Versatile Synthesis of Asymmetrical Dendron-Like/Dendron-Like Poly(ε-Caprolactone)-*b*-Poly(γ-Benzyl-L-Glutamate) Block Copolymers

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ABSTRACT: Dendron-like/dendron-like poly(ε-caprolactone)-*b*-poly(γ-benzyl-L-glutamate) block copolymers with asymmetrical topology (PCL^8_{20}-*b*-$PBLG^n$, both the subscript and the superscript denote the degree of polymerization and the branch number, respectively; $n = 1$, 2, and 4) were synthesized by combining ring-opening polymerization (ROP) and click chemistry. The dendron-like propargyl focal point PCL^8_{20} precursor with eight branches was synthesized from the controlled ROP of ε-caprolactone, and then click conjugated with azido focal point poly(amido amine) dendrons to generate the PCL^8_{20}-dendrons with multiple primary amine groups. The PCL^8_{20}-dendrons were further used as macroinitiators for the ROP of γ-benzyl-L-glutamate *N*-carboxyanhydride to produce the targeted asymmetrical block copolymers. Their molecular structures and physicochemical properties were thoroughly characterized by means of FT-IR, ^{1}H NMR, gel permeation chromatography, differential scanning calorimetry, and wide angle X-ray diffraction. Both the maximal melting temperature and the degree of crystallinity of PCL block within copolymers decreased with increasing the PBLG branches and/or the chain length, demonstrating that the crystallinity of PCL block was progressively suppressed by PBLG block. Meanwhile, the PBLG block within copolymers progressively transformed from β-sheet to α-helical conformation with increasing the PBLG chain length. Consequently, this provides a versatile strategy for the synthesis of biodegradable and biomimetic block copolymers with asymmetrical dendritic topology. © 2011 Wiley Periodicals, Inc. J Polym Sci Part A: Polym Chem 49: 3491–3498, 2011

KEYWORDS: biodegradable; dendritic block copolymers; ring-opening polymerization; synthesis

INTRODUCTION Over the past three decades, dendritic polymers (e.g., dendrimers, hyperbranched polymers, dendronized polymers, and linear-dendritic copolymers) received much attention because of their unique solution, bulk, and hierarchical self-assembly properties, enabling them as a versatile tool to tune the properties of complex functional materials.[1–8] In particular, they have been fabricated into multiscale micro-/nano-structures and soft gels, which are useful modalities for diagnosis, drug/gene delivery, nanomedicine, and tissue engineering.[9–12]

Owing to their biodegradability and biocompatibility, both aliphatic polyesters [e.g., poly(ε-caprolactone), PCL] and synthetic polypeptides have been widely investigated for nanomedicine and medical scaffolds,[13–15] and some of them entered clinical trials.[16] To take advantage of synthetic polymers and biomimetic polypeptides, increasing efforts are made on the hybrids of polypeptides with biomedical polymers [e.g., poly(ethylene oxide) and PCL].[17–21] Therefore, the merger of dendritic polypeptides with dendritic aliphatic polyesters affords an asymmetrical macromolecular topology with tunable composition and accessible peripheries, which holds great potentials in biomedical applications. The synthesis and properties of linear-dendritic PCL and/or polypeptide copolymers were studied by several groups;[1,22–25] however, no studies on dendritic/dendritic polypeptide/PCL block copolymers were reported until now.

Since the introduction of "click chemistry" methodology, both copper-catalyzed azide-alkyne cycloaddition (CuAAC) and thiol-ene/-yne reactions proved to be the robust and modular strategies for the synthesis of dendritic architectures.[26–35] The intensive efforts were also made on the syntheses and modifications of biodegradable aliphatic polyesters (e.g., PCL, polylactides, and polyglycolide) by utilizing click chemistry.[36–40] Our group recently designed and synthesized a novel class of dendron-like/linear PCL- and polypeptide-based block copolymers by combining CuAAC and ring-opening polymerization (ROP), which established a platform for nanomedicine and stimuli-sensitive hydrogels.[22–25,41–46] Herein, the versatile synthesis of dendron-like/dendron-like PCL-*b*-poly(γ-benzyl-L-glutamate) block copolymers with asymmetrical topology (i.e., PCL^8_{20}-*b*-$PBLG^n$, both the subscript and the superscript denote the degree of polymerization and the branch number, respectively; $n = 1$, 2, and 4) was developed by combining ROP and CuAAC (Scheme 1),

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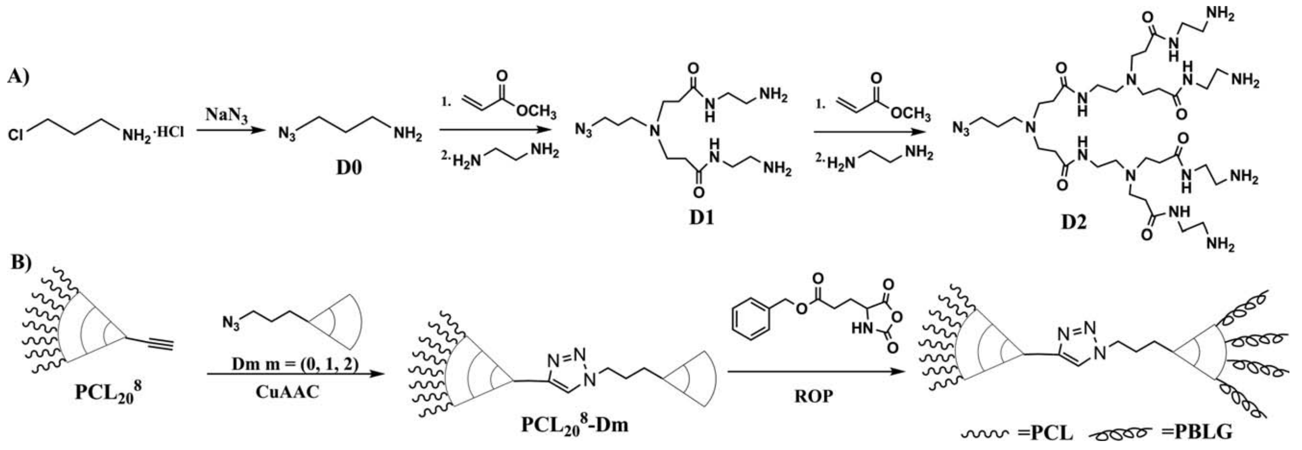

SCHEME 1 A: Synthesis of azido focal point PAMAM dendrons D_m (m = 0, 1, and 2); B: Synthesis of dendron-like/dendron-like PCL^8_{20}-*b*-$PBLG^n$ ($n = 2^m$ = 1, 2, and 4) block copolymers.

and their molecular structures and physicochemical properties were thoroughly characterized by means of FT-IR, ^{1}H NMR, gel permeation chromatography, differential scanning calorimetry, and wide angle X-ray diffraction. Importantly, this establishes a versatile strategy for the synthesis of biodegradable and biomimetic block copolymers with asymmetrical dendritic topology.

EXPERIMENTAL SECTION

Materials

ε-Caprolactone (CL, Aldrich, 99%) and dimethylformamide (DMF, ≥99.5%) were distilled from calcium hydride under reduced pressure and stored over molecular sieves, respectively. Dichloromethane (≥99.5%) and toluene (≥99.5%) were directly distilled from calcium hydride. Phosphorous trichloride (PCl_3, 95.5%) was distilled and diluted in dried dichloromethane (PCl_3:CH_2Cl_2 = 1:3, v/v) before use. 3-Chloropropylamine hydrochloride (Aldrich, 98%), copper (I) bromide (Aldrich, 99.999%), *N,N,N′,N″,N″*-pentamethyldiethylenetriamine (PMDETA, Aldrich, 99%), propargyl amine (Aldrich, 99%), and stannous octoate ($SnOct_2$, Aldrich, 95%) were used as received. Ethylenediamine (99%) and methyl acrylate (98%) were purchased from Shanghai Sinopharm Chemical Reagent Corporation and distilled before use. γ-Benzyl-L-glutamate *N*-carboxyanhydride (BLG-NCA) monomer was synthesized from *N*-tert-butyloxycarbonyl-γ-benzyl-L-glutamic acid and phosphorous trichloride.[24] The propargyl focal point poly(amido amine) (PAMAM) typed dendrons with eight primary amine groups were synthesized as detailed in our previous publication.[22]

Methods

^{1}H NMR spectroscopy was performed on a Varian Mercury-400 spectrometer. Tetramethylsilane was used as an internal standard. Molecular weight and polydispersity (M_w/M_n; M_w: weight-average molecular weight, M_n: number-average molecular weight) of polymer were determined on a gel permeation chromatograph (GPC, Perkin-Elmer Series 200) equipped with two linear Mixed-B columns (Polymer Lab Corporation, pore size: 10 μm, column size: 300 × 7.5 mm) and a refractive index detector (model) at 30 °C. The elution phase was DMF (0.01 mol/L LiBr, elution rate: 1.0 mL/min), and polystyrene was used as the calibration standard. The differential scanning calorimetry (DSC) analysis was carried out using a Perkin-Elmer Pyris 1 instrument under nitrogen flow (10 mL/min). All samples were first heated from 20 °C to 140 °C at 10 °C/min and held for 3 min to erase the thermal history, then cooled to 20 °C at 10 °C/min, and finally heated to 140 °C at 10 °C/min. Wide angle X-ray diffraction (WAXD) patterns of powder samples were obtained at room temperature on a Shimadzu XRD-6000 X-ray diffractometer with a CuKα radiation source (wavelength = 1.54 Å). The supplied voltage and current were set to 40 kV and 20 mA, respectively. Samples were exposed at a scan rate of 2θ = 4°/min between 2θ = 5 and 40°.

Preparation of Azidopropylamine

3-Chloropropylamine hydrochloride (1.0 g, 7.7 mmol) and sodium azide (1.5 g, 23.1 mmol) were added into 8 mL distilled water in a round flask. The solution was stirred vigorously at 80 °C for 24 h. After cooling in an ice-water bath, sodium hydroxide (0.46 g) was added into the solution. The solution was extracted by 30 mL diethyl ether for three times, and then the combined organic layer was dried by sodium sulfate. After removing diethyl ether under reduced pressure, azidopropylamine was obtained in a yield of 83.2% (663.7 mg). Azidopropylamine was stable if it was stored in refrigerator at about 4 °C. ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.70−1.76 (q, 2H, $CH_2\mathit{CH_2}CH_2$), 2.79−2.83(t, 2H, $\mathit{CH_2}NH_2$), 3.35−3.39 (t, 2H, $N_3\mathit{CH_2}$). TOF-MS, *m/z*: calcd for $C_3H_8N_4$, 101.0749; found, 101.0841 $[M + H]^+$. FT-IR (KBr, cm^{-1}): 3434 ($\nu_{N\text{-}H}$); 2926, 2852($\nu_{C\text{-}H}$), 2102 ($\nu_{N\equiv N}$), 1634 ($\nu_{C=O}$), 1469 ($\nu_{CO\text{-}NH}$).

Preparation of Azido Focal Point PAMAM Typed Dendron D1

The azido focal point PAMAM typed dendrons groups (i.e., **D1**and **D2**) were synthesized using a protocol similar to that described by Lee et al.,[47] as shown in Scheme 1. Under vigorous stirring, a solution of azidopropylamine (denoted as **D0**, 275.9 mg, 2.76 mmol) in methanol (2 mL) was added dropwise to a cooled solution (ice-water bath) of methyl acrylate (1.34 mL, 6.9 mmol) in methanol (2 mL) over 60 min. The reaction solution was stirred vigorously for 1 h at 0 °C and then for an additional 20 h at room temperature under nitrogen atmosphere. The solution was evaporated, and then the residue was purified by column chromatography (EtOAc/n-hexane, 1:1, v:v) to afford the desired methyl ester terminated dendron D0.5 (534.1 mg, 75% yield). ^{1}H NMR ($\mathrm{CDCl_3}$): δ (ppm) = 1.65–1.74 (t, 2H, $\mathrm{CH_2}\mathit{CH_2}\mathrm{CH_2}$), 2.38–2.52 (m, 6H, $\mathrm{CH_2CH_2}\mathit{CH_2}\mathrm{N}+\mathit{CH_2}\mathrm{CO}$), 2.68–2.78 (t, 4H, $\mathit{CH_2}\mathrm{CH_2CO}$), 3.28–3.35 (t, 2H, $\mathrm{N_3}\mathit{CH_2}$), 3.65–3.70 (s, 6H, $\mathrm{O}\mathit{CH_3}$).

Under vigorous stirring, a solution of D0.5 (1.2413 g, 4.56 mmol) in methanol (6 mL) was added dropwise to a cooled solution of ethylenediamine (6.1 mL, 91.2 mmol) in methanol (6 mL) over 60 min. The reaction mixture was stirred vigorously for 1 h at 0 °C and then for further 96 h at room temperature under nitrogen atmosphere. The solution was evaporated, and then the residue was dried *in vacuo* at 35 °C to give the azido focal point dendron **D1** (1.495 g, 99% yield). ^{1}H NMR ($\mathrm{CDCl_3}$): δ (ppm) = 1.60–1.75 (q, 6H, $\mathrm{CH_2}\mathit{CH_2}\mathrm{CH_2}+\mathit{NH_2}$), 2.31–2.40 (t, 4H, $\mathit{CH_2}\mathrm{CO}$), 2.46–2.50 (t, 2H, $\mathrm{CH_2CH_2}\mathit{CH_2}\mathrm{N}$), 2.69–2.75 (t, 4H, $\mathit{CH_2}\mathrm{CH_2CO}$), 2.80–2.84 (t, 4H, $\mathit{CH_2}\mathrm{NH_2}$), 3.25–3.30 (m, 6H, $\mathrm{N_3}\mathit{CH_2}+\mathrm{CONH}\mathit{CH_2}$), 7.02–7.08 (s, 2H, $\mathrm{CO}\mathit{NH}$). TOF-MS, *m/z*: calcd for $\mathrm{C_{13}H_{28}N_8O_2}$, 329.2413; found, 329.2396 $[\mathrm{M + H}]^+$. FT-IR (KBr, $\mathrm{cm^{-1}}$): 3434 ($\nu_{\mathrm{N\text{-}H}}$); 2926, 2852($\nu_{\mathrm{C\text{-}H}}$), 2102 ($\nu_{\mathrm{N\equiv N}}$), 1634 ($\nu_{\mathrm{C=O}}$), 1469 ($\nu_{\mathrm{CO\text{-}NH}}$).

Preparation of Azido Focal Point PAMAM Typed Dendron D2

D2 was synthesized from **D1** (1.4520 g, 4.42 mmol) using same method as successive Michael addition of primary amines with methyl acrylate and amidation of methyl ester groups with a large molar excess of ethylenediamine (99% yield). ^{1}H NMR of D1.5 ($\mathrm{CDCl_3}$): δ (ppm) = 1.72–1.76 (q, 2H, $\mathrm{CH_2}\mathit{CH_2}\mathrm{CH_2}$), 2.35–2.42 (m, 12H, $\mathit{CH_2}\mathrm{CO}$), 2.50–2.56 (m, 6H, $\mathrm{CH_2CH_2}\mathit{CH_2}\mathrm{N}+\ \mathrm{CONHCH_2}\mathit{CH_2}\mathrm{N}$), 2.70–2.82 (m, 12H, $\mathit{CH_2}\mathrm{CH_2CO}$), 3.28–3.38 (m, 6H, $\mathrm{N_3}\mathit{CH_2}+\mathrm{CONH}\mathit{CH_2}$), 3.64–3.68 (s, 12H, $\mathrm{O}\mathit{CH_3}$), 6.94–7.00 (s, 2H, $\mathrm{CO}\mathit{NH}$). ^{1}H NMR ($\mathrm{CDCl_3}$) of **D2**: δ (ppm) = 1.52–1.66 (s, 8H, $\mathrm{NH_2}$), 1.68–1.76 (q, 2H, $\mathrm{CH_2}\mathit{CH_2}\mathrm{CH_2}$), 2.28–2.42 (m, 12H, $\mathit{CH_2}\mathrm{CO}$), 2.42–2.60 (m, 6H, $\mathrm{CH_2CH_2}\mathit{CH_2}\mathrm{N}+\ \mathrm{CONHCH_2}\mathit{CH_2}\mathrm{N}$), 2.61–2.78 (m, 12H, $\mathit{CH_2}\mathrm{CH_2CO}$), 2.78–2.90 (t, 8H, $\mathit{CH_2}\mathrm{NH_2}$), 3.20–3.40 (m, 14H, $\mathrm{N_3}\mathit{CH_2}+\mathrm{CONH}\mathit{CH_2}$), 7.50–7.58 (s, 4H, $\mathrm{CO}\mathit{NH}$), 7.88–7.95 (s, 2H, $\mathrm{CO}\mathit{NH}$). TOF-MS, *m/z*: calcd for $\mathrm{C_{33}H_{69}N_{16}O_6}$, 785.5508; found, 785.5568 $[\mathrm{M + H}]^+$. FT-IR (KBr, $\mathrm{cm^{-1}}$): 3434 ($\nu_{\mathrm{N\text{-}H}}$); 2926, 2852($\nu_{\mathrm{C\text{-}H}}$), 2102 ($\nu_{\mathrm{N\equiv N}}$), 1634 ($\nu_{\mathrm{C=O}}$), 1469 ($\nu_{\mathrm{CO\text{-}NH}}$).

Preparation of Dendron-Like Macroinitiators $\mathrm{PCL^8}$-D_m (m = 0, 1, and 2)

The multiple amine-terminated dendron-like macroinitiators $\mathrm{PCL^8}$-D_m (m = 0, 1, and 2) were successfully synthesized in two steps by combining ROP and CuAAC. First, according to our previous publication,[22] the clickable dendron-like $\mathrm{PCL^8}$ with eight branches was synthesized by the controlled ROP of ε-caprolactone using propargyl focal point PAMAM typed dendron with eight primary amines as initiator and stannous octoate as catalyst at 130 °C ($\mathrm{PCL^8_{20}}$, 87.7% yield). ^{1}H NMR ($\mathrm{CDCl_3}$) of $\mathrm{PCL^8_{20}}$: δ (ppm) = 4.00–4.12 (m, 320H, $\mathrm{COCH_2CH_2CH_2CH_2}\mathit{CH_2}\mathrm{O}$), 3.59–3.68 (t, 16H, $\mathit{CH_2}\mathrm{OH}$), 3.39–3.47 (t, 2H, $\mathrm{CHC}\mathit{CH_2}\mathrm{N}$), 3.25–3.38 (m, 18H, $\mathrm{CH_2}$), 2.48–2.80 (m, 4H, $\mathrm{CH_2}$), 2.25–2.40 (m, 320H, $\mathrm{CO}\mathit{CH_2}\mathrm{CH_2CH_2CH_2CH_2O}$), 2.15–2.22 (m, 17H, $\mathrm{NHCO}\mathit{CH_2}\mathrm{CH_2CH_2}\mathit{CH_2}$ + $\mathit{CH}\mathrm{CCH_2N}$), 1.50–1.70 (m, 640H, $\mathrm{COCH_2}\mathit{CH_2}\mathrm{CH_2}\mathit{CH_2}\mathrm{CH_2O}$), 1.30–1.44 (m, 320H, $\mathrm{COCH_2CH_2}\mathit{CH_2}\mathrm{CH_2CH_2O}$). $M_{\mathrm{n,GPC}}$ = 13,820, $M_{\mathrm{w}}/M_{\mathrm{n}}$ = 1.60.

Then, the propargyl focal point $\mathrm{PCL^8_{20}}$ precursor was click conjugated with azido focal point PAMAM typed dendrons D_m (m = 0, 1, and 2) to generate the macroinitiators $\mathrm{PCL^8_{20}}$-D_m. A typical procedure was started with the feed ratio of reagents $[\mathrm{D}_m]/[\mathrm{PCL^8_{20}}]/[\mathrm{CuBr}]/[\mathrm{PMDETA}] = 2/1/2/2$. As a representative example, the click coupling reaction between D0 (2 mg, 0.02 mmol) and $\mathrm{PCL^8_{20}}$ (199.0 mg, 0.01 mmol alkyne unit) was conducted at 35 °C in a 25 mL Schlenk flask with 2 mL of DMF as solvent, and both CuBr (2.9 mg, 0.02 mmol) and PMDETA (88 μL, 0.02 mmol, diluted by 20-fold DMF) as catalyst. After 48 h, the copolymer solution was precipitated in diethyl ether. The white powder was then dried *in vacuo* at 40 °C to give 176.0 mg of $\mathrm{PCL^8_{20}}$-D0 (88% yield). ^{1}H NMR ($\mathrm{CDCl_3}$) of $\mathrm{PCL^8_{20}}$-D0: δ (ppm) = 4.00–4.12 (m, 320H, $\mathrm{COCH_2CH_2CH_2CH_2}\mathit{CH_2}\mathrm{O}$), 3.73–3.76 (t, 2H, $\mathit{CH_2}$-triazole), 3.59–3.68 (t, 16H, $\mathit{CH_2}\mathrm{OH}$), 3.25–3.38 (m, 14H, $\mathrm{CH_2}$), 2.48–2.80 (m, 4H, $\mathrm{CH_2}$), 2.25-2.40 (m, 320H, $\mathrm{CO}\mathit{CH_2}\mathrm{CH_2CH_2CH_2CH_2O}$), 2.15–2.22 (m, 16H, $\mathrm{NHCO}\mathit{CH_2}\mathrm{CH_2\,CH_2}\mathit{CH_2}$), 1.50–1.70 (m, 640H, $\mathrm{COCH_2}\mathit{CH_2}\mathrm{CH_2}\mathit{CH_2}\mathrm{CH_2O}$), 1.30–1.44 (m, 320H, $\mathrm{COCH_2CH_2}\mathit{CH_2}\mathrm{CH_2CH_2O}$).

Synthesis of Dendron-Like/Dendron-Like Block Copolymers $\mathrm{PCL^8_{20}}$-*b*-PBLG^n ($n = 2^m$ = 1, 2, and 4)

The block copolymers $\mathrm{PCL^8_{20}}$-*b*-PBLG^n were synthesized from the ROP of BLG-NCA using primary amine-terminated $\mathrm{PCL^8_{20}}$-D_m as the macroinitiators in DMF solution at room temperature. In a representative reaction, $\mathrm{PCL^8_{20}}$-D0 (200.3 mg, 0.01 mmol) was dissolved completely in 2 mL of DMF under nitrogen atmosphere, and then a degassed solution of BLG-NCA (65.8 mg, 0.25 mmol) in 1 mL of DMF was added via a syringe. The resulting solution was allowed to stir vigorously at room temperature for 24 h, diluted with THF (3 mL), and then precipitated dropwise into a large excess of cold methanol (50 mL). The white precipitate was filtered and dried *in vacuo* at 40 °C to give 217.4 mg of $\mathrm{PCL^8_{20}}$-*b*-$\mathrm{PBLG^1_{17}}$ (85.2%, yield = $W_{\mathrm{copolymer}}/[W_{\mathrm{NCA}} - (W_{\mathrm{NCA}}/M_{\mathrm{NCA}} \times M_{\mathrm{CO2}}) + W_{\mathrm{PCL-D}_m}]$), in which the subscript and the superscript numbers represent the degree of polymerization and the branch number, respectively.

^{1}H NMR (DMSO-d_6): δ (ppm) = 8.0–8.20 (s, 17H, NH), 7.14–7.34 (m, 85H, Ph), 4.87–5.08 (t, 34H, $\mathit{CH_2}\mathrm{Ph}$), 4.19–4.36 (s, 17H, $\mathrm{COC}\mathit{H}\mathrm{NH}$), 3.92–4.02 (t, 320H, $\mathrm{COCH_2CH_2CH_2CH_2}\mathit{CH_2}\mathrm{O}$), 2.37–2.42 (m, 34H, $\mathrm{CH_2}\mathit{CH_2}\mathrm{COOCH_2Ph}$), 2.23–2.28 (t, 320H, $\mathrm{CO}\mathit{CH_2}\mathrm{CH_2CH_2CH_2CH_2O}$), 1.98–2.05 (d, 34H, $\mathit{CH_2}\mathrm{CH_2\,COOCH_2Ph}$), 1.45–1.60 (m, 640H, $\mathrm{COCH_2}\mathit{CH_2}\mathrm{CH_2}\mathit{CH_2}\mathrm{CH_2O}$), 1.22–1.30 (m, 320H, $\mathrm{COCH_2CH_2}\mathit{CH_2}\mathrm{CH_2CH_2O}$). $M_{\mathrm{n,GPC}}$ = 17,350, $M_{\mathrm{w}}/M_{\mathrm{n}}$ = 1.58.

RESULTS AND DISCUSSION

Synthesis of Dendron-Like/Dendron-Like Block Copolymers $\mathrm{PCL^8_{20}}$-*b*-PBLG^n (n = 1, 2, and 4)

From the synthetic viewpoint, the dendron-like/dendron-like poly(ε-caprolactone)-*b*-poly(γ-benzyl-L-glutamate) (PCL-

b-PBLG) block copolymers with asymmetrical topology can be designed by utilizing the well-known divergent and convergent methods, and the ring-opening polymerization (ROP).[1–18] Herein, the dendron-like/dendron-like block copolymers PCL_{20}^{8}-*b*-PBLG^{n} (both the subscript and the superscript denote the degree of polymerization and the branch number, respectively; $n = 1$, 2, and 4) were for the first time synthesized by combining controlled ROP of ε-caprolactone (CL), click chemistry for the propargyl focal point transformation into dendrons having primary amine periphery, and the ROP of γ-benzyl-L-glutamate *N*-carboxyanhydride (BLG-NCA), as shown in Scheme 1. First, the dendron-like propargyl focal point PCL_{20}^{8} with eight branches was synthesized by the controlled ROP of CL monomer using a propargyl focal point PAMAM typed dendron as initiator according to our previous publication,[22] and its actual polymer molecular weight could be easily determined by ^{1}H NMR spectroscopy [Fig. 1(A)]. Second, the azido focal point PAMAM typed dendrons D_m with primary amine terminal groups (D_m, $m = 0$, 1, and 2) were designed and synthesized using azidopropylamine as an azido focal point according to the divergent synthetic procedure,[47] as shown in Scheme 1A. The dendrons D_m were fully characterized by ^{1}H NMR, FT-IR, and MS (see Experimental Section), which demonstrates that they are pure for the following click reaction. The propargyl focal point PCL_{20}^{8} precursor was then click conjugated with the azido focal point D_m to produce primary amine-terminated PCL_{20}^{8}-dendrons (PCL_{20}^{8}-D_m, Scheme 1B). FT-IR is a simple and useful tool to verify the click conjugation and the presence of both PCL and D_m components in the purified PCL_{20}^{8}-D_m (Fig. 2). The propargyl focal point (i.e., alkyne group) within dendron-like PCL_{20}^{8} precursor at about 2098 cm^{-1} completely disappeared within PCL_{20}^{8}-D_m, suggesting that the click reaction is nearly quantitative within the error of FT-IR method. Moreover, ^{1}H NMR spectra of PCL_{20}^{8}-D_m confirmed that the PCL_{20}^{8} precursor was successfully coupled with azido

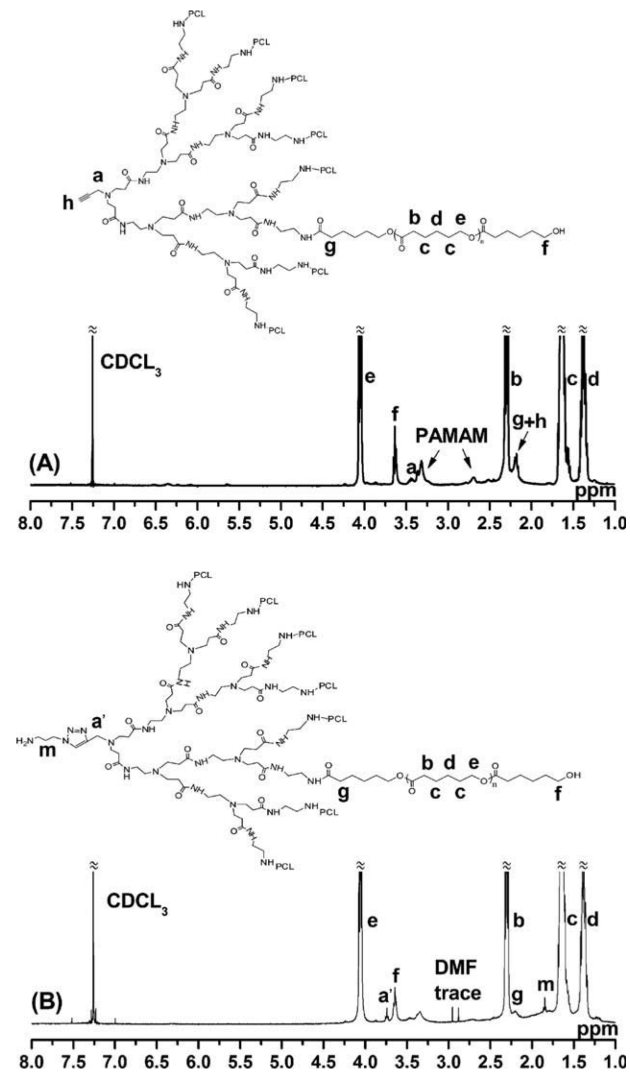

FIGURE 1 ^{1}H NMR spectra of PCL_{20}^{8} (A) and PCL_{20}^{8}-D0 (B).

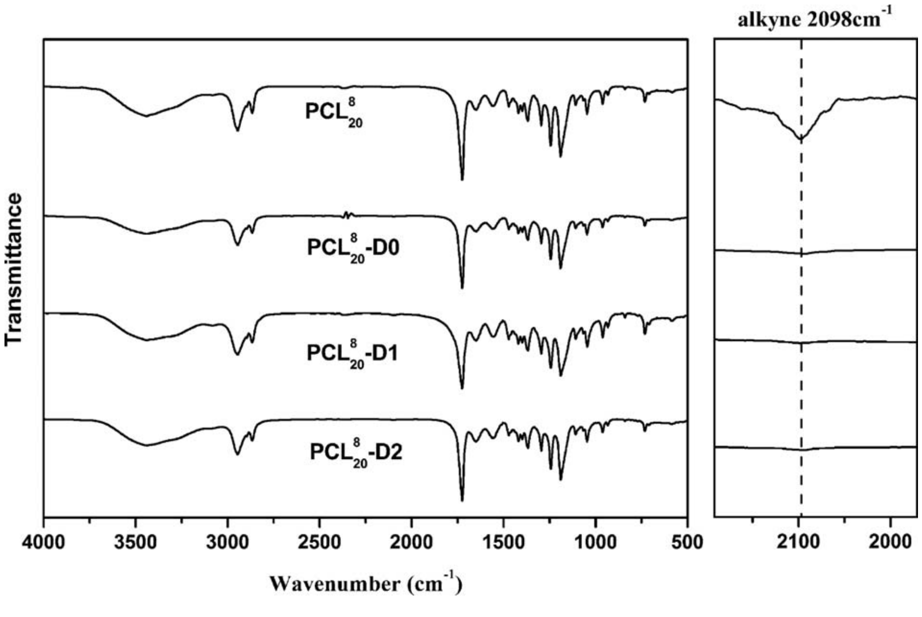

FIGURE 2 FT-IR spectra of PCL_{20}^{8} precursor and PCL_{20}^{8}-D_m macroinitiators.

TABLE 1 Synthesis of Dendron-Like/Dendron-Like PCL^{8}_{20}-*b*-PBLG^{n} (n = 1, 2, and 4) Block Copolymers with Asymmetrical Topology

Entry[a]	$M_{n,NMR}$[b]	$M_{n,GPC}$[c]	M_w/M_n[c]	$M_{n,PCL}$[b]	$M_{n,PBLG}$[b]	Yield[d]
PCL^{8}_{20}-*b*-PBLG^{1}_{3}	20,800	14,110	1.51	2,260	660	67.8%
PCL^{8}_{20}-*b*-PBLG^{1}_{17}	24,480	17,350	1.58	2,260	3,720	85.2%
PCL^{8}_{20}-*b*-PBLG^{2}_{10}	25,500	18,330	1.63	2,260	2,190	75.0%
PCL^{8}_{20}-*b*-PBLG^{4}_{14}	35,430	26,570	1.45	2,260	3,070	75.3%
PCL^{8}_{20}-*b*-PBLG^{4}_{22}	42,610	30,780	1.62	2,260	4,820	71.4%

[a] Both the subscript and the superscript numbers represent the degree of polymerization and the branch number of PCL and PBLG blocks, respectively.

[b] $M_{n,NMR}$, $M_{n,\ PCL}$, and $M_{n,PBLG}$ denote the molecular weights of copolymers and the related blocks determined by ^{1}H NMR (e.g., Fig. 4).

[c] Both molecular weight ($M_{n,GPC}$) and the polydispersity (M_w/M_n) of copolymers were determined by GPC.

[d] Yield $= W_{copolymer}/[(W_{monomer} - W_{monomer}/M_{monomer} \times M_{CO2}) + W_{macroinitiator}]$.

focal point D_m. Compared with the PCL^{8}_{20} precursor, the representative ^{1}H NMR spectrum of PCL^{8}_{20}-D0 clearly shows that new signals at about 1.85 ppm (a) typical of methene proton assignable to D0 appeared, and the original methylene peak adjacent to alkyne shifted down to 3.74 ppm (a′), which is indicative of the occurrence of triazole ring [Fig. 1(B)]. Taken together, these results indicate that the propargyl focal point PCL^{8}_{20} precursor was quantitatively transformed into PCL^{8}_{20}-D_m by the click conjugation with the azido focal point D_m.

The PCL^{8}_{20}-D_m with multiple primary amine groups were further used as the macroinitiators for the ROP of BLG-NCA monomer to produce the targeted asymmetrical block copolymers PCL^{8}_{20}-*b*-PBLG^{n}, and the detailed results are compiled in Table 1. Compared with that of the original PCL^{8}_{20} precursor, the elution peak of these block copolymers shifted toward a lower elution time region coupled with a moderate polydispersity, demonstrating the successful synthesis of the purified block copolymers (Fig. 3).

As a representative example (Fig. 4 and Supporting Information S1), the ^{1}H NMR spectrum of PCL^{8}_{20}-*b*-PBLG^{1}_{17} block copolymer clearly show the typical PBLG proton signals at 7.34 − 7.14 and 5.08 − 4.87 ppm assignable to the benzyl residue, those at 2.42 − 2.37 and 2.05 − 1.98 ppm assignable to the methylene groups ($-CH_2CH_2-$COOBz), and those at 4.36 − 4.19 ppm assignable to the backbone ($-CH-$) of PBLG, and the typical PCL proton signals. Note that the degree of polymerization of PBLG within these copolymers can be precisely calculated by the integral ratio of proton e to proton i or g. Moreover, FT-IR spectra confirmed the presence of both PCL and PBLG components in these block copolymers. As shown in Figure 5, the block copolymers exhibit the strong amide I bands at 1650 and 1625 cm^{-1}, and amide II bands at 1545 cm^{-1} for PBLG segments, the distinct stretching bands at 2946 cm^{-1}(CH) and 1727cm^{-1} (C=O) for PCL block, and the broad absorption at 3200 – 3600 cm^{-1} for the PBLG backbone (NH) and the PAMAM dendrons (NH and NH_2). Taken together, these results convincingly demonstrated that dendron-like/dendron-like PCL-*b*-PBLG block copolymers with asymmetrical topology were successfully synthesized by combining ROP and CuAAC, as shown in Scheme 1.

As the PBLG with different chain length assumes α-helix and/or β-sheet conformations, which characteristically presents the vibrational peaks assignable to the amide I band at ∼1650 cm^{-1} and amide II band at ∼1550 cm^{-1}, and the amide bands at ∼1630 cm^{-1} and ∼1530 cm^{-1},

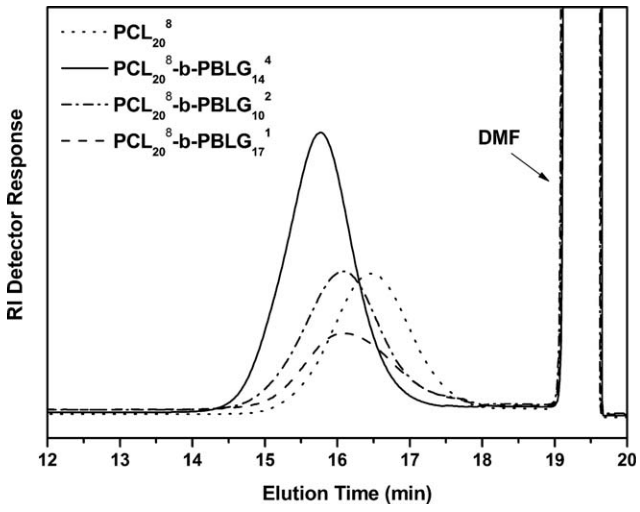

FIGURE 3 The GPC traces of PCL^{8}_{20} precursor and PCL^{8}_{20}-*b*-PBLG^{n} block copolymers.

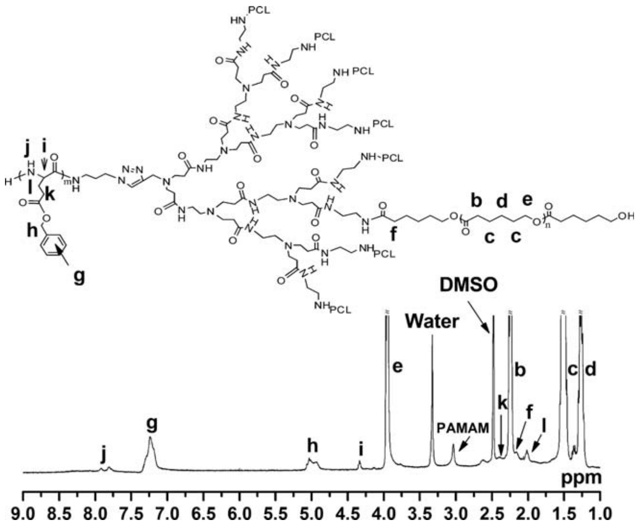

FIGURE 4 ^{1}H NMR spectrum of PCL^{8}_{20}-*b*-PBLG^{1}_{17}.

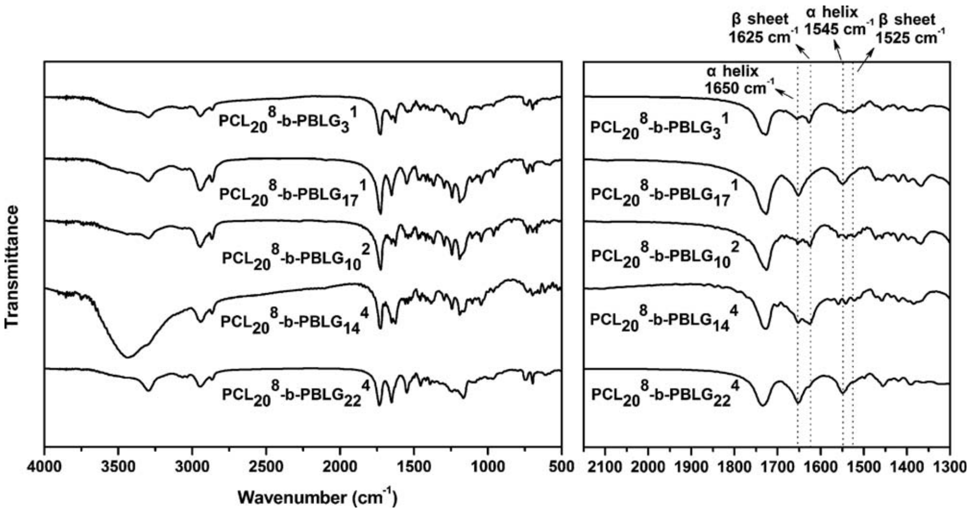

FIGURE 5 FT-IR spectra of PCL^{8}_{20}-*b*-$PBLG^{n}$ block copolymers.

respectively.[24,25,41] Thus, the secondary conformation of PBLG segment within these block copolymers can be easily characterized by FT-IR. As shown in Figure 5, it can be observed that the longer PBLG segment within PCL^{8}_{20}-*b*-$PBLG^{1}_{17}$ and PCL^{8}_{20}-*b*-$PBLG^{4}_{22}$ mainly assumed an α-helix conformation, while both α-helix and β-sheet conformations existed within PCL^{8}_{20}-*b*-$PBLG^{2}_{10}$ and PCL^{8}_{20}-*b*-$PBLG^{4}_{14}$. Note that the shorter PBLG segment within PCL^{8}_{20}-*b*-$PBLG^{1}_{3}$ mainly presented a β-sheet conformation. These results indicate that the secondary conformation of PBLG within copolymers can be tuned by changing the PBLG chain length, which is consistent with that reported in literature.[17,18,24,25,41] This result can be further clarified by the following DSC and WAXD analyses.

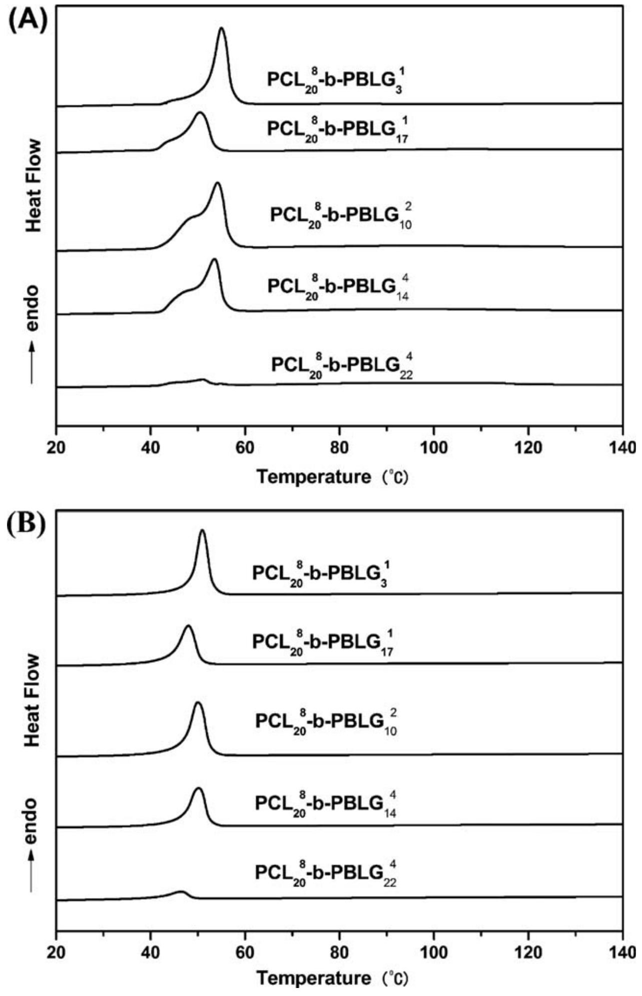

FIGURE 6 DSC curves of PCL^{8}_{20}-*b*-$PBLG^{n}$ copolymers in the first heating run (A) and in the second heating run (B), respectively.

DSC and WAXD Analyses

The PBLG with a long chain length often shows a liquid crystalline phase transition with a small endothermic enthalpy, which is indicative of its conformational transition from 7/2 α-helix to 18/5 α-helix.[24,25,41] Thus, the thermal behavior and conformation of both PCL and PBLG segments can be characterized by DSC (Fig. 6 and Table 2). As for PCL^{8}_{20}-*b*-$PBLG^{1}_{3}$ with shorter PBLG segment, the maximal melting temperature (T_m) of PCL segment was given at $T_m = 50.9$ °C, and no liquid crystalline phase transition temperature (T_{LC}) of PBLG was discerned. However, for the other block copolymers with

TABLE 2 The Melting and Crystallization Properties of PCL^{8}_{20}-*b*-$PBLG^{n}$ (n = 1, 2, and 4) Block Copolymers

Entry	$T_{m,\ PCL}$[a] (°C)	$T_{LC,PBLG}$[b] (°C)	ΔH_m[c] (J/g)	X_c[d] (%)
PCL^{8}_{20}-*b*-$PBLG^{1}_{3}$	50.9	–	54.5	39.0
PCL^{8}_{20}-*b*-$PBLG^{1}_{17}$	48.0	105.9	42.6	30.5
PCL^{8}_{20}-*b*-$PBLG^{2}_{10}$	50.0	95.8	45.4	32.5
PCL^{8}_{20}-*b*-$PBLG^{4}_{14}$	50.2	96.5	29.8	21.3
PCL^{8}_{20}-*b*-$PBLG^{4}_{22}$	47.6	109.1	3.0	2.1

[a] $T_{m,\ PCL}$ denotes the maximal melting temperature of PCL in the second heating run.

[b] $T_{LC,PBLG}$ denotes the liquid crystalline phase transition temperature of PBLG in the first heating run.

[c] ΔH_m denotes the melting enthalpy of PCL block in the second heating run.

[d] X_c denotes the degree of crystallinity of PCL block within these copolymers, where $X_c = \Delta H_m/\Delta H^{0}_{m,PCL}$, $\Delta H^{0}_{m,PCL} = 139.6$ J/g.

longer PBLG segment, the T_{LC} with a small and broad endothermic enthalpy could be observed at about 96–109 °C, suggesting at least a partial α-helical conformation for PBLG block. Note that the T_{LC} of PBLG slightly increased with increasing the PBLG chain length, and the liquid crystalline phase transition process was irreversible [Fig. 7(B)]. In addition, the liquid crystallinity (LC) of PBLG was characterized by polarized optical microscopy (POM), as shown in Supporting Information S2, which demonstrated that the LC phase of PBLG segment mainly occurred at about 120 °C. Moreover, both the T_m and the degree of crystallinity (X_c) of PCL block within copolymers decreased with increasing the PBLG branches and/or the chain length, demonstrating that the crystallinity of PCL block was progressively suppressed by PBLG block.

As shown in Figure 8, all the block copolymers exhibited the crystalline diffraction peaks at about 1.51 and 1.68 $Å^{-1}$ for the PCL block, while the diffraction intensity of PCL block was progressively attenuated with increasing the PBLG branches and/or the chain length. This result is in good agreement with that determined by DSC. Moreover, PCL$^8_{20}$-*b*-PBLG$^1_3$ presents a diffraction peak at about 0.39 $Å^{-1}$, suggesting a β-sheet conformation of PBLG segment.[24,25,41] However, the diffraction peak gradually shifted to about 0.45 $Å^{-1}$ with the increasing PBLG chain length, indicating an α-helical conformation of PBLG segment within PCL$^8_{20}$-*b*-PBLG$^4_{22}$. These results are consistent with the above FT-IR and DSC analyses.

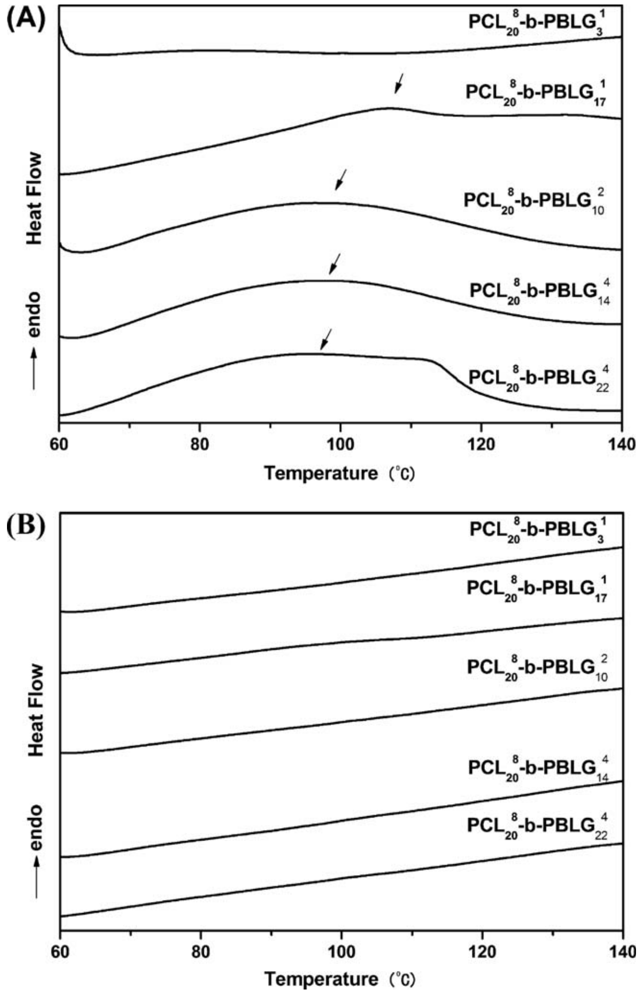

FIGURE 7 Expanded regions (60 °C–140 °C) of DSC curves of PCL$^8_{20}$-*b*-PBLG^n copolymers in the first heating run (A) and in the second heating run (B), respectively.

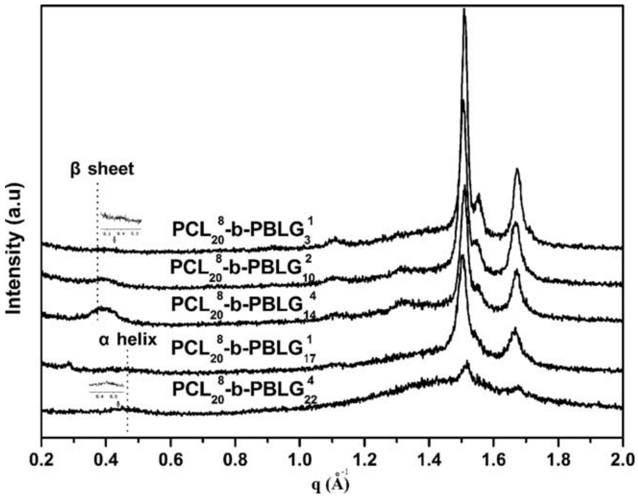

FIGURE 8 WAXD patterns of PCL$^8_{20}$-*b*-PBLG^n copolymers.

CONCLUSIONS

A new class of dendron-like/dendron-like PCL$^8_{20}$-*b*-PBLG^n (n = 1, 2, and 4) block copolymers with asymmetrical topology was successfully synthesized by combining CuAAC and ROP. The dendron-like propargyl focal point PCL$^8_{20}$ precursor with eight branches was click conjugated with azido focal point PAMAM dendrons to generate the PCL$^8_{20}$-D$_m$ with multiple primary amine groups, which were then used as macroinitiators for the ROP of BLG-NCA monomer to produce the targeted asymmetrical block copolymers. Both the maximal melting temperature and the degree of crystallinity of PCL block within copolymers decreased with increasing the PBLG branches and/or the chain length, demonstrating that the crystallinity of PCL block was progressively suppressed by PBLG block. Meanwhile, the PBLG block within copolymers progressively transformed from β-sheet to α-helical conformation with increasing the PBLG chain length. These results were concomitantly confirmed by FT-IR, DSC, and WAXD techniques. Importantly, this study establishes a versatile strategy for the synthesis of biodegradable and biomimetic block copolymers with asymmetrical dendritic topology.

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