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Synthesis of cyclam-capped β-cyclodextrin-bonded silica particles for use as chiral stationary phases in capillary electrochromatography

Yinhan Gong,[a] Guoping Xue,[b] Yanqiao Xiang,[b] Jerald S. Bradshaw,[b] Milton L. Lee[b] and Hian Kee Lee[a,*]

[a]*Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543*
[b]*Department of Chemistry and Biochemistry, Brigham Young University, Provo, UT 84602-5700, USA*

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Abstract—β-Cyclodextrin (β-CD) was anchored onto silica particles at its C(2) position, derivatized primarily at the C(6) position by treatment with bromoacetyl bromide, and finally reacted with two types of cyclams to form cyclam-capped β-CD-bonded silica particles. When used as chiral stationary phases in capillary electrochromatography, these novel bonded silica particles exhibited excellent enantioselectivities for chiral separations. © 2002 Elsevier Science Ltd. All rights reserved.

Development of new chiral stationary phases (CSP) with high selectivities to separate chiral molecules is one of the most active areas of liquid chromatography (LC); chiral LC is an important technique in the pharmaceutical industry. Many chiral separations have been accomplished using β-cyclodextrin-type bonded silica particles as CSPs in LC.[1] However, one drawback in utilizing cyclodextrins has been the low binding constants for most guest molecules.[2] It was reported that the crown ether-capped β-CDs[2–4] exhibited high binding constants for several guest molecules. Recently, it was shown that the combination of a crown ether and β-CD as a buffer additive in capillary electrophoresis (CE) sometimes produced better enantioseparations than did either selector alone due to cooperative functioning of the β-CD and the crown ether.[5–7] However, many crown ethers, cyclams and derivatized CDs cannot be used as CE additives due to their high UV–vis absorption or poor solubility in water. Alternatively, they can be bonded onto silica to use as CSPs in LC.

We have previously reported a method involving successive multiple-step liquid–solid phase reactions on the silica surface to prepare crown ether-capped β-CD-bonded silica particles for use as new CSPs in LC.[8] These CSPs have shown excellent enantioselectivities. Since cyclams have similar structures and properties to crown ethers, it was of interest to us to prepare cyclam-capped β-CD particles for comparison with our previously synthesized crown ether-capped β-CD particles. In this paper, we describe a synthetic method to prepare two types of cyclam-capped β-CD-bonded silica particles. Better enantioselectivities were obtained using the cyclam-capped β-CD-bonded phases compared to the crown ether-capped β-CD bonded phases in capillary electrochromatography.

The synthetic strategies for the synthesis of the required cyclam ligands **4** and **8** are outlined in Scheme 1. Tris-*t*-butyl carbamate-substituted cyclam **1** was synthesized as described.[9] Compound **3** was synthesized by reductive amination of 8-benzenesulfonamido-2-quinolinecarboxaldehyde **2**[10] with **1** using $NaBH(OAc)_3$ as the reducing agent in 85% yield. Removal of the Boc protecting groups was easily accomplished in an excellent yield (95%) using CF_3CO_2H to give ligand **4**.[11] Key intermediate **5** for ligand **8** has already been prepared using formaldehyde and cyclam as the starting reagents.[12] Treatment of **5** with 2-(bromomethyl)-6-(hydroxymethyl)-pyridine **6**[13] in CH_3CN gave disubstituted macrotricycle **7** in 90% yield. Ligand **8**[14] was obtained in quantitative yield after basic hydrolysis of **7** in NaOH (3 M) at room temperature. The synthetic details for the preparation of ligands **4** and **8** will be published in due course.

Keywords: chiral stationary phase; enantiomeric separation; cyclam; crown ether; β-cyclodextrin; capillary electrochromatography.

* Corresponding author. Tel.: (65)-6874-2995; fax: (65)-6779-1691; e-mail: chmleehk@nus.edu.sg

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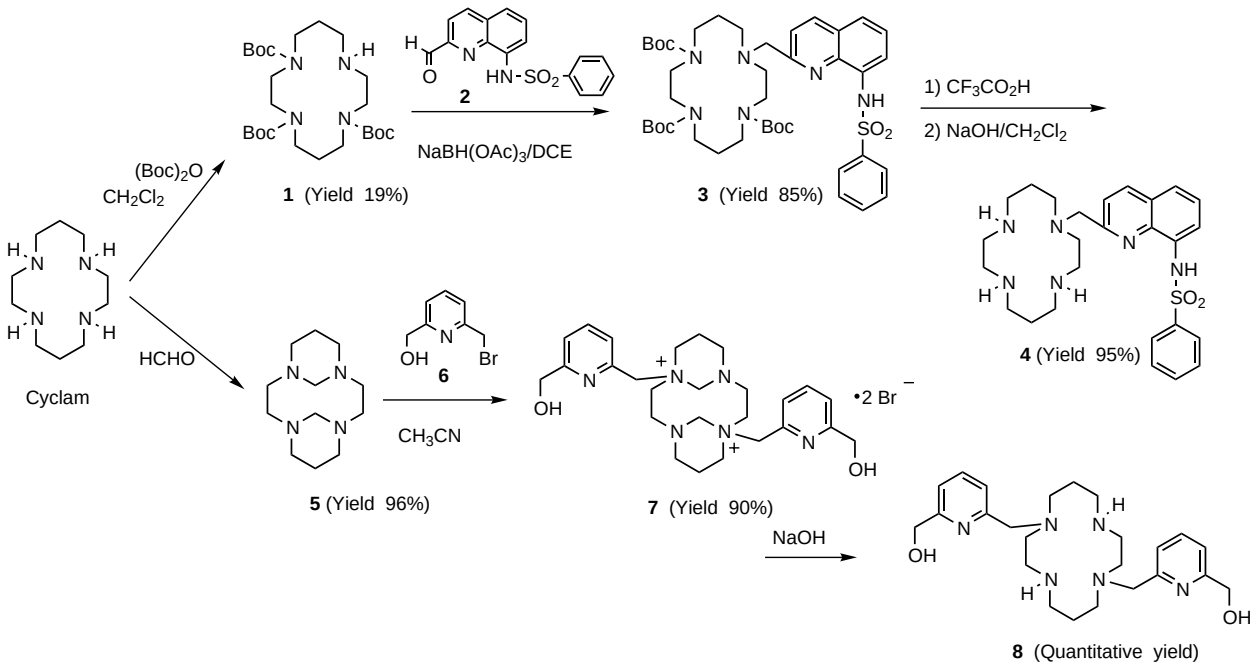
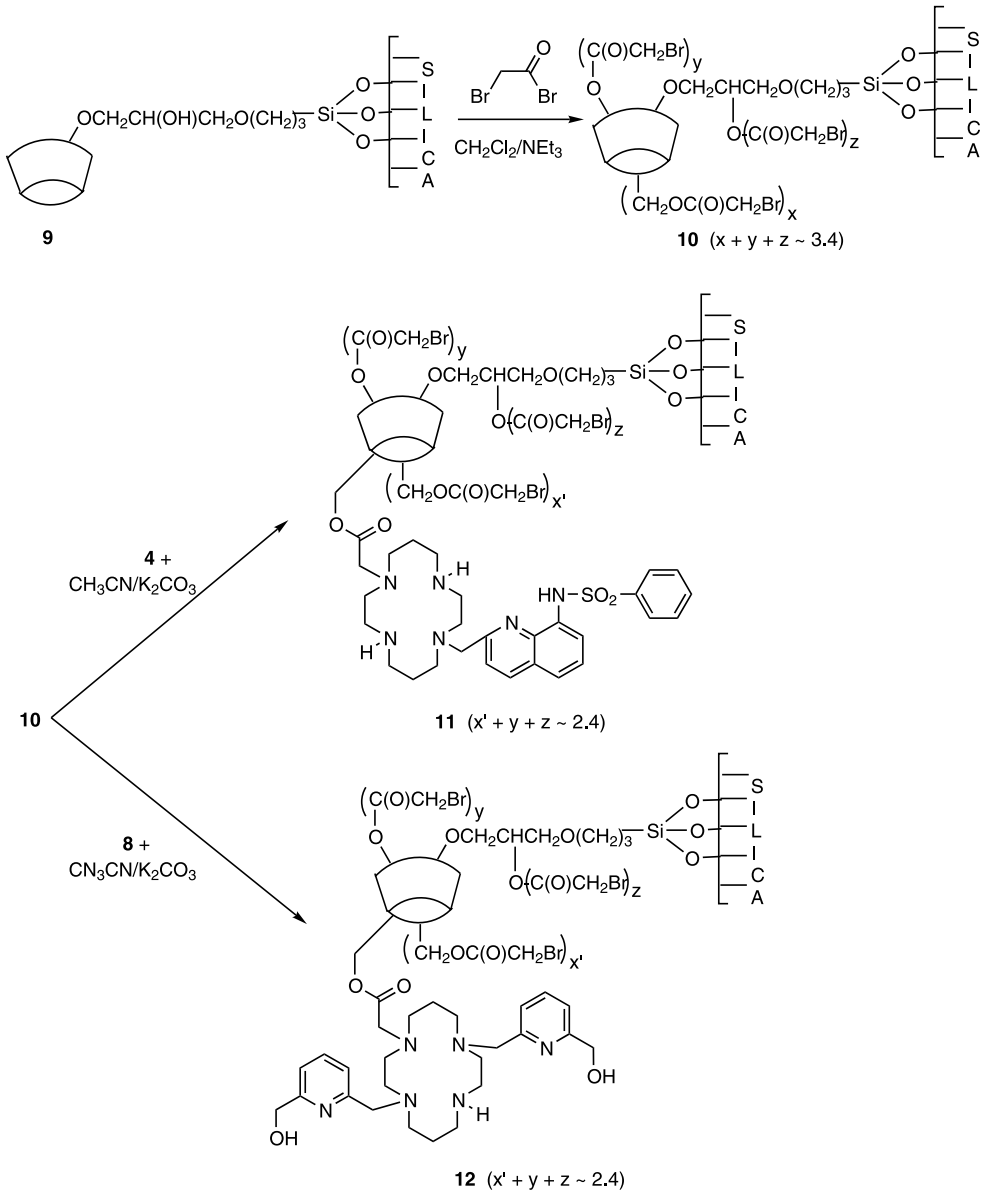


Scheme 1. Synthesis of cyclam derivatives **4** and **8**.

The β-CD was anchored onto the silica gel particles at the C(2) secondary hydroxyl position to form compound **9**[15] as reported.[8] The more reactive C(6) primary hydroxyl groups[16,17] are then available for further reactions. Compound **9** was first treated with seven equivalents of bromoacetyl bromide to form **10**[8] (see Scheme 2). Due to the fact that the seven C(6) hydroxyl groups of the attached CD are more reactive and less sterically hindered than those at C(2) or C(3),[16,17] and they are also less sterically hindered than the secondary hydroxyl group in the spacer arm, we believe that the majority of the bromoacetate units are attached at the C(6) positions. Thus, compound **10** has a β-CD containing some 6-*O*-bromoacetate groups and is attached to silica through its 2-O position, as shown in Scheme 2. Compound **10** was then treated with the two cyclams to form the cyclam-capped β-CD-appended silica materials **11** and **12**.[18] Since the amine groups in the cyclam ring are more reactive than the other functional groups in cyclams **4** and **8**, the two cyclams must be appended to the β-CD via the nitrogen atom(s) in the ring, as shown in Scheme 2. Because of steric constraints, it is unlikely that the cyclam is attached to the β-CD via two linkages, although there are two or three amine groups in the cyclam rings.

Since **11** and **12** have a chiral selector with three recognition sites, i.e. β-CD, cyclam and its side arm, they exhibit excellent enantioselectivities when used as CSPs in capillary electrochromatography (CEC).[19] After inclusion of the metal ion (Ni^{2+}) from the running buffer into the cyclam unit, particles **11** and **12** are positively charged. The positively charged cyclam-capped β-CD can supply extra electrostatic interactions with ionizable solutes and enhance the dipolar interactions with polar neutral solutes. This can enhance the host–guest interaction with the solute and improve chiral recognition and selectivity. Since the side arms in the cyclams can also include Ni^{2+} ions that have higher positive charges than Na^+ or K^+ ions, and the positively charged cyclam center is nearer to the β-CD compared to 4′-aminobenzo-18-crown-6 and 4′-aminobenzo-15-crown-5-capped β-CD-bonded particles,[8] particles **11** and **12** have stronger electrostatic and dipolar interactions with solutes and, accordingly, show better enantioselectivities than the crown ether-capped β-CD-bonded phases. It was found that, for labetalol and 2-amino-1,2-diphenylethanol which have two chiral centers, only partial separation of the four stereoisomers can be achieved on the 4′-aminobenzo-18-crown-6 and 4′-aminobenzo-15-crown-5 capped β-CD-bonded phases, however, baseline separation of the four stereoisomers is easily achieved on bonded phases **11** and **12** (shown in Fig. 1). The cooperative functionings of β-CD, cyclam and its side arms are important for chiral recognition.

In summary, cyclam-capped β-CD-bonded silica particles were synthesized using a convenient successive multiple-step liquid–solid phase reaction on the silica gel surface. These bonded silica materials have excellent enantioselectivities due to the cooperative functioning of the cyclam and β-CD when used as CSPs in CEC.



Scheme 2. Synthesis of the two cyclam-capped β-CD-bonded silica particles.

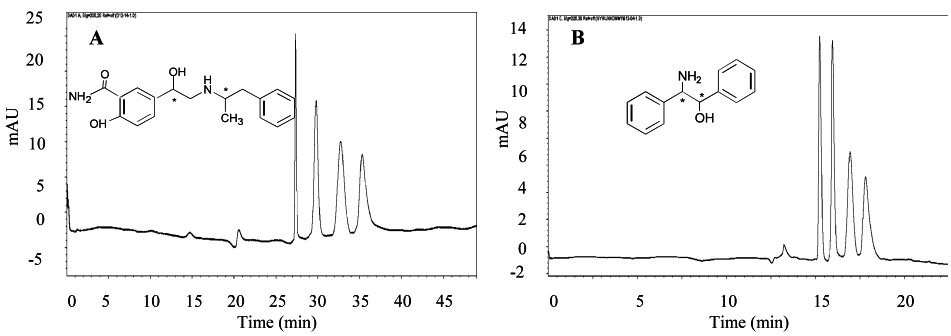


Figure 1. (A) CEC separation of the four stereoisomers of labetalol using compound **11** as stationary phase. Conditions: 75 μm i.d.×30 cm effective length fused silica column (38.5 cm total length) packed with **11** (1.5 μm, 100 Å on Alltech Exsil porous silica particles, Deerfield, IL, USA); 10 mM Tris buffer (pH 8.6) containing 2 mM $Ni(ClO_4)_2$/acetonitrile (30:70 v/v), 15 kV, 254 nm UV detection. (B) CEC separation of the four stereoisomers of 2-amino-1,2-diphenylethanol using compound **12** as stationary phase. Conditions: 75 μm i.d.×30 cm effective length fused silica column (38.5 cm total length) packed with **12** (1.5 μm, 100 Å on Alltech Exsil porous silica particles, Deerfield, IL, USA); 10 mM Tris buffer (pH 8.6) containing 2 mM $Ni(ClO_4)_2$/acetonitrile (40:60 v/v), 20 kV, 210 nm UV detection.

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11. Compound **4**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.95–7.90 (m, 3H), 7.50 (t, $J=3.2$, 1H), 7.32–7.16 (m, 5H), 7.10 (t, $J=3.2$ Hz, 1H), 3.92 (s, 2H), 3.05–2.96 (m, 8H), 2.81–2.68 (m, 8H), 1.99–1.87 (m, 4H); HRMS (FAB): m/z, calcd for $C_{26}H_{37}N_6O_2S$ $(M+1)^+$: 497.2702, found: 497.2698. Anal. calcd for $C_{26}H_{36}N_6O_2S$: C, 62.87; H, 7.31. Found: C, 62.63; H, 7.17%.
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14. Compound **8**: ^{1}H NMR (200 MHz) δ 7.40–7.10 (m, 6H); 4.76 (br., 2H); 4.65 (s, 4H), 3.82 (s, 4H), 2.80 (br., 2H), 2.72–2.70 (m, 12H), 2.59 (t, $J=4.4$ Hz, 4H), 1.81 (m, 4H); HRMS (FAB) m/z, calcd for $C_{24}H_{39}N_6O_2$ $(M+1)^+$: 443.3137, found: 443.3142. Anal. calcd for $C_{24}H_{38}N_6O_2$: C, 65.13; H, 8.65. Found: C, 64.95; H, 8.87.
15. Compound **9** was prepared using 1.5 μm porous silica. An elemental analysis of C, 7.75; H, 1.87 shows a concentration of anchored β-CD of 160 μmol g^{-1}.
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18. Cyclam-capped β-CD-bonded silica particles **11** and **12** were prepared as shown in Scheme 2. They were each washed successively with MeCN, water, acetone and MeOH and then extracted with acetone in a Soxhlet extractor overnight and dried in vacuum at 50°C for 6 h. An elemental analysis for **11** of C, 13.11; H, 1.89; N, 1.43 shows a concentration of the cyclam in **11** of 166 μmol g^{-1} (for C) and 170 μmol g^{-1} (for N) or about 1.05 cyclams per β-CD molecule. The elemental analysis for **12** of C, 13.57; H, 1.84; N, 1.32 shows a concentration of the cyclam in **12** of 158 μmol g^{-1} (for C) and 157 μmol g^{-1} (for N) or about 0.98 cyclams per β-CD molecule.
19. CEC was performed using an HP^{3D} CE instrument (Hewlett–Packard, Waldbronn, Germany) equipped with a UV diode-array detector. Supporting evidence for chiral separation was accomplished by comparing UV spectra for the stereoisomers from 200 to 254 nm wavelengths.