

Fully Degradable and Well-Defined Brush Copolymers from Combination of Living CO₂/Epoxide Copolymerization, Thiol–Ene Click Reaction and ROP of ϵ -caprolactone

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Supporting Information

Brush copolymers are a special class of grafting polymers with side chains densely linked to a polymer backbone that present a stretched brushlike conformation. Brush copolymers have attracted much attention over the past decades due to their unique architectures and potential applications in biomedicine and nanotechnologies.^{1–5} Many methods have been developed to synthesize well-defined brush copolymers.^{1,5} Thereof, the breakthrough of the controlled radical polymerization (CRP) techniques (e.g., atom transfer radical polymerization, ATRP)^{5–9} and ring-opening metathesis polymerization (ROMP)^{10–12} have led to a booming development of brush copolymers, and large numbers of well-defined brush copolymers with various architectures have been synthesized through three popular strategies of “grafting from”, “grafting onto” and “grafting through” methods.^{5–12} However, these brush copolymers are commonly composed of nondegradable vinyl (carbon–carbon) backbone or side chain. Therefore, it is an interesting and meaningful topic to develop methods for synthesizing fully (both side chain and backbone) degradable and well-defined brush copolymers.

Very recently, attempts have been made to prepare brush copolymers with degradable side chains or backbones. For example, degradable poly(ϵ -caprolactone) (PCL) was grafted to a nondegradable vinyl backbone via ring-opening polymerization (ROP) of ϵ -caprolactone (ϵ -CL) (i.e.: “grafting from” method).^{13–15} Alternatively, nondegradable poly(ethylene glycol) (PEG) was grafted to degradable backbones such as polylactide (PLA),^{16a} poly(ester-co-carbonate)^{16b} by “grafting onto” method, however, the length of the side PEG chain of these brush copolymers were usually small for achieving high grafting density (i.e.: number-average ratio of the side chains to backbone monomer units). Moreover, a brush copolymer with cellulose as backbone and dual side chains of poly(*N,N*-dimethylaminoethyl methacrylate) and PCL^{16c} was prepared by “grafting from” method. However, the side chains of these brush copolymers were random-distributed with low grafting density. Totally, the development of well-defined brush copolymers with carbon-heteroatom units (e.g.: C–O) as backbone and side chain is still at early stage.¹⁷ If we can prepare a brush copolymer with carbonate or ester units (e.g.: aliphatic polycarbonate (APC), PLA and PCL) as backbone and side chain in a living polymerization manner, fully degradable and well-defined brush copolymer could be obtained.

Since APC is structurally degradable and biocompatible and expected to have potential applications in biomedicine and nanotechnologies,^{18–20} it is a good choice for synthesizing the

aforesaid brush copolymers. Commonly, APC can be synthesized either by ROP of the cyclic carbonates^{16d} or by the alternating copolymerization of epoxides and CO₂.^{18–28} The route of ROP of the cyclic carbonates for APC generally requires multiple monomer synthesis using toxic phosgene derivatives. By alternating copolymerization of CO₂/epoxides with a living manner,^{21–24,26–28} APC with well-defined structure can be now prepared directly. Thus, it is worthwhile to develop a versatile method for synthesizing brush copolymers based on APC from CO₂/epoxide copolymerization, which may advance its properties and expand its applications.

In this communication, we report the example of well-defined brush copolymers with degradable C–O backbone and side chain. Such brush copolymers have an aliphatic polycarbonate as backbone and PCL as side chain. Three steps that are living alternating copolymerization of CO₂ and epoxides, thiol–ene click reaction and ϵ -CL ROP were used to afford the target brush copolymer with nearly 100% grafting density (Scheme 1). Both the backbone and side chain of such brush copolymers are structurally degradable and biocompatible, rendering them as potential biomedical materials.

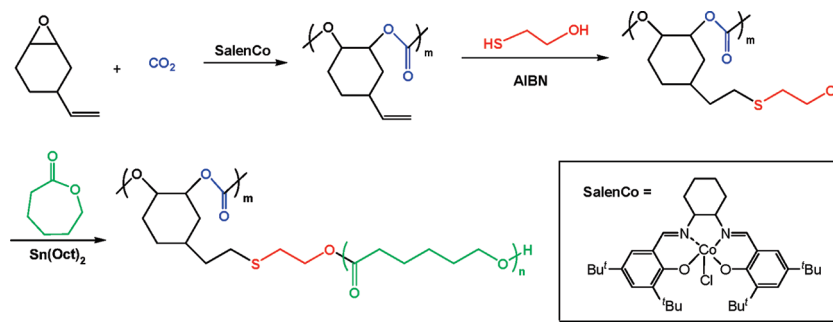
In order to obtain the aforesaid fully degradable and well-defined brush copolymers, a well-defined linear CO₂/epoxide copolymer with evenly spaced dangling functional groups (or as-synthesized side chain) should be first synthesized in a living manner. It required suitable epoxide monomers and available catalysts. The ideal monomer for our aim would be an epoxide containing hydroxyl (–OH) group (e.g.: 2, 3-epoxy-1-propanol) because the side –OH group linked to the backbone can directly either initiate the following ROP of ϵ -CL (“grafting from”) or couple with a carboxyl-terminated PCL (“grafting onto”), to afford a PCL side chain. However, it is hardly to use such epoxide directly because an inevitable chain transfer reaction between propagating chain and –OH group would occur during the CO₂/epoxide copolymerization.^{18,19} Moreover, very few of catalysts can be utilized to catalyze the copolymerization of CO₂ with epoxides with polar groups (e.g.: –CH₂Cl,^{23f} –CH₂Br, –CH₂COOR) in a well-controlled manner, which consequently limits the synthesis of side chains. Herein, 4-vinyl-cyclohexene-1, 2-epoxide (VCHO, Scheme 1) was selected

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Scheme 1. Synthetic Route of Degradable Brush Copolymers with Polycarbonate as Backbone and PCL as Side Chains



as the epoxide monomer for synthesizing a well-defined linear CO_2 /epoxide copolymer with anchored vinyl group. There were two reasons for choosing VCHO. One was that two kinds of homogeneous catalysts, (Salen) MX ($M = \text{Co}$, or Cr ; $X = \text{halide}$ or carboxylate)^{21–24} and Zn (β -diiminate)^{26–28} that present living nature for alternating copolymerization of CO_2 , cyclohexene oxide (CHO) and VCHO with high activity. The other was that the vinyl group of VCHO is inert to the available catalysts for CO_2 copolymerization and easy to be converted to $-\text{OH}$ group by thiol–ene click reaction with high efficiency. Herein, (salen)Co(III)–Cl complex (Scheme 1) was synthesized according to the literatures^{29–31} (see Supporting Information) and used as the catalyst for the alternating copolymerization of CO_2 /VCHO. The kinetic of CO_2 /VCHO copolymerization catalyzed by the (salen)Co(III)–Cl complex ($[\text{Co}]/[\text{VCHO}] = 1:2000$, 20°C and 2.0 MPa) was investigated by sampling at each 30 min with a high pressure sample collecting device. The living nature of this copolymerization was confirmed by the observation of a linear number-average molecular weight (M_n)–time curve and narrow polydispersity index (PDI) (see Figure S1 in the Supporting Information).

The (salen)Co(III)–Cl complex-catalyzed CO_2 /VCHO copolymerization was carried out with a $[\text{Co}]/[\text{VCHO}]$ molar ratio of 1:200 at 25°C in a predried autoclave at CO_2 pressure of 5.0 MPa for 6.0 h . VCHO and the catalyst were also predried completely. The conversion of VCHO was ca. 20%. The resultant poly(vinyl cyclohexene carbonate) (PVCHC) was fully alternating, which was evident by the fact that no proton signals at 3.5 ppm in its ^1H NMR spectrum (Figure 1A) that was attributed to the ether linkage in PVCHC.²⁵ Herein, two small peaks at 3.58 and 3.70 ppm in Figure 1A can be safely assigned to the methylene protons of the $-\text{OH}$ and $-\text{Cl}$ terminal groups in the copolymer, respectively. When using CDCl_3 as a solvent for ^1H NMR determination, the two small peaks were shifted to 3.74 and 3.90 ppm , respectively. The M_n of PVCHC was 6.6 kDa with a narrow PDI of 1.17 (Table 1) by GPC determination. The single GPC peak of this copolymer (Figure 2) accompanied by narrow PDI indicated that the chain transfer reaction of propagating chain to trace water was minimized, which allowed us to evaluate the number-average degree of polymerization (DP_n) based on the VCHO conversion. The calculated DP_n and molecular weight of this copolymer were ca. 40 and 6.7 kDa , respectively (see Table 1).

With PVCHC₄₀ in hand, thiol–ene click reaction^{32–35} was applied for converting side vinyl group to $-\text{OH}$ group. The choice of thiol–ene click reaction was due to that it is tolerant to moisture and air, high efficiency and no necessity for metal

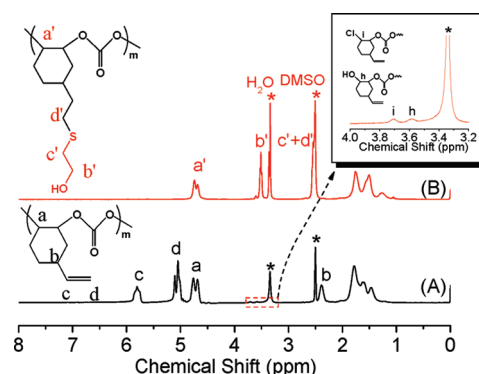


Figure 1. ^1H NMR spectra of (A) PVCHC₄₀ and (B) PVCHC–OH₄₀ ($\text{DMSO}-d_6$, 35°C).

catalysts. Although azide–alkyne cycloaddition is a well-known and efficient click reaction, it would require complex syntheses of epoxides containing alkyne group in our system, and copper catalyst should be used in the reaction.³⁶ The thiol–ene click reaction of β -mercaptoethanol and PVCHC₄₀ was performed using azodiisobutyronitrile (AIBN) as an initiator in predried THF at 70°C . In order to avoid possible cross-linking reaction caused by radical coupling reaction, excess β -mercaptoethanol (40 folds of the numbers of $-\text{OH}$ group) was added. Therefore, it was necessary to remove β -mercaptoethanol from the products completely for that the residual β -mercaptoethanol would initiate the ROP of $\epsilon\text{-CL}$. The polymeric product was purified completely by precipitation in THF/toluene system for several times. Because the dried product was not dissolved into CDCl_3 , we used $\text{DMSO}-d_6$ as the solvent for ^1H NMR test. As seen from Figure 1, the chemical shifts at 5.78 and 5.05 ppm of vinyl groups (curve 1A) completely disappeared after reaction, and the chemical shift at 3.50 ppm was appeared in curve 1B, which could be assigned to the methylene protons ($-\text{SCH}_2\text{CH}_2\text{OH}$, b') conjoint with the end $-\text{OH}$ group (Figure 1B). GPC results of the product showed a single narrow peak (PDI: 1.15) without a tail at high molecular weight part (Figure 2b), confirming that radical coupling reaction between chains was completely depressed. Possible intramolecular cyclization reaction of PVCHC₄₀ during thiol–ene click reaction could be depressed in a relative dilute reaction system because the space between two neighboring side double bonds of PVCHC₄₀ was clearly larger (about 5σ bonds) due to its unique alternating chain structure.^{35a,b} Moreover, as seen in Figure 1B, the integration area ratio of the methylene protons b' to the methylene protons a'

Table 1. Graft Copolymerization of ϵ -Caprolactone onto PVCHC Backbone^a

entry	samples	DP _n of PCL		reaction time (h)	$M_{n,th}$ ^d (kDa)	$M_{n,NMR}$ ^e (kDa)	$M_{n,GPC}$ ^f (kDa)	PDI ^f	grafting density (%) ^g	conv. (%)
		feed ^b	expt ^c							
1	PVCHC ₄₀	/	/	6.0	6.7	/	6.6	1.17	/	20
2	PVCHC–OH ₄₀	/	/	24.0	9.8	/	9.2	1.15	100	/
3	PVCHC ₄₀ -g-PCL ₈	30	8	3.5	53.6	46.3	32.1	1.12	100	32
4	PVCHC ₄₀ -g-PCL ₁₅	30	15	6.0	81.0	78.2	46.7	1.14	100	52
5	PVCHC ₄₀ -g-PCL ₂₂	30	22	10.0	116.5	110.2	65.7	1.13	100	78
6	PVCHC ₄₀ -g-PCL ₃₇	50	37	15.0	196.8	178.6	99.9	1.12	100	82
7	PVCHC ₄₀ -g-PCL ₈₇	100	87	15.0	411.1	406.6	241.4	1.21	100	88

^a For entries 3–7, bulk polymerization, 120 °C. Key: entries 3–5, [CL]/[Sn(Oct)₂] = 1000; entry 6, [CL]/[Sn(Oct)₂] = 250. The conversions are based on ϵ -CL; For entry 1, [Co]/[VCHO] = 1:200, 25 °C and 5.0 MPa, and the conversion is based on VCHO. For entry 2, [C=C]₀/[β -mercaptoethanol]₀/[AIBN]₀ = 1/40/0.33, 70 °C, in THF. ^b Feeding ratio of [CL]/[OH]. ^c DP_n of the side chain, determined by ¹H NMR spectrum. ^d For entries 3–7, $M_{n,th} = ([CL]/[OH])_{Feed} \times M_{n,CL} \times 40 \times \text{conversion}(\%) + M_{n,PVCHC-OH40}$, where $M_{n,CL}$ is the molecular weight of CL and $M_{n,PVCHC-OH40}$ is the molecular weight of PVCHC–OH₄₀. ^e $M_{n,NMR} = ([CL]/[OH])_{Exp} \times M_{n,CL} \times 40 + M_{n,PVCHC-OH40}$. ^f Determined by GPC against the standard monodispersed polystyrene (PS) samples. ^g The resonance signal of methylene protons of –SCH₂CH₂OH of PVCHC–OH₄₀ was not observed in ¹H NMR spectra, therefore, the grafting density of these brush copolymers was estimated to be close to 100%.

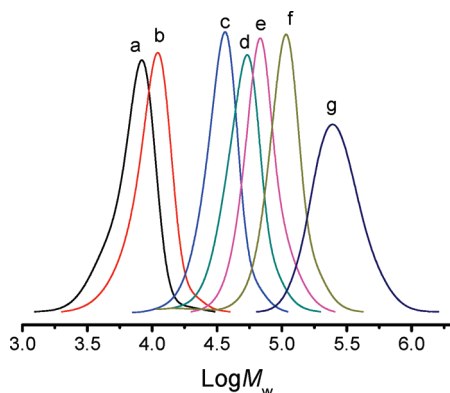


Figure 2. GPC curves of (a) PVCHC₄₀, (b) PVCHC–OH₄₀, (c) PVCHC₄₀-g-PCL₈, (d) PVCHC₄₀-g-PCL₁₅, (e) PVCHC₄₀-g-PCL₂₂, (f) PVCHC₄₀-g-PCL₃₇, and (g) PVCHC₄₀-g-PCL₈₇. THF was used as a solvent and monodispersed polystyrene as a standard.

was nearly 1.0, indicating that such intramolecular cross-linking was minimized. M_n of the resultant product was 9.2 kDa by GPC, which is consistent to the calculated M_n (9.8 kDa) based on 100% conversion of the vinyl group. Hereto, a macroinitiator PVCHC–OH₄₀ with well-defined structure was obtained.

Because PVCHC–OH₄₀ could be easily dissolved into ϵ -CL at room temperature, bulk ROP of ϵ -CL initiated by PVCHC–OH₄₀ was initially performed under the [CL]/[OH] feeding ratio of 30 by using Sn(Oct)₂ as the catalyst at 120 °C. The well-controlled chemical structure of the resulting PVCHC₄₀-g-PCL_n was verified by GPC (Figure 2) and ¹H NMR (Figure 3) characterizations. The integration area ratio of the methylene protons (CH₂) f from PVCHC₄₀-g-PCL_n at 4.21 ppm to the methylene protons from end –CH₂OH group (i) at 3.65 ppm (Figure 3) was 1.0, which indicates that PCL initiated from trace water could be minimized in this reaction. Therefore, on the basis of the resonance intensities of the methylene protons f at 4.21 ppm and b in the side chain at 4.06 ppm, DP_n of the side PCL of PVCHC₄₀-g-PCL_n was estimated to be 8, 15, and 22 for the brush copolymers of entries 3–5 respectively. One can see

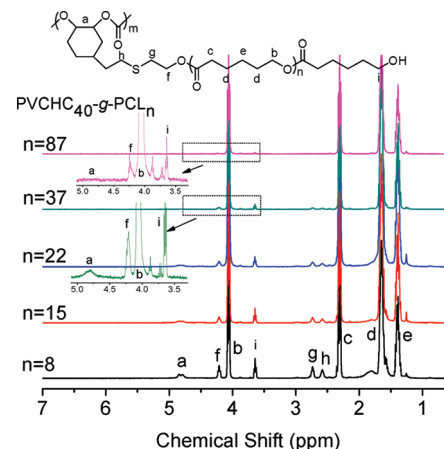


Figure 3. ¹H NMR spectra of PVCHC₄₀-g-PCL_n, n = 8, 15, 22, 37 and 87 (CDCl₃, 35 °C). Two small peaks at 3.74 and 3.90 ppm can be assigned to the methylene protons of CH–OH and CH–Cl at the terminal groups of the copolymer respectively (compared to ¹H NMR spectra of PVCHC₄₀ in CDCl₃, see Figure S2 in Supporting Information).

that DP_n of the side PCL increased by prolonging the polymerization times (Table 1). Moreover, the grafting density of these brush copolymers could be estimated by the integration area ratio of the methylene protons f to the possible residual methylene protons conjoint with the end –OH group of PVCHC–OH₄₀. However, the resonance signal of such methylene protons (–SCH₂CH₂OH, b') of PVCHC–OH₄₀ was not observed in ¹H NMR spectra even for PVCHC₄₀-g-PCL₈ with rather low DP_n of the side PCL chain. Therefore, the grafting density of these brush copolymers was estimated to be close to 100%.

As seen in Figure 2, GPC curves of PVCHC₄₀-g-PCL_n with DP_n of 8, 15, and 22 were single peaks with narrow PDIs of 1.12, 1.14 and 1.13, respectively (Table 1). $M_{n, GPC}$ and $M_{n, NMR}$ of these brush copolymers increased linearly with increasing the polymerization time and conversion of ϵ -CL, and the agreement between $M_{n, th}$ (based on ϵ -CL conversion) and $M_{n, NMR}$ of

PVCHC₄₀-g-PCL_n (DP_n = 8, 15 and 22) plus narrow PDIs of these brush copolymers proved that ϵ -CL ROP initiated by side —OH group of PVCHC—OH₄₀ was nearly living and in good control. Note that the difference between $M_{n, \text{GPC}}$ and $M_{n, \text{NMR}}$ can be attributed to the difference in hydrodynamic radii of the grafted chain and the backbone as compare with the linear monodispersed polystyrene GPC standards.³⁷

In comparison with poly(2-hydroxyethyl methacrylate)-graft-poly(ϵ -caprolactone) (PHEMA-g-PCL)¹⁴ with a vinyl backbone, the space between two neighboring side chains of PVCHC₄₀-g-PCL_n was clearly larger for their unique alternating chain structure. As a result, the steric repulsion between two side chains was greatly relaxed during chain propagation, which ensured the equal reactivity of the side —OH group and narrow PDIs and hence allowed for the synthesis of brush copolymers with nearly 100% grafting density. We considered that such minor steric repulsion effect may qualify the synthesis of brush copolymers with long side PCL chain in a controlled manner. As expected, PVCHC₄₀-g-PCL_n with $n = 37$ and 87 were successfully prepared in bulk under the [CL]/[OH] feeding ratios of 50 and 100, respectively. Both brush copolymers showed single elution peaks with narrow PDIs (1.12 and 1.21). It indicated a well-controlled propagating manner of ROP of ϵ -CL using PVCHC—OH₄₀ as a macroinitiator (cf. Figures 2 and 3).

Hereto, three steps were used for synthesizing well-defined brush copolymers in a controlled fashion. The obtained brush copolymer contained an aliphatic polycarbonate as backbone and PCL as side chain, presenting a good example of the designation and synthesis of well-defined brush copolymers with carbon-heteroatom backbone and side chain. In theory, “grafting through” method could synthesize such brush copolymers with one-step reaction. A recent work reported that the alternating copolymerization of CO₂ and 4-R-cyclohexene-1,2-epoxide (R = CH₃(CH₂CH₂O)₃, CHF₂(CF₂)₃) was catalyzed by a Zn(β -diiminate) catalyst, affording a well-defined copolymer with pendant functional moieties.²⁸ Thus, Zn(β -diiminate) catalyst might be a potential catalyst for preparing brush copolymers with CO₂/epoxide copolymer as backbone by “grafting through” method. Even so, it might be unpredictable to realize the copolymerization of CO₂ with an epoxy-capped PCL in a well-controlled manner. An early attempt has been made to synthesize a grafting polymer with CO₂/epoxide copolymer as backbone and a short PCL (M_n : 3.2 kDa, GPC) as side chain by “grafting through” method.¹⁷ However, the resultant brush copolymer had low MW (M_n : up to 11 kDa, GPC) and wide PDI, suggesting that the main chain had only several carbonate units.

Because PVCHC₄₀-g-PCL_n contained non-crystallizable PVCHC backbone²⁰ and crystallizable PCL side chain, herein, we preliminarily examined the crystallization behaviors of these new brush copolymers by DSC as shown in Figure 4 and Table 2. The crystallization and melting behaviors of PVCHC₄₀-g-PCL_n with various lengths of side PCL chains were investigated as shown in Figure 4. The crystallization temperature (T_c), the melting temperature (T_m) and the degree of crystallinity (X_c) of PVCHC₄₀-g-PCL_n increased clearly with increasing the length of the side PCL chain.¹⁴ X_c of PVCHC₄₀-g-PCL₈₇ was 46.5% (Table 2) and close to that of a linear PCL (48.8%) with $M_{n, \text{GPC}}$ of 10.8 kDa.¹⁴ Presumably, relative large space between two neighboring side chains of PVCHC₄₀-g-PCL_n may be unfavorable to the crystallization of the side chains. Since degradable rate of a polymer was closely related to the degree of crystallinity,³⁸ thus it

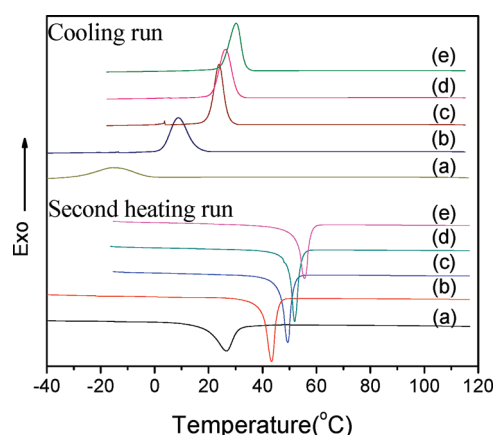


Figure 4. DSC curves of (a) PVCHC₄₀-g-PCL₈, (b) PVCHC₄₀-g-PCL₁₅, (c) PVCHC₄₀-g-PCL₂₂, (d) PVCHC₄₀-g-PCL₃₇, and (e) PVCHC₄₀-g-PCL₈₇ in the cooling run and the second heating run, respectively.

Table 2. Melting and Crystallization Behaviors of PVCHC₄₀-g-PCL_n ($n = 8, 15, 22, 37$, and 87) Brush Copolymers

sample	$T_{c, \text{PCL}}$ (°C) ^a	$T_{m, \text{PCL}}$ (°C) ^b	$\Delta H_{m, \text{PCL}}$ (J/g) ^c	$X_{c, \text{PCL}}$ (%) ^d
PVCHC ₄₀ -g-PCL ₈	−15.8	26.6	60.2	34.9
PVCHC ₄₀ -g-PCL ₁₅	8.8	43.4	66.3	42.6
PVCHC ₄₀ -g-PCL ₂₂	23.9	49.4	65.5	43.8
PVCHC ₄₀ -g-PCL ₃₇	26.2	51.9	64.5	44.8
PVCHC ₄₀ -g-PCL ₈₇	30.2	55.6	64.8	46.5

^a $T_{c, \text{PCL}}$ denote the crystallization temperatures of PCL segments in the cooling run, respectively. ^b $T_{m, \text{PCL}}$ are the melting points of PCL segments in the second heating run, respectively. ^c $\Delta H_{m, \text{PCL}}$ denote the fusion enthalpies of PCL segments in the second heating run, respectively. ^d $X_{c, \text{PCL}} = W_{t, \text{PCL}}\% \times \Delta H_{m, \text{PCL}} / \Delta H_{m, \text{PCL}}^0$, where $\Delta H_{m, \text{PCL}}^0$ is 136.1 J/g and $W_{t, \text{PCL}}\%$ is the mass fraction of PCL in PVCHC₄₀-g-PCL_n.

is now possible to synthesize PVCHC₄₀-g-PCL_n with controlled degradable rate by changing the length of the side chain.

In summary, we describe the synthesis of degradable brush copolymers with well-defined structure and nearly 100% grafting density through “grafting from” method via living alternating copolymerization of CO₂/VCHO, thiol–ene click reaction and ROP of ϵ -CL. These brush copolymers also showed relatively large space between two PCL side chains, which may be favorable to the formation of cavity for the accommodation of small molecules and present a clear superiority in potential application as biomedical materials with respect to traditional linear CO₂/epoxide copolymers.^{18–20} Investigation on the self-assembly, crystallization behaviors, and application of these brush copolymers are in progress.

■ ASSOCIATED CONTENT

S Supporting Information. Experimental details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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