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NEW CHIRAL STATIONARY PHASES FOR THE HIGH-PERFORMANCE LIQUID CHROMATOGRAPHIC RESOLUTION OF ENANTIOMERS

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Optically active polyamides were synthesized from (-)-1,2-diphenylethylenediamine and diacid chlorides by low temperature solution polycondensation. The polyamides were found to be effective as chiral stationary phases for direct HPLC resolution of enantiomers such as trans-1,2-cyclobutanedicarboxanilide, Tröger base, 2,2'-dihydroxy-1,1'-binaphthyl, mandelamide, benzyl mandelate, and benzoin.

The direct HPLC separation using a column packed with a suitable chiral stationary phase is one of the excellent methods for the rapid and convenient resolution of enantiomers with high enantiomeric purities.1) In most polymeric chiral stationary phases, chiral recognition depends on the secondary or higher-ordered structure,2) while that of low-molecular-weight chiral stationary phases results from simultaneous interactions with one of enantiomers.3) We previously reported that optically active polyamides having asymmetric centers in their main chains are useful as chiral stationary phases for HPLC.4) These polyamides act on enantiomers by several interactions and/or conformational constraint. As low-molecular-weight chiral stationary phases, N-benzoylated phenylglycine and valine derivatives are known to be very effective.3) Then, optically active polyamides having the structure similar to these amino acid derivatives in their main chains are expected to be applicable as chiral stationary phases. In this paper, we wish to report the synthesis and application as chiral stationary phases of optically active polyamides consisting of (-)-1,2-diphenylethylenediamine and dicarboxylic acid components, which possess the structure similar to N-acylated phenylglycine in their repeating units.

(-)-1,2-Diphenylethylenediamine [(-)-**1**] was obtained by fractional crystallization of the diastereomeric salts of racemic **1** with optically active mandelic acid.5) Optically active polyamides (**3**) were synthesized from (-)-**1** and diacid chlorides (**2**) by low temperature solution polycondensation. The general procedure is as follows: To a solution of **2** (ca. 4 mmol) in N,N-dimethylacetamide were added an equimolar amount of finely powdered (-)-**1** and then 2.5 equivalents of triethylamine. The final concentration was adjusted to 0.20 $\mathrm{mol \cdot L^{-1}}$. The reaction mixture was stirred for 30 min at 0 °C and overnight

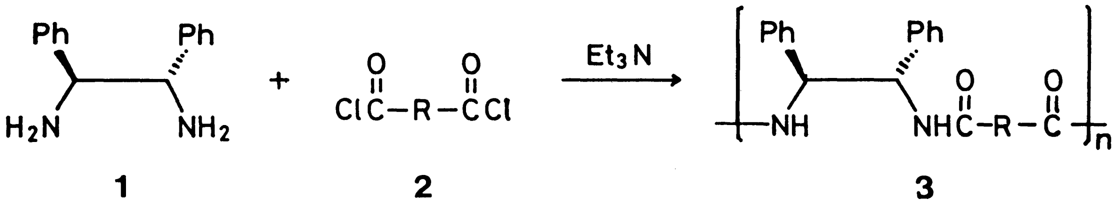
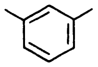
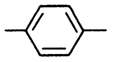


Table 1. Yield and properties of optically active polyamides (3)

3	-R-	Yield/%	η_{inh}/dL·g^{-1} at 35 °C	[m]$_D$/°
a		78	0.20$^{a)}$	-61$^{a)}$
b		100	0.20$^{a)}$	-164$^{a)}$
c	$-(CH_2)_4-$	100	0.11$^{b)}$	+109$^{b)}$
d	$-(CH_2)_{10}-$	98	0.12$^{b)}$	+551$^{b)}$

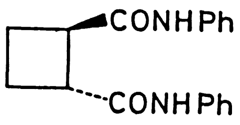
a) 0.50 g·dL^{-1} in concd H_2SO_4. b) 0.50 g·dL^{-1} in m-cresol.

at room temperature, and was poured into water (400 ml). The resulting insoluble mass was collected by centrifugation and dried at 80 °C overnight. The result is shown in Table 1.

Macroporous silica gel,[6] pretreated with diphenylsilane coupler, was coated with 15-20 wt% of the polyamide by using 1,1,1,3,3,3-hexafluoro-2-propanol or m-cresol as a solvent. The modified silica gel was packed in a stainless column [250 mm x 4.6 (i.d.) mm] by the slurry method.[7]

Figure 1 shows the chromatographic resolution of trans-1,2-cyclobutanedicarboxanilide (**4**), Tröger base (**5**), and 2,2'-dihydroxy-1,1'-binaphthyl (**6**) on the columns bearing polyamides **3a**, **3b**, and **3c**, respectively. The chromatographic parameters for the resolution of **4**-**9** using the polyamide columns are summarized in Table 2.

These polyamides could resolve enantiomers **4**-**9** with satisfactory separation factors. Polyamides **3a** and **3b** were more utilizable for these enantiomers than polyamides **3c** and **3d**. Polyamides **3a** and **3b** possess three possible interaction sites, i.e., amide carbonyl, amide hydrogen, and electron-deficient benzoyl, which play an important role in the chiral recognition using N-acylated phenylglycine derivatives as stationary phases, while polyamides **3c** and **3d** lack the third interaction site. This difference would affect strongly the chiral recognition ability of the polyamides. The unique resolving power of **3c** for **6** can be due to the high-ordered conformation of **3c**, which is presumed from the [m]$_D$ of **3c** in comparison with [M]$_D$ (+880°) of the corresponding model diamide, optically active N,N'-dipentanoyl-1,2-diphenylethylenediamine. The conformation would make the hydrophobic interaction suitable between phenyl groups of diamine component in **3c** and naphthyl groups of only one of the enantiomers of **6**.



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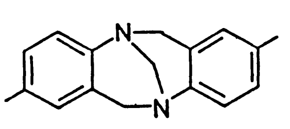

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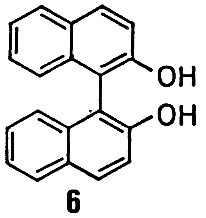

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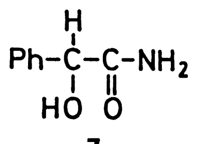
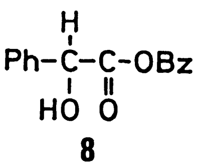


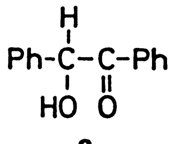
$\mathrm{Ph{-}CH(OH){-}C(=O){-}NH_2}$

7



$\mathrm{Ph{-}CH(OH){-}C(=O){-}OBz}$

8



$\mathrm{Ph{-}CH(OH){-}C(=O){-}Ph}$

9

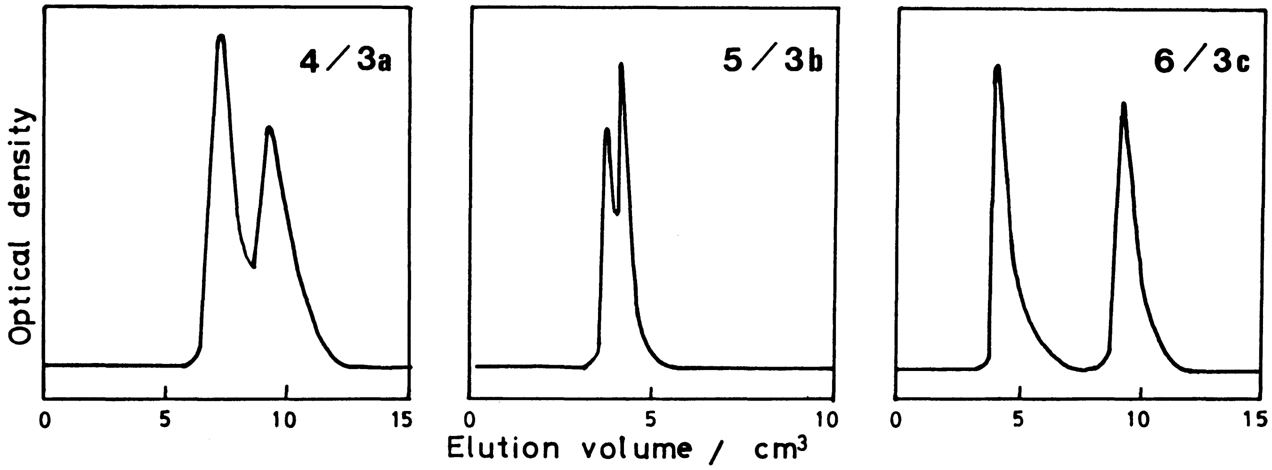


Fig. 1. Chromatographic resolution of **4**, **5**, and **6** on the columns of **3a**, **3b**, and **3c**, respectively.

Table 2. Chromatographic factors for the resolution of **4**-**9**$^{a)}$

Compd	Column **3a**		Column **3b**		Column **3c**		Column **3d**	
	α	Rs	α	Rs	α	Rs	α	Rs
4	1.39	0.96	1.48	0.64	b)		b)	
5	1	--	1.17	0.49	1	--	1.26	0.60
6	1	--	1.08	0.40	1.89	1.65	1	--
7	1.23	0.67	1.10	0.50	1	--	1.38	0.60
8	1.21	0.59	1.19	0.50	1	--	1	--
9	1.19	0.73	1	--	1	--	1	--

a) Eluent, hexane/2-propanol (v/v = 9/1); flow rate, 0.50 cm^3/min. α (separation factor) = (capacity factor for more retained enantiomer) / (that for less retained enantiomer). Rs (resolution factor) = 2 x (distance between the two peak positions) / (sum of band-widths of the two peaks). b) Not determined.

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6) Macroporous spherical silica gel has 10 μm of mean particle size with 100 nm of mean pore diameter and 20000 m^2/kg of specific surface area.

7) Theoretical plate number of the column **3a, 3b, 3c**, and **3d** for benzene were 1500, 500, 2150, and 210, respectively, at a flow rate of 0.50 cm^3/min.

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