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Note

N-(1*R*,3*R*)-*trans*-Chrysanthemoyl (*R*)-1-(α-naphthyl)ethylamine as a stationary phase for the separation of optical isomers by gas chromatography

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In the study of the direct separation of optical isomers by gas chromatography (GC), it is well established that it is sufficient for a chiral stationary phase to contain an amide group and an asymmetric carbon atom, attached to the nitrogen or carbon atom, in order to display selectivity in its interaction with the enantiomers of amides such as N-acyl amino acid esters, N-acyl amines and α-substituted carboxylic acid amides. Recently König and Sievers[1] reported that a second chiral constituent in the stationary phase does not necessarily improve but may influence the separation.

During the course of our research to examine influences on enantioselectivity where it has been verified that the structure of the stationary phase contains two asymmetric carbon atoms attached to both nitrogen and carbon atoms of the amide group, we have found that N-(1*R*,3*R*)-*trans*-chrysanthemoyl (*R*)-1-(α-naphthyl)ethylamine (phase I) shows excellent enantioselectivity compared to that of N-(1*R*,3*R*)-*trans*-chrysanthemoyl laurylamine[2] (phase II) or N-lauroyl (*R*)-1-(α-naphthyl)ethylamine (phase III) both of which contain only one asymmetric center.

EXPERIMENTAL

Synthesis of stationary phases

Phase I was obtained by coupling (1*R*,3*R*)-*trans*-chrysanthemic acid (0.006 mole) with (*R*)-1-(α-naphthyl)ethylamine (0.006 mole) in dry tetrahydrofuran in the presence of equimolar 1,1′-carbonyldiimidazole at room temperature for 3 h. The solvent was removed under reduced pressure at 50°C. The crude product was dissolved in 40 ml of chloroform. The solution was washed successively with 1 *N* hydrochloric acid and with water. After drying over sodium sulfate and evaporation, the amide was purified by column chromatography on silica gel. The fraction eluting with ethyl acetate–*n*-hexane (5:95) was the desired compound as demonstrated by nuclear magnetic resonance spectrometry (m.p. 111–114°C). Elemental analysis: found, C 81.3%, H 8.6%, N 4.2%; calculated for $C_{22}H_{27}NO$, C 82.2%, H 8.5%, N 4.4%, $[\alpha]_D^{25}$: 16.5° (C = 0.31% in chloroform). Phase III was prepared according to the procedure of Weinstein *et al.*[3]. Phase II was prepared as described previously[2].

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TABLE I

GAS CHROMATOGRAPHIC SEPARATION OF ENANTIOMERS

Chromatographed on 40 m × 0.25 mm, I.D. glass capillary columns. Column temperature: 100°C. Carrier gas: helium at 0.6–1.2 ml/min.

Compound	*Optically active stationary phase*									
	Phase I			*Phase II*			*Phase III*			
	*Retention time (min)**		α**	*Retention time (min)**		α**	*Retention time (min)**		α**	
	1st Peak	*2nd Peak*		*1st Peak*	*2nd Peak*		*1st Peak*	*2nd Peak*		
Amines										
2-Octyl amine***	47.64	49.91	1.048	106.2		1.000	41.91	44.42	1.060	
1-Phenyl ethylamine[§]	63.07	73.58	1.167	121.4	122.5	1.009	53.81	61.69	1.146	
*Amino acid isopropyl esters****										
Alanine	11.52	12.24	1.063	18.61	18.81	1.011	8.12	8.37	1.031	
Valine	13.58	14.38	1.059	22.37	22.79	1.019	9.86	10.29	1.044	
Leucine	40.27	42.03	1.044	73.26	74.85	1.022	29.49		1.000	
Carboxylic acid tert.-butyl amides										
3,3-Dimethyl-2-ethyl butyric acid	44.53	47.64	1.070	105.8	108.4	1.025	36.78		1.000	
2-Bromo-3,3-dimethyl butyric acid	76.70	88.37	1.152	170.0		1.000	61.38	69.31	1.129	
cis-Chrysanthemic acid	183.2	189.0	1.032	121.2		1.000	140.3	145.9	1.040	
trans-Chrysanthemic acid	248.3	271.1	1.092	182.8	196.3	1.074	212.8		1.000	

Carboxylic acid ethyl esters							
cis-Chrysanthemic acid	28.02	28.44	1.015	28.40	1.000	11.50	1.000
cis-3-(2,2-Dichlorovinyl)-cyclopropanecarboxylic acid	43.96	44.72	1.017	66.98	1.000	33.25	1.000
Nitriles							
2-Phenyl propiononitrile	38.41	39.02	1.016	47.70	1.000	41.80	1.000
2-(2-Fluorophenyl)-isovarelonitrile	51.01	52.42	1.028	21.34	1.000	27.18	1.000
2-(4-Chlorophenyl)-isovarelonitrile ‡‡	144.2	149.0	1.033	104.8	1.000	101.6	1.000
Alcohols							
1-Phenyl ethanol	17.56	17.81	1.014	23.22	1.000	18.42	1.000
Pantoyl lactone	51.98	53.52	1.030	54.21	1.000	52.00	1.000
Menthol	21.45	21.83	1.018	45.64	1.000	29.13	1.000

* Measured from solvent peak.
** Separation factor calculated by second peak/first peak.
*** Resolved as N-trifluoroacetyl derivatives.
‡ Resolved as N-pentafluoropropionyl derivative.
‡‡ Chromatographed at a column temperature of 120°C.

Gas chromatography

The experiments were carried out with a Shimadzu GC-7A gas chromatograph equipped with a flame ionization detector. The glass capillary columns (40 m × 0.25 mm I.D. and 20 m × 0.25 mm I.D.) were coated with a 5% solution of the stationary phase in chloroform.

RESULTS AND DISCUSSION

The GC results are given in Table I. It is notable that phase I shows higher separation factors (α) than II or III in the separation of racemic N-trifluoroacetyl (TFA) amino acid esters, N-TFA-amines and α-substituted carboxylic acid amides except in the case of racemic N-TFA-2-octylamine and *cis*-chrysanthemic acid *tert.*-butylamide. These results indicate that the second chiral constituent improves the enantioselectivity of phase I.

It is of some interest that phase I separates enantiomers of some chiral carboxylic acid esters, nitriles and alcohols in spite of the fact that these enantiomers could not be resolved with phase II or III. Three typical chromatograms are shown in Figs. 1–3.

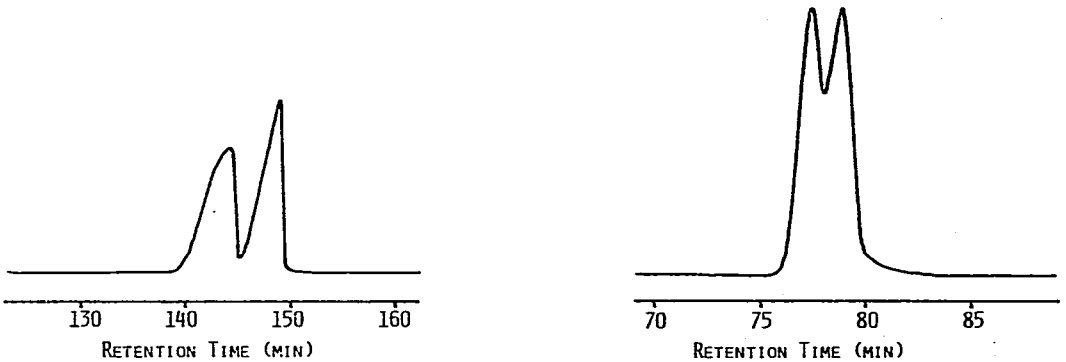

Fig. 1. Gas chromatogram of racemic 2-(4-chlorophenyl)isovarelonitrile. Column: glass capillary column (40 m × 0.25 mm I.D.) coated with N-(1*R*,3*R*)-*trans*-chrysanthemoyl (*R*)-1-(α-naphthyl)ethylamine. Temperature: 80°C. Carrier gas (helium) flow-rate: 1.0 ml/min.

Fig. 2. Gas chromatogram of racemic ethyl *cis*-chrysanthemate. Chromatographic conditions as in Fig. 1.

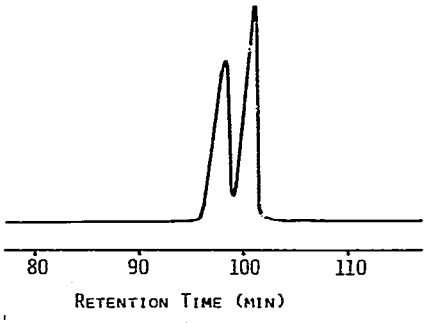

Fig. 3. Gas chromatogram of racemic menthol. Chromatographic conditions as in Fig. 1.

To our knowledge, this is the first separation of enantiomeric nitriles. Although it is known that enantiomers of N-acylamino acid esters[4], α-hydroxy carboxylic acid esters[5] and their O-acyl derivatives[1] can be resolved on some chiral phases, the separation of alkylcarboxylic acid ester enantiomers has never been reported. We have already accomplished the first successful direct separation of some alcohol enantiomers[6,7], but racemic menthol could not be resolved.

We consider that these results suggest that a direct separation of enantiomers of other alkylcarboxylic acid esters, nitriles and alcohols may be possible with some chiral carboxylic acid amides if their steric structures are composed of sufficiently energetically different diastereomeric complexes.

REFERENCES

1 W. A. König and S. Sievers, *J. Chromatogr.*, 200 (1980) 189.
2 N. Ôi, T. Doi, H. Kitahara and Y. Inda, *Bunseki Kagaku (Jap. Anal.)*, submitted for publication.
3 S. Weinstein, B. Feibush and E. Gil-Av, *J. Chromatogr.*, 126 (1976) 97.
4 E. Gil-Av, B. Feibush and Charles-Sigler, in A. B. Littlewood (Editor), *Gas Chromatography 1966*, Institute of Petroleum, London, 1967, p. 227.
5 N. Ôi, H. Kitahara, M. Horiba and T. Doi, *J. Chromatogr.*, 206 (1981) 143.
6 N. Ôi, T. Doi, H. Kitahara and Y. Inda, *Bunseki Kagaku (Jap. Anal.)*, 30 (1981) 79.
7 N. Ôi, T. Doi, H. Kitahara and Y. Inda, *J. Chromatogr.*, 208 (1981) 404.