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Chemically bonded cationic β-cyclodextrin derivatives as chiral stationary phases for enantioseparation applications

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ABSTRACT

Vinylene-functionalized cationic β-cyclodextrins are co-polymerized with vinylized silica in the presence of AIBN and conjugated monomers. The chemically immobilized cationic β-cyclodextrins were thereafter applied as chiral stationary phases in packed column supercritical fluid chromatography and demonstrated good and reproducible enantioseparations of racemic pharmaceutical compounds.

The use of cyclodextrin (CD) as a bonded chiral stationary phase (CSP) in chromatography for optical resolution has been studied extensively.[1,2] Considerable research was devoted to methods for immobilization of CD derivatives onto silica supports. Fujimura and others have reported the preparation of amino, urea, or amido linkages between CD and silica gel.[3–5] Earlier, we applied azido mono-substituted CD derivatives as reactive intermediates to afford a urea linkage with aminised silica gel via the Staudinger reaction.[6] Recently, Liang et al. employed a 'click' reaction to immobilize azido mono-substituted CD derivatives.[7,8] Araki and coworkers reported catalyzed hydrosilylation for the immobilization of CD containing a double bond.[9]

Many useful chiral selectors based on cyclodextrins have been reported. These include chemically bonded chiral stationary phases based on native-CDs (α-CD, β-CD, γ-CD),[10–12] neutral-CDs (acetyl-β-CD, hydroxypropyl-β-CD, 2,3-dimethyl-β-CD),[13–15] and polar-CD derivatives (phenylcarbamoyl-CDs).[16] In contrast, there are few literature reports on the application of anionic and cationic CD chiral selectors. Stalcup et al. reported a novel chemically bonded anionic-β-CD and its application as a stationary phase in HPLC demonstrating strong chiral separation abilities.[17] Surprisingly, there is no report on chemically bonded cationic β-CDs. A co-polymerization method was reported by Okamoto and coworkers for the preparation of cellulose- and amylose-based CSPs.[18–21] However, the preparation of CD-based CSPs via co-polymerization has rarely been investigated. Previous reports on CD-based polymers described physically coating CSPs onto silica gel and their use as CSPs.[22–24] Chemical co-polymerization represents the most direct and efficient method to achieve chemically bonded cationic β-CD CSPs. Accordingly, we have developed a chemical immobilization method for cationic CSPs to enable studies on the effect of the cationic charge on chiral recognition. Our prior research on coated cationic β-CD had showed better retention properties and selectivity in comparison to neutral CSPs, but they have limited solvent resistance. The coated CSPs were only useful for applications using mobile phases with a ratio of 2-propanol in *n*-hexane or CO_2 no higher than 4% (v:v), while methanol in supercritical fluid chromatography (SFC) could cause damage to the coated CSPs.[25] As such, these chemically bonded cationic β-CD CSPs would be expected to expand the application window toward a broader range of chromatographic conditions.

As depicted in Scheme 1, the starting material, *p*-toluenesulfonyl-β-CD (**1**) was reacted with 4-vinylpyridine or *N*-allyl-*N*-methylamine to afford the corresponding cationic intermediates **2a,b** with a vinyl group.[26,27] The tosylate anion was exchanged with chloride using Amberlite resin.[28] Subsequently, the remaining hydroxy groups on the cationic β-CD derivatives were fully derivatized with phenylisocyanate to obtain the vinylene-functionalized cationic β-CD derivatives **3a,b**.[29,30] Vinylized silica **4** was prepared by refluxing Kromasil porous spherical silica (particle size 5 μm) with 3-methacryloyltriethoxysilane in dry toluene.[31] Prior to chemical polymerization, the vinylene-functionalized cationic β-CD derivatives **3a,b** were physically coated onto **4**. The CD-coated silica was then co-polymerized in the presence of AIBN and a small amount of 2,3-dimethyl-1,4-butadiene (DMBD) to afford cationic β-CD CSPs **5a,b**.[32,33] The modified silica was wrapped in filter paper and extracted with MeOH in a Soxhlet extractor overnight.

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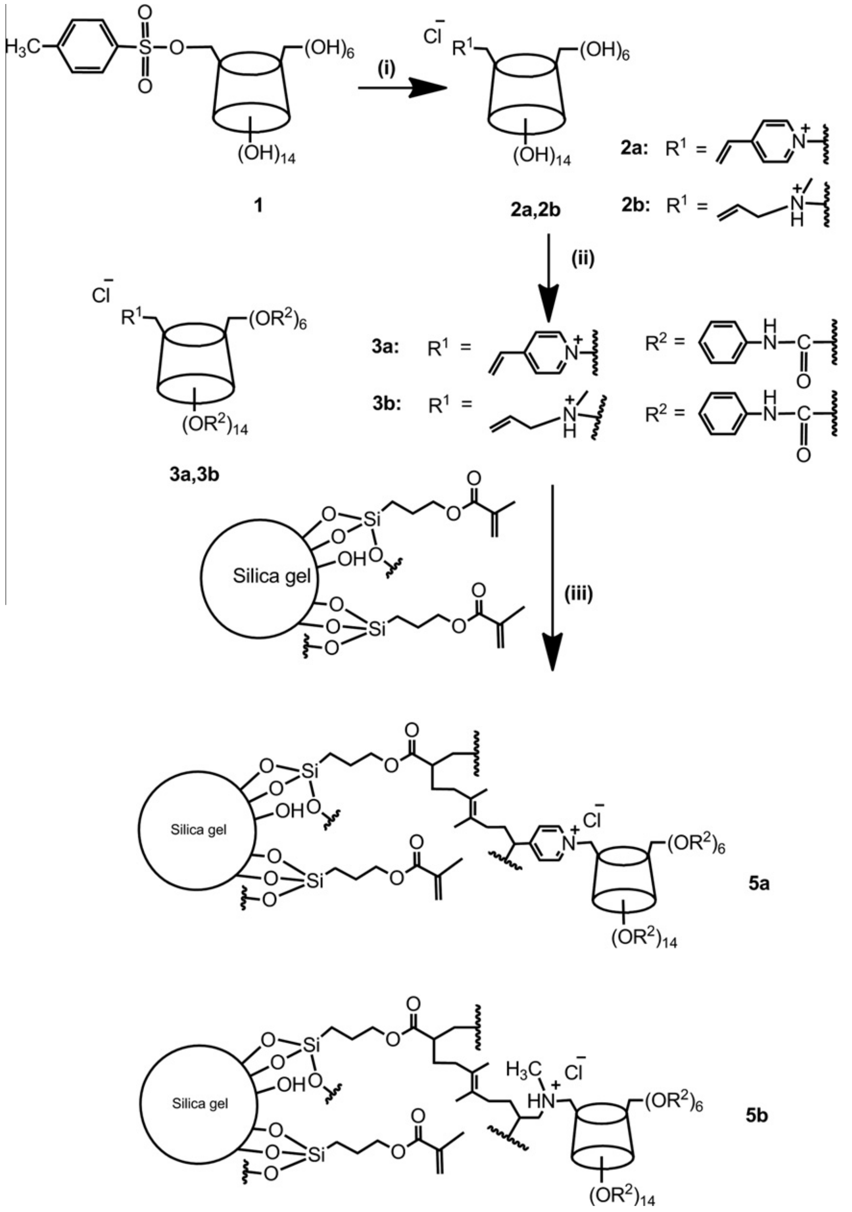

Scheme 1. Synthesis of vinylene functionalized phenylcarbamoyl-β-CD and their chemical immobilization onto silica. Conditions: (i) 4-vinylpyridine or *N*-allyl-*N*-methylamine, DMF/Δ; (ii) phenylisocyanate, pyridine/Δ; (iii) toluene/DMBD/AIBN/Δ.

Elemental analyses revealed that the cationic β-CD CSPs **5a,b** contained approximately 0.78–0.80% nitrogen contributed from the cationic β-CD moiety. Hence the %*N* in elemental analyses results can be used to determine the amount of CD derivative that is chemically bonded onto the silica gel. The surface coverage was calculated based on the %*N* to be 0.091–0.094 μmol m^{-2} using the equation shown below.[34]

$$\text{Surface coverage}(\mu mol\, m^{-2}) = \frac{(\%N)(10^6)}{(S.A.)(n_N)(14.0067)[100 - \frac{\%N}{(n_N)(14.0067)}(M_r)]}$$

The %C and %H for **5a,b** (9.43–9.50% C; 1.39–1.40% H) were significantly higher compared to **4** (5.81% C; 1.27% H). These results indicated successful formation of chemical linkages between the silica support and the chiral monomer. This is in agreement with the observation of characteristic IR peaks for the phenyl group (1631–1448 cm^{-1}, C=C) and carbonyl groups (1708 cm^{-1}, C=O) in **5a** and **5b**.

Chemically bonded cationic β-CD CSPs **5a,b** were then packed individually into stainless steel columns (Ø = 2.1, length = 150 mm) using the slurry method.[35,36] The chiral resolution abilities of the bonded cationic β-CD CSPs were investigated using a Jasco supercritical fluid chromatography system.

The chemically bonded cationic β-CD CSPs **5a**,**b** exhibited excellent chiral resolution abilities in SFC. Representative enantioseparation chromatograms are shown in Figure 1 for the pharmaceutical compounds bendroflumethiazide and trichlormethiazide which showed baseline chiral resolutions. We also demonstrated enantioseparations for the following classes of racemic compounds: α-phenyl alcohols, 2-phenoxypropionic acid and its derivatives, 2-phenylpropionic acid and its derivatives, flavanone derivatives, and dansyl D,L-amino acids. It was found that analytes undergoing good chiral resolution preferably contained phenolic, carboxylic acid, or other moieties which can undergo ionization to afford anions (such as the –SO$_2$-N*H*-moieties in bendroflumethiazide and trichlormethiazide) which take part in electrostatic attractions with the cationic moiety on the CSP. This can be explained by considering Pirkle's three-point interaction model required for enantioseparation,[37] wherein strong ionic interactions