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Novel cyclodextrin chiral stationary phases for high performance liquid chromatography enantioseparation: Effect of cyclodextrin type

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ABSTRACT

Three novel chiral stationary phases (CSPs) were prepared by regioselective chemical immobilization of mono(6^A-*N*-allylamino-6^A-deoxy)perphenylcarbamoylated (PICD) α-, β-, and γ-cyclodextrins (CDs) onto silica support via hydrosilylation. Their enantioseparation properties in high performance liquid chromatography (HPLC) were evaluated with a large spectrum of racemates including flavanone compounds, β-adrenergic blockers, amines and non-protolytic compounds. The effect of CD's cavity size on enantioseparation abilities was studied and discussed. The results indicated that CD's surface loading at silica support played an important role in the enantioseparation on these CSPs under normal-phase conditions while inclusion phenomena contributed the major driving force under reverse-phase conditions. As expected, α-PICD demonstrated the best resolutions towards flavonone and most aromatic alcohols under normal-phase conditions with the highest surface loading; while Fujimura's competitive inclusion model can be applied to explain the better enantioseparations towards β-adrenergic blockers, amines and non-protolytic compounds with α- and β-PICD CSPs. γ-PICD CSP showed superior enantioseparation ability for sterically encumbered analytes like flavanone compounds under both normal-phase and reversed phase conditions.

1. Introduction

With a growing demand for the exploration of different properties like toxicities and metabolic pathways of enantiomers, increasing efforts have been made on the resolution optically active compounds with respect to their optical purity. Direct enantioseparation by chiral stationary phases (CSPs) in high-performance liquid chromatography (HPLC) remains one of the most important techniques for both analysis of enantiomeric purity and quick obtainment of optically pure materials [1–3]. Several categories of chemically bonded CSPs such as Pirkle-type, protein-based, polysaccharide-based, macrocyclic antibiotic, crown ethers, imprinted polymers, chiral ligand exchange and cyclodextrin (CD)-based CSPs have been designed and applied for enantioseparation [4–13]. Among them, CD-base CSPs are especially attractive for their versatility and durability under all kinds of conditions [8–13].

Cyclodextrins (CDs) are chiral, toroid-shaped cyclic oligosaccharides comprising six, seven or eight glucopyranose units bonded via (1,4)-linkage, assigned as α-, β-, or γ-CD, respectively [2,14]. CDs and their derivatives are used extensively as chiral selectors for CSPs for HPLC chiral separation due to their natural chirality and ability to form inclusion complex with molecules via hydrophobic cavity [15–18]. It was reported that the combination of hydrophobic interactions and steric effects from the substituents present on the cavity entrance are believed to be responsible for the observed enantioselectivity in reversed-phases HPLC [15,18].

The chiral recognition of CD CSPs under reverse-phase conditions is thought to be driven by the inclusion complexation between the hydrophobic moiety of analyte and the relatively non-polar interior of the CD cavity [19]. Therefore, the dimension of CD-cavity is likely to have substantial effects on the enantioseparation ability of CD-bonded CSPs under reversed-phase conditions. Under normal-phase conditions, however, the CD-cavity is more likely to be occupied by the non-polar molecules of the mobile phase [20]; and the chiral recognition was mainly attributed to the π–π interaction and hydrogen bonding between sites provided by the aromatic and carbonyl substituents on the derivatized CD [21].

We previously reported a novel approach for preparing a CSP based on mono(6^A-*N*-allylamino-6^A-deoxy)perphenylcarbamoylated β-CD (β-PICD), which was immobilized onto porous silica via hydrosilylation [22,23]. This CSP exhibited outstanding enantioseparation abilities towards a wide range of chiral compounds. The effect of spacer length of mono(6^A-*N*-(ω-alkenylamino)-6^A-deoxy)perphenylcarbamoylated β-CD based

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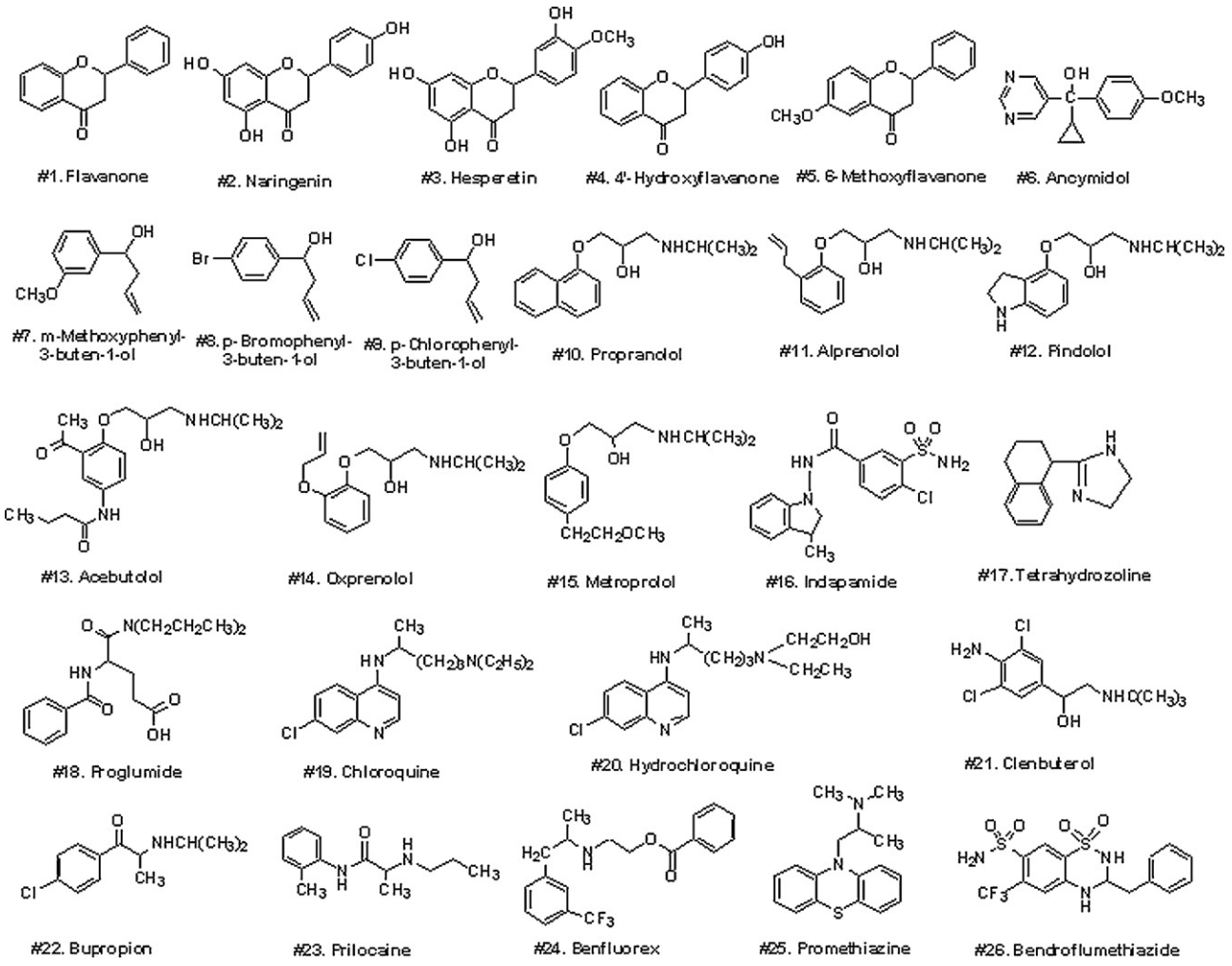

Fig. 1. Structure of flavanone, β-adrenergic blockers, amines and non-protolytic racemates studied.

CSPs was recently studied [24], which indicated an optimal spacer length (6–11 C atoms) existed. To further investigate the influence of CD cavity size on the enantioseparation performance, two analogue CSPs based on mono(6^A-*N*-allylamino-6^A-deoxy)perphenylcarbamoylated α-, and γ-CD (α-PICD and γ-PICD) were prepared in this paper. Enantioseparation of these three CSPs were presented herewith, and the effect of the CD-cavity dimension on the enantioseparation was discussed.

2. Experimental

2.1. Materials and instrumentation

α-, γ-cyclodextrins were purchased from TCI (Tokyo, Japan). All racemic samples (Fig. 1) and other reagents were procured from Sigma–Aldrich (Saint Louis, MO, USA) and used without further purification. Other chemicals and all instrumentations are the same as in Ref. [24].

2.2. Preparation of CSPs

Mono(6^A-*N*-allylamino-6^A-deoxy)perphenylcarbamoylated α-, β-, and γ-CD based CSPs were prepared according to the reported synthetic route by using different CD [22–24]. By refluxing mono[6^A-(*p*-tolysulfonyl)-6^A-deoxy]-α-, β-, or γ-CD **1** with allylamine [25–27], the key intermediate mono-(6^A-*N*-allylamino-6^A-deoxy)-α-, β-, or γ-CD **2** was obtained in high purity and good yield. Further reaction of **2** with phenyl isocyanate, (6^A-*N*-allylamino-6^A-deoxy)-heptakis (2,3-di-O-phenylcarbamate)-6^B, 6^C,6^D,6^E,6^F,6^G-hexakis-O-phenylcarbamoylated cyclodextrin **3** can be prepared. A further hydrosilylation of **3** with triethoxylsilane with 0.5% eq. tetrakis(triphenylphosphine)-platinum(0) gave the reactive siloxane, which was directly immobilized onto silica gel to afford the resultant CSPs.

Characterization data for mono-(6^A-*N*-allylamino-6^A-deoxy)-α-CD **2a**: IR (cm^{-1}, KBr): 3392 (O-H, str), 2935 (C–H, str), 1662 (C=C, m), 1024 (C–O str); ^{13}C NMR (75 Hz, DMSO-d_6) δ: 104.53 (C-1), 83.79 (C-4), 75.77 (C-2), 74.73 (C-3), 74.52 (C-5), 62.93 (C-6), 114.37(CH=$\underline{C}H_2$), 137.45 ($\underline{C}H$=CH_2); Anal. Calcd. (%) for $C_{39}H_{65}NO_{29}$: C 46.29, H 6.47, N 1.38, Found: C 45.01, H 6.59, N 1.19; ESI-MS for $C_{39}H_{65}NO_{29}$ (1012), *m*/*z*: 1013 for $[M]^+$.

Characterization data for mono-(6^A-*N*-allylamino-6^A-deoxy)-γ-CD **2c**: IR (cm^{-1}, KBr): 3401, 3308 (O-H, str); 2922 (C–H, str), 1640 (C=C, m), 1038 (C–O str); ^{13}C NMR (75 Hz, DMSO-d_6) δ: 101.63 (C-1), 80.86 (C-4), 73.81 (C-2), 73.48 (C-3), 72.84 (C-5), 61.77 (C-6), 114.99 (CH=$\underline{C}H_2$), 137.54 ($\underline{C}H$=CH_2); Anal. Calcd. (%) for $C_{51}H_{85}NO_{39}$: C 45.84, H 6.41, N 1.05; Found: C 44.01, H 6.63, N 1.09; ESI-MS for $C_{51}H_{85}NO_{39}$ (1336), *m*/*z*: 1337 for $[M]^+$.

Characterization data for (6^A-*N*-allylamino-6^A-deoxy)-heptakis (2,3-di-O-phenylcarbamate)-6^B,6^C,6^D,6^E,6^F,6^G-hexakis-O-phenylcarbamoylated α-CD **3a**: IR (cm^{-1}, KBr): 2920 (C–H, str), 1658 (C=C, m), 1045 (C–O str); ^{13}C NMR (75 Hz, DMSO-d_6) δ: