

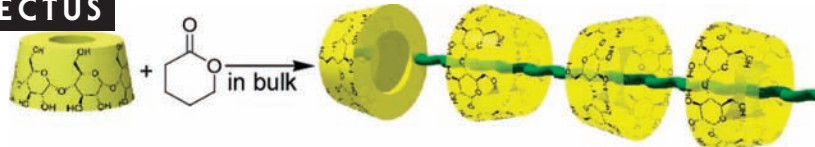
Ring-Opening Polymerization of Cyclic Esters by Cyclodextrins

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CONSPICUOUS



Synthetic polymers, typically prepared by addition polymerization or stepwise polymerization, are used constantly in our daily lives. In recent years, polymer scientists have focused on more environmentally friendly synthetic methods such as mild reaction conditions and biodegradable condensation polymers, including polyesters and polyamides. However, challenges remain in finding greener methods for the synthesis of polymers. Although reactions carried out in water are more environmentally friendly than those in organic solvents, aqueous media can lead to the hydrolysis of condensation polymers. Furthermore, bulk polymerizations are difficult to control.

In biological systems, enzymes synthesize most polymers (proteins, DNAs, RNAs, and polysaccharides) in aqueous environments or in condensed phases (membranes). Most enzymes, such as DNA polymerases, RNA polymerases, and ribosomes, form doughnutlike shapes, which encircle the growing polymer chain. As biopolymers form, the active sites and the substrate-binding sites are located at the end of the growing polymer chain and carefully control the polymerization. Therefore, a synthetic catalyst that could insert the monomers between the active site and binding site would create an ideal biomimetic polymerization system. In this Account, we describe cyclodextrins (CDs) as catalysts that can polymerize cyclic esters (lactones and lactides). CDs can initiate polymerizations of cyclic esters in bulk without solvents (even water) to give products in high yields.

During our studies on the polymerization of lactones by CDs in bulk, we found that CDs function not only as initiators (catalysts) but also as supporting architectures similar to chaperone proteins. CDs encircle a linear polymer chain so that the chain assumes the proper conformation and avoids coagulation. The CDs can mimic the strategy that living systems use to prepare polymers.

Thus, we can obtain polyesters tethered to CDs without employing additional solvents or cocatalysts. Although CD has many hydroxyl groups, only one secondary hydroxyl group attaches to the polyester chain. In addition, the polymerization is highly specific for monomer substrates. We believe that this is the first system in which the catalyst includes monomers initially and subsequently activates the included monomers. The catalyst then inserts the monomers between the binding site and the growing chain. Therefore, this system should provide a new environmentally friendly route to produce biodegradable functional polymers.

Introduction

In recent years, developing renewable polymers has received much attention from the viewpoints of environmental protection and efficient utilization of natural resources. Many researchers, including our group, have investigated renewable and biodegradable polymers like carbohydrates (polysaccharides) and polyesters. However, catalysts containing metal ions and some organic solvents are harmful and not suitable in the synthesis

of these polymers. In biological systems, enzymes such as DNA- or RNA-polymerases synthesize biomacromolecules with a high efficiency and selectivity. Enzymes and their models have been widely studied as new catalysts for organic syntheses with highly controllable reactivity and environmental affinity, and select enzymes have been used as catalysts in polymer syntheses.^{1–3} For example, we have examined cyclodextrins (CDs) as a catalyst to synthesize renewable polymers.^{4,5}

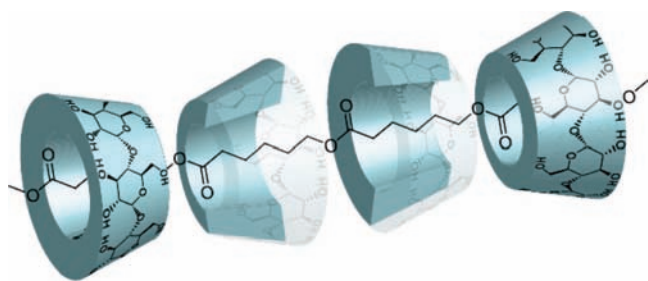


FIGURE 1. Inclusion complex of polyester with α -CD.

Although the unique inclusion properties and selective reactivities of CDs^{6,7} once attracted the attention of chemists as enzyme models, reactions promoted by CDs have been limited to the hydrolysis of activated esters like nitrophenyl esters in basic conditions. Moreover, although the acceleration and selectivity of ester hydrolysis by CDs have been somewhat improved, excessive amounts of CDs are required for these reactions. Accordingly, the utilization of CDs as synthetic reagents has been limited. Herein, we report that CDs initiate the ring-opening polymerization of cyclic esters without solvent to give polyester-tethered CD in high yield.

Cyclodextrin as an Initiator of Polymerization

Formation of Inclusion Complexes of CDs with Polymers. Previously, we have found that CDs form inclusion complexes with certain polymers with high selectivities in water. α -CD forms a complex with poly(ethylene glycol) (PEG) to give a crystalline compound in high yield.⁸ However, β -CD does not yield a complex with PEG. On the other hand, β -CD does provide a complex with poly(propylene glycol) (PPG) in high yield, whereas α -CD does not. γ -CD forms complexes with poly(methyl vinyl ether) (PMVE) efficiently, but α -CD does not provide complexes with PMVE, which have the same composition as PPG.⁹ Hence, the cross-sectional area of the polymer and the size of the CD cavity are well correlated. These results suggest that the polymer chain is included in the CD cavity. X-ray crystallographic data of the complex of α -CD with hexa(ethylene glycol) has demonstrated that CDs form a column, and ethylene glycol is included in a channel formed by CDs.^{10,11} A variety of supramolecular structures using CDs

have been investigated.¹² Recently, we successfully observed the threading process of CDs onto the polymer chain in real time.¹³ Threading dynamics have also been observed using a CD covalently attached to PEG,^{14,15} as well as the manipulation of CD ring entrapment on a polymer chain using a cantilever of a scanning tunneling microscope (STM).¹⁶

Later, we found that CDs form inclusion complexes not only with hydrophilic polymers but also with hydrophobic polymers to give inclusion compounds.¹⁷ CDs can form inclusion complexes even with inorganic polymers such as poly(dimethylsiloxane) and poly(dimethylsilane).^{18–20} Furthermore, CDs can form an inclusion complex even in the bulk state without water.²¹

Formation of Inclusion Complexes of CDs with Polyesters. Previously, we found that CDs form inclusion complexes with poly(ϵ -caprolactone) (poly(ϵ -CL))²² or poly(alkylene adipates) to give pseudo-polyrotaxanes (Figure 1).²³ Additionally, other researchers have also reported that other polyesters are included in CDs.²⁴

While preparing inclusion complexes of poly(ϵ -CL) with α -CD in an aqueous solution, we found that the polymer is easily hydrolyzed to give its oligomers and monomers under mild conditions. However, a polymer without CDs is not hydrolyzed under the same conditions.

Hydrolysis of Polyesters by Various Carbohydrates. Treating the polyesters with various carbohydrates (methyl glucoside, dextrin, dextran, and pululan) does not affect the hydrolysis of the polyester in a basic aqueous solution (pH = 12). In contrast, polyester is easily hydrolyzed to give its oligomers and monomer in CD cavities under the same mild conditions (Figure 2).

Interactions of CDs with Lactones. We found that CDs selectively form inclusion complexes with certain lactones (starting materials for polyesters). In addition, the hydrolyses of some lactones can be catalyzed according to the sizes of CDs in water (Scheme 1).²⁵ These behaviors are probably due to the high basicity of the secondary hydroxyl groups of CDs.

Polymerization of Lactones by CDs. CDs easily hydrolyze polyesters in water. Lactones are also hydrolyzed by CDs

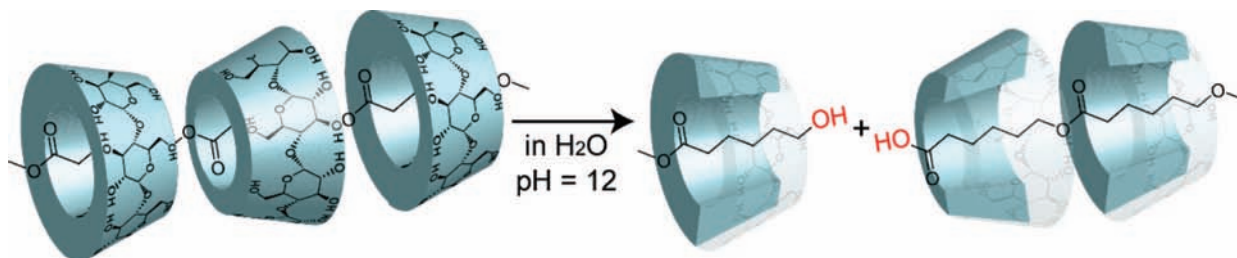
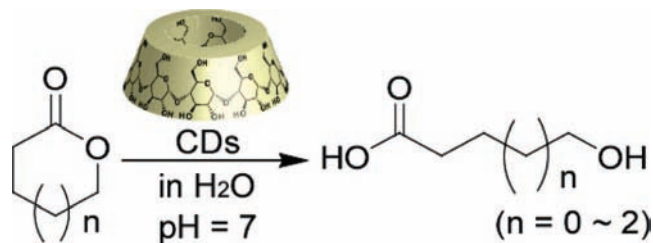
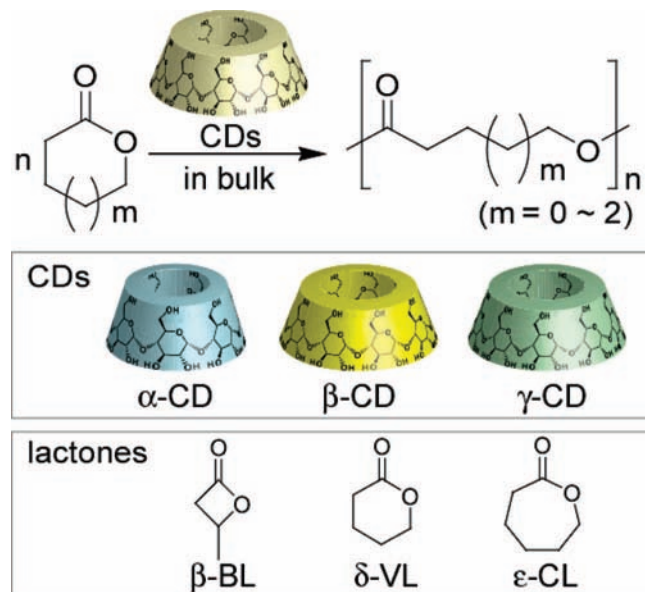


FIGURE 2. Hydrolysis products of polyesters in the presence of CDs.

SCHEME 1



SCHEME 2



in water. Hence, we speculated that if lactones are heated with CDs in bulk without water, they might form polymers because hydrolysis cannot occur. To examine this hypothesis, we employed α -, β -, and γ -CDs as catalysts, and β -butyrolactone (β -BL), δ -valerolactone (δ -VL), and ϵ -caprolactone (ϵ -CL) as monomers (Scheme 2).

Experimental Procedure. We carried out the polymerization of lactones with CDs using the following method. First, CDs were placed in a Schlenk tube and dried at 80 °C under a high vacuum. Then under an Ar atmosphere, lactone was added onto the CD without a solvent. Then the mixture of CD and lactone was stirred and heated at 100 °C under an Ar atmosphere. Although most cyclic esters are liquids, CD is insoluble in lactones. The heterogeneous mixture became viscous and solidified over time (Figure 3). The product was dissolved in *N,N'*-dimethylformamide (DMF), and the solution was poured into tetrahydrofuran (THF) to remove unreacted CD. The polymer was obtained after drying the THF solution.

Polymer Formation. When a mixture of δ -VL and β -CD was heated at 100 °C, poly(δ -VL) was obtained in a quantitative yield after 48 h. However, δ -VL did not yield a polymer without CDs under the same conditions. γ -CD also gave a

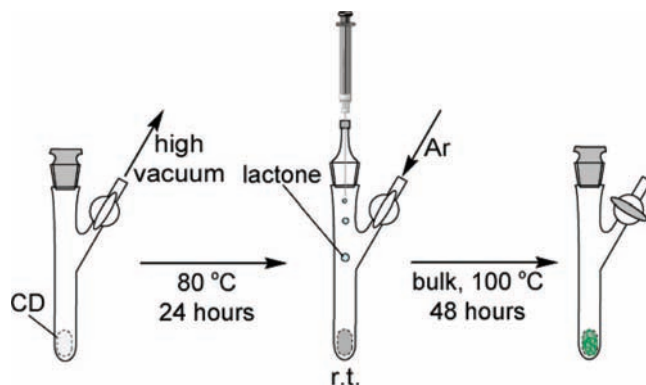
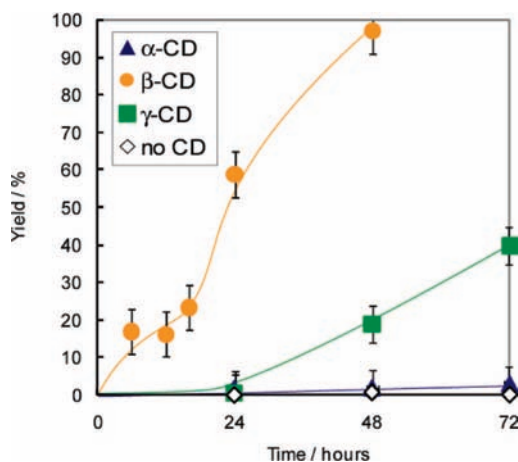
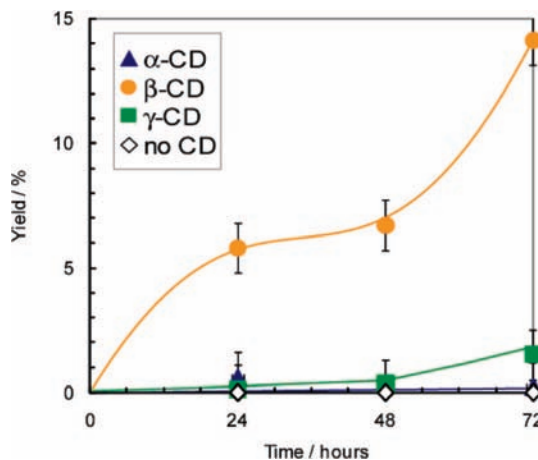


FIGURE 3. Polymerization of lactones with CDs.

FIGURE 4. Polymerization of δ -VL with CDs.FIGURE 5. Polymerization of ϵ -CL with CDs.

polymer but in a lower yield. In contrast, α -CD did not produce polymers (Figure 4).

Similar results were obtained in the case of ϵ -CL but with yields lower than those of δ -VL (Figure 5) due to the lower reactivity of ϵ -CL.

In contrast, when β -BL, a smaller lactone, was used, α -CD and β -CD gave poly(β -BL) in high yields. γ -CD gave poly(β -BL) in lower yields (Figure 6).

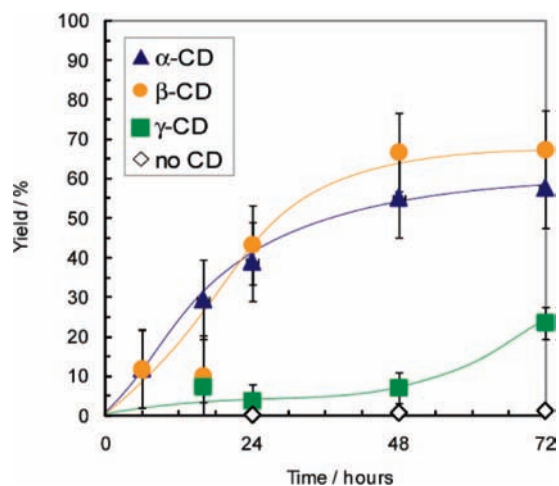
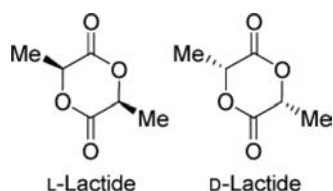


FIGURE 6. Polymerization of β -BL with CDs.

SCHEME 3



Whereas a smaller lactone (β -BL) gave polyester in higher yields with a smaller CD (α - and β -CD), a larger lactone (δ -VL) gave polyester in higher yields with a larger CD (β - and γ -CDs). These results indicate that the reactions occur by incorporating lactones into the CD cavities.²⁶

The polymerization behavior depended on temperature. Polymerization occurring below 100 °C had a decreased yield due to the low activity of the monomers. At higher temperatures (> 100 °C), CD decomposed during the reaction. Hence, 100 °C is the most appropriate condition for the reaction.

Polymerization of lactide (LA, Scheme 3), which is one of the most important monomers for biocompatible and biodegradable polymer synthesis,²⁷ was also successful using CDs. The polymerizations of LA were initiated by mixing with CD and heating at 100 °C in bulk. The order of the polymer yields with CDs was γ -CD > β -CD > α -CD. Furthermore, CDs initiated the polymerizations of D-LA more efficiently than those of L-LA, demonstrating chiral selectivity for the monomer. These results also indicate that the inclusion ability of the CD cavity is important in the polymerization. LA is solid at room temperature; hence, the reactivity is lower than those of liquid lactones due to its low mobility in the bulk reaction. However, when liquid δ -VL was added to the reaction mixture of CD and LA in bulk to perform copolymerization, the yield of poly(LA) increased. δ -VL probably assists in dissolving LA to enhance the mobility of LA in the bulk mixture.²⁸

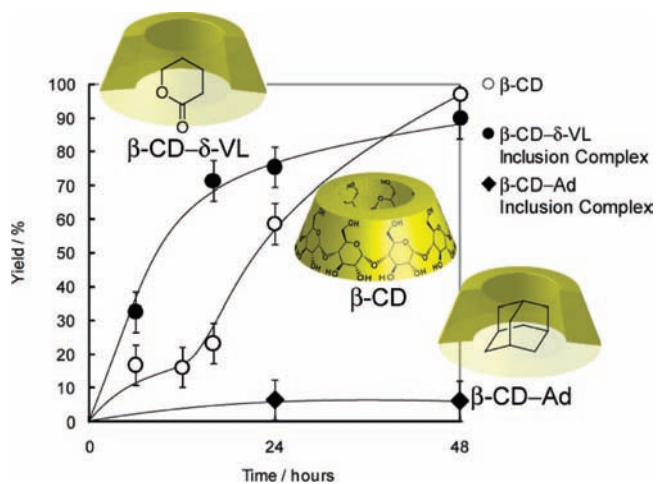


FIGURE 7. Polymerization of δ -VL in the presence of β -CD or its inclusion complexes with δ -VL or adamantane.

Polymerization of cyclic esters was also studied by Palmans and Meijer.²⁹ They used enzymes such as lipase or Novozym as a catalyst to show a high stereoselectivity for chiral lactones. These polymerizations do not require toxic metal catalysts. From the aspects of the highly controlled polymerization ability and environmental acceptability, organic polymerization catalysts like CDs and enzymes should receive much attention in the future.

Initiators. When intact β -CD was used as the initiator for the polymerization of δ -VL, there was an induction period before polymerization was initiated. In contrast, when inclusion complexes of δ -VL with β -CD were used as the initiator for the polymerization of δ -VL, polymerization started efficiently (Figure 7). On the other hand, when the inclusion complex of β -CD with adamantane (Ad), which is included in the β -CD cavity, was used as the initiator, polymerization of δ -VL did not occur. These results indicate that the formation of inclusion complexes is the rate-determining step for the polymerization reactions.

A model compound, mono-2-O-(6-benzyloxypentanoyl)- β -CD (2-BnOPen- β -CD),³⁰ was found to initiate the polymerization of lactones to give polyesters, despite the fact that there is not a hydroxyl group at the end of the polymer chain (Figure 8). The lactones were assumed to be inserted between CD and the polymer chain. This result indicates that polymerization proceeds via inclusion and insertion of the monomers between CD and the polymer chain.

Structures of the Polymers. We hypothesized the plausible structures of the polymers formed during polymerization. If inclusion polymerization occurs, then pseudopolyrotaxanes would be formed. If the hydroxyl group acts as a nucleophile for lactone, then polyesters covalently attached to CD would be formed.

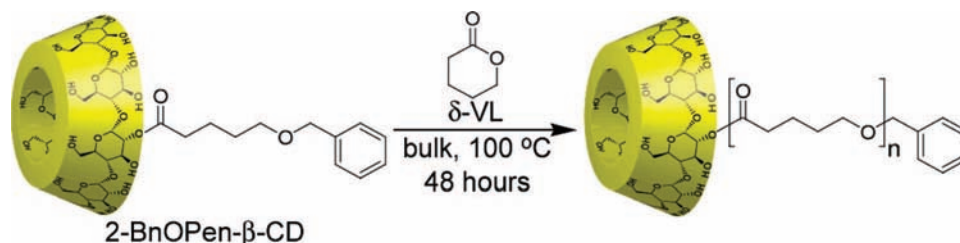


FIGURE 8. Polymerization of δ -VL initiated by the model compound, 2-BnOPen- β -CD.

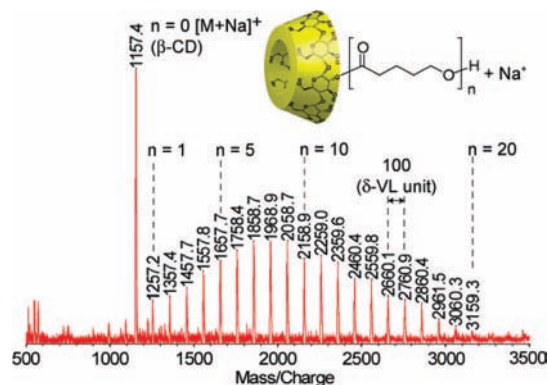


FIGURE 9. MALDI-TOF mass spectrum of the product obtained from the mixture of β -CD and δ -VL.²⁶

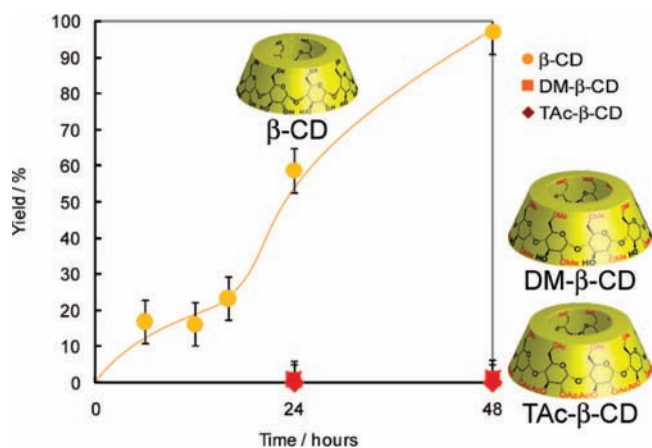


FIGURE 10. Polymerization of δ -VL with CD derivatives.

The matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrum of poly(δ -VL), which was obtained from the product of β -CD and δ -VL, showed that each signal appeared at 100 amu intervals (corresponding to a δ -VL monomer unit) from the signal of β -CD (Figure 9). It is noteworthy that other signals at a lower molecular weight than β -CD are not present, because this indicates that each polymer involves a single β -CD at the end of the polymer chain. Other polymers, poly(ϵ -CL) and poly(β -BL) initiated by CDs, gave similar mass spectra.

CD Derivatives as Initiators. 2,6-Di-*O*-methyl- β -CD (DM- β -CD) and 2,3,6-tri-*O*-acetyl- β -CD (TAc- β -CD) were unreactive in the polymerization of lactones (Figure 10). These results indicate that the inclusion of lactones in the CD cavity and sec-

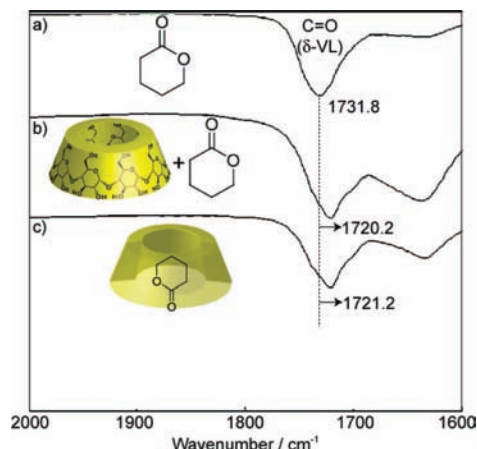


FIGURE 11. IR spectra of δ -VL (a), the bulk mixture of β -CD and δ -VL (b), and β -CD- δ -VL inclusion complex (c).

ondary hydroxyl group at the C₂-position of CDs play important roles in initiating polymerization.

Activation of Lactones in CDs. Figure 11 shows the FT-IR spectra of δ -VL, a bulk mixture of β -CD and δ -VL, and the inclusion complex of β -CD and δ -VL. δ -VL showed a characteristic band for the stretching mode of the C=O bond at 1731.8 cm⁻¹. However, this IR band shifted to a lower frequency in the presence of β -CD. The spectra showed that the lactone is included in the CD cavity by mixing CD and lactone.³¹ It has been reported that the IR band of the carbonyl group shifts to a shorter wavenumber upon forming a hydrogen bond between the hydroxyl group of CD and the carbonyl oxygen of the guest molecule^{32,33} and that lactones are activated by hydrogen bond formation.³⁴ These results indicate that lactones are activated in the CD cavity with a hydrogen bond between the carbonyl of δ -VL and the hydroxyl group of CD during polymerization.

The C=O band of lactones shifted according to the cavity sizes of CDs. These shifts can be seen in the presence of CD with polymerization activity for each lactone, supporting our hypothesis that CDs recognize lactones in bulk.

The band for a mixture of DM- β -CD with δ -VL, which did not display polymerization activity, did not shift, indicating that the C₃-position of CD does not form hydrogen bonds. However, the hydroxyl groups at the C₂-position of native CDs play

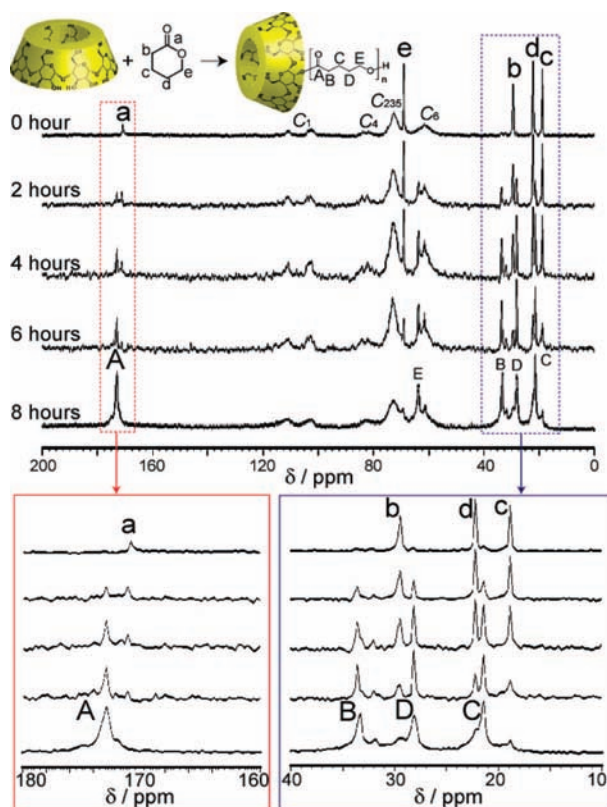


FIGURE 12. Time dependence of ^{13}C 1pda/MAS NMR spectra of the mixture of β -CD and δ -VL at 100°C .

a role in the activation of lactones by forming hydrogen bonds in the initiation step.

Observation of the Propagation of the Polyester. Figure 12 shows the 1pda/MAS (single pulse with ^1H decoupling/magic angle spinning) NMR spectra of a mixture of β -CD and δ -VL recorded every two hours at 100°C . The 1pda/MAS NMR spectra support bulk reactions because the 1pda/MAS NMR method enhances the peak intensity for mobile regions such as liquid and molten polymers with the nuclear Overhauser effect. Although signals (A–E) for poly(δ -VL) were not observed in the early stage, these signals increased with time, while the peaks (a–e) of δ -VL decreased with time. Figure 13 shows the time–conversion curve for this polymerization. The conversion was determined by the NMR integral values of the monomer (I_{monomer}) and the polymer (I_{polymer}) obtained in the solid-state NMR measurements. The conversion of poly(δ -VL) increased with time, indicating the propagation of poly(δ -VL) in bulk. The solid-state NMR measurement revealed chain growth of the polymer in the solid state.

Mechanism. Figure 14 shows plausible mechanisms for the formation of the polyester-tethered CD. The first step is the inclusion of lactone in the CD cavity to form a 1:1 inclusion complex. The carbonyl carbon of the included lactone is activated by forming a hydrogen bond between the carbonyl oxy-

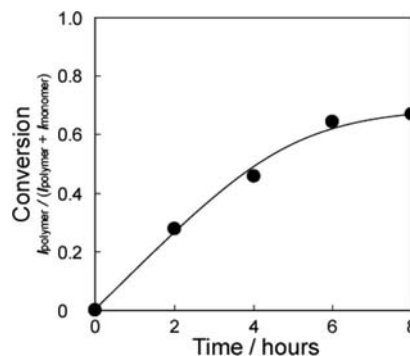


FIGURE 13. Time–conversion curve of the polymerization of δ -VL initiated by β -CD.

gen of lactone and the hydroxyl group of CD. A secondary hydroxyl group at the C_2 -position of a CD nucleophilically attacks the activated carbonyl carbon of the lactone to cleave the carbonyl–oxygen bond and form an ester bond. The monomer-attached CD is formed in the initial step.

Figure 14a–c shows three plausible propagating mechanisms. Mechanism a is unlikely because the model compound (2-BnPen- β -CD without hydroxyl groups at the end of the polymer chain) initiates polymerization of δ -VL. In mechanism b, recognition, activation, and insertion of the monomers serially occur to give 2-O-poly(ester)-CDs. Accordingly, the lactones are inserted into the ester bond between CD and the polyester chain. Generally, the oxygen next to a carbonyl group is weak for nucleophilic attack. The activation of monomers in the CD cavity might allow this mechanism. However, we propose another polymerization mechanism c. The hydroxyl group of the monomer-attached CD attacks the carbonyl group of the included lactone in the CD cavity to form a disubstituted CD. Then, the hydroxyl group of the monomer moiety immediately attacks the carbonyl carbon of the other monomer moiety so as to insert the lactone into the ester bond between CD and the polymer chain.³⁵

These processes are similar to enzymes that bind substrates noncovalently to their active site to catalyze target molecules and release products from the active site. Kobayashi et al. have employed enzymes to polymerize various monomers, phenol derivatives, sugars, and lactones.³⁶ CDs, which have a simple structure compared with enzymes, show a high activity for lactones.

Artificial Molecular Chaperone

Post-polymerizations by Polyester-Tethered CDs. After the monomers were completely consumed by the polymerization, new monomers were added to the reaction mixture, and further polymerization occurred (Figure 15).

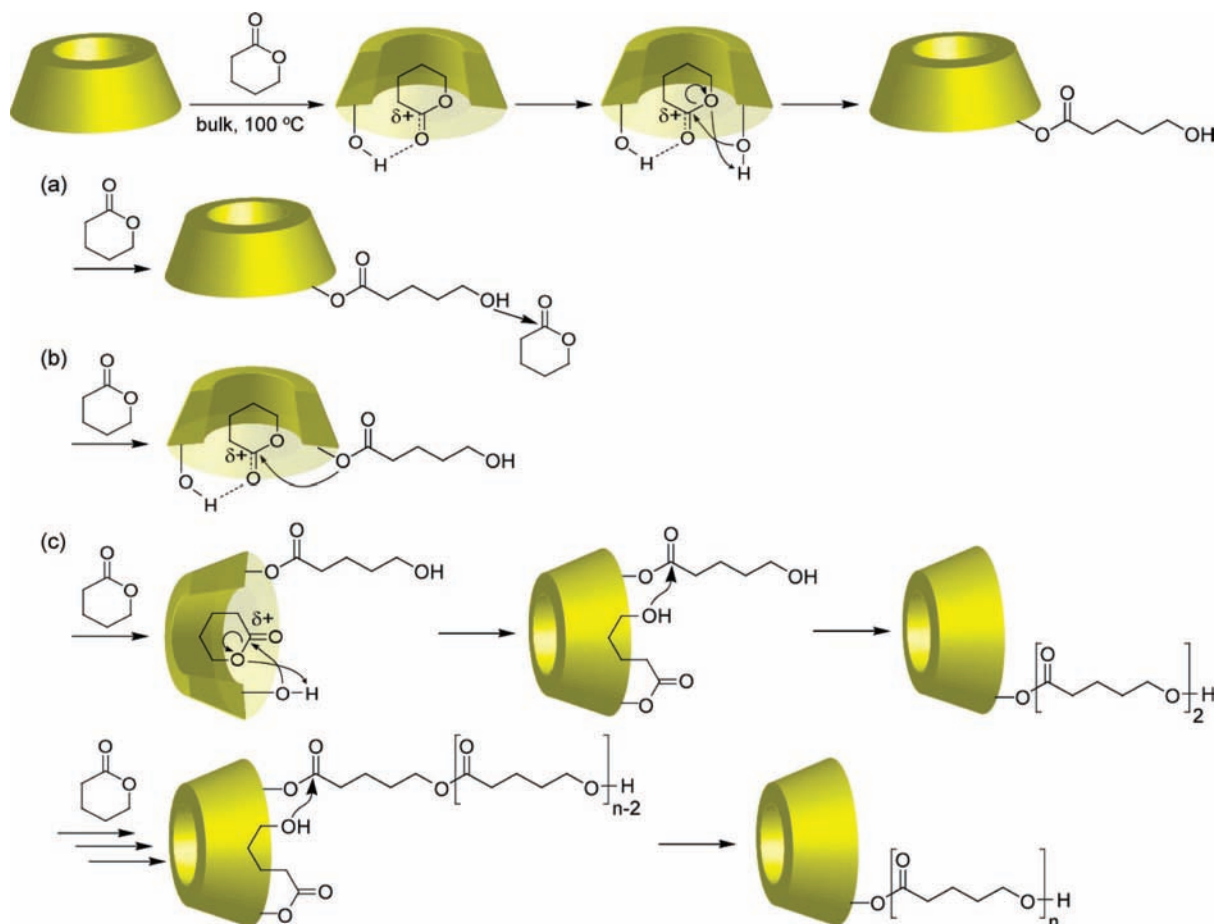


FIGURE 14. Proposed mechanism of the polymerization of lactone by CD.

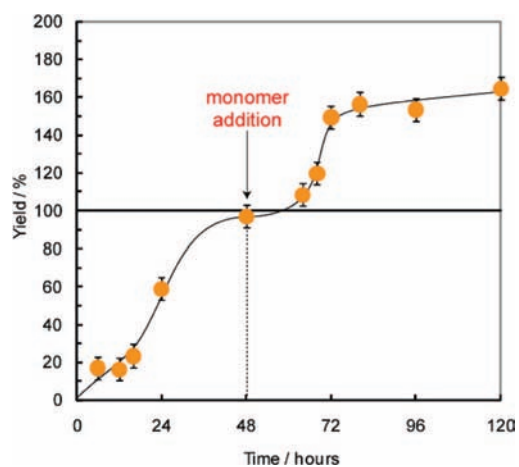
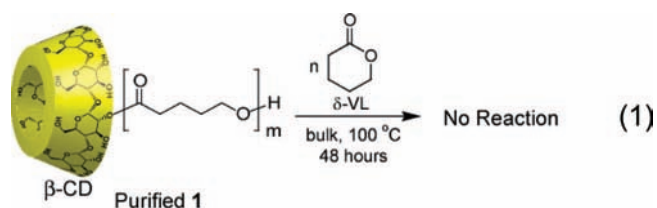


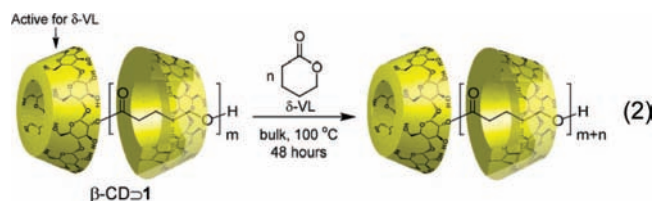
FIGURE 15. Post-polymerization of δ -VL by β -CD.

We speculated that the β -CD at the end of the polymer chain could include lactone and reinitiate polymerization. 2-*O*-poly(δ -VL)- β -CD (**1**) was isolated from the mixture of β -CD and δ -VL by precipitation with DMF and THF. However, once the product polymer was purified, purified **1** could not reinitiate the polymerization of the new monomers, and the polymer chain was not elongated (eq 1).

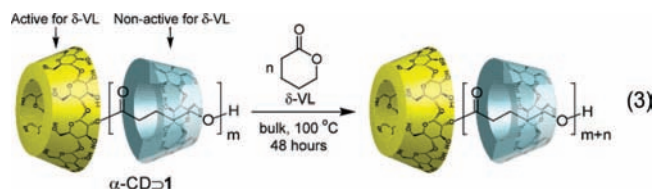


However, when we used the polymer washed only with water, further polymerization of new monomers was observed. In this case, the polyester chain was included by other β -CDs to give pseudo-polyrotaxane (β -CD \supset **1**). The molecular weight of the polymer increased compared with those by the first polymerization (eq 2). Thus, we propose that the polymer chain is extended, and the CD cavities are opened for the new monomers by polyrotaxane formation so as to reinitiate polymerization. We prepared pseudo-polyrotaxane β -CD \supset **1** from the purified **1** and new β -CD. Whereas purified **1** could not initiate the polymerization, β -CD \supset **1** reinitiated the polymerization to give polyesters with higher molecular weights.

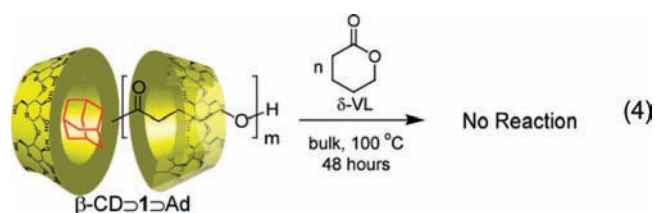
Although α -CD cannot initiate polymerization of δ -VL, when α -CD was added onto **1** to give pseudo-rotaxane (α -CD \supset **1**), α -CD \supset **1** reinitiated the polymerization of lactone (eq 3), indi-



indicating that β -CD at the end of the polyester chain reinitiates the polymerization of lactone.



Adamantane (Ad), which is strongly included in the cavity of β -CD, was used as a competitive guest.⁵ β -CD>1>Ad (β -CD>1 with Ad included in the β -CD cavity at the end of **1**) did not show polymerization activity for δ -VL (eq 4). Thus, δ -VL is not initiated by β -CDs on the polymer chain of β -CD>1>Ad.



These observations suggest that the β -CD at the end of **1** is the active site for polymerization and that the unmodified CDs threaded onto **1** do not have the polymerization activity. CDs threading onto **1** cannot include δ -VL because they have already a polymer chain in their cavities. Therefore, these threading CDs likely play a supplementary role to control the structure of **1** in the polymerization.

Structures of Pseudo-polyrotaxane CDs>1 and 1 in Bulk. The propagating behaviors of the polymer chain in the presence of the threading CDs were studied by spin–lattice

relaxation time (T_1) measurements with solid-state NMR spectroscopy. The T_1 value of polymer chain in β -CD>1 was shorter than that of **1**, indicating that β -CD>1 has a higher mobility than **1**. The increased mobility of β -CD>1 is probably because the polymer chain is isolated from the neighboring polymer chain upon forming a pseudo-polyrotaxane.

We proposed the mechanism to reinitiate polymerization of δ -VL by **1** or CDs>1 in bulk. Figure 16 shows the proposed structures of **1** and β -CD>1. The polymer chain of **1**, which forms a random coil conformation in an amorphous state, has a lower mobility, which is affected by inter- or intrapolymer chain interactions. Steric hindrance of the polymer chain attached to β -CD makes it difficult for monomers to approach the active site of β -CD at the end of **1**. The β -CD moiety at the end of **1** does not have an inclusion ability for a new δ -VL molecule. However, in pseudo-polyrotaxane β -CD>1, CDs threaded onto the polymer chain may prevent the polymer chain from taking a random coil conformation. Another new δ -VL is accessible to the β -CD cavity at the end of the polymer chain and is inserted at the ester bond between β -CD and the polymer chain. Thus, the polymer chain is extended with a higher mobility in the β -CD channel.³⁷

Conclusion

CDs selectively initiate ring-opening polymerizations of cyclic esters to give polyesters with a CD ring at the end of the polymer chain in high yields without cocatalysts or solvents. Monomers are included and activated in the appropriate CD cavity. This mechanism is similar to that of an enzyme because the substrate is noncovalently bound to the active site and the products are released from the active site.

Moreover, we found that β -CD-tethered poly(δ -VL) (**1**) propagates with the formation of pseudo-polyrotaxane (CDs>1), which is necessary to initiate further polymerization. β -CD at the end of CDs>1 is the active site for the polymerization. On the other hand, similar to a chaperone protein in a biological

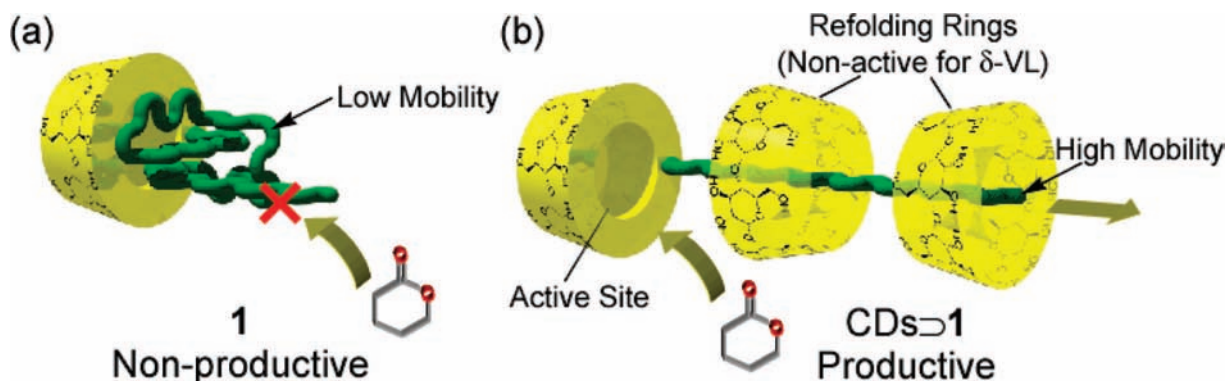


FIGURE 16. Schematic representations of the mechanism to reinitiate polymerization of δ -VL by **1** or CDs>1 in bulk at 100 °C.

system, which assists protein folding and allows the functional state of proteins, CDs threaded onto **1** are essential for maintaining the propagating state of the polyester. CDs showed activities not only to activate and transform monomers like enzymes but also to refold polymer chains as an artificial chaperone. Hence, this study should contribute to the development of new catalytic systems. Furthermore, this method has potential in the industrial syntheses of environmentally benign polymers and biodegradable polymers because the reaction occurs by heating the initiator and the monomer without solvent to give products with increasing molecular weights as the monomer feed increases.

BIOGRAPHICAL INFORMATION

Akira Harada (born in Osaka, Japan, in 1949) received his Ph.D. from Osaka University (1977). From 1979 to 1980, he worked for IBM Research, San Jose, CA, as a visiting scientist, and then served as a Postdoctoral Fellow at Colorado State University (1980–1981). Prior to joining the faculty of Science at Osaka University, he was a faculty member at the Institute of Scientific and Industrial Research, Osaka University. In 1990, he was a visiting scientist at the Scripps Institute. He is currently a Professor at the Graduate School of Science, Osaka University. He has received several awards, including the IBM Science Award (1993), the Osaka Science Award (1998), the Japan Polymer Society Award (1999), the Cyclodextrin Society Award (2004), and the Medals of Honour in Japan (Medal with Purple Ribbon) (2006). His research interests include supramolecular science, polymer synthesis, and biorelated polymers.

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