Conjugate substitution and addition of α-substituted acrylate: A highly efficient, facile, convenient and versatile approach to degradable polymer by dynamic covalent chemistry

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Electronic Supplementary Information

Experiments

Instruments

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (Across Organics) on an AVANCE 400 (Bruker) spectrometer. Chemical shifts in ^{1}H and ^{13}C NMR spectra were referred to the signal of tetramethylsilane (TMS) and solvent ($CDCl_3$), respectively. Molecular weight and its distributions were determined at 40 °C by size-exclusion chromatography (SEC) on an EXTREMA chromatograph (JASCO) equipped with two SEC columns [PL-gel, Mixed C (300 mm _7.5 mm), Polymer Laboratories], using tetrahydrofuran (THF, Wako Pure Chemical Industries, for HPLC grade) as an eluent (flow rate = 0.8 mL min^{-1}), and calibrated against standard polystyrene (PS) samples (TSK-gel oligomer kit, Tosoh, M_n: 1.03×10^6, 3.89×10^5, 1.82×10^5, 3.68×10^4, 1.36×10^4, 5.32×10^3, 3.03×10^3, 8.73×10^2) and detected with UV (UV-4070, JASCO) and RI (RI-4030, JASCO) detectors. IR spectra were recorded on a Cary 630 FTIR spectrometer equipped with a transmission attachment. Thermogravimetric /differential thermal analyses (TG/DTA) was carried out from room temperature to 500 °C at a heating rate of 10 °C with Rigaku Thermo plus II TG8120 under an N_2 atmosphere. Differential scanning calorimetry (DSC) was carried out at a heating rate of 10 °C with Rigaku Thermo plus II DSC8230 under an N_2 atmosphere.

Materials

tert-Butyl acrylate was a kind gift from Osaka Organic Chemical Industry Ltd. Methyl α-(hydroxymethyl)acrylate was a kind gift from Nippon Shokubai Co, Ltd. 1,4-Diazabicyclo[2.2.2]octane (DABCO) was purchased from Kanto Chemical Co, Inc. Formaldehyde aqueous solution (37 wt%), thionyl chloride and solvents were purchased from Wako Pure Chemical Industries, Ltd. Other chemicals were purchased from Tokyo Chemical Industry Co., Ltd.

tert-Butyl (α-hydroxymethyl)acrylate (9)[1]

Formaldehyde aqueous solution (37 wt%, 35.8 g, 0.441 mol) and *tert*-butyl acrylate (**8**, 51.3 g, 0.400 mol) was added to a solution of DABCO (9.62 g, 85.8 mmol) in 1,4-dioxane (300 mL)–water (300 mL). The reaction mixture was stirred at 60 °C for 33 h. The product was extracted with hexane (250 mL × 2) and the combined organic layer was concentrated. The residue oil was purified on silica gel column chromatography (eluent: hexane / EtOAc = 10 / 0, 8 / 1, and then 4 / 1) to give *tert*-butyl α-(hydroxymethyl)acrylate (**9**, 36.4 g) as colorless oil. Yield 57.2%; ^{1}H NMR (400 MHz, 26 °C, $CDCl_3$) δ/ppm 6.15 (s, 1H, CH_2=), 5.74 (s, 1H, CH_2=), 4.11 (s, 2H, CH_2OH), 1.51 (s, 9H, CH_3–).

α-(Chloromethyl)acryloyl chloride (10)[2,3]

Thionyl chloride (58 mL, 810 mmol) was added dropwise to **9** (36.4 g, 496 mmol). The reaction mixture was stirred for 24 h and concentrated. The residue was purified by distillation under reduced pressure to afford α-(chloromethyl)acryloyl chloride (**10**, 23.1 g) as colorless oil. Yield 72.3%; bp 62.5-67.0 °C / 11 mmHg.

1,4-butylene bis[α-(chloromethyl)acrylate] (4)

A solution of **10** (13.1 g, 94.0 mmol) in THF (25 mL) was added dropwise to a solution of 1,4-butanediol (3.61 g, 40.0 mmol) in THF (25 mL) under argon atmosphere at −10 °C. The reaction mixture was stirred for 45 h, diluted with diethyl ether (100 mL) and washed with *sat.* $NaHCO_3$ aq (100 mL). The organic layer was concentrated, and the residue was purified on silica gel column chromatography (eluent: hexane / EtOAc = 8 / 1) to yield **4** (4.73 g) as a colorless needle crystal. Yield: 40.0%; mp: 45.0-46.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 26 °C): δ/ppm 6.38 (s, 2H, C*H*H=), 5.98 (d, *J* = 0.76 Hz, 2H, CH*H*=), 4.29 (d, *J* = 0.76 Hz, 4H, CH_2Cl), 4.28-4.25 (m, 4H, OCH_2), 1.84-1.82 (m, 4H, CH_2);^{13}C NMR (100 MHz, $CDCl_3$, 26 °C): δ/ppm 164.8, 136.8, 128.7, 64.5, 42.5, 25.2; FTIR: υ/cm^{-1} 3039 (CH_2=), 2972 (C-H), 2959 (C-H), 2922 (C-H), 2984 (C-H), 2855 (OCH_2), 1714 (C=O), 1626 (C=C), 1336 (C-O), 1192 (C-O), 1144 (C-O), 816 (C-Cl).

Methyl α-(Chloromethyl)acrylate (11)[4]

Thionyl chloride (53.0 mL, 0.27 mol) was added to methyl α-(hydroxymethyl)acrylate (57.6 g, 0.496 mol) dropwise. The reaction mixture was stirred for 15 h and concentrated. The residue was purified by distillation under reduced pressure to yield methyl α-(chloromethyl)acrylate (**11**) as colorless oil (54.0g). Yield: 80.1 %; bp 58-60 °C / 7.5 mmHg; ^{1}H NMR (400 MHz, 26 °C, $CDCl_3$) δ/ppm 6.39 (s, 1H, C*H*H=), 5.99 (d, J = 1.4 Hz, 1H, CH*H*=), 4.29 (d, J = 1.4 Hz, 2H, CH_2Cl), 3.81 (s, 3H, OCH_3).

Polymerization of 2a and 4 (Table 1, Runs 1–3)

A typical procedure (Table 1, Run 3): A solution of Et_3N (0.10 g, 1.0 mmol) and 1,10-decanedithiol (**2a**) (83 mg, 0.40 mmol) in $CHCl_3$ (0.50 mL) was added dropwise to a solution of **4** (0.118 mg, 0.400 mmol) in $CHCl_3$ (0.50 mL). The reaction mixture was stirred for 24 h and poured into MeOH (50 mL). The precipitate was collected by filtration and dried *in vacuo* to yield the corresponding unsaturated polymer (153 mg) as white powder. Yield: 79%; M_n = 58000, M_w/M_n = 2.27.

Polymerization of 2b and 4 (Runs 4–6)

A typical procedure (Table 1, Run 4): Polymerization **2b** (61 mg, 0.40 mmol) and **4** (0.118 mg, 0.400 mmol) was conducted in a similar manner to that of **2a** and **4**. After 24 h, the reaction mixture was washed with 1 M HCl aq (5.0 mL), and the organic layer was concentrated and dried *in vacuo* to yield the corresponding polymer (137 mg) as white powder. Yield: 92%; M_n = 12000, M_w/M_n = 1.43

Polymerization of 2e and 4 without end-capping (Run 7).

Polymerization of **2e** (74 mg, 0.41 mmol) and **3** (0.118 mg, 0.400 mmol) was conducted in a similar manner to that of **2b** and **3** described above to yield the corresponding polymer (131mg) as a colorless elastomer. The product exhibited poor solubility in THF and $CHCl_3$.

Polymerization of 2e and 4 with end-capping (Run 8)

Polymerization of **2c** (74 mg, 0.41 mmol) and **4** (0.118 mg, 0.400 mmol) was conducted in a similar manner to that of **2b** and **4** described above. After 1 h, a solution of methyl α-(chloromethyl)acrylate (19 mg, 0.14 mmol) in $CHCl_3$ (0.40 mL) was added. The reaction mixture was stirred further 3 h and poured into MeOH (50 mL). The precipitate was collected by centrifugation to yield the corresponding polymer (137 mg) as a colorless sticky solid. Yield 84%; M_n =17000, M_w/M_n = 2.08.

Polymerization of 4 and 5 (Table 2, Run 9)

A solution of Et_3N (0.102 g, 1.00 mmol) and adipic acid (**5**) (58 mg, 0.40 mmol) in *N*,*N*-dimethylformamide (DMF, 0.50 mL) was added dropwise to a solution of **4** (0.118 mg, 0.400 mmol) in DMF (0.30 mL). The reaction mixture was stirred for 1 h and $CHCl_3$ (10 mL) was added. The solution was washed with water (10 mL × 3) and the organic layer was dried over Na_2SO_4 and concentrated. The residue was poured into water (40 mL). The precipitate was collected by filtration and dried *in vacuo* to yield the corresponding unsaturated polymer (78 mg) as white powder. Yield: 53%; M_n = 14000, M_w/M_n = 1.86.

Polymerization of 4 and 6 (Runs 10 and 11)

A typical procedure (Table 2, Run 11): A solution of DBU (0.156 g, 1.02 mmol) and *n*-propyl amine (**6**, 24 mg, 0.41 mmol) in 1,4-dioxane (0.50 mL) was added dropwise to a solution of **4** (0.119 mg, 0.403 mmol) in 1,4-dioxane (0.30 mL). The reaction mixture was stirred for 24 h and water (10 mL) was added. The solution was extracted with CH_2Cl_2 (30 mL) and the organic layer was washed with water (30 mL), dried over Na_2SO_4 and concentrated. The residue was dried *in vacuo* to yield the corresponding unsaturated polymer (78 mg) as white powder. Yield: 90%; M_n = 1900, M_w/M_n = 1.92.

Polymerization of 4 and 7 (interfacial polymerization, Run 12)

A solution of **4** (0.122 g, 0.413 mmol) in CH_2Cl_2 (0.80 mL) was added to a solution of bisphenol A (**7**) (0.94 mg, 0.41 mmol) and benzyltriethylammonium chloride (BTEAC, 20 mg, 88 mmol) in ca. 0.6 M NaOH aq (1.5 mL). The reaction mixture was vigorously stirred for 24 h and water (10 mL) was added. The solution was extracted with CH_2Cl_2 (10 mL) and the organic layer was concentrated. The residue was dried *in vacuo* to yield the corresponding unsaturated polymer (137 mg) as white powder. Yield: 74%; M_n = 2800, M_w/M_n = 1.56.

Polymerization of 4 and 7 (solution polymerization, Runs 13 and 14)

A typical procedure (Table 2, Run 14): A solution of Et_3N (0.105 g, 1.03 mmol) and **7** (91 mg, 0.40 mmol) in $CHCl_3$ (0.50 mL) was added dropwise to a solution of **4** (0.118 mg, 0.400 mmol) in $CHCl_3$ (0.50 mL). The reaction mixture was stirred for 24 h and water (5 mL) was added. The organic layer was concentrated and the residue was dried *in vacuo* to yield the corresponding unsaturated polymer (168 mg) as white powder. Yield: 93%; M_n = 32000, M_w/M_n = 1.98.

Synthesis of Prepolymer P7/12

A solution of adipoyl chloride (**12**, 0.293 g, 1.60 mmol) in $CHCl_3$ (2.0 mL) was added dropwise to a solution of **7** (0.457 g, 2.00 mmol) and Et_3N (0.508 g, 5.00 mmol) in $CHCl_3$ (2.0 mL). The reaction mixture was stirred for 2 h and water (4 mL) was added to quench the reaction. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (5 mL × 3). The combined organic layer was concentrated and the residue was dried *in vacuo* at 60 °C for 3 h. The residue was dissolved in $CHCl_3$ (5 mL) and washed with 0.16 M HCl aq (6 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (5 mL × 3). The combined organic layer was washed with brine (5 mL), concentrated and dried *in vacuo* to yield prepolymer **P7/12** as a mixture with Et_3N·HCl (0.847 g). The product was used in the next reaction without further purification. M_n = 750, M_w/M_n = 1.95 (SEC); M_n = 675 (NMR).

Synthesis of Terpolymer P4/(7/13)

A solution of **4** (0.118 g, 0.400 mmol) in $CHCl_3$ (0.50 mL) was added dropwise to a solution of prepolymer **P7/13** (0.328 g, 0.363 mmol) and Et_3N (0.108 g, 1.01 mmol) in $CHCl_3$ (0.30 mL). The reaction mixture was stirred for 1 h and water (1.5 mL) and 1 M HCl aq (0.5 mL) was added to quench the reaction. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (5 mL × 3). The combined organic layer was washed with brine (5 mL), dried over $MgSO_4$ and concentrated. The residue was dried *in vacuo* to yield terpolymer **P4/(7/13)** (0.403 g, 97%). M_n = 6420, M_w/M_n = 1.93 (SEC).

Model reaction for the polycondensation with dithiol monomer

A typical procedure (Table 1, Run 1): Model reaction of **11** (134 mg, 1.00 mmol) and benzyl mercaptan (**A**, 112 mg, 0.902 mmol) was conducted in a similar manner to the polymerization of **2a** and **4**. After 3 h, the reaction mixture was washed with 1 M HCl aq (0.5 mL), and the organic layer was concentrated in vacuo to yield a mixture of 5 and 6 (0.230 mg) as yellow oil.

Main-chain scission of obtained polymers

A typical procedure (Table 2, Run 7): A solution of Et_3N (15.2 mg, 0.150 mmol) and **13** (0.187 g, 1.50 mmol) in CH_3CN (0.6 mL) was added dropwise to a solution of **P4/5** (0.110 g, 0.400 mmol/unit) in $CHCl_3$ (0.6 mL). The reaction mixture was stirred at room temperature, and small portions were sampled at the determined time. After 24 h, 0.1 M HCl aq (1 mL) was added, and the product was extracted with $CHCl_3$ (3 mL). The organic layer was washed with brine (3 mL), concentrated and dried *in vacuo* to give viscous colorless liquid (0.216 g).

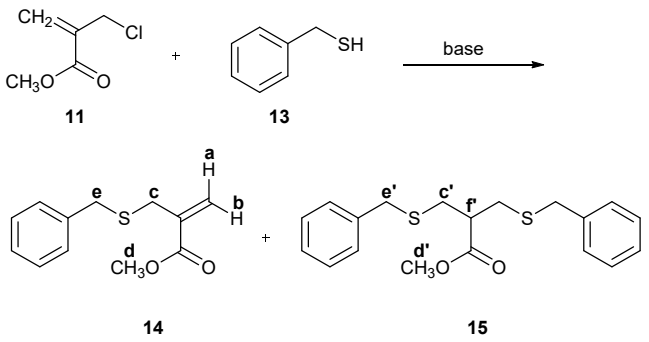
Decrosslinking of P2a/4-gel

A solution of Et_3N (10 mg, 0.11 mmol) and **13** (0.124 g, 1.00 mmol) in CH_3CN (0.4 mL) was added dropwise to a suspension of **P2a/4-gel** (86 mg) in $CHCl_3$ (0.4 mL). The reaction mixture was stirred at room temperature for 46 h. The obtained solution was poured into hexane to recover the product, and the precipitate was collected by decantation and dried *in vacuo* to give pale yellow viscous liquid (0.125 g).

Additional Results and Discussion

Kinetic control toward selective S_N2' reaction

In advance to the polymerization, we first investigate the selectivity of conjugate substitution and addition reactions by a model reaction of **11** and benzyl mercaptan (**13**) (Scheme S1, Table S1). Since the substitution reaction release the hydrochloride, the reaction should be employed in the presence of weak base such as amine. However, amine compounds can catalyse the conjugate addition, the substitution reaction of **11** is competitive with the addition reaction against the product, **14**. Figure 1 shows the ^{1}H NMR spectra of the products by the reaction of **11** and **14** with Et_3N. In addition to the signals assigned to **15** (labelled a-e), those of the addition product **16** (labelled c'-f') were observed. From the intensity ratio of signal a to signals d and d', the selectivity of substitution reaction against the subsequent addition reaction was evaluated. The products from an equimolar mixture of **1a** and **11** in CH_3CN included 98% of **14** and 2% of **15** (Table 1, Run 1). An excess amount of **13** afforded the addition product quantitatively (Runs 2 and 3). These results indicated that the substitution reaction of **11** and **13** preferentially proceeded, and thereafter the addition reaction of **13** and **14** followed. In other words, the conjugate substitution proceeds at much faster reaction rate than the conjugate addition. Similar tendency was found among the reactions in $CHCl_3$ (Runs 4-6), and notably, the equimolar mixture of **11** and **13** yielded the substitution product (**14**) selectively. As the Michael addition-type thiol-ene reaction proceeds very slow in low polar solvents such as $CHCl_3$,[15,16] these results seem to be reasonable. Therefore, $CHCl_3$ should be a suitable solvent and base to supress the crosslinking in the polymerization of **2** and **4**.



Scheme S1. Model reaction of the polymerization of **2** and **3**.

Table S1 Model reaction of **11** and **13** under the ambient conditions.

Run[a]	Solvent	[**13**]$_0$ / [**11**]$_0$	Product Composition[b] / %	
			14	**15**
1	CH_3CN	1.00	98	2
2	CH_3CN	1.05	95	5
3	CH_3CN	1.15	85	15
4	$CHCl_3$	1.00	>99	1 >
5	$CHCl_3$	1.06	94	6
6	$CHCl_3$	1.13	87	13

[a] **A**: 1.00 mmol, [**11**]$_0$/[**13**]$_0$/[Et_3N]$_0$ = 1/1.00/2.50, solvent: 1 mL, 3 h.

[b] Determined by ^{1}H NMR spectrum of the product extracted with $CHCl_3$ (400 MHz, $CDCl_3$, 26 °C)

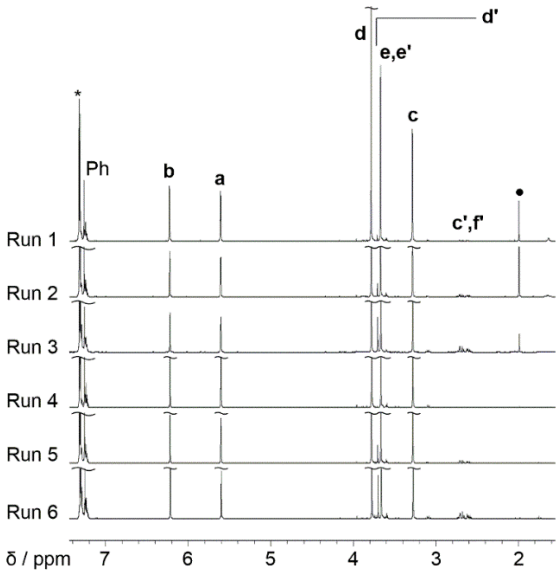


Figure S1 ^{1}H NMR spectra of the reaction products of **11** and **13** (400 MHz, $CDCl_3$, 26 °C). The experimental codes were corresponding to Table 1. Labels for the assignments were corresponding to Scheme S1 except the followings: *$CHCl_3$ and ●CH_3CN.

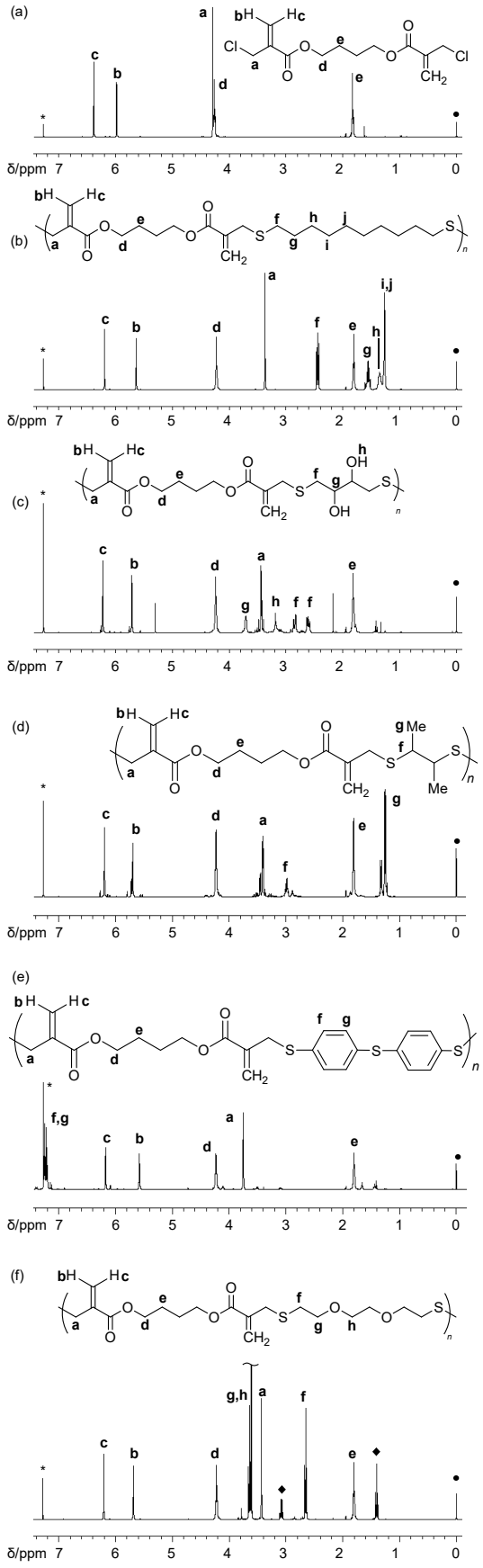


Figure S2 ^{1}H NMR spectra of (a) **4** and (b) **P2a/4**, (c) **P2b/4**, (d) **P2c/4**, (e) **P2d/4** and (f) **P2e/4** (400 MHz, $CDCl_3$, 26 °C). *: $CHCl_3$, •: tetramethylsilane and ♦: $Et_3N\cdot HCl$.

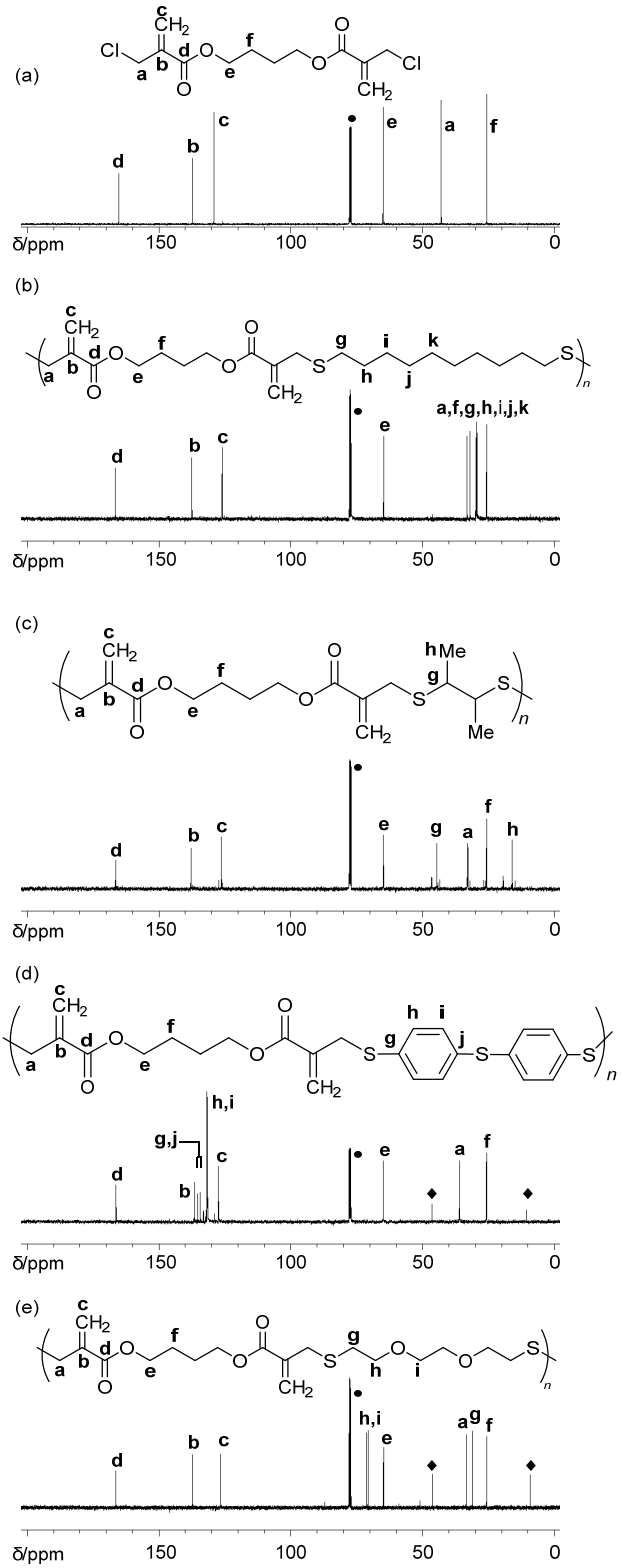


Figure S3 ^{13}C NMR spectra of (a) **4** and (b) **P2a/4**, (c) **P2c/4**, (d) **P2d/4** and (e) **P2e/4** (100 MHz, $CDCl_3$, 26 °C). *: $CHCl_3$, •: tetramethylsilane.

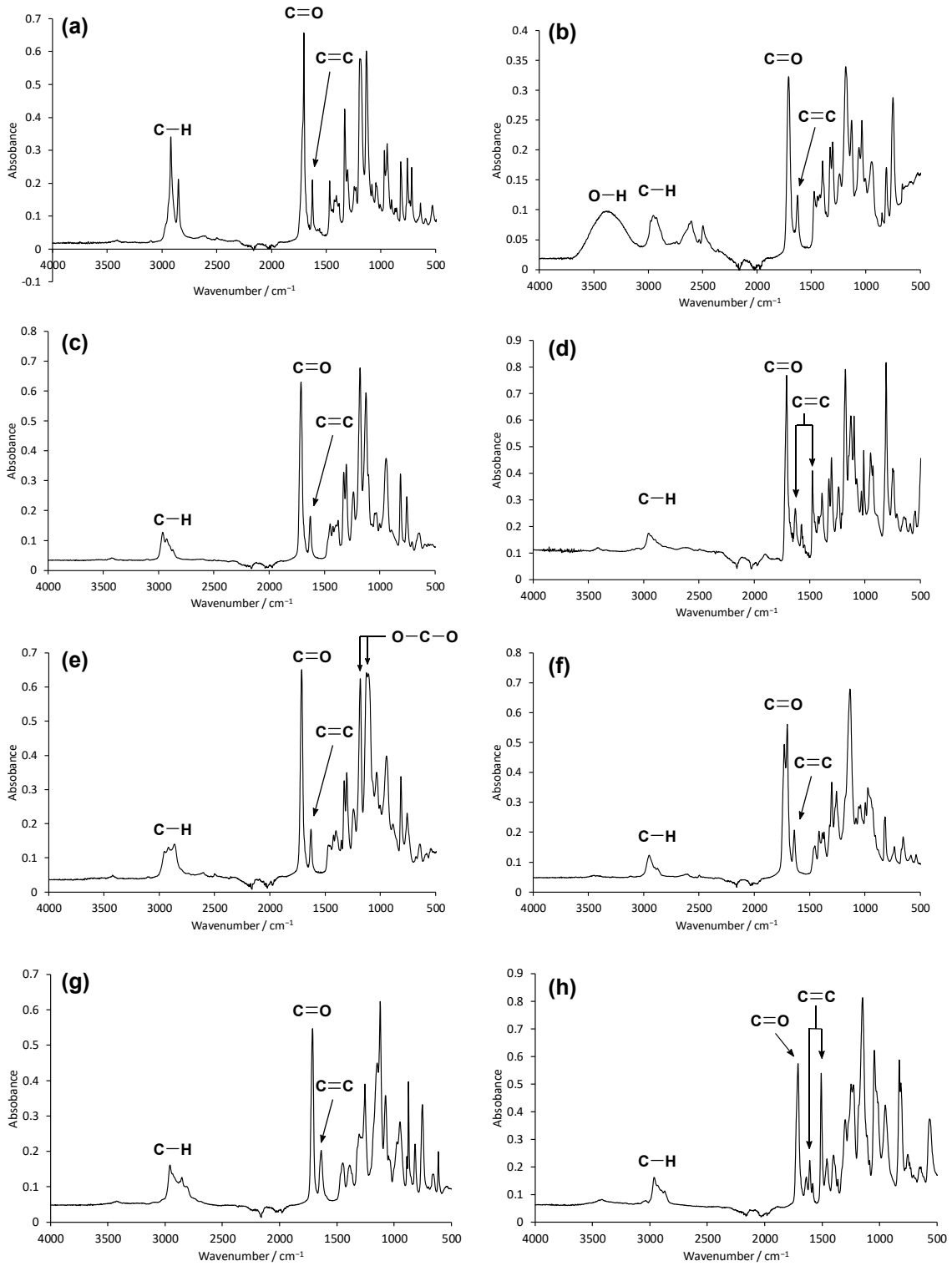


Figure S4 IR spectra of (a) **P2a/4**, (b) **P2b/4**, (c) **P2c/4**, (d) **P2d/4**, (e) **P2e/4**, (f) **P4/5**, (g) **P4/6**, and (h) **P4/7** (ATR).

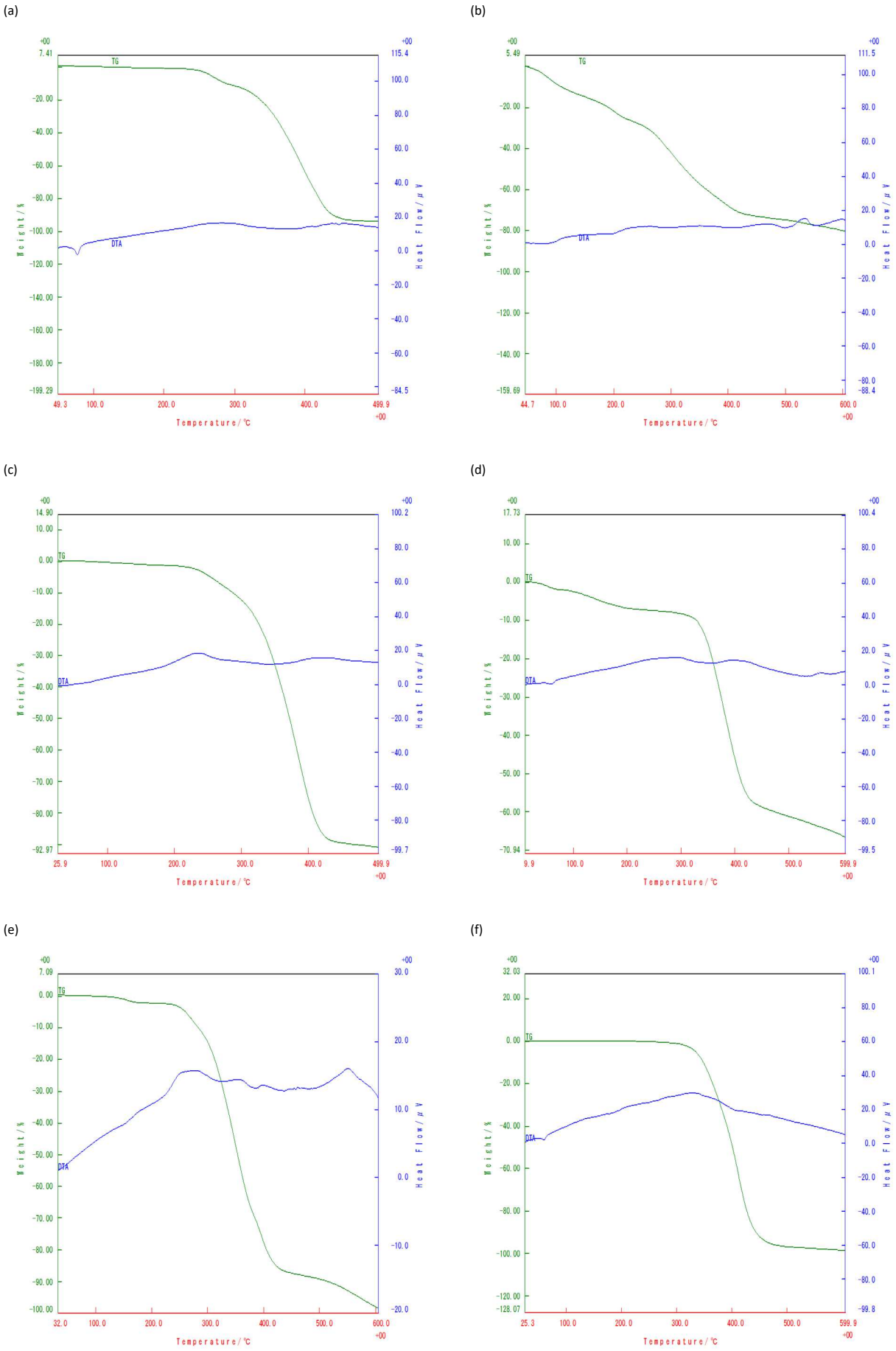
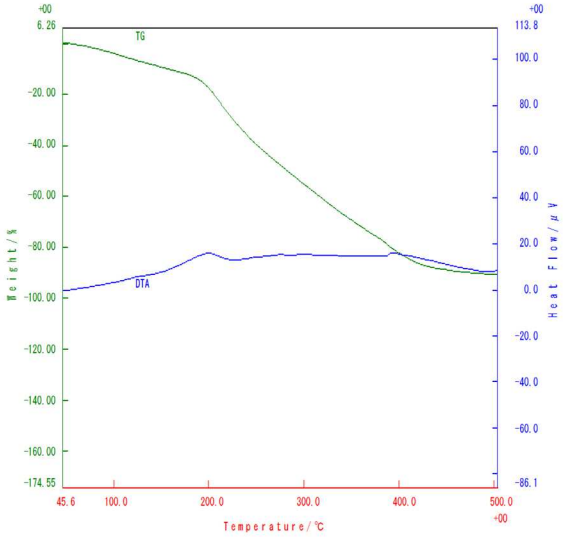


Figure S5 TGA/DTA charts of (a) **P2a/4**, (b) **P2b/4**, (c) **P2c/4** and (d) **P2d/4** (heating rate = 10 °C/min, under N_2 atmosphere).

(e)



(f)

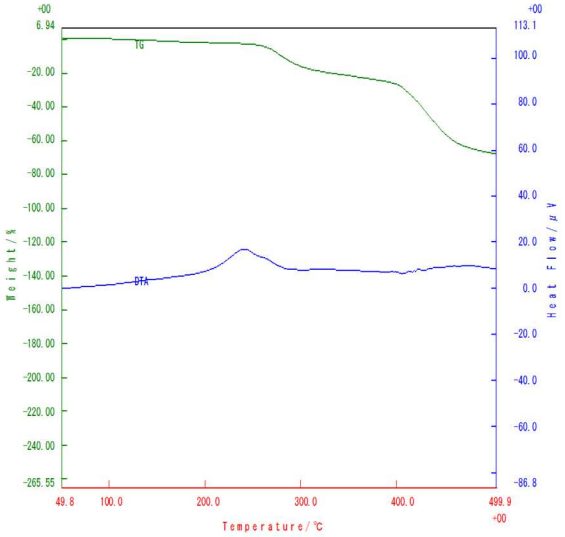
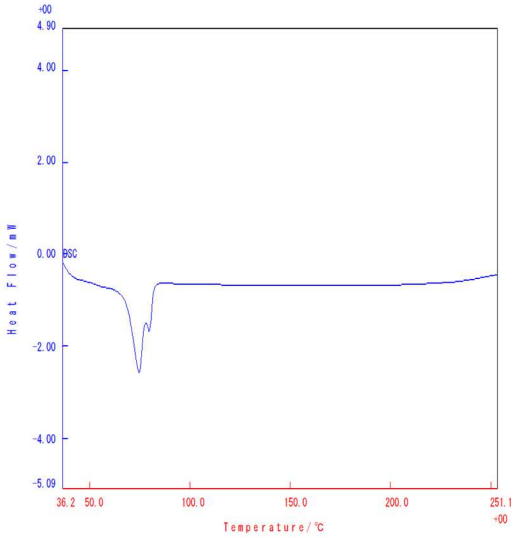
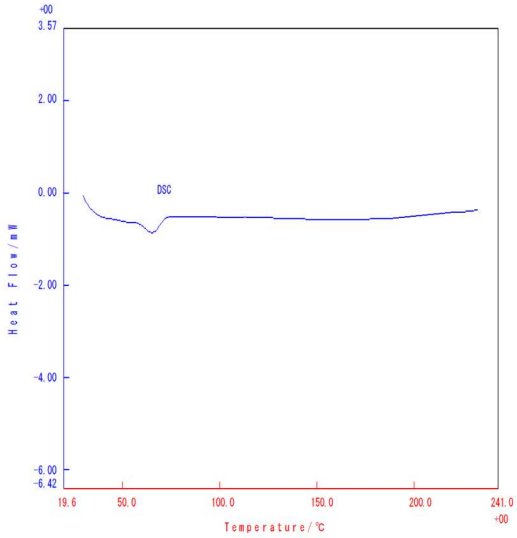


Figure S6 TGA/DTA charts of (e) **P2e/4**, (f) **P4/5**, (g) **P4/6**, and (h) **P4/7** (heating rate = 10 °C/min, under N_2 atmosphere).

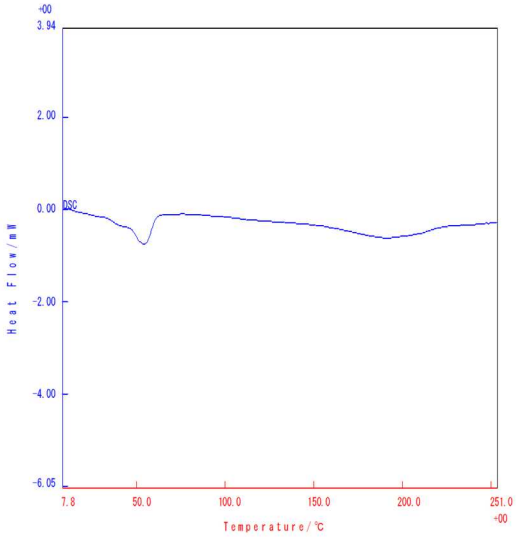
(a)



(b)



(c)



(d)

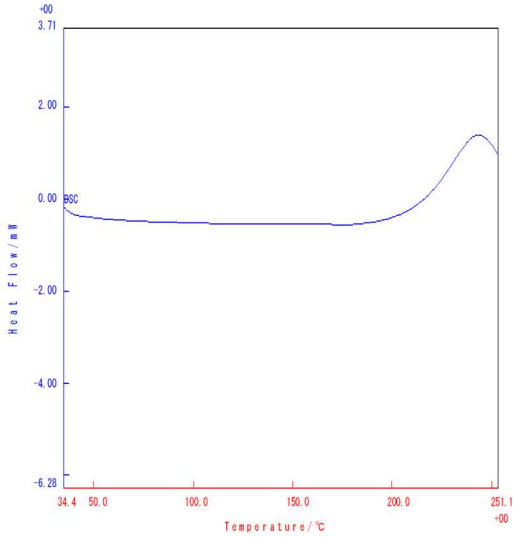


Figure S7 DSC charts of (a) **P2a/4**, (b) **P2d/4**, (c) **P4/5**, and (d) **P4/7** (heating rate = 10 °C/min, under N_2 atmosphere).

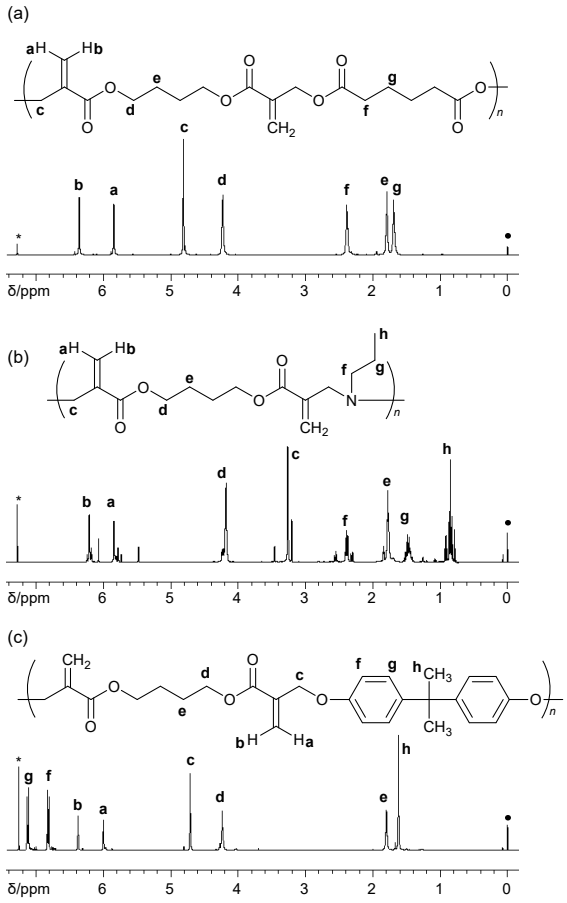


Figure S8 ^{1}H NMR spectra of (a) **P4/5**, (b) **P4/6**, and (c) **P4/7** (400 MHz, $CDCl_3$, 26 °C). •: Tetramethylsilane, *: $CHCl_3$.

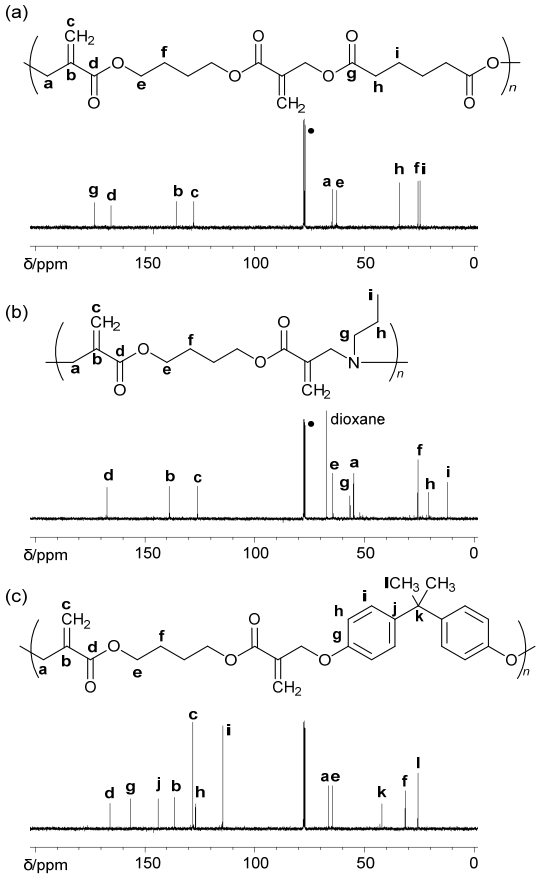


Figure S9 ^{13}C NMR spectra of (a) **P4/5**, (b) **P4/6**, and (c) **P4/7** (100 MHz, $CDCl_3$, 26 °C). *: $CHCl_3$.

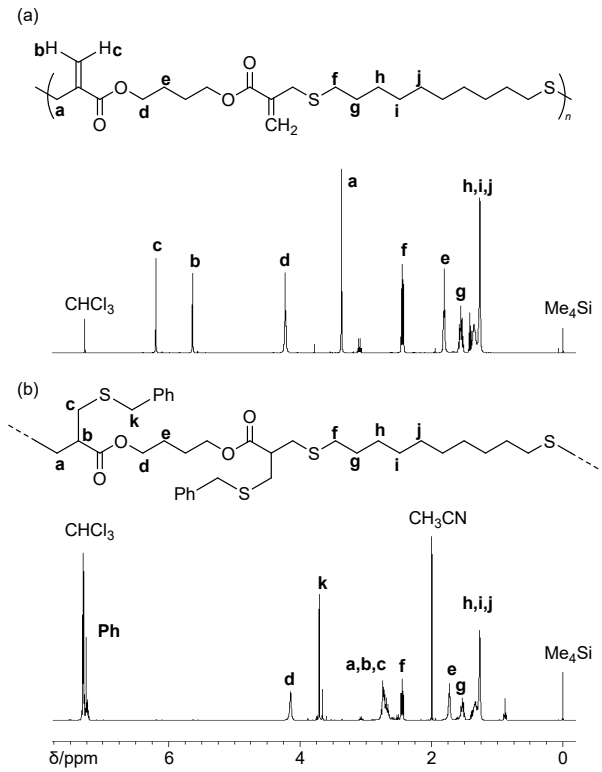


Figure S10 ^{1}H NMR spectra of **P2a/4** (a) before and (b) after the main-chain scission (400 MHz, $CDCl_3$, 26 °C).

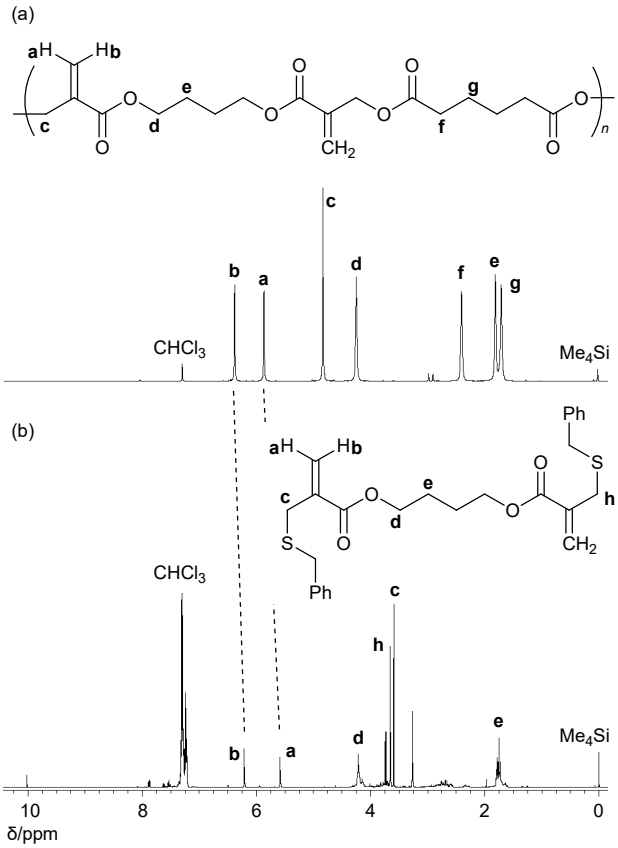


Figure S11 ^{1}H NMR spectra of **P4/5** (a) before and (b) after the main-chain scission (400 MHz, $CDCl_3$, 26 °C).

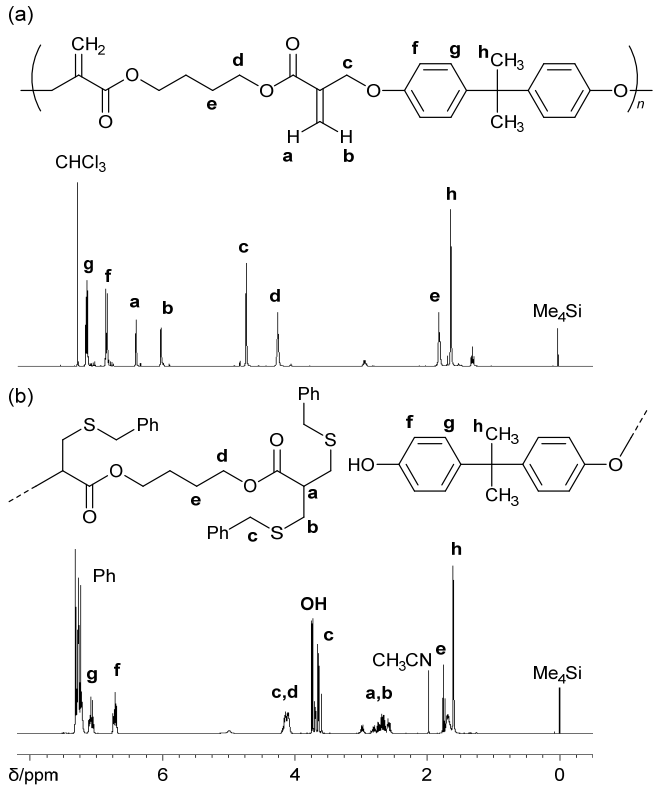


Figure S12 ^{1}H NMR spectra of **P4/7** (a) before and (b) after the main-chain scission (400 MHz, $CDCl_3$, 26 °C).

Notes and references

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