Optical Resolution of Some Racemates by HPLC Using Chiral Polymers Having (+)-5-Oxobornyl Moieties

JUI-HSIANG LIU, FU-JN TSAI

Department of Chemical Engineering, National Cheng Kung University, Tainan, Taiwan 70101, Republic of China

ABSTRACT: To investigate the stereo coordination effect on the optical resolution, chiral monomer (+)-5-oxobornyl methacrylate (OBMA) was synthesized and then polymerized under various conditions. In this work, optical resolution was carried out in the presence of chiral polymers having (+)-5-oxobornyl moieties as chiral stationary phase (CSP) for high-performance liquid chromatography (HPLC). Chiral polymer was immobilized on the surface of hydrophobic silica gel, and the chiral recognition ability of the chiral polymers was investigated. Effects of operation temperature and eluent flow rate on the chromatographic resolutions were investigated. The results of optical resolution were compared with those observed in our previous paper using chiral polymers (CSP-1 and CSP-2) having 2,3-dihydroxybornyl moieties as chiral stationary phases. It was found that the recognition ability of poly(OBMA) is greater than those of CSP-1 and CSP-2. © 1999 John Wiley & Sons, Inc. J Appl Polym Sci 72: 677–682, 1999

Key words: optical resolution; chiral polymer; chiral stationary phase; camphor; oxobornyl methacrylate

INTRODUCTION

Optical activity is a physical spectral property of chiral matter caused by asymmetrical configuration, conformations, and structures that have no plane and no center of symmetry and consequently have two mirror image enantiomeric forms of inverse optical rotation.[1] The racemic mixture of chiral enantiomers is optically inactive. The great majority of natural molecules contain chiral centers and are optically active. This is the case because living systems and their extracts as enzymes are able to produce completely stereoselective asymmetrical synthesis or transformations. This led Pasteur to say that "life is asymmetrical"[1]—at the molecular level. The majority of food and drug molecules of physiological activity are chiral.

Nonasymmetrical syntheses result in optically inactive racemic mixtures of the enantiomers. They can be separated by one of the three basic Pasteur methods (or their more recent variants) where, using asymmetrical chemical or biochemical agents, one of the optical isomers is stereoselectively extracted or transformed.[2-4] The much greater difference among the diastereomers obtained containing noninverse chiral centers (as between the two enantiomers) seems absolutely fundamental in all these methods and techniques based on specific interactions and reactions. The principle that asymmetry is generated or selected by asymmetry has not yet been contradicted. A wide variety of polymeric chiral stationary phases (CSPs) have been developed for the separation of enantiomers by means of high-performance liquid chromatography (HPLC).[5-8]

During the course of our investigations on the synthesis of both monomers and polymers containing chiral groups derived from (+)-camphor, it was found that polymers with pendant chiral

bornyl groups are effective for asymmetric induction reactions.[9–11] In a previous article, we reported the optical resolution of some racemates with the use of chiral poly(2,3-camphane diol [CPO]-co-toluene diisocyanate [TDI]) and poly-(CPO-co-isophorone diisocyanate [IPDI]).[12]

To investigate the stereo coordination effect on the optical resolution, the coodinative binding site of the bornane ring was changed from the 2,3- to the 2,5-position. In this article, optical resolution was carried out in the presence of chiral polymers having (+)-5-oxobornyl moieties as CSP for HPLC. Chiral polymer was immobilized on the surface of hydrophobic silica gel, and the chiral recognition ability of the chiral polymers was investigated. Effects of operation temperature and effluent flow speed on the chromatographic resolutions were also investigated. The results of optical resolution were compared with those observed in our previous paper using chiral polymers having 2,3-dihydroxybornyl moieties as CSPs.[12] From the results of the optical resolution, three points of acting sites of (+)-5-oxobornyl methacrylate (OBMA) unit were proposed.

EXPERIMENTAL

Materials

(+)-Camphor, sodium metal, ligroin, acetic anhydride, sodium sulphate, and all racemates purchased from Wako Chemicals Co., Ltd. (Japan), were marked EP grade. Selenium dioxide, lithium aluminium hydride, silica gel, and organic solvents were from Merck Co. (Germany); petroleum benzine [boiling point (b.p.) = 50–90°C] was from Hayashi Co. (GR grade). Organic solvent was dehydrated by distilling the solvent over magnesium sulfate and then redistilling in the presence of sodium metal. The anhydrous solvent was kept in the presence of sodium.

Measurements

Fourier transform infrared (FTIR) spectra were recorded on a Jasco VALOR III FT infrared spectrophotometer. Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker-100, high-resolution NMR spectrometer. Optical rotations were measured at 30°C in dimethylformamide (DMF) using a Jasco DIP-360 automatic digital polarimeter with readings to ±0.001°. Elemental analyses were conducted with a Heraeus

CHN-O rapid elemental analyzer. Gel permeation chromatography (GPC) measurements were carried out at 40°C on a Hitachi L-4200 instrument equipped with Tosoh Co. (Japan) TSK gel GMH and G2000H columns using tetrahydrofuran (THF) as an eluant. Chromatographic resolution was accomplished on a Hitachi L-6000 equipped with Shimadzu C-R4A data processor.

Parameters of Optical Resolution

The parameters are defined as follows: k_1, k_2, capacity factor of chiral compounds **1** and **2**; V_d, void volume; α, separation factor; V_1 and V_2, retention volume of compounds **1** and **2**.

$$k_1 = \frac{V_1 - V_d}{V_d}$$

$$k_2 = \frac{V_2 - V_d}{V_d}$$

$$\alpha = \frac{k_2}{k_1}$$

Preparation

OBMA (<u>10</u>)

(+)-5-Oxobornyl acetate (<u>8</u>), obtained from (+)-bornyl acetate (<u>7</u>) by chromium trioxide oxidation, was hydrolyzed to (+)-5-oxoborneol (<u>9</u>),[13,14] which was treated with methacrylic acid to yield OBMA (<u>10</u>).[15] The monomer was identified with elemental analysis, FTIR, and NMR spectra. A typical method was as follows. A mixture of (+)-5-oxoborneol (<u>9</u>) (8 g), methacrylic acid (1.5 g), and p-toluenesulfonic acid (1.5 g) was heated in 200 mL of benzene at 100°C in the presence of hydroquinone (3 g). Water, librated during the reaction, was removed by a Dean–Stark apparatus for 20 h. After completion of the reaction, the resulting mixture was washed with dilute aqueous sodium hydrogen carbonate solution and then with water. The oily layer was separated, dried over anhydrous magnesium sulfate, and distilled in vacuum to yield the product.

Yield: 67%, $[\alpha]_D$ = +103.5 (7.8 mg/mL; CHCl$_3$). FTIR: 1710, 1740 cm^{-1} (C=O). ^{1}H-NMR(CDCl$_3$): δ = 0.95 (s; 3H, 1CH$_3$), 1.02 (s; 6H, 7CH$_3$), 1.25 (d with fine coupling; 1H, 3-endo-H), 1.75 (s; 1H, 6-exo-H), 1.91 (s; 3H, C=C—CH$_3$), 2.13 (d; 1H, 4H), 2.45 (s; 1H, 6-endo-H), 2.51–2.95 (m, 1H, 3-exo-H), 5.17 (d; 1H, 2-exo-H), 5.61 and 6.1 (each s; 1H, C=CH$_2$).

poly(CPO-*co*-IPDI) (4)

poly(CPO-*co*-TDI) (5)

Scheme 1

ANAL. Calcd for $C_{14}H_{20}O_3$(236.3): C, 71.19%; H, 8.47%. Found: C, 70.98%; H, 8.39%.

Syntheses of Chiral Polymers (11)

Chiral monomer (10) (15 g, 0.06 mol) was polymerized in the presence of 2,2′-azobisisobutyronitrile (AIBN) in benzene (50 mL) at 60°C for a certain polymerization time. After polymerization, polymers were precipitated in a large amount of methanol. Copolymerization of chiral monomer (10) with various comonomers of methyl methacrylate (MMA), styrene (St), and acrylonitrile (AN) were carried out in benzene at 60°C for a certain polymerization time. The monomer, solvent, and AIBN were charged in this order into a polymerization tube, which was degassed in vacuo by a freeze–thaw technique and then sealed off. After a certain polymerization time, the tube was opened and the mixture was poured into a large excess of methanol to precipitate the chiral polymer. The crude polymer was purified by reprecipitation using the benzene/methanol system. The conversion was estimated by gravimetry, and the compositions of the chiral polymers were calculated from the values of the elemental analyses.

Preparation of Packing Materials and Column Packing

Macroporous silica gel (Merck Lichrospher SI-100: 10-μm mean particle size) was silanized

with dimethoxydiphenylsilane. The process of the pretreatment of packing materials is the same as those described in our previous paper.[12] The chiral polymer packing materials thus obtained were packed in a stainless steel HPLC column [0.46-cm inner diameter (i.d.), 25-cm length] by the slurry method. *n*-Hexane/2-propanol (v/v = 9/1) was used as the eluent at ambient temperature (28°C).

RESULTS AND DISCUSSION

Chiral poly(CPO-*co*-TDI) and poly(CPO-*co*-IPDI) were synthesized from (+)-camphor (1) as shown in Scheme 1, and were used as CSP-1 and CSP-2 for the chromatographic resolution. The detail conditions and recognition abilities are described in our previous article.[12] Scheme 2 shows the preparation of chiral monomer OBMA (10) by the esterification of 5-oxoborneol (9) with methacrylic acid. Structures of the synthesized compounds shown in Schemes 1 and 2 were all confirmed by elemental analyses, ^{1}H-NMR, and FTIR spectroscopy. As can be seen in the schemes, there are two polar coodinative sites in the 2,3- and 2,5-positions of the bornane ring for CPO (3) and OBMA (10), respectively. The results of the polymerization of chiral monomer (10) are summarized in Table I. Copolymers were confirmed by NMR and FTIR spectroscopy, and the compositions of the chiral copolymers were calculated from the values of elemental analyses.

OBMA (10)

Scheme 2

Table I   Polymerization of OBMA (10)[a]

Entry	Feed OBMA[b] (mol %)	Comonomer	Time (h)	Chiral Polymer		
				Conversion[c] (%)	Content of OBMA (mol %)	$[\alpha]_D$[d]
1	100	—	2	41	100	+127.8
2	100	—	8	72	100	+126.2
3	80	MMA	2	49	38	+47.2
4	80	MMA	6	76	45	+58.1
5	20	MMA	2	53	10	+11.9
6	20	MMA	6	85	12	+15.7
7	50	St	2	32	28	+35.1
8	50	St	8	64	32	+41.7
9	50	AN	8	61	19	+26.1

[a] At 60°C in benzene with 1 wt % AIBN.
[b] Feed OBMA.
[c] (Weight of polymer/total weight of monomer) × 100%.
[d] In CHCl$_3$ at room temperature.

As shown in Table I, conversions of the polymerization increased with increasing the polymerization temperature. The specific rotation of the chiral polymers depends on the chiral units contained in the copolymer. Observed rotation increased with increasing the OBMA units contained in copolymers. Homopolymer obtained in entry 2 was used to investigate the optical resolution of some racemates.

To study the chiral recognition ability of the chiral polymer, the chiral poly(OBMA) was immobilized on the surface of hydrophobic silica gel and then packed in a HPLC column as chiral stationary phase. To prevent the influence of the hydrophilic groups on the optical resolution, the surface of silica gel was modified. The hydrophilic hydroxy groups on the silica gel surface were substituted by hydrophobic phenyl groups.[12] The results of chromatographic resolution of racemates on chiral poly(OBMA) are summarized in Table II. The capacity factors (k_1 and k_2) and separation factor (α) of all the racemates were evaluated. The structures of the racemates used in this investigation are shown in Scheme 3. As can be seen in Table II, chiral poly(OBMA) is effective for separation racemates (1), (2), (7), (8), and (9). Poly(OBMA-co-MMA) and poly(OBMA-co-St) are all effective for the optical resolution (entries 13, 14, 15), although the separation factors (α) are lower than that of poly(OBMA) in entry 8. The results suggest that the existence of achiral segment in copolymer may hinder the coordination and decrease the recognition ability of the chiral copolymers.

Comparing these results with those observed in our previous article,[12] it was found that the recognition ability of poly(OBMA) is greater than those of CSP-1 and CSP-2. For the same racemates, the greater separation factors were observed in this investigation. The results suggest that racemates will coordinate with OBMA units

Table II   Chromatographic Resolution of Racemates on Chiral Poly(OBMA)[a]

Entry	Racemate	k_1	k_2	α
1	(1)	0.215	0.591	2.75
2	(2)	0.236	0.861	3.65
3	(3)	0.153	0.153	1.0
4	(4)	0.362	0.362	1.0
5	(5)	0.314	0.314	1.0
6	(6)	0.274	0.274	1.0
7	(7)	0.107	0.392	3.66
8	(8)	0.092	0.723	7.86
9	(9)	0.062	0.354	5.71
10	(10)	1.227	1.227	1.0
11	(11)	0.215	0.215	1.0
12	(12)	0.168	0.168	1.0
13[b]	(8)	0.132	0.859	6.51
14[c]	(8)	0.153	0.722	4.72
15[d]	(8)	0.258	1.07	4.15

[a] Eluant, n-hexane/2-propanol (v/v = 9/1); flow rate, 0.5 mL/min; void volume, 3.57 mL; k_1 and k_2, capacity factors; α, separation factor.
[b] Poly(OBMA-co-MMA) was used, OBMA content = 45 mol %.
[c] Poly(OBMA-co-MMA) was used, OBMA content = 10 mol %.
[d] Poly(OBMA-co-St) was used, OBMA content = 32 mol %.

in the *endo* position. The bulky bornane unit will provide an effective steric hindrance from top side of the coordinating intermediate. These hindrances lead to the result of greater recognition ability of the chiral poly(OBMA). From the three-point interaction theory, only one solute enantiomer possesses the correct chirality to have three simultaneous interactions with the resolving agent.[16] In this case, polar carbonyl groups in position 2 and 5 of the bornane ring and the bulky steric hindrance of the bornane group may act as the three points in the optical resolution.

Table III shows the results of the temperature effects on the optical resolution. As can be seen in the table, the capacity and separation factors decreased with increasing the operation temperature. In general, the larger the E_{act} of a reaction, the larger the increase in rate brought about by a given rise in temperature. Such phenomenon is considered as a leveling out effect on the reac-

Table III   Thermal Effects on the Optical Resolution Using the Chiral Poly(OBMA)^a

Entry	Racemate	T (°C)^b	k_1	k_2	α
1	(1)	28	0.215	0.591	2.75
2	(1)	35	0.224	0.486	2.17
3	(1)	40	0.198	0.368	1.86
4	(1)	28	0.198	0.491	2.48^c
5	(2)	28	0.236	0.861	3.65
6	(2)	35	0.203	0.644	3.17
7	(2)	28	0.215	0.720	3.35^c
8	(2)	35	0.189	0.512	2.71^c

^{a} Eluant, *n*-hexane/2-propanol (v/v = 9/1); flow rate, 0.5 mL/min; void volume, 3.57 mL; k_1 and k_2, capacity factors; α, separation factor.
^{b} Operation temperature.
^{c} Eluant flow rate, 0.8 mL/min.

tions. Similarly, the results obtained in Table III suggest that a rise in temperature should decrease the coordinating ability between the chiral poly(OBMA) and the enantiomers. Such thermal leveling out effects always are found in the enantioface differentiation by using chiral polymers as asymmetric inducing catalysts.[17–19] Enantioface differentiation occurred effectively at low temperature; however, the enantiomeric excess decreased with increasing the reaction temperature obviously. Dependence of the efficiency of optical resolution on eluant flow rate was also investigated. As shown in entries 4, 7, and 8, separation factor decreased with increasing the eluent flow rate.

Scheme 3

CONCLUSION

Chiral poly(OBMA) immobilized on the surface of hydrophobic silica gel can be used as a CSP for HPLC. Some racemates can be separated by the chromatographic resolution. The separation factor decreased with increasing the operation temperature and eluent flow rate. The recognition ability of poly(OBMA) is greater than those of CSP-1 and CSP-2.

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