Copolymerization of 3-(*S*)-[(benzyloxycarbonyl)methyl]-1,4-dioxane-2,5-dione and L-lactide: a facile synthetic method for functionalized bioabsorbable polymer

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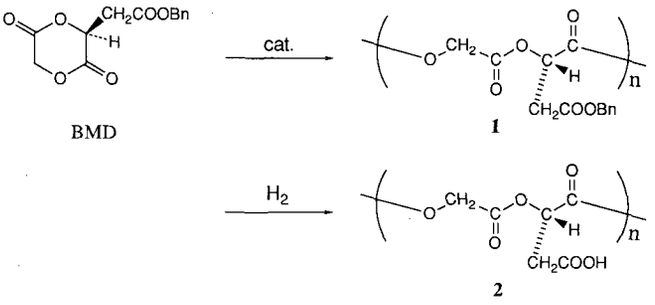
The copolymerization of 3-(*S*)-[(benzyloxycarbonyl)methyl]-1,4-dioxane-2,5-dione (BMD) and L-lactide (LAC) was carried out in bulk at relatively low BMD/LAC feed ratios with stannous 2-ethylhexanoate as the catalyst. The resulting copolymers were subjected to hydrogenolysis at atmospheric pressure in the presence of a palladium on charcoal catalyst to remove the pendant benzyl groups quantitatively. The deprotected copolymers consisted of L-lactic (L), glycolic (G) and L-α-malic acid (M) repeating units, with the copolymer composition being almost identical to the monomer feed composition. ^{13}C n.m.r. spectroscopy revealed that the BMD units (G–M) had been randomly incorporated into the copolymer (L–L). These poly(α-hydroxy acid)s with pendant carboxyl groups were found to hydrolyse more rapidly than poly(L-lactide), because of the water-absorbing and catalytic activities of the carboxyl moieties. They were allowed to react with *p*-azidophenacyl bromide in the presence of triethylamine to form photo affinity labelling groups at the carboxyl functionalities. These findings suggested that the malic-acid-containing poly(α-hydroxy acid)s should have a high potential for use as functionalized bioresorbable polymers.

(Keywords: α-malic acid unit; L-lactide; poly(α-hydroxy acid); carboxyl side group; copolymerization; catalytic hydrogenolysis)

INTRODUCTION

Poly(α-hydroxy acid)s such as poly(glycolic acid) (PGA) and poly(lactic acid) (PLA) have been widely used as bioresorbable polymers, from which a variety of medical products and drug delivery systems have been developed[1–8]. However, the biodegradation rates of these materials were difficult to control[9], because of their high crystallinity[10,11] and poor hydrophilicity[9,12]. In particular, poly(L-lactic acid) (PLLA) with hydrophobic methyl substituents has been shown to need more than two years for its complete absorption *in vivo*[13]. Consequently, recent work has focused on methods of imparting a hydrophilic nature to these polymers by suitable functionalization[14–16] and copolymerization techniques[17–24]. One of the promising methods for modification is to introduce another hydroxy acid metabolite, malic acid, in the polyesters[25–31]. The incorporation of malate repeating units into the copolymer places pendant carboxyl groups along the chain. These pendant carboxyl groups can work as the catalysts and sites of water absorption for hydrolysis, as well as functional groups for immobilizing other bioactive agents. However, few methods are known for introducing the malic acid units into poly(α-hydroxy acid)s, because of the difficulty in synthesizing polymerizable or copolymerizable malic-acid-containing monomers[32]. Recently[33], we reported the synthesis of a novel cyclic diester monomer consisting of both glycolate (G) and benzyl-α-L-malate (M*) units, i.e. 3-(*S*)-[(benzyloxycarbonyl)methyl]-1,4-dioxane-2,5-dione (BMD). This monomer polymerizes into poly[(glycolic acid)-*co*-(benzyl-α-L-malate)] **1** in the presence of such conventional catalysts as stannous 2-ethylhexanoate (*Scheme 1*). The pendant benzyl groups of **1** are readily deprotected by catalytic hydrogenolysis to give poly[(glycolic acid)-*co*-(α-L-malic acid)] **2** having free carboxyl groups. We therefore consider BMD as a useful monomer for incorporating α-malic acid units into poly(α-hydroxy



Scheme 1 Polymerization of BMD to give **1** and subsequent hydrogenolysis to give **2**

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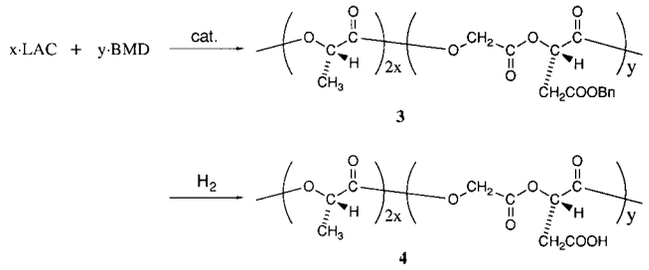


Scheme 2 Copolymerization of LAC and BMD to give **3** and subsequent hydrogenolysis to give **4**

acid)s. In the present paper, copoly(α-hydroxy acid)s with regulated amounts of α-malic acid units were prepared by the copolymerization of 3-(*S-cis*)-3,6-dimethyl-1,4-dioxane-2,5-dione (L-lactide: LAC) and BMD and by the subsequent hydrogenolysis of the pendant benzyl esters (*Scheme 2*). Since the reactivity of BMD is comparable with that of LAC, the copolymer composition was found to be controlled by adjusting the monomer ratio in the feed. The poly[(L-lactic acid)-*co*-(glycolic acid)-*co*-(α-L-malic acid)] **4**, which was obtained after the hydrogenolytic deprotection of **3**, was shown to be much more hydrophilic than PLLA.

EXPERIMENTAL

Materials

BMD was prepared as previously reported[33]. LAC of polymerization grade was provided by Mitsui Chemical Corp. (Tokyo, Japan). Stannous 2-ethylhexanoate was supplied by Nakarai Tesque Co. Ltd (Kyoto, Japan) and purified by distillation. The solvents (1,4-dioxane (DOX), diethyl ether, tetrahydrofuran (THF), chloroform, dimethylformamide (DMF), etc.) and palladium on charcoal (Pd–C) were used as received. *p*-Azidophenacyl bromide (APB) was supplied by Pharmacia Japan (Tokyo, Japan) and used as received.

Measurements

^{1}H and ^{13}C n.m.r. spectra were recorded on a Varian XL-200 spectrometer at 200 MHz and 50.3 MHz, respectively, with tetramethylsilane as the internal standard. I.r. spectra were measured by a JASCO IRA-1 spectrometer. G.p.c. was measured on a Toyo Soda HLC-802A analyzer fitted with an r.i. detector and a TSK-CP8000 data processor. The column (7.5 mm i.d., 60 cm length) contained polystyrene gel (TSK Gel G4000 H8) which was of 16000 t.p. with limited exclusion molecular weight of 4×10^5. The sample was injected at 38°C with THF as the eluent. The molecular weight was calibrated relative to mono-dispersed polystyrene standards. D.t.a. was performed on a Shimazu DT-30 thermal analyser for a 5.0 mg sample. The sample was heated at a rate of 10°C min^{-1} under a nitrogen atmosphere, and its thermographic change was recorded at both ranges of 25 and 100 μV. Scanning electron micrographs were recorded on a JASCO TSM-25S II microscope.

Copolymerization

Prescribed amounts of LAC and BMD were placed in a 100 ml round bottomed flask equipped with a mechanical stirrer. The flask was evacuated and filled with argon gas. The flask was heated up to 160°C, and the mixture was stirred. To this monomer mixture was added stannous 2-ethylhexanoate (0.1 mol%, relative to the total monomer concentration) and the mixture was stirred at this condition for a period of about 5 min. Then, the pressure of the system was gradually reduced to 100 mmHg by a vacuum pump. While the system was stirred under these conditions for 2 h, the viscosity of the system gradually increased. The final product was dissolved in 100 ml of DOX and poured into an excess of diethyl ether to precipitate out the product, which was filtered and dried *in vacuo*. **3** (crystalline powder) – ^{1}H n.m.r. (200 MHz in $CDCl_3$), δ (ppm): 1.48 (d, CCH_3), 2.90 (m, CH_2CO), 4.61 (q, OCH_2CO), 5.08 (q, $CHCH_3$), 5.51 (m, OCH), 7.23 (s, C_6H_5). ^{13}C n.m.r. (50.3 MHz in $CDCl_3$), δ (ppm): 16.5 (CCH_3), 35.2 (CH_2CO), 60.4 (OCH_2CO), 66.5 (CH_2Ph), 68.2 ($OCHCO$), 128.4 (CH of C_6H_5), 135.3 (C of C_6H_5), 166.2 (OCH_2CO), 167.5 ($OCHCO$ of the malate), 168.2 (CH_2CO), 169.4 ($OCHCO$ of the lactate). I.r. (KBr), cm^{-1}: 2980, 1760, 1730 (ester), 1270, 1160, 1070.

For comparison, homopolymerization of LAC was carried out under identical reaction conditions.

Hydrogenolysis

A solution of 8 g of **3** in 250 ml of an ethanol/DOX (25:75 v/v) mixture was transferred into a 1 l flask. After 1 g of palladium on charcoal catalyst had been dispersed in this solution, the flask was evacuated, connected to a hydrogen depot standing at atmospheric pressure by a rubber tube, and filled with hydrogen gas. The mixture was then stirred vigorously with a magnetic stirrer and reacted with hydrogen for 10 h. After the theoretical amount of hydrogen had been absorbed, the mixture was filtered to remove the catalyst. The filtrate was condensed at reduced pressure and poured into a large excess of diethyl ether to precipitate out the product, which was filtered and dried *in vacuo*. **4** (white crystalline powders) – ^{1}H n.m.r. (200 MHz in $CDCl_3$), δ (ppm): 1.47 (d, CCH_3), 3.08 (m, CH_2CO), 4.71 (q, OCH_2CO), 5.08 (q, $CHCH_3$), 5.66 (m, OCH). ^{13}C n.m.r. (50.3 MHz in $CDCl_3$), δ (ppm): 17.2 (CCH_3), 35.2 (CH_2CO), 60.4 (OCH_2CO), 69.6 ($OCHCO$), 166.9 (OCH_2CO), 168.2 ($OCHCO$ of the malate), 170.1 (CH_2COOH and $OCHCO$ of the lactate). I.r. (KBr), cm^{-1}: 3440 (OH), 1758 (ester), 1710 (shoulder, COOH), 1170, 1070.

Preparation of polymer film

A 20 wt% solution of **4** in DOX was prepared and cast on a glass plate. After the liquid layer solidified in air, the semi-solid film was peeled off from the plate and thoroughly dried *in vacuo*. The film was transparent with a thickness of about 0.1 mm. For comparison, a film of PLLA was prepared in the same manner.

Hydrolysis of the films

Several pieces of these films ($50 \times 5 \times 0.1$ mm) were placed in glass ampoules containing 10 ml of phosphate buffer (pH 7.2). The ampoules were sealed and dipped into a water bath thermostated at 37°C. After a prescribed time, the films were taken out from the ampoules and were subjected to analysis.

Table 1 Copolymerization of BMD and LAC[a]

Run no.	Monomer feed composition LAC/BMD	Yield (%)	Copolymer[b] composition LAC/BMD	M_n[c]	M_w/M_n[c]
1	100/0	94	100/0	39 500	2.4
2	95/5	81	95/5	57 200	2.4
3	90/10	85	91/9	43 200	2.0
4	85/15	98	86/14	36 800	2.1

[a] In bulk at 160°C with 0.1 mol% of $(C_7H_{15}COO)_2Sn$
[b] By ^1H n.m.r. spectroscopy
[c] Determined by g.p.c. relative to polystyrene standards

Reaction of **4** *with APB*

Next, 200 mg of **4** (sample: G/M/L = 7.0/7.0/86) and 90 mg of APB were dissolved in 4 ml of DMF, and 30 mg of $NaHCO_3$ were suspended in this solution. The mixture was then stirred vigorously at room temperature for a period of 2 days. After the reaction was over, the insoluble salts were filtered off, and the filtrate was poured into 30 ml of diethyl ether to precipitate out the product. The solid product was filtered and dried *in vacuo*. **5** – ^1H n.m.r. (200 MHz in $CDCl_3$), δ (ppm): 1.47 (d, CCH_3), 3.11 (m, CH_2CO), 4.71 (q, OCH_2CO), 5.08 (q, $CHCH_3$), 5.25 (s, CH_2CO of APB residue), 5.57 (m, OCH), 7.00 (d, aromatic *H* of C_3 and C_5), 7.80 (d, aromatic *H* of C_2 and C_6). ^{13}C n.m.r. (50.3 MHz in $CDCl_3$), δ (ppm): 16.6 (CCH_3), 35.5 (CH_2CO), 61.1 (OCH_2CO), 66.3 (CH_2CO for APB), 68.9 (OCHCO), 119.2 (aromatic C_3 and C_5), 129.7 (aromatic C_2 and C_6), 130.5 (aromatic C_4), 145.8 (aromatic C_1), 166.3 (OCH_2CO), 167.5 (OCHCO of the malate), 168.1 (CH_2CO), 169.5 (OCHCO of the lactate), 189.7 (COPh). I.r. (KBr) cm^{-1}: 2980, 1760, 1730 (ester), 1270, 1160, 1070.

RESULTS AND DISCUSSION

Copolymerization of BMD and LAC

The copolymerization of BMD and LAC was carried out in bulk with stannous 2-ethylhexanoate, known to be the most effective catalyst for the polymerization of both LAC and BMD. The BMD/LAC molar ratios in the feed were set below 0.2 because the present purpose was to modify the resorption profile of PLLA. *Table 1* shows the results of the copolymerization. In all of the runs, the copolymers were obtained in high yield (> 80%) as white crystalline powders. The molecular weight of the copolymers was over 30 000 as determined by g.p.c. and was even higher than that of the PLLA homopolymer prepared under identical conditions. *Figure 1* shows the typical ^1H and ^{13}C n.m.r. spectra of the copolymers **3** whose signals were assigned as described above. Here, the proton signal of the glycolate methylene was detected as an AB quartet. This may be because the two protons are diastereotopic with respect to the chiral centre in the neighbouring L-malate unit. By contrast, no splitting was observed in the proton-decoupled carbon signal of the same methylene. These results, combined with the other spectroscopic data previously summarized, indicate that the copolymer structure of **3** consists of lactate (L), glycolate (G) and benzyl-α-L-malate (M*) units. The copolymer compositions determined by ^1H n.m.r. spectroscopy were almost identical with the monomer feed composition. This indicates that the BMD ratio in the copolymer is readily controlled by changing the monomer ratio in the feed.

Figure 2a shows the enlarged spectrum of the carbonyl carbons of **3**. All of the signals are split into two or three lines due to the different diad sequences. With stannous 2-ethylhexanoate as the catalyst, the polymerization mechanism involves the transesterification reaction between the terminal hydroxy group and the monomer which is rendered more reactive by complexing to the Lewis acid catalyst. In the present copolymerization either LAC or BMD reacts with the terminal hydroxy group to form one diad. While LAC forms one homo-diad LL, BMD has two possibilities of forming the diad. If the ring-opening of BMD occurs at the carbonyl of the G unit (course a), the diad GM* is generated. In the alternative case where the carbonyl of M* is opened (course b), M*G is formed (*Scheme 3*). Here the units L, G, and M* are bonded with each other having the arrangement shown below. In addition, the probability of forming the homo sequence of BMD is negligibly small at the present relatively low BMD/LAC ratios in the feed composition. Therefore, the unit sequences formed by the copolymerization are thought to be **3a** and **3b**, depending on which carbonyl of BMD is attached. The diads involved in these sequences are shown in parentheses. Since the chemical shift of the ester carbonyls is slightly influenced by the ether units bonding to them[22–24], the observed signals should be assigned to the ester carbonyl carbons of the underlined units, as summarized in *Figure 2a*. The two signals for the chain carbonyls of G and M* units[23] are ascribed to a pair of diads L*G*/M**G* and G*M**/L*M**, respectively. The two

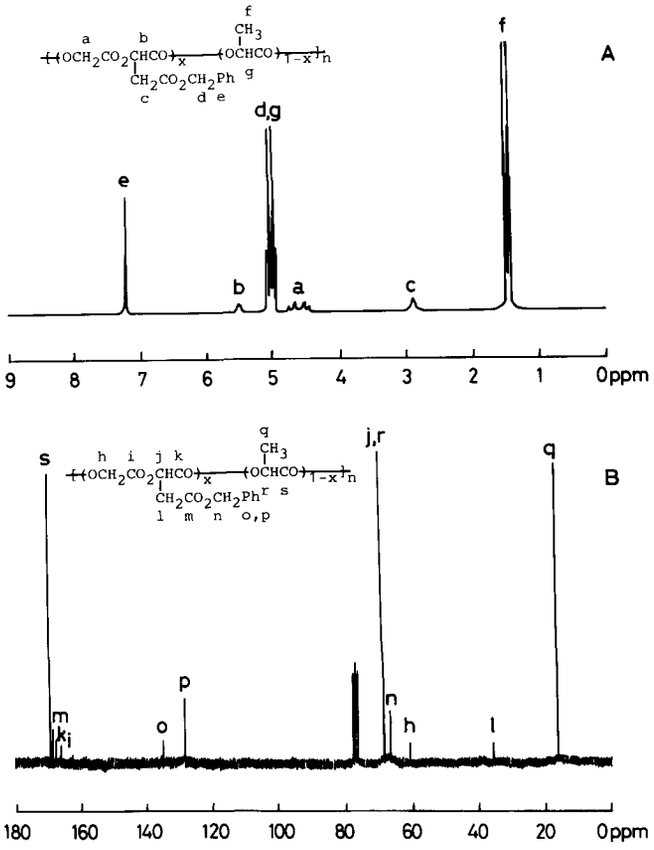


Figure 1 N.m.r. spectra of **3** ($CDCl_3$): (A) 200 MHz ^1H spectrum and (B) 50.3 MHz ^{13}C spectrum

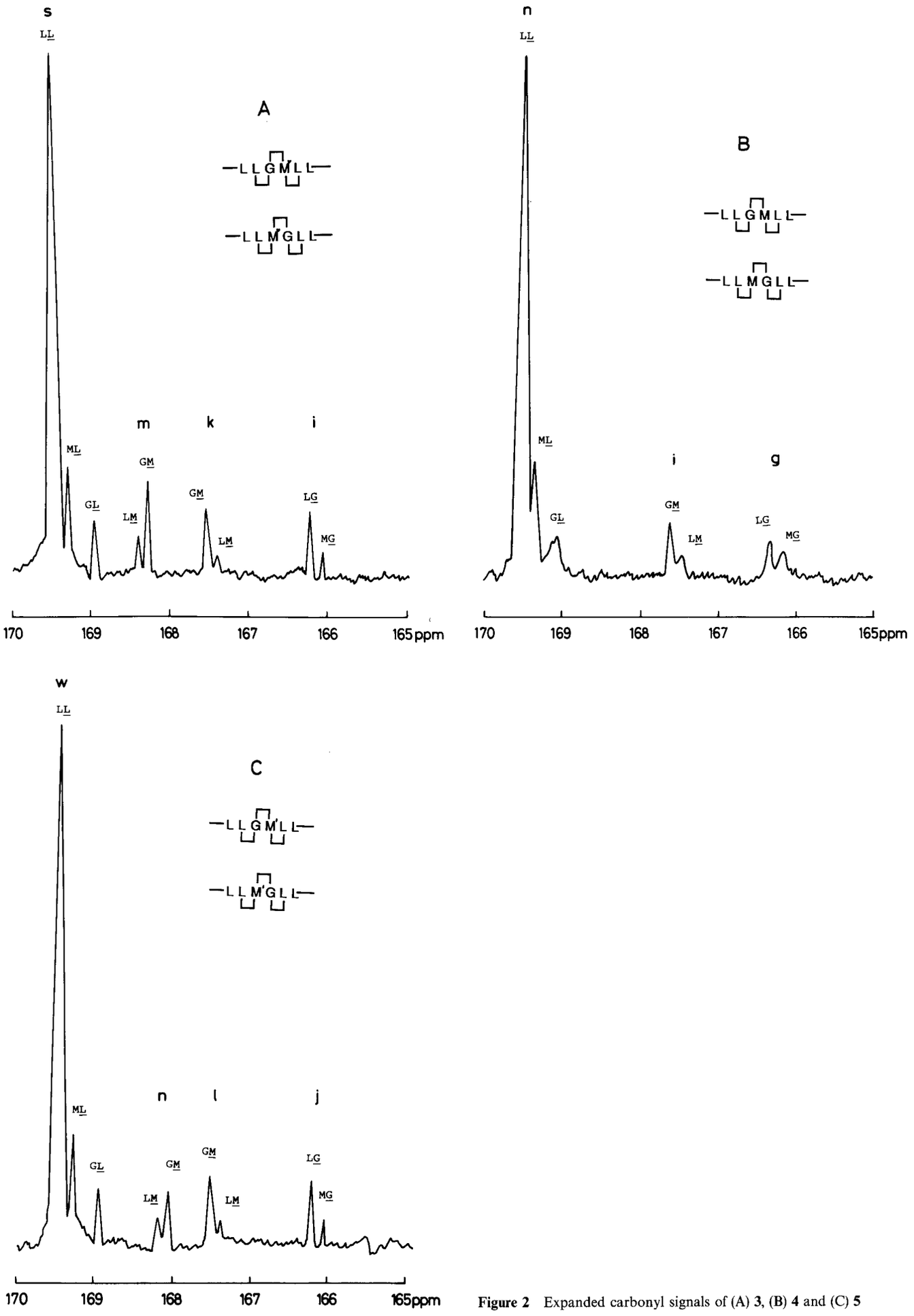


Figure 2 Expanded carbonyl signals of (A) **3**, (B) **4** and (C) **5**

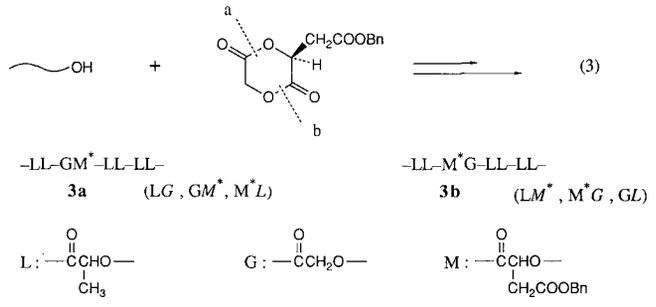
signals for the pendant ester groups of M* are also due to the G*M**/L*M** diads. For the carbonyls of the L units, a large signal due to the *LL* units is detected in addition to the two signals of M**L* and G*L*. The ratios of L*G*/M**G* and G*M**/L*M** were larger than unity, probably because of the higher probability of the ring-opening at the sterically less hindered G carbonyl of BMD (course a). The absence of G*G* and M**M** diads indicated that no ester interchange reactions occurred during the copolymerization.

Deprotection of 3 to 4

The copolymers **3** were subjected to catalytic hydrogenolysis at atmospheric pressure with palladium on charcoal as the catalyst[25–30]. The deprotection of the benzyl groups proceeded quantitatively to give **4**, whose characterization is summarized above. *Figure 2b* shows the carbonyl signals of the ^{13}C n.m.r. spectrum. The signals of the pendant carboxyl groups shifted to lower field and superimposed with those of L carbonyls. The other signals are identical to those of **3**. In *Table 2*, the molecular weights of **4** determined by g.p.c. are summarized. The observed values were found to be larger than the theoretical values calculated from those of the corresponding original copolymers **3**, because of the increased hydrodynamic volume or the intermolecular association by forming hydrogen bonds between the carboxyl groups. These data suggested that the benzyl groups of **3** are probably deprotected without scission of the polymer chain to form copolymer **4** consisting of lactic (L), glycolic (G) and α-L-malic acid (M) units quantitatively.

Thermal properties of 3 and 4

Figures 3 and *4* show d.t.a. curves of **3** and **4**, respectively. All polymers exhibited an endothermic peak due to melting of the PLLA crystallites. The melting temperature (T_m) was found to be lower with increasing BMD composition in the copolymers, as is known for the other conventional crystalline polymers. The crystallinity of **3** comprising 14 mol% of BMD units seemed to be very low. In the case of the deprotected polymers **4**, sharper peaks were noted at higher temperatures than those of the corresponding **3**. This is because the weight fraction of L units is comparably increased in **4** with the benzyl groups removed. The glass transition temperatures (T_gs) of **3** and **4** were also much lower than that of the PLLA homopolymer (~61°C), and no clear glass transition behaviour was noted in *Figures 3* and *4*. Analyses at a higher sensitivity revealed that all of these copolymers showed a T_g in the temperature range of 20–23°C, as summarized in *Table 2*. The similar T_g, regardless of the change in copolymer composition and of the substituents of the pendant groups, may possibly be due to the similar segment motion of the three-component polymer chains in the amorphous phase.



Scheme 3 Routes to formation of diads during ring-opening of BMD

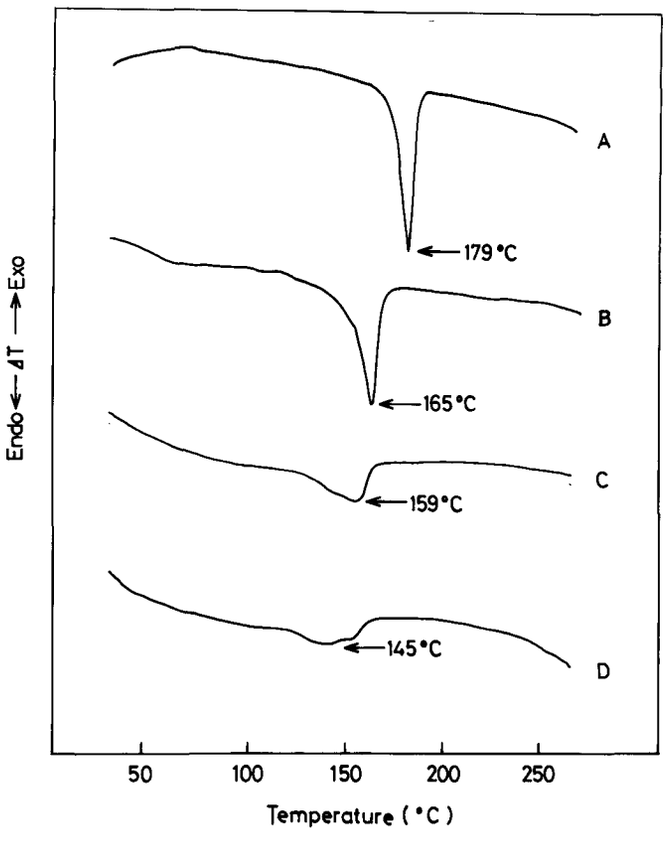


Figure 3 Typical d.t.a. curves of PLLA (A) and **3** with LAC/BMD ratios of 95/5 (B), 91/9 (C) and 86/14 (D)

Table 2 Molecular weight[a] and T_g[b] of **4** as compared with those of **3**

Run no.	Composition LAC/BMD	3			4			
		M_n	M_w/M_n	T_g (°C)	Calcd M_n[c]	M_n	M_w/M_n	T_g (°C)
1	95/5	57200	2.4	23	55400	79400	2.1	23
2	91/9	43200	2.0	21	40700	60700	1.8	20
3	86/14	36800	2.1	20	33700	54400	1.7	20

[a] By g.p.c. relative to polystyrene standards
[b] By d.t.a.
[c] Based on the M_n value of **3**

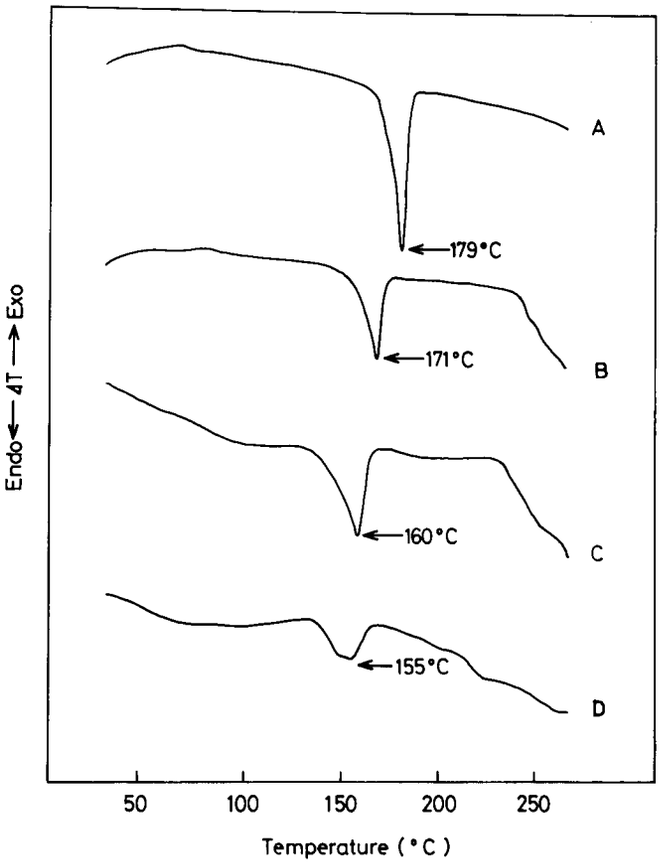


Figure 4 Typical d.t.a. curves of PLLA (A) and **4** with LAC/BMD ratios of 95/5 (B), 91/9 (C) and 86/14 (D)

Hydrolysis of 4

Films of **4** were prepared by solution casting and immersed in a phosphate buffer in order to investigate their *in vitro* hydrolysis rate. The film forming property of each **4** was excellent, and homogeneous transparent films were obtained in all cases. Since the film of PLLA was difficult to prepare, a polymer sample with higher molecular weight was used to obtain films for the control experiment. *Figure 5* shows the changes in molecular weight for the films as a function of immersion time. The hydrolysis of **4** was much faster than expected, and the molecular weight of **4** with BMD ratios of 9 and 14 mol% decreased less than 4000 after immersion for 1 week. Even in the case of **4** with BMD ratio of 5 mol% the half-life of the molecular weight was about 1 week. Since the control PLLA films showed no change in molecular weight in the period of this experiment, the extraordinarily large hydrolysis rate of **4** should be attributed to the function of the pendant carboxyl groups. These carboxyl groups may bind water in the interior of the film and catalyse the hydrolysis of the main chain esters, resulting in the sharp decrease in molecular weight of the polymers.

Figure 6 shows scanning electron micrographs of the films obtained after immersion for 1 week. In the films of **4** with higher BMD ratio a large number of cracks and holes were observed on the surface. Particularly in the case of **4** with BMD ratio of 14 mol%, the surface had been heavily eroded. After 3 weeks the surface of each film was covered with many grains which are derived from the PLLA spherulites. These data indicated that the introduction of α-malic acid units is quite effective for enhancing the *in vitro* hydrolysis rate of PLLA.

Introduction of APB into 4

The pendant carboxyl groups of **4** do not work as hydrophilic groups, but also as sites for chemical modification. Here, a model reaction was examined by reacting **4** with APB which is a photo affinity labelling agent[35] (*Scheme 4*). The reaction took place under mild conditions to give the product **5** quantitatively. Its characterization was described above. *Figure 2c* shows the carbonyl signals of **4**, which should be compared with *Figures 2a* and *2b*. Since all the carboxyl groups of **4** had been esterified, the signals around δ 168 ppm for the pendant carboxyl groups disappeared. In addition, carbonyl signals due to the phenacyl groups were detected at δ 189.7 ppm. These data were consistent with the structure **5** shown in *Scheme 4*. By analogous methods, other bioactive agents can be introduced on to **4** and utilized for drug delivery systems as well as for other biomedical materials and devices.

CONCLUSIONS

The malic-acid-containing poly(α-hydroxy acid)s were easily prepared by the copolymerization of BMD and LAC accompanied by the hydrogenolysis of the pendant benzyl groups. The copolymers were found to have an enhanced *in vitro* hydrolysis rate due to the water-

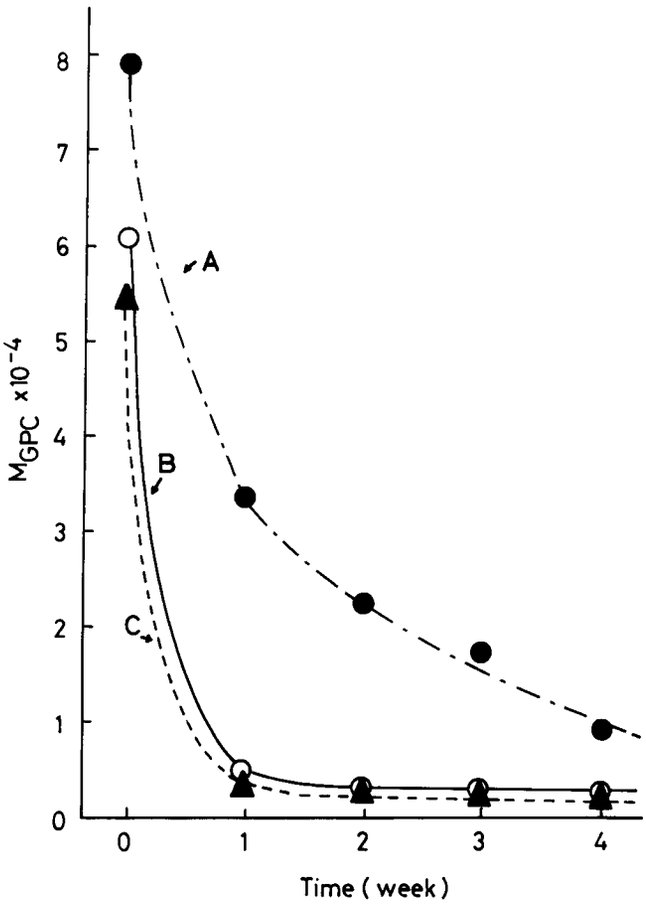


Figure 5 Decrease in molecular weight as a function of immersion time for films of **4** with LAC/BMD ratio of 95/5 (A), 91/9 (B) and 86/14 (C)

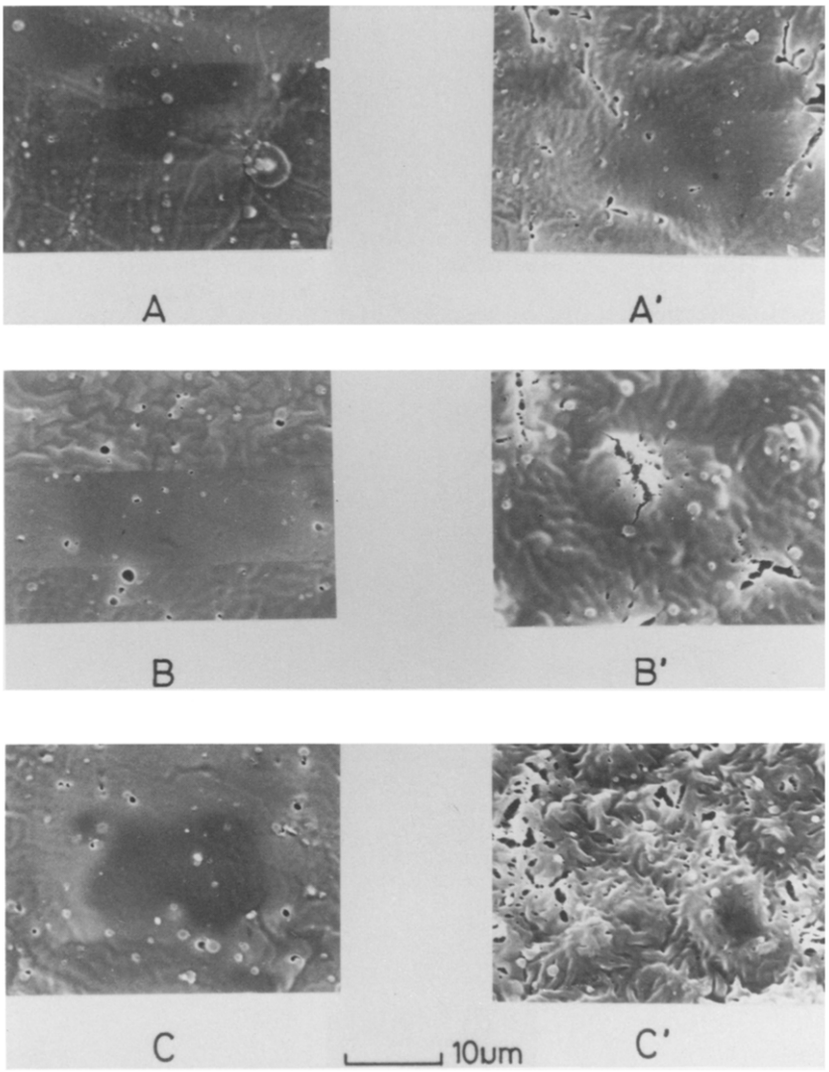
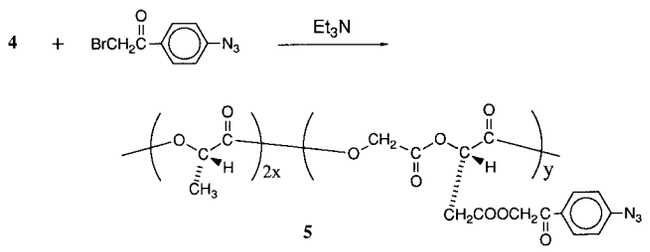


Figure 6 Scanning electron micrographs of the films (A'–C') immersed in phosphate buffer (pH 7.2) for 1 week compared with those (A–C) of control. LAC/BMD ratio of 95/5 (A, A'), 91/9 (B, B') and 86/14 (C, C')



Scheme 4 Functionalization of **4** with p-azidophenacyl bromide to give **5**

absorbing and catalytic activities of the pendant carboxyl groups. These carboxyl groups were also utilized for introducing functional moieties, such as photo affinity labelling groups. All of these novel copolymers could be used as bioabsorbable polymers. We are now studying the biodegradability and bioabsorbability of these copolymers.

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