Supplementary Information

Cyclic thioacetal carbonates for dual-stimuli degradable poly(vinyl ether)s with cleavable thioacetal and carbonate bonds evenly distributed in the main chains by cationic degenerative chain-transfer copolymerization

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Contents:

Experimental Section

Materials.

Ethyl vinyl ether (EVE) (Tokyo Chemical Industry (TCI), >98.0%), isobutyl vinyl ether (IBVE) (TCI, >99.0%), and 1,2-dichlorobenzene (TCI, >99.0%) were distilled over calcium hydride under reduced pressure before use. 4-Hydroxybutyl vinyl ether was kindly provided by Maruzen Petrochemical Co., Ltd. Bis(2-mercaptoethyl) ether (**DT-1**) (TCI, >95.0%), 1,1-carbodiimidazole (TCI, >97.0%), 3-chloro-1-propanol (TCI, >98.0%), potassium thioacetate (TCI, >97.0%), *n*-butylamine (TCI, >99.0%), benzenesulfonic acid anhydrous (TCI, >98.0%), *p*-toluenesulfonic acid monohydrate (PTSA) (TCI, >98.0%), triethylamine (TCI, >99.0%), sodium methoxide ($NaOCH_3$) (TCI, >96.0%), $ZnCl_2$ (Aldrich; 1.0 mM solution in diethyl ether), and silver nitrate ($AgNO_3$) (Aldrich, 99.9999%) were used as received. 2-Methoxyethyl vinyl ether (MOVE)[1] and the HCl adduct of IBVE (**1**)[2] were synthesized according to the literature. Toluene (KANTO, >99.5%; H_2O <10 ppm), *n*-hexane, diethyl ether, and dichloromethane (KANTO, >99.5%; H_2O < 10 ppm) were dried and deoxygenized by their passage through the columns of a Glass Contour systems before use.

Synthesis of 22-membered cyclic thioacetal carbonate (22-CTAC).

22-CTAC was synthesized by the following procedure. Bis[4-(vinyloxy)butyl] carbonate (**DVE-1**) was first synthesized by the reaction between 4-hydroxybutyl vinyl ether and 1,1-carbodiimidazole. 4-Hydroxybutyl vinyl ether (42.0 mL, 0.450 mol) was slowly added to a solution of 1,1-carodiimidazole (25.0 g, 0.150 mol) and THF (100 mL) in a 500 mL flask at 20 °C. After 24 h, the solvent was removed under vacuum to produce the crude product. After purification by column chromatography on silica gel with *n*-hexane/Et_2O (9/1) as the eluent, **DVE-1** was obtained as a colorless liquid (39.8 g, 0.150 mmol, yield > 99%) (Fig. S1).

Then, **22-CTAC** was synthesized via a cationic thiol-ene reaction between **DVE-1** and bis(2-mercaptoethyl) ether (**DT-1**) under dilution conditions. The cationic thiol-ene reaction was initiated by the dropwise addition of **DVE-1** (9.60 mL, 38.0 mmol) to a solution of **DT-1** (4.70 mL, 38.0 mmol) and benzenesulfonic acid (BSA) (28.0 g, 180 μmol) in CH_2Cl_2 (900 mL) at –40 °C. After 32 h, the reaction was quenched with triethylamine (10 mL). The solvent was removed under vacuum. The residue was extracted with Et_2O and washed with $NaHCO_3$ aqueous solution and water. The solvent was subsequently removed under vacuum to produce the crude product. After purification by column chromatography on silica gel with *n*-hexane/EtOAc (9/1), **22-CTAC** was obtained as a colorless liquid (7.50 g, 18.9 mmol, yield = 50%) (Figs. 1, S2, and S3). The ^1H NMR ($CDCl_3$, r.t.) results were as follows: δ 1.54 (d, 6H, CH_3CH, J = 6.4 Hz), 1.60-1.73 (m, 4H, $OCH_2CH_2CH_2$), 1.73-1.85 (m, 4H, SCH_2CH_2), 2.65-2.75 and 2.82-2.92 (m, 4H, SCH_2CH_2), 3.41-3.51 and 3.66-3.76 (m, 4H, CH_3CHOCH_2), 3.55-3.65 (m, 4H, OCH_2CH_2S), 4.19 (t, 4H, $CH_2OC(O)O$, J = 6.6 Hz), 4.65-4.74 (m, 2H, CH_3CH).

^{13}C NMR ($CDCl_3$, r.t.): δ 22.2 ($\mathit{C}H_3$), 25.7 and 26.0 ($OCH_2\mathit{C}H_2\mathit{C}H_2$), 27.2 and 27.4 ($S\mathit{C}H_2$), 66.1 and 66.2 ($\mathit{C}H_2OC(O)O$), 67.7 ($CHO\mathit{C}H_2CH_2$), 71.1 ($O\mathit{C}H_2CH_2CH_2S$), 81.3 and 81.4 ($CH_3\mathit{C}H$), 155.3 ($O\mathit{C}(O)O$).

Synthesis of 26-membered cyclic thioacetal carbonate (26-CTAC)

26-CTAC was synthesized by the following procedure. Bis(3-chloropropyl) carbonate was first synthesized by the reaction between 3-chloro-1-propanol and 1,1-carbodiimidazole. 3-Chloro-1-propanol (9.80 mL, 390 mmol) was slowly added to a solution of 1,1-carodiimidazole (10.0 g, 62.0 mmol) and THF (20.0 mL) in a 100 mL flask at 20 °C. After 48 h, the product was extracted with $CHCl_3$ and washed with water. The solvent was removed by evaporation to produce bis(3-chloropropyl) carbonate (11.0 g, 51.1 mmol, yield = 82%). (Fig. S4)

Thioacetylation of bis(3-chloropropyl) carbonate was conducted by the reaction between bis(3-chloropropyl) carbonate and potassium thioacetate. A solution of bis(3-chloropropyl) carbonate (10.3 g, 47.9 mmol) in $CHCl_3$ (9.60 mL) was slowly added to another solution of potassium thioacetate (16.4 g, 140 mmol) in DMF (86.0 mL) in a 200 mL flask at 0 °C. After 24 h at r.t., the product was extracted with Et_2O and washed with water. The solvent was removed by evaporation to produce bis[3-(acetylthio)propyl] carbonate (9.00 g, 30.6 mmol, yield = 64%) (Fig. S5).

Then, the acetyl group was deprotected by the addition of *n*-butylamine (9.10 mL, 93.0 mmol) to bis[3-(acetylthio)propyl] carbonate (7.22 g, 24.5 mmol) in $CHCl_3$ at 0 °C. After 24 h, the product was extracted with $CHCl_3$ and washed with water. The solvent was removed by evaporation to produce the crude product. After purification by column chromatography on silica gel with *n*-hexane/EtOAc (4/1), bis(3-mercaptopropyl) carbonate (**DT-2**) was obtained as a colorless liquid (1.00 g, 4.75 mmol, yield = 19%) (Fig. S6).

Finally, **26-CTAC** was synthesized via a cationic thiol-ene reaction between **DVE-1** and **DT-2** under dilution conditions. The cationic thiol-ene reaction was initiated by the dropwise addition of **DVE-1** (0.84 mL, 3.30 mmol) to a solution of **DT-2** (0.700 g, 3.30 mmol) and BSA (2.10 mg, 13.0 μmol) in CH_2Cl_2 (67.0 mL) at –40 °C. After 24 h, the reaction was quenched with triethylamine (10.0 mL). The solvent was removed under vacuum. The residue was extracted with Et_2O and washed with $NaHCO_3$ aqueous solution and water. The solvent was subsequently removed under vacuum to produce the crude product. After purification by column chromatography on silica gel with *n*-hexane/EtOAc (3/1), **26-CTAC** was obtained as a colorless liquid (0.770 g, 1.64 mmol, yield = 50%) (Figs. S7–S9). The ^{1}H NMR ($CDCl_3$, r.t.) were as follows: δ 1.54 (d, 6H, $C\mathit{H}_3CH$, J = 6.4 Hz), 1.60-1.80 (m, 4H, $OCH_2C\mathit{H}_2C\mathit{H}_2CH_2$), 1.97 (m, 4H, $SCH_2C\mathit{H}_2$), 2.58-2.76 (m, 4H, $SCH_2C\mathit{H}_2$), 3.41-3.51 and 3.44 and 3.69 (dt, 4H, $CH_3CHOC\mathit{H}_2CH_2$, J_{vic} = 6.0, and 6.4 Hz, J_{gem} = –9.2 Hz), 4.16 (t, 4H, $C\mathit{H}_2OC(O)O$, J = 6.4

Hz), 4.22 (m, 4H, $SCH_2CH_2CH_2OC(O)O$),4.68 (q, 2H, CH_3CH, J = 6.4 Hz). ^{13}C NMR ($CDCl_3$, r.t.): δ 22.2 (CH_3), 24.2 (SCH_2CH_2), 25.8 and 26.1 ($OCH_2CH_2CH_2CH_2$), 29.5 ($SCH_2CH_2CH_2$), 66.3 ($CH_2CH_2CH_2CH_2OC(O)O$), 66.8 ($SCH_2CH_2CH_2OC(O)O$), 67.8 ($CHOCH_2CH_2$), 81.4 (CH_3CH), 155.3 and 155.4 ($OC(O)O$).

Cationic Copolymerization of EVE and 22-CTAC

Cationic copolymerization of EVE and **22-CTAC** was carried out using the syringe technique under dry nitrogen in a baked glass tube equipped with a three-way stopcock. A typical example of the polymerization procedure is given below. Cationic copolymerization was initiated by sequentially adding **1** (0.20 mL of 400 mM in toluene solution, 80 μmol) and $ZnCl_2$ (0.20 mL of 40 mM in Et_2O solution, 8.0 μmol) via a dry syringe into a monomer mixture containing EVE (0.77 mL, 8.04 mmol), **22-CTAC** (0.26 mL of 1.52 M CH_2Cl_2 solution, 0.40 mmol), and 1,2-dichlorobenzene (0.10 mL) as an internal standard in CH_2Cl_2 (0.47 mL) at –40 °C. At the predetermined intervals, the polymerization was terminated with methanol (2.0 mL) containing a small amount of triethylamine. The monomer conversion was determined from the concentration of residual monomer measured by ^{1}H NMR with 1,2-dichlorobenzene as an internal standard (50 min, >99% for EVE and >99% for **22-CTAC**). The quenched reaction mixture was washed with dilute hydrochloric acid and distilled water to remove residual catalyst, evaporated to dryness under reduced pressure, and vacuum-dried to produce the product polymers (M_n = 11000, $Đ$ = 1.92).

Degradation of Poly(EVE-*co*-22-CTAC) with $AgNO_3$

The degradation of poly(EVE-*co*-**22-CTAC**) using $AgNO_3$ was carried out by the syringe technique under dry nitrogen in a baked glass tube equipped with a three-way stopcock. A typical example of the reaction procedure is given below. The degradation reaction was initiated by the addition of $AgNO_3$ (0.15 g, 0.88 mmol) into a polymer solution containing poly(EVE-*co*-**22-CTAC**) (100 mg, thioacetal: 90 μmol, M_n = 11400, $Đ$ = 1.85) in THF (17.0 mL) and H_2O (0.90 mL) at 20 °C. After 1 h, the reaction was quenched by dilution with *n*-hexane. The quenched reaction mixture was washed with dilute hydrochloric acid and distilled water to remove residual catalyst, evaporated to dryness under reduced pressure, and vacuum-dried to produce the product polymers (M_n = 2200, $Đ$ = 1.29).

Degradation of Poly(EVE-*co*-22-CTAC) with $NaOCH_3$

The degradation of poly(EVE-*co*-**22-CTAC**) with $NaOCH_3$ was carried out by the syringe technique under dry nitrogen in a baked glass tube equipped with a three-way stopcock. A typical example of the reaction procedure is given below. $NaOCH_3$ (24.0 mg, 0.44 mmol), poly(EVE-*co*-**22-CTA**) (100 mg, carbonate: 45.0 μmol, M_n = 11400, $Đ$ = 1.85), and CH_3OH

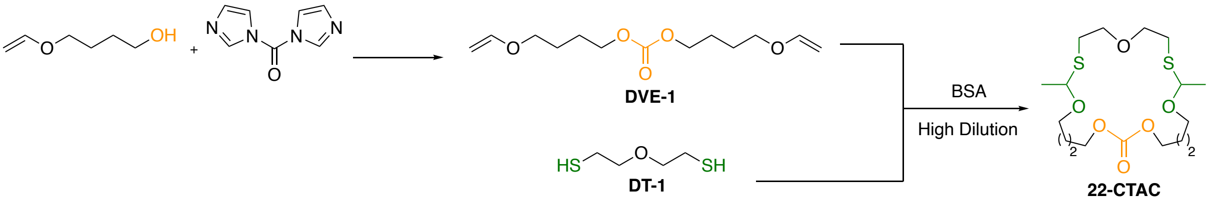
(9.00 mL) were added to a 25 mL round-bottom flask. The flask was subsequently immersed in a thermostatic oil bath at 60 °C. After 17 h, the reaction was quenched by dilution with *n*-hexane. The quenched reaction mixture was washed with dilute hydrochloric acid and distilled water to remove the residual catalyst, evaporated to dryness under reduced pressure, and vacuum-dried to afford the product polymers (M_n = 2400, $Đ$ = 1.25).

Measurement

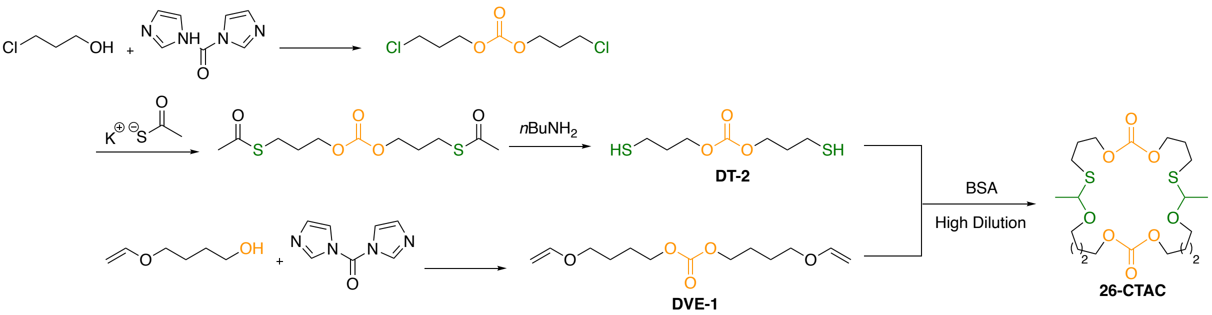
^{1}H and ^{13}C NMR spectra were recorded on a JEOL ECS-400 spectrometer operated at 400 MHz. The number-average molecular weight (M_n) and molecular mass dispersity ($Đ$) of the product polymer were determined by size-exclusion chromatography (SEC) in THF at 40 °C using two polystyrene gel columns [Shodex K-805L (pore size: 20–1000 Å; 8.0 mm i.d. × 30 cm)× 2] connected to a JASCO PU-2080 precision pump and JASCO RI-2031 detector. The columns were calibrated against 10 standard polystyrene samples (Agilent Technologies; M_p = 575–2783000, $Đ$ = 1.02–1.23, M_p: peak molecular weight). MALDI-TOF-MS was performed with a Bruker Autoflex mass spectrometer with dithranol as the ionizing matrix and sodium trifluoroacetate as the ion source.

References

1. S. Aoshima, H. Oda and E. Kobayashi, *J. Polym. Sci., Part A: Polym. Chem.* 1992, **30**, 2407–2413.
2. M. Kamigaito, Y. Maeda, M. Sawamoto and T. Higashimura, *Macromolecules* 1993, **26**, 1643–1649.



Scheme S1 Synthesis of 22-Membered Cyclic Thioacetal Carbonate (**22-CTAC**)



Scheme S2 Synthesis of 26-Membered Cyclic Thioacetal Carbonate (**26-CTAC**)

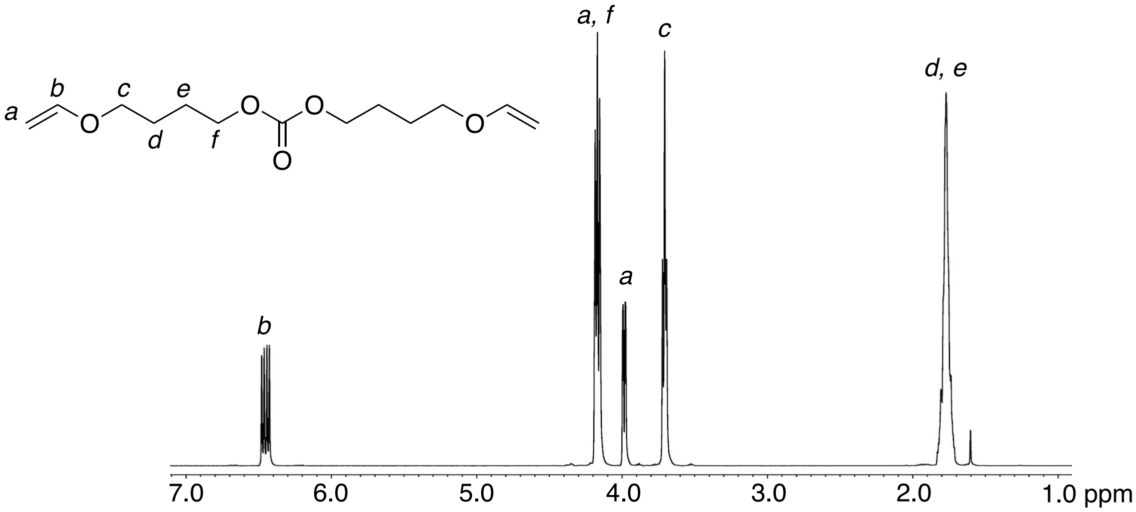


Fig. S1 ^{1}H NMR spectrum (CDCl$_3$, r.t.) of bis[4-(vinyloxy)butyl] carbonate (**DVE-1**).

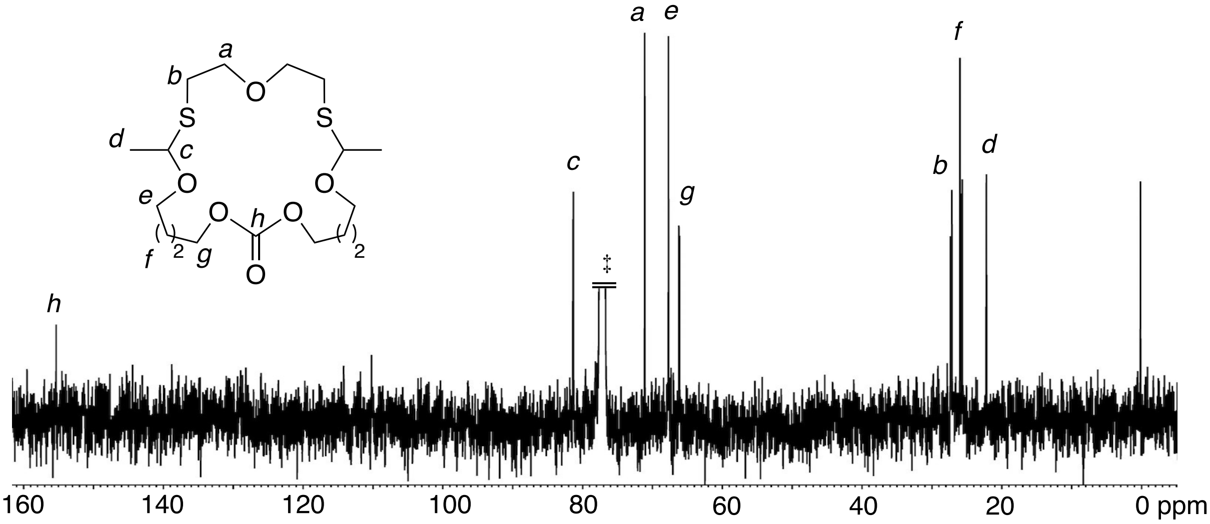


Fig. S2 ^{13}C NMR spectrum (CDCl$_3$, r.t.) of **22-CTAC**. ‡: CHCl$_3$.

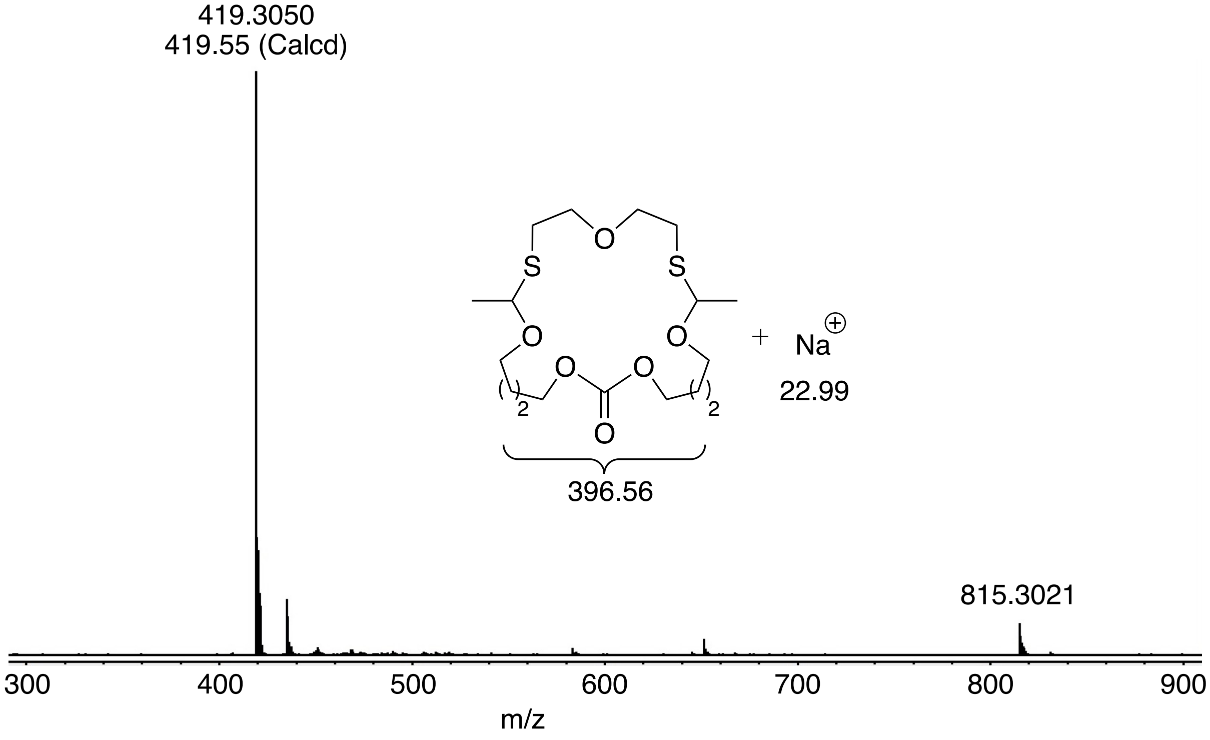


Fig. S3 MALDI-TOF-MS spectrum of **22-CTAC**.

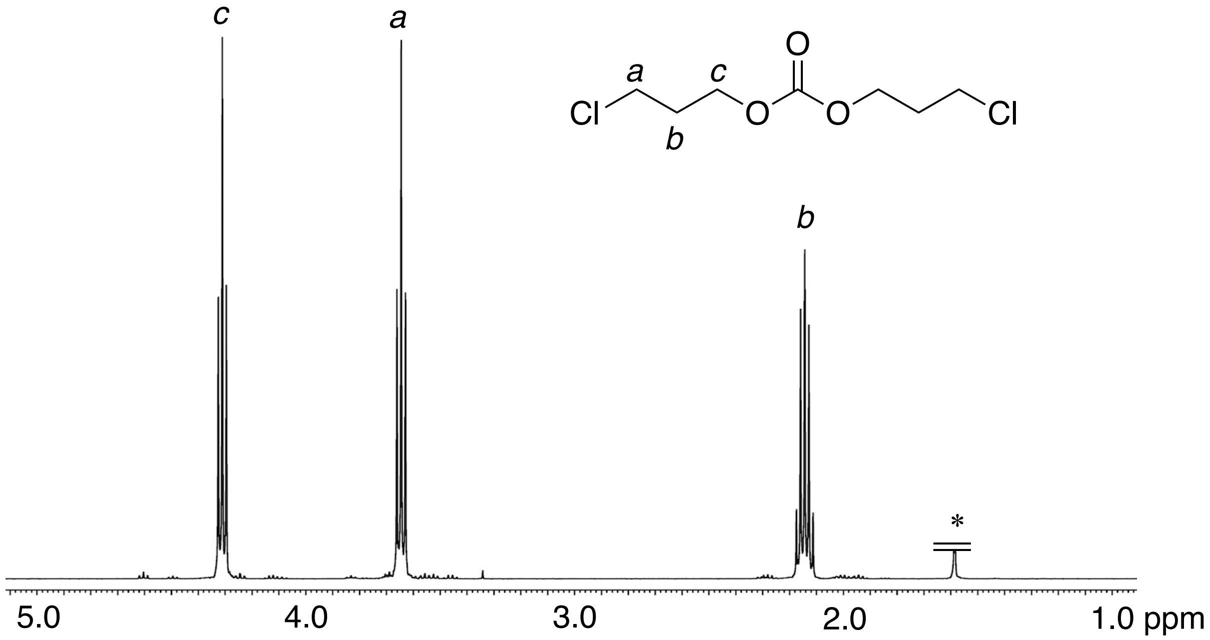


Fig. S4 ^{1}H NMR spectrum ($CDCl_3$, r.t.) of bis[3-chloropropyl] carbonate. ∗: H_2O.

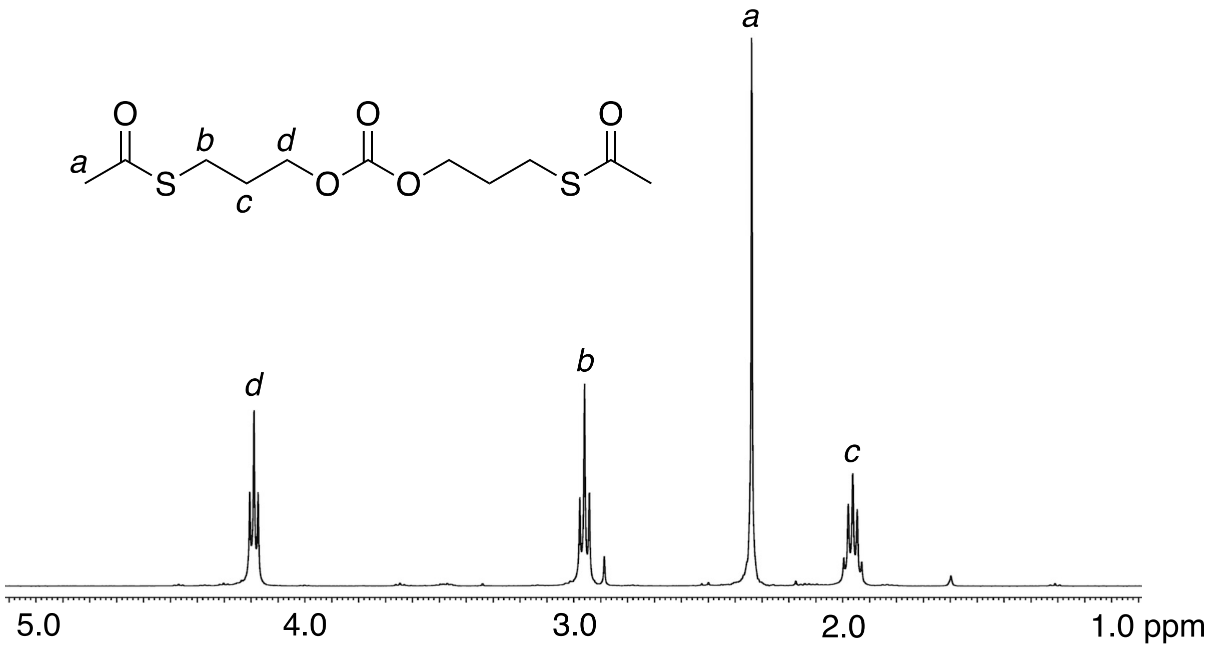


Fig. S5 ^{1}H NMR spectrum ($CDCl_3$, r.t.) of bis[3-(acetylthio)propyl] carbonate.

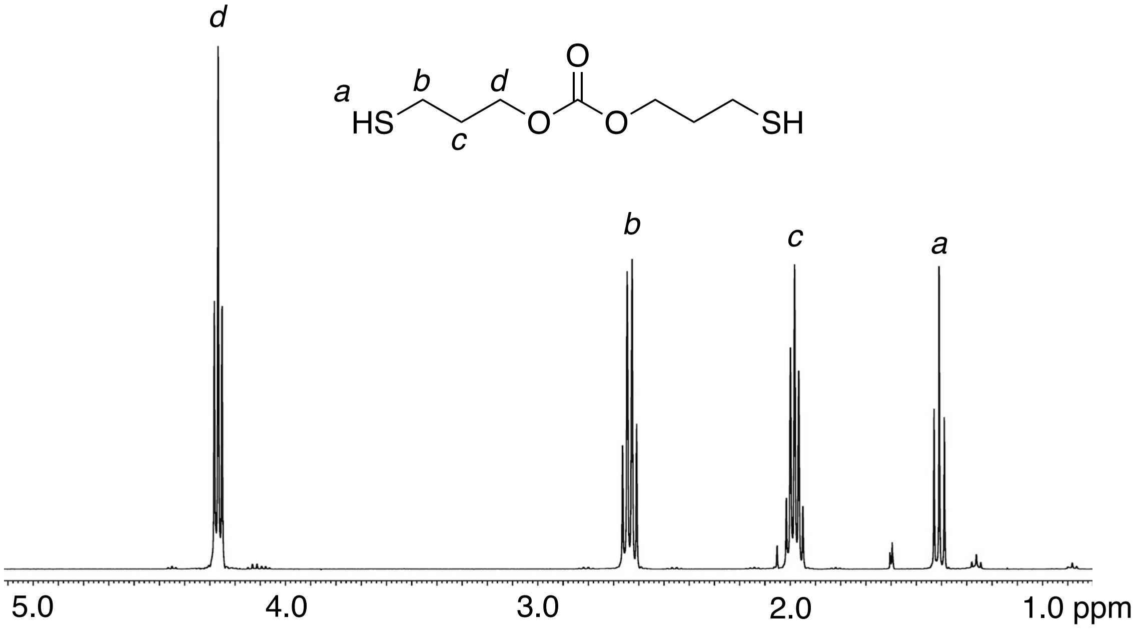


Fig. S6 ^{1}H NMR spectrum (CDCl$_3$, r.t.) of bis(3-mercaptopropyl) carbonate (**DT-2**).

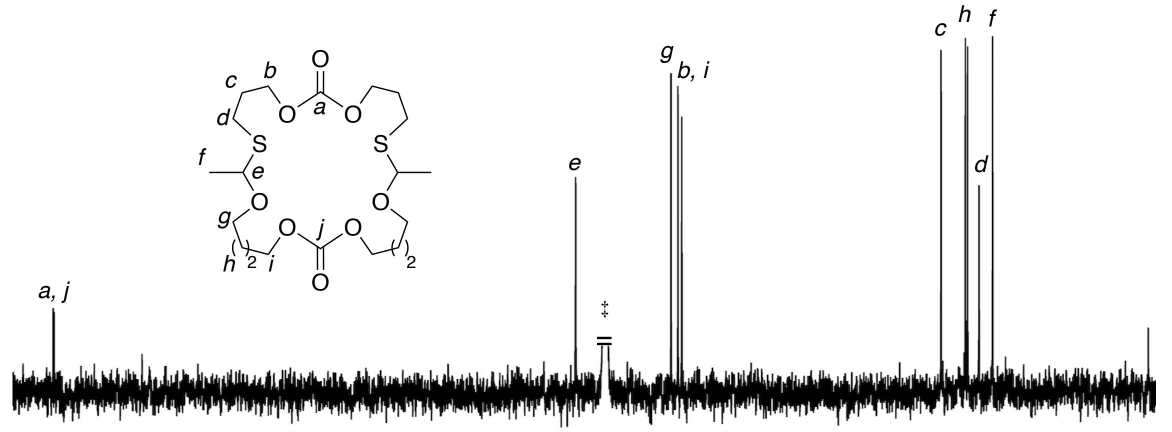


Fig. S7 ^{13}C NMR spectrum (CDCl$_3$, r.t.) of **26-CTAC**. ‡: CHCl$_3$.

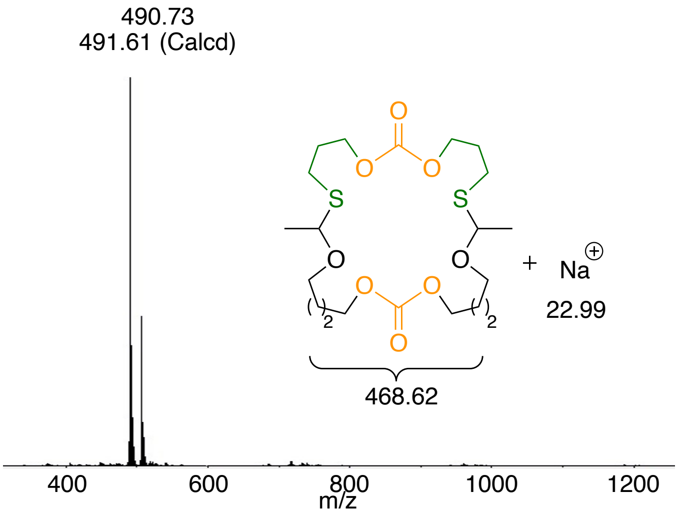


Fig. S8 MALDI-TOF-MS spectrum of **26-CTAC**.

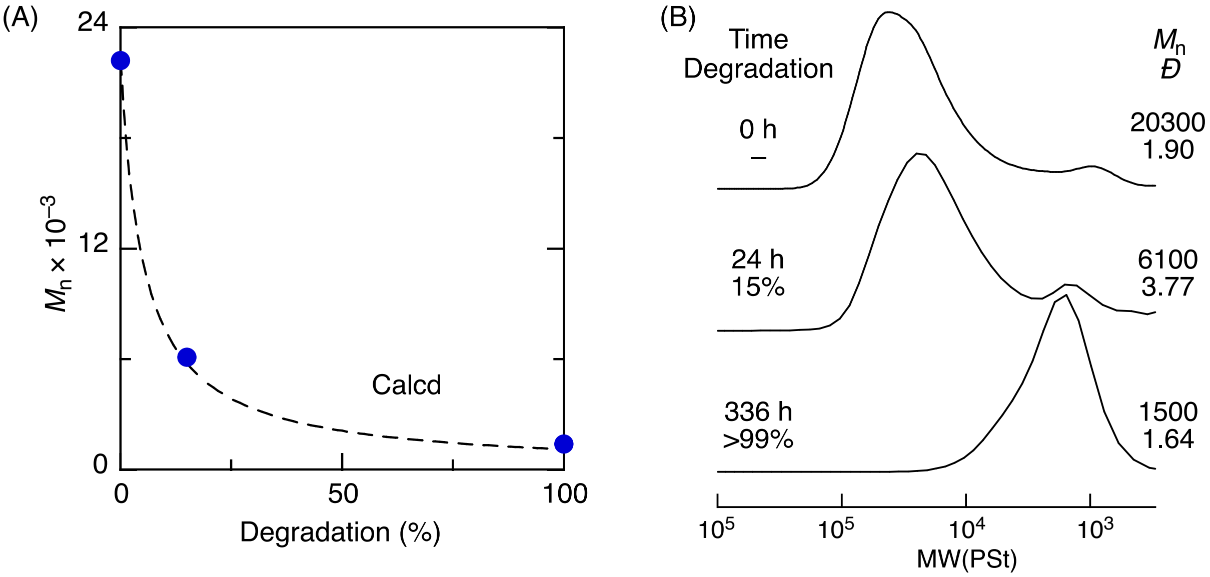


Fig. S9 M_n values (A) and SEC curves (B) of the polymers before and after degradation with PTSA: [thioacetal units]$_0$/[PTSA]$_0$ = 5.0/50 mM in THF/H_2O (19/1 vol%) at 20 °C.

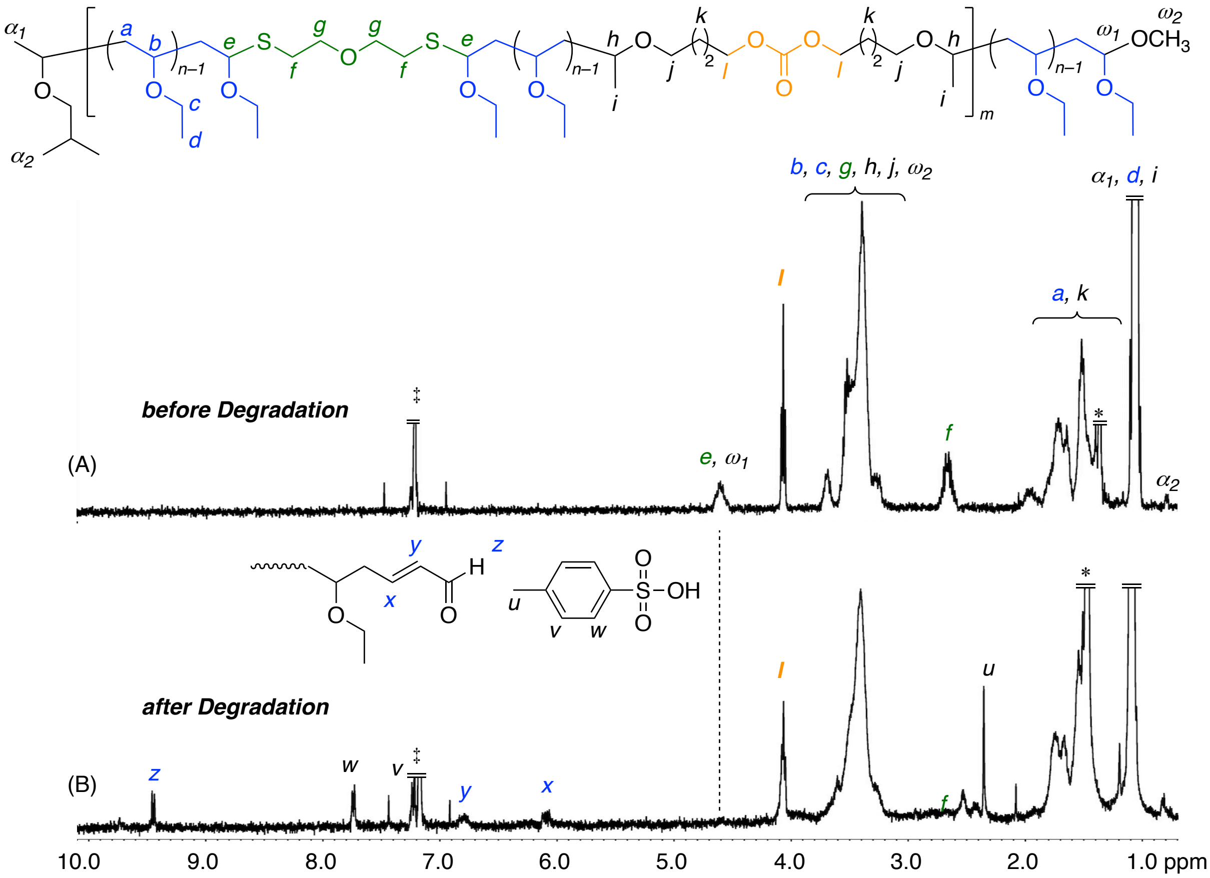


Fig. S10 ^{1}H NMR spectra (CDCl$_3$, 55 °C) of the polymers before and after degradation with PTSA: [thioacetal units]$_0$/[PTSA]$_0$ = 5.0/50 mM in THF/H$_2$O at 20 °C. ∗: H$_2$O, ‡: CHCl$_3$.

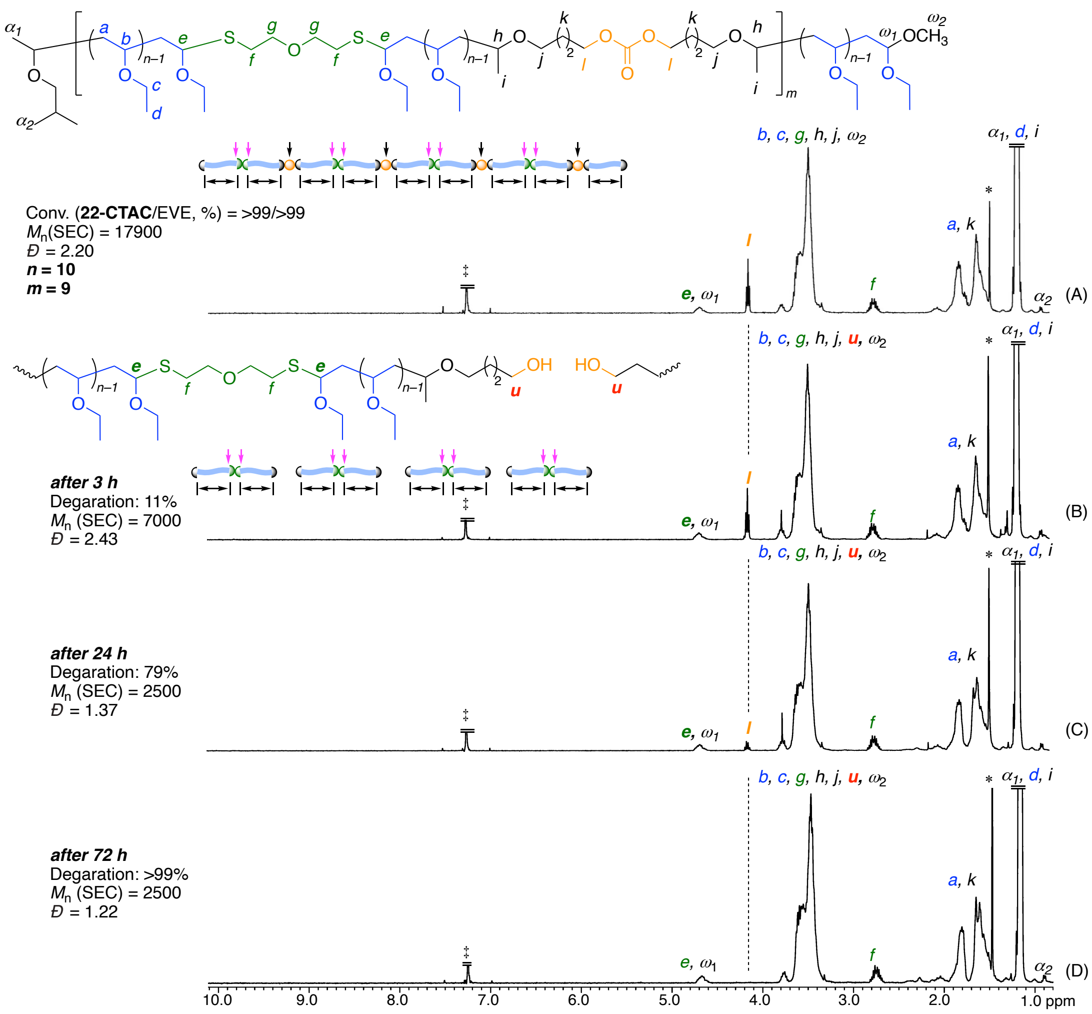


Fig. S11 ^{1}H NMR spectra (CDCl$_3$, 55 °C) of the polymers before (A) and after degradation (B-D) with NaOCH$_3$: [carbonate units]$_0$/[NaOCH$_3$]$_0$ = 5.0/50 mM in CH$_3$OH at 60 °C. ∗: H$_2$O, ‡: CHCl$_3$.

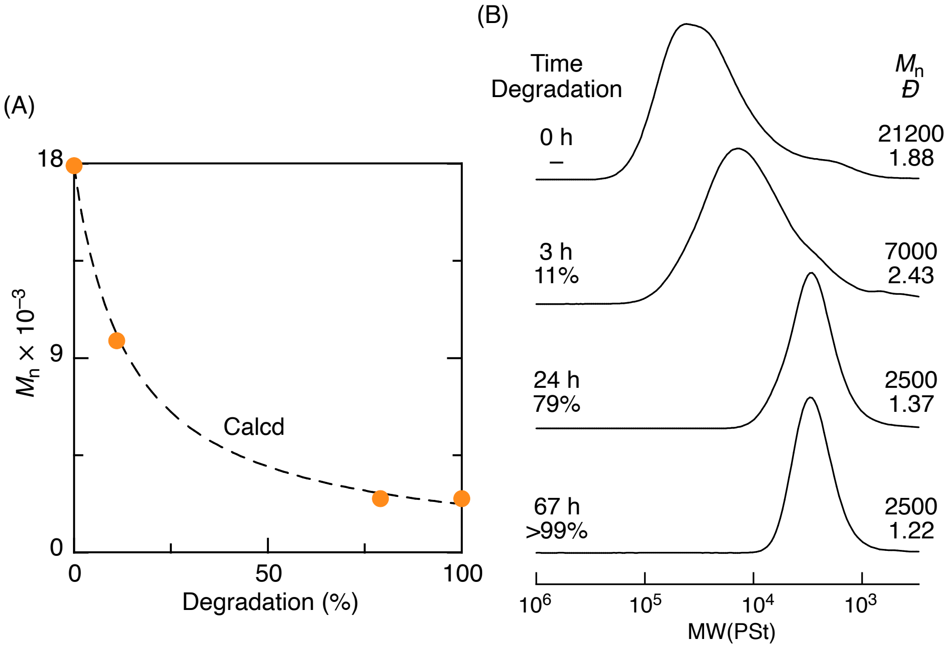


Fig. S12 M_n values (A) and SEC curves (B) of the polymers before and after degradation with $NaOCH_3$: [carbonate units]$_0$/[$NaOCH_3$]$_0$ = 5.0/50 mM in CH_3OH at 20 °C.

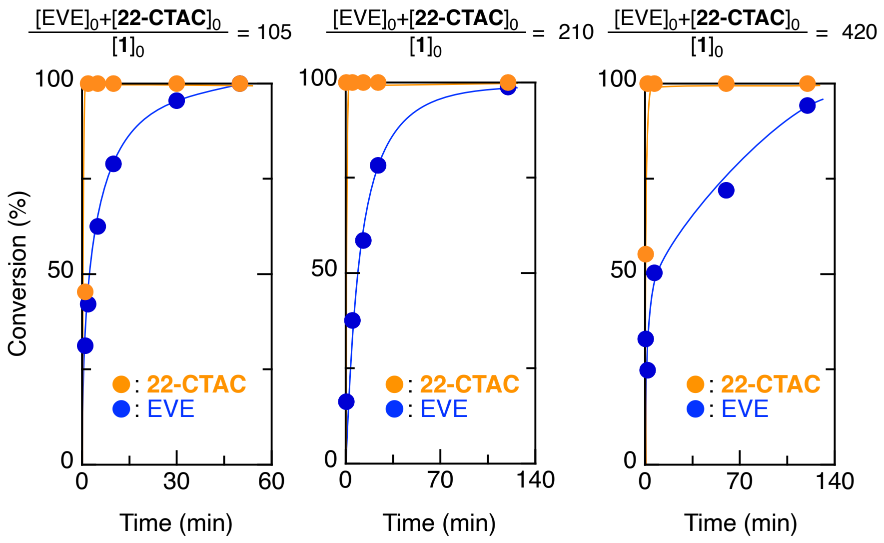


Fig. S13 Time-conversion curves of cationic DT copolymerization of EVE and **22-CTAC** varying the feed ratio of EVE to **22-CTAC**: [EVE]$_0$/[**22-CTAC**]$_0$/[**1**]$_0$/[$ZnCl_2$]$_0$ = 4000/200/40, 20, 10/4.0 mM in CH_2Cl_2/*n*-hexane/Et_2O (20/10/10) at –40 °C.

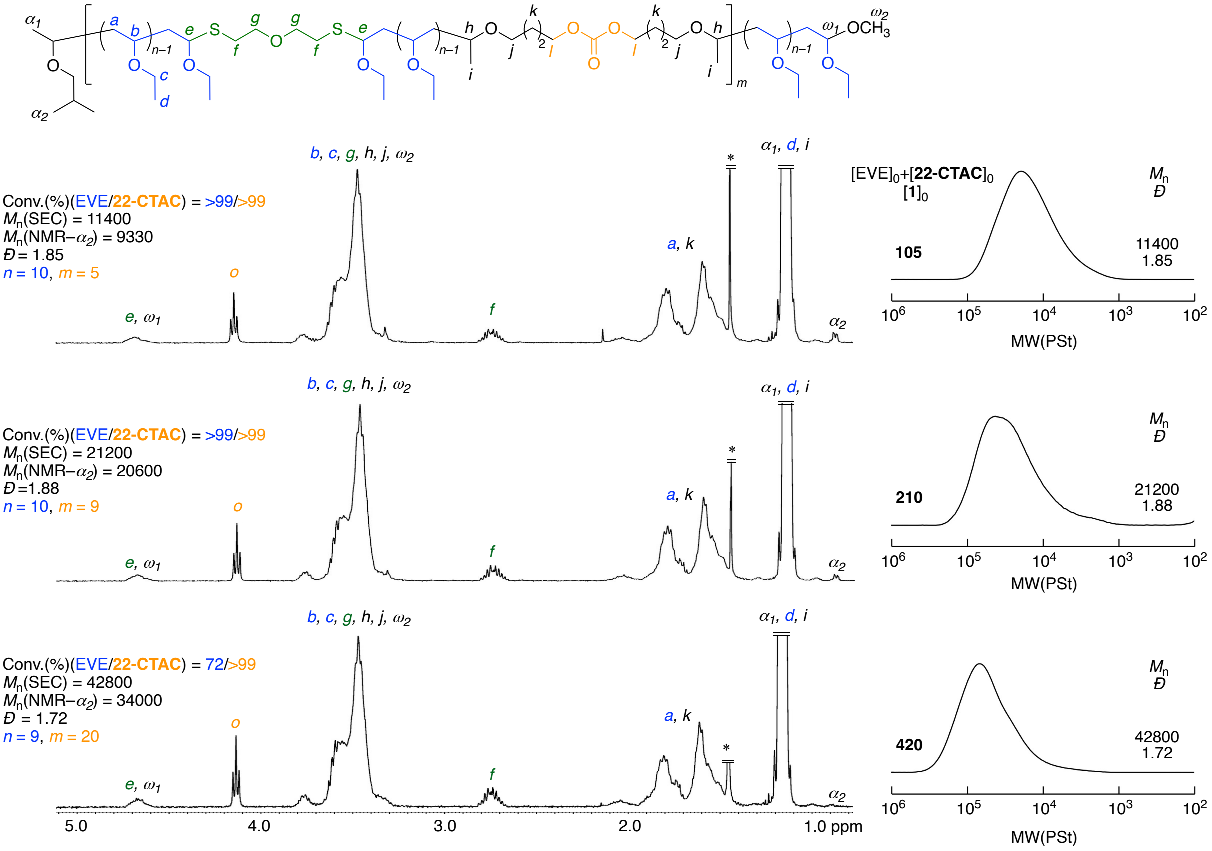


Fig. S14 ^{1}H NMR spectra ($CDCl_3$, 55 °C) and SEC curves of the copolymers obtained by cationic DT copolymerization of EVE and **22-CTAC** for Fig. S12 after purification by preparative SEC. *: H_2O.

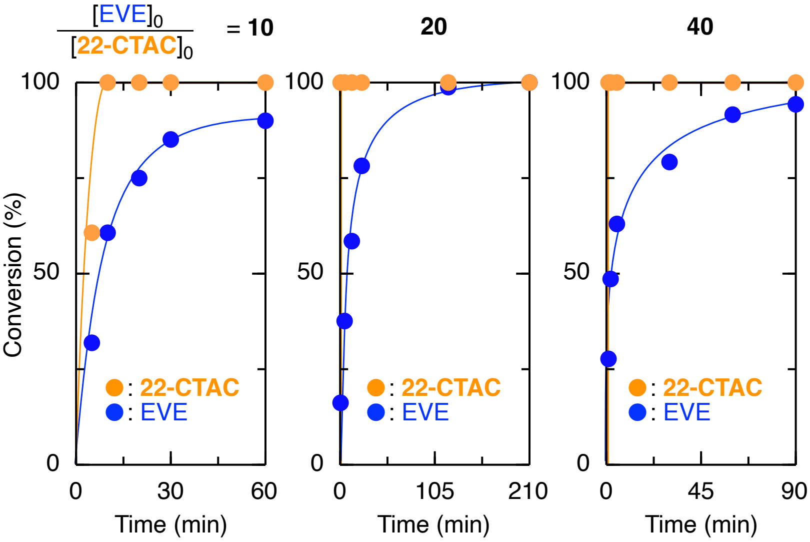


Fig. S15 Time-conversion curves of cationic DT copolymerization of EVE and **22-CTAC** varying the feed ratio of EVE to **22-CTAC**: [EVE]$_0$/[**22-CTAC**]$_0$/[**1**]$_0$/[$ZnCl_2$]$_0$ = 4000/400, 200, 100/20/4.0 mM in CH_2Cl_2/*n*-hexane/Et_2O (20/10/10) at –40 °C.

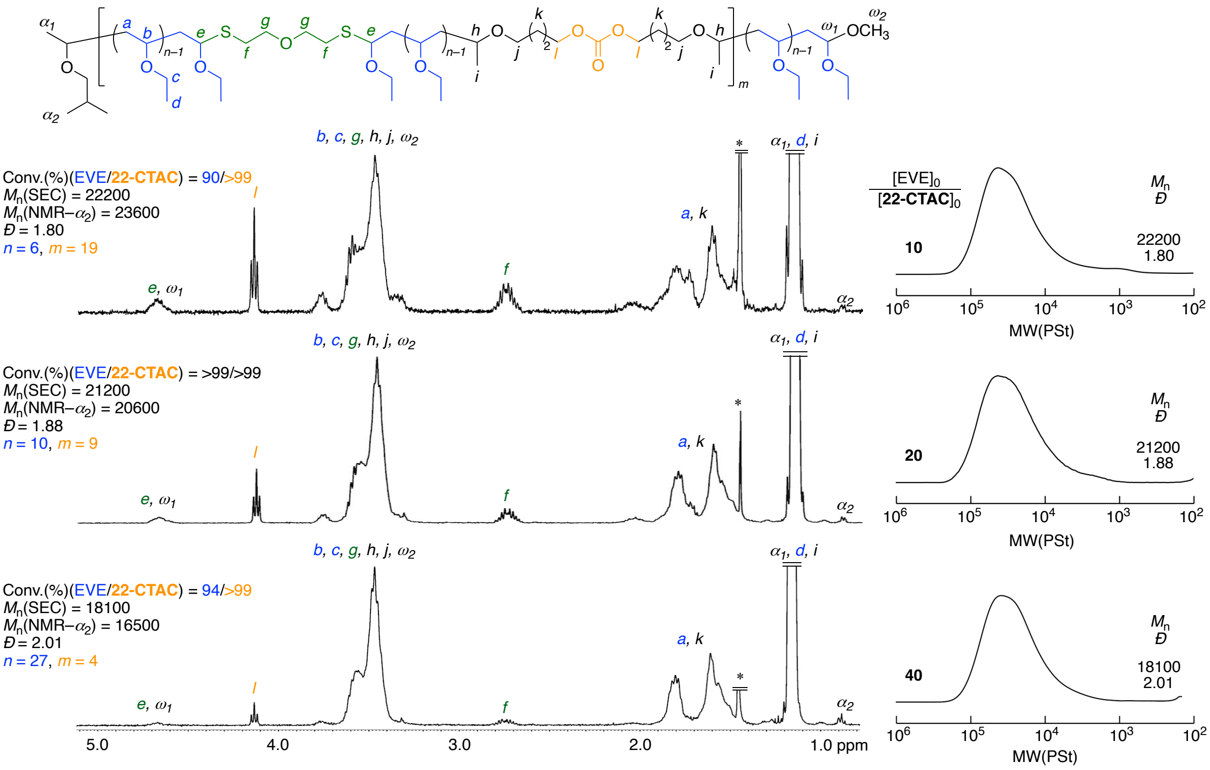


Fig. S16 ^{1}H NMR spectra ($CDCl_3$, 55 °C) and SEC curves of the copolymers obtained by cationic DT copolymerization of EVE and **22-CTAC** for fig. S14 after purification by preparative SEC. ∗: H_2O.

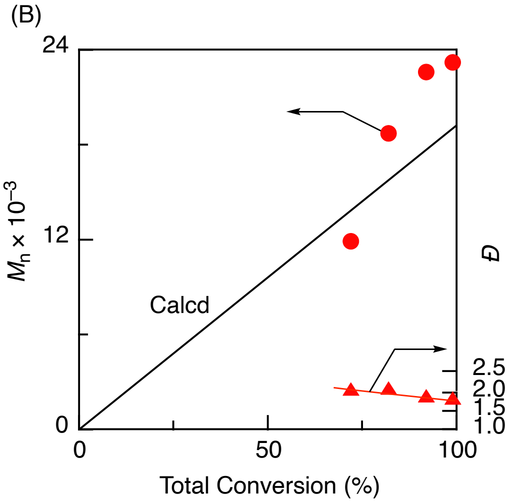


Fig. S17 M_n values of the polymers obtained by cationic DT copolymerization of EVE and **26-CTAC**: [EVE]$_0$/[**26-CTAC**]$_0$/[**1**]$_0$/[$ZnCl_2$]$_0$ = 4000/200/20/8.0 mM in CH_2Cl_2/*n*-hexane/Et_2O (20/10/10) at –40 °C.

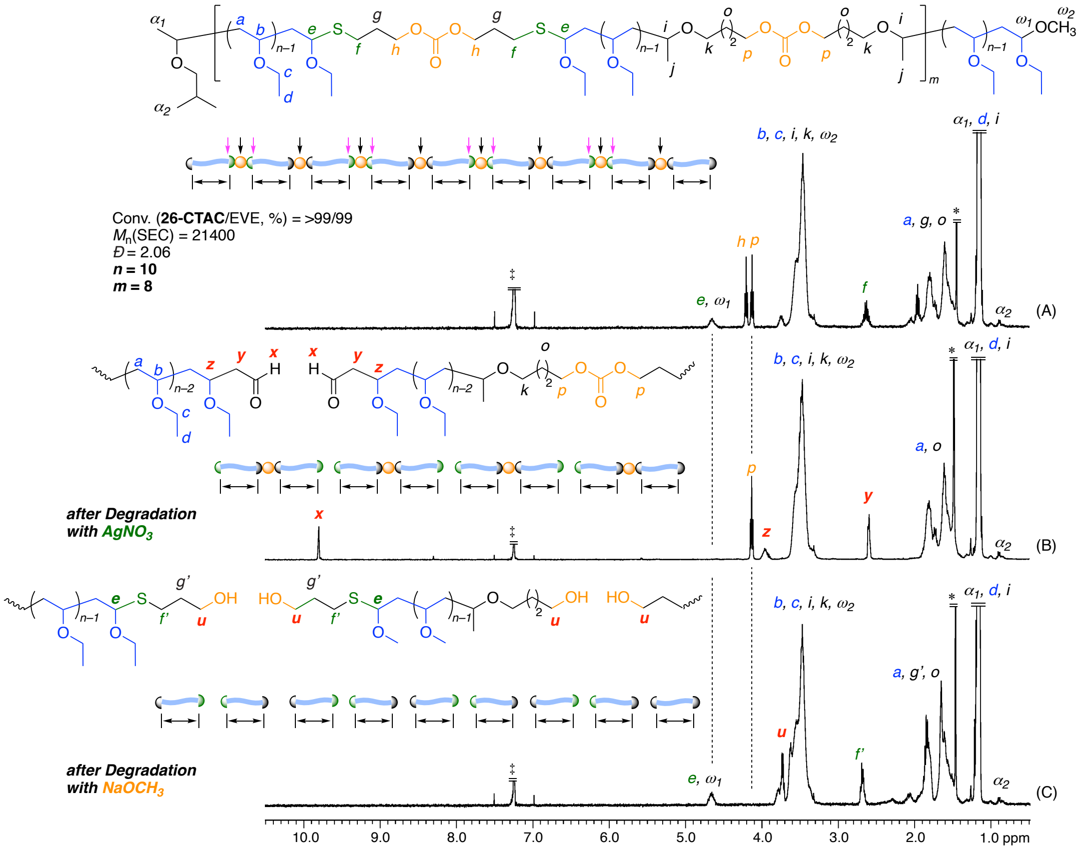


Fig. S18 ^{1}H NMR spectra ($CDCl_3$, 55 °C) of the products obtained by cationic DT copolymerization of EVE and **26-CTAC** and after degradation with $AgNO_3$ and $NaOCH_3$: $[\text{thioacetal unit}]_0/[AgNO_3]_0 = 5.0/50$ mM in THF/H_2O at 20 °C. $[\text{carbonate}]_0/[NaOCH_3]_0 = 5.0/50$ mM in CH_3OH at 60 °C. ∗: H_2O, ‡: $CHCl_3$.

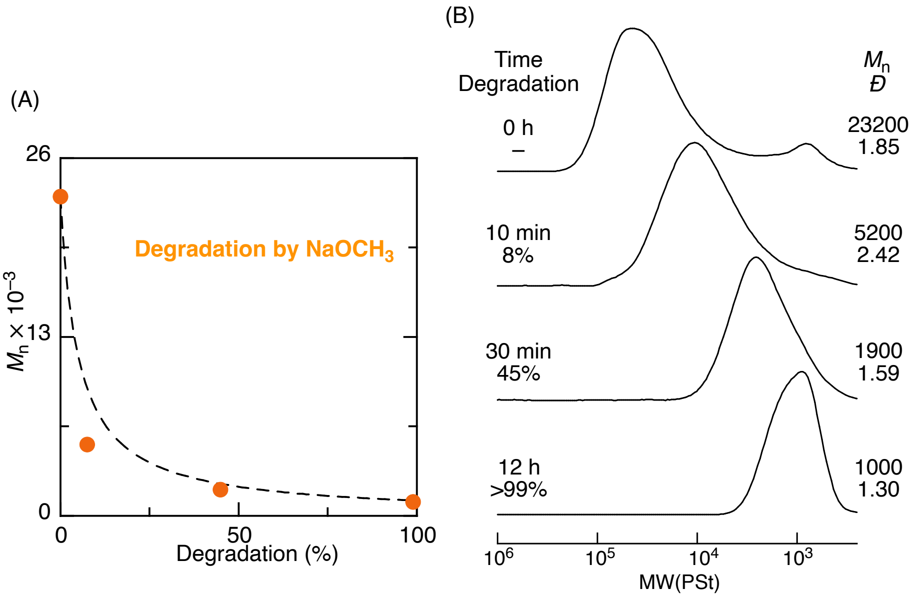


Fig. S19 M_n values (A) and SEC curves (B) of the polymers after methanolysis using a $NaOCH_3$ solution: $[\text{thioacetal units}]_0/[NaOCH_3]_0 = 5.0/50$ mM in CH_3OH at 60 °C.

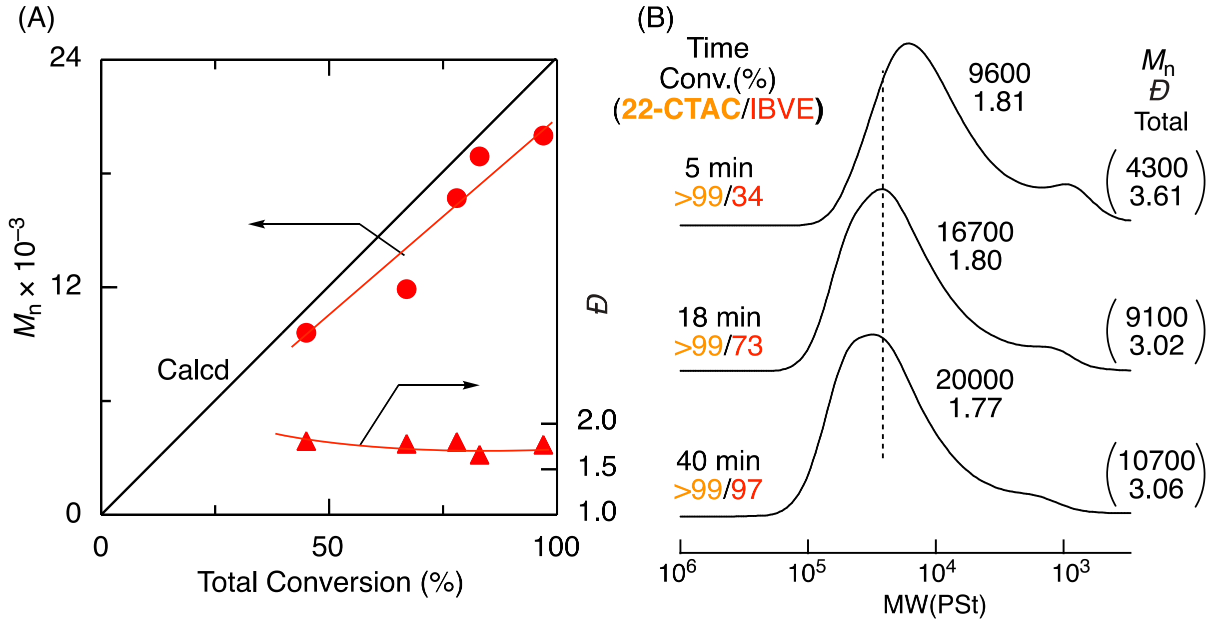


Fig. S20 M_n values (A) and SEC curves (B) of the polymers obtained by cationic DT copolymerization of IBVE and **22-CTAC**: [IBVE]$_0$/[**22-CTAC**]$_0$/[**1**]$_0$/[$ZnCl_2$]$_0$ = 4000/200/20/4.0 mM in CH_2Cl_2/*n*-hexane/Et_2O (20/10/10) at –40 °C.

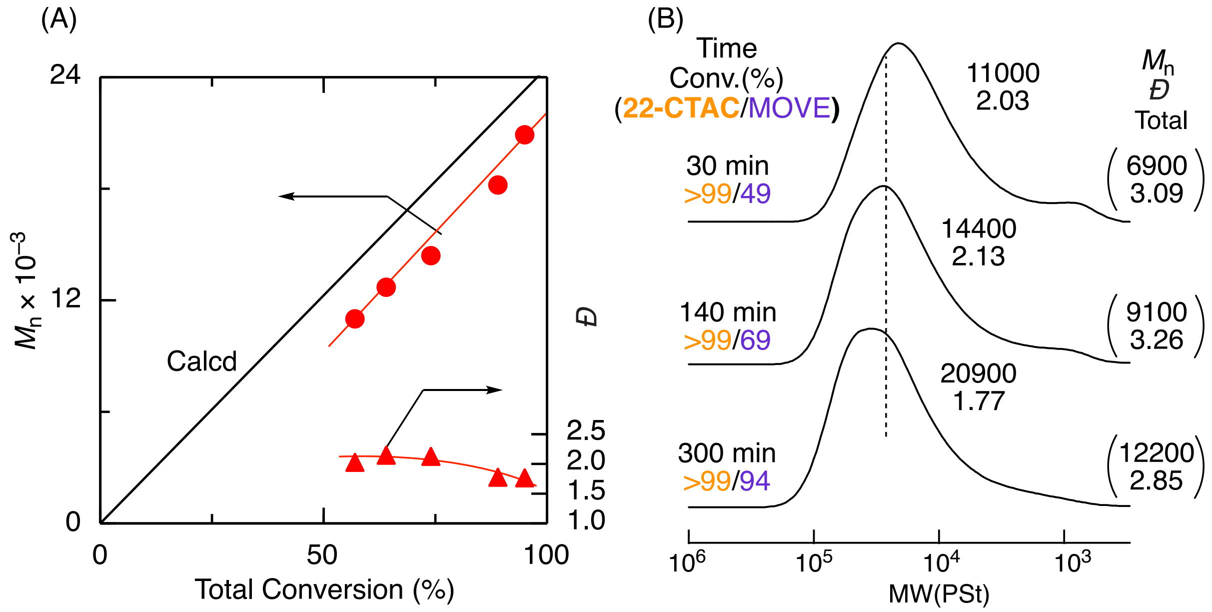


Fig. S21 M_n values (A) and SEC curves (B) of the polymers obtained by cationic DT copolymerization of IBVE and **22-CTAC**: [MOVE]$_0$/[**22-CTAC**]$_0$/[**1**]$_0$/[$ZnCl_2$]$_0$ = 4000/200/20/4.0 mM in CH_2Cl_2/*n*-hexane/Et_2O (20/10/10) at –40 °C.

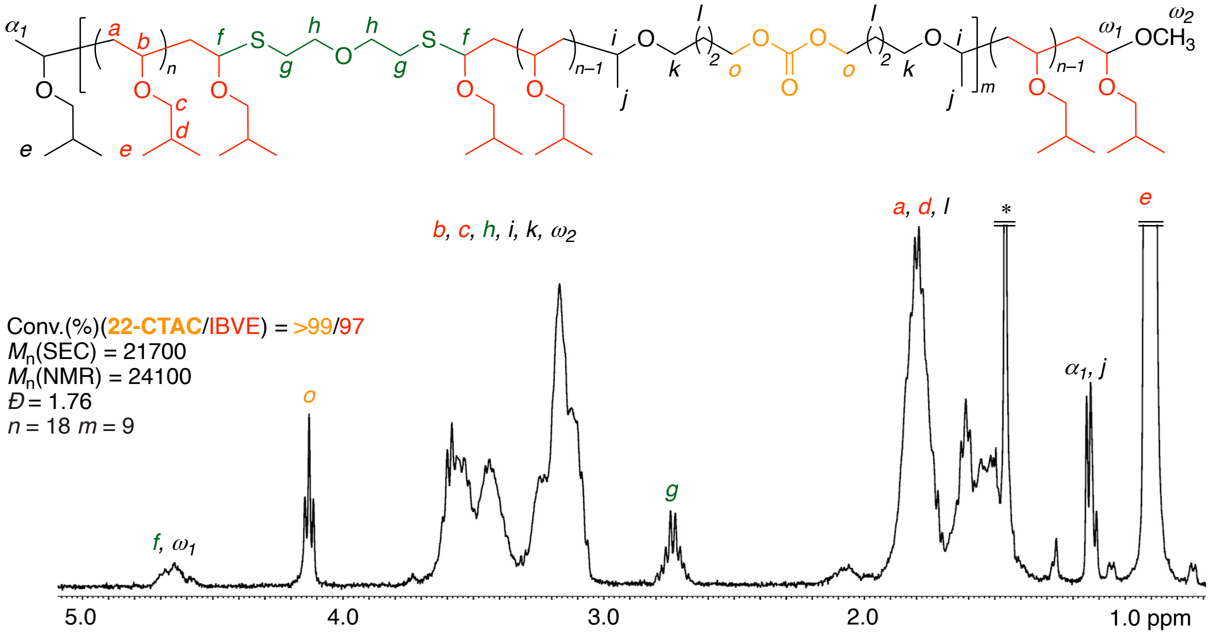


Fig. S22 ^{1}H NMR spectrum ($CDCl_3$, 55 °C) of dual-degradable poly(IBVE) obtained by cationic DT copolymerization of IBVE with **22-CTAC**. ∗: H_2O.

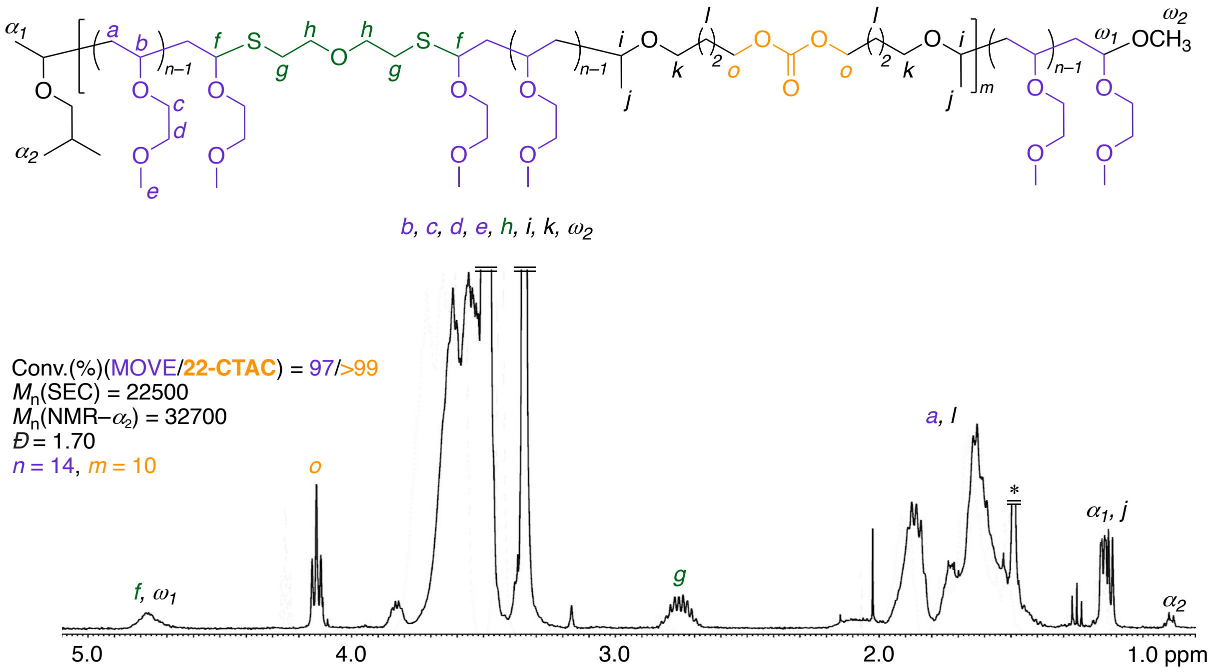


Fig. S23 ^{1}H NMR spectrum ($CDCl_3$, 55 °C) of dual-degradable poly(MOVE) obtained by cationic DT copolymerization of MOVE with **22-CTAC**. ∗: H_2O.

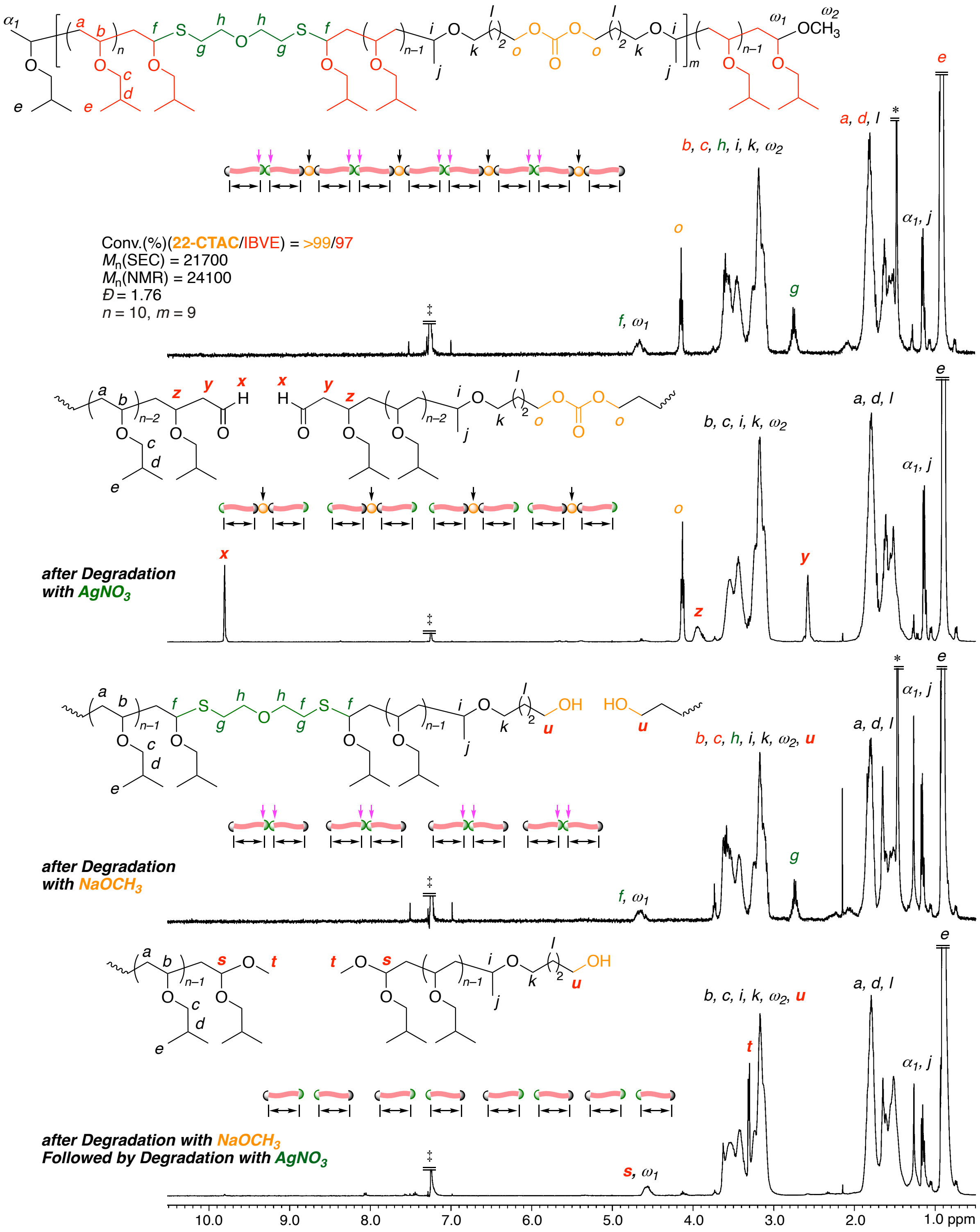


Fig. S24 ^{1}H NMR spectra ($CDCl_3$, 55 °C) of dual-degradable poly(IBVE) before and after degradation with $AgNO_3$ and $NaOCH_3$: [thioacetal unit]$_0$/[$AgNO_3$]$_0$ = 5.0/50 mM in THF/H_2O or CH_3OH at 20 °C. [carbonate]$_0$/[$NaOCH_3$]$_0$ = 5.0/50 mM in CH_3OH at 60 °C. ∗: H_2O, ‡: $CHCl_3$.

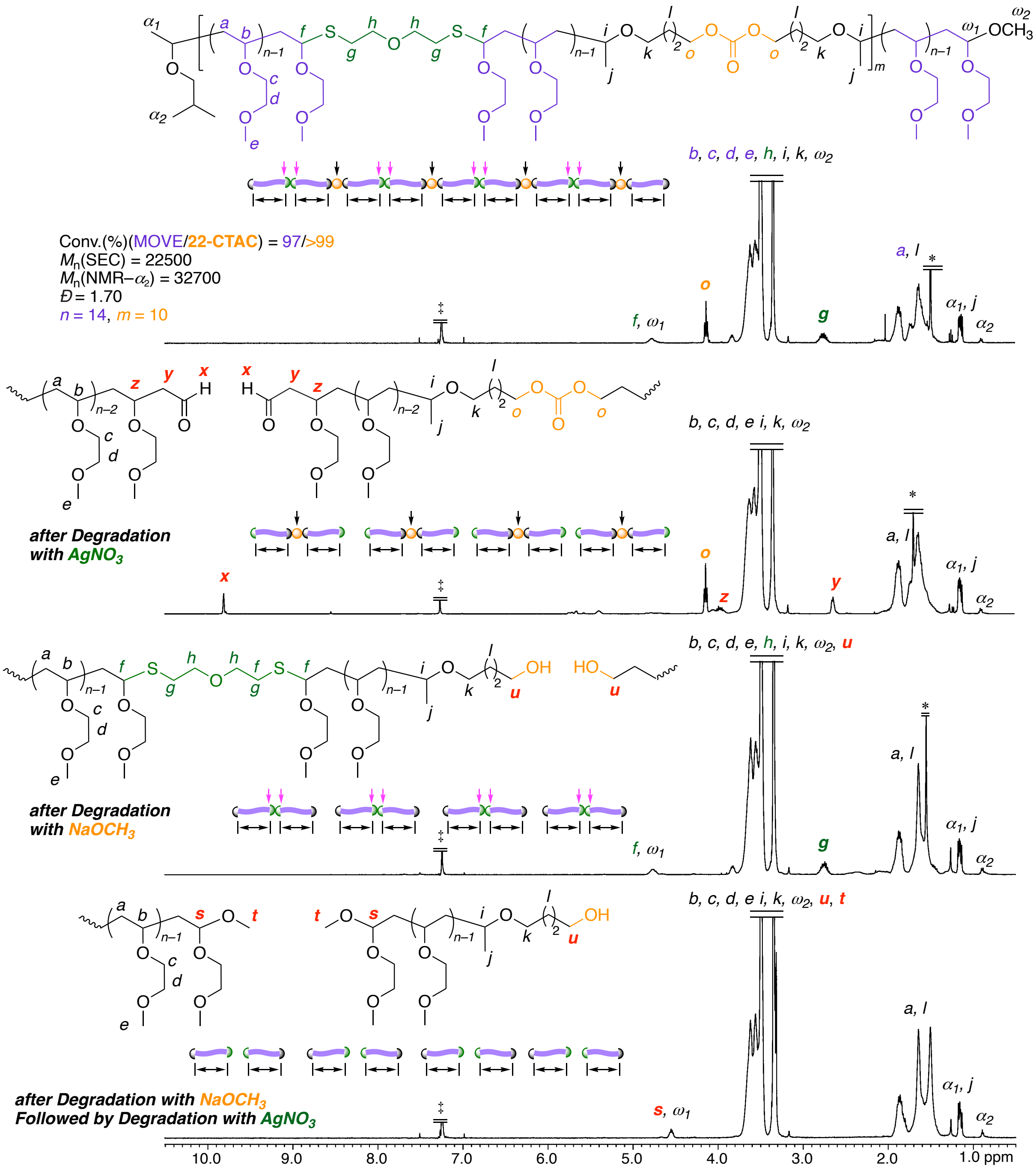


Fig. S25 ^{1}H NMR spectra ($CDCl_3$, 55 °C) of dual-degradable poly(MOVE) before and after degradation with $AgNO_3$ and $NaOCH_3$: [thioacetal unit]$_0$/[$AgNO_3$]$_0$ = 5.0/50 mM in THF/H_2O or CH_3OH at 20 °C. [carbonate]$_0$/[$NaOCH_3$]$_0$ = 5.0/50 mM in CH_3OH at 60 °C. *: H_2O, ‡: $CHCl_3$.

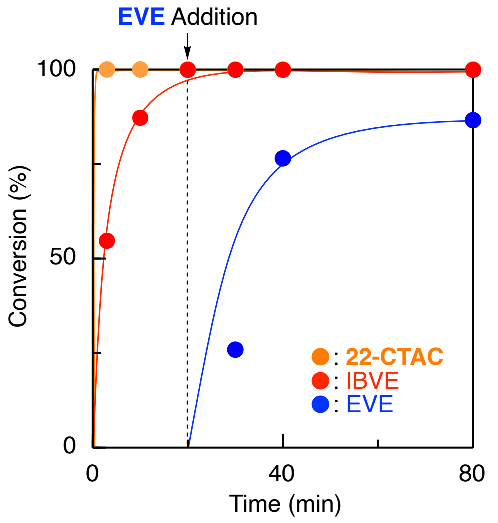


Fig. S26 Time-conversion curves for one-pot synthesis of dual-degradable multiblock copolymers of IBVE and EVE by cationic DT copolymerization with **22-CTAC**: $[\text{IBVE}]_0/[\text{EVE}]_{\text{add}}/[\textbf{22-CTAC}]_0/[\textbf{1}]_0/[\text{ZnCl}_2]_0$ = 2000/2000/200/20/4.0 mM in CH_2Cl_2/*n*-hexane/Et_2O (20/10/10) at –40 °C.

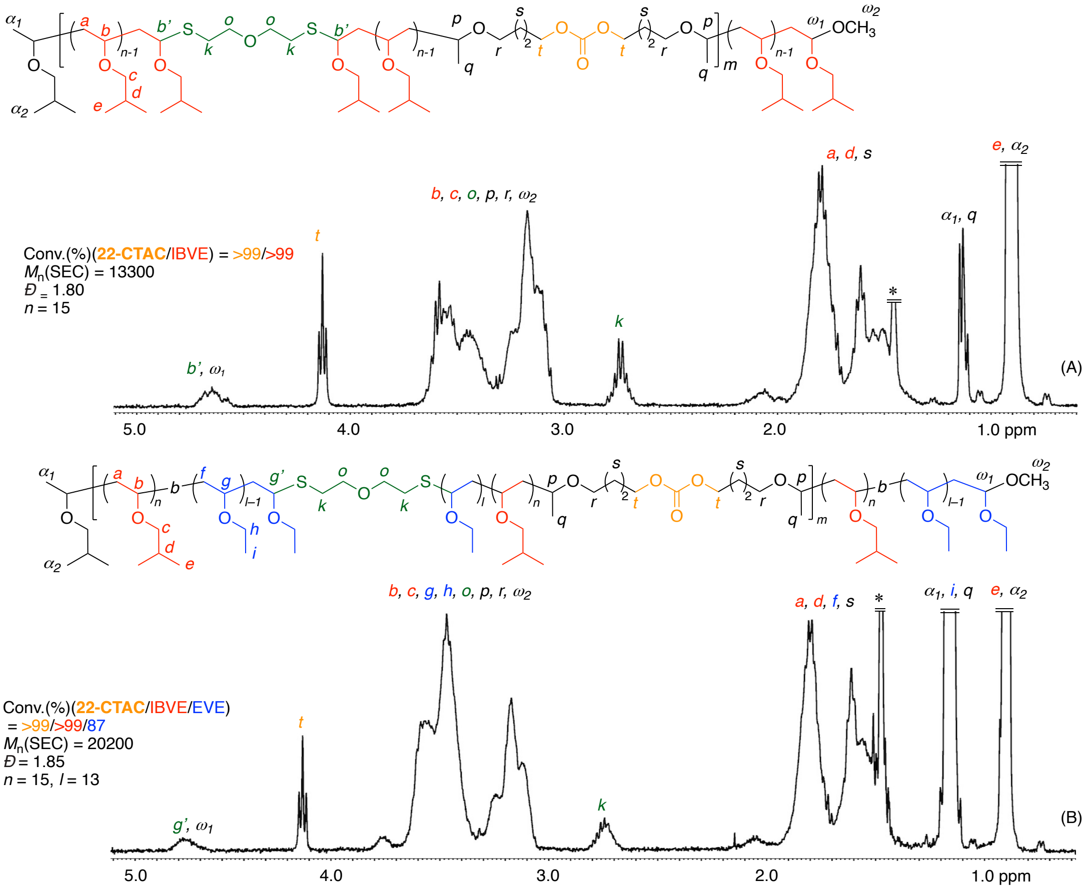


Fig. S27 ^{1}H NMR spectra ($CDCl_3$, 55 °C) of dual-degradable poly(IBVE) (A) and dual-degradable-multiblock poly(IBVE-EVE) (B). ∗: H_2O, ‡: $CHCl_3$.

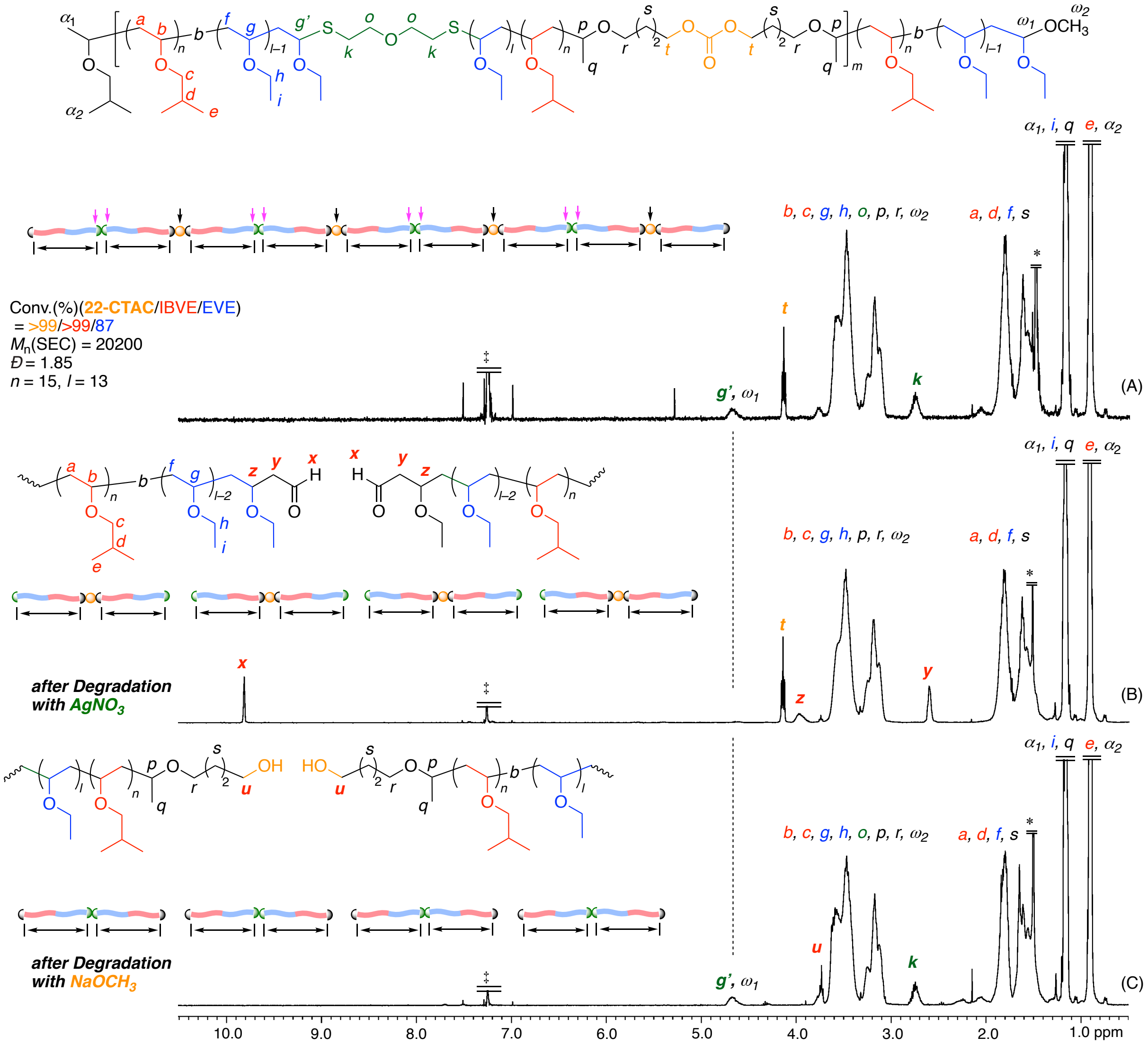


Fig. S28 ^{1}H NMR spectrum ($CDCl_3$, 55 °C) of dual-degradable multiblock poly(IBVE-EVE) before and after degradation with $AgNO_3$ and $NaOCH_3$: [thioacetal unit]$_0$/[$AgNO_3$]$_0$ = 5.0/50 mM in THF/H_2O at 20 °C. [carbonate]$_0$/[$NaOCH_3$]$_0$ = 5.0/50 mM in CH_3OH at 60 °C. $*$: H_2O, ‡: $CHCl_3$.