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Direct Enantiomer Separation of 2-Phenylcyclopropanecarboxylate Esters on Cyclodextrin Derivatives Stationary Phases in GC

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Abstract: Direct enantiomeric separation of all four optical isomers of 2-phenylcyclopropane carboxylate ester was first achieved on each of the three different β-cyclodextrin chiral stationary phases (CSPs) in GC. Using these CSPs, enantiomeric excess of the products of enantioselective cyclopropanation can be determined directly, conveniently and fast.

Keywords: Enantiomer separation, 2-phenylcyclopropanecarboxylates, cyclodextrin.

Introduction

The chiral cyclopropane subunit is found in a wide range of natural and unnatural products possessing important biological properties. Recently, many efforts have been focused on the development of stereoselective methods to facilitate access to enantioenriched cyclopropanes. As the pro-drugs and drug intermediates, 2-phenyl cyclopropanecarboxylates are the frequently reported products of enantioselective cyclopropanation of olefins[1,2]. However, so far, enantiomeric excess of these chiral compounds was usually determined by converting to the *L*-menthyl ester in GC[3]. In chiral HPLC, only *trans* 2-phenylcycloproanecarboxylic acid can be separated[4,5,6].

Direct gas chromatographic enantiomer separation of racemates using chiral stationary phases (CSPs) is a simple and effective method, and is extensively used for the determination of enantiomeric purity in asymmetric catalysis. Various types of cyclodextrin (CD) derivatives have been used as CSPs in GC. Herein, direct separation of all enantiomers and diastereomers of 2-phenylcycloproanecarboxylate esters were first investigated using three different β-CD CSPs.

Experimental

Column 1 with heptakis(2,6-di-*O*-pentyl)-β-CD (DPBCD): 38m×0.25mm i.d. deactivated fused-silica capillary was statically coated with pure DPBCD.

Column 2 with heptakis(2,6-di-*O*-pentyl-3-*O*-acetyl)-β-CD (DPABCD): 20m× 0.25mm i.d. deactivated fused-silica capillary was statically coated with mixture of DPABCD and SP-79[6] (50:50, w/w).

Column 3 with permethylated β-CD (PMBCD): 30m×0.25mm i.d. deactivated fused-silica capillary was statically coated with mixture of PMBCD and OV-1701 (15:85, w/w).

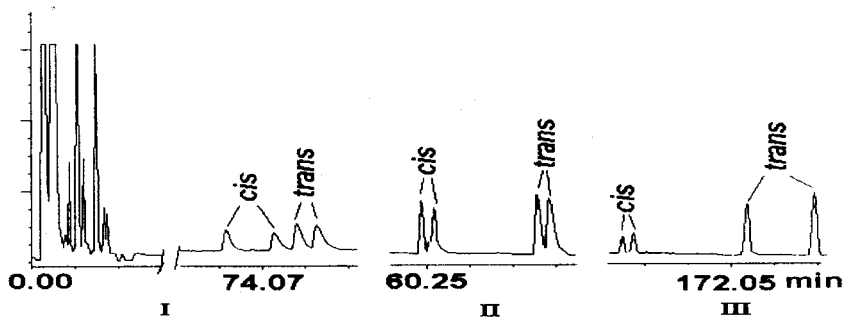
All chromatographic separations were performed with a GC1121 modified capillary gas chromatograph (Shanghai Analytical Instrument Factory, China) equipped with a flame ionization detector. The injector and detector were maintained at 250°C. With hydrogen as carrier gas, all separations were performed isothermally with a split ratio of 1:100.

All 2-phenylcyclopropanecarboxylate esters were the products of enantioselective cyclopropanation of styrene with the esters of diazoacetic acid.

Results and Discussion

The investigated compounds include ethyl 2-phenylcyclopropanecarboxylate **I**, *n*-butyl 2-phenylcyclopropanecarboxylate **II** and *L*-menthyl 2-phenylcyclopropanecarboxylate **III**. These compounds are products of enantioselective cyclopropanation of styrene with the corresponding esters of diazoacetic acid, and four optical isomers are usually present. Previously, the enantiomeric excesses of the cyclopropanation products were determined only after converting to *L*- or *D*-menthyl esters, which is very inconvenient and onerous. On CD CSPs, all four optical isomers of the product in GC can be resolved, as illustrated in **Table 1** and **Figure 1**.

Figure 1. Chromatograms of 2-phenylcyclopropanecarboxylates on PMBCD CSP.



Column temperatures for compounds **I, II** and **III** are 100, 130 and 150 °C, respectively. Other conditions: see experimental section.

From **Table 1**, it is observed that on DPBCD and DPABCD CSPs, direct baseline separations of all four optical isomers are obtained for compounds **I** and **III** respectively, but only *cis* and *trans* isomers are separated for compound **II**. On PMBCD CSP, direct baseline separation of all four optical isomers for all three compounds can be achieved. Moreover, almost all enantiomeric separation factors (α) for *cis*-isomers are greater than the corresponding values for *trans*-isomers at the same temperatures on the three different CD CSPs, except for the compound **III** separated on PMBCD CSP. Interestingly, it is noted that on both DPBCD and DPABCD CSPs, enantiomeric separation factors for all *trans*-isomers are almost constant over the investigated range of temperatures, which means that the differences of enthalpy change ($\Delta(\Delta H)$) during the chiral recognition process of *trans*-isomers with CDs are close to zero. This maybe infers that enantiomer separation of *trans*-isomers is an entropy-controlled process. The enantiomeric separation mechanisms of 2-phenylcyclopropanecarboxylates on CD CSPs will be further investigated. In addition, it is obviously seen in **Table 1** that the retention times of ethyl ester are significantly less than those of menthyl ester. This is very important in practical applications for timesaving and convenience, because the products of catalyzed cyclopropanation are usually ethyl ester.

Table 1. Separation results of 2-phenylcyclopropanecarboxylates on CD-CSPs.

		Column 1 (DPBCD)			Column 2 (DPABCD)			Column 3 (PMBCD)		
		k_1'	α	T/℃	k_1'	α	T/℃	k_1'	α	T/℃
	cis	7.212	1.021	140	5.916	1.042	140	6.073	1.042	140
I		46.873	1.033	100	39.593	1.087	100	45.997	1.103	100
	trans	8.787	1.014	140	7.387	1.016	140	7.124	1.012	140
		59.833	1.015	100	50.525	1.023	100	52.913	1.037	100
	cis	15.778	1.000	150	13.057	1.000	150	12.852	1.019	150
II		41.885	1.000	130	32.637	1.000	130	62.390	1.052	120
	trans	20.483	1.000	150	18.541	1.000	150	16.859	1.012	150
		55.747	1.000	130	47.649	1.000	130	84.515	1.032	120
	cis	32.512	1.156	180	43.410	1.110	170	61.478	1.016	160
III		51.653	1.174	170	121.087	1.129	150	111.149	1.027	150
	trans	45.435	1.046	180	62.121	1.064	170	78.995	1.114	160
		74.516	1.047	170	181.558	1.073	150	146.494	1.127	150

Notes: k_1' is the capacity factor of the first-eluted isomers; α is separation factor.

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