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Unzipping and Scrambling Reaction-Induced Sequence Control of Copolymer Chains via Temperature Changes during Cationic Ring-Opening Copolymerization of Cyclic Acetals and Cyclic Esters

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Abstract

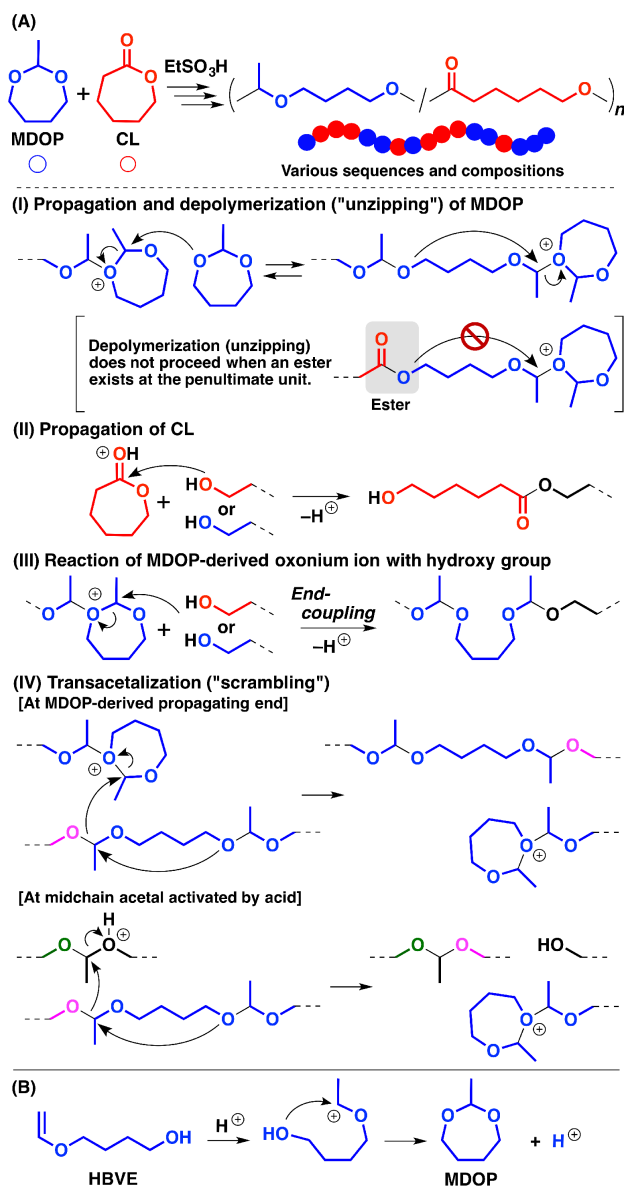
A temperature change-dependent sequence transformation of copolymer chains was demonstrated by a method based on tandem depolymerization and transacetalization reactions during the cationic ring-opening copolymerization of cyclic acetals and cyclic esters. In this study, the position of polymerization-depolymerization equilibrium was controlled by the reaction temperature rather than by the decrease in monomer concentration under vacuum conditions, as in our previous study. First, the conditions for efficient copolymerization were optimized, with a particular focus on the structures of cyclic acetals and cyclic esters. Subsequently, sequence transformation induced by temperature change was examined during the copolymerization of 2-methyl-1,3-dioxepane (generated in situ from 4-hydroxybutyl vinyl ether) and δ -valerolactone using EtSO_3H . The homosequence length of cyclic acetals decreased during depolymerization (unzipping) at the oxonium chain ends upon increasing the temperature from 30 to 90 °C, while transacetalization (scrambling) of the main chain transferred midchain cyclic acetal homosequences to the oxonium chain ends. As a result of the cycle of unzipping and scrambling reactions, an alternating-like copolymer was obtained. Interestingly, the possibility of reversible sequence transformation upon heating and cooling was also demonstrated.

1. Introduction

The synthesis of copolymers with desired sequences remains a challenge in the field of polymer science. In nature, biopolymers, such as proteins and nucleic acids, have strictly controlled sequences, which is the key for their sophisticated functions. In synthetic polymers, various kinds of well-defined diblock (or triblock) copolymers have been synthesized owing to the development of precision polymerization techniques and have been utilized for many applications, such as drug delivery systems,¹ thermoplastic elastomers,² and lithography.³ By contrast, there are limited examples of copolymers with more complex sequences, e.g., AB-,⁴⁻⁶ ABB-,^{7,8} or ABC-type⁹⁻¹¹ alternating structures, despite the potential high functionalities of these molecules. Sequence-regulated copolymers have been synthesized via several methods.¹²⁻²⁴ Each method has inherent advantages and disadvantages. For example, step-by-step monomer addition to a polymer chain (iterative method)^{12,13} is the most promising strategy for producing desired sequences, although a considerable amount of time and effort is necessary to generate a long chain. Polymerization of a monomer containing specific sequences of multiple monomer units is also very effective; however, the synthesis of such sequence-incorporated monomers usually requires cumbersome procedures.¹⁴⁻¹⁷ Polymerization of monomers with specific reactivities is the most practical method, although the need for very high selectivity during the propagation reactions limits the monomers that can be used.^{4-11,18,19} A new strategy and/or hybridization of existing methods are required for the synthesis of a much wider variety of sequence-regulated copolymers in a practical manner.

Previously, we demonstrated that the cationic ring-opening copolymerization of 2-methyl-1,3-dioxepane (MDOP) [generated via the isomerization of 4-hydroxybutyl vinyl ether (HBVE) in the very early stages of polymerization (**Scheme 1B**)] and ϵ -caprolactone (CL) with EtSO₃H produced copolymers with a wide variety of compositions and sequences (Scheme 1A).²⁵ Polymerization was initiated via the reaction of an MDOP monomer with protonated MDOP, forming a compound with an oxonium ion and a hydroxy group at each end. Starting from this compound, the propagation of MDOP and CL proceeded via the active chain end (ACE)²⁶ and activated monomer (AM)²⁷ mechanisms, respectively [Scheme 1A(I) and (II)]. Intra- and

intermolecular coupling reactions between the two ends also occurred [Scheme 1A(III)]. Interestingly, because of these copolymerization characteristics, a copolymer with alternating sequences was produced via an unprecedented strategy, as explained in the next paragraph.

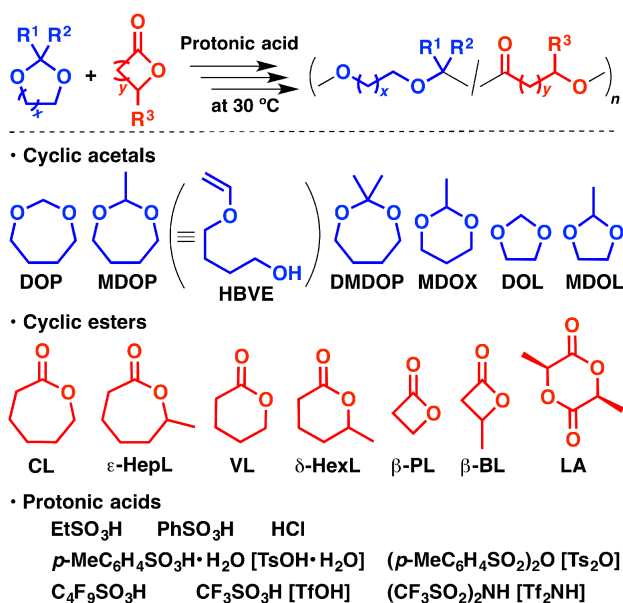


Scheme 1. (A) Cationic ring-opening copolymerization of MDOP and CL and (B) isomerization of HBVE to MDOP.

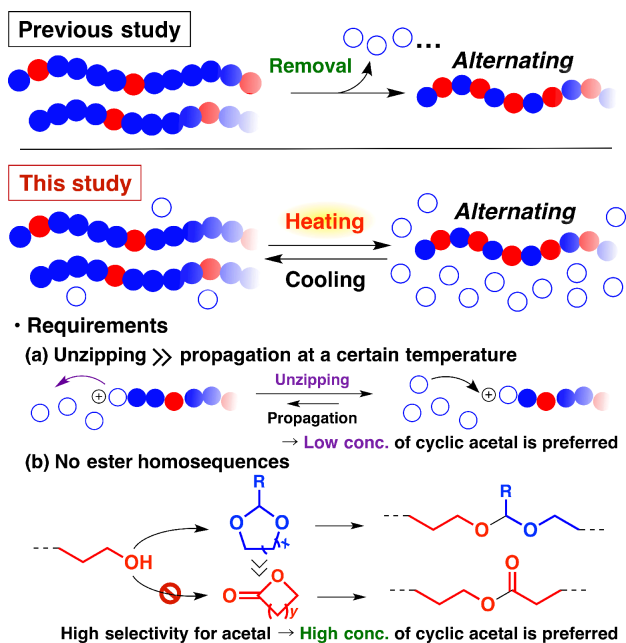
An alternating copolymer was synthesized via the preparation of a copolymer with no CL homosequences (prepolymer) and the subsequent removal of all the MDOP homosequences (Scheme S1).²⁵ The prepolymer was obtained by copolymerization with an excess of MDOP relative to CL. Subsequently, the pressure of the system was reduced by a vacuum pump, which

induced the transformation of the prepolymer to an alternating copolymer. This process was enabled by the combination of two reactions, i.e., depolymerization of MDOP at the oxonium end [unzipping; Scheme 1A(I)] and transacetalization [scrambling; Scheme 1A(IV)]. Specifically, the removal of MDOP monomers via vacuum promoted unzipping [Scheme S1(*i*)], although the unzipping stopped when an ester bond from a CL unit emerged next to an oxonium end [Scheme 1A(I), below]. Meanwhile, scrambling randomly rearranged the sequence and occasionally transferred MDOP homosequences from the midchain to the oxonium ends [Scheme S1(*ii*)], which led to immediate unzipping. The repetition of processes (*i*) and (*ii*) eventually removed all the MDOP homosequences, yielding an alternating copolymer. In this method, monomer pairs do not need to have specific selectivities in the propagation reactions; hence, a wide variety of copolymer sequences are achievable from a given monomer pair. The possibility of reversible sequence transformation is another advantage of this method.

In this study, we aimed to demonstrate the generality of the above-described sequence transformation. First, the copolymerization of a series of cyclic esters, cyclic acetals, and protonic acids was examined (**Scheme 2**) to observe the different kinetics. Then, alternating copolymer synthesis was investigated by changing the polymerization temperature (heating) instead of subjecting the samples to vacuum (**Scheme 3**). The temperature-dependent sequence transformation, which does not require the removal of cyclic acetals via vacuum, is very attractive because the copolymer sequences can be reversibly altered by changing the temperature. However, this method is more difficult than sequence transformation via vacuum because the unzipping of cyclic acetals needs to proceed predominantly over propagation at the oxonium ends even in the presence of cyclic acetal monomers. Thus, lower concentrations of cyclic acetals are desired [Scheme 3(a)]; however, the homopropagation of cyclic esters must be simultaneously prevented [Scheme 3(b)]. These requirements can be met when the crossover reaction from the cyclic ester-derived hydroxy ends to cyclic acetals is preferred over cyclic ester homopropagation. Thus, systematic investigations were performed with a specific focus on the selectivity of the propagation reaction from the cyclic ester-derived ends.



Scheme 2. Monomers and protonic acids used in this study.



Scheme 3. The goal of this study: sequence control in the copolymerization of cyclic acetals and cyclic esters via temperature change.

2. Experimental

2.1. Materials

HBVE (Aldrich; >99%), CL (TCI; >99.0%), β -propiolactone (β -PL; TCI; >95.0%), β -butyrolactone (β -BL; TCI; >95.0%), δ -valerolactone (VL; TCI; >98.0%), and δ -hexanolactone (δ -HexL; TCI; >99.0%) were distilled twice over calcium hydride under reduced pressure.

1,3-Dioxolane (DOL; TCI; >98.0%) was distilled twice over calcium hydride. Butyl acetate (Wako; >98.0%) was distilled over calcium hydride. 2-Methyl-1,3-dioxolane (MDOL; TCI; >98.0%) was distilled over calcium hydride and then lithium aluminum hydride. L-Lactide (LA; TCI; >98.0%) was recrystallized from 1,4-dioxane and then toluene before being dried for more than 3 h. 1,3-Dioxepane (DOP), 2-methyl-1,3-dioxane (MDOX), MDOP, and 2,2-dimethyl-1,3-dioxepane (DMDOP) were synthesized according to previously reported procedures.^{28–30} ϵ -Heptanolactone (ϵ -HepL) was synthesized by Baeyer–Villiger oxidation according to previously reported procedures.^{31,32} EtSO₃H (Aldrich; 95%), PhSO₃H (TCI; >98.0%), *p*-toluenesulfonic anhydride (Ts₂O; Aldrich; 97%), trifluoromethanesulfonic acid (TfOH; Aldrich; >99.0%), bis(trifluoromethanesulfonyl)imide (Tf₂NH; Wako; 98.0+%), and Ti(OBu)₄ (Alfa Aesar; 99+%) were used without further purification after preparing stock solutions in CH₂Cl₂. C₄F₉SO₃H (TCI; >98.0%) and *p*-toluenesulfonic acid monohydrate (TsOH·H₂O; TCI; >98.0%) were used without further purification after preparing stock solutions in CH₂Cl₂ (the acids were slightly insoluble). HCl (Aldrich; 1.0 M solution in diethyl ether) was used as received. Toluene (Wako; 99.5%) and CH₂Cl₂ (Wako; superdehydrated) were dried by passage through a solvent purification column (Glass Contour).

2.2. Polymerization Procedure

The following is a typical polymerization procedure. A glass tube equipped with a three-way stopcock was dried using a heat gun (Ishizaki; PJ-206A; the blowing temperature was ~450 °C) under dry nitrogen. CH₂Cl₂, HBVE, and CL were sequentially added to the tube using dry syringes. Polymerization was initiated by the addition of a solution of EtSO₃H in CH₂Cl₂. After predetermined intervals, aliquots were extracted from the reaction mixture using dry syringes and subsequently added to methanol containing a small amount of aqueous ammonia at room temperature. The quenched mixture was diluted with CH₂Cl₂ and then washed with water. The volatiles were removed under reduced pressure to afford the polymer. Monomer conversion was determined by ¹H NMR analysis of the quenched reaction mixture.

2.3. Acid Hydrolysis

Acid hydrolysis of the polymers was conducted with 0.5 M HCl(aq) in 1,2-dimethoxyethane at room temperature (except for the copolymer of HBVE and DOP) or 60 °C (for the copolymer of HBVE and DOP) for 3 h (polymer: approximately 0.5 wt%). The quenched mixture was diluted with CH₂Cl₂ and then washed with water. The volatiles were removed under reduced pressure at room temperature to yield the hydrolysis products.

2.4. Transesterification

Transesterification was conducted under a dry nitrogen atmosphere in a glass tube equipped with a three-way stopcock. The purified copolymer (16 mg) was dissolved in butyl acetate (5.2 mL), and then transesterification was initiated by the addition of a 200 mM Ti(OBu)₄ solution in CH₂Cl₂ (0.73 mL) at 70 °C. After 16 h, the reaction was quenched by diluting the reaction mixture with CH₂Cl₂, and then the mixture was washed with water to remove the resulting salt. The volatiles were removed under reduced pressure at 60 °C to yield the transesterification products.

2.5. Characterization

The molecular weight distribution (MWD) of each polymer was measured by gel permeation chromatography (GPC) in chloroform at 40 °C with two polystyrene gel columns [TSKgel GMH_{HR} × 2 (exclusion limit molecular weight = 4×10^6 ; bead size = 5 μm; column size = 7.8 mm I.D. × 300 mm); flow rate = 1.0 mL/min] connected to a Tosoh DP-8020 pump, a CO-8020 column oven, a UV-8020 ultraviolet detector, and an RI-8020 refractive-index detector. The number-average molecular weight (M_n) and polydispersity index [weight-average molecular weight/number-average molecular weight (M_w/M_n)] were calculated from the chromatographs with respect to 16 polystyrene standards (Tosoh; $M_n = 5.0 \times 10^2$ — 1.09×10^6 , $M_w/M_n < 1.2$). NMR spectra were recorded using a JEOL JNM-ECA 500 instrument (500.16 MHz for ¹H and 125.77 MHz for ¹³C) or a JEOL JNM-ECS 400 instrument (100.53 MHz for ¹³C). Electrospray ionization mass spectrometry (ESI-MS) was performed on an LTQ Orbitrap XL (Thermo Scientific). Polymer solutions in CH₂Cl₂/methanol (1/1 v/v) were used for the ESI-MS analysis. Differential scanning calorimetry (DSC) measurements were conducted using a Shimadzu DSC-60 Plus differential scanning calorimeter.

3. Results and Discussion

3.1. Cationic Copolymerization of Various Cyclic Acetals and Cyclic Esters with a Variety of Protonic Acids: Systematic Investigation of Effective Monomers and Catalysts for Copolymerization

We aimed to demonstrate the generality of the above-described sequence transformation. First, a series of cyclic esters, cyclic acetals, and protonic acids were examined for copolymerization (Scheme 2) to observe their different kinetics.

The copolymerization of HBVE (0.50 M) and CL (0.50 M) with EtSO₃H, which was studied previously²⁵ and is considered a standard system in this section, was conducted in CH₂Cl₂ at 30 °C. Both monomers were simultaneously consumed to yield a polymer with an M_n value of 3.8×10^3 (Figure 1A, black), and the average number of units per block was calculated to be 1.0/5.7 for HBVE/CL. However, to achieve alternating copolymer synthesis upon heating, more frequent crossover reactions from cyclic ester to cyclic acetal are needed. Therefore, in this first section, various kinds of monomers and catalysts were examined to determine the conditions needed to generate shorter cyclic ester blocks.

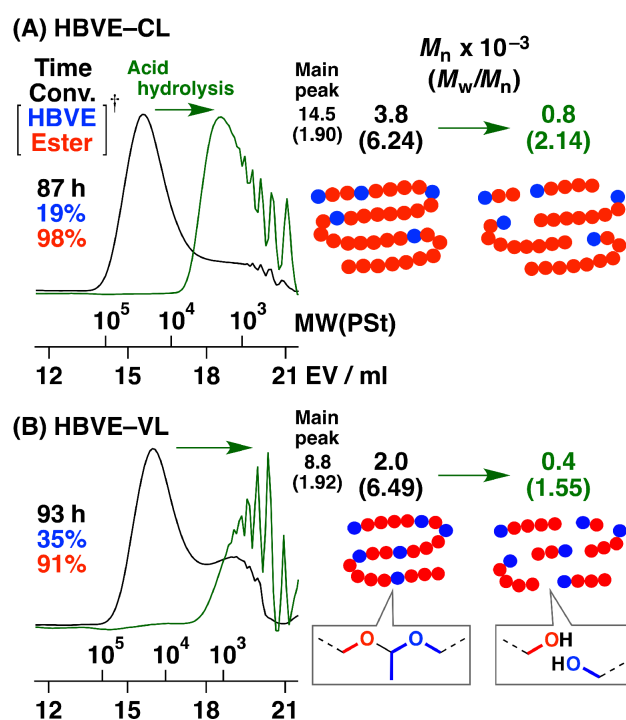


Figure 1. MWD curves of the copolymerization products (black) of HBVE with (A) CL (entry 1 in Table 1; the same sample as that reported in reference 25) or (B) VL (entry 5) and acid hydrolysis products (green); † conversion to polymer. See the footnote of Table 1 for the polymerization conditions.

3.1.1. Effects of Cyclic Esters

VL, a six-membered cyclic ester, was used for copolymerization with HBVE using EtSO₃H in CH₂Cl₂ or toluene (entries 4 and 5 in **Table 1**). Both monomers were simultaneously consumed in both solvents. The conversion of HBVE to polymer was relatively high compared to the standard system (entry 1), which suggested that crossover reactions occurred more frequently. The MWD curve of the product obtained in toluene (entry 5; Figure 1B, black) had a bimodal shape: the main products in the low-molecular-weight (MW) region were likely cyclic oligomers, as in the copolymerization of HBVE and CL (Figure 1A, black). The ¹H NMR spectrum of the product (**Figure 2A**) exhibited peaks derived from each monomer unit, and the integral ratio of each unit (not “units per block” but unit ratio) was calculated to be 1.0/3.4 for HBVE/VL. Direct evidence of copolymerization was, however, not provided by ¹H NMR analysis due to the overlap of crossover-derived peaks with the peaks of VL homosequences (for example, peaks *h* and *i*). In contrast, ¹³C NMR analysis suggested the generation of copolymers (Figure S2D).

Table 1. Cationic Copolymerization of HBVE and Various Cyclic Esters with EtSO₃H^a

entry	cyclic ester	solvent	time (h)	conv. to polymer (%) ^b		$M_n \times 10^{-3}$ ^c	M_w/M_n ^c	units per block ^{b,d}	
				HBVE	cyclic ester			HBVE	cyclic ester
1 ^e	CL	CH ₂ Cl ₂	87	19	98	3.8	6.24	1.0	5.7
2	ε-HepL	CH ₂ Cl ₂	162	8	39	1.3	2.17	n.d.	n.d.
3	ε-HepL	toluene	16	10	38	1.0	3.41	n.d.	n.d.
4	VL	CH ₂ Cl ₂	141	24	62	1.6	3.97	1.0–1.1	3.7–4.1
5	VL	toluene	93	35	91	2.0	6.49	1.0–1.1	3.4–3.7
6	δ-HexL	toluene	92	0	0	–	–	–	–
7	β-PL	CH ₂ Cl ₂	358	17	50	0.5	2.21	n.d.	n.d.
8	β-PL	toluene	310	14	54	0.3	2.37	n.d.	n.d.
9	β-BL	toluene	92	0	0	–	–	–	–
10	LA	CH ₂ Cl ₂	241	0	0	–	–	–	–

^a [HBVE]₀ = 0.50 M, [cyclic ester]₀ = 0.50 M, [EtSO₃H]₀ = 5.0 (entry 1) or 10 mM (entries 2–10), at 30 °C. See Figure S3 for ¹H NMR spectra and MWD curves (entries 2 and 7). ^b Determined by -

^1H NMR analysis. ^c Determined by GPC (polystyrene standards). ^d See the Supporting Information (Schemes S2 and S3, Figures S1 and S2, and a note on page S6) for the detail of these values. ^e The same sample as that reported in reference 25.

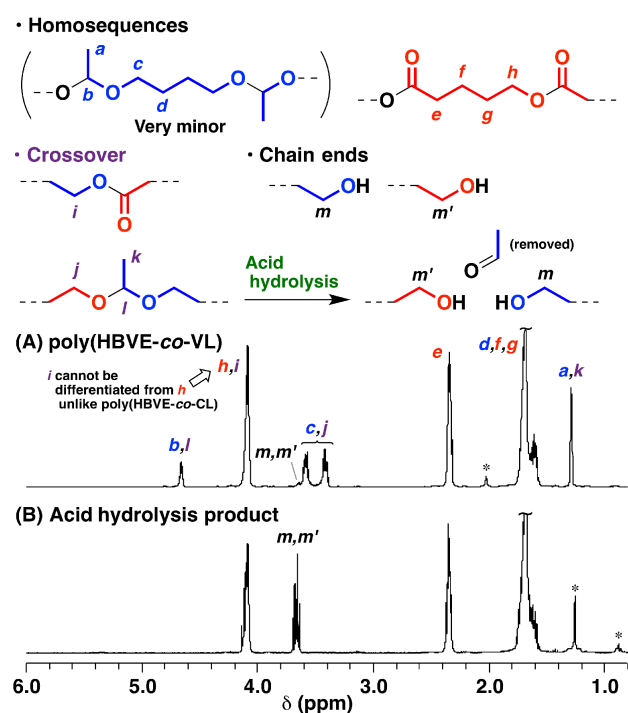


Figure 2. ^1H NMR spectra of (A) poly(HBVE-*co*-VL) (entry 5 in Table 1) and (B) its acid hydrolysis product. * Water or vaseline. Various structures resulting from transacetalization may be included in the main chain (see Schemes S2 and S3).

Acid hydrolysis of the product also revealed the successful formation of the copolymer. The MWD curve shifted significantly to the low-MW region after hydrolysis (Figure 1B, green) due to cleavage of the acetal moieties. The M_n value of the hydrolysis product, which mainly consists of VL homosequences, was 0.4×10^3 . This value is consistent with the copolymer structure having 1.0–1.1/3.4–3.7 HBVE/VL units per block (see page S6 in the Supporting Information for the determination of “units per block”). The presence of shorter VL blocks in the copolymer than in the CL counterpart indicates that VL has higher selectivity than CL for the crossover reaction in the copolymerization with HBVE, likely due to the lower reactivity of VL than of CL under the conditions examined because the chain end structures derived from each monomer do not have significant differences (Scheme S4).

The other cyclic esters were not effective for copolymerization with HBVE. δ -HexL, β -BL, and LA were not consumed at all (entries 6, 9, and 10 in Table 1). Copolymerization of ϵ -HepL or β -PL with HBVE proceeded slowly (entries 2, 3, 7, and 8). HBVE was more efficiently consumed in these copolymerization reactions than in the copolymerization with CL or VL, implying the occurrence of frequent crossover reactions. Indeed, the ^1H NMR spectra (Figure S3) showed that the peak intensities for the structure derived from cyclic ester-HBVE crossover were relatively strong. However, these copolymerizations suffered from low MWs. These cyclic esters would potentially be effective if copolymers with higher MWs are obtained, although the reason for the low MWs is currently unclear.

3.1.2. Effects of Cyclic Acetals

Next, various cyclic acetals were tested in the copolymerization with CL using EtSO_3H in CH_2Cl_2 at 30 °C (**Table 2**). All the cyclic acetals used were copolymerized with CL; however, in comparison with the standard system [entry 1 in Table 1 (HBVE was used); entry 2 in Table 2 (not HBVE but MDOP was used)], the conversions of cyclic acetals were lower, and the lengths of CL blocks were much longer. The MWD curves of the products obtained with DOP, DMDOP, MDOX, and DOL (entries 1, 3, 4, and 5; Figure S4) did not shift significantly and/or a part of the curves remained after acid hydrolysis, which indicated that these polymers had tiny amounts of CL-cyclic acetal heterosequences in a single chain and/or contained non-negligible amounts of CL homopolymers. The crossover reaction proceeded most frequently when MDOP was used (entry 2). The homosequences of cyclic acetals were not observed except in the case of DOP (entry 1).

The above-estimated copolymerizability of cyclic acetals with CL was less correlated to the homopolymerizability.^{30,33,34} For example, among all the cyclic acetals used, DOL was least consumed in the copolymerization with CL, although DOL has high homopolymerizability.³⁴ One possible pathway of the crossover reaction from CL to cyclic acetals is the nucleophilic attack of a CL-derived hydroxy end to a protonated cyclic acetal (Scheme 1A(III)), which corresponds to the AM propagation of cyclic acetals. By contrast, homopolymerization of cyclic acetals probably proceeds mainly via ACE propagation.³⁴ The inconsistency of the DOL homopolymerizability and

the copolymerization results likely stemmed from such differences. Further investigation is required for better understanding.

Table 2. Cationic Copolymerization of Various Cyclic Acetals and CL with EtSO₃H^a

entry	cyclic acetal	time (h)	conv. to polymer (%) ^b		$M_n \times 10^{-3}$ ($M_n \times 10^{-3}$ [hydrolysis]) ^c	M_w/M_n ^c	units per block ^b		equilibrium monomer conc. at 30 °C (M) ^d
			cyclic acetal	CL			cyclic acetal	CL	
1	DOP	47	14	100	1.6 (0.6)	3.24	n.d. ^e	n.d. ^e	0.84
2	MDOP	82	19	99	3.9 (0.8)	6.17	1.0	5.3	2.69
3	DMDOP	28	10	97	2.5 (1.7)	2.20	n.d. ^e	n.d. ^e	n.d.
4	MDOX	28	6	89	16.1 (9.8)	1.37	n.d. ^e	n.d. ^e	n.d.
5	DOL	47	6	97	23.3 (19.7)	1.79	n.d. ^e	n.d. ^e	2.08
6	MDOL	28	11	95	10.0 (5.5)	3.10	1.0	56	n.d.

^a [Cyclic acetal]₀ = 0.50 M, [CL]₀ = 0.50 M, [EtSO₃H]₀ = 5.0 (entry 2) or 10 mM (entries 1 and 3–6) in CH₂Cl₂ at 30 °C. See Figure S4 for ¹H NMR spectra and MWD curves. ^b Determined by ¹H NMR analysis. ^c Determined by GPC (polystyrene standards). ^d Calculated from previously reported ΔH and ΔS values (references 33 and 34). ^e Not determined because non-negligible amounts of CL homopolymer was likely generated as demonstrated by the results of acid hydrolysis (Figure S4).

3.1.3. Effects of Protonic Acids

Various kinds of sulfonic acids were effective for the copolymerization of HBVE and CL (**Table 3**). The M_n values of the copolymers obtained with these catalysts were comparable,^{35,36} whereas the MW of the main copolymer obtained with EtSO₃H was higher than those of the copolymers formed with all other sulfonic acids used. The polymerization rates were obviously different and varied according to the following order: PhSO₃H > EtSO₃H > TsOH·H₂O > Ts₂O. The concentration of EtSO₃H had little effect on the MWs and copolymer sequences (entries 1 and 2). Additionally, no significant difference in the length of the CL blocks was observed with these catalysts. By contrast, the other catalysts employed, such as TfOH and HCl, exhibited a strong tendency toward crossover. However, the MWs of the products obtained with TfOH and HCl were very low, most likely due to frequent hydrolysis during the polymerization (Figures S5 and S6), as in the case of copolymerization using ϵ -HepL or β -PL (entries 2 and 7 in Table 1). The hydrolysis was probably not derived from insufficient drying of reagents, considering a high-MW product obtained by the copolymerization with a monohydrate catalyst (entry 4 in Table 3).

Table 3. Cationic Copolymerization of HBVE and CL with Various Catalysts^a

entry	catalyst	(mM)	time (h)	conv. to polymer (%) ^b		$M_n \times 10^{-3}$ ^c	M_w/M_n ^c	$M_n \times 10^{-3}$ (main peak) ^c	units per block ^b	
				HBVE	CL				HBVE	CL
1	EtSO ₃ H	5.0	87	19	98	3.8	6.24	15.5	1.0	5.7
2	EtSO ₃ H	10	43	12	67	3.3	5.72	14.3	1.0	5.4
3	PhSO ₃ H	10	19	26	97	3.6	4.46	10.0	1.0	5.4
4	TsOH · H ₂ O	10	111	26	98	4.1	4.31	12.0	1.0	5.1
5	Ts ₂ O	10	112	16	79	2.9	5.33	9.8	1.0	5.5

^a [HBVE]₀ = 0.50 M, [CL]₀ = 0.50 M, in CH₂Cl₂ at 30 °C. See Figure S5 for MWD curves. ^b Determined by ¹H NMR analysis. ^c Determined by GPC (polystyrene standards).

3.1.4 Overview

The examined cyclic esters and cyclic acetals were categorized into three groups based on their effectiveness in copolymerization (Chart S1). In particular, the monomers satisfying the following three criteria were considered potentially effective for the synthesis of alternating copolymers via sequence transformation upon heating: (1) high selectivity for the crossover from cyclic ester-derived hydroxy ends to suppress ester homosequences, (2) high equilibrium concentration of cyclic acetals (because unzipping needs to proceed predominantly over propagation in the presence of cyclic acetal monomers), and (3) generation of high-MW polymers without frequent hydrolysis during polymerization. By employing these effective monomers and other optimized polymerization conditions, sequence transformation upon heating was examined, as described in the following section.

3.2. Sequence Transformation from a Copolymer with No Ester Homosequences to an Alternating Copolymer upon Heating

Based on the systematic investigations demonstrated above, HBVE, VL, and EtSO₃H were selected as potential monomers and catalysts for the synthesis of alternating copolymers via sequence transformation upon heating. Toluene was used as the solvent because its high boiling point is preferable for heating. To prevent homopropagation of VL, the initial monomer

concentrations were 2.5 M for HBVE and 0.50 M for VL. The reaction temperature was changed when the equilibrium between polymerization and depolymerization, which was judged from monomer conversion values, seemed to shift adequately.

A copolymer with negligible VL homosequences was produced under the above conditions at 30 °C, which was followed by the transformation of the copolymer to a copolymer with almost equivalent amounts of HBVE and VL units by increasing the polymerization temperature (**Figure 3A–D**). More than 90% of the VL monomers were consumed in 2 h at 30 °C, while 58% of the HBVE was polymerized (Figure 3B). The ¹³C NMR spectrum of the copolymer obtained at 30 °C exhibited negligible peaks attributed to the VL homosequences (**Figure 4D**, peaks 7–10). The HBVE/VL unit ratio of the copolymer was 3.4 at 2 h {Figure 3A, top; (peaks *b* + peak *l*)/[(peak *h* + peak *i*)/2]}, which gradually decreased with increasing reaction time, reaching 2.1 at 22 h (Figure 3C). This decrease corresponds to the gradual decrease in HBVE conversion to polymer (Figure 3B). Subsequently, to promote the depolymerization of HBVE, the polymerization temperature was increased from 30 to 60 °C (at 22 h) and finally to 90 °C (at 42 h). As the temperature increased, the conversion of HBVE decreased (Figure 3B), indicating that depolymerization gradually proceeded. At the same time, the HBVE/VL ratio decreased to 1.3 at 60 °C (Figure 3A, middle) and finally to 1.1 at 90 °C (Figure 3A, bottom), which implied the successful formation of an alternating copolymer. In addition, the MWD curves of the obtained copolymers shifted to the lower-MW region as the polymerization temperature increased (Figure 3D, black).

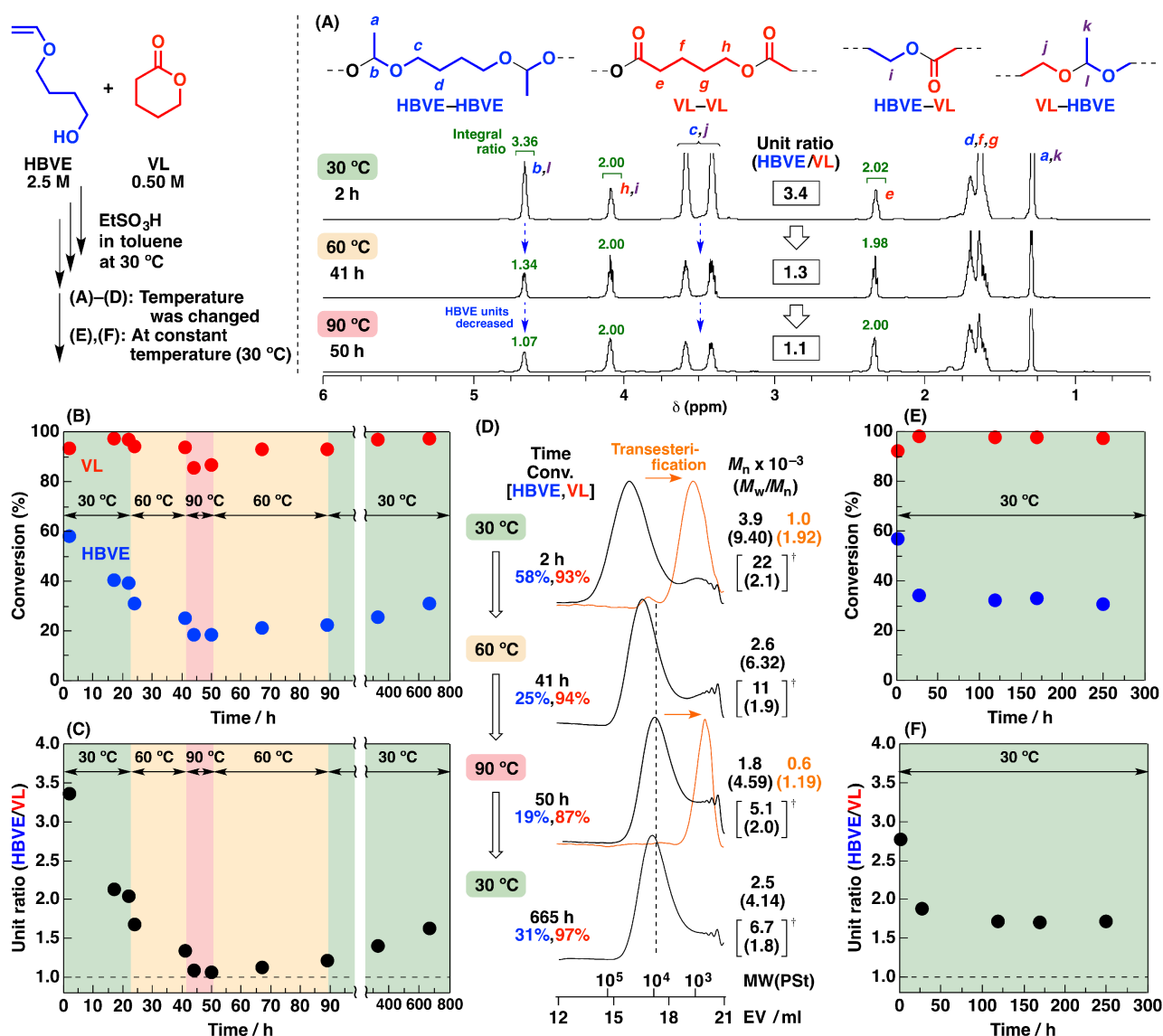


Figure 3. Copolymerization of HBVE and VL at varying or constant temperature: (A) ^1H NMR spectra of the products, (B), (E) monomer conversion (determined by ^1H NMR; conversion to polymer), (C), (F) the unit ratios of HBVE and VL in the products (determined by ^1H NMR), and (D) MWD curves of the copolymerization (black) and transesterification products (orange) (polymerization: $[\text{HBVE}]_0 = 2.5 \text{ M}$, $[\text{VL}]_0 = 0.50 \text{ M}$, $[\text{EtSO}_3\text{H}]_0 = 4.0 \text{ mM}$, in toluene at (A)–(D) varying temperature (30 → 60 → 90 → 60 → 30 °C) or (E)–(F) constant temperature (30 °C); transesterification: 25 mM $\text{Ti}(\text{O}i\text{Bu})_4$ in butyl acetate/ CH_2Cl_2 (7/1 v/v; 0.3 wt% polymer) at 70 °C for 16 h). † Values for the higher-MW peak.

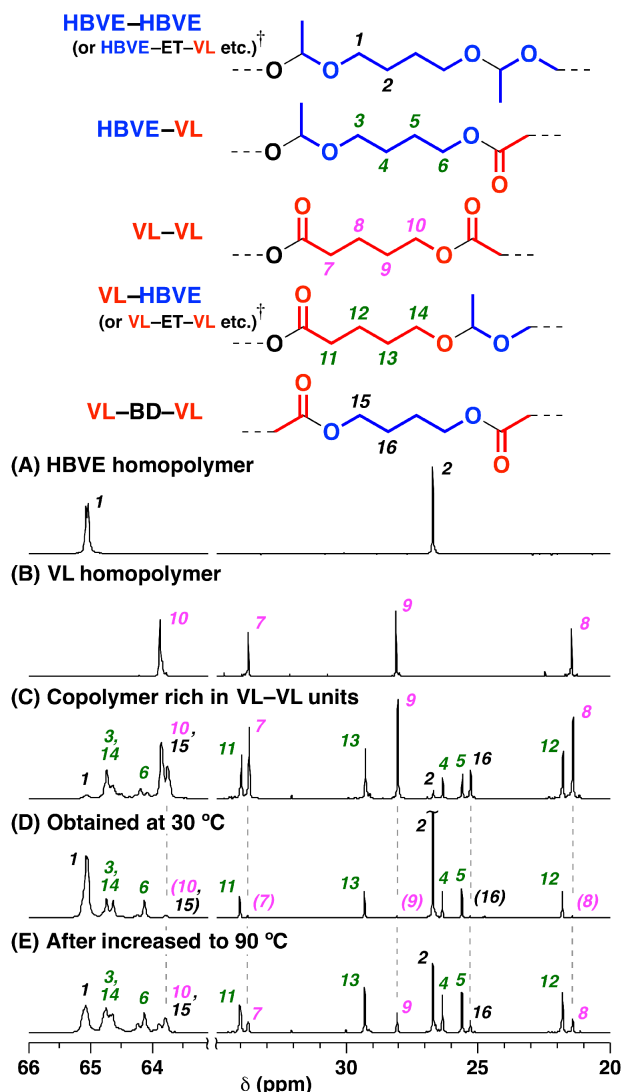
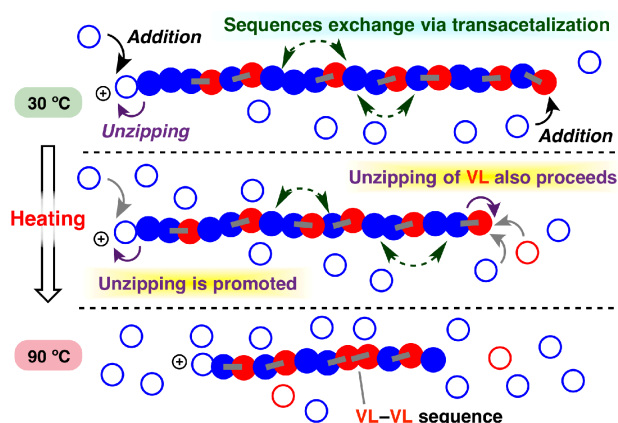


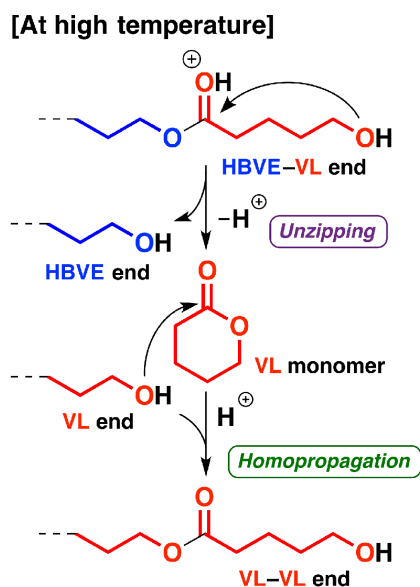
Figure 4. ^{13}C NMR spectra of (A) HBVE homopolymer, (B) VL homopolymer, and (C)–(E) poly(HBVE-*co*-VL)s [polymerization conditions: (A) $[\text{HBVE}]_0 = 2.5$ M, $[\text{EtSO}_3\text{H}]_0 = 5.0$ mM, in CH_2Cl_2 at 30 °C; (B) $[\text{VL}]_0 = 1.0$ M, $[\text{Ti}(\text{OBu})_4]_0 = 10$ mM, in toluene at 30 °C; (C) $[\text{HBVE}]_0 = 0.50$ M, $[\text{VL}]_0 = 0.50$ M, $[\text{EtSO}_3\text{H}]_0 = 10$ mM, in toluene at 30 °C (entry 5 in Table 1); (D) and (E) $[\text{HBVE}]_0 = 2.5$ M, $[\text{VL}]_0 = 0.50$ M, $[\text{EtSO}_3\text{H}]_0 = 4.0$ mM, in toluene at (D) 30 and (E) after increased to 90 °C (Figure 3)]. A, B, and C are the same as the spectra shown in Figure S2 (A, E, and D, respectively). † Ethylidene (ET) and butylenedioxy (BD) units are generated as a result of transacetalization (Scheme S2). Sequences such as HBVE–ET–VL and VL–ET–VL partly have the same structures to those of HBVE–HBVE and VL–HBVE, respectively.

The copolymerization results suggest that the copolymer sequence was successfully changed by controlling the propagation-depolymerization equilibrium by changing the temperature.³⁷ However, in contrast to the expected generation of an alternating copolymer, VL homosequences were found to be partly formed after increasing the temperature. The ^{13}C NMR

spectrum of the copolymer obtained at 90 °C exhibited small peaks assigned to VL homosequences (peaks 7–10, Figure 4E). In addition, the ESI-MS spectrum of the copolymer exhibited peaks with m/z values that correspond to polymer chains with more VL units than HBVE units (Figure S7B), unlike that of the copolymer obtained at 30 °C (Figure S7A). The VL homosequences most likely formed because a small number of VL monomers were regenerated by unzipping (depolymerization) after increasing the temperature and subsequently reacted with the VL-derived hydroxy end (**Scheme 4 and 5**). This mechanism is consistent with the decrease in VL conversion after increasing the temperature (Figure 3B). The unzipping is related to the equilibrium concentration of VL ($[VL]_e = 0.28$ M at 90 °C; calculated from the reported thermodynamic parameters³⁸), although not homopolymerization but copolymerization was conducted in the present study.



Scheme 4. Sequence transformation in the copolymerization of HBVE and CL at incrementally increased temperature. See also Scheme 5 for the unzipping of VL and the generation of a VL–VL sequence.



Scheme 5. Liberation of a VL monomer via unzipping at the HBVE–VL end and the generation of a VL–VL end.

Ester degradation of the obtained copolymers via transesterification with butyl acetate by $\text{Ti}(\text{OBu})_4$ corroborated the decrease in HBVE homosequences after increasing the temperature. ^1H NMR analysis of the transesterification products confirmed that the original ester moieties were quantitatively transformed into esters with butyl acetate-derived fragments (Figure S8). The MWD curves of the transesterification products clearly shifted to the low-MW region (Figure 3D, orange). The MW of the transesterification product obtained at 90 °C was lower than that of the product obtained at 30 °C, indicating a decrease in HBVE homosequences in the original copolymer. The MWD of the transesterification product of the copolymer obtained at 90 °C was slightly broader than that of the alternating copolymer obtained in the previous study,²⁵ likely due to the remaining HBVE homosequences. Indeed, the ESI-MS spectrum of the transesterification products also demonstrated the presence of HBVE homosequences (Figure S9B).

Based on the above results, a possible reaction mechanism was proposed (Scheme 4). First, copolymers with negligible VL homosequences were generated because VL-derived hydroxy chain ends predominantly reacted with MDOP monomers (derived from HBVE). The gradual decrease of HBVE conversion at 30 °C was most likely due to a change in the rate balance between the addition and unzipping reactions at the oxonium chain ends [Scheme 1A(I)]. Copolymerization gradually approached the equilibrium state, as indicated by the results of copolymerization at a constant

temperature of 30 °C (Figures 3E, 3F, and S10). After the temperature was increased, unzipping of HBVE was promoted as expected, which, in association with scrambling reactions, resulted in copolymer sequences more similar to alternating sequences; however, unzipping of VL also proceeded at higher temperatures, inducing the generation of VL homosequences. As a result of these reactions, an alternating-like copolymer with an HBVE/VL unit ratio of 1.1 was generated.

The possibility of reversible sequence transformation depending on the reaction temperatures was demonstrated by lowering the temperature from 90 °C to 60 °C (at 51 h) and then to 30 °C (at 90 h) (Figure 3B–D). After lowering the temperature, the conversion of HBVE to polymer gradually increased and finally reached 31% at 665 h, which is comparable to the conversion at a constant temperature of 30 °C (Figure 3E; 30% at 249 h). The HBVE/VL unit ratio reached 1.6, which is also similar to the value at a constant temperature (Figure 3F; 1.7 at 249 h). The conversion of VL also returned to 97% when the temperature was decreased, although the VL-VL homosequences generated at 90 °C remained in the copolymer chains.

3.3. Thermal Properties of poly(HBVE-co-CL)s with Various Compositions and Sequences

The DSC measurements of the poly(HBVE-co-CL)s with various compositions and sequences demonstrated that the thermal properties were tunable via the design of primary structures (Figure 5). All the tested poly(HBVE-co-CL)s showed single glass transition peaks, which suggested the miscibility of these amorphous segments. The copolymers have T_g s between those of HBVE and CL homopolymers (entries 1 and 8). In addition, the order of T_g values is likely related to the composition of the copolymers (the copolymers shown in Figure 5 are arranged in the order of high (upper) to low (lower) MDOP contents). The effects of MWs on T_g values are likely subtle. Melting peaks were observed only for copolymers having relatively long CL homosequences (entries 3, 6, 7, and 8), and the T_m values depended on the length of the CL block, both of which indicated that the crystalline region was derived from CL homosequences. The copolymers having short CL blocks (entry 5) and alternating sequences (entry 4) did not exhibit crystallinity, which demonstrated that the crystallinity was affected by the copolymer sequence rather than by the composition.

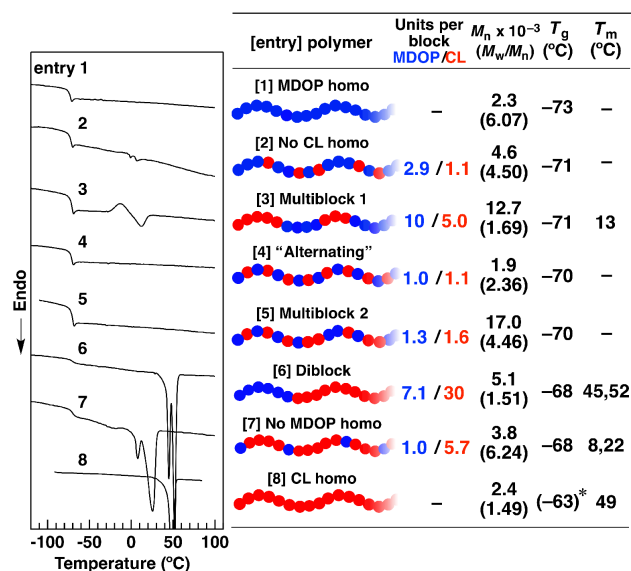


Figure 5. DSC curves and thermal properties of poly(HBVE), poly(CL), and poly(HBVE-*co*-CL)s with various compositions and sequences. ^1H NMR spectra and MWD curves of the polymers are summarized in Figure S11. * Glass transition was not clearly observed. The T_g value is from literature (reference 39).

4. Conclusion

The cationic ring-opening copolymerization of cyclic esters and cyclic acetals was performed using a series of monomers and protonic acids to demonstrate the generality of sequence control by unzipping and scrambling reactions. In particular, reaction conditions that result in the generation of shorter cyclic ester blocks were explored for the synthesis of alternating copolymers upon heating. Cyclic esters with moderate but sufficient reactivities were effective for copolymerization with fewer ester homosequences. The reactivity of cyclic acetals in copolymerization was not comparable to their homopolymerizability. The MWs, polymerization rate, and tendency to cross-propagate were slightly affected by the kinds of protonic acids. Under the optimum conditions based on these systematic studies, the sequence transformation from a copolymer with no ester homosequences to an alternating-like copolymer with an HBVE/VL ratio of 1.1 was achieved by changing the polymerization temperature from 30 °C to 90 °C, although the VL homosequences were partly generated due to the occurrence of depolymerization (unzipping) at the VL-derived chain ends as well as the HBVE-derived ends. For stricter sequence control, further optimization of the reaction conditions is required, which is currently being investigated by our

group. The possibility of reversible sequence transformation by heating and cooling cycles was also demonstrated. In addition, the thermal properties of poly(HBVE-*co*-CL)s were tunable by altering the compositions and sequences of the copolymer. These parameters can vary widely in the devised copolymerization system. Moreover, this sequence transformation concept is potentially applicable to other copolymerization systems involving unzipping and scrambling, which will increase the number of sequence-regulated copolymers obtainable from various monomer pairs.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

Acknowledgments

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Table of contents entry:

Sequence transformation from a prepolymer with no consecutive ester units to an alternating polymer is demonstrated by increasing the reaction temperature during cationic ring-opening copolymerization of cyclic acetals and cyclic esters. Tandem reactions of scrambling and unzipping of acetal units, which is promoted by heating, are the key for the sequence control. Reversible sequence transformation is also attempted by cooling.

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Unzipping and Scrambling Reaction-Induced Sequence Control of Copolymer Chains via Temperature Changes during Cationic Ring-Opening Copolymerization of Cyclic Acetals and Cyclic Esters

