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Synthesis of Ultrahigh Molecular Weight Polyphenols by Oxidative Coupling

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An oxidative polymerization of phenols is an environmentally benign synthetic process of polymeric materials owing to excellent economy on atoms (normally, only water as byproduct) and mild reaction conditions with low energy input, significantly contributing to green polymer chemistry.[1,2] Poly(1,4-phenylene oxide) (PPO) is used as a high-performance engineering plastic in various fields[3] and is the only example of an industrial polymer that can be produced by the oxidative polymerization of phenols. This may be because only 2,6-disubstituted phenols afford PPOs with high molecular weight, and the polymerization of the other phenols often produces insoluble products with uncontrolled structure.[4]

In the past decade, enzymatic syntheses of polyphenols have been developed extensively.[2,5,6] Peroxidases were often used as the catalyst for the oxidative polymerization of a variety of phenol derivatives to produce a new class of polyphenols showing high thermal stability.[6] This enzymatic process is highly anticipated to be an alternative for preparing conventional phenolic resins (novolak and resol resins),[7] owing to no use of toxic formaldehyde, mild reaction conditions (in neutral solvents at room temperature), and facile procedures. The enzymatically synthesized polyphenols are normally composed of a mixture of phenylene and oxyphenylene units, whose ratio can be precisely controlled by the nature of the solvent and the monomer substituent.[8] In most of the polyphenols, however, the molecular weight is in the range of several thousands, due to precipitation of the polymer during the polymerization. These low molecular weight polymers may limit their applications for structural materials.

We have used iron *N*,*N'*-ethylenebis(salicylideneamine) (Fe-salen) as a new catalyst for the oxidative polymerization of phenols,[9] yielding high-performance polymeric materials.[10] Fe-salen can be regarded as a mimic of peroxidases. Very recently, we reported that Fe-salen catalyzed an oxidative coupling of phenol-containing poly(asparagine) and poly(glutamine) derivatives to produce a new class of poly(amino acid)s.[11] In this study, we synthesized ultrahigh molecular weight polyphenols by the oxidative coupling of the enzymatically synthesized polyphenols using Fe-salen as a catalyst (Scheme 1). Under selected conditions, the molecular weight reached 6×10^6 without formation of insoluble gels.

Enzymatically synthesized poly(*m*-cresol)[12] (**1**) with $M_n = 2.5 \times 10^3$ was first used as a starting substrate. The oxidative coupling was carried out using hydrogen peroxide as an oxidant in the presence of small amount of pyridine in *N*,*N*-dimethylformamide (DMF) at room temperature under air.[13] The molecular weight of the product polymer was estimated by size exclusion chromatography (SEC).

Scheme 1

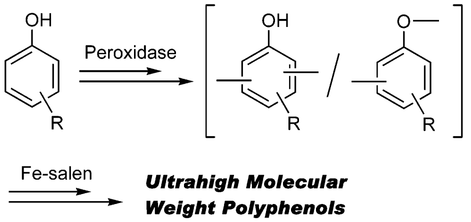

Table 1. Oxidative Coupling of Enzymatically Synthesized Polyphenols[a]

entry	substrate[b]	Fe-salen (µmol)	solvent (mL)	$M_n{}^c \times 10^{-3}$	$M_w/M_n{}^c$
1	**1** (0.5)	1.25	2.5	3.0	4.5
2	**1** (0.5)	2.5	1.25	*d*	*d*
3	**1** (0.5)	2.5	2.5	190	1.8
4	**1** (0.5)	2.5	5.0	15	3.0
5	**1** (0.5)	5.0	2.5	420	1.7
6	*m*-cresol (0.5)	5.0	2.5	17	4.3
7	**2** (0.50)	1.25	2.5	11	3.0
8	**2** (0.50)	2.5	2.5	200	1.6
9	**2** (0.50)	5.0	2.5	350	1.6
10	**2** (1.0)	5.0	2.5	*d*	*d*
11	bisphenol A (1.0)	5.0	2.5	33	9.2

[a] Oxidative coupling was performed in 0.4 vol % pyridine/DMF at room temperature under air, in which the substrate was quantitatively consumed. [b] In parentheses, phenol unit (mmol) of poly(*m*-cresol) (**1**) or poly(bisphenol A) (**2**). [c] Determined by SEC using DMF as eluent with polystyrene standards. [d] Gelation took place.

Polymers having a phenol group in the side chain were cross-linked by an oxidative coupling with Fe-salen catalyst.[11,14] To synthesize a soluble polymer without gelation, therefore, the reaction conditions were screened. Table 1 shows the effect of the amount of the substrate and catalyst in the oxidative coupling of **1**. In all cases, the precursor polymer was quantitatively consumed. The molecular weight of the product increased with decreasing solvent amount (increasing substrate concentration); however, gelation took place at higher concentrations (entry 2). The catalyst amount greatly affected the molecular weight of the product; the molecular weight increased as a function of the catalyst amount. Under selected conditions, the molecular weight reached 4.2×10^5 from **1** with molecular weight of 2.5×10^3 (entry 5). For comparison, *m*-cresol was oxidatively coupled under similar reaction conditions. The molecular weight of the polymer was much lower than that from **1** (entry 6). These data demonstrate that the molecular weight obtained by the oxidative coupling of the precursor polymer was much higher than that of the corresponding monomer. Enzymatically synthesized poly(bisphenol A)[12] (**2**) with $M_n = 3.8 \times 10^3$ was also oxidatively coupled, yielding a high molecular weight polymer under appropriate reaction conditions (entries 8 and 9). The reaction behaviors were similar to those of **1**.

Under the conditions of entry 5 in Table 1, the coupling reaction was monitored by SEC (Figure 1). The peak of **1** completely disappeared immediately after adding only a small amount of hydrogen peroxide, and a unimodal peak was newly observed at a lower elution

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Table 2. SEC-VISC-RALLS Analysis of Polyphenols Synthesized by Fe-salen Catalyzed Oxidative Coupling

sample	mol wt $M_w \times 10^{-5}$	intrinsic viscosity IV_w (dL/g)	radius R_{gw}[a] (nm)	R_{hw}[b] (nm)	Mark−Houwink−Sakurada values[c] *a*	log*K*
poly(**1**)[d]	63.9	0.199	32.0	24.6	0.344	−2.98
poly(**2**)[e]	38.2	0.166	25.7	19.7	0.389	−3.28
poly(bisphenol A)[f]	1.4	0.096	7.1	5.4	0.394	−2.99

[a] Radius of gyration. [b] Hydrodynamic radius. [c] Mark−Houwink−Sakurada equation; $[\eta] = KM^a$. [d] Sample of entry 5 in Table 1. [e] Sample of entry 9 in Table 1. [f] Sample of entry 11 in Table 1.

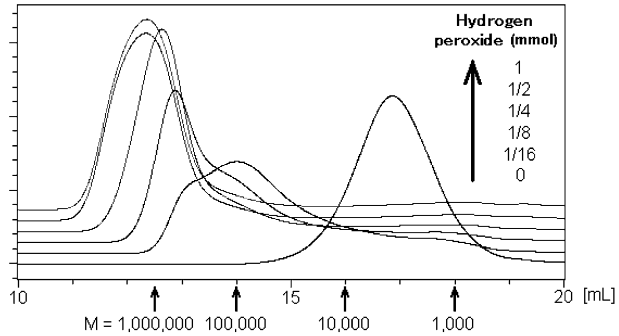

Figure 1. SEC traces of coupling products of **1** (1.0 mmol of phenol unit) under the conditions of entry 5 in Table 1.

time, indicating that the intermolecular oxidative coupling of **1** efficiently proceeded at the initial reaction stage to increase the molecular weight rapidly. With the addition of hydrogen peroxide, the molecular weight gradually increased by the intermolecular coupling of the resulting polymer.

The present high molecular weight polymers obtained by the intermolecular coupling of **1** or **2** should have a branched structure; thus, the molecular weight value determined by SEC may be underestimated. We measured the absolute molecular weight by a combination of SEC with an on-line viscometer (VISC) and a right angle laser light scattering (RALLS) detector (Table 2). For both poly(**1**) and poly(**2**), the molecular weight was very high ($M_w > 10^6$). To the best of our knowledge, this is the first example of the synthesis of phenolic polymers with ultrahigh molecular weight by an oxidative coupling; the molecular weight of the polymer obtained directly from bisphenol A was much lower than that from **2**. These data strongly indicate that using the polyphenol as a starting substrate was essential for the preparation of ultrahigh molecular weight polymers. The intrinsic viscosity, radius of gyration, and hydrodynamic radius of poly(**2**) were also larger than those synthesized directly from the monomer, supporting the formation of the higher molecular weight polymer by the oxidative coupling of **2**.

The parameters obtained by the Mark−Houwink−Sakurada equation ($[\eta] = KM^a$) are often used for the molecular conformation of polymers in solution. The *a* values of poly(**1**) and poly(**2**) were 0.344 and 0.389, respectively, which are much lower than that of a linear polymer (0.6−0.8).[15] These results strongly suggest that the resulting polyphenol with ultrahigh molecular weight has a spherical structure with densely branched three-dimensional topology in solution.

In conclusion, phenoloic polymers with ultrahigh molecular weight ($M_w > 10^6$) were prepared by an oxidative coupling of the enzymatically synthesized polyphenols for the first time. The present study clearly shows that polyfunctional macromolecules such as poly(**1**) and poly(**2**) can be polymerized to lead to exclusive production of soluble polymers with ultrahigh molecular weight, where a cross-linking is suppressed in the appropriate concentrations of the substrate and catalyst. SEC analysis showed that the intermolecular coupling of the substrate polyphenol proceeded efficiently at the initial stage of the reaction, leading to the rapid increase of molecular weight. The SEC-VISC-RALLS measurements suggest that the polymer is branched structure and its conformation in solution is compact like a sphere. Further studies, including applications of the present ultrahigh molecular weight polymers, are under way in our laboratory.

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References and Notes

(1) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 1998.
(2) (a) Kobayashi, S.; Uyama, H.; Kimura, S. *Chem. Rev.* **2001**, *101*, 3793. (b) Kobayashi, S.; Uyama, H.; Ohmae, M. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 613.
(3) Aycock, D.; Abolins, V.; White, D. M. *Encyclopedia of Polymer Science and Engineering*, 2nd ed.; John Wiley & Sons: New York, 1986; Vol. 13, pp 1−30.
(4) Hay, A. S. *J. Polym. Sci., Polym. Chem. Ed.* **1998**, *36*, 505.
(5) For reviews on enzymatic synthesis of polyphenols, see: (a) Kobayashi, S.; Shoda, S.; Uyama, H. *Adv. Polym. Sci.* **1995**, *121*, 1. (b) Kobayashi, S. *J. Polym. Sci., Polym. Chem. Ed.* **1999**, *37*, 3041. (c) Gross, R. A.; Kumar, A.; Kalra, B. *Chem. Rev.* **2001**, *101*, 2097.
(6) For recent papers on enzymatic polymerization of phenols, see: (a) Reihmann, M. H.; Ritter, H. *Macromol. Chem. Phys.* **2000**, *201*, 798. (b) Mandal, B. K.; Walsh, C. J.; Sooksimuang, T.; Behroozi, S. J. *Chem. Mater.* **2000**, *12*, 6. (c) Iwahara, K.; Honda, Y.; Watanabe, T.; Kuwahara, M. *Appl. Microbiol. Biotechnol.* **2000**, *54*, 104. (d) Reihmann, M. H.; Ritter, H. *Macromol. Biosci.* **2001**, *1*, 85. (e) Fukuoka, T.; Tachibana, Y.; Tonami, H.; Uyama, H.; Kobayashi, S. *Biomacromolecules* **2002**, *3*, 768. (f) Xu, P.; Kumar, J.; Samuelson, L.; Cholli, A. L. *Biomacromolecules* **2002**, *3*, 889. (g) Mejias, L.; Reihmann, M. H.; Sepulveda-Boza, S.; Ritter, H. *Macromol. Biosci.* **2002**, *2*, 24.
(7) Kopf, P. W. *Encyclopedia of Polymer Science and Engineering*, 2nd ed.; John Wiley & Sons: New York, 1986; Vol. 11, pp 45−95.
(8) (a) Oguchi, T.; Tawaki, S.; Uyama, H.; Kobayashi, S. *Macromol. Rapid Commun.* **1999**, *20*, 401. (b) Mita, N.; Tawaki, S.; Uyama. H.; Kobayashi, S. *Chem. Lett.* **2002**, 402. (c) Mita, N.; Tawaki, S.; Uyama. H.; Kobayashi, S. *Macromol. Biosci.* **2003**, *3*, 253.
(9) (a) Tonami, H.; Uyama, H.; Kobayashi, S.; Higashimura, H.; Oguchi, T. *J. Macromol. Sci., Pure Appl. Chem.* **1999**, *A39*, 719. (b) Tonami, H.; Uyama, H.; Oguchi, T.; Higashimura, H.; Kobayashi, S. *Polym. Bull. (Berlin)* **1999**, *42*, 125.
(10) (a) Ikeda, R.; Tanaka, H.; Uyama, H.; Kobayashi, S. *Macromolecules* **2000**, *33*, 6648. (b) Ikeda, R.; Tanaka, H.; Uyama, H.; Kobayashi, S. *Macromol. Rapid Commun.* **2000**, *21*, 496. (c) Ikeda, R.; Tanaka, H.; Uyama, H.; Kobayashi, S. *Polymer* **2002**, *43*, 3475.
(11) Fukuoka, T.; Uyama, H.; Kakuchi, T.; Kobayashi, S. *Macromol. Rapid Commun.* **2002**, *23*, 698.
(12) Poly(*m*-cresol) (**1**) was synthesized by an oxidative polymerization using horseradish peroxidase as a catalyst in an equivolume mixture of methanol and pH 7 phosphate

buffer: Tonami, H.; Uyama, H.; Kobayashi, S.; Kubota, M. *Macromol. Chem. Phys.* **1999**, *200*, 2365. The ratio of phenylene/oxyphenylene units was 63/37, determined by titration of the residual phenolic group. Poly(bisphenol A) (**2**) was synthesized similarly.[16]

(13) The following is a typical procedure for the oxidative coupling of the enzymatically synthesized polyphenol (entry 5 in Table 1). A mixture of **1** (108 mg, 1.0 mmol of phenol unit) and Fe-salen (1.6 mg, 5.0 μmol) was dissolved in DMF (2.5 mL) containing 10 μL of pyridine. The coupling started by the addition of a quarter molar amount of hydrogen peroxide (30%) for **1** under air. The same amount of hydrogen peroxide was further added three times in every 15 min. After 24 h, the reaction mixture was analyzed by SEC.

(14) Ikeda, R.; Tanaka, H.; Uyama, H.; Kobayashi, S. *Polym. J.* **2001**, *33*, 959.

(15) Yamaguchi, T.; Nomoto, M.; Yamashita, S.; Yamazaki, T.; Nakamoto, Y.; Ishida, S. *Macromol. Chem. Phys.* **1998**, *199*, 423.

(16) Uyama, H.; Maruichi, N.; Tonami, H.; Kobayashi, S. *Biomacromolecules* **2002**, *3*, 187.

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