Journal of Chromatography, 366 (1986) 385–390
Elsevier Science Publishers B.V., Amsterdam — Printed in The Netherlands

CHROM. 18 797

Note

Critical remarks on the interpretation of chiral stereodifferentiation in gas chromatography

WOLFGANG DEGER*, MARTIN GESSNER, GEORG HEUSINGER, GABRIELE SINGER and ARMIN MOSANDL*

Institut für Pharmazie und Lebensmittelchemie, Universität Würzburg, Am Hubland, D 8700 Würzburg (F.R.G.)

(Received May 16th, 1986)

Direct high-resolution gas chromatographic (HRGC) analysis on chiral stationary phases[1–3] and indirect methods via diastereomeric derivatives on achiral phases[4] have proved to be useful and efficient for aroma components. Facile and reliable methods for the determination of enantiomeric purities are essential to stereochemical analysis of flavour compounds. Therefore the correlation between absolute configuration and the order of elution of flavour antipodes is of fundamental importance. In some cases it seems to be possible to predict the elution order of optical isomers within a series of homologues[5–7]. But this must not be overestimated because for a reliable assignment optically pure references with definite chirality are needed.

In this paper, the gas chromatographic (GC) behaviour of diastereomeric carbamates of chiral secondary alcohols[8], chiral 1,3-oxathianes[2], 1-octen-3-yl esters[9] and 1,3-oxathiane-S-oxides[10] is investigated.

EXPERIMENTAL

Gas–liquid chromatography

A Hewlett-Packard 5830 A and a DANI 6500 gas chromatograph with a flame ionization detector, equipped with a fused-silica column (25 m × 0.32 mm I.D.) coated with SE 54, Carbowax 20M, DB 210 or $Ni(HFC)_2$ in OV-101 and a deactivated glass capillary column coated with $Ni(HFC)_2$ in OV-101 were used. For conditions see Figs. 1–3.

Synthesis and separation of compounds

Diastereomeric carbamates from (R)-1-phenylethyl isocyanate with chiral alkan-2-ols[11]. A 1.0-μl volume of the asymmetric alcohol and 1.5 μl of (*R*)-(+)-1-phenylethyl isocyanate were heated in a sealed GC reaction tube at 110°C for 7 h. Methanol (0.5 ml) was then added to convert the excess of the reagent into the corresponding methyl carbamate. For HRGC conditions, see Fig. 1a.

Similarly prepared were diastereomeric carbamates from (*R*)-1-(1-naphthyl)-ethyl isocyanate. For HRGC conditions, see Fig. 1b.

* Present address: Institut für Lebensmittelchemie, Universität Frankfurt, Robert-Mayer-Str. 7–9, D 6000 Frankfurt, F.R.G.

0021-9673/86/$03.50

Optically pure alkan-2-ols, which were not available, were synthesized via diastereomeric alkan-2-yl esters by reductive cleavage with $LiAlH_4$. Absolute configurations were ascertained by ^1H NMR spectroscopy of their optically pure diastereomeric esters of (*R*)-2-phenylpropionic acid with alkan-2-ols. Within the series of alkan-2-ols, the (*R*)-(−) and (*S*)-(+)-configurations were revealed for all optically pure references[8].

Chiral 1,3-oxathianes. Optically pure 2-methyl-4-propyl-1,3-oxathianes, 2,4-dimethyl-1,3-oxathianes, 4-propyl-1,3-oxathianes and 2-methyl-1,3-oxathianes were prepared as described[12].

The optical purity of 1,3-oxathiane references as well as of their racemic mixtures was tested by complexation GC[1,2] with the chiral $Ni(HFC)_2$ phase. For HRGC conditions, see Fig. 2a–d.

Chiral 1-octen-3-yl esters. (±)-1-Octen-3-ol (10 mmol) or 10 mmol (*R*)-(−)- and (*S*)-(+)-1-octen-3-ol respectively, according to the procedure of ref. 9, were dissolved in 10 ml tetrachloromethane, and 15 mmol acyl chloride (C_2–C_4) freshly distilled and diluted in 5 ml tetrachloromethane were added. Quantitative reaction took place within 2.5 h at 20°C. Work-up conditions: addition of water, extraction with saturated sodium bicarbonate solution and water; extraction with diethyl ether, washing organic layer with water and drying with sodium sulphate. Chromatographic purification on silica (63–200 μm). Eluent: light petroleum (30–50°C)–diethyl ether (99:1). HRGC behaviour: enantiodifferentiation of chiral 1-octen-3-yl esters on chiral phase $Ni(HFC)_2$; for conditions see Fig. 2e.

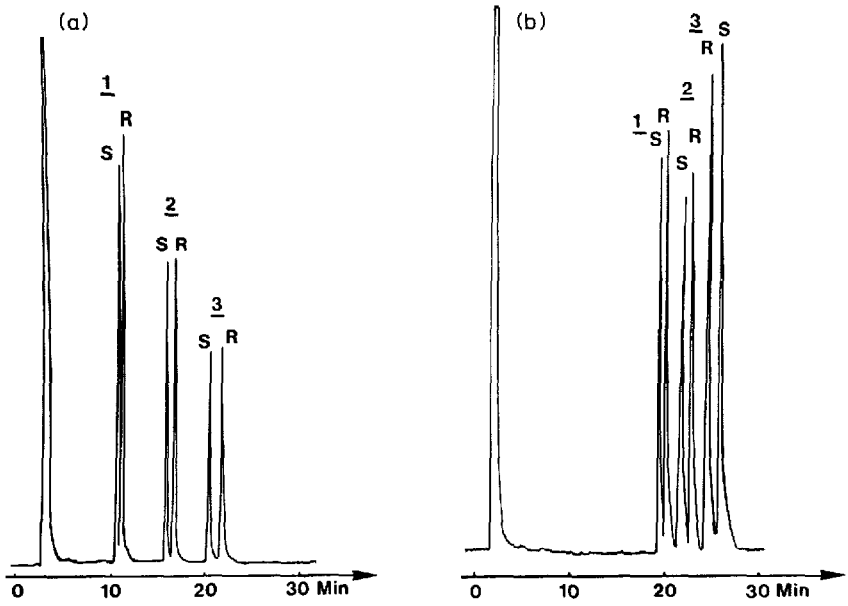

Fig. 1. Separation of secondary chiral alcohols as their urethane derivatives. Reagents (*R*)-(+)-1-phenylethyl isocyanate (a) and (*R*)-(−)-1-naphthylethyl isocyanate (b) on a DB 210 fused-silica column (25 m), carrier gas N_2, 0.8 bar. Conditions: (a): 170°C isothermal; 1 = hexan-2-ol (α = 1.0360); 2 = heptan-2-ol (α = 1.0510); 3 = octan-2-ol (α = 1.0671); (b) 180°C at 2°/min; 1 = hexan-2-ol (α = 1.0305); 2 = heptan-2-ol (α = 1.0363); 3 = octane-2-ol (α = 1.0412).

2-Methyl-4-propyl-1,3-oxathiane-S-oxides. These were synthesized according to refs. 10, 13, 14; see Fig. 3.

RESULTS AND DISCUSSION

Enantiodiscrimination of chiral carbamates of secondary asymmetric alcohols on a chiral phase has been described previously[3,11,15–18]. A further possibility for the analysis of chiral alcohols, relevant to flavour chemistry, should be applicable via diastereomeric urethanes: within a series of diasteromeric carbamates from alkan-2-ols with (*R*)-1-phenylethyl isocyanate, the order of elution of the diastereoisomers proved to be *R,S* (first) and *R,R* (second) (Fig. 1a). However, within a series of homologues of carbamates, derived from (*R*)-1-(1-naphthyl)ethyl isocyanate an inversion of elution order was observed in case of octan-2-ol enantiomers[8] (Fig. 1b).

In case of the well known chiral fruit flavourings of the 1,3-oxathiane type on the $Ni(HFC)_2$ phase, the assignment of absolute configurations according to the chromatographic behaviour was achieved by use of synthesized optically pure references[10,12–14,19] (Fig. 2a–c). Compared with 2-methyl-4-propyl-1,3-oxathiane iso-

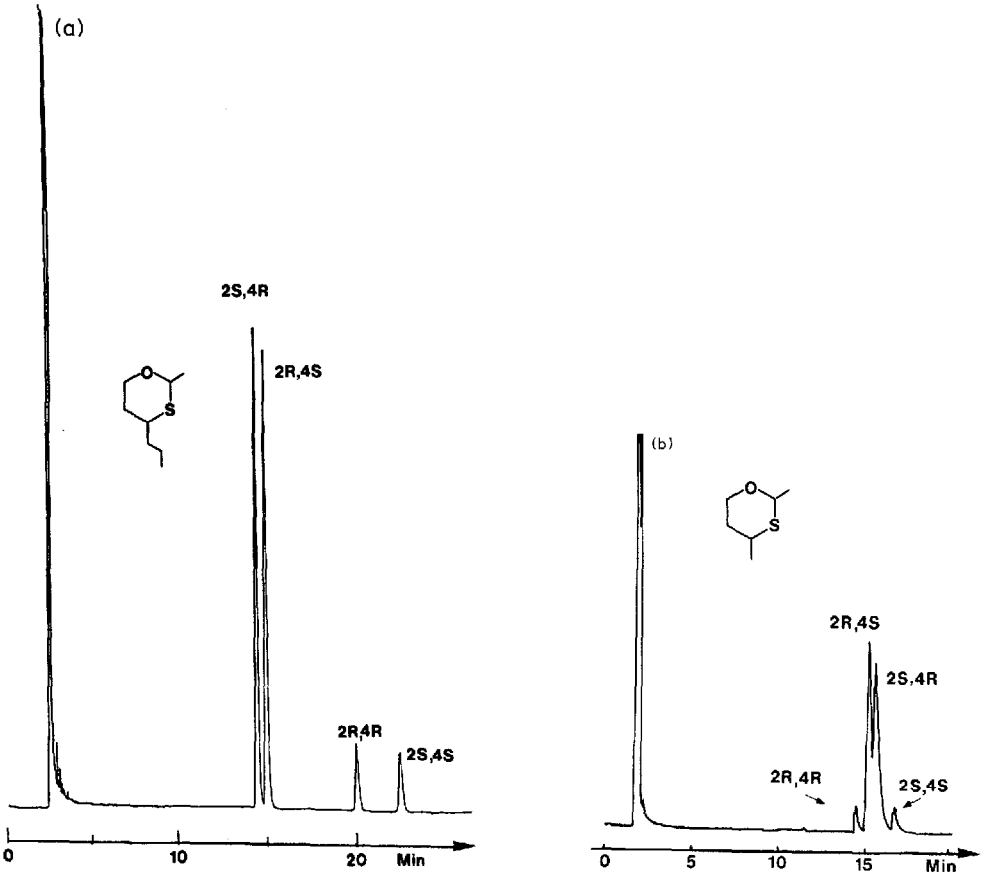

Fig. 3.

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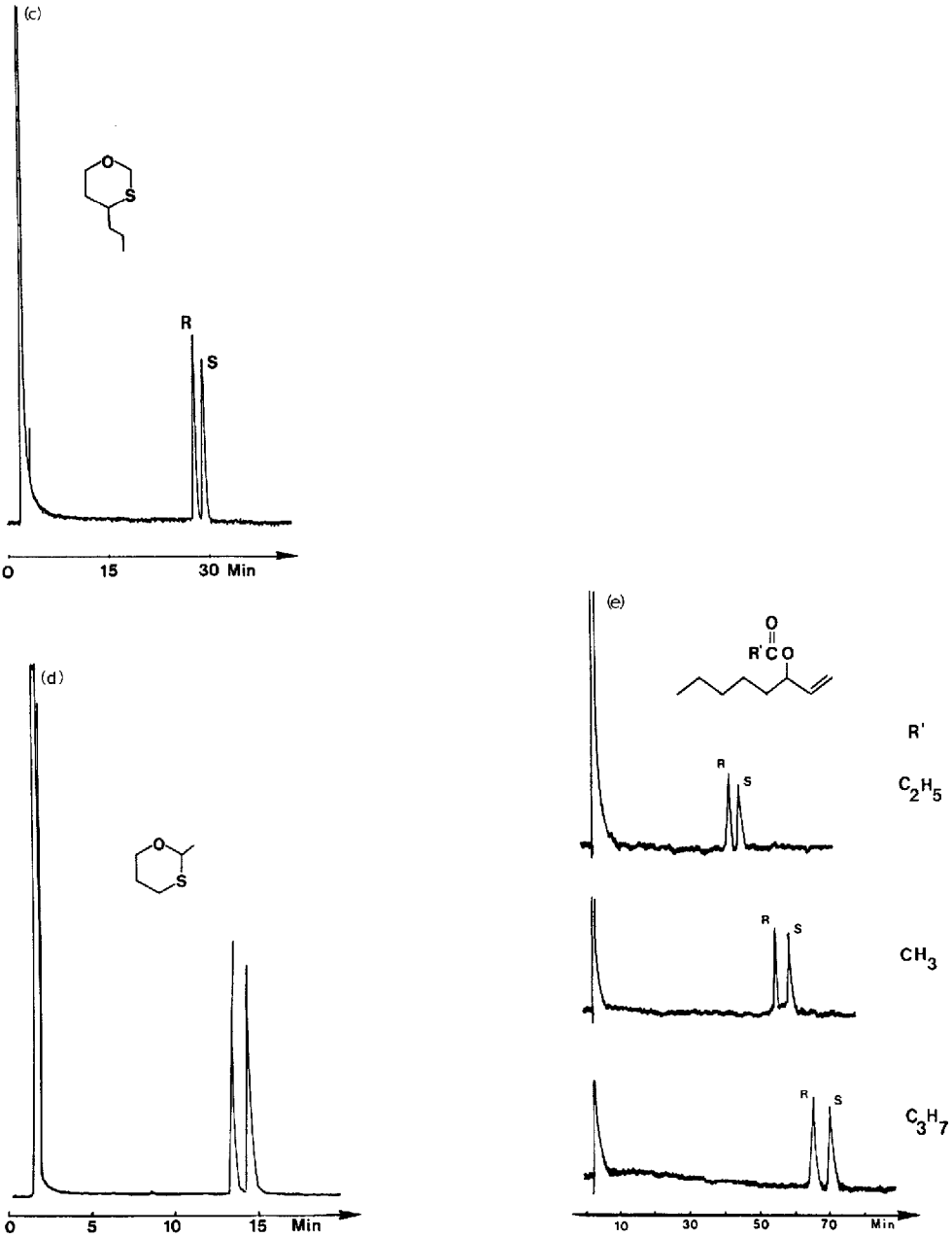

Fig. 2. Chiral resolution of 1,3-oxathiane derivatives on nickel(II) bis[3-heptafluorobutyryl-(1*R*)-camphorate], $Ni(HFC)_2$ (0.125 m in OV-101; deactivated capillary, 37 m × 0.25 mm). (a) 2-methyl-4-propyl-1,3-oxathiane (reproduced with permission from ref. 2). Conditions: 100°C isothermal; carrier gas N_2, 0.85 bar. (b) 2,4-Dimethyl-1,3-oxathiane. Conditions: 80°C isothermal; carrier gas N_2, 0.3 bar. (c) 4-Propyl-1,3-oxathiane (reproduced with permission from ref. 2). Conditions: 110°C isothermal; carrier gas N_2, 1.1 bar. (d) 2-methyl-1,3-oxathiane. Conditions: 80°C isothermal; carrier gas N_2, 0.35 bar; resolved, but without order of elution. (e) Separation of 1-octen-3-yl esters on fused-silica $Ni(HFC)_2$ column. Conditions: 95°C isothermal; carrier gas N_2, 0.8 bar.

mers (Fig. 2a), significant inversion of the elution order occurred for the lower homologue 2,4-dimethyl-1,3-oxathiane (Fig. 2b). 2-Methyl-1,3-oxathiane is very well resolved (Fig. 2d), but without elucidation of chirality, because the generation of this compound from 3-thiopropan-1-ol with the prochiral carbonyl compound acetaldehyde yields only a racemic mixture of 2-methyl-1,3-oxathiane and a prediction of chiral recognition of the $Ni(HFC)_2$ phase is not possible.

The enantiomeric composition of 1-octen-3-yl esters is of some interest with regard to their occurrence in essential oils, *e.g.*, 1-octen-3-yl acetate in lavender oil. Direct analysis of these esters with complexation HRGC on $Ni(HFC)_2$ is a highly sensitive and selective method for estimation of their optical purities, and it is conveniently applicable as an indirect method for resolution of 1-octen-3-ol, whose (*R*)(−)-antipode exclusively causes the impact flavour compound of mushrooms[20]. It seems remarkable that, within a series of 1-octen-3-yl ester homologues, in all cases the same chiral differentiation —first peak (*R*) and second peak (*S*)— was demonstrated by authentic optical isomers, but the enantiomers of 1-octen-3-yl acetate exhibit higher retention times than those of the higher homologues of 1-octen-3-yl propionate[9] (Fig. 2e).

Starting from optically pure (2*R*,4*S*)- and (2*S*,4*R*)-2-methyl-4-propyl-1,3-oxathiane enantiomers, the corresponding equatorial/axial (3:1) sulphoxides were generated by oxidation with $NaIO_4$ and chromatographic separation[10,13,14]. HRGC analysis with a Chirasil-Val phase[21] afforded quantitative resolution of all the four stereoisomers. The elucidation of the absolute configuration and chromatographic behaviour were carried by simultaneous chromatography of different amounts of optically pure equatorial/axial (3:1) sulphoxides of known configuration (Fig. 3).

The presented examples of enantiomers and diastereoisomers show that optically pure references with definite chirality are indispensable for reliable interpretation of chiral stereodifferentiation in flavour analysis.

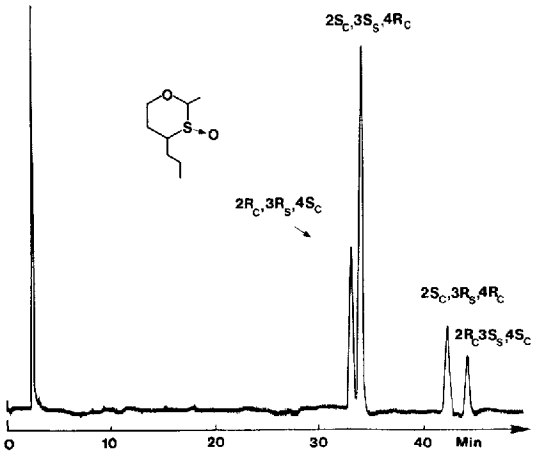

Fig. 3. Separation of 2-methyl-4-propyl-1,3-oxathiane-S-oxides, derived from *cis*-2-methyl-4-propyl-1,3-oxathiane enantiomers. Conditions: Chirasil-Val, fused-silica column (25 m); 120°C isothermal; carrier gas N_2, 0.8 bar.

ACKNOWLEDGEMENTS

This work was supported by the Bundesministerium für Jugend, Familie und Gesundheit and by the Deutsche Forschungsgemeinschaft.

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