Analytica Chimica Acta 912 (2016) 156–162

Contents lists available at ScienceDirect

Analytica Chimica Acta

journal homepage: www.elsevier.com/locate/aca

The CGC enantiomer separation of 2-arylcarboxylic acid esters by using β-cyclodextrin derivatives as chiral stationary phases

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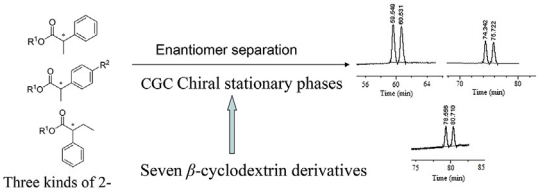
HIGHLIGHTS

- 2-arylcarboxylic acid esters were separated on CGC with CDs as stationary phases.
- 2,6-di-*O*-pentyl-3-*O*-butyryl-β-CD could separate 2-phenylpropionates enantiomers.
- 2,3,6-tri-*O*-methyl-β-CD separated 2-(4-substituted phenyl)propionates enantiomers.
- Supplied CGC option for enantioseparation problem of 2-arylcarboxylic acid esters.

GRAPHICAL ABSTRACT



CGC enantiomer separation of 2-arylcarboxylic acid esters

ARTICLE INFO

Article history:
Received 20 November 2015
Received in revised form
15 January 2016
Accepted 20 January 2016
Available online 27 January 2016

Keywords:
2-Arylcarboxylic acid esters
Enantiomer separation
Capillary gas chromatography
β-Cyclodextrin derivatives
Chiral stationary phases

ABSTRACT

Chiral 2-arylcarboxylic acid esters are important intermediates in preparation of enantioenriched 2-arylpropionic acids type Non-steroidal anti-inflammatory drugs (NSAIDs). Enantiomer separation of 2-arylcarboxylic acid esters is crucial for evaluation of the asymmetric synthesis efficiency and the enantiomer excess of chiral 2-arylcarboxylic acid derivatives. The capillary gas chromatography (CGC) enantiomer separation of 17 pairs of 2-arylcarboxylic acid esters enantiomers was conducted by using seven different β-cyclodextrin derivatives (CDs) as chiral stationary phases. It was found that for the 7 pairs of 2-phenylpropionates enantiomers, CDs with both alkyl and acyl substituents especially 2,6-di-*O*-pentyl-3-*O*-butyryl-β-cyclodextrin exhibited better enantiomer separation abilities than the other CDs examined. For the 7 pairs of 2-(4-substituted phenyl)propionates enantiomers, 2,3,6-tri-*O*-methyl-β-cyclodextrin possessed better enantiomer separation abilities than the other CDs. Among the 3 pairs of 2-phenylbutyrates enantiomers examined, only methyl 2-phenylbutyrate enantiomers could be separated by three CDs among the 7 CDs tested, while enantiomers of ethyl 2-phenylbutyrate and isopropyl 2-phenylbutyrate couldn't be separated by any of the 7 CDs tested. Besides the structures of CDs, the structures of 2-arylcarboxylic acid esters including different ester moieties, substituents of phenyl, and different carboxylic acids moieties in 2-arylcarboxylic acid esters also affected the enantiomer separation results greatly. The CGC enantiomer separation results of 2-arylcarboxylic acid esters on different CDs are useful for solving the enantiomer separation problem of 2-arylcarboxylic acid esters.

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used as therapeutic agents for the treatment of fever, pain and

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http://dx.doi.org/10.1016/j.aca.2016.01.037
0003-2670/

inflammation. NSAIDs are divided into several types based on their chemical structures, with ibuprofen, 2-(4-isobutylphenyl)propionic acid, belongs to the 2-arylpropionic acid type NSAIDs [1–3].

The importance of chiral center of 2-arylpropionic acid type profens at the 2-position has been recognized in pharmaceutical sciences. It has been established that (+)-(*S*)-enantiomer of ibuprofen is almost entirely responsible for the anti-inflammatory action of racemic ibuprofen [2–4], because the (+)-(*S*)-isomer of ibuprofen possesses an inhibitory effect on cyclooxygenases (COX-1 and/or COX-2) that mediate the generation of prostanoids and thromboxanes, though the antitumor activity and the effect towards Alzheimer's disease involve COX-independent pathways of some profens were also elucidated [3,4]. Moreover, ibuprofen undergoes enantioselective metabolism and disposition in organism. An unidirectional metabolic inversion of the inactive (−)-(*R*)-enantiomer of ibuprofen in vivo to its active form [3,4], and the disposition of (−)-(*R*)-ibuprofen with biotransformation inversion of configuration at the chiral center to yield (+)-(*S*)-enantiomer of the drug [1], were reported.

With the two enantiomers of 2-arylpropionic acid type NSAIDs differ greatly in their pharmacological and pharmacokinetic properties, versatile methods for enantioselective synthesis of individual enantiomer of 2-arylpropionic acid type NSAIDs have been developed. Chiral 2-arylcarboxylic acid esters are important intermediates in the synthesis of enantioenriched 2-arylpropionic acids type NSAIDs. By using new asymmetric synthesis with the catalyst of Cobalt-complex, enantioenriched 2-arylcarboxylic acid esters were successfully synthesized [5]. This novel method has been applied to the asymmetric synthesis of (*S*)-fenoprofen and the total synthesis of (*S*)-ar-turmerone [5]. Therefore, enantiomer separation of 2-arylcarboxylic acid esters is crucial for evaluation of the asymmetric synthesis efficiency and the enantiomer excess of chiral 2-arylcarboxylic acid derivatives, which were the raw materials for synthesizing NSAIDs.

With ibuprofen as one of the most important 2-arylpropionic acid type of NSAIDs, many enantioselective separation methods have been developed for analysis of ibuprofen enantiomers in biological samples. Oliveira et al. [1] developed a chiral HPLC method for analysis of ibuprofen enantiomers in urine by using a Chiralpak AD-RH column after solid-phase microextraction. By using chiral HPLC with a semi-preparative reversed-phase CHIRALPAC OJ-RH column, the two enantiomers of ^{11}C-labeled ibuprofen were successful obtained and used as tracer for positron emission tomography (PET) measure [4]. HPLC-MS/MS method on Lux Cellulose chiral column was used for direct determination of the two ibuprofen enantiomers in human plasma [2].

The fast chiral separation of ibuprofen enantiomers by nano-liquid chromatography were achieved in an analysis time of less than 3 min, by using a novel sub-2 μm chiral stationary phase prepared by immobilizing vancomycin onto diol hydride-based silica particles [6]. By using a novel β-cyclodextrin derivative functionalized polymethacrylate-based monolithic columns, enantioselective separation of ibuprofen and naproxen enantiomers were achieved by capillary electrochromatography [7]. In addition, the (*R*)- and (*S*)-enantiomer of ibuprofen were separated and analyzed by achiral gas chromatography tandem mass spectrometry (GC–MS/MS) after being derived to diastereomers with (*R*)-1-phenylethylamine or (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl) ethanol as chiral deriving reagent [8,9].

Capillary gas chromatography (CGC) with chiral stationary phases is a powerful measure for direct separation of enantiomers of volatile and thermal stable compounds, with advantages of easy, high enantioseparation efficiency and no use of organic solvent. The enantiomer separation of 2-bromo, chloride, hydroxyl or methoxyl substituted propionic acid esters by CGC on chiral stationary phase was reported widely. For example, methyl 2-chloride, bromide or hydroxyl propionates were well separated on 2,3-di-*O*-allyl-6-*O*-acylated-β-cyclodextrin [10]. Excellent CGC enantiomer separation of 2-hydroxyl propionates was achieved on 2,3,6-tri-*O*-valeryl-β-cyclodextrin and 2,3,6-tri-*O*-octanoyl-β-cyclodextrin [11].

However, enantiomer separation of 2-arylcarboxylic acids and their esters by CGC with chiral stationary phase was less reported. Only enantiomers of methyl 2-phenylpropionates and methyl 2-phenylbutyrates were separated on chiral CGC with β-cyclodextrin derivatives as chiral stationary phases. The enantiomers of methyl 2-phenylpropionates were well separated on permethylated-β-cyclodextrin [12] and 2,3-di-*O*-methyl-6-*O*-tert-butyldimethylsilyl-β-cyclodextrin [13]. Moreover, by using the mixture of 2,3-di-*O*-ethyl-6-*O*-*tert*-butyldimethylsilyl-β-cyclodextrin and PS-086 or OV-1701, and the mixture of 2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl-γ-cyclodextrin and PS-347.5, PS-086 or OV-1701 as CGC chiral stationary phases, the enantiomers of methyl 2-phenylbutanoate were separated [14].

In order to develop CGC enantiomer separation methods for 2-arylcarboxylic acid esters, the enantiomer separation of 17 pairs of enantiomers of 2-arylcarboxylic acid esters were examined on seven different CDs chiral CGC columns, including one commercial 2,3,6-tri-*O*-methyl-β-cyclodextrin column and six self-prepared CDs columns, which are 2,3,6-tri-*O*-pentyl-β-cyclodextrin column, 2,6-di-*O*-pentyl-3-*O*-butyryl-β-cyclodextrin column, 2,3-di-*O*-pentyl-6-*O*-octanoyl-β-cyclodextrin column, 2,6-di-*O*-benzyl-3-*O*-heptanoyl-β-cyclodextrin column, 2,3,6-tri-*O*-valeryl-β-cyclodextrin column and 2,3,6-tri-*O*-octanoyl-β-cyclodextrin column.

The results showed that some 2-arylcarboxylic acid esters enantiomers could be successfully separated by CGC with CDs as chiral stationary phases. Among the 7 CDs examined, 2,6-di-*O*-pentyl-3-*O*-butyryl-β-cyclodextrin possessed good enantiomer separation abilities to some 2-phenylpropionic acid esters, while 2,3,6-tri-*O*-methyl-β-cyclodextrin exhibited good separation abilities to 2-(4-substituted phenyl)propionic acid esters. The CGC enantiomer separation results of 2-arylcarboxylic acid esters on different CDs are useful for solving the enantiomer separation problem of 2-arylcarboxylic acid esters.

2. Materials and methods

2.1. Apparatus

HP 6890plus gas chromatograph (Agilent) equipped with a capillary split-splitless injection system and a flame-ionization detector (FID) was used. Agilent chromatographic Data Station was used for data collection. Carrier gas was high purity helium gas (99.99%). The constant pressure mode was used with the column inlet pressure as 0.095 MPa. Sample was prepared by dissolving individual racemic mixture in acetone. The inject volume for each sample is 1 μL. The injection split ratio was 30:1. Both the injector and detector temperature were 250 °C. All measurements were performed at isothermal conditions. The column temperature was chosen and tested according to the properties of different solutes firstly, and then was changed in order to optimize enantiomer separation results.

2.2. Chemicals

All reagents used were analytical reagent grade (Sinopharm chemical reagent Co., Beijing, China). 2-arylcarboxylic acid esters were synthesized and characterized following procedures described in Ref. [5], and kindly provided by the Department of Chemistry at China Agricultural University.