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Note

Cyclodextrins as chiral stationary phases in capillary gas chromatography

I. Pentylated α-cyclodextrin

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Carbohydrates have repeatedly been used as chiral selectors for the separation of enantiomers by liquid chromatography. A large number of racemic compounds have recently been resolved on microcrystalline triacetylcellulose[1,2], α- and β-cyclodextrins[3,4], carbohydrate derivatives covalently connected to aminopropyl silica gel[5,6] and polysaccharide derivatives adsorbed on silica gel[7,8].

Of these carbohydrate selectors, cyclodextrins are especially important. In addition to a large number of chiral centres for enantioselective interaction, these macrocyclic molecules may form diastereomeric inclusion complexes resulting in the selective retention of one enantiomer. The solubility of cyclodextrins in organic solvents also allows their application as stationary phases for gas chromatography. Koscielski *et al.*[9] have demonstrated the separation of enantiomers of terpenoid hydrocarbons on a packed column. We have increased the hydrophobicity of cyclodextrins by alkylation and used these derivatives as liquid phases for capillary gas chromatography. The fully pentylated α-cyclodextrin (Fig. 1) shows a remarkable enantioselectivity towards the enantiomers of carbohydrate derivatives and some nitrogen compounds.

EXPERIMENTAL

Gas chromatography

A Carlo Erba Model 2101 gas chromatograph with split inlet and a flame ionization detector was used.

Preparation of chiral capillary columns

Pyrex glass capillary columns were coated according to the static procedure[10] as described previously[11].

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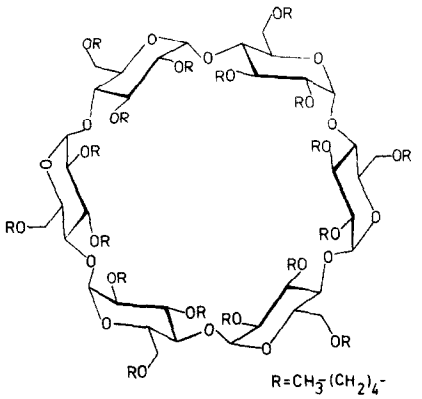

Fig. 1. Structure of per-O-pentyl-α-cyclodextrin used as chiral stationary phase.

Preparation of derivatives

Fully trifluoroacetylated sugars were prepared by heating samples of about 0.5 mg of carbohydrate in a mixture of 200 μl of dichloromethane and 50 μl of trifluoroacetic acid anhydride for 1 h at 100°C in a glass vial with a PTFE-lined screw-cap. Methylglycosides were prepared by heating sugars in 0.5 ml of dry hydrogen chloride in methanol (1.5 *M*) for 1 h at 100°C in glass vials. 1.5-Anhydroalditols (or 1,4-anhydroalditols) were formed according to the method described by Gray and co-workers[12,13]. For peralkylation of glucose a three-fold excess of the corresponding alkyl iodides, in the case of α-cyclodextrin pentylbromide, was added to the samples in dimethyl sulphoxide in the presence of 3 equiv. of sodium hydroxide, according to Ciucanu and Kerek[14].

RESULTS AND DISCUSSION

In most chiral stationary phases used for enantiomer separation by capillary gas chromatography, amino acids were used as optically active ligands[15]. Enantiomer resolution is mainly due to the formation of diastereomeric association complexes based on hydrogen bonding interactions. Only a few instances are known in which hydrogen bond association could definitely be ruled out but enantiomer separation is still observed[16,17]. In these instances dipole–dipole interactions may be responsible for chiral recognition.

The sepration of trifluoroacetylated hydroxy esters in capillary columns using stationary phases with optically active hydroxy acid derivatives as chiral selectors[18,19] and the separation of proline enantiomers on N-trifluoroacetyl-L-prolyl-L-proline cyclohexyl ester[16] demonstrates the beneficial effect of a close structural relationship between the chiral selector and the chiral substrate. This concept also seems to apply to the separation of carbohydrate derivatives on modified cyclodextrins. As shown in Figs. 2–6, the enantiomers of various carbohydrate derivatives can be separated on fully O-pentylated α-cyclodextrin. O-Trifluoroacetylated methylglycosides have also been separated on XE-60–L-valine-(*S*)-α-phenylethylamide[18,19], while pertrifluoroacetylated sugars could be separated particularly well

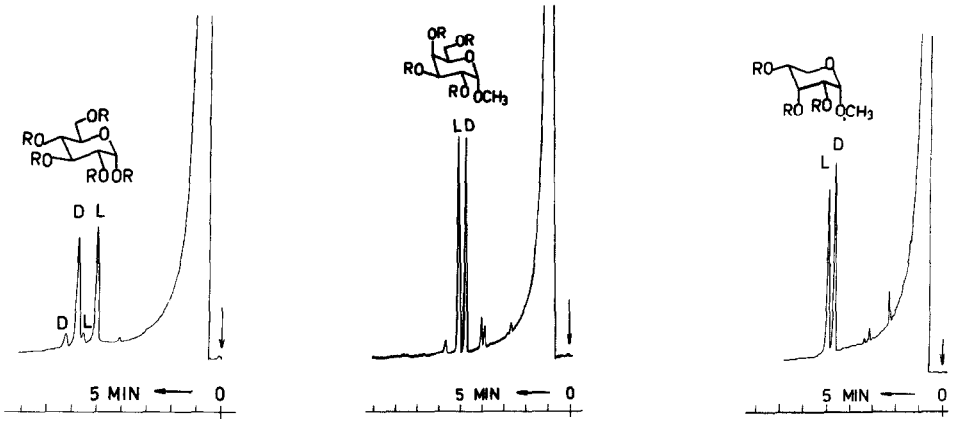

Fig. 2. Enantiomer separation of α- (large peaks) and β-glucopyranose (small peaks). R = CF_3CO. 20-m glass capillary column, coated with perpentylated α-cyclodextrin; column temperature, 100°C; carrier gas, 0.8 bar hydrogen.

Fig. 3. Enantiomer separation of α-methylgalactopyranoside. R = CF_3CO. Column as in Fig. 1; column temperature, 110°C.

Fig. 4. Enantiomer separation of α-methylribopyranoside. R = CF_3CO. Column as in Fig. 1; column temperature, 110°C.

on OV-225–L-valine-(*R*)-α-phenylethylamide[20]. Some polyols, including trifluoroacetylated arabinitol, were separated on XE-60–L-valine-(*R*)-α-phenylethylamide[21]. The 1,5-anhydroalditols (or 1,4-anhydroalditols) were formed during reductive depolymerization[22,23] in the course of structural investigations of complex polysaccharides. An example of the separation of these derivatives is shown in Fig. 6.

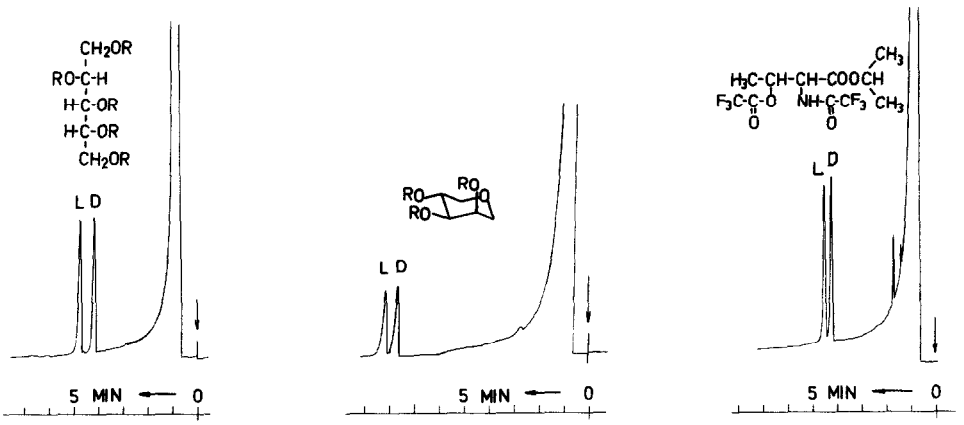

Fig. 5. Enantiomer separation of arabinitol. R = CF_3CO. Column as in Fig. 1; column temperature, 100°C.

Fig. 6. Enantiomer separation of 1,5-anhydrolyxitol. R = CF_3CO. Column as in Fig. 1; column temperature, 80°C.

Fig. 7. Enantiomer separation of N,O-trifluoroacetylthreonine isopropyl ester. Column as in Fig. 1; column temperature, 85°C.

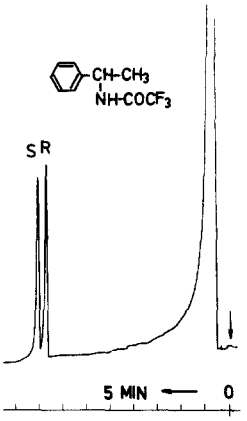

Fig. 8. Enantiomer separation of N-trifluoroacetyl-1-phenylethylamine. Column as in Fig. 1; column temperature, 100°C.

TABLE I

SEPARATION FACTORS, α, COLUMN TEMPERATURES AND ORDER OF ELUTION IN THE ENANTIOMER SEPARATION OF TRIFLUOROACETYLATED CARBOHYDRATE DERIVATIVES ON A 20-m GLASS CAPILLARY COLUMN, COATED WITH PER-*n*-PENTYL-α-CYCLODEXTRIN

Carbohydrate	α	*Column temperature (°C)*	*First peak eluted*
α-Glucose	1.119	100	L
β-Glucose	1.140	100	L
α-Galactose	1.070	100	L
β-Galactose	1.080	130	L
α-Allose	1.171	120	D
β-Allose	1.064	120	D
α-Mannose	1.000	100	—
β-Mannose	1.110	100	L
α-Gulose	1.000	120	—
β-Gulose	1.043	120	D
α-Talose	1.099	110	D
β-Fucose (f)*	1.039	100	L
α-Methylgalactoside	1.091	100	D
α-Methylglucoside	1.035	100	L
α-Methylmannoside	1.051	100	L
α-Methylidoside	1.040	90	D
α-Methylriboside	1.075	110	D
Sorbitol	1.042	100	D
Mannitol	1.019	90	D
Arabinitol	1.175	100	D
1,5-Anhydrofucitol	1.035	80	D
1,5-Anhydrolyxitol	1.064	80	D
1,5-Anhydroarabinitol	1.074	80	D
1,4-Anhydroribitol**	1.060	90	L
1,4-Anhydroxylitol**	1.029	80	L

* f = Furanoside.

** The corresponding 1,5-anhydro derivatives are non-chiral.

Compared with previous results with chiral polysiloxane phases, it can be stated that the separation of pertrifluoroactylated aldohexoses, aldopentoses and polyols is superior on perpentylated α-cyclodextrin. The methylglycosides of aldohexoses and some aldopentoses are also well separated on the cyclodextrin phase (Figs. 3 and 4). The results in terms of separation factors (α) are given in Table I.

In addition to carbohydrate derivatives, some trifluoroacetylated amines, amino alcohols and amino acid esters could be separated on perpentylated α-cyclodextrin, although the separation factors are generally lower than on the XE-60 phases. Fig. 7 shows an example of the separation of an amino acid derivative (DL-threonine). In Fig. 8 the separation of 1-phenylethylamine is shown.

The thermal stability of perpentylated α-cyclodextrin is remarkably high. No deterioration of column performance was observed after operation of the columns at 200°C. In conclusion, it can be stated that chemically modified cyclodextrins may well serve as chiral stationary phases in capillary gas chromatography.

Attempts to separate peralkylated glucose derivatives (permethyl, -ethyl and -propyl) failed. Therefore, it seems to be questionable whether the enantiomers are really separated owing to the formation of inclusion complexes inside the cavity of the macrocyclic cyclodextrin molecule or whether a more general type of diastereomeric association applies in this system.

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