Separation of Cyclopropane Derivatives with Multichiral Centers by Gas Chromatography on Modified β-Cyclodextrin Stationary Phase

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A new pyridine heterocyclic β-cyclodextrin derivative, heptakis[2,6-di-*O*-pentyl-3-*O*-(2-chloro-5-pyridyl)methyl]-β-CD, was synthesized and explored as chiral stationary phase in capillary gas chromatographic separation. Cyclopropane derivatives with two chiral centers including four configurational isomers or three chiral centers including eight configurational isomers were well separated, which indicated the new pyridyl β-CD derivative possessing excellent chiral selectivity for separation of complex compounds including multichiral centers.

Because having good biological properties,[1,2] substituted cyclopropanes are widely used as chiral building blocks in insecticides and medicines. Most of chiral cyclopropane derivatives such as the photodegradable and low mammalian-toxic pyrethroids are prepared by the method of asymmetric synthesis but a few of them are purified from natural products.[3] Therefore, an attempt has been focused on the stereo-controlled synthesis for high optical pure substituted cyclopropanes.[4] Many methods for monitoring the reaction progress and determinating enantiomeric purity have also been developed.[5–7] Among them, chiral gas chromatography (GC) technique is a very important analytical method for separating chiral compounds.[8]

The characterization of stationary phase is the key to enantioselective separation in chiral GC. Although different kinds of materials have been prepared as chiral stationary phases, modified β-cyclodextrins (β-CDs) are the most frequently used for their excellent chiral separation abilities.[9–12] However, it is difficult to choose an appropriate and efficient stationary phase for separating chiral cyclopropane compounds.[13] So far, there are few reports on the separation of cyclopropane compounds with multichiral centers in GC.

In this study, we explored a new pyridyl β-CD derivative, heptakis[2,6-di-*O*-pentyl-3-*O*-(2-chloro-5-pyridyl)methyl]-β-CD, as a chiral stationary phase to separate cyclopropane derivatives with multichiral centers. The results show that this β-CD derivative possesses excellent chiral recognition and cyclopropane derivatives with three-chiral centers including eight configurational isomers could be separated.

The synthesis of the β-CD derivative was as follows: In the protection of nitrogen gas, 2.6 g (14.9 mmol) of sodium hydride was transferred into a three-necked, round-bottomed flask. The prepared 3.0 g (1.4 mmol) of 2,6-di-*O*-pentyl-β-CD dissolved in 50 mL of anhydrous tetrahydrofuran (THF) was added to the reaction flask via the dropping funnel under nitrogen atmosphere. When the vigorous reaction ceased gradually, 2.5 g (14.9 mmol) of 2-chloro-5-chloromethylpyridine dissolved in anhydrous THF was added to the reaction flask via the dropping funnel. After the reaction mixture was refluxed for 35 h under nitrogen atmosphere, anhydrous alcohol was added to react with the excess sodium hydride. After the mixture was poured into 100 mL of water, the aqueous phase was extracted three times with 90-mL chloroform. The organic phase was dried with anhydrous sodium sulfate and subsequently filtrated. After the solution was concentrated and purified on silica chromatographic column, a yellow viscous liquid (3.8 g) was obtained. The structure of produce was checked by means of IR and NMR. IR (cm^{-1}): 3030, 2900, 2850, 1670, 1600, 1590, 1460, 1160–1020, 820, 740. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.33 (s, 1H, pyridine C_6–H), 7.67–7.64 (d, 1H, pyridine C_4–H), 7.32–7.29 (d, 1H, pyridine C_3–H), 5.07–4.91 (m, 1H), 4.57 (s, 2H), 3.98–3.33 (m, 11H), 1.59–1.20 (m, 12H, $-(CH_2)_3$), 0.91–0.89 (t, 6H, CH_2CH_3).

Fused-silica capillary chromatography column ((i.d.,

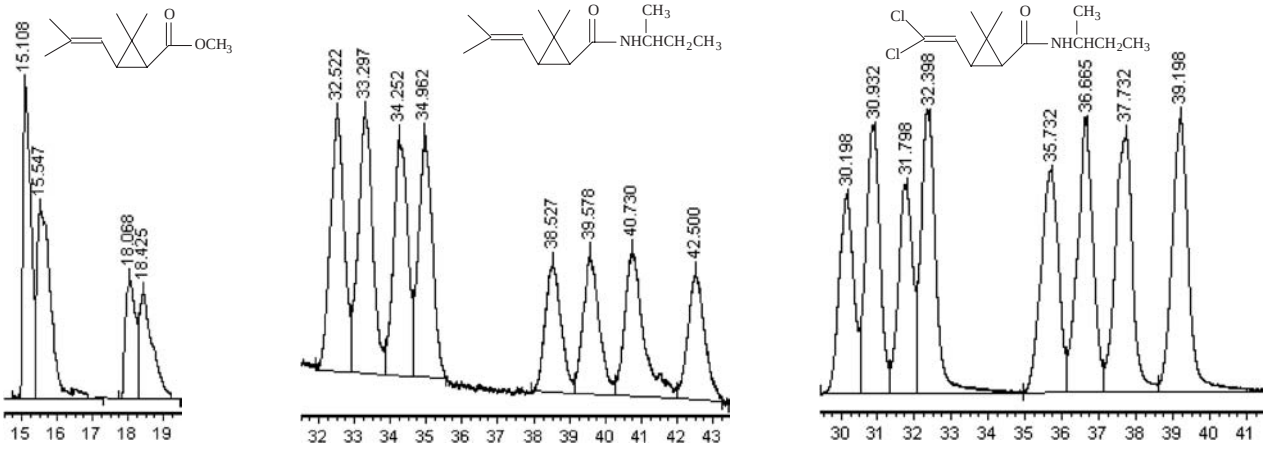

Figure 1. Gas chromatographic separation of three kinds of cyclopropane derivatives.

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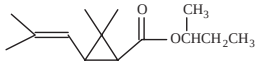
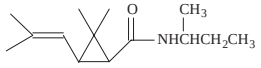
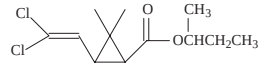
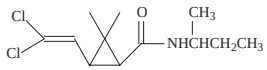
Table 1. Retention factor (k) and separation factor (α) of cyclopropane derivatives tested on the chiral colum

Solutes	Temp / °C	Retention factor		Separation factor	
 Methyl 2,2-dimethyl-3-(2-methylpropenyl)-cyclopropanecarboxylate	120	k_1	9.14		
		k_2	9.43	$\alpha_{2/1}$	1.03
		k_3	11.13		
		k_4	11.37	$\alpha_{4/3}$	1.02
 1-Methylpropyl 2,2-dimethyl-3-(2-methylpropenyl)-cyclopropanecarboxylate	140	k_1	8.41		
		k_2	8.41	$\alpha_{2/1}$	1.00
		k_3	8.76		
		k_4	8.76	$\alpha_{4/3}$	1.00
		k_5	9.42		
		k_6	9.42	$\alpha_{6/5}$	1.00
		k_7	9.72		
		k_8	9.88	$\alpha_{8/7}$	1.02
 *N*-(1-Methylpropyl)-2,2-dimethyl-3-(2-methylpropenyl)-cyclopropanecarboxamide	160	k_1	20.95		
		k_2	21.47	$\alpha_{2/1}$	1.03
		k_3	22.11		
		k_4	22.59	$\alpha_{4/3}$	1.02
		k_5	25.10		
		k_6	25.71	$\alpha_{6/5}$	1.03
		k_7	26.48		
		k_8	27.68	$\alpha_{8/7}$	1.05
 1-Methylpropyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate	130	k_1	14.25		
		k_2	14.43	$\alpha_{2/1}$	1.01
		k_3	15.06		
		k_4	15.06	$\alpha_{4/3}$	1.00
		k_5	16.01		
		k_6	16.01	$\alpha_{6/5}$	1.00
		k_7	16.53		
		k_8	16.91	$\alpha_{8/7}$	1.02
 *N*-(1-Methylpropyl)-3-(2,2-dichloroethenyl)-2,2-dimethyl-cyclopropanecarboxamide	160	k_1	17.41		
		k_2	17.86	$\alpha_{2/1}$	1.03
		k_3	18.39		
		k_4	18.76	$\alpha_{4/3}$	1.02
		k_5	20.79		
		k_6	21.36	$\alpha_{6/5}$	1.03
		k_7	22.01		
		k_8	22.90	$\alpha_{8/7}$	1.04

0.25 mm; length, 20 m) was purged with nitrogen gas at 240 °C for 4 h before being coated at 35 °C with 0.45% (w/v) stationary phase in dichloromethane. The column was then flushed with nitrogen gas under a slow flow (8–10 cm/s) for 2 h and conditioned between 60 and 220 °C, increasing its temperature in 20 °C increments, keeping at each temperature for 2 h, and finally at 220 °C for 6 h.

The chromatographic measurements were carried out on Model GC-9900 gas chromatograph (Beijing Jiafen Analytical Instrument Factory, Beijing China) equipped with FID detector. The carrier gas was pure nitrogen gas at a linear velocity of 23–24 cm/s. The injector split ratio was 60:1. Both the injector and detector temperatures were all maintained at 250 °C.

The tested cyclopropane compounds were supplied by the China Agricultural University. The purity and structures of samples were approved with ^{1}H NMR and MS.

Figure 1 shows chromatographic separation results of chiral cyclopropane derivatives on the new stationary phase. Cyclopropane derivatives with two chiral centers including four configurational isomers or three chiral centers including eight configurational isomers can be well separated, which indicates that the pyridyl β-CD possesses excellent selectivity and chiral separation ability. As the kind of heterocyclic compound, pyridine contains nitrogen heteroatom, which has strong induction effect and is the receptor of hydrogen bond. The introduced pyridine group to β-CD may increase special interaction between the stationary phase and the target molecules.

It also can be found in Table 1 that the separation results of amides are better than that of esters. The hydrogen bond between the CD derivative and the amide group may increase the chiral separation ability.

In conclusion, the new β-CD derivative, heptakis[2,6-di-*O*-pentyl-3-*O*-(2-chloro-5-pyridy)methyl]-β-CD has been synthesized. It showed good separation ability for compounds as the chiral stationary phase in GC. Cyclopropane compounds with multichiral centers were well separated. This new pyridyl β-CD can thus be expected as a useful stationary phase for separation of other complex compounds with multichiral centers.

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