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Synthesis and characterization of novel random copolyesters from *trans*-4-hydroxy-L-proline and functional cyclic esters

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Abstract

The melt polycondensation reaction of *trans*-4-hydroxy-*N*-benzyloxycarbonyl-L-proline (*N*-CBz-Hpr) and functional cyclic esters containing protected functional groups (carboxyl, and amino) at a wide range of molar fractions in the feed produced new degradable poly(*N*-CBz-Hpr-*co*-functional-ε-CL)s with stannous 2-ethylhexanoate ($Sn(Oct)_2$) as a catalyst. The optimal reaction conditions for the synthesis of the copolymers were obtained with 1.5 wt% $Sn(Oct)_2$ at 140 °C for 24 h. The copolymers obtained were characterized by Fourier transform infrared spectroscopy (FT-IR), ^{1}H NMR, differential scanning calorimetry, gel permeation chromatography, and Ubbelohde viscometry. The copolymers synthesized exhibited oligomeric molecular weights (3000–5000 g mol^{-1}) with modestly narrow molecular weight distributions (1.11–1.37). The values of the glass-transition temperature (T_g) of the copolymers depend on the compositions, and the molar fractions of cyclic lactone. For the poly(*N*-CBz-Hpr-*co*-4-EtC-ε-CL) system, with a decrease in 4-EtC-ε-CL contents from 79 to 3 mol%, the T_g increased from −34 to 67 °C In vitro degradation of these copolymers was evaluated from weight-loss measurements.

Keywords: *trans*-4-Hydroxy-L-proline; Functional cyclic ester; Copolymer

1. Introduction

The past two decades have seen increasing attention paid to synthetic polyesters for biomedical applications including surgery and medicine [1]. Many of these polymers are readily hydrolyzed to their constituent α-hydroxy acids which are eliminated by general metabolic pathways [2]. However, the biodegradation rates of these polyesters are difficult to control due to their hydrophobicity and semicrystalline morphology [3]. The impetus for research in this area has focused on the need for functional polyesters. Toward this end, advances in the field will require new functional monomers/polymers, which permit subsequent transformations to allow desirable solubility/property enhancements. The availability of functional pendant groups along the polymer backbone would be a highly efficient means of tailoring the properties of polyesters including features such as hydrophilicity, biodegradation rates, bioadhesion, drug attachment, etc.

There are numerous reports of functional polyesters prepared from protected monomers by both condensation and ring-opening polymerization techniques. In one example, Jérôme et al. [4–8] used 5-ethylenedioxycaprolactone as a comonomer in the synthesis of aliphatic polyesters and subsequent deketalization and reduction of the generated ketone functionality produced multihydroxyl functional polyester. These hydrophilic polymers can be used for applications that utilize this developed functionality including the preparation of amphiphilic block copolymers and nanoparticles. Kimura et al. [9,10] reported the synthesis of pendant carboxyl functional polyesters through the ring-opening polymerization (ROP) of 3-(**S**)-[(benzyloxycarbonyl)methyl]-1,4-dioxane-2,5-dione with lactide in the presence of stannous 2-ethylhexanoate ($Sn(Oct)_2$). The benzyl protecting groups were readily removed by catalytic hydrogenolysis to give the highly functionalized bioresorbable polyester. Recently, Hedrick et al. [11,12] described one of the most exquisite routes to functional hydrophilic polyesters from new cyclic esters

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containing protected functional groups. Controlled generation of pendant hydroxy, carboxylic and amino functionality was demonstrated.

Pseudo-poly(amino acid)s belong to a new class of biodegradable polymers that has the advantage of being nontoxic, biodegradable, biocompatible, and fitted with pendant functional groups on the backbone. In our previous articles [13–18], we reported the synthesis of polyesters, poly(ester-urethane)s, and poly(ester-amide)s bearing pendant amino functional groups on the backbone from pseudo amino acid. The hydroxyproline (Hpr) was chosen as a model monomer because of the structural simplicity and it is a major constituent of collagen.

The object of this study was to synthesis of poly(Hpr-*co*-functional-ε-CL)s bearing two kinds of pendent amino, and carboxylic groups by the polycondensability of *N*-CBz-Hpr and protected functional lactones (carboxyl-, and amino-substituted) with large variations of molar fractions in the feed. These new copolymers were identified by ^{1}H NMR, FT-IR, differential scanning calorimetry (DSC), and gel permeation chromatography (GPC). The effects of the comonomers on the inherent viscosity (η_{inh}), glass transition temperature (T_g) and degradation rate were also examined.

2. Experimental

2.1. Materials

Hpr, benzyloxychloroformate, ethyl-4-hydroxycyclohexanecarboxylate, 1,4-dioxa-7-azaspiro [4,5] decane, pyridinium chlorochromate (PCC), *m*-chloroperoxybenzoic acid (*m*-CPBA), benzyl bromide, and 1,4-cyclohexadiene were obtained from Aldrich Chemical Co. The stannous 2-ethylhexanoate ($Sn(Oct)_2$) was used as obtained from Strem Chemical Co. Organic solvents (e.g. tetrahydrofuran (THF), *N*,*N*-dimethyl formamide (DMF), methanol, chloroform, diethyl ether, and ethyl acetate) and inorganic compounds (e.g. magnesium sulfate, sodium bicarbonate, and potassium carbonate) were reagent or high-pressure liquid chromatography (HPLC) grade.

2.2. Characterization

IR spectra were measured on a Brucker TENSOR 27 Fourier transform infrared (FT-IR) spectrophotometer. Samples were either neatly placed on NaCl plates or pressed into KBr pellets. ^{1}H NMR spectra were recorded in solution at 500 MHz (Brucker WB/DMX-500 spectrometer) with tetramethylsilane as an internal standard. Elemental analyses were run on a Perkin–Elmer model 2400 CHN analyzer. The η'_{inh}s were measured with an Ubbelohde viscometer at 30 °C. A thermal analysis of the polymer was performed on a DuPont 9900 system that consisted of a DSC. The heating rate was 20 °C min^{-1}. T'_gs were read at the middle of the change in the heat capacity and were taken from the second heating scan after quick cooling. Number- and weight-average molecular weights (M_n and M_w, respectively) of the polymer were determined by a GPC system. It was carried out on a Jasco HPLC system equipped with a model PU-2089 separation module, and a model RI-2031 refractive- index detector. Five Jordi Gel DVB columns (250 × 10 mm) connected in series in order of increasing pore size (100, 500, 1000, 10^4, 10^5 A) were used with $CHCl_3$ (or DMF) as the eluent at a flow rate of 0.5 ml min^{-1}. Polystyrene standards with a low dispersity (Polymer Science) were used to generate a calibration curve. Data were recorded and manipulated with the windows-based software package (Scientific Information Service Co.).

2.3. Preparation of trans-4-hydroxy-N-benzyloxycarbonyl-L-proline (N-CBz-Hpr) **1**

1 was prepared according to the method described in our previous article [13].

2.4. Preparation of functional cyclic esters **2**

Ethyl γ-(ε-caprolactone)carboxylate **2a**, benzyl γ-(ε-caprolactone)carboxylate **2b**, and 4-benzyloxycarbonyl-7-oxo-1,4-oxazaperhydroepine **2c** were prepared according to the modified method of the Hedrick [12].

2.5. Synthesis of copolymers **3**

In general, the polymerization was conducted in a round-bottom flask with a side arm. Typically, the purified monomer *N*-CBz-Hpr (**1**; 2.6 mmol) and 4-functional-ε-CL (**2**; 2.6 mmol) as a comonomer were added to the flask. Then, the catalyst $Sn(Oct)_2$ (1.5 wt%) was added. The flask was purged with nitrogen and reacted at 140 °C for 24 h. The crude polymer was dissolved in THF and then precipitated into excess *n*-hexane with stirring. After purification, the polymer was dried in vacuo for 24 h and analyzed. Representative ^{1}H NMR and IR spectra of the copolymer **3I** are shown in Figs. 1(A) and 2(A).

2.5.1. Poly(N-CBz-Hpr-co-4-EtC-ε-CL) **3E**

^{1}H NMR ($CDCl_3$) δ 7.27–7.17 (m, 5H, Ph), 5.27–5.21 (m, 1H, –C*H*–OCO–), 5.07–5.00 (m, 2H, –CH_2Ph), 4.34–4.25 (m, 3H, –CO–C*H*–N, –CH_2–O), 4.08–4.02 (m, 2H, –CO_2CH_2), 3.67–3.50 (m, 2H, N–CH_2–), 3.25 (bs, 1H, O*H*), 2.42–2.40 (m, 1H, –C*H*–CO–), 2.30–2.25 (m, 2H, –CH_2–CHO–), 2.08–2.05 (m, 2H, –CO–CH_2–), 1.94–1.72 (m, 4H, –CH_2–CH_2–CH–CH_2–), 1.19 (q, 3H, –CH_3).

2.5.2. Poly(N-CBz-Hpr-co-4-BzC-ε-CL) **3I**

^{1}H NMR ($CDCl_3$) δ 7.21–7.11 (m, 10H, Ph), 5.24–5.18

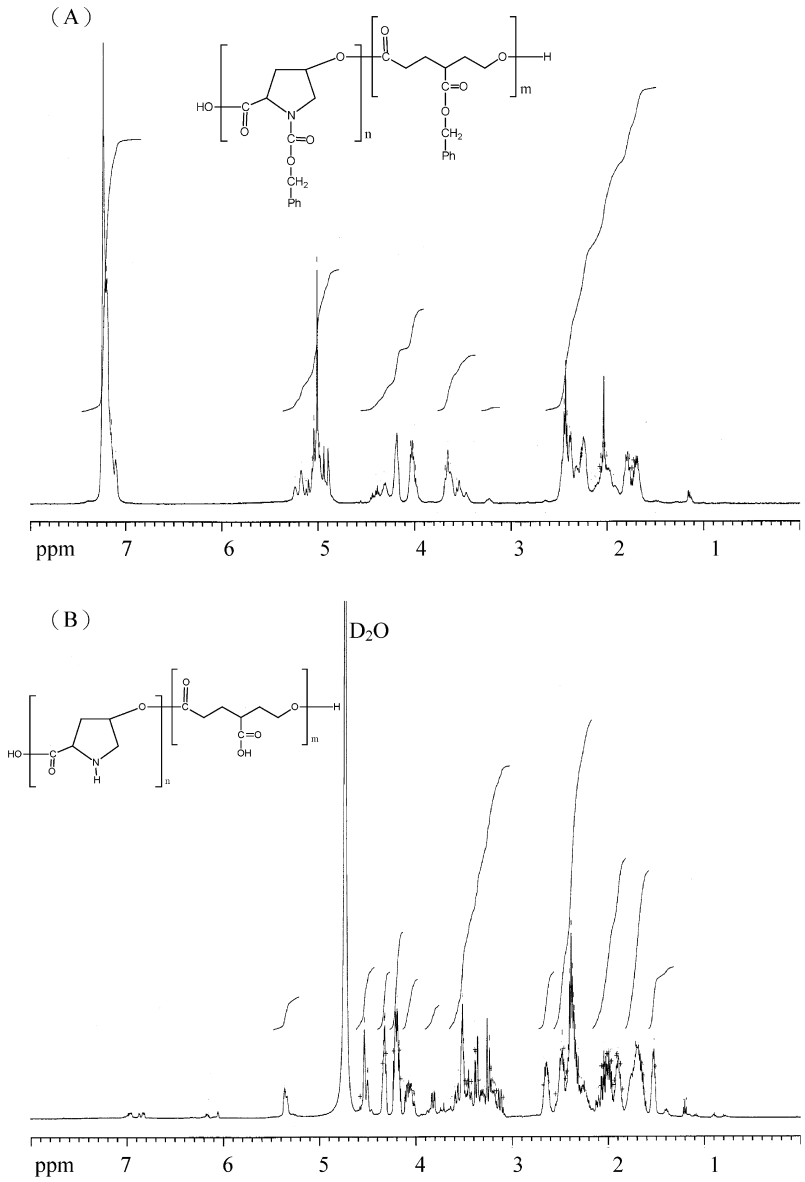


Fig. 1. ^{1}H NMR spectra of (A) copolymer **3I** in $CDCl_3$, and (B) deprotected copolymer **4I** in D_2O/CD_3OD.

(m, 1H, –C*H*–OCO–), 5.10–4.90 (m, 4H, –CH_2Ph), 4.59–4.30 (m, 1H, –CO–C*H*–N), 4.19–3.99 (m, 2H, –CH_2–O), 3.69–3.54 (m, 2H, N–CH_2–), 3.21 (bs, 1H, O*H*), 2.45–2.38 (m, 2H, –CH_2–CO–), 2.32–2.25 (m, 1H, –C*H*–CO–), 2.07–1.99 (m, 2H, –CH–CH_2–CHO–), 1.81–1.77 (t, 2H, –CH_2–CH$_2$–O–), 1.71–1.69 (t, 2H, –CH_2–CH).

2.5.3. Poly(N-CBz-Hpr-co-4-BzCN-ε-CL) ***3K***

^{1}H NMR ($CDCl_3$) δ 7.27–7.24 (m, 10H, Ph), 5.28–4.94 (m, 1H, –C*H*–OCO–), 5.13 (m, 4H, –CH_2Ph), 4.37 (bs, 1H, –CO–C*H*–N), 4.14–4.13 (m, 2H, –CH_2–O), 3.68–3.47 (m, 6H, CH_2–N–CH_2–, N–CH_2–), 2.50 (bs, 2H, –CH_2–CO–), 2.30 (bs, 1H, –O*H*), 2.05–1.96 (m, 2H, –CH–CH_2–CH–).

2.6. Deprotection of the benzyl-protecting group of the new copolymer

A 10 wt% palladium-on-charcoal catalyst (1 g) was added to a solution of the copolymer **3** (3.1 mmol) in THF (10 ml). With vigorous stirring, 1,4-cyclohexadiene was slowly added to the mixture. Stirring was continued at room temperature for 68 h. After the deprotection reaction, the palladium catalyst was removed by filtration and the solution was concentrated to approximately one-fourth the volume by partial evaporation under reduced pressure. The concentrated solution was added dropwise into excess of *n*-hexane to precipitate, and the deprotected polymer **4** was dried in vacuum for 24 h and then analyzed by ^{1}H NMR (Fig. 1(B)), and IR (Fig. 2(B)).

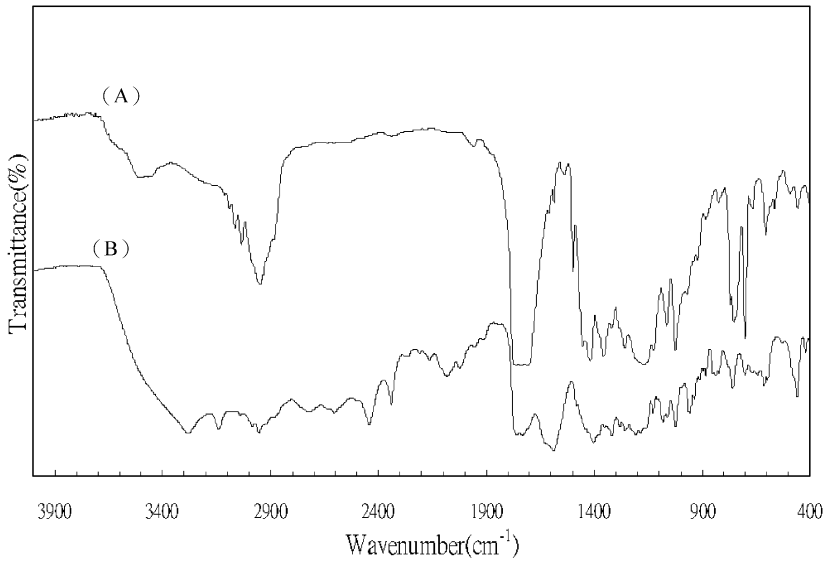


Fig. 2. IR spectra of polymer **3I** (A) before, and (B) after deprotection.

2.6.1. Poly(Hpr-co-4-EtC-ε-CL) ***4E***

^{1}H NMR (D_2O/CD_3OD) δ 5.51–5.29 (m, 1H, –C*H*–OCO–), 4.49–4.45 (m, 1H, –CO–C*H*–N), 4.20–4.14 (m, 2H, –CO_2CH_2), 4.01–3.99 (m, 2H, –CH_2–O–), 3.89–3.69 (m, 1H, N*H*), 3.47–3.20 (m, 2H, N–CH_2–), 2.61–2.22 (m, 3H, –C*H*–CO–, –CO–CH_2–), 2.09–1.78 (m, 2H, –CH_2–CHO–), 1.68–1.48 (m, 4H, –CH_2–CH_2–CH–CH_2–), 1.10 (q, 3H, –CH_3).

2.6.2. Poly(Hpr-co-4-HO$_2$C-ε-CL) ***4I***

^{1}H NMR (D_2O/CD_3OD) δ 5.36–5.33 (m, 1H, –C*H*–OCO–), 4.53–4.50 (m, 1H, –CO–C*H*–N), 4.33–4.18 (m, 2H, –CH_2–O), 3.52–3.23 (m, 2H, N–CH_2–), 2.48–2.47 (m, 1H, –C*H*–CO–), 2.41–2.35 (m, 2H, –CH_2–CO–), 2.04–1.99 (m, 2H, –CH–CH_2–CHO–), 1.90–1.52 (m, 4H, –CH_2–CH–CH_2–).

2.6.3. Poly(Hpr-co-4-HN-ε-CL) ***4K***

^{1}H NMR (D_2O/CD_3OD) δ 5.03 (m, 1H, –C*H*–OCO–), 4.56 (bs, 1H, N*H*), 4.30–4.23 (bs, 1H, –CO–C*H*–N), 4.10 (bs, 1H, N*H*), 3.63–3.61 (m, 2H, –CH_2–O), 3.52–3.13 (m, 6H, CH_2–N–CH_2–, N–CH_2–), 2.75–2.32 (m, 2H, –CH_2–CO–), 2.08–1.93 (m, 2H, –CH–CH_2–CH–).

2.7. Degradation of copolymer

The *N*-protected copolymer films were prepared by the pressing technique. Forty milligrams of powdered polymer were pressed into a solid pellet under vacuum for 5 min. For the degradation study, each film was placed in a small bottle containing 5 ml of M/15 phosphate buffer solutions (pH 7.4). The bottle was then incubated at 37 °C. At time intervals the specimen was removed, washed with distilled water, lyophilized, and weighed. The degree of degradation was estimated from:

$$\text{degree of degradation (\%)} = 100(D_0 - D)/D_0$$

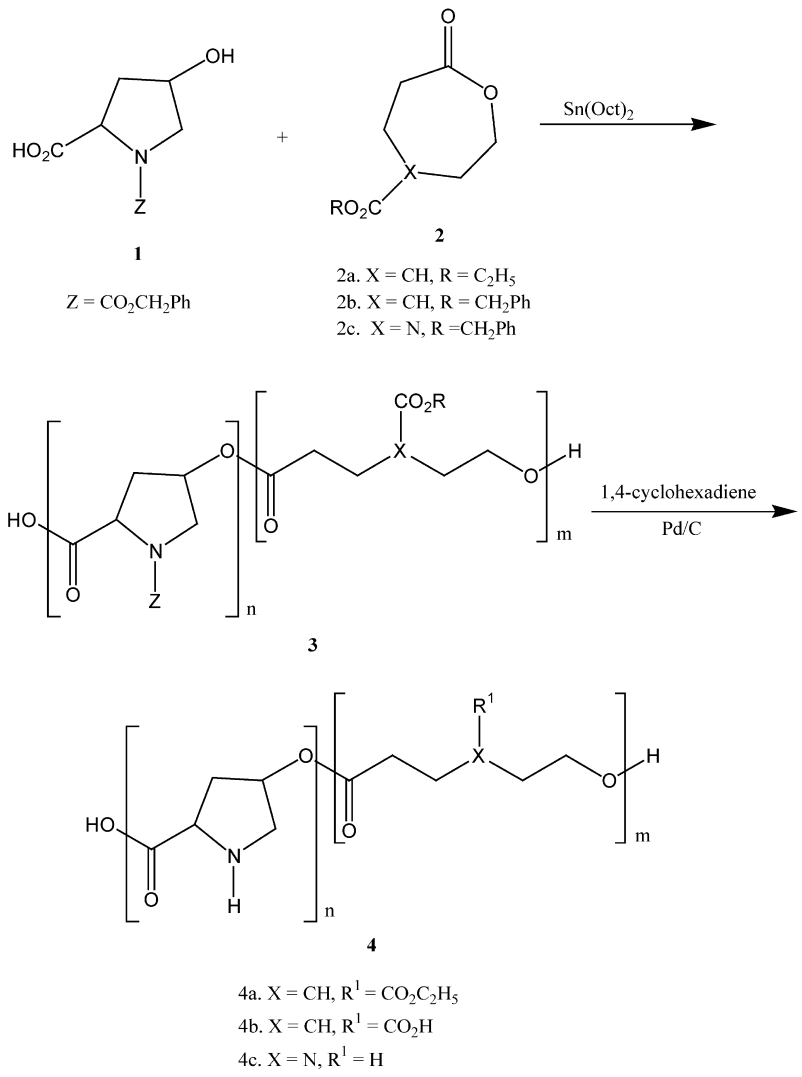
where D_0 is the weight of copolymer before degradation and D is the weight of copolymer after degradation for a certain period.

3. Results and discussion

The functionalized caprolactone comonomers [ethyl γ-(ε-caprolactone)carboxylate **2a** (4-EtC-ε-CL), benzyl γ-(ε-caprolactone)carboxylate **2b** (4-BzC-ε-CL), and 4-benzyloxycarbonyl-7-oxo-1,4-oxazaperhydroepine **2c** (4-BzCN-ε-CL)] were prepared from commercially available ethyl 4-hydroxycyclohexanecarboxylate and 1,4-dioxa-7-azaspiro [4,5] decane, respectively, according to the modified method of Hedrick [12].

3.1. Copolymerization

The copolymerizations of *trans*-4-hydroxy-*N*-benzyloxycarbonyl-L-proline (*N*-CBz-Hpr) **1** and functionalized ε-caprolactone **2** were investigated over a wide range of compositions via a ring-opening/condensation mechanism, where the active hydroxy group of *N*-CBz-Hpr induces a selective acyl-oxygen cleavage of the lactone ring, forming an external ester block, and were accompanied by the homo- and copolycondensation polyester chain growth (Scheme 1). The polymerization was performed in bulk using $Sn(Oct)_2$ as a catalyst, and the results of copolymerization are listed in Tables 1 and 2. There are a number of catalysts that are effective for ring-opening/condensation polymerization. However, $Sn(Oct)_2$ was selected as the catalyst in the following study because of its high efficiency and has U.S. Food and Drug Administration approval used in the



Scheme 1. Condensation copolymerization of *trans*-4-hydroxy-*N*-benzyloxycarbonyl-L-proline **1** and functional cyclic esters **2**.

preparation of polymers for biomedical applications. The optimal catalyst level (1.5 wt%) was determined according to the previous reported [16,18]. So, in order to find the optimum copolymerization conditions, the influence of the polymerization time, and temperature on the inherent viscosity (η_{inh}) and molecular weight (M_n, M_w) were investigated by copolymerizing *N*-CBz-Hpr **1** and functionalized ε-caprolactone **2a** (4-EtC-ε-CL) or **2b** (4-BzC-ε-CL)

Table 1
Effect of the reaction time a nd temperature on the yield, inherent viscosity (η_{inh}), and molecular weight of the copolymer **3**

Entry	Comonomer	Reaction time (h)	Reaction temperature (°C)	^{1}H NMR composition in copolymer *N*-CBz-Hpr/cyclic ester (mol%)	Yield (%)	η_{inh} (dL g^{-1})[a]	M_n[b]	M_w/M_n[b]
1	**2a**	12	140	73:27	81	0.66	1124	1.37
2	**2a**	18	140	74:26	78	0.73	1778	1.20
3	**2a**	24	140	83:17	73	1.06	3849	1.16
4	**2a**	36	140	75:25	68	0.72	1644	1.20
5	**2a**	48	140	80:20	75	0.78	2353	1.35
6	**2b**	24	140	59:41	73	0.85	3359	1.14
7	**2b**	24	110	67:33	79	0.55	996	1.26
8	**2b**	48	110	64:36	74	0.69	835	1.15
9	**2b**	24	170	54:46	69	0.69	2013	1.32

Were prepared by polymerization of *N*-CBz-Hpr **1** and functional cyclic esters **2a**–**b** with an equivalent molar ratio, with 1.5 wt% $Sn(Oct)_2$ as a catalyst.
[a] Measured at 0.1 g dL^{-1} in $CHCl_3$ at 30 °C.
[b] Number-average molecular weight and molecular weight distribution determined by GPC with $CHCl_3$ as the eluent.

Table 2
Results of the melt copolymerization of *N*-CBz-Hpr (**1**) and functional cyclic ester (**2a–c**)

Copolymer **3**	Comonomer **2a–c**	Monomer composition in feed (mol%)[a] *N*-CBz-Hpr/comonomer	^{1}H NMR composition in copolymer (mol%) *N*-CBz-Hpr/comonomer	Yield (%)	M_n[b]	M_w/M_n[b]	T_g[c] (°C)	Elemental analysis					
								C (%)		H (%)		N (%)	
								Calcd.	Found	Calcd.	Found	Calcd.	Found
3A	**2a**	10:90	21:79	61	3625	1.23	−34	59.38	58.76	6.98	6.85	1.48	1.25
3B	**2a**	20:80	40:60	58	3870	1.27	−13	60.45	59.32	6.51	6.83	2.66	2.54
3C	**2a**	30:70	55:45	62	3834	1.24	4	61.21	60.22	6.17	6.38	3.51	3.55
3D	**2a**	40:60	81:19	69	3063	1.12	16	62.39	61.73	5.64	5.97	4.81	3.38
3E	**2a**	50:50	83:17	73	3849	1.16	27	62.47	61.63	5.60	5.98	4.91	4.82
3F	**2a**	60:40	85:15	92	4386	1.29	36	62.88	62.84	5.42	5.57	5.36	4.46
3G	**2a**	80:20	92:8	95	5166	1.29	66	62.84	62.35	5.44	6.40	5.32	4.19
3H	**2a**	90:10	97:3	96	5078	1.37	67	63.14	62.76	5.19	6.06	5.55	4.94
3I	**2b**	50:50	59:41	73	3359	1.14	−8	65.03	64.88	5.79	5.81	3.34	2.75
3J	**2b**	80:20	70:30	84	3281	1.11	50	64.53	63.07	5.66	5.86	3.96	4.64
3K	**2c**	50:50	53:47	93	4048	1.13	8	62.91	61.97	5.66	5.99	5.64	5.64
3L	**2c**	80:20	70:30	96	5170	1.36	41	61.80	61.82	5.43	5.74	5.54	5.19

The reaction was performed with 1.5 wt% $Sn(Oct)_2$ as a catalyst at 140 °C 24 h.

[a] Molar ratio percentage of *N*-CBz-Hpr **1** over the comonomer functional cyclic ester **2a–c** was fed in the polymerization.

[b] Number-average molecular weight and molecular weight distribution determined by GPC with $CHCl_3$ as the eluent.

[c] Determined from DSC thermograms at 10 °C/min^{-1}.

with an equivalent molar ratio, with 1.5 wt% $Sn(Oct)_2$ as a catalyst. The results are shown in Table 1. For the poly(*N*-CBz-Hpr-*co*-4-EtC-ε-CL) system, the η'_{inh}s of the copolymers ranged from 0.66 to 1.06 dL g^{-1} and the M_n of the copolymers ranged between 1124 and 3849 g mol^{-1} with M_w/M_n between 1.16 and 1.37 were observed when the polymerization time varied from 12 to 48 h (entries 1, 2, 3, 4, and 5). The maximum M_n was obtained about at 24 h (3849 g mol^{-1}). The η_{inh} of the poly(*N*-CBz-Hpr-*co*-4-EtC-ε-CL) is significant lower than the poly(*N*-CBz-Hpr-*co*-ε-CL) [18] because of the functional lactones polymerized generally react slower than the ε-CL [11]. From the ^1H NMR analysis, the conversions of the functional lactones lower than the feed were observed. If the comonomer was transferred from **2a** to **2b**, the η_{inh} of the copolymers increased from 0.74 to 0.85 dL g^{-1} at the same polymerization condition (entries 3 and 6). As the polymerization temperature was decreased from 140 to 110 °C, the η_{inh} and the M_n of the copolymers decreased from 0.85 to 0.55 dL g^{-1} and from 3359 to 996 g mol^{-1}, respectively (entries 6 and 7). Although the polymerization time was increased to 48 h at 110 °C, the η_{inh} of the copolymers only slightly increased from 0.55 to 0.69 dL g^{-1} (entries 7 and 8). But, if the reaction temperature enhanced from 140 to 170 °C, a decrease in the η_{inh} and the M_n of the copolymers from 0.85 to 0.69 dL g^{-1}, and from 3359 to 2013 g mol^{-1} were observed, respectively (entries 6 and 9). This may be due to the transesterification of the copolymer at 170 °C. Therefore, the optimum copolymerizations of *N*-CBz-Hpr **1** with functional ε-caprolactone **2a–c** were performed at 140 °C for 24 h with 1.5 wt% $Sn(Oct)_2$ as a catalyst.

The effect of monomer compositions in feed, the copolymerization of *N*-CBz-Hpr **1** and functional ε-caprolactone **2a–c** were investigated at a wide range of compositions. The results are summaried in Table 2. The M'_ns of the copolymers were measured by GPC with universal curves calibrated with standard polystyrene. The copolymers synthesized exhibited oligomeric molecular weights with narrow molecular weight distributions. Compared the molecular weight of copolymers with homopolymers, the M_n of the copolymers (M_n = 3063–5170 g mol^{-1}) are higher than the homopoly(functional ε-CL) (M_n = 820 g mol^{-1}), but lower than the homopoly(*N*-CBz-Hpr) (M_n = 32,000 g mol^{-1}) [13]. For the *N*-CBz-Hpr/4-EtC-ε-CL system, the M_n of the copolymers ranged between 3063 and 5166 g mol^{-1} with polydispersities between 1.12 and 1.37 were observed when the composition molar ratios (*N*-CBz-Hpr/4-EtC-ε-CL) varied from 21/79 to 97/3 (copolymers **3A** to **3H**). Similarly, as the comonomer was transferred from **2a** to **2b** or **2c**, for the *N*-CBz-Hpr/4-BzC-ε-CL or *N*-CBz-Hpr/4-BzCN-ε-CL system, the M_n of the copolymers ranged between 3281 and 5170 g mol^{-1} with polydispersities between 1.11 and 1.36, (copolymers **3I** to **3L**) were obtained. The molecular weights of the copolymers were lower than expected, presumably due to the functional cyclic lactones have more steric hindrance and less reactive than the ε-CL.

3.2. Thermal analysis

DSC was used to analyze the temperature corresponding to the copolymer glass transition (T_g). The results of the DSC analyses are complied in Table 2. For *N*-CBz-Hpr/4-EtC-ε-CL, *N*-CBz-Hpr/4-BzC-ε-CL, and *N*-CBz-Hpr/4-BzCN-ε-CL the copolymers exhibited only T_g. Therefore, all the copolymers were amorphous. With a decrease in the contents of functional ε-CL incorporated into the copolymers, an increased T_g of the copolymers was observed. For *N*-CBz-Hpr/4-EtC-ε-CL the copolymers, the values of T_g increased from −34 to 67 °C when the molar ratio percentages of 4-EtC-ε-CL decreased from 79 to 3 mol% (copolymers **3A** to **3H**). Similar results were observed for *N*-CBz-Hpr/4-BzC-ε-CL, and *N*-CBz-Hpr/4-BzCN-ε-CL copolymers, the values of T_g increased from −8 to 50 °C, and 8 to 41 °C when the molar ratio percentages of 4-BzC-ε-CL **2b**, and 4-BzCN-ε-CL **2c** decreased from 41 to 30 mol% (copolymers **3I**, and **3J**), and 47 to 30 mol% (copolymers **3K**, and **3L**), respectively. This is due to the fact that functional ε-CL **2a**, **2b**, and **2c** can be considered as soft component as compared with *N*-CBz-Hpr. Therefore, larger amounts of loose linkage, such as methylene groups, were incorporated into the macromolecular backbone that had larger free rotation of the copolymer chain and caused a decrease in T_g.

3.3. Structure characterization

The structure of the copolymer was confirmed by ^1H NMR. The data from NMR spectroscopy of the copolymer are fully consistent with the anticipated chemical structure as compared to the spectrum of the homopolymer. Representative ^1H NMR spectrum of the copolymer poly(*N*-CBz-Hpr-*co*-4-BzC-ε-CL) **3I** with monomer compositions 59/41 mol% is depicted in Fig. 1(A). Characteristic resonance peaks at δ = 7.21–7.11 ppm (due to the protons of aromatic rings of the CBz protecting group), δ = 5.24–4.90 ppm (due to the C4 methine proton of Hpr and the benzylic protons of the CBz protecting group), δ = 4.59–4.30 ppm (due to the C2 methine proton of Hpr), δ = 4.19–3.99 ppm (due to the C6 methylene protons of ε-CL), δ = 3.69–3.54 ppm (due to the C5 methylene protons of Hpr), δ = 3.21 ppm (due to the hydroxy proton), δ = 2.45–2.38 ppm (the C2 methylene protons of ε-CL), δ = 2.32–2.25 (due to the C4 methine proton of ε-CL), δ = 2.07–1.99 (due to the C3 methylene protons of Hpr), and δ = 1.81–1.69 ppm (due to the C3, and C5 methylene protons of ε-CL) can be seen.

All of the copolymers obtained have similar FT-IR, which showed the characteristic absorption bands of the ester around 1750 cm^{-1} and the aromatic C–H (out-of-plane bending) absorptions at 699, and 745 cm^{-1} from the

CBz protecting group. A representative IR spectrum of the poly(*N*-CBz-Hpr-*co*-4-BzC-ε-CL) **3I** with monomer compositions 59/41 mol% is shown in Fig. 2(A). Also, an elemental analysis of the copolymers indicated that the experimental and calculated values were close to each other (Table 2).

3.4. Deprotection of the benzyl groups of copolymers

The benzyl protecting groups of copolymers **3E**, **3I**, and **3K** were removed by catalytic transfer hydrogenation. 1,4-Cyclohexadiene was used as an effective hydrogen donor under mild conditions. Palladium over activated carbon (10 wt%) was used as the catalyst for the hydrogenolysis of the benzyl protected group.

In a comparison with the ^{1}H NMR spectra of the benzyl protected copolymers, we found that the peaks around $\delta =$ 5.06 and 7.21 ppm, which were assigned to the hydrogen atoms of the benzyl protecting group, disappeared in the spectra of the deprotected copolymers after 68 h of hydrogenation. The representative IR spectra of the benzyl protected copolymer **3I** and the deprotected polymer **4I** exhibit strong ester carbonyl bands at 1740 cm^{-1}. The most distinctive features of the **4I** were the almost complete absence of aromatic C–H (out-of-plane bending) absorption at 699 and 750 cm^{-1} from the benzyl protected group and the presence of a broad carboxylic and amino band at 2400–3400 cm^{-1} (superimposed with aliphatic C–H stretching). This indicated the successful removal of the benzyl group and the formation of the pendant amino and (or) carboxylic group.

A decrease in the η_{inh} and M_n of the copolymers were observed in compared before and after deprotection. The results are shown in Table 3. As the benzyl and (or) benzyloxycarbonyl groups of the copolymers were deprotected, a decrease in the η_{inh} of the copolymers from 1.06 to 0.78 dL g^{-1} (copolymers **3E**, and **4E**), from 1.13 to 1.04 dL g^{-1} (copolymers **3I**, and **4I**), and from 0.95 to 0.91 dL g^{-1} (copolymers **3K**, and **4K**) were observed, respectively. Similarly, a decrease in the M_n's of the copolymers from 3849 to 1246 g mol^{-1} (copolymers **3E**, and **4E**), and from 3359 to 2182 g mol^{-1} (copolymers **3I**, and **4I**) was also observed when the copolymers were deprotected. For *N*-CBz-Hpr/4-BzC-ε-CL, and *N*-CBz-Hpr/4-BzCN-ε-CL the polymers, the values of T_g increased from −8 to 48 °C, and from 8 to 33 °C after deprotection, respectively. This may be due to the deprotected copolymer harder than the protected copolymer when the benzyl and (or) benzyloxycarbonyl groups were removed. In contrast, for *N*-CBz-Hpr/4-EtC-ε-CL the copolymers, the values of T_g decreased from 27 to 12 °C, presumably because of the degradation of the *N*-CBz-Hpr/4-EtC-ε-CL polymer in the deprotection.

Table 3
Buck properties of protected copolymers **3** and deprotected copolymers **4**

Copolymer	η_{inh} (dL g^{-1})[a]	M_n[b]	M_w/M_n[b]	T_g (°C)[c]
3E	1.06	3849	1.16	27
4E	0.78	1246	2.57	12
3I	1.13	3359	1.14	−8
4I	1.04	2182	1.51	48
3K	0.95	4048	1.13	8
4K	0.91	–[c]	–	33

[a] The η_{inh}'s of the protected copolymers **3**, and the deprotected copolymers **4** were measured at 0.1 g dL^{-1} in $CHCl_3$, and CH_3OH at 30 °C, respectively.
[b] The M_n's of the protected copolymers **3**, and the deprotected copolymers **4** were determined by GPC with $CHCl_3$, and DMF as the eluent, respectively.
[c] Determined from DSC thermograms at 10 °C/min^{-1}.
[d] Coplymer **4K** doesn't dissolve in DMF.

3.5. Preliminary in vitro degradation study

In vitro degradation of the protected poly(*N*-CBz-Hpr-*co*-4-EtC-ε-CL), poly(*N*-CBz-Hpr-*co*-4-BzC-ε-CL), and poly(*N*-CBz-Hpr-*co*-4-BzCN-ε-CL) were evaluated from weight loss of the sample. The degradation profiles of the poly(*N*-CBz-Hpr-*co*-4-EtC-ε-CL) **3G** with monomer compositions of 92/8 mol%, the poly(*N*-CBz-Hpr-*co*-4-BzC-ε-CL) **3J** with monomer compositions of 70/30 mol%, and the poly(*N*-CBz-Hpr-*co*-4-BzCN-ε-CL) **3L** with monomer compositions of 70/30 mol% at 37 °C under physiological condition (pH 7.4) are portrayed in Fig. 3. The results indicated that the degradation rate showed a gradual increase with time, and was affected by the composition of the polymers. The degradability of **3J** was higher than **3L**, and **3G**. The major reason is due to the M_n of **3J** (3281 g mol^{-1}) lower than **3L** (5170 g mol^{-1}), and **3G** (5166 g mol^{-1}). As for the degradability of **3L** was higher than **3G**. This may be due to the compositions of *N*-CBz-Hpr in the **3G** (92 mol%) higher than the **3L** (70 mol%) because the *N*-CBz-Hpr is more rigid than the functional ε-CL.

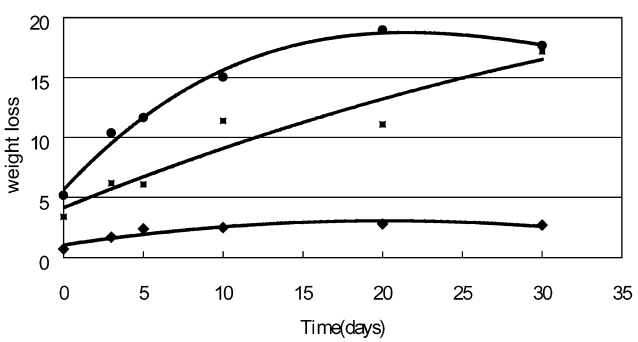


Fig. 3. Weight loss of copolymer **3G** (◆), **3J** (□), and **3L** (■) with monomer compositions 92:8, 70:30, and 70:30 mol% in which it was treated in M/15 phosphate buffer solution (pH 7.4) at 37 °C.

4. Conclusions

A series of poly(*N*-CBz-Hpr/functional cyclic ester)s with various compositions were synthesized from *N*-CBz-Hpr **1** and cyclic esters **2** containing protected functional groups (carboxyl, and amino). The copolymers synthesized exhibited oligomeric molecular weights with modestly molecular weight distribution. The T_g values of the resulting copolymers were controlled by the amounts of the comonomers added. These copolymers degraded under physiological conditions. The degradability of poly(*N*-CBz-Hpr-*co*-4-BzC-ε-CL) was higher than poly(*N*-CBz-Hpr-*co*-4-BzCN-ε-CL), and poly(*N*-CBz-Hpr-*co*-4-EtC-ε-CL).

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