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SHORT COMMUNICATIONS

# Solvent-Free Synthesis of Unmodified Cyclodextrin-Based Pseudopolyrotaxane and Polyrotaxane by Grinding

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Harada *et al.* first reported that cyclodextrin (**CD**)-polymer complexes as pseudopolyrotaxanes are formed between **CD**s and linear polymers such as poly(ethylene glycol) (**PEG**),[1] poly(tetrahydrofuran) (**PTHF**),[2] and poly(propylene glycol)[3] in aqueous solution. Recently, Harada *et al.* have found the formation of self-assembled tubular complexes by mixing **CD**s and solid polymers such as **PEG** and **PTHF** without solvent.[4] Tonelli *et al.* have reported the formation of inclusion compounds by mixing of low-molecular-weight liquid **PEG** and **α-CD** without solvent.[5] Solvent-free reactions have various advantages such as simple economical processes without recovery, storage, and disposal of solvent, being compatible to green chemistry.[6] Solid-state reactions[7] activated by grinding or milling are known to often cause mechanochemical reactions.[8] Takata *et al.* have recently disclosed the solid-state end-capping method of pseudopolyrotaxnae to polyrotaxane consisting of permethylated cyclodextrin (**PMCD**) and **PTHF** by simple grinding in a mortar.[9] While **PMCD** as the wheel component[10] is easy and convenient to use due to the protected OH groups, use of unmodified **CD** seems quite advantageous from viewpoint of potential application of polyrotaxane using the OH functionality. It is expected some difficulty, however, in solvent-free end-capping of unmodified **CD**-based pseudopolyrotaxane because of the reactive OH groups. Recently we have first succeeded in preparing polyrotaxane bearing unmodified **CD**s by solvent-free threading of linear polymer into wheel components to pseudopolyrotaxane and successive end-capping of it by simple grinding, which are described in this paper.

## EXPERIMENTAL

### *Materials and Methods*

α-Cyclodextrin (**α-CD**) was purchased from Nacalai Tesque Inc. Bis(3-aminopropyl)-terminated polytetrahydrofuran (**APTHF**) ($M_n = 1100$), 3,5-dinitrobenzoyl chloride (**DNBC**) (>98%), and 2,4-dinitrofluorobenzene (**DNFB**) (100%) were purchased from Aldrich. Water was used after deionization by ion-exchange resin.

$^1$H NMR spectra were recorded on a JEOL GSX-400 NMR spectrometer operating at 400 MHz with tetramethylsilane as an internal standard. IR spectra were obtained with a JASCO FT/IR-460 Plus spectrometer. UV-vis spectra were measured by a JASCO Ubest V-550 spectrophotometer. Powder X-ray diffraction patterns were taken by CuKα irradiation with a Rigaku X-ray diffractometer (voltage, 30 kV; current, 100 mA; scanning speed, 3°/min).

### *A Typical Procedure for Preparation of Pseudopolyrotaxane (**PPRX**) in Aqueous Solution*[3]

To a solution of **α-CD** (2.92 g, 3.00 mmol) in water (25 mL) was added bis(3-aminopropyl)-terminated polytetrahydrofuran (**APTHF**, $M_n$ 1100, 302 mg, THF unit 4.20 mmol). The resulting suspension was sonicated for 30 min at room temperature. The milky mixture was allowed to stand overnight, and the precipitate formed was collected by decantation after centrifugation. The residue was washed repeatedly with water[11] and dried under vacuum at 60 °C to give white powdery pseudopolyrotaxane (**PPRX**, 2.26 g, 70%).

### *Preparation of **PPRX** in Solid-State*

A mixture of **α-CD** 2.92 g (3.00 mmol) and **APTHF** ($M_n$ 1100, 302 mg, THF unit 4.20 mmol) was grinded for 1 h in a mortar at room temperature. The resulting mixture was directly used for the preparation of polyrotaxane (**PRX**).

### *Synthesis of **PRX** by Grinding a Mixture of **PPRX** and an End-Capping Agent*

A mixture of **PPRX** (0.400 g, 0.0400 mmol) and 10 eq. (*vs.* $NH_2$ group) of an electrophile (0.800 mmol) (**DNBC** or **DNFB**) was grinded for 1 h at room temperature. The solid mixture was dissolved in DMSO and precipitated with diethyl ether and methanol. The collected white solid was washed with chloroform and water, respectively, and finally dried *in vacuo* at 60 °C to give **PRX** (0.194 g, 46% for **DNBC**) as white solid or **PRX** (0.284 g, 67% for **DNFB**) as pale yellow solid.

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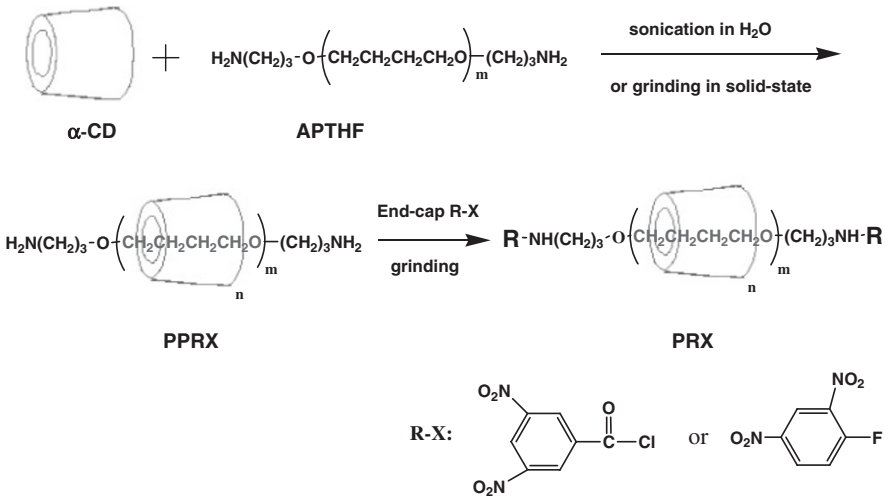


**Scheme 1.** Solvent-free synthesis of polyrotaxane. **APTHF**: Bis(3-aminopropyl)-terminated polytetrahydrofuran; **PPRX**: pseudopolyrotaxane; **PRX**: polyrotaxane.

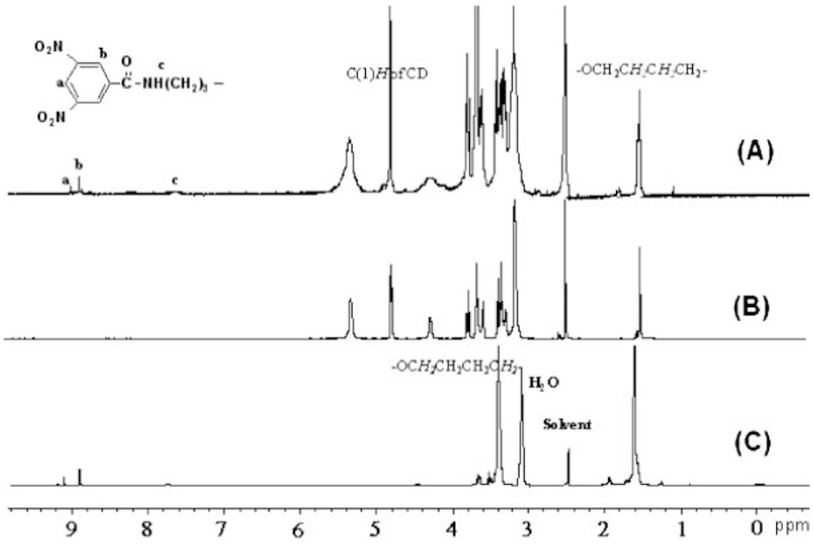


**Figure 1.** $^1$H NMR spectra of **PRX** (**A**), **PPRX** (**B**), and **APTHF** (**C**) in DMSO-$d_6$ at 60 °C (400 MHz). **PRX**: polyrotaxane; **PPRX**: pseuopolyrotaxane; **APTHF**: Bis(3-aminopropyl)-terminated polytetrahydrofuran.

## RESULTS AND DISCUSSION

**PPRX** consisting of **α-CD** as a wheel and **APTHF** ($M_n$ 1100) as an axle, was first prepared from a mixture of these components by sonication in aqueous solution. As shown in Scheme 1, a solid mixture of **DNBC** and **PPRX** thus obtained was grinded for 1 h at room temperature in a mortar to afford a white solid. The solid product was purified by precipitation and washing with water and a few organic solvents to give the corresponding **PRX** in 46% yield. The product was confirmed as **PRX** of which structure is discussed below.

Figure 1 shows the $^1$H NMR spectra of **PRX**, **α-CD**, and dumbbell-shaped axle derived by the reaction of **APTHF** with **DNBC**. The spectrum of **PRX** strongly revealed the incorporation of each moiety of **α-CD**, **APTHF** and the terminal aryl group. Namely, the aromatic proton signals appeared at 9.08 and 8.92 ppm in 1:2 integration ratio. Whereas the proton signal of C(1)H of **α-CD** was confirmed at 4.81 ppm, the methylene proton signals of **APTHF** appeared at 3.35 and 1.58 ppm, respectively. The chemical shifts were consistent with those of each component. Meanwhile, the broad signals in the spectrum of **PRX** suggest that **α-CD**s can hardly move on the **APTHF** axle. In fact, it was calculated that **PRX** had *ca.* 10 **α-CD**s wheels per one axle and therefore, the coverage ratio was more than 95%.

The X-ray diffraction pattern of **PRX** is shown in Figure 2 along with that of **α-CD**. A strong peak at $2\theta = 20^\circ$ is observed for **PRX** characteristic of the channel type **CD** arrangement, clearly indicating the formation of **PRX**. An additional evidence was confirmed in the UV-vis spectrum of **PRX** which contained typical absorptions of dinitrophenyl group at 360 and 430 nm (solvent: DMSO) and in the IR spectrum in which a weak absorption of the amide carbonyl group appeared at 1546 cm$^{-1}$.

To establish an all-solid-state process, solvent-free synthesis of **PPRX** was examined using **α-CD** and **APTHF**. According to our solid-state synthetic method with permethylated **α-CD**,[9] a mixture of **α-CD** and **APTHF** was grinded in a mortar for 1 h at room temperature without any solvent. To the result-

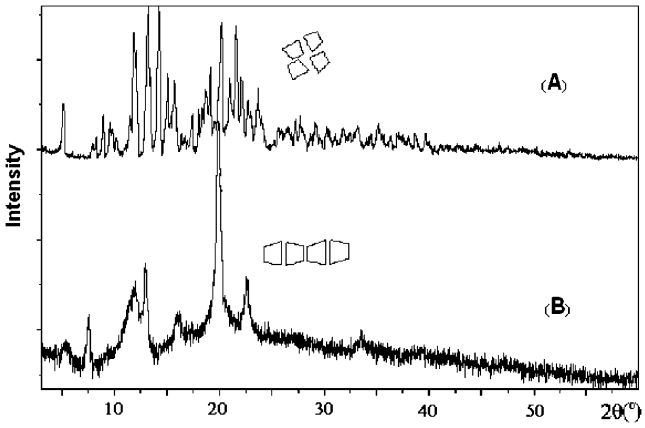


**Figure 2.** Powder X-ray spectra of **α-CD** (**A**) and **PRX** (**B**). **PRX**: polyrotaxane.

ing solid material in a mortar, **DNBC** was directly added and the mixture was grinded for 1 h similarly to the above procedure in the same mortar at room temperature. The collected organic solvent- and water-insolube material was polyrotaxane **PRX** (5.6% yield), of which structure was determined by $^1$H NMR, X-ray diffraction, IR, and UV-vis spectra. The formation of **PRX** unambiguously indicated the initial formation of **PPRX** by simple grinding of a mixture of two components, although the yield was low. The low yield can be attributed to the low efficiency of the **PPRX**-forming process because most of **α-CD** was actually recovered.[12]

**DNFB** which is often used as an end-capping agent in solution[3] was employed instead of **DNBC**, where the corresponding **PRX** was obtained in 67% yield by similar grinding of **PPRX** prepared by the aqueous solution method. Meanwhile, the totally solvent-free process afforded 12% yield of **PRX** end-capped with **DNFB** *via* the successive grindings. This result also suggests the low efficiency of the initial threading of linear polymer leading to **PPRX** as discussed above, whereas the efficiency of the end-capping with **DNFB** is fairly higher than that with **DNBC**,[13] although it is not clear whether the difference comes from use of "liquid" electrophile or not.

In this paper, we have demonstrated the efficient synthesis of pseudopolyrotaxane and polyrotaxane consisting of unmodified **α-CD** and a linear polymer by simple grinding of a mixture of the components and/or reagent in a mortar without any solvent. The end-capping of the pseudopolyrotaxane with a bulky electrophile has been achieved in a fairly good yield by grinding, although the threading complexation of the two components to pseudopolyrotaxane by grinding requires some improvement in yield. The present polymer synthesis by simple grinding of materials without solvent may provides a chance to have a new understanding of the utility and significance of solvent-free process.

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11. Even if APTHF remains in the product, APTHF remained is removed during the purification process of PRX.
12. The efficiency of the solid-state end-capping reaction of PPRX obtained by solution process is high enough. However, the yield of PRX becomes low when the two step reaction was carried out in solid state. Therefore, it is obvious that the threading efficiency of APTHF into CD as the first process is low. Such low efficiency in heterogeneous system is well understandable, although we did not study the detailed reason for it.
13. We carried out the reaction of APHF with the end-capping agents (DNBC and DNFB) under the same conditions as a control experiment, and obtained the corresponding acylated products in 60% (DNBC) and 75% (DNFB), respectively.