Electronic Supplementary Material (ESI) for Chemical Communications

Supplementary Information

Cyclodextrin-centered star polymers synthesized *via* a combination of thiol-ene click and ring opening polymerization

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Materials

Methyl acrylate (MA, 99%), Methyl methacrylate (MMA, 99%), Di(ethylene glycol) methyl ether methacrylate (DEGMEMA, 95%) and Poly(ethylene glycol) methyl ether acrylate ($PEGMEA_{480}$, average M_n 480 g mol^{-1}. PDI=1.05) were obtained from Sigma-Aldrich and the inhibitor was removed by passing the monomer through a column filled with basic alumina prior to use. ε-Caprolactone(ε-CL, 97%, Sigma-Aldrich) was distilled under reduced pressure before use. β-Cyclodextrin (β-CD, 97%, Sigma-Aldrich) was recrystallized twice from water and dried in a vacuum oven at 100 ^oC for two days before use. Dimethylphenylphosphine (DMPP, 97%, Sigma-Aldrich) was stored under nitrogen. Triphenyl phosphine (Ph_3P, 98.5%, Sigma-Aldrich), sodium methoxide (5.4 M in methanol), hexylamine (HA, 99%, Sigma-Aldrich), stannous octanoate($Sn(Oct)_2$, 97%, Sigma-Aldrich) and dimethyl sulfoxide-d_6 (DMSO-d_6, 99.9% atom D%, Sigma-Aldrich) were used as received. Membrane dialysis (1K MWCO) was obtained from Spectrum Laboratories. All other reagents and solvents were obtained at the highest purity available from Sigma-Aldrich and used without further purification unless otherwise stated.

Instruments and analysis

^1H and ^{13}C NMR spectra were recorded on Bruker DPX-300 and DPX-400 spectrometers using deuterated solvents obtained from Aldrich.

SEC was conducted on Varian 390-LC system in DMF (1 g/L LiBr) at 50 ^oC, equipped with refractive index and viscometry detectors, 2 × PLgel5 μm mixed-D columns (300 × 7.5 mm), 1 × PLgel5 μm guard column (50 × 7.5 mm) and autosampler. Narrow linear poly(methyl methacrylate) standards in the range of 200 to 1.0× 10^6 $g.mol^{-1}$ were used to calibrate the system.

MALDI-ToF MS was recorded in linear or reflex mode on a BrukerDaltonicsUltraflex II MALDI-ToF mass spectrometer, equipped with a nitrogen laser delivering 2 ns laser pulses at 337 nm with positive ion ToF detection performed using an accelerating voltage of 25 kV. The matrix solution was prepared by dissolving α-cyano-4-hydroxycinnamic acid (CHCA) or *trans*-2-[3-(4-*tert*-Butylphenyl)-2-methyl-2-propenylidene]malononitrile(DCTB) in THF(10 mg/mL solution). Sodium iodine was added at a 0.1% overall concentration to improve the ionization. CDs or polymer analytes were dissolved ata concentration of 1 mg/mL. Samples were prepared by layering matrix solution and analyte solution on the stainless steel slide. Calibration was performed with different linear poly(ethylene glycol) methyl ether standards.

Infrared absorption spectra were recorded on a Bruker VECTOR-22 FTIR spectrometer using a Golden Gate diamond attenuated total reflection cell.

The transmittance of the solution at a concentration of 1 mg/mL was measured at λ=500 nm through 10 mm path length cuvettes with a micro-stir bar and total volumes of 2 mL, using a PerkinElmer Lambda 35 UV-VIS spectrometer. The cloud points (CP) were defined as the temperature corresponding to a 50% reduction in the original transmittance of the solution.

Synthesis of per-6-iodo-β-cyclodextrin (CD-I)

This compound was prepared from β-CD according to procedures reported by Defaye andKaifer et al.[1-2] Ph_3P (13.3 g, 48 mmol) was dissolved in anhydrous DMF (30 mL) under stirring, I_2 (13.5 g, 53 mmol) dissolved in anhydrous DMF (30 mL) was added dropwise to the Ph_3P solution under nitrogen protection. Heat evolved during the addition and the solution was heated to 80 ^oC after addition. Anhydrous β-CD (4.0 g, 3.3 mmol) was then added to this dark brown solution and stirred at 80 ^oC for 15 h. After that, the solution was concentrated under vacuum to half of its original volume and the pH was adjusted to 9-10 by the addition of sodium methoxide under cooling with ice-water bath. The reaction mixture was stirred at ambient temperature for 30 min and was then poured into methanol (500 mL) to form a precipitate, which was filtered and washed with methanol. The product was purified by Soxhlet extract with methanol for 1 day and recovered as white powder after drying under vacuum (yield: 69%).

^1H NMR (DMSO-d_6, 298 K, 400 MHz): δ (ppm) =6.03 (d, J=6.8 Hz, 7 H, OH-2), 5.92 (d, J=1.7 Hz, 7 H, OH-3), 4.99 (d, J=3.3 Hz, 7 H, H-1), 3.80 (d, J=9.4 Hz, 7 H, H-6a), 3.54-3.68 (m, 14 H, H-3,H-5), 3.22-3.49 (m, 21 H, H-2, H-4, H-6b).

^{13}C NMR (DMSO-d_6, 298 K, 400 MHz): δ (ppm) =102.1 (C-1), 86.0 (C-4), 72.2 (C-5), 71.9 (C-3), 71.0 (C-2), 9.5 (C-6).

FT-IR ν: 3328.5 (OH), 2910.3 (CH) cm^{-1}.

MALDI-TOF MS m/z: calcd for $C_{42}H_{63}O_{28}I_7$ ($M+Na^+$), 1926.7; found, 1926.7.

Synthesis of per-6-thio-β-cyclodextrin (CD-$(SH)_7$)

This compound was prepared according to previous report by Stoddart and Kaifer et al.[2] Compound CD-I (3.86 g) and thiourea (1.21 g) were dissolved in DMF (40 mL) and the mixture was heated to 70 ^oC under nitrogen atmosphere. After 19 h, DMF was removed under reduced pressure and the obtained yellow oil was dissolved in water (200 mL). Sodium hydroxide (1.04 g) was then added and the reaction mixture was heated to a gentle reflux under nitrogen atmosphere. After 1 h, the resulting suspension was acidified with aqueous $KHSO_4$ and white precipitate was got, which was then filtered and washed thoroughly with water and dried under vacuum. Compound CD-SH was recovered as white powder (yield: 81%).

^1H NMR (DMSO-d_6, 298 K, 400 MHz): δ (ppm) =5.94 (d, J=7.0 Hz, 7 H, OH-2), 5.83 (d, J=2.0 Hz, 7 H, OH-3), 4.93 (d, J=3.5 Hz, 7 H, H-1), 3.67 (t, J=8.8 Hz, 7 H, H-5), 3.60 (t, J=9.8 Hz, 7 H, H-3), 3.27-3.45 (m, 14 H, H-2, H-4), 3.19 (m, 7 H, H-6 a), 2.75 (m, 7 H, H-6 b), 2.13 (t, J=8.2 Hz, 7 H, SH).

^{13}C NMR (DMSO-d_6, 298 K, 400 MHz): δ (ppm) =102.2 (C-1), 85.0 (C-4), 72.6 (C-2), 72.3 (C-3), 72.1 (C-5), 26.0 (C-6).

FT-IR ν: 3310.1 (OH), 2929.5 (CH), 2566.7 (SH) cm^{-1}.

MALDI-TOF MS m/z: calcd for $C_{42}H_{70}O_{28}S_7$ ($M+Na^+$), 1269.2; found, 1269.2.

However, previous research [3] has pointed out that less than seven-thiolated CD could exist when same synthetic route was used and CD dimers containing disulfide linkages could be obtained due to the oxidative coupling of thiol groups under similar reaction conditions.[4-5] MALDI-ToF MS spectrum (Figure. S1) also confirmed the existence of impurities such as six-thiolatedβ-CD and β-CD dimmer after reaction. When CD-$(SH)_7$ was characterized via SEC (Fig. 1), a small shoulder peak at higher molecular weight was detected, which was attributed to the existence of impurities. Due tothe poor solubility of CD-$(SH)_7$ in commonorganic solvents and the low amountof impurities, it was used without any further purification in the next step of the synthesis.

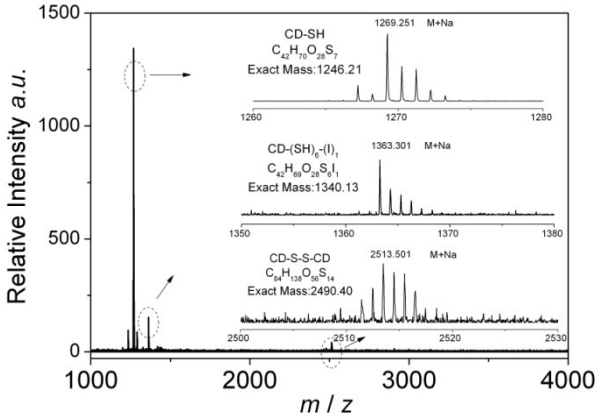


Figure S1. MALDI-ToF MS spectrum of CD-$(SH)_7$.

Synthesis of diMMA *via* CCTP

Methyl methacrylate dimer(diMMA) was prepared by CCTP of MMA with CoBF aschain transfer agent and AIBN as the initiator. MMA (250 mL)was used as received and degassed by bubbling through withnitrogen for at least 2 hours prior to use, then CoBF (0.25 g) andAIBN (0.5 g) were added to the Schlenk tube filled with nitrogenprior to addition of MMA. The reaction was carried out in an oilbath at 60 °C for three days, after which the unreactedMMA wasremoved by a rotary evaporator. Hydroquinone (100 ppm)was added to inhibit subsequent polymerization of productsduring the removal of MMA dimer. A crude separation wascarried out using a Kugelrohr apparatus and MMA dimer wascollected at 125-135 °C, 0.12 mbar. MMA dimer was furtherpurified by reduced pressure distillation at 130 °C, 0.12 mbar, The purity of the MMA dimer was confirmed by ^{1}H NMR,^{13}CNMR and ESI-MS.

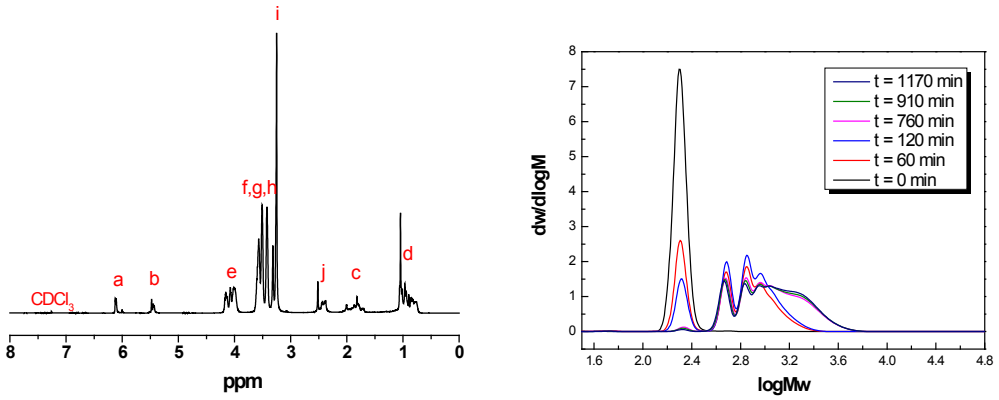
^{1}H NMR (400 MHz, acetone-d_6, 298 K), δ(ppm) = 6.15 (d, J = 1.6 Hz, 1H, 1/2 CH_2=C), 5.57 (d, J = 1.3 Hz, 1H, 1/2 CH_2=C), 3.69 (s, 3H, CH_2=C-COOCH_3), 3.59 (s, 3H, CH_3-C-COOCH_3), 2.59 (s, 2H, CH_2=C-CH_2), 1.12 (s, 6H, C(CH_3)$_2$).

^{13}C NMR (100 MHz, acetone-d_6, 298K), δ (ppm) = 177.44 (1C, CH_3-C-C=O), 168.26 (1C, CH_2=C-C=O), 138.74 (1C, CH_2=C), 128.25 (1C, CH$_2$=C), 52.36 (1C, CH_3-C-COOCH$_3$), 52.06 (1C, CH_2=C-COOCH$_3$), 43.46 (1C, CH_2), 42.02 (1C, C(CH$_3$)$_2$), 25.40 (2C, C(CH$_3$)$_2$).

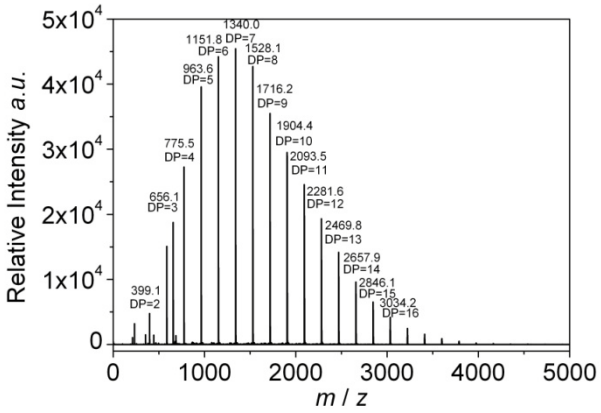
Mass spectrometry: ESI-MS Calcd. for $C_{10}H_{16}NaO_4^+$ ($M+Na^+$)=223.09, Found 223.09.

Synthesis of PDEGMEMA *via* CCTP

DEGMEMA monomers (15 g) and methanol (35 mL) mixture were purged with nitrogen for at least an hour prior to use. Stock solutions of CoBF were also weighed and purged with nitrogen prior to use. ACVA (0.14 g) was weighed into Schlenk flasks. All reaction mixtures were then mixed under nitrogen. To ensure the absence of oxygen, the reaction mixtures were subjected to at least three freeze-pump-thaw cycles. Polymerizations were performed at a constant temperature of 80 °C. The polymerization mixture was sampled periodically using an airtight degassed syringe for molecular weight and conversion analysis. Polymerizations were stopped by cooling and subsequent exposure to air. Polymers were then purified by precipitation and dialysis. PDEGMEMA was precipitated in cold petroleum ether (40-60 °C).



(a) (b)



(c)

Figure S2. (a) ^{1}H NMR spectrum, (b) GPC spectra and (c) MALDI-ToF MS spectrum of PDEGMEMA *via* CCTP at 80 ºC, [CoBF]/[Monomer] = 1.34×10^{-4}.

Thiol-ene reactions of CD-$(SH)_7$ with vinyl monomers and CCTP polymers

The reactions were carried out at ambient temperature and monitored by ^{1}H NMR spectroscopy.

For the reactions of CD-$(SH)_7$ with MA, MMA, DEGMEMA, $PEGMEA_{480}$ and CCTP MMA dimer, DMPP was used as the catalyst. In a typical reaction, CD-$(SH)_7$ (125 mg, 0.7 mmol SH groups), MA (86 mg, 1 mmol) and DMPP (10 μL, 0.07 mmol) were dissolved in DMSO (2 ml).and stirred at ambient temperature. A part of the solution (0.1 mL) was taken out for ^{1}H NMR analysis. After 24 h, ^{1}H NMR showed no more decrease of vinyl groups, then the mixture was directly transformed to a dialysis tubing (MWCO 1000, Spectrum Laboratories) and dialyzed against water for two days. 120 mg product was recovered after drying under vacuum.

For the reaction of CD-$(SH)_7$ with CCTP PDEGMEMA (M_n=900 g mol^{-1}, PDI=1.40), HA was used as the catalyst and mole ratio of thiol-ene was kept as 1:1 to avoid the purify procedure of excess polymer. In a 20 ml vial, CD-$(SH)_7$ (100 mg, 0.56 mmol SH groups), CCTP PDEGMEMA (504 mg, 0.56 mmol vinyl groups) and HA (0.15 mL, 1.12 mmol) were dissolved in DMSO (3 ml).and stirred at ambient temperature. After 90 h, ^{1}H NMR showed more than 99% of vinyl groups had disappeared, then the mixture was diluted with water and transformed to a dialysis tubing and dialyzed against water for two days. 260 mg product was recovered after freeze drying.

The obtained products are named as CD-$(S\text{-}MA)_7$, CD-$(S\text{-}MMA)_7$, CD-$(S\text{-}DEGMEMA)_7$, CD-$(S\text{-}PEGMEA_{480})_7$, CD-$(S\text{-}diMMA)_7$ and CD-$(S\text{-}PDEGMEMA)_7$ in turn. Obvious solubility change was observed during the thiol-ene reaction. CD-SH has good solubility in high polarity organic solvents (DMF, DMSO) but poor solubility in general solvents (water, acetone, methanol, $CHCl_3$, THF et al). After reaction with MA, MMA, DEGMEMA and CCTP diMMA, the products showed to have good solubility in acetone, methanol, $CHCl_3$, THF et al due to the addition of hydrophobic part. After reaction with $PEGMEA_{480}$ and CCTP PDEGMEMA, the products became more hydrophilic and were soluble in water, which also proved the success of thiol-ene reaction.

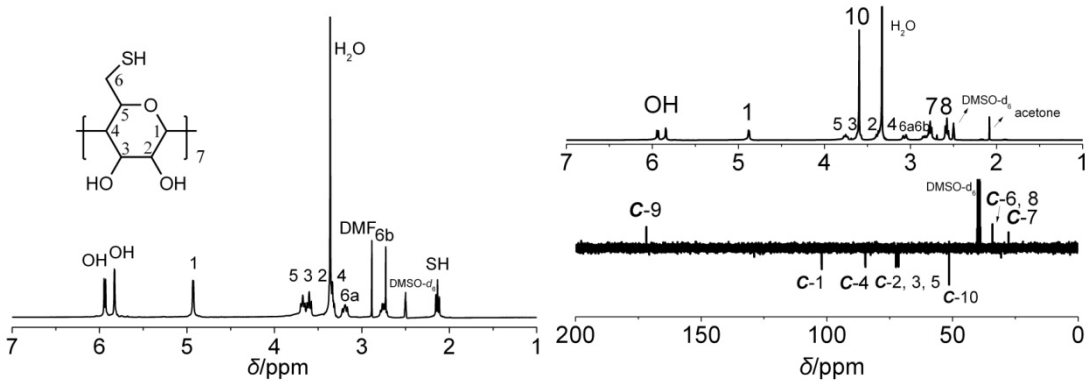


Figure S3. ^{1}H &^{13}C NMR spectra of CD-(SH)$_7$ (left) and CD-(S-MA)$_7$ (right) in DMSO-d_6.

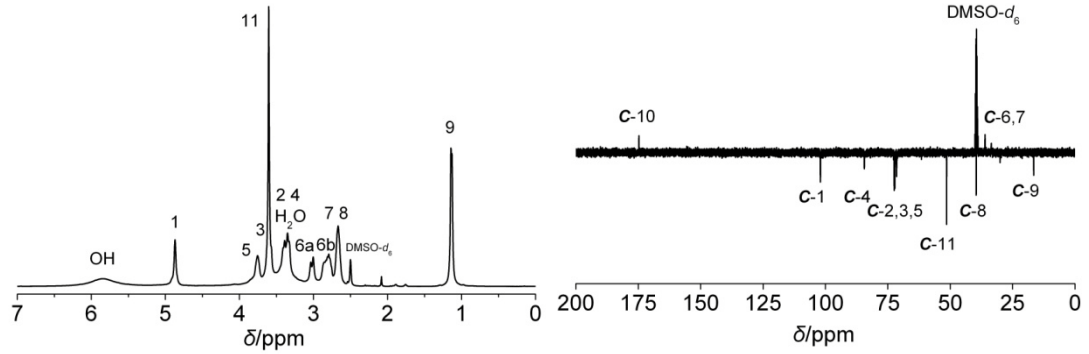


Figure S4. ^{1}H (left) &^{13}C (right) NMR spectra of CD-(S-MMA)$_7$ in DMSO-d_6.

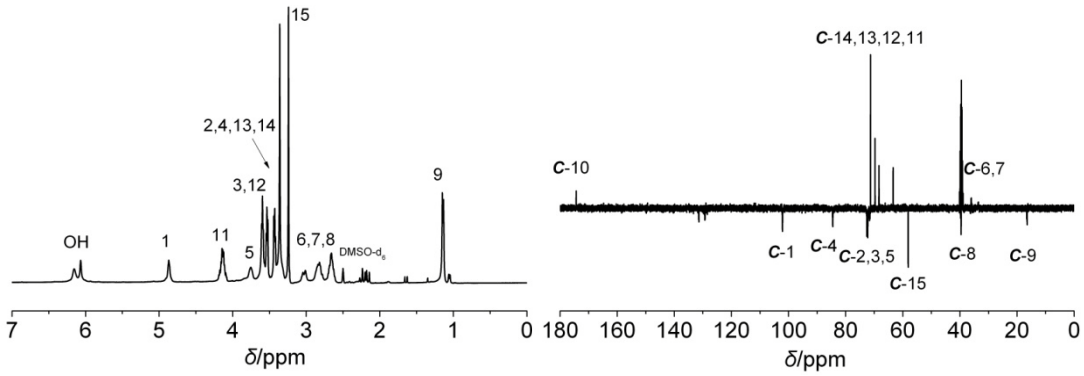


Figure S5. ^{1}H (left) &^{13}C (right) NMR spectra of CD-(S-DEGMEMA)$_7$ in DMSO-d_6.

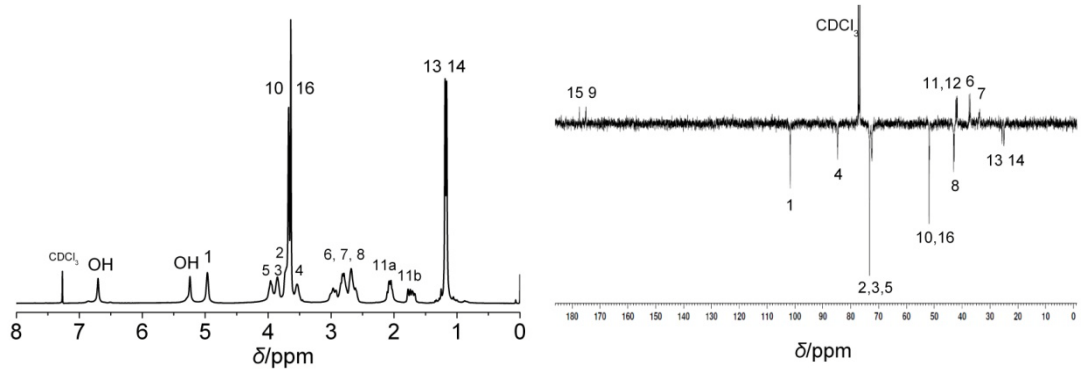


Figure S6. ^{1}H (left) &^{13}C (right) NMR spectra of CD-(S-diMMA)$_7$ in $CDCl_3$.

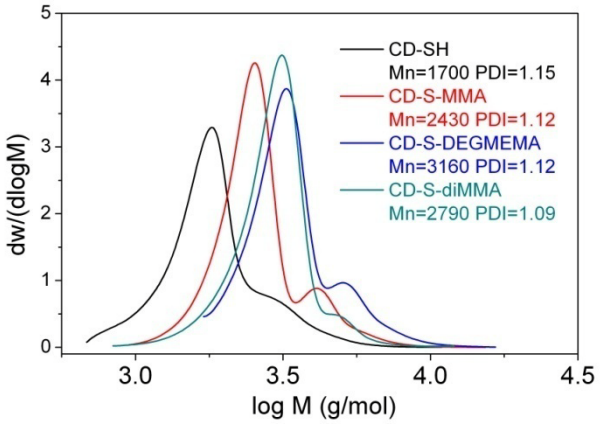


Figure S7. DMF SEC traces of CD-$(SH)_7$, CD-$(S\text{-}MMA)_7$, CD-$(S\text{-}DEGMEMA)_7$ and CD-$(S\text{-}diMMA)_7$.

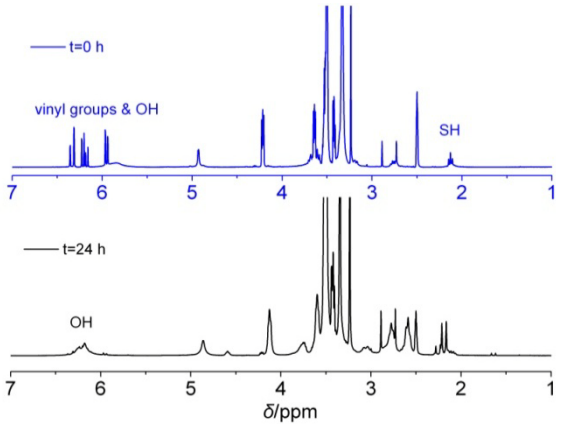


Figure S8. ^{1}H NMR spectra with time at 0 h and 24 h in the reaction of CD-$(SH)_7$ with $PEGMA_{480}$(thiol:ene:DMPP=1:1:0.05) in DMSO-d_6 at 25 ^{o}C.

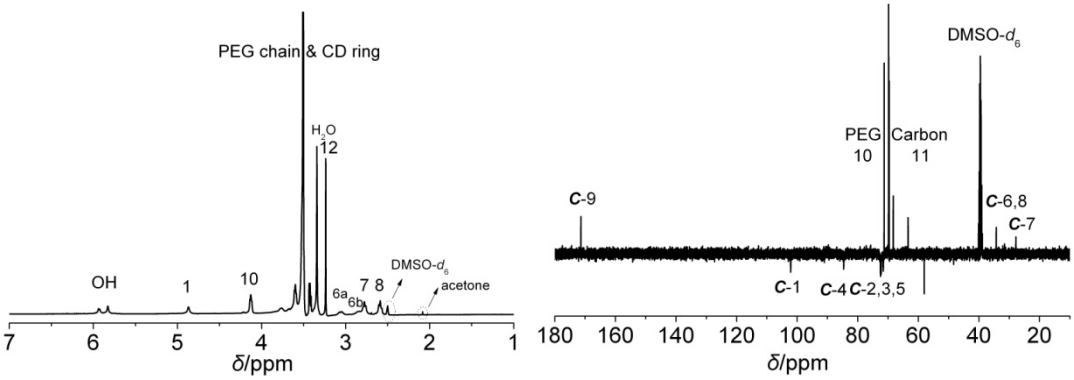


Figure S9. ^{1}H (left) &^{13}C (right) NMR spectra of CD-$(S\text{-}PEGMA_{480})_7$ in DMSO-d_6.

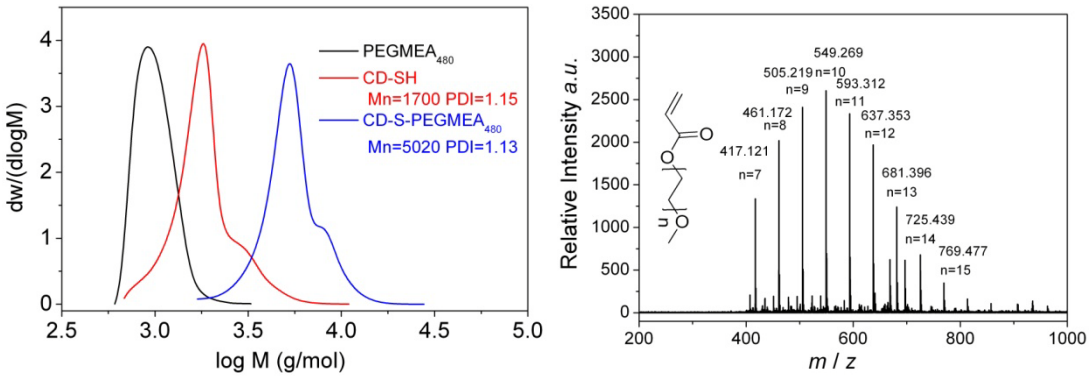


Figure S10. DMF SEC traces (left) of CD-$(SH)_7$, $PEGMEA_{480}$ and CD-$(S\text{-}PEGMEA_{480})_7$ and MALDI-ToF MS Spectrum (right) of $PEGMEA_{480}$.

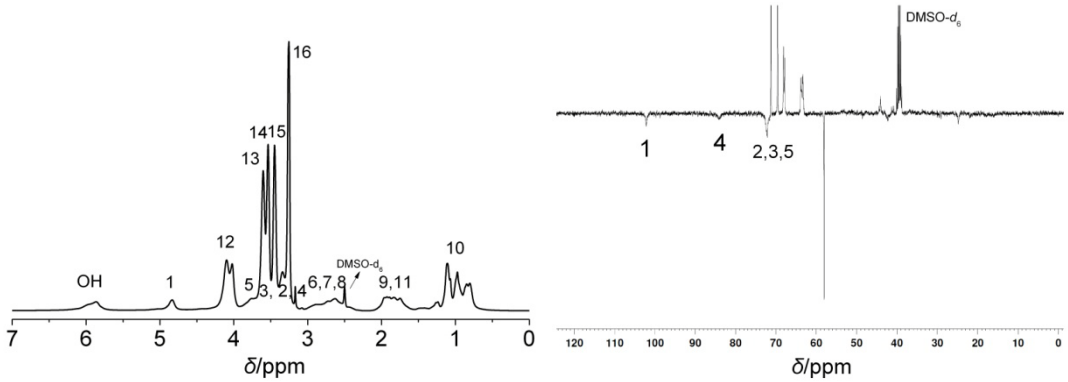


Figure S11. ^{1}H (left) &^{13}C (right) NMR spectra of CD-$(S\text{-}PDEGMEMA)_7$ in DMSO-d_6.

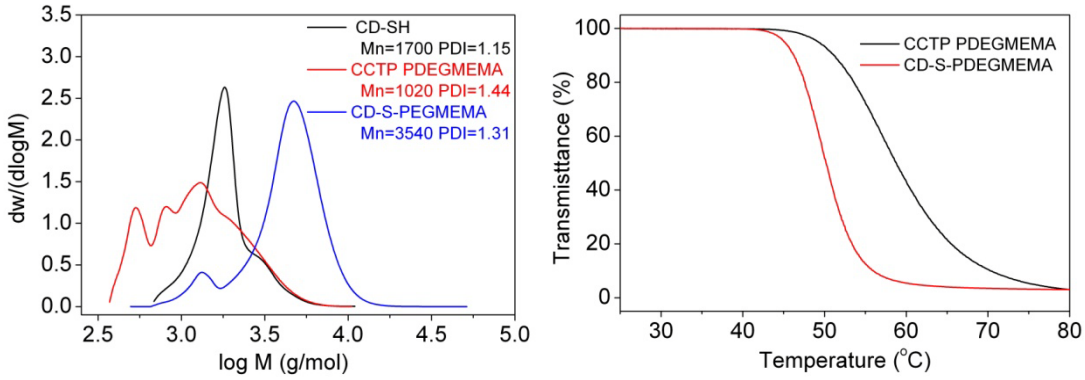


Figure S12. DMF SEC traces (left) of CD-$(SH)_7$, CCTP PDEGMEMA and CD-$(S\text{-}PDEGMEMA)_7$ and cloud point measurements (right) of CCTP PDEGMEMA & CD-$(S\text{-}PDEGMEMA)_7$ by UV/vis spectroscopy at 500nm & 1 mg/mL.

Ring opening polymerization (ROP) of ε-CL initiated by CD-(S-MA)$_7$

The ROP of ε-CL was conducted according to the procedure reported by Zhu et al.[6] In anoven dried Schlenk tube, 100 mg CD-(S-MA)$_7$ (0.76 mmol OH group) was dried at 70 ^{o}C under vacuum for one day. 519 mg ε-CL (4.6 mmol, DP=6) was then added to the tube and stirred until CD-(S-MA)$_7$ dissolved completely. Then an exhausting-refilling process was conducted for three times. After that, 3mg Sn(Oct)$_2$in 0.5 mL anhydrous toluene was added to the mixture and the exhausting-refilling process was repeated to remove the toluene. Then the tube was immersed in a thermostated oil bath at 120 ^{o}C and stirred at this temperature for 12 h. After reaction, the mixture was diluted with THF and poured into methanol to form a precipitate, which was then filtered and washed thoroughly with methanol. 210 mg product was obtained after drying under vacuum. ^{1}H NMR analysis of the product revealed the average DP=3.1 per chain by comparing the proton area of 8 to 12 shown in Figure S13.

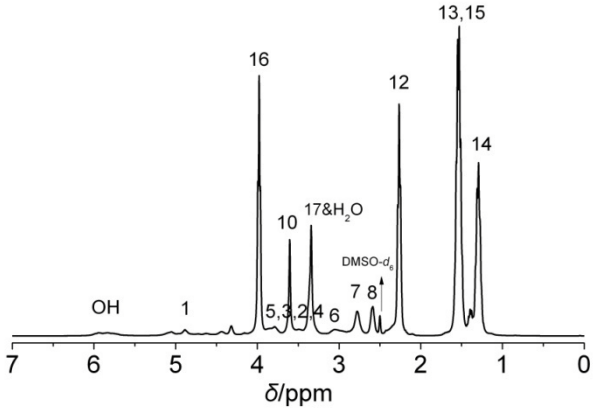


Figure S13. ^{1}H NMR spectrum of PCL-CD-(S-MA)$_7$ in DMSO-d_6.

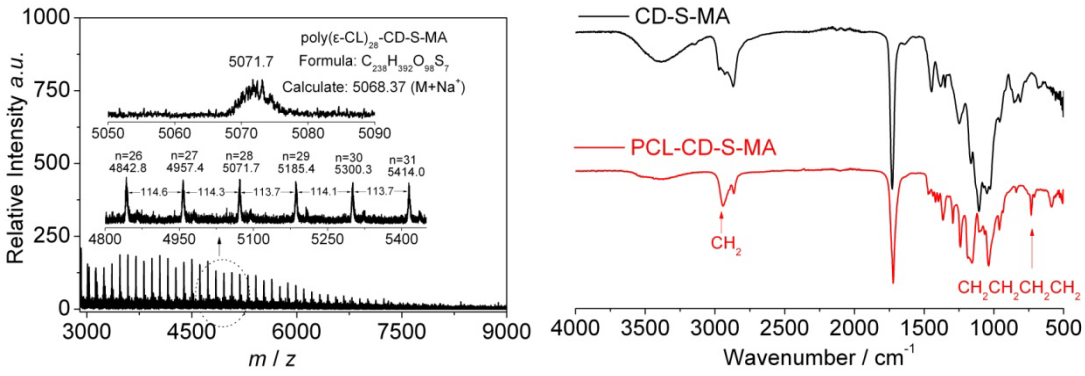


Figure S14. MALDI-ToF MS (left) and FTIR (right) Spectra of PCL-CD-(S-MA)$_7$.

References

1. A. Gadelle and J. Defaye, *Angewandte Chemie International Edition in English*, 1991, 30, 78-80.
2. M. T. Rojas, R. Koeniger, J. F. Stoddart and A. E. Kaifer, *Journal of the American Chemical Society*, 1995, 117, 336-343.
3. Y. Domi, Y. Yoshinaga, K. Shimazu and M. D. Porter, *Langmuir*, 2009, 25, 8094-8100.
4. L. s. Kumprecht, M. Buděšínský, J. i. Vondrášek, J. i. Vymětal, J. i. Černý, I. Císařová, J. i. Brynda, V. r. Herzig, P. Koutník, J. i. Závada and T. s. Kraus, *The Journal of Organic Chemistry*, 2008, 74, 1082-1092.
5. A. Wang, W. Li, P. Zhang and C.-C. Ling, *Organic Letters*, 2011, 13, 3572-3575.
6. P.-F. Gou, W.-P. Zhu and Z.-Q. Shen, *Polymer Chemistry*, 2010, 1, 1205-1214.