

CHROM. 13,236

Note

Direct separation of α -hydroxycarboxylic acid ester enantiomers by gas chromatography with optically active copper(II) complexes

NAOBUMI ÔI*, MASAO HORIBA, HAJIMU KITAHARA, TADASHI DOI, TORU TANI and TAKAAKI SAKAKIBARA

Institute for Biological Science, Sumitomo Chemical Co. Ltd., 4-2-1 Takatsukasa, Takarazuka-shi, Hyogo-ken 665 (Japan)

(First received April 15th, 1980; revised manuscript received August 11th, 1980)

Hitherto gas chromatographic (GC) separation of enantiomers of hydroxycarboxylic acids, including lactic acid which is an important biological substance, has been achieved by forming derivatives with some optically active reagents, such as *l*-menthol, and separating the resulting mixture of diastereoisomers with the usual optically inactive stationary phases^{1,2}. However, using this method, α -hydroxycarboxylic acid ester enantiomers must be hydrolysed before the derivatization to diastereoisomers.

The enantiomers of α -hydroxycarboxylic acid esters have never been resolved as such on optically active stationary phases. It is considered that the reason is that almost all known optically active stationary phases are derivatives of amino acids or dipeptides for which resolution has been attributed to diastereoisomeric interactions involving hydrogen bonds between CONH groups. Therefore, in order to resolve the enantiomers of α -hydroxycarboxylic acids, which have no NH group, it is necessary make the corresponding acid amides. For example, the enantiomers of *O*-pentafluoropropionyl lactic acid cyclohexyl amide were resolved with a high resolution factor on Chirasil-Val³.

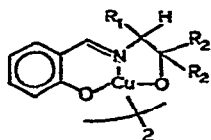
In the present paper we report the direct resolution of some chiral lactic acid esters by GC on copper(II) complexes of optically active Schiff's bases⁴.

EXPERIMENTAL

Chemicals

The methyl, ethyl and isobutyl esters of DL-lactic acid were purchased from Wako (Osaka, Japan). *L*- and *DL*-lactic acid isopropyl ester and *DL*- α -hydroxybutyric acid isopropyl ester were synthesized by esterification of each carboxylic acid.

The binuclear copper(II) complexes of *N*-salicyliden-(*R*)-2-amino-1,1-bis-(*S*-*tert*-butyl-2-octyloxyphenyl)-propan-1-ol and *N*-salicyliden-(*S*)-2-amino-1,1-bis-(*S*-*tert*-butyl-2-heptyloxyphenyl)-3-phenyl-propan-1-ol (I and II) were prepared by Dr. T. Nagase as reported previously⁵.



I : $R_1 = \text{CH}_3$

$R_2 = \text{tert-C}_4\text{H}_9$ -- H_{17}

II : $R_1 = \text{CH}_2$ -

$R_2 = \text{tert-C}_4\text{H}_9$ -- H_{15}

Gas Chromatography

The experiments were carried out with a Shimadzu Model GC-7A gas chromatograph equipped with a flame ionization detector. Glass capillary columns (40 m \times 0.25 mm I.D.) coated with the mixture of the copper complex (I or II) and silicone OV-101 (1:1), and packed columns (2 m \times 3 mm I.D.) filled with Chromosorb W AW DMCS (80-100 mesh) coated with 6% of the mixture of I and silicone OV-101 (5:1), were used.

GC mass spectrometric (MS) measurements were performed on a Shimadzu Model LKB-9000 GC-MS instrument.

RESULTS AND DISCUSSION

The results of the GC separation are given in Table I. The DL-lactic acid esters and a DL- α -hydroxybutyric acid ester were resolved into their antipodes with good separation factors. An example of a chromatogram is shown in Fig. 1.

As the optically active copper complex (I) shows a relatively large selectivity for the lactic acid esters, their enantiomers can be also separated on packed columns, as shown in Fig. 2. In these chromatograms of racemic isobutyl lactate, peak areas

TABLE I

GAS CHROMATOGRAPHIC SEPARATION OF α -HYDROXYCARBOXYLIC ACID ESTER ENANTIOMERS

Glass capillary columns, 40 m \times 0.25 mm I.D. Carrier gas, helium at a flow-rate of 0.6 ml/min. Stationary phases: A, Mixture of the copper complex of I and silicone OV-101 (1:1). B, Mixture of the copper complex of II and silicone OV-101 (1:1).

| Compound | Stationary phase | Column temp. ($^{\circ}\text{C}$) | Retention time* | | Ratio of retention times (second/first) |
|---|------------------|-------------------------------------|-----------------|-------------|--|
| | | | First peak | Second peak | |
| Lactic acid esters, $\text{CH}_3\text{CH}(\text{OH})\text{COOR}$: | | | | | |
| $\text{R} = \text{CH}_3$ | A | 70 | 3.6 | 4.2 | 1.17 |
| C_2H_5 | A | 70 | 6.3 | 7.1 | 1.13 |
| iso- C_3H_7 | A | 70 | 7.3(D) | 8.5(L) | 1.16 |
| | B | 110 | 2.4(L) | 3.2(D) | 1.33 |
| iso- C_4H_9 | A | 70 | 21.9(D) | 24.8(L) | 1.13 |
| | B | 110 | 4.3(L) | 5.8(D) | 1.35 |
| α -Hydroxybutyric acid isopropyl ester | A | 70 | 15.7 | 16.8 | 1.07 |

* Measured from solvent peak.

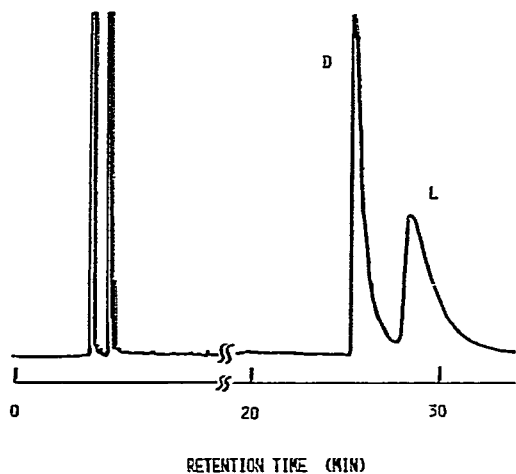


Fig. 1. Gas chromatogram of DL-isobutyl lactate. Conditions: see Table I.

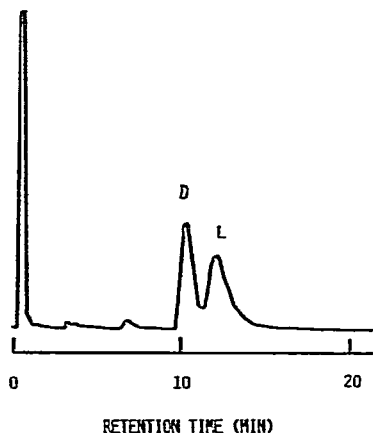


Fig. 2. Gas chromatogram of DL-isobutyl lactate. GC conditons: glass column (2 m \times 3 mm I.D.) containing 80–100 mesh Chromosorb W AW DMCS coated with 6% of the mixture of the copper complex I and silicone OV-101 (5:1); temperature, 70°C; carrier gas, nitrogen at a flow-rate of 30 ml/min.

of enantiomers were nearly equal, although the longer-retained L enantiomer had a much broader peak, accompanied by tailing, than the D enantiomer. Such an anomalous peak shape shows that the numbers of theoretical plates for enantiomers are not equal. Similar results have been reported by Lochmuller and Souter⁶ for the GC resolution of enantiomers with optically active mesophases. The mass spectra obtained from two separated peaks were identical (Fig. 3), and consistent with the standard spectrum of the racemic lactic acid ester.

Peak identifications were made by chromatographing successively racemic and 1:3 mixture of enantiomers of lactic acid isopropyl and isobutyl esters. On the copper complex I, the D isomers eluted before the L isomers. Supporting evidence for the

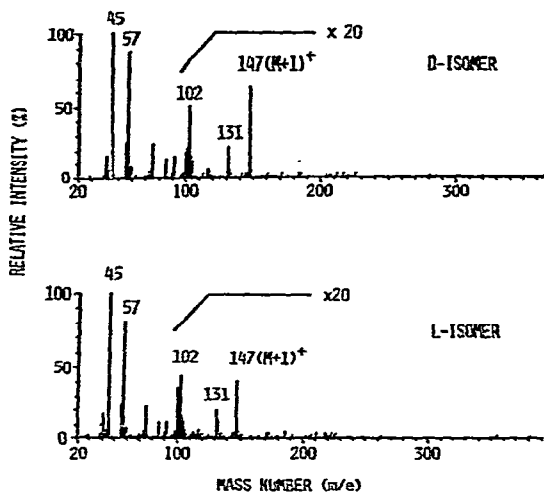


Fig. 3. Mass spectra of D- and L-isobutyl lactate. Operational conditions: electron energy, 70 eV; trapping current, 60 μ A; inlet system, GC on a glass column as described in Fig. 2.

successful resolution of DL-lactic acid ester was produced by use of the copper complex II, which possesses the opposite configuration (*S*) from I; the order of appearance of the peaks was reversed when the complex II was used.

It is convenient for practical purposes that these racemic esters can be resolved without any pretreatment such as acylation or hydrolysis. It is notable that the optically active copper complexes, which were found to be useful primarily as catalysts for asymmetric synthesis⁵, are also valuable as optically active stationary phases for the separation of enantiomers by GC.

ACKNOWLEDGMENT

The authors thank Dr. T. Nagase, Dr. T. Aratani and Mr. Y. Yoneyoshi for gifts of the optically active copper complexes used in this work.

REFERENCES

- 1 E. Gil-Av and D. Nurok, *Advan. Chromatogr.*, **10** (1974) 99.
- 2 J. P. Kamerling, G. J. Gerwig, J. F. G. Vliegthart, M. Duran, D. Ketting and S. K. Wadman, *J. Chromatogr.*, **143** (1977) 117.
- 3 H. Frank, G. J. Nicholson and E. Bayer, *J. Chromatogr.*, **146** (1978) 197.
- 4 N. Ōi, M. Horiba, H. Kitahara, T. Doi and T. Tani, *Bunseki Kagaku (Jap. Anal.)* **29** (1980) 156.
- 5 T. Aratani, Y. Yoneyoshi and T. Nagase, *Tetrahedron Lett.*, (1975) 1707.
- 6 C. H. Lochmuller and R. W. Souter, *J. Chromatogr.*, **88** (1974) 41.