# Acid-Sensitive Polypseudorotaxanes Based on Ortho Ester-Modified Cyclodextrin and Pluronic F-127

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S *Supporting Information*

ABSTRACT: We demonstrate a new type of acid-sensitive amphiphilic polypseudorotaxanes (PPRs) formed via inclusion complexation between Pluronic F127 and the hydrophobic β-cyclodextrin (CD) derivative in alcoholic solvents. The 6-OH ortho ester-substituted hydrophobic β-CD derivative (EMD-CD) was prepared by "click" reaction of β-CD with 2-ethylidene-4-methyl-1,3-dioxalane under mild conditions. The water-insoluble EMD-CD (host) is capable of forming PPRs with F127 (guest) in ethanol or methanol but not in water, which is confirmed by ^{1}H NMR, wide-angle X-ray diffraction, small-angle X-ray scattering, and the time-dependent threading kinetics. Depending on the host/guest ratio, the PPRs self-assembled into sheet-like structure or vesicular nanoparticles with different sizes in water. These PPR assemblies were stable at pH 8.4 but quickly dissociated into biocompatible products in neutral or in acidic buffers due to the hydrolysis of the ortho ester groups. Good biocompatibility, ease of fabrication, and extremely pH-sensitive character make the PPRs promising carriers for anticancer drug delivery. Moreover, the present work provides an alternative method for the preparation of PPRs composed of water-insoluble CD derivatives.
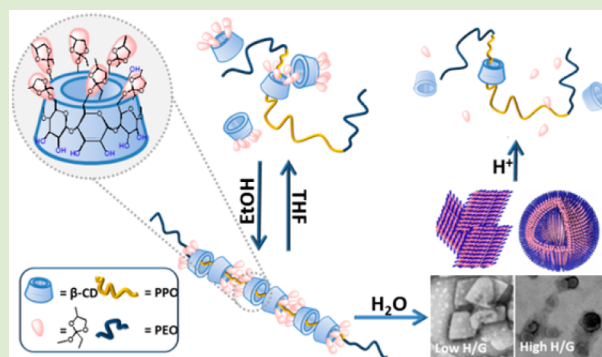
Poly(pseudo)rotaxanes represent the important branch of supramolecules.[1] Among them, cyclodextrin (CD)-based polyrotaxanes (PRXs) and polypseudorotaxanes (PPRs) show great potential in biomedical applications because of the excellent biocompatibility of CDs.[2] For example, various cationic PRXs or PPRs have been used for delivery of nucleic acids or proteins.[3] Hydrogels or nanoassemblies formed by the CD-containing PRXs or PPRs have also been widely investigated as carriers of sustained drug/protein delivery systems.[4] In general, the CD- or its hydrophilic derivative-based PPRs or PRXs were prepared in water.[5] While some of the CD-based PPRs or PRXs could be fabricated in the mixture of water and organic solvent or in bulk,[6] only several papers reported the formation of PPRs containing permethylated β-CD in organic solvents.[7]

pH-sensitive materials including supramolecular systems have been studied extensively as the vehicles of intelligent nanomedicines because of the numerous pH gradients in the human body.[8] Considering the unique necklace-like structure and channel topology, pH-sensitive PPRs or PRXs may possess interesting properties to construct various pH-responsive nanoparticles or hydrogels. However, only limited publications reported the CD-based pH-sensitive PPRs composed of polyamines as the guest polymers[9] and the acid-labile PRXs that contain acid-cleavable stoppers at both ends.[10]

Ortho esters, one type of the most acid-labile motifs, have been thoroughly studied regarding their applications in various pH-sensiti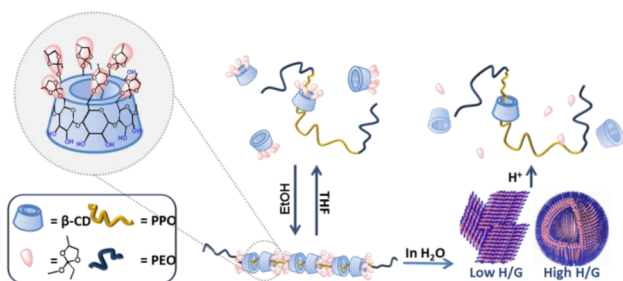ve delivery systems.[11] Recently, we have developed a simple method to synthesize asymmetrically ortho ester-modified β-CD derivatives by the selective reaction between the primary hydroxyl groups (6-OH) of β-CD and various cyclic ketene acetals.[12] It is interesting to explore whether these asymmetrically modified β-CD derivatives are capable of forming a new type of pH-sensitive PPRs. In the current work, the 6-OH ortho ester-modified β-CD derivative (EMD-CD) with an average substitution degree of 6.2 was prepared by "click" reaction of β-CD and 2-ethylidene-4-methyl-1,3-dioxalane (EMD) under mild conditions. EMD-CD is soluble in many organic solvents such as tetrahydrofuran (THF), ethanol, dimethyl sulfoxide (DMSO), and so forth but not in water. We found that EMD-CD can form amphiphilic PPRs with the PEO–PPO–PEO copolymer (Pluronic) F127 via host–guest interaction in ethanol or methanol. Depending on the host/guest ratio, the PPRs can self-assemble into sheet-like structure or vesicular nanoparticles in water. These PPR nanoassemblies are acid-sensitive and dissociated under a very mild acid triggering (Scheme 1). To our best knowledge, this is the first paper reporting the formation of PPRs via the host–guest interaction between the hydrophobic CD derivatives and the Pluronic copolymers in the selected organic solvents.

Scheme 1. Formation and Self-Assembly of Polypseudorotaxane Based on EMD-CD and Pluronic F127

Figure 2. (a) WAXD powder diffraction patterns of **PPR4**, F127, and EMD-CD and (b) SAXS spectrum of **PPR4**.

It is well-known that β-CD and its hydrophilic derivatives including 2,6-O-dimethyl-β-CD (DM-β-CD) and hydroxypropyl-β-CD (HP-β-CD) are able to form PPRs directly in water with PPO or PEO-b-PPO-b-PEO (Pluronic) copolymers.[13] Herein, EMD-CD is insoluble in water and thus cannot form PPR with Pluronic F127 directly in water even under ultrasonication.[14] However, PPR composed of EMD-CD as the host (H) and F127 as the guest (G) can be prepared in ethanol. In this context, EMD-CD and F127 were first dissolved in ethanol in a H/G molar feed ratio of 27:1, and the solution was incubated at 40 °C for 12 h. After removal of ethanol on a rotary evaporator, the obtained thin film was hydrated in cold phosphate buffer (pH 8.4, ~4 °C) under ultrasonication to afford a turbid dispersion. Further incubation of the dispersion at 4 °C for 24 h resulted in the formation of the PPR aggregate as a white precipitate which can be redispersed in the same buffer at 37 °C, affording a stable bluish dispersion. The PPR was characterized by ^{1}H NMR, wide-angle X-ray diffraction (WAXD), small-angle X-ray scattering (SAXS), and transmission electron microscope (TEM).

As shown in Figure 1, the proton signals of both EMD-CD and F127 are clearly observable in DMSO-d_6 where the PPR
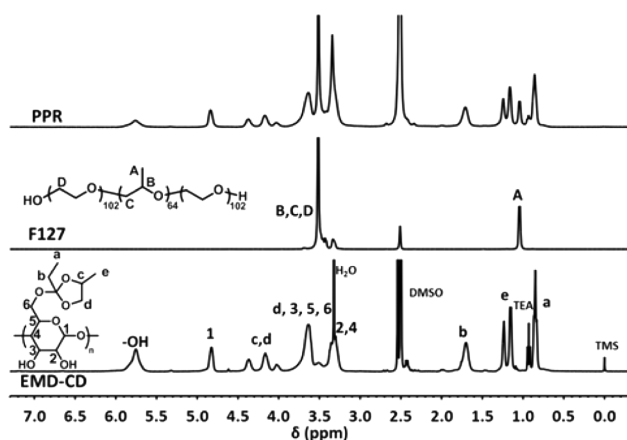

Figure 1. ^{1}H NMR spectra of **PPR4**, F127, and EMD-CD in DMSO-d_6.

was completely dissociated into free EMD-CD and F127. The H/G molar ratio in the PPR was calculated to be 28:1 by comparing the peak intensities of the C1 proton of the CD ring at 4.86 ppm and the proton A ($-CH_3$ of F127) at 1.05 ppm.

The phase structure of the PPR aggregate was first studied by WAXD. As shown in Figure 2a, EMD-CD is amorphous, and F127 shows two prominent peaks at $2\theta = 19°$ and 23°, respectively, which are assigned as the reflections of PEO

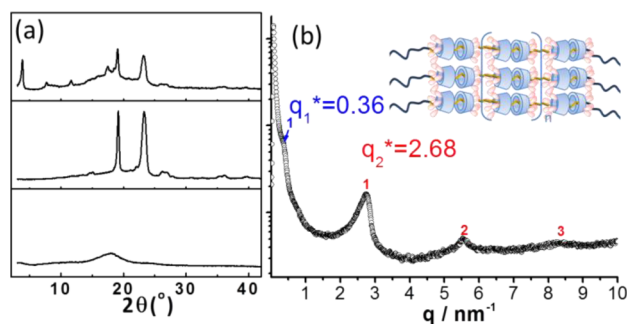crystalline. The diffraction pattern of the PPR was different from that of EMD-CD or F127. Besides the strong reflection peaks of PEO crystalline, there were several additional peaks ($2\theta = 3.96°$, 7.9°, 11.8°, and 17.9°), indicating the formation of new ordered structures in the PPR. Since PEO itself cannot form PPR with EMD-CD,[15] we rationally speculate that EMD-CDs were threaded onto the PPO block of F127 in a head-to-head manner, in which the hydrogen bonding between the secondary hydroxyl groups and the solvophobic interaction between the ortho ester groups of the neighbored EMD-CD molecules are beneficial for the threading.

The PPR was further characterized by SAXS (Figure 2b). A group of peaks with an approximate q ratio of 1:2:3 ($q = 2.68$, 5.54, 8.21) were observed, implying the lamellar phase with a calculated d-spacing of 2.3 nm. This phase is also represented in the WAXD pattern ($2\theta = 3.96°$, 7.9°, and 11.8°). The d-spacing 2.3 nm can be assigned to the length of two EMD-CD molecules arranged in the head-to-head manner (2.12 nm as estimated through the molecular dynamics simulation, Figure S3, Supporting Information) threaded onto the PPO block.[16] This spacing is larger than the height (1.52 nm) of two head-to-head arranged β-CD molecules along the PPO block, which can be attributed to the presence of the cyclic ortho ester substituents. In addition, there is another weak but obvious scattering peak with the q value of 0.36 nm^{-1} which is probably related to the length (~17 nm) of the poorly ordered polymeric inclusion complexes of many EMD-CDs threaded onto one PPO block, assuming that the possible contribution of PEO crystalline could be negligible. The average number of EMD-CDs threaded onto one F127 chain was calculated to be ~15 (17 nm × 2/2.3 nm). According to the result of computer simulation,[13a] the extended PPO length of F127 in its free energy minimized conformation is estimated to be ~23 nm (64 PO units). Assuming that the PPO block is fully threaded and the EMD-CD pairs are closely arranged, there will be ~20 EMD-CD molecules threaded onto one F127 chain at most. Both the calculated values are much smaller than the number 28 as previously determined by ^{1}H NMR, which indicates that some of the EMD-CD molecules were not threaded onto the PPO block but physically entrapped in the PPR aggregates.

In order to further demonstrate the formation of PPR, the time-dependent threading experiments were carried out in ethanol at 40 °C. As determined by ^{1}H NMR spectroscopy (Figure 3), the contents of F127 compared to EMD-CD in the obtained PPRs increase with time until 12 h, after which they almost level off. The normalized WAXD patterns of the PPRs reveal that the diffraction peaks associated with the lamellar phase also increased gradually with time, which indicates that
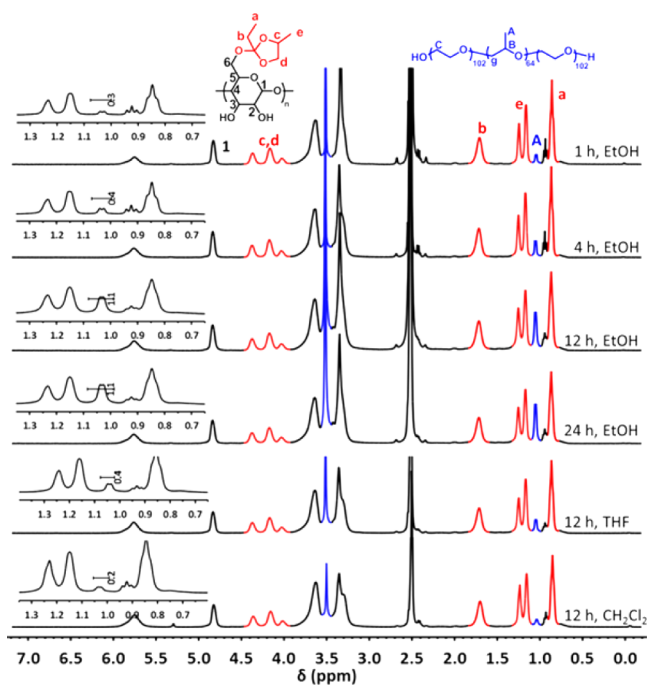
Figure 3. ^{1}H NMR spectra of the PPRs prepared in different conditions. The solvent for ^{1}H NMR measurements was DMSO-d_6.

at 37 °C (Table 1), approximately 1 order of magnitude lower than that of F127.[19] These PPR aggregates were further studied

Table 1. Characterization of the PPR Aggregates with Different H/G Ratios

	n_H:n_G[a]		yield[b] (%)	R_h[c] (nm)	R_g/R_h[c]	CAC[d]
	in feed	in PPR				
PPR1	9.0:1	8.3:1	75	150	1.12	9.2
PPR2	14:1	13:1	93	120	1.08	7.0
PPR3	16:1	16:1	90	100	1.06	5.5
PPR4	27:1	28:1	76	83	1.02	n.d.[e]

[a]Molar ratio of EMD-CD to F127 in feed and in the PPR aggregate. [b]The yields of the PPR aggregates. [c]Measured by LLS (concentration of PPR: 1.0 mg/mL; 37 °C). [d]Critical aggregation concentration (μg/mL) determined by the fluorescent method using pyrene as a probe (Figure S6, Supporting Information). [e]Not determined.

by TEM and laser light scattering (LLS) (Table 1 and Figure 4). With increasing the H/G ratio from ∼9:1 to ∼27:1, the

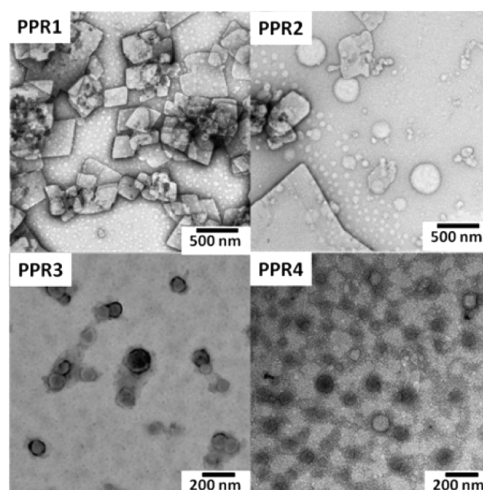**Figure 4.** TEM images of PPR aggregates with different H/G ratios. The samples were stained with uranyl acetate.

more EMD-CD molecules were threaded onto one F127 chain at a longer time (Figure S4, Supporting Information). These results are consistent with the formation of other PPR systems such as α-CD/PEO or β-CD/PPO.[6d,17]

Solvents were reported to influence the formation of CD-based poly(pseudo)rotaxanes, kinetically and/or thermodynamically.[7,17b] In the present work, besides in ethanol, the PPR composed of EMD-CD and F127 was also successfully prepared in methanol. However, when THF or CH$_2$Cl$_2$ was used as a solvent, we did not find obvious evidence indicating the formation of PPR. There are no diffraction peaks (2θ = 3.96°, 7.9°, and 11.8°) associated with the PPR formation in the WAXD patterns of the precipitates that were obtained using the same procedure and feed ratio (EMD-CD:F127 = 27:1) as in ethanol (Figure S5, Supporting Information). Moreover, when the PPR aggregate prepared in ethanol was redissolved in THF, incubated for 12 h at 40 °C, and treated by the same preparation procedure, the obtained precipitate did not show diffraction peaks of the PPR. ^{1}H NMR spectra reveal that the molar ratios of EMD-CD to F127 in the precipitates obtained from THF and CH$_2$Cl$_2$ were ∼76:1 and ∼150:1, respectively (Figure 3). These results indicate that the precipitate obtained in THF or CH$_2$Cl$_2$ is most likely a physical mixture of EMD-CD and F127 but not a typical PPR structure. It can be explained by the weak host−guest interaction in the less polar solvents, probably due to the competitive complexation of EMD-CD and the solvent molecules.[18]

The effect of H/G feed ratio on the formation and property of the PPR aggregates was also investigated in ethanol. When the H/G molar feed ratio was 4:1 or smaller, the PPRs could not precipitate out of the cold buffer even for a long incubation time (>24 h). At the feed ratio of 9:1 or more, PPR aggregates were obtained in high yields, and the H/G ratios in the PPRs are approximately equal to that in the feed. All the PPR aggregates can be redispersed well in PB at 37 °C. They possess critical aggregation concentrations in the range of 5−10 μg/mL

morphologies of the PPR aggregates evolved from a sheet-like structure for **PPR1** to the vesicular nanoparticles for **PPR3** and **PPR4**, and the sizes showed a decreasing trend. The morphologies of some PPR aggregates were supported by the freeze-fracture TEM image (for **PPR3**) and the TEM images without staining (for **PPR1** and **PPR3**) (Figure S7, Supporting Information). The unique morphologies of these PPR aggregates can be attributed to the combined effect of the relative rigidity of the EMD-CD/PPO (inclusion complex) segment and the crystallization of the PEO block.[13a,20] We speculate that at an appropriate H/G ratio such as in **PPR1** there was little unthreaded EMD-CD molecules in the aggregate, and the PPRs arranged side-by-side to pack into a sheet-like structure. With increasing H/G feed ratio, the amount of unthreaded EMD-CD molecules in the aggregates would increase, which may disturb the dense packing of the PPRs and force them to form vesicles.

The acid-triggered dissociation of the PPR aggregates was investigated by ^{1}H NMR and LLS. The dispersion of **PPR3** aggregates was stable at pH 8.4, with only ∼15% decrease in the scattered intensity in 24 h. By contrast, the intensity of the dispersion decreased rapidly with a pH decrease and dropped

more than 90% in 1 h at pH 5.0, indicating the dissociation of the PPR aggregates due to the acid-triggered hydrolysis of the ortho ester groups (Figure 5a). This explanation is further
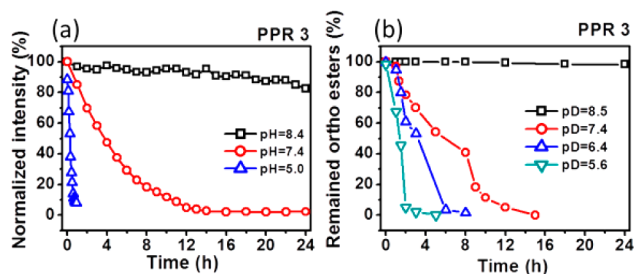

Figure 5. Effect of pH on the kinetics of dissociation of **PPR3** aggregate (a) and hydrolysis of the ortho ester groups (b).

confirmed by the pH-dependent hydrolytic kinetics of the ortho esters monitored by ^{1}H NMR spectroscopy (Figure 5b). For the **PPR3** aggregate, less than 10% of the ortho ester groups hydrolyzed in 24 h at pH 8.5, while the acid-triggered hydrolysis of the ortho esters was completed within 2 h at pH 5.6. At the same pH, the hydrolysis rate of the ortho esters decreased with increasing H/G ratio, which is attributed to the more hydrophobic character of the PPR with a higher H/G ratio (Figure 5b vs Figure S10, Supporting Information). As we reported previously, the hydrolysis rate of the ortho esters is highly dependent on the microenvironment, and a hydrophobic environment retards the hydrolysis.[21]

In summary, we demonstrate for the first time that the 6-OH ortho ester-substituted hydrophobic β-CD derivative is capable of forming amphiphilic acid-sensitive PPRs with Pluronic F127 in the alcoholic solvents. In weakly basic aqueous buffer, the PPRs can self-assemble into nanoassemblies whose morphology and size are dependent on the composition of the PPRs and can be adjusted by varying the H/G feed ratio. These extremely pH-sensitive PPRs have potential for anticancer drug delivery as well as for other biomaterials due to their promising features. In addition, the method of PPR preparation may be expanded to other PPRs formed by water-insoluble CD derivatives threaded onto polymer chains in organic solvents.

■ ASSOCIATED CONTENT

⑤ Supporting Information

Experimental part, more results of ^{1}H NMR, WAXD, and TEM measurements, CONTIN result, and more hydrolysis kinetic curves. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

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(14) F127 (25 mg, 1.98 μmol) was dissolved in 1 mL of PB (10 mM, pH 8.4), to which EMD-CD (29.0 mg, 15.8 μmol) was added. The mixture was ultrasonicated for 30 min and stirred at 40 °C for 12 h, affording a turbid dispersion. After centrifugation and being washed with PB, the white precipitate was analyzed by ^{1}H NMR to be EMD-CD only, without F127. The upper clear solution was lyophilized to afford white powder. ^{1}H NMR result reveals that this powder is mainly composed of F127 with little EMD-CD.

(15) PEO (M_w = 2000, 4.0 mg, 2.0 μmol) and EMD-CD (29.0 mg, 15.8 μmol) were completely dissolved in 2 mL of ethanol and the solution was stirred at 40 °C for 12 h. After the same procedure for the preparation of EMD-CD/F127 PPR, the obtained precipitate was analyzed by ^{1}H NMR. There was only EMD-CD in the precipitate without PEO. On the other hand, in the upper supernant, there was mainly PEO with little EMD-CD.

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