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Short communication

Direct separation of carboxylic acid and amine enantiomers by high-performance liquid chromatography on reversed-phase silica gels coated with chiral copper(II) complexes

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Abstract

Excellent direct separation of various carboxylic acid and amine enantiomers was accomplished by HPLC on reversed-phase silica gels coated with copper(II) complexes of N,S-dioctyl-D-penicillamine and (*R*,*R*)-tartaric acid mono-(*R*)-1-(α-naphthyl)ethylamide. The chiral recognition mechanism is discussed. These copper(II) complexes are promising as chiral stationary phases for the separation of a variety of racemic carboxylic acids and amines in which copper(II) complex formation can be assumed.

1. Introduction

It is well known the chiral ligand-exchange high-performance liquid chromatography (HPLC) using copper(II) complexes of chiral ligands is a powerful tool for the direct separation of various enantiomers [1,2], and this technique is usually applied for the separation of racemic amino acids, hydroxy acids [3] and amino alcohols [4,5]. Recently, it was shown some other racemic compounds, such as pyridonecarboxylic acids [6] and 3-amino-ε-caprolactam [7], were also resolved. These results suggest that chiral ligand-exchange HPLC is suitable for the separation of a wide range of enantiomers in which copper(II) complex formation can be assumed.

In this paper, we report the direct separation of various racemic carboxylic acids and amines by HPLC on reversed-phase silica gels coated with copper(II) complexes of N,S-dioctyl-D-penicillamine (**1**) [7] and (*R*,*R*)-tartaric acid mono-(*R*)-1-(α-naphthyl)ethylamide (**2**) [8], developed previously.

2. Experimental

Chiral ligands **1** and **2** were prepared as described previously [7,8]. Commercially available Sumipax ODS columns (150 and 50 mm × 4.6-mm I.D.) packed with octadecylsilanized silica (5 μm) were coated with **1** and **2** and treated with copper(II) ion. These columns are commercially available from Sumika Chemical Analysis Service (Osaka, Japan) as Sumichiral OA-5000 and OA-6000. All chemicals and solvents of analytical-reagent grade were purchased

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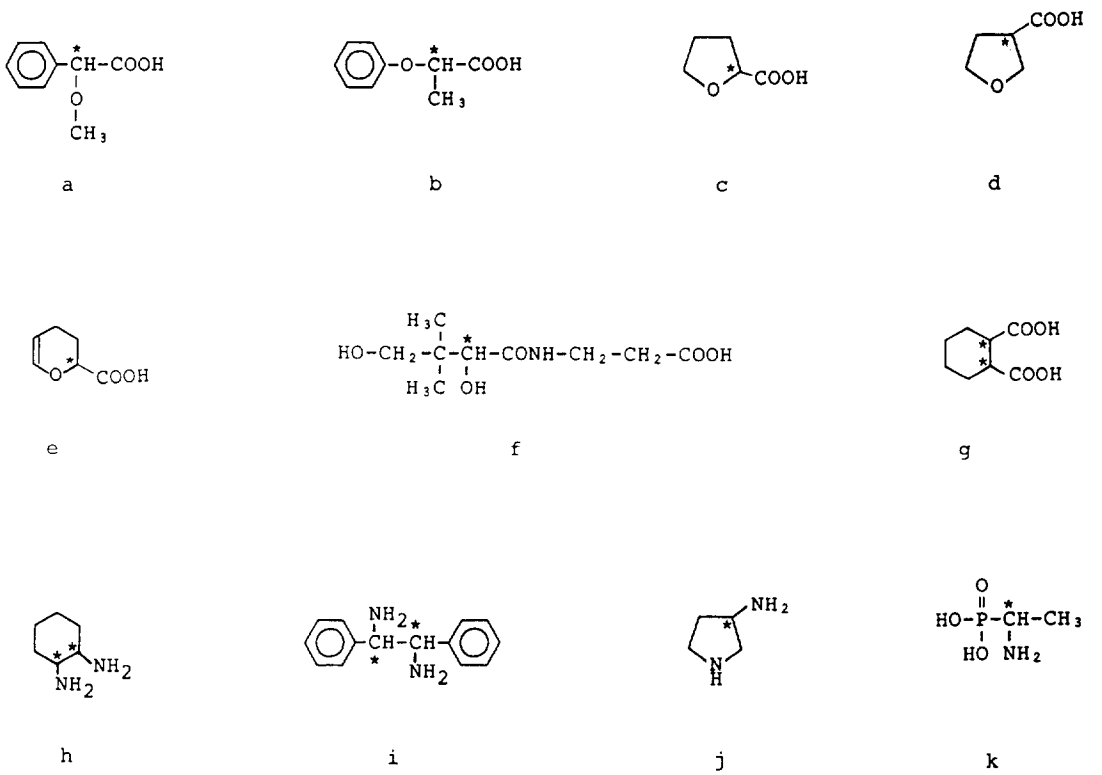


Fig. 1. Structures of racemic compounds.

from Wako (Osaka, Japan). Structures of the racemic carboxylic acids and amines used in this study are shown in Fig. 1.

The experiments were carried out using a Waters Model 510 high-performance liquid chromatograph equipped with a variable-wavelength UV detector (operated at 254 and 280 nm). The chromatographic conditions are given in Table 1.

3. Results and discussion

The chromatographic results are summarized in Table 1. Excellent direct separation of various racemic carboxylic acids and amines was accomplished. We can assume the formation of diastereomeric copper(II) complexes with the stationary phases for the chiral recognition of these enantiomers.

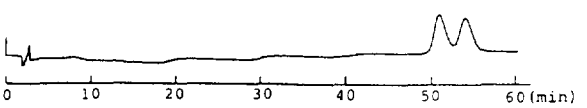
The separation of α-methoxyphenylacetic acid enantiomers (Fig. 2) suggests that the methoxy group attached to the asymmetric carbon atom may contribute to the complexation in place of the hydroxy group in mandelic acid. Similar complexations are assumed with racemic 2-phenoxypropionic acid, tetrahydro-2-furoic acid and tetrahydro-3-furoic acid. The difference in separation factors between tetrahydro-2- and -3-furoic acid shows that the positions of the carboxyl group and the oxygen atom of the ether linkage around the asymmetric carbon atom are important for the formation of the complex.

In the separation of racemic *trans*-1,2-diaminocyclohexane, 1,2-diphenylethylenediamine and 3-aminopyrrolidine (Fig. 3), two amino or imino groups may play an effective cooperative role for the complexation. The phosphoric acid group may contribute to the formation of the complex for the separation of 1-aminoethylphosphonic acid (Fig. 4).

Table 1
Enantiomer separations by HPLC with copper(II) complexes of chiral ligands

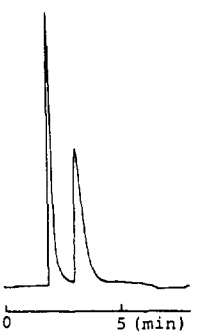
Compound[a]	Name	k_1'	k_2'	α	Chiral ligand	Mobile phase
a	α-Methoxyphenylacetic acid	35.20	37.31	1.06	**1**	D
b	2-Phenoxypropionic acid	60.78	72.94	1.20	**1**	E
c	Tetrahydro-2-furoic acid	6.90	12.97	1.88	**2**	B
d	Tetrahydro-3-furoic acid	13.26	14.59	1.10	**2**	A
e	3,4-Dihydro-2*H*-pyran-2-carboxylic acid	9.54	10.97	1.15	**2**	C
f	Pantothenic acid	7.29(−)	7.95(+)	1.09	**2**	B
g	*trans*-1,2-Cyclohexanedicarboxylic acid	91.10	109.32	1.20	**1**	F(pH 6.4)
h	*trans*-1,2-Diaminocyclohexane	9.81	11.48	1.17	**2**	A
i	1,2-Diphenylethylenediamine	3.64	4.00	1.10	**1**	F(pH 4.5)
j	3-Aminopyrrolidine	0.51	1.33	2.61	**2**	A
k	1-Aminoethylphosphonic acid	6.67	8.67	1.30	**1**	B

Mobile phase: A = 1 m*M* copper(II) sulfate in water; B = 2 m*M* copper(II) sulfate in water–acetonitrile (95:5); C = 2 m*M* copper (II) sulfate in water–acetonitrile (90:10); D = 2 m*M* copper(II) sulfate in water–2-propanol (85:15); E = 2 m*M* copper(II) sulfate in water–2-propanol (80:20); F = 1 m*M* copper(II) acetate + 0.1 *M* ammonium acetate in water–2-propanol (85:15). Column temperature: 25°C (40°C for compound **i**). A flow-rate of 1.0 ml/min was used for the 150 × 4.6 mm I.D. column. An injection volume of 5 μl (2 mg/ml) was typically used. k_1', k_2' = Capacity factors of first- and second-eluted isomer, respectively α = separation factor (k_1'/k_2').
[a] See Fig. 1.



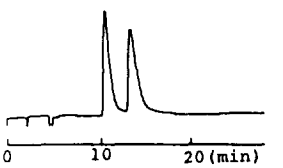
Retention time

Fig. 2. HPLC separation of racemic α-methoxyphenylacetic acid with **1**. Chromatographic conditions as in Table 1.



Retention time

Fig. 3. HPLC separation of racemic 3-aminopyrrolidine with **2**. Chromatographic conditions as in Table 1.



Retention time

Fig. 4. HPLC separation of racemic 1-aminoethylphosphonic acid with **1**. Chromatographic conditions as in Table 1.

4. Conclusion

Excellent direct separation of the enantiomers of various carboxylic acids and amines containing some other polar groups was accomplished on copper(II) complexes of chiral ligands **1** and **2**. The results showed that the carboxyl or amino group attached to the asymmetric carbon atom may play the main role and some other polar groups may play a cooperative role in forming the complexes with chiral stationary phases. It is emphasized that the positions of these groups around the asymmetric carbon atom are very

important stereochemically for chiral recognition.

These chiral copper(II) complexes of chiral ligands **1** and **2** are very promising as chiral stationary phases for the direct separation of the enantiomers of a variety of carboxylic acids and amines in which copper(II) complex formation can be assummed.

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