Found: C, 70.7; H, 11.1; N, 2.2; Br, —. Calcd for $C_{46}H_{87}NO_3S{\cdot}H_2O$ (2C18N2C1-PSS): C, 73.7; H, 11.6; N, 1.9. Found: C, 74.0; H, 12.2; N, 1.6; Br, 0.10.
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(7) Industrial Products Research Institute.
(8) Department of Polymer Chemistry.

Kazuhiro Taguchi,*[7] Syoichi Yano,[7] Kazuhisa Hiratani,[7] Norihiko Minoura,[7] and Yoshio Okahata[8]

Industrial Products Research Institute Higashi 1-1-4, Tsukuba-shi, Ibaraki 305, Japan

Department of Polymer Chemistry, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo 152, Japan

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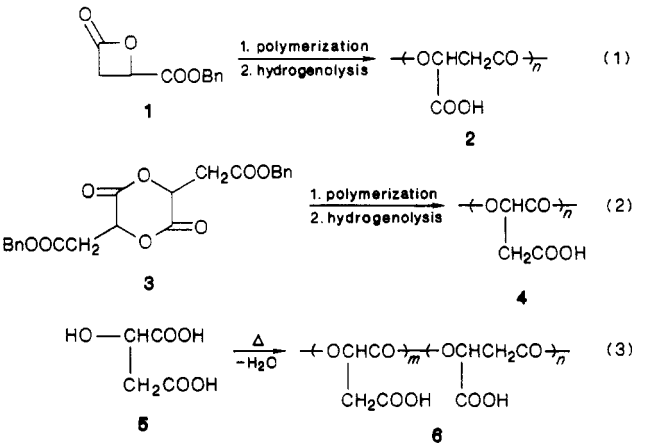
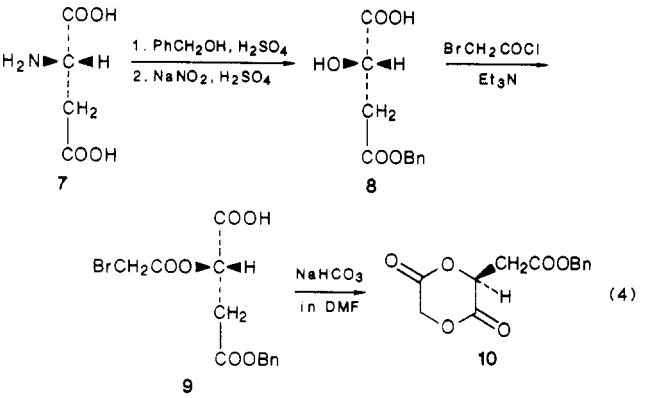
Ring-Opening Polymerization of 3(*S*)-[(Benzyloxycarbonyl)methyl]-1,4-dioxane-2,5-dione: A New Route to a Poly(α-hydroxy acid) with Pendant Carboxyl Groups

Poly(α-hydroxy acid)s[1] such as poly(glycolic acid) (PGA) and poly(lactic acid) (PLA) are not only biocompatible but also bioresorbable. When they are implanted in living organisms including the human body, they are hydrolyzed to their constituent α-hydroxy acid which is eliminated by general metabolic pathways.[2] Based on these intriguing properties, various biomedical and pharmaceutical applications of poly(α-hydroxy acid)s have recently been developed including their use as polymeric drug carriers[3] and bioresorbable sutures.[4] The hydrolysis rates of the widely used poly(α-hydroxy acid)s are too slow because of their high crystallinity and water insolubility,[5] and this slow biodegradation interferes with the controlled release of drugs chemically bound to the polymers.[2,3,5] Consequently, recent work has focused on methods of imparting a hydrophilic nature to these polymers by suitable functionalization. For this purpose, Vert and Lenz have prepared poly(β-malic acid) (**2**) by the ring-opening polymerization of benzyl malolactonate (**1**) and the subsequent hydrogenolysis of the pendent benzyl ester.[6] Ouchi and Fujino have also prepared poly(α-malic acid) (**4**), from the cyclic diester **3** called malide,[7] although its preparation is quite difficult. Recently,[8] we have reported the preparation of the copolymer poly(α,β-malic acid) (**6**) by direct condensation of malic acid **5**. All these polymers have a pendant carboxyl group in every repeat unit which can be used to impart water solubility and to attach drugs for sustained release.

For the purpose of manipulating the hydrophilicity of these biodegradable polyesters, the copolymers containing a variable degree of functionality should be developed. Gross et al. have recently prepared such copolymers by the combination of **1** and other lactones.[9] However, the reactivities of the monomers **1**, **3**, and **5** are quite different from those of the common glycolide and lactide,[10] and application of the conventional copolymerization techniques fails to yield a copolymer. In this paper, we discuss the synthesis of a six-membered cyclic diester, 3(*S*)-[(benzyloxycarbonyl)methyl]-1,4-dioxane-2,5-dione (**10**), which polymerizes to the alternating copolymer **11** consisting of glycolic acid and benzyl α-(*S*)-malate units. This monomer has a comparable ring-opening polymerizability with glycolide and lactide. The pendant benzyl ester can readily be removed by catalytic hydrogenolysis after polymerization to yield poly[(glycolic acid)-*co*-(α-(*S*)-malic acid)] (**12**), which is a new carboxyl-functionalized poly(α-hydroxy acid).



The synthesis of the monomer **10** was accomplished according to eq 4. The optically pure benzyl α-(*S*)-malate



(**8**) ($[\alpha]^{25}_D$ = −8.6° (in MeOH, *c* = 1.0 g/dL), ref[12b] −8.6° (the same conditions)) was prepared from (*S*)-aspartic acid (**7**) by the methods reported previously.[11,12] Twenty grams of **8** was mixed with 18.4 g of bromoacetyl chloride in 300 mL of diethyl ether. With this mixture stirred vigorously, a solution of 9.9 g of triethylamine in 50 mL of diethyl ether was added dropwise at a temperature not exceeding 5 °C over a period of 30 min. After the addition was over, stirring was continued at room temperature for 6 h, and triethylamine hydrochloride precipitate was removed by filtration. The filtrate was then washed with the same volume of water several times, dried over sodium sulfate, and evaporated in vacuo. A pale yellow viscous liquid was obtained in a yield of 96%, which was identified as **9** by ^{1}H NMR spectroscopy (200 MHz in acetone-d_6): δ 3.02 (q, CH_2, 2 H), 4.02 (s, OCH_2CO, 2 H), 5.12 (s, CH_2Ph, 2 H), 5.50 (q, CH_2, 1 H), 7.35 (s, C_6H_5, 5 H). This compound **9** was not further purified, for the contaminant, bromoacetic acid, did not produce a side reaction in the following cyclization.

In the next step, a solution of 10 g of **9** in 50 mL of DMF was added dropwise to a mixture of 3.7 g of sodium bicarbonate in 950 mL of DMF with vigorous stirring at room temperature over a period of 8 h. The mixture was further stirred for 12 h and filtered to remove the crystals of NaBr and excess sodium bicarbonate. The filtrate was then evaporated in vacuo, and the residue was washed with isopropyl alcohol and sublimed at 0.01–0.001 mmHg. The sublimate was recrystallized from isopropyl alcohol to give

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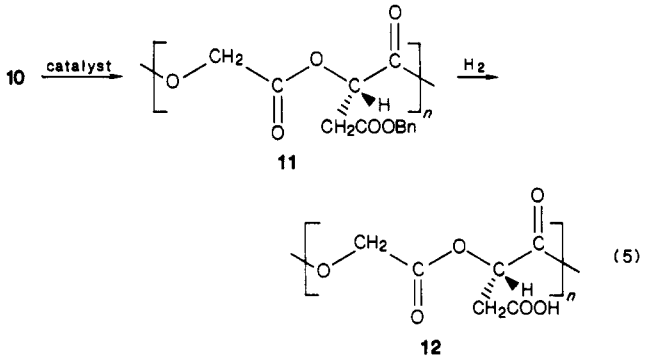
Table I
Ring-Opening Polymerization of 10[a]

run	initiator (mol %)[b]	rctn condtn[c]	time, min	conv, %	M_n	M_w/M_n[d]	$[\alpha]^{25}_D$,[e] deg
1	$(C_7H_{15}CO_2)_2Sn$ (1.0)	A	360	90	10500	2.0	-30.0
2	$(C_7H_{15}CO_2)_2Sn$ (2.0)	A	180	88	13500	2.5	-31.9
3	$(C_7H_{15}CO_2)_2Sn$ (1.0)	B	10	94	21400	3.4	-33.3
4	$(C_7H_{15}CO_2)_2Sn$ (0.1)	B	90	92	16900	2.3	-32.2
5	$(i\text{-PrO})_3Al$ (1.0)	A	480	51	4200	1.4	-33.5
6	$(i\text{-PrO})_3Al$ (2.0)	A	120	86	4500	1.6	-32.2
7	Et_2Zn (1.0)	A	180	92	5000	2.9	-30.7
8	Et_2Zn (2.0)	A	180	96	2000	2.3	-31.3

[a] 0.2 g (0.76 mmol). [b] Initiator to monomer ratio in mol %. [c] A, in 3 mL of toluene at 100 °C; B, in bulk at 160 °C. [d] M_n and M_w were determined by GPC relative to polystyrene standard (THF eluent). [e] In acetone (c = 0.2 g/dL).

needlelike crystals of **10** (27% yield), mp 150 °C. The structure **10** was supported by the data shown in Table II. Observation of the characteristic AB quartet at δ 5.16 ppm in the ^1H NMR spectrum was good proof for its cyclic structure as previously reported for a similar derivative.[13] The optical rotation $[\alpha]^{25}_D$ of this compound was -127° (in acetone, c = 1.0 g/dL). The optical purity was confirmed by 200-MHz ^1H NMR spectroscopy of the compound complexed with a chiral europium shift reagent, tris[3-[(heptafluoropropyl)hydroxymethylene]-(+)-camphorato]europium (Eu(hfc)$_3$). This shift reagent (30 mg) interacted with the racemic compound of **10** (10 mg) in $CDCl_3$ (0.5 mL) and split the benzylmethylene singlet into two peaks separated by 19 Hz (appearing at ca. δ 6.4 ppm). Under the same conditions the signal of the present optically active compound showed no splitting. From this result the optical purity of **10** was supposed to be ca. 100% within experimental error. Although partial racemization had occurred during the cyclization and sublimation, the racemic isomer was removed completely by repeated recrystallizations. The conversion of **9** into **10** was over 80%, but a significant fraction of the crude product decomposed during the sublimation. When triethylamine was used as the base in the cyclization of **9**, only polymeric product was obtained.

The polymerization of **10** was carried out both in solution and in bulk (eq 5). The solution polymerization was



(5)

done by heating a mixture of 0.2 g of **10** and 1–2 mol % of initiator (relative to **10**) in 3 mL of toluene at 100 °C for 2–8 h. After the toluene was evaporated, the residue was redissolved in 3 mL of acetone, reprecipitated into an excess of diethyl ether, and dried in vacuo. The bulk polymerization was done by heating a mixture of 0.2 g of **10** and the initiator (0.1–1.0 mol % relative to **10**) at 160 °C for 10–90 min. The product was isolated by precipitation as previously described. As in the polymerizations of glycolide and lactide,[5b,10] salts of tin, aluminum, and zinc were effective initiators. Some results are shown in Table I. The polymers were isolated in high yield as white powders which softened at 60–80 °C. Their WAXS revealed that the products, as isolated, were in an amorphous state. The number-average molecular weight was in the range 2000–21000, as determined by GPC using polystyrene standards, and the optical rotation was in the range -30 to -33°. Among the three catalysts examined, tin octylate[1a] was the most active. The rate of the bulk polymerization was much higher than that of the solution polymerization. Higher molecular weight polymers were also formed in the bulk polymerizations. These results imply that the polymerization proceeded in a similar manner to that of glycolide and lactide polymerizations.

Table II
Characterizations of the Compounds 10, 11, and 12

compd	spectroscopic data and elem anal.
10	^1H NMR (200 MHz in acetone-d_6) δ 3.18 (q, CH_2CO, 2 H), 5.16 (AB q, J = 76, 18 Hz, OCH_2CO, 2 H), 5.20 (s, CH_2Ph, 2 H), 5.68 (t, OCH, 1 H), 7.38 (s, C_6H_5, 5 H) IR (KBr) 2980, 1760 (lactone), 1720 (benzyl ester), 1295, 1200 cm^{-1}, etc. Anal. Calcd for $C_{13}H_{12}O_6$: C, 59.06; H, 4.58. Found: C, 59.09; H, 4.58.
11	^1H NMR (200 MHz in acetone-d_6) δ 3.08 (m, CH_2CO, 2 H), 4.80 (s, OCH_2CO, 2 H), 5.15 (s, CH_2Ph, 2 H), 5.66 (m, OCH, 1 H), 7.35 (s, C_6H_5, 5 H) ^{13}C NMR (50.3 MHz in $CDCl_3$) δ 35.2 (CCH_2CO), 60.4 (OCH_2CO), 66.5 (OCH_2Ph), 68.2 (OCHCO), 128.0 (CH for C_6H_5), 134.7 (C for C_6H_5), 165.3 (OCH_2CO), 166.7 (OCHCO), 167.8 (CO_2CH_2Ph) IR (KBr) 2980, 1760, 1730 (ester), 1270, 1160, 1170 cm^{-1}, etc. Anal. Calcd for $(C_{13}H_{12}O_6)_n$: C, 59.06; H, 4.58. Found: C, 58.96; H, 4.40.
12	^1H NMR (200 MHz in CD_3OD) δ 3.18 (d, CH_2CO, 2 H), 4.97 (d, OCH_2CO, 2 H), 5.82 (m, OCH, 1 H). IR (KBr) 3440 (OH), 2980, 1758 (ester), 1710 (shoulder, COOH), 1170, 1070 cm^{-1}, etc.

The polymer structure was determined by spectroscopy and elemental analysis. The data including the peak assignments of the spectra are summarized in Table II. From these data the polymer was supposed to consist of glycolate units (G) and benzyl α-(*S*)-malate units (M). In the ^1H NMR spectrum the signal of the methylene protons of the G units appeared at δ 4.80 ppm as a singlet. The ^{13}C NMR spectrum showed the single signal for each carbonyl carbon. These signals can be attributed to the sole diad G–M or the possible triads G–*M*–G and M–*G*–M.[14] Therefore, it was reasonably deduced that the polymer has an alternating sequence of G and M. Within the limit of the present analyses, no signal indicating the presence of disordered sequence or the formation of branch from the β-carbonyl of the M unit was detected. In addition, the asymmetric centers of the M units were found to be preserved without significant racemization occurring in the polymerization.[15]

Although the mechanism of the present polymerization has not yet been clarified, it can be said that the formation of the alternating sequence was allowed by the exclusive scission of the sterically less hindered ester bond between

the glycolate carboxyl and malate hydroxy groups of the monomer. Random transesterification[10] to give the random sequence or to propagate the branch seemed to be negligible under the present polymerization conditions.[16] Since the polymerization temperature and time were relatively low, as compared to those of the polymerization of glycolide and lactide, the rate of the transesterification involving the polymer chain and pendant esters might be much slower than that of the ring opening of **10**. The molecular weight distributions of the polymers were relatively broad, which may be attributed to the reversible depolymerization process that has been known in this type of ring-opening polymerization.[5b,10]

The polymer **11** was subjected to catalytic hydrogenolysis by using platinum oxide and palladium carbon as the catalysts.[6,7] For example, 0.09 g of **11** (sample, the product of run 8) was dissolved in a mixed solvent (20 mL) of methanol/ethyl acetate (1:3) and was reacted with hydrogen at atmospheric pressure and at 30 °C in the presence of 10 mg of PtO_2 for 4 h. After the theoretical quantity of hydrogen was absorbed, the catalyst was filtered off and the filtrate was poured into an excess of diethyl ether to isolate the white crystalline product of **12** in quantitative yield: mp 85–110 °C, $[\alpha]^{25}_D = -43.5°$ (in acetone, c = 0.2 g/dL); M_n (by GPC) 1200 (calcd M_n = 1320). The characterization of its structure is shown in Table II. The benzyl groups of **11** were completely deprotected and the formation of the alternating copolymer **12** consisting of glycolic and (*S*)-malic acids was confirmed. Since the polymer was water soluble and self-hydrolizable,[15] it should have some potential applications as a new bioresorbable material. We are now studying the polymerization mechanism of **10** in more detail as well as the copolymerization of **10** and other lactones.

Registry No. **7**, 56-84-8; **8**, 66178-06-1; **9**, 117098-33-6; **10**, 117098-34-7; **10** (homopolymer), 117098-35-8; $PhCH_2OH$, 100-51-6; $BrCH_2COCl$, 22118-09-8.

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(14) If the polymer had a random sequence, the signals of the main-chain carbonyls should be split into four lines corresponding to the four possible triads (e.g., G–*M*–G, G–*M*–M, M–*M*–G, and M–*M*–M), as observed in the copolymer of glycolide and lactide.[10b]

(15) The polymer **12**, obtained by the catalytic hydrogenolysis of **11**, was dissolved in a mixture of acetone/water (1:1 in volume) and hydrolyzed to the constituents hydroxy acids at 50 °C. After 3 days, the hydrolysis was complete. Then the solution was directly subjected to the measurement of the optical rotation of (*S*)-malic acid contained. The value $[\alpha]^{25}_D$ observed was −3.2° (c = 0.12 g/dL). The optical rotation of the authentic solution containing the same concentrations of (*S*)-malic acid (c = 0.12 g/dL) and glycolic acid (c = 0.07 g/dL) in the same mixed solvent was found to be −3.3°. Since both values were identical within experimental error, it was supposed that no racemization of the asymmetric center had occurred during the reactions.

(16) When the bulk polymerization was carried out at higher temperature, e.g., 180 °C, for prolonged time, randomization of the sequence was found. The polymer obtained in this case showed complex signals for the methylene protons of the G units in its ^1H NMR spectrum.

Yohiharu Kimura,* Kenji Shirotani, Hideki Yamane, and Toshio Kitao

Department of Polymer Science and Engineering
Kyoto Institute of Technology
Matsugasaki, Kyoto 606, Japan

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Verification of the Contour Length Fluctuation Mechanism in Polystyrene/Polyisoprene Block Copolymers by an NMR Experiment

In a series of previous papers[1–3] we have developed the three-component/three-block concept of chain fluctuations. It takes into account the special structure/dynamics relationship caused by topological restraints such as the tube.[4] The outstanding elements of this dynamic scheme are the reptation[5] and the contour length fluctuation[6] mechanisms.

The concept has been tested by studies of diverse dependences of NMR quantities. Thus we were able to describe the frequency,[7] molecular weight,[3] temperature,[8] and concentration[9] dependences of NMR relaxation times in melts or solutions of homopolymer standards. Special limiting cases characteristic for motions restricted by the tube topology could well be identified. The existence of characteristic molecular weights, for instance, has been explained in this way. The so-called critical molecular weight, which is well-known in rheology,[10] in particular can be understood as a crossover from Rouse-like to reptational dynamics mediated by the influence of contour length fluctuation.[1] In structural terms, one can speak of three dynamic chain blocks, the lengths of which vary nonlinearly with molecular weight.[1,2,6] Thus at low molecular weights, the end blocks with Rouse-like dynamics are expected to dominate, while in the limit of long chains the reptational dynamics of the central block becomes relevant.

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