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Novel Chiral Stationary Phases for the Resolution of the Enantiomers of Amino Acids by Ligand Exchange Chromatography

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Novel chemically bonded chiral stationary phases (CSP's) derived from (1R,2S)-2-carboxymethylamino-1,2-diphenylethanol and from (1S,2S)-2-carboxymethylamino-1,2-diphenylethanol were prepared. The ligand exchange chromatography on these CSP's was found to be effective for the direct resolution of the enantiomers of amino acids.

The chromatographic resolution of the enantiomers of amino acids is conventionally carried out by ligand exchange chromatography using copper(II) complexes of chiral amino acids bonded on a support. Among these chiral stationary phases (CSP's), copper(II) complexes of L-proline and L-hydroxyproline show an efficient chiral recognition ability when they are covalently bonded to silica gel pretreated with 3-glycidoxypropyltrimethoxysilane. However, some amino acids such as alanine and glutamic acid could not be resolved on both the CSP's.[1,2]

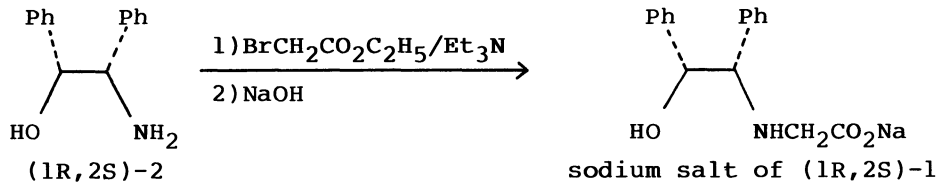
Between copper(II) complexes of L-proline and L-hydroxyproline, there is somewhat difference in the chiral recognition ability, that is, the hydroxyl group in the chiral moiety plays an important role in the recognition.[2] On the other hand, hydrophobic interaction is known to contribute significantly to the chiral recognition ability of some CSP's.[3] These facts indicate that the compounds having a hydroxyl group and a hydrophobically interactive site other than chelating site with copper(II) would be suitable as CSP's.

Highly effective CSP's were designed by the use of optically active 2-carboxymethylamino-1,2-diphenylethanol (**1**) with enhancement of the participation of a hydrogen bonding and a hydrophobic interaction.

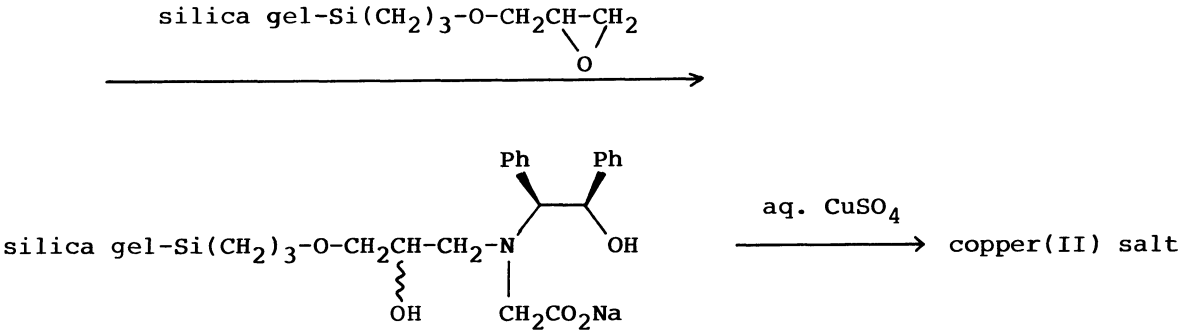
The CSP having (1R,2S)-**1** moiety was easily prepared as follows: Racemic 2-amino-1,2-diphenylethanol (**2**) was prepared by Pd/C catalized hydrogenation of benzoin α-oxime under an ordinary pressure.[4] Optically active **2** was obtained by the reciprocal crystallization on alternate seeding of the diastereomeric salts of racemic **2** with (-)-mandelic acid.[5] N-Alkylation of (1R,2S)-**2** with ethyl bromoacetate in the presence of Et_3N in CH_2Cl_2 at room temperature gave (1R,2S)-2-ethoxycarbonylmethyamino-1,2-diphenylethanol.[6] The ester was converted to the mono sodium salt of (1R,2S)-**1** on treatment with NaOH in

H_2O/MeOH.[7] The salt was covalently bonded to silica gel[8] (LiChrosorb SI-100, 10 μm), pretreated with 3-glycidoxypropyltrimethoxysilane, in benzene under refluxing.[9] The copper(II) complex was formed by treatment with aqueous copper(II) sulfate solution. Similarly, (1S,2R)-1 bonded CSP was prepared.

The diastereomeric (1S,2S)- and (1R,2R)-2 were easily obtained from (1R,2S)- and (1S,2R)-2, respectively.[10] The synthesis of bonded CSP's derived from (1S,2S)- and (1R,2R)-1[11] was carried out in the same manner as the case of (1R,2S)-1.[12]



(1R,2S)-2 sodium salt of (1R,2S)-1



The modified silica gel was packed into a stainless steel column [250 mm x 4.6 (i.d.) mm] by the slurry method.

The enantiomers of amino acids were sufficiently resolved on the copper(II) complexes of these CSP's by means of ligand exchange chromatography using an aqueous copper(II) sulfate solution as a mobile phase. The chromatographic parameters for the resolution of amino acids on the CSP's derived from (1R,2S)-1 (CSP-I) and (1S,2S)-1 (CSP-II) are summarized in Table 1.

A number of amino acids, including alanine and glutamic acid, which are very difficult to resolve by known CSP's, could be resolved on CSP-I. But, the resolution of serine, threonine, aspartic acid, phenylalanine, histidine, and cystine[13] was unable. The L-enantiomers always appeared with higher k' value than D-isomers except for tyrosine and tryptophan. By contrast, CSP-II was capable of resolving serine, threonine, aspartic acid, and phenylalanine, which could not be resolved on CSP-I, although histidine and cystine[13] were also unable to be resolved on CPS-II. Thus, the two CSP's, diastereomeric each other, showed significant difference in selectivity for amino acids, and the selectivity was highly complementary. The differences of chiral recognition between CSP-I and CSP-II may be caused by the difference of configuration of the polar hydroxyl group and the hydrophobic phenyl group at C_1.

Table 1. Chromatographic Parameters for the Resolution of Amino Acids[a)]

CSP	Racemate	Capacity Factor		Separation Factor	Resolution Factor
		k'_D	k'_L	α	Rs
I	Alanine	6.2	7.6	1.22	1.36
	Leucine	10.4	14.1	1.35	1.83
	Isoleucine	9.7	13.5	1.39	1.40
	Valine	8.4	11.3	1.35	1.57
	Methionine	11.3	13.6	1.21	1.25
	Arginine HCl	10.9	13.6	1.25	1.50
	Glutamine	8.1	10.1	1.24	1.53
	Glutamic acid	8.9	11.0	1.25	0.84
	Citrulline	9.2	11.7	1.27	1.54
	Ornitine HCl	8.0	9.8	1.23	0.99
	Proline	8.1	18.0	2.22	3.49
	Lysine HCl	7.8	9.7	1.25	1.16
	Tyrosine	12.2	10.3	1.19	1.20
	Tryptophan	19.6	16.4	1.19	1.25
	Indoline-2-carboxylic acid[b)]	25.1	38.4	1.53	3.00
II	Threonine	5.9	7.7	1.31	1.74
	Serine	5.5	6.4	1.16	--
	Tyrosine	12.0	9.9	1.22	--
	Phenylalanine	11.1	9.8	1.13	--
	Citrulline	9.4	10.2	1.09	--
	Aspartic acid	4.3	5.0	1.16	--
	Indoline-2-carboxylic acid[b)]	17.1	28.5	1.66	2.31

a) Eluent, 2.5×10^{-4} mol dm^{-3} $CuSO_4$; flow rate, 1.00 cm^3 min^{-1} (30 °C).
k'_D or k'_L (capacity factor for D- or L-amino acid, respectively) = (retention volume - dead volume)/dead volume; the dead volume was estimated to be 3.00 cm^3 with water.
α (separation factor) = (capacity factor for more retained enantiomer)/(capacity factor for less retained enantiomer).
Rs (resolution factor) = 2 x (distance of the two peak position)/(sum of band-widths of the two peaks); 1.0×10^{-1} cm^3 of the sample (1.00 g dm^{-3}) was injected in each case.

b) Eluent, 5.0×10^{-4} mol dm^{-3} $CuSO_4$; flow rate, 1.50 cm^3 min^{-1} (50 °C).

References

1) G. Gübitz, W. Jellenz, G. Löfler, and W. Santi, J. High Resol. Chromatogr., Chromatogr. Commun., 2, 145 (1979); G. Gübitz, W. Jellentz, and W. Santi, J. Liquid Chromatogr., 4, 701 (1981); G. Gübitz, W. Jellenz, and W. Santi, J. Chromatogr., 203, 377 (1981).

2) G. Gübitz, F. Juffmann, and W. Jellentz, Chromatographia, 16, 103 (1982); G. Gübitz and S. Mihellyes, ibid., 19, 257 (1984).

3) L. R. Gelber, B. L. Kager, J. L. Neumeyer, and B. Feibush, J. Am. Chem. Soc., 106, 7729 (1984); P. Roumeliotis, K. K. Unger, A. A. Kurganov, and V. A. Davankov, Angew. Chem., Int. Ed. Engl., 21, 930 (1982); V. A. Davankov, A. S. Bochkov, A. A. Kurganov, P. Roumeliotis, and K. K. Unger, Chromatographia, 13, 677 (1980).

4) K. Saigo, S. Ogawa, S. Kikuchi, A. Kasahara, and H. Nohira, Bull. Chem. Soc. Jpn., 55, 1568 (1982).

5) K. Saigo, I. Sugiura, I. Shida, K. Tachibana, and M. Hasegawa, Bull. Chem. Soc. Jpn., accepted.

6) (1S,2R)-1: mp 126.5-127 °C (hexane); $[\alpha]_D^{22}$ -2.5° (c 1.01, EtOH); IR (KBr) 3180, 1745, 765, and 705 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ=1.17 (t, 3H, J=7 Hz), 2.35 (bs, 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), and 7.20 (s, 10H); Anal. ($C_{18}H_{21}HO_3$) C, H, N. (1R,2S)-1: mp 125-126 °C (hexane); $[\alpha]_D^{18}$ +2.4° (c 1.00, EtOH); the IR and ^{1}H-NMR spectra were identical with those of (1S,2R)-1.

7) The mono sodium salts of (1S,2R)- and (1R,2R)-1 could not be purified. Then, the crude salts were used for the preparation of CSP's, and the structures were identified after converting them to 2-carboxymethylamino-1,2-diphenylethanol (3). (1S,2R)-3: mp 250-251.5 °C (decomp) (ethanol); $[\alpha]_D^{21}$ -3.4° (c 1.00, 1 mol dm^{-3} NaOH); IR (KBr) 3320, 3050, 2890, 1625, 1570, 1390, 760, 710, and 700 cm^{-1}; Anal. ($C_{16}H_{17}NO_3$) C, H, N. (1R,2S)-3: mp 249-251 °C (decomp) (ethanol); $[\alpha]_D^{21}$ +3.3° (c 1.00, 1 mol dm^{-3} NaOH); the IR and ^{1}H-NMR were identical with those of (1S,2R)-3.

8) On the basis of the elemental analysis, it was found that 0.59 mmol of 3-glycidoxypropyltrimethoxysilane was bound to 1.00 g of the silica gel.

9) The elemental analysis showed that the mono sodium salt of (1R,2S)-1 (0.11 mmol) was bound to 1.00 g of the silica gel on the average.

10) J. Weijlard, K. Pfister, E. F. Swanezy, C. A. Robinson, and M. Tishler, J. Am. Chem. Soc. 73, 1216 (1951).

11) (1S,2S)-1: oil; $[\alpha]_D^{17}$ -33.8° (c 1.03, MeOH); IR (neat) 3350, 1740, 1205, 765, and 705 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ=1.20 (t, 3H, J=7 Hz), 3.02 (bs, 2H), 3.66 (d, 1H, J=8 Hz), 4.07 (q, 2H, J=7 Hz), 4.59 (d, 1H, J=8 Hz), and 7.05 (s, 10H); Anal. ($C_{18}H_{21}NO_3$) C, H, N. (1S,2S)-3: mp 226-228 °C (decomp) (water); $[\alpha]_D^{18}$ -52.1° (c 1.02, 1 M NaOH/MeOH = 1/1); IR (KBr) 3270, 3120, 1610, 1385, 1075, 765, 705 cm^{-1}; Anal. ($C_{16}H_{17}NO_3$) C, H, N.

12) The elemental analysis showed that the mono sodium salt of (1S,2S)-1 (0.08 mmol) was bound to 1.00 g of the silica gel on the average.

13) Cystine could not be determined because of its low solubility in the solvent.

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