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Hydrolytic degradation of poly[(*R*)-3-hydroxybutyric acid] in the melt

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Abstract

Poly[(*R*)-3-hydroxybutyric acid] [*R*-P(3HB)] was hydrolyzed in high-temperature and high-pressure water at the temperature range of 180–300 °C and for a period of 360 min. The formation, racemization, and decomposition of 3-hydroxybutyric acids (3HBs) and molecular weight change of *R*-P(3HB) were investigated. The highest yield of (*R*)-3-hydroxybutyric acid (*R*-3HB), ca. 80%, was obtained at 200 °C in the hydrolytic degradation periods of 240–360 min. Too-high hydrolytic degradation temperature such as 300 °C induced the decomposition and racemization of formed 3HBs, resulting in decreased yield of *R*-3HB. The hydrolytic degradation of *R*-P(3HB) proceeds homogeneously and randomly via a bulk erosion mechanism. The molecular weight of *R*-P(3HB) decreased exponentially without formation of low-molecular-weight specific peaks originating from crystalline residues. The hydrolytic degradation rates in the melt estimated from M_n changes were lower for *R*-P(3HB) than for poly(L-lactide) (PLLA) in the temperature range of 180–220 °C. The activation energy for the hydrolytic degradation (ΔE_h) of *R*-P(3HB) in the melt (180–250 °C) was 30.0 kcal mol^{-1}, which is higher than 12.2 kcal mol^{-1} for PLLA in the melt in the temperature range (180–250 °C). This study reveals that hydrolytic degradation of PHB in the melt is an effective and simple method to obtain (*R*)-3HB and to prepare *R*-P(3HB) having different molecular weights without containing the specific low-molecular-weight chains, because of the removal of the effect caused by crystalline residues.

Keywords: Hydrolytic degradation; Poly[(*R*)-3-hydroxybutyric acid]; Racemization

1. Introduction

Poly[(*R*)-3-hydroxybutyrate] [*R*-P(3HB)] or poly[(*R*)-3-hydroxybutyric acid] is one of the simplest and most common member of the poly(hydroxyalkanoate) (PHA) family and can be produced from a variety of renewable resources by fermentation [1–8]. Having been made by bacteria, *R*-P(3HB) can be completely degraded to carbon dioxide and water by environmental microbes such as bacteria and fungi. As no such microbes are present in the human body, degradation of *R*-P(3HB) is expected to proceed via non-enzymatic hydrolytic degradation [9]. *R*-P(3HB) has a high potential for applications as degradable implant materials with excellent biocompatibility as evidenced by lack of toxicity [10–12] and compatibility in contact with tissue [13–15] and blood [16,17] as well as with appropriate hydrolyzability and mechanical performance. By selecting the culture conditions of microorganisms, PHB-related copolymers with different co-monomer units and compositions can be produced by fermentation to some extent. However, if the monomer of *R*-P(3HB) can be easily obtained by the present procedure, it can be utilized for the chemical synthesis of PHB-related copolymers having a wide variety of co-monomer units and compositions.

With respect to the hydrolytic degradation of *R*-P(3HB), a number of articles have been published [18,19]. In vitro degradation study on *R*-P(3HB) films in buffer solution at 37 °C showed no mass loss after 180 days, but a decrease in molecular weight started after an induction period of about 80 days [20]. This induction period was attributed to the time required for water to permeate the polymer matrix. It was concluded that the hydrolytic degradation of microbial polyesters proceeds in two steps. First, there is random chain scission both in the amorphous and crystalline regions of the polymer matrix accompanied with a decrease in molecular weight with unimodal distribution and of relatively narrow

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polydispersity. Mass loss begins below a molecular weight M_n of about 13,000 in the second step.

On the other hand, in recent years, a considerable number of studies have been conducted on the use of hydrothermal treatment process for thermal decomposition [21,22], organic synthesis [23,24], and recovery of useful materials from various organic waste [25–28]. This method has been also applied to chemical recycling processes such as hydrolytic degradation of polyethylene terephthalate (PET) into ethylene glycol and terephthalic acid [29]. Park et al. showed the ability of supercritical and near-critical water to decompose the styrene-butadiene rubber (SBR) into a range of lower molecular weight organic compounds [30]. Thus, water under hydrothermal conditions provides excellent properties (i.e. high ion product, low solvent polarity, high solubility for oil, etc.) for hydrolytic degradation [31]. In our previous study, we have applied high-temperature and high-pressure water to poly(L-lactide) [i.e. poly(L-lactic acid) (PLLA)] at the temperature exceeding its melting temperature (T_m) and found that the hydrolytic degradation in the melt at a temperature range of 180–250 °C is an effective method to recycling PLLA to its monomer (L-lactic acid) and to prepare PLLA having different molecular weights and that too high temperature exceeding 300 °C causes racemization and degradation of formed L-lactic acid [32,33].

With regard to aromatic and optically inactive PET, its hydrolytic degradation or solvolysis to the monomers and the monomer-based compounds has been intensively studied [34] and some commercial processes have been already established for the solvolysis (methanolysis [35] and glycolysis [36]). These industrial processes by solvolysis were successfully utilized because the monomers and the monomer-based compounds have relatively high stability at high temperature and the monomers contain no asymmetric carbon that can cause racemization during the solvolysis. However, terephthahlic acid formed by the hydrolytic degradation is reported to enhance the degradation of the formed ethylene glycol, resulting in its low yields, such as 50 and 20% at 300 and 400 °C, respectively, [37], though careful selection of reaction temperature and period gives high yields of terephthahlic acid (ca. 100% at 265 °C, Campanelli et al. [38]; 91% at 400 °C, Adschiri et al. [37]). The hydrolytic degradation or solvolysis of PET gives two monomers or monomer-based compounds and, therefore, should be followed by several-step separation processes in obtaining pure monomers for further polymer synthesis [35,36,39]. No such process is required for the hydrolytic degradation of *R*-P(3HB) and PLLA, because formed monomer and oligomers are expected to be readily polymerized to give *R*-P(3HB) and PLLA by the aforementioned one-step condensation polymerization after the removal of impurities [40], if procedure, catalyst, and conditions are scrupulously selected. The hydrolytic degradation of P-(3HB) is anticipated to proceed faster in the melt than as a solid [38,41], as reported for that of PET and PLLA.

In this study, hydrolytic degradation of microbially produced and optically active *R*-P(3HB) was carried out in the melt in high-temperature and high-pressure water was applied at the temperatures exceeding melting temperature (T_m) of *R*-P(3HB). The hydrolytic degradation behavior of *R*-P(3HB), the formation of its monomers 3-hydroxybutyric acids (3HBs), and the racemization of 3HBs have been investigated by the use of total organic carbon (TOC) measurements, high performance liquid chromatography (HPLC), and gel permeation chromatography (GPC).

2. Experimental section

2.1. Materials

R-P(3HB) [natural origin, number-average molecular weight (M_n) = 2.96×10^5 g mol^{-1}, weight-average molecular weight (M_w)/M_n = 1.62, T_m = 172 °C] was purchased from Sigma-Aldrich Co. and utilized without further purification.

2.2. Hydrolytic degradation

The hydrolytic degradation of *R*-P(3HB) was performed in a reactor (100×8 mm i.d.) made of SUS-316 in the temperature range of 180–300 °C at corresponding saturated vapour pressures according to previously reported procedure [32]. The hydrolytic degradation temperature was set to be higher than the T_m of *R*-P(3HB) (172 °C). The reactor was charged with 0.24 g of *R*-P(3HB) and 4.8 g of distilled water, and the air inside was replaced by argon gas. After being sealed, the reactor was immersed in the preheated molten salt bath (TSC-B600, Taiatsu Techno, Japan) containing a mixture of potassium nitrate and sodium nitrate. After the hydrolytic degradation for a predetermined period, the reactor was removed from the salt bath and quenched at 25 °C to stop further hydrolytic degradation.

2.3. Measurements

The yield of 3HBs (*R*- and S-3HB) was evaluated using a Shimadzu HPLC system (LCl0A, electroconductivity detector CDD-6A) with ion-exclusion columns (Shim-Pack SCR-102Hx2, Shimadzu Co.), while the fraction of *R*-3HB in the 3HBs was estimated using the LC-10A system (UV multiwavelength detector MD-1510, JASCO) with a Sumichiral OA-6100 (5 μm, 4.6 mm i.d., Sumika Chemical Analysis Service Ltd, Japan). The total organic carbon (TOC) of the water after the hydrolytic degradation was monitored by a Shimadzu TOC-5000 analyzer. The M_n, M_w and the molecular weight distribution of *R*-P(3HB) before and after the hydrolytic degradation were evaluated in chloroform at 40 °C by a Tosoh GPC system (refractive

index monitor RI-8020) with two TSK gel columns (GMH_{XL}) using polystyrene standard.

3. Results and discussion

3.1. Formation of water-soluble oligomers and monomers

Fig. 1 shows the TOC of the surrounding water after the hydrolytic degradation of *R*-P(3HB) at different temperatures as a function of hydrolytic degradation time. The TOC value can be an index of the content of water-soluble 3HB oligomers and monomers formed by the hydrolytic degradation and then released from the mother specimens into the surrounding water. The broken line in the figure indicates the theoretical TOC value (2.8 g l^{-1}) when all of the *R*-P(3HB) chains are hydrolyzed to water-soluble oligomers and monomers. The induction period until the onset of weight loss became longer with decreasing hydrolytic degradation temperature, but a significant increase was observed at 120 min even when hydrolytic degradation temperature was lowered to 180 °C. The TOC values at 200 °C approached the theoretical value within 300 min meaning that all of the *R*-P(3HB) chains in the melt can be hydrolyzed to water-soluble oligomers and monomers in relatively short period compared with those as a solid at low temperatures below 70 °C (2 and 4 weeks at 70 °C, respectively) [42]. The decrement in TOC values at 250 and 300 °C for long hydrolytic degradation periods can be ascribed to the formation of volatile compounds such as CO_2, CO, and CH_4, which are formed by decomposition of 3HBs and further decomposition of the decomposed compounds [43].

The dependence of TOC on hydrolytic degradation temperature and time dependences are analogous with those reported by Tsuji et al. and Saeki et al. for the hydrolytic degradation of PLLA in the melt [32,33]. However, probably due to the low stability of formed 3HBs at high temperature, to attain a high TOC value the hydrolytic degradation temperature should be set to be lower compared with that of PLLA and, therefore, requires the long period to reach the theoretical value. Adschiri et al. showed that increasing reaction pressure is effective for suppressing char and carbon dioxide formation during the hydrolytic degradation of PET [37]. This is applicable to the hydrolytic degradation of *R*-P(3HB) to maintain the theoretical TOC value for a long period after the saturation.

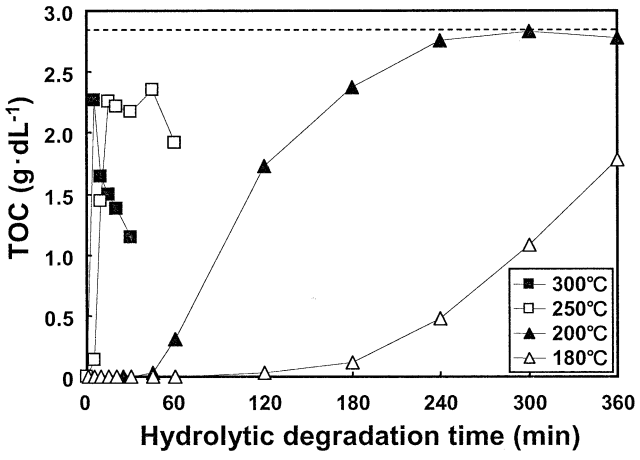

Fig. 1. TOC of the surrounding water after the hydrolytic degradation of *R*-P(3HB) at different reaction temperatures as a function of hydrolytic degradation time.

3.2. Formation of 3HBs

Fig. 2 gives the yield of 3HBs for the hydrolytic degradation of *R*-P(3HB) at different temperatures as a function of hydrolytic degradation time. The hydrolytic degradation temperature range of 190–220 °C was selected here because too high temperature will cause decomposition of the formed 3HBs as suggested by TOC results. As can be seen, the yield of 3HBs increased without any induction periods and gave maximums around 60, 80, 55, and 35% at 360, 240, 180, and 120 min for the hydrolytic degradation temperatures of 190, 200, 210, and 220 °C, respectively. The lower values of 3HBs compared with those of TOC may be due to the fact that TOC values contain not only those of 3HBs but also those of water-soluble oligomers, which require an additional period to be hydrolyzed to 3HBs, and a part of the oligomers may remain unhydrolyzed. The decrement of 3HB yield at longer hydrolytic degradation periods can be attributed to the decomposition of 3HBs. Such decomposed compounds include organic acids. The maximum yield of 3HBs ca. 80% is lower than 95% of lactic acids from PLLA at 250 °C for 15 min, confirming the lower stability of 3HB compared with that of lactic acids. The finding obtained here reveals that the highest maximum yield of 3HBs can be attained at around 200 °C and too high or low hydrolytic degradation temperatures result in the low yields of 3HBs.

Fig. 3 illustrates the fraction of *R*-3HB in the obtained 3HBs as a function of hydrolytic degradation time. In this

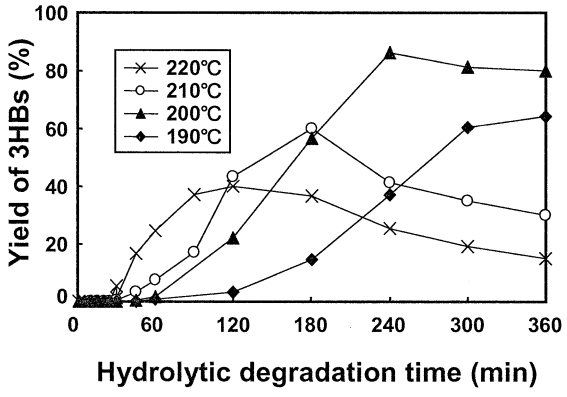

Fig. 2. The yields of 3HBs for the hydrolytic degradation of *R*-P(3HB) at different reaction temperatures as a function of hydrolytic degradation time.

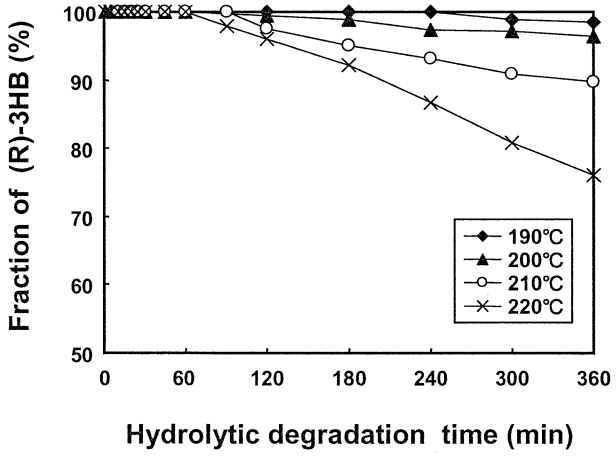

Fig. 3. *R*-3HB fraction in the formed 3HBs at different reaction temperatures as a function of hydrolytic degradation time.

figure, we assume that the fraction of *R*-3HB is 100% when we could not estimate the accurate fraction of S-3HB because of a low yield of 3HBs or of a low amount of S-3HB in the obtained 3HBs at a short hydrolytic degradation period. At the hydrolytic degradation temperature of 180 °C, the fraction of *R*-3HB remained unchanged for the period studied here, meaning no racemization of the formed *R*-3HB occurred during the hydrolytic degradation. In contrast, at hydrolytic degradation temperatures exceeding 190 °C, significant decrements in the fraction of *R*-3HB were observed. Namely, the fraction of *R*-3HB started to decrease at 300, 120, 120, and 90 min and reached 97, 93, 79, and 52% at 360 min, when hydrolyzed at 190, 200, 210, and 220 °C, respectively. This reflects that the racemization of 3HBs occurs at temperatures exceeding 190 °C. The hydrolytic degradation temperature above which significant racemization takes place is higher for PLLA (260 °C) than for *R*-P(3HB) [32,33]. The racemization of 3HBs indicates the rapid completion at the higher temperature. In terms of racemization, it is inappropriate to elevate the hydrolytic degradation temperature exceeding 200 °C.

The *R*-3HB yield was calculated from Figs. 2 and 3 according to the following equation:

$$\text{Yield of } R-3\text{HB } (\%) = \frac{\text{Yield of 3HBs } (\%) \times \text{fraction of } R-3\text{HB } (\%)}{100}$$

This reveals that the hydrolytic degradation of *R*-P(3HB) in the melt is an effective and simple method to obtain *R*-3HB and that 200 °C and 240 min are the most appropriate conditions for the highest maximum yield. The relatively low maximum yield of *R*-3HB 12% at 220 °C can be ascribed to the rapid decomposition and racemization of the formed 3HBs. Such racemization of the 3HBs at higher temperature can also occur through the radical scission and enolization of *R*-P(3HB) chains as suggested for PLLA by McNeill and Leiper [44] and by Kopinke and Mackenzie [45], respectively. The highest yield of *R*-3HB (ca. 84%) at 200 °C is comparable with that of L-lactic acid (ca. 90%) [33] those of terephthalic acid (ca. 100% and 91%) [37] formed as a result of hydrolytic degradation of PLLA at 250 °C and PET at 265 and 400 °C, respectively, though the yield of ethylene glycol, which is susceptible to further decomposition, has rarely been estimated and the reported highest value was 50 and 20% at 300 and 400 °C, respectively, [37].

3.3. Molecular weight change of R-P(3HB)

The molecular weight distribution of *R*-P(3HB) shifted as a whole to a lower molecular weight during the hydrolytic degradation without formation of any low-molecular-weight specific peaks arising from the chains in the crystalline residues (data not shown here). No formation of any low-molecular-weight peaks is an important feature of the hydrolytic degradation of *R*-P(3HB) above T_m, which must contribute to its efficient hydrolytic degradation, resulting in rapid saturation of yields of 3HBs and *R*-3HB, as shown in Fig. 2. The result obtained here reflects that the hydrolytic degradation of *R*-P(3HB) in the melt proceeds homogeneously and randomly in the specimen via a bulk erosion mechanism.

The M_n change of *R*-P(3HB) during the hydrolytic degradation at different temperatures is given in Fig. 4 as a function of hydrolytic degradation time. Here, we assumed that 1 min is required for the specimens to reach degradation temperature because no significant change in M_n was recognized in the first 1 min. The M_w/M_n value remained in the range of 1.5–1.8 during the hydrolytic degradation as long as M_n was higher than 1×10^4 g mol^{-1}, while it increased to about 2.7 when M_n became lower than 1×10^4 g mol^{-1}. The M_n decreased exponentially with the

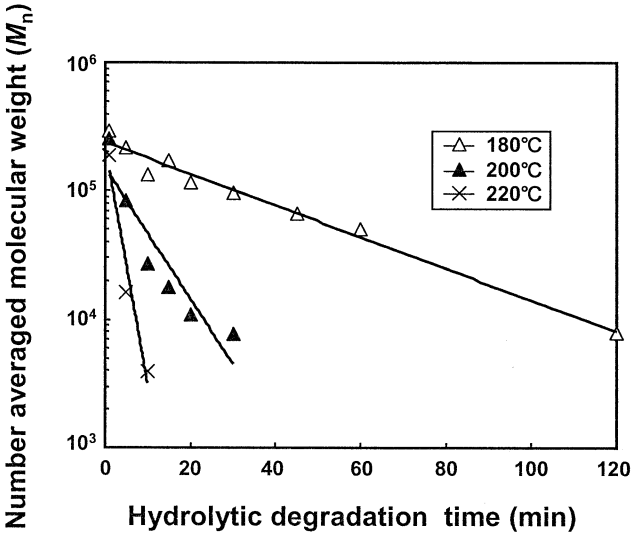

Fig. 4. M_n changes of *R*-P(3HB) hydrolyzed at different reaction temperatures as a function of hydrolytic degradation time.

hydrolytic degradation time and the decrease rates of M_n increased monotonically with the hydrolytic degradation temperature. This figure reveals that the hydrolytic degradation of *R*-P(3HB) in the melt at different temperatures and times yields the *R*-P(3HB) having different M_n values. In other words, the hydrolytic degradation of *R*-P(3HB) in the melt is an effective and simple method to prepare *R*-P(3HB) having different M_n values without containing the specific low-molecular-weight chains due to the chains in the crystalline residues. This effective and simple method is supported by the homogeneous and random features of the hydrolytic degradation in the melt. It should be noted that low hydrolytic degradation temperature such as 180 °C and short hydrolytic degradation period are appropriate to reduce the formation of 3HBs and other organic compounds and that the obtained low-molecular-weight *R*-P(3HB) may contain 3HBs and other organic compounds, which must be removed by precipitation or extraction for some biomedical and pharmaceutical applications.

The hydrolytic degradation rate constant (k) values of the *R*-P(3HB) at different temperatures were estimated assuming the exponential decreases in M_n of the specimens during the hydrolytic degradation and using the following equation:

$$\ln M_n(t_2) = \ln M_n(t_1) - k(t_1 - t_2)$$

where $M_n(t_2)$ and $M_n(t_1)$ are M_n values at the hydrolytic degradation times of t_2 and t_1, respectively. The Arrhenius plot of the obtained k values as presented in Fig. 5 gives activation energy of hydrolytic degradation (ΔE_h) for *R*-P(3HB) in the melt. For comparison this figure includes the reported data for PLLA [32]. As seen the estimated k values estimated for *R*-P(3HB) was lower than reported those for PLLA, when compared at the same hydrolytic degradation temperature, reflecting the lower hydrolytic degradation rate of *R*-P(3HB) than that of PLLA. The obtained ΔE_h values was 30.0 kcal mol^{-1} for *R*-P(3HB) in the melt in the temperature range of 180–250 °C, which is higher than 12.2 kcal mol^{-1} for PLLA in the melt in the temperature range of 180–250 °C [32] and is lower than 55.7 kcal mol^{-1} for PET in the melt in the temperature range of 250–280 °C [39]. This reflects that in the melt *R*-P(3HB) is much more susceptible to hydrolytic degradation than PET but more hydrolytic degradation-resistant than PLLA. These susceptibility difference must be due to the hydrophilicity difference, i.e. PET containing highly hydrophobic and bulky phenylene groups is more resistant to hydrolytic degradation than *R*-P(3HB), while *R*-P(3HB), while *R*-(3HB) having an additional hydrophobic methylene group in a monomer unit compared with a lactyl unit of PLLA, is hydrolytic degradation-resistant than PLLA.

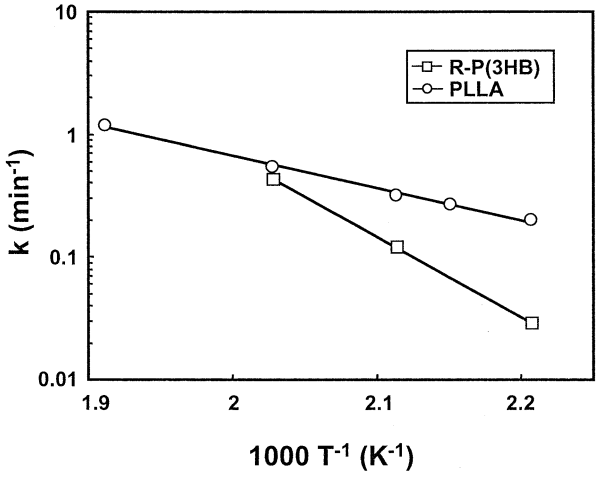

Fig. 5. Arrhenius plot of the hydrolytic degradation constant (k).

4. Conclusions

From the results mentioned above the following conclusions can be derived for the hydrolytic degradation of *R*-P(3HB) in the melt in high-temperature and high-pressure water: (1) More than 90% of *R*-P(3HB) was hydrolyzed to water-soluble oligomers and monomers within 300 min when hydrolyzed at 200 °C. (2) The 3HBs were obtained at the maximum yields exceeding 60% when hydrolyzed in the temperature range of 190–210 °C, whereas, the maximum yield decreased to 50% when hydrolytic degradation temperature was elevated to 220 °C. (3) The highest maximum yield of *R*-3HBs (ca. 84%) was attained at 200 °C and 240 min, while the hydrolytic degradation at high temperatures such as 220 °C resulted in the low maximum yield of *R*-3HB (ca. 30%) due to the racemization and decomposition of 3-hydroxybutyric acids. Moreover, the hydrolytic degradation at low temperature below 190 °C required long periods to give the maximum yield of *R*-3HB, and the maximum yields were lower than that obtained at 200 °C. (4) Significant racemization of the formed 3HBs occurred at hydrolytic degradation temperatures above 190 °C. (5) The hydrolytic degradation rates in the melt estimated from M_n changes were lower for *R*-P(3HB) than for PLLA in the temperature range of 180–220 °C. (6) The ΔE_h for *R*-P(3HB) in the melt in the temperature range of 180–250 °C was 30.0 kcal mol^{-1}, which is higher than 12.2 kcal mol^{-1} for PLLA in the melt in the temperature range of 180–250 °C and is lower than 55.7 for PET in the melt in the temperature range of 250–280 °C.

Acknowledgements

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