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# Measurement of Monomer Reactivity Ratios of D,L-3-Methylglycolide with Glycolide or D,L-Lactide

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**Abstract:** For monomer reactivity ratios study, the copolymerization of D,L-3-methylglycolide (MG) with glycolide (GA) or D,L-lactide (LA) was carried out in bulk to a certain low conversion in the presence of stannous octoate at 140 °C. The copolymer compositions were determined by $^1$H NMR spectroscopy. The monomer reactivity ratios were evaluated by Fineman-Ross method, Kelen-Tüdös method and linear least-squares method. The monomer reactivity ratios of D,L-3-methylglycolide and glycolide or D,L-lactide are $r_{mg}$= 0.73, $r_{ga}$= 1.47; $r_{mg}$= 1.71, $r_{la}$= 0.92, respectively.

**Keywords:** D,L-3-methylglycolide, glycolide, D,L-lactide, ring-opening copolymerization, monomer reactivity ratios.

Polylactides, polyglycolide and copolymers based on them, are still gaining interest because of the numerous applications in the biomedical and pharmaceutical fields[1]. They are usually prepared by bulk homo- and co-polymerizations of lactides, glycolide initiated with stannous octoate ($SnOct_2$) because $SnOct_2$ is a highly efficient commercial catalyst and a permitted food additive in numerous countries[1-2]. However, the properties of poly(D,L-lactic acid-co-glycolic acid) (D,L-PLGA) have widely varied from batch to batch because of the random block nature of polymer which is attributed to the higher reactivity ratios of glycolides[3-4]. Recently, different compositional D,L-PLGA has been commercialized[5]. The study of parameters influencing the degradation behavior of D,L-PLGA was the subject of numerous papers. The most effective influencing factors are the copolymer composition, the molecular weight and molecular weight distribution, and the polymer sequence structure[6]. Therefore, it is urgent to synthesize D,L-PLGA with regular sequence structure.

MG is the 6-membered lactone consisting of one lactic acid unit and one glycolic acid unit. D,L-PLGA (50:50, mol:mol) can be obtained from the homopolymerization of MG, which can also copolymerize with lactides or glycolide in the presence of $SnCl_2.2H_2O$ or $SnOct_2$[7-8], but the monomer reactivity ratios were not determined. The monomer reactivity ratios of MG and GA or LA are apparently important for the synthesis of D,L-PLGA with expected sequence structure. Until now, several methods have been proposed for calculating the monomer reactivity ratios from the feed monomer

composition and the copolymer composition. Among them, the methods used widely are Fineman-Ross method and Kelen-Tüdös method for the copolymerization of lactides or lactones[9-11]. In this communication, the evaluations of monomer reactivity ratios were described.

## Experimental

### *Materials and Methods*

Stannous octoate (Aldrich) was used as received. GA and LA were synthesized and recrystallized sequentially from dry ethyl acetate and toluene, the melting point was 82.5-83.5 °C, 129-130 °C, respectively.

$^1$H NMR spectroscopy was performed on a Bruker ARX-400 spectrometer. Molecular weights and molecular weight distributions of the polymers were determined on a Waters 150C gel permeation chromatograph equipped with three Waters Styragel columns ($10^2$, $10^3$, and $10^4$nm, respectively), using THF as eluent (1.0mL/min) at 35 °C. Calibration was made with monodispersed polystyrenes as the standards.

### *Monomer synthesis and Copolymerization*

D,L-3-methylglycolide (mp:62-63.5°C) was successfully synthesized with 40% yield according to the references[3,12] with some modification. $^1$H NMR ($CF_3COOD$): δ $CH_3$, 1.79-1.81 ppm (d, 3H); δ $CH_2$, 5.12-5.29 ppm (pseudo-q, 2H); δ CH, 5.34-5.38 ppm (q, 1H).

MG and GA or LA were put into the tube with a dry stirring bar. The tube was then connected to a Schlenkline, where an exhausting-refilling process was repeated three times. The monomers in the tube melted completely after the tube was put into an oil bath (140 °C). After vigorous stirring for about five minutes, a certain amount of stannous octoate in dry toluene was added to the melt mixture. The copolymer mixtures of GA and MG were extracted for 72h using ethyl acetate and petroleum ether (60-90 °C) mixed solvent (50:50, V:V). The copolymer mixtures of LA and MG were dissolved in $CH_2Cl_2$, then precipitated in petroleum ether (30-60 °C), finally shaked with methanol. The monomer conversion was determined gravimetrically.

## Results and Discussion

**Tables 1** and **2** give the molar ratio in the monomer feed, the resulting polymer composition and the monomer conversion. The molecular weight and molecular weight distribution are also given because the copolymers of MG and LA are soluble in THF. $^1$H NMR ($CF_3COOD$) of poly(MG-co-GA): δ CH, 5.50-5.55 ppm; δ $CH_2$, 4.97-5.15 ppm; δ $CH_3$, 1.68-1.75 ppm. $^1$H NMR ($CDCl_3$) of poly(MG-co-LA): δ CH, 5.15-5.30 ppm; δ $CH_2$, 4.62-4.90 ppm; δ $CH_3$, 1.40-1.73 ppm. The molar ratio of the copolymer composition can be calculated from the integral intensities of δ CH and δ $CH_2$.

*Fineman-Ross (F-R) method*

The Fineman-Ross equation: $F(f-1)/f = (r_1 \times F^2/f) - r_2$ (1)

where $F = [M_1]/[M_2]$, $f = d[M_1]/d[M_2]$, and $[M_1]$ and $[M_2]$ are the initial concentrations of $M_1$ and $M_2$ monomers, respectively. In **Table 1**, $M_1$, $M_2$ denote GA and MG, $r_1 = r_{ga}$ , $r_2 = r_{mg}$ ; in **Table 2**, $M_1$, $M_2$ denote MG and LA, $r_1 = r_{mg}$, $r_2 = r_{la}$. The monomer reactivity ratios: $r_{ga} = 1.44$, $r_{mg} = 0.70$ ; $r_{mg} = 1.64$, $r_{la} = 0.87$ are obtained from **Figures 1** and **2**, respectively.

**Table 1.** Copolymerization of GA and MG with $SnOct_2$ as initiator ($M/I^a = 1000$) at 140°C

| GA in monomer feed (mol %) | Conversion (%) | GA in copolymer (mol %) |
|---|---|---|
| 20 | 7.96 | 25.13 |
| 40 | 9.72 | 47.96 |
| 50 | 10.30 | 61.01 |
| 70 | 13.31 | 76.84 |
| 80 | 12.11 | 85.20 |

a: M= the mixture of monomers, I= $SnOct_2$

**Table 2.** Copolymerization of LA and MG with $SnOct_2$ as initiator (M/I=1000) at 140°C

| MG in monomer feed (mol %) | Conversion (%) | MG in copolymer (mol %) | $M_n$ | MWD |
|---|---|---|---|---|
| 10 | 6.64 | 10.32 | 2216 | 1.18 |
| 30 | 11.12 | 37.40 | 1439 | 1.13 |
| 50 | 7.98 | 60.73 | 2329 | 1.22 |
| 60 | 9.80 | 68.01 | 2216 | 1.21 |
| 80 | 8.66 | 86.06 | 2153 | 1.16 |

**Figure 1.** Fineman-Ross plot for the copolymerization of MG and GA

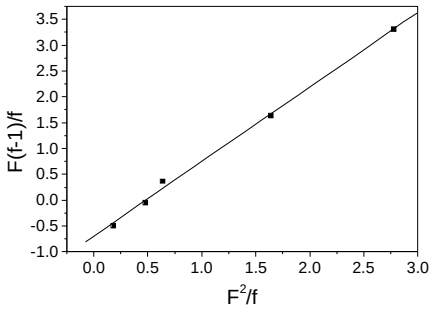
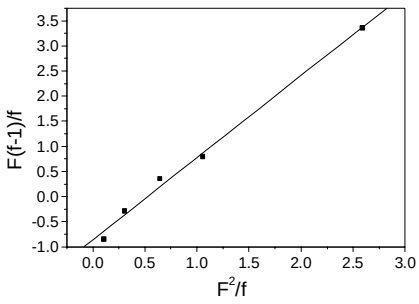



**Figure 2.** Fineman-Ross plot for the copolymerization of MG and LA




*Kelen-Tüdös (K-T) method*

Kelen-Tüdös equation : $\eta = (r_1 + r_2/\alpha)\xi - r_2/\alpha$ (2)

where $\eta = G/(\alpha+Q)$, $\xi = Q(\alpha+Q)$, $Q = F^2/f$ , $G = F(f-1)/f$, $\alpha = (Q_M Q_m)^{1/2}$ ($Q_M$ and $Q_m$ are the maximum and the minimum values of Q , respectively). The monomer reactivity

ratios : $r_{ga}$= 1.48, $r_{mg}$= 0.74; $r_{mg}$= 1.75, $r_{la}$= 0.95 are obtained from **Figures 3** and **4**, respectively.

*Linear Least-Squares (L-S) method*

On the basis of equation 2 and linear L-S method, the following equation was obtained,

$$A=\left[n\sum_i^n \eta_i\xi_i-\sum_i^n \eta_i\sum_i^n \xi_i\right]\Big/\left[n\sum_i^n \xi_i^2-\left(\sum_i^n \xi_i\right)^2\right], B=\left[n\sum_i^n \eta_i\xi_i\sum_i^n \xi_I-\sum_i^n \eta_i\sum_i^n \xi_i\right]\Big/\left[n\sum_i^n \xi_i^2-\left(\sum_i^n \xi_i\right)^2\right] \quad (3)$$

**Figure 3.** Kelen-Tüdös plot for the copolymerization of MG and GA

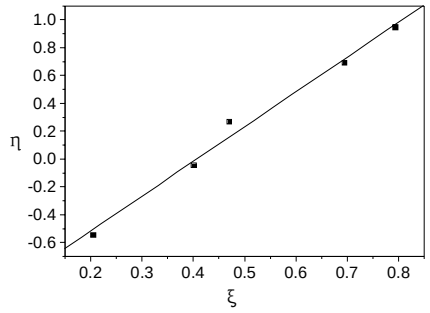
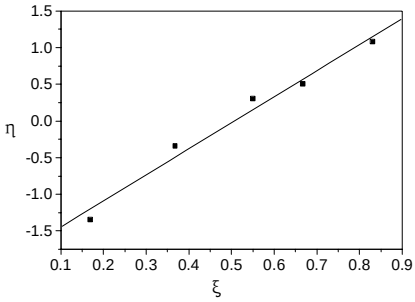



**Figure 4.** Kelen-Tüdös plot for the copolymerization of MG and LA




where A = $r_1$+$r_2/\alpha$, B = $r_2/\alpha$. The monomer reactivity ratios : $r_{ga}$= 1.48, $r_{mg}$= 0.74; $r_{mg}$= 1.75, $r_{la}$= 0.95 are obtained from **Tables 1** and **2**, respectively.

In summary, all of the three methods (F-R, K-T, L-S) gave the similar monomer reactivity ratios of D,L-3-methylglycolide with glycolide or D,L-lactide. That is to say, the results are reasonable and accurate. The average values from the three methods can be shown as the final monomer reactivity ratios : $r_{mg}$= 0.73, $r_{ga}$= 1.47; $r_{la}$= 0.92, $r_{mg}$= 1.71.

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