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Note

Acylation effects on chiral recognition of racemic amines and alcohols by new polar and non-polar cyclodextrin derivative gas chromatographic phases

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Various derivatives of amino acids and peptides have been used as chiral stationary phases (CSPs) for gas chromatography (GC) since the initial work in the area[1–8]. The most widely used CSP of the genre, today, is Chirasil-Val (*i.e.*, L-valine-*tert.*-butylamide coupled to a siloxane copolymer[9,10]. Also, at that time, a number of investigators were attempting to use cyclodextrins as GC stationary phases[11–16]. Although interesting selectivities were obtained, the crystalline cyclodextrins were sometimes difficult to use and coat and were inefficient. In general, they had to be dissolved or dispersed in another solvent prior to use[11–18]. Of these, the permethylated cyclodextrins dissolved in traditional achiral GC liquid stationary phases seemed to give the best enantiomeric separations[17,18]. The role of cyclodextrins in chromatography paralleled that of other CSPs in that liquid chromatographic developments occurred much more rapidly in the last decade.

Recently, there have been reports on hydrophobic cyclodextrin derivatives that are effective CSPs in GC[19–22]. These liquid derivatives were directly coated on glass capillaries and shown to resolve a number of racemic solutes. We have developed a new polar, hydrophilic cyclodextrin derivative and have compared it to the alkyl derivative[23,24]. Very different properties and enantioselectivities were observed.

Often in chiral, as in achiral, GC analysis, it is necessary to increase the volatility of polar analytes by making less polar derivatives. For example, it is common practice to make acetyl or trifluoroacetyl derivatives of amines and alcohols, or esters from carboxylic acids. These reactions are simple and quantitative and go rapidly to completion under proper conditions. One factor which generally is not appreciated is that these achiral derivative groups can play a significant role in enantioselective separations. As will be shown in this communication, the choice of an acylation reagent can mean the difference between success or failure in obtaining an enantiomeric separation. In addition, an optimal acyl derivative for one CSP may be marginal or poor for another CSP. In a previous work, Charles and Gil-Av[3] found that the resolution of enantiomeric aminoalcohols improved somewhat as the size of the acyl derivative increased from propionyl to pivaloyl.

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EXPERIMENTAL

Materials

Fused-silica capillary tubing (0.25 mm I.D.) was obtained from Alltech. Dipentyl cyclodextrins (DP-CDs) were made as previously reported[22,24]. The heptakis (2,6-di-O-pentyl) cyclodextrins were made by reacting excess 1-bromopentane with 3.0 g of the desired cyclodextrin in 30 ml of dimethyl sulfoxide (DMSO) at 50°C for 2 h, then at room temperature for 24 h. The product was isolated by precipitation with water. The precipitate was washed and dissolved in chloroform. The chloroform solution was washed with water and the chloroform was evaporated to leave the product, which was subsequently vacuum-dried. Permethyl derivatives of O-[(*S*)-2-hydroxypropyl] cyclodextrin (PMHP-CD) mixtures were made in two steps. First, the respective cyclodextrin was dissolved in aqueous sodium hydroxide (5%, w/w) and the solution cooled in an ice-bath; then (*S*)-propylene oxide was slowly added while stirring. After about 6 h in an ice-bath the reaction was allowed to proceed for a day at room temperature, neutralized and dialyzed briefly in order to remove the contam-

TABLE I

COMPARISON OF GC SEPARATION DATA FOR DIFFERENT ACYL DERIVATIVES OF CHIRAL AMINES AND ALCOHOLS

Compound	*Optimal acyl group*[a]	α	R_s	*Range of R_s for other acyl derivatives*[b]	*Column*[c]
1-Aminoindane	$-\overset{\overset{O}{\|}}{C}-CH_3$	1.03	1.6	0–0.9	PMHP-β-CD
1,2,3,4-Tetrahydro-α--naphthylamine	$-\overset{\overset{O}{\|}}{C}-CH_3$ or $-\overset{\overset{O}{\|}}{C}-CF_3$	1.04	1.5	0.7–1.2	PMHP-β-CD
1-Phenylethylamine	$-\overset{\overset{O}{\|}}{C}-CH_3$	1.03	1.3	0–0.9	PMHP-β-CD
1-Methoxy-2-aminopropane	$-\overset{\overset{O}{\|}}{C}-CH_2Cl$	1.07	1.5	0–1.1	PMHP-β-CD
2-Amino-1-propanol	$-\overset{\overset{O}{\|}}{C}-CH_3$	1.04	1.5	0.8–1.2	PMHP-β-CD
1-(α-Naphthyl)-ethylamine	$-\overset{\overset{O}{\|}}{C}-CH_3$	1.02	1.4	0	PMHP-β-CD

(Continued on page 156)

TABLE I *(continued)*

Compound	*Optimal acyl group*[a]	α	R_s	*Range of R_s for other acyl derivatives*[b]	*Column*[c]
α-Amino-γ-butyro-lactone	O ‖ –C–CH_3	1.03	1.2	0–0.6	PMHP-β-CD
1,2,3,4-Tetrahydro-α-napthylamine	O ‖ –C–CH_3	1.02	1.4	0–0.5	DP-β-CD
2-Amino-1-hexanol	O ‖ N–C–CH_2Cl	1.01	1.1	0	PMHP-β-CD
1-Indanol	O ‖ –C–CF_3	1.01	1.0	0	PMHP-β-CD
1-Aminoindan	O ‖ –C–CF_3	1.31	2.8	1.1–1.3	DP-α-CD
2-Amino-4-methyl-1-butanol	Underivatized	1.11	1.5	0.4–1.3	PMHP-β-CD
trans-Cyclohexane-1,2-diol	O ‖ –C–CH_2Cl	1.05	1.4	0–1.0	PMHP-β-CD
1,2,3,4-Tetrahydro-1-naphthol	O ‖ –C–CH_3	1.07	1.2	0–0.6	DP-α-CD

[a] The optimal acyl group is the derivative that gave the best separation factor (α) and resolution (R_s) on the indicated column under optimized conditions.

[b] This resolution range was for all the other acyl derivatives tested (see Experimental for complete list)

[c] The abbreviation PMHP-β-CD stands for the permethyl-(*S*)-hydroxypropyl-β-cyclodextrin stationary phase. These columns were 30 m in length. The abbreviation DP-α-CD stands for the 2,6-O-dipentyl-α-cyclodextrin stationary phase. These columns were 20 m in length.

inating salts. The reformed solution was filtered and the product obtained by freeze-drying. Permethylation was achieved by a reaction with methyl iodide after the dissolution of cyclodextrin derivative in a solution of sodium hydride in DMSO[24,25]. Additional data on the make-up and properties of this compound are to be published subsequently. The capillaries were coated via the static method as previously reported[26].

Acetic anhydride, trifluoroacetic anhydride, chloroacetic anhydride, dichloro-

acetic anhydride and trichloroacetic anhydride were obtained from Aldrich. In each case, approximately 1.0 mg of the racemic analyte was dissolved in 0.5 ml of methylene chloride and 200 μl of the desired anhydride were added. After reaction, dry nitrogen was bubbled through the solution to remove excess reagent.

Methods

Both Hewlett-Packard (5710A) and Varian (3700) gas chromatographs were used for all separations. Split injection and flame ionization detection were utilized. The injection port temperature was 200°C and nitrogen was used as the carrier gas.

RESULTS AND DISCUSSION

A comparison of enantiomeric separation data for a variety of acyl-derivatized analytes is given in Table I. In each case the temperature was optimized to produce the highest resolution. It is apparent that enantioselectivity can be very dependent on the type of acylation reagent used. Indeed, in some cases, it can mean the difference between obtaining or not obtaining a separation of enantiomers. For the majority of compounds listed in Table I, there were one or more common racemic acyl derivatives that could not be resolved. Fig. 1 nicely illustrates this phenomenon. In this case, the

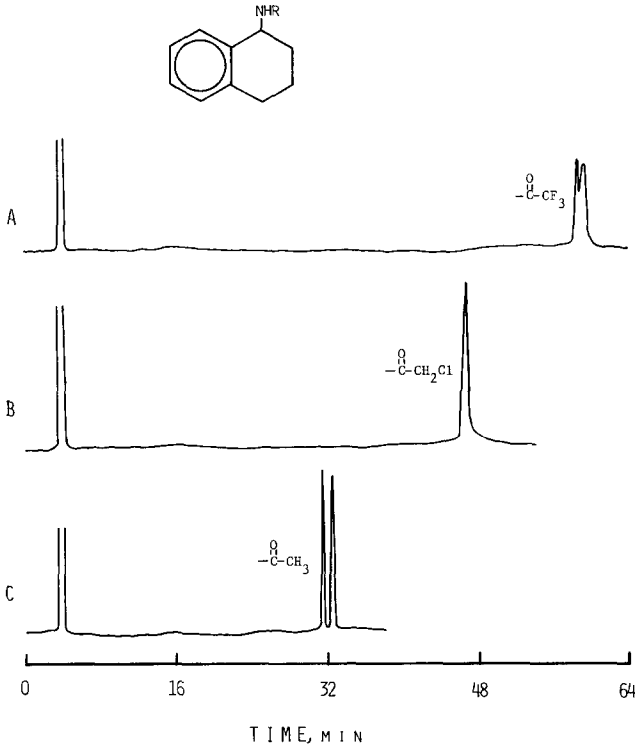

Fig. 1. Chromatograms comparing the resolution of three different acyl derivatives of racemic 1,2,3,4-tetrahydro-1-naphthylamine. The acetyl derivative (A) gave the best resolution while the monochloroacetyl derivative was unresolved (B). All separations were done on a 30-m fused-silica capillary coated with DP-β-CD. The column temperature for (A) was 130°C while it was 180°C for (B) and (C).

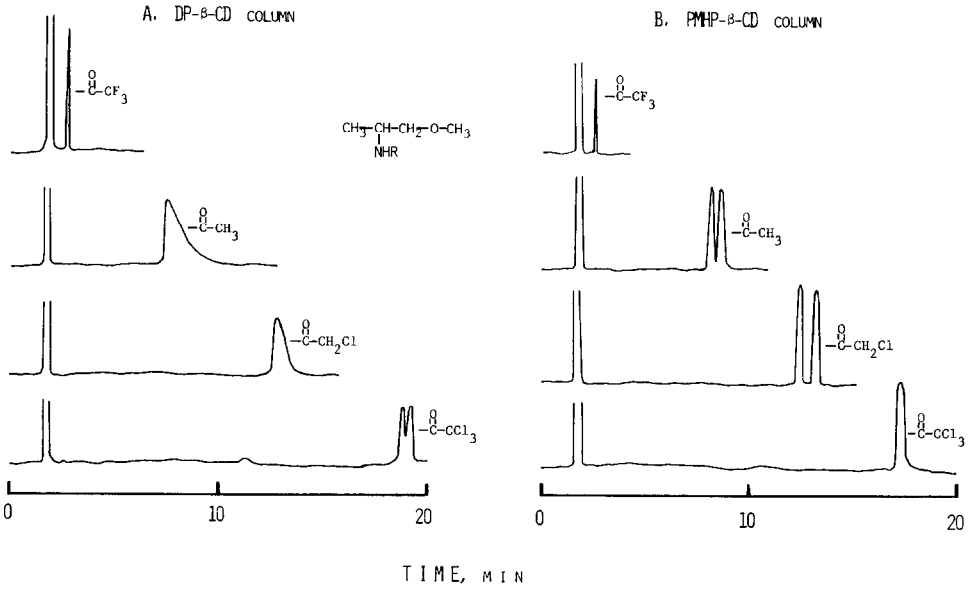

Fig. 2. Chromatograms showing the separation of different acyl derivatives of racemic 1-methoxy-2-aminopropane on two different cyclodextrin CSPs. On column A (DP-β-CD) only the trichloroacetyl derivative shows any resolution. On column B (PMHP-β-CD) only the monochloroactyl and acetyl derivative show resolution. Both columns were 30 m in length. The separations were done at 130°C.

monochloroacetyl-1,2,3,4-tetrahydro-1-naphthylamine was not resolved, while the trifluoroacetyl derivative shows partial resolution and the acetyl derivative is baseline-resolved.

Another interesting fact is that the best derivative of a racemate for one CSP may, or may not, be optimal for another CSP, even if the stationary phases are related as in the case of substituted cyclodextrins. Occasionally, one particular derivative resolves best on different CSPs; see, for example, the separation data for 1,2,3,4-tetrahydro-1-naphthylamine (acetyl derivative) on PMHP-β-CD and DP-β-CD columns (Table I). In other cases, completely different derivatives give better separations on these columns. This trend is shown for racemic 1-methoxy-2-aminopropane in Fig. 2. The acetyl derivative is baseline-separated on the PMHP-β-CD column but is unresolved on the DP-β-CD column. Conversely, the trichloroacetyl derivative is partially resolved on the DP-β-CD phase but is unresolved on the PMHP-β-CD column.

It is clear that when making simple acyl derivatives for chiral GC analysis, volatility cannot be the only consideration. Since one acyl derivative is as simple as another to make, it provides an additional parameter by which these separations can be optimized. Not only can a separation be improved by selecting the best derivative for a particular CSP, but sometimes it can mean the difference in obtaining any resolution. It has been reported that acylation of hydroxy compounds can lead to small separation factors when using the Chirasil-Val column[27]. This was thought to be due to the elimination of the donor functions for hydrogen bonding to the CSP[27]. This does not seem to be the case with the new derivatized cyclodextrin stationary phases. Indeed, there have been a number of separations of racemates that contain no hydrogen bonding groups, on these columns[17–24].

It is interesting to consider the role these closely related acyl groups play in chiral recognition. For example, the trifluoroacetyl and acetyl groups have about the same size and geometry. Any difference in the enantioselectivity of their analogues must be due to differences in polarity and hydrogen-bonding ability. On the other hand, the chlorinated acyl groups are much bulkier and steric factors may be important when they are used. In at least one case (1-methoxy-2-aminopropane, Fig. 2B) the trichloroacetyl derivative gave the best separation, possibly because it decreased the volatility of the solute, allowing it to interact with the CSP longer. In order to better understand these effects as they relate to cyclodextrins, thorough thermodynamic studies must be completed. Plots of retention *versus* the inverse of temperature have yet to show enantiomeric reversals for these CSPs[23,24]. However, one thing is clear. From a practical stand-point, acylation offers the chromatographer a facile way to improve marginal separations when all other parameters have been optimized. Currently, we are further evaluating the role of different acyl groups in chiral recognition using gas phase calorimetry, computer modeling and energy minimization calculations.

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