

SYNTHESIS OF NOVEL HYDROPHILIC BIODEGRADABLE POLYESTER WITH FUNCTIONALIZED SIDE CHAIN GROUPS*

Ji-yuan Yang^{a,b}, Jian Yu^a, Huai-zhong Pan^b, Zhong-wei Gu^b, Wei-xiao Cao^a and Xin-de Feng^{a**}

^a Department of Polymer Science and Engineering, Peking University, Beijing 100871, China

^b National Research Institute for Family Planning, Beijing 100081, China

Abstract A substituted glycolide, 3-benzyloxymethyl-1,4-dioxane-2,5-dione, was synthesized. It is a suitable precursor for the preparation of a new hydrophilic biodegradable poly(α -hydroxy acid). The polymerizations were carried out in bulk in the presence of $\text{Sn}(\text{Oct})_2$ at 120–140°C. The resulting polymers were subjected to hydrogenolysis with a Pd/C catalyst in a mixed solvent to remove the protecting benzyl groups. A novel poly(α -hydroxy acid) with pendant hydroxy groups was obtained. The hydrophilicity of the resulting polymer was evaluated preliminarily.

Keywords Biodegradable polyester, Hydrophilicity, Functional pendant group

INTRODUCTION

Aliphatic polyesters, such as polyglycolide (PGA), polylactides (PLA) and their copolymers (PLGA), are of great interest for biomedical applications, because of their low toxicity, approved biocompatibility and the property of being degradable to α -hydroxy acid which can be removed easily by the usual metabolic pathways^[1, 2]. However, the modulation of their degradation rate has been interfered with by their hydrophobic and semicrystalline nature. In addition, they have no pendant reactive groups as triggers, limiting their application regions^[3]. Research on the modification of these polyesters has been mainly focused on improving the hydrophilicity of the polymers and on developing functional monomers/polymers, leading to improvement of cell adhesion, drug attachment and release profile. To this end, two major strategies have been proposed. One is to introduce water-soluble segments, such as poly(vinyl alcohol) (PVA) or poly(ethylene glycol) (PEG) through branching or blocking into polymer chain^[4, 5]. Another one is to introduce the functional pendant groups along the backbone of the polymers. There are numerous reports relating the introduction of the functional groups onto the polylactide chain. Following the synthesis of biodegradable polyesteramides reported by Feijen *et al.*^[6], a series of polyesteramides with pendant functional groups were synthesized, and lysine, aspartic acid and serine were used to introduce pendant functional groups onto polymer backbones by Langer^[7], Ouchi^[8] and Morita^[9]. Langer reported the application of the reaction between free amino group and bioactive peptide GRGDY to improve the affinity between the polyesters and the cell. Kimura *et al.*^[10, 11] described the synthesis of pendant carboxyl functional polyesters through the ring-opening polymerization of 3-(s)-[(benzyloxycarbonyl)methyl]-1,4-dioxane-2,5-dione with lactide using stannous octanoate ($\text{Sn}(\text{Oct})_2$) as the catalyst. The benzyl protecting groups were readily removed by catalytic hydrogenolysis to give the highly functionalized bioresorbable polyester. Recently, Hedrick and Jerome^[12–15] synthesized a series of ϵ -caprolactone derivatives with functional pendant groups along the polyester backbone. There are several other potentially degradable polyesters containing functional side chains that have been synthesized^[16–18].

* This work was supported by the Major State Basic Research Program of China (No. G1999064704).

** Corresponding author: Xin-de Feng (冯新德)

Received June 11, 2001; Revised June 18, 2001; Accepted June 21, 2001

Surprisingly there is no report about the synthesis of poly(cyclic diester) with hydroxy pendant groups. The increased hydrophilicity resulted from functional side groups will lead to higher water absorption, promoting the degradation rates of polyester.

In the present paper, we introduce the synthesis of a substituted glycolide, 3-benzyloxymethyl-1,4-dioxane-2,5-dione (3-BMG), which has superior ring-opening polymerizability comparable to that of glycolide and lactides in bulk using $\text{Sn}(\text{Oct})_2$ as the catalyst. The polymerization of 3-BMG results in an alternating copolymer consisting of glycolic acid and benzyloxymethyl glycolic acid units. Subsequently, a new hydroxyl-functionalized poly(α -hydroxy acid), *i.e.* poly[(glycolic acid)-*alt*-(hydroxymethyl glycolic acid)] was obtained after removing the benzyl protective group by catalytic hydrogenolysis, and the hydrophilicity of the polymer was evaluated by water sorption and static contact angle test.

EXPERIMENTAL

Materials

3-Chloro-1,2-propanediol (98%) was purchased from Merck and used as received. Benzyl alcohol, triethylamine, tetrahydrofuran (THF) and *N,N*-dimethyl formamide (DMF) were dried over and distilled from calcium hydride. 2-Bromoacetyl bromide (Across) was distilled under vacuum. $\text{Sn}(\text{Oct})_2$ and PLGA (Lactel BP-0100, a lactide-glycolide copolymer 50:50 mol) were obtained from Sigma. Lactide-glycolide alternative copolymer poly(GA-*alt*-LA) was synthesized in our laboratory. Palladium absorbed on carbon (10%) was obtained from Across. All other chemicals and solvents were reagent grade and used without further purification.

Characterization

The ^1H - and ^{13}C -NMR spectra were recorded with a Bruker ARX-400 spectrometer. Tetramethylsilane was used as the internal standard. The molecular weights and molecular weight distributions of the polymers were determined on a Waters 515 gel permeation chromatograph equipped with three Waters Styragel columns (HT2, HT3 and HT4) at 35°C, using THF as eluent (1.0 mL/min) and polystyrene as calibration standards. Differential scanning calorimetric (DSC) measurements were carried out with a TA DSC 2910 differential scanning calorimeter under the protection of N_2 at a heating/cooling rate of 10 K/min. The glass transition temperature (T_g) of polymers were determined from the second scanning cycle.

Monomer Synthesis

Synthesis of β -chlorolactic acid (2)

β -Chlorolactic acid (2) was synthesized according the method of Koelsch^[19] with some modifications. Briefly, 350 g (3.70 mol) of concentrated HNO_3 was added portionwise over 3 days to a solution containing 250 g (1.85 mol) of 3-chloro-1,2-propanediol (1) in 250 g of water. The mixture was kept at room temperature until the color remained unchanged. Then the solvent was removed under vacuum. The residue was kept at 4°C to form white solid, which was recrystallized from isopropyl alcohol to give white crystals 2 150 g (yield 53%) with mp 77.5–79.0°C. Elemental analysis for $\text{C}_3\text{H}_5\text{O}_3\text{Cl}$ (Cald., %): C 28.90, H 4.05 and Cl 28.50. (Found, %): C 28.81, H 4.05, Cl 28.56.

Synthesis of 3-benzyloxy-glyceric acid (3-O-BGA) (3)

Under N_2 atmosphere, 15.5 g (0.67 mol) of sodium was added to 250 mL purified benzyl alcohol and heated until all the sodium was dissolved to form a pale yellow solution, to which 21.0 g (0.17 mol) of 2 in 100 mL benzyl alcohol was added dropwise with vigorous stirring. After reflux for 30 h the reactant was cooled to room temperature, an excess amount of water was added to destroy the remainder of sodium benzyl alcohol. The aqueous layer was separated and subsequently extracted with diethyl ether to remove benzyl alcohol. The aqueous layer was acidified with 6 mol/L HCl and then extracted again with diethyl ether. The diethyl ether layer was dried with MgSO_4 and evaporated under vacuum to yield the crude product, which was recrystallized from ethyl acetate to yield a white crystalline solid 3 (yield 47%). The characterization results are shown in Table 1.

3-Benzoyloxymethyl-1,4-dioxane-2,5-dione (3-BMG) (5)

In a typical reaction, to a solution of 19.6 g (0.10 mol) of **3** and 24.2 g (0.12 mol) bromoacetyl bromide in 150 mL diethyl ether, 19.2 g (0.19 mol) of triethylamine in 50 mL of diethyl ether was added dropwise with stirring at a temperature not exceeding 5°C over a period of 30 min. The mixture was continuously stirred at room temperature for 6 h, and filtered to remove triethylamine hydrobromide. The filtrate was evaporated in vacuo to remove the excess of 2-bromoacetyl bromide. The residue was redissolved in diethyl ether and washed with distilled water three times, dried with anhydrous Na₂SO₄ and concentrated in vacuo to give a yellow oil of 3-benzoyloxy-2-bromoacetyl propionic acid (**4**). A solution of **4** in 100 mL DMF was added dropwise to a solution of 8.7 g (0.086 mol) triethylamine in 400 mL of DMF under vigorous stirring at 90°C over a period of 3 h. The reaction mixture was further stirred for 5 h. After removal of the solvent in vacuo, the reddish residue was washed with diethyl ether. The combined organic fractions was then washed with the same volume of water several times, dried with Na₂SO₄, and evaporated in vacuo. The product was recrystallized from diethyl ether to give needle-like crystals of **5** in 40% yield. The characterization results are shown in Table 1.

Table 1. Characterization results of 3-O-BGA and 3-BMG

	3-O-BGA	3-BMG
Appearance	White needle-like crystal	
Solubility	Soluble in THF, chloroform, acetone etc.	
Melt point (°C)	52–53	49.5–50
¹ H-NMR (δ)	4.57 (phCH ₂ , 2.0) 3.80 (phCH ₂ OCH ₂ , 2.0) 4.38 (OCH(CH ₂ OBz)COO, 1.0)	4.57 (phCH ₂ , 2.0) 3.93–4.09 (phCH ₂ OCH ₂ , 2.0) 4.77–5.07 (OCH ₂ COO, 2.0) 5.06 (OCH(CH ₂ OBz)COO, 1.0)
Elemental analysis (%)	C 61.20, H 6.12 (Calculated) C 60.90, H 6.29 (Found)	C 60.17, H, 5.05 (Calculated) C 61.00, H, 5.08 (Found)

Polymerization of 3-BMG

All polymerization tubes were silanized using trimethylsilyl chloride (20 vol% in toluene), followed by repeated washings with toluene and methanol. The tube equipped with a stirring bar was heated above 130°C over 8 h, and cooled to room temperature in a desiccator before use.

Freshly crystallized 3-BMG was weighed and added to the polymerization tubes. Then the tubes were connected to the Schlenk-line and flushed 3 times with argon. A calculated amount of Sn(Oct)₂ in dry toluene was added using a dry syringe. The toluene was removed under vacuum for 1 h and then the tubes were sealed. The polymerization was conducted in an oil bath at constant temperature. After a given time, the polymerization was stopped and the polymer was dissolved in dichloromethane, then precipitated with methanol and filtered. The polymer was then dried in vacuo to constant weight. The results are given in Table 2.

Table 2. Ring-opening polymerization of 3-benzoyloxymethyl-1,4-dioxane-2,5-dione (3-BMG)

No.	[3-BMG]/[Sn] (mol/mol)	<i>T</i> (°C)	<i>t</i> (h)	Yield (%)	<i>M_n</i>	<i>M_w</i>	<i>M_w/M_n</i>
1	250	130	26	50.6	3500	5000	1.43
2	500	130	26	60.2	8000	13900	1.74
3	1000	130	26	85.7	10500	21100	2.01
4	2000	130	26	50.1	10800	21900	2.03
5	1000	120	26	75.1	9700	19700	2.03
6	1000	140	5	73.9	16000	31600	1.97
7	1000	140	10	79.5	15200	29400	1.93
8	1000	140	15	73.8	14300	26900	1.88
9	1000	140	26	79.5	11500	21800	1.90

Deprotection of PBMG

The poly(3-benzoyloxymethyl-1,4-dioxane-2,5-dione) (PBMG) was subjected to catalytic hydrogenolysis by using

10% palladium carbon (Pd/C) as the catalyst. The Pd/C was activated before use. Briefly, 40 mg Pd/C was dispersed in a 10 mL mixed solvent of dioxane/95% ethanol/acetic acid (6:3:1 vol). The system was evacuated and flushed with argon gas alternately for three times. Subsequently, hydrogen was bubbled into the suspension with stirring for 2 h at room temperature. A solution of 0.2 g PBMG in 10 mL of the above mixed solvent was added from a syringe. The reaction was conducted for 3 days at 35°C. The catalyst was removed by filtration and the filtrate was condensed in vacuo and then poured into excess chloroform. The deprotected polymer poly(3-hydroxymethyl-1,4-dioxane-2,5-dione) (PHMG) as a precipitate was collected and dried in vacuo.

Preparation of Films

The PBMG and PHMG were dissolved in chloroform and DMF, respectively, to prepare 5% (W/V) solution and then cast on a silanized glass plate. The films were obtained by drying the plates in air for 24 h and then in vacuo at 30°C for 48 h to remove residual solvent. The lactide-glycolide random copolymer 50:50 mol PLGA (Sigma) and lactide-glycolide alternative copolymer poly(GA-*alt*-LA) were adopted as control.

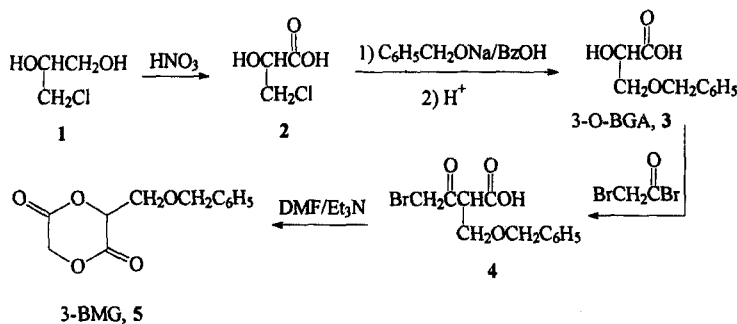
Evaluation of Hydrophilicity of the Polymer

Static contact angle and water absorption were used to evaluate the hydrophilicity of polymer. Contact angle was measured with more than five water drops for each sample on the coated plate using an OSA20 system (Physica Data Co.). The pure water dosing value was 20 μ L. All experiments were carried out at room temperature. After the contact angle test, the film was immersed in distilled water for several minutes and then peeled off the plate. For water uptake studies, three specimens of each sample were placed in the distilled water at 37°C for 8 h. After blotting up the water, the specimens were weighed, then vacuum-dried at 30°C to constant weight, and weighed again. The water absorption represents the average of the measurements from three specimens.

RESULTS AND DISCUSSION

Synthesis of 3-BMG

In the present study, a novel monomer, 3-benzyloxymethyl-1,4-dioxane-2,5-dione (3-BMG), has been successfully synthesized. It is a six-membered cyclic ester composed of glycolyl and benzyl protected glyceryl unit. An outline of the synthesis of 3-BMG is shown in Scheme 1. The overall yield was 40%.



Scheme 1 The synthetic route of 3-benzyloxymethyl-1,4-dioxane-2,5-dione

As a fundamental step for synthesizing of 3-BMG, the preparation of 3-O-BGA is the key step to improve the purity and the yield of 3-BMG. Though it is an important intermediate in drug preparation, only a few routes for the preparation of 3-O-BGA have been reported so far. Most of these syntheses start from the expensive *L*-serine and yield an oily product without further purification^[20–22]. In this article, we obtain, for the first time, the white solid of 3 through the reaction of sodium benzyl alcohol with β -chlorolactic acid derived from the oxidation of 3-chloro-propanediol. The structure of 3 is confirmed by the NMR spectrum (Fig. 1) and elemental analysis (see Table 1).

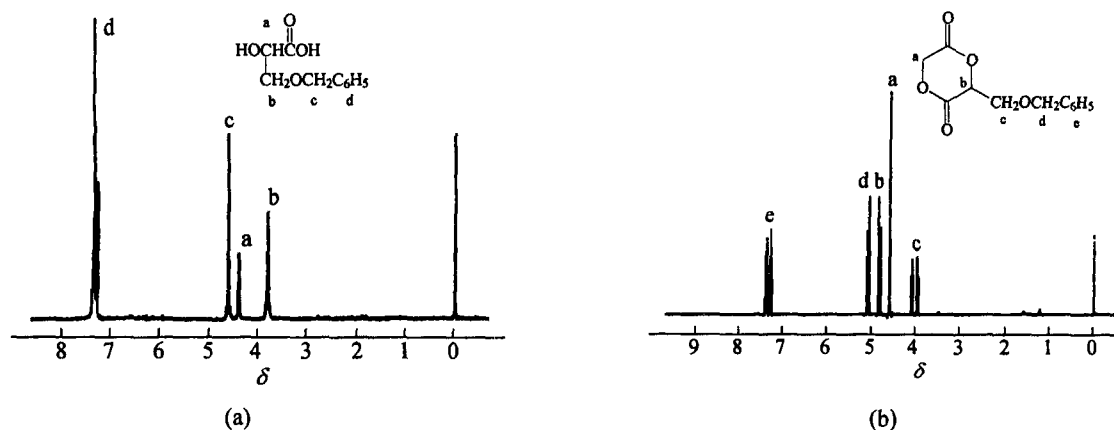
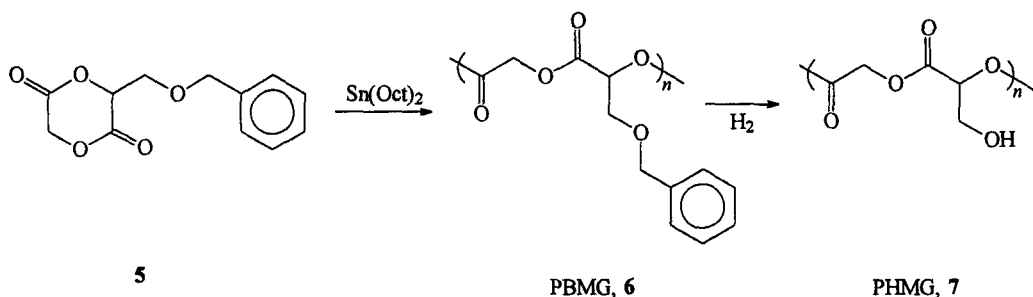


Fig. 1 ^1H -NMR spectrum of (a) 3-O-BGA; (b) 3-BMG (CDCl_3 as solvent)

Synthesis of Polymers

$\text{Sn}(\text{Oct})_2$ is one of the most often used catalysts for the ring-opening polymerization of cyclic esters such as lactides and ϵ -CL with high polymerization rate and high monomer conversion. In this study, homopolymerization of 3-BMG with $\text{Sn}(\text{Oct})_2$ catalyst was carried out in bulk between 120–140°C, as shown in Scheme 2. Figure 2 is the typical ^1H -NMR of PBMG. The results summarized in Table 2 show that both the yield and the M_n of polymer decrease with decreasing $[\text{3-BMG}]/[\text{Sn}]$ ratio (from 1000 to 250), indicating that $\text{Sn}(\text{Oct})_2$ is responsible for the formation of dead end-groups^[23]. At lower $\text{Sn}(\text{Oct})_2$ concentration ($[\text{3-BMG}]/[\text{Sn}] = 2000$), the yield decreases and M_n remains almost unchanged. Therefore, other polymerizations carried out in this study were conducted using the $[\text{3-BMG}]/[\text{Sn}]$ ratio of 1000. With increasing of temperature (from 120 to 140°C), the yield approximately keeps stable and M_n is increasing slightly. The effect of polymerization time shows that over 5 h the yield is almost unchanged while M_n decreases with increasing time due to transesterification reactions. It implies that the polymerization of 3-BMG is an reversible reaction, similar to the behavior of lactides^[24]. The GPC profile of the polymer shows a symmetrical single peak. The molecular weight data shown in Table 2 indicate that the polymerization activity of 3-BMG is similar to that of lactides or lactones in the presence of $\text{Sn}(\text{Oct})_2$.



Scheme 2 Ring-opening polymerization of 3-BMG and hydrogenolysis of PBMG

In the ^{13}C -NMR spectrum (Fig. 3) of PBMG, there are only two carbonyl signals appeared at $\delta = 163.4$ and $\delta = 163.1$. This result indicates that in the presence of $\text{Sn}(\text{Oct})_2$ the ring-opening polymerization of 3-BMG proceeds exclusively through the cleavage of the ester bond, similar to the results of lactide reported by Feijen *et al.*^[25]. In the recent work of Feng *et al.*^[26], the possibility of ring-opening polymerization of 3-methylglycolide (MG) through acryl-oxygen cleavage from the least hindered side of the MG ring was found to be about 85% when $\text{Sn}(\text{Oct})_2$ was used as catalyst. In the present study, due to the larger steric hindrance of

benzyloxymethyl group of 3-BMG compare with the methyl group of MG, the possibility of ring-opening occurs at the least hindered carbonyl groups. It means that the polymers consist of completely alternating distribution of glycolic and glyceric acid units.

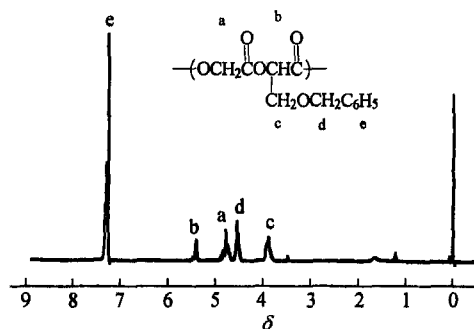


Fig. 2 ^1H -NMR spectrum of PBMG ($M_n = 1.5 \times 10^4$)

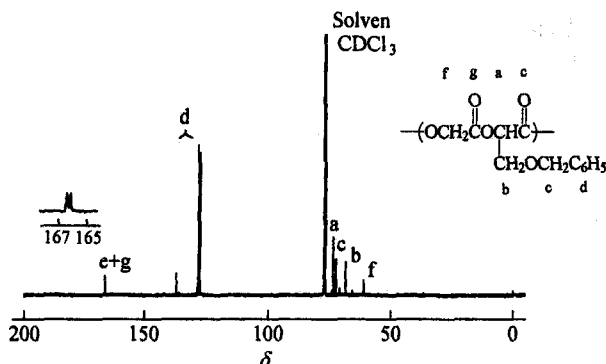


Fig. 3 ^{13}C -NMR spectrum of PBMG ($M_n = 1.5 \times 10^4$)

Removal of the Benzyl Protecting Groups

Catalytic hydrogenation was considered to be a selective and facile method to remove the pendant benzyl protecting groups present in the polymer^[10, 14]. In this study, palladium carbon was used as the catalyst to remove the benzyl group from PBMG. From the ^1H -NMR spectra, we can see that the protecting groups were almost completely removed because no proton signals of the benzyl group appear at $\delta = 7.2$ ($-\text{ph}$) and 4.57 ($-\text{CH}_2\text{ph}$) (DMSO as solvent).

Hydrophilicity of the Polymer

Films, cast from polymer solution, were used to measure the water absorption and contact angle. The data are shown in Table 3. A typical hydrophobic polyester, 50:50 PLGA, which had a contact angle of 96.7° (see Fig. 4a) and a water absorption less than 10% after 8 h immersion in water at 37°C , was used as a control. The contact angles of poly(GA-*alt*-LA) and PBMG were determined to be 77.3° and 89.8° , respectively, slightly lower than that of PLGA. However, PBMG had much higher water absorption (58.4 wt%) than poly(GA-*alt*-LA), which is 26.6 wt%. PBMG is an amorphous polymer with $T_g = 33.7^\circ\text{C}$, therefore, under the conditions of the water uptake test (37°C), it should be in a viscoelastic state. On the other hand, the ether bond of the benzyloxymethyl pendant group was liable to be attacked by water to form hydrate. Both reasons may be responsible for the drastic increase of water absorption. The deprotected polymer has a contact angle of only 20° (see Fig. 4b) and turns into a water-soluble polymer due to its dense hydroxyl pendant groups. Consequently, the hydrophilicity of polyester could be controlled within a wide range from very hydrophobic to water-soluble through copolymerization of 3-BMG with lactides or lactones followed by deprotection. This variability should

be of interest in practical usage of biomedical materials.

Table 3. Contact angles and water absorption of different samples

Sample	T_g (°C)	Contact angle (°)	Water uptake (%)
50:50 PLGA	48.5	96.7	5.0
Poly(GA- <i>alt</i> -LA)	42.3	77.8	26.6
PBMG	33.7	89.8	58.4
PHMG	19.6	20.0	– *

* Soluble in water during the water uptake test

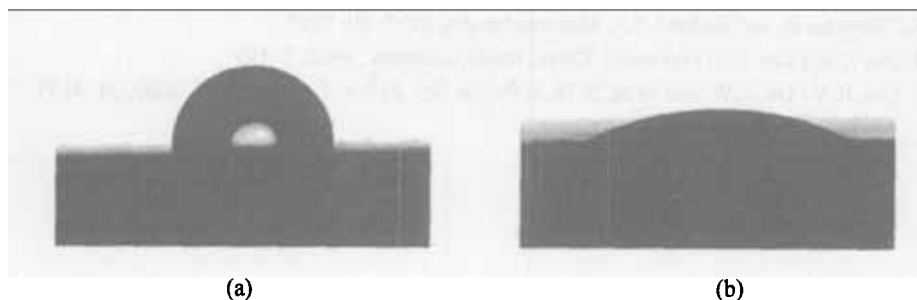


Fig. 4 Images of water drop on the surface of polymer film during contact angle analysis
a) 50:50 PLGA; b) PHMG

CONCLUSIONS

A new cyclic ester containing protected functional hydroxyl group was synthesized for the first time. The new monomer was polymerized in bulk under different conditions using $\text{Sn}(\text{Oct})_2$ as catalyst. The high molecular weight of the polymer shows that 3-BMG has high polymerizing power. The availability of hydroxyl pendant groups in poly(α -hydroxyl acid) has great potential for applications in drug delivery and tissue engineering.

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