Trends in Analytical Chemistry 65 (2015) 22–29

Contents lists available at ScienceDirect

Trends in Analytical Chemistry

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

Recent development of cationic cyclodextrins for chiral separation

Jie Zhou, Jian Tang, Weihua Tang *

Key Laboratory of Soft Chemistry and Functional Materials (Ministry of Education of China), Nanjing University of Science and Technology, Nanjing 210094, China

ARTICLE INFO

Keywords:
Cationic cyclodextrin
Chiral additive
Chiral recognition
Chiral separation
Complexation
Enantioselectivity
Mobile phase
Monocationic cyclodextrin
Polycationic cyclodextrin
Stationary phase

ABSTRACT

Cationic cyclodextrins (CDs) have attracted considerable interest in the field of chiral separation. Targeting effective modulation of the interactions between chiral selectors and analytes for enhanced chiral recognition, a growing library of positively charged CDs has been developed for different analytical techniques. This review updates the research endeavors of synthetic and analytical chemists in evaluating enantioselectivity of cationic CDs using different analytical methods and the study of the chiral recognition mechanism. We pay specific attention to the structurally defined cationic CDs, which have been explored for versatile chiral separation in a variety of techniques when subject to further modification.

Contents

1. Introduction

Chiral discrimination has attracted considerable attention in academia and industry, especially in biological, pharmaceutical and agrochemical fields [1–3]. This interest is attributed to heightened awareness that any compounds of biological and pharmaceutical interest are chiral and their enantiomers often exhibit different bioactivities and biotoxicities. The demand for single enantiomers in developing chiral drugs is met by the development of new strategies toward asymmetric synthesis and new methods of chiral separation. To date, chiral separation on analytical or semi-preparative scales has been achieved using gas chromatography (GC) [4], high-performance liquid chromatography (HPLC) [5], supercritical-fluid chromatography (SFC) [6] and capillary electrophoresis (CE) [7] to meet the need to characterize chiral compounds to a greater extent and with greater accuracy and precision. Among these techniques, CE stands out due to its advantages in affording rapid separations with high resolution and efficiency at elevated electric fields and selective separation modes.

Successful chiral separation with various chromatographic and electromigration techniques strongly relies on the chiral selectors used in mobile phases (mainly CE) or stationary phases (GC, HPLC and SFC). Among all chiral selectors explored in the literature, cyclodextrins (CDs) and their derivatives are among the most widely used in CE [8]. Called structural and functional straightjackets, CDs are chiral in nature and feature a hydrophobic interior cavity and hydrophilic edges. The hydrophobic cavity endows CDs with the capability to form "host-guest" inclusion complexes with a wide range of guest molecules, which is of great significance for chiral separation. The hydrophilic exterior paves the way to chemical modification of native CDs to pursue higher solubility in desired solvents and to improve enantioselectivities towards chiral analytes.

For consideration of solubility and enantioselectivity, charged CDs have been developed to exhibit better chiral recognition ability in comparison to their neutral counterparts. They are advantageous in forming additional electrostatic interactions with ionic guests to

* Corresponding author. Tel.: +86 25 84317311; Fax: +86 25 84317311.
E-mail address: whtang@mail.njust.edu.cn (W. Tang).

http://dx.doi.org/10.1016/j.trac.2014.10.009
0165-9936/

enhance the chiral separation. Several reviews have given good overviews on the application of CE for chiral separation [9,10].

This review updates on recent advances in developing cationic CD-based chiral selectors for enantioseparation using different analytical techniques.

2. Cationic CDs

Cationic CDs present as randomly multi-substituted and selectively substituted (i.e., bis-, mono-, or per-substituted), with most of them obtained via modification at the C6 position. Enhanced chiral recognition ability of these CDs compared to native CD is usually achieved due to the ability of the grafted groups to interact with the guest molecules (especially anionic ones) and to lower the symmetry of the CD. In most cases, positive charge directly linked to the CD rim affords an enantioselective electrostatic interaction with anionic analytes. Compared with anionic CD derivatives, the great advantage is the shorter analysis time due to cationic CDs migrating towards the cathode. However, the limited application of cationic CDs might be due to their stronger absorbing nature to the capillary wall and their more complicated synthesis procedure. By adding inhibitors into the mobile phase or coating the capillary, the adsorption might be suppressed. To address the concerns about repeatability and reproducibility in synthesis and applications, researchers are actively engaged in the development of selectively modified CDs.

2.1. Polycationic CDs as chiral additives

Polycationic CDs comprise multi- or per-substituted CD derivatives. A representative multi-substituted cationic CD is quaternary ammonium β-CD (QA-β-CD), where the hydroxyl groups of the CD are randomly converted to quaternary ammonium centers. QA-β-CD was utilized as a chiral selector to separate dianionic disodium 3-(*p*-isothiocyanatophenoxy)-3-(*p*-isothiocyanatophenyl)propane-1,2-disulfate by CE [11]. A parallel two-step complexation model was proposed on the basis of chiral discrimination together with ^{1}H NMR COSY and NOESY spectra.

Gil et al. investigated the influence of a series of quaternary ammonium CD nanoparticles (NPs) with different charge density on the integrity of bovine brain microvessel endothelial cell (BBMVEC) monolayer and blood-brain barrier (BBB) permeability of CD-NPs alone and the BBB permeability of doxorubicin [12]. The cationic CD-NPs exhibited non-toxicity to BBMVEC when their concentrations were increased to 500 μg/mL and would not change the integrity of them. The permeability of CD-NPs across the BBMVEC monolayer was improved with an increased number of quaternary ammonium groups, achieving the maximum when the molar ratio of quaternary ammonium groups to CD was 2.0.

By amination at all C6 positions, per-substituted polycationic CDs can be obtained, demonstrating good batch-to-batch reproducibility and enantioseparation ability. Budanova et al. [13] reported on the enantioseparations of anionic drugs with heptakis(6-amnio-6-deoxy)-β-CD (per-6-NH_2-β-CD) in the pH range 4.0~7.0 by CE. Electroosmotic force (EOF) reversal was observed due to the adsorption of the chiral selector onto the capillary wall. Ibuprofen with one phenyl ring was found to fit the CD cavity better than ketoprofen and fenoprofen. The results assumed that the chiral separation mechanism of per-6-NH_2-β-CD largely depended on sterically controlled inclusion complexation and hydrogen bonding.

The chiral recognition of α-amino-acid derivatives by protonated heptakis(6-amino-6-deoxy)-β-cyclodextrin (per-NH_3^+-β-CD) has been investigated with ^{1}H NMR spectroscopy [14]. The structure of per-NH_3^+-β-CD was also predicted from molecular mechanics-molecular dynamics (MM-MD) calculations. The NH_3^+-group side was expanded due to the electrostatic repulsion. The NMR study revealed that (S)-enantiomers in their anionic forms more preferentially formed complexes with per-NH_3^+-β-CD than the (R)-enantiomers. In addition, the binding constants (K values) for the per-NH_3^+-β-CD/guest-anion complexes were much larger than those for the mono-NH_3^+-β-CD ones. Aminated CDs could afford superior enantioselectivities due to the potential formation of electrostatic binding with guest molecules. Per-NH_2-CD demonstrated improved chiral recognition ability towards protected amino acids, including phenylalanine, methionine and histidine [15].

2.2. Monocationic and dual-cationic CDs as chiral additives

This sub-section presents chiral separation based on structurally-defined cationic CD derivatives including mono- or di-cationic CDs (selected cases are summarized in Table 1).

In terms of dual-cationic CDs, the traditional preparation is to produce AB, AC and AD bis-substituted CD sulfonates with different capping reagents (i.e., arenedisulfonyl chlorides) to build a versatile platform for further modification. For example, 6,6′-dideoxy-6,6′-$_L$-diamino-β-CDs (AB, AC, and AD) were developed via this strategy for the enantioseparation of hydroxyl acids and carboxylic acids in CE [41].

Enantioseparation significantly depended upon the position of cationic centers, which took part in the formation of electrostatic interactions with the carboxylate of analytes to enhance the chiral recognition. Interestingly, the best enantioselectivities for hydroxy acids were achieved by AC regioisomer, while carboxylic acids were well resolved by only AB regioisomer. The development of AC, AB or AD disubstituted CDs via the capping method is limited with low yield and difficulties in introducing different cationic centers.

To solve the above issue, a feasible methodology for the preparation of asymmetrically AC disubstituted CD regioisomers, mono-6^A-ammonium-6^C-alkylimidazolium-β-cyclodextrin chlorides, was developed by using 2-mesitylenesulfonyl chloride as the positioning reagent [42]. Among them, 6-ACNH_2BIMCD demonstrated excellent good chiral recognition towards acidic and neutral racemates, even at concentrations as low as 0.5 mM [16].

Aiming to obtain versatile cationic CDs for improved molecular recognition towards ampholytic and acidic racemates, monosubstituted dicationic CD containing both imidazolium and ammonium moieties in the sidearm on the primary rim of the CD was developed [17]. In the synthesis, alkylamine-linked imidazole or imidazole-linked alkylamine functionalities were directly launched onto the C6 position to afford dual-cationic CDs with multi-action sites for electrostatic interactions, hydrogen bonding and π-π interactions. The potential of dual-cationic mono-substituted CDs (e.g., AMBIMCD) was explored for the enantioseparations of dansyl (Dns-) amino acids and acidic compounds, where baseline enantioseparations were achieved at 2.5 mM CD. Impressively, AMBIMCD exhibited excellent enantioselectivities for acidic racemates, even at 1.0 mM CD, with the chiral resolution of mandelic acid achieved as high as 8.1.

Similarly, the chiral separation of α-hydroxy acids and carboxylic acids was achieved using 6-deoxy-6-N-histamino-β-cyclodextrin (CDhm) and 6-deoxy-[4-(2-aminoethyl)imidazoyl]-β-cyclodextrin (CDmh) [18]. CDhm proved to be a better chiral selector towards selected analytes than CDmh due to the different proximity of the positive charge to the cavity. The number of positive charges could be modulated via the pH of buffer, according to the different pKa of the amino and imidazolyl groups, which would directly affect both enantioselectivity and resolution.

Thermodynamic stereoselectivity was observed for tryptophan and phenylalanine enantiomers using a C3-histamine-substituted β-CD (CDhm3), and that was verified using chiral ligand-exchange CE (CLECE) [19]. Impressively, the stability order of the complexes of CDhm3 with L- and D-amino acids is the same as those with