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Enzyme-catalyzed polymerization to functional polymers☆

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Abstract

In this article, described are our recent advances in enzymatic polymerization, defined as chemical polymer syntheses in vitro (in test tubes) via non-biosynthetic pathways catalyzed by an isolated enzyme. The major target macromolecules formed via the enzymatic polymerizations in this article are polyesters and polyphenols. For synthesis of polyesters, hydrolases are used as catalyst; hydrolases, enzymes catalyzing a bond-cleavage reaction by water, induce the reverse reaction of hydrolysis, leading to polymer production by a bond-forming reaction. Specific enzyme catalysis provides a novel synthetic route for useful polyesters, many of which are difficult to be synthesized by conventional methodologies. Peroxidase and laccase act as catalyst for oxidative polymerization of various phenol derivatives to produce a new class of phenolic polymers without use of toxic formaldehyde under mild reaction conditions. Artificial urushi has been developed by laccase-catalyzed curing of new urushiol analogues.

Keywords: Enzymatic polymerization; Polyester; Polyphenol; Lipase; Peroxidase

1. Introduction

Enzymes have several remarkable catalytic properties such as high catalytic power and high selectivities under mild reaction conditions, as compared with those of chemical catalysts. In the field of organic synthesis, enzymes have been often employed as catalyst; functional organic compounds were synthesized by the enzymatic selective reactions [1].

Production of all naturally occurring polymers is in vivo catalyzed by enzymes. Polymerizations catalyzed by an enzyme ("enzymatic polymerizations") have received much attention as new methodology [2–8], since in recent years structural variation of synthetic targets on polymers has begun to develop highly selective polymerizations for the increasing demands in the production of various functional polymers in material science. So far, in vitro syntheses of not only biopolymers but also non-natural synthetic polymers through the enzymatic catalysis have been achieved [2–8].

Enzymes are generally classified into six groups. Table 1 shows typical polymers produced with catalysis by respective enzymes. The target macromolecules for the enzymatic polymerization have been polysaccharides, poly(amino acid)s, polyesters, polycarbonates, polyaromatics, vinyl polymers, etc. In many cases, enzymatic polymerization enables the synthesis of polymers, which otherwise are difficult to prepare. Furthermore, enzymatic polymerization often provides an environmentally benign process,

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Table 1
Classification of enzymes and in vitro production of typical polymers catalyzed by respective enzymes

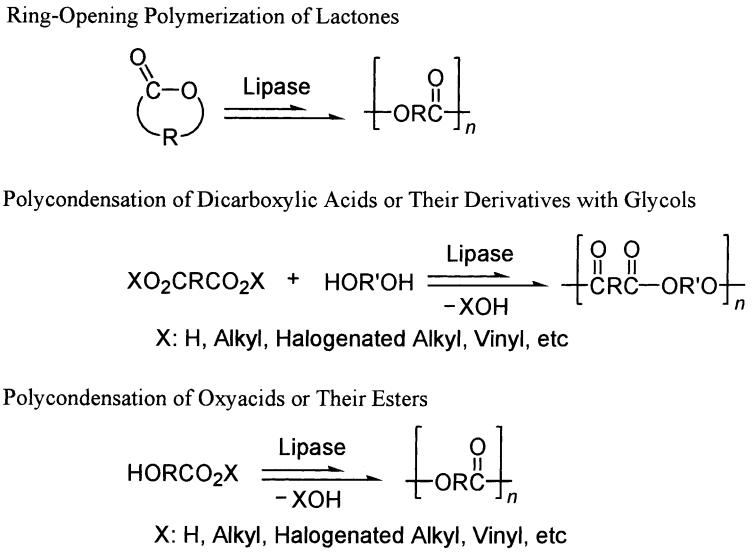
Enzymes	Typical polymers
Oxidoreductases	Polyphenols, polyanilines, vinyl polymers
Transferases	Polysaccharides, cyclic oligosaccharides polyesters
Hydrolases	Polysaccharides, polyesters, polycarbonates, poly(amino acid)s
Lyases	
Isomerases	
Ligases	

where starting materials and products are within the natural material cycle; this is in the context of "green polymer chemistry." This article deals with our recent topics on synthesis of polyesters and polyaromatics by using enzymes as catalyst. Studies on enzymatic polymerizations by other groups are referred in recent reviews [6–8].

2. Polyesters

There have been many works on syntheses of aliphatic polyesters by fermentation and chemical processes in viewpoint of biodegradable materials. Recently, lipase-catalyzed synthesis of aliphatic polyesters has been established as another approach to biodegradable polymer production. Lipase is an enzyme that catalyzes the hydrolysis of fatty acid esters normally in an aqueous environment in living systems. However, lipases are sometimes stable in organic solvents and can be used as catalyst for esterifications and transesterifications [1]. By utilizing such catalytic specificities of lipase, polyester syntheses have been achieved by various polymerization modes. Typical three reaction types of lipase-catalyzed polymerization leading to polyesters are given in Scheme 1 [6,8–11].

Various cyclic esters have been subjected to lipase-catalyzed ring-opening polymerization. Lipase catalyzed the ring-opening polymerization of 4–17-membered non-substituted lactones [9–11]. In 1993, we and Gutman's group first demonstrated that medium-size lactones, δ-valerolactone (δ-VL, 6-membered) and ε-caprolactone (ε-CL, 7-membered), were polymerized by lipases derived from *Candida cylindracea*, *Pseudomonas cepacia* (lipase PC), *Pseudomonas fluorescens* (lipase PF), and porcine pancreas [12,13], which are powdery and commercially available crude enzymes. The terminal structure of the polymer obtained in bulk was alcohol at one end and carboxylic acid at the other. In the polymerization without the enzyme or using the deactivated enzyme,



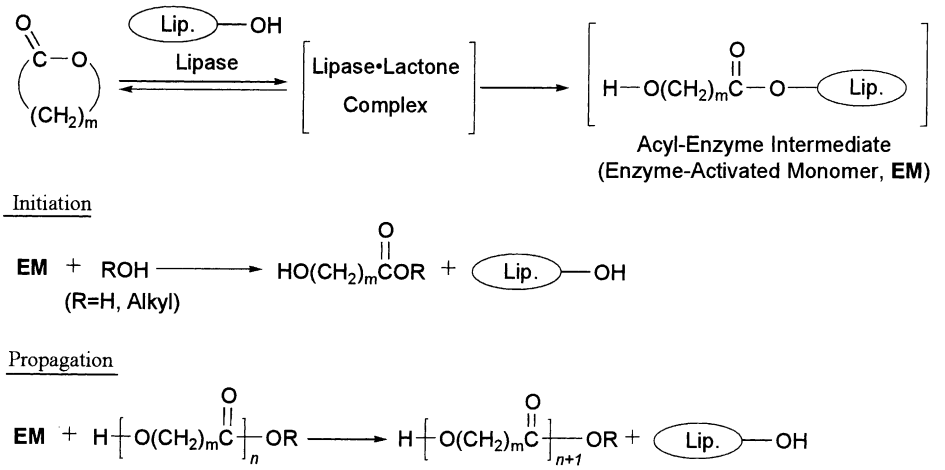
Scheme 1.

which was prepared by thermal treatment at 100 °C in water, all the monomers were recovered unreactedly, indicating that the polymerization proceeded through the lipase catalysis.

In the polymerization of lactones by these lipases, the catalyst amount was relatively large, often 20–50 wt.% for the monomers, which is due to the slow polymerization rate. We have first demonstrated efficient catalysis of *Candida antarctica* lipase immobilized on macroporous acrylic resins (lipase CA, tradename: Novozym® 435) [14]; a small amount of this enzyme (<1%) induced the polymerization of ε-CL and the polymerization rate using lipase CA was much larger than that by lipase PF under the same reaction conditions. These data clearly indicate the high catalytic activity of lipase CA. Furthermore, lipase CA could be repeatedly used for the polymerization of ε-CL. In the range of five cycles, the polymerization results hardly changed. Under appropriate reaction conditions, number-average molecular weight (M_n) of poly(ε-CL) reached more than 4×10^4 [15]. The lipase CA-catalyzed polymerization of ε-CL also took place in supercritical carbon dioxide, yielding poly(ε-CL) with relatively high molecular weight [16].

It is well known that catalytic site of lipase is a serine residue and lipase-catalyzed reactions proceed via an acyl-enzyme intermediate. The enzymatic polymerization of lactones is explained by considering the following reactions as the principal reaction course (Scheme 2) [17–19]. The key step is the reaction of lactone with lipase involving the ring-opening of the lactone to give an acyl-enzyme intermediate ("enzyme-activated monomer," EM). The initiation is a nucleophilic attack of water, which is contained partly in the enzyme, onto the acyl carbon of the intermediate to produce ω-hydroxycarboxylic acid ($n = 1$); the shortest propagating species. In the propagation stage, the intermediate is nucleophilically attacked by the terminal hydroxyl group of a propagating polymer to produce a one-unit-more elongated polymer chain. The kinetics of the polymerization showed that the rate-determining step of the over-all polymerization is the formation of the enzyme-activated monomer [20]. Thus, the polymerization probably proceeds via an "activated monomer mechanism."

Reactivity of cyclic compounds generally depends on their ring size; small and intermediate ring-size compounds possess higher ring-opening reactivity than macrocyclic lactones (macrolides) due to their larger ring strain. Table 2 summarizes dipole moment values and reactivities of lactones with different ring size. The dipole moment (indication of ring strain) of the macrolides is lower than that of ε-CL and close to that of an acyclic fatty acid ester (butyl caproate). The rate constants of the macrolides in alkaline hydrolysis and anionic polymerization are much smaller than those of ε-CL. These data clearly show that the macrolides have much lower ring strain, and hence, show less anionic reactivity and polymerizability than ε-CL.



Scheme 2.

Table 2
Dipole moments and reactivities of unsubstituted lactones

Ring size of lactone	Rate constant			Michaelis–Menten kinetics[a]		
	Dipole moment (Cm)	Alkaline hydrolysis (10^4 l mol^{-1} s^{-1})[b]	Propagation (10^3 s^{-1})[c]	$K_{m(lactone)}$ (mol l^{-1})	$V_{max(lactone)}$ (10^2 mol l^{-1} h^{-1})	$V_{max(lactone)}/K_{m(lactone)}$ (10^2 h^{-1})
6	4.22	55000	–	–	–	–
7	4.45	2550	120	0.61	0.66	1.1
12	1.86	3.3	2.2	0.58	0.78	1.4
13	1.86	6.0	15	1.1	2.3	2.1
16	1.86	6.5	–	0.80	6.5	8.1
17	–	–	–	0.63	7.2	11
Butyl caproate	1.75	8.4	–	–	–	–

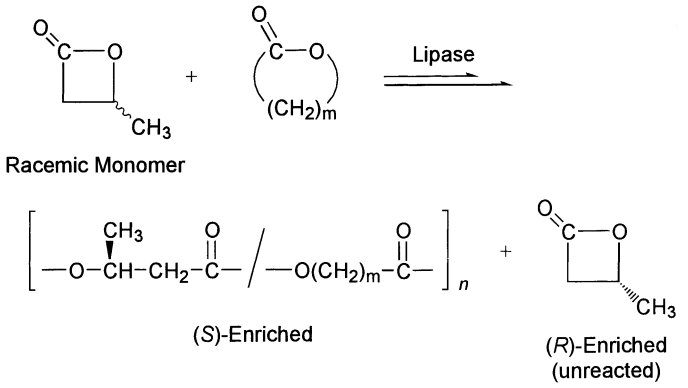
[a] Kinetics of the polymerization was carried out using lipase PF (200 mg) as catalyst in the presence of 1-octanol (0.03 mol l^{-1}) in diisopropyl ether (10 ml) at 60 °C.
[b] Alkaline: NaOH. Measured in 1,4-dioxane/water (60/40 vol.%) at 0 °C.
[c] Measured using NaOMe initiator (0.06 mol amount) in THF at 0 °C.

On the other hand, the macrolides showed unusual enzymatic reactivity. Lipase PF-catalyzed polymerization of the macrolides proceeded much faster than that of ε-CL. The lipase-catalyzed polymerizability of lactones was quantitatively evaluated by Michaelis–Menten kinetics. For all monomers, linearity was observed in the Hanes–Woolf plot, indicating that the polymerization followed Michaelis–Menten kinetics [20]. The $V_{max(lactone)}$ and $V_{max(lactone)}/K_{m(lactone)}$ values increased with the ring size of lactone, whereas the $K_{m(lactone)}$ values scarcely changed. These data imply that the enzymatic polymerizability increased as a function of the ring size, and the large enzymatic polymerizability is governed mainly by the reaction rate (V_{max}), but not to the binding abilities, i.e. the reaction process of the lipase–lactone complex to the acyl-enzyme intermediate is the key step of the polymerization [17–21].

We have first examined lipase-catalyzed ring-opening copolymerization of lactones. In the lipase PF-catalyzed copolymerization of δ-VL and ε-CL, the copolymer having random structure of both units was obtained [22]. The copolymerization of 8-octanolide with ε-CL or 12-dodecanolide (DDL, 13-membered) also produced random copolyesters [23]. The formation of the random copolymers in spite of the different enzymatic polymerizability of these lactones suggests the frequent occurrence of transesterification during the copolymerization. By utilizing this specific lipase catalysis, random ester copolymers were synthesized by the lipase-catalyzed polymerization of lactones in the presence of poly(ε-CL) [24]. Furthermore, we have first demonstrated that the intermolecular transesterification between two different aliphatic polyesters occurred via lipase catalysis [24–26]. Under the selected conditions, the random copolyesters were formed [26].

Lipase induced enantioselective ring-opening polymerization of racemic lactones. Polyesters with high optical purity were synthesized by lipase CA-catalyzed copolymerization of racemic substituted lactones with achiral unsubstituted lactones. In the lipase CA-catalyzed copolymerization of β-butyrolactone (β-BL) with DDL, (*S*)-β-BL was preferentially reacted to give the (*S*)-enriched optically active copolymer with enantiomeric excess (ee) of β-BL unit = 69% (Scheme 3) [27]. δ-CL (6-membered) was also enantioselectively copolymerized with achiral lactones by the lipase catalyst to give the (*R*)-enriched optically active polyesters reaching ee value to 76%.

Lipase PC induced the enantioselective polymerization of 3-methyl-4-oxa-6-hexanolide (MOHEL) [17]. The initial reaction rate of the *S*-isomer was seven times larger than that of the *R*-isomer, indicating that the enantioselective polymerization of MOHEL took place through lipase catalysis. (*S*)-MOHEL was also polymerized by lipase PF, whereas no polymerization of the *R*-isomer took place with lipase PF. Lipase catalysis chemoselectively induced the ring-opening polymerization of a lactone having exo-methylene group to produce a polyester having the reactive exo-methylene group in the main chain [28].



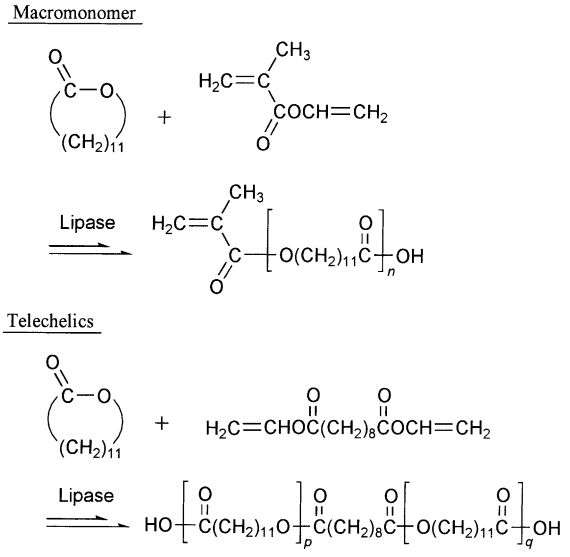
Scheme 3.

We developed a single-step, convenient production of end-functionalized polyesters by lipase-catalyzed ring-opening polymerization of lactones. As shown in Scheme 2, an alcohol could initiate the ring-opening polymerization of lactones by lipase catalyst. The lipase CA-catalyzed polymerization of DDL in the presence of 2-hydroxyethyl methacrylate gave the methacryl-type polyester macromonomer, in which 2-hydroxyethyl methacrylate acted as initiator to introduce the methacryloyl group quantitatively at the polymer terminal ("initiator method") [29]. This methodology was expanded to synthesis of ω-alkenyl- and alkynyl-type macromonomers by using 5-hexen-1-ol and 5-hexyn-1-ol as initiator.

A methacryl-type polyester macromonomer was synthesized by lipase PF-catalyzed polymerization of DDL using vinyl methacrylate as terminator ("terminator method"), in which the vinyl ester terminator was present from the beginning of the reaction (Scheme 4) [30]. In using divinyl sebacate as terminator, the telechelic polyester having a carboxylic acid group at both ends was obtained [31].

In using lipase CA as catalyst, the polycondensation of dicarboxylic acids and α,ω-glycols proceeded without organic solvents, despite the heterogeneous mixture of the monomers and catalyst (lipase and diacid: solid, glycol: solid or liquid depending on the chain length) [32,33]. The methylene chain length of monomers greatly affected the polymer yield and molecular weight. The polymer with M_n higher than 1×10^4 was obtained by the reaction under reduced pressure. A small amount of adjuvant was effective for the polymer production when both monomers were solid at the reaction temperature. This solvent-free system claimed a large potential as an environmental-friendly synthetic process of polymeric materials owing to the mild reaction conditions and no use of organic solvents and toxic catalysts.

A dehydration reaction is generally realized in non-aqueous media. Since a product water of the dehydration is in equilibrium with starting materials, a solvent water disfavors the dehydration to proceed in an aqueous medium due to the law of mass



Scheme 4.

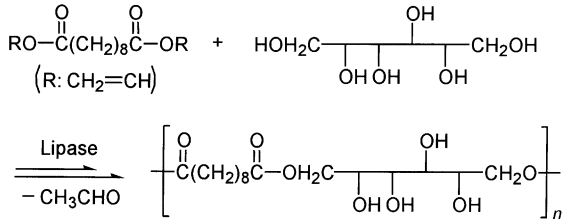
action. However, lipase catalysis achieved synthesis of aliphatic polyesters by dehydration polycondensation of dicarboxylic acids and glycols in water [34,35]. Various lipases such as lipases CA, PC and PF were active for the polymerization of sebacic acid and 1,8-octanediol. In the polymerization of α,ω-dicarboxylic acid and glycol, the polymerization behavior greatly depended on the methylene chain length of the monomers. The polymer was obtained in good yields from 1,10-decanediol, whereas no polymer formation was observed in using 1,6-hexanediol.

Transesterifications using lipase catalyst are often very slow owing to the reversible nature of the reactions. An irreversible procedure for the lipase-catalyzed acylation using vinyl esters as acylating agent has been developed, where a leaving group of vinyl alcohol tautomerizes to acetaldehyde. In these cases, the reaction with the vinyl ester proceeds much faster to produce the desired compound in higher yields, in comparison with the alkyl esters.

We have first demonstrated the high enzymatic reactivity of divinyl esters for synthesis of polyesters. The polymerization of divinyl adipate and 1,4-butanediol proceeded in the presence of lipase PF at 45 °C [36]. Under the similar reaction conditions, adipic acid and diethyl adipate did not afford the polymeric materials, indicating the high polymerizability of vinyl esters toward lipase catalyst. A combination of divinyl adipate, 1,4-butanediol, and lipase PC afforded the polymer with M_n of 2.1×10^4 [37]. Vinyl ester of 12-hydroxydodecanoic acid was also enzymatically polymerized to give the corresponding polyester [38].

Lipase-catalyzed copolymerization of lactones, divinyl esters, and glycols produced ester copolymers with M_n higher than 1×10^4 [39]. Lipases CA and PC showed high catalytic activity for this copolymerization. ^{13}C NMR analysis showed that the resulting product was not a mixture of homopolymers, but a copolymer derived from the monomers, indicating that two different modes of polymerization, ring-opening polymerization and polycondensation, simultaneously take place through enzyme catalysis in one-pot to produce ester copolymers.

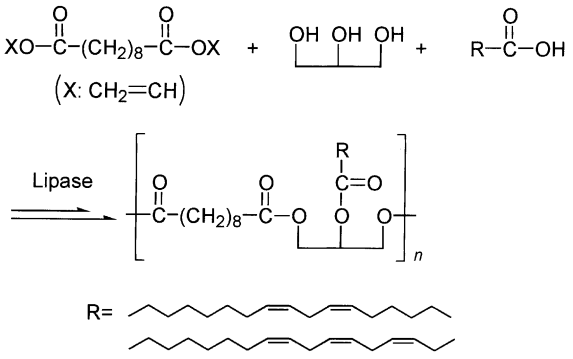
Polymerization of divinyl esters and triols regioselectively proceeded via lipase catalysis to give the soluble polymers with relatively high molecular weight. NMR analysis of the polymer obtained from divinyl sebacate and glycerol using lipase CA catalyst



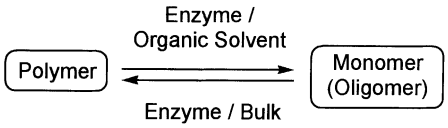
Scheme 5.

at 60 °C showed that 1,3-diglyceride was a main unit and a small amount of the branching unit (triglyceride) was contained [40]. The regioselectivity of the acylation between primary and secondary hydroxy groups was 74:26. In the polymerization at 45 °C, the regioselectivity was perfectly controlled to give a linear polymer consisting exclusively of 1,3-glyceride unit [41]. Lipase CA produced the sugar-containing polyesters regioselectively from divinyl sebacate and sorbitol, in which sorbitol was regioselectively acylated at the 1 and 6 positions (Scheme 5) [42]. Mannitol and meso-erythritol were also regioselectively polymerized with divinyl sebacate.

New cross-linkable polyesters were synthesized by lipase-catalyzed polymerization of divinyl sebacate and glycerol in the presence of unsaturated higher fatty acids derived from renewable plant oils (Scheme 6) [43]. Single-step synthesis of the cross-linkable polyester having the unsaturated group in the side chain was achieved by using lipase CA as catalyst. The polymerization under reduced pressure improved the polymer yield and molecular weight. The curing of the polymer obtained using linoleic or linolenic



Scheme 6.



Scheme 7.

acid proceeded by cobalt naphthenate catalyst or thermal treatment to give a cross-linked transparent film.

Aliphatic polyesters from lactones were subjected to hydrolytic degradation by lipase catalyst in organic solvents [44]. The lipase CA-catalyzed degradation of poly(ε-CL) with molecular weight of 4×10^4 readily took place in toluene at 60 °C to give oligomers with molecular weight <500. The degradation behavior catalyzed by lipase was quite different from an acid-catalyzed degradation (random bond cleavage of polymer). After the removal of the solvent from the reaction mixture, the residual oligomer was polymerized in the presence of the same catalyst of lipase. These data provide a basic concept that the degradation–polymerization could be controlled by presence or absence of the solvent, providing a new methodology of plastics recycling (Scheme 7). The enzymatic degradation of poly(ε-CL) also took place in supercritical carbon dioxide [45].

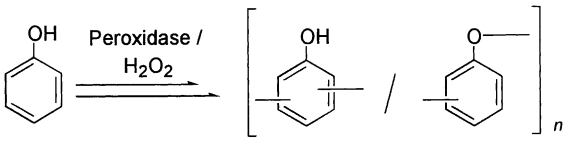
3. Polyaromatics

Phenol–formaldehyde resins using prepolymers such as novolaks and resols are widely used in industrial fields. These resins show excellent toughness and temperature-resistant properties. However, toxic nature of formaldehyde has problems in their manufacture and use. Therefore, an alternative process for preparation of phenol polymers without using formaldehyde is strongly desired.

For the last decades, enzymatic synthesis of polyphenols has been extensively investigated [46,47]. In living cells, various oxidoreductases play an important role in maintaining the metabolism of living systems. So far, several oxidoreductases, peroxidase, laccase, bilirubin oxidase, etc. have been reported to catalyze oxidation polymerization of phenol derivatives, and among them, peroxidase is most often used. Peroxidase is an enzyme whose catalysis is an oxidation of a donor to an oxidized donor by the action of hydrogen peroxide, liberating two water molecules. Horseradish peroxidase (HRP) is a single-chain β-type hemoprotein that catalyzes the decomposition of hydrogen peroxide at the expense of aromatic proton donors.

Phenol, the simplest and most important phenolic compound in industrial fields, is a multifunctional monomer for oxidative polymerization, and hence, conventional polymerization catalysts afford an insoluble product with non-controlled structure. On the other hand, the peroxidase catalysis induced the polymerization in an aqueous organic solvent to give a powdery polymer consisting of phenylene and oxyphenylene units showing relatively high thermal stability (Scheme 8) [48]. In the HRP and soybean peroxidase (SBP)-catalyzed polymerization in the aqueous 1,4-dioxane, the resulting polymer showed low solubility; the polymer was partly soluble in *N*,*N*-dimethylformamide (DMF) and dimethyl sulfoxide, insoluble in other common organic solvents. On the other hand, the aqueous methanol solvent afforded the DMF-soluble polymer with M_n of 2100–6000 in good yields [49,50]. Furthermore, the unit ratio (regioselectivity) could be controlled by changing the solvent composition to give the polymer in the range of the phenylene unit from 32 to 66%. Molecular weight control of the polyphenol was achieved by the copolymerization with 2,4-dimethylphenol [51].

The soluble polyphenols were enzymatically obtained from *m*-substituted phenols [52]. The HRP-catalyzed polymerization of *m*-cresol in an equivolume mixture of methanol and phosphate buffer (pH 7) produced the polymer with glass transition temperature (T_g) of 204 °C in a high yield, which was readily soluble in polar solvents such as methanol, acetone, DMF, and DMSO. As to *m*-alkyl substituted phenols, the enzyme origin strongly influenced the polymer yield; HRP could readily polymerize the monomer



Scheme 8.

having a small substituent, whereas in the case of large substituent monomers, the high yield was achieved by using SBP as catalyst. Bisphenol-A was polymerized by SBP catalyst to give a soluble polymer with molecular weight of several thousands [53]. Interestingly, the polymer was subjected to thermal curing at 150–200 °C.

Advantages for enzymatic synthesis of polyphenols are summarized as follows [46]: (i) the polymerization of phenols proceeds under mild reaction conditions without use of toxic reagents (environmentally benign process); (ii) phenol monomers having various substituents are polymerized to give a new class of functional polyaromatics; (iii) the structure and solubility of the polymer can be controlled by changing the reaction conditions; (iv) the procedures of the polymerization as well as the polymer isolation are very convenient.

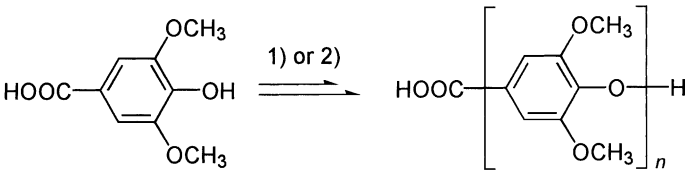
Poly(2,6-dimethyl-1,4-oxyphenylene) (poly(phenylene oxide), PPO) is widely used as high-performance engineering plastics, since the polymer has excellent chemical and physical properties, e.g. a high T_g (ca. 210 °C) and mechanically tough property. PPO was first prepared from 2,6-dimethylphenol monomer using a copper/amine catalyst system. 2,6-Dimethylphenol was also polymerized through HRP catalysis to give the polymer consisting of exclusively 1,4-oxyphenylene unit [54], on the other hand, a small amount of Mannich-base and 3,5,3′5′-tetramethyl-4,4′-diphenoquinone units are contained in the commercially available PPO. The polymerization also proceeded in the presence of laccase derived from *Pycnoporus coccineus* under air without the addition of hydrogen peroxide.

HRP, SBP, and laccase catalysis induced a new type of oxidative polymerization of 4-hydroxybenzoic acid derivatives, 3,5-dimethoxy-4-hydroxybenzoic acid (syringic acid) and 3,5-dimethyl-4-hydroxybenzoic acid. The polymerization involved elimination of carbon dioxide and hydrogen from the monomer to give PPO derivatives with molecular weight up to 1.8×10^4 (Scheme 9) [38,55,56].

We have first demonstrated that in the HRP-catalyzed oxidative polymerization of 4,4′-dihydroxydiphenyl ether in an aqueous methanol, α,ω-hydroxy-oligo(1,4-oxyphenylene)s were obtained in moderate yields [57]. During the reaction, the redistribution and/or rearrangement of the quinone-ketal intermediate take place, involving the elimination of hydroquinone to give oligo(1,4-oxyphenylene)s.

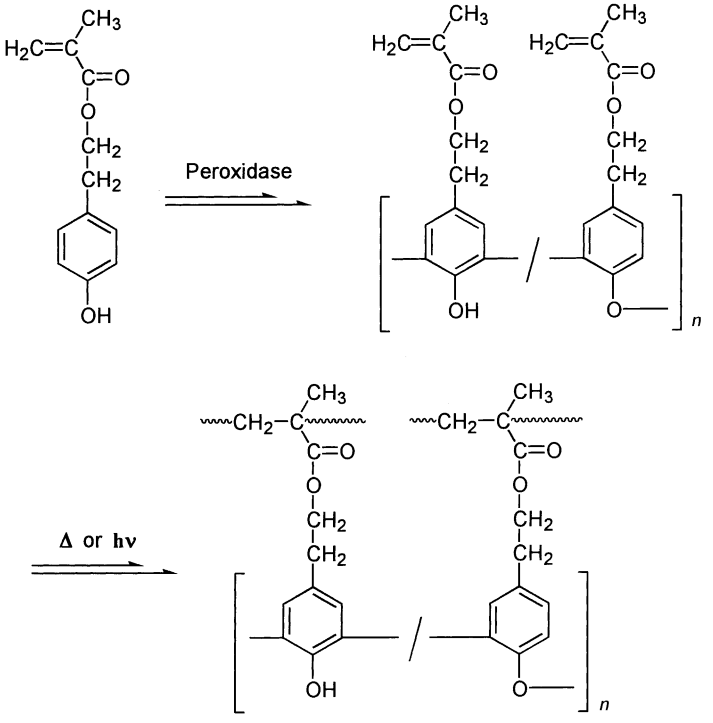
HRP catalysis induced a chemoselective polymerization of a phenol derivative having methacryloyl group [58]. Only the phenol moiety was polymerized without involving vinyl polymerization of methacryl to give a polymer having the methacryloyl group in the side chain (Scheme 10). The resulting polymer was subjected to thermal and photochemical curings. *m*-Ethynylphenol was also chemoselectively polymerized to give the polyphenol having the acetylenic group [59]. For reference, the copper/amine catalyst system induced the selective oxidative coupling of the acetylene group of the monomer to yield the dimer. Thermal treatment of the resulting polymer produced a carbonized polymer in a much higher yield than that of enzymatically synthesized poly(*m*-cresol).

Morphology of the enzymatically synthesized polyphenol was controlled under the selected reaction conditions. Monodisperse polyphenol particles in the sub-micron range were produced by HRP-catalyzed dispersion polymerization of phenol using poly(vinyl methyl ether) as stabilizer in an aqueous 1,4-dioxane [60–62]. The particle size could be controlled by



1) : Peroxidase + H_2O_2,− H_2O,− CO_2
2) : Laccase + O_2,− H_2O,− CO_2

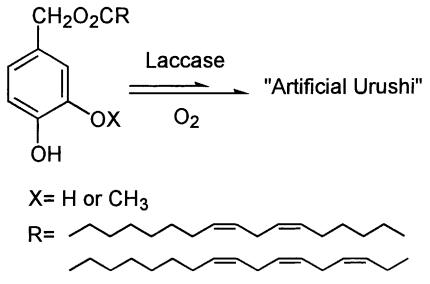
Scheme 9.



Scheme 10.

the stabilizer concentration and solvent composition. Thermal treatment of these particles afforded uniform carbon particles. The particles were also formed from *m*-cresol and *p*-phenylphenol.

A novel system of enzymatic polymerization, i.e. a laccase-catalyzed cross-linking reaction of new "urushiol analogues" for the preparation of "artificial urushi" has been demonstrated (Scheme 11) [63–66]. Single-step synthesis of the urushiol analogues was achieved by using lipase as catalyst. These compounds were cured in the presence of laccase catalyst under mild reaction conditions without use of organic solvents to produce the cross-linked polymeric film with high gloss surface and good elastic properties.



Scheme 11.

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