Supporting Information

In-situ generating redox responsive and acid labile nanogels/microgels simply *via* directly adding water into polymerization system

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Experimental section

Materials. *N*,*N*'-dimethyldipropylenepropanetridiamine (DMDPTA, Aldrich, 99%), *N*,*N*'-methylenebisacrylamide (MBA, Sigma-Aldrich, 99%), 1,6-hexanediol diacrylate (HDDA, Alfa Aesar, 98%), 2-methoxy propene (Alfa Aesar, 98%), dithiothreitol (DTT, Sigma, ≥98%), 3-(4,5-dimethylthiazol-2-yl)- 2,5-diphenyltetrazolium bromide (MTT, Solarbio), Dulbecco's modified Eagle's medium (DMEM, Hyclone), fetal bovine serum (FBS, Hyclone), branched polyethylenimine (bPEI, *M*_w~25000, Aldrich) were used as received. Ethyl trifluoroacetate was purchased from Shanghai ZhuoRui Chemical Co., LTD. Acryloyl chloride was distilled in the presence of hydroquinone before use. 2-Aminoethanol, molecular sieves (5 Å), cysteamine hydrochloride, sodium hydroxide, dichloromethane, triethylamine, ethyl acetate, methanol, n-hexane, diethyl ether, potassium carbonate and anhydrous sodium sulfate were purchased from Sinopharm Chemical Reagent Co., LTD and used as received. Water was deionized to 18MΩ•cm resistivity using nanopure system. Synthesis of control polymer without disulfide bond. Acid labile monomer N,N'-((propane-2,2-diylbis(oxy))bis(ethane-2,1-diyl))diacrylamide (270.7 mg, 1.0 mmol) was added into a vial containing N,N'-dimethyldipropylenepropanetridiamine (318.0 mg, 2.0 mmol) in methanol/water mixed solvents (4.60 mL, 5/5, v/v). After the mixture has been polymerized for 96 h at 50 °C, DMDPTA (247.6 mg, 1.5 mmol) was added to terminate vinyl groups, and polymer obtained has molecular weight of 15600.

Characterizations. ¹H NMR was recorded on a Bruker AV 300 (300 MHz) instrument. Molecular weight and molecular weight distribution were determined by gel permeation chromatography (GPC) performed with three linear Styragel columns and a Waters 2414 differential refractive index (RI) detector (flow rate of 1.0 mL/min, DMF as eluent). The cloud points of the polymer solutions were measured using a Beckman DU 640 UV spectrophotometer equipped with a digital temperature controller. Transmission electron microscopy (TEM) was performed on a JEM-2100F field emission transmission electron microscope with an accelerating voltage of 200 KV. Dynamic light scattering (DLS) was carried out on a Malvern Zetasizer Nano ZS90 with a He-Ne laser (633 nm) and 90° collecting optics. The rheological measurements for hyperbranched polymer was performed on a rheometer (TA-AR2000, TA Instruments) to detect evolutions of storage elastic modulus (G') and loss elastic modulus (G'') versus time at different temperatures at a fixed frequency of 10 rad/s.



Figure S1. ¹H NMR spectrum of *N*,*N*'-cystamine bisacrylamide in DMSO-d₆.



Scheme S1. Synthesis of acid-labile bis(acrylamide) monomer.



Figure S2. ¹H NMR spectrum of 2,2,2-trifluoro-*N*-(2-hydroxyethyl) acetamide in CDCl₃.



Figure S3. ¹H NMR spectrum of *N*,*N*'-(2,2'-(propane-2,2-diylbis(oxy)) bis(ethane-2,1-diyl)) bis(2,2,2-trifluoroacetamine) in DMSO-d₆.



Figure S4. ¹H NMR spectrum of 1,1'-(2,2'-(propane-2,2-diylbis(oxy))bis(ethane-2,1-diyl))diurea in CDCl₃.



N,*N*'-((propane-2,2-diylbis(oxy))bis(ethane-2,1-diyl))diacrylamide in acetone-d₆.



Figure S6. ¹H NMR spectrum of the formed hyperbranched polymer in DMSO-d₆.

Pyrene Fluorescence Measurements.

The pyrene stock solution prepared with acetone was added into volumetric flasks, then the acetone was evaporated and subsequently a predetermined amount of the formed hyperbranched polymer stock solutions and water were added to each flask. As a result, the polymer concentrations were ranging from 0.001 to 1 mg/mL and the concentration of pyrene was fixed at 6.0×10^{-7} mol/L. Then the flasks were heating at 50 °C for 40 min. The emission spectra were recorded at 20 °C on a Shimadzu RF-5301PC spectrofluorophotometer with λ_{ex} at 333 nm and a slit width of 5 nm. The obtained curve was fitted by Boltzmann fuction.



Figure S7. I1/I3 ratio in pyrene emission spectra as a function of hyperbranched polymer concentration.



Figure S8. The images of nanogels/microgels formed via adding water to disulfide contained polymerization system at 4 °C and after treated with DDT and HCl, and the images of nanoparticles formed via adding water to polymerization system with disulfide at 4 and 50 °C.



Figure S9. The variations of G' and G" of the hyperbranched polymers without disulfide bond with time at 50 °C. (Oscillatory Frequency $\omega = 10$ rad s⁻¹, Gap= 625 µm).



Figure S10. TEM of nanogels formed at polymer concentration of 0.1 mg/mL.

Synthesis of dibenzyl trithiocarbonate (DBTTC).

Carbon disulfide (4.84 g, 63.73 mmol) was added to a solution of benzyl chloride (6.76 g, 53.64 mmol) in N,N-dimethylformamide (DMF) (80 mL) and stirred at room temperature for about 5 min, then potassium carbonate (K₂CO₃) (7.38 g, 53.5 mmol) was added. After the mixture was stirred at 40 °C for 24 h, the reaction was quenched by pouring into 100 mL ice-water. After being extracted with 3×100 mL of ethyl acetate, the organic layers were dried by anhydrous sodium sulfate followed by evaporating. The crude product was purified by silica gel chromatography using hexane. ¹H NMR (300 MHz, CDCl₃): δ =4.62 (s, 4 H, -CH2-), 7.25–7.35 (m, 10 H, aromatic H).



Scheme S2 Synthesis of dibenzyl trithiocarbonate (DBTTC).

One-pot and *in-situ* generating bioreducible nanogels/microgels simply *via* adding water into RAFT polymerization system. A representative example is as follows: after NIPAM (56.5 mg), BCA (26.0 mg), acid labile monomer (5.0 mg), DBTTC (0.5 mg) and THF (0.5 mL) have been polymerized for 7 h at 60 °C preheated oil for 7 h, 80 mL of water with small amount of triethylamine was added into this polymerization, and the mixture was kept at 60 °C for 40 min, nanogels with ~50 nm *in-situ* generated.

References

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