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Note

Separation of chiral ketones by enantioselective gas chromatography

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Since thermostable polymer chiral stationary phases have become available[1,2], less volatile and more polar derivatives of chiral substrates are now accessible to gas chromatographic enantiomer separation. We have recently reported some general methods for the resolution of carbohydrates[3,4], chiral alcohols[5], amines[6], α- and β-hydroxy acids[6,7] and N-methylamino acids[7]. These separations have in most cases been possible after the introduction of carbamate, ureido or amide functions into chiral molecules. By these functional groups the formation of diastereoisomeric association complexes with the chiral stationary phase is strongly supported, probably by hydrogen-bond interaction. In this work we demonstrate for the first time that chiral ketones can be separated on chiral stationary phases after conversion into polar oxime derivatives.

EXPERIMENTAL

Materials

(+)- and (−)-fenchone, (+)- and (±)-camphor and 2-methylcyclohexanone were obtained from Fluka (Buchs, Switzerland), 2-methylcyclopentanone was purchased from Ventron (Karlsruhe, G.F.R.) and 3-methyl-2-pentanone from E. Merck (Darmstadt, G.F.R.). 3,4-Dimethyl-2-pentanone and 3-ethyl-4-methyl-2-pentanone were synthesized according to the method of Nenitzescu and Chicos[8]; 4-methyl-3-heptanone was obtained by oxidation of 4-methyl-3-heptanol (Aldrich, Milwaukee, WI, U.S.A.) with potassium dichromate in sulphuric acid. Samples of 2-methyl-3-oxobutanoic acid ethyl ester and 2-allyl-3-oxobutanoic acid ethyl ester were supplied by Professor P. Margaretha (University of Hamburg, Hamburg, G.F.R.).

Formation of derivatives

The oxime derivatives were prepared by dissolving 1 mg of hydroxylammonium chloride in a mixture of 100 μl of pyridine and 100 μl of dichloromethane and addition of 0.5 mg of chiral ketone to this mixture. After either 30 min at 100°C or 4 h at room temperature an appropriate amount of the solution was injected into the gas chromatograph. The products were also investigated by combined gas chromatography–mass spectrometry (GC–MS).

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Gas chromatography

Glass capillary columns were prepared and coated with XE-60–S-valine-S-α-phenylethylamide as described previously[9]. Fused silica columns with the same stationary phase were obtained from Chrompack (Middelburg, The Netherlands). A Carlo Erba Model 2101 gas chromatograph with hydrogen as carrier gas and, for GC–MS, a Hewlett-Packard 5985 A quadrupole mass spectrometer were used.

RESULTS AND DISCUSSION

Fig. 1 shows the results of the enantiomer separation of fenchone oximes. Both the (+)- and the (−)-enantiomer form *syn*- and *anti*-oximes, when the oxime formation takes place at room temperature. After injection of a mixture of (+)- and (−)-enantiomers two pairs of stereoisomers are separated, the (+)-isomers being eluted after the (−)-isomers. If the derivatization is performed at 100°C, predominantly one geometrical isomer (probably the thermodynamically more stable *anti*-isomer) of the oximes is formed, as demonstrated in Fig. 2. The same result is obtained after keeping a sample, originally derivatized at room temperature, for several days in pyridine solution.

Besides cyclic chiral ketones branched aliphatic ketones and α-branched β-keto acid esters could be separated into their enantiomers. The results are presented in

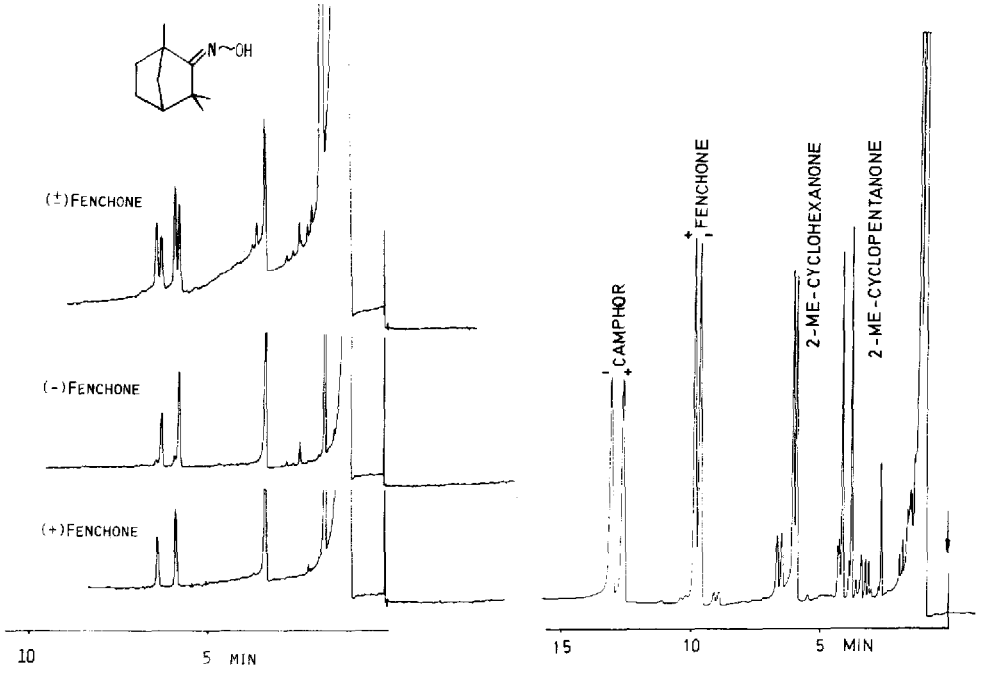

Fig. 1. Separation of enantiomers of fenchone oximes. Fused silica capillary column (25 m × 0.2 mm I.D.), coated with XE-60–S-valine-S-α-phenylethylamide. Column temperature, 140°C.

Fig. 2. Separation of some chiral ketone oximes. Column as in Fig. 1. Column temperature, 120°C; temperature programme, 1°C/min to 140°C. ME = Methyl.

TABLE I

SEPARATION FACTORS FOR SOME KETONE OXIMES ON A 25-m FUSED SILICA COLUMN COATED WITH XE-60–S-VALINE-S-α-PHENYLETHYLAMIDE

Racemate	*Separation factor, α*	*Column temperature (°C)*
Fenchone*	1.030 1.024	140
Camphor	1.046	140
2-Methylcyclopentanone	1.114	120
2-Methylcyclohexanone*	1.026 1.035	120
3-Methyl-2-pentanone	1.075	80
3,4-Dimethyl-2-pentanone	1.082	100
3-Ethyl-4-methyl-2-pentanone	1.055	125
4-Methyl-3-heptanone	1.036	110
2-Methyl-3-oxobutanoic acid ethyl ester	1.019	120
2-Allyl-3-oxobutanoic acid ethyl ester	1.015	120

* *syn*- and *anti*-isomers are formed.

Table I. The investigation of the enantiomers of fenchone and camphor clearly showed that the formation of the oximes proceeds without racemization. Also there is no racemization detectable after keeping the derivatives in pyridine solution for several weeks. The order of elution of the enantiomers could so far only be determined for the fenchone and camphor oximes. In both cases the enantiomer with *R*-configuration at the asymmetric centre next to the carbonyl function is eluted before the *S*-enantiomer.

The N–OH function seems to be essential for the formation of diastereoisomeric association complexes with the chiral phase. Neither the less polar O-methyl- and O-trimethylsilyl oximes nor the free ketones themselves are separated into enantiomers.

Chiral ketones such as 4-methyl-3-hexanone or 4-methyl-3-heptanone have repeatedly been identified as important alarm pheromones in ants of *Pogonomyrmex*[10], *Atta*[11] and *Manica*[12] species. 4,6-dimethyl-3-octanone and 4,6-dimethyl-3-nonanone were shown to have alarm pheromone properties in wasps of the *Dasymutilla occidentalis* species[13]. Only in the case of natural 4-methyl-3-heptanone has the *S*-configuration been proved[11].

Besides stereochemical investigations of insect communication systems and the analysis of flavour constituents this new case of chiral recognition may contribute to the understanding of enantioselective molecular interaction in a gas chromatographic system.

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