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Catalyst- and Solvent-Free Click Synthesis of Cyclodextrin-Based Polyrotaxanes Exploiting a Nitrile *N*-Oxide

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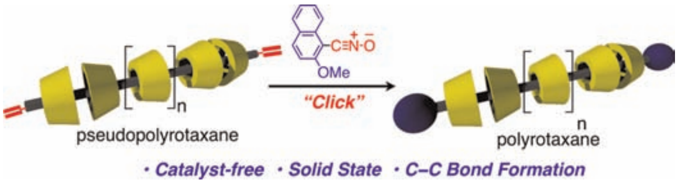
ABSTRACT



A catalyst- and solvent-free synthesis of cyclodextrin-based polyrotaxanes exploiting a stable nitrile *N*-oxide as an end-capping agent was achieved. The C−C bond-forming end-capping reaction of an allyl-terminated pseudopolyrotaxane with the nitrile *N*-oxide proceeded smoothly by solid-state grinding in a mortar to afford a polyrotaxane.

Main chain-type polyrotaxanes (PRXs) consisting of cyclodextrin (CD) as the wheel component have attracted much interest in various fields, such as supramolecular and polymer chemistry,[1] since Harada's original report.[2] Polyrotaxanes can be obtained by an end-capping reaction of the corresponding pseudopolyrotaxane (PPRX) with a bulky end-capping agent.[3] However, the end-capping method is difficult owing to the inclination of the axle to dethread from the wheel. Therefore, amine-terminated polymers have long been employed as axles of PPRXs with both CD and permethylated α-CD (PMα-CD) wheels to enable rapid and efficient end-capping.[2a,4]

We have previously disclosed a solid-state end-capping method for PPRXs consisting of PMα-CD and a hydroxyl-terminated linear polymer. This method is executed by solid-state grinding of a mixture of the PPRX and a bulky isocyanate in the presence of a Lewis acid to induce urethane formation.[5] This method is simple, economical, practical for manufacturing purposes, and widely applicable to various polymers, in contrast to methods requiring amine-terminated polymers. However, native α-CD is not

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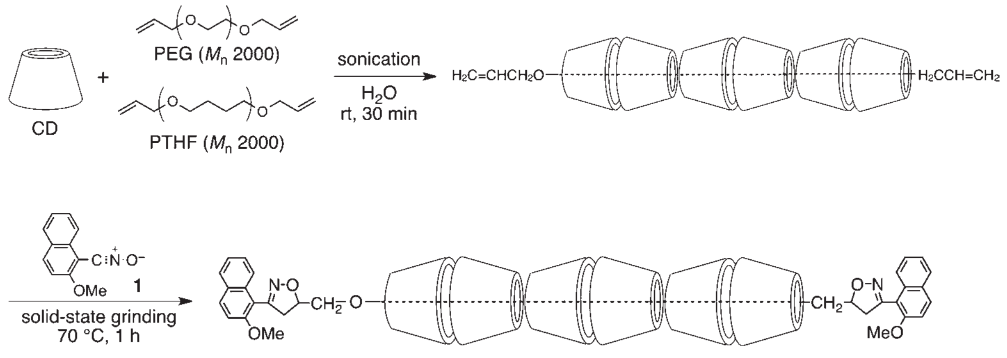
Table 1. Synthesis of PRXs with Native α-CD and PMα-CD Exploiting Nitrile *N*-Oxide **1** as an End-Capping Agent[a]



entry	CD	axle polymer ($M_n \times 10^{-3}$)	nitrile *N*-oxide **1**/equiv	product	yield/%[b]	coverage ratio/%[c]
1	α-CD	PEG (2.0)	10	**PRX1**	40	98
2	α-CD	PEG (2.0)	5	**PRX1**	36	100
3	α-CD	PEG (2.0)	2.5	**PRX1**	20	75
4	α-CD	PTHF (2.0)	5	**PRX2**	48	13
5	PMα-CD	PEG (2.0)	5	**PMPRX1**	2	63
6	PMα-CD	PTHF (2.0)	5	**PMPRX2**	28	35

[a] The threading reaction was carried out by sonicating an allyl-terminated axle polymer with α-CD or PMα-CD at room temperature for 30 min and subsequently stirring the mixture overnight. The resulting PPRX precipitate was filtered and dried in vacuo overnight. The end-capping reaction of PPRX with **1** was performed by solid-state grinding in a mortar at 70 °C for 1 h. [b] The yield was calculated on the basis of the amount of the axle component. [c] The coverage (%) was calculated from the ratio of the NMR integrals of the wheel and axle using the following complexation ratios: 2.0 PEG repeating units per α-CD, 2.7 PEG repeating units per PMα-CD, 1.5 PTHF repeating units per α-CD, and 2.0 PTHF repeating units per PMα-CD.

amenable to the solid-state method owing to the troublesome side reaction in which the hydroxyl groups of α-CD undergo urethane formation by reaction with the isocyanate.

Furthermore, we have also developed an effective synthesis of [2]rotaxanes consisting of a crown ether and *sec*-ammonium salt via 1,3-dipolar cycloaddition. This method exploits a kinetically stabilized nitrile *N*-oxide[6] for the end-capping reaction, which is accomplished in the absence of any catalyst.[7] The use of the kinetically stabilized nitrile *N*-oxide as the end-capping agent enabled the catalyst-free, chemoselective, and high-yield synthesis of [2]rotaxanes from pseudorotaxanes bearing unsaturated bonds, such as C═C, C≡C, and C≡N groups at the axle terminus.

Herein, we report that the click end-capping method using the stable nitrile *N*-oxide with CD-based PPRXs worked efficiently for the synthesis of α-CD- and PMα-CD-containing PRXs. We have further elucidated that the click end-capping method enables the manufacture of byproduct-free PRXs in which catalyst- and solvent-free conditions are applied throughout the process including both the threading and end-capping reactions.

Table 1 shows the synthesis of PRXs via 1,3-dipolar cycloaddition of kinetically stabilized nitrile *N*-oxide **1** to an allyl-terminated axle polymer. The stable nitrile *N*-oxide **1** was prepared from commercially available 2-hydroxy-1-naphthaldehyde according to the literature.[6a] The PPRX consisting of α-CD as the wheel and allyl-terminated PEG (M_n 2000) as the axle was prepared from a mixture of these components in H_2O by sonication. We have previously reported that the reaction rate of the 1,3-dipolar cycloaddition of nitrile *N*-oxides to dipolarophile-containing polymers is remarkably accelerated by employing a solid-state process.[8e,f] As a first attempt, a solid mixture of **1** (10 equiv) and PPRX in a mortar was well ground in the absence of any catalyst for 1 h at 70 °C to afford a pale yellow solid. After washing the solid with H_2O and THF to remove unreacted CD, the axle polymer, and **1**, we found that the solid-state grinding afforded **PRX1** as a H_2O- and THF-insoluble part. The yield was 40% from the axle polymer, and the coverage ratio was 98% (entry 1), which was calculated from the ratio of the

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Table 2. One-Pot Synthesis of PRXs with Native α-CD and PMα-CD under Solvent-Free Conditions[a]

entry	CD	axle polymer ($M_n \times 10^{-3}$)	nitrile *N*-oxide **1** /equiv	product	yield/%[b]	coverage ratio/%[c]
1	α-CD	PEG (2.0)	5	**PRX3**	20	26
2	α-CD	PTHF (2.0)	5	**PRX4**	14	34
3	PMα-CD	PEG (2.0)	5	**PMPRX3**	61	26
4	PMα-CD	PTHF (2.0)	5	**PMPRX4**	37	72

[a] The threading reaction was carried out by a solid-state process using allyl-terminated axle polymers with α-CD or PMα-CD at room temperature for 30 min. The nitrile *N*-oxide **1** (5 equiv) was directly added to the mixture and ground in a mortar at 70 °C for 1 h. [b] The yield was calculated on the basis of the amount of the axle component used. [c] The coverage (%) was calculated from the ratio of the NMR integrals of the wheel and axle using the following complexation ratios: 2.0 PEG repeating units per α-CD, 2.7 PEG repeating units per PMα-CD, 1.5 PTHF repeating units per α-CD, and 2.0 PTHF repeating units per PMα-CD.

^{1}H NMR integrals of the wheel and axle components by assuming that one α-CD molecule is threaded onto 2.0 repeating units of PEG. Notably, the 1,3-dipolar cycloaddition reaction of the nitrile *N*-oxide to terminal olefins proceeded chemoselectively in the presence of the alcohols on CD in spite of the solvent-free conditions. As shown in entries 1–3, PRXs were preprared using different equivalents of **1** in which the corresponding **PRX1** was similarly obtained. Both the yield and coverage ratio of entry 3 were slightly lower than those of entries 1 and 2, in which the PEG chains were completely covered with α-CD. From these results, we concluded that the use of 5 equiv of **1** was sufficient for completion of the end-capping reaction. The other PRXs were similarly prepared, as listed in entries 4–6.

When allyl-terminated PTHF (M_n 2000) was employed as the axle polymer, **PRX2** was obtained in 48% yield (entry 4). Next, the synthesis of PRXs consisting of PMα-CD was investigated. The use of PEG afforded a very low yield of **PMPRX1** (2%, entry 5), although the combination of PTHF with PMα-CD gave **PMPRX2** in 28% yield (entry 6). The yield and coverage ratio of all PRXs obtained in Table 1 would be probably dependent on the solubility of the intermediary PPRX in water.

Figure 1 shows the ^{1}H NMR spectrum of **PRX1** in DMSO-d_6, together with those of allyl-terminated PEG and **1** in $CDCl_3$. In spectrum c, the signals originating from the α-CD, PEG, and the skeleton of **1** along with the disappearance of the olefinic signals of the axle polymer are in good accordance with the structure of **PRX1**.

The IR spectrum of **PRX1** indicates the absence of the characteristic peak of a nitrile *N*-oxide around 2200 cm^{-1}.[9] The structure of **PRX1** was also confirmed by X-ray powder diffracton (XRD). The XRD pattern showed a main crystalline peak at $2\theta = 20°$ attributed to the channel structure of α-CD,[2a] strongly indicating the threading structure of **PRX1** into the CD cavities.[9] These results clearly suggest that the solid-state 1,3-dipolar cycloaddition of **1** to terminal olefins successfully afforded **PRX1**.

To establish an all-solid-state process, solvent-free conditions for the preparation of PPRX were incorporated into the procedure according to previous reports,[5] as summarized in Table 2. A mixture of CD and an allyl-terminated polymer was ground in a mortar for 1 h at room temperature in the absence of solvent. To the resulting solid product, **1** was directly added and the mixture was ground for 1 h in the same mortar at 70 °C. The results show the feasibility of the all-solid-state process for the PRX synthesis. In fact, the combination of α-CD and PEG gave **PRX3** in 20% yield. Moreover, a combination of PTHF with α-CD under the present conditions also afforded the corresponding polyrotaxane **PRX4** with a higher coverage ratio (34%) than that obtained in the aqueous system in Table 1 (entry 2, 14% yield).

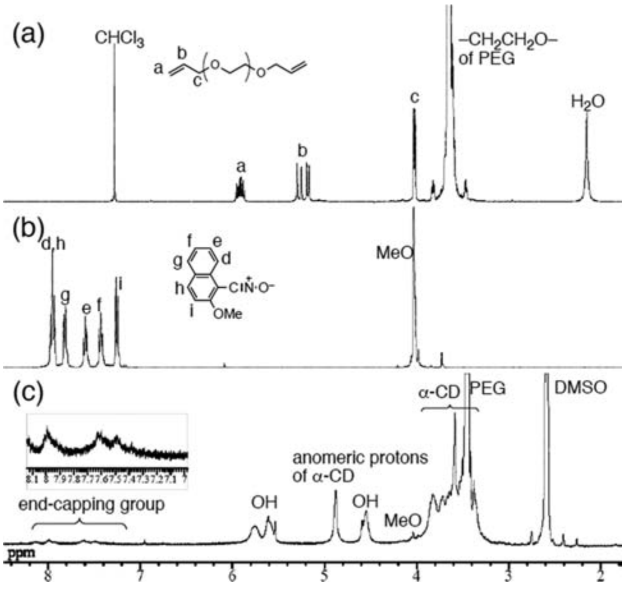

Figure 1. ^{1}H NMR spectra of (a) allyl-terminated PEG in $CDCl_3$, (b) **1** in $CDCl_3$, and (c) **PRX1** in DMSO-d_6 (400 MHz, 298 K).

Next, we investigated the synthesis of PMα-CD-based PRXs. Surprisingly, the combination of PMα-CD with either PEG or PTHF as the axle polymer afforded the corresponding **PMPRX3** and **PMPRX4** (entries 3 and 4), respectively, in higher yields than those reported in Table 1 for **PMPRX1** and **PMPRX2**.[4f,5b] The results emphasize

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(9) See Supporting Information.

the advantages of the all-solid-state process for the synthesis of the PMα-CD-based PRXs on the basis of not only the high reaction efficiency of the threading reaction under solid state but also the certain applicability to the water-soluble PPRX intermediates. The structures of these PRXs were estimated by ^{1}H NMR and IR and were ultimately confirmed by size-exclusion chromatography (SEC) analysis. The ^{1}H NMR spectra of the PRXs showed the existence of PMα-CD and the polymer axle as broadened signals,[9] which was probably due to structural disorder related to the directions of PMα-CD in the PRXs in addition to the slow motion of the polymer in solution relative to the NMR time scale. On the other hand, we found that the SEC profiles of **PMPRX3** and **PMPRX4** clearly indicate the formation of the polyrotaxane structure, because each peak of the PRXs appeared in a region of higher molecular weight than those of PMα-CD and PTHF.[9]

As for the XRD patterns of **PMPRX3** and **PMPRX4**, the main crystalline peak is observed at positions that are different ($2\theta = 8.4°$) from those of PMα-CD itself and α-CD-based PRX. The value was in good agreement with that reported by Ito et al. ($2\theta = 8.7°$).[10]

We also examined the synthesis of PRXs consisting of β-CDs and PPG using the same procedure. However, the reaction did not yield the corresponding PRX. This can probably be attributed to the low efficiency of PPRX formation in the absence of water and/or the favorable formation of an inclusion complex between naphthalene skeleton **1** and β-CD, thereby decreasing the reactivity of the nitrile *N*-oxide.[11]

In conclusion, the present click end-capping method utilizing the 1,3-dipolar cycloaddition reaction of a nitrile *N*-oxide to terminal olefins features the following characteristics in contrast to the Huisgen reaction-based click chemistry:[12] (i) catalyst-free conditions, (ii) byproduct-free results, (iii) chemoselective reaction even in the presence of alcohols, (iv) solvent-free conditions for each step of the process, and (v) favorable C–C bond formation. Such features afford a simple and powerful synthetic method for the preparation of versatile CD-based PRXs. Further studies directed toward the synthesis of new types of PRXs consisting of unprecedented axle polymers such as vinyl polymers or condensation polymers are currently underway.

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Supporting Information Available. Full experimental details for all new compounds are provided, including ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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