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Triply-responsive boronic acid block copolymers: Solution self-assembly induced by changes in temperature, pH, or sugar concentration

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Materials. 2-Dodecylsulfanylthiocarbonylsulfanyl-2-methylpropionic acid (DMP) chain transfer agent (CTA) was prepared as previously reported.\(^1\) \(N\)-Isopropylacrylamide (NIPAM) (TCI) was recrystallized twice from hexane. 2,2'-Azobisisobutyronitrile (AIBN, Sigma, 98%) was recrystallized from ethanol. 3-Aminophenyl boronic acid (Boron Molecular), acryloyl chloride (Alfa Aesar, 96%), 1,3,5-trioxane (Acros Organics, 99.5%), pinacol (Acros Organics, 99%), sodium hydrogen carbonate (Acros Organics, 99.5%), hydrochloric acid (Alfa Aesar, 36% (w/w) aq. solution), sodium hydroxide pearl (Alfa Aesar, 97%), \(N,N\)-dimethylformamide (DMF) (Aldrich 99.9%), tetrahydrofuran (THF) (Acros Organics, 99.9%), diethyl ether, dimethylsulfoxide-\(d_6\) (DMSO-\(d_6\), Cambridge Isotope, 99.9% D), CDCl\(_3\) (Cambridge Isotope, 99% D), methanol-\(d_4\) (Cambridge Isotope, 99.8% D), deuterium chloride (DCl, Sigma Aldrich, 35 wt. % in D\(_2\)O, 99% D), sodium deuteroxide (NaOD, Sigma Aldrich, 30 wt. % in D\(_2\)O, 99% D), and D\(_2\)O (Cambridge Isotope, 99.9% D) were used as received.
Analyses. SEC was conducted in DMF (with 0.05 M LiBr) at 55 °C with a flow rate of 1.0 mL/min (Viscotek SEC Pump; Columns ViscoGel I-Series G3000 and G4000 mixed bed columns: molecular weight range 0 – 60 $\times$ $10^3$ and 0 – 400 $\times$ $10^3$ g/mol, respectively). Detection consisted of a Viscotek refractive index detector operating at $\lambda = 660$ nm, a Viscotek UV-Vis detector operating at $\lambda = 254$ nm, and a Viscotek Model 270 Series Platform, consisting of a laser light scattering detector (operating at 3 mW, $\lambda = 670$ nm with detection angles of 7° and 90°) and a four capillary viscometer. Molecular weights were determined by the triple detection method. For the PAPBA homopolymers a $dn/dc = 0.121$ mL/g was employed. Block copolymer molecular weights were determined by in situ calculation of $dn/dc$, assuming 100% mass recovery. $^1$H NMR spectroscopy was conducted with a Bruker Avance 400 spectrometer operating at 400 MHz and a JEOL ECA-500 operating at 500 MHz. Dynamic light scattering was conducted with a Malvern Zetasizer Nano-S equipped with a 4 mW, 633 nm He-Ne laser, and an Avalanche photodiode detector at a constant angle of 173°. UV-Vis measurements were conducted using a Beckman Coulter DU 800 UV-Vis spectrophotometer equipped with a temperature controller.

Synthesis of 3-acrylamidophenylboronic acid monomer (APBA). APBA (3.0 g, 0.022 mol) was dissolved in a round bottom flask containing a 1:1 mixture of THF (40 mL) and water (40 mL). Sodium hydrogen carbonate (3.7 g, 0.044 mol) and acryloyl chloride (4.0 g, 0.044 mol) were added to the flask at 0-5 °C. The solution was stirred for 4 h, and THF was subsequently evaporated. A solid crude product was obtained and stirred in ethyl acetate for 2 h. After filtering the solid materials, the ethyl acetate layer
was washed with water (50 mL), saturated sodium bicarbonate solution (50 mL), water (50 mL), and brine (50 mL). The ethyl acetate layer was concentrated under reduced pressure providing the 3.5 g of orange solid in 84 % yield. The monomer was purified by recrystallization from hot water (×3). \(^1\text{H NMR (400 MHz, DMSO-}d_6\text{): }\delta=10.07 \text{ (s, 1H, NH), 8.00 (s, 2H, B(OH)\textsubscript{2}), 7.89, 7.83-7.81, 7.51-7.49, 7.31-7.29 (s, d, d, t, 1H each, ArH), 6.46-6.42, 6.27-6.22 (2d, dd, 1H each, vinyl CH\textsubscript{2}), 5.75-5.72 (dd, 1H, vinyl CH).}

![Figure S1. \(^1\text{H NMR spectrum of 3-acrylamidophenylboronic acid monomer (APBA) in DMSO-}d_6\text{.}](image-url)
RAFT homopolymerizations of APBA. An example RAFT polymerization of APBA was as follows. APBA (1.5 g, 7.9 mmol), DMP (0.028 g, 0.079 mmol), 2,2′-azo bis(isobutyronitrile) (AIBN) (0.86 mg, 0.0079 mmol), DMF/water mixture (15 mL 95/5 vol.-%) and trioxane (36 mg) were sealed in a 20 mL vial ([APBA]/[CTA]/[AIBN] = 100/1/0.1). The solution was deoxygenated by purging with nitrogen for approximately 30 min and then placed in a preheated reaction block at 70 °C. Samples were removed periodically by syringe to determine molecular weight, polydispersity index (PDI) by size exclusion chromatography (SEC) and monomer conversion and 1H NMR spectroscopy. The final polymer was isolated by removing DMF/water under vacuum, dissolving in methanol, and precipitating into diethyl ether. The resulting polymer was washed with acetone, dried, dissolved in dioxane/water, and isolated by freeze-drying.
RAFT block copolymerization of NIPAM with a PAPBA macroCTA. An example block copolymerization procedure was as follows. NIPAM (0.274 g, 2.42 mmol), PAPBA macro-CTA (0.402 g, 0.0242 mmol) and AIBN (0.8 mg, 0.005 mmol) were added to a 20 mL vial ([NIPAM]/[macroCTA]/[AIBN] = 100/1/0.2. DMF/water (4 mL, 95/5 vol.-%) mixture was used as the polymerization solvent. Trioxane (11 mg) was used as an internal standard. The sealed vial was deoxygenated with nitrogen for approximately 30 min and then placed in a preheated reaction block at 70 °C. The polymerization was quenched after 20 h by removing the polymerization vial from the heating block and exposing the reaction solution to air. The resulting PAPBA-b-PNIPAM (90% conversion; molar composition calculated by $^1$H NMR spectroscopy (methanol-$d_4$): PAPBA=50% and PNIPAM=50%; and by SEC: PAPBA=43%, and PNIPAM= 57%;
$M_{n, \text{protected}} = 34,700 \text{ g/mol; } M_w/M_n = 1.15$) was isolated by precipitating into diethyl ether, filtering, and drying under vacuum.

**Figure S3.** $^1$H NMR spectrum of PAPBA-$b$-PNIPAM in methanol-$d_4$. 
**Figure S4.** SEC traces for PAPBA macroCTA and block copolymer with poly(N-isopropylacrylamide) (PNIPAM).

**Protection of PAPBA and PAPBA-b-PNIPAM.** A typical protection procedure for boronic acid containing (co)polymers is described as follows. PAPBA-b-PNIPAM (0.10 g, 0.52 mmol) and pinacol (0.19 g, 1.6 mmol) were placed in a Schlenk flask. Anhydrous DMF (7 mL) and molecular sieves were added, and the reaction was carried out at 105 °C for 16 h under N₂. After reaction, the protected copolymer was precipitated into cold diethyl ether from THF (×2). The resulting block copolymer was dried in a vacuum oven. Methanol-d₄ was used as the solvent for ¹H NMR spectroscopy.
Figure S5. $^1$H NMR spectrum of protected PAPBA-$b$-PNIPAM in methanol-$d_4$.

**Dynamic light scattering (DLS) measurements of block copolymers.** A 1% weight solution of PAPBA$_{81}$-$b$-PNIPAM$_{109}$ (0.12 g, $M_n = 28,100$ g/mol, $M_w/M_n = 1.15$) in basic water (12 mL, pH $\approx 10.5$) was prepared. The resulting solution was sonicated for 1 h and then filtered with a 0.45 μm nylon syringe filter. The pH was adjusted to 11.0, and DLS measurements on this solution were recorded at 25 and 50 °C. A 2 wt.-% solution of PAPBA$_{81}$-$b$-PNIPAM$_{109}$ (0.2 g, $M_n = 28,100$ g/mol, $M_w/M_n = 1.15$) in basic water (10 mL, pH $\approx 10.5$) was placed in 3,500 MWCO dialysis tubing and dialyzed overnight against deionized water with constant stirring. The resulting solution was sonicated for 1 h and filtered with a 0.45 μm nylon syringe filter. The pH was adjusted to 8.7 and DLS
measurements on the solution were recorded at 25 °C. A 0.1% weight solution of PAPBA$_{89}$-b-PNIPAM$_{91}$ (0.0051 g, $M_n = 27,600$ g/mol) in basic water (5 mL, pH $\approx 11.0$) was placed in 3,500 MWCO dialysis tubing and dialyzed overnight against deionized water with constant stirring. The resulting solution was sonicated for 1 h and filtered with a 0.45 µm nylon syringe filter. The pH was adjusted to 8.7 and DLS measurements on the solution were recorded at 25 °C. A total of 135 mM of glucose was added, and DLS measurements on the solution were recorded at 25 °C.

**Determination of thermal transition temperature for block copolymers via turbidity measurements.** A 2.0% weight solution of PAPBA$_{81}$-b-PNIPAM$_{109}$ (25 mg, $M_n = 28,100$ g/mol) was dissolved in basic water (1.2 mL, pH $\approx 11.0$). The sample was used as a blank for the UV measurements. Absorbance measurements at 600 nm were taken from 25 to 75 °C with a ten minute equilibration period between each sample measurement.

**Temperature-dependent $^1$H NMR measurements for block copolymers.** A sample of PAPBA$_{81}$-b-PNIPAM$_{109}$ ($M_n = 28,100$ g/mol) was dissolved in D$_2$O/NaOD at pH 11.0. $^1$H NMR measurements were taken from 25 to 60 °C in 5 °C increments. After reaching 60 °C, the temperature was returned to 25 °C and $^1$H NMR measurements were taken. DCl was added to the sample to bring the pH to 8.0. $^1$H NMR were taken at 25 °C. The ratio of the integration of the phenyl protons for PAPBA ($^6$H$_4$) and the integration of the proton on PNIPAM ($^2$H$_2$) were compared to see how they changed at each temperature.
**Figure S6.** Ratio of the integration of the phenyl protons for PAPBA (C₆H₄) and the integration of the proton on PNIPAM (-CH-) versus temperature.

**References**