

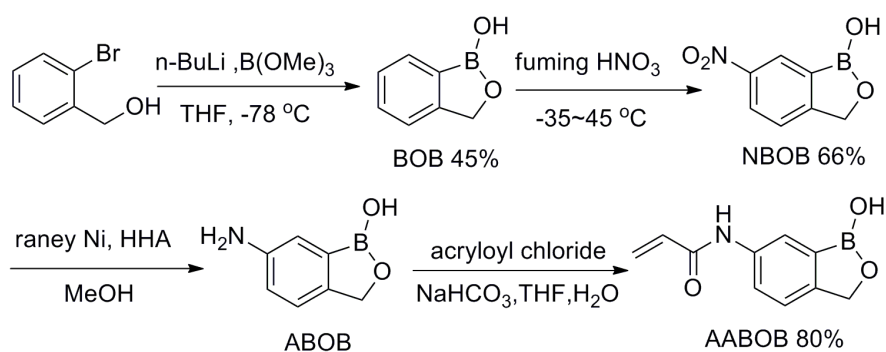
Supporting information
of
Direct and Indirect Core-Shell Inversion of
Block Copolymer Micelles

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Materials. *N*-Isopropylacrylamide (NIPAM) purchased from Tokyo Kasei Kagyo Co. was recrystallized three times from benzene/hexane (65:35 v/v) prior to use. Azobisisobutyronitrile (AIBN, CP) supplied by Sinopharm Chemical Reagent Co., was recrystallized from ethanol before use. DMP (2-dodecylsulfanylthiocarbonylsulfanyl-2-methylpropionic acid) was synthesized following procedures in literature.¹ DCM, DMF and THF were distilled before use. Unless specially mentioned, all other chemicals were used as received. The reactions were monitored and the R_f values were determined using analytical thin layer chromatography (TLC). The TLC plates were visualized by UV-light.

Characterization. ¹H NMR spectra were recorded with a JEOL ECA-400 spectrometer. Gel permeation chromatography (GPC) analysis was carried out with a Waters Breeze 1515 GPC analysis system with two PL mix-D columns, using DMF with 0.5 M LiBr as eluents at the flow rate of 1 mL/min at 80 °C and PEO calibration kit (purchased from TOSOH) as the calibration standard. UV-vis spectroscopy was recorded in a conventional quartz cell (light path 10 mm) on a Perkin-Elmer Lambda 35 spectrophotometer. Dynamic light scattering studies were conducted using ALV/5000E laser light scattering (LLS) spectrometers at scattering angle of 90°, CONTIN analysis was used for the extraction of R_h data. Aqueous solution (pH = 11) and PBS buffer was used for characterizations, including fluorescence spectroscopy, to ensure the dynamic covalent bond between boron and sugars. Zeta potential measurements were carried out on a Zetasizer Nano ZS90 instrument.



Scheme S1 Synthetic route of monomer AABOB

Synthesis of benzoboroxole (BOB). The compound was synthesized according to the procedures in literature^{2,3}. To a cooled (0 °C) suspension of sodium hydride (1.5 g, 50% solution, 63.6 mmol) in 10 mL THF, a solution of 2-bromobenzyl alcohol (10 g, 53.0 mmol) in THF (60 mL) was added with stirring for 1 h. The reaction was cooled to -78 °C and n-butyl lithium (25.4 mL, 2.4 M solution, 63.6 mmol) was added dropwise and stirred for 1 h. Then triisopropylborate (14.6 mL, 63.6 mmol) was added to the mixture at -78 °C and stirred for 6 h while gradually warming to room temperature. The reaction mixture was acidified to pH 1 using 2 M H₂SO₄ and THF was evaporated afterward. The mixture was extracted with EtOAc (3*100 mL) and washed with water. The organic layer was dried over anhydrous MgSO₄, filtered and evaporated. Purification using silica gel column chromatography (Hex/EtOAc = 4:1) yielded BOB (45% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.74–7.76 (d, 1H), 7.47–7.51 (m, 1H), 7.35–7.39 (m, 2H), 5.11 (s, 2H), 4.94 (br s, 1H).

Synthesis of 6-nitrobenzoboroxole (NBOB). The compound was synthesized according to the procedures in literature.⁴ To 10 mL of fuming nitric acid maintained at -45 to -40 °C, 1.6g (11.5 mmol) of BOB was added dropwise with stirring. Then the mixture was stirred and maintained at -45 to -30 °C for 20 min. It was poured into ice water and stirred at 0-10 °C for 2 h. The precipitated pale yellow compound was filtered, washed with 25 mL of water, and dried in vacuum. (1.3 g; 66% yield).

¹H NMR (400 MHz, CDCl₃): δ 8.60 (s, 1H), 8.35–8.37 (dd, 1H), 7.50-7.52 (d, 1H), 5.18 (s, 2H), 4.99 (br,1H);

Synthesis of 6-aminobenzoboroxole (ABOB). The compound was synthesized by an adapted procedure in literature.⁵ To a solution of NBOB (3.4 g, 20.2 mmol) in methanol (90 ml), 3 mL of Raney nickel (50% slurry in H₂O) was added. The resulting mixture was stirred, then 6.6 mL of hydrazine monohydrate was added dropwise in portions over 2 h (gas evolution). After the reaction was completed, the mixture was filtered through Celite

and evaporated to a light-brown solid. This compound was ABOB and used in further reaction without any purification.

^1H NMR (400 MHz, DMSO- d_6): δ 8.89 (s, 1H), 7.00–7.02 (d, 1H), 6.86 (s, 1H), 6.67–6.69 (dd, 1H), 4.95 (br, 2H), 4.79 (s, 2H);

Synthesis of 5-acrylamidobenzoboroxole (AABOB). The compound was synthesized following procedures in literature. To the solution of ABOB (3.0 g, 20 mmol) in a 1:1 mixture of THF (35 mL) and water (35 mL), sodium hydrogen carbonate (6.8 g, 80 mmol) and acryloyl chloride (3.2 mL, 40 mmol, 2.0 equiv.) was added dropwise at 0 °C - 5 °C. The solution was stirred for 4 h, when TLC indicated the complete conversion of the starting material. A solid crude product was obtained after THF was evaporated and extracted by EtOAc for 2 h. After filtering the solid materials, the EtOAc layer was washed continuously with water (50 mL), saturated sodium bicarbonate solution (50 mL), water (50 mL), and brine (50 mL). The organic layer was dried over MgSO_4 , filtered and evaporated and further purified by recrystallization from hot water ($\times 3$).

^1H NMR (400 MHz, DMSO- d_6): δ 10.19 (s, 1H), 9.22 (s, 1H), 8.06 (s, 1H), 7.67–7.70 (dd, 1H), 6.42–6.49 (q, 1H), 6.22–6.26 (dd, 1H), 5.72–5.75 (dd, 1H), 6.86 (s, 1H), 6.67–6.69 (dd, 1H), 4.93 (s, 2H);

RAFT homopolymerization of ABOB. A typical RAFT polymerization of AABOB is as follows. AABOB (0.5333 g, 2.6333 mmol), DMP (0.0093 g, 0.0263 mmol), and AIBN (0.5734 mg, 0.00032 mmol) were dissolved in DMF/water ($v:v = 95/5$, 5 mL) in a sealed 20 mL vial ([AABOB]: [CTA]: [AIBN] = 100: 1: 0.2). The vial was deoxygenated with nitrogen for approximately 30 min and then placed in a pre-heated oil bath at 70 °C for polymerization. The reaction was then quenched by removing the vial from heat followed by cooling in liquid nitrogen immediately after 4 h. The reaction mixture was concentrated in vacuum and precipitated into cold diethyl ether, filtrated and then dissolved in DMF and precipitated again. The procedure was repeated for three times and the polymer was obtained as lemon yellow powder after drying in vacuum at room temperature for 12 h. (Yield: 59%)

RAFT polymerization of PNIPAm Macro-CTA. A typical RAFT polymerization of PNIPAm Macro-CTA is as follows. NIPAm (1.0 g, 8.8 mmol), DMP (16.1 mg, 0.044 mmol) and AIBN (1.45 mg, 0.0088 mmol) were dissolved in dioxane (5 mL) in a sealed 20 mL vial ([NIPAm]: [CTA]: [AIBN] = 200: 1: 0.2). The vial was deoxygenated with nitrogen for approximately 30 min and then placed in a preheated oil bath at 70 °C. The polymerization was quenched after 4 h, by removing the reaction flask from heat followed by cooling in liquid nitrogen immediately. The reaction mixture was concentrated in vacuum and precipitated into cold diethyl ether, filtrated and then dissolved in THF and precipitated again. The procedure was repeated for three times and the polymer was obtained as lemon yellow powder after drying under vacuum at room temperature for 12 h. (Yield: 43%).

RAFT polymerization of PNIPAm-*b*-PBOB AABOB (300 mg, 2.4 mmol), PNIPAm-CTA (181.3 mg, 0.03 mmol) and AIBN (0.61 mg, 0.006 mmol) were dissolved in 95/5 DMF/water (5 mL) in a sealed 20 mL vial ([AABOB]: [CTA]: [AIBN] = 80: 1: 0.2). The vial was deoxygenated with nitrogen for approximately 30 min and then placed in a preheated oil bath at 70 °C. The polymerization was quenched after 20 h, by removing the reaction flask from heat followed by cooling in liquid nitrogen immediately. The reaction mixture was concentrated in vacuum and precipitated into cold diethyl ether, filtrated and then dissolved in THF and precipitated again. The procedure was repeated for three times and the polymer was obtained as lemon yellow powder after drying under vacuum at room temperature for 12 h (Yield: 90%).

Typical procedure for the self-assembly of PNIPAm-*b*-PBOB. The block copolymer (12 mg) was dissolved in DMF (4 mL). Water was added dropwise until opalescence appeared, followed by addition of equal volume of water to “freeze” the self-assembled structures. Then the solution was dialyzed in a dialysis bag (MWCO 3500 Da) against deionized water to remove DMF. After 48 h, the volume of the solution was increased to 24 mL to obtain the micelle solution with a concentration of 0.5 mg/mL for further experiments.

Sugar responsive of homopolymer The homopolymer was dispersed in PBS buffer (pH = 7.4, 7.6 or 7.8) with vigorous stirring. The specific monosaccharide was added and stirred.

Micelle dissociation and inversion at high pH The pH of micelle solution was adjusted to 11 with addition of aqueous solution of NaOH (1 M). Then the solution was centrifuged for 30 min. The pH of the solution was adjusted to 11 again and filtered through Millipore membrane (pore size 450 nm). The filtrate was used for DLS measurement including heating (30 min standing of the solution at a given temperature). For pH-triggered reversible micelle dissociation experiment, the solution pH was adjusted to 7.4 with aqueous solution of HCl (1 M) for the DLS measurement and was adjusted back to 11 with aqueous solution of NaOH (1 M).

Sugar (Fru) responsive property of the micelles A 1.5 mL solution of 200 mM Fructose (Fru) in PBS (pH = 7.4, 0.1 M) buffer was added into the micelle **M-BOB** solution (1.5 mL, 0.5 mg/mL) immediately to obtain the micelle solution with a concentration of 0.25 mg/mL with 100 mM Fru in PBS buffer (pH 7.4, 0.05 M). The micelle solution was filtered through Millipore membrane (pore size 450 nm) before DLS measurement.

Zeta potential measurement The solution (0.5 mL) of **M-BOB** with a concentration of 0.5 mg/mL with 100 mM Fru in pH 7.4 PBS buffer (0.05 M) was added to 2 mL deionized water to decrease the concentration of salt into appropriate range for zeta potential measurement. Final micelle concentration of 0.1 mg/mL (20 mM Fru and PBS 0.01 M) was used. The temperature was increased from 24 °C to 50 °C with 2 °C in each step with 30 min standing before each measurement. Measurements were repeated for 3 times at each temperature.

VT-NMR measurement The block copolymer PNIPAm-*b*-PBOB (2.5 mg) were dissolved in 10 mL, pH 7.4 PBS buffer (0.05 M) prepared by D₂O then the solution pH was adjusted to 11 with addition of aqueous solution of deuterium and sodium hydroxide

(1 M), then the polymer solution was treated by sonication for 30 minutes. The pH of the polymer solution was adjusted back to 7.4 by aqueous solution of DCI followed by sonication for 30 minutes. Thus micelles were prepared in deuterium solution and the required Fru was added for VT-NMR measurement. The temperature was increased from 25 °C to 50 °C with 5 °C in each step. The measurements were started after standing 30 minutes at a certain temperature and each measurement last 20 minutes.

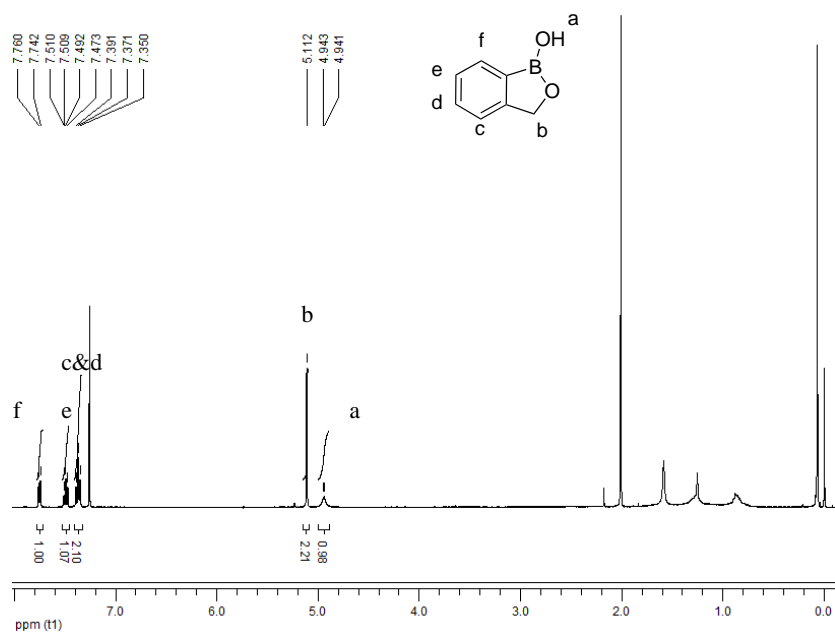


Figure S1. ^1H NMR of BOB in CDCl_3 .

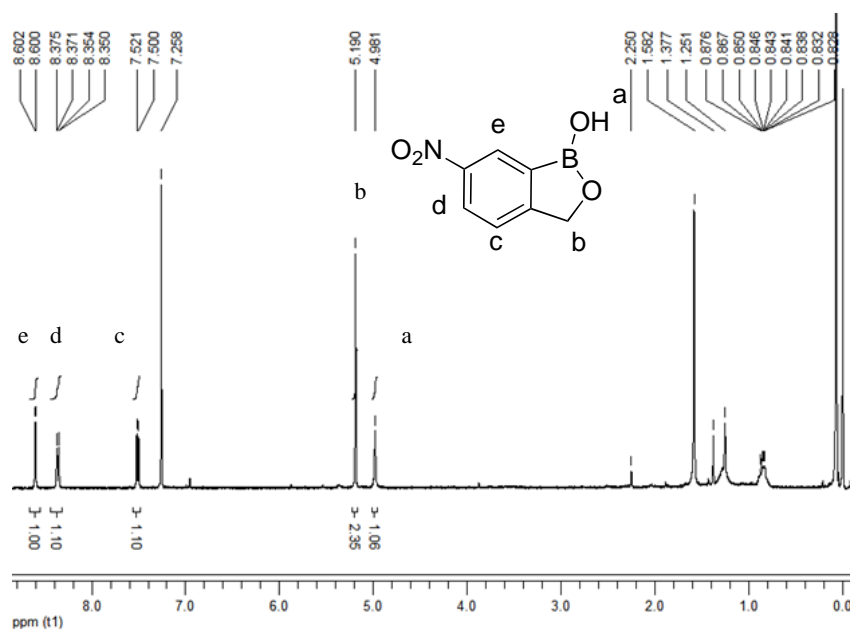


Figure S2. ^1H NMR of NBOB in CDCl_3 .

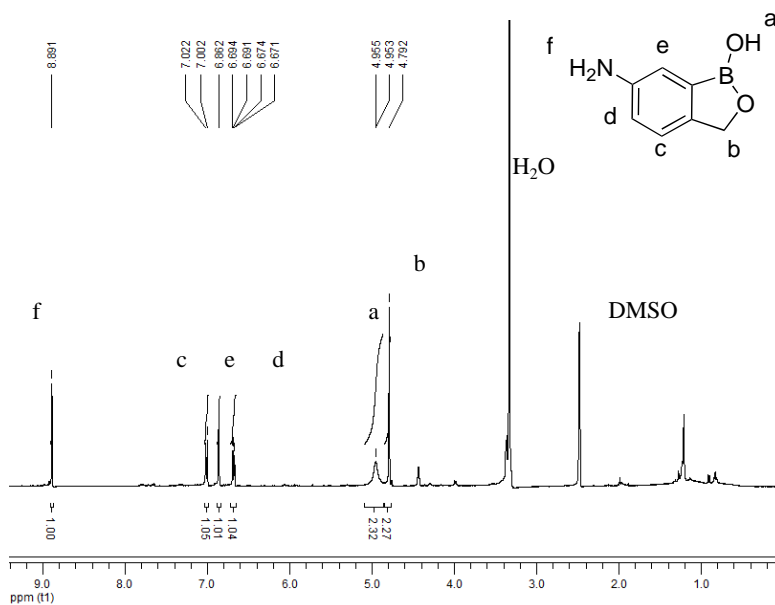


Figure S3. ^1H NMR of ABOB in $\text{DMSO}-d_6$.

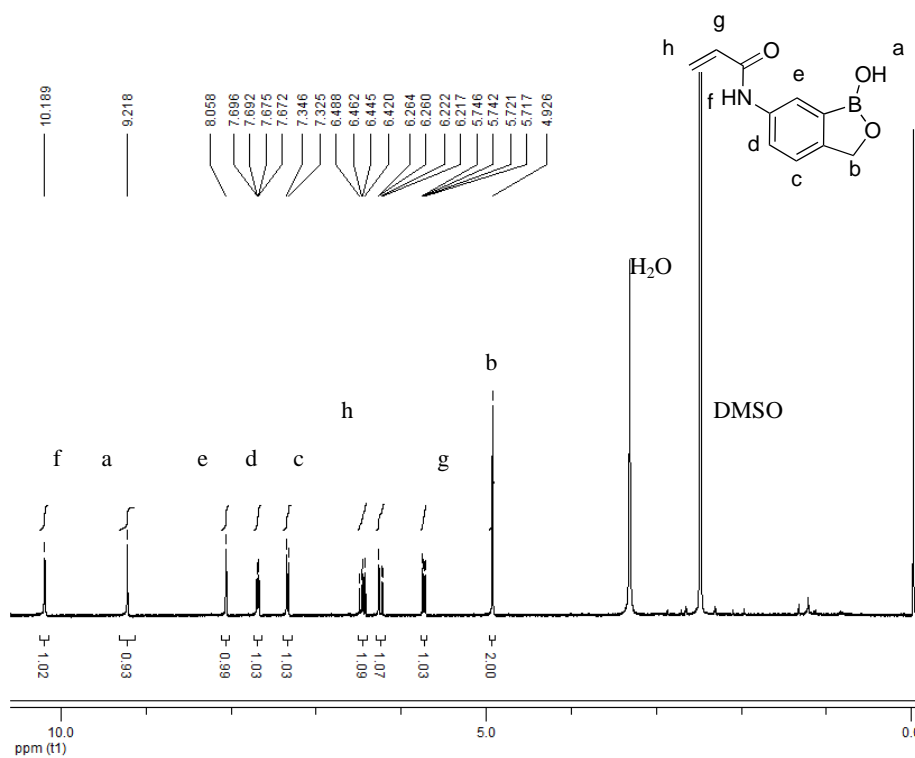


Figure S4. ^1H NMR of AABOB in $\text{DMSO}-d_6$

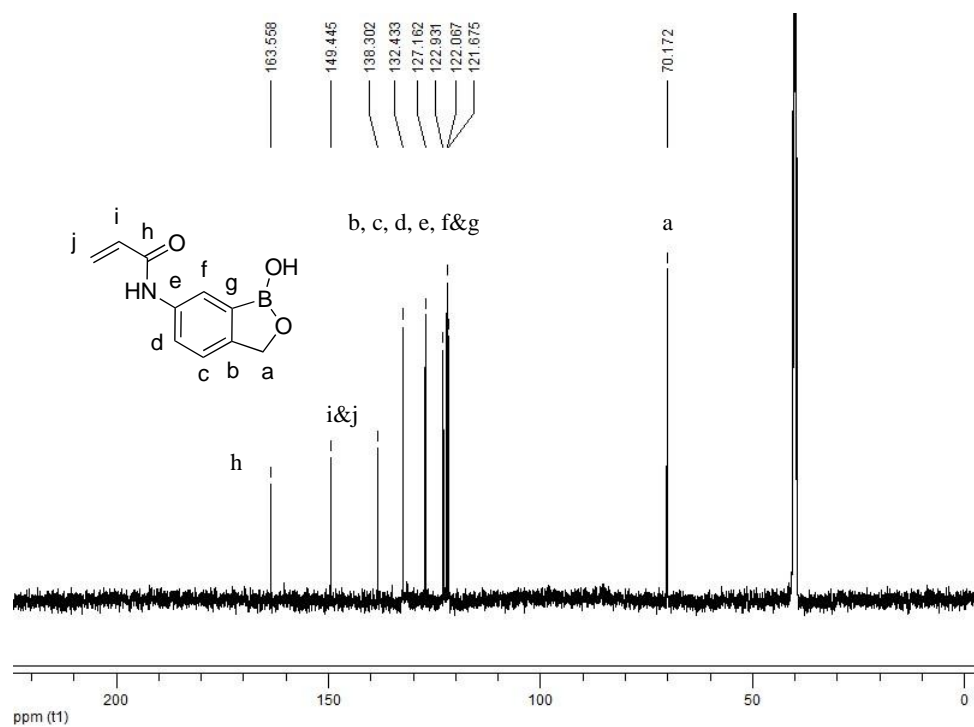


Figure S5. ^{13}C NMR of AABOB

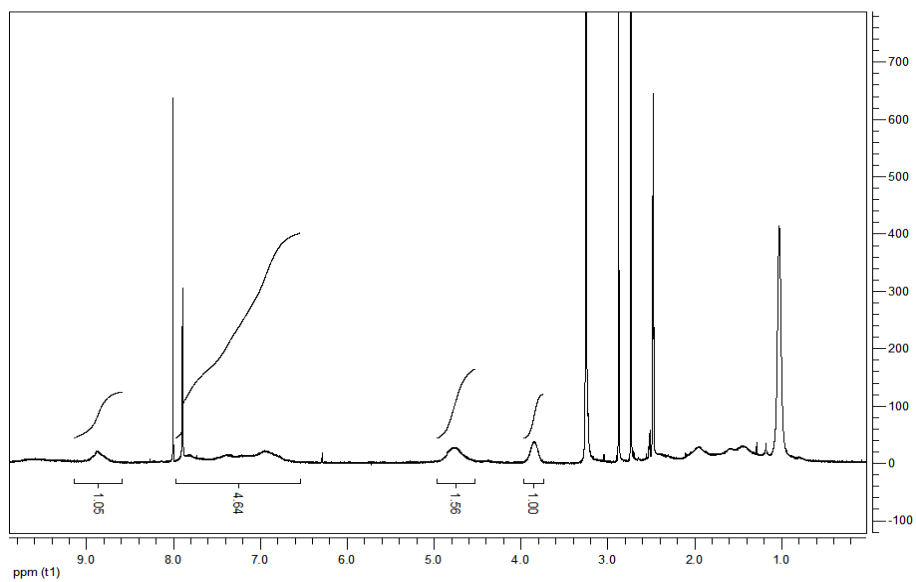


Figure S6. ^1H NMR of PNIPAm-*b*-PBOB

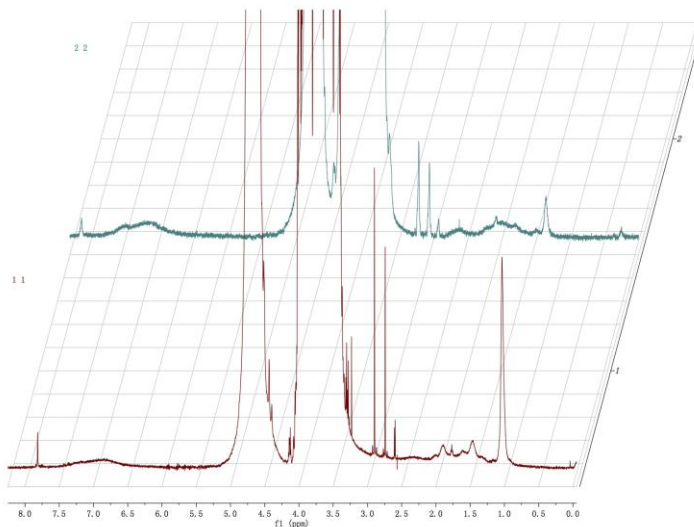


Figure S7. ^1H NMR of **M-BOB** (red line) and after direct micelle inversion (blue line) at 50°C in PBS (pH 7.4) with 200 mM Fru.

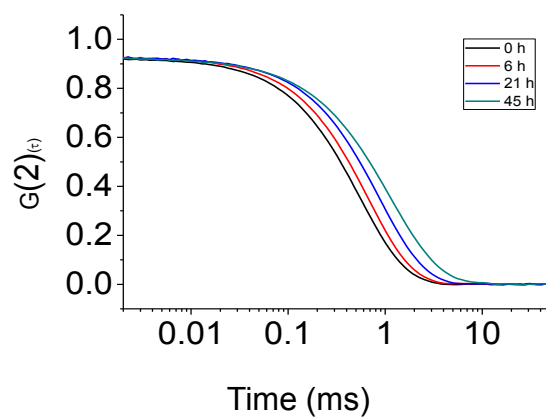


Figure S8. Correlation function of the dissociation process of **M-BOB** at 25°C in PBS (pH 7.4) with 200 mM Fru. (Corresponding scattered light intensity changes are plotted in Figure 5a)

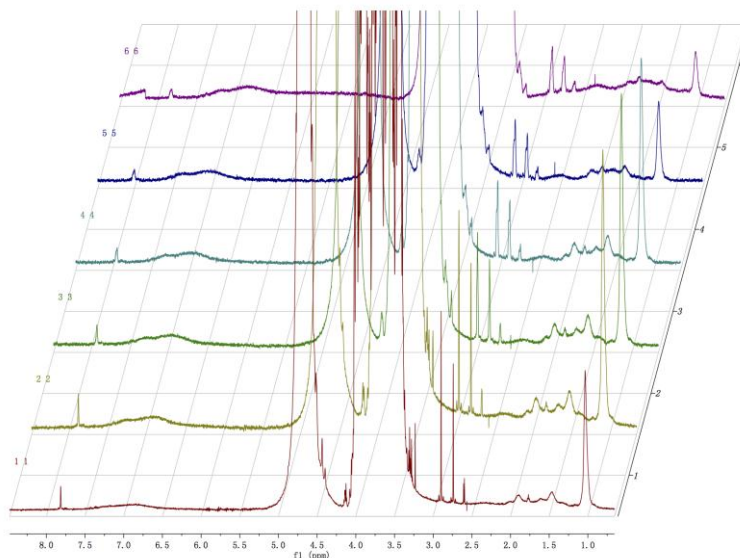


Figure S9. (from bottom to top) ^1H NMR of self-assembled **M-BOB** at 25 °C, 30 °C, 35 °C, 40 °C, 45 °C, 50 °C.

References:

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