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Versatile Strategy for the Synthesis of Hyperbranched Poly(ε-caprolactone)s and Polypseudorotaxanes Thereof

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ABSTRACT: A novel class of hyperbranched poly(ε-caprolactone)s (HPCLs) and polypseudorotaxanes (HPPRs) thereof was synthesized through the polycondensation of AB_2 type poly(ε-caprolactone) or polypseudorotaxanes macromonomers with α-thiol and ω-alkyne terminal groups (thiol is A unit, and each π bond in alkyne is B unit) by using thiol−yne chemistry. Their molecular structures and physical properties were characterized in detail by FT-IR, NMR, time-of-flight mass spectrometry, gel permeation chromatography, differential scanning calorimetry, and wide-angle X-ray diffraction. The molecular weights of HPCLs gradually increased over the irradiation time, while weight-average molecular weight grew faster than number-average molecular weight, resulting in broadening their polydispersities. The cross-linking side reaction occurred in the polycondensation of poly(ε-caprolactone) with α-thiol and ω-alkyne terminal groups (PA-PCL-SH); however, this side reaction was prohibited if PA-PCL-SH was completely threaded by α-cyclodextrin to form the rigid polypseudorotaxanes. Both the maximal melting point and the crystallization point of HPCLs gradually decrease with increasing their molecular weights, and they are in the order of PA-PCL-SH > HPCL-3 > HPCL-6 > HPCL-10 > HPCL-15 > HPCL-30 (the number within sample denotes the irradiation time used). Furthermore, the degree of crystallization of HPCLs decreases from 51.4% to 30.4% with increasing the molecular weights.

Introduction

Over the past decades, dendritic polymers such as dendrimers and hyperbranched polymers received much attention in the scientific and industrial communities because of their three-dimensional topologies, easily tailored functional periphery, and especially unique solution, bulk, and self-assembly properties.[1−18] For example, dendritic polymers are demonstrated to be versatile building blocks for fabricating hierarchical micro/nanostructures and smart devices for molecular diagnosis and drug/gene delivery vesicles.[9−17] Several dendrimers, e.g., polyamidoamine and polypropylenimine, are commercially available; however, their iterative and time-consuming synthesis procedures greatly hampered their wide application. Alternative to dendrimer is the hyperbranched polymer, which can be easily synthesized by one-pot polycondensation of AB_2 monomer and has been increasingly studied for various applications.[18]

As a U.S. Food and Drug Administration approved biomedical polymer, biodegradable poly(ε-caprolactone) has been used in clinical trials for surgical sutures and screws;[19] however, its intrinsically slow biodegradation and hydrophobicity limited the biomedical applications to some extent.[20] For solving these problems, the dendritic poly(ε-caprolactone) polymers that can tune the physical and biodegradation properties of linear counterparts have been studied by several research groups.[21−27] For example, Fréchet et al. synthesized dendrimer-cored and hyperbranched poly(ε-caprolactone)s (HPCLs).[21] Hedrick et al. synthesized dendrimer-like star poly(ε-caprolactone)s by a divergent growth approach[22] and then prepared HPCLs by the polycondensation of AB_2 macromonomers.[23] Kwak et al. reported the synthesis of HPCLs by a catalyst-free polycondensation method, and thoroughly studied the structure−property relationship.[24] Interestingly, the hyperbranched polyesters containing ε-caprolactone units were synthesized by an enzymatic method.[26,27] However, the degree of branching (DB) for HPCLs is often lower than 0.5.[21,23,25]

As a widely used click reaction, the copper-catalyzed azide−alkyne cycloaddition (CuAAC) is demonstrated to be a powerful and orthogonal tool for the synthesis and functionalization of various complex architectures, including dendritic polymers.[28−36] However, the products synthesized by CuAAC often contain a residual amount of copper catalyst, inducing toxicity and being incompatible with living systems.[37,38] Contrary to the aforementioned click reaction, both thiol−ene and thiol−yne chemistry are emerging as other click reactions for the synthesis and functionalization of polymers, dendrimers, and networks.[39−47] The thiol−yne reaction is highly efficient and easy to carry out under light irradiation without the use of metal catalyst; however, scare studies on the synthesis of hyperbranched polymers are reported by utilizing thiol−yne chemistry.[43] With these in mind, herein, a versatile strategy to synthesize hyperbranched HPCLs from an AB_2 macromonomer was successfully developed by using the thiol−yne chemistry (Scheme 1), and their molecular structures and physical properties were thoroughly characterized. The as-synthesized HPCLs have a clickable periphery terminated by multiple alkyne groups, which can be further modified by thiol−yne and/or azide−alkyne chemistry. Moreover, they should have a DB close to 1,[43] which is higher than that of HPCLs reported in the literature.[21,23,25] To clarify the effect of the rigidity of poly(ε-caprolactone) branches on the polycondensation, the necklace-like hyperbranched polypseudorotaxanes (HPPRs) of HPCLs threaded with α-cyclodextrin was further prepared via the thiol−yne chemistry (Scheme 2).

Experimental Section

Materials. ε-Caprolactone (Aldrich, 99%), dimethylformamide (DMF, ≥99.5%), and tetrahydrofuran (THF, ≥99%)

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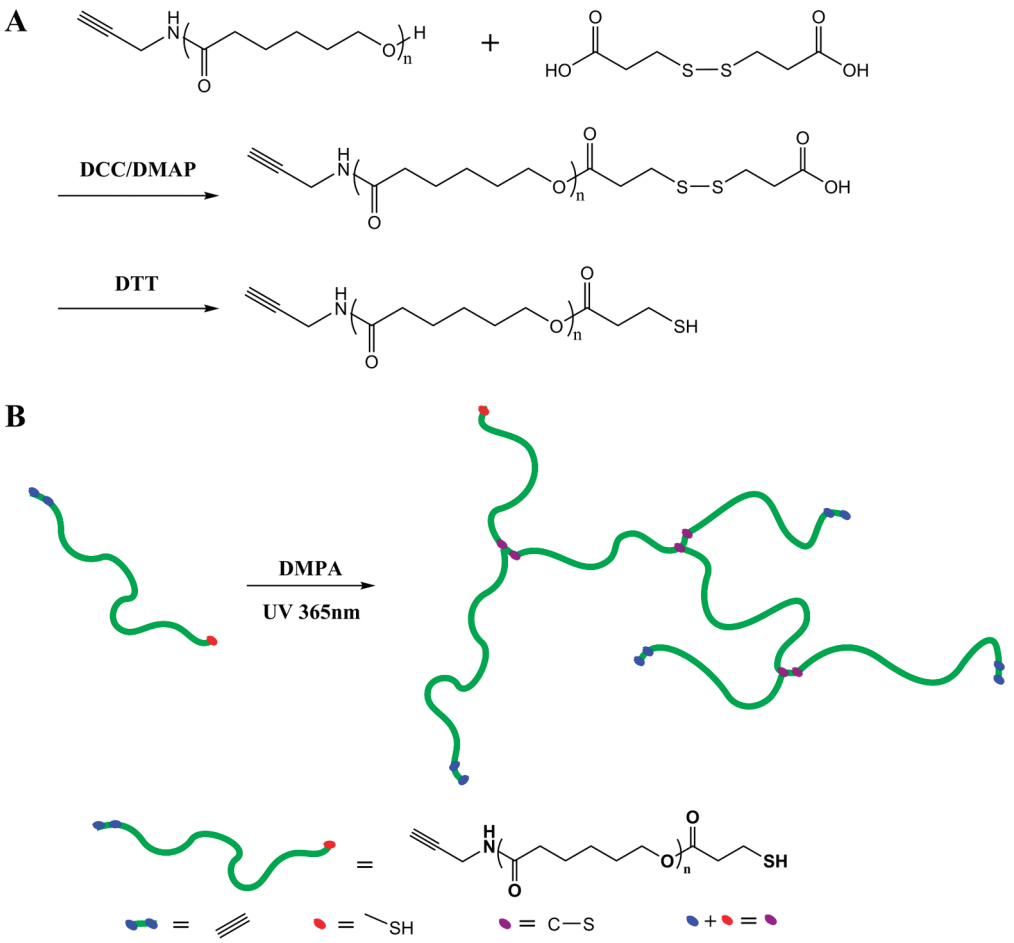
Scheme 1. Synthesis of Hyperbranched Poly(ε-caprolactone)s (HPCLs) via Thiol−Yne Chemistry: (A) Dicyclohexylcarbodiimide (DCC), 4-(Dimethylamino)pyridine (DMAP), 1,4-Dithiothreitol (DTT); (B) 2,2-Dimethoxy-2-phenylacetophenone (DMPA)

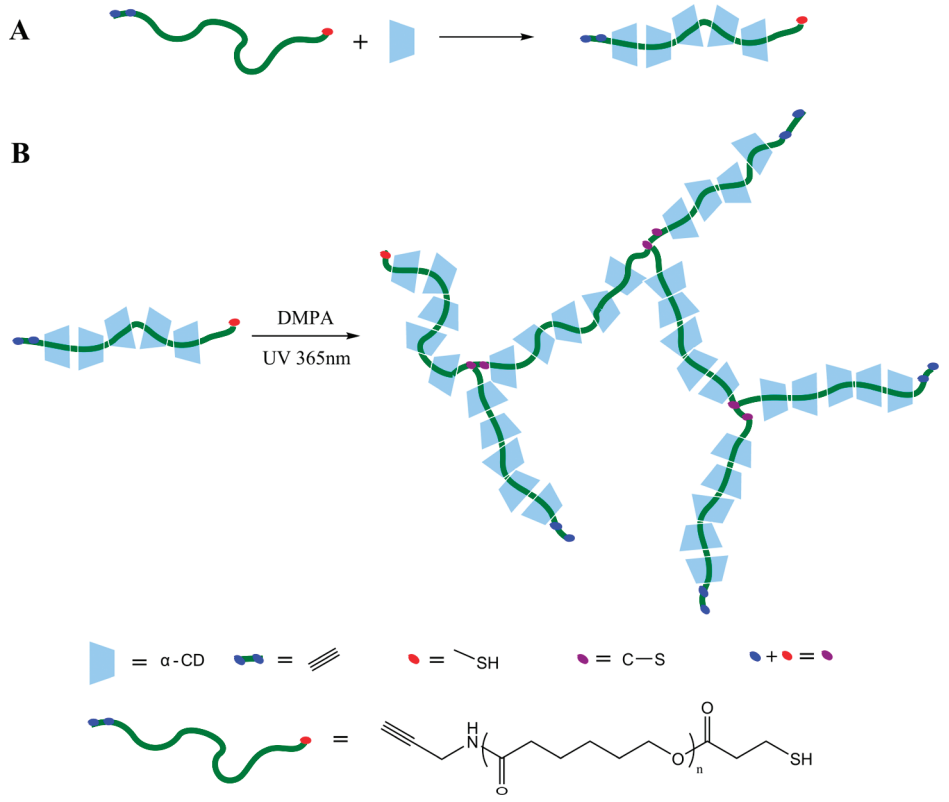


were distilled from calcium hydride under reduced pressure and stored over molecular sieves, respectively. α-Cyclodextrin hydrate (α-CD, ≥98%) was purchased from Acros and used without further purification. Dichloromethane (≥99.5%) and toluene (≥99.5%) were directly distilled from calcium hydride. Dicyclohexylcarbodiimide (DCC, 99.2%) and 4-(dimethylamino)-pyridine (DMAP, 99.1%) were purchased from GL Biochem (Shanghai, China) and used as received. 2,2-Dimethoxy-2-phenylacetophenone (DMPA, Aldrich, 99%), 3,3′-dithiobis(propionic acid) (DTPA, 99%, Aldrich), 1,4-dithiothreitol (DTT, Aldrich, ≥99%), propargylamine (PA, 99%, Acros), and stannous octoate ($SnOct_2$, Sigma, 95%) were used as received. Ethylenediamine (99%) and methyl acrylate (98%) were purchased from Shanghai Sinopharm Chemical Reagent Corporation and distilled before use.

Methods. FT-IR spectra were recorded on a Perkin-Elmer Paragon 1000 spectrometer at frequencies ranging from 400 to 4000 cm^{-1}. Samples were thoroughly mixed with KBr and pressed into pellet form. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) 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) equipped with two linear Mixed-B columns (Polymer Lab Corporation, pore size 10 μm, column size 300 × 7.5 mm, molecular weight range 500−800 000 Da) and a refractive index detector (Perkin-Elmer Series 200) at 30 °C. The elution phase was DMF (0.01 mol·L^{-1} LiBr, elution rate 1.0 mL/min), and polystyrene was used as the calibration standard. Time-of-flight mass spectrometry was performed on a Waters Acquity UPLC-QTOFMS Premier. The differential scanning calorimetry (DSC) analysis was carried out using a Perkin-Elmer Pyris 1 instrument under a nitrogen flow (10 mL/min). All samples were first heated from −20 to +80 °C at 10 °C/min, held for 3 min to erase the thermal history, then cooled to −20 at 10 °C/min, and finally heated to 90 at 10 °C/min. The melting temperature (T_m) and the crystallization temperature (T_c) were taken as the maximal points of both endothermic and exothermic peaks, respectively. The indium standard was used for temperature and enthalpy calibrations. 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 2θ = 5 and 40°.

Preparation of Poly(ε-caprolactone) with α-Hydroxyl and ω-Alkyne Terminal Groups (PA-PCL-OH). PA-PCL_{15}-OH (the subscript number denotes the degree of polymerization) was synthesized from controlled ring-opening polymerization of ε-caprolactone monomer using PA as initiator and $SnOct_2$ as catalyst according to our previous publication.[35] A typical polymerization procedure follows: 3.8 mg (4.7 μmol) of the $SnOct_2$ catalyst in dry toluene was added to the melt mixture of the PA initiator (34.2 μL, 501.1 μmol) and ε-caprolactone (1.03 g, 9.02 mmol), where the freeze−pump−thaw process was carried out three times using a Schlenk line. The polymerization mixture was stirred moderately in bulk at 120 °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

Scheme 2. Synthesis of Hyperbranched Polypseudorotaxanes (HPPRs) of HPCLs Threaded with α-Cyclodextrin (α-CD) via Thiol−Yne Chemistry



870.4 mg of PA-PCL_{15}-OH (82% yield). ^{1}H NMR of PA-PCL_{15}-OH ($CDCl_3$): δ (ppm) = 1.32−1.44 ($COCH_2CH_2CH_2$-CH_2CH_2O, m), 1.55−1.70 ($COCH_2CH_2CH_2CH_2CH_2O$, m), 2.18−2.25 ($NHCOCH_2$, q), 2.26−2.38 ($COCH_2CH_2CH_2$-CH_2CH_2O, t), 3.62−3.67 (CH_2OH, t), 4.02−4.10 ($COCH_2$-$CH_2CH_2CH_2CH_2O$, m). FT-IR (KBr, cm^{-1}): 3440 ($\nu_{N—H}$), 2946 ($\nu_{C—H}$), 2098($\nu_{C\equiv C}$), 1722 ($\nu_{C=O}$). $M_{n,GPC}$ = 5130, M_w/M_n = 1.22.

Preparation of AB_2 Type Poly(ε-caprolactone) with α-Thiol and ω-Alkyne Terminal Groups (PA-PCL-SH). PA-PCL_{15}-OH (707.0 mg, 0.4 mmol) and DTPA (168.2 mg, 0.8 mmol), DCC (329.6 mg, 1.6 mmol) ,and DMAP (8 mg, mmol) were completely dissolved in 10 mL of THF under a N_2 atmosphere. The reaction mixture was stirred vigorously at room temperature for 48 h. After several drops of acetone were addded, the mixture was filtered to remove dicyclohexylurea. The solution was concentrated under reduce pressure, and then precipitated into a large excess of cold ether (~0 °C, 20 mL). The precipitate was washed three times with cold methanol (~0 °C, 10 mL) and then dried in vacuo to give the product PA-PCL_{15}-DTPA (662.0 mg, yield 85%). ^{1}H NMR of PA-PCL_{15}-DTPA ($CDCl_3$): δ (ppm) = 1.32−1.44 ($COCH_2CH_2CH_2CH_2CH_2O$, m), 1.58−1.70 ($COCH_2$-$CH_2CH_2CH_2CH_2O$, m), 2.18−2.25 ($NHCOCH_2$, q), 2.28−2.34 ($COCH_2CH_2CH_2CH_2CH_2O$, t), 2.71−2.79 ($COCH_2CH_2SS$-CH_2CH_2COOH, m), 2.90−2.97 ($COCH_2CH_2SSCH_2CH_2CO$-OH, m), 4.02−4.12 ($COCH_2CH_2CH_2CH_2CH_2O$, m).

PA-PCL_{15}-DTPA (574.5 mg, 0.295 mmol) and DTT (182.0 mg, 1.18 mmol) were completely dissolved in 8 mL of DMF under a N_2 atmosphere. The reaction mixture was stirred vigorously at room temperature for 24 h. The solution was concentrated under reduced pressure and then precipitated into a large excess of cold ether (~0 °C, 20 mL). The precipitate was washed three times by using cold ether (~0 °C, 20 mL) and then dried in vacuo to give the product PA-PCL_{15}-SH (482.5 mg, yield 88%). ^{1}H NMR of PA-PCL_{15}-SH ($CDCl_3$): δ (ppm) = 1.32−1.42 ($COCH_2CH_2CH_2CH_2CH_2O$, m), 1.58−1.70 ($COCH_2CH_2$-$CH_2CH_2CH_2O$, m), 2.18−2.23 ($NHCOCH_2$, q), 2.27−2.34 ($COCH_2CH_2CH_2CH_2CH_2O$, t), 2.62−2.66 ($COCH_2CH_2SH$, m), 2.74−2.80 ($COCH_2CH_2SH$, m), 4.03−4.12 ($COCH_2CH_2CH_2$-CH_2CH_2O, m). FT-IR (KBr, cm^{-1}): 3440 ($\nu_{N—H}$), 2946 ($\nu_{C—H}$), 2575 ($\nu_{S—H}$), 2098 ($\nu_{C\equiv C}$), 1722 ($\nu_{C=O}$). $M_{n,GPC}$ = 6450, M_w/M_n = 1.33.

Synthesis of Hyperbranched Poly(ε-caprolactone)s (HPCLs) via Thiol−Yne Chemistry. A typical click polycondensation example follows: both PA-PCL_{15}-SH (50 mg) and 1.0 mg (2%) of the DMPA photoinitiator were completely dissolved in 1 mL of THF in a 5 mL tube, where the freeze−pump−thaw process was carried out three times using a Schlenk line. The solution tube was then irradiated under a 365 nm high-pressure mercury lamp (150 w) for a predetermined time (i.e., 3, 6, 10, 15, 30, 60 min), where the distance between the lamp and tube was 15 cm. The resulting solution was precipitated into a large excess of cold methanol (~0 °C, 10 mL) to give the final product HPCLs, and the polymer yield varied from 39% to 84%. ^{1}H NMR ($CDCl_3$) of a representative HPCL-3: δ (ppm) = 1.30−1.42 ($COCH_2CH_2CH_2CH_2CH_2O$, m), 1.55−1.70 ($COCH_2$-$CH_2CH_2CH_2CH_2O$, m), 2.20−2.35 ($COCH_2CH_2CH_2CH_2$-CH_2O, t), 2.60−2.67 ($COCH_2CH_2S$, m), 2.69−2.79 ($COCH_2$-CH_2S, m), 2.80−2.88 (SCH_2CHS, m), 2.88−2.90 (SCH_2CHS, m), 4.01−4.20 ($COCH_2CH_2CH_2CH_2CH_2O$, m). FT-IR (KBr, cm^{-1}): 3440 ($\nu_{N—H}$), 2940 ($\nu_{C—H}$), 1722 and 1734 ($\nu_{C=O}$). $M_{n,GPC}$ = 13 580, M_w/M_n = 1.84.

Synthesis of Hyperbranched Polypseudorotaxanes (HPPRs) of HPCLs Threaded with α-Cyclodextrin via Thiol−Yne Chemistry. HPPRs were prepared according to the following two steps. First, the polypseudorotaxanes (PPR) of PA-PCL-SH with α-cyclodextrin (α-CD) were prepared as follows. PA-PCL-SH (27.8 mg) was dissolved in 2.8 mL of acetone at 50 °C, and α-CD (146.0 mg) was dissolved in 1.5 mL of distilled water at 60 °C. Then the PA-PCL-SH solution was added dropwise to the α-CD solution at 60 °C with vigorous stirring. After being stirred at 60 °C for 8 h, the mixture was cooled to room temperature and stirred vigorously for 32 h. The precipitated product was collected by centrifugation and three times washed with acetone

(10.0 mL) to remove free polymer and then three times washed with distilled water (10.0 mL) to remove uncomplexed α-CD. The white powder was then dried overnight in vacuo to give 133.8 mg of PPR (77% yield). ^{1}H NMR of PPR (DMSO-d_6): δ (ppm) = 1.24−1.32 ($COCH_2CH_2CH_2CH_2CH_2O$, m), 1.44−1.56 ($COCH_2CH_2CH_2CH_2CH_2O$, m), 2.20−2.28 ($COCH_2CH_2CH_2CH_2CH_2O$, t), 2.60−2.68 ($COCH_2CH_2SH$, m), 2.84−2.88 ($COCH_2CH_2SH$, m), 3.20−3.28 ($CH(CH_2OH)CHCH(O)CH(OH)$, m), 3.33−3.40 ($CH(O)CH(OH)CH(OH)$, t), 3.52−3.60 (CH_2OH, d), 3.60−3.69 ($CH(O)CH_2OH$, m), 3.72−3.80 ($CH(O)CH(OH)CH(OH)$, t), 3.86−4.00 ($COCH_2CH_2CH_2CH_2CH_2O$, t), 4.44−4.49 (CH_2OH, t), 4.75−4.82 ($OCH(O)CH(OH)$, d), 5.40−5.44 ($CH(O)CH(OH)CH(OH)$, d), 5.48−5.54 ($CH(O)CH(OH)CH(OH)$, d), 8.19−8.21 ($NHCO$, s). FT-IR (KBr, cm^{-1}): 3440 (ν_{N-H}), 3415 (ν_{O-H}), 2946 (ν_{C-H}), 1730 ($\nu_{C=O}$), 1650 (ν_{CO-NH}), 1402 (ν_{O-H}), 1155 (ν_{C-O-C}), 1089 (ν_{C-C}), 1031 (ν_{C-O}).

Second, a typical click polycondensation example follows: both PPR (50 mg) and 5.0 mg (9%) of the DMPA photoinitiator were completely dissolved in 1 mL of DMF in a 5 mL tube, where the exhausting−refilling process was carried out three times using a Schlenk line. The solution tube was then irradiated under a 365 nm high-pressure mercury lamp (150 w) for 180 min, where the distance between the lamp and tube was 15 cm. The resulting solution was precipitated into a large excess of acetone (10 mL) to give the final product HPPR-180 (47.5 mg, 95% yield). ^{1}H NMR of HPPR-180 (DMSO-d_6): δ (ppm) = 1.22−1.32 ($COCH_2CH_2CH_2CH_2CH_2O$, m), 1.44−1.57 ($COCH_2CH_2CH_2CH_2CH_2O$, m), 2.20−2.28 ($COCH_2CH_2CH_2CH_2CH_2O$, t), 3.21−3.30 ($CH(CH_2OH)CHCH(O)CH(OH)$, m), 3.32−3.42 ($CH(O)CH(OH)CH(OH)$, t), 3.52−3.60 (CH_2OH, d), 3.60−3.70 ($CH(O)CH_2OH$, m), 3.71−3.80 ($CH(O)CH(OH)CH(OH)$, t), 3.92−4.00 ($COCH_2CH_2CH_2CH_2CH_2O$, t), 4.44−4.50 (CH_2OH, t), 4.76−4.82 ($OCH(O)CH(OH)$, d), 5.40−5.46 ($CH(O)CH(OH)CH(OH)$, d), 5.48−5.56 ($CH(O)CH(OH)CH(OH)$, d), 7.93−7.95 ($NHCO$, s). FT-IR (KBr, cm^{-1}): 3440 (ν_{N-H}), 3415(ν_{O-H}), 2946 (ν_{C-H}), 1730 ($\nu_{C=O}$), 1650 (ν_{CO-NH}), 1402 (ν_{O-H}), 1155 (ν_{C-O-C}), 1089 (ν_{C-C}), 1031 (ν_{C-O}). $M_{n,GPC}$ = 14 580, M_w/M_n = 2.34.

Results and Discussion

Synthesis of AB_2 Type Macromonomer Poly(ε-caprolactone) with α-Thiol and ω-Alkyne Terminal Groups (PA-PCL-SH). The AB_2 type macromonomer PA-PCL-SH was designed and synthesized by the following three steps. First, the poly(ε-caprolactone) with α-hydroxyl and ω-alkyne terminal groups (PA-PCL-OH) with 15 repeating units and a polydispersity of 1.22 was synthesized by the controlled ring-opening polymerization of ε-caprolactone using propargylamine (PA) as initiator according to our previous publications.[35] The actual polymer molecular weight or the degree of polymerization of PA-PCL_{15}-OH could be easily determined by means of ^{1}H NMR spectroscopy (Figure A). Then the PA-PCL_{15}-OH precursor was conjugated with 3,3′-dithiobis(propionic acid), followed by the reduction of disulfide bonds by 1,4-dithiothreitol at room temperature to generate the targeted PA-PCL_{15}-SH,[48] as shown in Scheme 1. Comparing the ^{1}H NMR spectrum of the resulting PA-PCL_{15}-SH with that of the PA-PCL_{15}-OH precursor, the triple proton signals at 3.62−3.67 ppm assignable to the primary hydroxymethylene end group ($HOCH_2$) of PA-PCL_{15}-OH wholly disappeared, while new signals corresponding to the thiol−methylene end group ($HSCH_2CH_2COO$) appeared at 2.77 and 2.64 ppm for PA-PCL_{15}-SH (Figure 1B). Moreover, the integral ratio of the repeating methylene unit (CH_2) of PA-PCL_{15}-SH to the methylene proton signals on HS-CH_2CH_2-COO was very close to the theoretical value ($H^d/H^i/H^j$ = 30/2/2). These results demonstrate that the hydroxyl end group

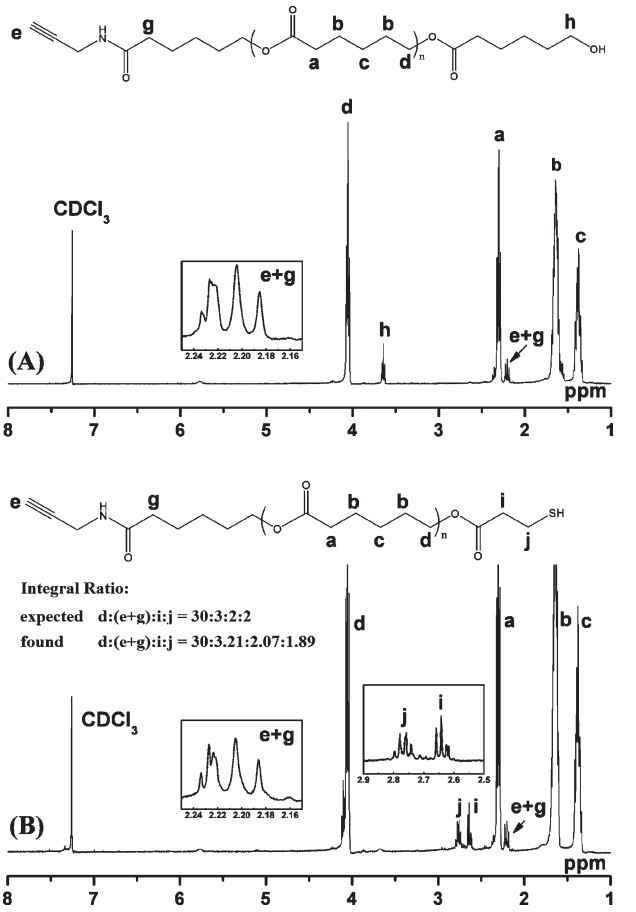


Figure 1. ^{1}H NMR spectra of the poly(ε-caprolactone) with α-hydroxyl and ω-alkyne terminal groups (PA-PCL-OH, A) and the poly(ε-caprolactone) with α-thiol and ω-alkyne terminal groups (PA-PCL-SH, B).

of the PA-PCL_{15}-OH precursor was quantitatively converted into the thiol end group within PA-PCL_{15}-SH. Moreover, compared with PA-PCL_{15}-OH, PA-PCL_{15}-SH showed the vibrational peak at about 2575 cm^{-1} for the thiol terminal group in FT-IR spectra (Figure 2), also suggesting that PA-PCL_{15}-OH was successfully transformed into PA-PCL_{15}-SH. Furthermore, time-of-flight mass spectrometry (TOF-MS) convincingly confirmed the successful synthesis of purified PA-PCL-SH (Figure 3). Note that the TOF-MS determined molecular weight of PA-PCL-SH was lower than that determined by ^{1}H NMR, which is due to PA-PCL-SH having a relatively high polydispersity (M_w/M_n = 1.33). This phenomenon has been often observed for the polymers with $M_w/M_n > 1.2$.[49,50] It should be noted that this is the first report on the synthesis of an AB_2 type PA-PCL-SH macromonomer with α-thiol and ω-alkyne terminal groups,[35,48] which can be used for synthesizing hyperbranched polymers via thiol−yne chemistry.[39−47]

Synthesis of Hyperbranched Poly(ε-caprolactone)s (HPCLs) via Thiol−Yne Chemistry. The AB_2 type macromonomer PA-PCL-SH was photoinitiated by 2,2-dimethoxy-2-phenylacetophenone (DMPA) under UV irradiation at 365 nm to generate HPCLs, and the detailed results were summarized in Table 1. It is observed that the molecular weights of HPCLs gradually increased with the irradiation time or the polymer yield, while weight-average molecular weight (M_w) grew faster than number-average molecular weight (M_n), resulting in broadening the polydispersity (M_w/M_n) (see Supporting Information, Figure S1) of HPCLs. The gel permeation chromatography (GPC)

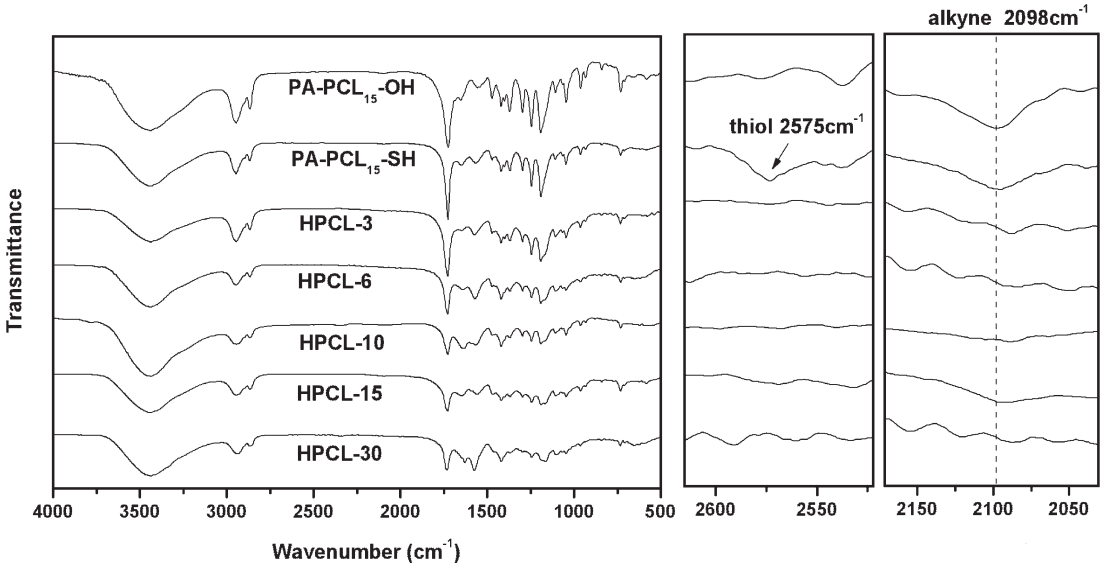


Figure 2. FT-IR spectra of PA-PCL-OH, PA-PCL-SH, and the related HPCLs.

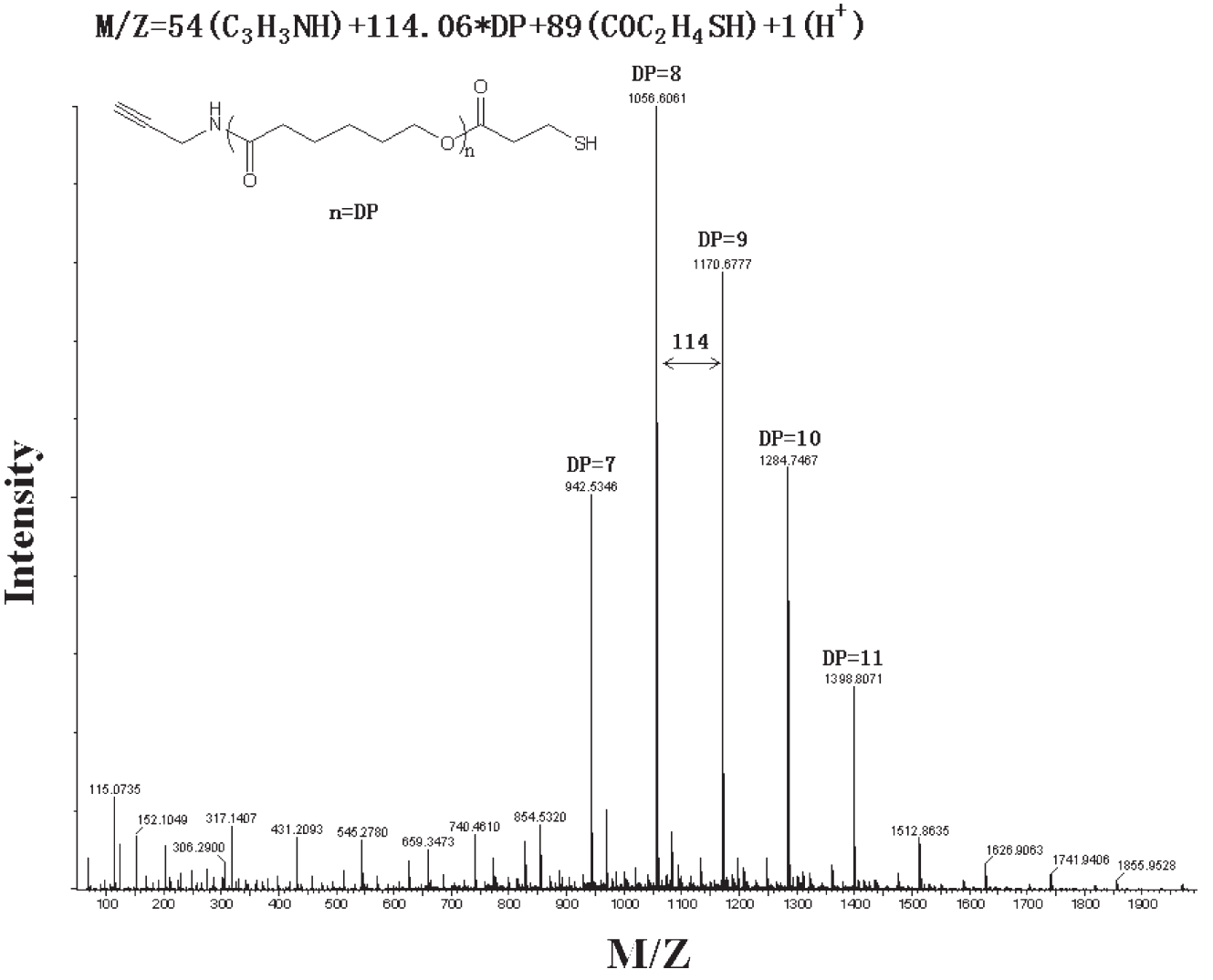


Figure 3. Time-of-flight mass spectrometry spectrum of PA-PCL-SH.

traces of HPCLs showed that the unimodal elution peak gradually shifted toward the higher molecular weight region with a broad polydispersity compared with that of the original PA-PCL_{15}-SH precursor (Figure 4). These results convincingly verified the successful synthesis of HPCLs.

Table 1. Synthesis of Hyperbranched Poly(ε-caprolactone)s (HPCLs) by Using Thiol−Yne Chemistry[a]

sample	irradiation time (min)	$M_{n,GPC}$[b]	$M_{w,GPC}$[b]	M_w/M_n[b]	alkyne[c] periphery	yield[d] (%)
PA-PCL$_{15}$-SH	0	6450	8950	1.33		
HPCL-3[e]	3	13580	24940	1.84	4	39
HPCL-6[e]	6	15170	27080	2.08	7	40
HPCL-10[e]	10	18710	43150	2.31	13	52
HPCL-15[e]	15	20090	47580	2.37	15	54
HPCL-30[e,f]	30	16530	36660	2.22		78
HPCL-60[e,f]	60	18560	40890	2.20		84

[a] The reaction was irradiated under 365 nm using 2% 2,2-dimethoxy-2-phenylacetophenone (DMPA) photoinitiator. [b] Both the molecular weights ($M_{w,GPC}$ and $M_{n,GPC}$) and the polydispersity (M_w/M_n) of HPCLs were determined by the GPC technique. [c] Alkyne periphery denotes the alkyne number per HPCLs macromolecule, which was determined by the Ellman method. [d] The yield of HPCLs was determined gravimetrically. [e] The number within sample denotes the irradiation time used. [f] After the reaction was irradiated by 30 or 60 min, about 5% and 40% cross-linked products were produced, respectively.

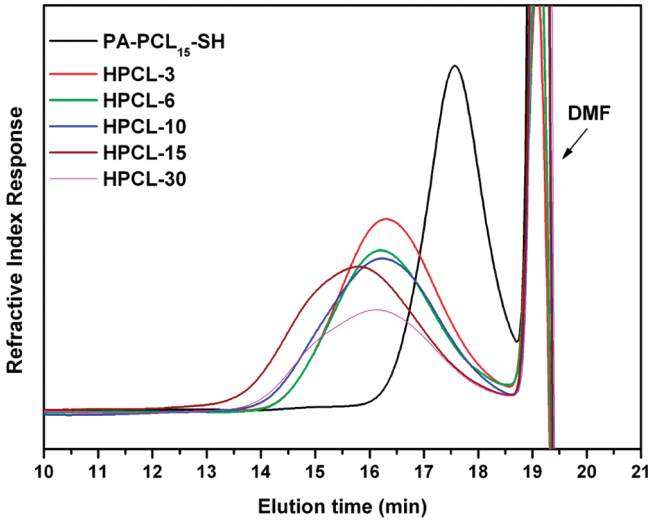


Figure 4. Gel permeation chromatography (GPC) traces of the PA-PCL-SH precursor and HPCLs.

Note that the molecular weights of HPCLs (e.g., HPCL-30 and HPCL-60) decreased reversely when the irradiation time was increased to 30 and 60 min, respectively. This is attributable to the fact that some cross-linked products were produced when the polymer yield was high (e.g., 78% and 84%) and that the soluble part showed a relatively lower molecular weight. As for the HPCL-60 sample, the cross-linked product accounted for about 40 wt %, which could not be dissolved in THF, DMF, and DMSO solvents. In addition, the polymerization system easily gelled if a lesser amount of solvent (e.g., THF or DMF) was added (Supporting Information, Table S1). As the HPCLs solution became more viscous, the focal point thiol (SH) might add to the intermediate vinyl sulfide (−HC═CH—S−) during the polycondensation process, resulting in the cross-linking side reaction (Supporting Information, Scheme S1). Note that the temperature of the polymerization system remained below 45 °C even if the irradiation time was extended to 240 min, which suggests that the intra/intermolecular transterification-triggered cross-linking was negligible within the polycondensation system.[51]

From the above results, we reason that the rigidity of the PA-PCL-SH precursor should affect the cross-linking. To further clarify this question, we designed and synthesized the hyperbranched polypseudorotaxanes (HPPRs) of HPCLs threaded with α-cyclodextrin. α-Cyclodextrin (α-CD) was threaded onto the backbone of PA-PCL$_{15}$-SH to form the rigid necklace-like polypseudorotaxanes (PPR),[52] which was then irradiated to produce the HPPRs via the thiol−yne chemistry (Scheme 2 and Table 2). Compared with that of the

Table 2. Synthesis of Hyperbranched Polypseudorotaxanes (HPPRs) of HPCLs Threaded with α-Cyclodextrin by Using Thiol−Yne Chemistry[a]

sample	irradiation time (min)	$M_{n,GPC}$	$M_{w,GPC}$	M_w/M_n
PPR[b]	0	6070	8210	1.35
HPPR-180	180	14580	34080	2.34
control[c]	180	7740	11320	1.46

[a] The reaction was irradiated under 365 nm using 9% DMPA photoinitiator. [b] Polypseudorotaxane (PPR) denotes the inclusion complexes formed between the poly(ε-caprolactone) with α-thiol and ω-alkyne terminal groups (PA-PCL-SH) and α-cyclodextrin. [c] The control was irradiated under 365 nm using 2% DMPA photoinitiator, which was equal to that used in the polycondensation of AB_2 type macromonomer PA-PCL-SH.

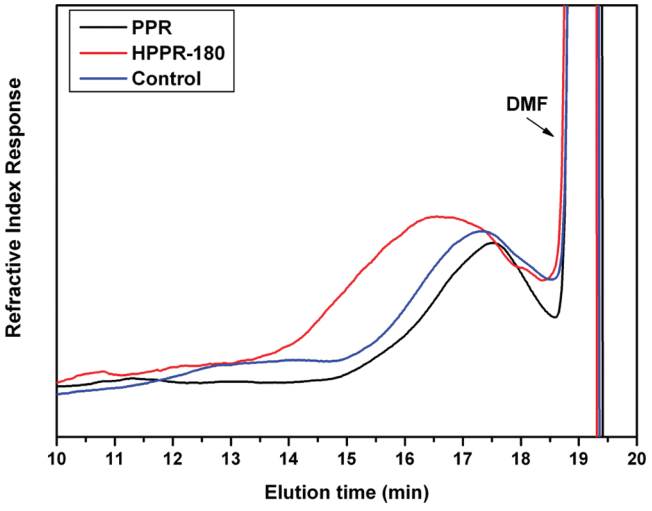


Figure 5. GPC traces of the polypseudorotaxanes (PPR) precursor, control, and HPPRs.

PPR precursor, the unimodal elution peak of the as-synthesized HPPRs shifted toward a lower elution time region with a broad polydispersity, which convincingly verified the successful synthesis of the target (Figure 5). No cross-linking phenomenon was observed during the polycondensation process even if the polymer yield was higher (95%) with the irradiation of 180 min, which suggests that the PPR backbone was rigid enough to prohibit the cross-linking side reaction. However, the molecular weight of PPR did not change obviously when 2% DMPA photoinitiator was used (control, Table 2). This indicates that the reactivity of addition between alkyne and thiol within PPR was greatly attenuated compared with that of PA-PCL-SH, which was due to the steric shielding effect of α-CD cavities.[46]

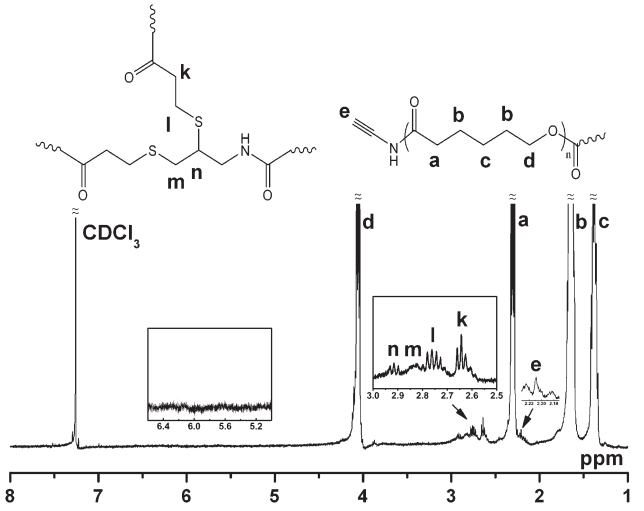


Figure 6. ^{1}H NMR spectrum of a representative HPCL-3 sample.

As shown in Figure 2, FT-IR spectra also confirmed the click polycondensation. Compared with the PA-PCL-SH precursor, the typical thiol group (−SH) at about 2575 cm^{-1} disappeared within HPCLs, and the peak at 2098 cm^{-1} associated with alkyne (HC≡C) gradually attenuated, suggesting the occurrence of click polycondensation.[43,46] Note that the intense stretching bands at 2946 cm^{-1} (CH) and 1722 cm^{-1} (C═O) for PCL block and the broad band at 3200−3600 cm^{-1} (NH) remained in HPCLs. Besides the typical proton signals of PCL, the ^{1}H NMR spectra of HPCLs clearly show new signals at 2.92 and 2.84 ppm assignable to methine proton (S—CH, n) and methylene protons (S—CH_2, m) (Figure 6). The degree of branching (DB) of hyperbranched polymers as originally defined by Fréchet et al.[53] is expressed as

$$\mathrm{DB} = \frac{S_n(\text{dendritic}) + S_e(\text{terminal})}{S_n + S_e + S_{alkene}(\text{linear})}$$

The ^{1}H NMR of Figure 6 can be utilized to determined DB, where S denotes the integral values of protons. The alkene peak ranging within 5−6.5 ppm can be negligible (i.e., $S_{alkene}(\text{linear}) = 0$) for HPCLs within the error of ^{1}H NMR measurement, suggesting that the alkyne group within HPCLs was either fully saturated or unreacted.[43] No alkene would be produced by one thiol addition to the alkyne, which implies that the degree of branching (DB) of these HPCLs is close to 1.[43] With the Ellman method,[54] the multiple alkyne periphery groups within HPCLs could be calculated, ranging from 4 to 15 (Table 1). In addition, ^{1}H NMR spectroscopy also confirmed the chemical structure of the hyperbranched HPPRs (Supporting Information, Figure S2). Taken together these results indicate that the click polycondensation of PA-PCL-SH and/or PPR indeed occurred and produced HPCLs and HPPRs, respectively, as shown in Schemes 1 and 2. To the best of our knowledge, this is the first report that describes the synthesis of hyperbranched and biodegradable HPCLs with tunable alkyne periphery and the HPPRs thereof by utilizing thiol−yne chemistry,[39−47] which can be further modified via thiol−yne and/or azide−alkyne chemistry.[28−47]

In addition, FT-IR can also characterize the crystallization behavior of the synthesized HPCLs in solid state and at room temperature. It is known that both crystalline and amorphous poly(ε-caprolactone) usually give the stretching peaks of carbonyl (C═O) at 1722 and 1734 cm^{-1}, and those of C—C and C—O at 1192 and 1160 cm^{-1}, respectively.[55] As shown in Figure 7, it can be seen that the relative intensity

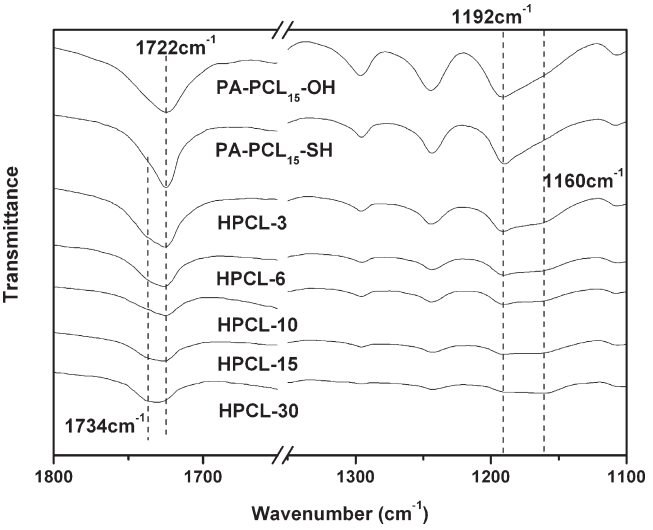


Figure 7. Expanded FT-IR of PA-PCL-OH, PA-PCL-SH, and HPCLs.

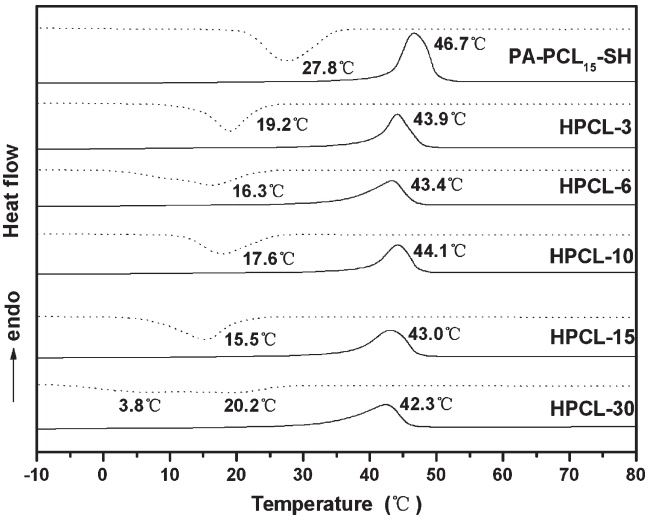


Figure 8. Differential scanning calorimetry (DSC) curves of PA-PCL-SH and HPCLs in the cooling run (dot lines) and in the second heating run (solid lines), respectively.

of the carbonyl peak at 1722 cm^{-1} to that at 1734 cm^{-1} within HPCLs gradually decreased with increasing molecular weight, indicating the decreasing crystallinity. A similar trend is also observed for the stretching peaks of C—C and C—O. These results demonstrate that the crystallinity of HPCLs can be tuned by changing the irradiation time, which provides a convenient tool to control the physical properties of poly(ε-caprolactone)-based biomaterials. This can be further clarified by the following DSC and WAXD analyses.

DSC and WAXD Analyses. The melting and crystallization behaviors of these HPCLs were investigated by DSC, as shown in Figure 8 and Table 3. Compared with the PA-PCL-SH precursor having a higher maximal melting point (T_m) at 46.7 °C and a higher crystallization point (T_c) at 27.8 °C, all hyperbranched HPCLs gave a monomodal T_m ranging from 43.9 to 42.3 °C and T_c at 19.2−15.5 °C. Moreover, both T_m and T_c of HPCLs gradually decreased with increasing molecular weight, and they are in the order PA-PCL-SH > HPCL-3 > HPCL-6 > HPCL-10 > HPCL-15 > HPCL-30 (Figure 8). This is attributed to the fact that the increasing poly(ε-caprolactone) branches

Table 3. Melting and Crystallization Behaviors of PA-PCL-SH Precursor and the Hyperbranched HPCLs

samples	T_m (°C)[a]	T_c (°C)[b]	ΔH_c (J/g)[c]	X_c (%)[d]
PA-PCL$_{15}$-SH	46.7	27.8	74.5	54.6
HPCL-3	43.9	19.2	70.1	51.4
HPCL-6	43.4	16.3	52.6	38.6
HPCL-10	44.1	17.6	48.6	35.6
HPCL-15	43.0	15.5	45.8	33.6
HPCL-30	42.3	3.8, 20.2	41.5	30.4

[a] T_m denotes the maximal melting temperature of poly(ε-caprolactone) (PCL) in the second heating run. [b] T_c denotes the maximal crystallization temperature of PCL in the cooling run. [c] ΔH_c denotes the crystallization enthalpy of PCL in the cooling run. [d] X_c denotes the degree of crystallinity of HPCLs, where $X_c = \Delta H_c/\Delta H^0_{c,PCL}$, $\Delta H^0_{c,PCL} = 136.4$ J/g.

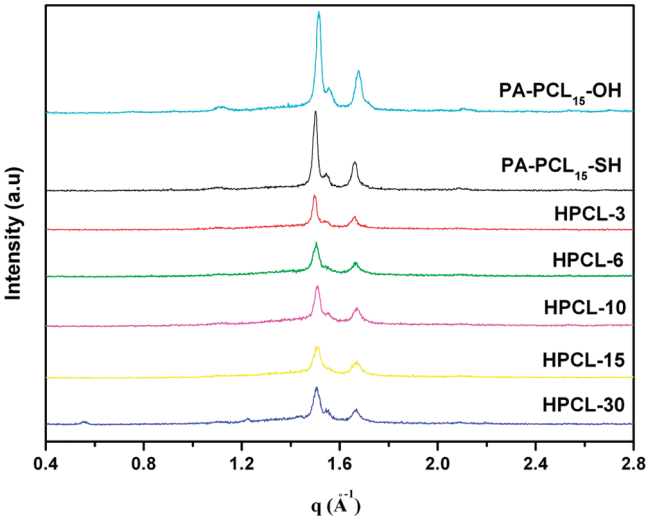


Figure 9. Wide-angle X-ray diffraction (WAXD) patterns of PA-PCL-SH and HPCLs.

within HPCLs rendered the crystallization more difficult, decreasing the melting and crystallization temperatures.[24,35,56] Furthermore, the degree of crystallization (X_c) of HPCLs decreases from 51.4% to 30.4% with increasing molecular weights of HPCLs, and its variation trend is the same as that of T_m or T_c.

As shown in Figure 9, WAXD was used to demonstrate the crystalline structure of HPCLs in the solid state and at room temperature. The PA-PCL-SH precursor exhibited prominent diffraction peaks at about 1.51 and 1.67 Å^{-1} (or $2\theta = 21.4°$ and 23.8°), which is characteristic of the poly(ε-caprolactone) crystal.[35,56] All HPCLs presented a similar diffraction mode, while the relative intensity is greatly attenuated compared with its linear PA-PCL-SH precursor. Taken together, the above analyses indicate that the crystallization properties of these HPCLs homopolymers (e.g., T_m, T_c, and X_c) can be easily tuned by changing the irradiation time. This provides a versatile strategy for designing hyperbranched poly(ε-caprolactone)-based biomaterials with controllable physical properties for biomedical applications.

α-CD can thread onto the backbone of poly(ε-caprolactone) to form supramolecular polypseudorotaxanes, providing a powerful tool to generate the necklace-like materials.[52] Compared with the case for PA-PCL-SH, no melting point and crystallization point were observed for PPR and HPPR-180, demonstrating that the crystallization of poly(ε-caprolactone) segments was completely suppressed within the cavities of α-CD (Figure 10A). Moreover, both PPR and HPPR-180 showed new strong diffraction peaks at 1.40 and 1.58 Å^{-1} (or $2\theta = 19.8°$ and 22.4°), while the major crystalline peaks

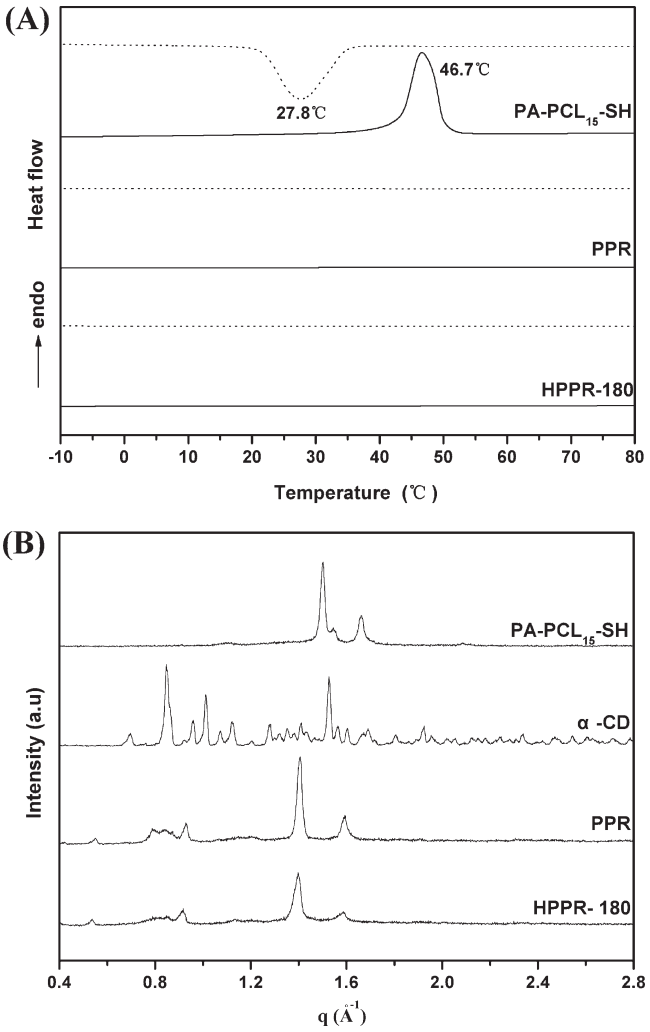


Figure 10. (A) DSC curves of PA-PCL-SH, PPR, and HPPRs in the cooling run (dot lines) and in the second heating run (solid lines), respectively. (B) WAXD patterns of PA-PCL-SH, α-CD, PPR, and HPPRs.

for PA-PCL-SH wholly disappeared. These results convincingly verified the successful preparation of PPR and HPPRs, which adopted a channel-type crystalline structure.[52] Note that the diffraction intensity of HPPR-180 was greatly attenuated in comparison with that for the PPR precursor, which is due to the hyperbranched architecture.

Conclusions

A novel class of hyperbranched HPCLs with tunable alkyne periphery and HPPRs thereof was successfully synthesized through the polycondensation of AB_2 type poly(ε-caprolactone) or polypseudorotaxane macromonomers with α-thiol and ω-alkyne terminal groups by utilizing thiol−yne chemistry. The molecular weights of HPCLs gradually increased over the irradiation time or polymer yield, while M_w grew faster than M_n, resulting in broadening the polydispersities. The cross-linking side reaction would occur over the polymer yield more than 70%; however, this side reaction was prohibited if the poly(ε-caprolactone) backbone was completely threaded by α-CD to form the rigid polypseudorotaxanes. The maximal melting point, the crystallization point, and the degree of crystallization of HPCLs gradually decrease over their molecular weights, which can be easily tuned by changing the irradiation time. This establishes a versatile platform for synthesizing hyperbranched biodegradable

poly(ε-caprolactone)-based biomaterials with tunable alkyne periphery, which might be further modified by thiol−yne and/or azide−alkyne chemistry.

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Supporting Information Available: Curve of M_w yield, effect of solvent on polycondensation, the postulated cross-linking mechanism, and ^{1}H NMR for HPPRs. This material is available free of charge via the Internet at http://pubs.acs.org.

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