

Short Communication

Improved enantiomeric separation with a 2,6-di-O-pentyl-3-O-trifluoroacetylated β -cyclodextrin and OV-7 mixed stationary phase chiral capillary column

Hong Wan, Yi Wang, Qingyu Ou* and Weile Yu

Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000 (China)

(First received November 9th, 1992; revised manuscript received March 1st, 1993)

ABSTRACT

2,6-Di-O-pentyl-3-O-trifluoroacetylated β -cyclodextrin (DP-TFA- β -CD) as a chiral stationary phase was synthesized and characterized by two-dimensional NMR spectrometry. A chiral fused-silica capillary column prepared by using a mixed stationary phase of DP-TFA- β -CD and OV-7 possesses a high column efficiency of >4100 plates/m and displays better thermal stability than a column coated with DP-TFA- β -CD alone. Enantiomers such as alcohols, diols, γ -lactones and amines could be separated in relatively short time.

INTRODUCTION

Cyclodextrin (CD) derivatives as chiral stationary phases (CSPs) for the gas chromatographic (GC) separation of enantiomers have attracted interest in recent years. Much progress has been made since Juvancz *et al.* [1] used permethylated β -CD for separating some optical isomers on glass capillary columns in 1987, and König and co-workers [2,3] introduced hydrophobic groups into CDs in 1988. Since then, a variety of derivatized α -, β -, and γ -cyclodextrin CSPs have been synthesized [4–10] and used in GC separations of chiral components in foods and beverages [11], essential oils [12], petroleum

and coal [13]. Permethylated β -CD and dipentyl acetylated- β -CD have been used extensively. Owing to their high melting points, permethylated CDs are usually dissolved in polysiloxanes such as OV-1701 to obtain a high column efficiency [14]. Schmarr *et al.* [15] showed that the diluted cyclodextrin derivatives decreased the enantioselectivity for enantiomers. Keim *et al.* [10] demonstrated however, that in some instances, the dilution could improve the physical properties of cyclodextrin derivatives even for these viscous fluids by dissolving them in a polysiloxane liquid phase. Li *et al.* [9] demonstrated the high enantioselectivity of dipentyl trifluoroacetylated cyclodextrin for a number of enantiomers, but the thermal stability of column was below 180°C.

In this work, 2,6-di-O-pentyl-3-O-trifluoro-

* Corresponding author.

acetylated β -CD(DP-TFA- β -CD) was synthesized and characterized by two-dimensional NMR. The enantioselectivity and thermal stability of a chiral column coated with a mixed stationary phase of DP-TFA- β -CD and conventional OV-7 were examined.

EXPERIMENTAL

Synthesis of 2,6-di-O-pentyl-3-O-trifluoroacetylated- β -CD

A 5.6-g (5-mmol) amount of dry β -CD was dissolved in 100 ml of dry dimethyl sulphoxide and 8 g (20 mmol) of pulverized NaOH and 30 ml of 1-bromopentane were added. The mixture was stirred at room temperature for 5 days, then poured into water and extracted three times with chloroform. The organic layer was washed with water until neutral and dried over Na_2SO_4 . After evaporating the solvent, the product was dried at 60°C for 8 h under vacuum and further purified by gel chromatography, giving 9.3 g of 2,6-di-O-pentyl- β -CD (DP- β -CD) with a yield of 88%. Elemental analysis gave C 63.44, H 9.66; required for $(\text{C}_{16}\text{H}_{30}\text{O}_5)_7$, C, 63.54, H 10.00%.

A 4-g amount of DP- β -CD was dissolved in 80 ml dry tetrahydrofuran, a fivefold excess of trifluoroacetic anhydride was added and the mixture was refluxed for 8 h, then poured over ice to precipitate the product. The product was extracted with diisopropyl ether and washed with 5% aqueous NaHCO_3 and water. The organic layer was dried over Na_2SO_4 and concentrated by evaporation of the solvent. The raw product was dried at 50°C for 6 h under vacuum, purified by gel chromatography and a viscous liquid of DP-TFA- β -CD was obtained with a yield of 82%; $R_f = 0.56$ [*n*-hexane–diisopropyl ether (4:6)]. Elemental analysis gave C 49.25, H 6.64; $(\text{C}_{18}\text{H}_{29}\text{O}_6\text{F}_3)_7$ requires C 54.26, H 7.34%. $[\alpha]_D^{21} = +42.5$ (*c* 0.41, CHCl_3). ^1H NMR (400 MHz, CDCl_3) δ (ppm) 0.81–0.98 (m, 6H, H-5'), 1.10–1.94 (m, 12H, H-2', H-3', H-4'), 3.30–4.48 (m, 4H, H-1'), 3.30–4.48 (m, 5H, H-2, H-4, H-5, H-6), 5.01 (d, 1H, $^3J = 3.4$ Hz, H-1), 5.37 (m, 1H, H-3). ^{13}C -NMR (100 Hz, CDCl_3) δ (ppm) 13.80, 13.96 (C-5'), 22.35, 22.48 (C-4'), 24.49, 25.19, 25.75 (C-3'), 27.61, 28.36, 29.00, 29.34 (C-2'), 67.19, 68.02, 69.98, 71.69, 71.91 (C-1'), 68.92 (C-6), 71.25 (C-5), 76.69 (C-4),

76.18 (C-3), 77.72 (C-2), 98.78 (C-1), 114.48, 114.55, 114.68 (dd, C-2', $J_{\text{C-F}} = 285.3$ Hz), 1550.03, 157.40, 157.71 (dd, C-1', $^2J_{\text{C-F}} = 42.7$ Hz).

Preparation of chiral capillary columns

A 38 m \times 0.26 mm I.D. glass capillary tube was first coated with a layer of Celite 545 by the organic gel method, then deactivated with DPTMDS–HMDS (1:2, v/v)^a at 400°C for 12 h. The pretreated glass capillary tube was coated with a 3% solution of DP-TFA- β -CD in diisopropyl ether by a superdynamic method as described [16].

A 40 m \times 0.26 mm I.D. fused-silica capillary tube was coated as above by using a 3% solution of a mixed stationary phase of DP-TFA- β -CD and OV-7 (2:1, w/w) in diisopropyl ether after it had been heated at 280°C for 2 h under a flow of nitrogen. It took only 1 h to coat the column. The finished columns showed a high column efficiency of above 4100 plates/m at 140°C using *n*-dodecane as the test solute.

Instrumentation

All chromatographic measurements were performed on a Model 1001 gas chromatograph (Shanghai Analytical Instrumentation Factory), equipped with a flame ionization detector and an HP-3390A integrator. High-purity nitrogen was used as the carrier gas at a velocity of ca. 25 cm/s, with a splitting ratio of 1:60.

Racemates

Most of the volatile racemates were commercial products. Some diols and amines were synthesized by Dr. Zhao Jun of this Institute. All compounds containing hydroxyl and/or amine functional groups were converted into their trifluoroacetyl derivatives before chromatographic analysis.

RESULTS AND DISCUSSION

Some peralkylated cyclodextrins have been characterized by NMR spectrometry [10,17], but

^a DPTMDS = 1,3 - diphenyl - 1,1,3,3 - tetramethyldisilane, HMDS = hexamethyldisilane.

TABLE I
 α , k'_1 AND R_s VALUES FOR SOME ENANTIOMERS






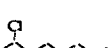


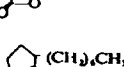



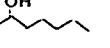




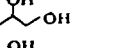
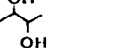
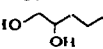
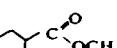
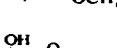


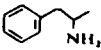



Racemate	Structure	Temperature (°C)	α	k'_1	R_s
2-Bromobutane		40	1.078	2.14	1.12
2-Bromopentane		40	1.030	3.96	0.88
2-Bromoheptane		80	1.039	2.40	2.45
2-Bromooctane		80	1.040	5.00	2.58
2-Chloroheptane		60	1.058	1.63	2.31
2-Chlorooctane		60	1.052	4.34	1.97
Epichlorhydrin		70	1.260	1.47	3.89
γ -Heptalactone		140	1.282	1.92	7.42
γ -Undecalactone		170	1.043	4.48	2.09
2-Butanol		40	1.302	0.42	4.24
2-Pentanol		40	1.290	0.88	6.85
2-Heptanol		50	1.270	3.51	11.6
2-Octanol		80	1.180	2.51	7.18
3-Methyl-2-Butanol		40	1.243	0.81	4.42
2-Methyl-3-Butanol		40	1.023	3.26	0.81
1,2-Propanediol		60	1.290	3.40	9.02
2,3-Butanediol		60	1.964	1.52	20.6
1,2,4-Butanetriol		130	1.071	2.48	1.53
Methyl 2-Methylbutyrate		80	1.025	5.14	1.51
Ethyl 2-hydroxypropionate		70	1.074	2.42	1.80
Methyl 2-aminobutyrate		140	1.178	1.76	10.1
Methyl 2-aminoisobutyrate		140	1.280	1.60	12.2
1-Phenylethanol		80	1.051	3.18	3.25

TABLE I (continued)

Racemate	Structure	Temperature (°C)	α	k'_1	R_s
1-Phenylethylamine		125	1.042	3.32	2.77
1-Phenyl-2-propylamine		125	1.036	5.81	2.41
2,4-Pentanediol		90	1.110	1.57	4.81
2,5-Hexanediol		90	1.060	2.70	2.43
2-O-Acetylated propion aldehyde		140	1.221	1.77	8.55

no NMR or elemental analysis data have been reported for dipentylacetylated or trifluoroacetylated cyclodextrins, probably it was too difficult to obtain these derivatives in pure form. Our results with two-dimensional NMR with ^1H - ^1H COSY, ^1H - ^{13}C HETCOR and DEPT techniques showed that DP- β -CD was relatively pure and its ^1H and ^{13}C NMR data were consistent with published data [18]. With DP-TFA- β -CD we were puzzled at the fact that its elemental analysis data were much lower than the calculated values as no impurities were detected in DP-TFA- β -CD by NMR spectrometry. Considering that the sample had been carefully dried before analysis, the most likely explanation

would be inclusion of solvent. The enantiomeric separation data on the mixed stationary phase for some resolved compounds are given in Table I.

Figs. 1–4 illustrate some typical enantiomeric separations on a 40-m fused-silica capillary column coated with a mixed stationary phase of DP-TFA- β -CD and OV-7, with nitrogen at 24 p.s.i. as the carrier gas.

Table II gives a comparative separation of four enantiomers with different functional groups using DP-TFA- β -CD alone and a mixed stationary phase of DP-TFA- β -CD and OV-7. A better enantiomeric separation was obtained with the

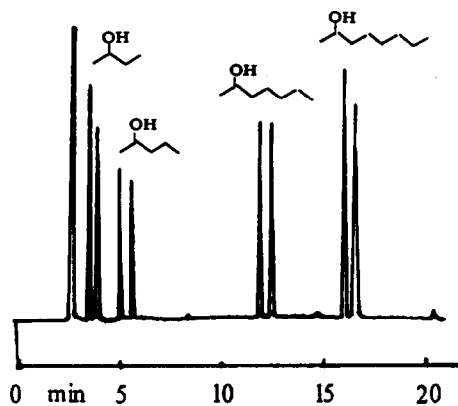


Fig. 1. Enantiomer separation of trifluoroacetylated alcohols. Column temperature, 40°C held for 4 min, then programmed to 80°C at 3°C/min.

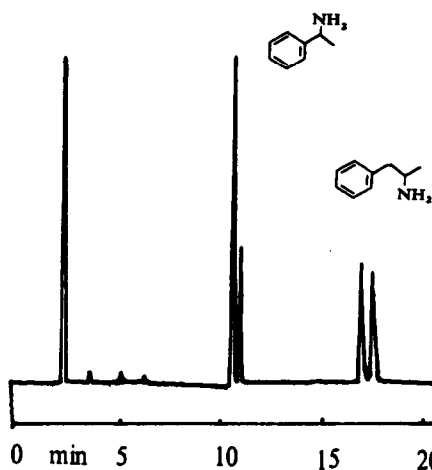


Fig. 2. Enantiomer separation of trifluoroacetylated amines. Column temperature, 125°C.



Fig. 3. Enantiomer separation of 2-O-acetylated propion aldehyde. Column temperature 150°C.

mixed stationary phase at lower temperature and in a shorter time, and the enantioselectivity of the DP-TFA- β -CD stationary phase was less affected when it was mixed with a small proportion of conventional polysiloxane OV-7.

Although Li *et al.* [9] found that DP-TFA- β -CD wets an untreated fused-silica capillary wall, the film was unstable above 180° and the column efficiency decreased dramatically after it had been used above 200°C. In this work, using a

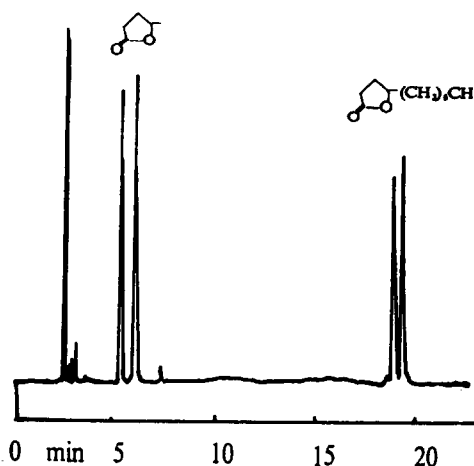
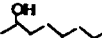
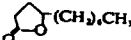




Fig. 4. Enantiomer separation of γ -lactones. Column temperature, programmed from 140 to 190°C at 2°C/min.

column coated with DP-TFA- β -CD alone, we also observed apparent droplets of stationary phase on the capillary wall after raising the column temperature to above 180°. However by using the mixed stationary phase, an easily prepared column with high efficiency can be used continuously at 210°C for 4 h without a decrease in efficiency. We have used this fused-silica capillary column for 6 months with over 2000 injections with virtually no decrease in k'_1 . These

TABLE II

ENANTIOMERIC SEPARATION DATA OBTAINED ON SINGLE AND MIXED STATIONARY PHASES

Enantiomer	Column							
	DP-TFA- β -CD (38 m \times 0.26 mm I.D.)			DP-TFA- β -CD + OV-7 (40 m \times 0.26 mm I.D.)				
	Temperature (°C)	t'_R (min)	α	R_s	Temperature (°C)	t'_R (min)	α	R_s
	80	8.09	1.068	4.14	70	7.54	1.078	4.84
	180	15.1	1.043	1.91	170	12.6	1.043	2.09
	140	8.56	1.035	1.59	130	6.32	1.038	2.66
	90	3.84	1.190	6.49	80	2.77	1.200	6.91

results demonstrate that the thermal stability of the chiral column was improved considerably by mixing a polysiloxane with a viscous liquid cyclodextrin derivative.

ACKNOWLEDGEMENT

This work was supported by the National Natural Science Foundation of China.

REFERENCES

- 1 Z. Juvancz, G. Alexander and J. Szejtli, *J. High Resolut. Chromatogr. Chromatogr. Commun.*, 10 (1987) 105.
- 2 W.A. Konig, S. Lutz and G. Wenz, *Angew. Chem., Int. Ed. Engl.*, 27 (1988) 979.
- 3 W.A. Konig, S. Lutz, P. Mischnick-Lubbecke, B. Brassat and G. Wenz, *J. Chromatogr.*, 447 (1988) 193.
- 4 W.A. Konig, S. Lutz, C. Colberg and N. Schmidt, *J. High Resolut. Chromatogr. Chromatogr. Commun.*, 11 (1988) 621.
- 5 W.A. Konig, R. Krebber and P. Mischnick-Lubbecke, *J. High Resolut. Chromatogr.*, 12 (1989) 732.
- 6 W.A. Konig, *J. High Resolut. Chromatogr.*, 12 (1989) 790.
- 7 D.W. Armstrong, W. Li, C.-D. Chang and J. Pitha, *Anal. Chem.*, 62 (1990) 914.
- 8 W.A. Konig, D. Ichtlef, T. Runge, I. Pforr and A. Krebs, *J. High Resolut. Chromatogr.*, 13 (1990) 702.
- 9 Y. Li, H.-L. Jin and D.W. Armstrong, *J. Chromatogr.*, 509 (1990) 303.
- 10 W. Keim, A. Konnes, W. Meltzow and H. Romer, *J. High Resolut. Chromatogr.*, 14 (1990) 507.
- 11 A. Mosandl, U. Plener, U. Hagerauer-Hener and A. Kusterman, *J. High Resolut. Chromatogr.*, 12 (1989) 532.
- 12 W.A. Konig, R. Krebber, P. Evers and G. Brachn, *J. High Resolut. Chromatogr.*, 13 (1990) 328.
- 13 D.W. Armstrong, Y.-B. Tang and J. Zukonski, *Anal. Chem.*, 63 (1991) 2858.
- 14 H.-P. Nowotny, D. Schmalzing, D. Wistuba and V. Schurig, *J. High Resolut. Chromatogr. Chromatogr. Commun.*, 12 (1988) 383.
- 15 H.-G. Schmarr, A. Mosandl, H.-P. Neukom and K. Grob, *J. High Resolut. Chromatogr.*, 14 (1991) 207.
- 16 H. Wan and Q. Ou, *Fenxi Huaxue*, 20 (1992) 394.
- 17 G. Wenz, P. Mischnick-Lubbecke, R. Krebber, M. Richters and W. A. Konig, *J. High Resolut. Chromatogr.*, 13 (1990) 724.
- 18 W. Meier-Augenstein, B.V. Burger and H.S.C. Spies, *Magn. Reson. Chem.*, 29 (1991) 681.