Supporting Information

Alkyl α-Hydroxymethyl Acrylate Monomers for Aqueous Dispersion Polymerization-Induced Self-Assembly

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Content

1. Materials

Acryloyl chloride (96%), n-butyl acrylate (nBA, 99%), 1,4-diazabicyclo[2.2.2]octane (DABCO), dicyclohexylcarbodiimide (DCC, 99%), and 4-dimethylaminopyridine (DMAP, 99%) were purchased from Aladdin Reagents. Lithium phenyl(2,4,6-trimethylbenzoyl)phosphinate (LiPTP, 98%) was purchased from TCI Shanghai. 2,2′-Azobis(2-methylpropionamidine) dihydrochloride (V-50, 97%), 2,2′-azobis(2,4-dimethylvaleronitrile) (ABVN, 97%), and super dry isopropanol (99.5%) were purchased from J&K Scientific. Poly(ethylene glycol) monomethyl ether (PEG_{45}-OH, M_n = 2 kg/mol and PEG_{113}-OH, M_n = 5 kg/mol), methyl α-hydroxymethyl acrylate (MHMA, 95%), and ethyl α-hydroxymethyl acrylate (EHMA, 97%) were purchased from Sigma-Aldrich. 2,2′-Azobis(2-methylpropionitrile) (AIBN, CP) was purchased from Sinopharm Chemical Reagent and recrystallized twice from methanol. To remove the cross-linker impurities, the as-received MHMA and EHMA were purified by column chromatography (ethyl acetate/petroleum ether = 4/6). 4-Cyano-4-(ethylthiocarbonothioylthio) pentanoic acid was synthesized as previously reported.[1]

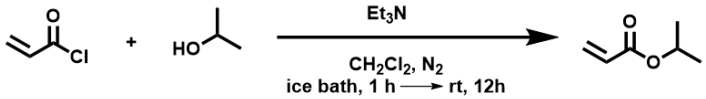
2. Characterization and methods

^{1}H NMR and ^{13}C NMR spectra were acquired on a JEOL resonance ECZ400S 400 MHz spectrometer using $CDCl_3$ or DMSO-d_6 as the solvent. ^{1}H NMR spectrum of PEG_{45}-$PEHMA_{100}$ dispersion in D_2O was performed on a Bruker Avance III HD 600 MHz spectrometer. Gel permeation chromatography (GPC) characterization was performed on a Waters Alliance e2695 instrument at 45 ℃ using DMF as the eluent (0.7 mL/min, [LiBr] = 20 mM). A 2414 refractive index (RI) detector (Waters Alliance) and a light scattering (LS) detector (90 ºand 7 º

angles) (TDA 305 Malvern Instruments Ltd., UK) were utilized for the detection. Two columns (D2500 and D5000) were equipped for separation. Dynamic light scattering (DLS) analysis of the nano-object dispersions (diluted to 0.1% w/v solids) was conducted on a Malvern ZS90 with a He-Ne laser (633 nm, 4 mW) at a detection angle of 90 °. After being equilibrated at 25 ℃ for 30 s, the dispersions were measured three times for an automatically optimized run duration by the Malvern zetesizer software. Polydispersity index (PDI) and Z-average diameter (D_h) were determined by the Malvern zetasizer software. Transmission electron microscopy (TEM) micrographs were obtained on a Hitachi HT7700 microscope operating at 100 kV. Nano-object dispersions were diluted to 0.2% w/v and used for the preparation of samples on carbon-coated copper grids followed by drying at 40 ℃ for 12 h.

3. Synthesis procedure

Synthesis of isopropyl acrylate (iPrA)



iPrA was synthesized by adapting a reported protocol.[2] Under nitrogen atmosphere, super dry isopropanol (10.0 g, 1.0 equiv) and Et_3N (1.7 equiv) were dissolved in CH_2Cl_2 (150 mL) and placed in ice bath. Then acryloyl chloride (1.5 equiv) in CH_2Cl_2 (50 mL) was dropwise added into the reaction mixture and stirred at 0 ℃ for 1 h. The reaction mixture was further stirred at room temperature for 24 h. The reaction was washed with aqueous NaCl solution and dried over anhydrous $MgSO_4$. The solvent was removed via rotary evaporation give a colorless oil. The ^1H NMR spectrum shown in **Figure S1** confirmed the structure of iPrA (9.5 g, 50 %).

Synthesis of isopropyl α-hydroxymethyl acrylate (iPrHMA)

iPrHMA was prepared via Baylis−Hillman reaction by reacting iPrA with formaldehyde. Specifically, iPrA (9.5 g, 83.25 mmol), formaldehyde aqueous solution (6.2 mL, 83.25 mmol), and 1,4-dioxane (7.0 mL) were added to a round-bottom flask under stirring. Then DABCO (3.1 g, 27.75 mmol) was added and the reaction was stirred at room temperature for 18 h. The mixture was extracted with ethyl acetate, washed with saturated brine and subsequently dried over anhydrous $MgSO_4$. The filtrate was then concentrated via rotary evaporation and purified by column chromatography (ethyl acetate/petroleum ether = 3/7) to give a colorless liquid. The ^{1}H NMR (**Figure S2A**) and ^{13}C NMR spectra (**Figure S3A**) confirmed the structure of iPrHMA (2.3 g, 20%). ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 1.27 (d, 6H), 2.40 (t, 1H), 4.30 (d, 2H), 5.09 (m, 1H), 5.78 (s, 1H), 6.21 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 21.83 (s), 62.33 (s), 68.48 (s), 77.48 (s), 125.23 (s), 139.98 (s), 165.98 (s).

Synthesis of n-butyl α-hydroxymethyl acrylate (nBHMA)

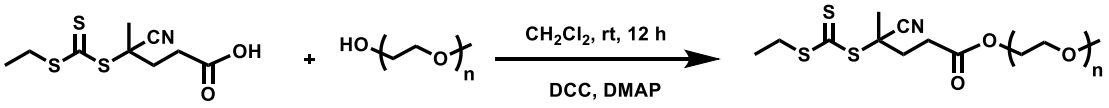
nBHMA was synthesized via Baylis−Hillman reaction by adapting a protocol previously reported.[3] In detail, n-butyl acrylate (nBA, 14.0 g, 0.109 mol), formaldehyde aqueous solution (8.1 mL, 0.109 mol), DABCO (4.1 g, 0.036 mol), and 1,4-dioxane (10.0 mL) were added to a round-bottom flask with stirring. After stirring at room temperature for 15 h, the reaction was extracted with ethyl acetate, washed with saturated brine and then dried over anhydrous $MgSO_4$. The filtrate was concentrated and purified by column chromatography (ethyl acetate/petroleum ether = 3/7) to afford a colorless liquid. The ^{1}H NMR (**Figure S2B**) and ^{13}C NMR spectra (**Figure S3B**) confirmed the structure of nBHMA (8.1 g, 47%). ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 0.92 (t, 3H), 1.38 (m, 2H), 1.64 (m, 2H), 2.53 (t, 1H), 4.16 (t, 2H), 4.30 (d, 2H), 5.81

(s, 1H), 6.22 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 13.76 (s), 19.24 (s), 30.62 (s), 62.32 (s), 64.82 (s), 125.49 (s), 139.66 (s), 166.52 (s).

Aqueous insolubility of PMHMA and PEHMA

$PMHMA_{25}$ was prepared via RAFT solution polymerization of MHMA in DMF at 70 ℃ for 24 h ([M] = 20% w/v, [CTA]:[MHMA]:[ABVN] = 1:30:0.3). The monomer conversion was determined to be 82% by ^{1}H NMR spectroscopy analysis. Similarly, $PEHMA_{16}$ was prepared via RAFT solution polymerization of EHMA at 70 ℃ in 1,4-dioxane for 24 h ([M] = 30% w/v, [CTA]:[EHMA]:[AIBN] = 1:30:0.3). The monomer conversion was determined to be 53% by ^{1}H NMR spectroscopy analysis. The DPs were estimated as the product of target DP and monomer conversion. The reaction solution in DMF or 1,4-dioxane was dropwise added into water to precipitate the polymers, which were further washed with water and dried to provide $PMHMA_{25}$ and $PEHMA_{16}$. The polymers were dispersed in water (0.1% w/v solids) and appeared to be insoluble over the temperature range 20−70 °C (**Figure S4**), thus indicating that they are insoluble in water.

Synthesis of PEG_{45}-CTA and PEG_{113}-CTA



1 5 6.5 1 PEG-CTA, n=45, 113

PEG-based macro-CTAs were synthesized via esterification of corresponding poly(ethylene glycol) monomethyl ether (PEG-OH, M_n = 2 kg/mol or 5 kg/mol) with 4-cyano-4-(ethylthiocarbonothioylthio) pentanoic acid (CTA) according to a protocol previously reported.[4] Specifically, poly(ethylene glycol) monomethyl ether (20.0 g, 1.0 equiv), CTA (5.0

equiv) and DMAP (1.0 equiv) were dissolved in CH_2Cl_2 (150 mL). Then DCC (6.5 equiv) in CH_2Cl_2 (50 mL) was dropwise added into the reaction mixture under stirring. After 24 h, the reaction was filtered to remove the white precipitate. Then the filtrate was concentrated via rotary evaporation and precipitated into excess cold diethyl ether 3 times. ^{1}H NMR analysis shown in **Figure S5** suggested near-quantitative functionality was achieved for PEG_{45}-CTA (94%) and PEG_{113}-CTA (97%).

RAFT Aqueous PISA of alkyl α-hydroxymethyl acrylate monomers.

RAFT aqueous polymerization of MHMA, EHMA and iPrHMA was conducted employing either PEG_{45}-CTA or PEG_{113}-CTA at various temperatures via either thermal or photo-initiation. Thermally initiated RAFT aqueous dispersion polymerization of EHMA was conducted using PEG_{113}-CTA at 70 ℃. Taking the synthesis of PEG_{113}-$PEHMA_{100}$ at 15% solids (**Table S1**, entry 1) as a representative example, PEG_{113}-CTA (0.0647 g, 12.3224 μmol) and EHMA (0.1603 g, 1.2322 mmol) were dissolved in water (1.4 mL). After being degassed with nitrogen for 20 min, the mixture was immersed into a preheated oil bath at 70 ℃. After the temperature was stabilized, a degassed V-50 aqueous solution (100 μL, 2.46 μmol) was injected and then left to continue for 12 h. The synthesis of PEG_{45}-$PEHMA_{100}$ at 15% solids (**Table 1**, entry 2) at 40 ℃ was taken as a representative example for photo-initiated dispersion polymerization. Specifically, PEG_{45}-CTA (0.0110 g, 4.9150 μmol) and EHMA (0.0640 g, 0.4915 mmol) were dissolved in water (0.41 mL). The vessel was sealed and degassed with nitrogen for 10 min. Then the mixture was immersed into a preheated oil bath surrounded with a violet-light LED strip at 40 ℃. After the temperature was stabilized, a degassed LiPTP aqueous solution (90 μL, 1.47 μmol) was injected via a microsyringe, and the reaction was then left to continue for 3 h.

4. Figures

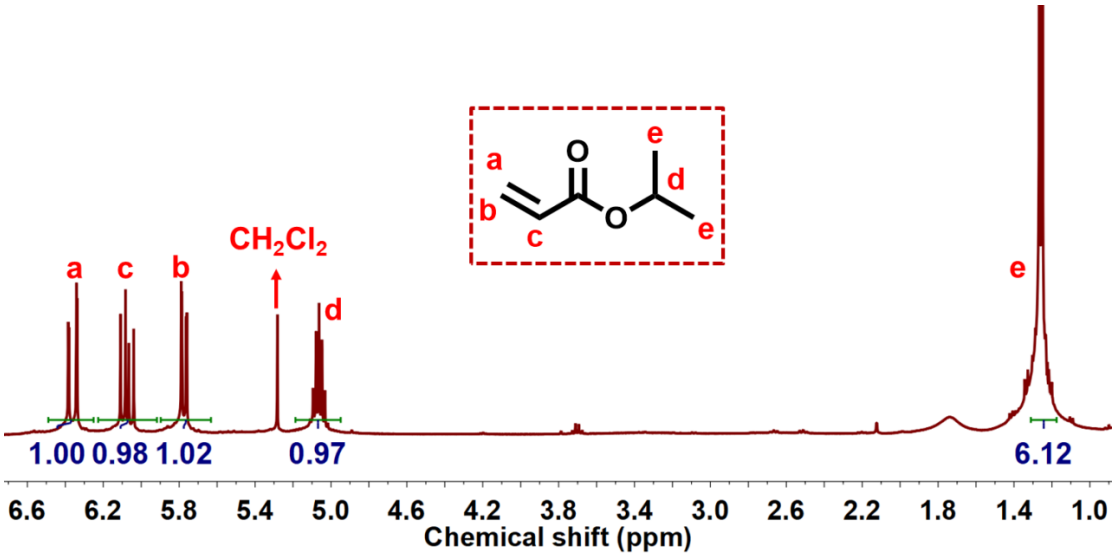


Figure S1. ^{1}H NMR spectrum of synthesized iPrA in $CDCl_3$.

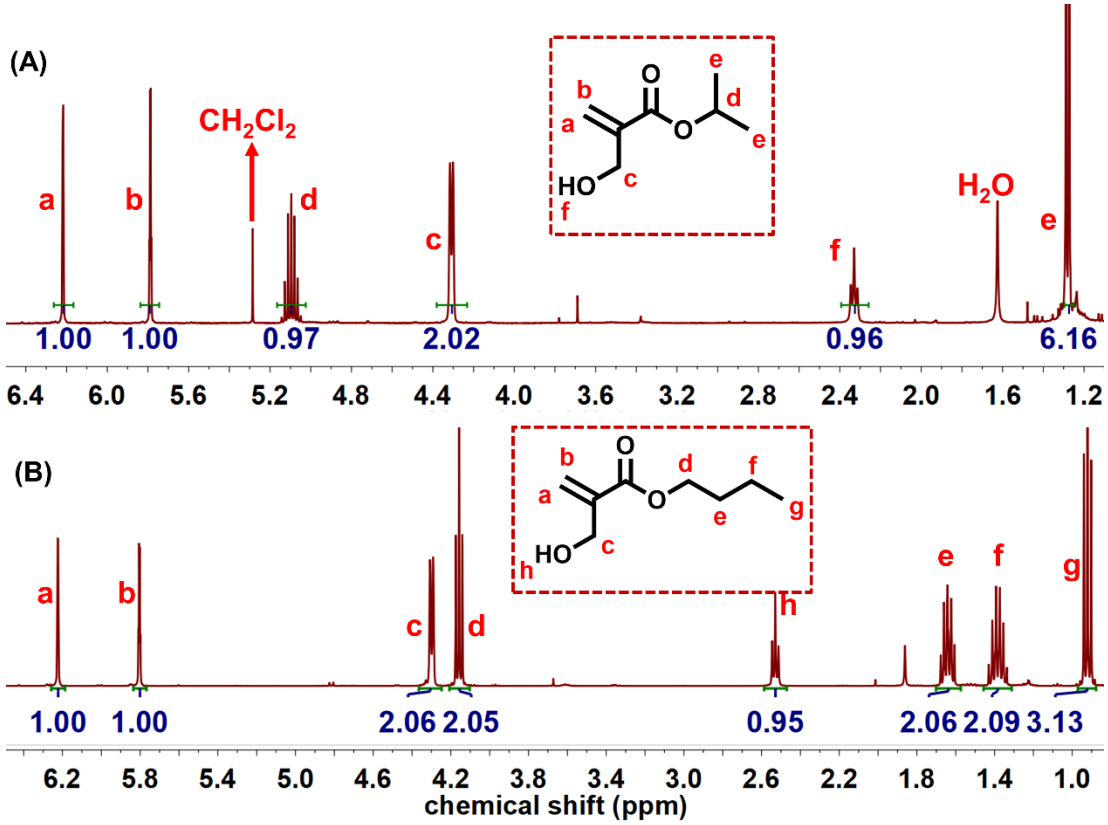


Figure S2. ^{1}H NMR spectra of synthesized iPrHMA (A) and nBHMA (B) in $CDCl_3$.

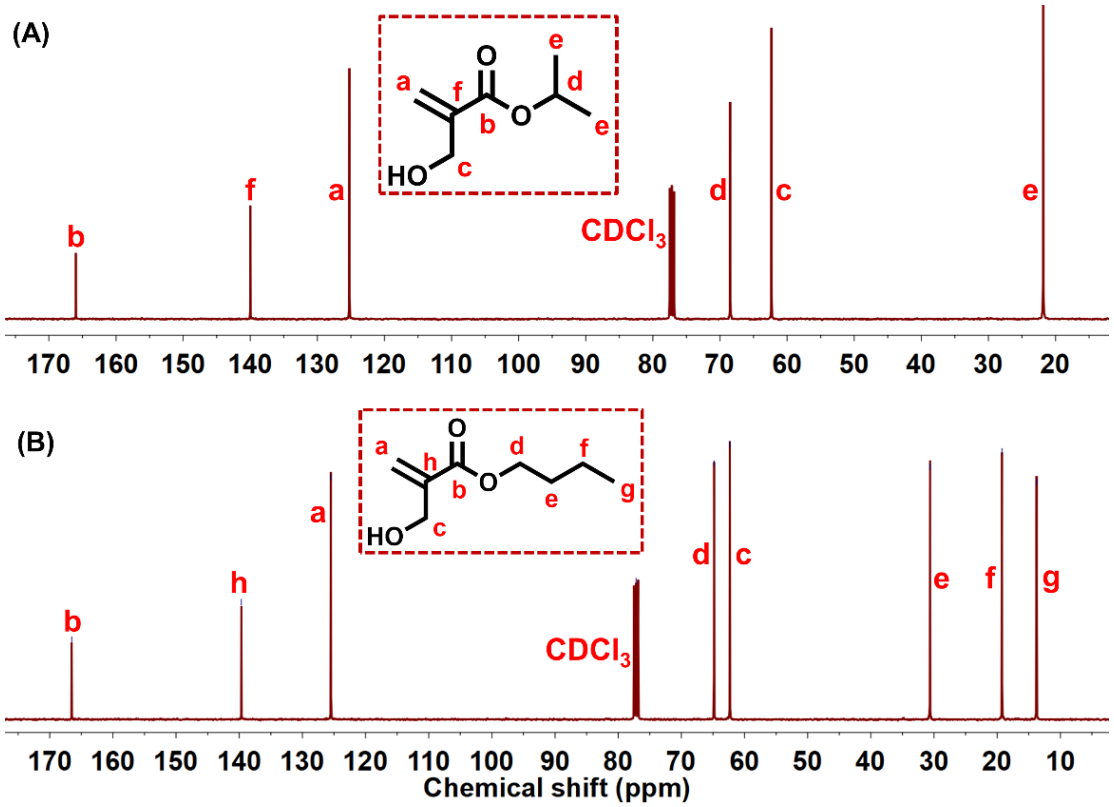


Figure S3. ^{13}C NMR spectra of synthesized iPrHMA (A) and nBHMA (B) in $CDCl_3$.

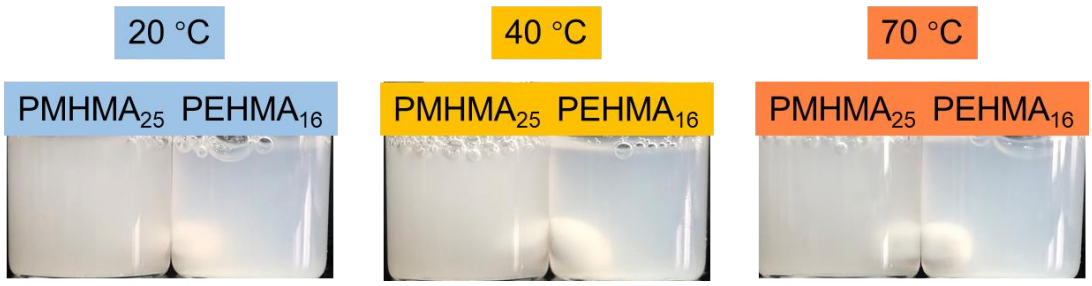


Figure S4. Photographs for $PMHMA_{25}$ and $PEHMA_{16}$ dispersions in water (0.1% w/v solids) at different temperatures under stirring for 15 min.

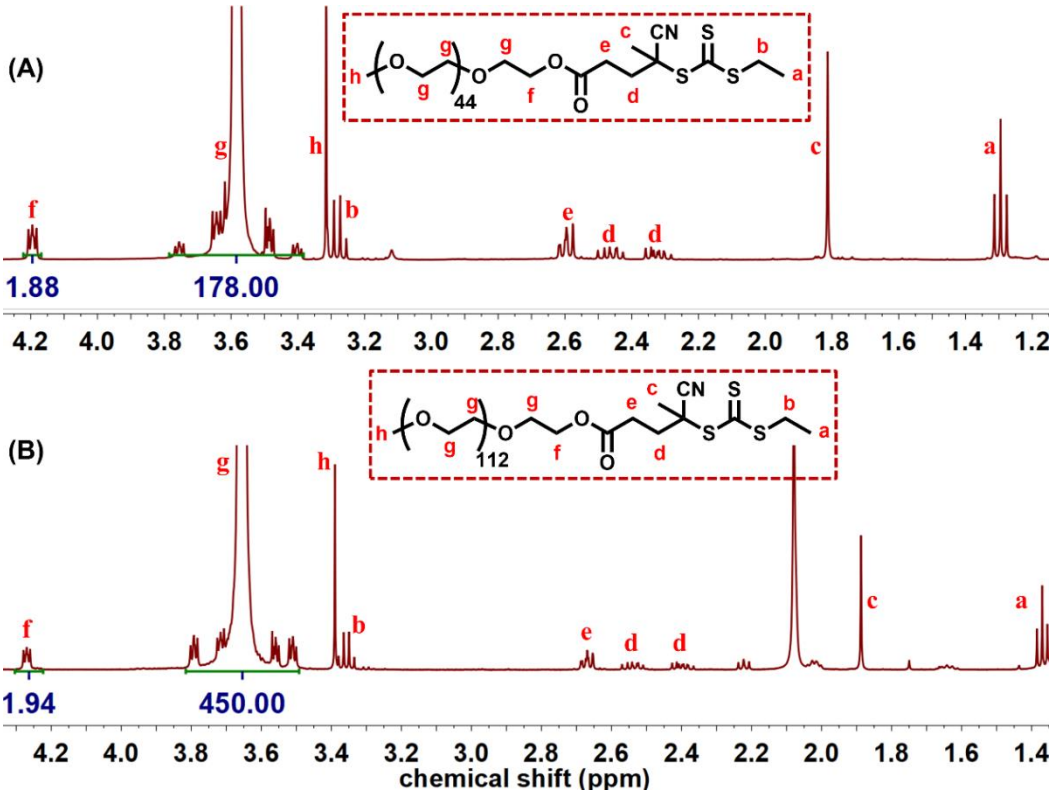


Figure S5. ^{1}H NMR spectra of synthesized PEG_{45}-CTA (A) and PEG_{113}-CTA (B) in $CDCl_3$.

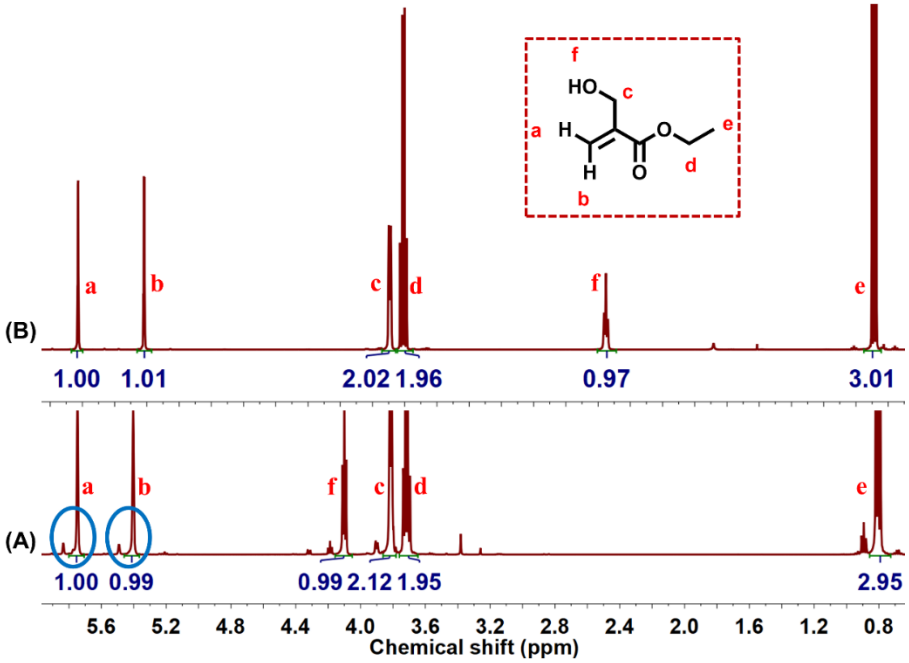


Figure S6. ^{1}H NMR spectra of as-received (A) and purified (B) EHMA in $CDCl_3$.

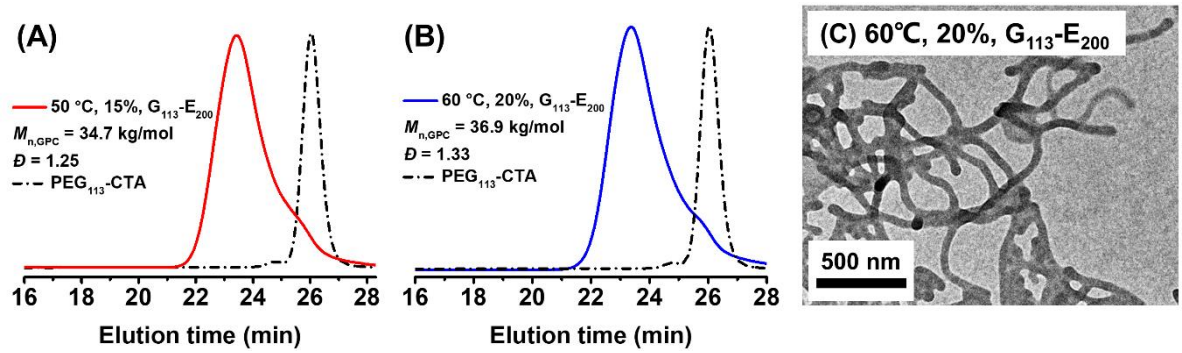


Figure S7. GPC traces (A) of PEG_{113} macro-CTA and PEG_{113}-*b*-$PEHMA_{200}$ prepared at 50 ℃, 15% w/v solids. GPC traces (B) and TEM image (C) for PEG_{113}-*b*-$PEHMA_{200}$ prepared at 60 ℃, 20% w/v solids, [LiPTP]/[PEG_{113}-CTA] = 0.3 (G stands for PEG block and E for PEHMA block).

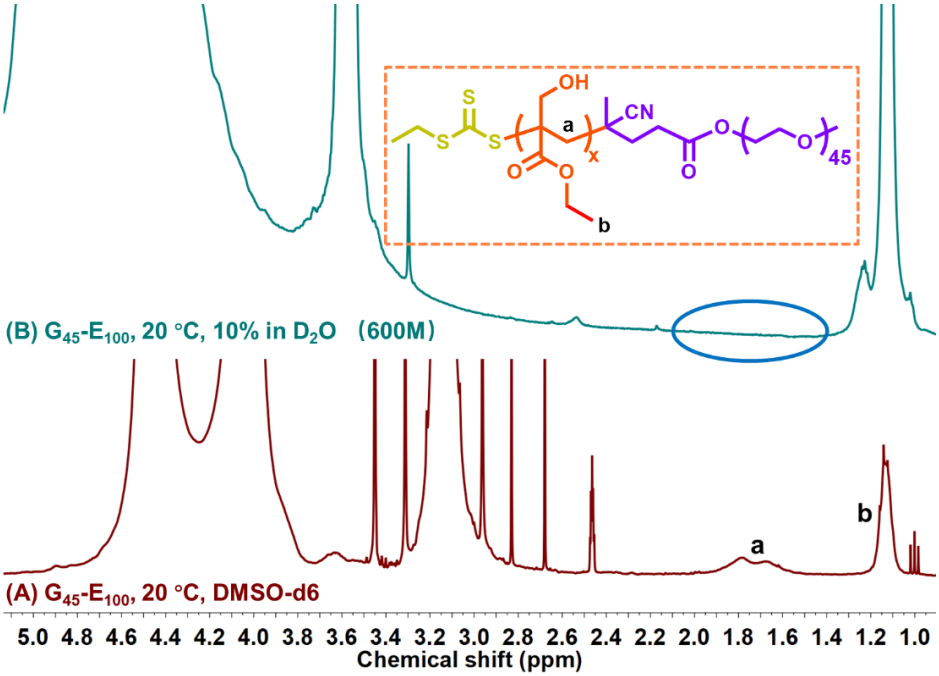


Figure S8. ^{1}H NMR spectra of PEG_{45}-$PEHMA_{100}$ (**Table 1**, entry 1) at 20 ℃ in DMSO-d_6 (A) and D_2O (B).

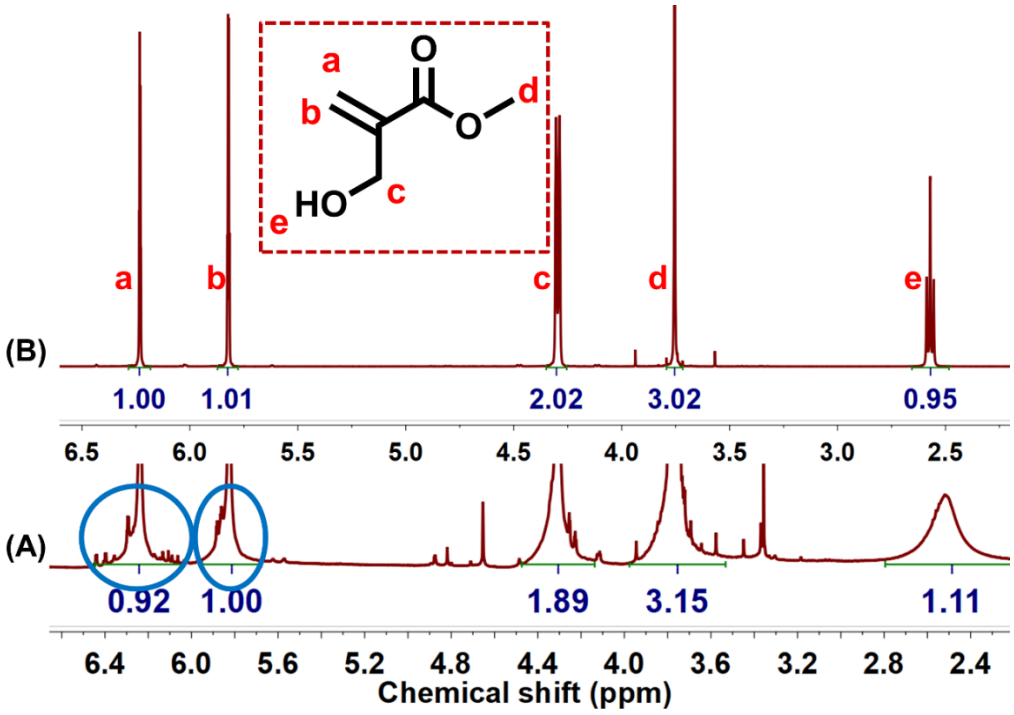


Figure S9. ^{1}H NMR spectra of as-received (A) and purified (B) MHMA in $CDCl_3$.

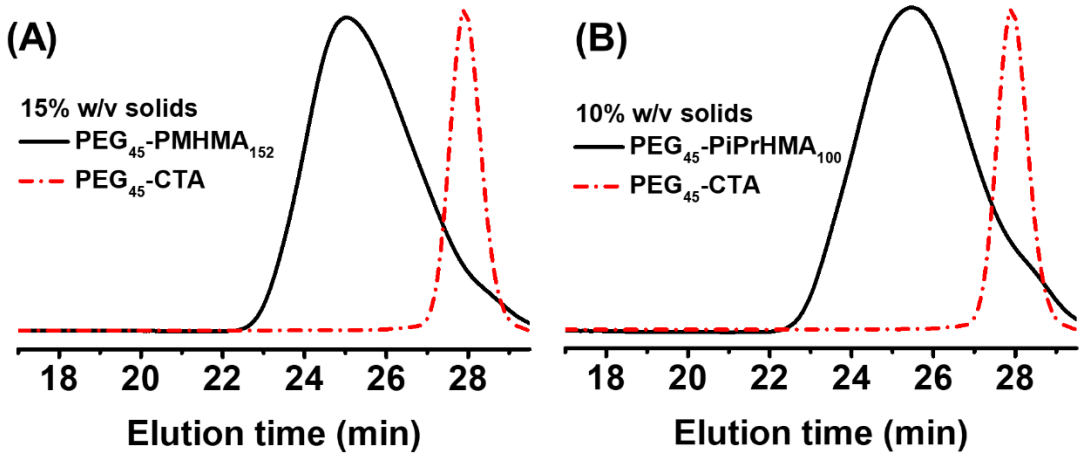


Figure S10. GPC traces of PEG_{45}-$PMHMA_{152}$ (A) and PEG_{45}-$PiPrHMA_{100}$ (B) prepared via RAFT aqueous dispersion polymerization at 40 °C.

5. Tables

Table S1. Characterization data for thermally initiated RAFT aqueous dispersion polymerization of EHMA using **PEG_{113}-CTA** at 70 ℃.

Entry	Solids (% w/v)	[V-50]/ [PEG_{113}-CTA]	Target DP	Time (h)	Conv. (%)	D_h (nm) (PDI)[a]	Morphology[b]
1	15	0.2	100	12	91	47 (0.25)	spheres
2	15	0.2	150	12	97	57 (0.22)	spheres
3	15	0.3	180	20	99	118 (0.08)	spheres
4	15	0.3	210	18	99	236 (0.24)	worms
5	15	0.3	250	12	99	438 (0.47)	vesicles
6	15	0.3	300	18	99	556 (0.14)	vesicles
7	15	0.3	150	12	99	240 (0.26)	worms
8	15	0.3	200	12	99	303 (0.19)	worms+ vesicles
9	20	0.3	150	12	99	240 (0.26)	worms
10	20	0.3	200	12	99	303 (0.19)	worms + vesicles

[a]Hydrodynamic diameter D_h and polydispersity index (PDI) determined by DLS. [b]Morphology of nano-objects judged by DLS results and TEM micrographs.

Table S2. Characterization data for photo-initiated RAFT aqueous dispersion polymerization of EHMA using **PEG$_{113}$-CTA** at 50 or 60 ℃.[a]

Entry	T (℃)	Solids (% w/v)	Target DP	$M_{n,GPC}$ (kg/mol) ($Đ$)[b]	D_h (nm) (PDI)[c]	Morphology[d]
1	50	15	200	34.7 (1.25)	53 (0.36)	spheres
2	50	20	200	-	47 (0.39)	spheres
3	50	20	300	-	70 (0.42)	spheres
4	50	25	200	-	64 (0.58)	spheres
5	50	25	300	-	92 (0.19)	spheres
6	60	20	150	28.5 (1.32)	89 (0.14)	spheres
7	60	20	200	36.9 (1.33)	180 (0.21)	worms

[a]Photo-initiated RAFT aqueous dispersion polymerizations of EHMA were conducted for 3 h, [LiPTP]/[PEG$_{113}$-CTA] = 0.3. Monomer conversions were determined to be > 92% by ^{1}H NMR characterization. [b]$M_{n,GPC}$ and MW distribution ($Đ$) obtained via GPC analysis. [c]Hydrodynamic diameter D_h and polydispersity index (PDI) determined by DLS. [d]Morphologies of nano-objects judged by DLS results and TEM micrographs.

Table S3. Characterization data for photo-initiated RAFT aqueous dispersion polymerization of EHMA using **PEG$_{45}$-CTA** at 40 or 50 ℃.[a]

Entry	T (℃)	Solids (% w/v)	Target DP	$M_{n,th}$ (kg/mol)	$M_{n,GPC}$ (kg/mol) ($Đ$)[b]	D_h (nm) (PDI)[c]	Morphology[d]
1	50	10	100	-	-	130 (0.16)	spheres
2	50	10	150	21.8	21.5 (1.19)	160 (0.14)	lamellae
3	50	10	200	28.3	28.1 (1.18)	250 (0.26)	vesicles
4	50	15	100	15.3	17.8 (1.20)	390 (0.36)	vesicles
5	50	15	200	28.3	29.9 (1.19)	370 (0.16)	vesicles
6	40	10	200	28.3	28.5 (1.19)	96 (0.15)	spheres
7	40	15	50	-	-	90 (0.24)	spheres
8	40	15	100	15.3	14.6 (1.12)	580 (0.28)	lamellae
9	40	15	200	28.3	26.8 (1.14)	280 (0.26)	vesicles

[a]Photo-initiated RAFT aqueous dispersion polymerizations of EHMA were conducted for 3 h, [LiPTP]/[PEG$_{45}$-CTA] = 0.3. Monomer conversions were determined to be > 95% by ^{1}H NMR characterization. [b]$M_{n,GPC}$ and MW distribution ($Đ$) obtained via GPC analysis. [c]The hydrodynamic diameter D_h and polydispersity (PDI) determined by DLS. [d]The morphologies of nano-objects were judged by DLS results and TEM images.

Table S4. Characterization data for photo-initiated RAFT aqueous polymerization of MHMA and iPrHMA at 40 ℃.[a]

Entry	Monomer	Solids (% w/v)	Target DP	Conv. (%)[b]	$M_{n,th}$ (kg/mol)	$M_{n,GPC}$ (kg/mol) ($Đ$) [c]	D_h (nm) (PDI)[d]	Morphology[e]
1	MHMA	15	200	76	19.9	20.4 (1.21)	95 (0.18)	spheres
2	iPrHMA	10	100	92	15.4	16.6 (1.25)	1310 (0.42)	vesicles

[a]Photo-initiated RAFT aqueous dispersion polymerization conducted at 40 ℃ for 3 h, [LiPTP]/[PEG_{45}-CTA] = 0.3. [b]Monomer conversions were determined by ^{1}H NMR characterization. [c]$M_{n,GPC}$ and MW distribution ($Đ$) obtained via GPC analysis. [d]Hydrodynamic diameter D_h and polydispersity (PDI) determined by DLS. [e]Morphology of nano-objects were judged by DLS results and TEM images.

6. References

1. Thang, S. H.; Chong, Y. K.; Mayadunne, R. T. A.; Moad, G.; Rizzardo, E., A Novel Synthesis of Functional Dithioesters, Dithiocarbamates, Xanthates and Trithiocarbonates. *Tetrahedron Lett.* **1999**, *40* (12), 2435-2438.
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4. Zhang, B.; Lv, X.; An, Z., Modular Monomers with Tunable Solubility: Synthesis of Highly Incompatible Block Copolymer Nano-Objects via RAFT Aqueous Dispersion Polymerization. *ACS Macro Lett.* **2017**, *6* (3), 224-228.