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Synthesis and degradation of novel photocrosslinkable aromatic copolyanhydrides

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Abstract

Novel photocrosslinkable degradable aromatic copolyanhydrides have been prepared by melt-polycondensation from 1,6-bis(*p*-carboxyphenoxy)hexane (CPH) and 4,4′-(sebacoyldioxy)dicinnamic acid (CSC) derived from 4-hydroxycinnamic acid and sebacoyl chloride. FT–IR and ^{1}H NMR confirmed the copolymer structures. These copolymers were subsequently irradiated with a 400 W high-pressure mercury lamp ($\lambda > 28$ nm) to produce crosslinked materials. The gel yields of copolymers increased with increasing irradiation time and/or CSC contents. The photocrosslinking significantly enhanced the tensile strength at break (σ_b) and tensile modulus (E), but decreased the elongation at break (ε_b). The crosslinked CPH/CSC(25/75) film with gel content of 90% showed the highest σ_b of 28 MPa and E of 742 MPa. The degradation characteristics of copolymer films was investigated in a phosphate buffer solution (pH 7.2 and 10.0) at 37 °C by mass loss, molecular weight reduction by GPC and contact angle measurement. The induction period was detected for all copolyanhydrides, and the rate of degradation of copolyanhydrides was much higher than that of PCPH.

Keywords: Cinnamic acid; Photocrosslinkable; Aromatic copolyanhydride; Mechanical properties; Hydrolytic degradation

1. Introduction

Bioerodible polyanhydrides have been used for various applications such as temporary replacement of bone and controlled drug release [1,2]. Polyanhydrides of aromatic acids show better mechanical properties and stability and longer release and degradation time than aliphatic polyanhydrides. However, aromatic polyanhydrides are insoluble in common organic solvents and melt at higher temperatures, which limits their use. By contrast, aliphatic polyanhydrides show much faster degradation and lower melting points. Thus, some copolymers based on aliphatic and aromatic diacids have been synthesized to improve physical and mechanical properties and control the degradation rates of polyanhydrides [3,4].

The introduction of crosslinking into polyanhydrides would be expected to improve the physical and mechanical properties. Domb et al. prepared polyanhydrides from unsaturated dicarboxylic acids such as fumaric acid and stilbenedicarboxylic acid, which were radically crosslinked [5]. The crosslinked polyanhydrides have been also synthesized from

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crosslinkable anhydride prepolymers that possess methacrylate end groups [6–8]. These prepolymers have been cured by photoinitiated polymerization of the methacrylic end groups. As an alternative approach we have synthesized a new class of copolyanhydrides that possess cinnamate groups in polymer main chains, which could be readily photocured to produce a polyanhydride network [9]. Incorporating a cinnamoyl moiety into the polyanhydride chain would be convenient way to obtain bioerodible crosslinkable polymers, since polycinnamates can be readily photochemically crosslinked, and the cinnamoyl moiety is metabolized into safe products in the body.

In this paper, we wish to report novel biodegradable photocrosslinkable aromatic copolyanhydrides from 4,4′-(sebacoyldioxy)dicinnamic acid (CSC) and 1,6-bis(*p*-carboxyphenoxy)hexane (*p*-CPH). The effects of copolymer compositions and crosslinking density on thermal and mechanical properties as well as degradation profiles of copolyanhydrides are examined.

2. Experimental

2.1. Materials

p-Hydroxybenzoic acid, 1,6-dibromohexane, acetic anhydride and 4-hydroxycinnamic acid were purchased from Tokyo Kasei Kogyo Co., Ltd. and used without further purification. Sebacoyl chloride from Wako Pure Chemical Industry, Ltd. was redistilled prior to use 1,6-bis(*p*-carboxyphenoxy)hexane (*p*-CPH) was synthesized from *p*-hydroxybenzoic acid and 1,6-dibromohexane as described elsewhere [10]. mp; 290–293 (lit. 294–295 °C). 4,4′-(Sebacoyldioxy)dicinnamic acid (CSC) was synthesized by condensation of sebacoyl chloride and 4-hydroxycinnamic acid. This synthetic procedure was described in detail in our previous paper [9]. mp.: 269–272 °C. The prepolymers of CSC [9] and *p*-CPH [11] were synthesized as described elsewhere.

2.2. Preparation of copolyanhydrides

A typical procedure for the synthesis of the photosensitive copolyanhydrides is described below: A mixture of 2 mmol of CSC prepolymer and 8 mmol of *p*-CPH prepolymer was placed in a polymerization glass tube equipped with a capillary inlet tube for the gas and a side arm for the vacuum. The mixture was then heated to 180 °C for 0.5 h in a stream of nitrogen and further heated at the same temperature *in vacuo* for 0.5–3 h in a silicon oil bath. Copolymer composition is denoted as CPH/CSC(80/20), where 20 refers to the mole percent of CSC used in the feed composition.

2.3. Characterization

Fourier transform infrared spectra (FTIR) were recorded on a JEOL spectro-photometer using a thin film on a KRS substrate. ^{1}H NMR spectra were obtained at 25 °C in $CDCl_3$ using a JEOL JNM-EX90A FT–NMR spectrometer with TMS as the internal standard. Gel permeation chromatography (GPC) was carried out on a Waters system. Three styragel columns (300 mm × 7.8 mm) were placed in a series and operated at a flow rate of 1 ml/min in chloroform at 35 °C. Polystyrene standards with low polydispersities were used for calibration. Differential scanning calorimetry (DSC) was made on a Shimadzu DSC-50 differential scanning analyzer controlled by a TA-50 work station at a heating rate of 10 °C/min in a nitrogen atmosphere. Wide angle X-ray scattering (WAXD) was performed for film samples using a Rigaku Denki model RAD-IA X-ray diffractometer with nickel-filtered CuK_α radiation. Drop contact-angle measurements were obtained with a NRL Goniometer (Rame-Hart. Inc.,). Tensile properties of film specimens (length, 10 mm; width, 5 mm; thickness, 0.20–0.22 mm) were investigated at room temperature (20 ± 2 °C) using a Shimadzu AG-1 autograph equipped with a 1 kN load-cell and a crosshead speed of 20 mm/min. An average of five measurements was taken with no more than 15% deviation from the mean.

2.4. Film preparation

Copolyanhydride films of about 200 μm were prepared by the melt-press method at 120–150 °C, followed by quenching in an ice-cooled bath, then dried for 24 h *in vacuo*.

2.5. Photocuring and gel fraction

The photocuring was conducted using a 400 W high-pressure mercury lamp (SEN LIGHT Co. Ltd.; Osaka, Japan) through a water jacket and Pyrex to cut off wavelengths below 280 nm. The UV light intensity (1.00 mW/cm^2) was measured on a photometer (SPECTRONICS DRC100X, NY).

The gel fractions were measured for melt-pressed films (200–220 μm). After the films were irradiated for various times, they washed thoroughly with chloroform to remove the unreacted soluble part of the polymer, and then the gels were dried *in vacuo* and weighed. The gel fraction was defined as the weight percentage of insoluble part (W_g) against that of the polymer (W): $W_g/W \times 100$.

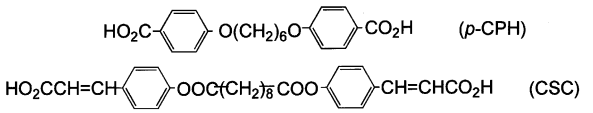
2.6. Hydrolytic degradation

The film specimen (10 mm × 10 mm, about 200 μm thickness) was placed in a small bottle containing 10 ml of 1/15 mol phosphate by a buffer solution (pH 7.2 and 10.0). The bottle was then incubated at 37 °C with shaking for various times. After incubation the film was washed with water extensively and dried overnight at room temperature *in vacuo*. The degree of degradation was estimated from the weight loss according to the following equation. Weight loss (%) $= 100(W_0 - W_t)/W_0$, where W_0 and W_t are the dry sample weight before and after the degradation. The weight loss averaged for two specimens was employed.

3. Results and discussion

3.1. Synthesis

Copolyanhydrides of CSC and *p*-CPH were prepared by a melt-polycondensation at 180 °C for 90–120 min under vacuum. The chemical structures of CSC and *p*-CPH are shown in Scheme 1. Fig. 1 shows the effects of polymerization time on the molecular weight (MW) and polydispersity of polymers. The MW increases rapidly at initial stage of polymerization and levels off after approximately 180 min. Therfore, the polymerizations were performed at 180 °C for 120 min for all copolymers



Scheme 1. Chemical structures of *p*-CPH and CSC.

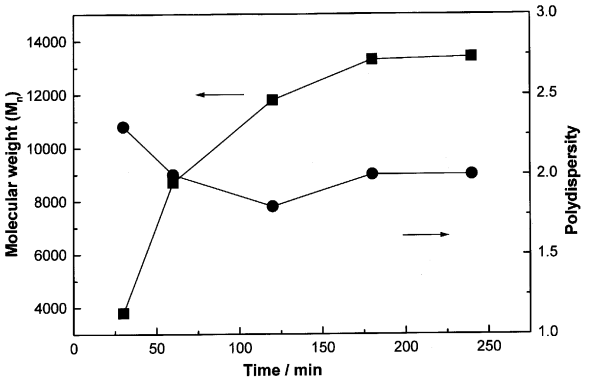


Fig. 1. Changes in molecular weight and polydispersity against polymerization time.

unless otherwise noted. Table 1 summarizes MWs and chemical compositions of the copolyanhydrides. The MWs of all the polymers were evaluated by GPC using PS calibration and the number average MWs prior to ranged from 8300 to 13,300. Careful purification and storage of the prepolymers was necessary to obtain high-molecular-weight polyanhydrides. All the copolyanhydrides were soluble in chloroform and methylene chloride, but insoluble in tetrahydrofuran, diethyl ether and methanol. The chemical structures of copolyanhydrides were confirmed by FTIR and ^{1}H NMR spectra. The IR spectra of all copolyanhydrides showed characteristic absorption bands at 1810 cm^{-1} and 1740 cm^{-1} due to the anhydride groups. The absorption at 1780 cm^{-1} corresponded to the ester carbonyl stretching bands. The sharp absorptions due to the

Table 1
Compositions and molecular weights of copolyanhydrides

Copolymer code[a]	Copolymer composition CPH/CSC[b] (mol%)	M_n[c] (g/mol)	M_w[c] (g/mol)	M_w/M_n[c]
PCPH	–	13,300	26,800	2.01
CPH/CSC(90/10)	87/13	9700	19,300	1.98
CPH/CSC(80/20)	76/24	10,300	26,800	2.60
CPH/CSC(70/30)	71/29	9500	46,300	4.88
CPH/CSC(50/50)	50/50	10,800	41,500	3.84
CPH/CSC(25/75)	24/76	8800	41,500	4.72

[a] Prepolymer feed ratio (mol%).
[b] Determined by ^{1}H NMR.
[c] Determined by GPC with polystyrene standards.

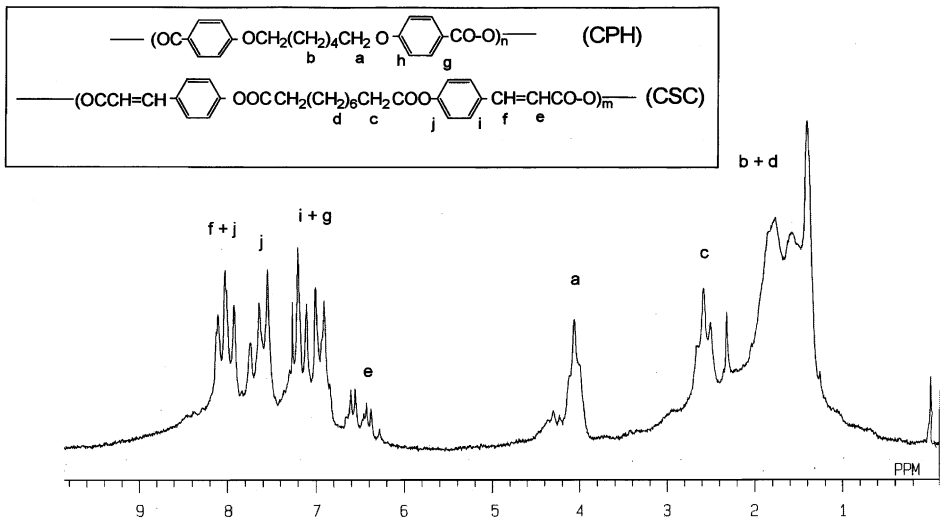


Fig. 2. ^{1}H NMR spectrum of CPH/CSC(50/50) in *d*-chloroform.

trans ethylene group appeared at 1638 cm^{-1} and 1308 cm^{-1}, respectively, indicating that the *trans* cinnamoyl group was successfully introduced into the polymer backbone. The typical ^{1}H NMR spectrum of CPH/CSC(50/50) is shown in Fig. 2. Two doublet signals characteristic for *trans* cinnamoyl group appeared at 6.39 ppm and 7.66 ppm with a coupling constant of 16 Hz, which also demonstrates the presence of cinnamoyl group in the polymer backbone. The copolymer composition were determined by the integral peak ratio of 4.08 ppm (4H, —CH_2O— of CPH) and 6.39 pm (2H, —CH=CH— of CSC) in the ^{1}H NMR spectrum. The copolymer compositions, listed in Table 1, are good agreement with the feeding monomer compositions.

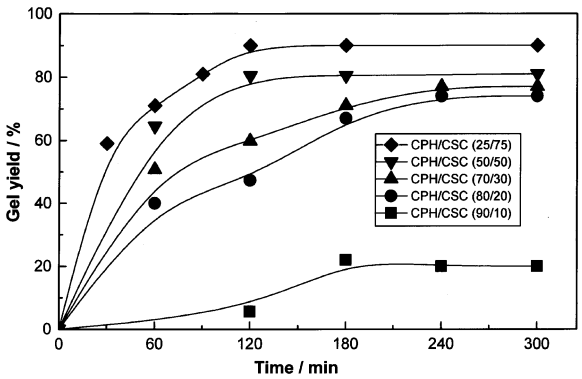


Fig. 3. Gel yields of copolyanhydride films against polymerization time.

3.2. Photocuring

The photochemical reaction of the cinnamate group is well known for undergoing a [2 + 2] cycloaddition reaction [12]. The melt-pressed copolyanhydride films were irradiated by a 400 W high-pressure mercury lamp at $\lambda > 280$ nm to form a network. Fig. 3 shows the gel yields for various copolyanhydride films *versus* irradiation time. The gel yields increase rapidly at the early stage of irradiation and level off for 2–4 h. They increase with increasing CSC contents in the copolyanhydride due to the increase in the concentration of the photocrosslinkable cinnamate moiety. CPH/CSC(25/75) attains a gel content of *ca.* 90% after 2 h irradiation, whereas, the gel content of CPH/CSC(90/10) is only *ca.* 20% after 5 h irradiation.

3.3. Thermal and mechanical properties

Thermal properties of copolyanhydrides were determined for melt-quenched samples by DSC. PCPH and all copolymers showed glass transition temperatures (T_g), but no melting endotherm, suggesting that they are amorphous. WAXS curves of these melt-pressed films also exhibited only an amorphous halo. In contrast, as-polymerized PCPH and CPH/CSC(90/10) samples exhibited a melting peak at 133 °C with a heat of fusion of 27 j/g and at 109 °C with that of 24 j/g, respectively. T_g values of the copolymers were in the range of 33–30 °C, and decreased slightly with an increased CSC component. The decrease in T_g would be caused by the decrease in aromatic anhydride linkages in the copolymers.

Table 2
Gel contents and tensile properties of melt-pressed films before and after photocuring[a]

Copolymer code	Gel content (wt.%)	σ_b (MPa)	E (MPa)	ε_b (%)
PCPH	–	16	762	3
CPH/CSC(80/20)	–	18	597	38
	50	22	550	24
	80	24	605	21
CPH/CSC(50/50)	–	17	540	16
	80	30	640	8
CPH/CSC(25/75)	–	9	305	32
	90	28	742	25

σ_b; Tensile strength at break, E; Young's modulus, ε_b; tensile elongation at break.
[a] Film thickness; 200–220 μm. UV intensity; 1.0 mW/cm^2.

Table 2 shows the tensile properties of melt-pressed copolyanhydride films before and after photocrosslinking. Before photocrosslinking, the tensile modulus (E) decreased markedly with increasing CSC content. Because the copolymers possess approximately similar molecular weights, the observed decrease in E is likely due to changes in chemical structure. This decrease would be ascribed to the decrease in aromatic anhydride linkages. As anticipated, crosslinking increased the tensile strength at break (σ_b) and the tensile modulus (E), but decreased the elongation at break (ε_b). The crosslinked CPH/CSC(25/75) and CPH/CSC(50/50) films with gel content of 80–90% shows a much larger σ_b of 28–30 MPa and E of 640–742 MPa with an ε_b of 8–25%. It is noteworthy that the tensile strength of these photocrosslinked films is close to the tensile strength of poly(lactic acid) (30–22 MPa) which is used as an absorbable suture in surgery [13].

3.4. Hydrolytic degradation

The degradation characteristic of copolyanhydride films was investigated in a buffer solution (pH 7.2 and 10.0) at 37 °C. The degradation was monitored by weight loss of the sample, MW reduction by GPC and contact angle measurement. The weight loss was hardly observed for all films during a 20 day incubation at pH 7.2. Thus, we measured the changes of MW and the contact angle during the incubation. Fig. 4 shows the changes of MWs and contact angles of CPH/CSC(50/50) film against the incubation time. Both the MWs and contact angles decreased with increasing time, indicating that scission of the polymer backbone occurred and

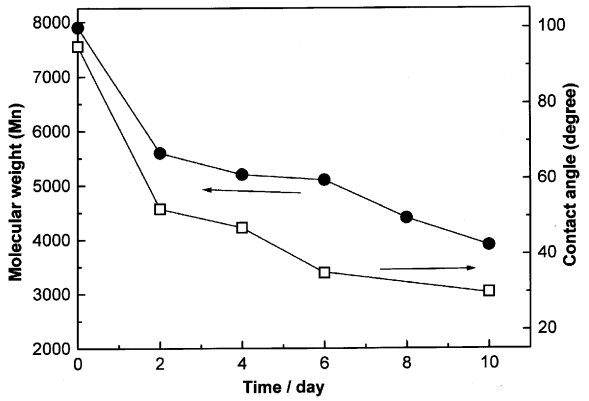


Fig. 4. Changes in molecular weight and contact angle of CPH/CSC(50/50) films against incubation time.

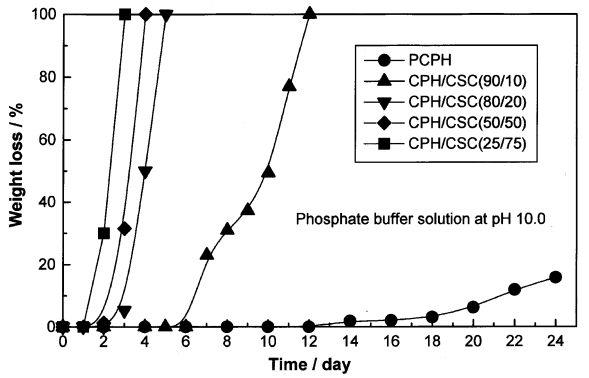


Fig. 5. Weight loss of copolymer films against incubation time degraded in the phosphate buffer solution (pH 10.0) at 37 °C.

the surface of the film became more hydrophilic with no weight loss. It is expected that the degradation rate is accelerated at higher pH. Fig. 5 shows the weight loss of various copolyanhydride films degraded in a phosphate buffer solution of pH 10 at 37 °C against incubation time. PCPH showed no weight loss, while the copolymer films degraded rapidly after an induction period. This induction period has been characterized by a rapid decrease in polymer MW without weight loss [14]. A similar induction period has previously been observed for copolyanhydrdes prepared from sebacic acid prepolymer and CSC prepolymer [9]. The lag time is detected in all copolyanhydrides. They decrease with increasing CSC content, which would be ascribed to the increase in concentration of more susceptible aliphatic-aliphatic anhydride linkages (CSC–CSC) and/or ester linkages between hydroxycinnamic acid and sebacic acd in the CSC component. The degradation rate of copolyanhydrides is

much higher than that of PCPH. The degradation behaviors of photocrosslinked copolyanhydride films are in progress.

In summary, novel photocrosslinkable degradable aromatic copolyanhydride based on 1,6-bis(*p*-carboxyphenoxy)hexane (CPH) and 4,4′-(sebacoyldioxy)dicinnamic acid (CSC) were synthesized and characterized. The photocrosslinking significantly enhanced the tensile strength at break (σ_b) and the tensile modulus (E), but decreased the elongation at break (ε_b). The crosslinked CPH/CSC(25/75) and CPH/CSC(50/50) films with gel contents of 80–90% showed the highest σ_b of 28–30 MPa. The degradation rate of copolyanhydrides was much higher than that of PCPH. These copolymers may be useful in applications such as absorbable sutures and orthopedic bioerodible bone cements with good mechanical strength. The availability of novel photocrosslinkable copolyanhydrides may make possible a variety of new applications of biodegradable polyanhydrides.

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