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Carbamate Derivatives of β-Cyclodextrin as Chiral Stationary Phases for Metal Capillary Gas Chromatography

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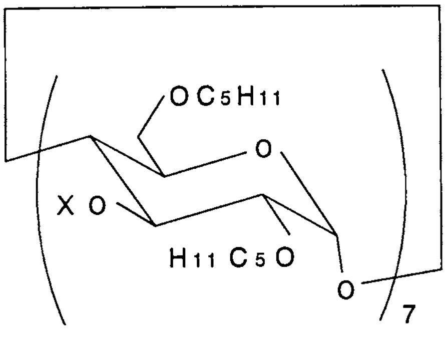
Three kinds of novel chiral stationary phases for capillary gas chromatography, heptakis(2,6-di-*O*-pentyl)-β-cyclodextrin hepta(3-n-propyl, 3-isopropyl, and 3-phenylcarbamate), were prepared. Metal capillary columns coated with the stationary phases showed impressive enantioseparation toward many kinds of racemic compounds.

Chiral separation by gas chromatography (GC) is a simple and effective method for the determination of enantiomer enrichment.1) The chiral stationary phases are, however, very limited. Polysiloxanes coupled with L-valine derivatives, Chirasilval2) and XE-60-L-valine-(*S*)-α-phenylethylamide,3) that utilize hydrogen bonding interactions for the enantiomer separation, had been the only available chiral stationary phases for GC. Recently, new types of chiral stationary phases were prepared from cyclodextrin (CD), namely, perpentylated CD and 2,6-di-*O*-pentyl-3-*O*-acetyl-CD.4) The fused silica capillary columns coated with them showed impressive enantiomer separations of many kinds of enantiomers by the mechanism of formation of inclusion complex, and it is now possible to separate samples that do not have hydrogen bonding interactions, such as alkenes and alkyl halides. Various types of CD derivatization are being investigated extensively as chiral stationary phases for GC.5) In this report, we would like to present our attempt to prepare new chiral stationary phases for GC that utilize both inclusion and hydrogen bonding interactions by introducing carbamate functions to CD.

CD carbamates were prepared as follows. β-CD was reacted with NaOH and n-amyl bromide in dry DMSO to give 2,6-di-*O*-pentyl-β-CD,6) which was heated to reflux with three kinds of isocyanates in pyridine for 2 days. Three CD derivatives, heptakis(2,6-di-*O*-pentyl)-β-CD hepta(3-n-propyl(**1**), 3-isopropyl(**2**), and 3-phenylcarbamate(**3**)), were obtained as yellow viscous oil. The structure was confirmed by IR7) and ^{1}H-NMR. Perpentylated β-CD(**4**) and acetylated β-CD(**5**) also were prepared for comparison. They were coated statically on deactivated metal capillary columns (35 m, 0.25 mm i.d.). The thickness of the chiral stationary phases were 0.2 μm.



1 : $X = CONH(CH_2)_2CH_3$
2 : $X = CONHCH(CH_3)_2$
3 : $X = CONHC_6H_5$
4 : $X = C_5H_{11}$
5 : $X = COCH_3$

Grob's test of the columns gave sharp peaks, which guarantees that the columns were well coated and extremely inert. Polarity value, k' (1–octanol) / k' (n–decane), measured at 100 °C was 7.26, 7.27, and 6.31 for **1**, **2**, and **3**, respectively. Those for **4** and **5** were 4.44 and 7.60. This means that the polarity of the carbamates are close to the acetyl derivative.

The columns were evaluated with several kinds of racemic compounds. The results, together with those using commercial Chirasil–val (**6**) obtained from Alltech Applied Science (25 m, 0.25 mm i.d.), are shown in Table 1. Full (base–line) resolution was always achieved when α was more than 1.06, and often achieved even when α was as small as 1.02. Moderate resolution was achieved when α was between 1.01 and 1.05. Slight resolution, which means that only the top of the peak was resolved, was achieved when α was less than 1.01. α value of 1.00 (actually α<1.005) means slight resolution, while α value of 1 means no resolution.

Chiral recognition of the carbamates (**1**, **2**, and **3**) was found to be different from that of the previously known CD derivatives (**4** and **5**). CD carbamates enabled good separation of samples that have amide or urethane functions, such as **12** and **15**, as shown in Fig. 1. This may be due to the hydrogen bonding interactions caused by the introduction of urethane linkages to CD. Free carboxylic acid (**21**), free alcohols (**13**, **16**), and free amine (**11**), that cannot be separated by the perpentyl (**4**) or acetyl CD (**5**), can be separated by these urethane CDs. The chiral recognition of n–propyl and isopropylcarbamates (**1** and **2**) is almost the same. Phenylcarbamate (**3**) is somewhat different from the above two carbamates; it enables separation of samples, 2–nonanol (**16**) and lactones (**19**, **20**) for example, that cannot be separated by the alkyl carbamates. Commercial Chirasil–val (**6**) could not seperate most of the above compounds, though it is very effective toward amino acid derivatives, and most of the amino acids, derivatized by reacting first with isopropyl alcohol and then with trifluoroacetic anhydride, were fully resolved. Urethane CDs (**1**–**3**) resolved amino acid derivatives better than **4** and **5**. Alanine derivative was resolved with every chiral column. Out of the other five amino acid derivatives examined (valine(**22**), phenylalanine(**23**), aspartic acid(**24**), serine(**25**), and 3–amino–n–butyric acid(**26**)), **1** resolved three compounds (**24**, **25**, and **26**), **2** resolved four compounds (**22**, **24**, **25**, and **26**), **3** resolved four compounds (**22**, **23**, **25**, and **26**), **4** resolved two compounds (**23** and **25**), and **5** resolved two compounds (**22** and **26**).

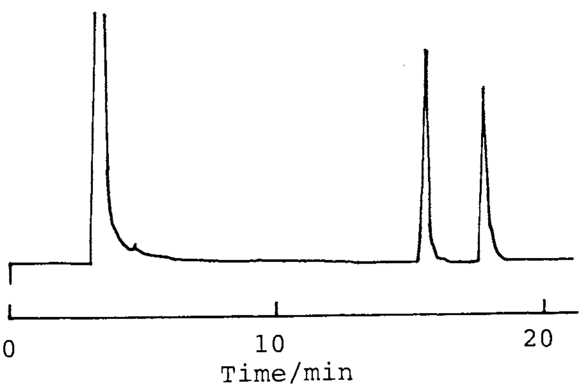


Fig.1. Chromatogram of trifluoro–acetylated α–phenylethylamine(**12**) on a metal capillary column coated with **3**. Column temp 150 °C const.

The mechanism of enantiomer separation with CD derivatives is not fully understood, but the size of the cavity is apparently working in most cases. As demonstrated above, these carbamate derivatives of CD are promising as chiral stationary phases for GC. The preparation and characterization of carbamate derivatives of α– and γ–CD are currently under way.

Table 1. Enantiomer separation by chiral metal capillary columns[a)]

Sample		Chiral column					
		1	**2**	**3**	**4**	**5**	**6**
α-Phenylethylamine (**11**)	α	1.02	1	1	1	1	1
	temp	130	130	120	130	140	1.40
	k'	4.88	3.31	3.10	2.95	2.04	1.23
α-Phenylethylamine (**12**) (Trifluoroacetylated)	α	1.06	1.20	1.18	1.05	1.07	1.05
	temp	145	145	150	115	150	120
	k'	9.90	8.51	4.18	5.91	4.50	5.34
α-Phenylethylalcohol (**13**)	α	1.03	1.01	1.02	1	1	1
	temp	120	120	120	130	130	110
	k'	5.49	8.82	5.97	2.42	3.23	1.58
α-Phenylethylalcohol (**14**) (Trifluoroacetylated)	α	1	1.05	1.03	1	1	1
	temp	100	100	90	100	100	80
	k'	4.59	4.27	4.92	2.04	2.46	1.23
α-Phenylethylalcohol (**15**) (isopropyl carbamate)	α	1.04	1.03	1.02	1	1.00	1.03
	temp	170	170	170	160	160	150
	k'	13.3	9.33	6.51	5.42	15.1	4.50
2-Nonanol (**16**)	α	1	1	1.04	1	1	1
	temp	120	120	100	130	130	80
	k'	11.1	8.59	13.4	1.87	2.07	1.56
Propylene carbonate (**17**)	α	1	1	1	1.04	1.13	1
	temp	150	150	140	100	180	110
	k'	2.25	2.19	2.34	3.09	0.72	0.96
2,3-Butylene carbonate (**18**)	α	1	1	1.05	1.21	1.14	1.00
	temp	140	140	140	100	180	80
	k'	3.02	3.31	2.58	2.69	1.71	3.28
γ-n-Octalactone (**19**)	α	1	1	1.01	1	1.02	1
	temp	170	170	170	160	160	150
	k'	3.67	4.58	3.27	1.79	2.73	2.10
γ-Decalactone (**20**)	α	1	1	1.02	1	1.01	1.01
	temp	170	170	170	160	170	150
	k'	12.2	13.6	10.1	5.41	5.74	6.48
2-Ethyl hexanoic acid (**21**)	α	1.01	1.02	1.01	1	1	1
	temp	130	140	150	150	160	150
	k'	14.6	9.17	4.57	2.11	5.98	2.33

a) k' is for the first eluting isomer.

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7) 3400 cm^{-1}(νN-H), and 1700 cm^{-1}(νC=O).

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