

Chromatographic Optical Resolution by Optically Active Poly(diphenyl-2-pyridylmethyl methacrylate) with a Highly One-Handed Helical Structure

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ABSTRACT: The ability of optical resolution of (–)-poly(diphenyl-2-pyridylmethyl methacrylate) (PD2PyMA) with highly one-handed helicity was investigated by using it as a chiral stationary phase for high-performance liquid chromatography. The optically active polymer was prepared with an organolithium complex of (+)-(2*S*,3*S*)-dimethoxy-1,4-bis(1-perhydroazepinyl)-butane. When methanol was used as an eluent, PD2PyMA resolved many racemic compounds completely and several binaphthyl derivatives were better resolved than in resolution by optically active poly(triphenylmethyl methacrylate) (PTrMA). When a non-polar eluent, hexane–2-propanol mixture was used, PD2PyMA exhibited higher optical resolving power to several alcohols than PTrMA. This was ascribed to the strong interaction between the 2-pyridyl group of the PD2PyMA and the hydroxy group of the racemate in the non-polar eluent. In order to evaluate the durability of the column in methanol, the solvolysis rates of the monomer and chiral stationary phase were measured. This revealed that PD2PyMA has higher durability in methanol than PTrMA.

KEY WORDS Optical Resolution / Chiral Stationary Phase / High Performance Liquid Chromatography / Diphenyl-2-pyridylmethyl Methacrylate / Optically Active Polymer / Helix / Solvolysis /

Optically active poly(triphenylmethyl methacrylate) (PTrMA) with a helical structure shows unique chiral recognition ability,^{1,2} and a practically useful chiral stationary phase for high-performance liquid chromatography (HPLC) has been prepared by adsorbing it on macroporous silica gel.³ This resolves many racemic compounds.^{3–7} The PTrMA column is particularly useful for the optical resolution of the racemic compounds which are difficult to resolve by other methods because of the lack of functionality. In many cases, effective separation can be attained with a polar eluent, methanol. Non-polar or hydrophobic interaction between the triphenylmethyl group of the PTrMA and the non-polar moieties of racemates seems to play an important role for the chiral recognition on the PTrMA.

Optically active PTrMA is thus one of the most valuable chiral stationary phases for optical resolution. However, this stationary phase has a defect that the ester group of PTrMA undergoes solvolysis in methanol.^{4,8} This means that the PTrMA column will lose its optical resolving ability slowly when methanol is used as an eluent. This defect can be improved by replacing one of the phenyl groups of PTrMA with 2-pyridyl group.^{9,10} However, the highly helix-sense-selective or atropogenic polymerization of diphenyl-2-pyridylmethyl methacrylate (D2PyMA) was more difficult than that of triphenylmethyl methacrylate,^{9,10} and therefore highly one-handed helical polymer (PD2PyMA) was obtained only by fractionation of the polymer in a rather low yield.¹⁰ The optical resolving

ability of this fractionated polymer has been briefly reported.¹⁰

Quite recently, we found a new chiral initiator system that gave the polymer with higher one-handedness in a high yield.¹¹ In this study, using this polymer, we carried out more detailed investigation on the stability of PD2PyMA as a chiral stationary phase and its optical resolving ability.

EXPERIMENTAL

Material

Optically active PD2PyMA was prepared by the asymmetric polymerization of D2PyMA with (+)-(2*S*,3*S*)-dimethoxy-1,4-bis(piperidino)butane-fluorenyllithium (FILI) complex or (+)-(2*S*,3*S*)-dimethoxy-1,4-bis(1-perhydroazepinyl)butane-FILI complex in toluene at -78°C.¹¹ Fractionation of the obtained polymers with benzene-hexane (9:1) mixture gave (-)-polymer as an insoluble part in a yield of about 80%. The specific optical rotation of the polymer was $[\alpha]_{365}^{25} - 1400^\circ$ and $[\alpha]_{\text{D}}^{25} - 350^\circ$. The degree of polymerization was 40, which was determined by gel permeation chromatography of the poly(methyl methacrylate) derived from the original PD2PyMA. The PD2PyMA fractionated was used for the preparation of a chiral packing material.

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

Packing Material and Column Packing

Macroporous silica gel, LiChrospher Si 4000 (particle size 10 μm , pore size 400 nm) was treated with 3-aminopropyltriethoxysilane in benzene. PD2PyMA (0.6 g) was dissolved in chloroform-2,2,2-trifluoroethanol (9:1) (10 ml). The silanized silica gel (3.0 g) was uniformly wetted with half of the polymer solution and then dried under reduced pressure. This process was repeated with the remaining polymer solution.

The chiral packing material thus obtained

was packed in a stainless steel tube (25 \times 0.46 (i.d.) cm) by a slurry method. The plate number of the column was about 3600 for acetone using methanol (0.5 ml min⁻¹) as an eluent.

PTrMA column was prepared with (+)-PTrMA ($[\alpha]_{\text{D}}^{25} + 350^\circ$) and the silica gel silanized with dichlorodiphenylsilane in the same manner reported previously.⁴

Measurement

Chromatographic analysis was conducted on a JASCO TRIROTAR-II chromatograph equipped with UV (UVIDEC-100-III) and polarimetric (JASCO DIP-181C) detectors. A flow cell (5 \times 0.2 (i.d.) cm) was used for the polarimetric detector. The optical resolution was studied at a flow rate of 0.5 ml min⁻¹ at 15°C. Dead time (t_0) was estimated with water when methanol was the eluent, and with 1,3,5-tri-*tert*-butylbenzene when a hexane-2-propanol mixture was the eluent.

¹H NMR spectra were measured on a JEOL JNM-MH-100 (100 MHz) spectrometer and UV spectra on a JASCO UVIDEC-610 spectrophotometer.

Measurement of Solvolysis

The solvolysis rate of D2PyMA was measured in an NMR sample tube by ¹H NMR spectroscopy in CDCl₃-CD₃OD (3:2, v/v) at 35°C. The relative intensities of olefinic protons of the monomer and methacrylic acid formed were used for determining the solvolysis rate.⁸

The solvolysis rates of the PD2PyMA and PTrMA supported on the silica gel were measured by monitoring the amount of the triarylmethyl methyl ethers produced by solvolysis. The chiral packing material (0.1 g) was soaked in methanol (5 ml) and heated at 60°C, and the UV absorption of the supernatant methanol solution was measured to determine the amount of the ethers. The molar extinction coefficient at 260 nm was determined to be 4300 for diphenyl-2-pyridylmethyl methyl ether, and 825 for triphenylmethyl methyl

ether.

RESULTS AND DISCUSSION

Durability of Packing Materials

The durability of the packing materials was evaluated by measuring the solvolysis rates of the ester groups of the monomers and the stationary phases. The solvolysis rate of D2PyMA was measured in $\text{CDCl}_3\text{-CD}_3\text{OD}$ (3:2, v/v) at 35°C by ^1H NMR spectroscopy. A good first-order rate plot was obtained. Table I shows the rate constants (k) and half life periods of the solvolysis. The solvolysis rate of D2PyMA was about one-hundred and tenth of that of TrMA. Figure 1 shows the time-conversion curves in solvolysis of the packing materials. The amounts of the solvolyzed ethers were proportional to the reaction times at low conversions (<15%). The

ester groups of the PD2PyMA phase were solvolyzed 16-fold slower than those of PTrMA. Thus, the PD2PyMA phase must be more durable than the PTrMA phase against the solvolysis by methanol. Therefore, PD2PyMA was relatively unstable against the solvolysis in comparison with the monomer.

Optical Resolution with Methanol as Eluent

Figure 2 shows the chromatogram in the resolution of *N*-(1-phenylethyl)aniline (**11**) on the (-)-PD2PyMA column using methanol as an eluent. Complete resolution was attained and (+)-isomer eluted at 12.2 min (t_1) and (-)-isomer at 15.2 min (t_2). Capacity factors $k'_1 = (t_1 - t_0)/t_0$ and $k'_2 = (t_2 - t_0)/t_0$ were obtained as 0.85 and 1.31, respectively. The separation factor ($\alpha = k'_2/k'_1$) and the resolution factor ($R_s = 2(t_2 - t_1)/(W_1 + W_2)$) for this ra-

Table I. Methanolysis of methacrylates in $\text{CDCl}_3\text{-CD}_3\text{OD}$ (3:2, v/v) at 35°C^a

Methacrylate	k^b	Half-life period
	h^{-1}	min
D2PyMA	0.0256	1620
TrMA	2.86 ^c	14.5 ^c

^a Concentration, 0.39–0.40 mol l⁻¹.

^b First-order rate constant.

^c Data in ref 8.

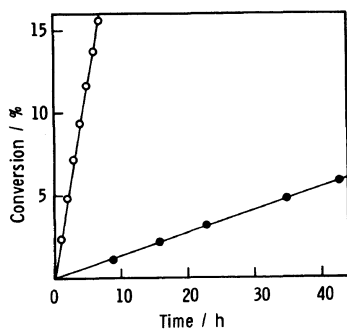


Figure 1. Solvolysis of chiral stationary phases supported on silica gel in methanol at 60°C. ●, PD2PyMA; ○, PTrMA.

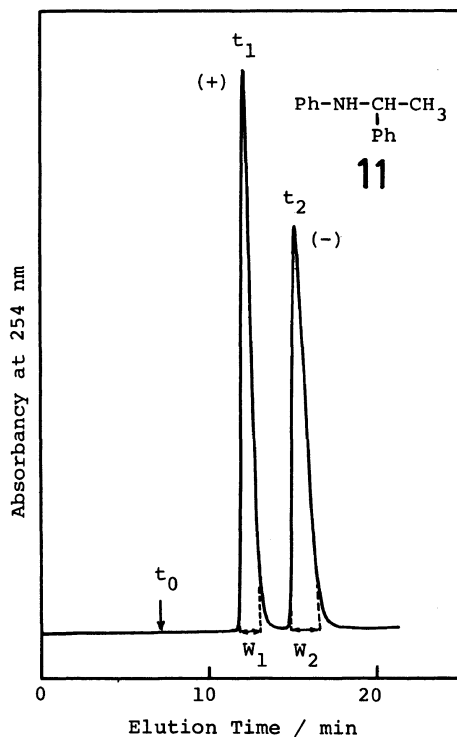
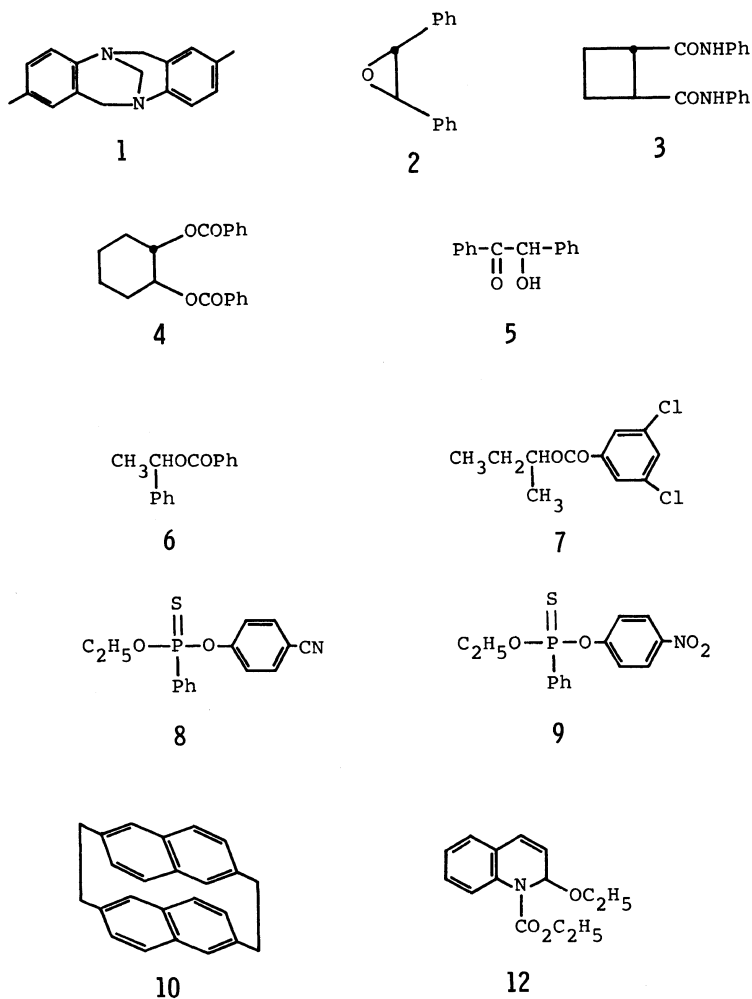


Figure 2. Optical resolution of *N*-(1-phenylethyl)aniline (**11**) on the (-)-PD2PyMA column. Eluent, methanol (0.5 ml min⁻¹).

Chromatographic Optical Resolution by PD2PyMA



cemate were calculated to be 1.54 and 2.11, respectively.

Table II shows the results of the optical resolution of the twelve racemates (1–12) on the (–)-PD2PyMA column. Data on the resolution on the PTrMA column are also shown for comparison. Most of the racemates listed in Table II were resolved better on optically active PTrMA, except for *O*-(4-cyanophenyl) *O*-ethyl phenylphosphonothionate (cyanofenfos, 8), *O*-ethyl *O*-(4-nitrophenyl) phenylphosphonothionate (EPN, 9), 10, and 11. If a racemate is not retained effectively, one can add water in the methanol eluent. In

the resolution of *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ, 12), the capacity and separation factors became large by using methanol–water (80:20) compared with $k'_1=0.31$ and $\alpha=1.0$ with methanol alone and almost complete separation was attained.

Several binaphthyl derivatives were separated on the PD2PyMA column as shown in Table III. PD2PyMA resolved 14, 16, 17, 19, and 20 better than PTrMA. PD2PyMA seems to show higher resolving power for the non-polar derivatives, and PTrMA exhibited better resolution for 13 and 18 bearing hydroxy or amino groups. This indicates that the chiral

recognition of the binaphthyl derivatives must be mainly controlled through non-polar interaction between the binaphthyl moieties and triarylmethyl groups of stationary phases. The interaction of polar groups of **13** and **18** with the 2-pyridyl group of the PD2PyMA phase increases retention time without increasing the chiral recognition.

Table II. Resolution of racemates (**1–12**) on (–)-PD2PyMA and (+)-PTrMA columns^a

Racemate	PD2PyMA			PTrMA		
	k'_1	α	R_s	k'_1	α	R_s
1	0.53 (–)	1.74	2.37	0.59 (+)	1.75	3.38
2	1.06 (+)	2.71	6.45	0.82 (–)	5.21	5.30
3	0.82 (+)	1.22	0.87	0.45 (–)	1.78	3.03
4	3.00 (–)	1.36	1.85	2.71 (+)	2.16	4.26
5	0.97 (+)	1.27	1.21	0.39 (–)	1.34	1.30
6	1.35	1.73	4.19	2.16	2.42	6.19
7	0.37 (–)	1.28	0.70	1.17 (+)	1.36	1.47
8	0.55 (–)	1.32	1.02	1.09 (+)	1.10	0.30
9	0.73 (–)	1.40	1.50	1.03 (+)	1.14	0.77
10	1.28	1.39	1.09	1.02	1.10	0.50
11	0.85 (+)	1.54	2.11	0.60	1.15	0.58
12^b	1.21 (+)	1.21	1.11	0.92 (–)	1.0	—

^a Eluent, methanol.

^b Eluent, methanol–water (80:20).

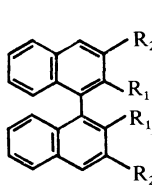
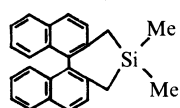
Optical Resolution with Hexane–2-Propanol as Eluent

In order to assess the polar effect of the 2-pyridyl group on the chiral recognition, a hexane–2-propanol mixture was used as an eluent, in which a polar interaction such as a hydrogen bond between a solute and the stationary phase must be enhanced.

In most cases, optically active PD2PyMA separated racemates more effectively with methanol than with non-polar eluents. This indicates that non-polar or hydrophobic interaction between a racemate and the chiral stationary phase is the more important factor for chiral discrimination.

However, PD2PyMA separated certain racemates effectively, when hexane–2-propanol was used as an eluent. Table IV shows the results of the resolution for the six racemates, which gave larger separation factors and resolution factors with hexane–2-propanol than with methanol. In particular, racemic alcohols, **22**, **23**, and **24** were resolved better on PD2PyMA with hexane–2-propanol than on PTrMA with methanol and hexane–2-propanol.¹³ Table V shows the results of the resolution of 1,2-diphenylethanol (**22**) and 1,2-

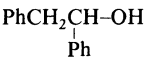
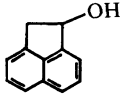
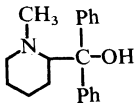
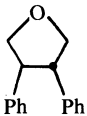
Table III. Resolution of 1,1'-binaphthyl derivatives (**13–21**) on (–)-PD2PyMA and (+)-PTrMA columns using methanol as eluent

Racemate	PD2PyMA			PTrMA						
	$R_1 =$	$R_2 =$	Entry	k'_1	α	R_s	k'_1	α	R_s	
	OH	H	13	1.41	2.06	2.62	0.50 ^a	2.37 ^a	3.83 ^a	
	OCH ₃	H	14	2.45	2.48	2.55	4.76 ^a	1.73 ^a	0.93 ^a	
	CH ₃	H	15	1.67	1.43	1.30	3.01 ^a	1.43 ^a	1.63 ^a	
	Br	H	16	2.30	2.01	3.71	3.77 ^a	1.41 ^a	1.06 ^a	
	CO ₂ CH ₃	H	17	1.69	2.80	2.16	3.85	1.67	1.79	
	NH ₂	H	18	1.91	1.29	1.54	1.67 ^a	1.39 ^a	1.08 ^a	
	OH	CH ₃	19	1.42	2.13	2.65	1.98	1.25	0.70	
	OH, OCH ₃	H	20	1.73	2.16	2.22	1.52	1.91	1.59	
				21	1.82	1.48	1.17	2.47 ^b	1.78 ^b	2.46 ^b

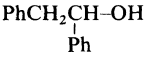
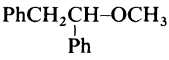
^a Data in ref 3.

^b Data in ref 12.

Table IV. Resolution of racemates (**22**–**27**) on (–)-PD2PyMA column

Racemate	Entry	Hexane–2-PrOH (95 : 5)			MeOH		
		k'_1	α	R_s	k'_1	α	R_s
	22	2.13 (+)	1.43	3.73	2.70 (+) ^a	1.34 ^a	1.59 ^a
	23	1.55	1.36	1.88	0.92 ^a	1.28 ^a	0.74 ^a
	24	0.86 (+)	1.38	1.55	0.94	1.0	—
	25	0.78 (+) ^b	1.24 ^b	1.14 ^b	2.04	1.0	—
Co(acac) ₃	26	1.82 (–) ^b	1.22 ^b	1.0 ^b	0.33	1.0	—
Cr(acac) ₃	27	2.02 (–) ^b	1.20 ^b	1.0 ^b	0.35	1.0	—

^a Eluent, methanol–water (80 : 20).^b Eluent, hexane–2-propanol (80 : 20).**Table V.** Resolution of racemates (**22**, **28**) on (–)-PD2PyMA column

Racemate	Entry	Eluent	k'_1	α	R_s
	22	MeOH	0.51 (+)	1.19	0.50
		MeOH–H ₂ O (80 : 20)	2.70 (+)	1.34	1.59
		Hex–2-PrOH (95 : 5)	2.13 (+)	1.43	3.73
	28	MeOH	0.58 (+)	1.17	0.63
		MeOH–H ₂ O (80 : 20)	4.12 (+)	1.28	0.96
		Hex–2-PrOH (95 : 5)	0.44	1.0	—

diphenylethyl methyl ether (**28**). In the methanol eluent system, these two racemates gave almost the same capacity and separation factors, whereas in hexane–2-propanol system, the racemic alcohol **22** was more retained and better resolved than its methyl ether derivative, **28**. These results indicate that the hydroxyl group of the alcohol interacts with the 2-pyridyl group of PD2PyMA, and this polar interaction or hydrogen-bonding must be the most important factor for attaining the efficient chiral recognition of **22** on PD2PyMA with a non-polar eluent.

Thus, PD2PyMA as well as PTrMA generally showed excellent chiral recognition ability with a polar eluent such as methanol, although PD2PyMA could resolve certain racemates effectively with a non-polar eluting system. The racemates which can interact with the triarylmethyl groups of the stationary phases through non-polar interaction could be resolved well. In contrast, the chiral stationary phases consisting of the derivatives of polysaccharide tris(phenylcarbamate)⁶ developed in our laboratory show high ability for the racemates bearing polar groups in a non-

polar eluent system. In the polysaccharide phases, the polar interaction between the carbamate groups of the polymers and the polar groups of racemates plays an important role for chiral recognition. Thus, with these two chiral stationary phases, rather wide range of racemic compounds are now able to be resolved.

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