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Supplementary Information

Ring Opening Copolymerization of *ε*-Caprolactone and Diselenic Macrolide Carbonate for Well-Defined Poly(ester-*co*-carbonate) : Kinetic Evaluation and ROS/GSH Responsiveness

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1. Experimental Section

1.1 Materials

Polyethylene glycol monomethyl ether (mPEG, M_n=2000) was purified by azeotropic distillation with toluene. ε-caprolactone (ε-CL) was dried over calcium hydride for 48 h followed by distillation under reduced pressure prior to use. Diselenic macrocyclic carbonate monomer (M_{SeSe}) was synthesized according to our previous work.[1] Lipase CA: Novozym 435 from Candida antarctica was dried under reduced pressure at 60 °C for 12 h. Toluene (Shanghai Guoyao Chemical Regent Company) was distilled with sodium for 6 h to remove the moisture followed by distillation. All reagents were available as analytical-grade products from Sigma-Aldrich, Aladdin or Shanghai Chemical Reagents Company and used as received unless otherwise noted.

1.2 Methods

Synthesis of mPEG-*b*-poly(CL-*co*-SeSe) copolymer

The copolymerization was executed *via* ring opening polymerization (ROP) and initiated by mPEG (M_n=2000). Typically, M_{SeSe} (110mg, 0.2 mmol), anhydrous ε-CL (136.8 mg,1.2 mmol), mPEG (40 mg, 0.02 mmol) and dried lipase CA (25 mg, 10 wt % relative to the total monomer) were added to a 10-mL dried flask equipped with a stir bar under Ar atmosphere rapidly. Then, anhydrous toluene (1.2 mL, solvent / monomer (mL / g) = 5) were introduced to the system. Subsequently, the flask was closed with a glass stopper and immersed in an oil bath at 70 °C for 24 h. The resulting product was dissolved with 2 mL dichloromethane and the insoluble enzyme was removed by filtration. The filtrate was precipitated into cold anhydrous diethyl ether and further dried in *vacuo* to obtain yellow viscous product with yield about 60%.

Polymerization kinetics

The polymerization kinetics of ε-CL (M_1) and M_{SeSe} (M_2) was monitored using Nuclear Magnetic Resonance (NMR) technology. During the reaction, the solution (25μL) was taken out at regular time intervals for ^{1}H NMR spectrum analysis to determine the monomer conversion. The composition of copolymers with different monomer feeds were obtained by analyzing the ^{1}H NMR spectrum of the reaction mixture. The specific behaviors of two monomers in the initial and late stage of polymerization were studied separately by analyzing the reaction solution at different time points. The reactivity ratio was calculated utilizing mathematical method according to the previous literature,[2-4] and the parameters were determined *via* the computational process expressed as follows:

(1) Fineman-Ross (F-R)

$$G1 = r_1H - r_2 \tag{1}$$

$$G = \frac{X(Y-1)}{Y}, \quad H = \frac{X^2}{Y}$$

(2) Kelen-Tüdös (K-T)

$$\eta = \left(r_1 + \frac{r_2}{\alpha}\right)\xi - \frac{r_2}{\alpha} \tag{2}$$

$$\eta = \frac{G}{\alpha + H}, \quad \xi = \frac{H}{\alpha + H}, \quad \alpha = \sqrt{H_m \times H_M}$$

$$G = \frac{X(Y-1)}{Y}, \quad H = \frac{X^2}{Y}$$

(3) Ext.Kelen-Tüdös (eK-T)

$$\eta = \left(r_1 + \frac{r_2}{\alpha}\right)\xi - \frac{r_2}{\alpha} \tag{3}$$

$$\eta = \frac{G}{\alpha + H}, \quad \xi = \frac{H}{\alpha + H}, \quad \alpha = \sqrt{H_m \times H_M}$$

$$G = \frac{Y-1}{z}, \quad H = \frac{Y}{z^2}$$

$$z = \frac{lg(1-\tau_1)}{lg(1-\tau_2)}, \quad \tau_2 = \left(\frac{\mu + X}{\mu + Y}\right)\omega, \quad \tau_1 = \tau_2\frac{Y}{X}$$

Where *X* is the monomer feed composition (M_1/M_2, mole ratio), *Y* is the copolymer composition (M_1'/M_2', mole ratio).

H_M and H_m represent the maximum and minimum values of the parameters *H,* respectively.

μ represents the molar mass ratio between M_1 and M_2. ω represents the total monomer conversion (wt. %).

Quantum chemistry calculation

The molecular structure of ε-CL and M_{SeSe} was calculated using the quantum chemistry methods. All the calculation was performed on the Gaussian 09 software and used density functional theory (DFT) B3LYP method. In the calculation, the 6-311++g** basis set was used for C, H and O atoms while the aug-cc-pvdz-pp basis set was used for Se atom. Meanwhile, the frequency was calculated to ensure the molecular structure at the lowest energy state.

Fabrication of the self-assembled mPEG-*b*-poly(CL-*co*-SeSe) micelles

The mPEG-*b*-poly(CL-*co*-SeSe) micelles were prepared by dialysis method. Typically, 25 mg copolymer was fully dissolved in 2 mL THF. Then, the solution was added dropwise to 15 mL of double-distilled water, subsequently, dialysis (MWCO = 3500 Da) was used to remove the organic solvent. After 48 h, the volume of the micelle solution was fixed at 25 mL to obtain the solution with a concentration of 1 mg mL^{-1} for further experiments.

The oxidation process

The oxidation behavior of mPEG-*b*-poly(CL-*co*-SeSe) copolymer by H_2O_2 was analyzed by monitoring the transmittance changes of mPEG-*b*-poly(CL-*co*-SeSe) micelles aqueous solution at 37 °C. Typically, 4mL copolymer micelle aqueous solution (ε-CL:M_{SeSe}=90:10, mole ratio) was added into 5-mL sample vial. Then 40 μL, 20 μL, 8 μL, 4 μL and 0.4 μL of 30 wt.% H_2O_2 were added to the solution and the mixture was stirred at 37 °C.

Similarly, the copolymer micelles with different feed ratios of CL/M_{SeSe} were oxidized by 20 μL H_2O_2 through the similar procedure.

The reduction process

The reduction behavior of mPEG-*b*-poly(CL-*co*-SeSe) copolymer by GSH was also conducted similarly as the oxidation process. Typically, 4mL copolymer micelle aqueous solution (ε-CL:M_{SeSe}=90:10, mole ratio) was added into 5-mL sample vial. Then 61.4 mg GSH (50 mM) were added to the solution and the mixture was stirred at 37 °C and transmittance changes were monitored to trace the reduction process.

1.3 Characterization

Structure and composition

Nuclear Magnetic Resonance (^{1}H, ^{13}C, ^{77}Se) spectra were recorded on a Bruker Avance 400 or 600 spectrometer. Deuterated chloroform ($CDCl_3$), deuterated dimethyl sulfoxide (DMSO-d_6) were used as solvents, tetramethylsilane (TMS) and diphenyl diselenide were used as the internal standard respectively.

Fourier transform infrared spectrometer (FT-IR) was carried out on a Nicolet 5700 FT-IR spectrometer by KBr sample holder method.

Gel permeation chromatograph (GPC) was performed using DMF as the eluent at a flow rate of 1.0 mL min^{-1} and polymethyl methacrylate (PMMA) as the standard to obtain the molecular weight and molecular-weight distribution.

Thermal properties and crystallization behaviors

Differential scanning calorimetry (DSC) was performed on TA-Instruments Q2000. The measurements were carried out at a scan rate of 10 ^{o}C / min under nitrogen flow. Samples were firstly heated from -60 ^{o}C to 80 ^{o}C followed by cooling to -60 ^{o}C to erase the thermal history and then heated to 80 ^{o}C.

Wide angle X-ray diffraction (WAXD) was performed over the range 2θ from 10^{o} to 60^{o} at room temperature, using Rigaku max 2550VB diffractometer with Nifiltered Cuka radiation.

Particle size, morphology and oxidation-responsive behavior

Particle size and size distribution of the micelles were measured by dynamic light scattering (Nano-ZS ZEN 3600, Malvern) under the He-Ne (λ = 633 nm) laser at 25 ^{o}C. The morphologies of micelles were observed using a JEOL/JEM 1400 microscope operated at 120 kV.

The oxidation-responsive behavior of copolymer micelles was characterized by UV-Vis, DLS and TEM. The turbidimetric experiment was performed by UV-Vis spectrometer (SP-1900, Shanghai Spectrum) at 450 nm.

2. Spectroscopic Characterization and Computational Data

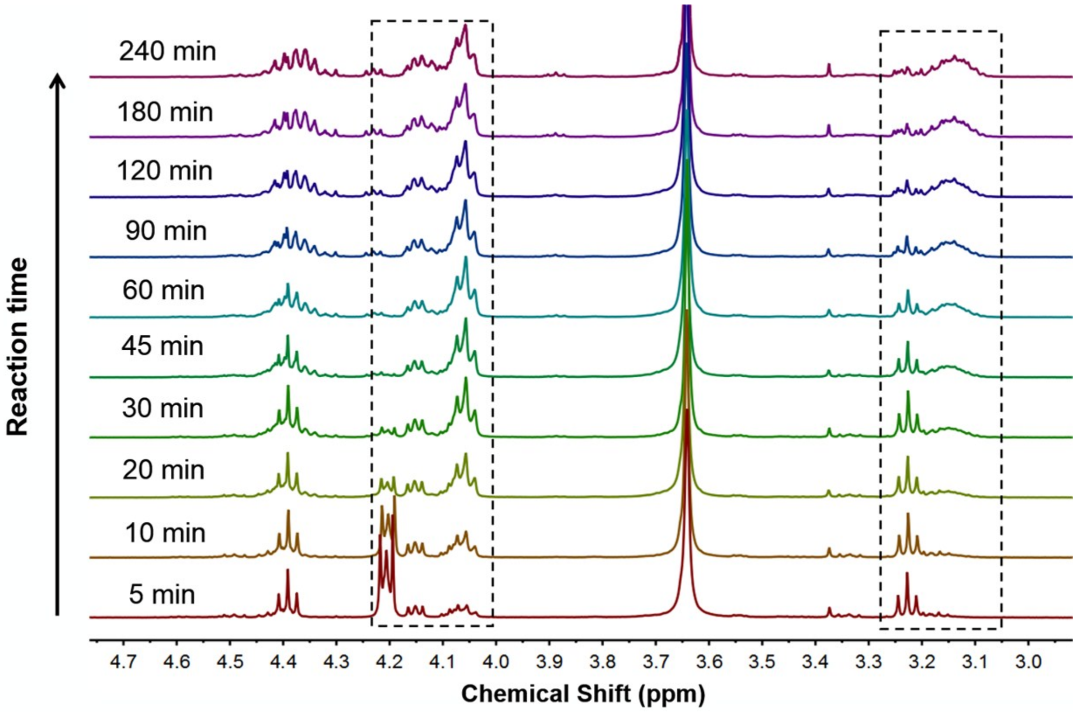

Figure S1 The copolymerization process of mPEG-*b*-poly(CL-*co*-SeSe) traced by ^{1}H NMR spectra ($CDCl_3$, 400 MHz)

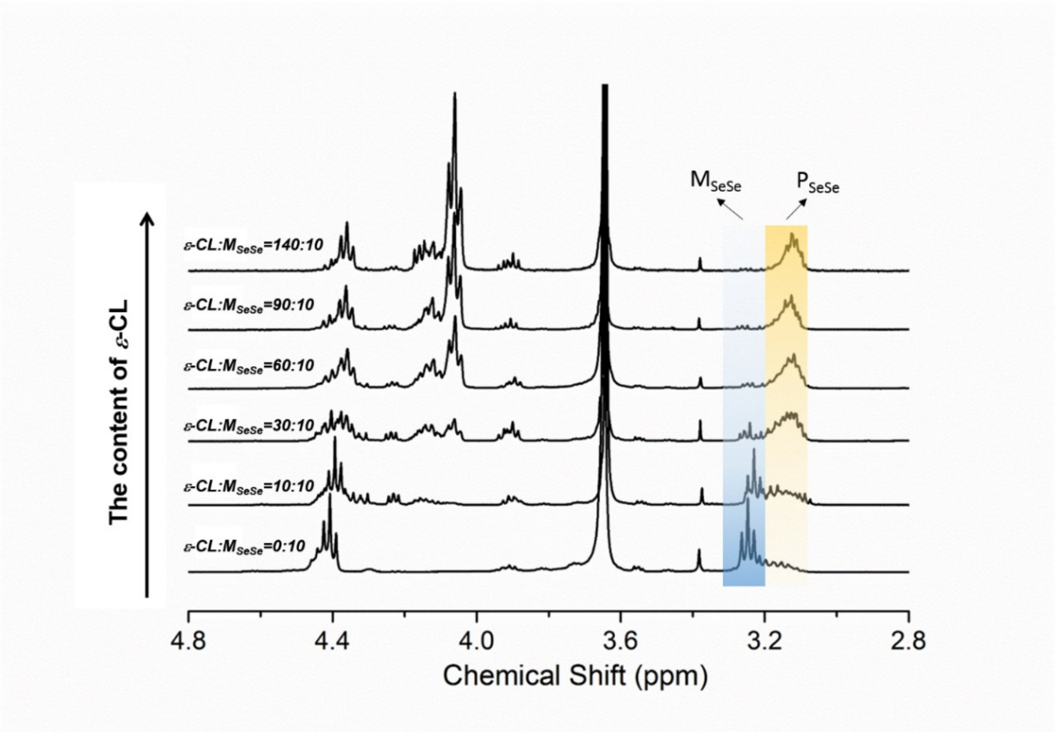

Figure S2 The ^{1}H NMR spectra ($CDCl_3$, 400 MHz) of 24-hour reaction mixture of different copolymers

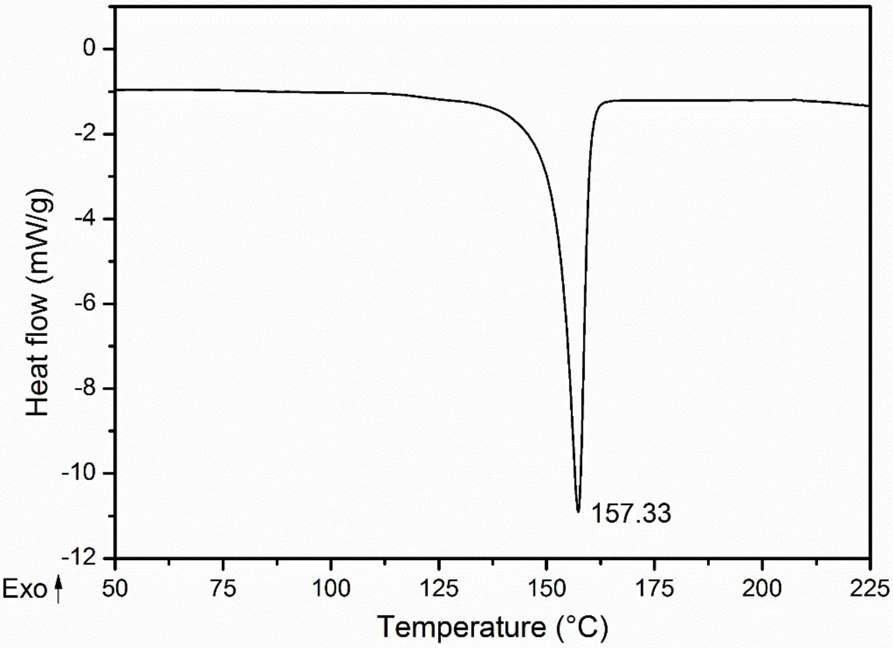

Figure S3 DSC curve of M_{SeSe}

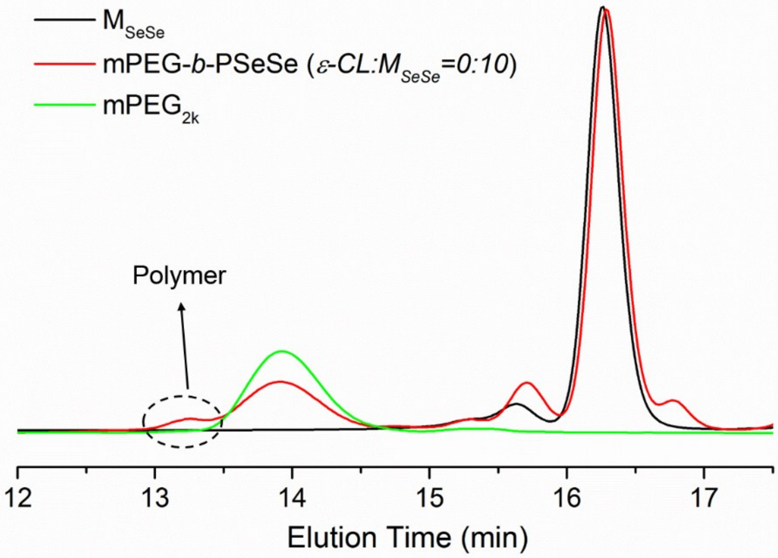

Figure S4 The GPC curve of mPEG-*b*-PSeSe

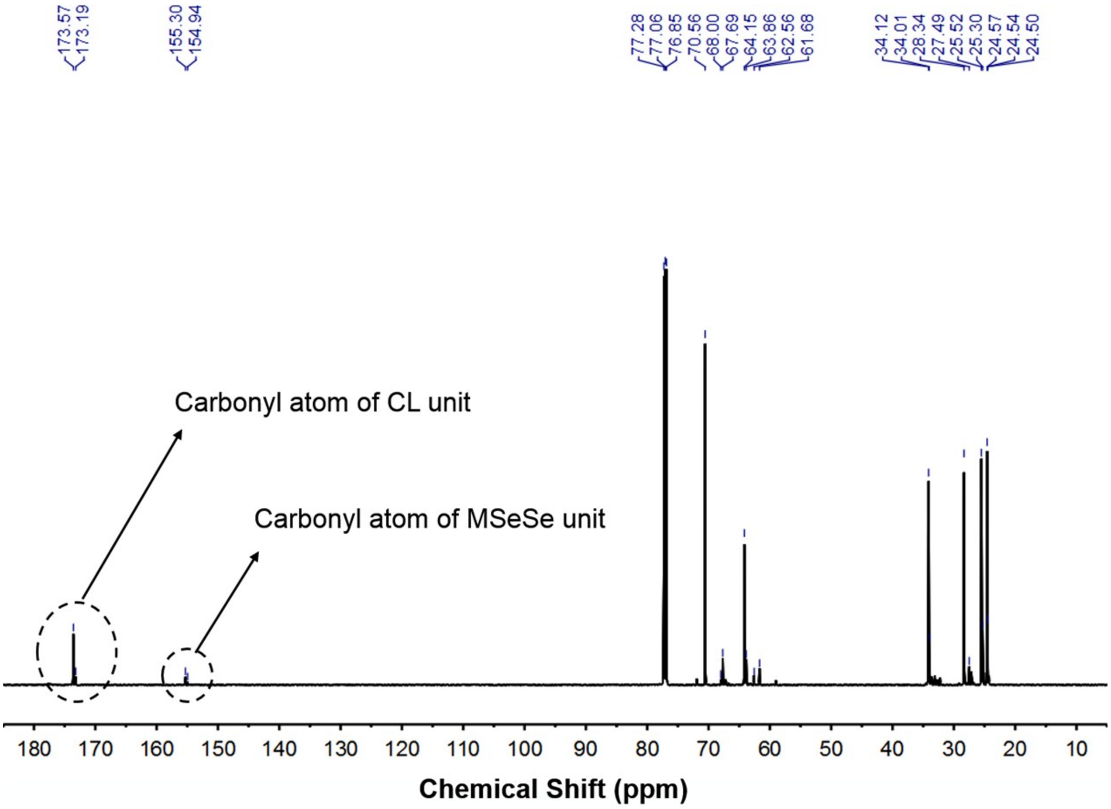

Figure S5 ^{13}C NMR spectra of mPEG-*b*-poly(CL-*co*-SeSe) copolymer (600 MHz, $CDCl_3$).

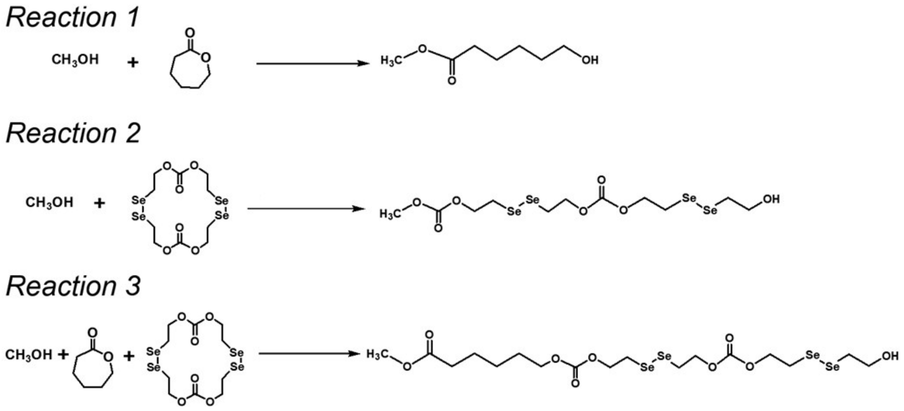

Figure S6 The model reaction in homo- or co-polymerization used for calculation.

Table S1. Ring-opening polymerization energy of different reaction[a]

Reaction	Δ*E(kcal/mol)*	ΔH*(kcal/mol)*	ΔG*(kcal/mol)*
Reaction 1	-46.58	-43.52	-38.66
Reaction 2	-35.16	-31.75	-34.58
Reaction 3	-101.67	-93.94	-92.77

[a]All the calculation was under 298 K and 1 atm

Table S2. F-T and K-T parameters for the ROP of CL with M_{SeSe}[a]

Entry	**X**	**Y**	**G**	**H**	**η**	**ξ**
1	10.1237	22.3250	9.6703	4.5908	1.7955	0.8524
2	4.8494	11.1764	4.4155	2.1041	1.5230	0.7257
3	1.0251	2.4682	0.6098	0.4257	0.4995	0.3487
4	0.6080	1.3705	0.1644	0.2697	0.1544	0.2533
5	0.2646	0.5084	-0.2559	0.1377	-0.2743	0.1476

[a]The copolymerization conducted in anhydrous toluene system, initiated with the $mPEG_{2k}$ and catalyzed by Novozym 435

Table S3. eK-T parameters for the ROP of CL with M_{SeSe}[a]

Entry	**X**	**Y**	**ω**	**τ_2**	**τ_1**	**z**	**G**	**H**	**η**	**x**
1	10.1237	11.9680	0.8878	0.7902	0.9342	1.7422	6.2956	3.9431	1.3061	0.8181
2	4.8494	5.6880	0.8049	0.7406	0.8686	1.5043	3.1164	2.5135	0.9192	0.7413
3	1.0251	1.2686	0.6549	0.6286	0.7779	1.5192	0.1768	0.5497	0.1239	0.3853
4	0.6080	0.8265	0.4758	0.4573	0.6217	1.5903	-0.1091	0.3268	-0.0906	0.2715
5	0.2646	0.3223	0.3401	0.3363	0.4096	1.2854	-0.5272	0.1950	-0.4918	0.1819

[a]The copolymerization conducted in anhydrous toluene system, initiated with the $mPEG_{2K}$ and catalyzed by Novozym 435

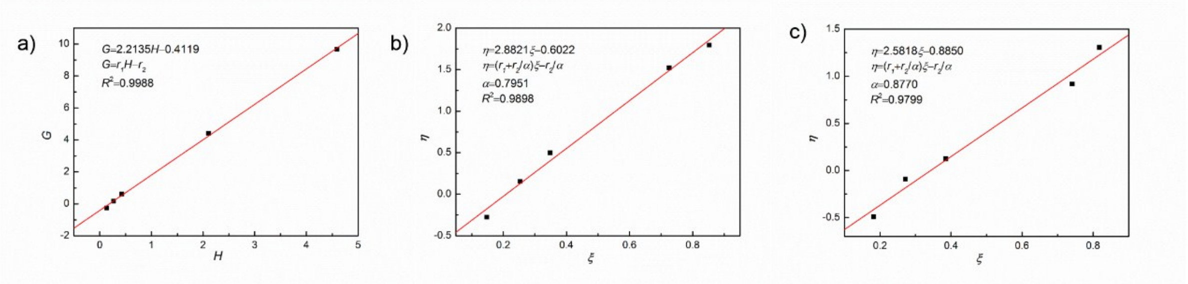

Figure S7 The linear regression analysis of (a) F-R method (b) K-T method (c) eK-T method.

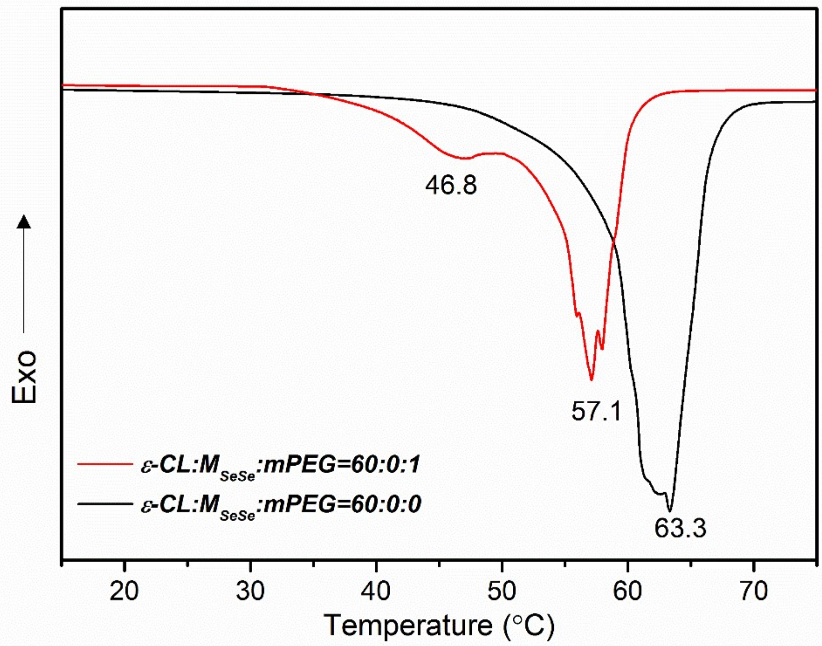

Figure S8 DSC curves for PCL polymers initiated with/without mPEG

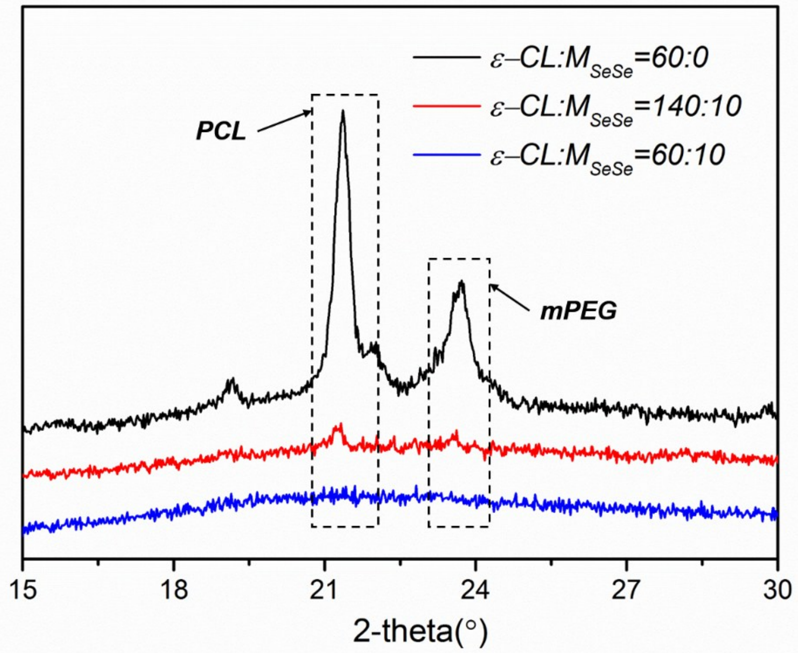

Figure S9 WAXS patterns for polymers with different monomer feeds initiated by mPEG

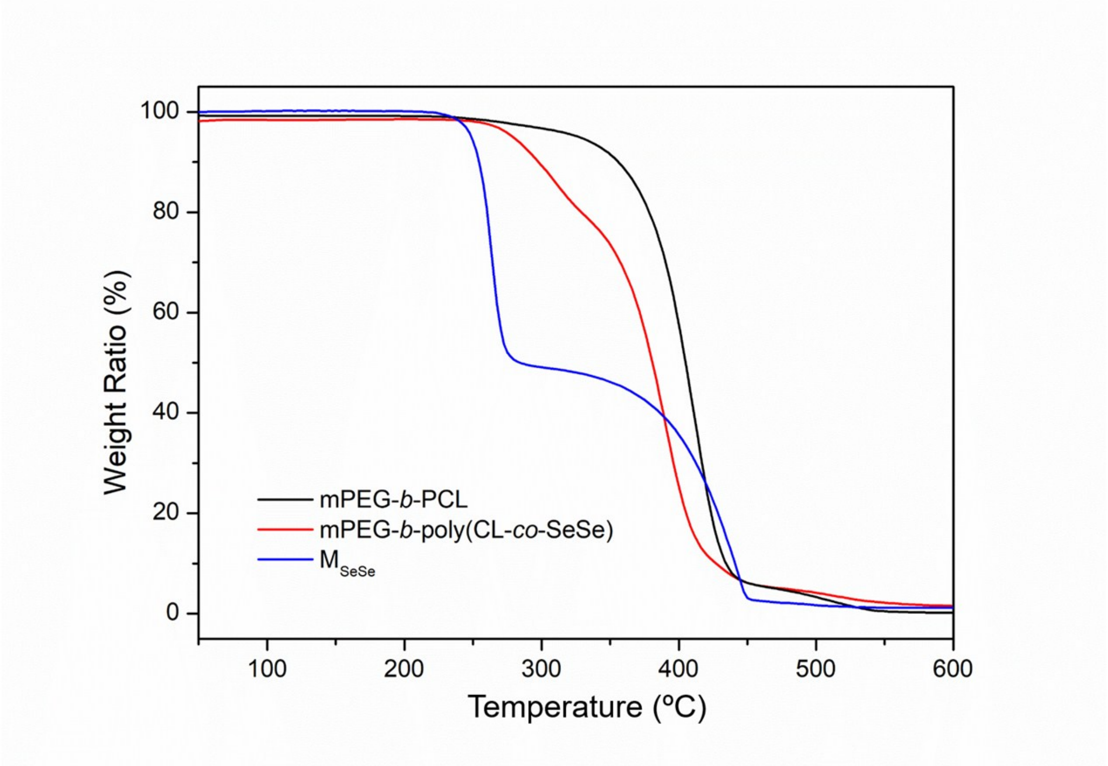

Figure S10 The TG curves of different polymers and monomer.

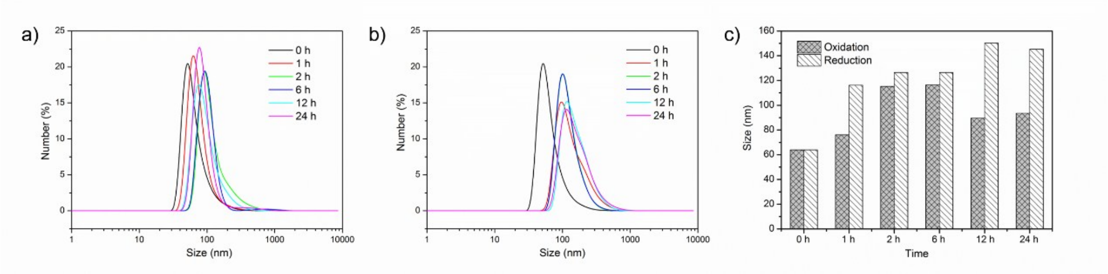

Figure S11 DLS results of copolymer (ε-CL:M_{SeSe}=90:10) micelle with different environments at 37 ^{o}C. (a) Oxidation by 50 mM H_2O_2. (b) Reduction by 50 mM GSH. (c) The average diameter of copolymer micelles over time in different environments at 37 ^{o}C.

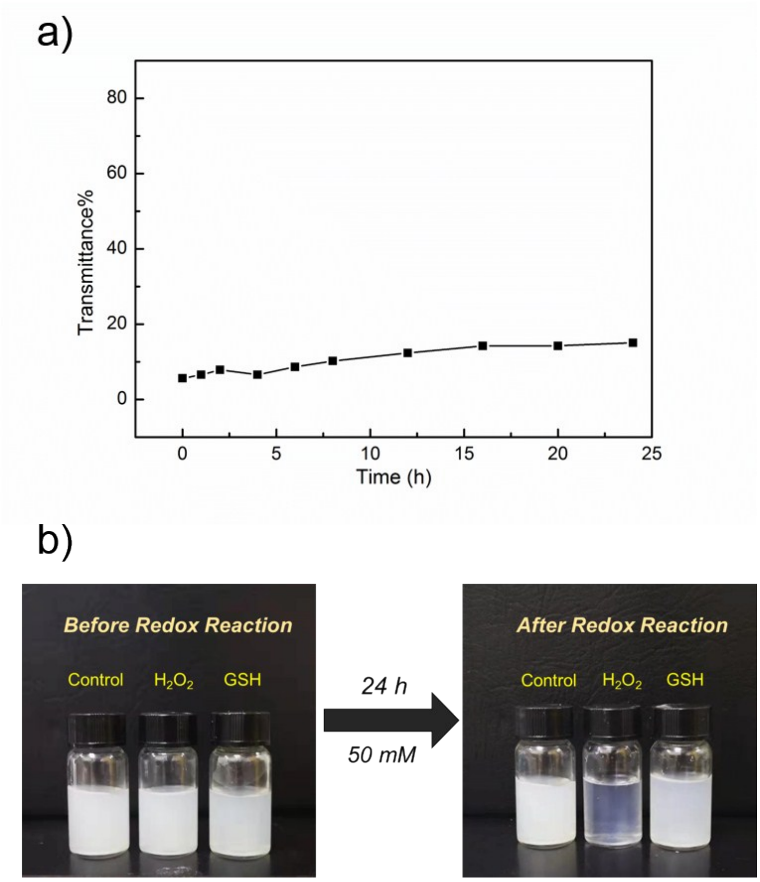

Figure S12. (a) The transmittance change of copolymer (ε-CL:M_{SeSe}=90:10) under 50 mM GSH. (b)The turbidity variation of the copolymer (ε-CL:M_{SeSe}=90:10) micelle conducted by redox reactions at 37 ^{o}C.

3. References

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