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Desilylation-Triggered Degradable Silylacetal Polymers Synthesized via Controlled Cationic Copolymerization of Trimethylsilyl Vinyl Ether and Cyclic Acetals

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ABSTRACT: Silylacetal was demonstrated to function as a promising cleavable moiety for preparing polymers degradable via desilylation under diverse, mild conditions. The silylacetal moieties were installed in the main chain of the polymers via the controlled cationic copolymerization of trimethylsilyl vinyl ether (TMSVE) and a cyclic acetal under appropriately designed conditions. Importantly, desilylation reactions of the silylacetal units occurred under weak acid, base, or fluoride ion conditions, which triggered the degradation of the polymer via the spontaneous cleavage of the unstable hemiacetal moieties generated by the desilylation. Moreover, silylacetal moieties were successfully incorporated at the desired positions in the main chain via the addition of a small portion of TMSVE during the controlled cationic copolymerization of a vinyl ether and cyclic acetal. The strategy devised in this study will allow the design of elaborate polymers that undergo degradation triggered by various stimuli.

Degradable polymers have been attracting considerable interest due to both the functions derived from their degradability, such as for drug delivery systems, and the widely recognized problems caused by plastic waste derived from commodities. Several functional groups, such as esters, acetals, and disulfides, have been employed for the design of degradable polymers.[1–6] The incorporation of degradable moieties into the desired positions in a polymer chain is also possible via the careful design of the structures of initiators and monomers or the polymerization reactions.[7–9] In general, degradable moieties of polymers are cleavable under specific conditions, such as either acidic or basic conditions, or under harsh conditions, such as extremely high temperature. Indeed, such specificity in the degradation conditions is of importance for achieving the desired function of the polymeric materials. However, degradability under diverse and/or extremely mild conditions is also highly attractive for some purposes.

Silyl groups, which are widely used for protecting hydroxy group in organic synthesis,[10–14] are highly promising as cleavable moieties because deprotection reactions of silyloxy groups can be achieved under various conditions using weak acids, bases, or fluoride ion. Moreover, the strength of the silyl-oxygen bonds can be tuned by changing the alkyl groups on the silyl atom. For example, the resistance to deprotection increases with increasing steric hindrance in the order trimethylsilyl < triethylsilyl < *t*-butyldimethylsilyl. The selective deprotection of a particular silyl group among several kinds of silyl groups is also possible by carefully selecting the desilylation conditions.[13] In addition, a desilylation reaction was reported to be effective as a trigger of subsequent chemical reactions. For example, the desilylation of a silylacetal moiety, which generates an unstable, spontaneously cleavable hemiacetal, induced a ring rearrangement[15] and a cycloaddition reaction mediated by an aryne intermediate.[16]

Silyl groups have been applied in degradable polymers with silyl ether or silyl ester moieties in the main chain. The polymers are degraded via the cleavage of the silicon–oxygen bonds with an acid, a base, or an alcohol. In most cases, poly(silyl ether)s and poly(silyl ester)s are synthesized via the polycondensation of dichlorosilanes or dihydrosilanes with difunctional alcohols, carboxylic acids, silyl esters, or ketones[17–22] or the polyaddition of dichlorosilanes and bis(cyclic ether)s.[23,24] Polyurethanes that degrade via the desilylation of a silyl-protected phenol moiety were also synthesized via polyaddition.[25] The step-growth mechanisms, however, complicate controlling the molecular weights and molecular weight distributions (MWDs), controlling the distances between the cleavable units without changing the structures of the monomers, and introducing cleavable silyl moieties at the desired positions.

In this study, we focused on silylacetal as a degradable moiety that can be incorporated into polymer chains by chain-growth copolymerization. The desilylation of a silylacetal moiety generates an unstable hemiacetal, which is expected to spontaneously cleave into aldehyde and hydroxy moieties. For this purpose, we devised the cationic copolymerization of a silyl vinyl ether (VE) and a cyclic acetal[26,27] because the crossover reactions from the silyl VE-derived propagating carbocation to a cyclic acetal can potentially generate silylacetal moieties in the main chain (Scheme 1). In particular, we focused on trimethylsilyl VE (TMSVE), which has a more labile silyl group compared to bulkier silyl groups, because the generated silyl acetal is expected to be cleaved under milder conditions. Silyl VEs undergo homopolymerization via cationic[28–30] or group-transfer[31,32] mechanisms; however, controlled cationic polymerizations[33] of TMSVE have not been achieved.[34–36] Thus, we first examined effective conditions for the cationic polymerization of TMSVE. Subsequently, the copolymerization of TMSVE with a cyclic acetal was

Scheme 1. (A) Cationic Homopolymerization of TMSVE and the Synthesis of PVA via Subsequent Desilylation, (B) Cationic Copolymerization of TMSVE and Cyclic Acetals, and (C) Cleavage of a Silylacetal Unit in the Main Chain via Desilylation by Acid, Base, or Fluoride Ion.

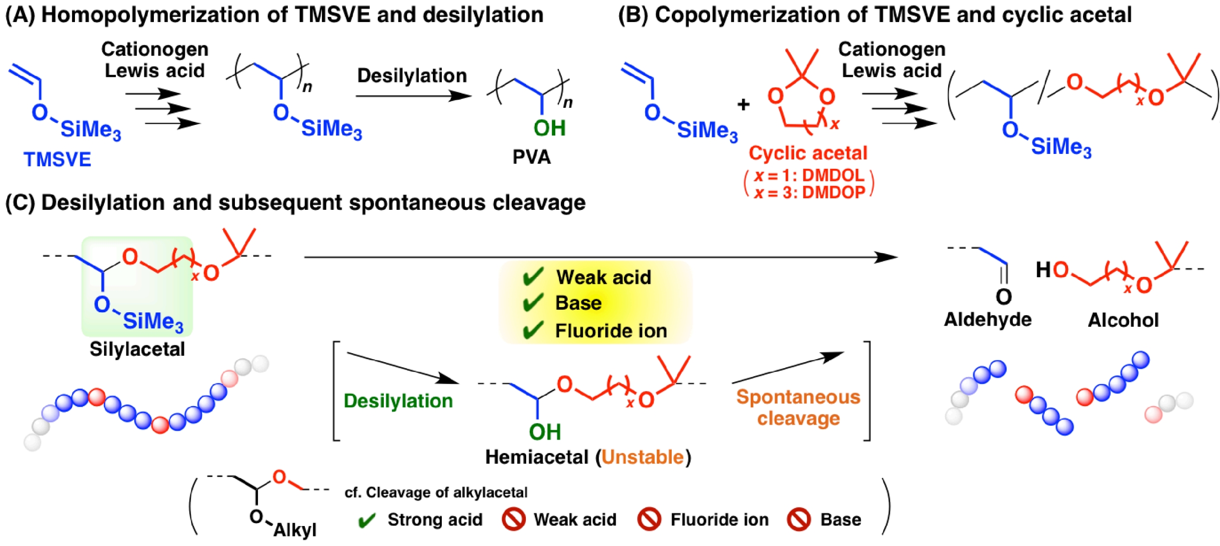

Table 1. Cationic Homopolymerization of TMSVE Using Various Lewis Acids[a]

entry	Lewis acid	additive	temp (°C)	time	conv (%)	M_n $\times 10^{-3}$ [b]	M_w/M_n [b]
1	$SnCl_4$	None	–78	10 s	98	9.5	1.35
2	$SnCl_4$	None	–40	10 s	83	4.9	1.50
3	$SnCl_4$	None	0	10 s	44	2.5	1.43
4[c]	$SnCl_4$	None	–78	1 min	87	7.5	1.36
5	$SnCl_4$	EA 1.0 M	–78	2 h	7	–	–
6	$SnCl_4$	EA 4.0 mM	–78	2 h	29	2.6	2.35
7	$SnCl_4$	Py 4.0 mM	–78	90 s	89	9.2	1.36
8	$SnBr_4$	None	–78	5 min	81	4.1	1.46
9	$TiCl_4$	None	–78	4 h	93	8.0	1.38
10	$GaCl_3$	None	–78	2 min	80	33.6	1.84
11	$EtAlCl_2$	None	–78	30 min	99	23.4	1.80

[a] $[TMSVE]_0 = 0.44$ M, $[IBVE–HCl]_0 = 4.0$ mM, $[Lewis\ acid]_0 = 5.0$ mM, in CH_2Cl_2 (except for entry 4). EA: ethyl acetate, Py: pyridine. [b] Determined by GPC (polystyrene standards). [c] In toluene.

conducted to afford desilylation-triggered silylacetal polymers. The copolymer was successfully degraded via desilylation with weak acid, base, or fluoride ions.

The control of polymerization reactions is fundamental for both the synthesis of polymers with controlled molecular weights and the introduction of cleavable points at the desired positions in main chains; hence, we first investigated initiating systems for the controlled cationic polymerization of TMSVE (Scheme 1A). The polymerization was conducted using various Lewis acid catalysts in conjunction with an HCl adduct of isobutyl VE (IBVE–HCl) as a cationogen in dichloromethane at –78 °C. Polymers were obtained with $SnCl_4$, $SnBr_4$, $TiCl_4$, $GaCl_3$ or $EtAlCl_2$, as the catalysts (entries 1, 8, 9, 10, and 11 in Table 1). Among the active catalysts, $SnCl_4$ was superior to the other catalysts because it afforded polymers with controlled molecular weights. Moreover, the M_n values of the products changed linearly with the $[monomer]_0/[cationogen]_0$ ratio (Figure S1). NMR analysis of the polymers (Figures S2 and S3) indicated that the cationogen fragment was incorporated into a polymer chain and that side reactions such as β-proton elimination were negligible. Unlike at –78 °C, the polymerizations at higher temperatures were inefficient both in terms of activity and the molecular weights of the products (entries 2 and 3). The use of toluene instead of dichloromethane as a solvent resulted in a similar product (entry 4). These results suggest that the cationic polymerization of TMSVE proceeded in a controlled manner with $SnCl_4$ as a catalyst at low temperature. The obtained poly(TMSVE) can be converted into poly(vinyl alcohol) (PVA) by desilylation (Figure S4).[28,29]

Weak Lewis bases, such as esters and ethers, which are used for living cationic polymerizations of various VEs,[37] were not effective for the polymerization of TMSVE. The polymerization was negligible in the presence of ethyl acetate regardless of the amount of base (1.0 M or 4.0 mM; entries 5 and 6 in Table 1). 1,4-Dioxane and diethyl ether (Table S1) were also ineffective for the polymerization at 1.0 M. These weak Lewis bases may induce side reactions by interacting with the silyl group of the propagating chain end (Scheme S1), although the details are not clear. In contrast, strong Lewis bases, such as pyridine (entry 7 in Table 1; see Table S1 for other bases), did not disturb the polymerization when the catalyst was present in excess relative to the base, as in the case of the polymerizations of isobutene or alkyl VEs.[38–40] The M_n values of the products increased as the monomer conversion increased (Figure S5), which indicates the occurrence of controlled polymerization. Unlike the weak Lewis bases, strong bases such as pyridine strongly interact with the catalyst, which likely prevented the bases from reacting with the TMSVE-derived propagating species. However, the controllability of the polymerization in the presence of strong bases was comparable to that in the absence of additives; hence, additives were not used for the copolymerizations described below.

To synthesize polymers with silylacetal moieties in the main chain, the cationic copolymerization of TMSVE with cyclic acetals (Scheme 1B) was investigated based on the results of the homopolymerization. First, 2,2-dimethyl-1,3-dioxolane (DMDOL), which is a five-membered cyclic acetal with two methyl substituents at the 2-position, was employed as a comonomer. The copolymerization proceeded under conditions suitable for homopolymerization of TMSVE (entry 1 in Table 2; Figure S6A). ^{1}H NMR analysis of the product (Figure S7) suggested that both monomers were incorporated into the polymer chains. The average numbers of monomer units per block were calculated to be 3.1 and 1.0 for TMSVE and DMDOL, respectively. These values are also consistent with the nonhomopolymerizability of DMDOL.[27] However, the molecular weight of the product was extremely low (M_n = 1.0 × 10^3), which indicates that side reactions likely occurred (Figure S7) in a manner similar to the case of the polymerization of TMSVE in the presence of weak Lewis bases such as esters and ethers (vide supra).

Table 2. Cationic Copolymerization of TMSVE and Cyclic Acetals[a]

				conv (%)				units per block[c]	
entry	cyclic acetal	solvent	time	VE	cyclic	M_n $\times 10^{-3\,b}$	M_w/M_n[b]	VE	cyclic
1	DMDOL	CH_2Cl_2	30 s	85	29	1.0	1.26	3.1	1.0
2	DMDOP	CH_2Cl_2	10 s	89	38	7.0	2.49	2.3	1.0
3	DMDOP	tol/CH_2Cl_2	15 s	36	10	4.8	1.74	3.6	1.0
4	DMDOP	tol/CH_2Cl_2	60 s	80	23	8.5	1.54	3.5	1.0

[a] $[TMSVE]_0$ = 0.44 M, [cyclic acetal]$_0$ = 0.44 M, $[IBVE–HCl]_0$ = 4.0 mM, $[SnCl_4]_0$ = 5.0 mM, in dichloromethane (entries 1 and 2) or in toluene/dichloromethane (8/2 v/v; entries 3 and 4) at –78 °C. [b] Determined by GPC (polystyrene standards). [c] Estimated by ^{1}H NMR analysis; the values correspond to the unit numbers per acetal.

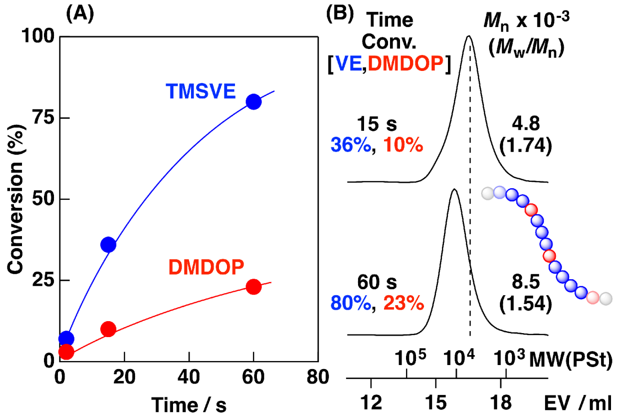

Figure 1. (A) Time–conversion plots of the polymerization of TMSVE and DMDOP and (B) the MWD curves of the obtained polymers (entries 3 and 4 in Table 2; $[TMSVE]_0$ = 0.44 M, $[DMDOP]_0$ = 0.44 M, $[IBVE–HCl]_0$ = 4.0 mM, $[SnCl_4]_0$ = 5.0 mM, in toluene/dichloromethane (8/2 v/v) at –78 °C).

Unlike DMDOL, the copolymerization proceeded effectively when 2,2-dimethyl-1,3-dioxepane (DMDOP), a seven-membered analogue of DMDOL, was used as the cyclic acetal monomer. Polymers with M_n values of several thousand were obtained in the polymerization using $SnCl_4$ in dichloromethane at –78 °C (entry 2 in Table 2; Figure S6B). In addition, the controllability was better in less polar solvents, such as toluene/dichloromethane (8/2 v/v), resulting in narrower MWDs (entries 3 and 4 in Table 2; Figure 1A, B). The MWD curve of the product shifted to the higher-molecular-weight region with increasing monomer conversion while maintaining a unimodal

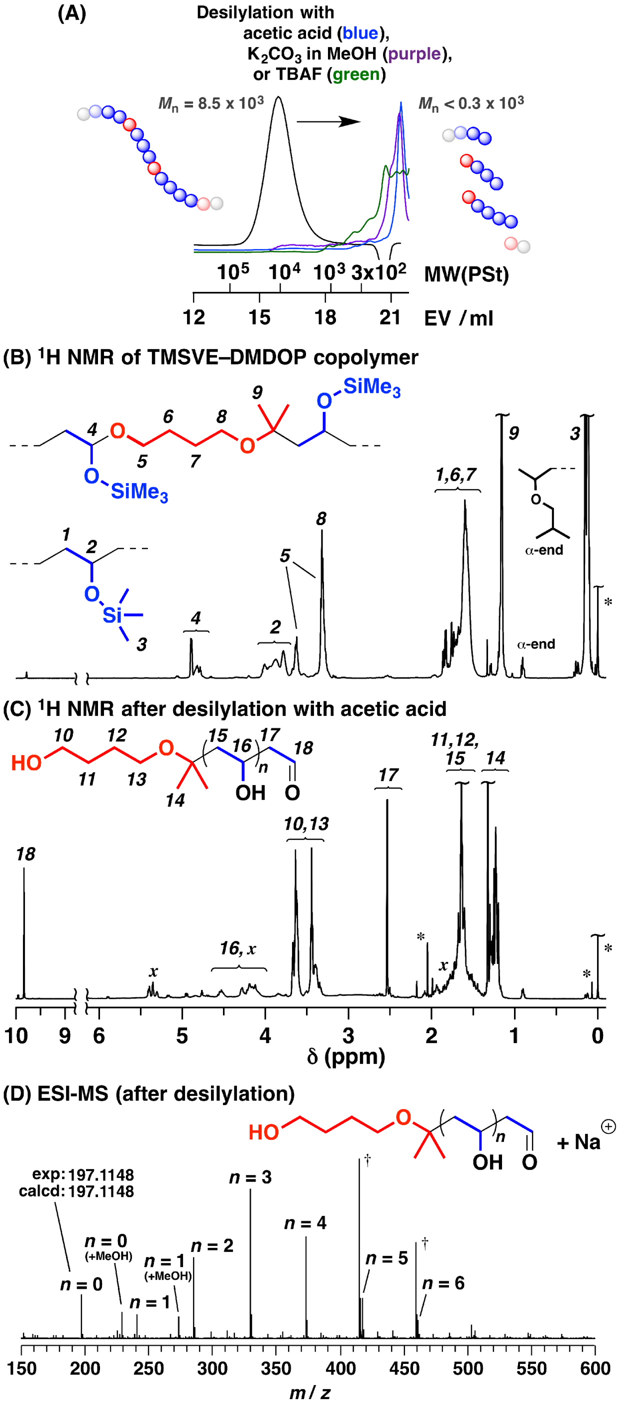

Figure 2. (A) MWD curves of poly(TMSVE-*co*-DMDOP) (black; entry 4 in Table 2; the same curve to that in Figure 1B [bottom]) and products obtained by desilylation with acetic acid (blue), K_2CO_3 (purple), or TBAF (green). ^{1}H NMR spectra of (B) poly(TMSVE-*co*-DMDOP) (entry 4 in Table 2) and (C) a product obtained by desilylation of the polymer with acetic acid [in $CDCl_3$ at 30 °C; * TMS, grease. Peaks with *x* are most likely assigned to six-membered hemiacetal structures (references 41 and 42). See Figure S13 and Scheme S3 for the detail]. (D) ESI-MS spectrum of a product obtained by desilylation of the polymer with acetic acid (see Figure S14 for peaks with †).

shape (Figure 1B), which indicates that the copolymerization was mediated by a long-lived species (see Figure S8 for the comparison of the experimental and theoretical M_n values).

Silylacetal moieties were successfully generated in the main chain of the copolymer, as confirmed by NMR analysis. The peaks at 4.7–4.9 ppm (peak 4) in the ^{1}H NMR spectrum (Figure 2B) were assigned to a methine proton of the silylacetal moiety. ^{13}C and 2D NMR analysis (Figures S9–S12) supported this assignment. The average numbers of TMSVE and DMDOP units per block were calculated to be 3.5 and 1.0, respectively, from the integral ratios of peaks 2, 4, 5, 8, and 9. Thus, copolymers were generated via frequent crossover reactions between the two monomers, and these reactions were estimated to occur several tens of times per chain.

In this copolymerization reaction, the silylacetal units are generated via the reaction of the TMSVE-derived propagating carbocation with a DMDOP monomer (Scheme S2). After the crossover reaction, the ring-opening of the DMDOP-derived oxonium ion generates a tertiary carbocation. This carbocation reacts not with DMDOP but with TMSVE due to the nonhomopolymerizability of DMDOP,[27] which is consistent with the absence of DMDOP homosequences in the copolymer chain.

The copolymer of TMSVE and DMDOP was degraded into low-molecular-weight compounds via desilylations triggered by weak acid, base, or fluoride ion (Scheme 1C). The MWD curve (M_n = 8.5 × 10^3) shifted significantly to the lower-molecular-weight region (less than 0.3 × 10^3) after desilylation of the copolymer with 5 M acetic acid in diethyl ether/water (6/1 v/v), K_2CO_3 in MeOH, or tetrabutylammonium fluoride (TBAF) in diethyl ether (Figure 2A).[43] In addition, the ^{1}H NMR peak of the silylacetal moiety disappeared, and instead, a peak attributable to an aldehyde was observed (Figures 2C and S12), which suggests that the silylacetal units were degraded via desilylation into aldehyde and alcohol moieties. The structure of the degradation product most likely consists of one DMDOP unit, a few or several units of vinyl alcohol, and an aldehyde moiety. The integral ratios of the silylacetal (peak 4) in the original copolymer and the aldehyde [peak 18; the six-membered hemiacetal (peak *x*) was also considered for the calculation] in the desilylation product to the cationogen fragment at the α-end (0.9 ppm) were comparable (35.8 and 38.8, respectively), which indicates that the copolymerization and the desilylation proceeded in a designed manner. Peaks with *m*/*z* values consistent with those structures were detected by ESI-MS analysis (Figures 2D and S14). Thus, as expected, the copolymer was degraded under diverse, mild conditions via the desilylation of the silylacetal moieties and subsequent spontaneous cleavage of the unstable hemiacetal units (Scheme 1C). The durability of the silylacetal moieties can potentially be tuned by changing the type of silyl group,[10–14] which will be investigated by our group in the future.

Polymers that have degradable silylacetal moieties at desired positions in the main chain were also successfully synthesized based on a controlled cationic polymerization mediated by a long-lived species (Figure 3A). A small portion of TMSVE (5 eq relative to the cationogen) was added when the conversion of 2-chloroethyl VE (CEVE) reached approximately 50% in the living cationic polymerization of CEVE and DMDOP.[27] After the addition, TMSVE was preferentially consumed and copolymerized with DMDOP because TMSVE is more reactive than CEVE (monomer reactivity ratios: r_{TMSVE} = 2.5, r_{CEVE} = 0.32; Figure S15). Thus, silylacetal moieties

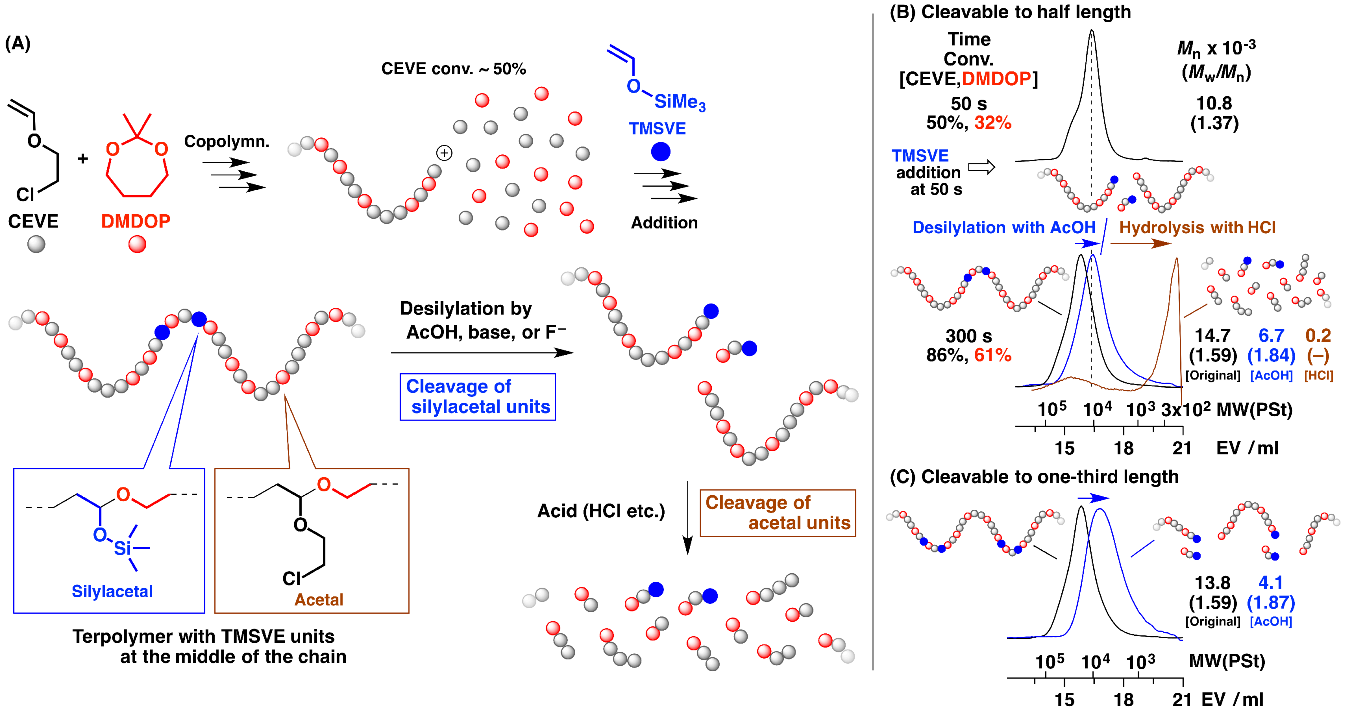

Figure 3. (A) Schematic illustration of the synthesis of a polymer with silylacetal units at the middle of the main chain via the addition of TMSVE during the cationic copolymerization of CEVE and DMDOP. (B) and (C) MWD curves of the polymers cleavable to half or one-third lengths [(B) poly(CEVE-*co*-DMDOP) obtained before the addition of TMSVE (upper), a polymer obtained after the addition of TMSVE (lower, black), a product obtained by desilylation with acetic acid (blue), and a product obtained by subsequent acid hydrolysis with hydrochloric acid (brown); see Figure S18 for the detail of (C); $[\text{CEVE}]_0$ = 0.44 M, $[\text{DMDOP}]_0$ = 0.44 M, $[\text{IBVE–HCl}]_0$ = 4.0 mM, $[\text{SnCl}_4]_0$ = 5.0 mM, $[\text{TMSVE}]_{\text{add}}$ = 20 mM [+ 20 mM for (C)], in toluene at –78 ºC).

were smoothly generated in the main chain, which was followed by the copolymerization of the remaining CEVE and DMDOP monomers. As a result, a terpolymer containing silylacetal moieties in the middle of the chain was obtained (lower black curve in Figure 3B; see Figure S16 for the ^{1}H NMR spectrum). Importantly, the polymer was selectively cleaved in the middle position via desilylation with acetic acid (blue curve in Figure 3B), K_2CO_3 in MeOH, or TBAF (Figure S17), which yielded polymer chains with molecular weights one-half of that of the original polymer. Polymers that are degraded into one-third of the original chain were also produced when TMSVE was fed into the reaction twice (Figures 3C and S18). Moreover, the desilylation-triggered degradation product retained its acetal units, which were generated via the crossover reaction from CEVE to DMDOP in the main chain; hence, the polymer chains were further degraded with hydrochloric acid into very low-molecular-weight compounds (brown curve in Figure 3B).

In conclusion, desilylation-triggered degradable polymers with silylacetal moieties in the main chain were successfully synthesized via the controlled cationic copolymerization of TMSVE and DMDOP. The copolymerization proceeded via frequent crossover reactions under appropriately designed conditions and yielded polymers that have several tens of silylacetal units per chain. The copolymer was successfully degraded into low-molecular-weight compounds via desilylation with acetic acid, K_2CO_3, or TBAF and subsequent spontaneous cleavage of the generated hemiacetal moieties. The silylacetal moieties were incorporated at the desired positions in the polymer chains via the addition of small portions of TMSVE during the copolymerization of VE and the cyclic acetal. The desilylation-triggered degradable polymers will be further developed by tuning the degradability of the silylacetal moieties by changing the alkyl groups on a silyl atom and the incorporation of functional groups via the structural modification of the cyclic acetals, which are synthesized from a diol and a carbonyl compound. In addition, thermoresponsive water-soluble polymers are potentially obtained via the terpolymerization with hydrophilic VEs having an oxyethylene moiety or the introduction of hydrophilic groups into cyclic acetals. The copolymerization of silyl VEs with other promising comonomers, such as conjugated aldehydes, oxiranes, and oxetanes, instead of cyclic acetals is also an attractive strategy for obtaining polymers with tunable degradability and various functionalities.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental section, polymerization data, ^{1}H, ^{13}C, and 2D NMR spectra, and ESI-MS spectra (PDF)

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Notes

The authors declare no competing financial interest.

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Desilylation-Triggered Degradable Silylacetal Polymers Synthesized via Controlled Cationic Copolymerization of Trimethylsilyl Vinyl Ether and Cyclic Acetals

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