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Molecular Design of Photocurable Liquid Biodegradable Copolymers. 2. Synthesis of Coumarin-Derivatized Oligo(methacrylate)s and Photocuring

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ABSTRACT: Photocurable, biodegradable liquid copolymers, which undergo liquid-to-gel transformation upon ultraviolet (UV) light irradiation, may find versatile biomaterial applications. A multifunctionally derivatized liquid prepolymer that is oligo(2-hydroxyl methacrylate) grafted with oligo(ϵ-caprolactone) and subsequently end-capped with a photodimerizable group, coumarin, at the terminal ends of the side chains, was prepared. UV irradiation produced a cross-linked solid.

Introduction

Photocurable biodegradable liquid precursors, oligomers or prepolymers, may be used for surface layering and microfabrication of medical devices and drug microencapsulation in biomedical fields.[1] We have prepared such oligomers by ring-opening polyaddition of trimethylene carbonate (TMC) with ϵ-caprolactone (CL) using appropriate hydroxyl group-bearing low-molecular-weight substances as initiators and subsequent end-capping with coumarin groups at their terminal ends.[2−4] These oligomers were di-, tri-, and tetrafunctional viscous liquid copolymers with molecular weights of the order of a few thousands to tens of thousands. Ultraviolet (UV) irradiation of thin liquid films of tri- or tetrafunctional photoreactive copolymers produced highly cross-linked solid films due to intra- and intermolecular photodimerization of the coumarin groups, which resulted in both chain extension and cross-linking. Since the photocuring rate is critical for processing, development of a faster photocuring system is an objective that must be pursued for next-generation products.

In this paper, we molecularly designed a protocol to prepare more functional liquid biodegradable copolymers that may be expected to provide increased curing photocharacteristics. The designed copolymers had oligo(methacrylate) as the main chain and oligo(CL) as the side chain, each terminal end of which was end-capped with coumarin groups. The preparation method and photocuring characteristics are reported in this paper.

Experimental Section

General Procedure. All the solvents and reagents were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan), or Sigma-Aldrich Japan, Inc. (Tokyo, Japan). Trimethylene carbonate (TMC) and 7-chlorocarbonylmethoxycoumarin (coumarin acid chloride) were prepared according to a previously reported method, and TMC was recrystallized from a mixed solvent of ethyl acetate and hexane.[2,4] Other solvents and reagents were purified by distillation. ^{1}H NMR spectra were recorded on a JEOL JNM-GX270 FT-NMR spectrometer (270 MHz, Tokyo, Japan). The chemical shifts were expressed in δ values compared to Me_4Si, which was used as the internal standard. IR spectra were recorded on a Shimadzu DR-8020 FT-IR spectrophotometer (Kyoto, Japan). UV absorption spectra were recorded on a JASCO Ubest-30 UV/vis spectrophotometer (Tokyo, Japan). The molecular weight (M_n) of the polymer was determined by GPC analysis, which was carried out on a Toso SC-8020 (Tokyo, Japan) (poly(ethylene glycol) standard; eluent, DMF). UV light (250 W Hg−Xe lamp: Hamamatsu Photonics L5662-02, Shizuoka, Japan) was irradiated through a Pyrex filter. The intensity of the UV light source was measured at 250 nm on a TOPCON UVR-25 (Tokyo, Japan).

Synthesis of Oligo(2-hydroxylethyl methacrylate) (OHEMA). A typical procedure for preparation is as follows. A mixture of 2-hydroxylethyl methacrylate (HEMA) (2.02 g, 17.2 mmol), 2,2′-azobis(isobutyronitrile) (AIBN) (113 mg, 688 μmol), 2-mercaptoethanol (120 μL, 1.71 mmol), and DMF (8.60 mL) was sealed in a glass tube under reduced pressure after three freeze/thaw cycles and then heated for 15 h at 60 °C. The obtained prepolymer, OHEMA, was isolated by precipitation in diethyl ether. The yield was 1.94 g (96.1%). Number-average molecular weight (M_n) = 1220. ^{1}H NMR (DMSO-d_6, ppm): $\delta = 0.78$ (multiplet), 1.80 (multiplet), 3.58 (multiplet), 3.90 (multiplet), and 4.79 (multiplet).

Synthesis of Grafted OHEMA. A typical procedure for preparation is as follows. A reaction mixture of 0.33 M tin(II) 2-ethylhexanoate solution in toluene (100 μL, 34 μmol), OHEMA (3.21 g, 2.63 mmol), and ϵ-caprolactone (CL) (4.56 g, 40.0 mmol) was stirred for 8 h at 160 °C under N_2 atmosphere. After vacuum distillation of unreacted CL, CL-grafted OHEMA was isolated by precipitation in methanol. The yield was 7.27 g (94%). $M_n = 3200$. ^{1}H NMR ($CDCl_3$, ppm): $\delta = 1.39$ (multiplet), 1.65 (multiplet), 2.29 (multiplet), 3.62 (multiplet), 4.04 (multiplet), and 4.28 (multiplet).

Synthesis of Coumarin End-Capped Grafted OHEMA (Coumarinated OHEMA). A mixture of grafted OHEMA (7.27 g, 2.27 mmol), 7-chlorocarbonylmethoxycoumarin (7.00 g, 29.3 mmol), and pyridine (2.0 mL, 24.7 mmol) was stirred for 12 h at room temperature under N_2 atmosphere. The product was isolated by precipitation in methanol. The yield was 17.8 g (82%). Coumarin content = 1.91×10^{-3} mol/g. Molecular weight (determined based on coumarin content as described below) = 4700. ^{1}H NMR ($CDCl_3$, ppm): $\delta = 1.39$ (multiplet), 1.65 (multiplet), 2.29 (multiplet), 3.62 (multiplet), 4.04 (multiplet), 4.28 (multiplet), 4.69 (doublet), 6.26 (doublet, $J = 9.3$ Hz), 6.79 (doublet, $J = 2.4$ Hz), 6.87 (quartet, $J = 2.4$,

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Scheme 1. Preparation of Grafted OHEMAs and Coumarinated OHEMA

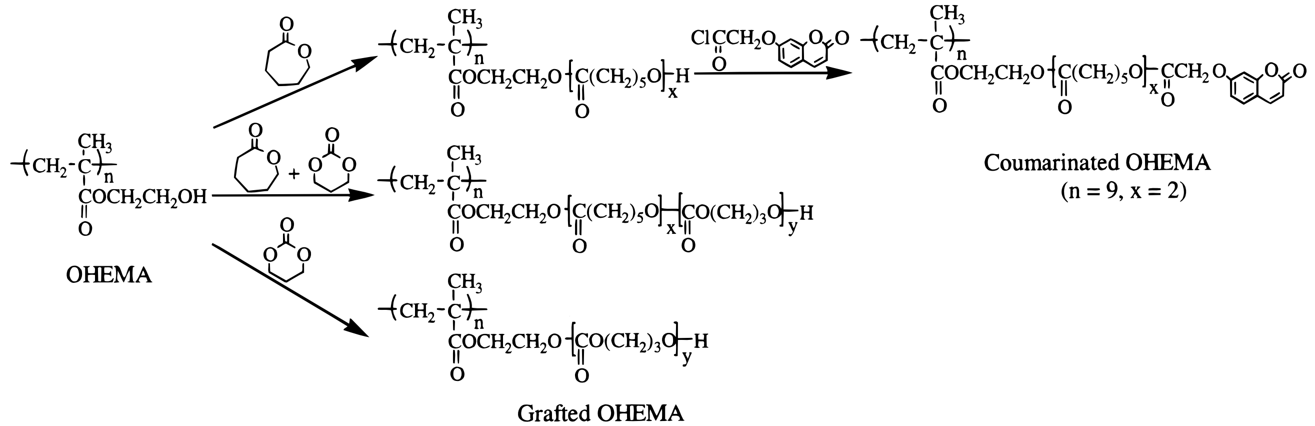


Table 2. OHEMA-Based Copolymers[a]

run	no. of OH groups of OHEMA[b]	monomer molar feed CL:TMC	molar ratio of monomer to OH group	grafted OHEMA	
				state	M_n[c]
1	6	1:0	2.0	viscous liquid	2500
2	6	1:0	5.2	waxy solid	7200
3	6	1:0	10.0	waxy solid	15000
4	6	1:1	2.0	solid	
5	6	1:1	5.0	solid	
6	6	0:1	2.0	solid	
7	6	0:1	5.0	solid	
8	9	1:0	2.0	viscous liquid	3200
9	9	1:0	4.5	waxy solid	6600
10	9	1:1	9.4	solid	

[a] Catalyst: tin(II) 2-ethylhexanoate (Sn-oct); 160 °C and 8 h. [b] Molecular weight of OHEMAs used were 8.1×10^2 (runs 1−7) and 1.2×10^3 (runs 8−10). [c] Number-average molecular weight determined by GPC (PEO standard).

Table 1. Oligomerization of HEMA[a]

run	[HEMA] (mmol)	[initiator] (mmol)	[transfer agent] (mmol)	OHEMA	
				M_n[b]	av no. of hydroxyl groups[c]
1	17.2	0.688	0.43	2.7×10^3	21
2	17.2	0.688	0.86	2.1×10^3	16
3	17.2	0.688	1.72	1.2×10^3	9
4	17.2	0.688	2.58	8.1×10^2	6
5	17.2	0.688	3.44	6.3×10^2	5

[a] Initiator: 2,2′-azobis(isobutyronitrile) (AIBN). Transfer agent: 2-mercaptoethanol. DMF solution, 60 °C, and 15 h. [b] Number-average molecular weight determined by GPC (PEO standard). [c] Average number of hydroxyl groups per molecule, which was calculated from M_n.

and 8.3 Hz), 7.39 (doublet, $J = 8.3$ Hz), and 7.62 (doublet, $J = 9.3$ Hz).

Synthesis of Coumarin End-Capped Poly(ε-caprolactone-*co*-trimethylene carbonate) (Poly(CL/TMC)). Tetrabranched poly(CL/TMC) end-capped with coumarin was prepared according to a previously described method.[4] Coumarin content = 7.90×10^{-4} mol/g. Molecular weight (determined based on coumarin content) = 5100.

Determination of the Coumarin Content of the Copolymers. The UV spectrum was recorded for a solution with coumarin end-capped copolymer dissolved in 1,4-dioxane. The coumarin content of grafted copolymer (number of coumarin per weight) was determined using an ϵ_{max} of 1.35×10^4 (318 nm). The molecular weight of grafted copolymer was calculated from multiplying the inverse of coumarin content with number of graft chain per molecule which is determined from the GPC measurement (Table 1).

Photocuring Characteristics. Coumarin end-capped copolymer, coated on a cover glass, was irradiated by a UV light. After immersion into dichloromethane, the weight of insoluble copolymer was determined. The photocuring yield was expressed as the weight percentage of the insoluble part (W_g) against that of the coated copolymer (W): $W_g/W \times 100$.

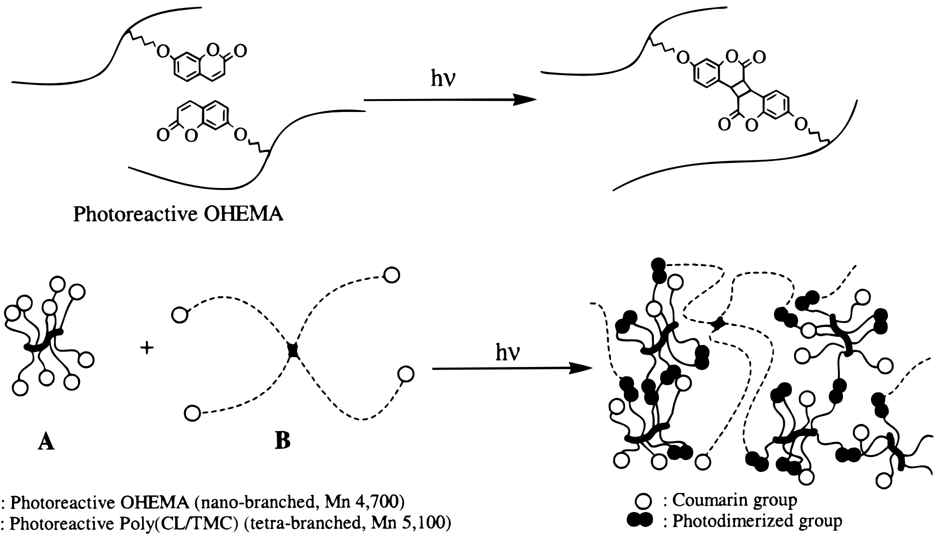
Results and Discussion

The synthetic strategy for the preparation of multifunctional photoreactive liquid oligomers is as follows (Scheme 1). At first, an oligomer of hydroxyethyl methacrylate (OHEMA) was prepared by radical polymerization in the presence of a chain transfer agent. Then, using OHEMA as a polyfunctional initiator, a ring-opening polyaddition reaction with CL, TMC, or a mixture of the two, initiated from hydroxyl groups of side chains of OHEMA, was carried out to produce OHEMAs with biodegradable pendant copolymers. Finally, these derivatized OHEMAs were further derivatized to have coumarin group at the ends of the pendant groups.

Table 1 lists the oligomerization conditions and average molecular weights of the oligomers produced using AIBN as a radical initiator and 2-mercaptoethanol as a transfer agent. As shown in Table 1, increase in the feed molar ratio of transfer agent to monomer decreased the average molecular weight of the produced oligomer. The transfer agent used effectively functioned to reduce the molecular weight. The molecular weights of the OHEMAs thus obtained were of the order of several hundreds to a few thousands. This indicates that these OHEMAs may have 5−21 hydroxyl groups per molecule.

The second step of the molecular architecture as mentioned above is summarized as follows. The molecular weights of the OHEMAs used for the second step, which contained 6 and 9 hydroxyl groups per molecule, were approximately 800 and 1200, respectively. As listed in Table 2, when TMC or an equimolar mixture of TMC and CL was used, the synthesized materials

Scheme 2. Photo-Cross-Linking via Photodimerization of a Pair of Coumarin Groups (Upper) and Photopolymerization of the Mixture of Coumarinated OHEMA and Poly(CL/TMC) (Lower)



were solid at room temperature. On the other hand, when a few CL units were derivatized on side chains, viscous liquids were formed. Although we did not determine the number of hydroxyl groups per molecule, OHEMAs derivatized with CL could have the same number of hydroxyl groups as that in nontreated OHEMAs, according to Scheme 1, since the growing chain end of poly(CL) always contains hydroxyl group. Our previous study showed that end-capping of the terminal hydroxyl groups of multibranched copolymers composed of CL and TMC with coumarin acid chloride resulted in complete coumarination under appropriate conditions.[4] The reaction of coumarin acid chloride with OHEMA (M_n 3200) resulted in full end-capping of the terminal hydroxyl groups with coumarin groups, which was determined according to a previously reported method by UV analysis. The resultant polymer (M_n 4700), which contained nine coumarin groups derivatized at the terminal ends of each side chains, was a viscous liquid.

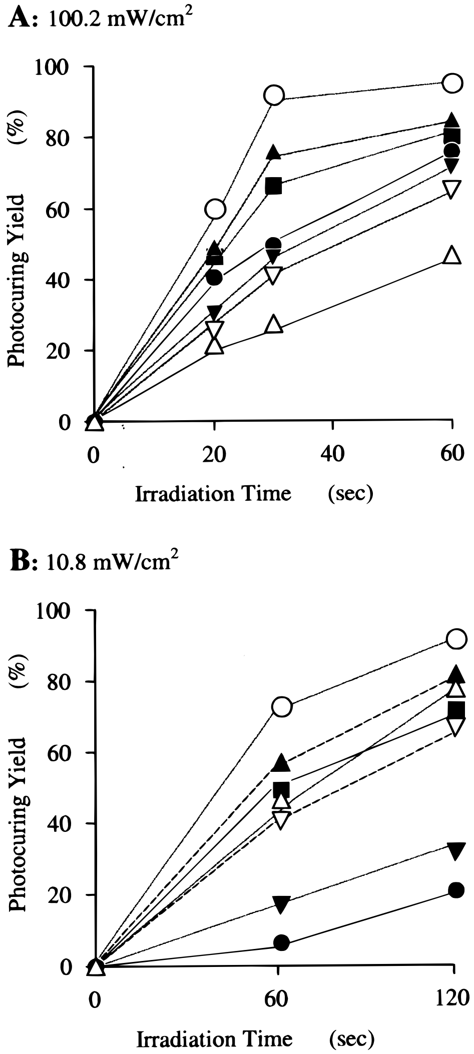


Figure 1. Photocuring yield of coumarinated OHEMA mixed with coumarinated poly(CL/TMC) at the UV intensity of 100 mW/cm^2 (A) and 10.8 mW/cm^2 (B). The feed ratios of coumarinated OHEMA and poly(CL/TMC) were 1.00:0.00 (△), 0.90:0.10 (■), 0.80:0.20 (○), 0.70:0.30 (▲), 0.50:0.50 (▽), 0.25:0.75 (▼), and 0.00:1.00 (●). Film thickness: 0.03 mm.

Thin liquid films (thickness: 0.03 mm) cast on cover glasses were subjected to UV irradiation. The gel yield, which was determined by measuring the weight of the insoluble residue in the organic solvent, increased with irradiation time. This photocuring is due to dimerization as shown in Scheme 2. The photocuring characteristics of these multifunctionally coumarinated copolymers were compared with those of tetrafunctional coumarinated copolymers composed of CL and TMC in the molar ratio 1:1 (poly(CL/TMC)) which were prepared in our previous study.[4] Figure 1 shows the time-dependent photocuring characteristics of coumarinated OHEMA, coumarinated poly(CL/TMC) (M_n 5100), and a mixture of the two under UV light irradiation at high (100.2 mW/cm^2) and low (10.8 mW/cm^2) UV intensities. Photocuring extent increases with intensity of UV light and longer irradiation time, regardless of the type of coumarinated oligomers or their mixture ratios. Figure 2 shows the photocuring characteristics of coumarinated oligomers and mixtures containing the two at both low and high UV intensities for 1 min irradiation. The maximum photocuring appears to occur at the composition of around 80 wt % of coumarinated OHEMA and 20 wt % of poly(CL/TMC), irrespective of the UV intensity. At low UV intensities, photocuring of coumarinated poly(CL/TMC) was very poor, but at high UV intensities, significantly more pronounced photocuring was observed. On the contrary, there was little appreciable

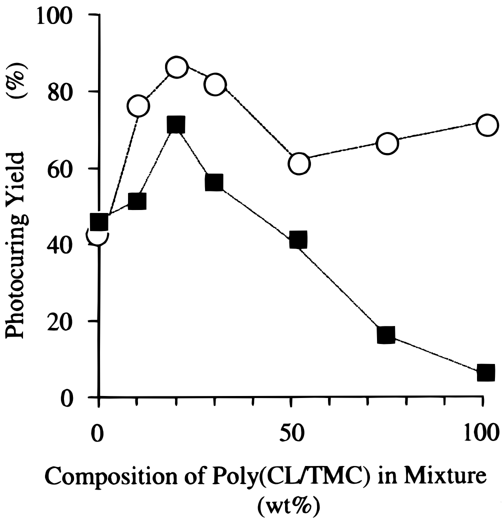


Figure 2. Photocuring yield of coumarinated OHEMA mixed with coumarinated poly(CL/TMC) as a function of the content of poly(CL/TMC) after UV light irradiation for 1 min. UV intensity: 10.8 mW/cm^2 (■) and 100.2 mW/cm^2 (○). Film thickness: 0.03 mm.

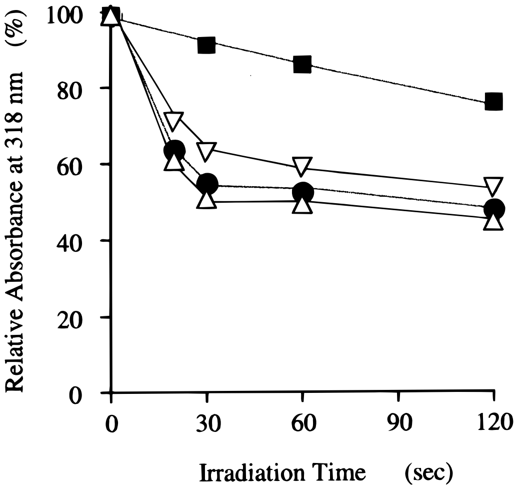


Figure 3. Time-dependent changes in absorbance at 318 nm of coumarinated OHEMA (▽) and poly(CL/TMC) (■) films at the UV intensity of 10.8 mW/cm^2 and OHEMA (△) and poly(CL/TMC) (●) films of 100.2 mW/cm^2. Film thickness was adjusted to obtain the same absorbance (<1.0 μm).

photointensity dependence of photocuring for the case of coumarinated OHEMA. To study these differences in the photointensity response between coumarinated OHEMA and poly(CL/TMC), the time-dependent changes of the UV absorption intensity of the thin liquid films, which were cast in a UV vessel, were measured at high and low UV intensities. The UV absorption intensity at 318 nm (attributed to coumarin groups) decreased with time, irrespective of the UV intensity or the type of coumarinated substance. The dependence of photodimerization on UV intensity was much stronger for coumarinated poly(CL/TMC) than that for coumarinated OHEMA, the photodimerization rate of which appears to exhibit little UV intensity dependence. These results indicate that the differences in photocuring dependence on UV intensity between coumarinated OHEMA and poly(CL/TMC), as are evident in Figure 3, may be partly attributable to the different aggregation state of coumarin groups in the liquid films as well as different macroscopic and microscopic viscosities of the films.

In conclusion, multifunctionally coumarinated liquid prepolymers based on oligo(2-hydroxylethyl methacrylate) derivatized with oligomers of ε-caprolactone were prepared. UV irradiation resulted in the production of cross-linked solid copolymers. This photoinduced liquid-to-solid conversion is expected to be useful for biomaterial applications.

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