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Note

Gas chromatographic separation of amino acid, amine and carboxylic acid enantiomers with α-hydroxycarboxylic acid esters as chiral stationary phases

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The optically active stationary phases used hitherto for the separation of amino acid, amine and carboxylic acid enantiomers by gas chromatography involve NH groups linked to the asymmetric carbon atom, which form diastereomeric hydrogen bonds with solutes. Examples are N-acyl amino acid esters[1], N-acyl dipeptide esters[2] and N-acyl amines[3].

Recently we found that α-hydroxycarboxylic acid ester enantiomers can be resolved on amino acid derivatives[4]. This suggested that some α-hydroxycarboxylic acid esters would be effective as optically active stationary phases and led us to this work.

In this paper we describe the separation of amino acid, amine and carboxylic acid enantiomers with di-*l*-menthyl (+)-tartrate and di-*dl*-menthyl (−)-malate as stationary phases.

EXPERIMENTAL

Gas chromatography was carried out with a Shimadzu GC-7A gas chromatograph equipped with a flame-ionization detector. Glass capillary columns (40 m × 0.25 mm I.D.) coated with α-hydroxycarboxylic acid esters were used.

Di-*l*-menthyl (+)-tartrate was prepared from (+)-tartaric acid by treatment with *l*-menthol in the presence of concentrated sulphuric acid for several hours at 100°C. The ester was extracted with chloroform and the solution was washed successively with water, 1 *N* hydrochloric acid and water. After drying over sodium sulphate and evaporation, the ester was purified by column chromatography with silica gel and *n*-hexane–ethyl acetate as the eluent. Di-*dl*-menthyl (−)-malate was similarly prepared from (−)-malic acid by treatment with *dl*-menthol. The structures of these esters were confirmed by infrared and nuclear magnetic resonance spectroscopy and microanalysis. Their specific rotations were $[\alpha]_D^{25} = -69°$ ($c = 1.0\%$, chloroform) in di-*l*-menthyl (+)-tartrate and $[\alpha]_D^{25} = -8°$ ($c = 1.2\%$, chloroform) in di-*dl*-menthyl (−)-malate.

(+)-Tartaric acid, (−)-malic acid and *l*- and *dl*-menthol were commercially available. Various racemic amino acids, amines and carboxylic acids shown in Table I were also commercially available. α-Bromo-β,β-dimethylbutyric acid was prepared in our laboratory.

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RESULTS AND DISCUSSION

The gas chromatographic results are summarized in Table I. Enantiomers of amino acids, amines and carboxylic acids were resolved into their antipodes. Typical gas chromatograms are shown in Figs. 1–3.

TABLE I

GAS CHROMATOGRAPHIC SEPARATION OF AMINO ACID, AMINE AND CARBOXYLIC ACID ENANTIOMERS ON OPTICALLY ACTIVE α-HYDROXYCARBOXYLIC ACID ESTERS

Glass capillary columns, 40 m × 0.25 mm I.D. Column temperature, 100°C. Carrier gas, helium at a flow-rate of 0.7 ml/min. Stationary phases: A, di-*l*-menthyl (+)-tartrate; B, di-*dl*-menthyl (−)-malate.

Compound	*Stationary phase*	*Retention time* (min)*		*Separation factor, α (second/first)*
		First peak	*Second peak*	
Amino acids**:				
Alanine	A	22.26 (L)	22.71 (D)	1.020
	B	111.60 (L)	112.80 (D)	1.011
Valine	A	33.54 (L)	33.97 (D)	1.013
	B	191.00 (L)	192.50 (D)	1.008
Leucine	A	67.07 (L)	68.93 (D)	1.028
Amines:				
α-Phenylethylamine***	A	82.34 (−)	84.39 (+)	1.025
α-(2,5-Xylyl)ethylamine§	A	272.00 (−)	281.20 (+)	1.034
α-Phenylpropylamine§	A	164.01 (−)	169.63 (+)	1.034
Carboxylic acids:				
α-Phenylpropionic acid§§	A	176.00 (−)	178.80 (+)	1.016
α-Bromo-β,β-dimethylbutyric acid§§§	A	62.10 (+)	63.60 (−)	1.024

* Measured from solvent peak.
** Resolved as N-trifluoroacetyl isopropyl ester.
*** Resolved as N-pentafluoropropyl derivatives.
§ Resolved as N-trifluoroacetyl derivatives.
§§ Chromatographed on 20 m × 0.25 mm I.D. glass capillary column using helium at a flow-rate of 1.3 ml/min. Resolved as isopropylamide.
§§§ Resolved as *tert.*-butylamide.

In 1959 Karagounis and Lippold[5] reported the successful of separation of some racemic compounds by gas chromatography with ethyl *d*-tartrate as a chiral stationary phase, but Goldberg and Ross[6] reported that such results could not be reproduced. Berrod *et al.*[7] studied the resolution of some chiral compounds by gas chromatography on chiral stationary phases derived from (+)-tartaric acid, such as (+)-dodecyl tartrate, and achieved a partial separation of the enentiomers of some alcohols by measuring the optical activities of trapped fractions at the beginning and end of the peak corresponding to the racemic compounds, but the separation was insufficient to observe the commencement of resolution.

To our knowledge this is the first successful gas chromatographic separation of racemic compounds with α-hydroxycarboxylic acid esters, which possess OH

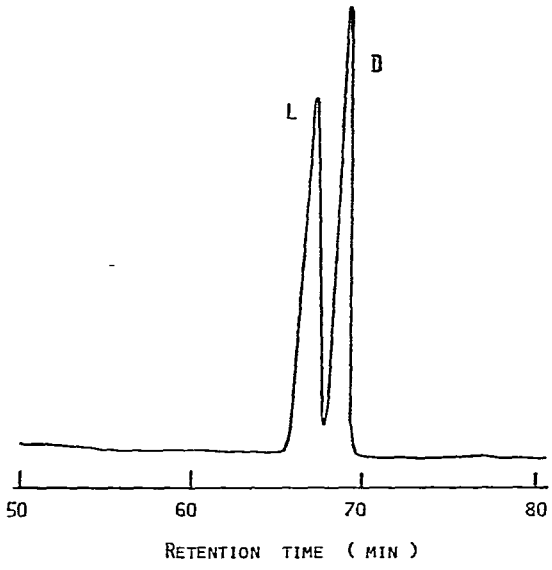
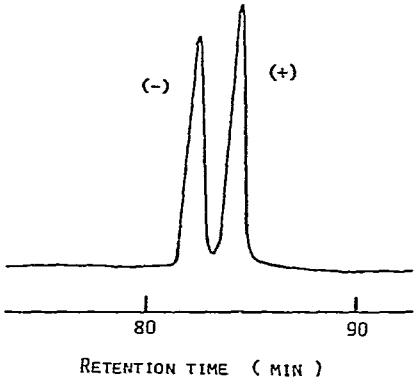


Fig. 1. Gas chromatogram of N-trifluoroacetyl-DL-leucine isopropyl ester. Glass capillary column (40 m × 0.25 mm I.D.) coated with di-*l*-menthyl (+)-tartrate. Temperature: 100°C. Carrier gas (helium) flow-rate: 0.7 ml/min.



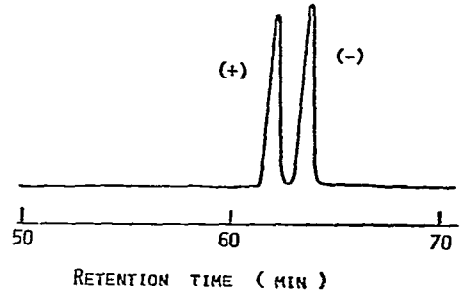


Fig. 2. Gas chromatogram of racemic N-pentafluoropropyl-α-phenylethylamine. Chromatographic conditions as in Fig. 1.

Fig. 3. Gas chromatogram of racemic α-bromo-β,β-dimethylbutyric acid *tert.*-butylamide. Chromatographic conditions as in Fig. 1.

groups linked to the asymmetric carbon atoms, as chiral stationary phases. This result supports the conclusion reported previously[4] that OH groups contribute to the formation of diastereomeric association complexes for the separation of enantiomers.

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