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NOVEL CHIRAL STATIONARY PHASES FOR OPTICAL RESOLUTION BY LIGAND-EXCHANGE HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY

YOICHI YUKI
Research Centre, Daicel Chemical Industries Ltd., Shinzaike, Aboshi-ku, Himeji, Hyogo 671-12 (Japan)
KAZUHIKO SAIGO* and HIROKI KIMOTO
Department of Synthetic Chemistry, Faculty of Engineering, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113 (Japan)
KOUZOU TACHIBANA
Research Centre, Daicel Chemical Industries Ltd., Shinzaike, Aboshi-ku, Himeji, Hyogo 671-12 (Japan)
and
MASAKI HASEGAWA
Department of Synthetic Chemistry, Faculty of Engineering, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113 (Japan)

SUMMARY

Novel chiral stationary phases, (1*R*,2*S*)- and diastereomeric (1*S*,2*S*)-2-carboxymethylamino-1,2-diphenylethanol, were prepared from (1*R*,2*S*)- and (1*S*,2*S*)-2-amino-1,2-diphenylethanol, respectively, and were bound to silica gel pretreated with 3-glycidoxypropyltrimethoxysilane. The chiral stationary phases were found to be very effective for the optical resolution of amino acids, amino acid derivatives and hydroxy acids by ligand-exchange high-performance liquid chromatography.

INTRODUCTION

Recently, the chromatographic resolution of the enantiomers of amino acids and 2-hydroxy acids was achieved by conventional ligand-exchange chromatography, using copper(II) complexes of chiral amino acids as chiral stationary phases (CSPs). Gübitz and co-workers[1–5] developed practically useful high-performance liquid chromatography (HPLC) columns, in which copper(II) complexes of various amino acids are covalently bonded to silica gel pretreated with 3-glycidoxypropyltrimethoxysilane. Among these CSPs, the copper(II) complex of L-proline or L-hydroxyproline shows an efficient chiral recognition ability. Even though the hydroxyl group of L-hydroxyproline is located far from the copper(II) atom, the L-hydroxyproline bonded packing shows better chiral recognition ability for some amino acids than the L-proline bonded packing[3–5]. This means that the hydrogen bonding of the hydroxyl group in the chiral moiety may play an important rôle in the chiral recognition. On the other hand, hydrophobic interaction is known to contribute significantly to the

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enantioselectivity of some CSPs[6–8]. These facts indicate that the compounds, having an hydroxyl group and an hydrophobically interactive site other than the chelating site with copper(II), are suitable as CSPs.

Several naturally occurring chiral compounds, such as ephedrine, cinchona alkaloids and *allo*-hydroxyproline, have an hydroxyl group and an hydrophobic site, and are effective as chiral auxiliaries in asymmetric syntheses[9–12], indicating that they are applicable as CSPs in ligand-exchange chromatography. However, the derivatization of some of these compounds to CSPs is difficult due to their chemically complicated structure and/or the limitation in practical use. We have therefore designed new CSPs consisting of synthetic optically active compounds and have applied them to the optical resolution of amino acids, amino acid derivatives and hydroxy acids by ligand-exchange HPLC.

EXPERIMENTAL

Materials

Silica gel, Develosil 100-5 (5 μm), obtained from Nomura (Aichi, Japan) was used as the support. In our previous report[13], LiChrosorb Si 100 (10 μm), from E. Merck (Darmstadt, F.R.G.), was used as the support. The difference in the silica gel did not have a large influence on the resolving ability, although the separation coefficients changed slightly.

3-Glycidoxypropyltrimethoxysilane was obtained from Shin-Etsu (Tokyo, Japan), amino acids from the Peptide Institute (Osaka, Japan), amino acid derivatives from Sigma (St. Louis, MO, U.S.A.) and hydroxy acids from Aldrich (Milwaukee, WI, U.S.A.).

All solvents were of reagent grade.

(1*R*,2*S*)-2-Amino-1,2-diphenylethanol[14,15] and (1*S*,2*S*)-2-amino-1,2-diphenylethanol[16] were synthesized and optically resolved as described.

Instruments

Infrared spectra were recorded on an IRA-1 or IR-810 infrared spectrophotometer (Jasco, Tokyo, Japan). Optical rotations were recorded on a Jasco DIP 360 digital polarimeter. ^{1}H NMR spectra were recorded on a R-40 instrument (Hitachi, Tokyo, Japan). A Jasco Trirotar-V liquid chromatograph, a 7125 injector (Rheodyne, Cotati, CA, U.S.A.), a Jasco Uvidec-100-IV UV detector and a CDS 86 Ver. 2.7 data processor (NIHON Chromato, Tokyo, Japan) were used for HPLC. The column temperature was maintained at 35°C by a Jasco TU-100 column oven.

(1R,2S)-2-Ethoxycarbonylmethylamino-1,2-diphenylethanol

(1*R*,2*S*)-2-Amino-1,2-diphenylethanol (2.10 g) was dissolved in dichloromethane (30 ml) and stirred at room temperature. Ethyl bromoacetate (2.00 g), dissolved in dichloromethane (15 ml), was added to the solution. The mixture was stirred at room temperature for 7 days, and then triethylamine (1.5 ml) was added and stirred at room temperature for an additional day. When the starting material disappeared [no spot upon thin-layer chromatography (TLC)], dichloromethane was evaporated under reduced pressure. Benzene (100 ml) was added to the residue, and triethylamine hydrobromide was washed out with water. The organic layer was washed with brine

and dried over anhydrous sodium sulphate. The solution was filtered and evaporated. The residue (2.60 g, 88%) was recrystallized from hexane (*ca.* 300 ml). The crystals were collected and dried under reduced pressure. Yield 2.20 g (75%), m.p. 123–125°C, $[\alpha]_D^{18}$ +2.4° (*c* 1.00, ethanol). IR (potassium bromide): 3180, 1745, 765, 705 cm^{-1}. ^1H NMR (deuterochloroform): 1.17 (t, 3 H, *J* = 7 Hz), 2.35 (br s, 2H), 3.16 (pseudo s, 2H), 3.98 (q, 2H, *J* = 7 Hz), 4.15 (d, 1H, *J* = 6 Hz), 4.76 (d, 1H, *J* = 6 Hz), 7.20 (s, 10H) ppm. Elemental analysis (%) for $C_{18}H_{21}NO_3$: calc. C, 72.22; H, 7.07; N, 4.68; found C, 72.43; H, 7.11; N, 4.47.

(1R,2S)-2-Carboxymethylamino-1,2-diphenylethanol monosodium salt

(1*R*,2*S*)-2-Ethoxycarbonylmethylamino-1,2-diphenylethanol (2.20 g) was suspended in methanol (20 ml), and 1 *M* sodium hydroxide (7.3 ml) was added with stirring. After stirring the suspension at room temperature for 3 days, the precipitate was completely dissolved. The solution was evaporated and dried *in vacuo* at 70°C for 12 h. Yield 2.09 g (97%), m.p. 231–235°C (decomp.), $[\alpha]_D^{17}$ + 3.8° (*c* 0.83, water). IR (potassium bromide): 3280, 1600, 1415, 760, 700 cm^{-1}.

(1S,2S)-2-Ethoxycarbonylmethylamino-1,2-diphenylethanol

(1*S*,2*S*)-2-Amino-1,2-diphenylethanol (2.10 g) was dissolved in dichloromethane (30 ml) and stirred at room temperature. Ethyl bromoacetate (2.00 g), dissolved in dichloromethane (15 ml), was added to the solution. The mixture was stirred at room temperature for 5 days, and then triethylamine (1.5 ml) was added and stirred at room temperature for an additional day. When the starting material had disappeared (TLC), dichloromethane was evaporated under reduced pressure. Benzene (100 ml) was added to the residue, and the solution was worked up in a manner similar to that for the (1*R*,2*S*)-form. The crude product (2.9 g) was purified by silica gel column chromatography using dichloromethane–methanol (19:1) as an eluent, to give the pure product as an oil. Yield 2.51 g (85%), $[\alpha]_D^{17}$ −33.8° (*c* 1.03, methanol), IR (neat): 3350, 1740, 1205, 765, 705 cm^{-1}. ^1H NMR (deuterochloroform): 1.20 (t, 3H, *J* = 7 Hz), 3.02 (br s, 2H), 3.66 (d, 1H, *J* = 8 Hz), 4.07 (q, 2H, *J* = 7 Hz), 4.59 (d, 1H, *J* = 8 Hz), 7.05 (s, 10H) ppm. Elemental analysis (%) for $C_{18}H_{21}NO_3$: calc. C, 72.22; H, 7.07; N, 4.68; found C, 72.48; H, 7.21; N, 4.42.

(1S,2S)-2-Carboxymethylamino-1,2-diphenylethanol monosodium salt

(1*S*,2*S*)-2-Ethoxycarbonylmethylamino-1,2-diphenylethanol (2.51 g) was dissolved in methanol (20 ml), and 1 *M* sodium hydroxide (8.4 ml) was added with stirring. The mixture was stirred at room temperature for 12 h, and then evaporated and dried *in vacuo* at 70°C for 12 h. Yield 2.35 g (95%), m.p. 222–225°C (decomp.), $[\alpha]_D^{18}$ −43.3° (*c* 1.06, methanol). IR (potassium bromide): 3305, 1590, 1415, 770, 700 cm^{-1}.

Coating on silica gel

To a suspension of silica gel (7.0 g), dried for 3 h at 120°C, in dry benzene (50 ml) was added 3-glycidoxypropyltrimethoxysilane (3.5 ml), and the suspension was refluxed for 8 h with removal of methanol formed from the mixture. After cooling, the benzene was removed by filtration, and the silica gel was suspended in methanol (20 ml). Then, the monosodium salt of (1*R*,2*S*)- (CSP-I) (2.1 g) or (1*S*,2*S*)-2-carbox-

ymethylamino-1,2-diphenylethanol (CSP-II) (2.3 g) was added, and the mixture was shaken for 3 days at room temperature. The CSP bonded silica gel was collected by filtration, washed with methanol and poured into 0.10 *M* copper(II) sulphate solution. The copper-loaded chiral support was collected by filtration and washed successively with water and the mobile phase. Elemental analysis (%) for the copper-loaded CSP-I gave C, 6.01; H, 1.31; N, 0.21 (C, 3.08; H, 1.16 for the silanized silica gel), and for CSP-II gave C, 5.99; H, 1.40; N, 0.14 (C, 3.80; H, 1.24 for the silanized silica gel).

Chromatography

The silica gel, bonded to the stationary phase, was packed in a stainless-steel column, 25 cm × 0.46 cm I.D., by the ascending slurry technique. The void volumes of the columns were estimated to be 3.00 ml by injecting water.

The chromatography was carried out at 35°C at a flow-rate of 1.00 ml/min using 0.25 m*M* copper(II) sulphate solution as a mobile phase. The results for the resolution of amino acids, amino acid derivatives and hydroxy acids are shown in Tables I–VI.

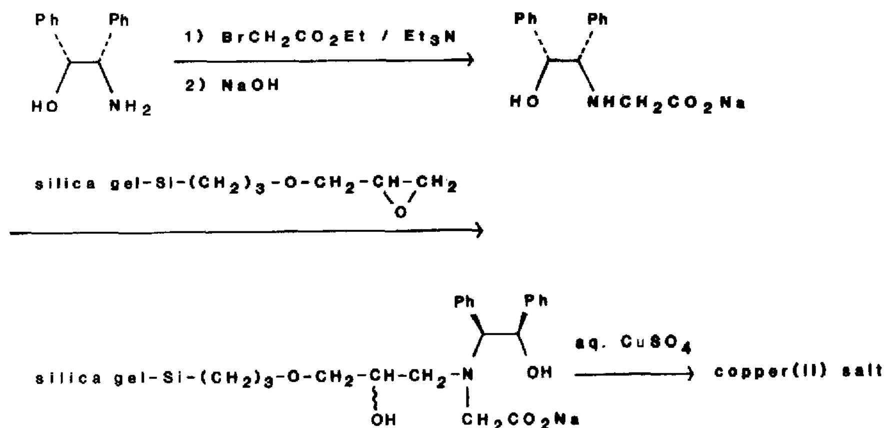
The k' values of amino acids, unresolved on CSP-I, were as follows: serine (4.2), threonine (5.0), aspartic acid (3.3), asparagine (4.1) and histidine (11.2). Those on CSP-II were: alanine (12.2), valine (9.0), leucine (11.4), isoleucine (11.1), proline (16.8), arginine hydrochloride (21.8), glutamic acid (16.2), histidine (16.8), methionine (11.2), phenylglycine (12.2) and tryptophan (20.7).

RESULTS AND DISCUSSION

As the model optically active compound, we chose 2-amino-1,2-diphenylethanol, since it has an hydroxyl group and hydrophobic phenyl groups. Both enantiomers, (1*R*,2*S*)- and (1*S*,2*R*)-2-amino-1,2-diphenylethanol, are easily and practically obtained from benzoin α-oxime via optical resolution by preferential crystallization[14] or by reciprocal crystallization on alternate seeding[15]. The diastereomers, (1*S*,2*S*) and (1*R*,2*R*), are also easily formed from the (1*R*,2*S*)- and (1*S*,2*R*)-forms, respectively[16]. To introduce a chelating site with copper(II), (1*R*,2*S*)- and (1*S*,2*S*)-2-amino-1,2-diphenylethanol were treated with ethyl bromoacetate and hydrolyzed to give new CSPs, (1*R*,2*S*)- (CSP-I) and (1*S*,2*S*)-2-carboxymethylamino-1,2-diphenylethanol (CSP-II), respectively. The CSPs were covalently bonded to silica gel, Develosil 100-5 (5 μm), pretreated with 3-glycidoxypropyltrimethoxysilane as a coupler. The preparation of the CSP having the (1*R*,2*S*) moiety is outlined in Scheme 1.

Typical chromatograms for the HPLC resolution of α-amino acids using CSP-I and CSP-II as chiral stationary phases are shown in Figs. 1 and 2. The corresponding resolution data are given in Tables I and II.

Most amino acids could be resolved on CSP-I except for DL-serine, DL-threonine, DL-aspartic acid, DL-asparagine and DL-histidine. On the other hand, CSP-II showed a chiral recognition ability quite different from that of CSP-I. It could resolve not only DL-glutamine, DL-tert-leucine and DL-tyrosine but also DL-serine, DL-threonine, DL-aspartic acid and DL-asparagine. Thus, CSP-I and CSP-II could resolve efficiently neutral α-amino acids and α-amino acids having a coordinatable function in the side chain, respectively. Moreover, on both CSP-I and CSP-II, D-α-amino acids



Scheme 1. Et = ethyl, Ph = phenyl.

a

0 20 40 (min)

b

0 20 40 60 (min)

a

0 20 40 (min)

b

0 20 40 (min)

Fig. 1. Chromatograms of (a) alanine and (b) glutamic acid (D/L = 1/2) by ligand-exchange HPLC using (1*R*,2*S*)-2-carboxymethylamino-1,2-diphenylethanol (CSP-I) as a chiral stationary phase. Eluent: 0.25 m*M* copper sulphate. Flow-rate: 1.00 ml/min. Temperature: 35°C.

Fig. 2. Chromatograms of (a) threonine and (b) asparagine (D/L = 1/2) by ligand-exchange HPLC using (1*S*,2*S*)-2-carboxymethylamino-1,2-diphenylethanol (CSP-II) as a chiral stationary phase. Conditions as in Fig. 1.

TABLE I

RESOLUTION OF α-AMINO ACIDS ON CSP-I

Eluent: 0.25 mM copper sulphate. Flow-rate: 1.00 ml/min (35°C).

Racemate	*Capacity factor*		*Separation coefficient,*	*Resolution,*
	k'_D	k'_L	α	R_s
Alanine	5.9	7.4	1.25	1.96
Valine	7.7	10.2	1.32	1.86
Leucine	10.3	13.5	1.31	1.70
Isoleucine	9.4	12.4	1.32	1.13
tert.-Leucine	6.1	7.3	1.20	1.10
Methionine	9.3	11.4	1.23	1.50
Arginine hydrochloride	11.6	13.9	1.20	1.07
Ornithine hydrochloride	7.4	9.0	1.22	1.37
Lysine hydrochloride	7.9	9.7	1.23	1.17
Citrulline	8.2	10.3	1.26	1.69
Glutamic acid	7.4	9.3	1.27	0.96
Glutamine	5.0	8.0	1.59	1.94
Proline	6.5	14.0	2.15	3.85
Phenylglycine	7.5	10.1	1.35	2.10
Phenylalanine	11.2	10.0	1.12	0.85
Tyrosine	12.6	10.0	1.26	1.45
DOPA	23.2	19.9	1.16	—
Tryptophan	25.0	19.3	1.29	1.57

had lower k' values than the L-isomers, except for phenylalanine, tyrosine, DOPA and tryptophan. The trend and the elution order can be explained as follows.

The carboxyl oxygen, the amino nitrogen and the hydroxyl oxygen of C_1 in copper(II)-loaded CSP-I can be positioned at three corners of a square plane, and the hydroxyl oxygen of the spacer portion at the apical position. This structure seems to be more stable than that in which the hydroxyl oxygens of the spacer portion and

TABLE II

RESOLUTION OF α-AMINO ACIDS ON CSP-II

Eluent as in Table I.

<table>
<tr><th>Racemate</th><th colspan="2">Capacity factor</th><th>Separation coefficient,</th><th>Resolution,</th></tr>
<tr><th></th><th>k'_D</th><th>k'_L</th><th>α</th><th>R_s</th></tr>
<tr><td>Serine</td><td>5.7</td><td>6.5</td><td>1.14</td><td>0.93</td></tr>
<tr><td>Threonine</td><td>6.0</td><td>7.6</td><td>1.28</td><td>1.07</td></tr>
<tr><td>Aspartic acid</td><td>5.5</td><td>6.8</td><td>1.24</td><td>0.95</td></tr>
<tr><td>Asparagine</td><td>5.6</td><td>6.9</td><td>1.24</td><td>0.98</td></tr>
<tr><td>Glutamine</td><td>13.4</td><td>16.9</td><td>1.26</td><td>1.04</td></tr>
<tr><td>tert.-Leucine</td><td>7.1</td><td>7.8</td><td>1.11</td><td>—</td></tr>
<tr><td>Citrulline</td><td colspan="2">9.0</td><td>1.00</td><td>—</td></tr>
<tr><td>Phenylalanine</td><td colspan="2">13.7</td><td>1.00</td><td>—</td></tr>
<tr><td>Tyrosine</td><td>12.8</td><td>10.3</td><td>1.24</td><td>—</td></tr>
</table>

of C_1 are situated at the corner and the apical position, respectively, since the bulky 2-amino-1,2-diphenylethanol moiety in the former structure is on the square plane. For this coordination system, there are two possible structures according to the position of the hydroxyl oxygen of the spacer portion. However, considering the influence of two phenyl groups of C_1 and C_2 on the stability of the chelate, the structure illustrated in Fig. 3 would be the most stable.

On the approach of an α-amino acid, the carboxyl oxygen and the amino nitrogen of the α-amino acid may coordinate to copper(II) at the corners of the square plane in *cis* (N,N) configuration as observed for an L-proline bonded chiral stationary phase[3]. Simultaneously, the hydroxyl oxygen of C_1 would move from the corner to the apical position of the square plane as shown in Fig. 4. The structure is quite similar to that proposed for the L-plorine bonded chiral stationary phase[3]. In this chelate, one of the phenyl groups of C_1 and C_2 should be equatorial and the other axial to the five-membered chelating ring, resulting in two possible conformations where the steric environment of one side of the α-amino acid chelated plane is quite different from that of the other side. This steric difference results in the wide-ranging resolving ability of CSP-I for neutral α-amino acids. Moreover, the complexes involving D-α-amino acids are less stable than those with the L-isomers as is seen from Fig. 4, resulting in faster elution of the D-isomers. By contrast, with CSP-II, both phenyl groups of C_1 and C_2 should be equatorial, and the phenyl groups merely sterically influence the enantiomers of neutral α-amino acids. Thus, CSP-II has low resolving ability for neutral α-amino acids.

On the other hand, in the case of α-amino acids having a coordinatable function in the side chain, this function may coordinate to copper(II). On coordination of either the L- or D-α-amino acid, cleavage of the coordination of the hydroxyl oxygen of C_1 (chelate A) and that of the spacer portion (chelate B) would occur, respectively, and the eliminated hydroxyl group would interact with the amino hydrogen in the α-amino acid and/or the function in the side chain by hydrogen bonding. Comparing chelates A and B of CSP-I, there seems little difference in stability, arising from the steric environment, since the bulky phenyl groups of C_1 and C_2 in chelate A are out of the chelating region of the α-amino acid. By contrast, chelate A

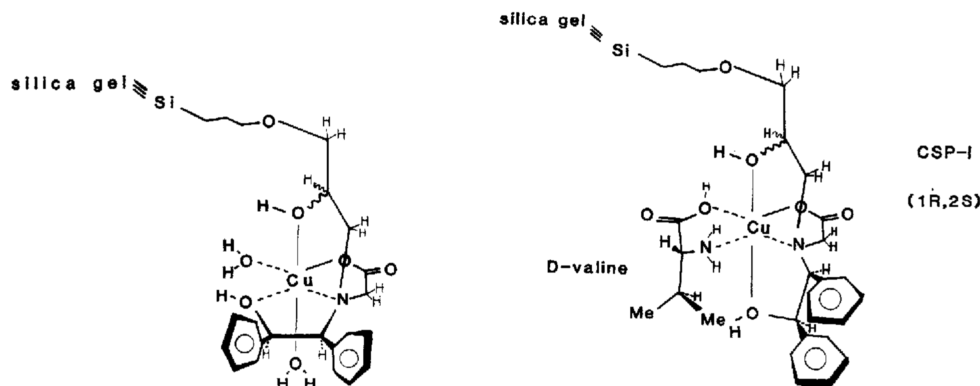


Fig. 3. The proposed coordination structure for copper(II)-loaded CSP-I.

Fig. 4. The proposed coordination structure of copper(II), CSP-I and D-valine.

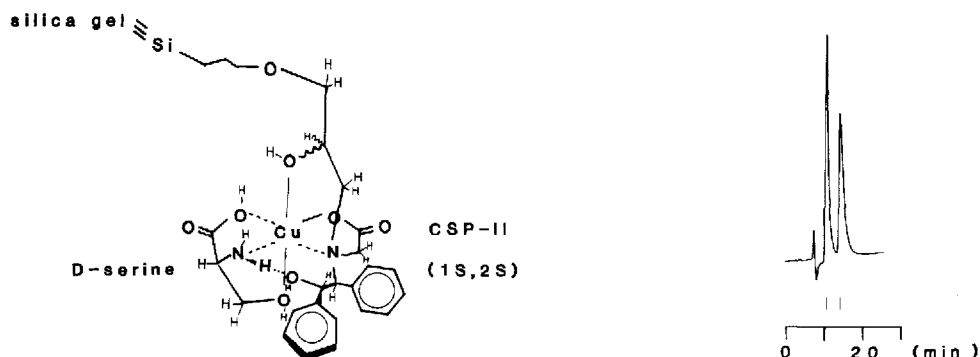


Fig. 5. The proposed coordination structure of copper(II), CSP-II and D-serine.

Fig. 6. Chromatogram of tropic acid (D/L = 1/1) by ligand-exchange HPLC using (1*S*,2*S*)-2-carboxymethylamino-1,2-diphenylethanol (CSP-II) as a chiral stationary phase. Conditions as in Fig. 1.

of CSP-II seems to be less stable than chelate B of CSP-II due to the steric repulsion between the side chain of the α-amino acid and the phenyl group of C_1 in chelate A, as shown in Fig. 5. Thus, CSP-II gives better resolution than CSP-I for α-amino acids having a coordinatable function in the side chain, and D-α-amino acids are eluted faster than the L-isomers.

The α-amino acids, which are the exceptions in the elution order, commonly have an arylmethyl moiety in the side chain. Thus, the reversed elution order may be due to an hydrophobic interaction, such as the plane-to-plane interaction between the phenyl group of C_1 and the aromatic side chain of these α-amino acids, which compensates for the cleavage of the coordination between the hydroxyl oxygen of C_1 and copper(II).

Thus, CSP-I and CSP-II show significant differences in their resolving ability for α-amino acids. It is noteworthy that CSP-I can resolve DL-alanine and DL-glutamic acid, which are very difficult to resolve by known CSPs.

Moreover, the CSP were applicable to the resolution of hydroxy acids. A typ-

TABLE III

RESOLUTION OF HYDROXY ACIDS ON CSP-I

Eluent as in Table I.

Racemate	*Capacity factor*		*Separation coefficient*, α	*Resolution*, R_s
	k'_1	k'_2		
Lactic acid	2.8 (D)	3.3 (L)	1.20	1.30
2-Hydroxybutyric acid	3.0	4.0	1.35	1.82
2-Hydroxycaproic acid	5.0	6.4	1.26	1.32
Malic acid	13.4	17.5	1.31	0.82
Mandelic acid	4.4	6.0	1.34	1.32
4-Hydroxymandelic acid	4.4	6.0	1.36	1.15
Tropic acid	3.0	3.5	1.18	–

TABLE IV

RESOLUTION OF HYDROXY ACIDS ON CSP-II

Eluent as in Table I.

Racemate	*Capacity factor*		*Separation coefficient,*	*Resolution,*
	k'_1	k'_2	α	R_s
Glyceric acid	3.0	3.3	1.09	–
2-Hydroxybutyric acid	3.0	3.4	1.12	0.63
2-Hydroxycaproic acid	4.7	5.3	1.14	0.71
Mandelic acid	7.2	8.3	1.16	–
4-Hydroxymandelic acid	6.7	7.7	1.15	–
Atrolactic acid	6.1	6.5	1.06	–
Tropic acid	2.5	3.7	1.47	1.91

TABLE V

RESOLUTION OF α-AMINO ACID DERIVATIVES ON CSP-I

Eluent as in Table I.

Racemate	*Capacity factor*		*Separation coefficient,*	*Resolution,*
	k'_1	k'_2	α	R_s
N-Benzyloxycarbonylalanine	3.07		1.00	–
N-Benzyloxycarbonylphenylalanine	7.4	8.6	1.17	–
Phenylalanine amide	3.4	4.1	1.21	0.80
N-Acetyltryptophan	4.5	5.5	1.22	–

TABLE VI

RESOLUTION OF α-AMINO ACID DERIVATIVES ON CSP-II

Eluent as in Table I.

Racemate	*Capacity factor*		*Separation coefficient,*	*Resolution,*
	k'_1	k'_2	α	R_s
N-Benzyloxycarbonylalanine	2.6	2.9	1.09	0.72
N-Benzyloxycarbonylvaline	3.1	3.5	1.12	0.84
N-Benzyloxycarbonylnorvaline	4.0	4.4	1.09	–
N-Benzyloxycarbonylleucine	5.0	5.2	1.04	–
N-Benzyloxycarbonylmethionine	4.5	4.8	1.08	–
N-Benzyloxycarbonylasparagine	2.2	2.6	1.17	1.31
N-Benzyloxycarbonylglutamine	2.3	2.6	1.13	1.09
Phenylalanine amide	8.2	9.7	1.19	0.75
Benzylhydantoin	0.84	0.96	1.15	–
N-Acetyltryptophan	3.5	3.9	1.10	–

ical chromatogram on CSP-II is shown in Fig. 6, and the chromatographic data are listed in Tables III and IV.

α-Amino acid derivatives were also optically resolved on CSP-I and CSP-II. The chromatographic data are listed in Tables V and VI.

As the Tables show, CSP-II gave better resolution than CSP-I for N-benzyloxycarbonylated α-amino acids. This result is quite different from that for the resolution of α-amino acids, and seems to suggest that the coordination system is also different. The reason why CSP-I does not show the wide-ranging resolving ability for the α-amino acid derivatives, which could be resolved by CSP-II, can be explained as follows.

The benzyloxycarbonyl group, attached to the amino nitrogen of the α-amino acids, is large and hydrophobic. It is considered that, in the case of CSP-I, the α-amino acid derivatives would not be able to coordinate to copper(II) in *cis* (N,N) configuration due to the steric repulsion. Consequently, the α-amino acid derivatives would coordinate in *trans* (N,N) configuration, in which the steric environment seems not to distinguish between the isomers of the α-amino acid derivatives. Another possibility is that the α-amino acid derivatives are unable to coordinate to copper(II) sufficiently due to the strong hydrophobic interaction between the phenyl groups in CSP-I and in the benzyloxycarbonyl group. On the other hand, in the case of CSP-II, the α-amino acid derivatives seem to be able to coordinate in *cis* (N,N) configuration, and the phenyl group of benzyloxycarbonyl can interact with the phenyl group of C_1. This situation should result in a good resolving ability of CSP-II for the α-amino acid derivatives.

CONCLUSION

Ligand-exchange high-performance liquid chromatography on the novel chemically bonded CSPs offers high efficiency for the rapid separation of various racemates. All four diastereomers for the synthesis of the CSP can easily be obtained. The results show that there is a significant difference in the resolving abilities of the chiral phases.

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