

Synthesis of Chiral Polymers Having Camphanediol Moieties and Their Applications on the Optical Resolution of Some Racemates

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SYNOPSIS

Optically active *exo-exo*-2,3-camphanediol (CPO) (**3**) was synthesized from (+)-camphor. Chiral polymers poly(CPO-*co*-TDI) (**6**) and poly(CPO-*co*-IPDI) (**7**) were synthesized by the step polymerization of chiral compound CPO (**3**) with toluene-2,4-diisocyanate (TDI) and isophorone diisocyanate (IPDI). To investigate the stereo structure of the chiral polymers, two kinds of model compounds, *exo-exo*-2,3-di[(phenylamido)oxy]camphane (**4**) and *exo-exo*-2,3-di[(propylamido)oxy]camphane (**5**), related to polymers (**6**) and (**7**) were synthesized. Chiroptical characteristics and stereo structures of the chiral polymers were investigated using a circular dichroic spectrometer. The results obtained in this investigation suggest that the chiral polymers (**6**) and (**7**) have no one-handed helix conformation. The optical resolution ability as chiral adsorbent for HPLC of the chiral polymers was investigated. It was found that chiral polymers (**6**) and (**7**) are effective for the optical resolution of some racemates. © 1995 John Wiley & Sons, Inc.

INTRODUCTION

Optically active compounds have attracted great attention because living systems are chiral. Proteins and nucleic acids process chiral characteristic structures that are related closely to their functions. Because of chirality, living organisms usually show different biological responses to one or the other of a pair of enantiomers or optical isomers, be they drugs, pesticides, or wastes. Synthesis of chiral compounds from achiral reagents always yields the racemic modification. This is simply one aspect of the more general rule: optically inactive reagents yield optically inactive products. Optically inactive racemates, however, can be separated in the chiral environment. A wide variety of polymeric chiral stationary phases (CSP) have been developed for the separation of enantiomers by means of high-performance liquid chromatography (HPLC).¹⁻⁴

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.⁵⁻⁷ In connection with the studies on the chiral recognition of chiral polymers having bornyl moieties, the synthesis and characterization of poly(CPO-*co*-TDI) and poly(CPO-*co*-IPDI) were studied.

In this article, the optically active compound CPO was synthesized from (+)-camphor and copolymerized with toluene-2,4-diisocyanate (TDI) and isophorone diisocyanate (IPDI). To compare the stereo structures of the chiral polymers, two kinds of model compounds related to poly(CPO-*co*-TDI) and poly(CPO-*co*-IPDI) were synthesized. Chiroptical characteristics and stereo structures of the chiral polymers were investigated by using a circular dichroic spectrometer. The optical resolution ability as chiral adsorbent for HPLC of the chiral polymers was investigated.

EXPERIMENTAL

Materials

(+)-Camphor, ligroin, acetic anhydride, sodium sulfate, and all racemates purchased from Wako

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Table I Results of Polymerization of Poly(CPO-co-TDI) (6)

Entry	Solvent	Time (h)	Temp (°C)	Conversion	$[\alpha]_D^a$
1	MEK	20	80	92.3	-27.6
2	DMF	20	80	71.6	-5.0
3	DMSO	20	80	85.1	-7.0
4	MEK	3	80	85.8	-19.6
5	MEK	6	80	89.5	-22.8
6	MEK	10	80	92.6	-24.4
7	MEK	20	80	93.7	-27.6
8	MEK	30	80	94.3	-8.0
9	MEK	20	50	91.7	-18.2
10	MEK	20	60	92.1	-18.2
11	MEK	20	70	92.8	-20.2
12	MEK	20	80	93.7	-27.6 ^b

^a Specific rotation of the product, $c = 10$ mg/mL in DMF.

^b Number average molecular weight = 8.6×10^4 , evaluated by GPC at 40°C on a Hitachi L-4200 with TSK GMH and G2000H columns.

Chemicals Co., Ltd. were marked EP grade. Selenium dioxide and lithium aluminium hydride were from Merck Co.; petroleum benzine (bp = 50–90°C) was from Hayashi Co. (GR grade).

Measurement

IR spectra were recorded on a Jasco VALOR III FTIR spectrophotometer. NMR spectra were performed on a Bruker-100, high-resolution NMR spectrometer. Optical rotations were measured at 30°C in DMF using a Jasco DIP-360 automatic digital polarimeter with readings to $\pm 0.001^\circ$. Elemental analyses were calculated with a Heraeus CHN-O

rapid elemental analyzer. Circular dichroic spectra of the chiral polymers were measured with a Jasco J-720 spectropolarimeter. GPC measurement were carried out at 40°C on a Hitachi L-4200 instrument equipped with TSK gel GMH and G2000H columns using DMF as an eluent. Chromatographic resolution was accomplished on a Hitachi L-6000 equipped with Shimadzu C-R4A dataprocessor.

Parameters of Optical Resolution

The parameters are k_1 , k_2 , capacity factor of chiral compound 1 and 2; V_d , void volume; α , separation factor; and V_1 , V_2 , volume of compounds 1 and 2.

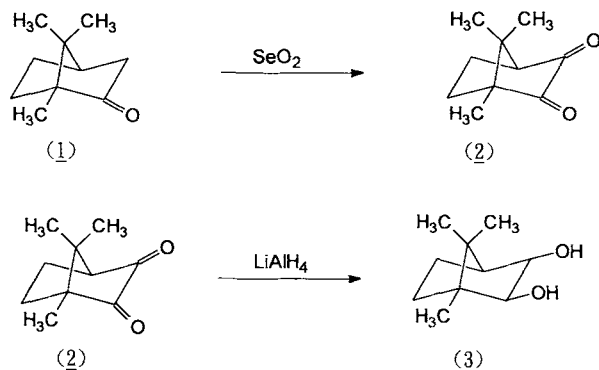
Table II Results of Polymerization of Poly(CPO-co-IPDI) (7)

Entry	Solvent	Time (h)	Temp (°C)	Conversion	$[\alpha]_D^a$
1	MEK	20	80	84.1	-7.4
2	DMF	20	80	71.5	-4.6
3	DMSO	20	80	86.7	-3.4
4	MEK	3	80	—	— ^b
5	MEK	6	80	72.0	-7.6
6	MEK	10	80	76.0	-7.8
7	MEK	20	80	84.1	-7.4
8	MEK	30	80	90.7	-7.0
9	MEK	20	50	62.0	-7.6
10	MEK	20	60	66.3	-9.2
11	MEK	20	70	68.4	-9.6
12	MEK	20	80	84.1	-7.4 ^c

^a Specific rotation of the product, $c = 10$ mg/mL in DMF.

^b Only a trace of product can be obtained.

^c Number average molecular weight = 5.2×10^4 , evaluated by GPC at 40°C on a Hitachi L-4200 with TSK GMH and G2000H columns.



Scheme 1 Preparation of exo-exo-2,3-camphane-diol (CPO).

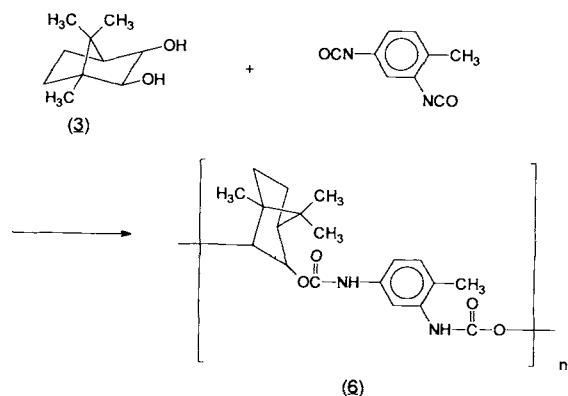
$$K_1 = \frac{V_1 - V_d}{V_d}; \quad K_2 = \frac{V_2 - V_d}{V_d}$$

$$a = \frac{K_2}{K_1}$$

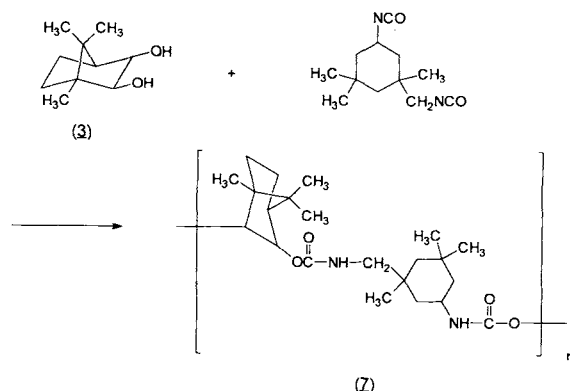
Preparation

Camphorquinone (2)

Selenium dioxide (50 g) was added to the mixture of (+)-camphor (1) (42 g) in 45 mL of acetic anhydride and then refluxed at 145°C for 7.5 h. After the reaction, the selenium was filtered off and was washed with acetic acid. The filtrate was neutralized with a cold saturated potassium hydroxide solution in an ice bath. A large amount of yellow precipitate was obtained during the neutralization. After a filtration, the crude product was recrystallized from petroleum benzene. Yield: 84.2%. $[\alpha]_D = -107.4^\circ$ (*c*



Scheme 2 Preparation of poly(CPO-co-TDI).



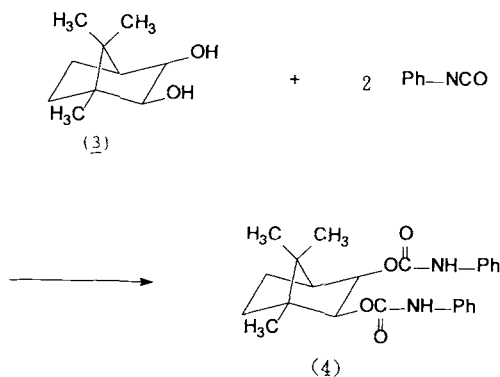
Scheme 3 Preparation of poly(CPO-co-IPDI).

= 10 mg/mL, DMF); FTIR (KBr): 1748 cm⁻¹ (C=O); ¹H-NMR (acetone-d₆): δ = 0.88, 1.04, 1.08 ppm (m, 9H, —CH₃), δ = 1.58–2.23 (m, 4H, —CH₂—), δ = 2.59, 2.60 ppm (d, 2H, —CH—).

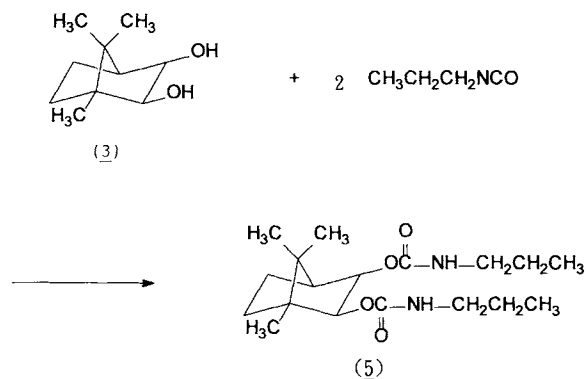
C₁₀H₁₄O₂ (166.2): Calc.: C 72.26, H 8.49; Found: C 72.32, H 8.45.

exo-exo-2,3-Camphane-diol (CPO) (3)

Camphorquinone (3) (30 g) in 360 mL of dry ether was cooled to about 0°C in an ice bath and lithium aluminium hydride (9 g) suspended in 100 mL of dry ether was added to it. After an exothermic reaction the mixture was kept at 0°C for an additional 20 min and then refluxed for 1 h. The excess amount of lithium aluminium hydride was decomposed with 1N sulfuric acid solution in an ice bath. The reaction mixture was washed several times with dilute sodium hydroxide solution and water, then it was dried over magnesium sulfate and evaporated. The crude product was recrystallized from ligroin, and then sublimed at 110°C; 26.3 g (yield: 85.6%) of colorless prisms were obtained; $[\alpha]_D = -12.0^\circ$ (*c* = 10 mg/mL, DMF); FTIR (KBr): 3358 cm⁻¹ (—OH), 1070



Scheme 4 Preparation of Model-1.



Scheme 5 Preparation of Model-2.

cm^{-1} (C—O); $^1\text{H-NMR}$ (acetone- d_6): $\delta = 0.78, 0.87, 1.07$ ppm (m, 9H, —CH₃), $\delta = 1.36\text{--}1.67$ (m, 4H, —CH₂—; 1H, —CH—), $\delta = 3.51, 3.73$ ppm (d, 2H, endo-H).

$\text{C}_{10}\text{H}_{18}\text{O}_2$ (170): Calc.: C 70.55, H 10.66; Found: C 70.56, H 10.68.

exo-exo-2,3-Di[(phenylamido)oxy]camphane (4)

A mixture of exo-exo-2,3-camphanediol (**3**) (1 g), phenyl isocyanate (1.6 g), and 20 mL of chloroform was heated at 80°C and was refluxed for 24 h. After completion of the reaction, the excess amount of phenyl isocyanate and chloroform solvent was evaporated at 80°C in vacuum. The crude product was dissolved in 20 mL of chloroform and then reprecipitated from 500 mL of *n*-hexane. The crystalline solid was recrystallized from 50 mL of *n*-hexane/acetone (v/v = 4/1) solution and was dried in vacuum. Yield = 59.3%; $[\alpha]_D = -14.8^\circ$ ($c = 10$ mg/mL, DMF); FTIR (KBr): 3298 cm^{-1} (—NH), 2963 cm^{-1} (—CH₂, —CH₃), 1706 cm^{-1} (C=O), 1596 cm^{-1} (monosubstituted C₆H₅); $^1\text{H-NMR}$ (acetone- d_6): $\delta = 0.83, 0.90, 1.25$ ppm (m, 9H, —CH₃), $\delta = 1.25\text{--}1.87$ ppm (m, 4H, —CH₂; 1H, —CH—), $\delta = 4.84$ ppm (d, 2H, endo-H), $\delta = 6.93\text{--}7.44$ ppm (m, 10H, C₆H₅).

$\text{C}_{27}\text{H}_{24}\text{O}_4\text{N}_2$ (440.5): Calc.: C 73.62, H 5.49, N 6.36; Found: C 73.58, H 5.51, N 6.37.

exo-exo-2,3-Di[(propylamido)oxy]camphane (5)

A mixture of exo-exo-2,3-camphanediol (**3**) (1 g), propyl isocyanate (1.2 g), and 20 mL of chloroform was refluxed at 80°C for 30 h. After completion of the reaction, the excess amount of phenyl isocyanate and chloroform solvent was evaporated at 80°C in vacuum. A colorless oily product was obtained. The crude product was distilled in vacuum to yield exo-exo-2,3-di[propylamido]oxy]camphane (**5**). Yield:

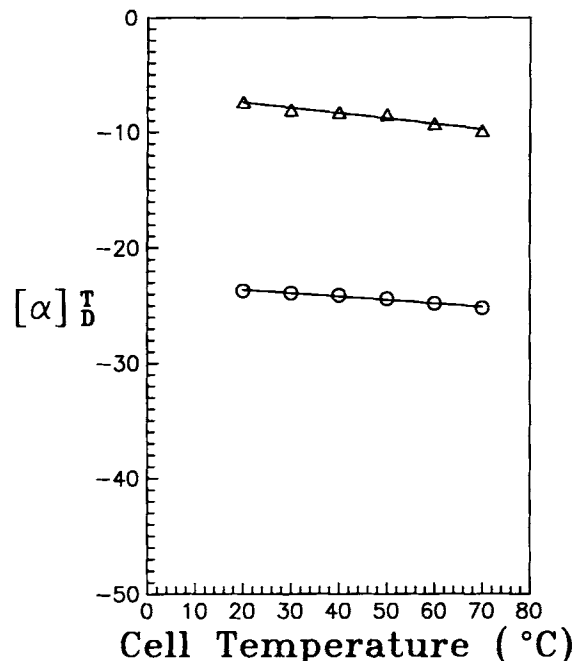


Figure 1 Temperature dependence of the specific rotation of poly(CPO-co-TDI) (**6**) (○) and poly(CPO-co-IPDI) (**7**) (Δ).

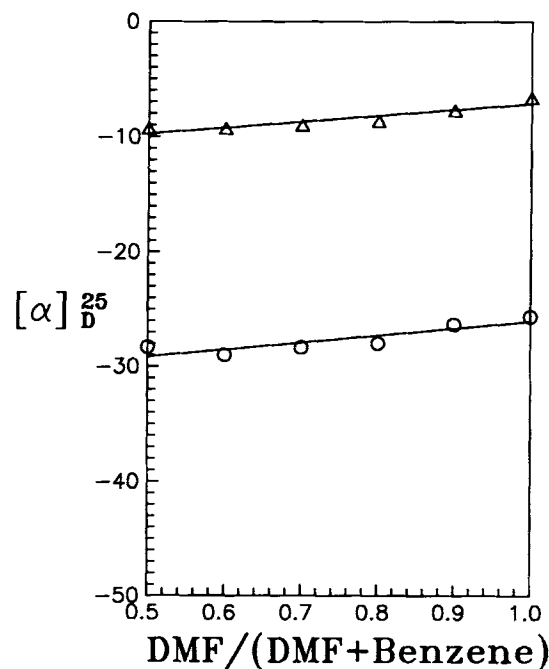


Figure 2 Solvent effect of the specific rotation of poly(CPO-co-TDI) (**6**) (○) and poly(CPO-co-IPDI) (**7**) (Δ).

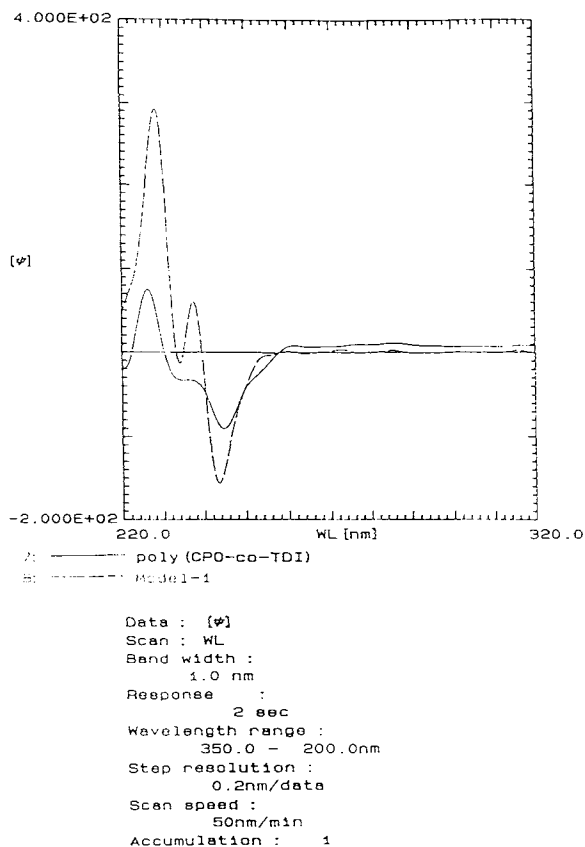


Figure 3 CD spectra of poly(CPO-co-TDI) (**6**) and model compound (**4**) in ethanol.

68.2%; $[\alpha]_D = -11.67^\circ$ ($c = 10$ mg/mL, DMF); FTIR(KBr): 3342 cm^{-1} (—NH), 2958 cm^{-1} (—CH₂, —CH₃), 1705 cm^{-1} (C=O); ¹H-NMR (CDCl₃): $\delta = 0.74\text{--}0.86$ ppm (m, 15H, —CH₃), $\delta = 1.41\text{--}1.75$ ppm (m, 8H, —CH₂; 1H, —CH—), $\delta = 3.02\text{--}3.05$ ppm (m, 4H, N—CH₂), $\delta = 4.66\text{--}4.99$ ppm (m, 2H, endo-H).

C₁₈H₃₂O₄N₂ (340.4): Calc.: C 63.50, H 9.41, N 8.23; Found: C 63.61, H 9.45, N 8.19.

Syntheses of Chiral Polymers

Chiral polymers poly(CPO-co-TDI) (**6**) and poly(CPO-co-IPDI) (**7**) were synthesized in various solvents. A typical method is as follows. In a four-necked flask provided with a stirrer and a reflux condenser, 1 g of exo-exo-2,3-camphanediol (CPO) in 15 mL of methyl ethyl ketone (MEK) was added to 1.024 g TDI under nitrogen atmosphere. The mixture was stirred at 80°C for 20 h and then an excess amount of 0.2 g of TDI was added and stirred for further 1 h. After completion of the reaction, 10 mL of methanol was added. The reaction mixture

was cooled to room temperature and then it was poured into 50 mL of water to precipitate the chiral polymers. The crude polymers were purified by reprecipitation using MEK/water as nonsolvents. Effects of solvents, reaction time, and reaction temperature on the copolymerization were investigated. The results are summarized in Tables I and II.

Preparation of Packing Materials and Column Packing

Macroporous silica gel (Merck Lichrospher SI-100: mean particle size, 10 μm; pore size, 100 nm) was silanized with dimethoxydiphenylsilane. A typical method is as follows. To remove water adsorbed on gel, silica gel (SI-100) (10 g) was heated at 150°C in nitrogen gas flow for 30 min. The silica gel was then mixed with 225 mL of toluene and was heated at the azeotropic temperature of water and toluene. After the azeotropic distillation, the remaining 50 mL of toluene was cooled to 90°C. Dimethoxydiphenylsilane (7 mL) was added and reacted at 90°C for 12 h. After the reaction, the silica gel was filtered,

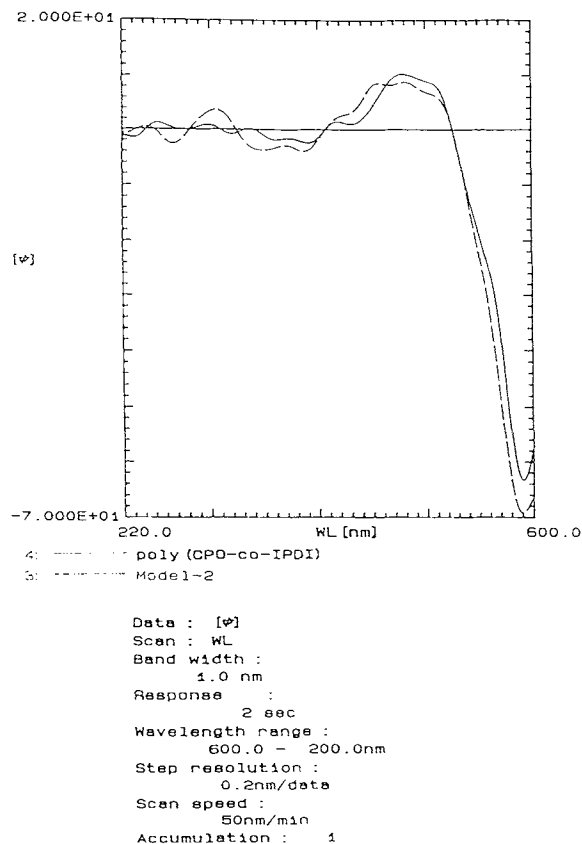
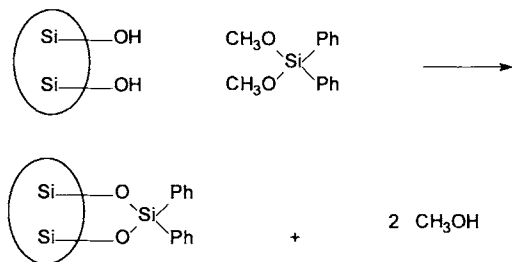


Figure 4 CD spectra of poly(CPO-co-IPDI) (**7**) and model compound (**5**) in ethanol.



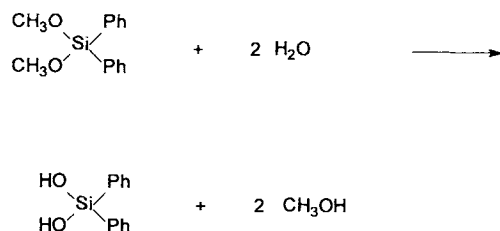
Scheme 6 Reaction of the modification on the silica gel surface.

washed with toluene and dichloromethane, and was then dried *in vacuo* at 60°C for 5 h.

Chiral polymer (**6**) or (**7**) (0.7 g) was dissolved in 10 mL of DMF and the silanized silica gel (2.5 g) was wetted with the chiral polymer solution. The solvent was removed *in vacuo*. The polymer-coated silica gel was dried *in vacuo* at 60°C for 5 h and then dispersed in 30 mL of methanol with sonication during 5 min. After filtration and washing with methanol, the silica gel was dried at 60°C for 5 h. The chiral polymer packing materials thus obtained were packed in a stainless-steel HPLC column (i.d. 0.46 cm, length 25 cm) by the slurry method. The plate numbers of the columns packed with poly(CPO-*co*-TDI) (**6**) (CSP-I) and poly(CPO-*co*-IPDI) (**7**) (CSP-II) were about 1438 and 1220, respectively, for benzene using *n*-hexane and 10% 2-propanol in *n*-hexane as the eluent at ambient temperature.

RESULTS AND DISCUSSION

Chiral exo-exo-2,3-camphanediol (CPO) (**3**) was synthesized from (+)-camphor by using selenium dioxide and lithium aluminium hydride in dry ether as shown in Scheme 1. As seen in Schemes 2 and 3, chiral polymers poly(CPO-*co*-TDI) (**6**) and poly(CPO-*co*-IPDI) (**7**) were prepared by the step polymerization of chiral compound CPO (**3**) with



Scheme 7 Side reaction of the modification on the silica gel surface.

Table III Chromatographic Resolution of Racemates on the CSP-1

Entry	Racemate	k_1	k_2	α
1	(1)	0.306	0.706	2.307
2	(2)	0.173	0.574	3.318
3	(3)	1.487	1.487	1.0
4	(4)	0.091	0.091	1.0
5	(5)	0.295	0.695	2.356
6	(6)	0.110	0.110	1.0
7	(7)	0.181	0.181	1.0
8	(8)	0.213	0.213	1.0
9	(9)	0.228	0.228	1.0
10	(10)	0.119	0.589	2.960
11	(11)	0.292	0.292	1.0
12	(12)	0.142	0.142	1.0
13	(13)	0.185	0.185	1.0
14	(14)	0.221	0.221	1.0
15	(15)	0.238	0.238	1.0
16	(16)	0.206	0.206	1.0

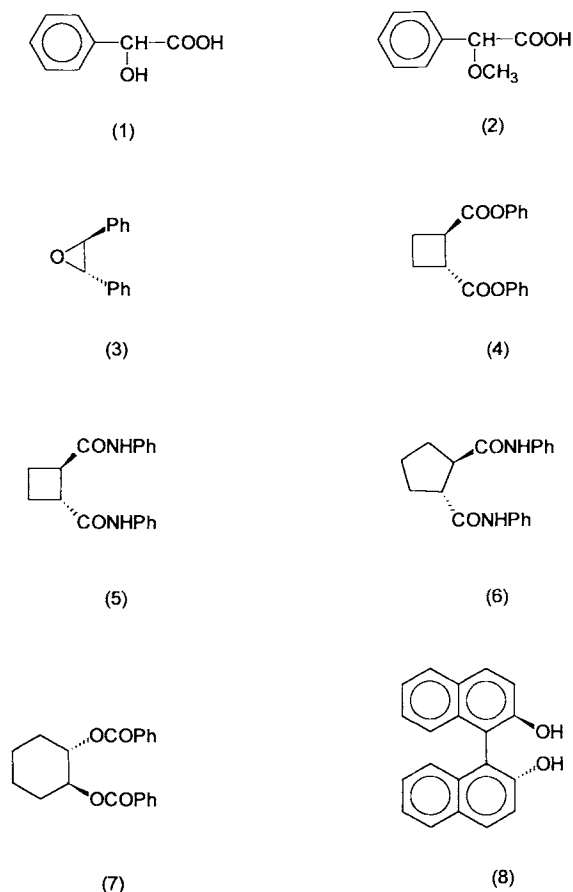
Eluent, *n*-hexane; flow rate, 0.5 mL/min; void volume, 3.59 mL; k_1 , k_2 , capacity factor; α , separation factor.

toluene-2,4-diisocyanate (TDI) and isophorone diisocyanate (IPDI), respectively. Effects of solvent, reaction time, and temperature on the polymerization were investigated. The results are summarized in Tables I and II. As shown in Tables I and II, optical rotation of the chiral polymers were affected by the polymerization conditions.

Table IV Chromatographic Resolution of Racemates on the CSP-2

Entry	Racemate	k_1	k_2	α
1	(1)	0.098	0.098	1.0
2	(2)	0.670	0.670	1.0
3	(3)	0.131	0.131	1.0
4	(4)	0.215	0.215	1.0
5	(5)	0.395	0.395	1.0
6	(6)	0.221	0.221	1.0
7	(7)	0.203	0.203	1.0
8	(8)	0.429	0.429	1.0
9	(9)	0.048	0.218	1.0
10	(10)	0.119	0.589	4.542
11	(11)	1.011	1.011	1.0
12	(12)	0.062	0.518	8.355
13	(13)	0.053	0.206	3.887
14	(14)	1.153	1.153	1.0
15	(15)	2.401	2.401	1.0
16	(16)	1.012	1.012	1.0

Eluent, *n*-hexane/2-propanol (*v/v* = 9/1); flow rate, 0.5 mL/min; void volume, 3.23 mL; k_1 , k_2 , capacity factor; α , separation factor.



Scheme 8 Structures of racemates (1) ~ (8).

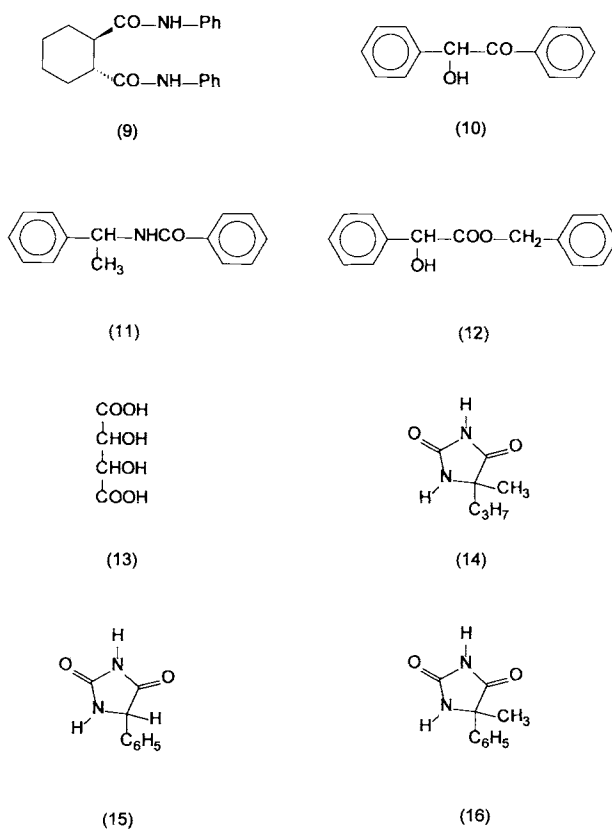
To investigate the stereo structure of the chiral polymers, two kinds of model compounds, exo-exo-2,3-di[(phenylamido)oxy]camphane (**4**) and exo-exo-2,3-di[(propylamido)oxy]camphane (**5**), related to chiral polymers (**6**) and (**7**) were synthesized as shown in Schemes 4 and 5. Structures of the synthesized compounds were all confirmed by elemental analysis, $^1\text{H-NMR}$, and IR spectroscopy. The $^1\text{H-NMR}$ signal of the exo-hydrogen in positions 2 and 3 of the CPO (**3**) showed the same chemical shift as those described in the literature.⁸

The temperature dependence and solvent effect on the specific rotation for the poly(CPO-co-TDI) (**6**) and poly(CPO-co-IPDI) (**7**) were investigated. As illustrated in Figure 1, a dependence of the specific rotation on temperature was observed over the range 20–70°C. The values of the temperature coefficient ($\Delta[\alpha]/\Delta T$) for the systems were all small. The dependence of the specific rotation on temperature for the polymers is shown in Figure 2. The specific rotation for the copolymers increased linearly with increasing DMF. As pointed out by Oishi

et al.,^{9,10} the results suggest that the helical conformation in the chiral polymers may not be present.

To get further information on the stereo structure of the chiral polymers, chiral polymers (**6**) and (**7**) were prepared in MEK at 80°C for 20 h. The comparison of the chiroptical properties of the poly(CPO-co-TDI) (**6**) and poly(CPO-co-IPDI) (**7**) to the corresponding model compounds exo-exo-2,3-di[(phenylamido)oxy]camphane (**4**) and exo-exo-2,3-di[(propylamido)oxy]camphane (**5**) was carried out. The value of the specific rotation of (**6**) (-27.6°) is comparable to that of the model compound (**4**) (-14.8°). The CD spectrum of polymer (**6**) in ethanol is almost comparable to that of model compound (**4**) as shown in Figure 3. Much the same, the value of the specific rotation of (**7**) (-7.4°) is comparable to that of the model compound (**5**) (-11.67°). As can be seen in Figure 4, the CD spectrum of polymer (**7**) is also comparable to that of model compound (**5**). These results suggest that chiral polymers (**6**) and (**7**) may have no one-handed helix conformation.

To study the chiral recognition ability of the chiral polymers, the chiral poly(CPO-co-TDI) (**6**) and poly(CPO-co-IPDI) (**7**) were immobilized on



Scheme 9 Structures of racemates (9) ~ (16).

the surface of hydrophobic silica gel and then packed in a high-performance liquid chromatograph (HPLC) column as chiral stationary phases, CSP-1 and CSP-2, respectively. The modification reaction on the silica gel surface is shown in Scheme 6; hydrophilic hydroxy groups were substituted by hydrophobic phenyl groups. As shown in Scheme 7, a side reaction may occur in the progress of the surface modification. The results of chromatographic resolution of racemates on CSP-1 and CSP-2 are summarized in Tables III and IV. The capacity factor (k') and separation factor (α) of all the racemates were evaluated. The structures of the racemates used in this investigation are shown in Schemes 8 and 9.

As can be seen in Tables III and IV, CSP-1 is effective for the racemates (1), (2), (5), and (10), and CSP-2 is effective for the racemates (10), (12), and (13) (Schemes 8 and 9). Amino groups in CSP-1 can provide a hydrogen-bonding site, and a benzene ring may act as a π -electron acceptor group. Thus, a main control factor for the chiral discrimination of CSP-1 seems to be the hydrogen-bonding site, π - π interaction, dipole-dipole interaction, and chiral stereo factors. For CSP-2, however, it may be only the hydrogen-bonding site, dipole-dipole interaction, and chiral stereo factors.

CONCLUSION

Chiral polymers poly(CPO-*co*-TDI) (**6**) and poly(CPO-*co*-IPDI) (**7**) can be synthesized by the step polymerization of chiral compound CPO (**3**) with toluene-2,4-diisocyanate (TDI) and isophorone diisocyanate (IPDI), respectively. The results of the

CD spectra investigation suggest that chiral polymers poly(CPO-*co*-TDI) (**6**) and poly(CPO-*co*-IPDI) (**7**) may not exist in a one-handed helix conformation. Chiral polymers poly(CPO-*co*-TDI) (**6**) and poly(CPO-*co*-IPDI) (**7**) immobilized on silica gel packed in a high-performance liquid chromatograph (HPLC) column can be used as chiral stationary phases, CSP-1 and CSP-2, respectively. CSP-1 and CSP-2 are effective for the optical resolution of some racemates.

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