

Supplementary Information

Diselenide Covalent Chemistry at the Interface: Stabilizing Asymmetric Diselenide-containing Polymer via Micelle Formation

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S1 Materials

Selenium powder, styrene, (1-Bromoethyl) benzene, N,N,N',N',N''-pentamethyldiethylenetriamine (PMDETA), copper bromide (CuBr) and Sodium borohydride were purchased from Aladdin Chemical Reagent Co. Ltd. Dibenzyl diselenide ((BnSe)₂) were purchased from TCI. Poly (ethylene glycol) methyl ether (average M_n= 1000, 2000, 5000) were products from Sigma-Aldrich Co. LLC. Tosyl chloride, tetraethylene glycol and all deuterated solvents were purchased from J&K Chemical. All other organic solvents used in this study were analytical-grade products from the Beijing Chemical Reagent Company, Beijing, China. Dialysis bags (Molecular weight cutoff 5KDa and 1000KDa) were purchased from Spectrum Laboratories, Inc.

S2 Instruments and methods

The ¹H NMR and ⁷⁷Se NMR spectra were recorded on a BRUKER AVANCE III HD 400 (400 MHz) spectrometer. Electrospray ionization mass spectrometry (ESI-MS) spectra were measured on a LTQ LC/MS apparatus. Gel permeation chromatography (GPC) measurements were performed on a breeze system, Waters Corporation (Styragel[®] Columns), using polystyrene as a standard and dimethyl formamide (DMF) as an eluent. Dynamic light scattering (DLS) tests were measured on a Malvern 3000HS Zetasizer at 25 °C using a monochromatic coherent He-Ne laser (633 nm) as the light source. Transmission electron microscopy (TEM) images were recorded using a JEM-2010 microscope with an accelerating voltage of 80 kV. Fluorescence spectra was obtained from a Hitachi F-7000 spectrofluorometer. Pendant Drop tests were performed on a Drop Shape Analyzer (DSA30S, KRUSS, GmbH). All the light irradiations were conducted under a light bulb with the intensity of 8500 Lux unless otherwise stated.

S3 Experiments and results

3.1 Synthetic procedures

The synthetic route of di-(tetraethylene glycol) diselenide (HOEG4Se)₂ were shown on Fig. S1(A). First 1.0017 g (0.0250 mol) NaOH, 3 mL deionized water, 22 mL (0.1274 mol)

tetraethylene glycol and 3 mL THF were put into a 100 mL flask in sequence. Then 3.0040 g (0.0158 mL) Tosyl chloride were dissolved in 8 mL THF and dropwisely added into the flask within 30min. The reaction was performed on room temperature. After 6h 80 mL deionized water were poured into the flask to quench the reaction. The mixture was extracted by 150 mL CH₂Cl₂ in total for three times and washed with 900 mL saturated NaCl solution in total for six times. After drying by anhydrous sodium sulphite, the solvent was evaporated to obtain a colorless oil-like liquid (HOEG4OTs, 3.5041g). The crude product was directly used without further purification. Yield 63.9%.

In the next step, Se powder 0.3800 g (0.0048 mol) and sodium borohydride 0.1701 g (0.0045 mol) were reacted with water (5 mL) for 30 minutes in nitrogen atmosphere to obtain disodium diselenide. THF solution of HOEG4OTs (1.5200 g, 0.0044 mol) was then added under nitrogen flow and reacted at 50 °C overnight. The product was purified by column chromatography using a 20:1 mixture of CH₂Cl₂ and methanol as eluent. At last 0.3436 g golden oil-like liquid was obtained. ESI-MS and NMR results are shown on Figure S1(B), (C), (D). Yield 30.7%.

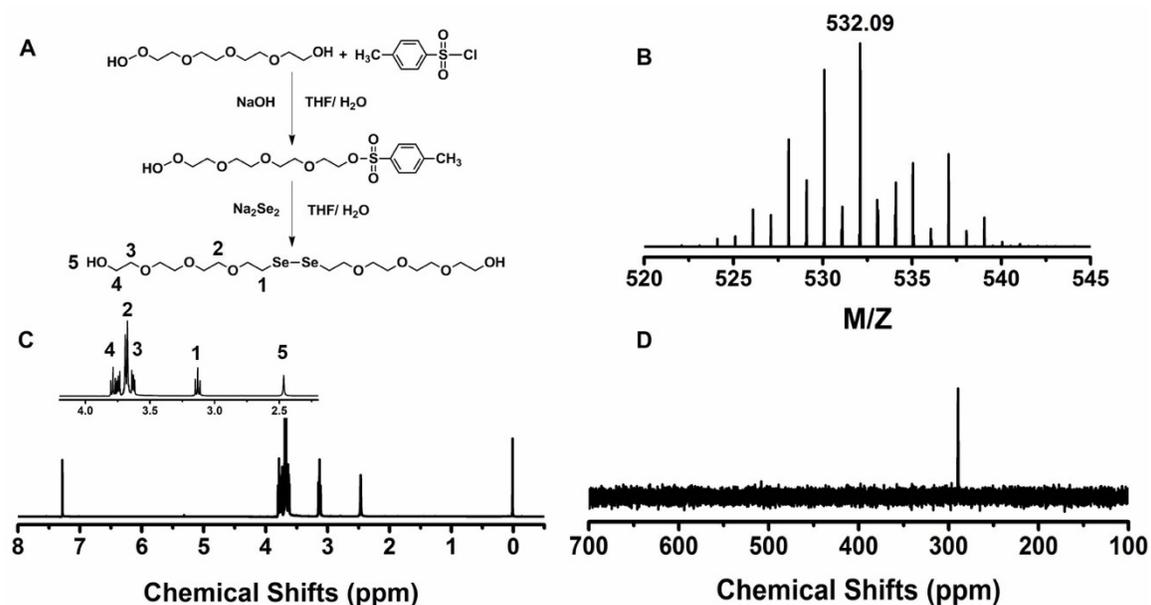


Figure S1 Synthetic procedure and NMR, ESI-MS results of (HOEG4Se)₂. (A) Synthetic procedure of (HOEG4Se)₂. (B) ESI-MS result of (HOEG4Se)₂. Calc. (M⁺ = 514.06), obsvd. (M+NH₄)⁺ = 532.09. (C) ¹H NMR (400M CDCl₃) of (HOEG4Se)₂. (D) ⁷⁷Se NMR (CDCl₃) of (HOEG4Se)₂.

The synthetic route of di- (poly (ethylene glycol) methyl ether) diselenide (mPEGSe)₂ (average M_n= 4000 and 2000) were shown on Figure S2(A). 0.2000 g NaOH, 2.5 mL H₂O, 2.0000 g mPEG (average M_n= 2000) and 20 mL THF were put into a 100 mL flask in sequence. Then 1.9064 g tosyl chloride (10 equivalence) were dissolved in 5 mL THF and dropwisely added into the flask within 30min. The reaction was performed on room temperature for 24h. After the reaction the solvents were removed and the obtained substance was re-dissolved in dry CH₂Cl₂. The salts generated from reaction were removed after a simple silica gel column using a 10:1 mixture of CH₂Cl₂ and methanol as eluent. The obtained clear solution was concentrated and precipitated in cold diethyl ether four times. The crude product was directly used without further purification. NMR and GPC results are shown on Figure S2(C), (D), (E), (F). Yield 86.9% and 82.4%, respectively for (mPEGSe)₂ (average M_n= 4000 and 2000).

The synthetic route of di- (poly (ethylene glycol) methyl ether) diselenide (mPEGSe)₂ (average M_n= 10000) were shown on Figure S2(B). 2.0000 g mPEG (average M_n= 5000) was previously dried by azeotropic distillation with toluene. Then 10 mL CH₂Cl₂ was added to dissolve mPEG and the bottle was quickly sealed with a rubber plug to prevent from moisture. 0.7626 g tosyl chloride was dissolved in 6.7 mL dry pyridine and carefully injected into the bottle. The reaction was performed on room temperature for 24h. After the reaction the solvents were removed and the obtained substance was re-dissolved in dry CH₂Cl₂. The product was purified by column chromatography using a 12:1 mixture of CH₂Cl₂ and methanol as eluent and precipitated in cold diethyl ether. Yield 82.1%.

In the next step, Se powder 0.1580 g and sodium borohydride 0.0378 g were reacted with ethanol (5 mL) for 30 minutes in nitrogen atmosphere to obtain disodium diselenide. H₂O solution of mPEGOTs (1.0000 g) was then added under nitrogen flow and reacted at 50 °C for 24h. The product was purified by column chromatography using a 10:1 mixture of CH₂Cl₂ and Methanol as eluent and precipitated in cold diethyl ether. At last 0.2841 g white powder was obtained. NMR and GPC results are shown on Figure S2(G), (H). Yield 28.4%.

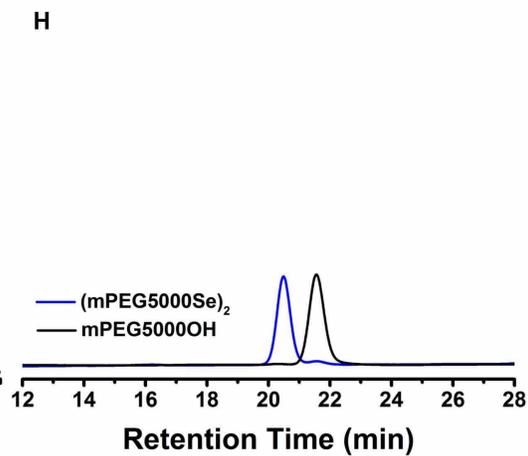
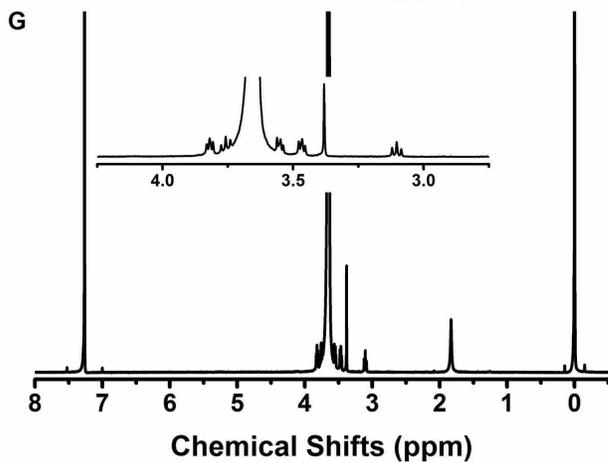
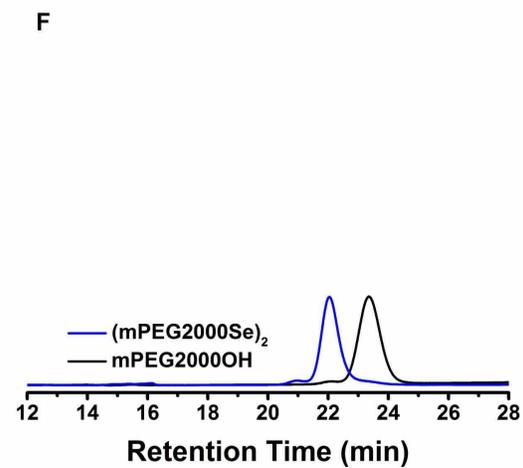
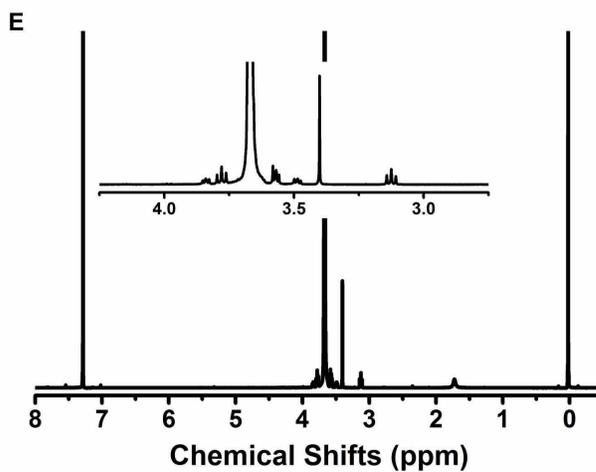
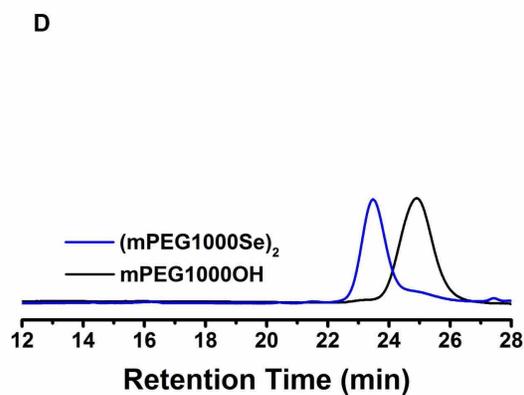
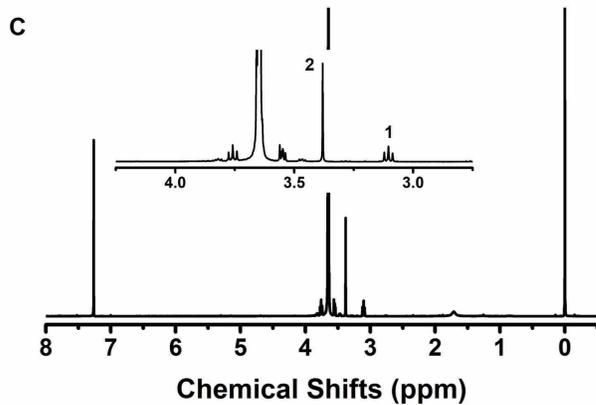
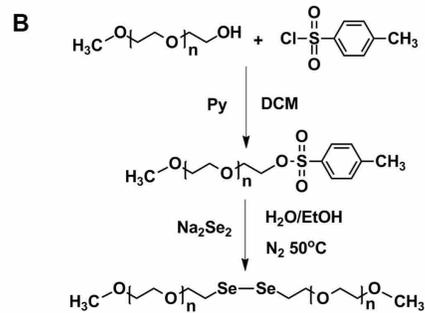
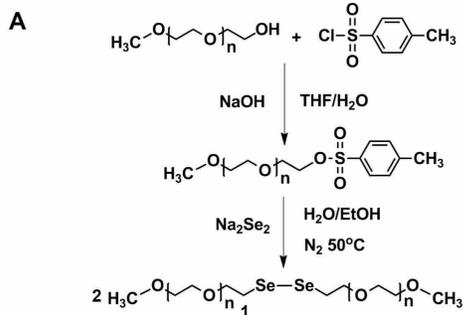


Figure S2 Synthetic procedure and NMR, GPC results of (mPEGSe)₂. (A) Synthetic procedure of (mPEGSe)₂ (average M_n= 4000 and 2000). (B) Synthetic procedure of (mPEGSe)₂ (average M_n= 10000). ¹H NMR (400M CDCl₃) of (mPEG1000Se)₂ (C), (mPEG2000Se)₂ (E), (mPEG5000Se)₂ (G). GPC (DMF as eluent) of (mPEG1000Se)₂ (D), (mPEG2000Se)₂ (F), (mPEG5000Se)₂ (H).

The synthetic route of di-(polystyrene) diselenide (PSSe)₂ was shown on Figure S3(A). Bromine ended polystyrene (PSBr) was prepared via ATRP method^{s1} and directly used after purification. Specifically, the formula for preparing PSBr was [styrene]:[PEBr]:[CuBr]:[PMDETA]= 100:1:1:1. The solution was deoxygenated by three standard freeze–pump–thaw cycles and then reacted for 6h at 90 °C. The GPC result showed that the M_n and M_w of PSBr were 5100 Da and 5500Da, respectively. And the PDI of PSBr was 1.08. In the next step, Disodium diselenide ethanol solution was prepared following the procedure above and DMF solution of PSBr (0.5000 g) was added and reacted at 50 °C overnight. The disodium diselenide was 10 equal to PS-Br for a complete yield of (PSSe)₂. After reaction, solvents were evaporated and dry THF was used to dissolve the product. The undissolvable substance like salts and selenium powder were removed by filtration. The clear solution was dropwisely added into methanol to obtain faint yellow powder (PSSe)₂. The product was further purified by precipitation for three times. NMR and GPC results are shown on Figure S3(B), (C). The GPC result showed that the M_n and M_w of (PSSe)₂ were 9300 Da and 10000Da, respectively. And the PDI of (PSSe)₂ was 1.07. Yield 74.4%.

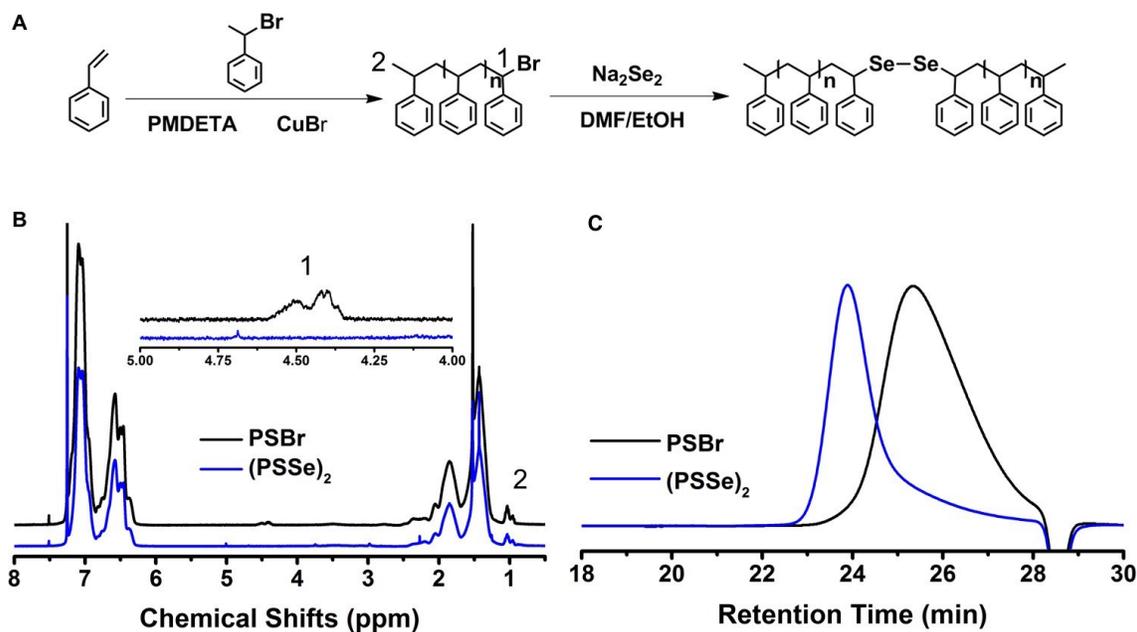


Figure S3 Synthetic procedure and NMR, GPC results of $(PSSe)_2$. (A) Synthetic procedure of $(PSSe)_2$. (B) 1H NMR (400M $CDCl_3$) of $(PSSe)_2$. (C) GPC (DMF as eluent) of $(PSSe)_2$ $M_w=10$ KDa, $M_n=9300$ KDa, PDI=1.07.

3.2 Diselenide metathesis

For small molecule system HOEG4SeSeBn, 15 mM of $(HOEG4Se)_2$ and 15 mM of $(BnSe)_2$ were dissolved in 0.5 mL CD_2Cl_2 in a 1.5 mL vial. The vial was then put under light bulb with intensity of 8500 Lux for three hours to reach an equilibrium. For macromolecule system mPEG5000SeSePS, 0.5 mM $(mPEG5000Se)_2$ and 0.5 mM $(PSSe)_2$ were dissolve in 0.5 mL CD_2Cl_2 in a 1.5 mL vial. The vial was then put under the same light bulb as above. In the meantime, 1H NMR spectra was used to monitor the kinetics of the reaction.

3.3 Preparation of assemblies.

In a standard operation of preparing mPEG5000SeSePS assemblies, 5 mg $(mPEG5000Se)_2$ and 5 mg $(PSSe)_2$ were dissolved in 1 mL THF and irradiated for 3h to reach metathesis equilibrium. Then polymer solution was dropwisely added into 10 mL deionized water under sonication within 10 mins. The turbid mixed solution was then dialyzed against deionized water in a dialysis bag (Molecular weight cutoff 5KDa) for 24h to remove THF completely. As shown in Figure S4, the obtained micelle solution showed

an obvious Tyndall effect which implied the micelle solution formation. The final obtained micelle solution was stored in refrigerator for further usage. The preparation of mPEG1000SeSePS and mPEG2000SeSePS were similar to mPEG5000SeSePS.

Before the light stability test, the micelle solution was further dialyzed against deionized water in a dialysis bag (Molecular weight cutoff 1000KDa) for 48h to completely remove the unreacted (mPEG5000Se)₂. After the dialysis, 5 mL of the micelle solution was freeze-dried for GPC and NMR test. The rest of the solution was stored in refrigerator for further usage.



Figure S4 Photograph of Tyndall effect of the micelle solution.

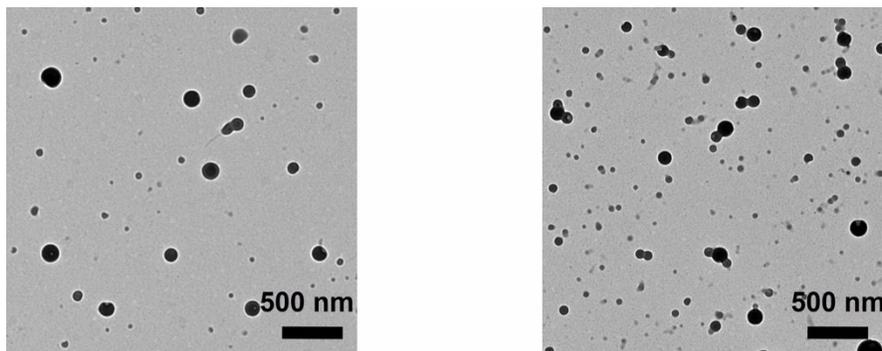


Figure S5 TEM images of micelle solutions mPEG1000SeSePS (left) and mPEG2000SeSePS (right).

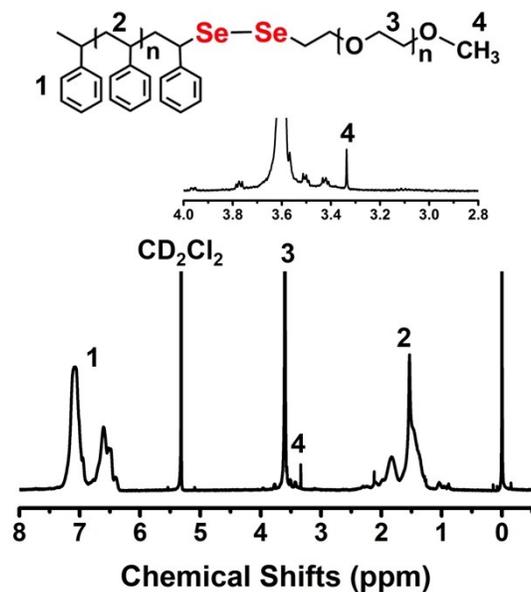


Figure S6 ^1H NMR (400M CD_2Cl_2) NMR spectra of mPEG5000SeSePS micelle after freeze-drying.

3.4 Determination of critical micelle concentration (CMC) of assemblies.

Firstly 2 mL of micelle solution samples were freeze-dried in order to calculate the concentration of micelle solutions. The as-prepared concentrations of mPEG5000SeSePS, mPEG2000SeSePS and mPEG1000SeSePS were 0.42 mg/mL, 0.27 mg/mL and 0.23 mg/mL. Then The CMC multiplier “m” were measured by recording the concentration-dependent count rates in the DLS measurement of the micelle suspensions. The final CMC were calculated by equation $\text{CMC} = m \times C_0$. The CMC of mPEG5000SeSePS, mPEG2000SeSePS, mPEG1000SeSePS were 6.3×10^{-4} mg/mL, 1.8×10^{-4} mg/mL and 7.6×10^{-5} mg/mL respectively.

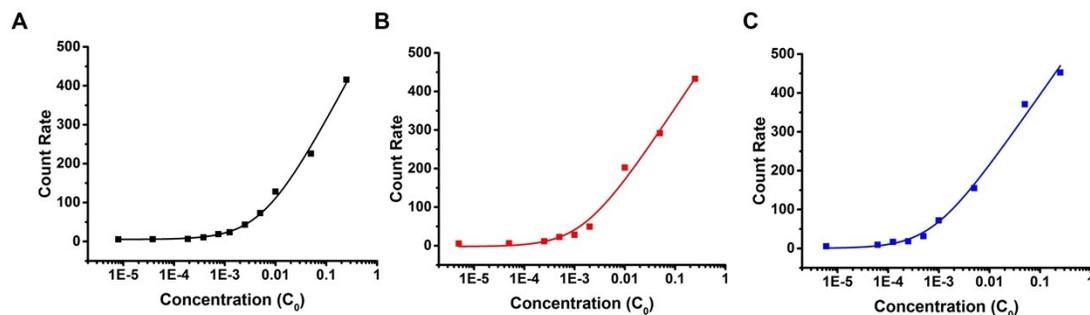


Figure S7 CMC of the micelle suspensions determined by recording the concentration-

dependent count rates in DLS. A: mPEG5000SeSePS. B: mPEG2000SeSePS. C: mPEG1000SeSePS.

3.5 Photographs of the redox-responsive micelle solutions.

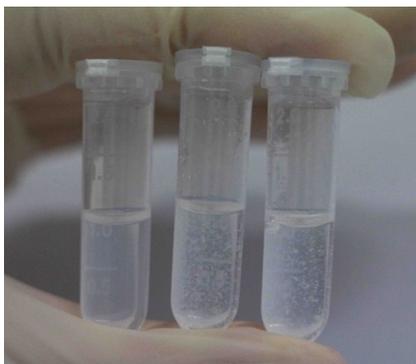


Figure S8 Photographs of the redox-responsive micelle solutions. (Control, H₂O₂ and GSH groups from left to right)

3.7 Micelle stability at different concentrations

The micelle suspension was diluted by 10 and 100 folds, named 0.1C₀ and 0.01C₀ respectively. They were then exposed to visible light irradiation for 12h. After that, DLS measurements were recorded.

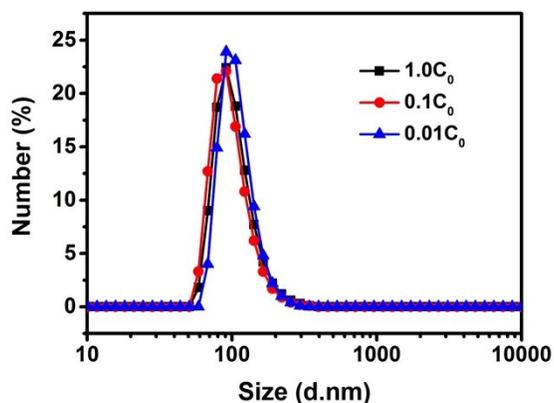


Figure S9 DLS results of mPEG5000SeSePS assemblies at different concentrations under visible light irradiation.

Reference

1s J. S. Wang, K. Matyjaszewski, *J. Am. Chem. Soc.* **1995**, 117, 5614-5615