Supporting Information

Temperature, pH, and Glucose Responsive Gels via Simple Mixing of Boroxole- and Glyco-Based Polymers

Yohei Kotsuchibashi[a], Roman Vincent C. Agustin[a], Jin-Yong Lu[b], Dennis G. Hall[b], Ravin Narain[a,]*

[a]*Department of Chemical and Materials Engineering and Alberta Glycomics Centre, University of Alberta, Edmonton, Alberta, T6G 2G6, Canada*

[b]*Department of Chemistry, W5-07 Gunning-Lemieux Chemistry Centre, University of Alberta, Edmonton, Alberta, T6G 2G2 Canada*

* Corresponding author.

Department of Chemical and Materials Engineering and Alberta Glycomics Centre, University of Alberta, Edmonton, Alberta, T6G 2G6, Canada

Telephone: +1-780-492-1736, Fax: +1-780-492-2881

E-mail: narain@ualberta.ca

Materials

The *N*-isopropylacrylamide (NIPAAm) was obtained from Sigma-Aldrich (Canada) and purified by recrystallization from hexane. The 5-methacrylamido-1,2-benzoxaborole (MAAmBO) was synthesized and purified according to the protocol given in report.[1] The 4-cyanopentanoic acid dithiobenzoate (CTP) was synthesized and purified according to the protocol given in previous reports.[2] All other chemicals and solvents were used as received. Distilled water used in this study was purified with a Millipore Milli-Q system.

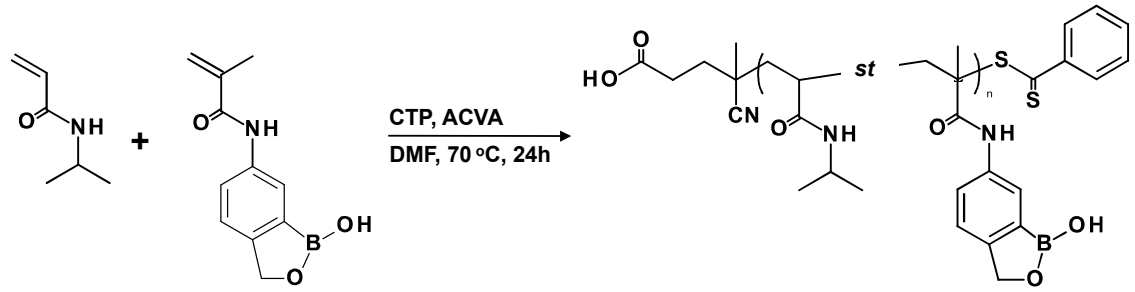
Synthesis of 5-methacrylamido-1,2-benzoxaborole (MAAmBO)

5-Amino-2-hydroxymethylphenylboronic acid HCl salt (1.0 g, 5.39 mmol) was added to an aqueous solution of NaOH (1.16 g, 29.0 mmol) in H_2O (17 mL), and the reaction mixture was cooled down to 0 ºC and stirred for 15 min. Methacryloyl chloride (1.1 mL, 11.3 mmol) was added via a syringe pump over a period of one hour, after that the reaction mixture was stirred for another 3 h, and acidified slowly with concentrated HCl at 0 ºC. The white precipitate was filtered and washed with cold water (2 × 5 mL). High vacuum removal of water yielded a white solid (1.14 g, 97%).

^{1}H NMR (500 MHz, DMSO-d*6*): δ[ppm] = 9.80 (s, 1H), 9.16 (s, 1H), 8.04 (d, *J* = 1.8 Hz, 1H), 7.66 (dd, *J* = 2.1, 8.2 Hz, 1H), 7.32 (dd, *J* = 0.7, 8.2 Hz, 1H), 5.79 (t, *J* = 1.0 Hz, 1H), 5.48 (dt, *J* = 1.5 Hz, 1H), 4.93 (s, 2H), 1.94 (dd, *J* = 0.9, 1.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d*6*): δ[ppm] = 166.6, 148.8, 140.3, 137.6, 123.4, 122.2, 121.1, 119.7, 69.6, 18.6. The NMR data were in agreement with a previous report.[3]

Synthesis of P(NIPAAm-*st*-MAAmBO)

To achieve a narrow distribution of molecular weight, we employed the RAFT polymerization for the synthesis of the polymers. A typical polymerization method *i.e.* 5 mol% of MAAmBO content in P(NIPAAm-*st*-MAAmBO) was shown below (Scheme S1). NIPAAm (1.04 g, 9.2 mmol), MAAmBO (105 mg, 0.48 mmol), CTP (8.6 mg, 0.031 mmol), ACVA (3.4 mg, 0.012 mmol) were dissolved in 5 mL *N*,*N*-dimethylformamide (DMF). After degassing with nitrogen gas for 30 min, the mixture was allowed to polymerize for 24 h at 70 °C. The resulting P(NIPAAm-*st*-MAAmBO) was purified by reprecipitation using diethyl ether (Figure S1).



Scheme S1. Synthesis of P(NIPAAm-*st*-MAAmBO)s by RAFT polymerization.

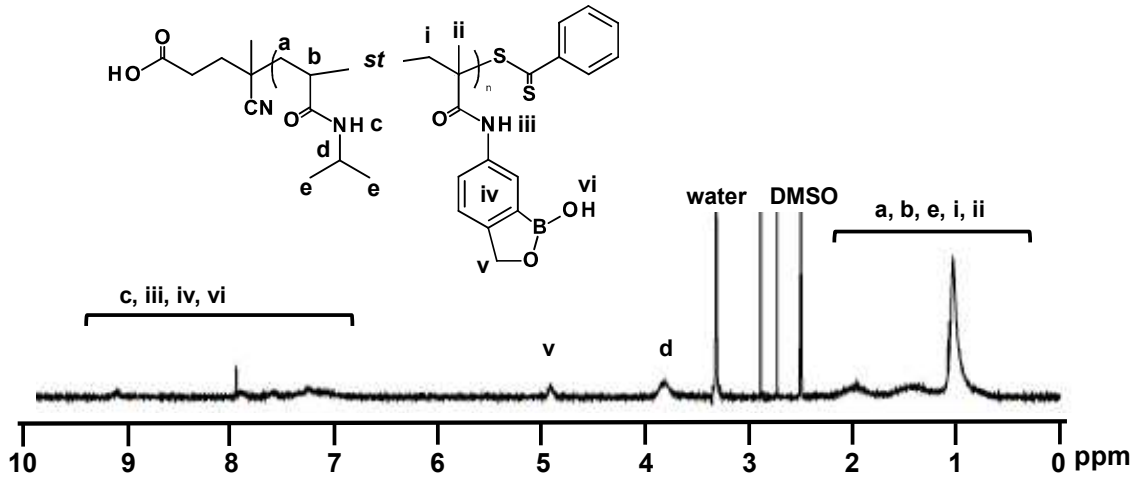


Figure S1. NMR spectra of P(NIPAAm$_{90}$-*st*-MAAmBO$_{12}$).

Characterization

^{1}H Nuclear Magnetic Resonance (^{1}H NMR) spectra of polymers were recorded with a 500 MHz Varian spectrometer to confirm successful chemical composition of the synthesized polymers. The molecular weight and polydispersity of the polymers were determined by gel permeation chromatography (GPC) with two Waters Ultrahydogel linear WAT011545 columns and Viscotek model 270 dual detector for sugar polymers or I-MBLMW-3078 and I-MBHMW-3078 columns and Viscotek model 250 dual detector for P(NIPAAm-*st*-MAAmBO)s. 0.50M sodium acetate/0.50M acetic acid buffer or 10 mM LiBr DMF were used as eluent respectively through a flow rate of 1.0 mL/min. Dynamic light scattering (DLS) was performed with a ZetaPlus-Zeta Potential Analyzer (Brookhaven Instruments Corporation) at a scattering angle $\theta = 90$ °. All samples were kept in a given temperatures to reach the equilibrium prior to the measurements. The samples were prepared using KBr. Transmission electron microscopy (TEM) images were obtained on a transmission electron microscope Morgaghi 268 (FEI) with an accelerating voltage of 80 kV. The samples were coated on a carbon coated copper grids and allowed to dry before analysis.

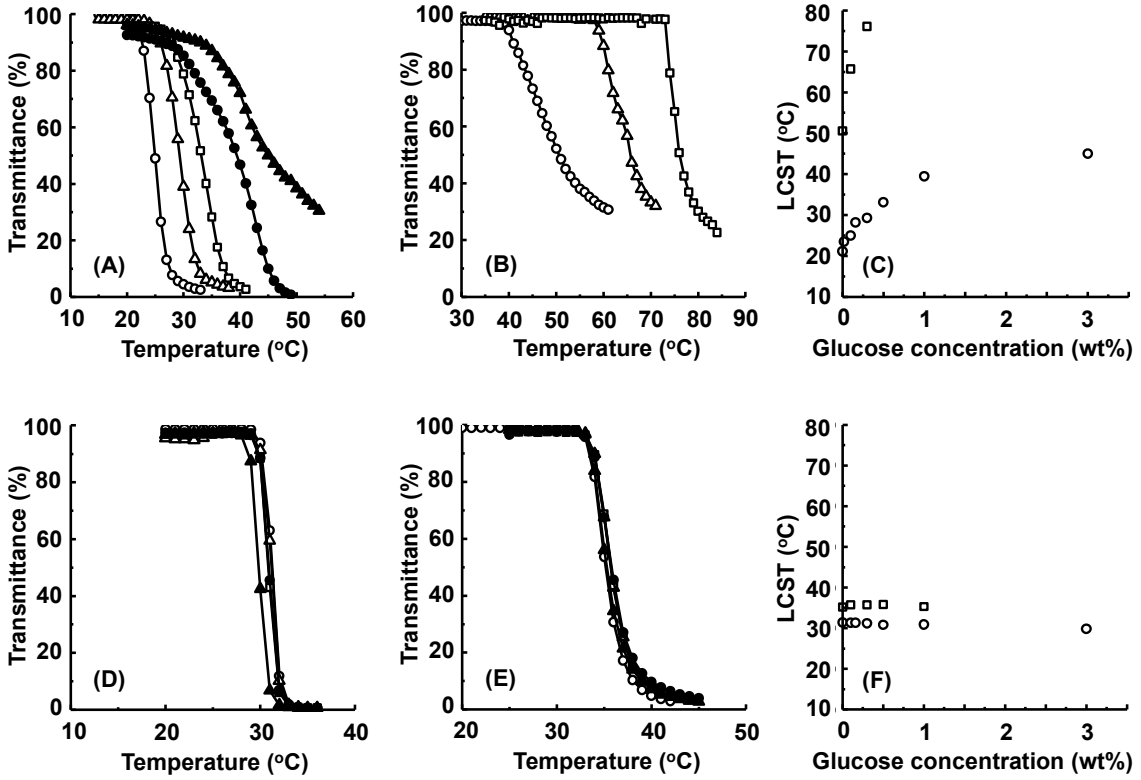


Figure S2. Transmittance change of 0.1wt% P(NIPAAm$_{90}$-*st*-MAAmBO$_{12}$) (A) in pH 7.4 PBS with glucose at different concentrations (○) 0.1wt%, (Δ) 0.3wt%, (□) 0.5wt%, (•) 1wt%, and (▲) 3wt%, (B) in pH 12 NaOH solution with glucose at different concentrations (○) non-glucose, (Δ) 0.1wt%, and (□) 0.3wt%. (C) LCSTs of 0.1wt% P(NIPAAm$_{90}$-*st*-MAAmBO$_{12}$) as a function of the glucose concentration (○) in pH 7.4 PBS and (□) in pH 12 NaOH solution. Transmittance change of 0.1wt% PNIPAAm$_{178}$ (D) in pH 7.4 PBS with glucose at different concentrations (○) 0.1wt%, (Δ) 0.3wt%, (□) 0.5wt%, (•) 1wt%, and (▲) 3wt%, (E) in pH 12 NaOH solution with glucose at different concentrations (○) non-glucose, (Δ) 0.1wt%, (□) 0.3wt%, (•) 5wt%, and (▲) 1wt%. (F) LCSTs of 0.1wt% PNIPAAm$_{178}$ as a function of the glucose concentration (○) in pH 7.4 PBS and (□) in pH 12 NaOH solution.

References

(1) Jay, J. I.; Lai, B. E.; Myszka, D. G.; Mahalingam, A.; Langheinrich, K.; Katz, D. F.; Kiser, P. F. *Mol. Pharmaceutics* **2010**, *7*, 116–129.

(2) (a) Mitsukami, Y.; Donovan, M. S.; Lowe, A. B.; McCormick, C. L. *Macromolecules,* **2001**, *34*, 2248-2256. (b) Lai, J. T.; Filla, D.; Shea, R. *Macromolecules*, **2002**, *35*, 6754-6756.

(3) Schumacher, S.; Grueneberger, F.; Katterle, M.; Hettrich, C.; Hall, D. G.; Scheller, F. W.; Gajovic-Eichelmann, N. *Polymer*, **2011**, *52*, 2485-2491.