Single Cyclized Molecule Structure From RAFT Homopolymerization of Multi-vinyl Monomers

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† Electronic Supplementary Information

Supplementary Methods

Materials

Ethylene glycol dimethacrylate (EGDMA), *p*-Methoxybenzaldehyde (*p*-MBA) and 2-hydroxyethyl acrylate (HEA) were purchased from Sigma-Aldrich. The *p*-MBA and HEA were dried with a molecular sieve (4 Å) for 24 h before using. The 1,1'-Azobis (cyclohexane carbonitrile) (ACHN, 99%, Aldrich) were used as the initiator. 2-Cyano-2-propyl benzodithioate (CPBDT, 97%, Aldrich); 2-Cyano-2-propyl dodecyl trithiocarbonate, (CPDTC, 97%, Aldrich), *p*-toluene sulfonic acid monohydrate, *d*-Chloroform (99.8%, Aldrich), toluene (HPLC grade, Aldrich) and *n*-hexane (ACS reagent grade, Aldrich), dichloromethane (ACS reagent grade, Aldrich) were used as received.

FRP of EGDMA: ACHN (48.8 mg, 0.2 mmol, 0.4 equiv), EGDMA (9.9 g, 50 mmol, 100 equiv, [EGDMA]=1.67 $molL^{-1}$ or 33.3% w/v) and toluene (20 ml) was added into the 50ml flask and oxygen was removed by bubbling argon through the solutions for 30 min in ice bath. The solution was stirred at 800 rpm and the polymerization was conducted at 70 ^{o}C in an oil bath for the desired reaction time.

RAFT1 (CPBD) of EGDMA : The polymers were prepared in a two-necked round bottom flask. CPDB (110 mg, 0.5 mmol, 1 equiv), EGDMA (9.9 g, 50 mmol, 100 equiv), toluene (20 ml, [EGDMA]=1.67 M or 36.6% wt) were added into the flask and oxygen was removed by bubbling argon through the solutions for 30 mins. ACHN (48.8 mg, 2 mmol, 0.4 equiv) was added into the flask under positive pressure of argon before the flask was immersed in a preheated oil bath. The solution was stirred at 800 rpm and the polymerization was conducted at 70 ^{o}C in an oil bath for the desired reaction time.

RAFT2 (CPDTC) of EGDMA: The polymers were prepared in a two-necked round bottom flask. CPDTC (172.8 mg, 0.5 mmol, 1 equiv), EGDMA (9.9 g, 50 mmol, 100 equiv), toluene (20 ml, [EGDMA]=1.67 M or 36.6% wt) were added into the flask and oxygen was removed by bubbling argon through the solutions for 30 mins. ACHN (48.8 mg, 2 mmol, 0.4 equiv) was added into the flask under positive pressure of

argon before the flask was immersed in a preheated oil bath. The solution was stirred at 800 rpm and the polymerization was conducted at 70 ^{o}C in an oil bath for the desired reaction time.

PolyEGDMA purification: The experiment was stopped by opening the flask and exposing the catalyst to air. Samples taken from reaction at different reaction time points were diluted with acetone and precipitate into a large excess of cold hexane to remove EGDMA monomer. The precipitated mixture was filtered using filter paper (Whatman®, Qualitative-1) followed by vacuum evaporation at room temperature for 6 hrs and weighed to obtain the final yields.

Preparation and purification of the acid cleavable divinyl (ACD) monomer: the ACD monomer was prepared by the reported method.[1] Briefly the monomers of *p*-MBA (0.1 mol) and HEA (0.8 mol) were added in a single-necked round bottom flask, with *p*-toluene sulfonic acid (0.015 mol) as a catalyst and molecular sieves as the drying agent. The mixture was stirred in an ice bath overnight and the reaction was stopped by adding 3 ml of TEA. The molecular sieve was removed by filtering under reduced pressure. The reaction mixture was extracted with potassium carbonate aqueous solution (K_2CO_3, 0.1 M), then purified by basic alumina column with *n*-hexane/dichloromethane/TEA mixtures of 85/5/10 as eluents. The obtained product of di(2-acry-loyloxy ethoxy)-[4-methoxy-phenyl]methane) was determined by ^{1}H NMR in $CDCl_3$: 3.7 ppm t (4H), 3.8 ppm s (3H), 4.3 ppm t (4H), 5.6 ppm s (1H), 5.8 ppm d (2H), 6.1 ppm q (2H), 6.4 ppm d (2H), 7.4 ppm d (2H).

FRP of ACD monomer: ACHN (7.6 mg, 0.03125 mmol, 0.5 equiv), bisacrylate acetal monomer (2.19 g, 6.25 mmol, 100 equiv, [ACD]=1.2 molL^{-1} or 45.7% wt.) and Toluene (3 ml) was added into the flask and oxygen was removed by bubbling argon through the solutions for 15 min in ice bath. The solution was stirred at 800 rpm and the polymerization was conducted at 70 ^{o}C in an oil bath for the desired reaction time.

Synthesis of ACD homopolymer via RAFT2 (CPDTC): The polymers were prepared in a two-necked round bottom flask. ACHN (7.6 mg, 0.03125 mmol, 0.5 equiv), CPDTC (21.6 mg, 0.0625 mmol, 1 equiv), bisacrylate acetal monomer (2.19 g, 6.25 mmol, 100 equiv, [ACD]=1.2 molL^{-1} or 45.7% wt.) and Toluene (3 ml) was added into the flask and oxygen was removed by bubbling argon through the solutions for 15 min in ice bath. The solution was stirred at 800 rpm and the polymerization was conducted at 70 ^{o}C in an oil bath for the desired reaction time. Samples taken from the reaction at different reaction time points were diluted with acetone and dialyzed for 48 hours in excess amount of acetone with TEA to remove ACD monomer and toluene. The ACD polymer was cleaved in acid condition (add 0.5 M HCl into solution to PH=3). The polymer was completely cleaved after 2 hrs which confirmed by both the GPC and ^{1}H NMR.

Characterizations of poly(EGDMA)

The polymers were characterized by gel permeation chromatography (GPC) and ^{1}H NMR spectroscopy. Weight average molecular weight (M_w), number average molecular weight (M_n) and polydispersity (M_w/M_n) were obtained by GPC (Varian 920-LC) equipped with a RI detector. The columns (30 cm PLgel Mixed-C, two in series) were eluted using dimethylformamide (DMF) and calibrated using a series of 12 near-monodisperse PMMA standards (M_p from 690 to 1,944,000 gmol^{-1}). The polymers were analyzed in DMF at a concentration of 5.0 mg/ml. All calibrations and analysis were performed at 50 ^{o}C and a flow rate of 1 ml/min. The laser light scattering (LS) detector (mini-Dawn) was supplied by Wyatt Technology. The Astra software package for Windows was used to process the data from the detector systems. For LS calculation, a mean refractive index increment (d_n/d_c, measured by refractometer) of 0.059 was used for polyEGDMA samples. ^{1}H NMR spectroscopy was carried out on a 300 MHz Bruker NMR with MestReC processing software. The chemical shifts were referenced to the lock chloroform (7.26 ppm).

Functionalization of PolyEGDMA with 2-Mercaptoethanol via Michael addition

Poly(EGDMA) of RAFT1 reaction obtained after 3 hrs (0.2g, M_w=26.7 kDa) were diluted with 3 ml THF (Fisher, Chromatography grade), and excess 2-Mercaptoethanol (0.352g, 4.5 mmol) was added. The oxygen was removed by bubbling argon through the solutions for 3 min in ice bath. The solution was then stirred for 24 hours at 60 ^{o}C in oil bath. Final product (pink polymer) was diluted with THF and precipitate into a large excess of cold hexane. The functionalized polyEGDMA was filtered using filter paper (Whatman®, Qualitative-1) followed by vacuum evaporation at room temperature for 6 hrs and characterized by ^{1}H NMR (see Figure S6).

Supplementary Data

Table S1. Detailed results of the polymerization and polymeric materials from FRP and RAFT, respectively. FRP, ACHN:EGDMA=0.4:100, T=70 ^{o}C; RAFT, ACHN: RAFT: EGDMA = 0.4: 1: 100, T=70 ^{o}C. All polymerizations were conducted in toluene and [EGDMA]=1.67M or 36.6% wt.

		RI detector			***LS detector***					
	Time	M_n[a] (KDa)	M_w[a] (KDa)	PDI[a]	M_n[b] (KDa)	M_w[b] (KDa)	PDI[b]	Yield[c] (%)	Conv[d] (%)	Branch Ratio[e]
FRP	10 m		N/A[f]							
	12 m	26	75	2.8				3	7	4.2%
	25 m	32	140	4.4				5.6	10	4%
	30 m		Gel							
RAFT1	2 hr	5.3	6.7	1.3	5.9	7.1	1.2	3	7.5	14%
(CPBD)	2.5 hr	6.9	9.8	1.4	7.2	9.4	1.3	17	21.9	16.8%
	3 hr	7.4	11.4	1.5	8.0	11.2	1.4	21	29	18.5%
	3.5 hr	8.9	16.4	1.8	10.1	16.2	1.6	31	39.6	20%
	4 hr	11.5	26.7	2.3	12.6	25.2	2	37	48.2	20%
	5 hr	16.7	69.5	4.2	26.3	97.3	3.7	45	56	21%
	5.5 hr		Gel							
RAFT2	2 hr	10.3	13.7	1.3	12.7	16.5	1.3	2	8.2	9.6%
(CPDTC)	2.25 hr	11.9	17.6	1.5	13.1	18.3	1.4	8	16.6	11%
	2.5 hr	11.6	19.8	1.7	13.3	22.6	1.7	17	22.5	11%
	2.75 hr	12.6	24.7	1.9	14.2	24.1	1.7	24	32.7	12.5%
	3 hr	18.1	72.7	4.1	23.2	67.3	2.9	38	48.9	12%
	3.5 hr		Gel							

[a].M_n, M_w and PDI results were obtained by GPC equipped with a RI detector. [b]. M_n, M_w and PDI results were obtained by the laser light scattering (LS) detector. [c]. Polymer yield was calculated gravimetrically. [d]. Monomer conversion was calculated by the comparison of peak area of monomer and polymer. [e]. Calculated from ^{1}H NMR spectroscopy, see Figure S1 and Eq. S1. [f]. No polymer was obtained

at 10mins due to the slow initiation effect in FRP.

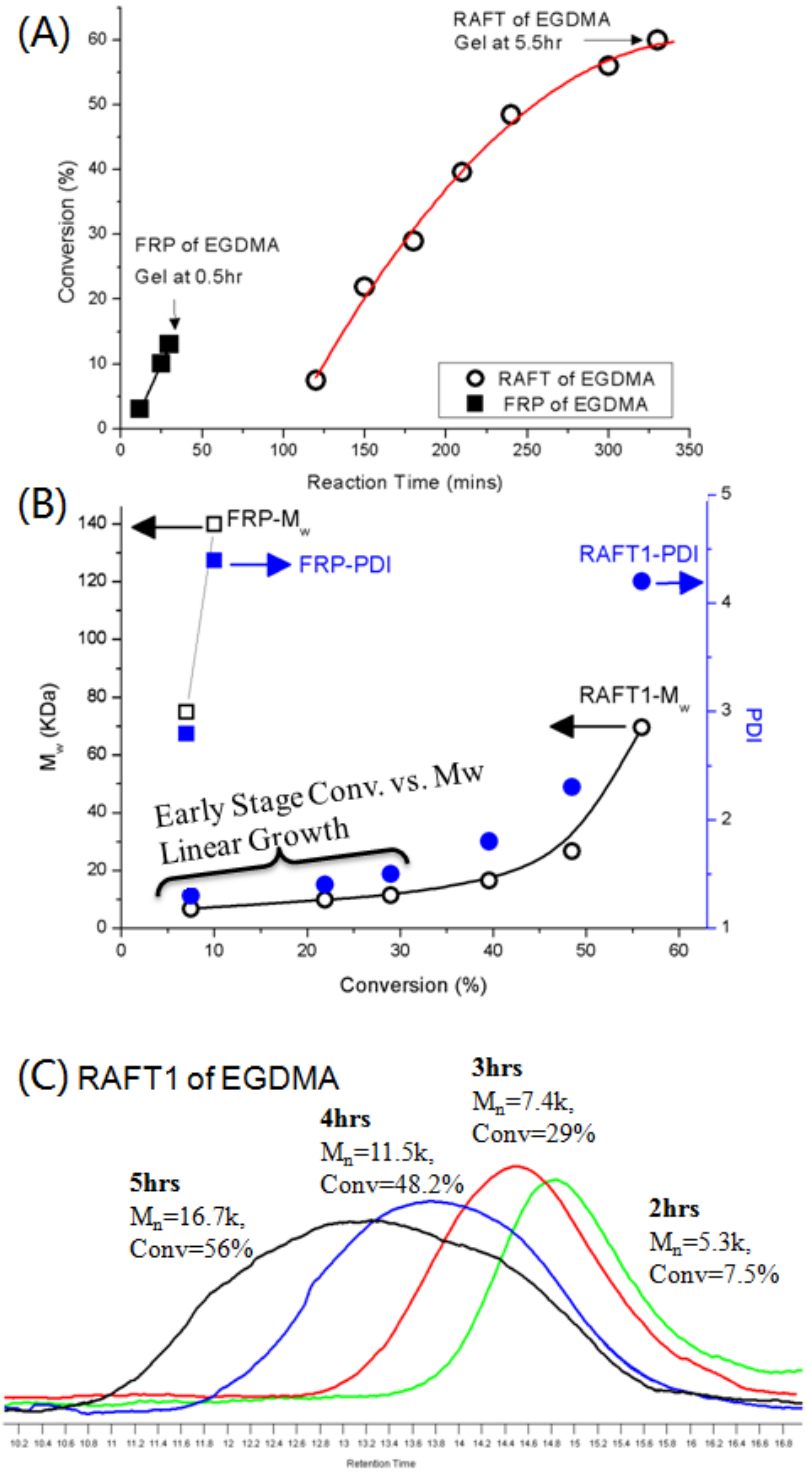

Fig. S1 (A) Time-conversion plots for conventional FRP and RAFT1 polymerization with of EGDMA (Table 1). (B) Dependence of the weight-average molecular weight (M_w) and polydispersity index (PDI) on the monomer conversion, for the polymers formed by FRP and RAFT1. (C) Time dependence of the composition of the polymerization mixtures monitored by GPC equipped with a RI detector, showing the unimodal peaks at initial stages (<3hrs) and multi-modal peaks appearing later (>3 hrs) in the RAFT1 of EGDMA.

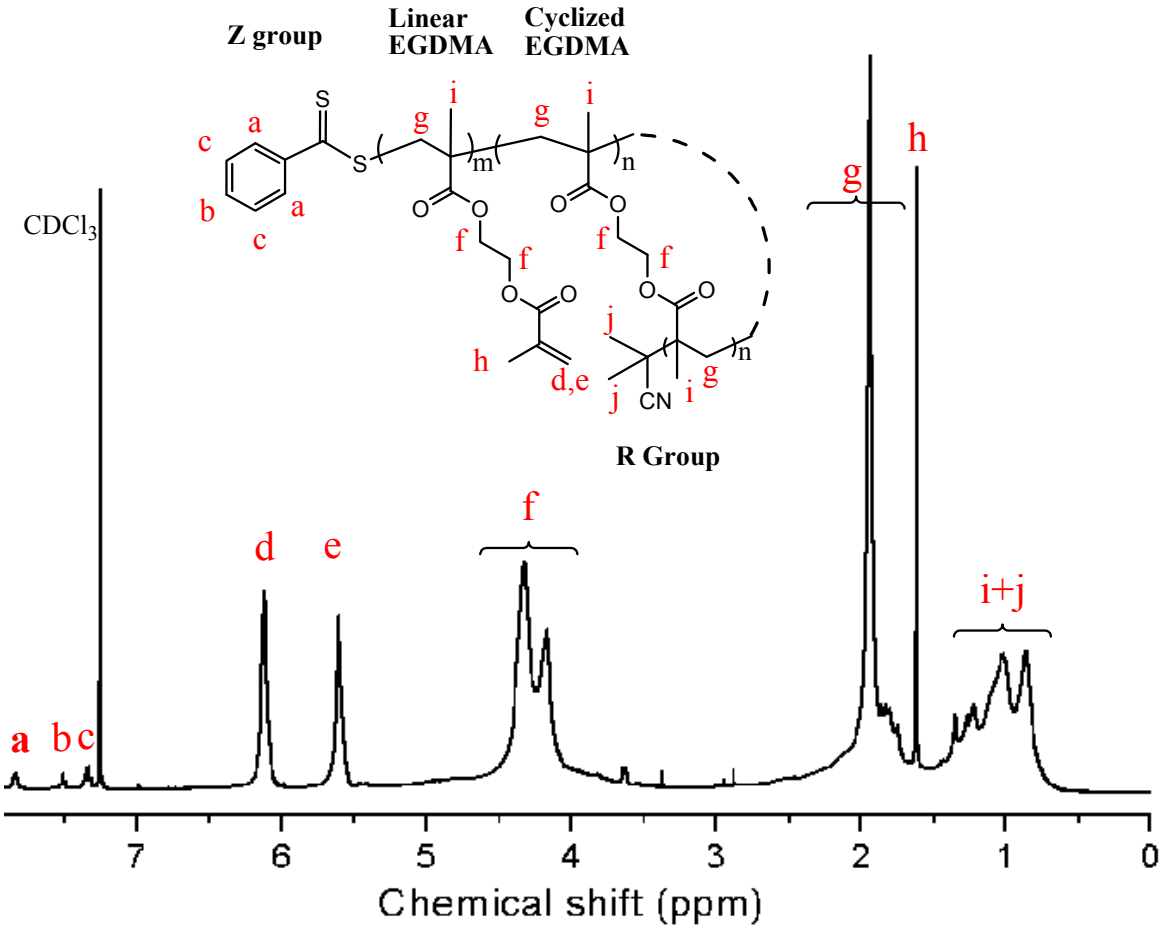

Fig. S2 ^{1}H NMR spectrum of purified polyEGDMA prepared via RAFT1 in $CDCl_3$ at 300 MHz (entry 2, Table 1). The resonances of protons d relative to proton f demonstrate clearly the presence of vinyl functionalities and also a high branch ratio (14%) for the polyEGDMA even at the very beginning of the reaction (Conv.=7.5 %, M_w=6.7 KDa, PDI=1.3).

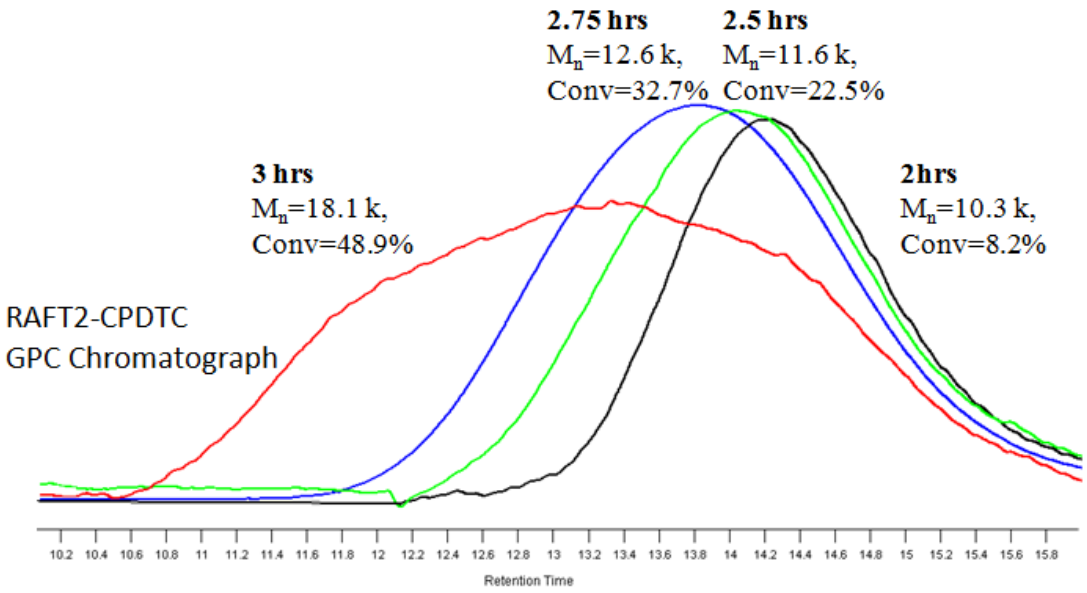

Fig.S3. GPC traces of the polymerization of EGDMA via RAFT2 (CPDTC) at different time points (Table S1).

NMR spectroscopy of polyEGDMA via RAFT1 (Figure 3, CPBD)

The branching ratio is defined as the ratio of branched EGDMA units to all the EGDMA units, as shown in Eq. S1

$$\text{Branch ratio} = \frac{\text{Branched EGDMA units}}{\text{All EGDMA units}} = 1 - \frac{\text{integrals of e}}{(\text{integrals of f})/4} \quad \text{(Eq.S1)}$$

The molecular weight calculated by ^{1}H NMR of polyEGDMA prepared via RAFT1 as shown in Eq. S2

$$MW_{NMR} = FW_{EGDMA} \times DPn + FW_{RAFT} = 198.22 \times \frac{(\text{integrals of f})/4}{\text{integrals of b}} + 221.34 \quad \text{(Eq.S2)}$$

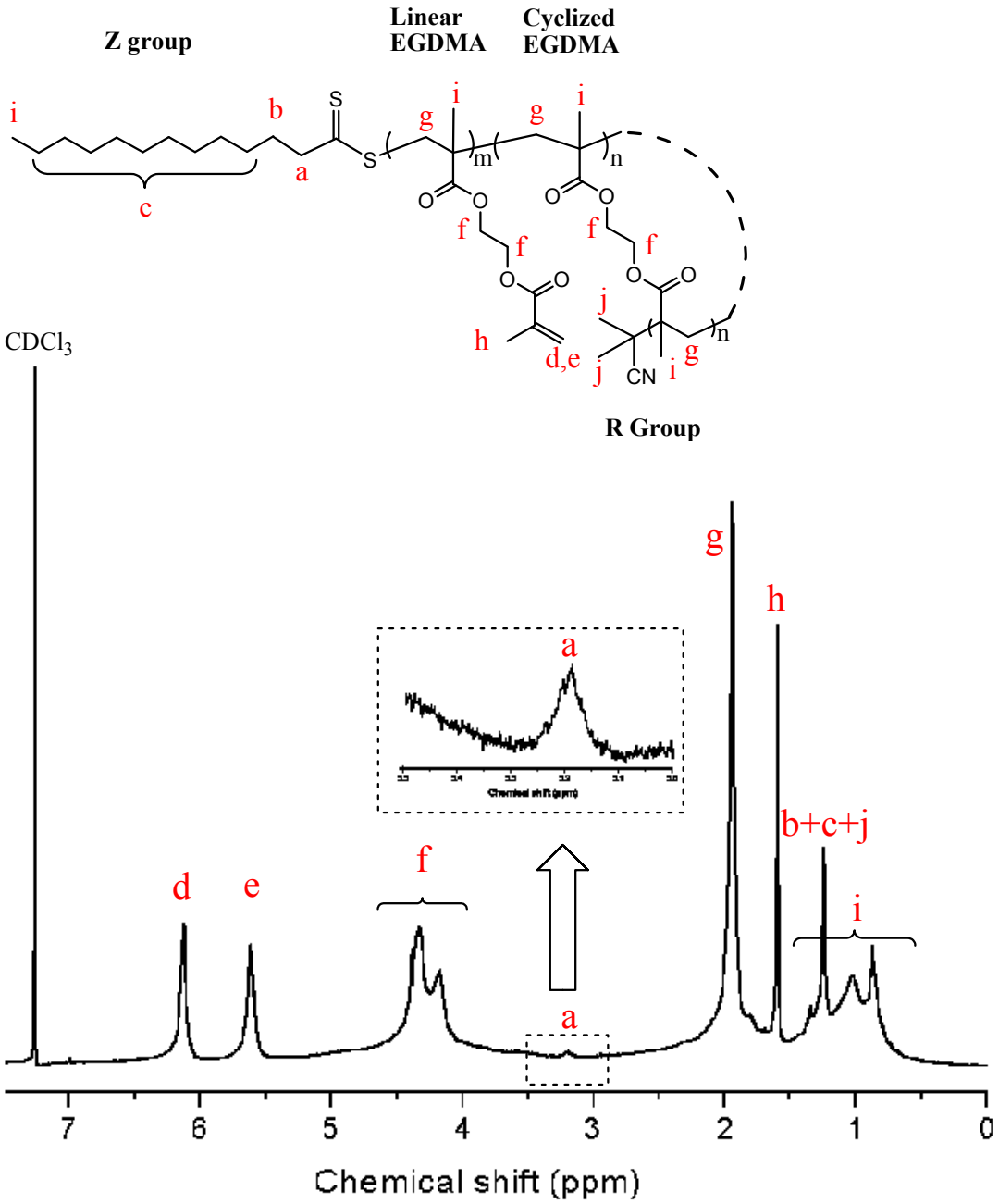

Fig.S4 ^{1}H NMR spectrum of poly(EGDMA) prepared via RAFT2 (CPDTC) in $CDCl_3$ at 300 MHz (3hrs, conversion=48.9%, Table 1 and Table S1).

NMR spectroscopy of polyEGDMA via RAFT2 (Figure S2, CPDTC)

The branching ratio of polyEGDMA prepared via RAFT2, as shown in Eq. S3

$$\text{Branch ratio} = \frac{\text{Branched EGDMA units}}{\text{All EGDMA units}} = 1 - \frac{\text{integrals of e}}{(\text{integrals of f})/4} \quad \text{(Eq.S3)}$$

The molecular weight calculated by ^{1}H NMR of polyEGDMA prepared via RAFT1 as shown in Eq. S2

$$MW_{NMR} = PW_{EGDMA} \times DPn + PW_{RAFT}$$

$$= 198.22 \times \frac{(\text{integrals of f})/4}{(\text{integrals of a})/2} + 345.63 \quad \text{(Eq. S4)}$$

Kinetic Study

For FRP, the kinetic chain length (ν_{FRP}) is given by Eq. S5,[2] where R_p is the rate of propagation, R_t is the rate of termination, k_p is the constant of propagation, [M] is the concentration of monomer, [P*] is the concentration of radicals, k_t is the constant of termination.

$$\nu_{FRP} = \frac{R_p}{R_t} = \frac{k_p[M][P*]}{2k_t[P*]^2} = \frac{k_p[M]}{2k_t[P*]} \quad \text{(Eq. S5)}$$

For RAFT, the instantaneous kinetic chain length is defined as the average number of monomer units added to the propagating radical during each radical transfer cycle. The kinetic chain length (ν_{RAFT}) is given by Eq. S6,[3] where R_p is the rate of propagation, R_{tr} is the rate of chain transfer, k_p is the constant of propagation, [M] is the concentration of monomer, [P$^{\bullet}$] is the concentration of radicals, [RAFT] is the concentration of RAFT agent, k_{tr} is the constant of RAFT chain transfer. The chain transfer rate is related to the absolute concentration of RAFT agent ([RAFT]) and the chain transfer constant (k_{tr}). Thus, the CPDB RAFT reagent displayed better control and intermolecular suppressed effect than the CPDTC.

$$\nu_{RAFT} = \frac{R_p}{R_{tr}} = \frac{k_p[M][P*]}{k_{tr}[RAFT][P*]} = \frac{k_p[M]}{k_{tr}[RAFT]} \quad \text{(Eq. S6)}$$

RAFT of Acid Cleavable Divinyl monomer

Table S2. Detailed results of RAFT2 and FRP of the acid cleavable divinyl monomer (ACD). RAFT, ACHN: CPDTC: ACD = 0.5:1:100, T=70 °C; FRP, ACHN: ACD=0.5: 100. The polymerizations were conducted in Toluene and [ACD]=1.2 M or 45.7% wt.

		RI			MALLS					
Entry	**Reaction Time (hr)**	**M_n[a] (KDa)**	**M_w[a] (KDa)**	**PDI[a]**	**M_n[b] (KDa)**	**M_w[b] (KDa)**	**PDI[b]**	**Branch Ratio[c]**	**Yield[d] (%)**	**Conv[e] (%)**
1	2.5	1.4	1.5	1.1				-	-	1
2	3.5	3.1	4.1	1.4				17%	6	14.8
3	4	3.4	4.7	1.4				16.7%	8.9	18.6
4	4.25	4.6	6.9	1.5	5.2	7.2	1.4	19%	16.1	22.6
(After cleavage)		3.4	5.2	1.5	3	4.2	1.4	-	-	-
5	4.75	9.4	20.8	2.2	10.8	20.5	1.9	20%	24.3	37.2
(After cleavage)		6.8	12.7	1.8	5.9	10	1.7	-	-	-
6	5	14.2	41.1	2.9				21%	35	45.5
7	5.25		Gelation					-		
8 FRP	0.4	17.1	73.6	4.3	27.2	110	4	6.7%	4.1	10.7
(After cleavage)		8	14.4	1.8	11.3	21.6	1.9	-	-	-
9	0.6		Gelation							

[a].M_n, M_w and PDI results were obtained by GPC equipped with a RI detector. [b].M_n, M_w and PDI results were obtained by GPC equipped with a LS detector. [c]. Calculated from ^{1}H NMR spectroscopy, see Figure S4 and Eq. S7. [d].Polymer yield was calculated gravimetrically. [e].Monomer conversion was calculated by the comparison of peak area between monomer and polymer from GPC.

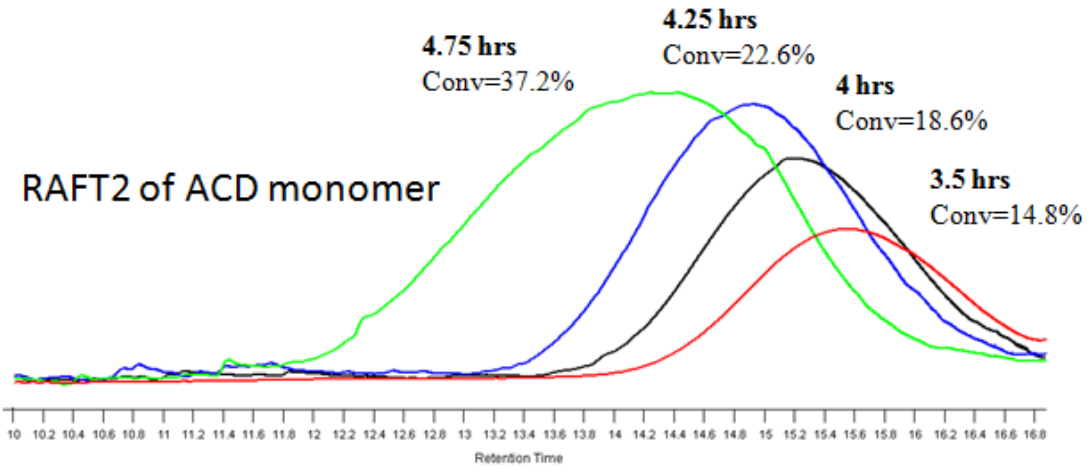

Fig.S5 GPC traces of the polymerization of acid cleavable divinyl monomer via RAFT2 (CPDTC) at different time points (Entry 2, 3, 4 and 5 in Table S2).

NMR spectroscopy of polyACD via RAFT2

The branching ratio is defined as the ratio of branched EGDMA units to all the EGDMA units, as shown in Eq. S7

$$\text{Branch ratio} = \frac{\text{Branched EGDMA units}}{\text{All EGDMA units}} = 1 - \frac{\text{Integrals of h}}{(\text{Integrals of e})/2} \quad \text{(Eq. S7)}$$

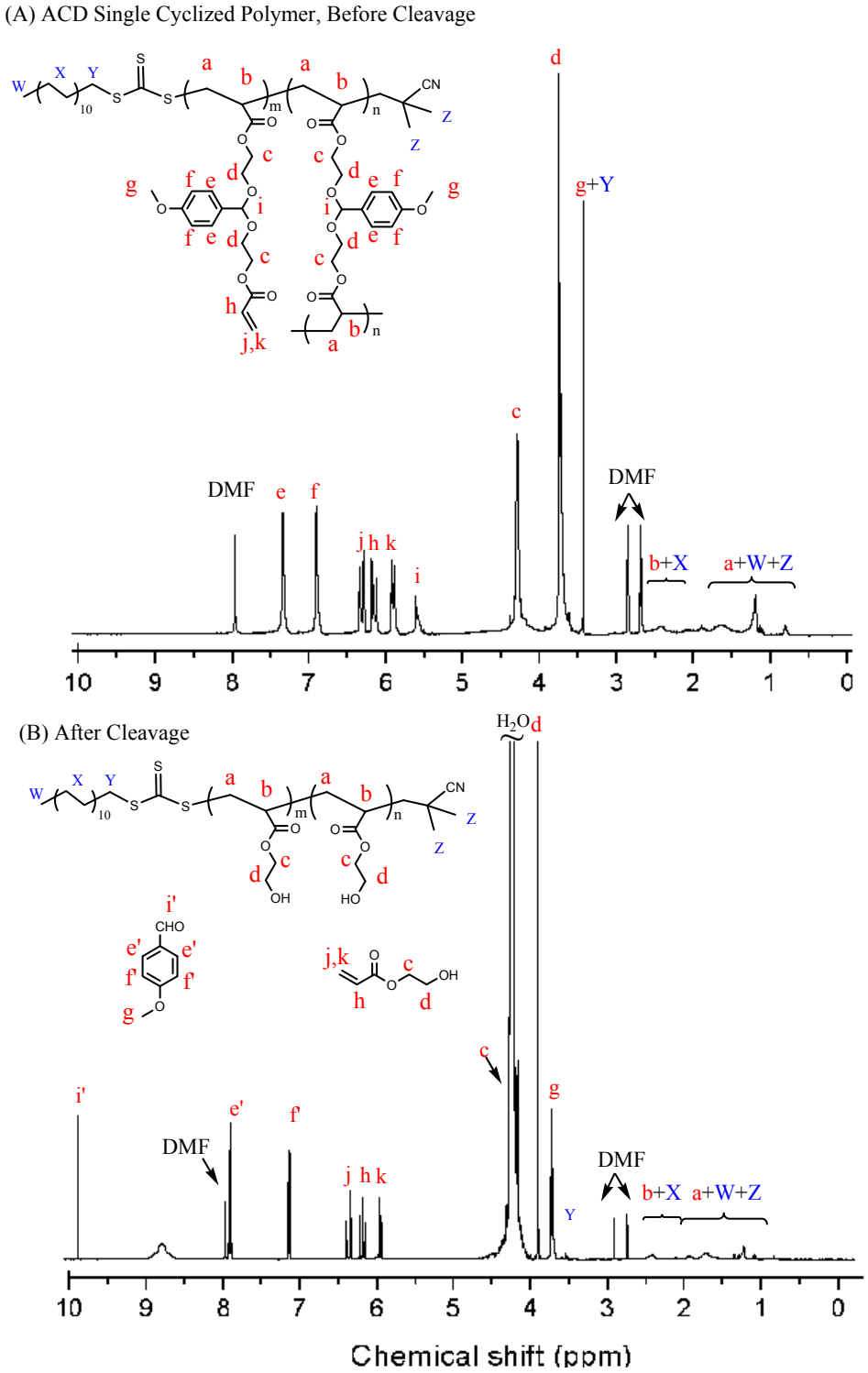

Fig.S6 ^{1}H NMR spectrum of polyACD prepared via RAFT2 (CPDTC), and after degradation in acidic conditions in $CDCl_3$ at 300 MHz (Entry 5, conversion=37.2 %, Table S2).

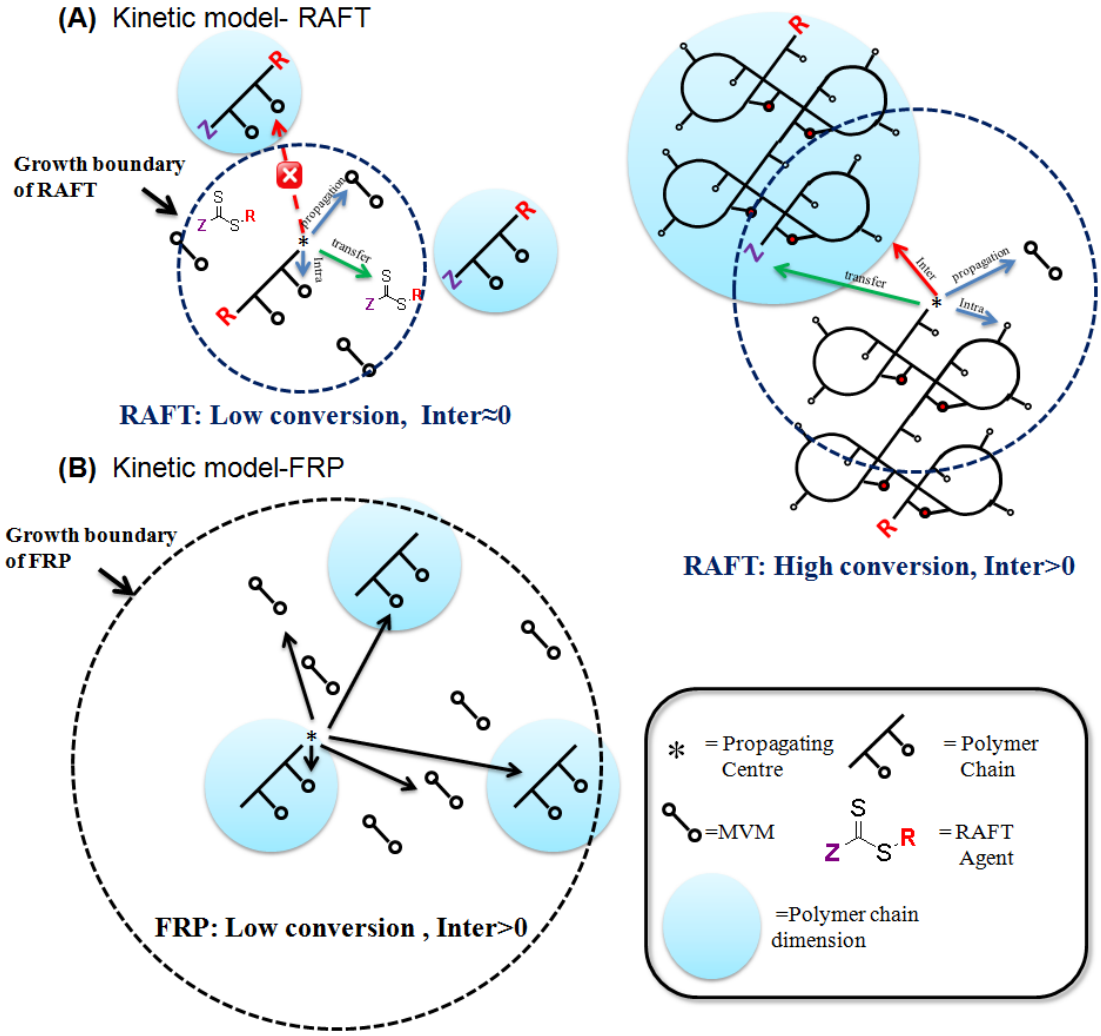

Fig.S7 (A) Model of RAFT and (B) Model of FRP based on the kinetics model. The kinetic model consideres two parameters: the growth boundary which depends on the kinetics chain length of the polymerization (dotted circle) and polymer dimension depends on the polymer chain length and concentration (shaded part). The maximum growth of a polymer chain (defined as the instantaneous kinetics chain length), which depends on the possible number of vinyl groups reacted during its active life time during the propagation process. The probability of monomer addition to the chain decreases with distance from the active propagation centre up to the maximum growth boundary, past which the probability of monomer addition tend towards zero.

Calculation of Critical overlap concentration of RAFT of EGDMA

The critical overlap concentration of polyEGDMA, C*, is related to the molecular volume, V_m, and the radius of gyration, R_g, by the Equation S8.[4]

$$C^* = \frac{\frac{V_m}{N_A}}{R_g^3} = \frac{M \times N}{d \times N_A \times \left[\frac{b \times (2N)^{0.6}}{2.45}\right]^3} \quad \text{(Eq. S8)}$$

where M is the molecular weight of EGDMA monomer, N_a is Avogadro's constant, N=mean degree of polymerization, d is the density of polyEGDMA, R_g=b x $[(2N)^{0.6}]/(6^{0.5})$, where b is the distance between the monomer unit (0.65 nm for PMMA). According to the calculation, the critical overlap DP_n of the RAFT of EGDMA is 58.

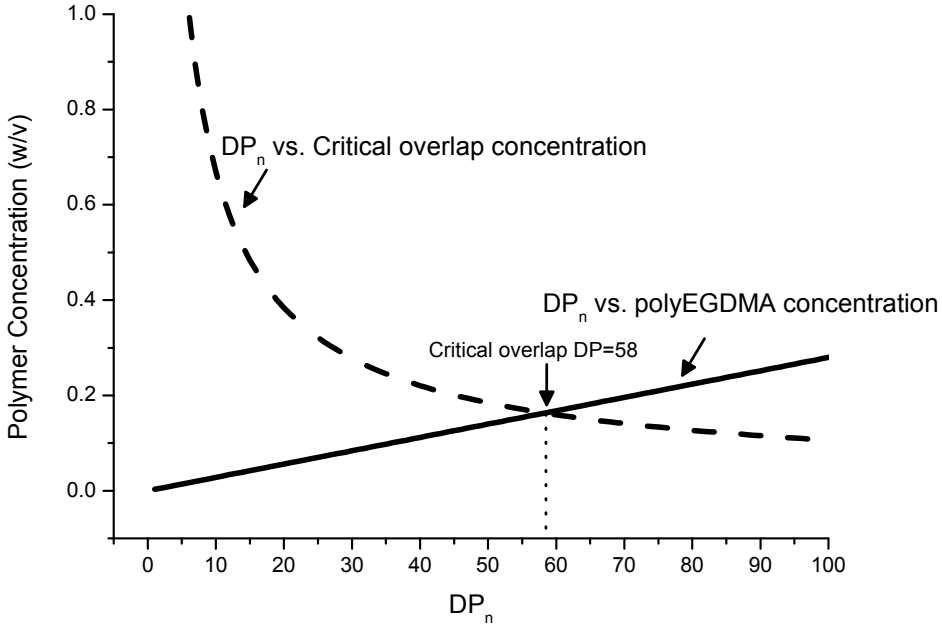

Fig.S8 The critical overlap degree of polymerization (DP_n) of the RAFT of EGDMA. It shows the critical overlap DP_n of the polyEGDMA is 58 in the reaction.

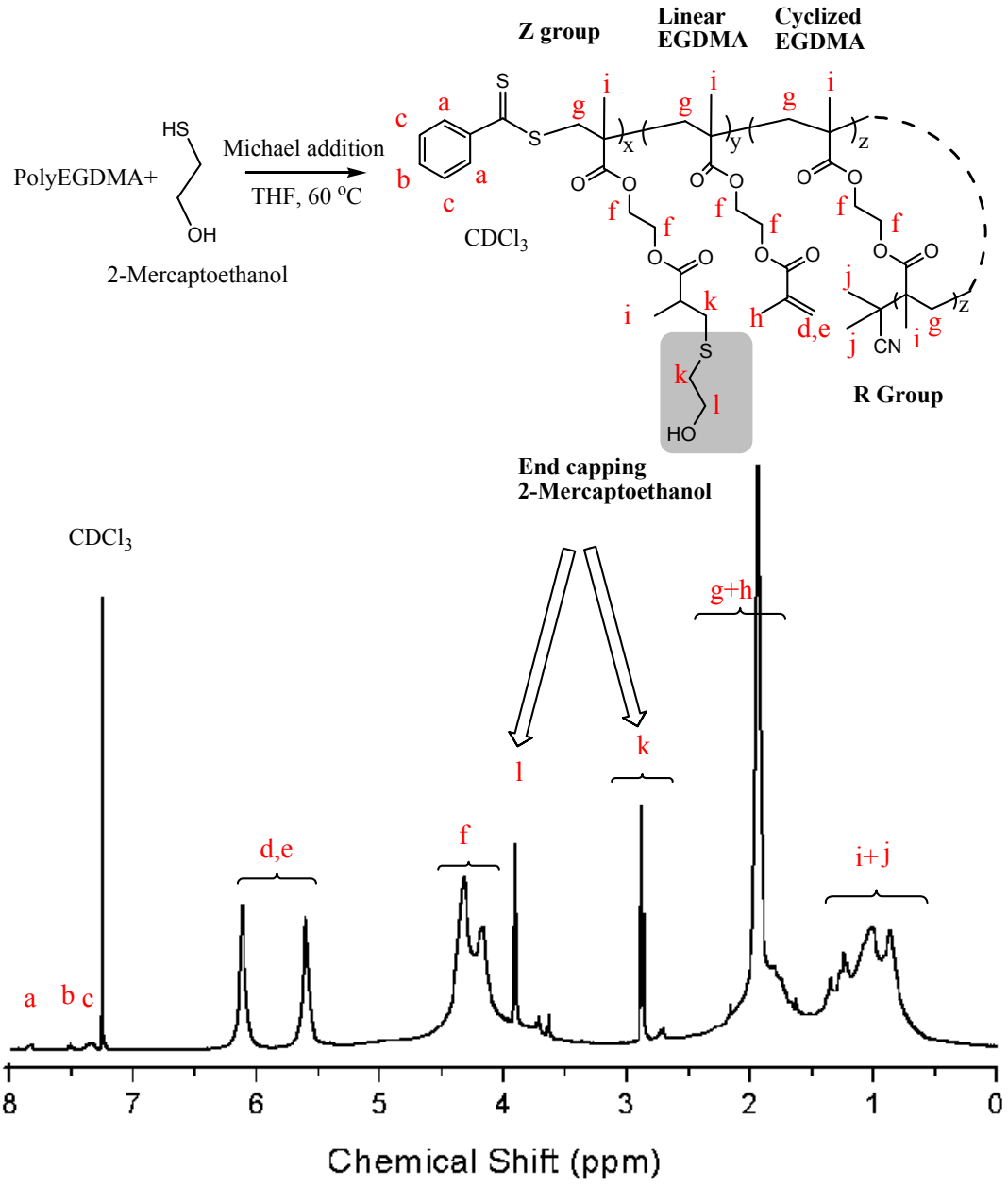

Fig.S9 ^{1}H NMR spectrum of functionalized RAFT1 poly(EGDMA) by 2-Mercaptoethanol in $CDCl_3$ at 300 MHz. The resonance of proton k and l indicate that the single cyclised polyEGDMA was successfully functionalized by thiol group via Michael addition.

$$\text{End}-\text{Capping ratio} = \frac{(\text{integrals of k})/4}{(\text{integrals of f})/4} \times 100\% = 10.1\ \%\ (\text{Eq.S9})$$

Additional References

[1] Y. Chan, V. Bulmus, M. H. Zareie, F. L. Byrne, L. Barner, M. Kavallaris, *Journal of Controlled Release* **2006**, *115*, 197-207.

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[4] Y. T. Li, A. J. Ryan, S. P. Armes, *Macromolecules* **2008**, *41*, 5577-5581.