Chemoselective Polymerization of a Phenol Derivative Having a Methacryl Group by Peroxidase Catalyst

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There has been much interest in polymerizations catalyzed by enzymes ("enzymatic polymerizations") as new methodology of polymer syntheses.[1−3] Chemical synthesis of cellulose was first achieved by cellulase-catalyzed polycondensation of β-cellobiosyl fluoride in an aqueous acetonitrile.[4] Other polysaccharides, e.g., maltooligosaccharide, xylan, and chitin, were synthesized from designed unnatural monomers by using hydrolase catalyst via a nonbiosynthetic pathway.[1,5] Lipase catalysis induced enantioselective polymerization of an epoxide-containing diester with glycol monomers as well as the ring-opening polymerization of lactones of various ring-sizes and six-membered cyclic carbonate.[1,6] Regioselective polymerization of sucrose with an activated diester was achieved by using protease catalyst.[7]

Typical conventional polymers using phenolic compounds as monomer are phenol−formaldehyde resin[8] and poly(1,4-phenylene oxide).[9] These polymers are widely used in various fields. However, there are several concerns for them: the former involves use of toxic formaldehyde for its production, and in the latter case, the polymer is obtained from only 2,6-disubstituted phenols. After Klibanov reported that the peroxidase-catalyzed polymerization of *p*-phenylphenol proceeded in an aqueous organic solvent to produce a new class of polyphenol,[10] enzymatic oxidative polymerization of phenol derivatives has been extensively investigated.[3,11] Peroxidase and laccase were often used as catalysts. This process has several features, compared with the conventional methods: polymers are conveniently obtained under mild reaction conditions without use of formaldehyde; various phenol derivatives polymerize to a new class of polyphenols, most of which are difficult to be synthesized by conventional polymerizations; the resulting polymers have relatively high thermal stability.

Chemoselective polymerizations of monomers having more than two polymerizable groups are expected to afford a new class of highly reactive polymers having a polymerizable group in the side chain. In case of such monomers having an unsaturated polymerizable group, however, it is often difficult to achieve the chemoselective polymerization involving no reaction of the unsaturated groups because of their high reactivity toward various polymerization catalysts. For example, in the oxidative polymerization of a thiophene derivative including a methacryl group using ferric chloride catalyst, vinyl polymerization also took place.[12]

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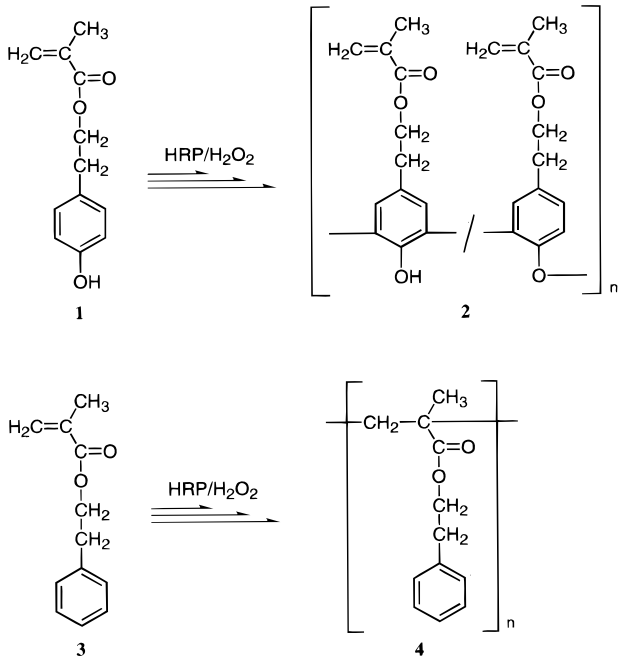
Scheme 1



1 2 3 4

It was reported that peroxidase mediates polymerization of vinyl monomers.[13] (Meth)acrylic monomers polymerized in the presence of peroxidase and hydrogen peroxide. The present study deals with peroxidase-catalyzed polymerization of 2-(4-hydroxyphenyl)ethyl methacrylate (**1**).[14] **1** possesses two functional groups, methacryl and phenolic groups, which are known to be reacted through peroxidase catalysis. We have found that the phenolic moiety of **1** was chemoselectively polymerized by using horseradish peroxidase (HRP) as catalyst to give the polymer having methacryl group in the side chain (Scheme 1). This is the first example of chemoselective polymerization with enzyme catalysis.

The HRP-catalyzed polymerization of **1** was carried out using hydrogen peroxide as oxidizing agent in acetone/acetate buffer (pH 7) (50:50 vol %) at room temperature under air for 24 h.[15] During the polymerization, powdery materials were formed. The isolated yield was 77%. The polymer was soluble in acetone, chloroform, *N*,*N*-dimethylformamide, and dimethyl sulfoxide (DMSO) and insoluble in water, methanol, diethyl ether, and hexane. The molecular weight and polydispersity were determined by size exclusion chromatography to be 1400 and 1.7, respectively.

The polymer structure was confirmed by ^{1}H NMR spectroscopy. Figure 1 shows ^{1}H NMR spectra of monomer **1** and polymer **2**. Assignment of monomer peaks is shown in Figure 1A. The pattern of the peaks of **2** was similar to that of **1**, although all the peaks became broader. The ratios of the integrated area of peaks B, C, and F due to protons of methacryl group toward peak D ascribed to β-methylene protons of phenyl group were 0.5, 0.5, and 1.5, respectively, indicating that the methacryl group did not react during the polymerization.

In most cases, the structures of the enzymatically obtained polyphenols were complicated;[1,11] we have reported that the polymer from phenol was mainly

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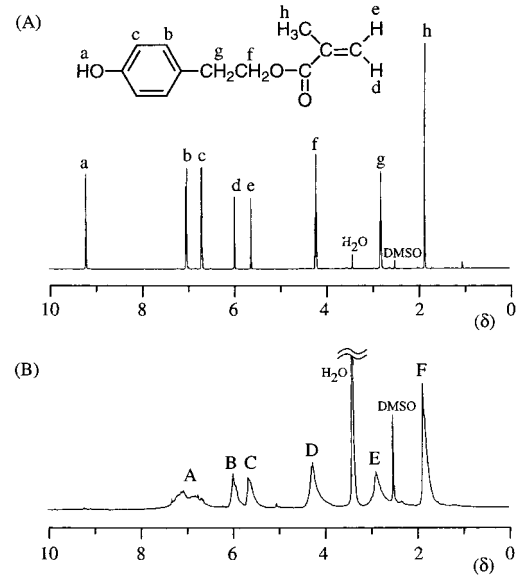

Figure 1. ^{1}H NMR spectra of (A) monomer **1** and (B) polymer **2** in DMSO-d_6.

composed of a mixture of phenylene and oxyphenylene units.[11a] The integrated area between peak A due to the aromatic protons and peak D was 53:47, implying that polymer **2** was also of a mixture of phenylene and oxyphenylene units (70:30).

Next, radical polymerization of **1** was investigated. The polymerization was carried out by using AIBN initiator (2 wt % for **1**) in THF at 70 °C for 14 h. 80% of the monomer was consumed, and the molecular weight of the resulting polymer was 3.5×10^4. ^{1}H NMR analysis showed that the vinyl polymerization of the methacrylate ester of **1** took place by AIBN.

As described above, the phenolic moiety of **1** was subjected to HRP-catalyzed oxidative polymerization, without involving the vinyl polymerization of the methacryl group. To confirm that the present polymerization proceeded chemoselectively with enzyme catalysis, the HRP-catalyzed polymerization of 2-phenylethyl methacrylate (**3**) was carried out. HRP afforded poly(methacrylate) (**4**) in 43% yield under the similar reaction conditions. A trace of **1** or **3** (less than 5%) was polymerized in the vinyl polymerization fashion without the enzyme. From these results, it is obvious that HRP could catalyze the vinyl polymerization of a methacrylate ester such as **3**; however, in the case of **1** the phenolic moiety was chemoselectively polymerized by HRP catalyst. This may be because HRP had a larger catalytic activity for oxidative polymerization than for vinyl polymerization.

The thermal properties of **2** was evaluated by differential scanning calorimetry (DSC) and thermogravimetry (TG). Figure 2 shows DSC traces of **2**, measured under nitrogen. In the first scan, a large exothermic peak was observed at 100 °C, whereas there was no peak in the second scan below 300 °C. The product after the first scan was insoluble in organic solvents. The IR spectrum of the cross-linked material was very close to that of **2**, suggesting that a small amount of the methacryl group in **2** was subjected to the hardening. In case of the enzymatically obtained polymer from phenol, the exothermic peak was detected at higher temperature (238 °C) in the first scan.[11c] These results indicate that the present polymer was thermally cured at a relatively low temperature. The decrease of the

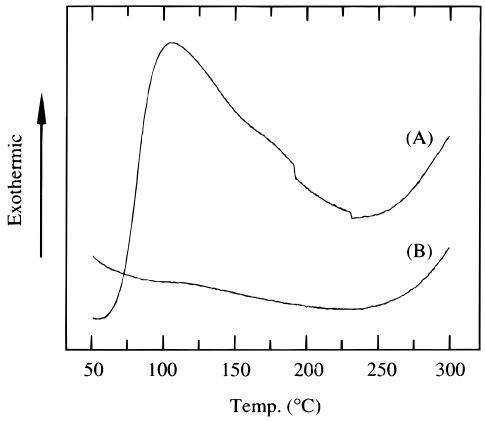

Figure 2. DSC traces of **2**: (A) first scan; (B) second scan. The measurement was carried out at a heating rate of 10 °C/min under nitrogen.

curing temperature is probably due to the thermal reaction of the methacryl group of **2**. The polymer was found to be stable at 330 °C by TG analysis under nitrogen.

In conclusion, the phenolic moiety was chemoselectively reacted in the HRP-catalyzed polymerization of **1** in an aqueous acetone. The polymer was thermally cross-linked at a relatively low temperature. The resulting polymer possessed a methacryl group in the side chain and, hence, is expected to have various applications as a highly reactive polymer. For example, the polymer was subjected to the photochemical hardening, suggesting the possibility to use **2** as a new photoresistant material. Further investigations on the polymerization behavior of **1** and applications of **2** are under progress in our laboratory.

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(15) The following is a procedure for the polymerization. **1** (0.41 g, 2.0 mmol) and HRP (4 mg) was dissolved in a mixture of acetone (5.0 mL) and phosphate buffer (5.0 mL). The polymerization was started by the addition of 30% hydrogen peroxide (23 μL, 0.20 mmol). The same amount of hydrogen peroxide was added every 15 min for 9 times. The reaction mixture was vigorously stirred under air at room temperature. After 24 h, the polymer was isolated by centrifugation. The residue was dried in vacuo to give 0.32 g of the polymer (yield 77%).

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