

COPOLYMERIZATION AND DETERMINATION OF MONOMER REACTIVITY RATIOS OF *DL*-LACTIDE WITH 3-BENZYLOXYMETHYL-1,4-DIOXANE-2,5-DIONE*

Ji-yuan Yang^{a, b}, Jian Yu^a, Mei Li^a, Zhong-wei Gu^b 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 The copolymerization of *DL*-LA and 3-BMG was carried out in bulk with stannous 2-ethylhexanoate as the catalyst. A series of copolymers with pendant protected groups were obtained and characterized by ¹H-NMR and GPC analysis. The monomer reactivity ratios were evaluated by the Fineman-Ross method and the Kelen-Tüdös method and found to be $r_{\text{BMG}} = 1.96$ and $r_{\text{LA}} = 0.37$, respectively.

Keywords 3-Benzyloxymethyl-1,4-dioxane-2,5-dione, *DL*-Lactide, Reactivity ratios

INTRODUCTION

Poly(lactic acid) (PLA) is a versatile, well-characterized material, from which a variety of medical products and drug delivery systems have been developed^[1, 2]. However, because of its hydrophobicity, the release of proteins and peptides based on PLA could not be satisfactorily controlled, leading to undesired discontinuous or polyphasic release patterns. Increasing the hydrophilicity of the polymer will result in a faster water uptake and swelling of the polymer matrix, causing a faster and more prolonged drug release during the initial pore diffusion phase. Thus, the introduction of certain functional groups into polylactide for the modification of its properties has been investigated^[3–6].

Recently, we^[7] have reported a new cyclic diester monomer, 3-benzyloxymethyl-1,4-dioxane-2,5-dione (3-BMG), which can be ring-opening polymerized in bulk using stannous 2-ethylhexanoate ($\text{Sn}(\text{Oct})_2$) as catalyst. The resulting polymer was an alternating copolymer of glycolic acid and benzyloxymethyl glycolic acid units. Subsequently, a new hydroxyl-functionalized poly(α -hydroxy acid) was obtained after removing the benzyl protective group by catalytic hydrogenolysis. The contact angle of the copolymer decreases from 89.8° to only 20° on deprotection and the deprotected polymer became a water-soluble material due to its pendant hydroxyl groups^[7].

On the basis of these studies, we suppose that the hydrophilicity of polyesters could be controlled in a wide range from very hydrophobic to water-soluble through copolymerization of 3-BMG with *DL*-lactide (*DL*-LA) followed by deprotection, which would be of interest in practice for producing biomedical materials. In this research, copolymers of *DL*-LA and 3-BMG were synthesized and their reactivity ratios were determined.

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

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

Received September 6, 2001; Revised October 9, 2001; Accepted November 19, 2001

EXPERIMENTAL

Materials

As described in our former paper, 3-BMG was prepared from 3-benzyloxy-glyceric acid, which was obtained through the reaction of sodium benzyl alcohol with β -chlorolactic acid derived from the oxidation of 3-chloropropanediol^[7]. The product was recrystallized from diethyl ether and its characterization results are shown in Table 1. *DL*-LA was synthesized from *DL*-lactic acid^[8]. The crude product was purified by recrystallization from toluene, followed by sublimation three times under reduced pressure. The melting point of the purified *DL*-LA is 128–128.5°C. Stannous 2-ethylhexanoate (Sigma) was used as received. Toluene was refluxed over CaH₂ and distilled under nitrogen prior to use.

Table 1. Characterization results of 3-BMG

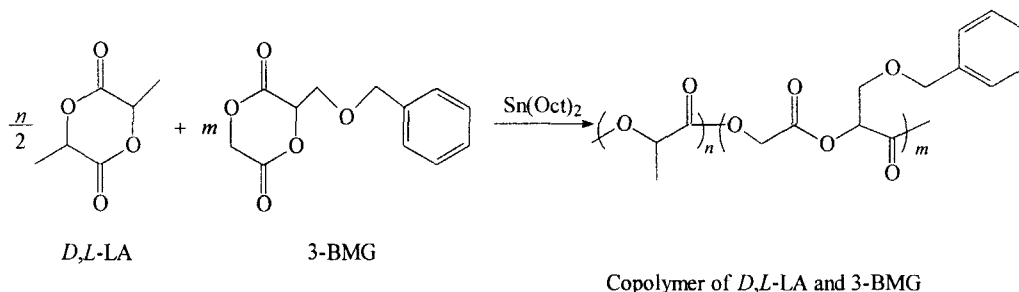
Appearance	White needle-like crystal
Solubility	Soluble in THF, chloroform, acetone <i>etc.</i>
Melt point (°C)	49.5–50
¹ H-NMR (δ)	4.57 (phCH ₂ , 2.0), 3.93–4.09 (BzOCH ₂ , 2.0) 4.77–5.07 (OCH ₂ COO, 2.0) and 5.06 (OCH(CH ₂ OBz)COO, 1.0)
¹³ C-NMR (δ)	65.5 (BzOCH ₂); 70.8 (OCH ₂ CO); 74.0 (phCH ₂); 76.5 (OCH(CH ₂ OBz)CO); 127.8–136.2 (ph); 163.6 (CH ₂ COO) and 164.5 (CHCOO)
FT-IR (neat, cm ⁻¹)	3029, 3011, 2974, 2870, 1766, 1750, 1608, 1494, 1447, 1378, 1070, 729 and 692
Elemental analysis (%)	C 60.17, H 5.05 (Calculated); C 61.00, H 5.08 (Found)
Mass (<i>E</i> / <i>I</i> , <i>m/z</i>)	236 (<i>M</i> ⁺)

Characterisation

¹H-NMR and ¹³C-NMR spectra of the copolymer were recorded with a Bruker ARX-400 spectrometer using tetramethylsilane (TMS) as the internal reference. FTIR spectra were measured on a Nicolet Magna-IR 750 spectrometer. The molecular weights and molecular weight distributions of the polymers were determined with a Waters 515 gel permeation chromatograph equipped with three Waters Styragel columns (10², 10³, and 10⁴) using THF as eluent (1.0 mL/min) at 35°C. Calibration was made with polystyrene standards.

Copolymerization of *DL*-LA and 3-BMG

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



Scheme 1

Freshly purified and thoroughly dried *DL*-LA and 3-BMG were weighed and added to the polymerization tubes. Then the tubes were connected to the Schlenk line, where evacuating-flushing with argon was repeated for 3 times. Next, a specific amount of Sn(Oct)₂ in dry toluene was injected into the tubes using a dry syringe. The toluene was removed under vacuum for 1 h and then the tubes were sealed. The copolymerization shown in Scheme 1 was conducted in an oil thermostat. After a given time, the polymerization was terminated and the resulting polymer was dissolved in dichloromethane, then precipitated with methanol and filtered. The polymer

obtained was then dried *in vacuo* until constant weight. The monomer conversion was determined gravimetrically. The results of copolymerization are summarized in Table 2. In the study of monomer reactivity ratios, the copolymerization of *DL*-LA and 3-BMG was conducted at 140°C and stopped at its initial stage of reaction in order to ensure the conversion of monomers below 10 percent.

Table 2. Copolymerization of 3-BMG and *DL*-LA^a

Run no.	Monomer feed LA/BMG (mol/mol)	Copolymer ratio ^b LA/BMG (mol/mol)	Yield (%)	M_n	M_w/M_n
1	100/0	100/0	96.5	28000	1.51
2	90/10	89.0/11.0	87.7	30000	1.82
3	85/15	84.9/15.1	73.4	36500	1.61
4	75/25	75.0/25.0	79.5	27500	1.73
5	50/50	48.0/52.0	73.8	21000	1.64
6	30/70	25.3/74.7	72.0	13500	1.73
7	20/80	11.5/88.5	82.2	12000	1.70
8	10/90	7.3/92.7	71.0	11000	1.76
9	0/100	0/100	85.7	10500	2.00

^a [M]/[Sn] = 1000, 130°C, 26 h

^b Determined by ¹H-NMR

RESULTS AND DISCUSSION

Copolymerization of *DL*-LA and 3-BMG

Both *DL*-LA and 3-BMG are six-membered cyclic monomers and can be homopolymerized in the bulk with Sn(Oct)₂, known to be one of the most effective catalysts for the ring-opening polymerization of cyclic diesters. Figure 1 shows the ¹H-NMR spectrum of a poly(*DL*-LA-co-3-BMG) (PLB) copolymer. The molar composition of PLB copolymer was calculated according to the following equation:

$$BMG(\%) = \frac{I_c}{I_c + I_f} \times 100$$

where I_c and I_f are the relative signal intensities at $\delta = 3.9$ (3-BMG) and 5.2 (lactide), respectively.

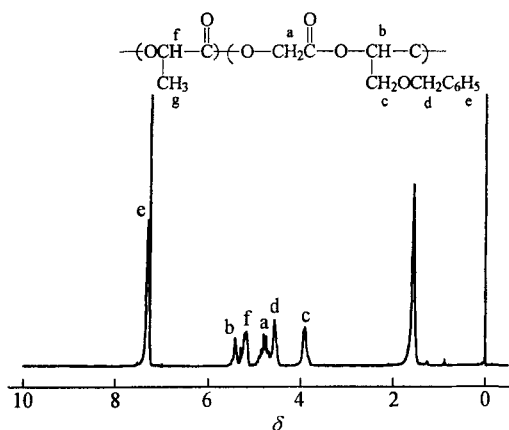


Fig. 1 ¹H-NMR spectra of copolymer of *DL*-LA and 3-BMG (50/50) in CDCl₃

Table 2 gave the molar ratio in the monomer feed, the composition and the molecular weight of resulting copolymers. The results indicate that the copolymerization of *DL*-LA and 3-BMG could be also conducted under similar condition as in homopolymerization of *DL*-LA or 3-BMG. Moreover, it can be seen that the molecular weight of the polymers gradually decreases with the increase of molar ratio of 3-BMG in the feed, while the 3-

BMG molar content in copolymers is higher than that in their monomer feed, especially when the 3-BMG feed ratio is higher than 50%. These results may reflect the difference of reactivity between 3-BMG and *DL*-LA.

Determination of Monomer Reactivity Ratios

Several procedures are available for the determination of monomer reactivity ratios, r_1 and r_2 . But all of them depend on careful analysis of the copolymer formed from mixtures of two monomers in varying ratios. Since the composition of copolymer changes with conversion, it is necessary either to control the copolymerization to very low conversion or to treat the integral composition. Table 3 is the data for copolymerization of 3-BMG and *DL*-LA at low conversion.

Table 3. Determination of reactivity ratios of 3-BMG (M_1) and *DL*-LA (M_2)

M_1 in monomer feed (mol%)	M_1 in copolymer (mol%)	r_1		r_2	
		F-R	K-T	F-R	K-T
20	34.6				
40	60.3				
50	67.6	1.88	2.04	0.31	0.43
70	84.5				
80	88.4				

* Copolymerization was conducted with Sn(Oct)₂ as catalyst at 140°C, ([M₁] + [M₂])/[Sn] = 1000

Fineman-Ross(F-R) method

The Fineman-Ross method has been widely used for deriving r_1 and r_2 of lactides or lactones^[9, 10]. In this method, r_1 and r_2 can be calculated from copolymer composition and monomer feed by using the Fineman-Ross equation as follows:

$$F(f-1)/f = (r_1 \cdot F^2/f) - r_2$$

where $F = [M_1]/[M_2]$, $f = d[M_1]/d[M_2]$, $[M]$ and $d[M]$ represent the initial concentration of monomer and instantaneous copolymer concentration, respectively.

In this study, M_1 and M_2 represent 3-BMG and *DL*-LA, respectively. The copolymer compositions were determined by ¹H-NMR. The points in Fig. 2(a) were obtained by plotting $F(f-1)/f$ against F^2/f and a straight line can be drawn through the points using the method of least squares. From the slope and the intercept of the line, the reactivity ratios of 3-BMG and *DL*-LA are found to be $r_1 = 1.88$ and $r_2 = 0.31$, respectively.

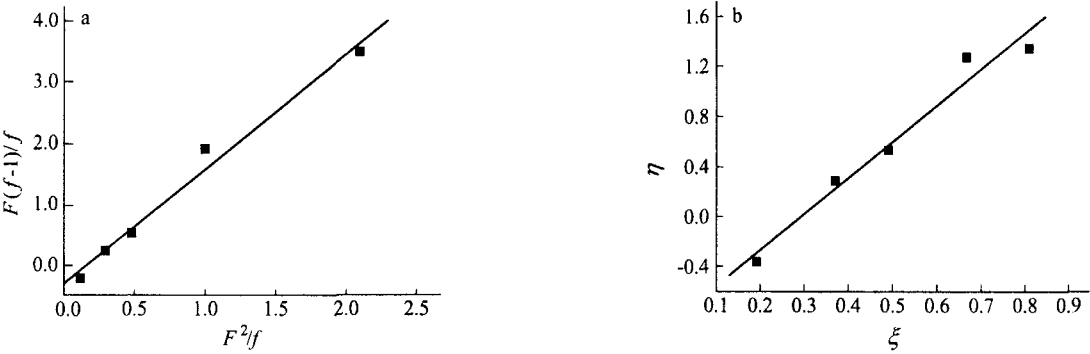


Fig. 2 Plots for computing reactivity ratios of 3-BMG and *DL*-LA, obtained by (a) Fineman-Ross method and (b) Kelen-Tüdös method

Kelen-Tüdös (K-T) method

Kelen-Tüdös equation:

$$\eta = (r_1 + r_2/\alpha)\xi - r_2/\alpha$$

where $\eta = G/(\alpha + Q)$, $\xi = Q/(\alpha + Q)$, $Q = F^2/f$, $G = (Q_M Q_m)^{1/2}$ (Q_M and Q_m are the maximum and the minimum values of Q , respectively). Similarly, the reactivity ratios of 3-BMG and DL-LA are obtained from Fig. 2(b), i.e. $r_1 = 2.04$ and $r_2 = 0.43$, respectively.

Accordingly, the values of monomer reactivity ratio ($\bar{r}_1 = 1.96$, $\bar{r}_2 = 0.37$) are obtained by averaging the r_1 and r_2 , calculated from the F-R method and the K-T method.

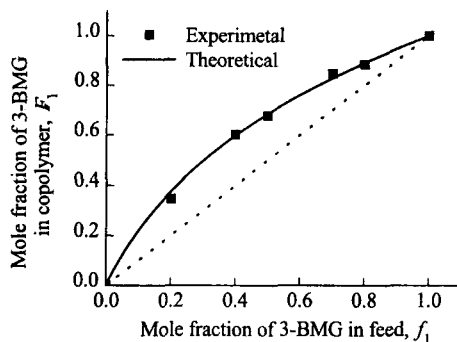


Fig. 3 Plot of molar ratio of 3-BMG in the copolymer against that in the monomer feed, obtained theoretically (solid line) and experimentally (dotted line)

The theoretical composition curve obtained according to the r_1 and r_2 is shown in Fig. 3, which coincide well with the experimentally observed composition curve.

REFERENCES

- 1 Vert, M., *Macromol Symp.*, 2000, 153: 333
- 2 Maquet, V. and Jerome, R., *Material Science Forum*, 1997, 250: 15
- 3 In't Veld, P.J.A., Dijkstra, P.J. and Feijen, J., *Makromol. Chem.*, 1992, 193: 2713
- 4 Barrera, D.A. and Langer, R., *Macromolecules*, 1995, 28: 425
- 5 Ouchi, T., Shiratani, M., Jinno, M., Hirao, M. and Ohya, Y., *Makromol. Chem. Rapid Commun.*, 1993, 14: 825
- 6 John, G., Tsuda, S. and Morita, M., *J. Polym. Sci. A: Polym. Chem.*, 1997, 35: 1901
- 7 Yang, J.Y., Yu, J., Pan, H.Z., Gu, Z.W., Cao, W.X. and Feng, X.D., *Chinese J. Polym. Sci.*, 2001, 19(5): 509
- 8 Kulkarni, R.K., Pani, K.C., Neuman, C. and Leonard, F., *U.S. Nat. Tech. Inform. Serv., AD Rept.* 1969, No.636,716
- 9 Albertsson, A.C. and Lofgren, A., *J. Macrom. Sci. Pure Appl. Chem.*, 1995, A32: 41
- 10 Dong, C.M., Qiu, K.Y., Gu, Z.W. and Feng, X.D., *Chinese Chem. Letter*, 2000, 11: 9