Synthesis of Degradable Polymer Exhibiting LCST-type Phase Separation by Radical Copolymerization of Sorbic Esters and Molecular Oxygen

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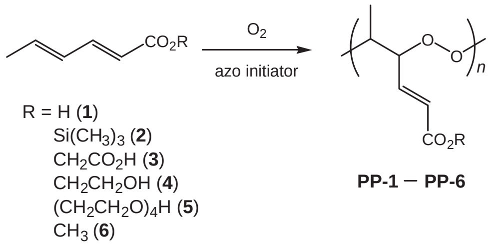
We synthesized water-soluble polyperoxides (**PP**) by radical copolymerization of hydrophilic sorbic esters with oxygen. A phase separation with a lower critical solution temperature (LCST) was observed under the onset temperature of thermal degradation for the aqueous solutions of **PP** containing a tetra(ethylene oxide) unit in the side chain. A critical temperature for the LCST-type phase separation depended on the composition of the hydrophilic and hydrophobic esters of **PP**.

Water-soluble polymers are important materials as the thicker and flocculating agent for an aqueous medium, the water-absorbent, the biomaterials, and the sequential components of block and graft copolymers used in various research fields.[1,2] Especially, thermosensitive water-soluble polymers and block copolymers have recently become the focus of much interest. Some water-soluble polymers become insoluble above a certain critical temperature, which is called the lower critical solution temperature (LCST). Hydrogels with a poly(*N*-isopropylacrylamide) segment exhibiting an LCST-type phase separation show many interesting features of mechanical, reological, and biomedical properties as the stimuli-responsive gel.[2] The fundamental properties and a wide scope of application of poly(*N*-isopropylacrylamide) and its gels have intensively been investigated by many researchers in synthetic chemistry, biochemistry, physics, and also medicine.[3] Poly(vinyl ether)s with a well-defined structure, which were prepared by living cationic polymerization, have also been reported to show an interesting LCST-type phase in water.[4]

Recently, we have succeeded in the fabrication of polyperoxides (**PP**) as a new class of degradable polymers via a conventional radical copolymerization process using 1,3-diene monomers including sorbic esters and oxygen as the starting monomers.[5] The rational design of **PP** was also carried out to provide environmentally friendly degradation products.[5e] When we synthesized water-soluble **PP** using sorbic ester monomers with a hydrophilic functional group in the ester group as shown in Scheme 1, we found that the aqueous solutions of **PP** containing a tetra(ethylene oxide) unit as the ester groups in the polymer side chain show an LCST-type phase separation. These water-soluble **PP** can be used as the thermo-responsive polymer around room temperature, and they are degradable upon further heating.

We first tried to directly polymerize **1** with oxygen, but it failed because of the low solubility of **1** toward organic solvents and difficulty with the isolation of the resulting **PP-1**. Therefore,



Scheme 1.

Table 1. Preparation, solubility, and thermal properties of polyperoxides with hydrophilic ester substituents[a]

Polyperoxide	Yield /%	$M_n \times 10^{-3}$	M_w/M_n	P_n	Solubility				DTA[b]		TG[b]	
					$CHCl_3$	THF	CH_3OH	H_2O	T_{init}/°C	T_{max}/°C	T_{95}/°C	T_{50}/°C
PP-2[c]	79.4	2.0	1.5	14	sol	sol	sol	insol	94.5	138.9	118.9	147.5
PP-3	21.5	3.3	2.0	16	sol	sol	sol	insol	93.0	143.2	116.1	260.3
PP-4	23.0	4.1	1.6	22	sol	sol	sol	insol	97.4	145.0	128.0	229.5
PP-5	29.1	3.9	1.7	12	insol	sol	sol	sol	107.2	146.5	152.3	340.9
PP-6[d]	49.3	3.2	1.6	20	sol	sol	insol	insol	107.9	147.5	119.5	149.8
PP-5/6-I (80/20)[e]	38.3	3.3	1.6	—	sol	sol	sol	sol	97.7	147.3	132.4	285.2
PP-5/6-II (75/25)[e]	41.9	3.8	1.7	—	sol	sol	sol	sol				
PP-5/6-III (50/50)[e]	44.7	4.1	1.8	—	sol	sol	sol	insol				

[a] Polymerization was carried out in 1,2-dichloroethane in the presence of 2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile) with bubbling oxygen for 6 h at 30 °C. Monomer/initiator = 50/1, monomer/solvent = 1/3 in weight. The M_n and M_w/M_n were determined by GPC calibrated with standard polystyrenes. [b] Differential thermal analysis (DTA) and thermogravimetric analysis (TG) were carried out in nitrogen stream at a heating rate of 10 °C/min. The initial and maximum degradation temperatures, T_{init} and T_{max}, respectively, were estimated from the onset and peak temperature of the exothermic peak in the DTA curve. T_{95} and T_{50} are the 95 and 50 wt % temperatures, respectively, determined by the TG. [c] **PP-2** was isolated as **PP-1** after hydrolysis in methanol. [d] Ref. 5e. [e] Values in parentheses indicate the comonomer ratio of **5** and **6** in the feed for the copolymerization with oxygen. The composition in the copolymers was not determined.

the carboxyl group was temporarily protected with a trimethylsilyl group, and then used for the polymerization. The trimethylsilyl ester **2** provided a polymer in a high yield, which was higher than the yield for the methyl ester **6**, as shown in Table 1. This is due to the electron-donating nature of the trimethylsilyl group because an electrophilic peroxy radical preferably adds to unsaturated compounds with electron-donating groups. The polymer was isolated as the powder by precipitation into water after deprotection was carried out with methanol under mild conditions at room temperature. **PP-1** was soluble in many organic solvents including chloroform, THF, and methanol, but insoluble in water. Other hydrophilic ester derivatives with carboxymethyl and 2-hydroxyethyl groups (**PP-3** and **PP-4**) also showed a solubility similar to that of **PP-1**. When a tetra(ethylene oxide) unit was introduced into the ester moiety to further increase the hydrophilicity of the resulting **PP**, a water-soluble polyperoxide **PP-5** was obtained.

Thermal degradation properties were investigated by TGA/DTA measurement in a nitrogen atmosphere at the heating rate of 10 °C/min. The degradation parameters are also summarized in Table 1. The degradation proceeds via a chain reaction mechanism, which has already been proposed for the **PP** with alkyl esters including **PP-6**.[5] The T_{init} were 93–107 °C for the **PP** prepared in this study, being the same as that for the **PP-6** previously reported. The $T_{\max}$ values also well agreed with each other, independent of the structure of the ester groups in the side chain. In contrast to the results from the DTA experiments, the T_{95} and T_{50} values by TG depended on the structure of the ester groups, being due to the high boiling point of the degradation products for **PP-3**–**PP-5**.

An aqueous solution of **PP-5** was turbid upon heating, similar to the solutions of the poly(*N*-alkylacrylamide)s[3] and poly(vinyl ether)s,[4] which are typical polymers exhibiting an LCST-type phase separation in water. The determination of LCST for **PP-5** was difficult because of its simultaneous thermal degradation. Therefore, we fabricated the copolyperoxides of **5** with **6** to decrease the hydrophilicity, thus leading to a decrease in the LCST due to an increase in the hydrophobic interaction in water. The copolymerization was carried out in the presence of monomers **5** and **6** with a different ratio in the feed. A water-soluble **PP** was obtained when the monomer ratios of **5**/**6** were 80/20 and 75/25 (Table 1). The copolyperoxides showed a phase separation around room temperature; LCST were determined to be 45 and 36 °C for **PP-5/6-I** and **PP-5/6-II**, respectively (Figure 1). The phase separation of **PP-5/6** was reversibly observed under the degradation temperature, but the turbid solution over LCST became a transparent solution upon further heating. It accompanies the degradation of **PP** leading to the production of low-molecular-weight compounds.

In conclusion, we synthesized several hydrophilic **PP** using sorbic esters with a functional group in the ester group by the radical copolymerization with bubbling oxygen based on a conventional radical polymerization process. We found an LCST-type phase separation for the aqueous solutions of **PP** including a tetra(ethylene oxide) unit in the side chain and the copolyperoxide with methyl sorbate. Polymers degradable via a radical chain reaction mechanism, triggered by various stimuli including not only heating but also biochemical and redox reactions, have great potential for their use in various fields. Further application as the degradable hydrogels is now under investigation.

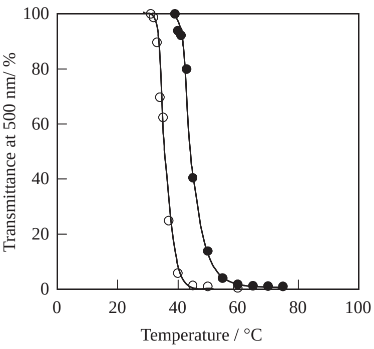


Figure 1. Phase diagrams for the 0.5 wt % aqueous solution of **PP-5/6-I** (●) and **PP-5/6-II** (○). Traced by turbidimetry at 500 nm.

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