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Cationic cyclodextrin clicked chiral stationary phase for versatile enantioseparations in high-performance liquid chromatography

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ABSTRACT

In this work, a novel cationic cyclodextrin (CD) chiral stationary phase (CSPs) has been developed by clicking 6^A-azido-6^C-[(3-methoxylpropyl)-1- ammonium]-heptakis[2,3-di-O-(3-chloro-4-methylphenylcarbamate)-6^B,6^D,6^E,6^F,6^G-pentakis-O-per(3-chloro-4-methylphenylcarbamate)-β-CD chloride onto alkynyl silica support. The enantioselectivies of the as-obtained novel CSP were evaluated using 21 model racemates including flavonoids, aromatic alcohols, acidic drugs, β-blocker and amino acids. Good enantioseparations were achieved in polar-organic phase high performance liquid chromatography (HPLC), with the highest resolution of 8.07 observed for 7-methoxyflavanone. The enantioseparations in normal-phase HPLC were fine-tuned with the polarity of the mobile phase with different alcohols as organic modifiers. Improved chiral resolutions of analytes but longer retention were observed in mobile phases with decreased polarity. On comparison with previously reported clicked CD CSP, the cationic CD clicked CSP exhibited better enenatioseparations for selected racemates even in normal-phase HPLC. The results indicate that 3-methoxypropylammonium and phenylcarbamoylated moieties of the cationic CSP may provide intermolecular interactions such as hydrogen bonding, π–π conjugation and dipole–dipole besides inclusion complexation to drive the enantioseparation.

1. Introduction

Chiral separations have attracted continuous interest in the field of pharmaceutical, agricultural and food science. Ever-increasing research efforts have been made to develop related methodologies and multifunctional separation materials for various chiral technologies [1–4]. Up to now, direct enantioseparations with high performance liquid chromatography (HPLC) coupled with derivatized cyclodextrins (CDs) chiral stationary phases (CSPs) has significantly evolved into one of the most popular and robust tools for both analysis and even large-scale preparation of pure enantiomers. Great progress has been made on the immobilization of CD derivatives onto silica support by forming ether [5], urea [6], amino [7], and newly established triazole [8–10] linkages. The click chemistry of Cu(I) catalyzed 1,3-dipolar cycloadditions has been extensively used for the effective immobilization of functional molecules onto substrate surfaces [11,12]. A large spectrum of clicked CD-CSPs has thus been generated for practical chromatographic separations [13–18].

Besides the substantial efforts undertaken to develop the linkage between CD and silica support, the chemical modification of natural CDs to improve their inherent chiral recognition ability is also a very valuable work for enantioseparations [19,20]. In general, the hydroxyl groups on CD rims can be substituted with diverse functionalities like methyl [21,22], phenyl [23] and phenyl isocyanate [24,25]. These functionalities can effectively enable the enantioseparation under mixed modes in HPLC by constructing multiple intermolecular interactions such as π–π conjugation, dipole-dipole, ion-pairing, hydrogen bonding, and electrostatic and steric repulsion interactions besides inclusion complexation. Among various chemical modifiers, phenyl isocyanate is a good modifying agent to afford versatile CD CSPs with compatibility and durability to execute enantioseparations under different separation conditions. Furthermore, the recognition abilities of the as-prepared phenylcarbamated CDs are greatly affected by the substituents on the phenyl groups. When electron-withdrawing or donating substitutes are introduced onto the phenyl ring, the change in acidity of N—H group and electron density of carbonyl group would affect the stability of inclusion complexes through other interactions such as hydrogen bonding and steric hindrance. The functionality tuned enantioseparations of CD clicked CSPs have been systematically reported in our recent study [26]. The phenylcarbamoylated CD bearing 3-chloro and 4-methyl functionalities

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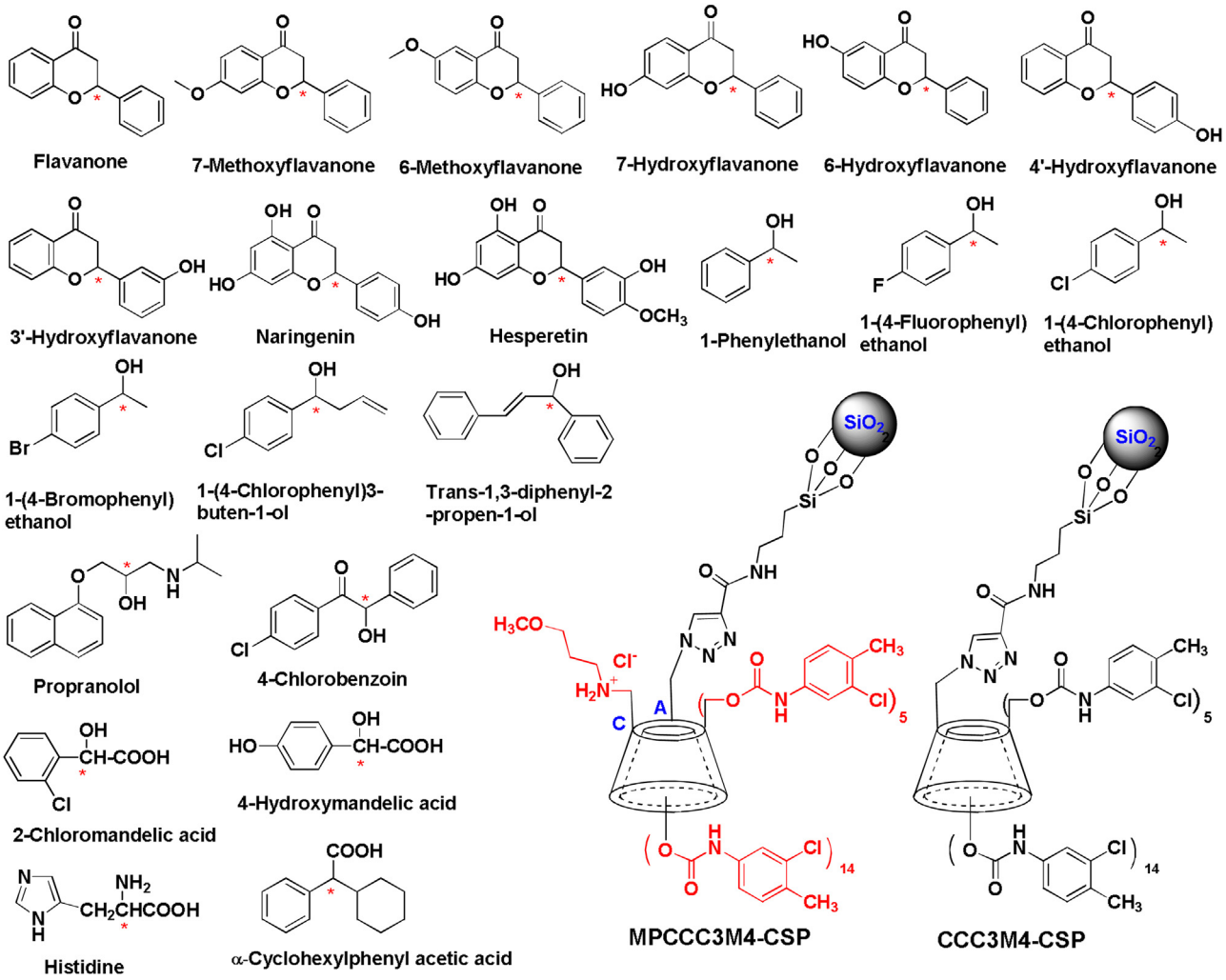

Fig. 1. Structure of model racemates, newly developed MPCCC3M4-CSP and reference CSP.

exhibited the best enantioselectivity and chiral resolution for CD clicked CSPs. The consequence of further incorporation of cationic moiety to CD rim on the enantioseparation of the CD clicked CSP has inspired us for this study.

The pursuit of single-isomer cationic CDs for enhanced chiral recognition has been launched in our group with the aim of constructing extra intermolecular interactions such as hydrogen bonding, π–π conjugation and dipole–dipole interactions between CD and guest molecules [27–31]. Impressively, 3-methoxypropylamino moiety at C6 position of CD has proved to be a versatile functionality in forming hydrogen bonding to enhance the enantioseparation [27]. To further excavate the role of 3-methoxypropylamino moiety in CD-CSPs for HPLC enantioseparations, we here report a cationic CD CSP by clicking 6^{A}-azido-6^{C}-[(3-methoxylpropyl)-1- ammonium]-heptakis[2,3-di-*O*-(3-chloro-4-methylphenylcarbamate)-6^{B},6^{D},6^{E},6^{F},6^{G}-pentakis-*O*-per(3-chloro-4-methylphenylcarbamate)-β-CD chloride onto silica support. The enantioseparation-performance of as-prepared cationic CSP towards various racemic analytes was further evaluated in HPLC, with the highest chiral resolutions over 8 achieved for 7-methoxyflavanone under both polar-organic (PO) and reversed-phase (RP) elution modes. The enantioselectivity of the cationic CD clicked CSP is strongly modulated by the polarity of the mobile phases.

2. Experimental

2.1. Materials

Kromasil spherical silica gel (5 μm, 100 Å with a surface area 300 m^2/g) was obtained from Eka Chemicals (Bohus, Sweden). HPLC-grade elution solvents including methanol (MeOH), acetonitrile (ACN), *n*-hexane (HEX), 2-propanol (IPA) and ethanol (EtOH) were purchased from Tedia (USA). HPLC-grade triethylamine (TEA) was obtained from J&K (Shanghai, China). The racemic enantiomers (see Fig. 1) were procured from Sigma-Aldrich (St. Louis, MO, USA) and J&K (Shanghai, China). The structures of cationic CD-based CSP, i.e., MPCCC3M4-CSP, and reference CCC3M4-CSP used are shown in Fig. 1.

The click preparation of MPCCC3M4-CSP was performed according to our recently reported procedure for CCC3M4-CSP [32–34]. As the synthetic route shown in Fig. 2, the cationic CD clicked CSP MPCCC3M4-CSP was prepared with 6^{A}-azido-6^{C}-3-methoxylpropyl-1-ammonium-β-CD chloride **2** as the key intermediate compound. The AC-disubstituted CD **2** was efficiently prepared with a nucleophilic substitution of **1** (6^{A}-azido-6^{C}-mesitylenesulfonyl-β-CD) with 3-methoxypropylamine to introduce the ammonium cationic center onto CD primary rim and a further ion-exchange process. The residual hydroxyl groups of **2** were further persubstituted using 3-chloro-4-methylphenyl isocyanate to attain compound **3**. The followed click anchoring of