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Mono(6^A-*N*-allylamino-6^A-deoxy)perphenylcarbamoylated β-cyclodextrin: synthesis and application as a chiral stationary phase for HPLC

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Abstract—A novel cyclodextrin derivative: mono(6^A-*N*-allylamino-6^A-deoxy)perphenylcarbamoylated β-cyclodextrin was synthesized. Hydrosilylation with $(EtO)_3SiH$ and then reaction of the reactive siloxane with pristine silica gel afforded a facile entry into a durable, structurally well-defined chiral stationary phase capable of enantioseparation of a variety of racemic drugs.

Cyclodextrins (CD) are cyclic oligosaccharides containing six or more D-(+) glucopyranose units, which are bonded through α-(1,4)-linkages. The structures of CDs give rise to their remarkable ability in forming inclusion complexes with a variety of molecules[1–3] as well as ions.[4,5] Meanwhile, the chirality of the CD moieties makes them amenable for application in enantioseparation processes. Accordingly, it is not surprising that CD and their derivatives are extensively used as chiral selectors in enantioselective chromatography.[6–9]

Previously, we have reported a facile procedure into structurally well-defined chiral stationary phases (CSPs) based on cyclodextrin derivatives using an extended application of the Staudinger reaction under extremely mild reaction conditions.[9–11] These CSPs exhibited good enantioseparation ability towards a wide variety of racemates. In the said procedure, the use of aminised silica gel was required for the immobilization reaction with CD-azido moieties. However, the use of aminised silica would invariably result in remnant unreacted amine moieties on the surface of the CSPs. The presence of free amine groups on the surface may be undesirable under some conditions, since they may interact with analytes via H-bonding affording a longer retention time and/or have an adverse influence on the selectivity of the CSP. We present herein an alternative facile approach that can effectively avoid the use of aminised silica gel. Thus, mono(6^A-*N*-allylamino-6^A-deoxy)perphenylcarbamoylated β-cyclodextrin was first synthesized. Hydrosilylation with triethoxysilane and then reaction of the reactive siloxane with pristine silica gel afforded a durable CSP without free amine groups on the surface.

Scheme 1 depicts the synthetic route to the CSP, starting from the readily available mono-6-deoxy-6-(*p*-tolylsulfonyl)-β-cyclodextrin **1**.[12,13]

Mono-6-deoxy-6-(*p*-tolylsulfonyl)-β-cyclodextrin **1** was readily converted to the key intermediate **2** in high purity and good yield by refluxing in allylamine for 5 h and then precipitating the product in acetonitrile.[14] Reaction of **2** with phenyl isocyanate afforded **3**. Thereafter, hydrosilylation of **3** with $(EtO)_3SiH$ in the presence of a catalytic amount of tetrakis(triphenylphosphine)platinum(0) gave the reactive siloxane **4**, which was directly immobilized onto the surface of silica gel to give the CSP **5** (elementary analysis: C, 4.98; H, 0.73; N, 0.45%).

The carbon content in the elemental analysis as well as the appearance of a FT-IR peak at 1733 cm^{-1} attributable to carbonyl stretching in the CSP **5** provides corroborating evidence that the cyclodextrin moieties have been successfully immobilized onto the surface of the silica gel. According to the microanalysis data, the surface concentration[15] of the cyclodextrin derivative on the silica gel is calculated to be 7.2×10^{-8} mol m^{-2}.

Keywords: cyclodextrin; hydrosilylation; chiral stationary phases; enantioseparation.

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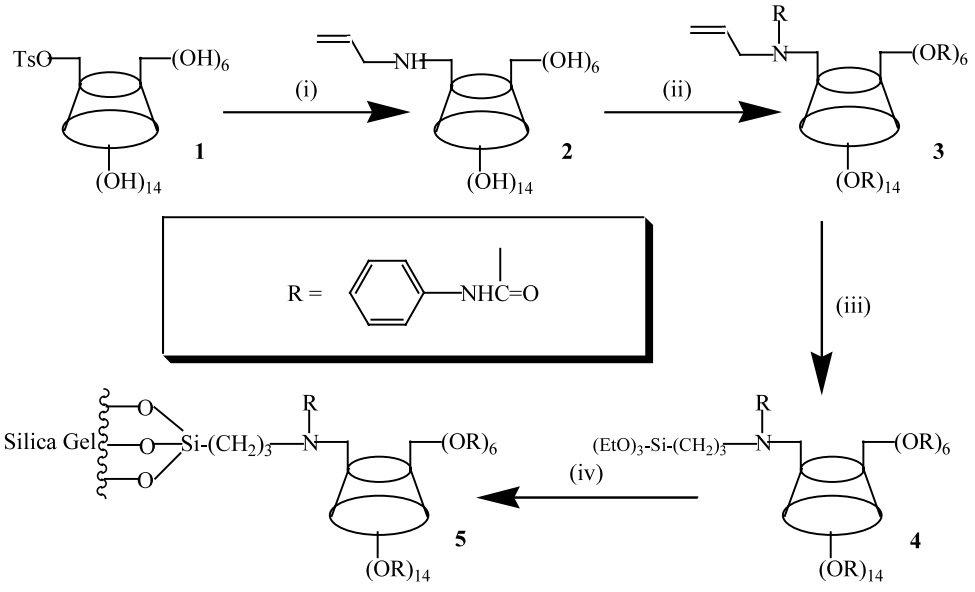


Scheme 1. Synthetic route to CSP **5**. *Reagents and conditions:* (i) CH_2=$CHCH_2NH_2$/Δ; (ii) PhN=C=O/C_5H_5N/Δ; (iii) $(EtO)_3SiH$/cat. $Pt(PPh_3)_4$/THF/Δ; (iv) silica gel/$CH_3C_6H_5$/Δ.

The slurry method (using CCl_4/dioxane) was applied to the packing of the derived CSP into HPLC columns using methanol as the packing solvent. After suspending the CSP in CCl_4/dioxane (20 ml/10 ml) and sonication for 20 min, the slurry of silica gel (3.5 g) was packed into a stainless steel column (∅4.6×250 mm) at a pressure of 7800 psi maintained for 20 min before gradual release of the pressure. The packed column afforded an efficiency of ca. 37,000 plates per meter using biphenyl as a test probe under normal phase (IPA and hexane in 5/95 v/v ratio).

The chromatographic properties of this column were tested with a range of structurally diverse racemic compounds and drugs. Representative chromatograms are depicted in Figure 1.

With a view of evaluating the enantioseparation ability of CSP **5**, we compared it with the SINU-PC column which was prepared by immobilization of mono(6^A-azido-6^A-deoxy)perphenylcarbamoylated β-cyclodextrin onto the same silica gel via the Staudinger reaction.[10,16] Table 1 summarizes representative separation data on

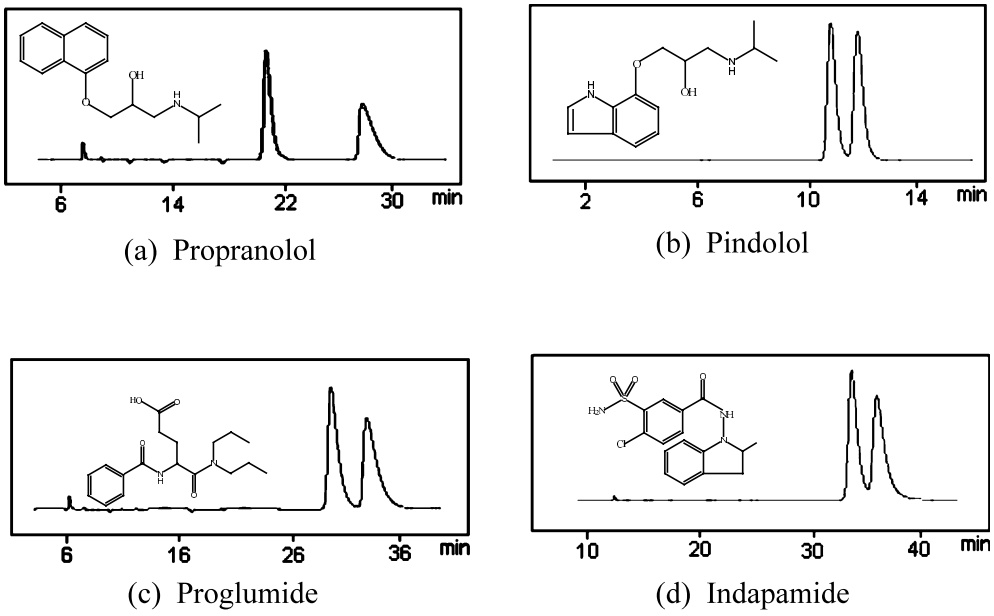
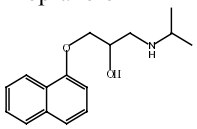
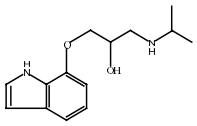
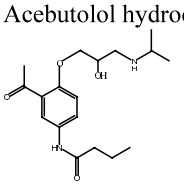
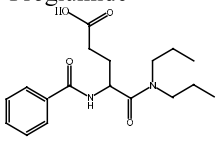
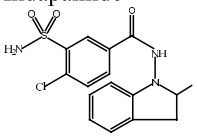
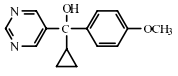
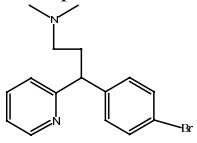
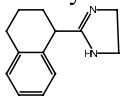


Figure 1. Chromatograms for some chiral drugs on the column packed with CSP **5**. **Conditions**: buffer (1% TEAA, pH 5.50)/methanol = 65/35, flow rate: 0.5 ml/min, UV detector: $\lambda = 240$ nm.

Table 1. Enantioseparation of chiral solutes on CSP **5** and SINU-PC columns

S/N	Chiral compounds	Separation data	
		CSP **5**	SINU-PC[16]
1	Propranolol 	k_1 =2.35 k_2 =3.56 α =1.51 R_s =4.70 Condition: **II**	k_1 =3.91 k_2 =4.97 α =1.27 R_s =3.08 H_2O/CH_3CN=70/30
2	Pindolol 	k_1 =0.71 k_2 =0.87 α =1.23 R_s =1.73 Condition: **II**	NA
3	Acebutolol hydrochloride 	k_1 =1.63 k_2 =1.79 α =1.10 R_s =0.95 Condition: **III**	NA
4	Proglumide 	k_1 =3.76 k_2 =4.29 α =1.14 R_s =1.66 Condition: **II**	NA
5	Indapamide 	k_1 =4.25 k_2 =4.76 α =1.12 R_s =1.33 Condition: **II**	NA
6	Ancymidol 	k_1 =6.66 k_2 =7.05 α =1.06 R_s =0.71 Condition: **III**	NA
7	Brompheniramine 	k_1 =5.57 k_2 =5.81 α =1.04 R_s =0.65 Condition: **I**	NA
8	Tetrahydrozoline 	k_1 =1.26 k_2 =1.35 α =1.07 R_s =0.86 Condition: **III**	NA

Conditions: **I**: Buffer (1% TEA, PH=4.75) / Methanol=70/30; **II**: Buffer (1% TEA, PH=5.50) / Methanol=65/35; **III**: Buffer (1% TEA, PH=5.50) / Methanol=75/25.

these two columns. It is evident that CSP **5** depicted better enantioresolution ability in comparison with the SINU-PC CSP, with several racemates which were not resolvable on the latter being now readily separated. It is also suggestive that for those racemates which can be separated on both of the columns, better separation factors (α) as well as resolutions (Rs) and shorter retentions (k) were achieved on CSP **5**. This indicates that the current synthetic procedure can be used to afford improved CSPs. Further investigations on the detailed chromatographic data as well as the separation mechanism involved will be reported elsewhere.

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