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SEPARATION OF MESO AND RACEMIC 2,3-DIBROMOBUTANE-1,4-DIOL BY GAS CHROMATOGRAPHY

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SUMMARY

Meso and racemic forms of 2,3-dibromobutane-1,4-diol were separated by gas chromatography, but only in the form of derivatives. Silyl, acetyl and trifluoroacetyl derivatives were investigated on stationary phases of varying polarity. The meso isomers exhibited higher retention times on each column studied than the corresponding racemic isomers. Possible conformations were deduced from the elution order.

INTRODUCTION

The separation of several diastereomers of alkanes¹, alkenes², alcohols^{3,4}, esters⁴, halides^{5,6} and amides^{7,8} has been realized by gas chromatography (GC). Feibush and Spialter⁹ studied the differential gas-liquid chromatographic (GLC) behaviour of diastereomers of 2,3-dipentylbutanes and 2,4-dipentylpentanes. Nurok *et al.*¹⁰ studied the GLC behaviour of the diastereomeric esters of butane-2,3-diol. The racemic form had a higher retention volume than the meso form. Pritchard and Vollmer¹¹ investigated halogenated butane and pentane isomers where the halogen atoms were not adjacent. In this type of derivative it was the meso isomer which exhibited the longer retention time. Similarly, in racemic butane-2,3-diol isomers where there is a possibility of intramolecular hydrogen bonding it was the racemic isomer which exhibited the shorter retention time¹¹. According to Karger *et al.*¹², the separation of diastereoisomers may be explained by the different accessibility of polar functional groups to the stationary phase. Stern *et al.*⁵ have separated meso and racemic 2,3-dichlorobutane by preparative GC where the racemic isomer exhibited higher retention than the meso one.

In the present study the effects of trimethylsilyl, acetyl and trifluoroacetyl groups on the separation of meso and racemic 2,3-dibromobutane-1,4-diol isomers were examined. An attempt has been made to explain the relationship between the order of elution and the preferred conformers of meso and racemic derivatives.

EXPERIMENTAL

Materials

The silylating agents hexamethyldisilazane (HMDS) and (trimethylchlorosilane) (TMCS) were purchased from Pierce (Rockford, IL, U.S.A.), trifluoroacetic anhydride and acetic anhydride from Fluka (Buchs, Switzerland), and the stationary phases QF-1, OV-1 and PEGA on Gas-Chrom Q (80–100 mesh) were obtained from Applied Science Labs. (State College, PA, U.S.A.). The solvents were analytical grade.

meso-2,3-Dibromobutane-1,4-diol, m.p. 131°C, was prepared by a method described in the literature¹³. Racemic 2,3-dibromobutane-1,4-diol was synthesized according to the following method: 80 g of *cis*-2-butene-1,4-diol were treated with 18% aqueous bromine solution until the yellow colour of bromine appeared. The precipitated product was filtered off, washed with ice-cold water and recrystallized from toluene, yield 80%, m.p. 88°C (identical with that published in the literature¹⁴). The purity of the isomers was confirmed by GC.

Gas chromatographic conditions

An HP 5830A gas chromatograph provided with a flame ionization detector was used. The glass column (6 ft. × 4.00 mm I.D.) was packed with the stationary phases QF-1, OV-1 or PEGA on Gas-Chrom Q (80–100 mesh). Carrier gas (nitrogen) flow-rate: 45 ml/min. Column, detector and injection temperatures: 150°C, 240°C and 240°C, respectively. Chart speed: 0.6 cm/min.

Derivatization

The 1,4-bis(trimethylsilyloxy) derivatives of the *meso* and racemic 2,3-dibromobutane-1,4-diol isomers were prepared according to Sweeley *et al.*¹⁵. The 1,4-diacetoxy and 1,4-bis(trifluoroacetoxy) derivatives were synthesized at room temperature using acetic anhydride–pyridine (2:1) or trifluoroacetic anhydride–pyridine (2:1), respectively. The structure of the acetylated derivatives was confirmed by NMR spectroscopy.

RESULTS

The *meso* and racemic 2,3-dibromobutane-1,4-diols have four polar groups. Due to their interaction with the stationary phases applied, as well as to their low volatility, they could only be studied in the form of derivatives. Consequently the factors determining the efficiency of resolution were not intra- or intermolecular hydrogen bonding but orientation forces (temperature-dependent dipole–dipole interaction), induction and dispersion (both independent of temperature), donor–acceptor interaction, etc.

In Table I the relative retentions of the compounds, in Table II the separation factors, of the isomers are given. Comparing data determined at identical temperatures but with different stationary phases, it could be concluded that in the presence of the bulky trimethylsilyl group the separation is rather poor on both polar stationary phases QF-1 and PEGA compared to OV-1. The acetyl and trifluoroacetyl groups, however, having a lower shielding effect, induce higher relative volatility on the polar stationary phases than on the apolar OF-1 phase.

TABLE I

RELATIVE RETENTION DATA (n -HEXADECANE = 1.00) OF MESO AND RACEMIC 2,3-DIBROMOBUTANE-1,4-DIOL DERIVATIVES AT 150°CCorrelated retention times of n -hexadecane: 2.2 min on QF-1; 16.5 min on OV-1 and 0.8 min on PEGA.

Derivative	10% QF-1		10% OV-1		20% PEGA	
	meso	racemic	meso	racemic	meso	racemic
1,4-Bis(trimethylsilyloxy)	1.62	1.59	0.80	0.78	2.77	2.74
1,4-Diacetoxy	7.60	7.20	0.91	0.86	6.51	5.31
1,4-Bis(trifluoroacetoxy)	1.93	1.70	0.16	0.15	5.18	4.66

TABLE II

SEPARATION FACTORS (α) OF MESO AND RACEMIC 2,3-DIBROMOBUTANE-1,4-DIOL DERIVATIVES AT 150°C

$$\alpha = t_{\text{meso}}/t_{\text{racemic}}$$

Derivative	10% QF-1	10% OV-1	20% PEGA
1,4-Bis(trimethylsilyloxy)	1.01	1.03	1.01
1,4-Diacetoxy	1.06	1.06	1.22
1,4-Bis(trifluoroacetoxy)	1.13	1.07	1.11

When comparing the separation factors obtained only on the OV-1 stationary phase, a decrease is found from the trifluoroacetyl to the silyl derivatives. It may be assumed that the silyl group, compared to other protecting groups, causes the greatest reduction in configurational effect *i.e.*, the bulky apolar groups "dominate" the properties of the molecules. It is expected that, in the presence of bulky protecting groups, the relative extent of the intermolecular interactions of the polar functional groups in the meso and the racemic series may decrease. This would mean that the increase in the importance of dispersion effects relative to the dipole forces may be greatest in the presence of trimethylsilyl groups.

As regards elution order (Table I), the racemic isomers precede the meso isomers on every stationary phase applied. The elution order is influenced by the combined effect of a number of factors. For example the molecule contains both strongly polar moieties and rather bulky protecting groups. Also the stationary phase may promote or eventually reduce the separation. It is known that on polar columns both vapour pressure and solubility contribute to the separation. In Table III the standard

TABLE III

 $\Delta(\Delta G^\circ)$ VALUES OF MESO AND RACEMIC 2,3-DIBROMOBUTANE-1,4-DIOL DERIVATIVES AT 150°C $\Delta(\Delta G^\circ)$ = standard molar free energy difference (cal/mol) of solution.

Derivative	10% QF-1	10% OV-1	20% PEGA
1,4-Bis(trimethylsilyloxy)	-8.4	-24.8	-8.4
1,4-Diacetoxy	-49.0	-49.0	-167.1
1,4-Bis(trifluoroacetoxy)	-102.6	-56.8	-87.7

molar free energy differences of the isomer pairs are listed. It is seen from the $\Delta(\Delta G^0)$ values that the higher the negative values the higher are the solubility differences between the isomer pairs. As the conformations and the standard molar free energy differences are strongly correlated¹⁶, it is assumed that the stronger the stabilizing effect exerted by the stationary phase on the preferred conformers formed the better is the separation. The $\Delta(\Delta G^0)$ values were calculated from:

$$\Delta(\Delta G^0) = -RT \ln \alpha$$

The α values are in Table II.

Fig. 1 shows all possible conformers in both the meso (A, B and C) and the racemic (D, E and F) series. When comparing the energetically most stable conformer (A) to D and E, it can be seen that in conformer A, *i.e.*, in the meso series, the polar groups are "symmetrically" arranged whereas with the racemate both the major conformers D and E are polar, due to the "asymmetric" arrangement of the functional groups. As the meso compounds exhibited higher retention times than the racemates, the "symmetric" conformers must be able to form stronger interactions with the stationary phases. Considering the groups having the gauche conformation in the meso series, conformer A should exhibit stronger interactions with the stationary phase than conformers of gauche conformation in the racemic series (D and E). The large steric and dipole-dipole repulsion in the compounds may favour the conformation in which the Br atoms are at their farthest distance from each other. In this conformation the $-\text{CH}_2\text{OR}$ groups are *anti* to each other in the meso isomer (A), but would be substantially closer in the racemic (D) isomer.

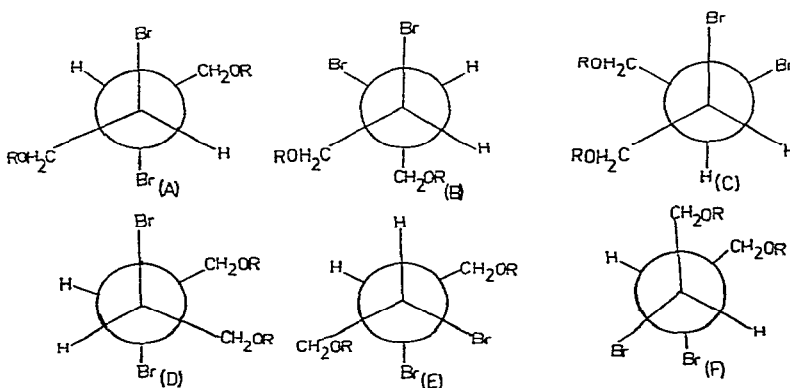


Fig. 1. The possible conformers of meso and racemic derivatives of 2,3-dibromobutane-1,4-diol. A, B and C = meso series; D, E and F = racemic series; R = trimethylsilyl, acetyl, trifluoroacetyl.

For 2,3-dibromobutane, *i.e.*, the same compound as in Fig. 1 but with $-\text{CH}_3$ substituted for $-\text{CH}_2\text{OR}$, Nurok *et al.*¹⁰ considered the population of conformers containing more gauche bromine groups in the racemic than in the meso series. The racemic series had a higher interaction with the stationary phase than the meso one on the basis of stabilization of aligned adjacent dipoles by the stationary phase. In the

2,3-dibromobutane-1,4-diol derivatives all the four polar groups have strong dipole interactions with the stationary phase. The stabilization of aligned and adjacent carbon-bromine dipoles by the stationary phases is hindered by the bulky $-\text{CH}_2\text{OR}$ groups. Due to the dispersion forces, the silyloxy, acetoxy as well as trifluoroacetoxy groups are relatively complex and this fact plays a significant role in the separation. It is supposed that the net attractive force may be greater in the racemic than in the meso series. This would mean a greater population of molecules with *syn*- CH_2OR groups in the racemic than in the meso series. Consequently an explanation for the trend may be that in the *gauche* conformation the interactions of the carbonyl group in the ester linkage and those of the oxygen atom in the ether linkage create an enhanced accessibility to the stationary phase with the meso series (A) compared with the racemic one (D).

Thus, it can be concluded that the separation of 2,3-dibromobutane-1,4-diol derivatives is rather poor in the presence of trimethylsilyl groups on the stationary phases studied. More efficient separation was attained with acetyl derivatives. The retention data and thermodynamic data obtained provide additional information on these molecules.

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