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CHROMATOGRAPHIC RESOLUTION

IX*. HIGH-PERFORMANCE LIQUID CHROMATOGRAPHIC RESOLUTION OF ENANTIOMERS ON OPTICALLY ACTIVE POLY(TRIPHENYLMETHYL METHACRYLATE)

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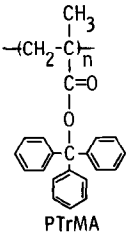
SUMMARY

Optically active (+)-poly(triphenylmethyl methacrylate) was coated on macroporous silica gel and used as a chiral stationary phase for high-performance liquid chromatographic resolution of enantiomers. The chiral polymer resolved various compounds particularly when a polar eluent such as methanol was employed. The influences of the kind of silica gel, column temperature and eluent on the separation were investigated.

INTRODUCTION

The liquid chromatographic separation of enantiomers is a practically important and useful method for the preparation and purity determination of optical isomers, and various types of chiral stationary phases have been made in the past ten years[1,2]. We reported that optically active poly(triphenylmethyl methacrylate)[3,4]



PTrMA

(PTrMA), particularly when coated on silica gel[5], can resolve various racemic compounds in high-performance liquid chromatography (HPLC). The stationary phase

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is able to resolve non-polar compounds for which other methods cannot be applied because of the lack of functional groups. The chirality of PTrMA arises only from the helicity of the polymer chain and is prepared by the asymmetric polymerization of triphenylmethyl methacrylate (TrMA) with chiral anionic initiators[6,7]. Although many enantiomers have been resolved on (+)-PTrMA[8–25], details of the chiral adsorbent have not yet been reported. In this paper, we report fundamental data for (+)-PTrMA coated on silica gel.

EXPERIMENTAL

Materials

(+)-PTrMA was prepared by the polymerization of TrMA with (S)-(+)-2,3-dimethoxy-1,4-bis(dimethylamino)butane-lithium (+)-N-(1phenylethyl)anilide complex in toluene at −78°C[7,26]. The polymer $\{[\alpha]_D^{25}$ +340° (tetrahydrofuran)$\}$ which was soluble in tetrahydrofuran but insoluble in hexane–benzene (1:1) was used for the preparation of the chiral packing material.

Most racemic compounds were commercially available or prepared by usual procedures. The reagents were purchased from Nakarai Chemicals Co.

Packing material

Macroporous silica gels, LiChrospher SI-1000 (10 μm, 1000 Å) and SI-4000 (10 μm, 4000 Å), were treated with a large excess of dichlorodiphenylsilane in toluene at 110°C. After 24 h, the silica gels were poured into methanol, filtered and dried. Found for SI-1000: C, 1.2; H, 0.17%. Found for SI-4000: C, 0.52; H, 0.07%.

LiChrospher SI-1000 was also silanized with (3-aminopropyl)triethoxysilane and trichlorooctadecylsilane. Found for the former: C, 0.52; H, 0.15; N, 0.10%. Found for the latter: C, 2.93; H, 0.54%.

(+)-PTrMA (0.55 g) was dissolved in tetrahydrofuran (10 ml) and the above silanized silica gel (SI-1000, 2.5 g) was wetted with the polymer solution (*ca.* 5 ml) as uniformly as possible. Then, the solvent was evaporated under reduced pressure. The remaining (+)-PTrMA solution (*ca.* 5 ml) was adsorbed on the silica gel using the same procedure.

Column packing

The packing material dispersed in methanol–ethyleneglycol (2:1) was packed in a stainless-steel column (25 × 0.46 cm I.D.) at 300 kg/cm^2 by a slurry method using methanol. The plate number of the column was 4000–7000 for acetone when methanol (0.5 ml/min) was used as eluent at 15°C.

Resolution

Chromatographic resolution was accomplished on a JASCO TRIROTAR-II chromatograph equipped with an UV (UVIDEC-V), an RI (Shodex SE-II) and a polarimeter (JASCO DIP-181) detector. A flow cell (5 × 0.3 cm I.D.) was used for the polarimeter detector.

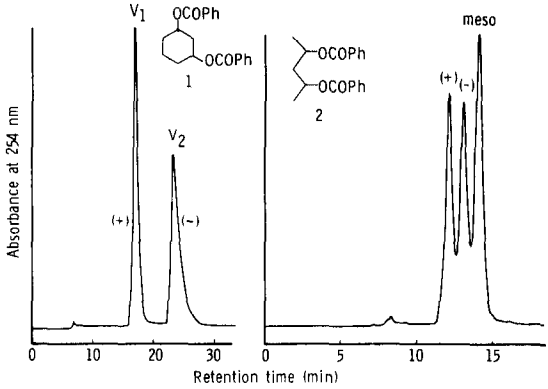


Fig. 1. Resolution of compounds 1 and 2 on a (+)-PTrMA column (25 × 0.46 cm). Eluent: methanol (0.5 ml/min), 15°C.

RESULTS AND DISCUSSION

Unless stated otherwise, the resolution of enantiomers was carried out on a stationary phase containing 22 wt. % of (+)-PTrMA on silica gel (SI-1000) using methanol (0.5 ml/min) as eluent at 15°C. The dead volume, V_0, of the system was estimated to be 3.3 ml using water as a non-retained compound.

Typical resolutions of *trans*-1,3-cyclohexylene dibenzoate (1) and 3,5-pentylene dibenzoate (2) are shown in Fig. 1. The cyclic diester was completely resolved but the linear diester containing the *meso* isomer was separated to a lesser extent. The capacity factors, k'_1 and k'_2, which are expressed as $(V_1 - V_0)/V_0$ and $(V_2 - V_0)/V_0$, respectively, were 1.57 and 2.56 for compound 1 and the separation factor, $\alpha = k'_2/k'_1$, was 1.63.

The influence of column temperature on the efficiency of the column was investigated (Fig. 2). The column efficiency was estimated from the theoretical plate numbers, N_a and N_b, for acetone and benzene, respectively. Acetone was weakly retained on the column and its retention time (7 min) was rather close to the dead time (6.6 min) for water; N_a was minimized at about 20°C. Benzene was more strongly retained and its retention time was about 8 min; N_b increased slightly with increasing temperature.

The effect of temperature on the resolution of enantiomers depended on the compounds (Fig. 3). The capacity factors for compound 2, 2,2'-dihydroxy-1,1'-binaphthyl (3) and *trans*-2,3-diphenyloxirane (4) decreased with increasing tempera-

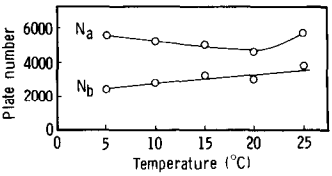


Fig. 2. Influence of temperature on the theoretical plate number of the column for acetone (N_a) and benzene (N_b).

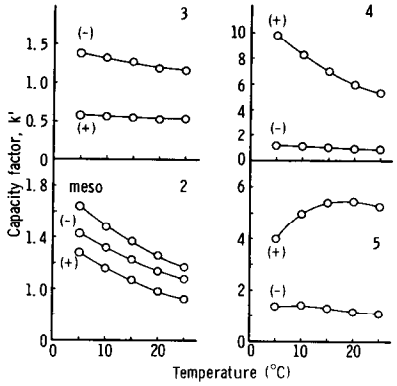
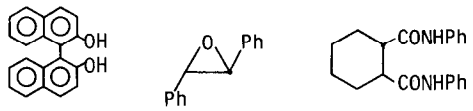


Fig. 3. Effect of temperature on the capacity factors in the resolution of racemic compounds 2–5.

ture, whereas those for *trans*-cyclohexanedicarboxylic acid dianilide (5) increased. The unusual temperature dependence of compound 5 may be due to a conformational change which would result in a more effective chiral discrimination at higher temperature.



3 4 5

The ester groups of (+)-PTrMA were slowly solvolyzed in methanol to form methyl triphenylmethyl ether. Therefore, the retention times and capacity factors, k', for enantiomers gradually decreased with time owing to a decrease in the amount of triphenylmethyl groups on the polymer. However, this did not lead to a steep decrease in the resolution factor. The amount of methyl triphenylmethyl ether eluted from the column increased (Fig. 4) as the column temperature increased. The formation of the ether by solvolysis was negligible at 5°C and 1 l of the methanol eluted from the column at 15°C contained about 8 mg of the ether. This means that during 1000 h

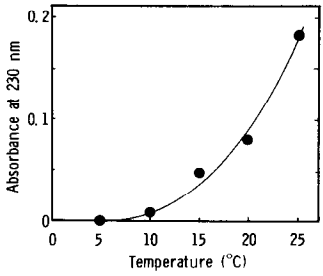


Fig. 4. UV absorbance of the eluent (methanol) eluted from the (+)-PTrMA column at various temperatures. Path length of UV cell: 1 cm. Chromatographic conditions: see Fig. 1.

TABLE I

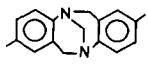
EFFECT OF DIFFERENT ELUENTS ON THE RESOLUTION OF RACEMATES 3, 4, 6, 7 AND $Cr(acac)_3$

C = Complete (baseline) separation; P = partial separation (two peaks); N = no separation.

Eluent	*3*	*4*	*6*	*7*	*$Cr(acac)_3$*
Hexane		C	P	N	P
Acetonitrile	N	C	P	N	N
Ethanol	C	C	C	P	P
Methanol	C	C	C	C	P
Methanol–water				C	C

of use of the column at 15°C about 30% of the triphenylmethyl groups of PTrMA are solvolyzed by methanol.

The effect of eluents on the resolution of compounds 3, 4, Tröger base (6), benzoin (7) and chromium(III) tris(acetylacetonate), $Cr(acac)_3$, is summarized in



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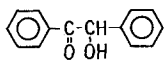

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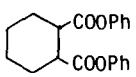
Table I. A baseline separation was observed for compound 4 in all eluent systems. Other compounds were better resolved with polar eluents than hexane, suggesting that hydrophobic interaction between the polymer, probably involving the triphenylmethyl groups, and the enantiomers plays an important rôle for effective chiral recognition.



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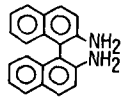

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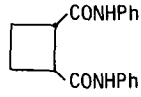

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The pore size of the macroporous silica gels LiChrospher Si-1000 and 4000 also influenced the resolution (Table II). Rather large differences in k'_1 for diphenyl

TABLE II

INFLUENCE OF THE PORE SIZE OF SILICA GEL ON THE SEPARATION

Racemate	k'_1		α	
	SI-1000	*SI-4000*	*SI-1000*	*SI-4000*
3	0.55	0.48	2.29	2.41
4	0.82	0.90	5.21	6.44
8	2.19	3.16	1.22	1.41
9	1.67	1.52	1.39	1.14
10	0.45	0.46	1.78	1.65

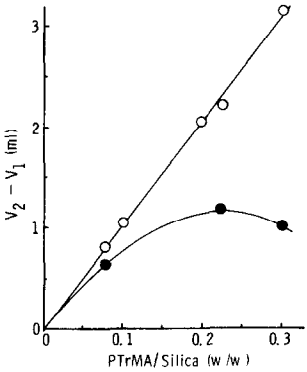

Fig. 5. Plots of the weight ratio of (+)-PTrMA to silica gel *vs.* the difference in retention volumes between the (+)- and (−)-isomers of compounds 3 (○) and 10 (●). For conditions see Fig. 1.

trans-1,2-cyclohexanedicarboxylate (8) and in α for 2,2'-diamino-1,1-binaphthyl (9), on the two chiral stationary phases, while compound 3 and 1,2-cyclobutanedicarboxylic acid dianilide (10) were resolved to a similar extent. The nature of (+)-PTrMA adsorbed on the two silica gels may be different. It must be more associated or aggregated in an ordered form on SI-4000 because the surface area of SI-4000 is about three times less than that of SI-1000 and (+)-PTrMA has a high degree of crystallinity. Non-associated (+)-PTrMA may show different chiral recognition from associated (+)-PTrMA. This speculation is also supported by the following experimental results. Chiral stationary phases which carried different amounts of (+)-PTrMA on the silica gel were prepared and their resolution abilities were investigated for compounds 3 and 10 (Fig. 5). The difference in retention volumes of the (+)- and (−)-isomers of compound 3 increased linearly as the amount of polymer on the silica gel (SI-1000) increased, whereas that of compound 10 showed a maximum when the weight ratio of the polymer to the silica gel was about 0.2. At low contents of (+)-PTrMA each polymer molecule may exist separately, and at high contents the polymer chains probably associate in an ordered structure, in which new chiral adsorption

TABLE III

INFLUENCE OF THE SILYLATION OF SILICA GEL ON THE RESOLUTION OF RACEMIC COMPOUNDS 2, 3, 4, 5 AND 10

Silica gel: SI-1000. DPhS = Dichlorodiphenylsilane; 3-APS = (3-aminopropyl)triethoxysilane; ODS = trichlorooctadecylsilane.

Racemate	k'_1			α		
	DPhS	*3-APS*	*ODS*	*DPhS*	*3-APS*	*ODS*
2	1.07	0.80	1.27	1.15	1.24	1.15
3	0.55	0.61	0.63	2.29	2.13	2.45
4	0.82	0.96		5.21	5.83	
5	1.30	0.93		4.14	4.61	
10	0.45	0.43		1.78	1.89	

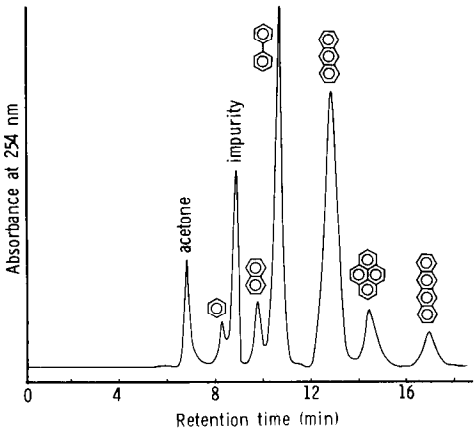

Fig. 6. Separation of aromatic compounds on a (+)-PTrMA column. For conditions see Fig. 1.

centres will be produced between the polymer chains. For some enantiomers these new centres may show chiral recognition oposite to that of the isolated polymer.

So far, silica gel (SI-1000) treated with dichlorodiphenylsilane was used to support (+)-PTrMA. We also treated the silica gel with (3-aminopropyl)triethoxysilane and trichlorooctadecylsilane. The results of the resolution of several racemic compounds on the three chiral stationary phases are summarized in Table III. Since the surface area of the macroporous silica gel is much smaller compared with usual silica gel, the influence of organic groups attached to the silica gels on the resolution is not considered to be large. Small differences in the α values might be due to the different morphology of the (+)-PTrMA on the three treated silica gels.

Besides racemic compounds, the column was also useful to separate achiral compounds. Several aromatic compounds were separated effectively without adding water to the methanol eluent as shown in Fig. 6.

Preparative resolution was investigated with a larger column (30 × 2.2 cm I.D.) at a methanol flow-rate of 10 ml/min at 10°C. A 40-mg amount of compound 3 or 200 mg of 4 were completely resolved in one injection.

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