Electronic Supplementary Material (ESI) for Polymer Chemistry

Controlled Cross-Linking Strategy: from Hybrid Hydrogels to Nanoparticle Macroscopic Aggregates

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1. Materials

(3-Mercaptopropyl) trimethoxysilane (97%, J&K Chemical), 2,2'-dithiodipyridine (98%, Energy Chemical), poly(ethylene glycol) methyl ether (PEG-OH, M_n = 750 g/mol, Alfa Aesor), glutathione (GSH, 99%, J&K Chemical), Methanesulfonyl chloride (98%, Beijing Chemical Works), potassium thioacetate (99%, Energy Chemical), triethylamine (TEA, 99%, Beijing Chemical Works), methanol, chloroform, hydrochloric acid and acetonitrile (Reagent Grade, Beijing Chemical Works), tetrahydrofuran (THF) and dichloromethane (DCM) were dried according to the typical procedures described in the literature.

2. Characterizations

Infrared spectra were recorded on an Excalibur Series FT-IR spectrometer (DIGILAB, Randolph, MA) by drop-casting sample films on a KBr plate from polymer solution in chloroform with subsequent drying by infrared lamp. All NMR spectra were obtained on a Bruker DRX-400 spectrometer. X-ray diffraction (XRD) data were obtained with a graphite monochromatic device and Cu Kα radiation α= 0.15406 nm) on the Rigaku D / max 2500, operated in the θ : 2θ mode primarily in the 3-60 ° (2θ) range and step-scan of 2θ = 0.04 °. The tube voltage was 40 kV, and the tube current was 200 mA. MALDI-TOF-MS measurements were carried out using a Bruker BIFLEX III equipped with a 337 nm nitrogen laser. Field emission scanning electron microscopy (SEM) images were obtained at acceleration voltage of 5 kV on a JSM-6700F microscope (JEOL, Japan). The samples were sputter-coated with a thin layer of Pt for 60 s to make the sample conductive before testing. Rheological

characterization was performed by using a Thermo Haake. Briefly, a small amount of aqueous solution (0.5 mL) was pipetted on the same holder (MP30 steel) and a parallel steer plate (30 mm) was loaded sample. The gap between the sample holder and the plate was maintained at 0.5 mm for the measurement performed. Maintaining a constant sheer force (0.3 Pa), the sample was measured at 25 ^{o}C using an oscillatory frequency of 1.0 rad s^{-1}. The differential scanning calorimetry (DSC, Mettler Toledo-822e) measurement was performed on a Perkin–Elmer Pyris-1 thermal analysis apparatus in a dry nitrogen atmosphere. The instrument was calibrated with standard indium. The sample (about 5 mg in weight) was heated from 30 to 270 ^{o}C and the thermogram was recorded using the heating rate of 10 ^{o}C /min. The hardness measurement was performed on a QualiRock Digital Rockwell Hardness Tester. The test piece was placed perpendicular to the indenter shaft, and the distance among the indentations was 4 d (‘d’ is the diameter of indentation). The density of the common glass and POSS aggregate were determined according to the method described below. Briefly, at 30 ^{o}C the density bottle was filled with ethanol (density ρ_e) and weighed (W_1). Then a sample (weight W_s) was immersed into the density bottle. The density bottle was kept at 30 ^{o}C again for 30 min; all the overflowed ethanol was cleaned away carefully. Then the density bottle was weighed again (W_2). The average density of whole sample (D_w) was calculated as follows:

$$D_w = W_s/V_s, \text{ wherein, } V_s = (W_1-W_2+W_s) / \rho_e.$$

3. Synthesis of PEG-SH

PEG-OH (15 g, 20 mmol) and triethylamine (8 mL, 100 mmol) were dissolved in anhydrous DCM (200 mL) and cooled down to 0 ^{o}C for 30 min. Methanesulfonyl chloride (14 mL, 100 mmol) was then added to the mixture. After stirring for 8 h at room temperature, the mixture was quenched with distilled water (150 mL), and extracted with DCM (3×50 mL). Then the combined organic layers were washed with distilled water (3×50 mL) and dried over $MgSO_4$. The final product, PEG-SO_3CH_3 (16.4 g, yield: 99%), was obtained in vacuo.

As-synthesized PEG-SO_3CH_3 (16.4 g, 20 mmol) and potassium thioacetate (7.07 g, 50 mmol) were dissolved in anhydrous THF (100 mL) under a nitrogen atmosphere. The reaction mixture was degassed three times with nitrogen and then heated to 60 ^{o}C. After stirring for 5 h, the mixture was quenched by DI water and extracted with

chloroform. The chloroform layer was collected, and residual water was removed with $MgSO_4$. The final product, PEG-$SCOCH_3$ (13.6 g, yield: 85%), was obtained in vacuo.

As-synthesized PEG-$SCOCH_3$ (13.7 g, 16.8 mmol) was dissolved in methanol under a nitrogen atmosphere and degassed three times. Concentrated hydrochloric acid (0.8 mL) was added to the solution. The mixture was refluxed at 80 ^oC for 24 h, quenched with DI water, and then extracted with chloroform. The chloroform layer was collected, and residual water was removed by $MgSO_4$. The final product, PEG-SH (10.2 g, yield: 80%), was obtained in vacuo.

4. Synthesis of Octa (3-Mercaptopropylsilsesquioxane), POSS-$(SH)_8$

Typically, 50 mL of methanol, 10 mL of acetonitrile, and 8 mL of concentrated hydrochloric acid were added in a 100 mL flask and mixed to get a heterogeneous solution. Then, (3-Mercaptopropyl) trimethoxysilane (8.5 g, 40 mmol) was added carefully to the solution. The mixture was refluxed at 80 ^oC for 5 days to produce white precipitates. The crude products were obtained after filtration, washing with cold MeOH and drying. Then recrystallization from acetone afforded the product, POSS-$(SH)_8$, as white solids (0.89 g, yield: 18%).

5. Synthesis of 2,2'-dithiodipyridine activated thiol-terminal PEG (PEG-SS-2TP)

Briefly, PEG-SH (10.2 g, 13.3 mmol) was dissolved in 50 mL of methanol and added dropwise to a stirred solution of 2, 2'-dithiodipyridine (8.8 g, 50 mmol) dissolved in 40 mL of methanol. The reaction was kept under an argon atmosphere to minimize free thiol oxidation. After 3 days, the mixture was concentrated under reduced pressure. The product was precipitated by addition of 50 mL of cold ether and purified by redissolving in 10 mL of methanol and precipitating into 50 mL of cold ether 3 times to give a white powder. The final product, PEG-SS-2TP (9.31 g, yield: 80%), was obtained in vacuo.

6. Synthesis of POSS-$(SS\text{-}PEG)_8$

POSS-$(SH)_8$ (0.89 g, 0. 88 mmol) was dissolved in 50 mL of chloroform and added

dropwise to a stirred solution of PEG-SS-2TP (9.31 g, 10.6 mmol) dissolved in 50 mL of chloroform. The reaction was kept under nitrogen atmosphere to minimize free thiol oxidation. The reaction mixture was stirred at 40 ^{o}C for 6 days and then concentrated by rotary evaporation to yield a viscous liquid. The product, POSS-(SS-PEG)$_8$ (4.2 g, yield: 68%), was purified by ultrafiltration (MWCO 2000) and collected after freeze-drying.

7. Preparation of the loose, compact hydrogels and POSS aggregate

50 mg of POSS-(SS-PEG)$_8$ was dissolved in 440 μL of deionized water and 10 μL of 5 M NaOH was added to adjust pH to 12. Then 5 mg of cysteamine was mixed to trigger the reaction. After ultrasonic processing and standing for ~10 min, the solution slowly became milky and turned into the loose hydrogel absorbing all water inside. The hydrogel further shrank into the compact hydrogel if aging longer. The stable loose and compact hydrogels can be obtained by neutralization of hydrogel system by 2 mL of saturated NH_4Cl solution at a predetermined time. If aging enough time like 10 days, the compact hydrogels turned into the glass-like POSS aggregate.

8. Measurement of swelling ratio

Four samples were prepared for measurement. The resulted hydrogels and aggregate after basification of 10 wt % POSS-(SS-PEG)$_8$ solution for 1, 8, 24, and 240 h with addition of cysteamine for testing. The samples were equilibrated in distilled water at 25 ^{o}C for 24 h, and water on the surface was removed by filter paper. The weights of the swollen products (W_s) were recorded. All of the dry products were obtained after freeze-drying for 48 h, and their weights were recorded as W_d. Swelling ratio (SR) is defined as follows:

$$SR = (W_s - W_d) / W_d$$

Where W_s and W_d are the weight of swollen and dry gels.

9. Degradation tests of the hybrid hydrogels and aggregate

The in vitro degradation tests of the hybrid hydrogels and POSS aggregate were evaluated in H_2O and $CHCl_3$ containing 10 mM GSH, respectively. Figure S8 demonstrated the hydrogels and the aggregate can decompose under treatment of

GSH, but the degradation rate is dependent on the medium and structures of the products. Due to high hydrophobicity of POSS cores, the dense and hydrophobic inside domains prevent the access of GSH when GSH was dissolved in water, so the composition only took place on the surface of the hybrid hydrogels and POSS aggregate step by step, resulting in low degradation rate and remain of some whole particles but smaller sizes as indicated in Fig. S8B. Chloroform is a good solvent both for POSS cores and PEG shells, and GSH in chloroform is easier to access inside domains to degrade the hydrogels quickly, even for the high hydrophobic aggregate as shown in Fig. S8C.

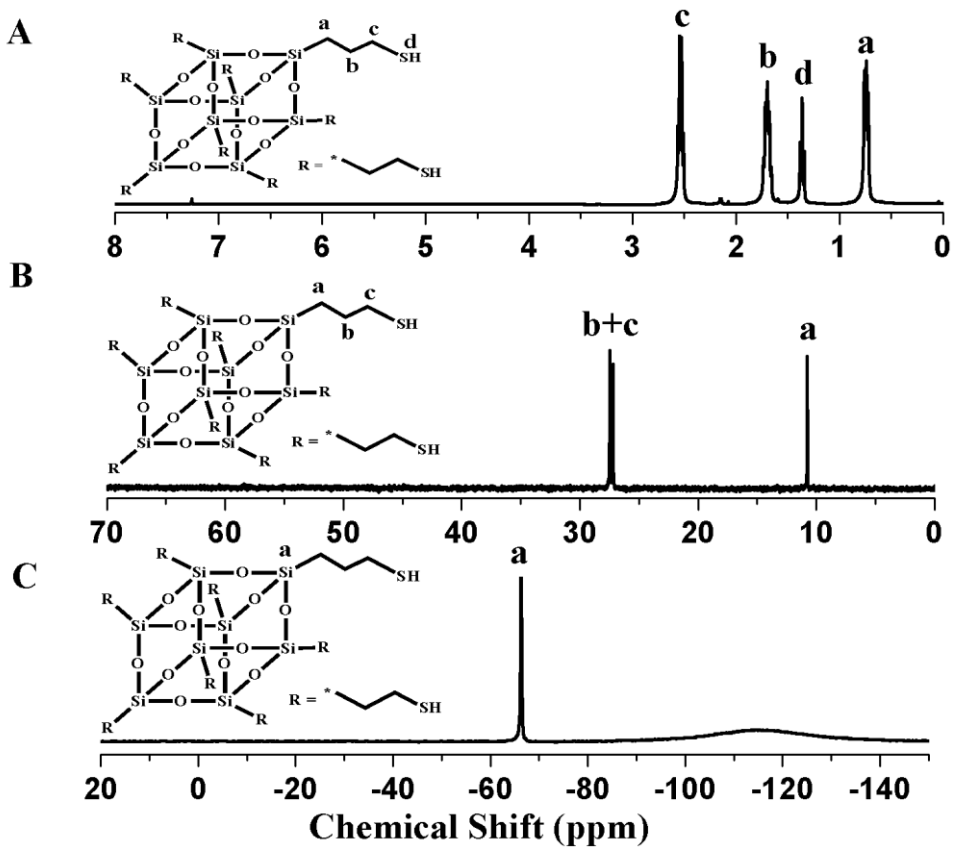

Fig. S1 (A) ^{1}H, (B)^{13}C and (C) ^{29}Si NMR spectra of POSS-$(SH)_8$ in $CDCl_3$.

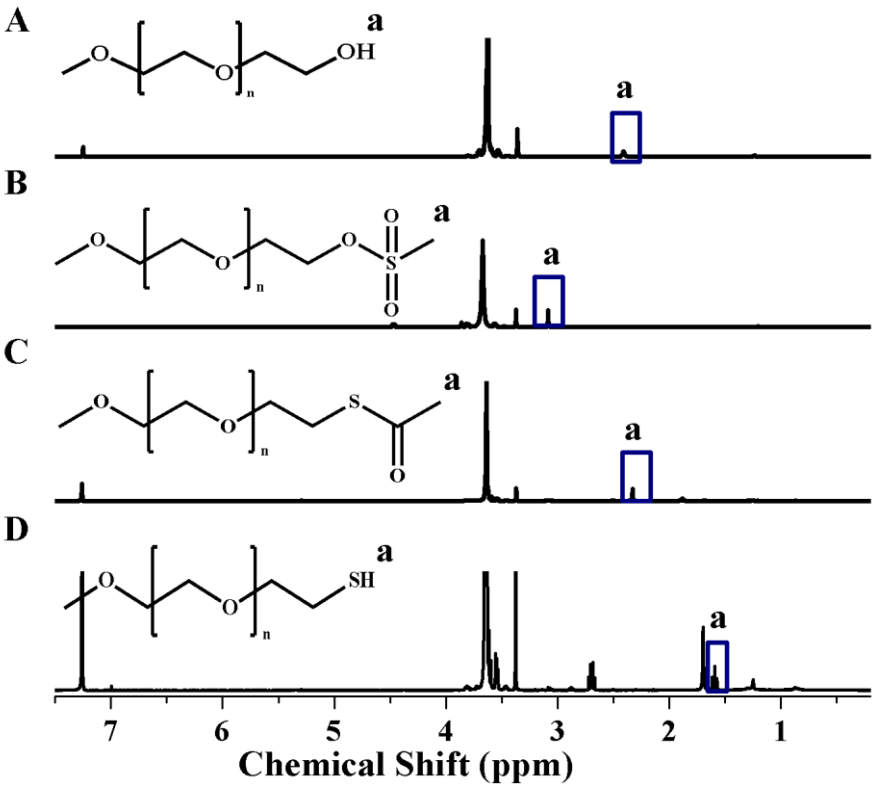

Fig. S2 Comparison of ^{1}H-NMR spectra of (A) PEG-OH, (B) PEG-SO_3CH_3, (C) PEG-$SCOCH_3$ and (D) PEG-SH in $CDCl_3$.

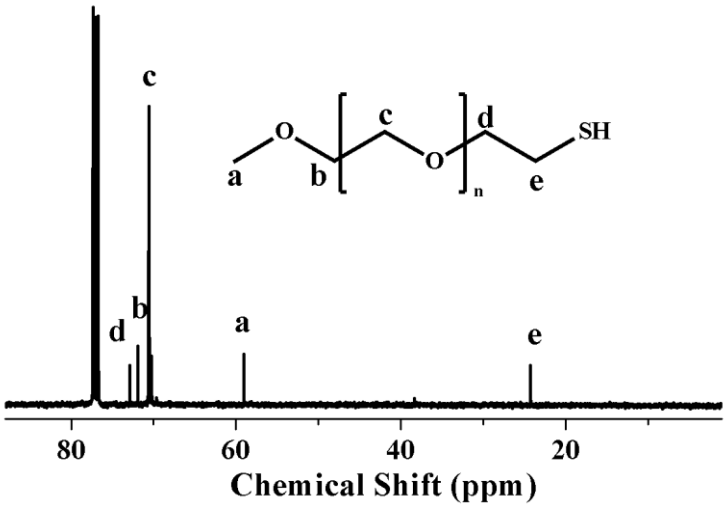

Fig. S3 ^{13}C NMR spectrum of PEG-SH in $CDCl_3$.

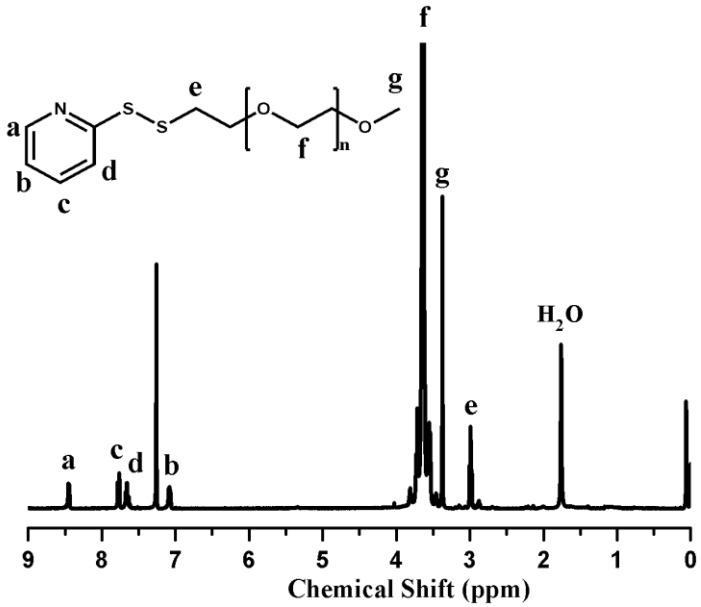

Fig. S4 ^{1}H NMR spectra of PEG-SS-2TP in $CDCl_3$.

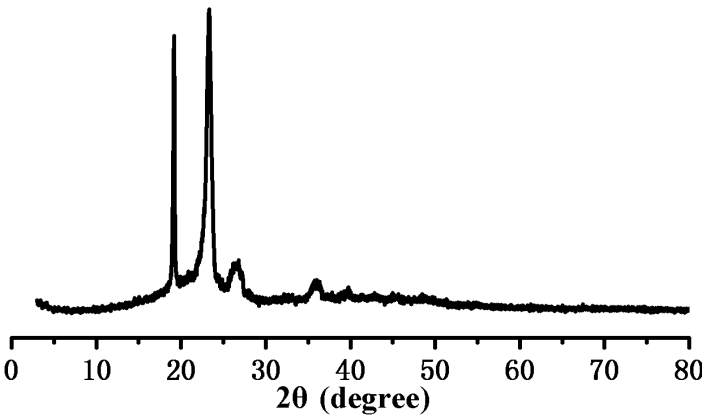

Fig. S5 XRD pattern of PEG-SH.

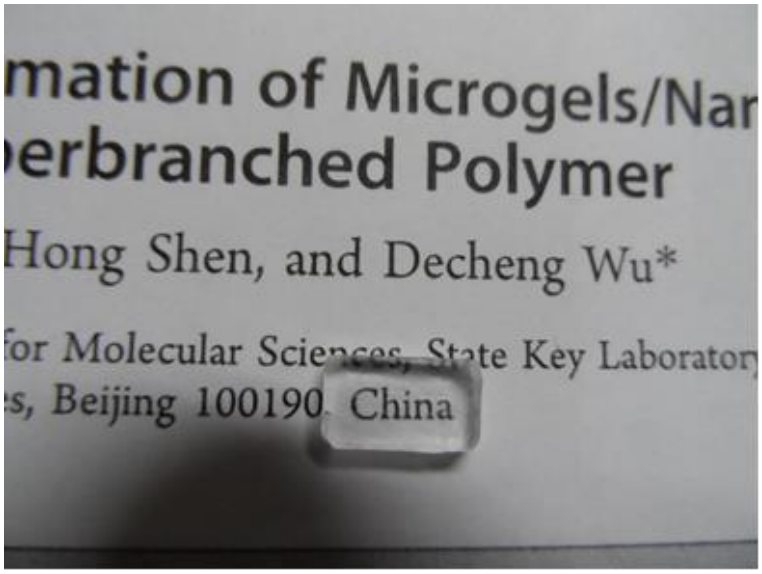

Fig. S6 Photographs of the POSS aggregate.

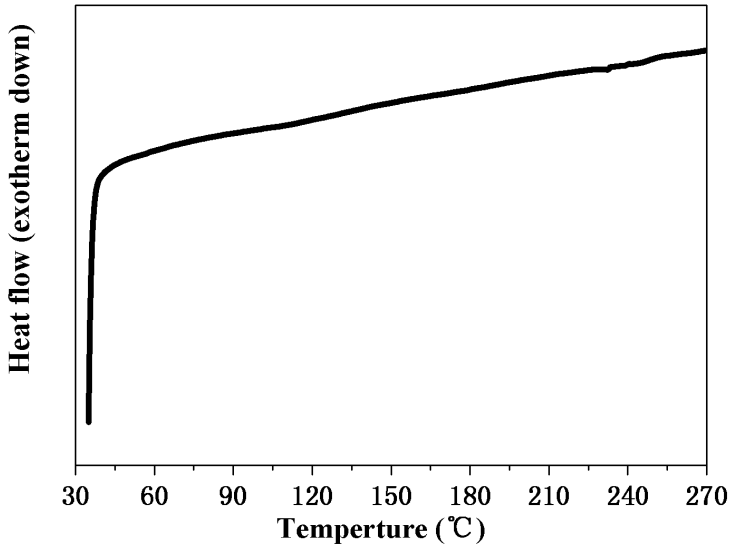

Fig. S7 DSC curve of the POSS aggregate.

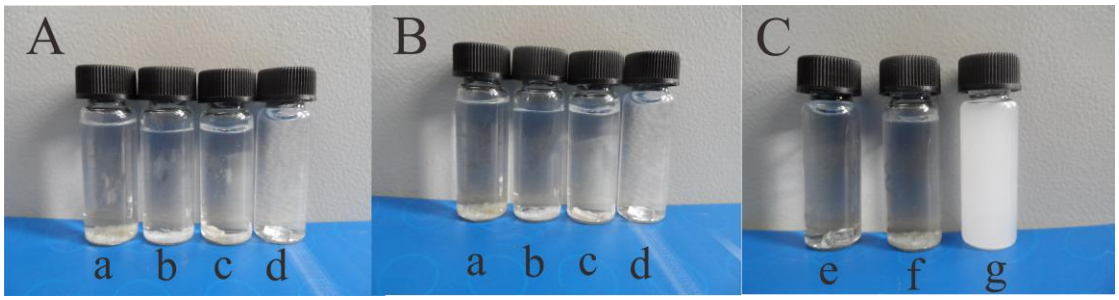

Fig. S8 Comparison of photographs of the hybrid hydrogels and POSS aggregate after cross-linking of (a) 1, (b) 8, (c) 24, and (d) 240 h in water containing 10 mM GSH for (A) 0 and (B) 360 h. (C) Comparison of photographs of the POSS aggregate after cross-linking of 240 h in $CHCl_3$ containing 10 mM GSH for (e) 1, (f) 24, and (g) 168 h.