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Baeyer−Villiger Oxidation of an Optically Active 1,4-Polyketone

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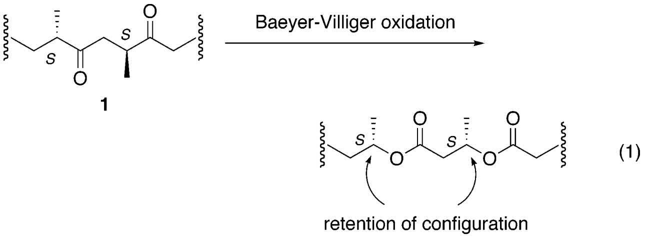
ABSTRACT: Baeyer−Villiger oxidation of poly[(*S*)-2-methyl-1-oxopropane-1,3-diyl] (**1**) with *m*-chloroperbenzoic acid provided poly(ketone/ester) (**2**) in a ratio of ketone/ester = 82/18 in 73% isolated yield. Methanolysis of **2** ($M_n = 8600$) gave only a trace amount of methyl 3-hydroxybutyrate (**5**) which resulted from neighboring two ester units, $-[OCH(CH_3)CH_2C(=O)]_2-$. The major product was oligoketone ($M_n = 650$). A low yield of **5** indicates that an ester unit likely exists to distribute randomly in **2** rather than to form a block copolymer of a polyketone and a polyester.

Introduction

Poly((*R*)-3-hydroxybutyrate) (PHB) is a naturally occurring polyester produced by a wide variety of bacteria.[1] Conventional synthetic routes to optically active PHB are ring-opening polymerization of optically pure (*R*)-3-butanolide without racemization of the stereogenic center[2] and kinetic resolution in the ring-opening polymerization of racemic 3-butanolide using a chiral catalyst.[3] On the other hand, the repeating unit of PHB might be produced, as we attempted here, by the Baeyer−Villiger oxidation of optically active α-methyl-γ-polyketone (**1**) transforming the ketone groups to the ester groups.

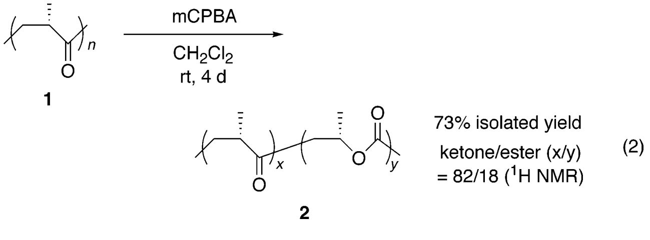
The polyketone **1** was synthesized in an optically active form by asymmetric alternating copolymerization of propene and CO.[4,5] The structure of **1** is almost completely controlled in a head-to-tail, isotactic, and enantiomerially pure manner. Chemical modification of the carbonyl group, a versatile functional group convertible to others, provides new classes of chiral polymers.[5e,6] Here we report the Baeyer−Villiger oxidation of optically active γ-polyketone **1** using *m*-chloroperbenzoic acid (mCPBA). Although the Baeyer−Villiger oxidation of polyketone was previously reported for the random copolymer of ethene and carbon monoxide or ethene-rich incompletely alternating copolymers, all of the precedent examples contain no stereogenic centers in the main chain.[8] The Baeyer−Villiger oxidation of dialkyl ketones is known to proceed with retention of configuration of the migrating group with migratory ability of tertiary > secondary > primary > methyl, namely, a more substituted alkyl group migrates favorably.[7] Thus, the oxidation of polyketone **1** was expected to provide with repeating unit of PHB (eq 1). Even a relatively low conversion of the oxidation might be enough to bestow biodegradable property on the original polyketone.



(1)

Results and Discussion

Baeyer−Villiger Oxidation of Polyketone 1 with mCPBA. We first employed mCPBA as an oxidant for the Baeyer−Villiger oxidation of polyketone **1**. Treatment of **1** ($M_n = 21\,400$, $M_w/M_n = 1.33$, $[\alpha]^{25}_D$ −58.1 (*c* 1.01, $CHCl_3$), $\Delta\epsilon = -1.52$ ($CHCl_3$, 23 °C))[4b] with 8 mol equiv of mCPBA in dichloromethane at room temperature for 4 days (eq 2),[9] followed by workup with aqueous Na_2SO_3 and then with aqueous K_2CO_3, afforded a crude polymer containing both ketone and ester moieties (ketone/ester = 82/18, determined by ^1H NMR). The crude polymer was purified by filtration through a column of Sephadex LH-20 SEC resin and then by preparative GPC to obtain poly(ketone/ester) **2** (ketone/ester = 82/18) in a 73% isolated yield.[10]



(2)

Figure 1 shows the ^1H NMR spectrum of **2** in $CDCl_3$. Signals of a methine proton in an ester unit were observed around 5.3 ppm. None of the peaks were attributable to methylene next to the ester oxygen. Thus, the oxidation proceeded exclusively at the site of the methyl-substituted α-carbon rather than the unsubstituted α-carbon. When the sample was left in a

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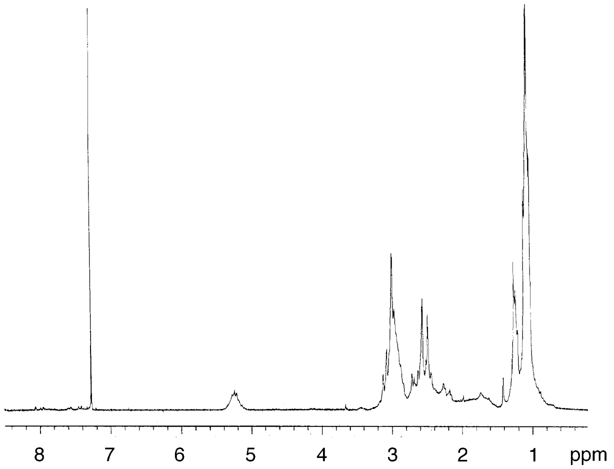
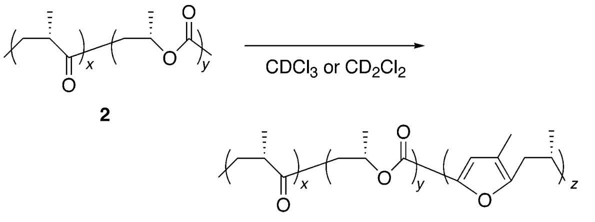


Figure 1. ^{1}H NMR spectrum of **2** in $CDCl_3$. Signals around 5.3 ppm correspond to a methine proton in an ester unit.

$CDCl_3$ or CD_2Cl_2 solution for several hours, the colorless solution changed into a black one: furan units likely formed from ketone units possibly due to acidic impurities (eq 3), as confirmed by observation of singlet signals in 1.8 and 5.7 ppm in ^{1}H NMR in $CDCl_3$.



2

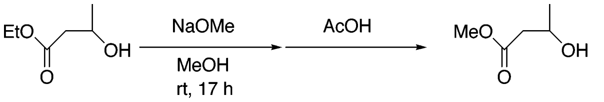
3

(3)

Distribution of Ester Unit in Polymer Chain. To investigate the distribution of an ester unit in **2**, we subjected the polymer to methanolysis and assayed the products (Scheme 1). When methanolysis was performed in a small scale, not only methanolysis but also hydrolysis occurred due to a slight amount of water in the reaction mixture. To test the feasibility of the assay method, we first examined the small-scale experiment of methanolysis using a low molecular weight model compound, ethyl 3-hydroxybutyrate **6** (eq 4). The results are shown in Table 1. Methanolysis of **6** (0.23 mmol) at room temperature and quenching with acetic acid gave **5** in a quantitative yield as revealed by GC (run 1). A smaller scale (0.040 mmol of **6**) experiment was carried out without any significant problem (run 2). Then, polymer **2** was subjected to methanolysis: Polymer **2** was treated with 10 mol equiv (per ester unit) of sodium methoxide for 44 h at room temperature. After quenching with AcOH, only a trace amount of **5** (2.1×10^{-4} mmol, 0.3% yield from ester unit in **2**) was obtained, indicating that consecutive ester units do exist but in an almost negligible amount.

Table 1. Methanolysis of Model Compound 6

run	**6** (mmol)	NaOMe (equiv)	GC yield of **5** (%)
1	0.23	3	>95
2	0.040	9	80



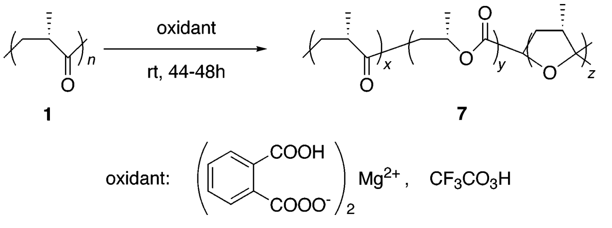
6

5

(4)

Next, we measured the molecular weight of poly(ketone/ester) **2** and the degraded oligoketone **4** to compare the data with that of the parent polyketone **1**. The size exclusion chromatography (SEC) charts of the samples are shown in Figure 2. The molecular weight of poly(ketone/ester) **2** ($M_n = 8600$) is found to be smaller than that of polyketone **1** ($M_n = 21\,400$). The SEC chart of **2** (Figure 2b) corresponds to an increase in low molecular weight components, which might be derived either from hydrolysis of the ester units in **2** under the oxidation conditions or from the overestimated molecular weight of polyketone **1** by SEC.[11] Methanolysis of **2** resulted in lowering the molecular weight to $M_n = 650$ (Figure 2c), no trace of high molecular weight components being observed. At this stage, no trace of signals of methine proton at 5.3 ppm was observed for the degraded oligomers by ^{1}H NMR, indicating that all the ester linkages in polymer **2** were cleaved by the methanolysis to give oligoketone **4**. Hence, the SEC studies also suggest that ester units are randomly distributed in the polymer chain rather than consecutively.

Baeyer−Villiger Oxidation of 1 with Other Oxidants. We further examined the Baeyer−Villiger oxidation of **1** using other oxidizing agents (eq 5).



1

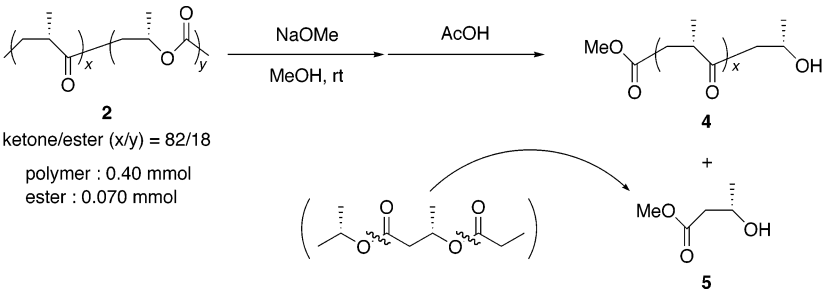
7

MMPP

(5)

Results are summarized in Table 2. Magnesium monoperoxyphthalate (MMPP)[12] was inert, and the substrate polyketone was recovered quantitatively (run 1). The use of trifluoroperacetic acid[13] along with Na_2HPO_4 or $CaCO_3$ as a buffer converted ca. 8% of the ketone units

Scheme 1. Methanolysis of Poly(ketone/ester) 2



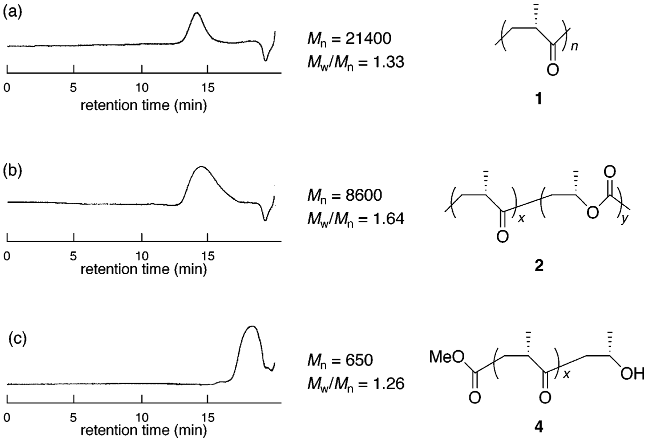


Figure 2. SEC charts (polystyrene standard) and molecular weights of (a) polyketone **1**, (b) poly(ketone/ester) **2**, and (c) methanolysates of poly(ketone/ester) **4**.

Table 2. Baeyer–Villiger Oxidation of 1 with Other Oxidants

run	oxidant	solvent	recovery (%)	*x*/*y*/*z*
1	MMPP (5 equiv to carbonyl)	CH_2Cl_2/DMF (1/1)	97	100/0/0
2	$(CF_3CO)_2O$ (14 equiv), H_2O_2 (4 equiv), Na_2HPO_4 (4 equiv)	CH_2Cl_2	73	<8/8/84
3	$(CF_3CO)_2O$ (14 equiv), H_2O_2 (4 equiv), $CaCO_3$ (4 equiv)	CH_2Cl_2	82	<8/8/84

to ester units as estimated by ^{1}H NMR (runs 2 and 3). The resulting polymer (**7**) exhibited peaks around 110 ppm in ^{13}C NMR, assignable to quarternary carbons as evidenced by DEPT. These peaks was assigned as a region of spiroketal units because quarternary spiro carbons in poly(ketone/spiroketal)s with methyl side chains exhibit ^{13}C NMR peaks around 113 ppm in solution[5e,14] or solid state.[5b,14b] Thus, most of the remaining ketone units were transformed to spiroketal units possibly due to the strong acidity of the reaction conditions. The spiroketal form is protected from oxidation, and thus no further reaction took place.

Conclusion

The Baeyer–Villiger oxidation of optically active γ-polyketone **1** with mCBPA gave poly(ketone/ester) **2** in a ketone/ester ratio of 82/18 in 73% isolated yield. The oxidation proceeded regioselectively, as was confirmed by ^{1}H NMR, although the stereochemistry of the resulting ester unit was unclear. Methanolysis of **2** afforded only a trace amount of methyl 3-hydroxybutyrate **5**, an expected product derived from a continuously oxidized moiety. The major product was oligomeric ketone **4**, which likely indicates that an ester unit distributes randomly in the polymer chain.

Experimental Section

General. Nuclear magnetic resonance spectra were taken with a JEOL JNM-ECP500 (^{1}H, 500 MHz; ^{13}C, 126 MHz), a JEOL EX-270 (^{1}H, 270 MHz; ^{13}C, 68 MHz), or a Varian Mercury 200 (^{1}H, 200 MHz; ^{13}C, 50 MHz) spectrometer using tetramethylsilane as an internal standard, and coupling constants are given in hertz. Infrared spectra were recorded on a Shimadzu FTIR-8400 spectrometer. Molecular weights were estimated by SEC (Shodex, KF-804L, THF as an eluent) using polystyrene as a standard. Preparative recycling GPC was performed with a JAI LC-908 chromatograph equipped with JAIGEL-1H and -2H columns (chloroform as an eluent). GC analysis was performed on a Shimadzu GC-14B gas chromatograph equipped with a flame ionization detector. Most of the reagents were purchased from Wako Pure Chemical Industries Ltd., Tokyo Kasei Kogyo Co., Ltd., Nacalai Tesque, Ltd., Kanto Chemical Co., Ltd., or Aldrich Chemical Co., Inc. All of the solvents used for the reactions were distilled under argon after drying over a suitable drying agent. Silica gel column chromatography was performed with Wako-gel C-200. Sephadex LH-20 resin was purchased from Amersham Biosciences.

Baeyer–Villiger Oxidation of Optically Active Polyketone 1 with mCPBA. Polyketone **1** (42 mg, 0.60 mmol of a repeating unit) was added to a solution of *m*-chloroperbenzoic acid (70%, 1.10 g, 4.8 mmol) in CH_2Cl_2 (8 mL) at room temperature, and the resulting mixture was stirred at the same temperature for 4 days before quenching with aqueous Na_2SO_3 (40 mL) and chloroform (40 mL). The separated organic layer was washed with aqueous K_2CO_3 (40 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated to afford a crude polymer (ketone/ester = 82/18 as determined by ^{1}H NMR). The crude polymer was filtered through a column of Sephadex LH-20 gel (gel bed, 2.4 × 32 cm; eluent, chloroform; flow rate, 0.3 mL/min) and then purified with preparative GPC to give poly(ketone/ester) **2** in a pure form (32 mg, 0.44 mmol of a repeating unit, ketone/ester = 82/18, 73% yield). ^{1}H NMR ($CDCl_3$) δ: 0.80–1.36 (m, 3H, CH_3), 2.13–2.77 (m, 1.1H), 2.77–3.15 (m, 1.5H), 5.10–5.42 (br m, 0.18H, C*H*OCO). ^{13}C NMR (C_6D_6) δ: 16.1, 16.5, 19.7, 19.9, 30.1, 37.2, 37.4, 40.2, 41.1, 41.6, 44.9, 45.1, 47.0, 47.2, 67.6, 67.7, 169.0, 171.3, 209.3, 210.9, 211.6. IR (CH_2Cl_2): 1730, 1709 cm^{-1}. $[\alpha]^{25}_D$ −40.4 (*c* 1.20, $CHCl_3$). Anal. Calcd for $(C_4H_6O)_{0.82n}(C_4H_6O_2)_{0.18n}$: C, 65.84%; H, 8.29%. Found: C, 62.92%; H, 7.86%.

Model Reaction of Methanolysis. A mixture of ethyl 3-hydroxybutyrate **6** (30 mg, 0.23 mmol) and sodium methoxide in methanol (0.143 M, 4.5 mL, 0.64 mmol) was stirred at room temperature for 17 h. 1,2-Diethoxyethane (42 mg) was added into the reaction mixture as an internal standard for GC analysis. A small amount of the solution (0.15 mL) was extracted from the reaction mixture and was mixed with acetic acid (0.01 mL). The resulting solution was analyzed with GC (DB-1, 0.53 mm × 30 m). The yield of methyl 3-hydroxybutyrate was estimated to be >95%.

A smaller scale experiment was also examined. A mixture of **6** (5.3 mg, 0.040 mmol) and sodium methoxide in methanol (0.143 M, 2.5 mL, 0.36 mmol) was stirred at room temperature for 17 h to give **5** (80% GC yield).

Methanolysis of Polymer 2. The mixture of polymer **2** (29 mg, ketone/ester = 82/18, corresponding to 0.070 mmol of ester unit) and sodium methoxide in methanol (0.143 M, 4.9 mL, 0.70 mmol) was stirred at room temperature for 44 h. 1,2-Diethoxyethane (21 mg) was added to the reaction mixture as an internal standard for GC analysis. A small amount of the solution (0.15 mL) was extracted from the reaction mixture and was added to acetic acid (0.01 mL). The resultant was assayed by GC (DB-1) to estimate 0.3% yield (2.1 × 10^{-4} mmol) of methyl 3-hydroxybutyrate **5**.

Baeyer–Villiger Oxidation of 1 with CF_3CO_3H–Na_2HPO_4. To a suspension of Na_2HPO_4 (0.37 g, 2.6 mmol) in dichloromethane (12 mL) was added trifluoroacetic anhydride (1.93 g, 9.2 mmol) and 30% aqueous H_2O_2 (0.30 mL, 2.7 mmol) at 0 °C. To the suspension was added polyketone **1** (45 mg, 0.64 mmol of a repeating unit) at 0 °C, and the resulting mixture was stirred at room temperature for 45 h and then treated with aqueous $NaHCO_3$ (40 mL) and $CHCl_3$ (40 mL) at 0 °C. Separated organic layer was washed with aqueous Na_2SO_3 (15 mL) and H_2O (25 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by preparatve GPC to afford polymer **7** in a pure form (33 mg, ketone/ester/spiroketal = <8/8/84 as determined by ^{1}H NMR and IR, 0.46 mmol of a repeating unit, 72% yield). ^{1}H NMR ($CDCl_3$) δ: 0.75–1.33 (m, 3H, CH_3), 1.33–3.08 (br m, 2.3H), 5.10–5.40 (br m, 0.08H, C*H*OCO). ^{13}C NMR ($CDCl_3$) δ: 11.4–15.3 (m), 29.6–43.5 (m), 67.6, 109.5–114.0 (m). IR

(CH_2Cl_2): 1790, 1736 cm^{-1}. $[\alpha]^{23}_{D}$ −143 (*c* 0.81, $CHCl_3$). $(C_4H_6O)_{0.92n}(C_4H_6O_2)_{0.08n}$: C, 67.32%; H, 8.47%. Found: C, 58.46%; H, 7.33%.

Baeyer−Villiger Oxidation of 1 with CF_3CO_3H−$CaCO_3$. To a suspension of $CaCO_3$ (0.26 g, 2.6 mmol) in dichloromethane (12 mL) was added trifluoroacetic anhydride (1.93 g, 9.2 mmol) and 30% aqueous H_2O_2 (0.30 mL, 2.7 mmol) at 0 °C. To the suspension was added polyketone **1** (45 mg, 0.64 mmol of a repeating unit) at 0 °C, and the resulting mixture was stirred at room temperature for 45 h. Workup described above afforded polymer **7** (37 mg, ketone/ester/spiroketal = <8/8/84 as determined by ^{1}H NMR and IR, 0.46 mmol of a repeating unit, 81% yield).

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(10) The product ratio was determined by comparing the integration of methine proton in ester units (around 5.3 ppm, 0.18 H) with methyl protons in the whole polymer chain (0.80−1.36 ppm, 3 H). The integration values of all of the peaks supported the ratio. Elemental analysis, however, did not match exactly.

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