Peroxidase-Catalyzed Oxidative Polymerization of 4,4′-Dihydroxydiphenyl Ether. Formation of α,ω-Hydroxyoligo(1,4-phenylene oxide) through an Unusual Reaction Pathway

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Introduction

Recently, enzymatic polymerizations have been paid much attention as new methods of polymer synthesis.[1] Enzymatic polymerization of phenols[2] is an environmentally benign production process of formaldehyde-free polyphenols with biodegradability[3] under mild reaction conditions; on the other hand, traditional phenolic resins are synthesized using toxic formaldehyde as comonomer under acidic or basic conditions.[4] The polyphenols enzymatically obtained have structures normally of a mixture of phenylene and oxyphenylene units, which are formed by C−C and C−O couplings of phenols. Recent investigations revealed that the coupling selectivity (regioselectivity) could be controlled by changing the solvent composition, yielding a DMF-soluble polyphenol.[5]

Poly(2,6-dimethyl-1,4-phenylene oxide) (PPO) was first synthesized by an oxidative polymerization of 2,6-dimethylphenol using a copper/amine catalyst.[6] Blends of PPO and polystyrene are widely used as engineering plastics in industrial fields.[7] PPO derivatives were also enzymatically prepared from 2,6-dimethylphenol[8] and 3,5-dimethoxy-4-hydroxybenzoic acid (syringic acid).[9] In the latter monomer, carbon dioxide and hydrogen as product water were eliminated from the monomer during the oxidative polymerization. We have achieved regioselective synthesis of crystalline unsubstituted PPO by an oxidative polymerization of 4-phenoxyphenol using a tyrosinase model complex as catalyst.[10] This complex also induced the regioselective polymerization of 2,5-dimethylphenol to give a PPO derivative having a melting point of more than 300 °C.[11] Furthermore, an iron−salen complex induced the oxidative polymerization of 2,6-fluorophenol to give the crystalline fluorinated PPO derivative, poly(2,6-difluoro-1,4-phenylene oxide), for the first time.[12]

In the present study, we used 4,4′-dihydroxydiphenyl ether (**1**) as a new monomer for the peroxidase-catalyzed oxidative polymerization, in which α,ω-hydroxyoligo(1,4-phenylene oxide)s having degree of polymerization of 3−5 were yielded. The formation of these products involves an unusual reaction pathway.

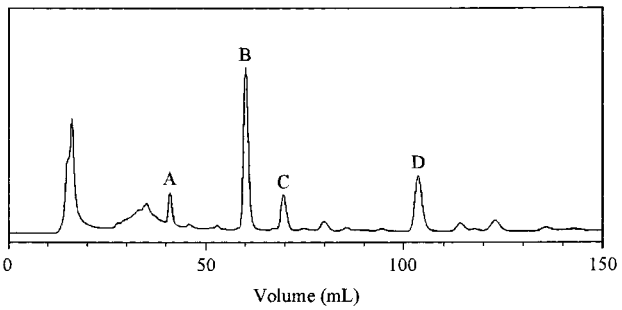

Figure 1. HPLC chart of the product enzymatically obtained from **1**.

Results and Discussion

Peroxidase-Catalyzed Polymerization of 4,4′-Dihydroxydiphenyl Ether. In this study, horseradish peroxidase (HRP) and hydrogen peroxide were used as catalyst and oxidizing agent, respectively. The HRP-catalyzed oxidative polymerization of **1** was carried out in an equivolume mixture of methanol and pH 7 phosphate buffer for 3 h under air. During the reaction, powdery materials were precipitated. After the reaction, the precipitates were collected by centrifugation to give the product (83% yield). The product was soluble in polar organic solvents such as acetone, acetonitrile, *N*,*N*-dimethylformamide, dimethyl sulfoxide, and methanol, and insoluble in chloroform, hexane, toluene, and water.

High-pressure liquid chromatography (HPLC) analysis of the product was performed using an inverse-phase silica gel column with acetonitrile/water (70:30 vol %) eluent. In HPLC chart of the reaction mixture, several peaks were observed (Figure 1). Main fractions A−D were separated by using preparative HPLC column, and their structure was analyzed by NMR spectroscopy. The yields of fractions A−D were 11, 25, 6, and 10%, respectively. The separation and analysis of other fractions have been examined; however, the isolation and/or structural characterization of the pure compounds have not been achieved. Beyond the elution volume larger than 150 mL, no clear peaks were detected.

Figure 2 shows the ^{1}H−^{1}H COSY NMR spectrum of fraction B. Two sets of cross-peaks (δ 6.76−6.87 and 6.91−6.97) were observed. Integrated areas of four peaks were very close to each other. The mass value determined by fast atom bombardment mass (FAB-MS) measurement was 386. From these data, fraction B was identified as 1,4-oxyphenylene tetramer having a phenolic hydroxy group at both ends (Chart 1). NMR and FAB-MS analysis showed that fractions A and D were trimer and pentamer of oligo(1,4-oxyphenylene), respectively.

The mass value of fraction C was 586, indicating the hexamer of phenol. In the ^{1}H−^{1}H COSY NMR spectrum, a doublet peak at δ 6.62 was due to a proton coupled only with m-substituted proton, indicating that 1,2,4-trisubstituted benzene unit was contained in the oligomer. Peaks at δ 6.71 and 6.98 were ascribed to other two protons of the 1,2,4-trisubstituted unit from analysis

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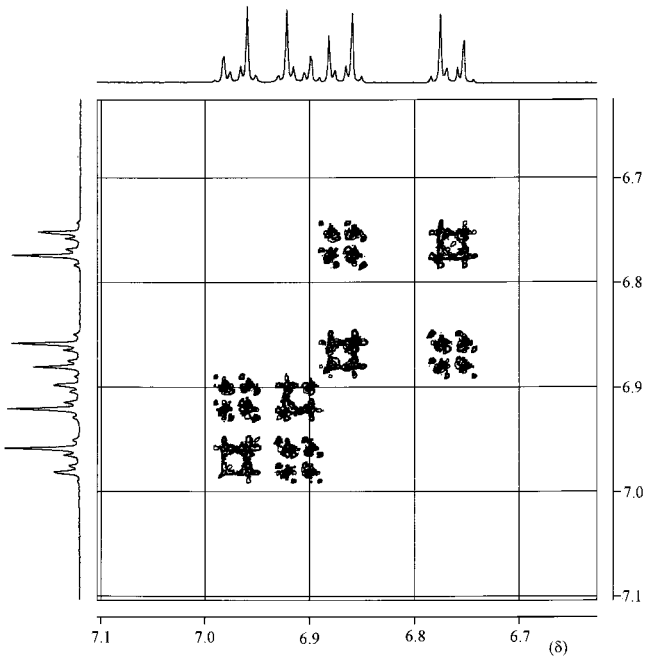


Figure 2. $^1H-^1H$ COSY NMR spectrum of fraction B.

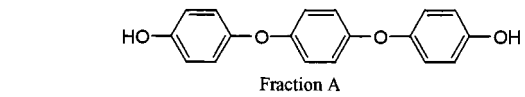
of the cross-peaks. NMR data of other peaks suggest the exclusive formation of the symmetric 1,4-oxyphenylene units except the trisubstituted unit. These data indicate that fraction C is the hexamer consisting of five 1,4-oxyphenylene units and one 1,2,4-trioxysubstituted unit as shown in Chart 2. The position of the 1,2,4-oxyphenylene unit in the hexamer of phenol could not be determined by NMR analysis.

Mechanism of Oligo(1,4-phenylene oxide) Formation. So far, the reaction mechanism on the oxidative polymerization of 2,6-dimethylphenol to PPO has been extensively investigated;[13] the quinone−ketal redistribution and rearrangement are involved for the formation of the polymer with a 1,4-oxyphenylene unit. Recent computational investigation on the PPO formation by the copper/amine catalyst shows that the quinone−ketal intermediate formation preferentially takes place via an ionic coupling.[14] However, the enzymatic oxidative polymerization, where only free radical species are exclusively involved as intermediate, produced PPO,[8] suggesting that the quinone−ketal intermediate is also derived by the free radical coupling.

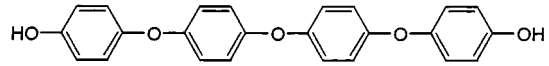
Based on the above results, the formation mechanism of 1,4-oxyphenylene trimer from **1** is proposed as follows (Scheme 1). First, the phenoxy radical species are formed through the HRP catalyst/hydrogen peroxide, and their coupling produces a quinone−ketal intermediate (the dimer of **1**). Similarly with the polymerization of 2,6-dimethylphenol, both redistribution and rearrangement are considered as a subsequent reaction pathway. The redistribution of the dimer produces radicals of hydroquinone and the 1,4-oxyphenylene trimer (route A). As to the rearrangement (route B), the unstable hemiketal species is formed, followed by the bond cleavage to give the same products. In the reaction mixture, hydroquinone was contained (ca. 5 wt % based on **1**), supporting the above reaction mechanism. Hydroquinone in situ formed during the polymerization might be partly subjected to the oxidative coupling.

For reference, the enzymatic polymerization of 4-phenoxyphenol was performed under the produced reaction conditions. Trimer and pentamer of the 1,4-oxyphenylene unit were not obtained, although the formation of the tetramer was observed at the initial stage of the polymerization. The tetramer formation is explained by the rearrangement of quinone−ketal and subsequent isomerization of the resulting hemiketal intermediate by hydrogen transfer onto oxygen of the hemiketal terminal (Scheme 2). No detection of the trimer means that the redistribution did not take place. As for the oxidative coupling of **1**, on the other hand, the hemiketal intermediate cannot be susceptible to the isomerization (transfer of OH group), resulting in the bond cleavage to the two radical species.

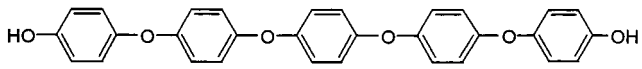
Chart 1



Fraction A

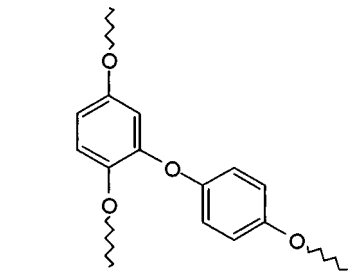


Fraction B



Fraction D

Chart 2



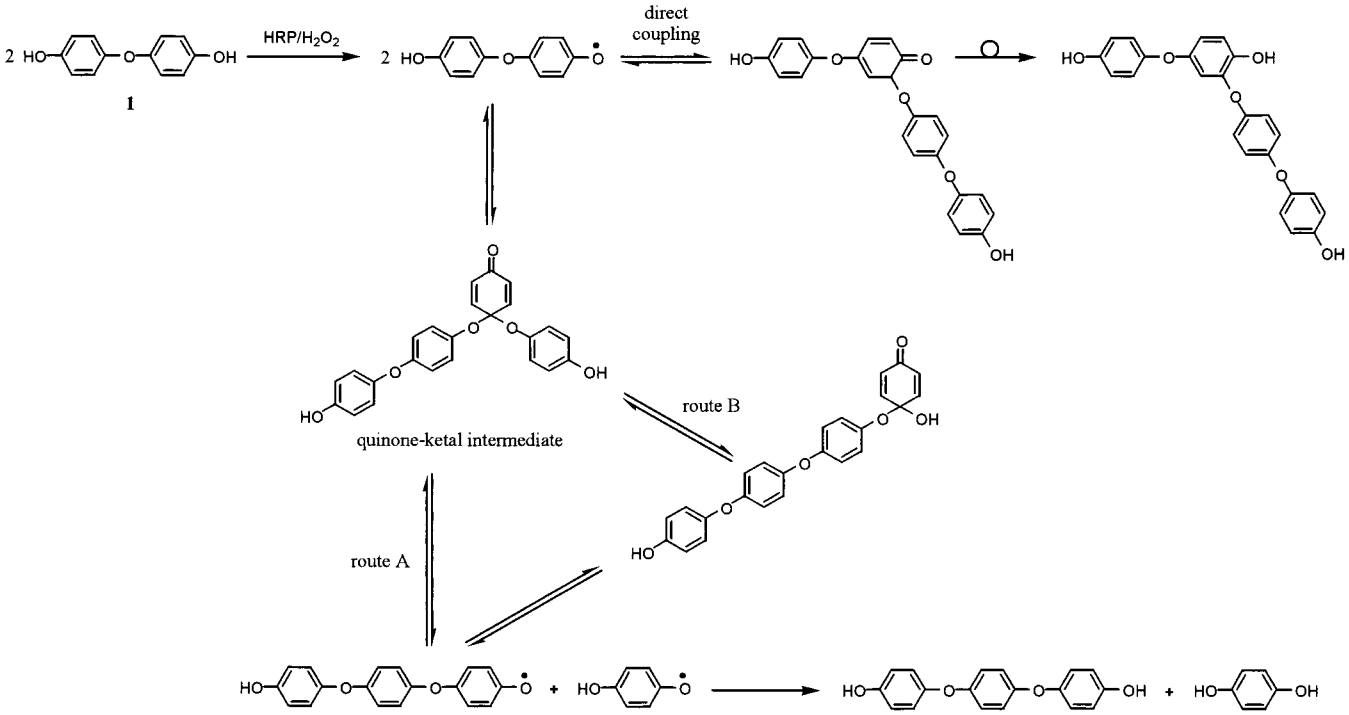
: Oligo(1,4-oxyphenylene) or H

The formation of the hexamer containing a branched structure from **1** indicates that a direct free radical coupling involving no quinone−ketal intermediate also took place during the reaction. The remaining OH content of the reaction mixture (before the purification) was determined by the titration with acetic anhydride/pyridine. The OH value (257 mg value of KOH required for neutralization of 1.0 g substrate) was much smaller than that of **1** (554). These data support that the HRP-catalyzed polymerization of **1** proceeded through the unique reaction pathways as well as the direct radical coupling.

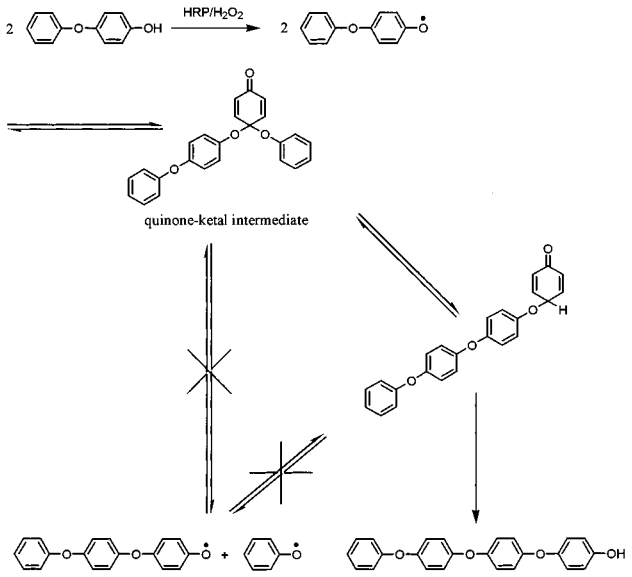
Conclusion

We have first demonstrated that, in the HRP-catalyzed oxidative polymerization of 4,4′-dihydroxydiphenyl ether in an aqueous methanol, α,ω-hydroxyoligo(1,4-phenylene oxide)s were formed in moderate yields. During the reaction, hydroquinone was formed. On the basis of these data, it is proposed that the redistribution and/or rearrangement of the quinone−ketal intermediate take place to give the oligomers and hydroquinone. To our knowledge, this is the first example of the oxidative polymerization involving the elimination of hydroquinone. The present unique reaction pathway will provide a new insight into oxidative polymerizations for production of functional materials.

Scheme 1



Scheme 2



Experimental Section

Materials. The monomers and solvents were commercially available reagents. HRP was purchased from Wako Pure Chemical Co. and used without further purification.

Enzymatic Oxidative Polymerization of 4,4′-Dihydroxydiphenyl Ether. Under air, 4,4′-dihydroxydiphenyl ether (4.04 g, 20.0 mmol) and HRP (4.0 mg) in a mixture of 50 mL of methanol and 50 mL of 0.1 M phosphate buffer (pH 7) were placed in a 50 mL flask. Hydrogen peroxide (5% aqueous solution, 13.6 mL, 20.0 mmol) was added dropwise to the mixture for 2 h at room temperature under air. After 3 h, polymer precipitates were collected by centrifugation. The polymer was washed with an aqueous methanol (50:50 vol %), followed by drying in vacuo to give 3.37 g of the polymer (yield 83%).

Fraction A: ^{1}H NMR ($CDCl_3$) δ 6.75, 6.85, 6.88. ^{13}C NMR ($CDCl_3$) δ 117.0, 119.6, 121.1, 149.6, 153.2.

Fraction B: ^{13}C NMR ($CDCl_3$) δ 117.1, 119.5, 120.6, 121.3, 149.4, 152.9, 154.5, 154.7.

Fraction D: ^{1}H NMR ($CDCl_3$) δ 6.76, 6.87, 6.92, 6.99, 7.00. ^{13}C NMR ($CDCl_3$) δ 117.1, 119.5, 120.5, 120.8, 121.3, 149.3, 152.3, 153.6, 154.5, 154.8.

Measurements. SEC analysis was carried out using a TOSOH SC8010 apparatus with a refractive index (RI) detector at 40 °C under the following conditions: TSKgel G3000H_{HR} column and THF eluent at a flow rate of 1.0 mL/min. The calibration curves for SEC analysis were obtained using polystyrene standards. HPLC analysis was performed using a TOSOH LC8020 system equipped with RI and UV detectors under the following conditions: TSKgel ODS-80Ts column and acetonitrile/water (70/30 vol %) eluent at a flow rate of 0.5 mL/min. NMR spectra were recorded on a Bruker DPX-400 spectrometer. FAB-MS was measured by a JEOL JMS-HX110 spectrometer with glycerol matrix.

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