

Synthesis and Direct Assembly of Linear-Dendritic Copolymer via CuAAC Click Polymerization-Induced Self-Assembly (CPISA)

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Experimental Section

Materials and Instrumentation. Poly(ethylene glycol)-N₃ (PEG₁₁₂-N₃),¹ 3-azidopropyl acetate,² and 3-azido-2-(azidomethyl)-2-(hydroxymethyl)propyl pent-4-ynoate³ were synthesized according to previous literature. Tripropargylamine (Sigma-Aldrich, 98 %), copper (II) sulfate pentahydrate (CuSO₄·5H₂O, BDH, ACS grade), ascorbic acid (Alfa Aesar, 99%), copper (I) acetate (CuOAc, Sigma-Aldrich, 97 %), ammonia solution (NH₃·H₂O, ACROS, 28-30 % in water), thionyl chloride (TCI America, > 98 %), sodium azide (VWR International, high purity grade), phenylacetyl chloride (Alfa Aesar, 98 %), *N,N,N',N',N''*-pentamethyldiethylenetriamine (PMDETA, Sigma-Aldrich, 99%), pyridine (Sigma-Aldrich, 99.8%), tetrahydrofuran (THF, Sigma-Aldrich, ≥ 99.0 %), *N,N*-dimethylformamide (DMF, Sigma-Aldrich, ≥ 99.8 %), methanol (Sigma-Aldrich, ≥ 99.8 %), ethyl ether (Sigma-Aldrich, ≥ 99.8 %), chloroform (CHCl₃, Sigma-Aldrich, ≥ 99.0 %), dimethyl sulfoxide (DMSO, VWR International, > 99.9 %) were used as received. Dichloromethane (CH₂Cl₂, Sigma-Aldrich, > 99.5 %) was distilled over CaH₂ before use.

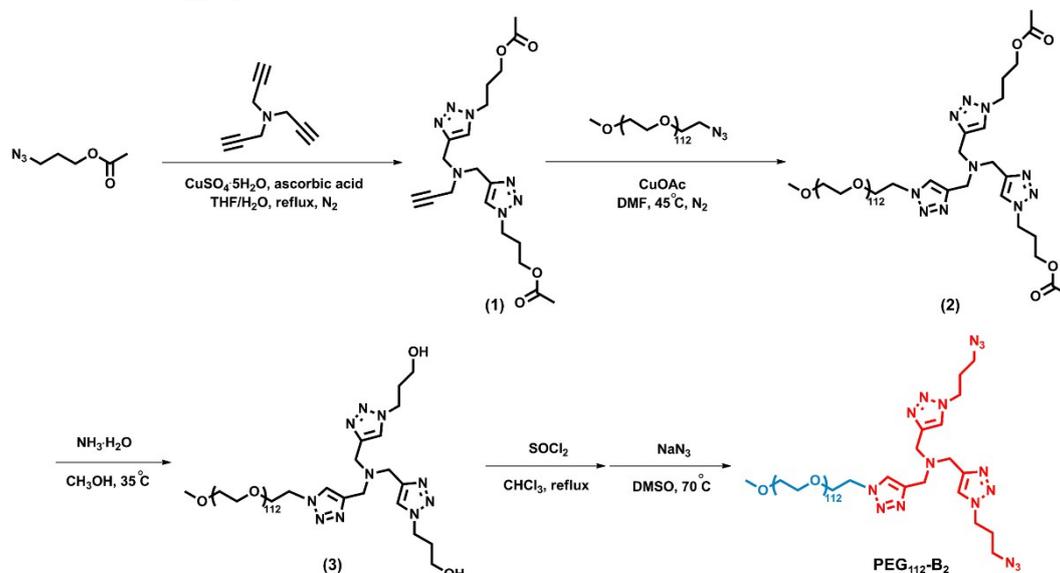
The proton nuclear magnetic resonance (¹H NMR) spectroscopy was performed on a Bruker 400 MHz spectrometer using CDCl₃ or DMSO-d₆ as solvent at 25 °C.

The size exclusion chromatography (SEC) analyses were conducted on a Waters SEC system at 55 °C with a DMF flow rate of 1 mL min⁻¹. The DMF SEC system was equipped with a Waters 515 HPLC pump, Polymer Standards Services columns, a Waters 2414 refractive index (RI) and a multi-angle laser light scattering (MALLS) detector. The apparent molecular weights were calculated based on linear poly(methyl methacrylate) PMMA standards. The absolute molecular weights were measured by RI detector and MALLS detector with the light wavelength at 658 nm using ASTRA software from Wyatt Technology. The used dn/dc value of 0.0422 mL g⁻¹ for the linear-dendritic copolymers as determined separately via on-line measurement.

The hydrodynamic size (*D_h*) of the assemblies was performed on a Malvern Zetasizer Nano ZS laser light scattering spectrometer equipped with 633 nm He-Ne laser. Scattering light at 173° angle was detected and analyzed.

Transmission electron microscopy (TEM) images were recorded on a 200 kV JEOL JEM-2010 high resolution transmission electron microscope. For the preparation of TEM samples, 10 μL of diluted colloidal solution was dropped onto a piece of copper grid, and the droplet was blotted up using filter paper after 1 min. This process was repeated for three times before staining with 10 μL of phosphotungstic acid (PTA) solution (0.5 wt %). After being stained by PTA solution, the copper grid was dried at room temperature before TEM observation.

Synthesis of PEG₁₁₂-B₂ macroinitiator



Scheme S1. The synthetic routes to PEG₁₁₂-B₂ macroinitiator.

Synthesis of compound (1). To solution of tripropargylamine (2.83 g, 21.56 mmol) and 3-azidopropyl acetate (6.20 g, 43.30 mmol) in a 250 mL THF/H₂O (4/1, v) mixture was added CuSO₄·5H₂O (0.27 g, 1.08 mmol) and ascorbic acid (0.38 g, 2.16 mmol) under N₂ atmosphere and the resulting solution was refluxed for 48 h under inert atmosphere. The reaction mixture was concentrated by rotary evaporation and purified via silica gel chromatography using CH₂Cl₂ as eluent to afford compound 1 (5.40 g, 60 % yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃, 25 °C) δ (ppm): 7.62 (s, 2H, CH₂C=CHN), 4.45 (t, 4H, NCH₂CH₂CH₂OCOCH₃), 4.09 (t, 4H, NCH₂CH₂CH₂OCOCH₃), 3.86 (s, 4H, NCH₂C=CH), 3.37 (d, 2H, NCH₂C≡CH), 2.29 (t, 1H, NCH₂C≡CH), 2.26 (m, 4H, NCH₂CH₂CH₂OCOCH₃), 2.07 (s, 6H, NCH₂CH₂CH₂OCOCH₃). ¹³C NMR (ppm, in CDCl₃) δ (ppm): 170.87, 144.51, 123.33, 78.47, 73.75, 60.87, 47.71, 47.10, 42.24, 29.41, 20.88.

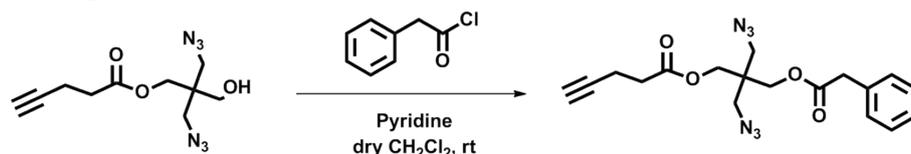
Synthesis of compound (2). To solution of compound 1 (0.80 g, 1.92 mmol) and PEG₁₁₂-N₃ (6.50 g, 1.28 mmol) in DMF (25 mL) was added CuOAc (12.0 mg, 98.00 μ mol) under N₂ atmosphere and the resulting solution was reacted at 45 °C for 24 h under inert atmosphere. The reaction mixture precipitated into ethyl ether to afford crude product. The crude product was dissolved in CH₂Cl₂ and 2 equiv. of PMDETA ligand was added before passing through a flash alumina column to remove the copper ions. The collected CH₂Cl₂ solution was concentrated to 20 mL before being precipitating into ethyl ether for three times. The final dried product of compound 2 was white solid (6.30 g, 90 %). ¹H NMR (400 MHz, DMSO, 25 °C) δ (ppm): 8.05 (s, 2H, CH₂C=CHN), 8.03 (s, 1H, CH₂C=CHN), 4.44 (t, 4H, NCH₂CH₂CH₂OCOCH₃), 3.99 (t, 4H, NCH₂CH₂CH₂OCOCH₃), 3.67 (m, 2H, NCH₂C=CH), 3.62 (s, 4H, NCH₂C=CH), 3.50 (m, CH₂CH₂O), 2.14 (m, 4H, NCH₂CH₂CH₂OCOCH₃), 1.98 (s, 6H, NCH₂CH₂CH₂OCOCH₃).

Synthesis of compound (3). To solution of compound 2 (4.20 g, 0.77 mmol) in 25 mL methanol was added NH₃·H₂O (5.00 mL) and the resulting solution was stirred at 35 °C overnight. The reaction mixture was precipitated into ethyl ether for three times and dried under vacuum to afford compound 3 as a white solid (3.50 g, 85 % yield). ¹H NMR (400 MHz, DMSO, 25 °C) δ (ppm): 8.03 (m, 3H, CH₂C=CHN), 4.67 (t, 4H, NCH₂CH₂CH₂OH), 4.52 (t, 4H, NCH₂CH₂CH₂OH), 3.68 (m, 2H, NCH₂C=CH), 3.61 (s, 4H, NCH₂C=CH), 3.50 (m, CH₂CH₂O), 1.96 (m, 4H, NCH₂CH₂CH₂OH).

Synthesis of macroinitiator PEG₁₁₂-B₂. Compound 3 (2.00 g, 0.37 mmol) and CHCl₃ (20 mL)

were added into a 250 mL flask. Thionyl chloride (0.36 g, 3.02 mmol) was diluted with CHCl_3 (20 mL) and then added dropwise to the flask at room temperature. After refluxing 24 h, the mixture was concentrated and then dissolved in DMSO (30 mL), to which NaN_3 (0.24 g, 3.72 mmol) was added and reacted at 70 °C for 24 h. The solution was precipitated into ethyl ether, and redissolved with CH_2Cl_2 , and then passed a neutral alumina column to remove unreacted NaN_3 . The CH_2Cl_2 was concentrated to 10 mL and precipitated into ethyl ether for three times to obtain $\text{PEG}_{112}\text{-B}_2$ as a white solid (1.58 g, 79 % yield).

Synthesis of $\text{AB}_2\text{-Bn}$ monomer



Scheme S2. Protocols for synthesis of $\text{AB}_2\text{-Bn}$ monomer.

Synthesis of $\text{AB}_2\text{-Bn}$ monomer. 3-azidopropyl acetate, 3-azido-2-(azidomethyl)-2-(hydroxymethyl)propyl pent-4-ynoate (6.00 g, 22.53 mmol), pyridine (15 mL) and dried CH_2Cl_2 (150 mL) were added into a 250 mL flask. Phenylacetyl chloride (4.18 g, 27.04 mmol) was diluted with CH_2Cl_2 (15 mL) and then added dropwise to the flask at 0 °C. Then the mixture was stirred at room temperature overnight. The solution was washed with 0.5 M HCl, water, and brine for three times, respectively. The CH_2Cl_2 solution was dried with MgSO_4 before purified via silica column chromatography (hexanes/ethyl acetate = 5/1, v) to afford the $\text{AB}_2\text{-Bn}$ as a pale yellow oil (6.26 g, 72.3 %).

Preparation of linear-dendritic $\text{PEG}_{112}\text{-p}(\text{AB}_2\text{-Bn})_x$ assemblies via dispersion CuAAC polymerization. Linear-dendritic copolymer $\text{PEG}_{112}\text{-p}(\text{AB}_2\text{-Bn})_x$ assemblies were prepared by CuAAC polymerization of the $\text{AB}_2\text{-Bn}$ monomer using $\text{PEG}_{112}\text{-B}_2$ as the macroinitiator. A typical synthetic procedure to synthesize $\text{PEG}_{112}\text{-p}(\text{AB}_2\text{-Bn})_{80}$ in $\text{CH}_3\text{OH}/\text{H}_2\text{O}$ (90/10, by wt) was as follows: $\text{PEG}_{112}\text{-B}_2$ (17.7 mg, 3.25 μmol), $\text{CuSO}_4\cdot 5\text{H}_2\text{O}$ (1.0 mg, 4.00 μmol), CH_3OH (0.90 mL) and H_2O (80.0 μL) were added into a 10 mL Schlenk flask. The $\text{AB}_2\text{-Bn}$ monomer (0.10 g, 0.26 mmol) was charged into the flask after the mixed solution was stirred for 15 min. The sealed flask was degassed by three freeze-pump-thaw cycles. At last cycle, the flask was opened when everything was frozen to quickly add ascorbic acid (3.5 mg, 20.00 μmol) into the flask before re-capping the flask. The flask was vacuumed and backfilled with N_2 for three cycles before being immersed in a thermostatic oil bath at 45 °C to thaw the mixture solution and initiate the polymerization. After 24 h, the polymerization was quenched by liquid nitrogen. The resulting dispersion was dialyzed against reaction solution to remove residual monomer and most Cu catalyst. After dialysis, excess PMDETA (two equivalents to originally added Cu amount) was added into the solution to exact the residue Cu out of the linear-dendritic copolymer before passing the polymer solution through neutral alumina column. And then, an aliquot of the colloidal solution was analyzed by ^1H NMR, SEC, DLS, and TEM.

Similarly, $\text{PEG}_{112}\text{-p}(\text{AB}_2\text{-Bn})_x$ assemblies were also synthesized in methanol at 45 °C.

Kinetic studies of linear-dendritic $\text{PEG}_{112}\text{-p}(\text{AB}_2\text{-Bn})_{80}$ assemblies via dispersion CuAAC polymerization. A typical procedure to the kinetic study of $\text{PEG}_{112}\text{-p}(\text{AB}_2\text{-Bn})_{80}$ in $\text{CH}_3\text{OH}/\text{H}_2\text{O}$ (90/10, by wt) was as follows: $\text{PEG}_{112}\text{-B}_2$ (35.3 mg, 6.50 μmol), $\text{CuSO}_4\cdot 5\text{H}_2\text{O}$ (2.0 mg, 8.00 μmol), trioxane (5.00 mg, using as internal standard for calculating the conversion of monomer), CH_3OH

(1.79 mL) and H₂O (0.16 mL) were added into a 10 mL Schlenk flask. The AB₂ monomer (0.20 g, 0.52 mmol) was charged into the flask after above mixed solution stirred for 15 min. The sealed flask was degassed by three freeze-pump-thaw cycles. At last cycle, the flask was opened when everything was frozen to quickly add ascorbic acid (7.1 mg, 40.00 μmol) into the flask before re-capping the flask. The flask was vacuumed and backfilled with N₂ for three cycles before being immersed in a thermostatic oil bath at 45 °C for 24 h. The reaction solution was periodically sampled for ¹H NMR, SEC, and DLS characterizations.

Similarly, the kinetic study of PEG₁₁₂-p(AB₂-Bn)₈₀ assemblies via CuAAC polymerization were also conducted in methanol, water, and methanol/water (95/5, by wt) at 45 °C.

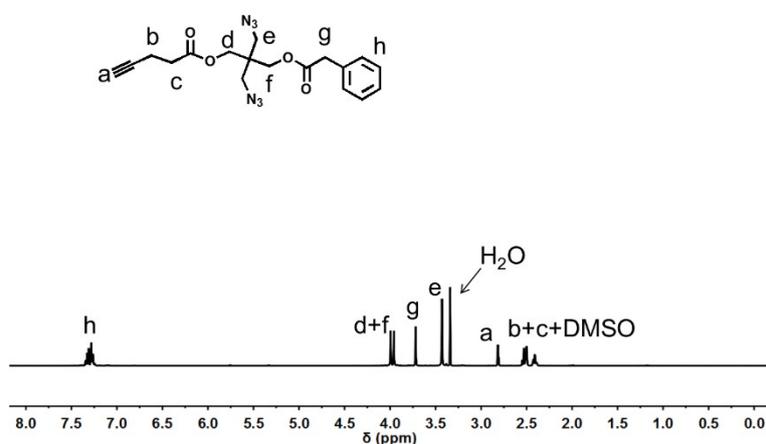


Fig. S1 ¹H NMR spectrum of AB₂-Bn monomer with DMSO-d₆ as solvent at 25 °C.

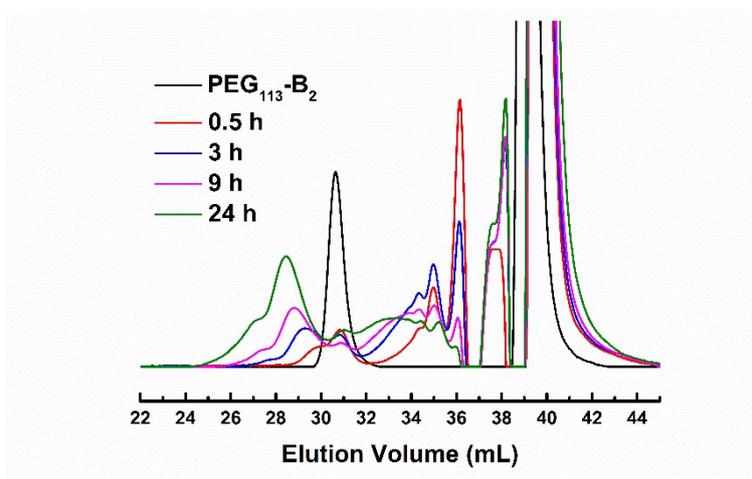


Fig. S2 SEC traces of the PEG₁₁₂-p(AB₂-Bn)₈₀ assemblies prepared via dispersion CuAAC polymerization in methanol/water (90/10, w) at 45 °C.

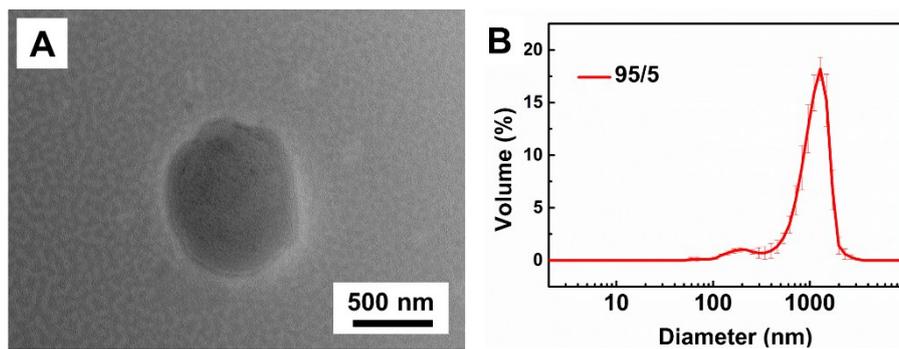


Fig. S3 A) TEM image and B) DLS characterization of the PEG₁₁₂-p(AB₂-Bn)₈₀ assemblies prepared via dispersion CuAAC polymerization in methanol/water (95/5, w) at 45 °C.

References

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