Electronic Supplementary Information

Effect of hydrophilic block end groups and block junction on block copolymer self-assembly in solution

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Materials

Unless otherwise stated, all reactions were carried out under N_2 atmosphere. All reagents and chemicals were purchased from Sigma Aldrich, Alfa Aesar, and TCI and used as received. Styrene (99+%) was purchased from Sigma Aldrich and filtered over a column of basic alumina before use. Dry solvents were obtained via distillation using Na and benzophenone as drying agents for tetrahydrofuran (THF) and CaH_2 for dichloromethane (DCM).

Experimental Procedures

General Information

^{1}H NMR spectra were recorded on Agilent 500-MR DD2 magnetic resonance system and Varian/Oxford As-500 using CD_2Cl_2 or $CDCl_3$ as solvents. Molecular weights of polymers were measured on Agilent 1260 infinity gel permeation chromatography (GPC) system equipped with a PL gel 5 μm mixed D column and differential refractive index detectors. DMF was used as the GPC eluent with a flow rate of 1 mL min^{-1} at 35 °C. A PS standard kit (Agilent Technologies) was used for calibration. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) was performed on Bruker Ultraflex II TOF/TOF mass spectrometer equipped with a nitrogen laser (335 nm). The analytical sample was prepared by mixing a THF solution of an analyte with a THF solution of sinapic acid.

Scanning electron microscopy (SEM) was performed on Hitachi S-4300 at an acceleration voltage of 15 kV. Typically, droplets of the sample solution were placed on a slide glass and then sputtered with Pt with a thickness of 3 nm by using Hitachi E-1030 ion sputter. Transmission electron microscopy (TEM) was performed on JEOL JEM-2100 microscope at

200 kV. Specimens were prepared by placing a droplet of the sample solution and drying it on a carbon-coated Cu grid (200 mesh, EM science).

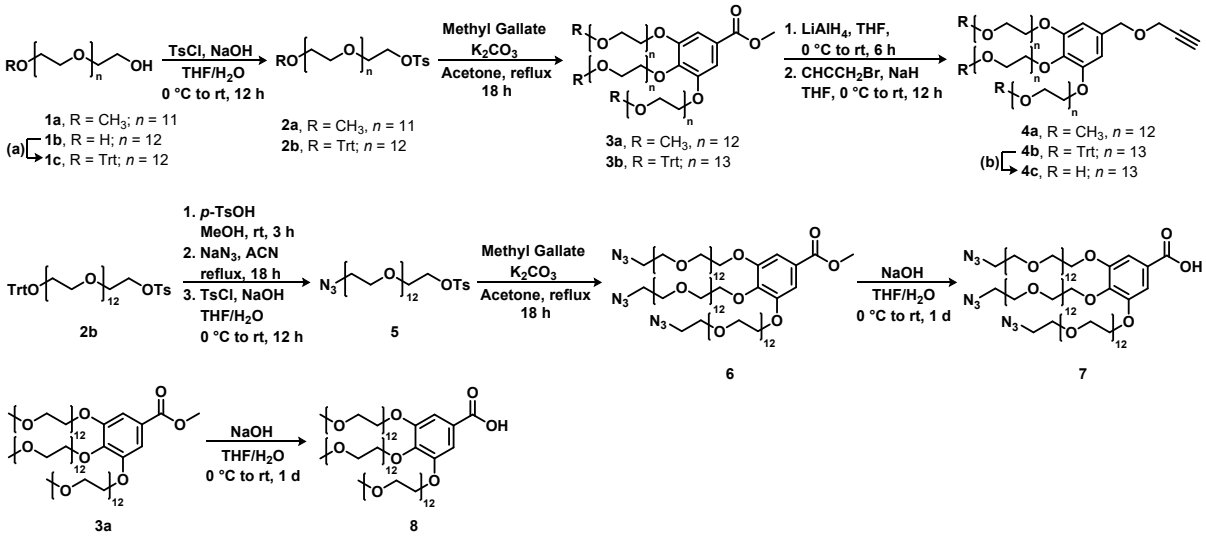

Fig. S1 Synthesis of hydrophilic PEG blocks (**4a**, **4c**, **7**, and **8**) with different end groups. Reagents and conditions: (a) Trityl chloride, DCM, rt, 8 h; (b) *p*-TsOH, MeOH, rt, 3 h.

Synthesis of a methoxy PEG block (4a)

The tosylation procedure was adapted from previous literature.[1,2] Poly(ethylene glycol) methyl ether (M_n = 550, **1a**, 10 g, 18.2 mmol) was dissolved in THF (50 mL) and cooled to 0 °C. A solution of NaOH (3.3 g, 81.9 mmol) in water (11 mL) was slowly added and the mixture was stirred at 0 °C. After 30 min, a solution of *p*-toluenesulfonyl chloride (TsCl, 2.7 g, 23.7 mmol) in THF (7 mL) was slowly added and the mixture was stirred for 6 h at 0 °C. After complete consumption of the starting compound (**1a**), which was confirmed by TLC (silica, DCM/MeOH, 9/1, v/v), the mixture was stirred at rt for 6 h to hydrolyze the excess TsCl. After the complete hydrolysis was confirmed by TLC (silica, DCM/MeOH, 9/1, v/v),

the mixture was diluted with water (20 mL) and diethyl ether (20 mL). The organic layer was separated, washed with a saturated $NaHCO_3$ (30 mL) and brine (30 mL), and was dried with anhydrous Na_2SO_4. The product was obtained as a pale yellow liquid (11.9 g, ca. 16.7 mmol, 92%). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): 7.79 (d, 2H, J = 8.0 Hz), 7.34 (d, 2H, J = 8.0 Hz), 4.15 (t, 2H, J = 5.0 Hz), 3.71–3.51 (m, 44H, -CH_2CH_2O-), 3.37 (s, 3H).

Methyl gallate (0.39 g, 2.1 mmol) and K_2CO_3 (2.35 g, 17.0 mmol) were added to a 250 mL two-neck flask charged with acetone under N_2. Compound **2a** (5.0 g, 7.0 mmol) was added to the flask, and the mixture was refluxed at 75 °C for 18 h. After the complete consumption of the methyl gallate confirmed by MALDI-TOF, the reaction was cooled to room temperature. The crude mixture was filtered through a filter paper and the solvent was removed under reduced pressure. The residue was extracted with DCM and washed with brine three times. The organic phase was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure.

Without further purification, the crude mixture containing **3a** (less than 2.1 mmol) was reduced by $LiAlH_4$ (0.24 g, 6.3 mmol) in THF under N_2 atmosphere for 6 h. The reaction mixture was quenched via Fieser workup and purified by column chromatography on silica (DCM/MeOH, 20/1 to 10/1, v/v) to obtain a pale yellow liquid (3.1 g, 1.76 mmol, 84% over 2 steps). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): 6.64 (s, 2H), 4.57 (d, 2H, J = 6.0 Hz), 4.17 (t, 4H, 4.0 Hz), 4.12 (t, 2H, 4.0 Hz), 3.83 (t, 4H, J = 5.0 Hz), 3.78 (t, 2H, J = 5.0 Hz), 3.74–3.51 (m, -CH_2CH_2O-), 3.38 (s, 3H), 2.46 (s, 1H).

The product (870 mg, 0.49 mmol) from the previous step was dissolved in dry THF (20 mL) and the solution was added dropwise to a suspension of NaH (60% suspension in oil, 40 mg, 1.0 mmol) in dry THF at 0 °C under N_2 atmosphere, and the mixture was stirred from 0

°C to rt for 2 h. Propargyl bromide (0.11 mL, 1.0 mmol) was added to the reaction mixture and stirred at room temperature for 12 h. The reaction mixture was cooled to 0 °C and saturated NH_4Cl solution was added. After evaporating THF under reduced pressure, the mixture was extracted with DCM, washed with brine, and dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography on silica (DCM/MeOH, 20/1 to 8/1, v/v) to obtain a yellow liquid (780 mg, 0.43 mmol, 89%). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): 6.60 (s, 2H), 4.50 (s, 2H), 4.20–4.08 (m, 8H), 3.84 (t, 4H, J = 5.0 Hz), 3.78 (t, 2H, J = 5.0 Hz), 3.74–3.51 (m, -CH_2CH_2O-), 3.39 (s, 9H), 2.51 (s, 1H).

Synthesis of a hydroxyl PEG block (4c)

Synthetic procedure of compound **4c** was adapted from previous literature, starting from poly(ethylene glycol) ($\boldsymbol{M}_n$ = 600, **1b**).[1–3] ^{1}H NMR (500 MHz, $CDCl_3$, ppm): 6.59 (s, 2H), 4.49 (s, 2H), 4.20–4.08 (m, 8H), 3.84 (t, 4H, J = 5.0 Hz), 3.77 (t, 2H, J = 5.0 Hz), 3.74–3.51 (m, -CH_2CH_2O-), 2.50 (s, 1H).

Synthesis of an azido PEG block (7)

Compound **2b** was prepared according to the literature.[1–3] Compound **2b** (10.0 g, 9.3 mmol) was dissolved in methanol (50 mL) and *p*-toluenesulfonic acid (0.18 g, 0.93 mmol) was added. The mixture was stirred at rt for 3 h, and quenched with $NaHCO_3$ (0.78 g, 9.3 mmol). After the removal of the solvent under reduced pressure, the mixture was purified by column chromatography on silica (DCM/MeOH, 20/1 to 8/1, v/v) to obtain a monotosyl PEG as a pale yellow liquid (6.0 g, 7.8 mmol, 84%). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): 7.78 (d,

2H, *J* = 6.8 Hz), 7.34 (d, 2H, *J* = 8.0 Hz), 4.16 (t, 4H, *J* = 8.0 Hz), 3.75–3.55 (m, -CH_2CH_2O-), 2.57 (s, 1H), 2.45 (s, 3H).

The product (6.0 g, 7.8 mmol) from the previous step was dissolved in acetonitrile (50 mL), and sodium azide (0.84 g, 14.0 mmol) was added. The mixture was reluxed for 18 h, and cooled to rt. The precipitate was filtered off and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica (DCM/MeOH, 20/1 to 10/1, v/v) to obtain an azido PEG as a pale yellow liquid (4.0 g, 6.1 mmol, 78%). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): 3.75–3.59 (m, -CH_2CH_2O-), 3.39 (t, 2H, *J* = 5.0 Hz), 2.79 (s, 1H).

The azido PEG (4.0 g, 6.1 mmol) was tosylated in the same way as previously described for the methoxy PEG to obtain compound **5** as a yellow liquid (4.7 g, 5.8 mmol, 95%). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): 7.80 (d, 2H, *J* = 8.0 Hz), 7.34 (d, 2H, *J* = 8.0 Hz), 4.16 (t, 4H, *J* = 5.5 Hz), 3.75–3.59 (m, -CH_2CH_2O-), 3.39 (t, 2H, *J* = 5.0 Hz), 2.45 (s, 3H).

Compound **5** (4.7 g, 5.8 mmol) was reacted with a methyl gallate according to the previously described procedure, and the crude product was purified by column chromatography on silica (DCM/MeOH, 20/1 to 8/1, v/v) to obtain compound **6** as a pale yellow liquid (1.9 g, 0.95 mmol, 54%). ^{1}H NMR (500 MHz, $CDCl_3$, ppm): 7.29 (s, 2H), 4.24–4.16 (m, 6H), 3.88 (s, 3H), 3.86 (t, 4H, *J* = 5.0 Hz), 3.79 (t, 2H, *J* = 5.0 Hz), 3.75–3.59 (m, -CH_2CH_2O-), 3.39 (t, 6H, *J* = 5.0 Hz).

Compound **6** (460 mg, 0.23 mmol) was dissolved in THF (2 mL) and cooled to 0 ℃. 0.8 mL of 12% aqueous NaOH solution was slowly added at 0 ℃, and the mixture was stirred for 1 day at rt. The solution was cooled to 0 ℃, and neutralized by slowly adding conc. HCl. The mixture was extracted with DCM to obtain compound **7** (310 mg, 0.16 mmol, 71%) as a

yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): 7.36 (s, 2H), 4.26–4.18 (m, 6H), 3.85 (t, 4H, J = 5.0 Hz), 3.79 (t, 2H, J = 5.0 Hz), 3.75–3.59 (m, -CH_2CH_2O-), 3.39 (t, 6H, J = 5.0 Hz).

Synthesis of a methoxy PEG block (8)

The crude mixture containing **3a** (less than 1.0 mmol) was dissolved in THF (6 mL) and cooled to 0 ℃. 3.3 mL of 12% aqueous NaOH solution was slowly added at 0 ℃, and the mixture was stirred for 1 day at rt. The solution was cooled to 0 ℃, and neutralized by slowly adding conc. HCl. After extraction with DCM, the crude product was purified by column chromatography on silica (DCM/MeOH, 20/1 to 8/1, v/v) to obtain compound **8** (1.1 g, 0.61 mmol, 60% over 2 steps) as a yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$, ppm): 7.37 (s, 2H), 4.26–4.18 (m, 6H), 3.86 (t, 4H, J = 5.0 Hz), 3.80 (t, 2H, J = 5.0 Hz), 3.75–3.53 (m, -CH_2CH_2O-), 3.39 (s, 9H).

General procedure for the synthesis of azido and amino polystyrenes

Azido polystyrenes were synthesized according to the previous literature.[3,4] CuBr (313 mg, 2.2 mmol) was charged in a 100 mL Schlenk flask, and dried under vacuum for 15 min. *N,N,N′,N″,N‴*-pentamethyldiethylenetriamine (PMDETA) (0.91 mL, 4.4 mmol) in anisole (2 mL) was added to the flask, and the mixture was gently stirred under N_2 for 10 min. (1-Bromoethyl)benzene (80 mg, 0.44 mmol) in anisole (1 mL) and styrene (50 mL, 440 mol) was added and the mixture was degassed via bubbling N_2 into the mixture for 15 min. ATRP reaction was carried out at 90 °C. The reaction was monitored by GPC and quenched by exposing it to air and cooling it in a liquid N_2 bath. The cooled mixture was filtered through a pad of aluminum oxide (basic) using DCM as an eluent for the removal of Cu ions. The

filtered solution was concentrated by rotary evaporation, diluted with a small amount of DCM, and then precipitated into methanol. Polystyrene end-functionalized with bromine was obtained as a white powder by filtration and dried in vacuo.

The obtained bromo end-functionalized polystyrene (10 g, ca. 0.44 mmol, 1 eq.) and sodium azide (0.283 g, 10 eq.) were dissolved in DMF (250 mL) and stirred at room temperature under N_2 for 12 h. After the removal of the solvent rotary evaporation, azido end-functionalized polystyrene was obtained as a white powder by precipitation in methanol.

Amino polystyrenes were obtained via reduction using $LiAlH_4$. An azido polystyrene was dissolved in dry THF, and LiAlH4 (10 eq.) was slowly added at 0 °C. After 6 h, the reaction was quenched via Fieser workup procedure and amino polystyrenes were obtained by precipitation in methanol in quantitative yields.

CUAAC of the PEG blocks and the azido PSs

Compound **4a** or **4c** (30 mg, 0.017 mmol), azido end-functionalized polystyrene (2.5 equivalents of compound **4**), $CuSO_4 \cdot 5H_2O$ (13 mg, 0.052 mmol), and sodium ascorbate (7 mg, 0.035 mmol) were dissolved in dry DMF under N_2 atmosphere. The mixture was stirred for 1 day at room temperature and the reaction was monitored by GPC. After consumption of the PEG block, DMF was removed by rotary evaporation. The crude product was purified by column chromatography on silica (DCM/MeOH, 30/1 to 9/1, v/v). After precipitation in methanol, a pure block copolymer was obtained as a white powder.

Amidation of the PEG blocks and the amino PSs

Compound **7** or **8** was dissolved in dry DCM and the solution was cooled to 0 °C. *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC·HCl, 1.5 eq.) and 4-(Dimethylamino)pyridinium 4-toluenesulfonate (DPTS, 0.5 eq.) were added to the solution, and the mixture was stirred for 1 day at rt. The mixture was washed with water and brine, and purified by column chromatography on silica (DCM/MeOH, 30/1 to 9/1, v/v). After precipitation in methanol, a pure block copolymer was obtained as a white powder.

General procedure for the BCP self-assembly

The synthesized BCPs were self-assembled as previously reported.[3] 5 mg of BCP was dissolved in 1 mL of acetone/dioxane solvent mixture followed by the addition of water at the rate of 0.25 mL/h for 4 h. The organic solvent was removed by subsequent dialysis against water for 24 h.

Table S1. MALDI-TOF profiles of PEG blocks.

Compound **4a**		Compound **4c**		Compound **7**		Compound **8**	
m/z	Intensity	m/z	Intensity	m/z	Intensity	m/z	Intensity
1671.3	183	1493.6	27	1469.4	102	1855.1	91
1715.5	626	1537.5	92	1513.4	262	1899.2	370
1759.5	1453	1581.5	243	1557.5	549	1943.2	868
1803.5	2430	1625.6	450	1601.5	934	1987.2	1357
1847.6	3522	1669.7	709	1645.5	1488	2031.3	1620
1891.6	4377	1713.7	988	1689.6	2038	2075.4	1660
1935.7	4774	1757.8	1190	1733.6	2581	2119.5	1539
1979.8	4737	1801.8	1378	1777.7	3023	2163.7	1200
2024.0	4370	1845.9	1436	1821.7	3301	2207.7	860
2067.9	3694	1890.0	1375	1865.8	3329	2207.5	749
2112.0	2934	1934.0	1183	1909.9	3048	2252.4	416
2156.4	2073	1978.1	954	1593.9	2593	2295.9	167
2200.3	1308	2022.2	701	1998.1	2054	2341.0	43
2244.7	748	2067.2	450	2042.1	1510		
2288.7	349	2111.2	248	2086.3	970		
2333.1	105	2154.7	117	2131.1	556		
		2199.2	38	2174.8	276		
				2219.4	111		

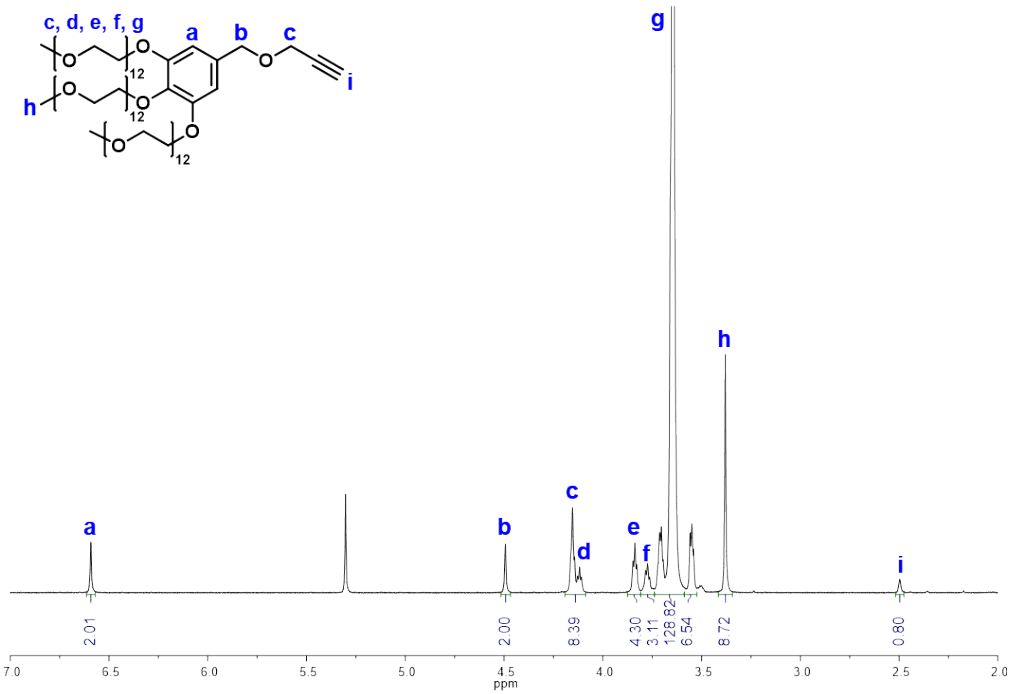

Fig. S2 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **4a**.

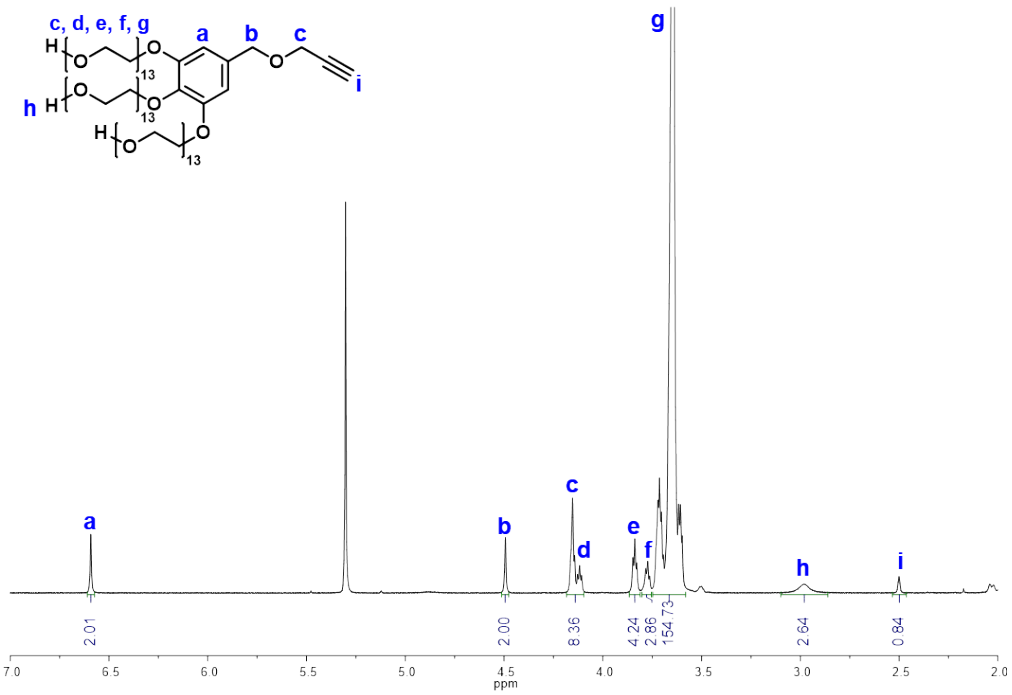

Fig. S3 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **4c**.

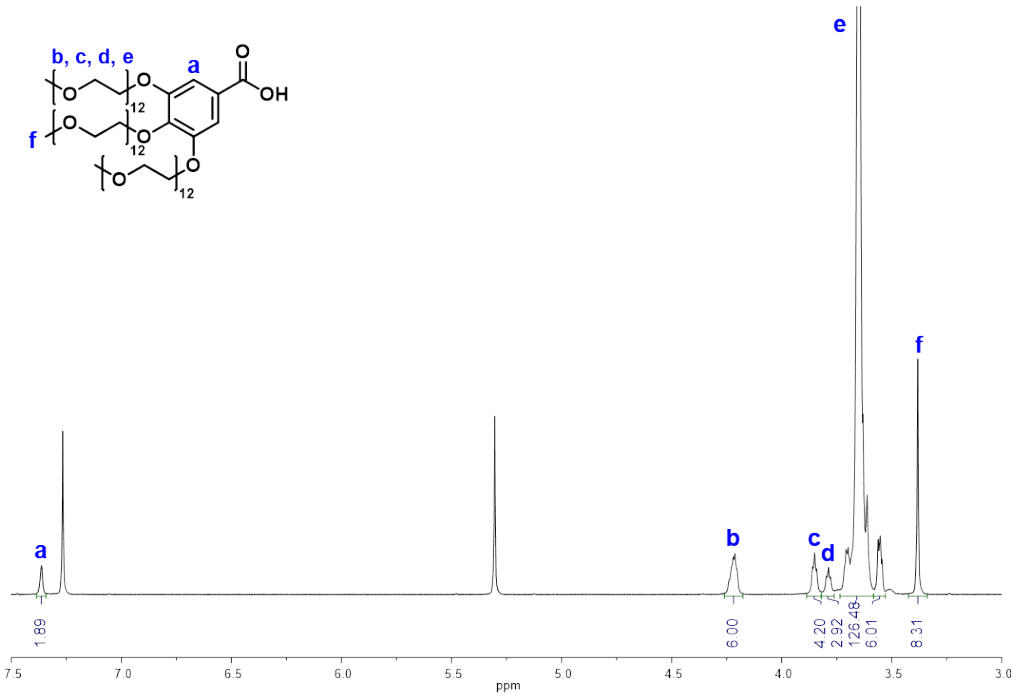

Fig. S4 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **7**.

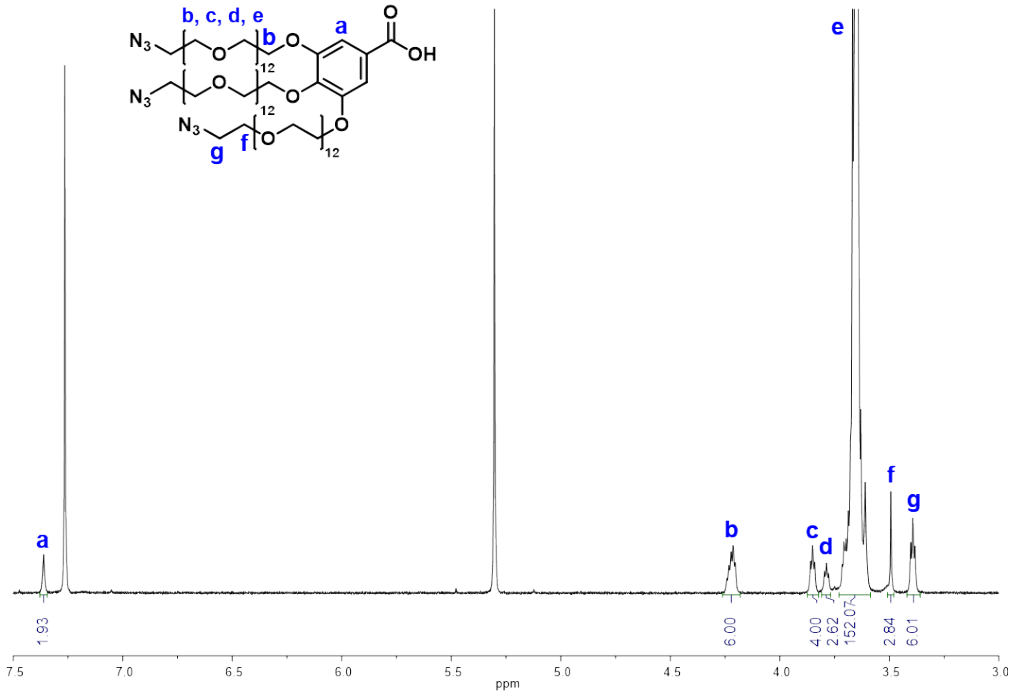

Fig. S5 ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of compound **8**.

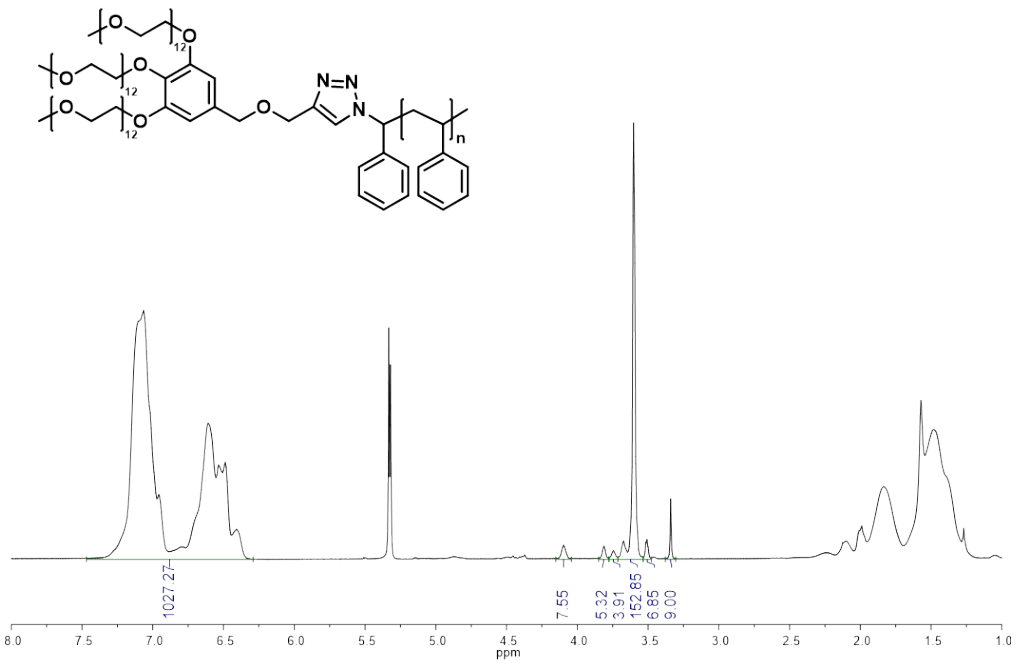

Fig. S6 ^{1}H NMR spectrum (500 MHz, CD_2Cl_2) of $(MeO\text{-}PEG)_3$-trz-PS.

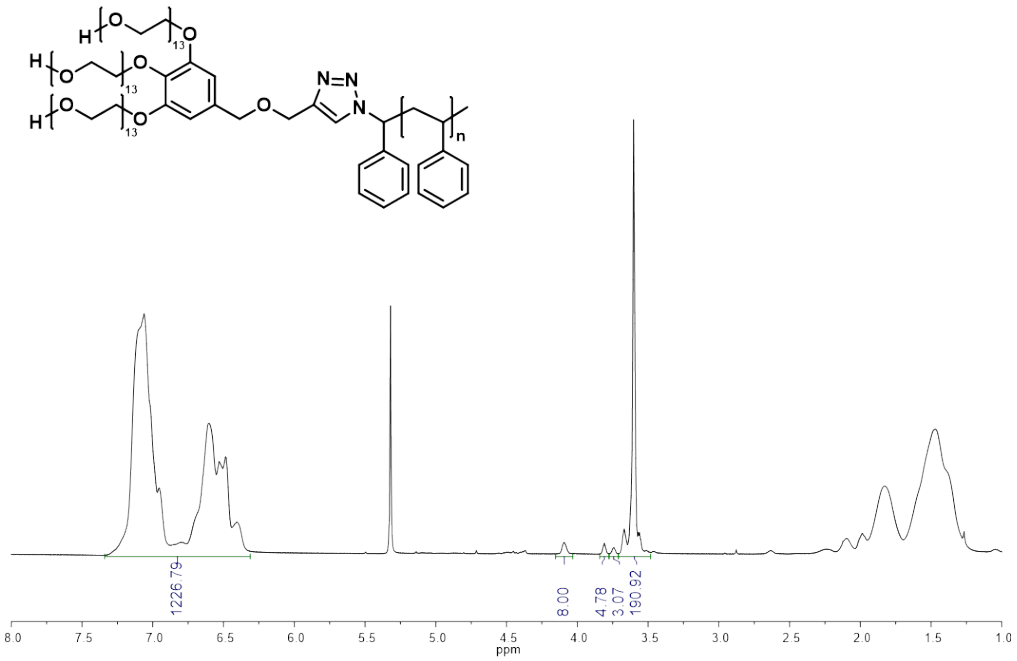

Fig. S7 ^{1}H NMR spectrum (500 MHz, CD_2Cl_2) of $(HO\text{-}PEG)_3$-trz-PS.

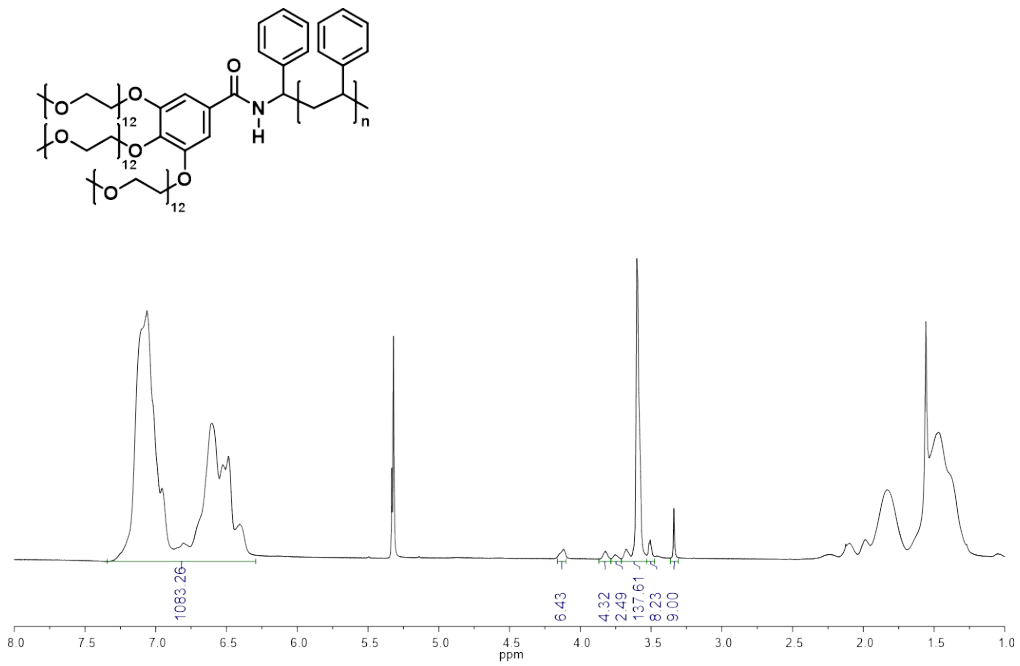

Fig. S8 ^{1}H NMR spectrum (500 MHz, CD_2Cl_2) of $(MeO\text{-}PEG)_3$-amd-PS.

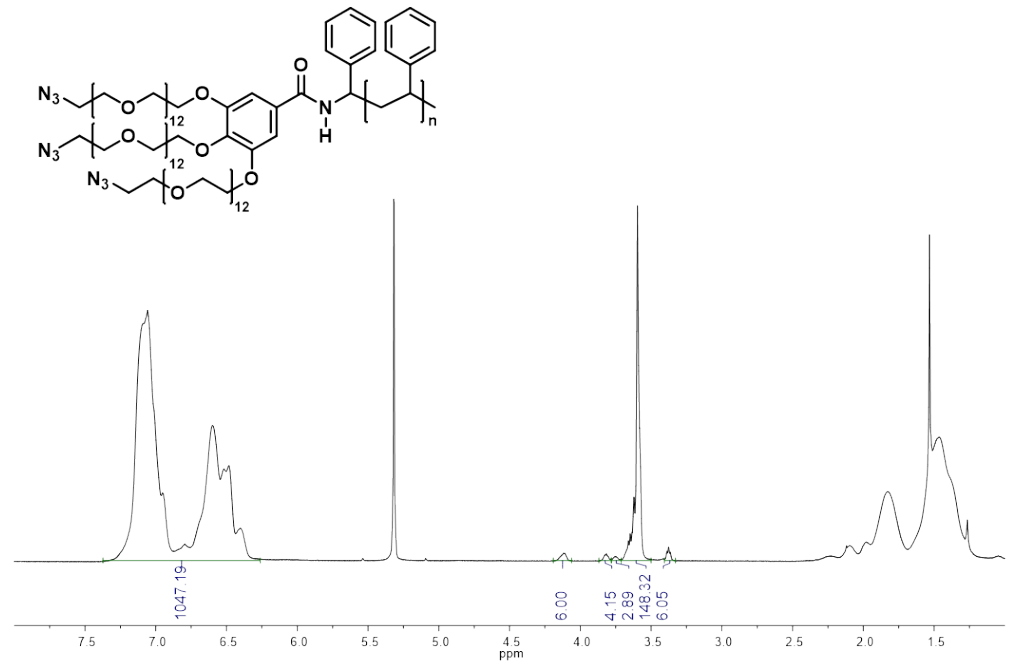

Fig. S9 ^{1}H NMR spectrum (500 MHz, CD_2Cl_2) of $(N_3\text{-}PEG)_3$-amd-PS.

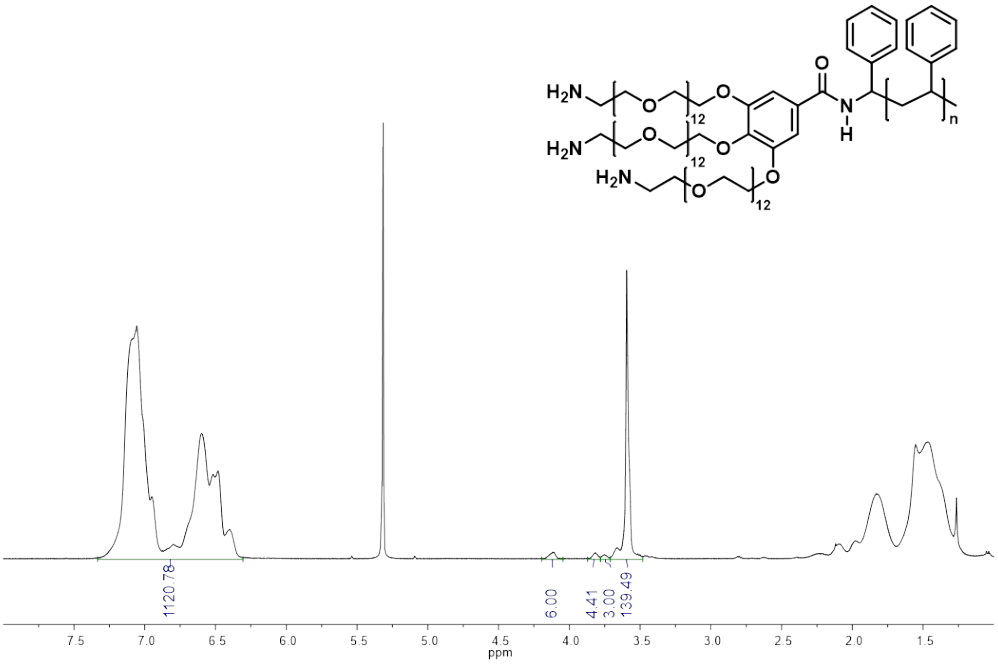

Fig. S10 ^{1}H NMR spectrum (500 MHz, CD_2Cl_2) of $(H_2N\text{-PEG})_3$-amd-PS.

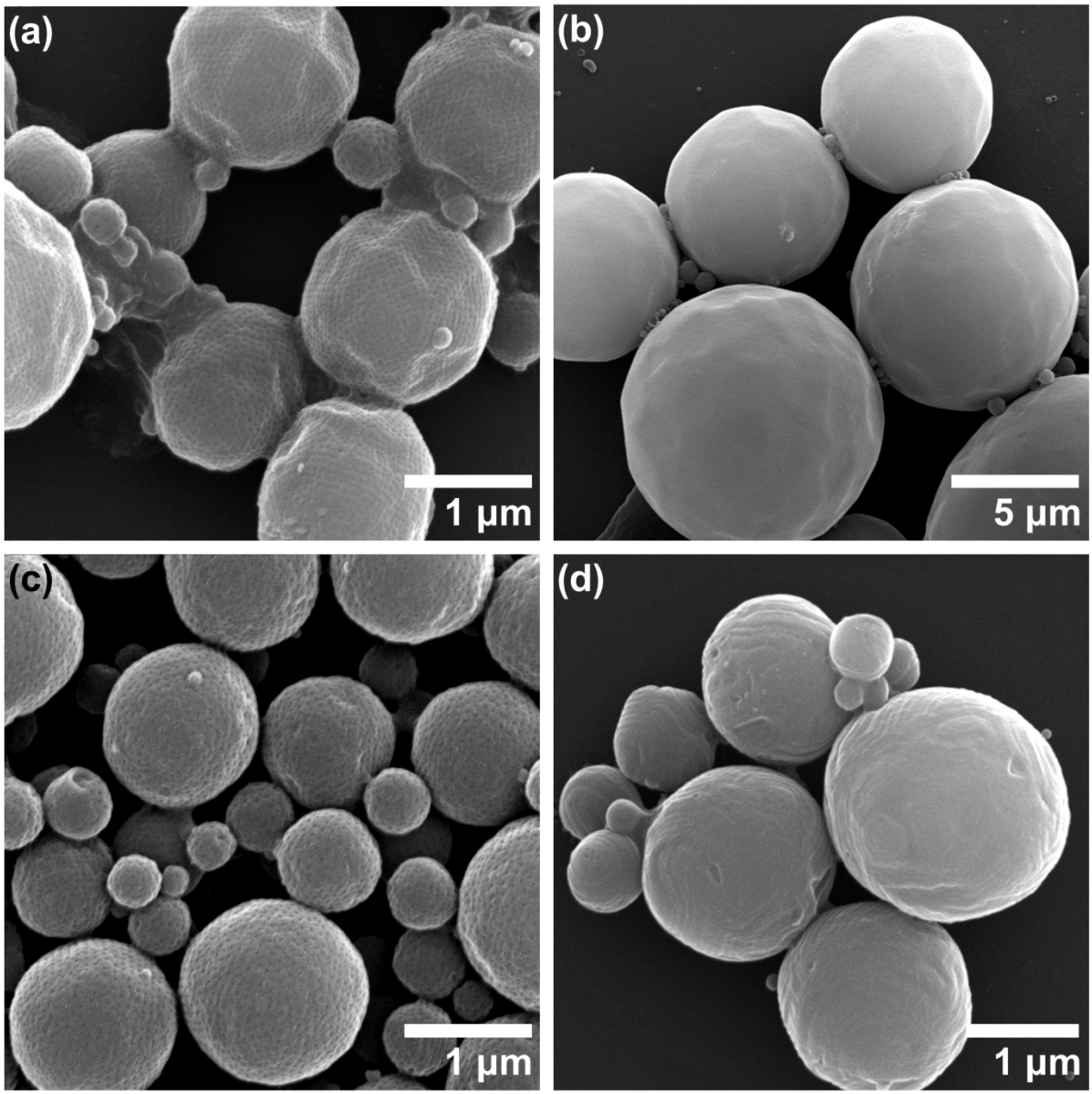

Fig. S11 SEM images of (a and b) $(MeO\text{-}PEG)_3$-trz-PS cubosomes self-assembled in (a) acetone and (b) dioxane, (c) $(HO\text{-}PEG)_3$-trz-PS cubosomes self-assembled in acetone, and (d) $(HO\text{-}PEG)_3$-trz-PS hexosomes self-assembled in dioxane.

Notes and references

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