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A Facile Immobilization Approach for Perfunctionalised Cyclodextrin onto Silica via the Staudinger Reaction

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Abstract: The Staudinger reaction was applied for the first time in the immobilization of mono-(6-azido-6-deoxy)-perfunctionalised cyclodextrins onto the surface of aminised silica gel under mild conditions. The composite materials obtained are applicable as chiral stationary phases for enantioseparation processes.

Functionalised cyclodextrins have been attracting burgeoning interests since the demonstration by Armstrong and co-workers [1] that immobilization of these chiral compounds onto inert support materials, such as silica gel afforded chiral stationary phases (CSP) which are amenable to both analytical and preparative scale enantioseparation of a broad range of racemic compounds. Previously, research efforts were directed mainly on chemically anchoring cyclodextrins (CD) onto solid matrices *via* amino linkages [2] and the solvolytically more stable carbamic acid moieties [3] involving post-immobilization derivatisation procedures. In all these approaches, regioselective immobilization of CD cannot be readily accomplished since reaction may occur indiscriminately at the 2, 3 or 6- position of cyclodextrin or result in a complex mixture of multi-anchored CD instead of one with well-defined chemical structure. In addition, subsequent chemical derivatisation of the immobilized CD also does not readily lead to materials with easily controllable batch-to-batch reproducibility on account of the invariable need of conducting heterogeneous solid-liquid reactions. These factors, in part, may have contributed to the high cost and poor availability of the CD-CSP.

We report herein a facile synthetic approach which effectively overcome the above shortcomings. In this, mono-

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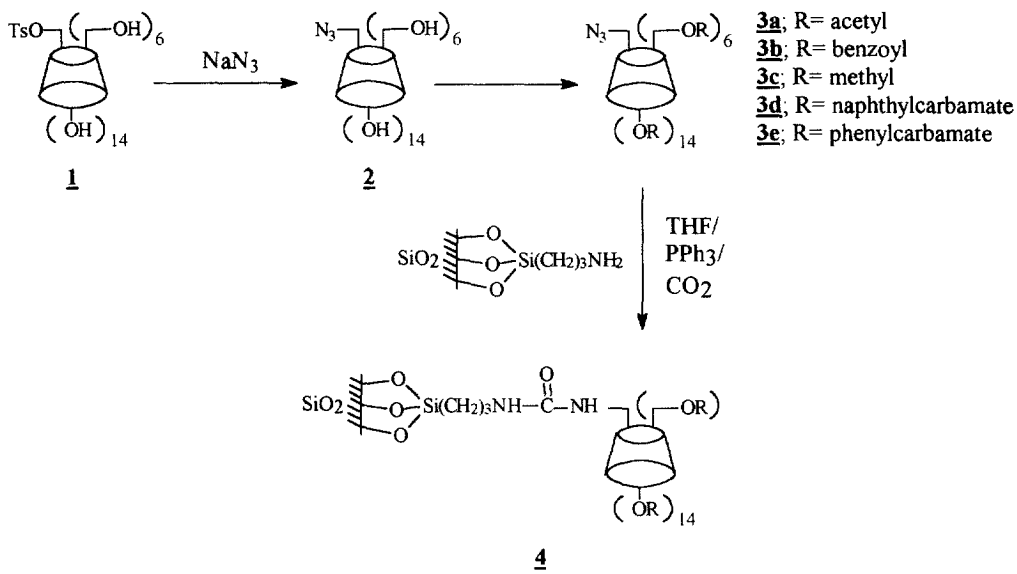
(6-azido-6-deoxy)perfunctionalised cyclodextrins were first synthesized, purified and characterized. Immobilization onto the surface of aminized silica gel can then be conveniently carried out on the CD-azido functionality using a Staudinger reaction [4] under extremely mild reaction conditions. Chemical anchoring of the CD moieties onto the support were effectively *via* the hydrolytically stable urethane linkage.

Scheme 1. Synthetic route to perfunctionalised cyclodextrin immobilised silica gel



The synthetic route used is depicted in Scheme 1 using the readily available mono-6-deoxy-6-(p-tolysulphonyl)cyclodextrin **1** [5] as starting material. Treatment of **1** with an excess of sodium azide in DMF at 95 ^{0}C for 10 hrs afforded mono-(6-azido-6-deoxy)-cyclodextrin **2** after purification by complex formation [6] with 1,1,2,2-tetrachloroethane in *ca* 90% yield. Thereafter, complete functionalisation of the remaining hydroxyl groups can be readily effected under a variety conditions [7] which afforded a range of mono-(6-azido-6-deoxy)-perfunctionalised-cyclodextrins **3** in good yields and high purities.

Aminized silica gel was prepared by stirring silica gel (dried overnight in 0.1 mmHg vacuum at 180 ^{0}C) with γ-aminopropyltriethoxysilane in accordance with a literature procedure [8]. Staudinger reaction of the CD-derivatives **3** were initiated by passage of CO_2 into a THF suspension of the aminized silica gel. At this stage, an infrared of a sample of the reacting silica gel depicted vibrational bands at 1560 cm^{-1} ascribed to the formation of the propylammonium propylcarbamate on the surface of silica, an expected intermediate in the reaction. Completion of the immobilization process was then effected by addition of a solution mixture of triphenylphosphine and the respective derivatives **3**. The crude CSPs were purified by soxhlet extraction with acetone to remove the triphenyphosphine oxide and any unreacted cyclodextrin by-products.

The obtainment of CSPs **4** were evident from the weak but characteristic FT-IR vibrational bands particularly in

the 1400-1800 cm^{-1} region, reminiscent of those present in the precursor compounds **3**. In addition, the significantly higher carbon contents in the elemental analyses for CSPs **4** as of the presence of determined surface concentration of CD-derivatives(*Table 1*) further corroborated the success of our immobilization approach. Since we have utilized only purified and characterized precursor compounds **3** and since there is only one azido functional group in every cyclodextrin molecule from which the Staudinger reaction can occur, the current procedure therefore afforded structurally well-defined CSPs.

Table 1 Charaterisation of the perfunctionalised cyclodextrin immobilised silica gel.

List of Bonded Sorbents	C%	H%	N%	Surface Concentration ($\mu mol\ m^{-2}$)
Aminised silica gel	5.43	1.82	2.11	---
Permethyl–β-CD immobilised silica gel	15.49	3.07	1.52	0.80
Peracetyl–β-CD immobilised silica gel	16.70	2.98	1.56	0.67
Perbenzoyl–β-CD immobilised silica gel	17.25	2.40	1.43	0.32
Perphenylcarbamate–β-CD immobilised silica gel	17.42	2.15	2.56	0.32
Pernaphthylcarbamate–β-CD immobilised silica gel	16.17	2.07	2.45	0.20

The respective CSPs when packed into stainless steel HPLC columns, depicted excellent enantioseparation of a board range of structurally diverse racemic compounds and drugs (representative chromatogram depicted in *Figure 1*). These analytical results will be reported elsewhere.

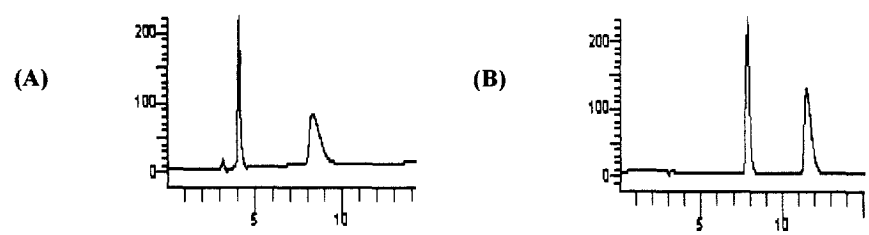


Figure 1. HPLC separation of the enantiomers on stainless column (ϕ4.6 × 250 mm) packed with perphenylcarbamate–β-CD immobilised silica gel. Flow rate: 1ml/ min. UV detector: λ= 230nm. (A) Atropine, mobile phase: Buffer(1% TEA aqueous adjusted with HOAc, PH= 4.65)/MeOH =65/35; (B) 1-(p-chlorophenyl) ethanol, mobile phase: Hexane/ IPA= 90/10.

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7. **3a** was prepared in $(CH_3CO)_2O$/ pyridine in yield of 82%,m.p. 133-135 ^{0}C; $[\alpha]_D$ +120.92 ^{0} ($C_{1.0}$, $CHCl_3$); IR (cm^{-1}): 2966 (C-H str), 2111 (-N_3 str), 1750 (C=O str), 1052 (C-O str); ^{1}H NMR ($CDCl_3$, TMS) δ (ppm): 5.33-5.26 (m, 7H), 5.13-5.01 (m, 7H), 4.85-4.77 (m, 7H), 4.58-4.54 (d, J= 12.3Hz, 7H), 4.32-4.18 (m, 7H), 4.15-4.10 (m, 7H), 3.80-3.66 (m, 7H), 2.16-2.02 (multi s, 60H); Anal. Calcd. for $C_{82}H_{109}O_{54}N_3$: C 49.23%, H 5.49%, N 2.10%; found: C 49.14%, H 5.64%, N 1.95%. **3b** was prepared in PhCOCl/ pyridine in the yield of 66%, m.p. 96-99°C; $[\alpha]_D$ +24.65 ° ($C_{1.0}$, $CHCl_3$); IR (cm^{-1}): 3071 (arom C-H str), 2105 (-N_3 str), 1729 (C=O str), 1603, 1449 (C=C arom ring str), 1273, 1097 (C-O-C str), 704 (C-H arom); ^{1}H NMR ($CDCl_3$, TMS) δ (ppm): 8.24-8.12 (m, 12H), 7.75-7.24 (m, 46H), 7.23-7.13 (m, 14H), 7.09-6.80 (m, 28H), 6.10-5.88 (m, 7H), 5.75-5.42 (m, 7H), 5.20-4.50 (m, 28H), 4.24-3.95 (m, 7H); Anal. Calcd. for $C_{182}H_{149}N_3O_{54}$: C 67.42%, H 4.63%, N 1.30%; found: C 66.91%, H 4.51%, N 1.25%. **3c** was prepared in CH_3I/DMF/NaH in the yield of 82%, m.p. 95-99 °C; $[\alpha]_D$ +157.00 ° ($C_{1.0}$, $CHCl_3$); IR (cm^{-1}): 2929 (C-H); 2103 (-N_3 str), 1034 (C-O str); ^{1}H NMR ($CDCl_3$, TMS) δ (ppm): 5.18-5.08 (m, 7H), 3.95-3.38 (m, 95H), 3.23-3.15 (m, 7H); Anal. Calcd. for $C_{62}H_{109}N_3O_{34}$: C 51.70%, H 7.62%, N 2.92%; found: C 51.43%, H 7.00%, N 2.76%. **3d** was prepared in naphthyl isocyanate/ pyridine in the yield of 55%, m.p. 192-199 °C; $[\alpha]_D$ +89.56 ° ($C_{1.0}$, $CHCl_3$); IR (cm^{-1}): 3401, 3308 (N-H str), 2110 (-N_3 str), 1738 (C=O str), 1549, 1505 (arom C=C str), 1215, 1043 (C-O-C str), 772 (C-H arom); ^{1}H NMR ($CDCl_3$, TMS) δ (ppm): 6.20-8.40 (m, 160H), 2.50-5.75 (m, 49H); Anal. Calcd. for $C_{262}H_{209}N_{23}O_{54}{\cdot}4H_2O$: C 68.17%, H 4.74%, N 6.98%; found: C 68.45%, H 4.93%, N 6.62%. **3e** was prepared in phenyl isocyanate/ pyridine in the yield of 57%, m.p. 220-227 °C; $[\alpha]_D$ +33.40 ° ($C_{1.0}$, $CHCl_3$); IR (cm^{-1}): 3393, 3313 (N-H str); 2102 (N_3 str), 1732 (C=O str), 1604, 1537, 1443 (arom C=C str), 1221, 1053 (C-O-C str), 750 (C-H arom); ^{1}H NMR ($CDCl_3$, TMS) δ (ppm): 7.48-6.55 (m, 120H); 5.65-5.50 (m, 7H), 5.32-5.08 (m, 14H), 4.82-4.25 (m, 21H), 4.05-3.90 (m, 7H); Anal. Calcd. for $C_{182}H_{169}N_{23}O_{54}{\cdot}8H_2O$: C 59.29%, H 5.06%, N8.73 %; found: C59.59 %, H5.34 %, N8.48 %.
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