The Chiral Recognition of Optically Active Poly(triphenylmethyl methacrylate) Derivatives as Stationary Phases for HPLC[1]

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Four *meta*-halogen- or *meta*-methyl-substituted optically active poly(triphenylmethyl methacrylate) [poly(TrMA)] derivatives with a one-handed helical structure were coated on macroporous silica gel and their chiral-recognition abilities as stationary phases for high-pherformance liquid chromatography were investigated with methanol or hexane-2-propanol (95:5(v/v)) as the eluent. The chiral-recognition abilities of poly(*m*-fluorophenyldiphenylmethyl methacrylate) and poly(*m*-chlorophenyldiphenylmethyl methacrylate) were slightly low compared with that of poly(TrMA) when methanol was used as the eluent. Poly[tris(*m*-chlorophenyl)methyl methacrylate] [poly(*m*-Cl_3TrMA)] showed no resolving ability, although poly[tris(*m*-tolyl)methyl methacrylate] [poly(*m*-Me_3TrMA)] had an effective chiral recognition ability and resolved some racemates more efficiently than poly(TrMA). When hexane–2-propanol (95/5) was used as the eluent, the optical-resolution abilities of all these chiral polymers except for poly(*m*-Cl_3TrMA) were rather similar to that of poly(TrMA) under the same eluent system. The chiral-adsorbing sites are considered to be the chiral triarylmethyl propellers in the methanol system; carbonyl groups may also be involved in the hexane-2-propanol system. The difference in the chiral-recognition abilities of the two tri-substituted chiral polymers were ascribed to their different propeller structures and/or the different conformations of their carbonyl groups. The optical-resolution abilities of poly[TrMA-*co*-(*m*-Cl_3TrMA)] and poly[TrMA-*co*-(*m*-Me_3TrMA)] were also investigated. From the results, the mechanism of the separation of enantiomers on poly(TrMA) was discussed.

Optically active poly(TrMA) is a unique polymer whose chirality is caused only by helicity; it is directly prepared by the asymmetric polymerization of TrMA with chiral anionic initiators, such as (−)-sparteine-butyllithium[2] and (+)-(2*S*,3*S*)- or (−)-(2*R*,3*R*)-dimethoxy-1,4-bis(dimethylamino)butane (DDB)–lithium amide complexes[3] in toluene at a low temperature. The polymer, especially when coated on macroporous silica gel,[4] can resolve many racemic compounds, including hydrocarbons, esters, amides, and alcohols, most of which were first resolved on a poly(TrMA) column.[5] As eluents, polar solvents like methanol are more effective than nonpolar solvents like hexane, indicating that the nonpolar interaction between the polymer, probably triphenylmethyl groups, and nonpolar groups of enantiomers plays an important role in chiral recognition.[5] However, when methanol is used as the eluent, the ester groups of poly(TrMA) are slowly solvolyzed to form methyl triphenylmethyl ether.[6] In order to improve this defect, we prepared (*m*-fluorophenyl)diphenylmethyl methacrylate (*m*-F_1TrMA), (*m*-chlorophenyl)diphenylmethyl methacrylate (*m*-Cl_1TrMA), tris(*m*-chlorophenyl)methyl methacrylate (*m*-Cl_3TrMA), tris(*m*-tolyl)methyl methacrylate (*m*-Me_3TrMA), and tris(*p*-chlorophenyl)methyl methacrylate (*p*-Cl_3TrMA), and then measured the rates of methanolysis by means of ^{1}H NMR spectroscopy.[7] The methacrylates with electron-withdrawing substituents like halogen were much more stable against methanolysis than those with electron-donating substituents like the methyl group. All the methacrylates except for *p*-Cl_3TrMA gave optically active isotactic one-handed helical polymers with chiral anionic initiators in toluene at −78 °C.[7] The CD spectra of these chiral polymers were greatly different from each other. We assumed that the difference is attributable to the different propeller structures and/or conformations of ester groups, including carbonyl groups.

In this article, we will investigate the optical-resolution abilities of these chiral polymers and chiral copolymers of TrMA; we will also discuss the mechanism of enantiomer recognition.

Experimental

Materials. Optically active poly(triphenylmethyl methacrylate) derivatives were prepared by the asymmetric polymerization of the corresponding monomer with chiral lithium initiators in toluene at −78 °C;[3,7] the $[\alpha]_D^{25}$ values of the polymer in tetrahydrofuran (THF) were +343° [poly(TrMA)], +330° [poly(*m*-F_1TrMA)], +356° [poly(*m*-Cl_1TrMA)], −284° [poly(*m*-Cl_3TrMA)], and $[\alpha]_{546}^{25}$ −310° [poly(*m*-Me_3TrMA)]. The fractions which were soluble in THF and insoluble in benzene–hexane (1:1(v/v)) were used for the preparation of the chiral stationary phases.

Poly(TrMA-*co*-*m*-Cl_3TrMA) and poly(TrMA-*co*-*m*-Me_3TrMA) were prepared by asymmetric copolymerization with (+)- or (−)-DDB and *N*,*N*′-diphenylethylenediamine monolithium amide complex in toluene at −78 °C, as previously reported.[7]

Most racemic compounds were commercially available or were prepared by the usual procedures.

Preparation of Stationary Phase. Macroporous silica gels, (Merck, LiChrospher SI 1000 (diameter, 10 μm; pore size, 100 nm) and SI 4000 (10 μm; 400 nm)), were treated

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with a large excess of dichlorodiphenylsilane in toluene at 110 °C for 24 h and with (3-aminopropyl)triethoxysilane in benzene at 80 °C for 24 h respectively. After the reaction, the silica gels were poured into methanol, filtered, and dried. Found for SI 1000: C, 2.93; H, 0.54%. Found for SI 4000: C, 0.23; H, 0.07%.

A chiral polymer (0.75 g) was dissolved in 10 ml of THF and the silanized silica gel (3.0 g) was wetted with the polymer solution (ca. 5 ml) as uniformly as possible. Then, the solvent was evaporated under reduced pressure. This process was repeated with the remaining polymer solution. The stationary phases contained 20—24.5 wt% of polymer on silica gel, judging from the elemental analyses. The packing materials thus obtained were packed in a stainless-steel column (25X0.46 (i.d.) cm) at 300 kg cm^{-2} by means of a slurry method using methanol. The plate number of a column was 3000—4500 for acetone when methanol (0.5 ml min^{-1}) was the eluent at 15 °C. The void volume (V_0) of the column was estimated to be 3.3 ml, with water as a non-retained compound.

Measurements. Chromatographic resolution was accomplished on a JASCO TRIROTAR-II chromatograph equipped with UV (JASCO UVIDEC-100-III) and polarimetric (JASCO DIP-181C) detectors. The optical rotation was followed in a flow cell (5X0.2 (i.d.) cm) at full lamp (mercury) intensity without filters. Resolution was carried out with methanol or a hexane-2-propanol (95:5 (v/v)) mixture at a flow-rate of 0.5 ml min^{-1} at 15 °C, unless otherwise stated.

Results and Discussion

Figure 1 shows the chromatogram of the resolution of *trans*-2,3-diphenyloxirane (**1**) on a poly(*m*-F$_1$TrMA) column. The enantiomers were eluted at the retention volumes, V_1 and V_2. The capacity factors, k_1' and k_2', were determined to be 0.66 and 1.20 respectively by using the following relations:

$$k_1' - \frac{(V_1 - V_0)}{V_0} \qquad k_2' = \frac{(V_2 - V_0)}{V_0}$$

The separation factor, α, and the resolution factor, R_s, were estimated to be 1.82 and 2.51 respectively from these equations:

$$\alpha = \frac{k_2'}{k_1'} \qquad R_s = \frac{2(V_2 - V_1)}{(W_1 + W_2)}$$

Table 1 shows the results of the optical resolution of racemates **1**, *trans*-cyclopropanedicarboxylic acid dianilide (**2**), the Tröger base (**3**), benzoin (**4**), 2,2′-dihydroxy-1,1′-binaphtyl (**5**), 2,2′-(2,2-dimethyl-2-silapropane-1,3-diyl)-1,1′-binaphthalene (**6**),[8] and tris(acetylacetonato)cobalt(III) (Co(acac)$_3$), with methanol as the eluent. All the compounds were almost completely resolved by the use of a (+)-poly(TrMA) column. When a polar solvent like methanol was used as the eluent, the driving force for the separation of the enantiomers on (+)-poly(TrMA) has been considered to be nonpolar interaction between the polymer, probably the chiral propeller of the triphenylmethyl group, and nonpolar groups of

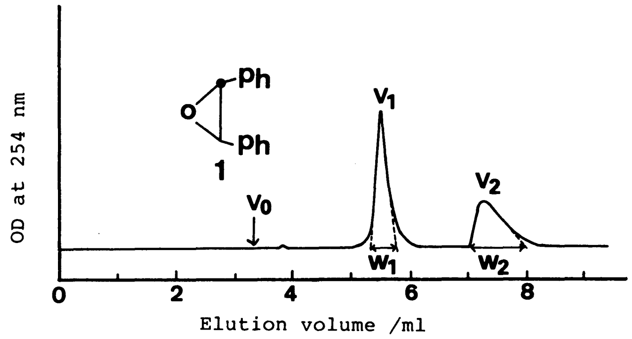


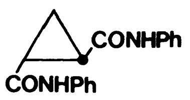
Fig. 1. Chromatographic resolution of *trans*-2,3-diphenyloxirane (**1**) on (+)poly(*m*-F$_1$TrMA) column. (Column: 25 cmX0.46 (i.d.) cm, eluent: methanol (0.5 ml min^{-1}), 15 °C).

Table 1. Resolution of Racemic Compounds on Optically Active Polymers[a)]

Racemate	(+)-Poly(TrMA)			(+)-Poly(*m*-F$_1$TrMA)			(+)-Poly(*m*-Cl$_1$TrMA)		
	k_1'(±)	α	R_s	k_1'(±)	α	R_s	k_1'(±)	α	R_s
1	0.82(−)	5.21	5.30	0.66(−)	1.81	2.51	0.48(−)	1.44	0.75
2	0.22(−)	1.24	0.50	0.53	1	0	0.17	1	0
3	0.59(+)	1.75	3.38	0.61(+)	1.51	1.71	0.72(+)	1.43	1.19
4	0.39(−)	1.34	1.30	0.27(−)	1	0	0.20	1	0
5	0.50(+)	2.37	3.83	0.47(+)	1.63	1.65	0.47(+)	1.60	1.23
6	2.47(−)	1.78	2.46	2.15(−)	1.26	1.14	2.24(−)	1.23	0.59
Co(acac)$_3$	0.46(+)	1.32	0.88	0.52(+)	1.09	0.26	0.72(+)	>1	0

	(−)-Poly(*m*-Cl$_3$TrMA)			(−)-Poly(*m*-Me$_3$TrMA)		
	k_1'(±)	α	R_s	k_1'(±)	α	R_s
1	0.44(+)	>1	0	0.59(+)	1.76	1.47
2	0.10	1	0	0.11	1	0
3	0.60	1	0	0.54(−)	1.14	
4	0.14	1	0	0.14	1	0
5	0.31	1	0	0.23	1	0
6	2.27	1	0	1.40(+)	1.49	2.07
Co(acac)$_3$	0.57	1	0	0.24	1	0

a) Operating conditions: column, 25X0.46 (i.d.)cm; eluent, methanol; flow rate, 0.50 ml min^{-1}; temperature, 15 °C.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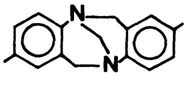
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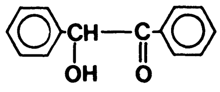
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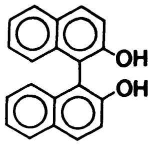
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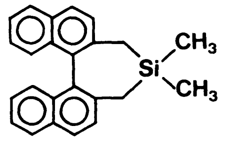
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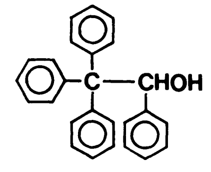
enantiomers.[5] The capacity factors (k_1') and the chiral-recognition abilities (α) decrease with an increase in the size and number of halogen substituents of the stationary phases. Poly(m-Cl$_3$TrMA) having a specific rotation as high as those of other chiral polymers, could not resolve any racemic compounds. However, poly(m-Me$_3$TrMA) showed a complete separation for Compounds **1** and **6** and a partial separation of **3**. Moreover, poly(m-Me$_3$TrMA) resolved 1,2,2,2-tetraphenylethanol (**7**, α=1.16) and methyl 2-(1-carbazolyl)propionate (**8**, α=1.45) more effectively than poly(TrMA) by using a mobile phase of methanol–H$_2$O=85/15 (v/v). These results indicate that the effects of the halogen and methyl substituents are greatly different from each other; this will be discussed later.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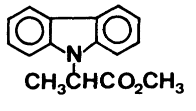
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In the resolution of **1**, all the (+)-polymers adsorbed the (+)-isomer more strongly than the (−)-isomer, while the two negative polymers adsorbed the (−)-isomer more strongly. Similar results were also obtained for the other compounds, indicating that the sign of the optical rotation of polymers reflects the helicity of the polymer chains.

In Table 2 are collected the results of the resolution of racemates **1**, **3**, **4**, and Co(acac)$_3$ on the chiral polymers, using hexane–2-propanol (95:5 (v/v)) as the eluent at 15 °C. Poly(TrMA) resolved all the racemates with a slightly low separation factor in comparison to that with the methanol eluent. The chiral-recognition abilities of the other polymers did not always decrease in hexane–2-propanol, and **3**, **4**, and Co(acac)$_3$ were more effectively resolved on the poly(m-F$_1$TrMA) and poly(m-Cl$_1$TrMA) columns than on the poly(TrMA) column. In this non-polar system, the ester group (COO) and the triarylmethyl group may both more effectively participate in chiral discrimination. This might bring about the similar optical resolving powers of poly(TrMA), poly(m-F$_1$TrMA), poly(m-Cl$_1$TrMA), and poly(m-Me$_3$TrMA). The extremely low chiral-recognition ability of poly(m-Cl$_3$TrMA) in both the eluent systems may be attributed to a different structure of the triarylmethyl group.

Previously, we proposed that the triphenylmethyl groups on the optically active poly(TrMA) may take either left- or right-handed propeller structures, accompanied by the formation of a one-handed helical polymer chain.[9] (+)-Poly(TrMA) has been considered to possess a right-handed helix on polymer chains and a left-handed propeller on the triphenylmethyl group, based on the results of the optical resolution of various racemic compounds.[5,9] Such a chiral propeller structure of the triphenylmethyl group has been demonstrated by Empirical Force Field Calculations,[10,11] while perchlorotriphenylamine has been

Table 2. Resolution of Racemic Compounds on Optically Active Polymers with Hexane-2-Propanol (95/5)[a]

Racemate	(+)-Poly(TrMA)			(+)-Poly(m-F$_1$TrMA)			(+)-Poly(m-Cl$_1$TrMA)		
	$k_1'(\pm)$	α	R_s	$k_1'(\pm)$	α	R_s	$k_1'(\pm)$	α	R_s
1	0.76(−)	1.54	1.96	0.82(−)	1	0	0.54(−)	1.38	1.19
3	0.66	1.44	1.30	0.57(+)	1.50	1.57	0.61(+)	1.43	0.84
4	1.88	1.13	0.59	1.33(−)	1.17	1.11	1.41	1.32	1.22
Co(acac)$_3$	2.21(+)	1.26	1.25	3.51(+)	1.19	1.00	4.40(+)	1.34	0.99
	(+)-Poly(m-Cl$_3$TrMA)			(−)-Poly(m-Me$_3$TrMA)					
	$k_1'(\pm)$	α	R_s	$k_1'(\pm)$	α	R_s			
1	0.31(+)	1	0	0.18(+)	1.25	0.15			
3	0.38	1	0	1.15(−)	1.32	0.96			
4	0.95	1	0	0.68(+)	1.16	0.56			
Co(acac)$_3$	3.58	>1	0	1.18	>1	0			

a) Operating conditions: see Table 1.

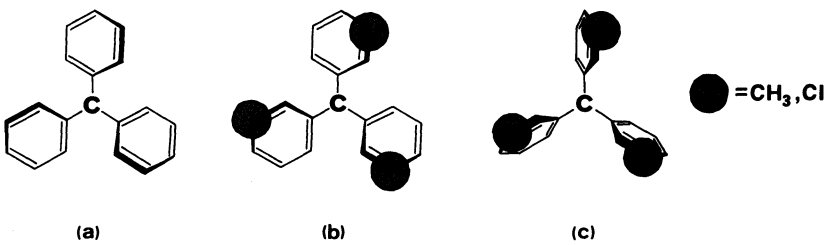

Fig. 2. Possible propeller structures of triphenylmethyl group (a), tris(*m*-tolyl)methyl group (b), and tris(*m*-chlorophenyl)methyl group (c).

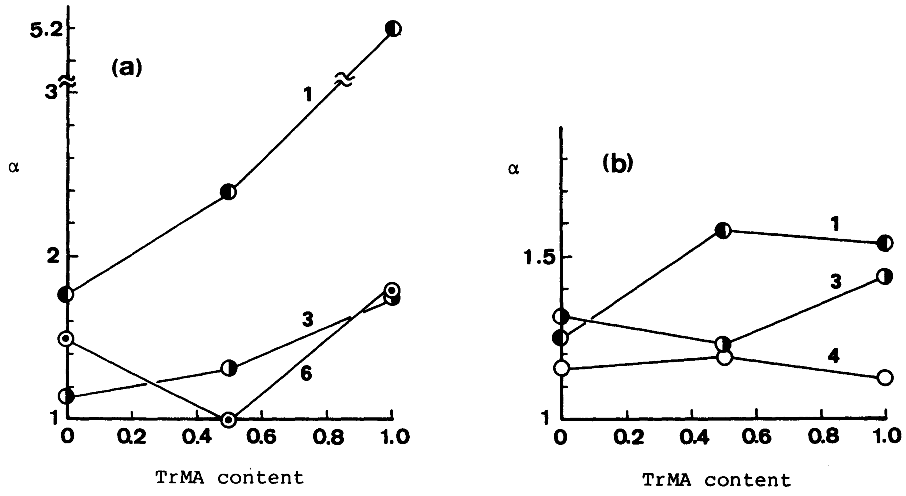

Fig. 3. Influence of TrMA content on separation factor (α) of poly(TrMA-*co*-*m*-Me_3TrMA). Eluent: (a), methanol; (b), hexane–2-propanol (95/5).

proved to take a stable propeller structure by its optical resolution.[12]

Figure 2 shows the possible left-handed propeller structures of the triphenylmethyl group and its derivatives. Three phenyl rings are likely to be twisted at some intermediate angle to each other for steric hindrance (Fig. 2(a)); the dihedral angle formed by the planes of the phenyl rings was calculated to be 35.7° for the most stable structure of triphenylmethane.[10] These chiral propeller faces must play the most important role in recognizing enantiomers, at least when methanol is used as the eluent. The three *m*-tolyl rings may also be twisted (Fig. 2(b)), because poly(*m*-Me_3TrMA) showed an effective chiral-recognition ability, similar to that of poly(TrMA) to some enantiomers. On the other hand, three *m*-chlorophenyl rings seem to be more upright, as is illustrated in Fig. 2(c). Therefore, enantiomers can not interact with chiral propeller faces and will be less retained in the stationary phase. This must lead to a poor separation of the enantiomers, regardless of the eluents.

The chiral recognition of the poly(triarylmethyl-methacrylate)s must be governed not only by a single triarylmethyl propeller but also by adjacent propellers. In order to investigate this, copolymers of TrMA and *m*-Cl_3TrMA or *m*-Me_3TrMA were prepared[7] and used as chiral stationary phases in the same manner as homopolymers. All the copolymers in our experiments showed almost the same optical rotation, regardless of the molar ratios, as has previously been reported.[7] Figure 3 shows the relationships between the TrMA content in poly(TrMA-*co*-*m*-Me_3TrMA) and the separation factors (α) for the three racemates **1**, **3**, and **4**. When methanol was used as the eluent (Fig. 3(a)), the α values for **1** and **3** were nearly equal to the average values of those on the two homopolymers. These compounds may be recognized on a single propeller unit. The copolymer could not resolve Compound **6**, although both the homopolymers resolved it well, indicating that continuous, same monomer units in polymer chains are necessary for the separation of **6**. On the other hand, **1** and **4** were better resolved on the copolymer than on either of the homopolymers in the hexane–2-propanol system (Fig. 3(b)). Those compounds seem to be recognized more effectively on chiral sites lying between TrMA and *m*-Me_3TrMA units.

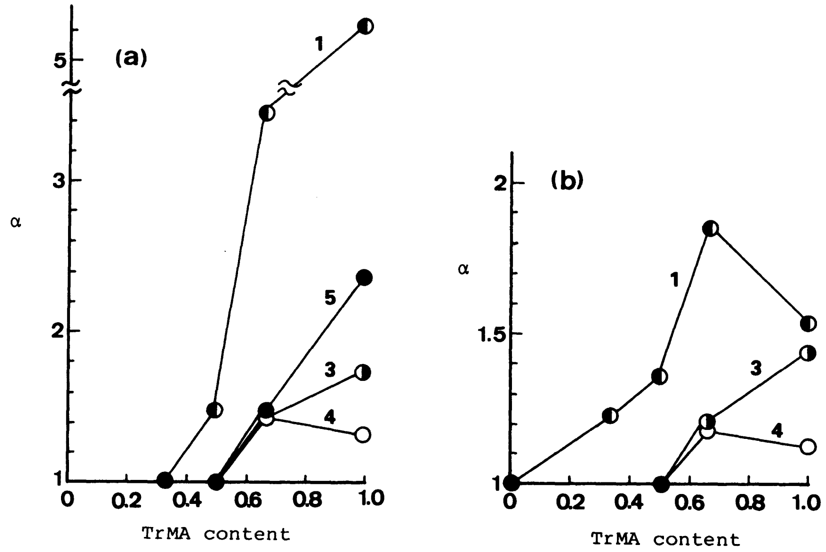

Fig. 4. Influence of TrMA content on separation factor (α) of poly(TrMA-*co*-*m*-Cl_3TrMA). Eluent: (a), methanol; (b), hexane–2-propanol (95/5).

Figure 4 shows the relationships between the TrMA content in poly(TrMA-*co*-*m*-Cl_3TrMA) and the α values for the four racemates **1**, **3**, **4**, and **5**. In both eluent systems, all of the racemates except **1** were not resolved on the copolymers containing less than 50% TrMA units; the resolution of **1** could be attained on the copolymers containing 50 and 33% TrMA units. These results suggest that two or more continuous TrMA units are necessary for the resolution of **3**, **4**, and **5**, while **1** can be resolved by only one TrMA unit in the copolymer.

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