Synthesis and Characterization of Linear-Dendron-like Poly(ε-caprolactone)-*b*-poly(ethylene oxide) Copolymers via the Combination of Ring-Opening Polymerization and Click Chemistry

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ABSTRACT: A new class of *linear-dendron-like* poly(ε-caprolactone)-*b*-poly(ethylene oxide) (PCL-*b*-PEO) copolymers with *unsymmetrical topology* was synthesized via controlled ring-opening polymerization (ROP) of ε-caprolactone (CL) followed by a click conjugation with azide-terminated PEO (PEO-N_3). The *dendron-like* PCL terminated with a clickable alkyne group (D*m*-PCL, $m = 0$, 1, 2, and 3) was for the first time synthesized from the ROP of CL monomer using a propargyl focal point dendrons D*m* with primary amine groups as the initiators and stannous octoate as catalyst in bulk at 130 °C. Then, the linear-dendron-like D*m*-PCL-*b*-PEO copolymers were obtained by the click conjugation of D*m*-PCL with PEO-N_3 using PMDETA/CuBr as catalyst in DMF solution at 35 °C. Their molecular structures and physical properties were in detail characterized by FT-IR, NMR, MALLS-GPC, DSC, and WAXD. Both DLS and TEM analyses demonstrated that the biodegradable micelles and vesicles with different sizes (less than 100 nm) self-assembled from these D*m*-PCL-*b*-PEO copolymers in aqueous solution, and both the PEO composition and the linear-dendron-like architecture of copolymers controlled the morphology and the average size of nanoparticles. To the best of our knowledge, this is the first report that describes the synthesis of linear-dendron-like PCL-*b*-PEO block copolymers via the combination of ROP and click chemistry. Consequently, this provides a versatile strategy not only for the synthesis of biodegradable and amphiphilic block copolymers with linear-dendron-like architecture but also for fabricating biocompatible nanoparticles with suitable size for controlled drug release.

Introduction

Dendritic polymers such as dendrimers, dendrons, dendronized polymers, and hyperbranched polymers have attracted much attention in the past decades because their compositions and architectures can be controlled by size, shape, chain flexibility, and surface functionality in the nanoscale region, which enable the fabrication of various micro/nanoscale devices and scaffolds for biomedical diagnosis, drug delivery, tissue engineering, nanoelectronics, and catalysis.[1−5] Moreover, the merger of dendrimers/dendrons with traditional linear polymers created not only the novel macromolecular architectures (e.g., linear-*b*-dendrimer/dendron block copolymers, dendronized polymers) but also the biomimetic nanostructures for biomedical studies.[6−9]

As a U.S. Food and Drug Administration approved biomedical polymer, biodegradable poly(ε-caprolactone) (PCL) and PCL-based biomaterials have been increasingly investigated for pharmacological and biomedical applications.[10,11] However, PCL and its related biomaterials usually presented uncontrollable biodegradation rate and undesirable biological response to cells and/or tissues because of high crystallinity, strong hydrophobicity, and lack of bioactive functions.[12−14] Fortunately, these drawbacks might be tackled through the adjustment of polymer hydrophilicity−hydrophobicity balance, the bioconjugation with bioactive proteins/peptides and/or polysaccharides, and the control of branched macromolecular architecture.[15−17] Because of the biocompatibility, the stealth property of poly(ethylene oxide) (PEO) shelled nanoparticles in vivo, and the ability to decrease protein absorption, the block and/or graft copolymerization of PEO with aliphatic polyesters (e.g., PCL, polylactides and copolymers) provided a facile strategy to improve the physical, degradation, and drug release properties of biodegradable polyesters. For example, amphiphilic copolymers containing both aliphatic polyesters and PEO components were intensively investigated for fabricating micellar and vesicular nanostructures and thermosensitive hydrogels.[18−23] However, these conventional polymeric micelles/vesicles are not stable in physiological conditions because of their relatively higher critical micelle concentration, which hindered their clinical applications in biomedical fields.[24−26] In addition, the injectable thermosensitive hydrogels are usually generated with a high polymer weight percent in solution, while it is important to fabricate hydrogels with quick response to stimuli at a lower gelation concentration for tissue engineering.[27,28] Thus, the rational design of dendritic PEO-containing copolymers provides a promising tool to generate unimolecular micelles/vesicles and high-performance hydrogels.[24−27]

Recently, the Huisgen 1,3-dipolar cycloaddition between azides and alkynes catalyzed by copper (Cu^+) ions, termed as "click chemistry" by Sharpless and colleagues, is proved to be a versatile method for complex polymers/materials syntheses and modifications, e.g., block and graft copolymers, star and dendritic polymers, and cross-linked networks and gels, demonstrating high efficiency and tolerance of functional groups under benign conditions.[29−33] For example, Emrick et al. reported the synthesis of PEO- and peptide-grafted aliphatic polyesters by click chemistry.[34] Jérôme et al. synthesized a novel ε-caprolactone-terminated PEO macromonomer and established a platform for the preparation of comblike biodegradable biomaterials.[35] As an extension of this synthetic effort, Jérôme's group in detail investigated the functionalization, grafting of PCL, and the synthesis of tadpole-shaped PCL-*g*-PEO copolymers via the combination of click chemistry and ROP.[36−38] Very recently, Baker et al. synthesized a clickable polyglycolide and the thermoresponsive polyglycolide-*g*-PEO copolymers.[39] In this article, using commercial and biocompatible PEO as the precursor, a versatile strategy to prepare the linear-dendron-

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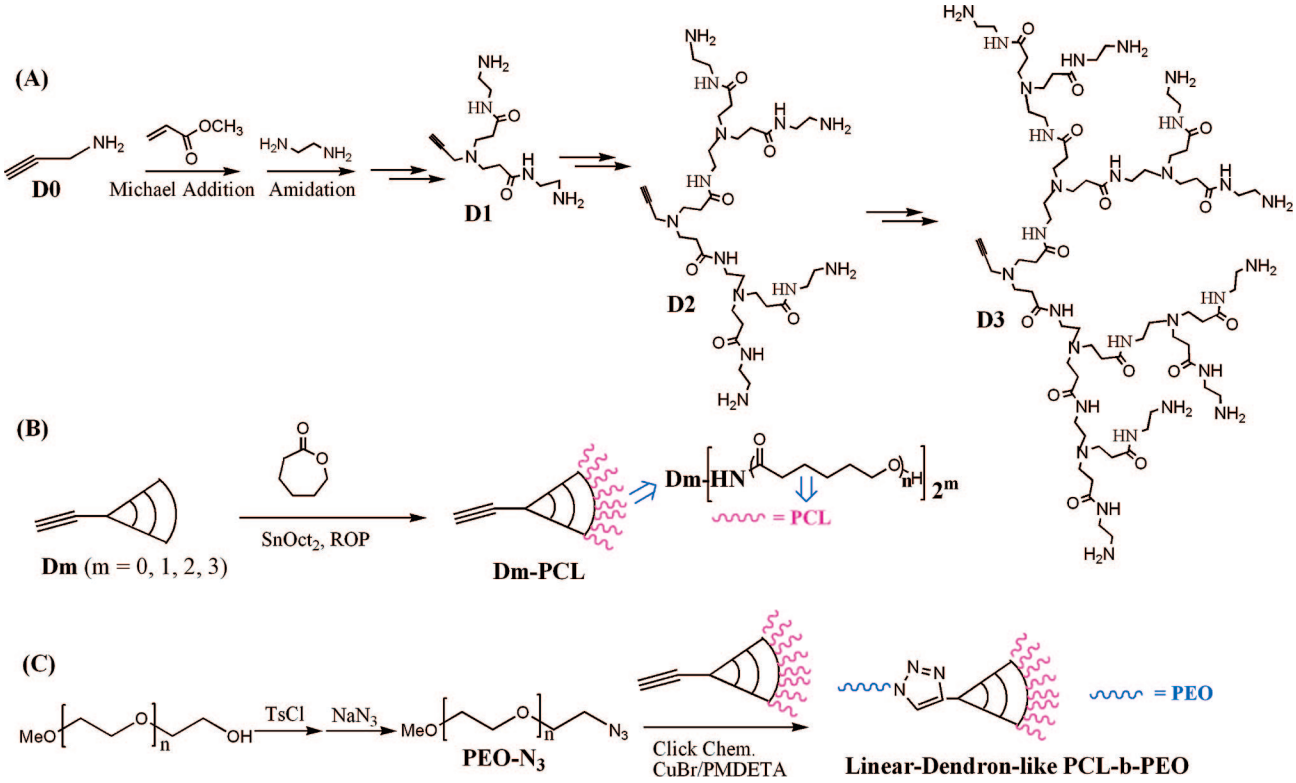
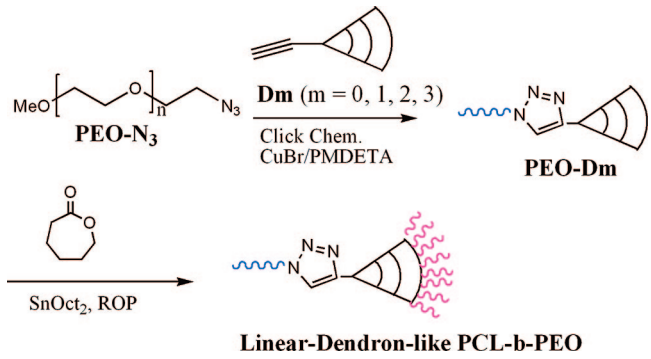
Scheme 1. Synthesis of Linear-Dendron-like D*m*-PCL-*b*-PEO Block Copolymers via the Combination of Controlled ROP and Click Chemistry Using the "Arm-First" Method



Scheme 2. Synthesis of Linear-Dendron-like D*m*-PCL-*b*-PEO Block Copolymers via the Combination of Click Chemistry and Controlled ROP Using the "Core-First" Method



like PCL-*b*-PEO block copolymers with *unsymmetrical topology* was successfully developed via the combination of controlled ROP and click chemistry, as shown in Scheme 1. The propargyl focal point dendrons D*m* terminated with primary amines (i.e., propargylamine denoted as D0, D*m*, $m = 0, 1, 2, 3$) were first synthesized and used for initiating the controlled ROP of CL monomer, generating the dendron-like PCL homopolymers having 1, 2, 4, and 8 branches (i.e., D*m*-PCL). These dendron-like D*m*-PCL homopolymers were then conjugated with azide-terminated PEO (i.e., PEO-N_3) to produce the targeted linear-dendron-like PCL-*b*-PEO copolymers by click chemistry. To the best of our knowledge, this is the first example to describe the synthesis of linear-dendron-like PCL-*b*-PEO with unsymmetrical topology via the combination of controlled ROP and click chemistry.[34−39]

Experimental Section

Materials. ε-Caprolactone (CL, Aldrich) and toluene were distilled from CaH_2. Poly(ethylene glycol) methyl ether ($M_n = 5000$, Aldrich) was dried at 50 °C in vacuo overnight, and its purity was 100% within the error of ^{1}H NMR measurement. Copper(I) bromide, 1,6-diphenyl-1,3,5-hexatriene (DPH), propargylamine, *N,N,N′,N″,N″*-pentamethyldiethylenetriamine (PMDETA), stannous octoate ($SnOct_2$), and toluene-4-sulfonyl chloride were purchased from Aldrich or Acros and used as received. Ethylenediamine (A.R.) and methyl acrylate (A.R.) were purchased from Sinopharm Chemical Reagent Corp. (Shanghai) and distilled under reduced pressure before use.

Table 1. Synthesis of the Dendron-like D*m*-PCL ($m = 0, 1, 2,$ and 3) Homopolymers from the Controlled ROP of CL Monomer in Bulk at 130 °C[a]

entry[b]	[CL]/[amine of D*m*] (mol/mol)	$M_{n,LLS}$[c]	M_w/M_n[c]	$M_{n,NMR}$[d]	yield[e] (%)
D0-PCL_{24}[f]	20			2770	77.9
D0-PCL_{68}	80	6910	1.47	7470	92.7
D1-PCL_{22}	20	6400	1.11	5400	79.2
D2-PCL_{19}	20	10200	1.01	9230	78.0
D2-PCL_7[f]	8			3750	94.9
D3-PCL_{13}	20	14900	1.01	13710	71.0

[a] [CL]/[$SnOct_2$] = 500/1, polymerization time = 24 h. [b] The subscript number represents the degree of polymerization of PCL branch, which was determined by ^{1}H NMR spectrum (e.g., D0-PCL in Figure 2A). [c] Both the actual molecular weight ($M_{n,LLS}$) and the polydispersity (M_w/M_n) of D*m*-PCL were determined by the MALLS-GPC technique. [d] $M_{n,NMR}$ was determined by ^{1}H NMR spectrum in Figure 2. [e] The yield of D*m*-PCL was determined gravimetrically. [f] The molecular weight of D0-PCL_{24} and D2-PCL_7 samples was less than the limit of MALLS-GPC-determined molecular weight.

Methods. ^{1}H NMR and ^{13}C NMR spectroscopy was performed on a Varian Mercury-400 spectrometer. Tetramethylsilane was used as an internal standard. The actual molecular weights ($M_{n,LLS}$) and polydispersities (M_w/M_n) of polymers were determined on a Waters 717 plus autosampler gel permeation chromatograph (GPC) equipped with Waters RH columns, a refractive index detector, and the DAWN EOS (Wyatt Technology) multiangle laser light-scattering (MALLS) detector at 30 °C, THF as the eluent (1.0 mL/min). 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 0 to 90 °C at 10 °C/min and held for 3 min to erase the thermal history, then cooled to 0 at 10 °C/min, and finally heated to 90 °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 Cu Kα radiation source (wavelength = 1.54 Å). The supplied voltage and current were set to 40 kV and 30 mA, respectively. Samples were exposed at a scan rate of $2\theta = 4°$ min^{-1} between $2\theta = 5°$ and 40°. The mean size of nanoparticles was determined by dynamic light scattering (DLS) using a Malvern Nano_S instrument (Malvern, UK). The solution of nanoparticles was performed at a scattering angle of 90° and at 25 °C. All the measurements were repeated three times, and the average values reported are the mean diameter ± standard deviation. Transmission electron microscopy (TEM) was performed using a JEM-2010/INCA OXFORD TEM (JEOL/OXFORD) at a 200 kV accelerating voltage. Samples were deposited onto the surface of 300 mesh Formvar-carbon film-coated copper grids. Excess solution was quickly wicked away with a filter paper. The image contrast was enhanced by negative staining with phosphotungstic acid (0.5 wt %).

Preparation of Propargyl Focal Point PAMAM Type Dendron D1. The propargyl focal point PAMAM type dendrons with methyl ester terminal groups were recently designed for synthesis of symmetrical and unsymmetrical PAMAM dendrimers by Lee et al.[40,41] The propargyl focal point PAMAM type dendrons with primary amine groups (D1, D2, and D3) were synthesized using a protocol similar to that described by Lee et al., as shown in Scheme 1A. A solution of propargylamine (denoted as D0, 311 μL, 4.6 mmol) in methanol (1 mL) was added dropwise to a cooled (ice−water bath), stirred solution of methyl acrylate (1.6 mL, 18.0 mmol) in methanol (2 mL) over 30 min. The reaction mixture was stirred vigorously for 1 h at 0 °C and then for an additional 24 h at room temperature under a nitrogen atmosphere. The reaction solution was evaporated, and then the residue was dried in vacuo at 35 °C to give the methyl ester-terminated dendron D0.5 (1.02 g, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.18-2.20$ (t, 1H), 2.43−2.48 (t, 4H), 2.80−2.85 (t, 4H), 3.40−3.42 (d, 2H), 3.66 (s, 6H).

A solution of D0.5 (951.5 mg, 4.2 mmol) in methanol (4 mL) was added dropwise to a cooled, stirred solution of ethylenediamine (3.4 mL, 50.4 mmol) in methanol (4 mL) over 45 min. The reaction mixture was stirred vigorously for 1 h at 0 °C and then for a further 48 h at room temperature under a nitrogen atmosphere. The reaction solution was evaporated, and then the residue was dried in vacuo at 35 °C to give the amino-terminated dendron D1 (1.17 g, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.46$ (s, 4H), 2.24 (t,1H), 2.38 (t, 4H), 2.83 (q, 8H), 3.29 (q, 4H), 3.43 (d, 2H), 7.30 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.64, 77.85, 73.96, 49.68, 42.31, 41.60, 38.05, 34.14. FT-IR (KBr, cm^{-1}): 3415, 3230 (ν_{N-H}); 2930, 2850 (ν_{C-H}), 2120 ($\nu_{C\equiv C}$), 1650 ($\nu_{C=O}$), 1560 (ν_{CO-NH}).

Preparation of Propargyl Focal Point PAMAM Type Dendron D2. D2 was synthesized from D1 (600.0 mg, 2.1 mmol) using the 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 (96% yield). ^{1}H NMR of D1.5 (400 MHz, $CDCl_3$): $\delta = 2.18$(t, 1H), 2.37 (t, 4H), 2.42 (t, 8H), 2.53 (t, 4H), 2.74 (t, 8H), 2.83 (t, 4H), 3.27 (q, 4H), 3.45 (d, 2H), 3.66 (s, 12H), 7.10 (s, 2H). ^{1}H NMR of D2 (400 MHz, $CDCl_3$): $\delta = 1.51$ (s, 8H), 2.20 (t, 1H), 2.34 (p, 12H), 2.50 (t, 4H), 2.71 (t, 8H), 2.81 (p, 12H), 3.26 (m, 12H), 3.42(d, 2H), 7.63 (t, 4H), 7.89 (t, 2H). ^{13}C NMR of D2 (100 MHz, $CDCl_3$): $\delta = 173.22$, 172.57, 77.95, 73.98, 53.15, 50.79, 49.44, 42.45, 41.73, 41.17, 38.05, 34.59, 33.92. FT-IR (KBr, cm^{-1}): 3416, 3262 (ν_{N-H}); 2934, 2841(ν_{C-H}), 2123 ($\nu_{C\equiv C}$), 1642 ($\nu_{C=O}$), 1556, 1386 (ν_{CO-NH}).

Preparation of Propargyl Focal Point PAMAM Type Dendron D3. D3 was synthesized from D2 (813.0 mg, 1.1 mmol) using the 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 (94% yield). ^{1}H NMR of D2.5 (400 MHz, $CDCl_3$): $\delta = 2.18$ (t, 1H), 2.37 (t, 4H), 2.42 (t, 8H), 2.53 (t, 4H), 2.74 (t, 8H), 2.83 (t, 4H), 3.27 (q, 4H), 3.45 (d, 2H), 3.66 (s, 12H), 7.10 (s, 2H). ^{1}H NMR of D3 (400 MHz, $CDCl_3$): $\delta = 1.51$ (s, 8H), 2.20 (t, 1H), 2.34 (p, 12H), 2.50 (t, 4H), 2.71 (t, 8H), 2.81 (p, 12H), 3.26 (m, 12H), 3.42(d, 2H), 7.63 (t, 4H), 7.89 (t, 2H). ^{13}C NMR of D3 (100 MHz, $CDCl_3$): $\delta = 173.27$, 172.94, 172.67, 78.07, 77.44, 53.14, 52.77, 50.75, 50.42, 49.64, 42.47, 42.31, 42.08, 41.63, 37.95, 34.52, 34.27, 34.02. FT-IR (KBr, cm^{-1}): 3416, 3262 (ν_{N-H}); 2934, 2841(ν_{C-H}), 2123 ($\nu_{C\equiv C}$), 1642 ($\nu_{C=O}$), 1556, 1386 (ν_{CO-NH}).

Preparation of Azide-Terminated PEO (PEO-N_3). Both poly(ethylene glycol) methyl ether ($M_n = 5000$; 1.00 g, 0.2 mmol) and toluene-4-sulfonyl chloride (381.0 mg, 2 mmol) were completely dissolved in CH_2Cl_2 (10 mL) under a N_2 atmosphere. Triethylamine (278 μL, 2 mmol) was added dropwise to the above solution at ice−water bath, and then the resulting solution was stirred for 24 h at room temperature. The reaction solution was centrifuged and precipitated into 80 mL of diethyl ether, and then the powder was dried in vacuo at 25 °C to give the monotosylated PEO (PEO-Ts, 968.0 mg, 94% yield). ^{1}H NMR of PEO-Ts (400 MHz, $CDCl_3$): $\delta = 2.44$ (s, 3H), 3.37 (s, 3H), 3.46 (t, 2H), 3.54 (t, 2H), 3.64 (s, 450H), 3.82 (t, 2H), 4.16 (t, 2H), 7.35 (d, 2H), 7.81(d, 2H). Thus, sodium azide (223.0 mg, 3.4 mmol) was added to a solution of the obtained PEO monotosylate (881.0 mg, 0.17 mmol) in dry DMF (10 mL) under a N_2 atmosphere, and the reaction mixture was stirred vigorously at room temperature for 24 h. DMF solvent was removed under reduced pressure, and then the product was dissolved in 80 mL of dichloromethane. The mixture was extracted sequentially with NaCl (5 wt %) solution and distilled water, dried with anhydrous Na_2SO_4, and then precipitated in diethyl ether to yield 687.2 mg of PEO azide (PEO-N_3, 80% yield). ^{1}H NMR of PEO-N_3 (400 MHz, $CDCl_3$): $\delta = 3.37$ (s, 3H), 3.39 (t, 2H), 3.46 (t, 2H), 3.54 (t, 2H), 3.64 (s, 450H), 3.82 (t, 2H).

Synthesis of Dendron-like PCL Terminated with Clickable Alkyne Group (D*m*-PCL). The dendron-like PCL homopolymers terminated with clickable alkyne groups (D*m*-PCL) were synthesized from controlled ring-opening polymerization of CL monomer using propargyl focal point PAMAM type dendrons (D*m*, $m = 0$, 1, 2, and 3) as initiators and $SnOct_2$ as catalyst in bulk at 130 °C. A typical example follows: 7.3 mg (9 μmol) of the $SnOct_2$ catalyst in dry toluene was added to the melt mixture of the D0 initiator (7.7 μL, 113 μmol) and CL monomer (1.03 g, 9.02 mmol), where the exhausting−refilling process was carried out for three times using a Schlenk line. The polymerization mixture was stirred moderately in bulk at 130 °C for 24 h. Then, the resulting product was dissolved in 5 mL of CH_2Cl_2 and poured dropwise into 50 mL of cold methanol under vigorous stirring. The precipitate was filtered and dried in vacuo at 40 °C to give 955.0 mg of D0-PCL sample (92.7% yield). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.30−1.44 (CH_2, m), 1.50−1.72 (CH_2, m), 2.17−2.23 (CH, t), 2.25−2.40 (CH_2, m), 3.60−3.70 (CH_2OH, t), 4.00−4.15 (CH_2, m). FT-IR (KBr, cm^{-1}): 3440 (ν_{N-H}), 2946 (ν_{C-H}), 1730 ($\nu_{C=O}$), 1650 (ν_{CO-NH}).

Synthesis of Linear-Dendron-like PCL-*b*-PEO Copolymers (D*m*-PCL-*b*-PEO) via Click Chemistry. A typical procedure for the synthesis of linear-dendron-like PCL-*b*-PEO copolymers was started with the feed ratio of reagents [PEO-N_3]/[Dm-PCL]/[CuBr]/[PMDETA] = 1.1/1/1.1/1.1. The click coupling reaction between PEO-N_3 (110.0 mg, 0.219 mmol) and D1-PCL (118.1 mg, 0.199 mmol alkyne unit) was conducted at 35 °C in a 25 mL Schlenk flask with 2 mL of DMF as solvent and CuBr/PMDETA as catalyst. After 24 h, the polymer solution was then precipitated in ethyl ether. The resulting copolymers were purified by solvent extraction using 10 mL of cold methanol (about 10 °C) to completely extract the excess PEO-N_3. The white powder was dried in vacuo at 40 °C to give 158.5 mg of D1-PCL-*b*-PEO (69.5% yield). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.30−1.44 (CH_2, m), 1.58−1.72 (CH_2, m), 2.14−2.22 ($NHCOCH_2$, t), 2.22−2.40 (CH_2, t), 2.70−2.76 (NCH_2CH_2CONH, t), 3.30−3.36 ($CONHCH_2CH_2NHCO$, s), 3.36−3.38 (CH_3, s), 3.50−3.74 (OCH_2CH_2O, s), 4.00−4.10 (CH_2, t), 4.50−4.56 (CH_2, t). FT-IR (KBr, cm^{-1}): 3440 (ν_{N-H}), 2946 (ν_{C-H} for PCL), 2888 (ν_{C-H} for PEO), 1725 ($\nu_{C=O}$), 1600 (triazole).

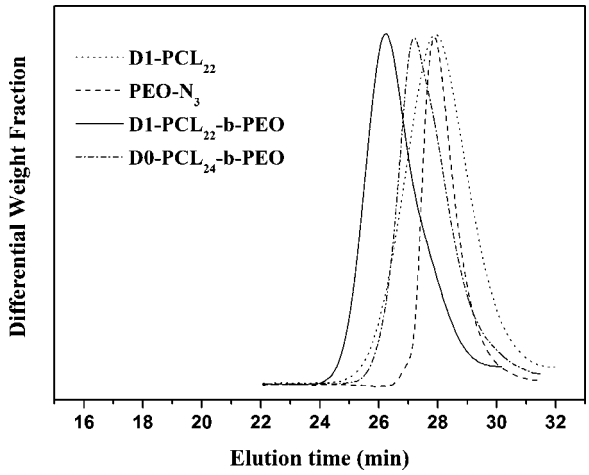


Figure 1. MALLS-GPC traces of the D*m*-PCL, PEO-N_3 precursors, and the D*m*-PCL-*b*-PEO block copolymers.

Self-Assembled Nanoparticles from D*m*-PCL-*b*-PEO Copolymers in Aqueous Solution. A typical procedure for the preparation of D*m*-PCL-*b*-PEO nanoparticles is as follows. 10 mg of D*m*-PCL-*b*-PEO sample was dissolved completely in 2 mL of acetone at room temperature, and then the resulting solution (5 mg/mL) was added dropwise to 10 mL of distilled water under vigorous stirring for about 15 min using a microsyringe. The solution was stirred vigorously for another 24 h at room temperature, and acetone was completely evaporated under reduced pressure. The obtained nanoparticles solution was stored at 4 °C before measurement, and both the mean size and morphology of nanoparticles were determined by DLS and TEM, respectively.

Results and Discussion

Synthesis of Linear-Dendron-like D*m*-PCL-*b*-PEO Copolymers via the Combination of Click Chemistry and ROP. In this article, using commercial and biocompatible PEO as the precursor, a versatile strategy to prepare the *linear-dendron-like* D*m*-PCL-*b*-PEO block copolymers with *unsymmetrical topology* was investigated based on the "arm-first" and the "core-first" synthetic strategies. In the "arm-first" method (Scheme 1), the propargyl focal point PAMAM type dendrons D*m* with primary amine terminal groups (i.e., commercial propargyl amine denoted as D0; D*m*, $m = 0$, 1, 2, and 3) were first synthesized and used for initiating the controlled ring-opening polymerization (ROP) of CL monomer, generating *dendron-like* D*m*-PCL homopolymers having 1, 2, 4, and 8 branches, which were then conjugated with azido-terminated PEO (i.e., PEO-N_3) to produce the targeted D*m*-PCL-*b*-PEO copolymers by click chemistry. This strategy was in detail investigated and proved to be successful, as shown in the following parts. As a note, in the "core-first" strategy (Scheme 2), the propargyl focal point PAMAM type dendrons D*m* with primary amine terminal groups were first synthesized and then conjugated with PEO-N_3 by click chemistry to generate primary amino-terminated PEO-dendrons (i.e., PEO-D*m*). The PEO-D*m* with primary amine terminal groups were further used as the macroinitiators for the controlled ROP of CL monomer to produce the targeted D*m*-PCL-*b*-PEO block copolymers (the bulk copolymerization conditions: [CL]/[$SnOct_2$] = 500/1, 120 and/or 130 °C, 24 h). However, both MALLS-GPC and NMR analyses indicated the targeted D*m*-PCL-*b*-PEO block copolymers with controlled molecular weights and narrow polydispersities could not be obtained (data not shown). This might be attributed to the relatively lower initiating activity of amine terminal groups of PEO-D*m* macroinitiators, which induced inter- and/or intramolecular esterification reactions in bulk at about 120 and/or 130 °C.[42−44]

It is known that biodegradable aliphatic polyesters (e.g., PCL and polylactides) with well-defined architecture can be synthesized from the controlled ROP of lactides and/or lactones using primary hydroxy- and/or amine-containing compound (especially small molecules) as initiator and $SnOct_2$ as catalyst.[42−48] Interestingly, Schubert et al. and Li et al. reported the synthesis of alkyne-terminated PCL using alkyne-containing alcohol as initiator, respectively.[49,50] However, the "clickable" PCL with dendron-like architecture has not been reported until now, which should provide a straight platform for functionalization of biodegradable polymers such as aliphatic polyesters, polypeptides, and natural polysaccharides (such as chitin and chitosan) by click chemistry. First, the propargyl focal point PAMAM-type dendrons D*m* with primary amine terminal groups (D*m*, $m = 0$, 1, 2, and 3) were designed and synthesized using propargyl amine as a propargyl focal point according to the divergent synthetic procedure,[40,41] as shown in Scheme 1A. These dendrons (i.e., D1, D2, and D3) were fully characterized by ^{1}H NMR, ^{13}C NMR, and FT-IR (see Experimental Section), which demonstrates they are pure and can be used as initiators for the following polymerization. Then, using these dendrons D*m* as initiators, the controlled ROP of CL monomer was carried out in bulk at 130 °C to obtain the dendron-like PCL homopolymers with a clickable alkyne group (D*m*-PCL), such as D0-PCL having one branch, D1-PCL having two branches, D2-PCL having four branches, and D3-PCL having eight branches (Scheme 1B), and the detailed results are summarized in Table 1. The typical MALLS-GPC curves of the resulting dendron-like D*m*-PCL homopolymers revealed a symmetrical elution peak with narrow polydispersity (M_w/M_n), as shown in Figure 1 and Table 1. Moreover, the actual molecular weights of these dendron-like D*m*-PCL homopolymers can be determined by ^{1}H NMR spectroscopy (i.e., $M_{n,NMR}$) and by MALLS-GPC (i.e., $M_{n,LLS}$), and the $M_{n,NMR}$ of D*m*-PCL is consistent with the $M_{n,LLS}$. These results indicate that the molecular weights of these dendron-like D*m*-PCL homopolymers can be accurately controlled by the molar ratio of CL monomer to the dendron D*m* initiator, and their polydispersities are narrow.

As a representative example (Figure 2A), the ^{1}H NMR spectrum of the D0-PCL homopolymer clearly shows that besides the typical proton signals of PCL main chain at 1.32−1.43 (δH^d), 1.59−1.70 (δH^f), 2.25−2.35 (δH^c), and 4.00−4.11 ppm (δH^e), there are additional proton signals of its end groups, i.e., the signals assigned to the protons on the primary hydroxy methylene end group ($HOCH_2$, $\delta H^{e'} = 3.64$ ppm) and the protons on clickable propargyl groups assigned to the dendron D*m* initiator residue (HC≡C, $\delta H^a = 2.22$ ppm, HC≡CCH_2NHCO, $\delta H^b = 5.79$ ppm). The ^{13}C NMR spectroscopy further verified the structure of as-synthesized D0-PCL, as shown in Figure 2B. Meanwhile, the NMR spectra of other D*m*-PCL homopolymers gave similar results (e.g., D2-PCL; Supporting Information, Figure S1). These results demonstrated that the propargyl focal point D*m* with primary amine terminal groups really played the role of initiator for the controlled ROP of CL monomer, and the dendron-like D*m*-PCL with different branch densities can be easily synthesized according to Scheme 1A,B. Moreover, the clickable alkyne group within these D*m*-PCL homopolymers can be discerned by ^{1}H NMR and ^{13}C NMR spectroscopy, which indicates that the clickable alkyne group did not change during the bulk polymerization at 130 °C. Thus, the above results demonstrate that the dendron-like D*m*-PCL with a clickable alkyne group can be successfully synthesized from the controlled ROP of CL monomer using propargyl focal point dendrons D*m* as initiators in bulk at 130 °C. To the best of our knowledge, this is the first report for the synthesis of dendron-like D*m*-PCL with a clickable alkyne group,[34−39,49,50] which can be used for the click conjugation with azide-

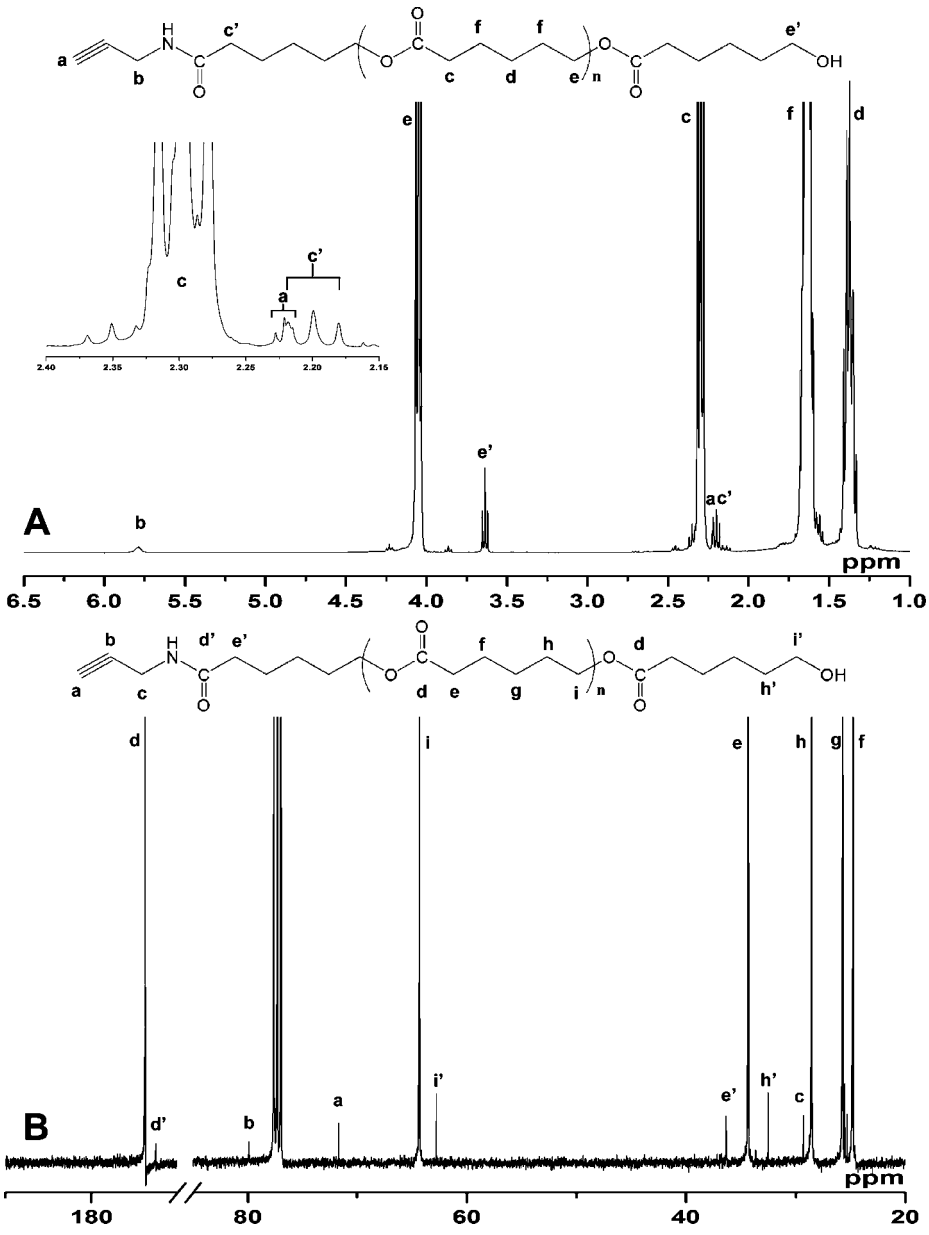


Figure 2. ^{1}H NMR (A) and ^{13}C NMR spectra (B) of D0-PCL$_{24}$ homopolymer.

Table 2. Synthesis of the Linear-Dendron-like D*m*-PCL-*b*-PEO Block Copolymers with Unsymmetrical Topology via the Click Chemistry

entry	$M_{n,LLS}$[a] copolymer	M_w/M_n[a] copolymer	$M_{n,NMR}$[b] copolymer	PEO/PCL in copolymer (wt %)[c]	yield (%)[d]
D0-PCL$_{24}$-*b*-PEO	7980	1.38	7800	65/35	91.7
D0-PCL$_{68}$-*b*-PEO	9940	1.32	12530	39/61	64.0
D1-PCL$_{22}$-*b*-PEO	10500	1.11	10420	50/50	69.5
D2-PCL$_{19}$-*b*-PEO	15200	1.10	14260	37/63	78.5
D2-PCL$_{7}$-*b*-PEO			8870	62/38	73.4
D3-PCL$_{13}$-*b*-PEO	17830	1.07	18730	29/71	81.9

[a] Both the actual molecular weight ($M_{n,LLS}$) and the polydispersity (M_w/M_n) of copolymer were determined by the MALLS-GPC technique. [b] $M_{n,NMR}$ was determined by the ^{1}H NMR spectrum (e.g., D0-PCL-*b*-PEO in Figure 5). [c] The weight percent of PEO or PCL in copolymer was calculated from the ratio of $M_{n,NMR}$ of PEO or PCL to that of copolymer. [d] The yield of these purified copolymers was determined gravimetrically.

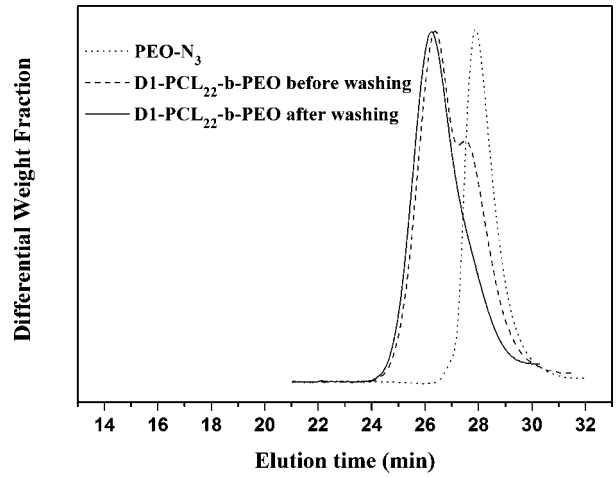


Figure 3. MALLS-GPC traces of as-synthesized D1-PCL$_{22}$-*b*-PEO copolymer before and after simple washing using cold methanol.

terminated PEO to produce *linear-dendron-like* D*m*-PCL-*b*-PEO block copolymers with *unsymmetrical topology* (Scheme 1C).

The click conjugation reaction between dendron-like D*m*-PCL with an alkyne group and PEO-N_3 was carried out using CuBr/PMDETA as catalyst in DMF solution at 35 °C, and the detailed results for the synthesis of linear-dendron-like D*m*-PCL-*b*-PEO copolymers are compiled in Table 2. It is known that

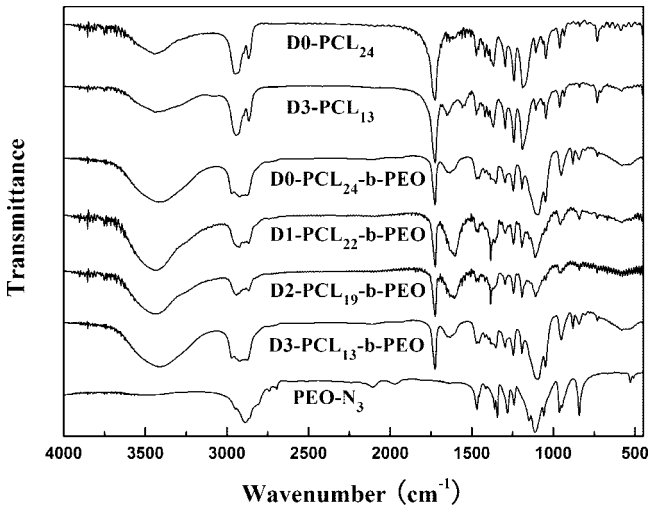


Figure 4. FT-IR spectra of PEO-N_3, D*m*-PCL, and the D*m*-PCL-*b*-PEO copolymers.

the equal molar ratio between D*m*-PCL (alkyne unit mole) and PEO-N_3 (azide unit mole) cannot be exactly realized in experiments based on the calculation of ^{1}H NMR and/or MALLS-GPC, and 10% excess PEO-N_3 precursor was used in order to prepare well-defined D*m*-PCL-*b*-PEO. The MALLS-GPC analysis proved that the excess PEO-N_3 component can be completely removed from the resulting products by simple washing using cold methanol (Figure 3), and the overall yield of these block copolymers was high (70−90 wt %). The actual molecular weights of these linear-dendron-like D*m*-PCL-*b*-PEO copolymers can be determined by ^{1}H NMR and by MALLS-GPC, and $M_{n,NMR}$ is in agreement with $M_{n,LLS}$ (Table 2). Moreover, the unimodal and symmetrical elution peak of the purified block copolymers apparently shifted toward a lower

Table 3. Melting and Crystallization Behaviors of the D*m*-PCL, PEO-N_3 Precursors, and the Linear-Dendron-like D*m*-PCL-*b*-PEO Copolymers

entry	$T_{c,PEO}$[a] (°C)	$T_{c,PCL}$[a] (°C)	$T_{m,PEO}$[b] (°C)	$T_{m,PCL}$[b] (°C)	ΔH_c[c] (J/g)	X_c[d] (%)
PEO	36.2		59.8		171.4	92.2
D0-PCL_{24}		32.4		52.0	80.6	59.1
D3-PCL_{13}		23.6		47.8	63.9	46.8
D0-PCL_{24}-*b*-PEO	29.2		52.6		108.2	64.3
D1-PCL_{22}-*b*-PEO	27.3		48.6		98.9	61.7
D2-PCL_{19}-*b*-PEO	25.9		47.9		76.3	49.6
D3-PCL_{13}-*b*-PEO	22.4		45.8		78.7	52.5

[a] $T_{c,PEO}$ and $T_{c,PCL}$ denote the crystallization temperature of PEO and PCL in the cooling run, respectively. [b] $T_{m,PEO}$ and $T_{m,PCL}$ denote the maximal melting temperature of PEO and PCL in the second heating run, respectively. [c] ΔH_c denotes the crystallization enthalpy of both PEO and PCL segments in the cooling run. [d] X_c denotes the degree of crystallinity of copolymers, where $X_c = \Delta H_c/(W_{PEO}\Delta H^\circ_{c,PEO} + W_{PCL}\Delta H^\circ_{c,PCL})$, $\Delta H^\circ_{c,PEO} = 186.0$ J/g, $\Delta H^\circ_{c,PCL} = 136.4$ J/g.

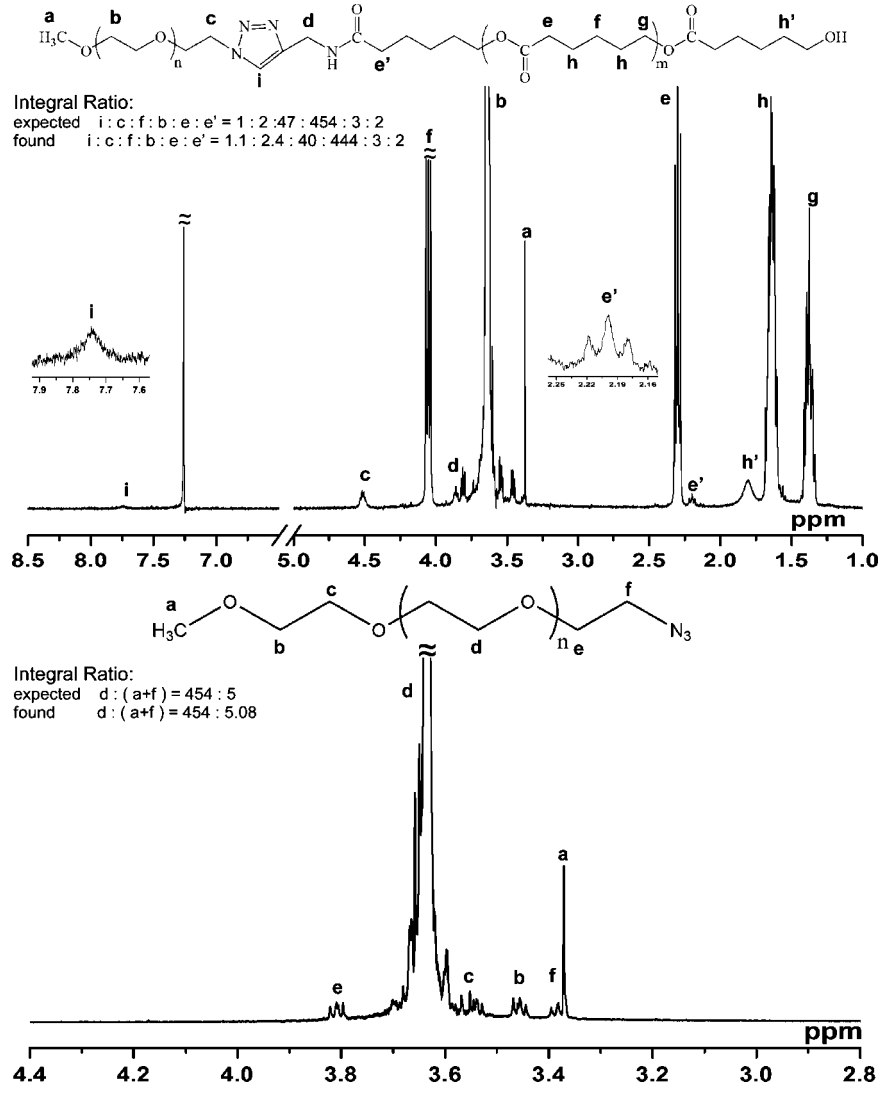


Figure 5. ^{1}H NMR spectra ($CDCl_3$) of PEO-N_3 and the D0-PCL_{24}-*b*-PEO copolymer.

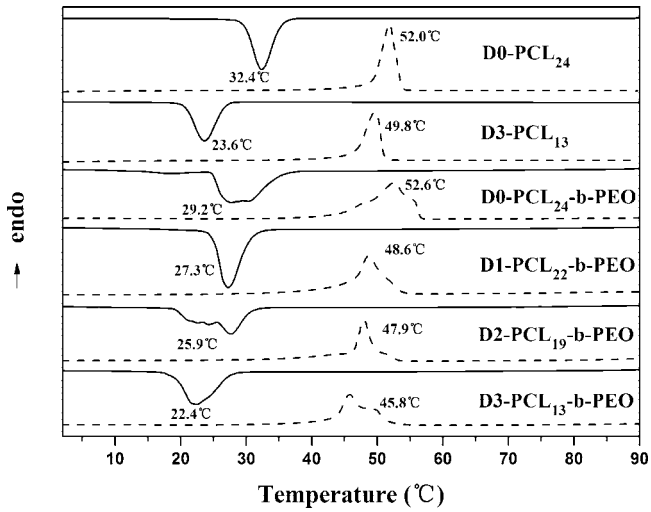


Figure 6. DSC curves of PEO-N_3, D*m*-PCL and the PCL-*b*-PEO copolymers in the cooling run (solid lines) and in the second heating run (dotted lines).

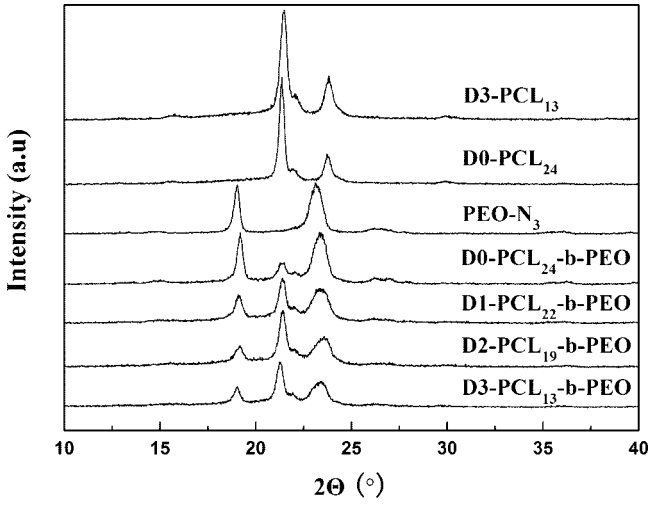


Figure 7. WAXD patterns of PEO-N_3, D*m*-PCL, and the D*m*-PCL-*b*-PEO copolymers.

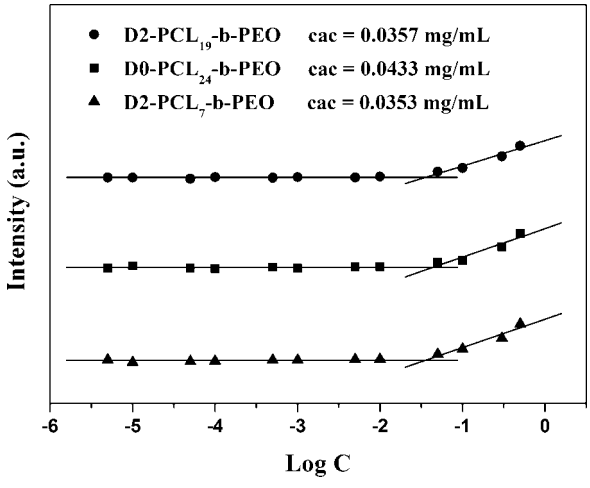


Figure 8. Relationship of the absorbance intensity of DPH as a function of the D*m*-PCL-*b*-PEO copolymer concentration in aqueous solution at room temperature (*C*: mg/mL).

elution time region coupled with a narrow polydispersity in comparison with that of the original D*m*-PCL and PEO-N_3 precursors, as shown in Figure 1. These results convincingly verified the successful synthesis of the purified D*m*-PCL-*b*-PEO block copolymers. As a note, for the D2-PCL-*b*-PEO and D3-PCL-*b*-PEO with more branches, their elution peaks did not shift toward a lower elution time region, although their $M_{n,LLS}$ apparently were greater than that of D1-PCL-*b*-PEO. This is attributable to both the compact conformation and the molecular interactions among these multihydroxyl-terminated copolymers, which resulted in a smaller hydrodynamic volume. This phenomenon has also been observed within the block and graft PCL/PEO copolymers and polyglycolide-*g*-PEO copolymers.[13,36−39]

FT-IR is a useful tool to verify the click conjugation and the presence of both PCL and PEO components in purified block copolymers (Figure 4). These purified block copolymers did not present the azide group at about 2096 cm^{-1}, and a new absorption at about 1600−1640 cm^{-1} typical of the triazole ring appeared. In addition, the linear-dendron-like D*m*-PCL-*b*-PEO block copolymers showed the distinct stretching bands at 2947 cm^{-1} (CH) and 1725 cm^{-1} (C═O) for PCL block, the intense stretching bands at 2883 and 840 cm^{-1} for PEO block, and the broad absorption at 3200−3500 cm^{-1} (NH) for the dendron D*m* initiators. Moreover, ^{1}H NMR spectra of these block copolymers confirmed that the dendron-like D*m*-PCL precursor was successfully coupled with PEO-N_3 after the click conjugation (Figure 5 and Supporting Information, Figure S2). Compared with the PEO-N_3 and D*m*-PCL precursors, the ^{1}H NMR spectra of these D*m*-PCL-*b*-PEO copolymers clearly show that, besides the typical proton signals of both PCL and PEO blocks, new signals at 7.74 ppm (singlet) typical of methine proton of the triazole ring and at 4.50 ppm of methylene protons (−CH_2−) adjacent to triazole ring clearly appeared, and the original peak (CH_2−N_3, 3.38 ppm) for PEO-N_3 disappeared (Figure 5). Furthermore, by taking into account the integration values of protons "i", "c", and "e′", the click conjugation is quantitative within the error of ^{1}H NMR measurement. Meanwhile, the compositions (PEO/PCL wt %) of these block copolymers can be easily calculated from the relative peak integrals of the methylene protons of both blocks. In all, these results indicate that the click conjugation between azide-terminated PEO and dendron-like D*m*-PCL with an alkyne group provides a versatile strategy for the synthesis of *linear-dendron-like* PCL-*b*-PEO block copolymers with *unsymmetrical topology*, as shown in Scheme 1. Notably, these block copolymers can be functionalized for the preparation of bioactive biomaterials because the multihydroxyl-terminated dendron-like PCL segments should be easily conjugated with carboxylic acid, *N*-hydroxysuccinimide (NHS) activated ester, and/or isothiocyanate derivatives of biological molecules (such as peptides, biotin, and folic acid).[51] To the best of our knowledge, this is the first report that describes the synthesis of amphiphilic *linear-dendron-like* PCL-*b*-PEO with *unsymmetrical topology* using the combination of controlled ROP and click chemistry.[34−39]

DSC and WAXD Analyses. The melting and crystallization behaviors of these linear-dendron-like D*m*-PCL-*b*-PEO copolymers were investigated by DSC, as shown in Table 3 and Figure 6. Compared with PEO and D*m*-PCL precursors, all D*m*-PCL-*b*-PEO copolymers with different compositions (PEO % = 64.8−29.3 wt %) presented a superposed melting peak (T_m) and crystallization temperature (T_c) in the second heating run and in the cooling run, respectively, which was attributed to that both PCL and PEO blocks had similar melting and crystallization temperature.[13,52] When the branch length of dendron-like D*m*-PCL segments was similar, both T_m and T_c of these block copolymers gradually decreased with the increasing branch densities of dendron-like D*m*-PCL segments, and they were in the order of D0-PCL_{24}-*b*-PEO > D1-PCL_{22}-*b*-PEO > D2-PCL_{19}-*b*-PEO > D3-PCL_{13}-*b*-PEO. This is attributable to the

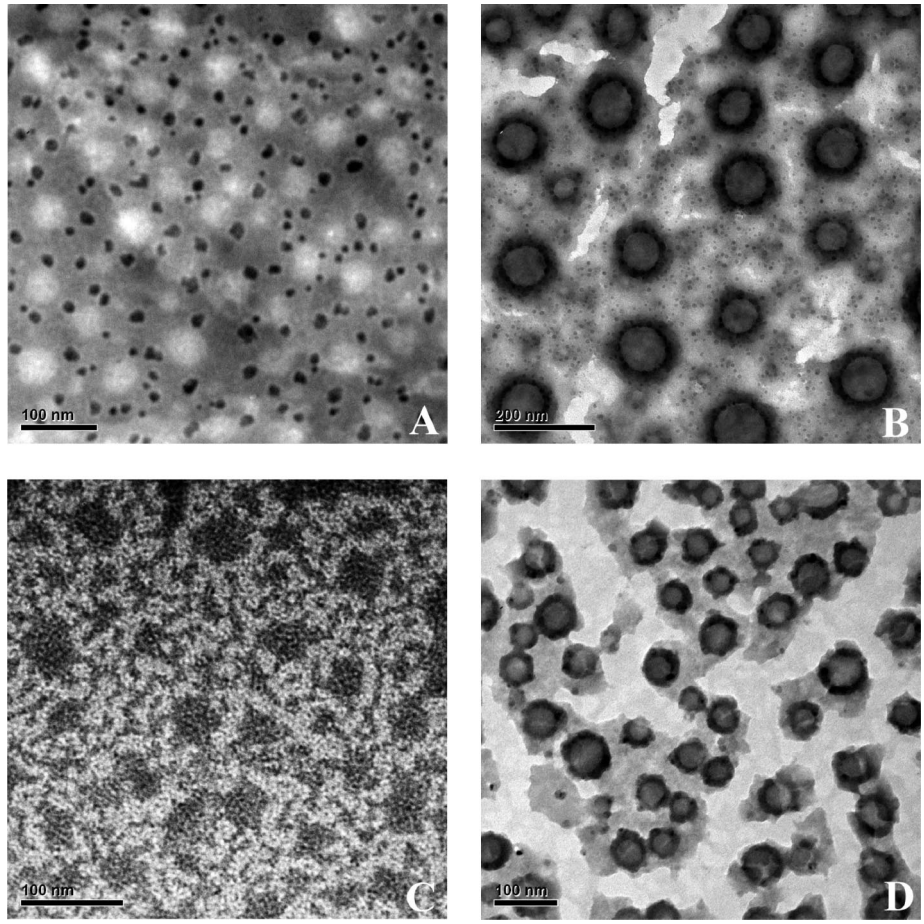


Figure 9. TEM photographs of the self-assembled nanoparticles from these D*m*-PCL-*b*-PEO copolymers in aqueous solution: A, D0-PCL$_{24}$-*b*-PEO; B, D0-PCL$_{68}$-*b*-PEO; C, D2-PCL$_{7}$-*b*-PEO; D, D2-PCL$_{19}$-*b*-PEO.

Table 4. Self-Assembled Nanoparticles from the Linear-Dendron-like D*m*-PCL-*b*-PEO Copolymers in Aqueous Solution

entry	average diameter (nm)[a]	PDI[b]
D0-PCL$_{24}$-*b*-PEO	32.9 ± 3.9	0.22
D0-PCL$_{68}$-*b*-PEO	47.7 ± 2.3	0.15
D1-PCL$_{22}$-*b*-PEO	31.0 ± 4.4	0.22
D2-PCL$_{19}$-*b*-PEO	28.1 ± 3.9	0.22
D2-PCL$_{7}$-*b*-PEO	89.4 ± 2.8	0.16
D3-PCL$_{13}$-*b*-PEO	24.6 ± 2.0	0.27

[a] The average diameter of nanoparticles was determined by the dynamic light scattering (DLS) technique. [b] PDI denotes the polydispersities of nanoparticles in aqueous solution.

following reasons. With the continuous increasing branch densities of copolymers (from D0-PCL-*b*-PEO to D3-PCL-*b*-PEO), both the intermolecular interactions (e.g., hydrogen-bonding, van der Waals, and/or dipole−dipole interactions) among these copolymers and the constrained geometry of dendron-like D*m*-PCL segments decreased the macromolecular mobility and rearrangement, suggesting a decreased crystallization tendency. Moreover, the degree of crystallinity (X_c) of both PCL and PEO blocks within these copolymers similarly showed a decreased tendency over the branch densities of copolymers. In contrast to the conventional linear polymer, these results suggest that the dendron-like D*m*-PCL segments with different branch densities provide a straight method for adjusting the crystallization properties of these block copolymers, which will be further clarified by the following WAXD analysis.

WAXD is another useful method to demonstrate the crystalline structure of these D*m*-PCL-*b*-PEO block copolymers in solid state and at room temperature, as shown in Figure 7. The D*m*-PCL and PEO-N_3 precursors presented prominent diffraction peaks at about 21.4° and 23.8° and about 19° and 23°, which are characteristic of the PCL and the PEO crystals, respectively.[13,52] Notably, the dendron-like D0-PCL having one branch and D3-PCL having eight branches showed similar diffraction peaks. This suggests that the D*m*-PCL homopolymers have similar crystalline structure in solid state and at room temperature, and both the dendron D*m* initiator and the dendron-like architecture have no apparent effect on it. Moreover, these D*m*-PCL-*b*-PEO copolymers approximately presented the diffraction peaks of both PCL and PEO blocks, which suggests that these D*m*-PCL-*b*-PEO block copolymers formed microphase-separated crystalline materials (i.e., both crystalline PCL and crystalline PEO within copolymers) in solid state and at room temperature. Comparing D0-PCL-*b*-PEO with both D0-PCL and PEO-N_3, it can be clearly observed that the diffraction intensity of PCL segment greatly decreased, suggesting that the crystallization of PEO segment heavily restrained the PCL crystallization. Furthermore, the relative peak intensity of PCL to PEO within these copolymers (from D0-PCL-*b*-PEO to D3-PCL-*b*-PEO) progressively increased with the increasing weight percent of PCL component, suggesting that the crystallization of the dendron-like PCL segments, to some extent, restricted reversely that of the PEO segments. In all, both DSC and WAXD analyses indicate that both PCL and PEO blocks within copolymers mutually influence each other, and the crystallization properties (T_m, T_c, and X_c) can be tuned from both macromolecular architecture (i.e., the branch density of dendron-like PCL) and copolymer composition. These are important parameters for adjusting the biodegradation rate and mechanical properties of biodegradable polymeric biomaterials.[10,11]

Self-Assembly of the Linear-Dendron-like D*m*-PCL-*b*-PEO Copolymers. The critical aggregation concentration (cac) of amphiphilic copolymers was an important parameter for the thermodynamic stability of self-assembled aggregates in aqueous solution, which was measured by the dye solubilization method.[23−26] 1,6-Diphenyl-1,3,5-hexatriene (DPH) was used as a probe molecule, and Figure 8 shows the relationship of the absorbance intensity of DPH as a function of copolymer concentration at room temperature. It can be clearly observed that the absorbance intensity values of DPH remained nearly constant below a certain concentration. Above that concentration, the absorbance intensity increased substantially, reflecting the incorporation of DPH in the hydrophobic region of aggregates. The cac of amphiphilic D*m*-PCL-*b*-PEO copolymers ranged from 3.53×10^{-2} to 4.33×10^{-2} mg/mL, suggesting that the self-assembled nanoparticles are thermodynamically stable in aqueous solution.[23−26] As a note, the cac of D2-PCL$_7$-*b*-PEO decreased about 18% in comparison with that of D0-PCL$_{24}$-*b*-PEO with similar composition (PEO % = 62.4−64.8 wt %), which demonstrated that the linear-dendron-like architecture was beneficial for the stability of nanoparticles in aqueous solution.[26]

Both the morphology and the average size of the self-assembled nanoparticles from these D*m*-PCL-*b*-PEO copolymers were investigated by the techniques of TEM and DLS, and the detailed results are shown in Figure 9 and Table 4. For the D0-PCL-*b*-PEO copolymer, when the weight fraction of hydrophilic PEO block was 65 wt % within D0-PCL$_{24}$-*b*-PEO sample, nearly spherical micelles with an average diameter of 32.9 ± 3.9 nm are shown in Figure 9A. However, when the weight fraction of PEO block decreased to 39 wt % within D0-PCL$_{68}$-*b*-PEO sample, the polymersomes and/or vesicles with an average diameter of 47.7 ± 2.3 nm were obtained (Figure 9B). This is attributed to both the decreased repulsion among the corona chains (i.e., hydrophilic PEO corona) and the increased surface tension resulting from the increased hydrophobicity−hydrophilicity balance.[23−25] Notably, these micellar and vesicular nanoparticles are similar to the conventional polymeric micelles usually with a diameter of 10−50 nm,[26] suggesting that they should have the simple core/shell structure (core: hydrophobic PCL segments; shell: water-soluble PEO segments). However, D2-PCL$_7$-*b*-PEO with a weight fraction of 62 wt % PEO presented a mixed morphology of nearly spherical micelles and worm-like micelles compared with D0-PCL$_{24}$-*b*-PEO having a similar PEO composition (Figure 9C). As for the D2-PCL$_{19}$-*b*-PEO copolymer having a weight fraction of 37 wt % PEO (Figure 9D, the self-assembled vesicles with an average diameter of 28.1 ± 3.9 nm were obtained in comparison with D0-PCL$_{68}$-*b*-PEO having similar PEO composition. Thus, these results indicate that both the PEO composition and the linear-dendron-like architecture of copolymers controlled the morphology and the average size of self-assembled nanoparticles. As a note, the effect of macromolecular architecture on the morphology of nanoparticles needs further investigation, which is ongoing in our laboratory. Moreover, the average size of these micellar and vesicular nanoparticles remained basically unchanged at least within 110 days at 4 °C and continuously within 7 days at 37 °C (Supporting Information, Figures S3 and S4). This suggests that they are very stable in vitro, which provides them suitable for drug delivery.[23−26] Therefore, these linear-dendron-like D*m*-PCL-*b*-PEO block copolymers will provide a convenient platform for fabricating biodegradable and biocompatible nanoparticles with controllable morphology and size for controlled drug release.

Conclusions

A new class of *linear-dendron-like* D*m*-PCL-*b*-PEO block copolymers with *unsymmetrical topology* was successfully synthesized via the combination of controlled ROP and click chemistry. The *dendron-like* D*m*-PCL terminated with a clickable alkyne group was for the first time synthesized from the controlled ROP of CL monomer using propargyl focal point dendrons D*m* with primary amine groups as the initiators and $SnOct_2$ as catalyst in bulk at 130 °C. The linear-dendron-like D*m*-PCL-*b*-PEO was obtained by the click conjugation of D*m*-PCL with PEO-N_3 using PMDETA/CuBr as catalyst at 35 °C. Both PCL and PEO blocks within these block copolymers mutually influence each other, and their crystallization properties (T_m, T_c, and X_c) can be tuned from both macromolecular architecture (i.e., the branch density of dendron-like PCL) and copolymer composition. Moreover, the biodegradable micelles and vesicles with different sizes (less than 100 nm) self-assembled from these D*m*-PCL-*b*-PEO copolymers in aqueous solution, and both the PEO composition and the linear-dendron-like architecture of copolymers controlled the morphology and the average size of nanoparticles. Consequently, this provides a versatile strategy not only for the synthesis of biodegradable and amphiphilic block copolymers with linear-dendron-like architecture but also for fabricating biocompatible nanoparticles with suitable size for controlled drug release.

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Supporting Information Available: ^{1}H NMR for D2-PCL, D2-PCL-*b*-PEO, and in vitro stability for nanoparticles. This material is available free of charge via the Internet at http://pubs.acs.org.

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