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Arylcarbamoylated allylcarbamido-β-cyclodextrin: synthesis and immobilization on nonfunctionalized silica gel as a chiral stationary phase

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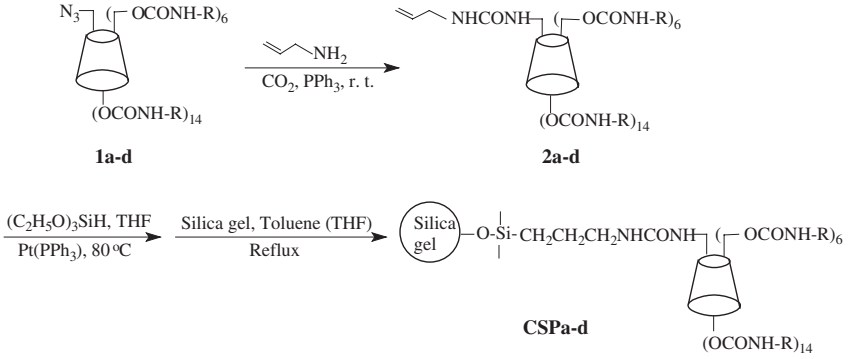
Abstract—Four new chiral stationary phases based on mono-(6^{A}-allylcarbamido-6^{A}-deoxy)-arylcarbamoylated β-cyclodextrin were synthesized. The chiral stationary phase of phenylcarbamoylated β-cyclodextrin exhibited excellent separation capability for a variety of chiral compounds. Compared with the previous work, it was found that the spacer remained on the surface of the silica gel and decreased the enantioseparation capability.

β-Cyclodextrin (β-CD) and its derivatives have been used as chiral selectors in several cases[1–4] owing to complexation between their hydrophobic cavities and organic molecules.[5] As a chiral selector, β-CD is usually derivatized and chemically bonded to silica gel. Derivatization includes alkylation,[6] acylation[7] and carbamoylation,[8] etc. In most cases, a spacer is pre-immobilized on the silica gel and used to connect the derivatized β-CD to the silica gel.[1,9,10] Hence, a disadvantage is that numerous reactive groups remain on the surface of the silica gel after immobilization of derivatized β-CD. The chiral stationary phases (CSPs) prepared are inappropriate for separation of those chiral compounds, which contain groups that can interact with these reactive groups. To resolve this problem, in our previous work, we put forward an alternative method to



Scheme 1. The synthesis of β-CD derivatives and CSP**a**–**d**: (a) R = phenyl; (b) R = 3,5-dimethylphenyl; (c) R = 1-naphthyl; (d) R = 2-methoxyphenyl.

Keywords: Allylcarbamido-β-cyclodextrin; Arylcarbamate; Hydrosilylation; Silanization; Chiral stationary phase; Enantioseparation.
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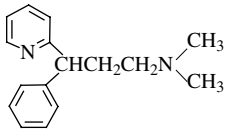
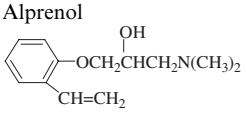
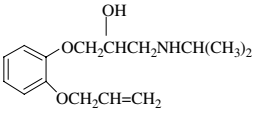
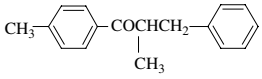
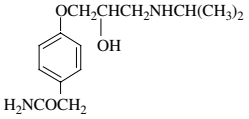
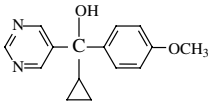
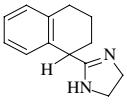
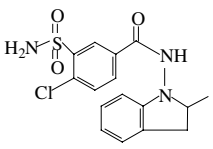
Table 1. Characterization data for CSP**a**–**d**

CSP	IR (cm^{-1})	Elemental analysis (%)			Surface concentration ($\mu mol\,m^{-2}$)
		C	H	N	
CSP**a**	3524–3106 (CONH); 1744 (O–C=O); 1631 (HN–C=O)	9.75	0.97	0.36	0.145
CSP**b**	3536–3002 (CONH); 1739 (O–C=O); 1634 (HN–C=O)	9.93	1.06	0.24	0.122
CSP**c**	3518–3086 (CONH); 1732 (O–C=O); 1638 (HN–C=O)	6.51	0.76	0.21	0.068
CSP**d**	3528–3063 (CONH); 1734 (O–C=O); 1635 (HN–C=O)	5.49	0.69	0.26	0.074

Table 2. Enantioseparation results of chiral compounds on CSP**a**, SINU-PC CSP and CSP**5**

	Chiral compounds	Separation data		
		CSP**a**	SINU-PC CSP	CSP**5**
1	Pheniramine 	k_1 = 2.18 k_2 = 2.42 α = 1.11 R_s = 0.58 Condition 1	NA	NA
2	Alprenol 	k_1 = 3.01 k_2 = 5.17 α = 1.72 R_s = 5.00 Condition 1	k_1 = 1.00 k_2 = 1.63 α = 1.63 R_s = 2.46 Condition 1	NA
3	Oxprenolol 	k_1 = 1.96 k_2 = 2.21 α = 1.13 R_s = 1.30 Condition 1	k_1 = 3.67 k_2 = 4.40 α = 1.20 R_s = 1.00 Condition 2	NA
4	Tolperisone 	k_1 = 5.76 k_2 = 6.17 α = 1.07 R_s = 1.14 Condition 1	NA	NA
5	Atenolol 	k_1 = 0.67 k_2 = 0.85 α = 1.27 R_s = 1.29 Condition 1	k_1 = 0.34 k_2 = 0.45 α = 1.31 R_s = 0.83 Condition 3	NA
6	Ancymidol 	k_1 = 5.88 k_2 = 6.50 α = 1.11 R_s = 0.92 Condition 1	NA	k_1 = 6.66 k_2 = 7.05 α = 1.06 R_s = 0.71 Condition 4
7	Tetrahydrozoline 	k_1 = 1.50 k_2 = 1.65 α = 1.10 R_s = 0.93 Condition 1	NA	k_1 = 1.26 k_2 = 1.35 α = 1.07 R_s = 0.86 Condition 4
8	Indapamide 	k_1 = 8.71 k_2 = 9.71 α = 1.11 R_s = 0.70 Condition 1	NA	k_1 = 4.25 k_2 = 4.76 α = 1.12 R_s = 1.33 Condition 5

Separation conditions: Condition 1: 1% TEAA buffer (pH = 4.65)/methanol = 65/35 (v/v); Condition 2: hexane/isopropanol = 95/5 (v/v); Condition 3: 1% TEAA buffer (pH = 5.15)/methanol = 70/30 (v/v); Condition 4: 1% TEAA buffer (pH = 5.50)/methanol = 75/25 (v/v); Condition 5: 1% TEAA buffer (pH = 5.50)/methanol = 65/35 (v/v).

immobilize phenylcarbamoylated β-CD, where the linker between the spacer and β-CD was an amine that was converted into a urea as a side chain of the spacer when modifying the hydroxyls of β-CD.[11] The CSP (referred to as CSP**5**) prepared by this route showed better chiral recognition than the CSP (referred to SINU-PC CSP) with a urea contained in the spacer chain,[9] although the modifying agent was the same. When SINU-PC CSP was prepared, the silica gel was pre-functionalized with 3-aminopropyltriethoxysilane but many spacers that is 3-aminopropyl groups, remained on the silica gel. Additionally, in these two CSPs, the linkages for connecting the β-CD were different. Thus the question arises, which factor caused the difference in chiral recognition, the residual spacer or the different linkages or both of them? To probe this problem, we designed another approach to immobilize β-CD derivatives to avoid pre-functionalization of the silica gel so as to ensure the same spacer and linkage but with no spacer remaining, cf. SINU-PC CSP;[9] and with a different linkage compared to CSP**5**.[11] In this case, a comparison of chiral recognition among these three CSPs can be made to find out, which factor causes the difference in chiral separation.

The synthetic route is shown in Scheme 1, which is based on the allylcarbamido-derivatization of arylcarbamoylated mono-azido-β-CD via the Staudinger reaction, followed by hydrosilylation of the double bond and silanization of silica gel. The precursor of carbamoylated mono-allylcarbamido-β-CD, mono-azido-β-CD[12] is easily available from tosylated β-CD.[13] The triethoxysilane moiety contained in derivatized β-CD has high reactivity towards the hydroxyls on the surface of silica gel. So the approach established herein is a useful alternative. The arylcarbamoylated mono-azido-β-CDs were prepared by following the method described in previous work.[9]

The arylcarbamoylated allylcarbamido-β-CDs were synthesized first. Allylamine was reacted with an equivalent of arylcarbamoylated mono-azido-β-CD in tetrahydrofuran (THF) at room temperature in the presence of triphenylphosphine with continuous bubbling of carbon dioxide. After completion of the reaction, the solution was concentrated and was subsequently precipitated from a mixture of ethyl acetate and hexane (1:5) to afford a white solid. The product was further purified by dissolving in THF followed by re-precipitation with ethyl acetate/hexane (1:5). The newly synthesized β-CD derivatives were characterized by NMR, FT-IR and elemental analysis.[14]

The double bond of the β-CD derivatives was hydrosilylated with triethoxysilane in dry THF at 80 °C in the presence of a Pt catalyst for at least 48 h. Excess triethoxysilane was removed under vacuum. The subsequent silanization reaction was conducted in dry toluene for the preparation of CSP**a**,**b** and in dry THF for the preparation of CSP**c**,**d** overnight at reflux. The CSPs prepared were washed thoroughly with acetone to remove unreacted hydrosilylated β-CD derivatives. Complete removal was determined by thin layer chromatography, where no organic compound could be detected in the filtrate. Successful immobilization was confirmed from IR spectra and elemental analysis. In the IR spectra, there were typical absorbances (~1732–1744 cm^{-1}) for the carbamate carbonyls of derivatized β-CD. The characterization data for CSP**a**–**d** are listed in Table 1.

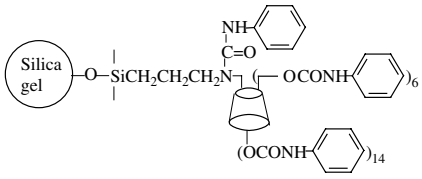


Figure 1. The structure of CSP**5**.

CSP**a** was packed into stainless steel columns (∅ 4.6 mm × 250 mm). The chiral recognition capability was evaluated with a variety of chiral compounds, and excellent enantioseparation results were obtained. For pyrimidine derivatives, CSP**a**, SINU-PC CSP and CSP**5** showed similar separation capabilities. Table 2 presents the representative separation results of some chiral compounds on these three CSPs. Of the chiral compounds listed, five chiral compounds could not be separated on the latter two CSPs, but could be separated on CSP**a**. Other enantioseparation results are not listed where CSP**a** showed better resolutions, in comparison with the latter two CSPs. It is evident that the chiral recognition capability of CSP**a** is better than those of the latter two CSPs. Accordingly we can conclude that the decrease in separation capability of SINU-PC CSP was caused by the residual spacer. The difference in separation capability between CSP**a** and CSP**5** was caused by the different linkages (Fig. 1). A urea linkage in the spacer chain is superior to one as a side chain of the spacer for chiral recognition.

In summary, CSP**a** has the best enantioseparation capability among these three CSPs. The synthetic approach described is very useful for the preparation of β-CD-based CSPs owing to the easy availability of the materials used.

Acknowledgements

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14. **2a**: Yield 95%; mp: 201–209 °C; $[\alpha]_D^{25}$ +42.86 (*c* 0.5, acetone); IR (cm^{-1}): 3419–3202 (amide N–H), 3146 (double bond C–H), 3064 (arom C–H); 2962 (C–H), 1734 (ester C=O), 1606, 1540, 1508 (arom C=C), 1233, 1059 (C–O–C); ^1H NMR ($CDCl_3$, TMS) δ (ppm): 8.05–6.61 (m, 100H), 5.60 (s, 1H), 5.32–3.13, (m, 73H), 2.06 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 153.9–152.9 (m, C=O), 137.6–136.8 (m, *C*H=CH$_2$), 133.5–123.4 (m, arom C), 119.6–118.9 (m, CH=*C*H$_2$), 98.9 (C1), 77.4–76.5 (m, C4), 73.2–70.0 (m, C2, C3, C5), 64.4–63.3 (m, C6), 41.8 (CH_2–NH); Elemental analysis for $C_{186}H_{176}N_{22}O_{55}\cdot 3H_2O$: Calcd C 61.15%, H 4.99%, N 8.44%; Found C 61.37%, H 5.17%, N 8.08%.
2b: Yield 87%; mp: 188–191 °C; $[\alpha]_D^{25}$ +20.76 (*c* 0.5, acetone); IR (cm^{-1}): 3406–3195 (amide N–H), 3094 (double bond C–H), 3018 (arom C–H), 2916 (C–H), 1739 (ester C=O), 1617, 1555 (arom C=C), 1223, 1044 (C–O–C); ^1H NMR ($CDCl_3$, TMS) δ (ppm): 7.73–6.28 (m, 60H), 5.57 (s, 1H), 5.31–3.71 (m, 73H), 2.35–1.57 (m, 122H); ^{13}C NMR ($CDCl_3$) δ (ppm): 153.7–152.7 (m, C=O), 138.5–136.7 (m, *C*H=CH$_2$), 132.1–125.1 (m, arom C), 117.2–116.5 (m, CH=*C*H$_2$), 98.7 (C1), 77.4–76.6 (m, C4), 73.3–69.9 (m, C2, C3, C5), 63.8–56.9 (m, C6), 42.0 (CH_2–NH), 31.6–20.8 (m, CH_3); Elemental analysis for $C_{226}H_{256}N_{22}O_{55}\cdot 4H_2O$: Calcd C 64.14%, H 6.24%, N 7.28%; Found C 64.65%, H 6.35%, N 6.98%.
2c: Yield 91%; mp: 136–139 °C; $[\alpha]_D^{25}$ +77.37 (*c* 0.5, acetone); IR (cm^{-1}): 3404–3227 (amide N–H), 3053 (double bond C–H), 3013 (arom C–H), 2956 (C–H), 1739 (ester C=O), 1596, 1545, 1504 (arom C=C), 1218, 1039 (C–O–C); ^1H NMR ($CDCl_3$, TMS) δ (ppm): 8.18–6.50 (m, 140H), 5.52 (s, 1H), 5.16–4.11 (m, 73H), 2.13 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 156.8–153.8 (m, C=O), 137.2–131.9 (m, *C*H=CH$_2$), 128.7–125.2 (m, arom C), 121.9–120.4 (m, CH=*C*H$_2$), 115.2 (C1), 77.4–76.6 (m, C4), 73.8–67.3 (m, C2, C3, C5), 64.2–63.3 (m, C6), 42.2 (CH_2–NH); Elemental analysis for $C_{266}H_{216}N_{22}O_{55}$:Calcd C 69.45%, H 4.70%, N 6.70%; Found C 69.87%, H 4.95%, N 6.35%.
2d: Yield of 93%; mp: 134–142 °C; $[\alpha]_D^{25}$ +36.72 (*c* 0.5, acetone); IR (cm^{-1}): 3421–3193 (amide N–H), 3141 (double bond C–H), 3008 (arom C–H), 2946 (C–H), 1750 (ester C=O), 1617, 1535 (arom C=C), 1233, 1044 (C–O–C); ^1H NMR ($CDCl_3$, TMS) δ (ppm): 8.17–6.29 (m, 80H), 5.62 (s, 1H), 5.34–3.18 (m, 133H), 1.82 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm): 152.9–151.7 (m, C=O), 148.7–147.6 (m, *C*H=CH$_2$), 137.2–119.7 (m, arom C), 110.0–108.9 (m, CH=*C*H$_2$), 99.0 (C1), 77.4–76.6 (m, C4), 72.4–70.3 (m, C2, C3, C5), 63.3 (C6), 55.6–54.8 (m, OCH_3), 42.4 (CH_2–NH); Elemental analysis for $C_{206}H_{216}N_{22}O_{75}$: Calcd C 58.91%, H 5.15%, N 7.34%; Found C 59.23%, H 5.28%, N 7.06%.