70[f]
2	**1**	PTHF, **2d**	1400	room temp	**4d**	48	11	7	62
3	**1**	PEGBA,[g] **2e**	1500	room temp	**4e**	18	5	2	46
4	PMβCD[h]	**2a**	1100	room temp	**4f**	0			
5	α-CD	**2a**	1100	room temp	**4g**	0			

[a] Substrates, reagents, and conditions: wheel (0.5 mmol), axle polymer (1.0 mmol/THF unit), solvent (2 mL), and **3** (1.3 mmol, 0.19 mL), 2 h. [b] Reaction temperature during the end-capping process. [c] Yield calculated on the basis of the weight of axle component used. [d] Yield based on the amount of PMαCD incorporated in **4a**. [e] Determined by ^{1}H NMR. Coverage ratio: percent ratio of covered length of axle polymer chain on the basis of the complexation ratio (PTHF repeating units per PMαCD). [f] Average value. [g] Poly(ethylene glycol) bisamine-terminated (PEGBA) (1.6 equiv/EG unit, 1 CD covers 3.3 units of PEG). [h] Tris(*p*-*tert*-butylphenyl)methylphenyl isocyanate (1.3 mmol, 0.66 g) was used instead of **3**.

Two factors controlling the yield and coverage ratio were identified in this system. One was temperature, and the other was the molecular weight of the axle polymer. We might expect the composition of **1** and **2** at the initial stage, i.e. the pseudopolyrotaxane formation, to be maintained at the second stage, i.e. the polyrotaxane formation, by fixation via the end-capping with **3**, because of the one-pot reaction under heterogeneous conditions. If this were true, both the final yield and the final coverage ratio would have reflected those of the pseudopolyrotaxanation step.[8] Although the higher temperature generally moves the threading equilibrium to the entropically favorable side—the dethreading side of the axle polymer, especially in a homogeneous system—, the present end-capping reaction favors higher temperatures because the yield and the coverage ratio of **2a** dramatically increased to 55% and 93% at 50 °C from 28% and 70% at room temperature (runs 1 and 3). The formation of pseudopolyrotaxane certainly reaches equilibrium in solution, but in this case, the dethreading would be somewhat suppressed due to the heterogeneous system, which can be regarded as a pseudosolid-state system. Therefore, the enhanced yield and coverage ratio can be attributed to the enhanced reaction rate of the axle termini of the pseudorpolyrotaxane with isocyanate **3** at higher temperatures, probably without accompanying its decomposition. In addition, the partial dissolution of the aggregates at higher temperatures may have occurred in this case.

Effects of the Axle Polymer and Its Terminal Functional Groups. To clarify the effects of the structures of axle polymer **4** and PMαCD wheel **1**, a few axle polymers and CDs were examined in the isooctane system (Table 4). When PTHF (M_n 1400, **2d**) was used instead of PTHFBA (**2a**) along with DBTDL (0.13 mL) as a catalyst, the corresponding polyrotaxane **4d** was actually isolated; however, the yield was low (11%, Run 1). A more electrophilic end-capping agent than **3** would be required to react with the OH group at the sterically hindered axle termini of pseudorotaxane in a none polar solvent like isooctane even in the presence of a Lewis acid. Meanwhile, axle polymer PEGBA (**2e**) afforded the corresponding polyrotaxane **4e**, the first polyrotaxane consisting of a PEG axle and PMαCD wheel, but neither the yield nor the coverage ratio were high (run 3). Whereas PEG is often used for the synthesis of polyrotaxanes with native α-CD, the synthesis of polyrotaxane from PMαCD and PEG has never been accomplished so far. The reason seemed to be either the low solubility of PEGBA and mismatch of the distance between the ether oxygen atoms of PEG and the inner interaction site of PMαCD, which is longer than native α-CD in size. As described in our previous report,[8] the hydrophilic polymers such as PEG could not effectively form inclusion complexes with PMαCD in aqueous solutions. In the present system (run 3), it was also unfavorable for PMαCD to form inclusion complexes with PEG in isooctane.

To examine the effects of the wheel component, permethylated β-CD (PMβCD) and native α-CD were used in the isooctane system, but they did not yield the corresponding polyrotaxane. Therefore, the combination of PMβCD and PTHF essentially had little interaction to form the inclusion complex. The reaction of native α-CD and PHFBA was not examined due to the purification problem.

Inspection of the data of Table 4 suggests that both the wheel and axle components, in addition to an effective attractive interaction between them, are required to hold some affinity to the solvent to obtain the corresponding polyrotaxane under the present conditions.

Conclusion

The present study has demonstrated the preparation of CD-containing polyrotaxanes in a nonaqueous heterogeneous system, especially in a hydrocarbon solvent. PMαCD-based polyrotaxane was obtained in high yields up to 71% by the one-pot reaction involving initial threading of the inclusion complex as

pseudopolyrotaxane, followed by end-capping to form polyrotaxane in isooctane. Because the addition of small amounts of water did not improve the yield of polyrotaxane, hydrophilic/hydrophobic interactions did not function as the main attractive interaction in this system. The almost heterogeneous reaction system suggested that the reaction occurred via a mechanism similar to that of the solvent-free reaction that we recently reported,[7] and could thereby be regarded as a quasi-solid-phase synthesis; although, the inclusion of solvent in PMαCD might also be important. In other words, the present organic solvent-assisted one-pot system can be considered a sophisticated system, replacing *air as the medium* in the solid-state synthesis with an *organic solvent* with a density larger than that of air by an amount significant enough to enhance the mixing efficiently. The present protocol can be applied to the syntheses of a variety of functionalized polyrotaxanes with modified cyclodextrines.

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