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Polymerization of Lactones Initiated by Cyclodextrins: Effects of Cyclodextrins on the Initiation and Propagation Reactions

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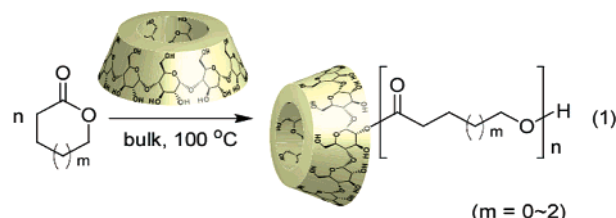
ABSTRACT: Cyclodextrins (CDs) were found to initiate ring-opening polymerizations of lactones selectively to give polyesters in high yields, although lactones did not give any polymers under the same conditions in the absence of CD. The order of the polymer yield of β -butyrolactone (β -BL) with CDs is α -CD \cong β -CD \gg γ -CD $>$ no CD. On the other hand, that of δ -valerolactone (δ -VL) is β -CD $>$ γ -CD \gg α -CD \cong no CD. The yields of the polyesters depend on the cavity size of CDs and structures of lactones, indicating that the reaction took place via inclusion of lactones in the CD cavity. The β -CD–adamantane inclusion complex did not show any polymerization activity for δ -VL under the same conditions because adamantane is strongly included in the cavity of β -CD to inhibit formation of the inclusion complex between β -CD and δ -VL. The included lactones in the CD cavity are activated by the formation of hydrogen bonds between the hydroxyl group of CDs and the carbonyl oxygen of lactones in the initiation step, which was observed by FT–IR spectroscopy. The products were found to be a polymer chain attached to the C₂-hydroxyl group of a single glucopyranose unit of CD via an ester bond. The lactones are activated by other remaining secondary hydroxyl groups to give the propagation step by way of insertions of monomers between CD and the polymer chain. The initiation and the propagation steps of the polymerization of lactones by CDs were observed by solid state ¹³C NMR techniques.

Introduction

Some enzymes, such as RNA polymerases, DNA polymerases, and λ -exonucleases, have cylindrical cavities in the substrate-binding site determined by X-ray crystallography.¹ These cyclic molecules might thread onto biological polymers to form rotaxane-like structures. Cyclodextrins (CDs) have a cylindrical structure and have been widely employed as substrate-recognition moieties in enzyme models, such as serine proteases, papain, and esterases, because of their well-defined molecular structures and hydroxyl groups around the rims of the cavities.^{2,3} Bender and Komiyama reported that CDs accelerate the hydrolysis of activated esters, such as *p*-nitrophenyl acetate.⁴ Over the past few decades, a large number of studies have been conducted on the effects of native CDs or modified CDs on the hydrolysis of the activated esters. However, the accelerated reactions have been limited to the degradation of the activated aryl esters in the presence of excess amounts of CDs.

We found that CDs selectively form inclusion complexes with some lactones (the starting materials of the polyesters) to promote or suppress the hydrolysis of lactones.⁵ To the best of our knowledge, the catalytic activities of sugars or CDs for the polymerization have not been reported. The polymerization of lactones could be selectively initiated by CDs without any cocatalysts or solvents, and the secondary hydroxyl group of CD attacks the activated carbonyl carbon (eq 1). This polymerization system requires neither a conventional metal catalyst, nor CDs with substituent groups.⁶ However, we could not reveal the details of the initiation and the propagation steps catalyzed by CDs. Herein, we have studied the details of the polymerization, and have obtained polyesters with molecular weights over 10000. We have found that CDs play important roles not

only in the initiation, but in the propagation step of the ring-opening polymerization of lactones.



Results and Discussion

Polymerization of Lactones by CDs. Lactones, β -butyrolactone (β -BL), δ -valerolactone (δ -VL), and ϵ -caprolactone (ϵ -CL), did not give any polyesters by heating at 100 °C for 48 h without CDs under an argon atmosphere (Table 1, entries 1–3). These lactones did not give poly(lactone)s in the presence of alcohol or water under the same conditions, although methanol and water gave only oligomeric ring-opened products (the number of the monomer units is 1–5). However, we found that these lactones gave polyesters with CDs under the same conditions. The yields of polyesters depended on the cavity size of CDs and the structure of the lactones. The order of the activity for β -BL with CDs was α -CD \cong β -CD \gg γ -CD (entries 4–6). The polymerization activity of β -CD for δ -VL was higher than that of γ -CD, whereas α -CD did not show any effects (entries 7–9). The activity for ϵ -CL was lower than those of β -BL and δ -VL because of the low Lewis basicity of the carbonyl oxygen of ϵ -CL as reported by Okamoto⁷ and Penczek.⁸ The order of the activities of CDs for ϵ -CL is similar to that of δ -VL (entries 10–12). The molecular weights (M_n) of the products depend on the [Monomer]/[Initiator] ratio in the feed. Some combinations of CD and lactone gave polyesters of higher M_n with an increase in the monomer feed. In the case of β -CD and δ -VL, the M_n increased with an increase in the [δ -VL]/[β -CD] ratio

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Table 1. Polymerizations of Lactones Initiated by Various CDs in Bulk at 100 °C

entry	monomer	initiator	[monomer]/[initiator]	time/h	yield/%	M_n^a	M_w/M_n^a
1	β -BL			48	0		
2	δ -VL			48	0		
3	ϵ -CL			72	0		
4	β -BL	α -CD	5	48	66	3600	2.4
5	β -BL	β -CD	5	48	56	3800	2.1
6	β -BL	γ -CD	5	48	6	2200	1.1
7	δ -VL	α -CD	5	48	1	1100	1.3
8	δ -VL	β -CD	5	48	97	2300	1.8
9	δ -VL	γ -CD	5	48	20	2900	1.6
10	ϵ -CL	α -CD	5	72	0		
11	ϵ -CL	β -CD	5	72	15	1700	1.1
12	ϵ -CL	γ -CD	5	72	3	1400	1.1
13	δ -VL	β -CD	10	96	95	3400	1.9
14	δ -VL	β -CD	30	96	29	7800	2.0
15	β -BL	α -CD	15	96	58	5700	2.3
16	β -BL	β -CD	15	96	61	4800	2.5

^a The molecular weights were calibrated by GPC calculated with polystyrene standard^{9,10} (eluent: THF).

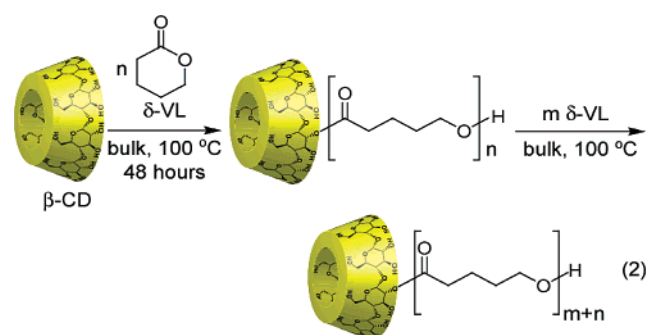
Table 2. Post-Polymerizations of δ -VL Initiated by β -CD in Bulk at 100 °C

entry	$[\delta\text{-VL}]/[\beta\text{-CD}]$	time/h	yield/%	M_n^a	M_w/M_n^a
1 (pre-polymer) ^b	5	48	97	2300	1.8
(post-polymer)	5 + 5	48 + 48	78	3700	2.2
2 (pre-polymer) ^b	30	96	29	7800	2.0
(post-polymer)	30 + 30	96 + 96	46	10400	1.8

^a The molecular weights were calibrated by GPC calculated with polystyrene standard^{9,10} (eluent: THF). ^b The pre-polymers correspond to entries 8 and 14 in Table 1, respectively.

to attain 7800 (entries 13 and 14). The reduction in yields of polyesters with higher M_n is supposed to be due to decrease in the mobility of the polyester with increasing in the M_n in the solid state. The M_n of poly(β -BL)s also increased with an increase in $[\beta\text{-BL}]/[\text{CD}]$ ratio in the feed (entries 15 and 16). The combination of β -BL and α -CD ($[\beta\text{-BL}]/[\alpha\text{-CD}] = 15$) gave poly(β -BL) with M_n of 5700. These results indicate that the formation of the inclusion complexes between CDs and lactones plays an important role in the polymerization.

After the monomers were consumed in the polymerization of δ -VL by β -CD, another δ -VL was added, and the mixture was heated at 100 °C again (eq 2). The yields and the M_n for the post-polymerizations are shown in Table 2. The M_n of the polymer obtained by the pre-polymerization ($[\delta\text{-VL}]/[\beta\text{-CD}] = 30$) reached 7800 within 96 h. After washing the pre-polymer with water and dried, another 30-equivalent of δ -VL was added and heated. Then, the second-polymerization took place to give a polyester with M_n of 10 400 (Entry 2). The M_n increased by the post-polymerizations, indicating that the polyester still possesses the ability to polymerize after the first polymerization.



Polymerization of δ -VL by the β -CD- δ -VL Inclusion Complex. To prove the importance of the inclusion of guest monomers during polymerization, the polymerization of δ -VL was conducted using the β -CD- δ -VL inclusion complex as an

initiator. The induction period was observed in the polymerization of δ -VL with β -CD, but the induction period was not observed in the polymerization of δ -VL with the β -CD- δ -VL inclusion complex (Figure 1). The polymerization of δ -VL was suppressed by using β -CD-adamantane (β -CD-Ad) inclusion complex as an initiator under the same conditions. This result shows that δ -VL was not included in the β -CD cavity because the adamantane guest is strongly included in the cavity of β -CD. These observations indicate that the formation of the inclusion complex is important to initiate the ring-opening polymerization of lactones.

Complex Formation and Activation of Lactones in the Solid State. Previously, we and other groups reported that CDs form inclusion complexes with some guest molecules at elevated temperature (80 °C) in a two-phase-system.¹¹ CDs could be used as reversed-two-phase catalysts in Wacker reactions at 80 °C. These reports suggest that CD forms a short-lived intermediate in two-phase systems. Nakai and his co-workers discussed the inclusion phenomena of CDs in solid state by the FT-IR spectroscopy.¹² There are few reports on an inclusion phenomenon of CDs at higher temperatures (100 °C) in organic media or solid state.

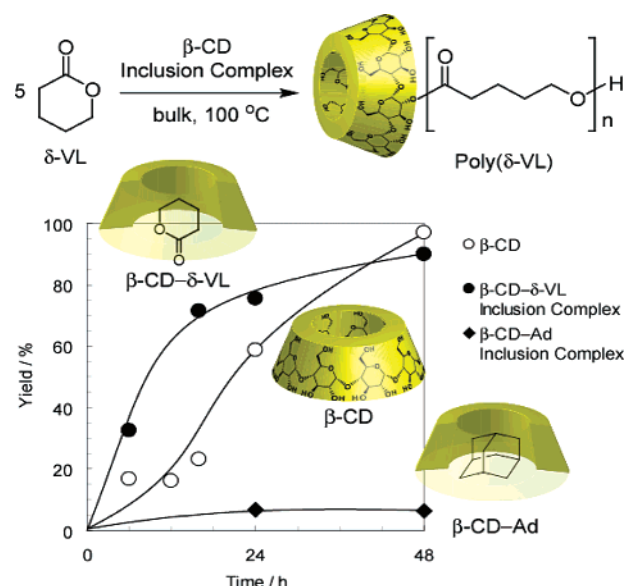


Figure 1. Time-yield plots of the polymerization of δ -VL initiated by β -CD (○), the β -CD- δ -VL inclusion complex (●), the β -CD-adamantane (β -CD-Ad) inclusion complex (◆) in bulk at 100 °C. $[\delta\text{-VL}]/[\beta\text{-CD}] = 5$.

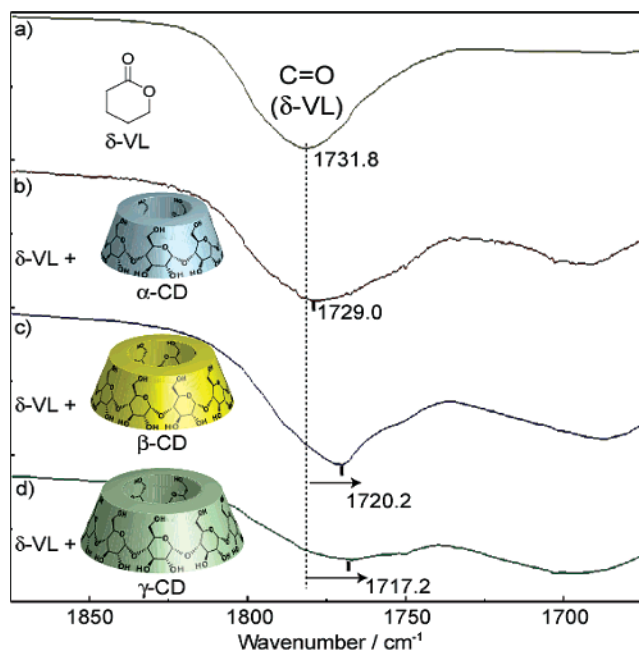


Figure 2. The FT-IR spectra of δ -VL (a), the mixture of α -CD and δ -VL (b), the mixture of β -CD and δ -VL (c), and the mixture of γ -CD and δ -VL (d).

The FT-IR spectrum of δ -VL showed a characteristic band of the stretching mode of the C=O bond at 1731.8 cm^{-1} (Figure 2a). The spectrum of the mixture of α -CD and δ -VL showed that the stretching mode of the C=O bond of δ -VL shifted to a slightly shorter wavenumber than that of native δ -VL (Figure 2b). In contrast, the C=O band in the mixture of β -CD (or γ -CD) and δ -VL shifted largely to a shorter wavenumber, indicating that the band shifts correspond to the polymerization activity of CDs for δ -VL (Figure 2, parts c and d). Some papers described that the stretching mode of carbonyl groups shifts to shorter wavenumber when a hydrogen bond is formed between the hydroxyl group of CD and the carbonyl oxygen of the guest molecule.¹³ Previously, the activated monomer mechanisms via hydrogen bond formation or the protonation were reported by Okamoto⁷ and Penczek.⁸ We suppose that hydrogen bonds between the hydroxyl group of CDs and the carbonyl oxygen of δ -VL are formed to activate δ -VL for the polymerization. The band shift of β -BL to a shorter wavenumber was observed with α -, β -, and γ -CDs. ϵ -CL also showed a band shift in the presence of β -CD and γ -CD (see Supporting Information in Figures S2 and S3). These results are in agreement with the polymerization activities of CDs for lactones. The mixture of 2,6-di-*O*-methyl- β -CD (DM- β -CD) and δ -VL, which shows no polymerization activity, did not show any band shifts (see Supporting Information in Figure S5). These data indicate that the hydrogen bond is not formed between the hydroxyl group at the C₃-position of each glucopyranose unit and δ -VL in the DM- β -CD cavity. Hydroxyl groups of C₂-position of each glucopyranose unit of native CDs play a role of the activation of lactones by the formation of hydrogen bond to activate the included lactones in the initiation step.

Reactions in the Solid State: ^{13}C CP/MAS NMR Spectroscopy and ^{13}C 1pda/MAS NMR Spectroscopy. When we studied the ring-opening behavior of lactones with CDs in water, we found that CDs promoted or suppressed the hydrolysis of lactones, but did not show the initiation of polymerization of lactones. To gain some insights into the initiation and propagation steps in the solid state, β -CD, the mixture of β -CD and δ -VL, and the β -CD- δ -VL inclusion complex were studied by

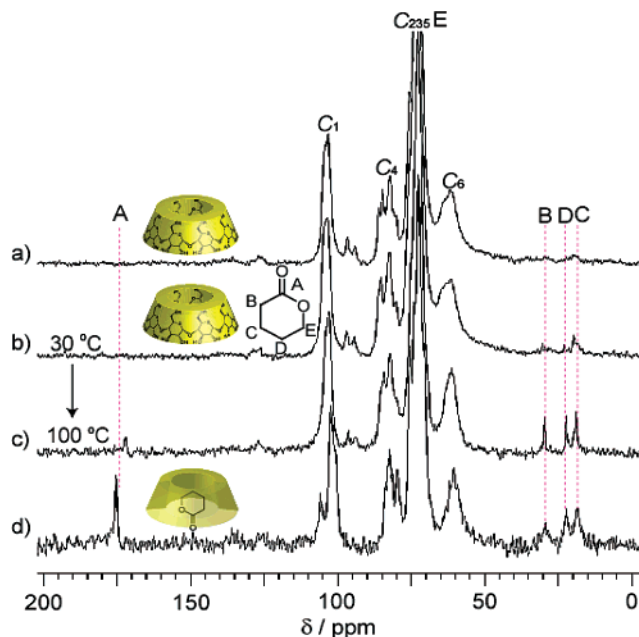


Figure 3. ^{13}C CP/MAS NMR spectra of β -CD (a), the mixture of β -CD and δ -VL at $30\text{ }^{\circ}\text{C}$ (b), the mixture of β -CD and δ -VL at $100\text{ }^{\circ}\text{C}$ (c), and the β -CD- δ -VL inclusion complex (d).

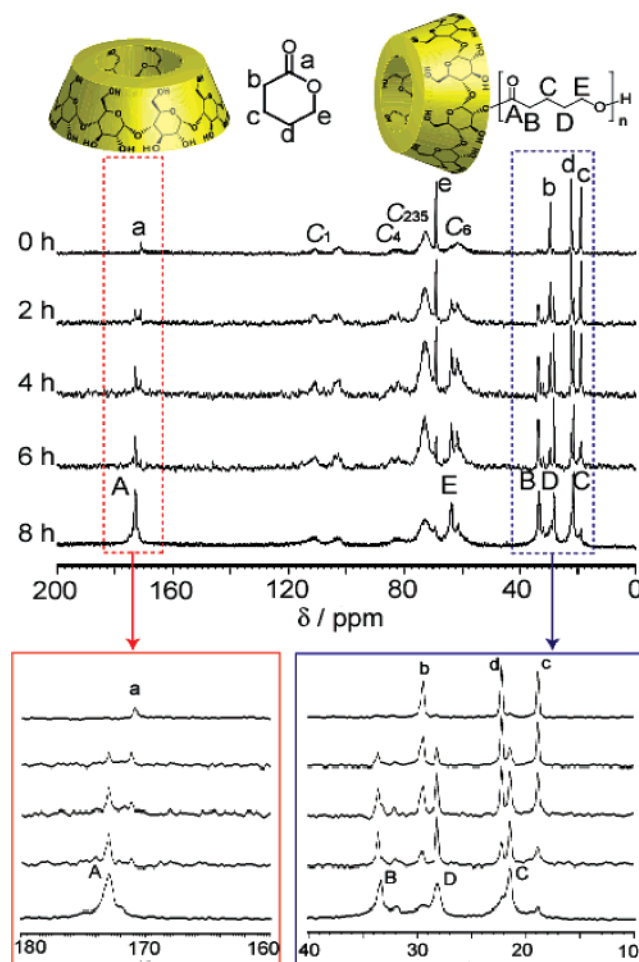
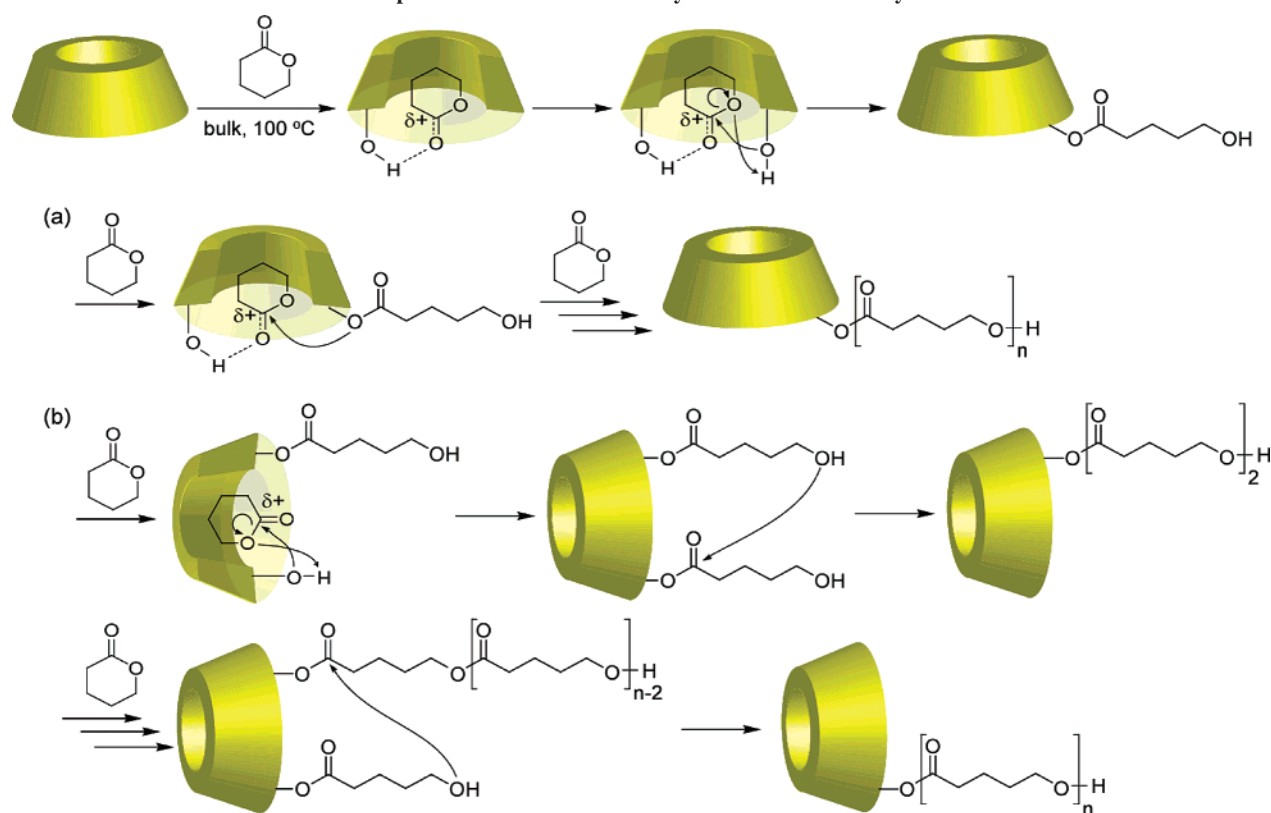


Figure 4. Time dependence of ^{13}C 1pda/MAS NMR spectra of the mixture of β -CD and δ -VL at $100\text{ }^{\circ}\text{C}$.

the time dependence of ^{13}C CP/MAS NMR and ^{13}C 1pda/MAS NMR as shown in Figures 3 and 4.

Figure 3 shows the ^{13}C CP/MAS NMR spectra of native β -CD (a), the mixture of β -CD and δ -VL at $30\text{ }^{\circ}\text{C}$ for an hour (b),

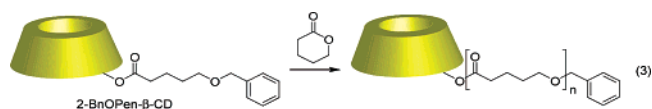
Scheme 1. Proposed Mechanism of the Polymerization of δ -VL by CD in Bulk

the mixture of β -CD and δ -VL at 100 °C for an hour (c), and the β -CD- δ -VL inclusion complex (d). The signals of native δ -VL are not observed by the ^{13}C CP/MAS NMR spectra because δ -VL cannot perform the cross-polarization in the liquid state. The signals of δ -VL guest molecules in the β -CD- δ -VL inclusion complex were observed as shown in Figure 3d, indicating that the mobility of δ -VL in the β -CD- δ -VL inclusion complex was restrained in the β -CD cavity. The mixture of β -CD and δ -VL standing at 100 °C for an hour showed larger peak intensity of δ -VL than that of the mixture of β -CD and δ -VL standing at 30 °C for an hour, indicating that β -CD forms inclusion complexes with δ -VL even at 100 °C in solid state. Moreover, the rate of the formation of the β -CD- δ -VL inclusion complex at 100 °C is faster than that at 30 °C in solid state.

Figure 4 shows the 1pda/MAS NMR spectra of the mixture of β -CD and δ -VL recorded every 2 h at 100 °C. The 1pda/MAS NMR spectra support the polymerization behavior of δ -VL at 100 °C in solid state because the 1pda/MAS NMR method, compared to the CP/MAS NMR method, enhances the peak intensity for mobile regions in the sample. Although the signals of poly(δ -VL) were not observed in the early stage, the peaks of poly(δ -VL) (A–E) increased with time and the peaks of δ -VL (a–e) decreased with time. Figure S6 shows the time–conversion curve for the polymerization of δ -VL using β -CD. The conversion of poly(δ -VL) increased with time, indicating the propagation of poly(δ -VL) in bulk.

Polymerization Mechanism. The polymers were characterized by the ^1H and ^{13}C NMR spectra, the MALDI–TOF mass spectra, and gel-permeation chromatography. The entire polymer chain was attached to a C_2 -position of a glucopyranose unit as a pendent. The proposed polymerization mechanism is refined as shown in Scheme 1. The first step is the inclusion of lactone in the CD cavity to form a 1:1 inclusion complex. The included lactone in the CD cavity is activated by the formation of a hydrogen bond between the carbonyl oxygen of lactone and

the hydroxyl group of CDs. A secondary hydroxyl group of a C_2 -position of a glucopyranose unit attacks the activated carbonyl carbon of the included lactone to cleave the carbonyl–oxygen bond. The monomer-attached CD is formed in the initial step.



A hydroxyl group at the end of the polymer chain might be able to attack the included lactone in the CD cavity. However, mono-2-*O*-(5-benzyloxypentanoil)- β -CD (2-BnOPen-poly(δ -VL)- β -CD), which does not have a hydroxyl group at the end, initiated the polymerization of δ -VL (eq 3). The result indicated that the hydroxyl group of the end of polymer did not have the polymerization activity. In Scheme 1a, the monomer recognition, the activation of the monomer and the insertion of monomers are serially repeated to give 2-*O*-poly(ester)-CDs in the propagation step. The lactones are supposed to be inserted at the ester bond between CD and a polyester chain. We proposed another possible polymerization mechanism in Scheme 1b. The hydroxyl group of the monomer-attached CD attacks the carbonyl group of the included lactone in CD cavity to form disubstituted CD. Then, the hydroxyl group of the monomer moiety attacked the carbonyl carbon of the other monomer moiety. The lactones are inserted between CD and the polymer chain to give 2-*O*-poly(ester)-CD. In the propagation step, the intermediate species (the disubstituted CDs) were not observed by the ^1H NMR spectroscopy so that the hydroxyl group of the disubstituted CD immediately attacks the other carbonyl carbon.

Conclusion

The appropriate combination of CDs and lactones (for example, the mixture of α -CD and β -BL and the mixture of

β -CD and δ -VL etc.) gives the CD-tethered polyesters in high yields without cocatalyst or solvent. β -CD- δ -VL inclusion complex showed a high initiation activity. On the contrary, adamantane inhibited the polymerization activity of β -CD. The formation of the inclusion complex between CD and lactone is important to initiate the ring-opening polymerization of lactones. The FT-IR spectra indicated that the appropriate combination of CDs and lactones forms a hydrogen bond between the carbonyl oxygen of lactones and the hydroxyl group of CDs to activate lactone in the CD cavity. The complex formation and the polymerization behavior in the mixture of β -CD and δ -VL were followed by the solid-state NMR techniques. On the basis of the above results, the polymerization mechanisms were proposed. These processes are similar such that the substrate is noncovalently bound to the active site on the enzyme to catalyze target molecules in the pocket, and the products are released from the active site. This study should contribute to the development of new catalytic systems. Now, we are studying the propagation of poly(lactone)s with high molecular weight using CDs.

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Supporting Information Available: Text giving the experimental method of the polymerizations of lactones with CDs and the polymerization of δ -VL with methanol and figures showing the FT-IR spectra of β -BL and ϵ -CL with CDs, text discussing the polymerization of δ -VL with DM- β -CD and figures showing the FT-IR spectra of δ -VL with DM- β -CD, The time-conversion curve for the polymerization of δ -VL with β -CD calculated by the integral value of the ^{13}C 1pda/MAS NMR spectra, and the characterization of the polyesters (^1H and ^{13}C NMR spectra of mono-2-*O*-poly(δ -VL)- β -CD, mono-2-*O*-BnOPen- β -CD, and mono-2-*O*-BnOPen-poly(δ -VL)- β -CD in DMSO- d_6 and the MALDI-TOF mass spectra of 2-*O*-poly(δ -VL)- γ -CD, 2-*O*-poly(ϵ -CL)- β -

CD, mono-2-*O*-BnOPen-poly(δ -VL)- β -CD). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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