Supporting Information

Multi-stimuli sensitive supramolecular hydrogel formed by host–guest interaction between PNIPAM-Azo and cyclodextrin dimmers

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Materials.

3-Mercaptopropionic acid, 4-Phenylazophenol, 2-bromoethanol, *N*-isopropyl acrylamide (NIPAM) and DL-Dithiothreitol (DTT) were purchased from Alfa Aesar. Acryloyl chloride and1-hydroxybenzotriazole (HOBT) were purchased from Aladdin. β-Cyclodextrin, *p*-Toluenesulfonyl chloride, azodiisobutyronitrile (AIBN) and *N,N′*-dicyclohexylcarbodiimide (DCC) were purchased from Signopharm Chemical Reagent Co, Ltd, (Shanghai, China). Potassium carbonate (K_2CO_3), triethylamine (TEA), ammonia and all other organic solvents used in this study were analytical-grade products from Kelong Chemical Reagent Co. Ltd. (Chengdu, China). *S,S′*-Bis(α,α′-dimethyl-α′′-acetic acid) trithiocarbonate (CTA) was prepared according

to the literature.[S1] TEA was dried over CaH_2 for 48 h, and then distilled just before use. *N,N*-Dimethylformamide (DMF) was dried by refluxing over P_2O_5 and distilled just before use. Tetrahydrofuran (THF) was dried by refluxing over metallic sodium and distilled just before use.

Synthesis

Synthesis of mono-deoxy-6-(*p*-toIylsulfonyl)-β-cyclodextrin.

β-Cyclodextrin (20.0 g, 17.6 mmol) was dispersed in 180 ml deionized water, and 7 ml NaOH (2.19 g, 54.8 mmol) aqueous solution was added dropwise slowly. The suspension became homogeneous and slightly yellow before the addition of NaOH aqueous solution was completed. *p*-Toluenesulfonyl chloride (3.36 g, 17.6 mmol) in 10 ml of acetonitrile was added dropwise over 4 min, causing immediate formation of a white precipitate. After vigorous stirring for 3 h at room temperature, diluted HCl (1 mol/L) solution was added dropwise until the reaction solution was acidized to pH=8 to terminate the reaction. Product solution refrigerated overnight at 4 ^{o}C then the white precipitate was resulted. The white precipitate was recovered by suction filtration and soaked in diethyl ether (Et_2O) for 48 h to remove the unreacted *p*-Toluenesulfonyl chloride. After recovered by suction filtration, the white precipitate was further purified by recrystallization from deionized water. ^{1}H-NMR (400 Hz, D_2O) 7.3-7.6 (Ar-H), 5.0 and 3.5-4.0 (CD-H), 2.3 (Ph-CH_3)

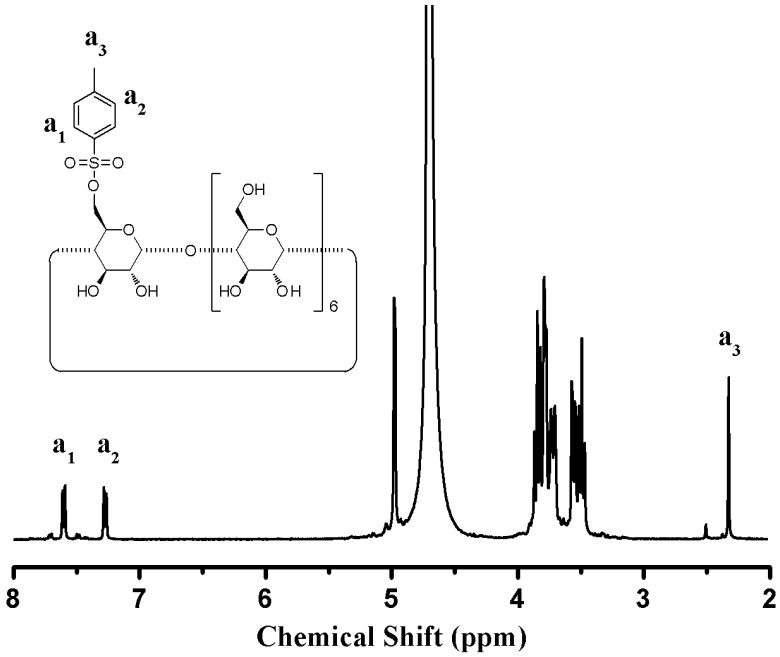

Figure S1. ^{1} H NMR spectrum of mono-Bdeoxy-6-(*p*-toIylsulfonyl)-β-cyclodextrin.

Synthesis of Mono-6-deoxy-6-amino-β-cyclodextrin.

Powdered 6-OTs-β-CD was dissolved in a substantial excess of ammonia at 75 ^{o}C. After stirring for 4 h at 75 ^{o}C, the reaction solution was cooled to room temperature. Added appropriate amount of acetone into the solution, a mass of white precipitate separated out immediately. After recovered by suction filtration, the white precipitate was dissolved in mixed solution of H_2O/CH_3OH (v/v=3:1) and precipitated by acetone. This operation was repeated several times to remove the unreacted 6-OTs-β-CD and ammonia. The white precipitate was recovered by suction filtration and dried at 50 ^{o}C in vacuum for 3 d. ^{1}H-NMR (400 Hz, D_2O) 5.0 and 3.5-4.0 (CD-H), 2.8 and 3.1 (-CH_2-N-),

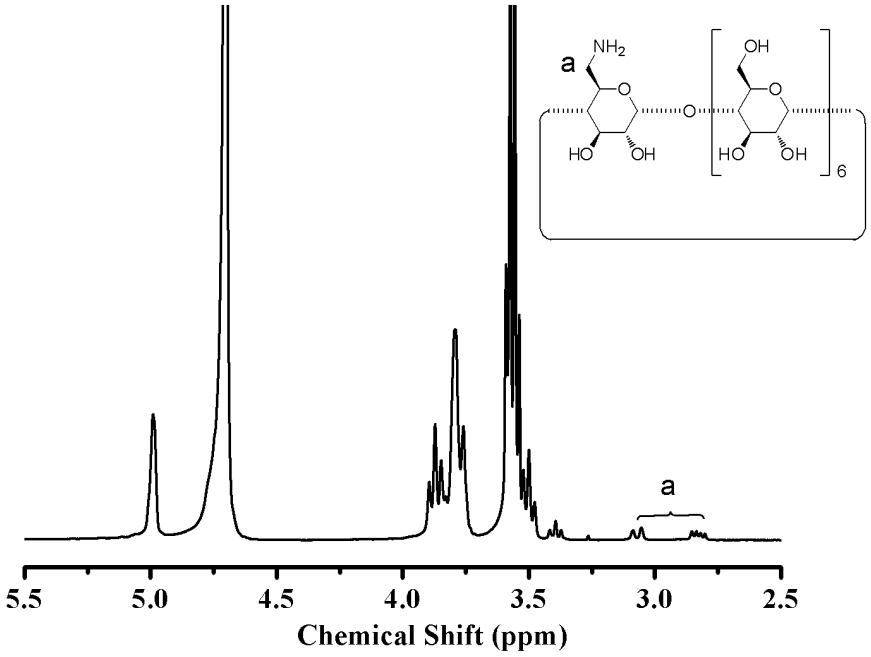

Figure S2. [1] H NMR spectrum of Mono-6-deoxy-6-amino-β-cyclodextrin.

Synthesis of bis(2-carboxyethyl) disulfide.

The 3-Mercaptopropionic acid (3.0 g, 28.3 mmol) was dissolved in 25 ml DMSO. The resulting solution was stirred for 8 h at 80 ^{o}C. The product solution was poured into a tenfold volume of ice-water and after 3 h standing, the precipitated disulfide was collected by filtration. After washing three times with water, the white precipitate was filtered and dried under vacuum. ^{1}H-NMR (400 Hz, DMSO-d_6) 2.9 (-CH_2-COO-), 2.6 (-CH_2-SS-)

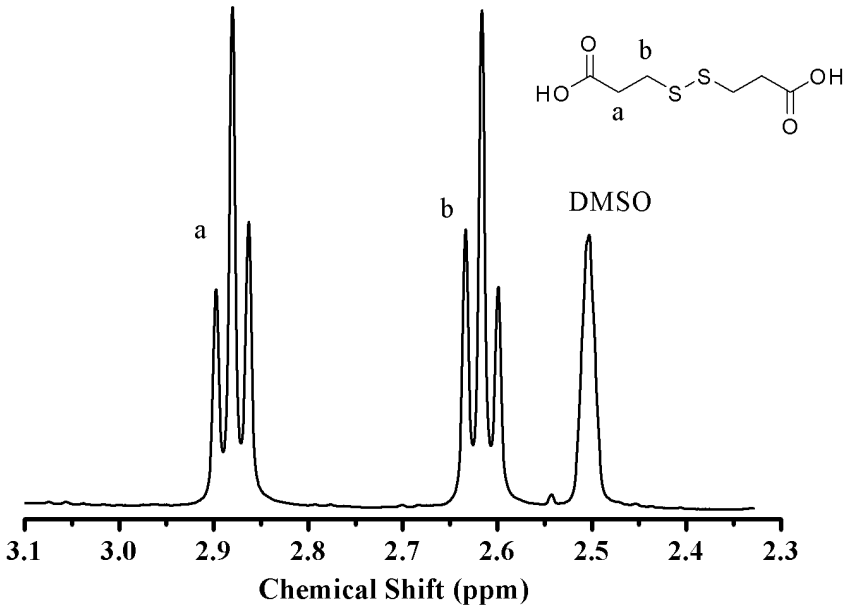

Figure S3. [1] H NMR spectrum of bis(2-carboxyethyl) disulfide.

Synthesis of bis(2-carboxyethyl) disulfide bridged β-CD Dimer.

6-NH_2-β-CD (2.27 g, 2mmol) and bis(2-carboxyethyl) disulfide(0.17 g, 0.8 mmol) were dissolved in 50 ml DMF. After the mixed solution was cooled below 0 °C, DCC (496 mg, 2.4 mmol) and HOBT (324 mg, 2.4 mmol) were added. The reaction solution was stirred at room temperature for 7 d. After the insoluble residues were removed by filtration, the filtrate was poured into acetone (1.5 L), and the precipitate was collected and washed with acetone and then dried under vacuum to give the crude product. The crude product was purified by column chromatography on DIAION HP-20. ^{1}H-NMR (400 Hz, DMSO-d_6) 8.0 (-NH-CO-), 5.6-5.8, 4.9, 4.5 and 3.0-3.9 (CD-H), 2.9 (-CH_2-CO-), 2.6 (-CH_2-SS-)

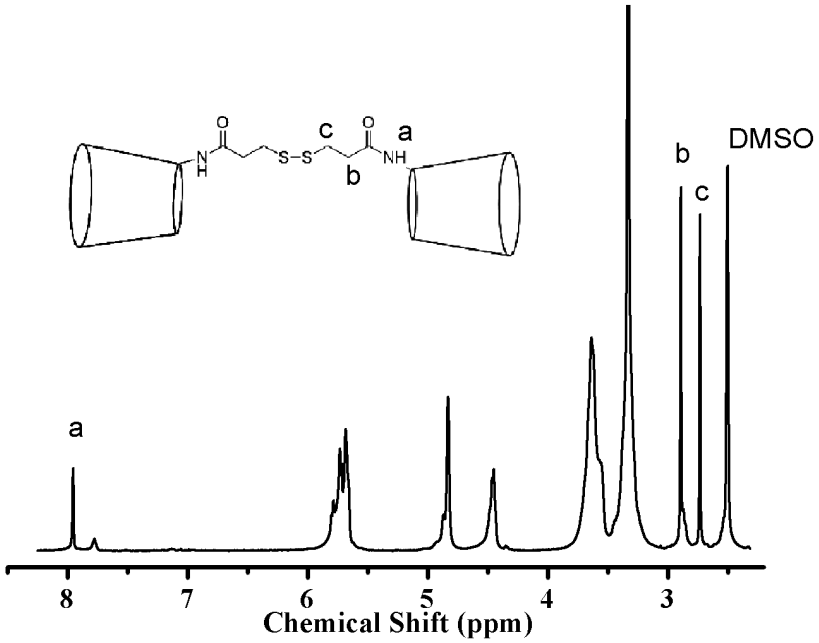

Figure S4. [1] H NMR spectrum of bis(2-carboxyethyl) disulfide bridged β-CD Dimer.

Synthesis of 4-Phenylazophenyl hydroxyethyl ether.

4-Phenylazophenol (1.98 g, 10 mmol), 2-bromoethanol (3.75 g, 30 mmol) and K_2CO_3 (4.14 g, 30 mmol) were dissolved in 25 ml 2-butanone. The mixed solution was refluxed for 12 h under a nitrogen atmosphere. After cooling to room temperature, the K_2CO_3 residue was filtered off and washed with 2-butanone. The filtrate solution was evaporated by rotary to remove solvent and excess 2-bromoethanol. The crude product was washed by Et_2O to get pure brown solid. ^{1}H-NMR (400 Hz, $CDCl_3$) 6.8-7.9 (Ar-H), 4.9 (-OH), 4.1 (Ar-O-CH_2), 3.8 (-CH_2-OH)

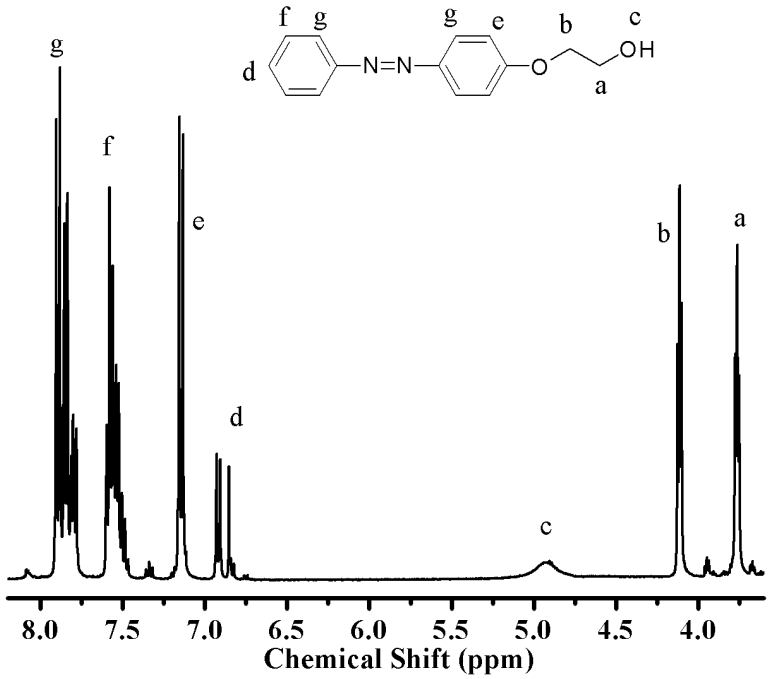

Figure S5. ^{1} H NMR spectrum of 4-Phenylazophenyl hydroxyethyl ether.

Synthesis of 2-(4-(phenyldiazenyl) phenoxy) ethyl acrylate.

4-Phenylazophenyl hydroxyethyl ether (3.34 g, 13.8 mmol) and TEA (2.76 ml) were dissolved in 50 ml THF. After the resulting solution was cooled to 0 °C, acryloyl chloride (4.99 g, 55.2 mmol) diluted in THF (15 ml) was added dropwise to the cool solution. The resultant mixture was vigorously stirred in an ice bath for 1 h and then at room temperature overnight. $CHCl_3$ (55 ml) was added and the mixture was washed by solution of HCl (138 ml, PH = 1) and 138 ml of 3% NaOH. The $CHCl_3$ phase was washed to neutrality with deionized water and the solvent was evaporated by rotary to give the crude product. The crude product was purified by recrystallization from $CHCl_3$ to give the desired product. ^{1}H-NMR (400 Hz, $CDCl_3$) 7.0-7.9 (Ar-H), 5.9-6.5 (-CO-CH=CH_2), 4.6 (Ar-O-CH_2), 4.3 (-CH_2-OH)

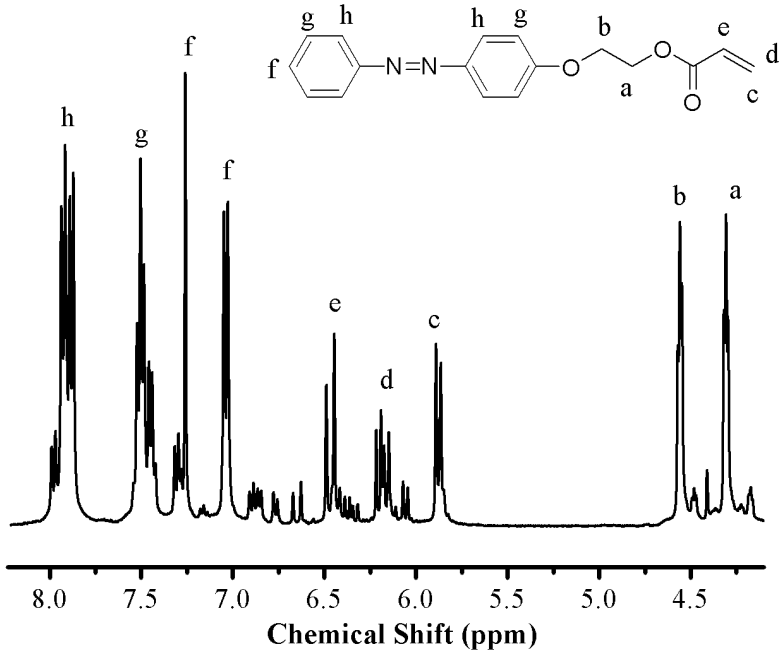

Figure S6. ^{1} H NMR spectrum of Azo modified crylic acid (AA-AZO).

Synthesis of PNIPAM-Azo copolymer.

The PNIPAM-Azo was prepared in DMF by RAFT copolymerization. NIPAM (2.0 g, 17,7 mmol), AA-AZO (0.18 g, 0.93 mmol), AIBN (6.0 mg, 3.66×10^{-2} mmol) and CTA (8.0 mg, 2.84×10^{-2} mmol) were added to a reaction tube and then dissolved by 5 ml DMF. The reaction solution was degassed by three freeze-pump-thaw cycles and then heated at 70 °C under nitrogen atmosphere overnight. The product was precipitated in anhydrous ethyl ether and the precipitate was filtered and dried under vacuum. GPC result showed a number-average molecular weight (Mn) of PNIPAM-Azo copolymer was 60912 g/mol. ^{1}H-NMR (400 Hz, $CDCl_3$) 7.0-7.9 (Ar-H), 6.0-6.5 (-CO-NH-), 4.2-4.6 ($-OCH_2-CH_2-O-$), 4.0 ($(CH_3)_2$-CH-N-), 1.5-2.5 (-CH2-CH-), 1.1 ($-CH_3$)

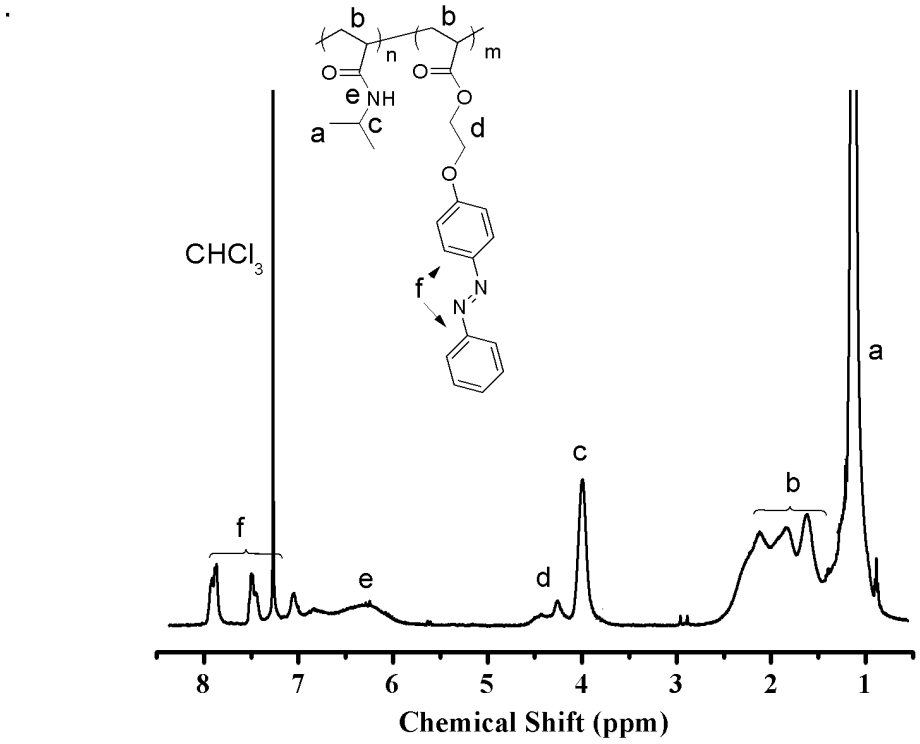

Figure S7. ^{1} H NMR spectrum of PNIPAM-Azo copolymer.

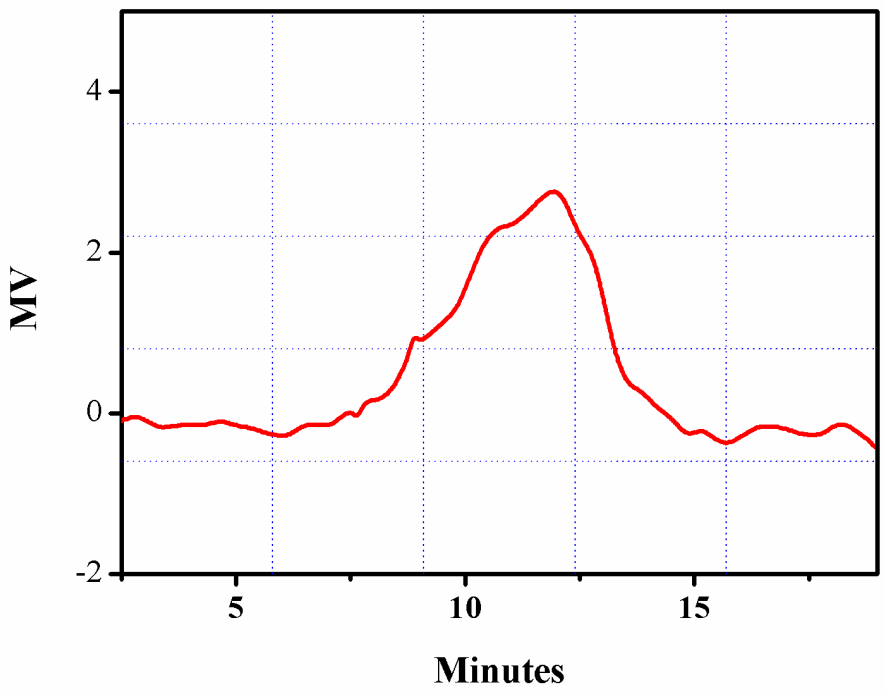

Figure S8. GPC spectrum of PNIPAM-Azo copolymer.

Electronic Supplementary Material (ESI) for RSC Advances

Instruments and methods

NMR spectrometer. ^{1}H-NMR spectra were measured in $CDCl_3$, DMSO-d_6 or D_2O with a Bruker AV II-400 MHz spectrometer. The chemical shifts are given in ppm from tetramethylsilane (TMS) as external standards.

UV-vis absorption spectrometer. The turbidity measurements were measured by monitoring the transmittance of a 600 nm light beam through a quartz sample cell. The transmittance was recorded on a VARIAN Cary 50 Probe spectrophotometer. The control of temperature was conducted by using a PolyScience temperature controller as the heating instrument. The systems were heated at a rate of 1^{o}C/min, and stabilized for 3 min before the data were recorded.

Rheometry. Value of η was measured using the Advanced Dynamic Rheometric Expansion System (ARES, Bohlin Gemini200). Oscillatory frequency sweep experiments were performed from 0.1 rad/s to 100 rad/s with a strain in the linear region at 10 °C. Figure S9 showed the Compllex viscosity of Rheology Measurements.

Photoisomerization. Photoisomerization of azo groups in azo-modified poly(N-iso-propyl acrylamide) (PNIPAM-Azo) was performed using a 300 W Xe lamp (CEL-HXUV300).

Gel permeation chromatography (GPC). GPC measurement was carried out on a Water 515 apparatus using polystyrene as a standard and $CHCl_3$ as an eluent. Figure S8 was the GPC spectrum of PNIPAM-Azo copolymer.

Redox and oxidation experiment. The reduction experiment: In general, 5 equiv reduction agent DTT was added into the hydrogel; The oxidation experiment: 5 equiv oxidation agent NaClO or H_2O_2 aq. was added into the sol. Figure S10 showed the photographs of the redox experiment.

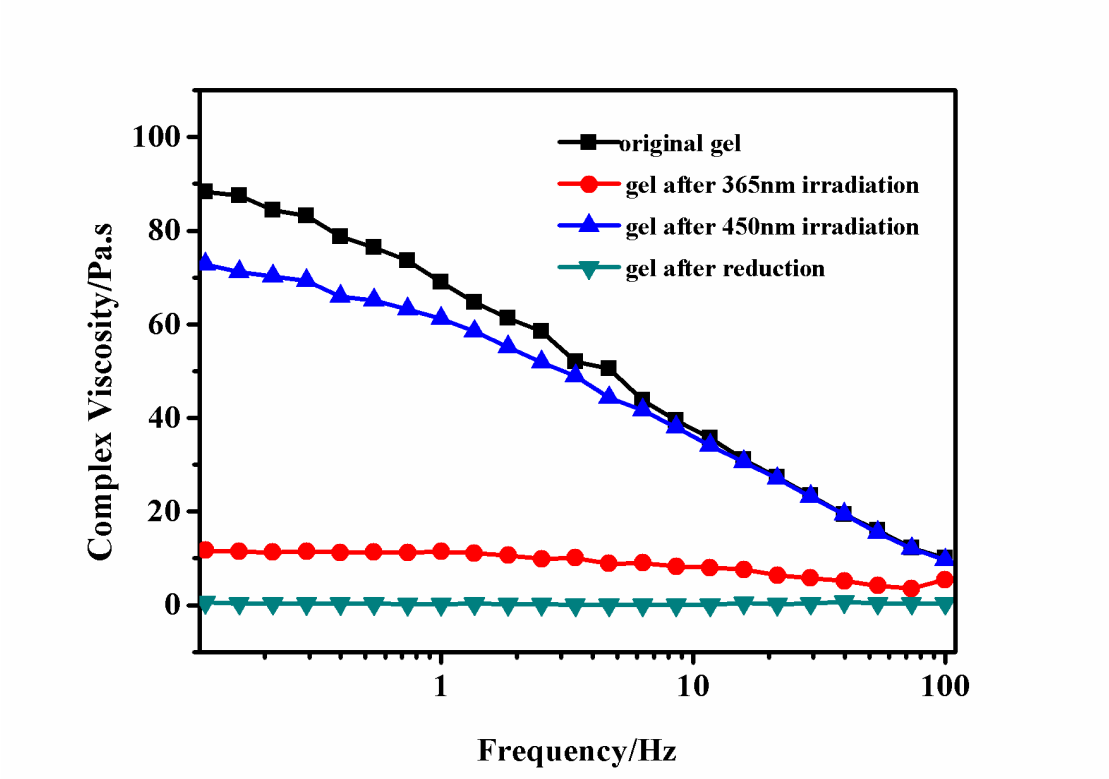

Figure S9. Compllex viscosity of Rheology Measurements.

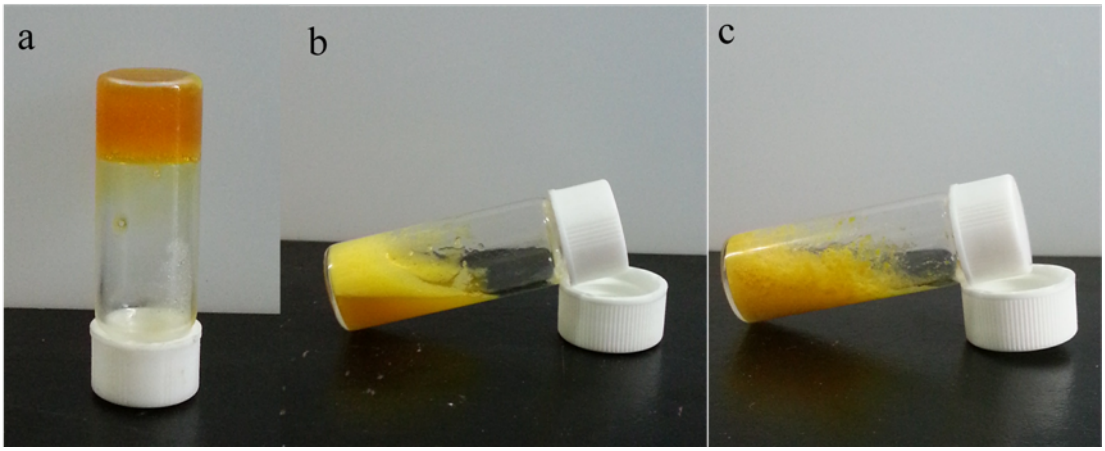

Figure S10. The photographs of the redox experiment. (a) the original hydrogel; (b) the hydrogel after reduction by DTT; (c) the sol(b) after oxidation by H_2O_2.

References:

S1. John T, Lai.; Debby, Filla.; Ronald, Shea. *Macromolecules.* **2002**, 35, 6754.