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Note

Gas chromatographic separation of enantiomeric sulphur compounds on Chirasil-Val

ERNST BAYER*, ERNST KÜSTERS and GRAEME J. NICHOLSON
Institut für Organische Chemie der Universität, Auf der Morgenstelle 18, D-7400 Tübingen-1 (F.R.G.)
and
HARTMUT FRANK
Institut für Toxikologie der Universität, Wilhelmstrasse 56, D-7400 Tübingen-1 (F.R.G.)
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The first synthesis of optically active sulphoxides was reported in 1926[1] and in 1948 both Stoll and Seebeck[2] and Karrer *et al.*[3] reported their occurrence in nature. Further, chiral sulphoxides are formed by the metabolism of thioesters[4]. Precise determination of the relative and absolute amounts of the enantiomers is difficult, however, because both polarimetry and NMR spectroscopy with application of shift reagents are too insensitive and are not exact.

Chromatography on stereoselective stationary phases offers an alternative method. Liquid chromatographic separations reported[5–7] are not applicable to the separation of aliphatic sulphoxides because chiral recognition requires an aromatic ring adjacent to the sulphoxide group. We report here the first gas chromatographic separation of sulphoxide antipodes[8], including aliphatic sulphoxides, on the chiral silicone Chirasil-Val[9–11].

EXPERIMENTAL

Materials

The following substances were purchased: D,L-methionine (Serva); D,L-2-methylmethionine (Schuchardt); D,L-methylsulphinylmethyl methyl sulphide (EGA); *d,l*-phenylisopropyl sulphoxide (Aldrich).

The following substances were synthesized according to methods described in the literature: L-methionine-*d,l*-S-oxide[12]; L-methionine-*d*-S-oxide[13]; *d,l*-2-aminoethyl methyl sulphoxide[3].

Derivatization of methionine-S-oxide, 2-methylmethionine-S-oxide and 2-aminoethyl methyl sulphoxide

D,L-Methionine-d,l-S-oxide-PFP-n-propyl ester. D,L-Methylmethionine-d,l-S-oxide-PFP-n-propyl ester (asymmetric oxidation). A 0.3-mg amount of D,L-methionine (or 2-methylmethionine) was heated for 30 min at 110°C with 1 ml of 4 *N* hydrochloric acid in *n*-propanol. Excess reagent was removed by a gentle stream of nitrogen at 110°C and the residue taken up in 0.25 ml of methylene chloride. After

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addition of 70 μl of pentafluoropropionic anhydride (PFPA), the mixture was heated again to 110°C for 10 min. After cooling to room temperature, the excess reagent and solvent were removed by a gentle stream of nitrogen, the residue taken up in 0.5 ml of methylene chloride, and a stoichiometric amount of hydrogen peroxide in 0.1 ml of glacial acetic acid added. After heating for 5 min at 110°C, the mixture was cooled to room temperature and the methylene chloride phase subjected to gas chromatographic analysis.

L-*Methionine-d-S-oxide-PFP-methyl ester (derivatization with retention of configuration without reduction to thioether)*. A 0.3-mg amount of L-methione-*d*-S-oxide was dissolved in 0.5 ml of methylene chloride and 70 μl of PFPA were added. After 10 min at room temperature, excess reagent was removed with a gentle nitrogen stream, and the sample taken up in 0.5 ml of methylene chloride. Diazomethane was added until a yellow colour persisted, the excess reagent and solvent were blown off and the residue was dissolved in methylene chloride.

Gas chromatography

Quartz fused silica capillaries (20 m × 0.25 mm I.D.) coated with Chirasil-Val are available from Chrompack, Middelburg, The Netherlands. The chromatograms were obtained on a Carlo Erba Model 2101 gas chromatograph equipped with a flame ionization detector, using hydrogen (0.4 bar) as carrier gas (split ratio 1:25).

RESULTS AND DISCUSSION

By asymmetric oxidation of methionine-PFP-*n*-propyl ester with hydrogen peroxide–acetic acid, we obtained the corresponding S-oxides which were found to be separable on Chirasil-Val. Coalescence of the gas chromatographic peaks was not observed, indicating high configurative stability of the chiral sulphur atom at 200°C. The order of elution of the diastereomeric S-oxides was determined after esterification with diazomethane, because esterification with acetyl chloride–*n*-propanol was accompanied by reduction to the corresponding thioether. The order of elution is *RR, SR, RS, SS*. It is interesting to note that the separation factors of the enantiomers of the diastereomeric pairs (*RR/SS* and *SR/RS*) differ greatly from one another. While the former pair (*RR/SS*) display unusually high resolution, the latter are characterized by a low degree of stereoselective recognition.

Apparently, the effect of the two chiral centres is cooperative in the former case, but competitive in the latter. Expressed differently, the antipode pair *RS/SR* display stronger "meso" character and the two enthalpy association vectors are thus closely similar in size, but antiparallel. The weak chiral recognition is thus not a consequence of the strength of the molecular interaction being too small. This is supported by the observation that the separation factor of S-dioxide enantiomers is even higher than that of methionine (Fig. 1).

Also noteworthy is the behaviour of the S-oxides of 2-methylmethionine. Whereas the enantiomers of 2-methylmethionine are not separated, the four S-oxide enantiomers and also the S-dioxide enantiomers are resolved. In general, the resolution of the 2-methylamino acids in chiral stationary phases is modest[14]. By the introduction of a further polar, hydrogen-bridging, yet non-chiral sulphone group, the separation is significantly improved. In this case also, the poor chiral recognition

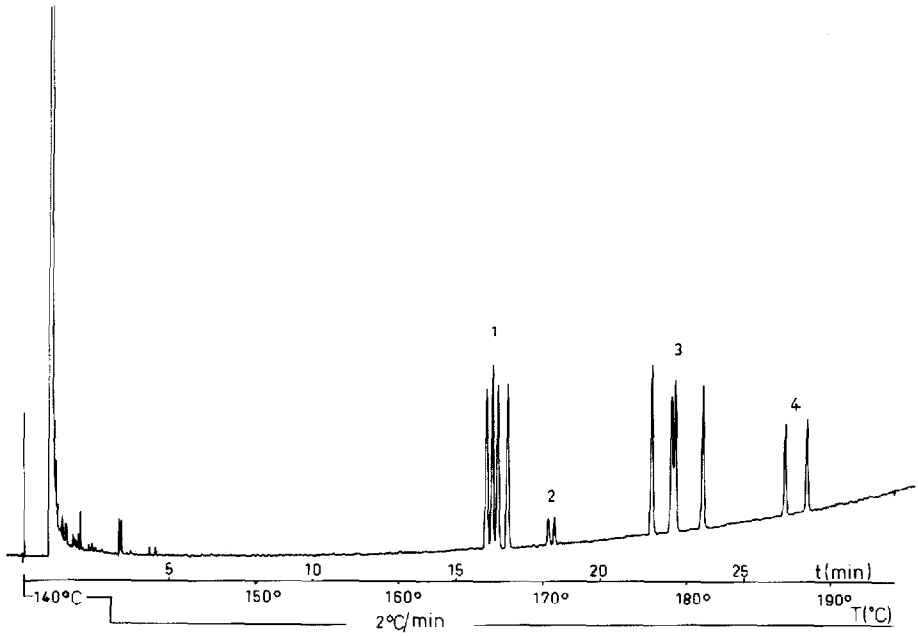

Fig. 1. Gas chromatographic separation of enantiomeric and diastereomeric pairs of (1) 2-methylmethionine-S-oxide (*RR*; *SR*; *RS*; *SS*), (2) 2-methylmethionine-S-oxide (*R*; *S*), (3) methionine-S-oxide (*RR*; *SR*; *RS*; *SS*), (4) methionine-S-dioxide (*R*: *S*); all N-(pentafluoropropionyl)-*n*-propyl ester derivatives. Conditions: column 20 m × 0.25 mm I.D. fused silica coated with Chirasil-Val; pressure, 0.4 bar; temperature of injector and detector, 250°C.

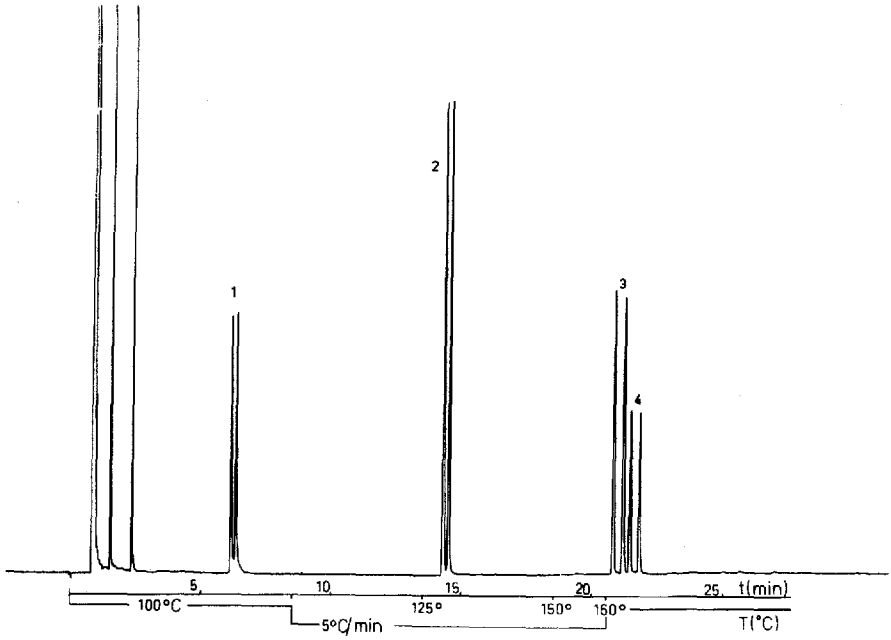

Fig. 2. Gas chromatographic separation of the enantiomers of (1) methylsulphinylmethyl methyl sulphide, (2) phenylisopropyl sulphoxide, (3) 2-aminoethyl methyl sulphoxide (PFP derivatives), (4) 2-aminoethyl methyl sulphoxide (TFA derivatives). Conditions as in Fig. 1.

is not due principally to an insufficiently strong association between selector and selectand, but rather to the possibility of competitive formation of two or more "elementary association complexes". The sulphone group leads to a stronger association and consequently to higher enthalpy differences.

Sulphoxides without a chiral carbon atom, such as N-PFP- (or TFA)-2-aminoethyl methyl sulphoxide, phenyl isopropyl sulphoxide and methylsulphinylmethyl methyl sulphide, may also be resolved into their enantiomers (Fig. 2). In the case of the sulphoxides without a further functional group, only one hydrogen bond from selector to selectand is possible; their resolution factors are lower, but nevertheless ample for complete resolution. This is probably due to a direct involvement of the chiral sulphur atom in the association complex, in contrast to carbon-centred chirality, where the association of chiral selector to selectand is brought about by neighbouring heteroatoms (C=O, N–H). Of particular interest is the separation of the enantiomers of methylsulphinylmethyl methyl sulphoxide, representative of the class of monooxodithioacetals, which, as protected aldehydes, are useful synthones[15,16].

CONCLUSIONS

S-Oxides (including purely aliphatic S-oxides) can be resolved by gas chromatography into their enantiomers on Chirasil-Val. The S-oxides are but one of many classes of chiral sulphur compounds; it is to be expected that further classes of chiral sulphur compounds (sulphoximines, sulphimines, etc.) are also amenable to enantiomeric resolution on Chirasil-Val.

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