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Chemical synthesis of high molecular weight poly(3-hydroxybutyrate-*co*-4-hydroxybutyrate)

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The reaction of optically active β-butyrolactone with γ-butyrolactone in the presence of a distannoxane complex as a catalyst at 100°C yielded a high molecular weight poly(3-hydroxybutyrate-*co*-4-hydroxybutyrate).

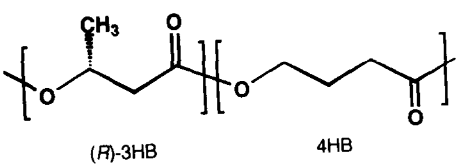
(Keywords: distannoxane; ring-opening copolymerization; poly(3-hydroxybutyrate-*co*-4-hydroxybutyrate))

Introduction

A wide variety of micro-organisms are known to produce intracellular energy and carbon storage products which have been generally described as being poly(*R*)-3-hydroxyalkanoates] (P(3HA)s)[1–3]. Imperial Chemical Industries (ICI) has developed a controlled fermentation process for the production of copolyesters of (*R*)-3-hydroxybutyrate and (*R*)-3-hydroxyvalerate [P(3HB-*co*-3HV)][4].

Doi *et al.* succeeded in the fermentation production of a new copolyester of (*R*)-3-hydroxybutyrate and 4-hydroxybutyrate [P(3HB-*co*-4HB)] (*Scheme 1*) (4HB content 0–82 mol%), by *A. eutrophus* from 4-hydroxybutyric and butyric acids[5,6].

In order to synthesize the P(3HB-*co*-4HB) by a chemical method, the ring-opening polymerization of (*R*)-β-butyrolactone [(*R*)-β-BL] with γ-butyrolactone (γ-BL, ring size 5) has to be carried out. In general, it is impossible to obtain a high molecular weight poly(4-hydroxybutyrate) [P(4HB)] by ring-opening polymerization of γ-BL, because of the small ring strain. Korte *et al.* successfully achieved the homopolymerization of γ-BL to yield P(4HB) with low molecular weight under special conditions, for example, under a pressure of 20 000 atm at 160°C (ref. 7). Kricheldorf *et al.* pointed out the low copolymerizability of γ-BL with other lactones by ring-opening polymerization[8]. Fukuzaki *et al.* reported the direct copolymerization of L-lactic acid with γ-BL in the absence of catalysts to afford low molecular weight poly(2-hydroxypropionate-*co*-4-hydroxybutyrate)[9,10].



Scheme 1

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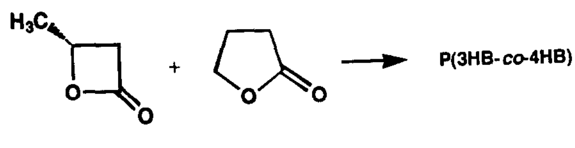
Recently, we reported that the highly efficient ring-opening polymerization of (*R*)-β-BL[11,12] and copolymerization of (*R*)-β-BL with ε-CL[12,13], δ-VL[12,13], β-methyl-δ-valerolactone[12,13], L-lactide[12,13] and (*R*)-3-methyl-4-oxa-6-hexanolide[14] in the presence of distannoxane catalysts gave a new series of copolyesters and poly(ester ether)s of high molecular weights.

We thought that it was a challenging subject to synthesize P(3HB-*co*-4HB) which was easy to obtain by a fermentation method but was difficult to obtain by ring-opening copolymerization of (*R*)-β-BL with γ-BL.



Here we report the synthesis of P(3HB-*co*-4HB) with high molecular weight catalysed by 1-ethoxy-3-chlorotetrabutyldistannoxane.

Experimental

Materials. 1-Ethoxy-3-chlorotetrabutyldistannoxane[15] was prepared using the literature methods. The catalyst was dried *in vacuo* at 80°C for 20 h. (*R*)-β-Butyrolactone[16] [(*R*)-β-BL, 92% enantio excess] and γ-BL were dried with CaH_2 and distilled under reduced pressure.

Measurements. Molecular weights of the polymers were determined by g.p.c. using a polystyrene calibration. Proton and carbon-13 nuclear magnetic resonance spectra were recorded on a Bruker AM-400 spectrometer. Calorimetric measurements (d.s.c.) of the polymers were carried out on a Shimadzu thermal analysis system over a temperature range of −50 to +200°C at heating and cooling rates of 10°C min^{-1}. The melting temperature (T_m) was taken as the peak temperature of the melting endotherm (first run). The glass transition temperature (T_g) was taken as the inflection point of the specific heat increment at the glass transition (second run).

Ring-opening copolymerization. (R)-β-BL (3.10 g, 36 mmol), γ-BL (0.34 g, 4 mmol), and 1-ethoxy-3-chlorotetrabutyldistannoxane (11.2 mg, 1×10^{-2} mmol) were heated in a 20 ml Shlenk tube at 100°C for 4 h. The resulting mixture was dissolved in trichloromethane and then was added to a mixture of diethyl ether and hexane (ratio 1:3) to afford the white solid of the P(3HB-*co*-6% 4HB) 3.29 g in 96% yield. ^{1}H n.m.r. (400 MHz, in $CDCl_3$): δ = 1.20–1.36 (m, 3H, CH_3 for 3HB unit), 1.88–2.00 (m, 2H, CH_2 for 4-hydroxybutanoate (4HB) unit), 2.31–2.42 (m, 2H, CH_2 for 4HB unit), 2.42–2.54 (m, 1H, CH_2 for 3HB unit), 2.54–2.68 (m, 1H, CH_2 for 3HB unit), 4.05–4.18 (m, 2H, CH_2 for 4HB unit), and 5.20–5.33 (m, 1H, CH for 3HB unit).

Results and discussion

(R)-β-Butyrolactone polymerized with γ-BL to give P(3HB-*co*-4HB)s in the presence of a catalytic amount of 1-ethoxy-3-chlorotetrabutyldistannoxane (*Table 1*). The proton n.m.r. of these P(3HB-*co*-4HB)s showed a structure quite similar to that of a P(3HB-*co*-4HB) which was produced by bacteria[5]. When the feed molar ratio of the (R)-β-BL and γ-BL was 90:10, the P(3HB-*co*-6% 4HB) showed the maximum molecular weight $M_n = 96\,000$ (entry 2 in *Table 1*). The yields and molecular weights of P(3HB-*co*-4HB)s decreased with increasing feed ratio of γ-BL. The observed ratios of 4HB units in P(3HB-*co*-4HB)s increased with increasing feed ratio of γ-BL (*Figure 1*). The maximum ratio of 4HB units was 35% when the feed ratio of γ-BL was 90%. The elasticity of P(3HB-*co*-4HB)s increases as the percentage of the 4HB units increases.

Figure 2 illustrates the relationship of T_m and T_g values to 4HB percentage content of P(3HB-*co*-4HB)s and P(3HB). All T_m and T_g values are directly related to

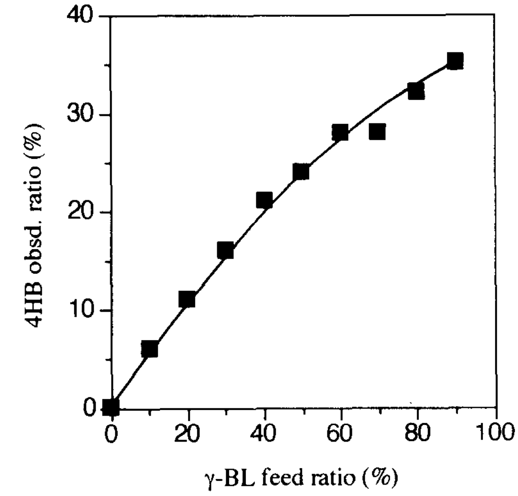


Figure 1 Relation between the feed ratio of γ-BL and the observed composition of 4HB units

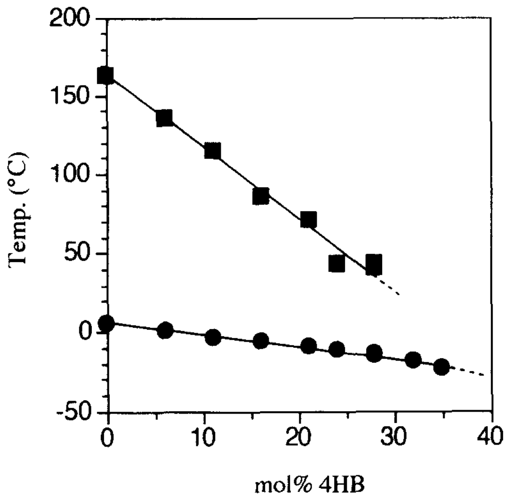


Figure 2 Relation of T_m (■) and T_g (●) values with composition of 4HB units

Table 1 Polymerization results of (R)-β-BL with γ-BL at 100°C[a]

Entry	Monomer (feed ratio)	Polymer (obsd ratio)[b]	T_m (°C)	T_g (°C)	M_w^c	M_n^c	Yield (%)	$[\alpha]_D^{25}$ (c = 1, $CHCl_3$)
1[d]	(R)-β-BL	(100/0)	163	5.3	424 000	178 000	99	−1.6[e]
2	(R)-β-BL/γ-BL (90/10)	(94/6)	135	0.8	156 000	96 000	96	−1.7
3	(80/20)	(89/11)	114	−3.6	108 000	64 000	95	−1.9
4	(70/30)	(84/16)	86	−6.0	120 000	72 000	81	−2.0
5	(60/40)	(79/21)	70	−9.0	98 000	59 000	79	−2.2
6[f]	(50/50)	(76/24)	43	−11.4	94 000	59 000	61	−2.1
7[f]	(40/60)	(72/28)	41	−14.3	72 000	42 000	50	−2.0
8[f,g]	(30/70)	(72/28)	43	−15.6	36 000	22 000	44	−1.5
9[f,g]	(20/80)	(68/32)		−18.5	19 600	6 700	21	−2.2
10[f,g]	(10/90)	(65/35)		−22.7	7 600	2 700	13	−1.7

[a] Polymerization conditions: catalyst 1×10^{-2} mmol; lactones 40 mmol; 4 h, no solvent was used
[b] Determined by ^{1}H n.m.r. analysis
[c] Determined by g.p.c. analysis, calibrated to a polystyrene standard
[d] Catalyst 5×10^{-3} mmol
[e] c = 0.25, $CHCl_3$
[f] 16 h
[g] Catalyst 2×10^{-2} mmol

the content of the 4HB unit. Thus, by increasing the 4HB content, polymers with both lower T_m and T_g values can be obtained. We have shown that the distannoxane catalyses the ring-opening polymerization of (*R*)-β-BL (entry 1 in *Table 1*) which proceeds by breaking the bond between the carbonyl carbon and oxygen atom of the (*R*)-β-BL ring (acyl cleavage) with retention of the configuration[11]. It is also considered that the copolymerization of (*R*)-β-BL with γ-BL proceeds by acyl cleavage with retention of the configuration because the decreases in T_m and T_g are not dramatic, and the optical rotation of polyesters shows negative values ranging from $-1.5°$ to $-2.2°$.

Conclusion

It has been disclosed that the reaction of the (*R*)-β-butyrolactone (92% ee) with γ-butyrolactone in the presence of a distannoxane catalyst at 100°C yielded the poly(3-hydroxybutyrate-*co*-4-hydroxybutyrate)s with various contents of the 4HB unit. P(3HB-*co*-6% 4HB) showed the maximum molecular weight ($M_n = 96\,000$). The P(3HB-*co*-4HB)s by the ring-opening polymerization showed a structure quite similar to that produced by bacteria.

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