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Chemospecific ring-opening polymerization of α-methylenemacrolides

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Abstract

α-Methylenemacrolides having various groups, such as aromatic, ether, and amine, were enzymatically, anionically, and radically polymerized. The polymerization with the lipase catalyst successfully afforded polymers only through the ring-opening process, whereas the vinyl polymerizations selectively proceeded by using anionic and radical initiators. The polyesters obtained by the enzymatic polymerization have a polymerizable methacrylic methylene group in the main-chain, in addition to the aromatic and polar groups, and were further radically polymerized to quantitatively produce a cross-linked polymer gel.

Keywords: Enzymatic polymerization; Ring-opening polymerization; Chemospecific polymerization

1. Introduction

Enzymatic polymerization has become a powerful tool for synthesizing useful macromolecules, which are often difficult to prepare by conventional polymerization procedures [1–4]. Although numerous studies on the ring-opening polymerization of lactones with small and medium ring-sizes using various chemical initiators and catalysts, including enzymes, have been reported, less attention has been paid to the polymerization of large-membered lactones. These enzymatic systems can also polymerize macrolides, such as 12-, 13-, 16-, and 17-membered lactones, to afford aliphatic polyesters [5–10], whereas the anionic methods [11–14] showed relatively lower polymerizability, probably due to the low ring-strain of the macrolides.

Macrocyclic α-(alkoxymethyl)acrylates [15–18] have two polymerizable groups, a lactone for the ring-opening process and a methacrylic *exo*-methylene group for the vinyl polymerization. For example, the chemospecific polymerizations of 2-methylene-4-oxa-12-dodecanolide (**1**) produce poly(ro-**1**) and poly(v-**1**), respectively, having a completely different and unique structure (Scheme 1). In the former, further facile transformations are possible due to the highly reactive methylene residue, while macrorings are perpendicularly fixed on the main-chain in the latter.

We recently reported that the anionic polymerization of macrocyclic α-(alkoxymethyl)acrylates proceeded in a chemospecific manner to give polymers having a normal vinyl polymer structure and, especially, the polymers having a crown-ether type side chain showed novel functions, such as selective alkali-ion extractabilities and cobalt ion transport abilities as a synthetic ion channel, based on the characteristic polymer structure [19–21]. On the other hand, *Candida antrarctica* lipase (lipase CA) chemospecifically polymerized **1** to afford poly(ro-**1**) [22], although the polymerization of the monomers with an unsaturated polymerizable group is quite difficult to chemoselectively produce a polymer without reactions of the unsaturated groups due to their high reactivity toward various polymerization catalysts [23].

In this study, the enzymatic polymerization of macrocyclic α-(alkoxymethyl)acrylates (α-methylenemacrolides) bearing various groups, such as ether, phenyl, amino, and binaphthyl, **2**–**5** (Scheme 2) was carried out, and the polymerizabilities and chemoselectivities were mainly investigated. The ring-opening polymerization of macrolides has been studied using the aliphatic ones and little data

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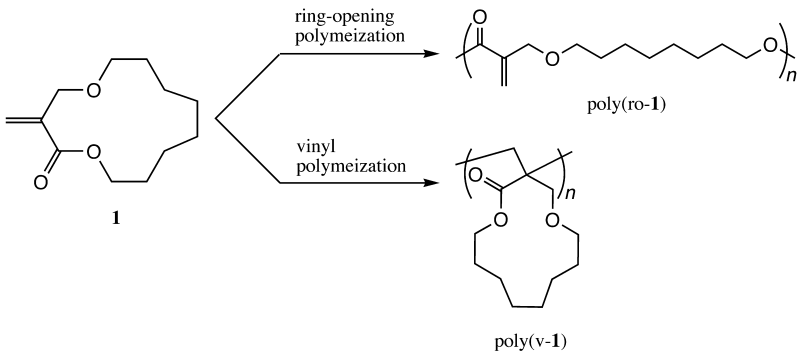


Scheme 1.

are available for monomers having aromatic and polar groups. The synthesis of polyesters with highly reactive groups by the ring-opening process is also interesting from the viewpoint of developing novel functional materials.

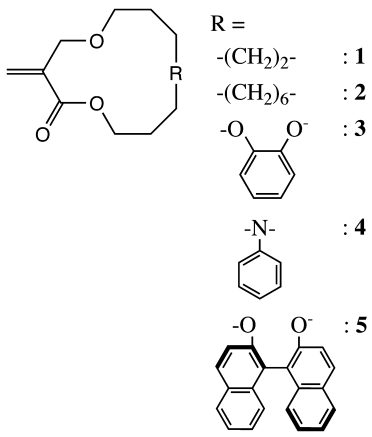
2. Experimental

2.1. Materials

The solvents, toluene and tetrahydrofuran (THF), used for enzymatic polymerization were purchased from Kanto Chem. Co, as the dehydrate grade. A catalyst, lipase CA, was kindly provided by Novozymes Japan, Ltd. The novel monomer **4** was synthesized from ethyl α-(bromomethyl)-acrylate with the corresponding diols according to a previously reported procedure [19–22].

2.1.1. 2-Methylene-8-phenyl-4-oxa-8-aza-11-undecanolide (*4*)

^{1}H NMR ($CDCl_3$): δ 1.86 (m, 2H, $-CCH_2C-$), 2.08 (m, 2H, $-CCH_2C-$), 3.42 (m, 4H, $-NCH_2C-$), 3.62 (t, $J = 5.4$ Hz, 2H, $-OCH_2C-$), 4.22 (s, 2H, $=CCH_2O-$), 4.34 (m, 2H, $-OCH_2C-$), 5.71 (m, 1H, vinyl), 6.30 (m, 1H, vinyl), 6.69 (m, 3H, aromatic), 7.22 (m, 2H, aromatic) ppm; ^{13}C NMR ($CDCl_3$): δ 28.3, 29.4, 48.0, 49.9, 63.3, 67.9, 70.3, 113.2, 116.7, 128.6, 129.1, 138.3, 149.2, 166.5 ppm. IR (neat): 2918, 1721, 1599, 1508, 1307, 1176, 1105, 748 cm^{-1}. Elemental analysis. Found: C, 69.30; H, 7.80; N, 4.96%. Calcd for $C_{16}H_{21}NO_3$: C; 69.79, H; 7.69, N; 5.09%.



Scheme 2.

2.2. Polymerization procedure

The enzymatic polymerization was carried out according to the following procedure [22]. A catalyst was placed in a glass ampoule equipped with a three-way stopcock under a dry nitrogen atmosphere, and a solution of a monomer (0.5 mmol) in toluene (0.2 ml) was introduced with a syringe. The mixture was gently stirred at 60 or 75 °C, and the organic solution was then filtered. After concentration, the polymers were precipitated in a large amount of hexane, separated by centrifugation, and dried in vacuo.

The anionic and radical polymerizations were performed in the same way as reported previously [17–21].

2.3. Measurements

^{1}H NMR spectra were measured on a Varian Gemini-2000 (400 MHz) spectrometer in $CDCl_3$ with tetramethylsilane as the internal standard. Infrared (IR) spectra were recorded on a JASCO FT/IR-620 spectrometer. The size exclusion chromatographic (SEC) analyses were performed on a Shodex GPC-System-21 equipped with Shodex UV-41 and Shodex RI-71S detectors using Shodex GPC KF-806L and KF-803 columns connected in series and THF was used as eluent (temp. = 40 °C, flow rate = 1.0 ml/min). Calibration was carried out using standard polystyrenes. Optical rotation was measured on a JASCO P-1030 polarimeter at 25 °C. Circular dichroism (CD) spectra were obtained with a JASCO J-720L apparatus.

3. Results and discussion

In a previous paper, we reported that poly(ro-**1**) was quantitatively obtained by the polymerization of **1**, having a 13-membered ring, with lipase CA in toluene [22], whereas the polymerization using tin(II) octanoate ($Sn(Oct)_2$) (in

Table 1
Chemospecific polymerizations of α-methylenemacrolides (**2**–**4**) in toluene (enzymatic polymerization: monomer = 0.5 mmol, toluene = 0.2 ml; anionic polymerization: [monomer]/[*n*-BuLi] = 20; radical polymerization: [monomer]/[(*i*-PrOCO$_2$)$_2$] = 30)

Entry	Monomer	Catalyst/initiator	Temp.(°C)	Time (h)	Yield[a] (%)	$M_n \times 10^3$ (M_w/M_n)[b]
1	**2**	Lipase CA (10 mg)	60	24	93	33 (8.7)
2[c]		*n*-BuLi[d]	−78	48	94	9.3 (17)[e]
3[c]		*c*-HexMgBr[d,f]	−78	48	17	11 (5.0)
4[c]		(*i*-PrOCO$_2$)$_2$	30	48	77	7.7 (2.4)
5	**3**	Lipase CA (10 mg)	60	24	7	1.0 (–)
6		Lipase CA (100 mg)	60	24	83	4.4 (1.6)
7		Lipase CA (100 mg)	60	48	90	6.5 (1.5)
8		Lipase CA (100 mg)	75	24	77	4.0 (1.2)
9		Lipase CA (100 mg)	75	48	75	4.5 (1.3)
10		Lipase CA (100 mg)[g]	60	24	84	3.9 (1.3)
11[c]		*n*-BuLi[d]	−78	48	>99	13 (5.4)
12		(*i*-PrOCO$_2$)$_2$	30	48	89	10 (2.5)
13	**4**	Lipase CA (10 mg)	60	24	11	1.5 (–)
14		Lipase CA (10 mg)	60	24	79	3.2 (1.3)
15		Lipase CA (10 mg)	60	48	81	5.9 (2.1)
16		*n*-BuLi	−78	48	99	12 (17)
17		(*i*-PrOCO$_2$)$_2$	30	48	8	3.1 (5.5)

[a] Hexane-insoluble part for enzymatic and radical polymerizations, methanol-insoluble part for anionic polymerization.
[b] Determined by SEC (polystyrene standard).
[c] Ref. [20].
[d] Solvent = THF.
[e] $CHCl_3$-soluble part.
[f] Cyclohexylmagnesium bromide, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) was used as a ligand.
[g] Toluene = 0.4 ml.

toluene at 100 °C for 24 h) [24–26] or scandium trifluoromethanesulfonate ($Sc(OTf)_3$) with benzyl alcohol (in toluene at 0 °C for 46 h), a typical initiator for the ring-opening polymerization of lactones [27,28], resulted in no yield. These results indicate that lipase CA is significantly effective for the α-methylenemacrolide polymerization. The polymerization of **2** with a 17-membered ring structure using the lipase catalyst at 60 °C for 24 h gave a polymer as the hexane-insoluble part in 93% yield (Table 1, entry 1). The results of the anionic and radical polymerizations of **2** are also listed in the table (entries 2–4) [20].

The ^{1}H NMR spectrum of the polymer obtained from **2** with the lipase catalyst is depicted in Fig. 1(b), together with those of the monomer (a) and polymers prepared by the anionic and radical systems ((c) and (d)). The spectral pattern of the polymer obtained by the enzymatic system is quite different from those of the polymers obtained with the anionic and radical initiators. In addition, the enzymatically obtained polymer clearly showed peaks based on the vinyl protons around 6 ppm and each peak is assigned as shown in the figure, indicating that the polymer has a polyester structure formed by the chemospecific ring-opening process [poly(ro-**2**)]. In contrast, no vinyl proton was observed for the anionically and radically obtained polymers, which have a normal vinyl polymer structure [poly(v-**2**)], although stereoregularities were very different between these two polymers. Therefore, the polyester and vinyl polymers were easily synthesized from the same monomer in a chemospecific manner and the former has a reactive methacrylic double bond in every monomer unit.

The polymerization of **3** with the lipase catalyst at 60 °C for 24 h was carried out under the same conditions as performed for **2** but resulted in a poor yield to give a low molecular weight oligomer as the hexane-insoluble part (Table 1, entry 5). By increasing the amount of the catalyst (by 10 times), the polymer was successfully obtained in a good yield (83%), and the 48 h polymerization afforded a polymer in 90% yield with a number average molecular weight (M_n) of 6.5×10^3 (entries 6 and 7). The polymerization at higher temperature (75 °C), however, slightly reduced the polymer yield and the M_n value (entries 8 and 9). On the other hand, the anionic polymerization with *n*-BuLi in THF at −78 °C and the radical one using (*i*-PrOCO$_2$)$_2$ at 30 °C gave polymers in high yields (entries 11 and 12).

Fig. 2 shows the ^{1}H NMR spectra of the monomer **3** and the polymers obtained by these three polymerization systems. The polymer obtained with the lipase catalyst again showed absorptions based on the vinyl protons around 6 ppm (b), whose chemical shifts are different from those of the monomer (a), clearly demonstrating that poly(ro-**3**) was chemospecifically produced through the ring-opening process during the enzymatic polymerization. Similar spectral patterns without the peaks based on the vinyl protons were observed for the anionically and radically obtained polymers (c and d), although the spectral pattern of

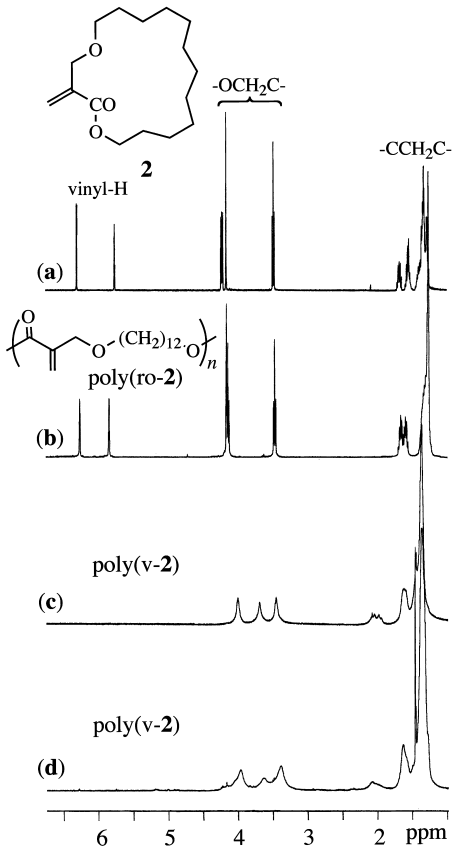


Fig. 1. ^{1}H NMR spectra of the monomer **2** (a), poly(ro-**2**) obtained with lipase CA (Table 1, entry 1) (b), poly(v-**2**) obtained with *c*-HexMgBr–TMEDA (Table 1, entry 3) (c), and poly(v-**3**) obtained with $(i\text{-PrOCO}_2)_2$ (Table 1, entry 4) (d) (in $CDCl_3$, 60 °C).

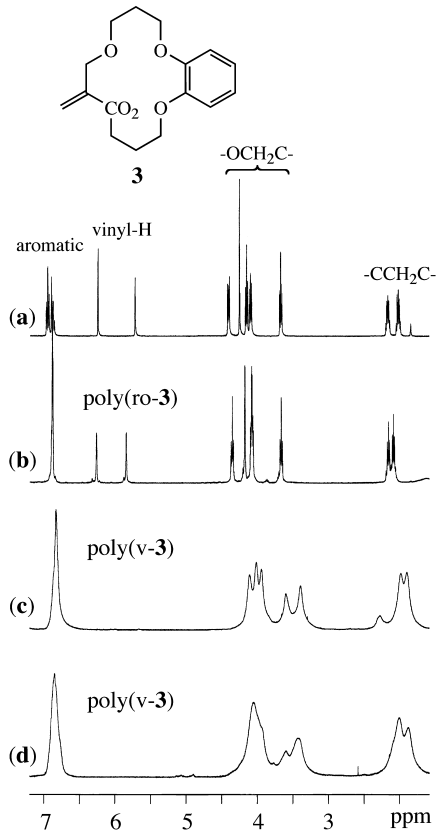
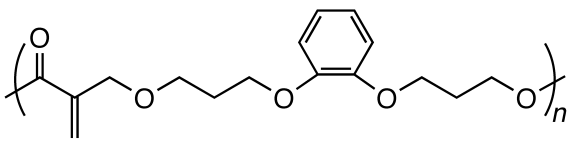
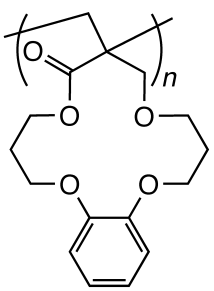


Fig. 2. ^{1}H NMR spectra of the monomer **3** (a), poly(ro-**3**) obtained with lipase CA (Table 1, entry 7) (b), poly(v-**3**) obtained with *n*-BuLi (Table 1, entry 11) (c), and poly(v-**3**) obtained with $(i\text{-PrOCO}_2)_2$ (Table 1, entry 12) (d) (in $CDCl_3$, 60 °C).

the latter was much broader than that of the former due to lower stereoregularity. The poly(v-**3**)s with a normal vinyl polymer structure are selectively obtained in these processes.



poly(ro-**3**)



poly(v-**3**)

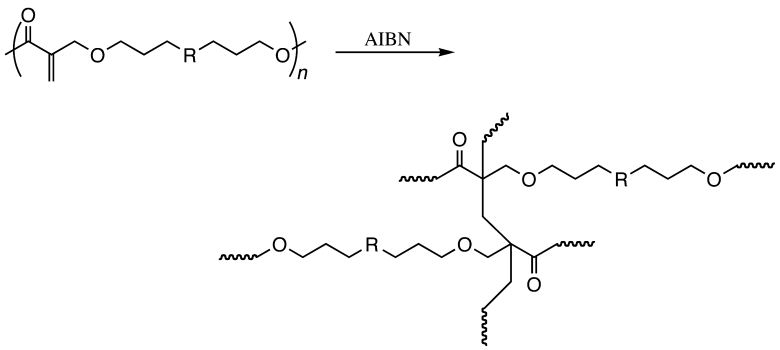
Poly(ro-**4**) was also selectively synthesized by the polymerization of **4** using lipase CA, while the anionic and radical polymerizations proceeded though a vinyl polymerization process to give poly(v-**4**)s (entries 13–17). These were confirmed by ^{1}H NMR analysis. Accordingly, the chemospecific ring-opening polymerization of the α-methylenemacrolides, bearing aromatic and polar groups, was attained by using the enzyme catalyst and produced the polymers with a polymerizable unsaturated group.

The copolymerizability of **2** and **3** with 12-dodecanolide (**6**) was examined. The enzymatic copolymerization was

Table 2
Enzymatic ring-opening copolymerization of α-methylenemacrolides (**2** and **3**) with **6** (monomers = 1 mmol, toluene = 0.4 ml, temp. = 60 °C, time = 24 h, lipase CA = 20 mg (entry 1) and 200 mg (entries 2–4))

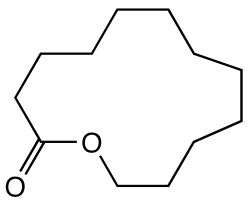
Entry	Monomers (ratio in feed)	Yield (%)[a]	Unit ratio in polymer[b]	$M_n \times 10^3$ (M_w/M_n)[c]
1	**2/6** (50/50)	79	50/50	14 (2.7)
2	**3/6** (52/48)	74	50/50	4.8 (2.3)
3	**3/6** (64/36)	80	63/37	5.3 (2.0)
4	**3/6** (29/71)	69	28/72	6.9 (2.0)

[a] Hexane-insoluble part.
[b] Determined by ^{1}H NMR analysis.
[c] Determined by SEC (polystyrene standard).



Scheme 3.

performed at 60 °C for 24 h. In the copolymerization of **3**, 10 times the amount of catalyst was used in the same way as its homopolymerization. The polymerizations proceeded in good yields to give copolymers as a hexane-insoluble fraction with almost a comparable monomer unit ratio to the ratio in the feed. The polyesters partially having a reactive double bond in the main-chain were synthesized (Table 2).



6

Because the polymers obtained from the α-methylene-macrolides through the ring-opening process have a polymerizable methacrylic methylene group in the main- chain, further vinyl polymerization will generate a polymer gel (Scheme 3). The gelation experiment was carried out using a polymer (0.5 mmol (monomer unit)) with 2,2′-azobisisobutyronitrile (AIBN, 0.025 mmol) in toluene (0.4 ml) at 60 °C. Poly(ro-**2**) (Table 1, entry 1) and poly(ro-**3**) (entry 10) were used for the reaction and the complete gelation was observed within 15 min. The insoluble gels were successfully obtained in quantitative yield after 24 h. On the other hand, the cross-linking reaction was not observed for the reaction of the vinyl polymers, poly(v-**1**), prepared with *n*-BuLi in toluene at − 78 °C (94% yield (methanol-insoluble part), $M_n = 2.3 \times 10^4$, $M_w/M_n = 10$) and poly(v-**3**) (Table 1, entry 11), using lipase CA (100 mg/0.5 mmol (monomer unit)) in toluene at 60 °C for 24 h, as well as using $Sn(Oct)_2$ in toluene at 100 °C for 24 h. The polyesters prepared from the α-methylenemacrolides should be useful as novel reactive polymers.

The polymerization of the optically active monomer **5** ($[\alpha]_D = +234°$ ($c = 1.0$, $CHCl_3$)) using lipase CA (200 mg/0.5 mmol (monomer unit), solvent: toluene/THF = 0.6 ml/0.1 ml) at 60 °C for 48 h afforded poly(ro-**5**) in 35% yield as a methanol-insoluble fraction ($M_n = 2.7 \times 10^3$, $M_w/M_n = 1.4$, $[\alpha]_D = +50°$ (in $CHCl_3$)), whereas poly(v-**5**) was selectively obtained by the anionic polymerization with the complex of Ph_2NLi with *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) in THF at − 78°C [82% yield (methanol-insoluble part), $M_n = 4.9 \times 10^3$, $M_w/M_n = 1.5$, $[\alpha]_D = +153°$ (in $CHCl_3$)] [21]. The CD spectra of these polymers in THF are shown in Fig. 3.

The enzymatically obtained poly(ro-**5**) was further polymerized using AIBN in toluene at 60 °C for 24 h to give a cross-linked gel in quantitative yield (gel(**5**)). The chiral recognition ability of the optically active polymers and gel derived from the same monomer **5** was examined by the enantiomer selective adsorption method [29]. The *trans*-stilbene oxide (**7**) was employed as the racemate. The chiral polymer (10 mg) and **7** (0.05 mg) are mixed in hexane-2-propanol (90/10 (v/v), 200 μl) or hexane, and after standing at room temperature for 4 h, the amount of the adsorbed **7** and its optical purity were determined by a high performance liquid chromatographic (HPLC) analysis of the supernatant solution using a chiral column (Chiralcel OD, Daicel).

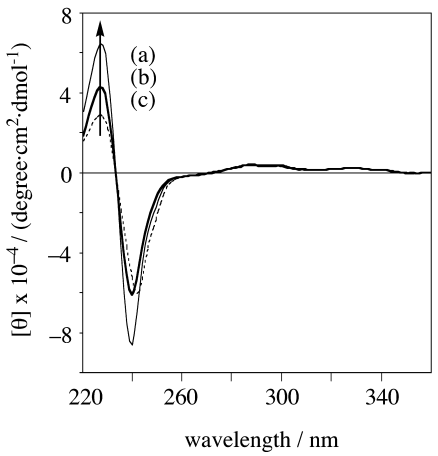
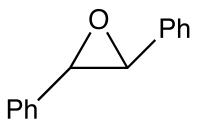


Fig. 3. CD spectra of the monomer **5** (a), poly(ro-**5**) (b), and poly(v-**5**) (c) (in THF).

Table 3
Chiral recognition by poly(ro-**5**), poly(v-**5**), and gel(**5**)

Entry	Polymeric material	Solvent hexane/2-propanol	Adsorbed **7** (%)[a]	ee of adsorbed **7** (%)[a]	Separation factor (α)[b]
1	Poly(ro-**5**)	100/0	6	0.2 (−)	~0
2	Gel(**5**)	90/10	22	3.5 (+)	1.09
3	Gel(**5**)	100/0	36	3.2 (+)	1.11
4[c]	Poly(v-**5**)	90/10	23	8.0 (−)	1.23

[a] Determined by HPLC analysis.
[b] Calculated according to $\alpha = [F_{major}(\%)/F_{minor}(\%)]/[A_{minor}(\%)/A_{major}(\%)]$ (F : free **7**; A : adsorbed **7**).
[c] Ref. [21].



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The results of the enantiomer selective adsorption experiments toward **7** are listed in Table 3. Chiral recognition was observed for gel(**5**) and poly(v-**5**), while poly(ro-**5**) showed almost no recognition power. Gel(**5**) preferentially adsorbed the (+)-isomer of **7** and the separation factor (α) was estimated to be about 1.1 (entries 2 and 3). In contrast, (−)-**7** was selectively recognized by poly(v-**5**) ($\alpha = 1.23$) (entry 4) [21].

4. Conclusion

α-Methylenemacrolides having 12–17 membered rings and various functional groups were chemospecifically polymerized to afford polyesters by enzymatic polymerization and vinyl polymers by the anionic and radical methods. The polymers obtained through the ring-opening process had a highly reactive methacrylic methylene group in the repeating unit, which was utilized for further polymerization to produce a cross-linked polymer gel. Therefore, the obtained polymers should be useful as novel reactive materials.

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