"Click" preparation of hindered cyclodextrin chiral stationary phases and their efficient resolution in high performance liquid chromatography

Yong Wang [a], David James Young [b], Timothy Thatt Yang Tan [a,*], Siu-Choon Ng [a,*]

[a] School of Chemical and Biomedical Engineering, Nanyang Technological University, 62 Nanyang Drive, Singapore, Singapore
[b] Faculty of Science, Universiti Brunei Darussalam, Jalan Tungku Link, Gadong BE1410, Negara Brunei Darussalam

ABSTRACT

This communication reports the preparation of two new cyclodextrin (CD) chiral stationary phases (CSPs): heptakis(6-deoxy-6-azido)-β-CD and heptakis(6-deoxy-6-azido-phenylcarbamoylated)-β-CD CSPs that perform quite differently to our previously reported "click" immobilized CD-CSPs. These CSPs are sterically congested at the narrow mouth of the CD and exhibit chiral discrimination between over 40 pairs of enantiomers in high performance liquid chromatography. The free hydroxyl CSP afforded better separation of indoprofen, ketoprofen, Tröger's base, hydroxyl, carboxylic and dansyl amino acids than did the phenylcarbamoylated CSP, while the latter was better at resolving aryl alcohols, flavonoids, β-blockers and β-agonists. The current work shows that enantiodiscrimination achieved with different CSPs for different classes of analyte may be correlated with CD accessibility and peripheral functionality.

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1. Introduction

"Click" chemistry–Cu(I) catalytic 1,3-dipolar cycloadditions, has been used in a diverse array of applications since it was first investigated in 2002 [1–7]. Resolution of chiral molecules by the differential formation of transient, diastereomeric cyclodextrin–analyte complexes is well known [8–12] and our group has reported HPLC enantioseparations on a "click" chemistry derived native cyclodextrin (CD) chiral stationary phase (**CCN-CSP**) tethered to silica via a single triazole linkage [13]. This CSP exhibited reasonable enantiorecognition for dansyl amino acids, flavanone and monohydroxyl substituted flavanones in reversed phase HPLC. However, the synthesis of mono-azido-CD derivatives requires the relatively low yielding synthesis of the intermediate mono-6-tosyl-β-CD. Moreover, the single triazole linkage may become unstable after long exposure to buffers.

To improve the efficiency of the preparation procedure and further investigate the inclusion mechanism, we have now prepared and tested two CSPs bonded to silica with multiple triazole linkages. The multiple linkages should improve stability in acidic and basic media. **CSP1** was prepared by immobilizing heptakis(6-deoxy-6-azido)-β-CD (heptakis-N$_3$-CD) by multiple "click" reactions with alkyne functionalized silica. **CSP2** was prepared using the same Cu(I) catalyzed reaction but of heptakis(6-deoxy-6-azido-phenylcarbamoylated)-β-CD (heptakis-N$_3$-Ph-CD) and so does not

bear any free hydroxyl groups. In both cases the smaller CD mouth is almost closed by the multiple triazole linkages. These materials demonstrate quite different enantioseparation properties to one another and to the previously reported "click" derived CD CSP.

2. Experimental

2.1. Chemicals and materials

Sodium azide, phenyl isocyanate, cuprous iodide and 3-aminopropyltriethoxysilane were purchased from Merck (Hohenbrunn, Germany). β-Cyclodextrin and iodine were obtained from Fluka (Buchs, Switzerland). HPLC-grade methanol (MeOH), acetonitrile (ACN) and triethylammonium were purchased from Fischer (Fair Lawn, New Jersey, USA) and used directly. Ultra-pure water was prepared with an Arium 611VF water system supplied by Sartorius Stedim Biotech (Göttingen, Germany). Chiral analytes were purchased from Sigma–Aldrich (Steinheim, Germany). Kromasil spherical silica gel (5 μm, 100 Å) was obtained from Eka Chemicals (Bohus, Sweden).

2.2. Instruments and measurements

Fourier-transform infrared (FTIR) spectra were collected on an FTS165 FT-IR supplied by Perkin-Elmer (Hercules, CA, USA). Elemental analysis was performed on a Vario EL universal CHNOS elemental analyzer (Elementar Analysensysteme, Hanau, Germany). The NMR spectra were recorded on a Bruker ACF300
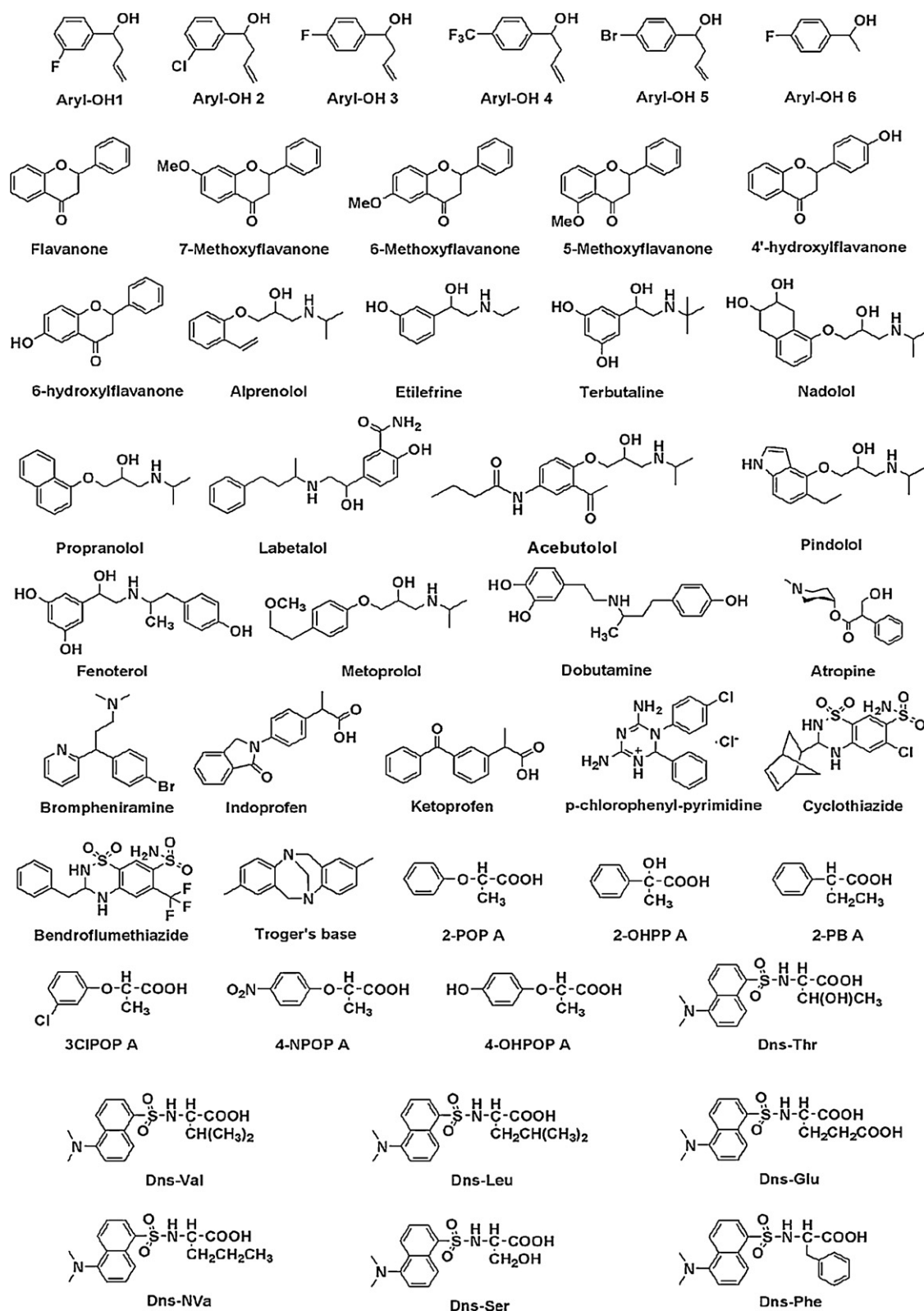
Fig. 1. Structures of the studied chiral compounds.

(300 MHz) supplied by Bruker Biospin (Fällanden, Switzerland). Mass spectra were obtained on a QSTAR XL LC/MS system purchased from Applied Biosystems (Foster City, CA, USA). All enantioseparations were performed on an HPLC system with a diode array detection (DAD) system (Hitachi, Tokyo, Japan). The structures of the analytes are presented in Fig. 1.

Mobile phases were prepared by mixing different amounts of ACN/MeOH with ultra-pure water or 1 wt.% triethylamine buffer adjusted with acetic acid to the desired pH (denoted as TEAA). All buffers were filtered through a 0.45 μm membrane. The detection wavelength ranged from 200 to 300 nm. The test samples were dissolved in MeOH or ACN/water (v/v = 1:1) at a concentration of
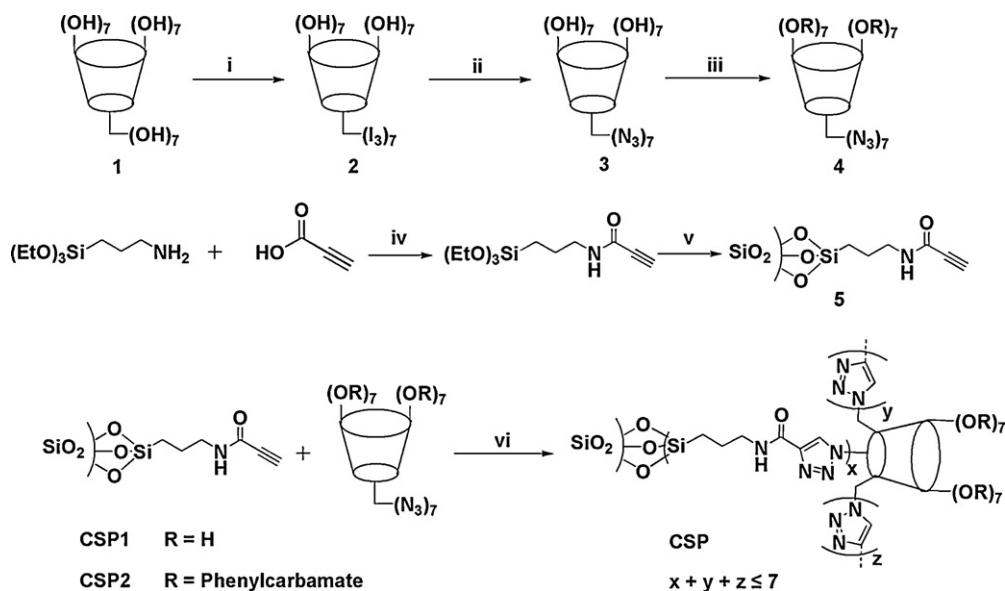
Scheme 1. Preparation of the CSPs. Conditions: (i) I_2/PPh$_3$/DMF/12 h; (ii) NaN$_3$/DMF/16 h; (iii) phenyl isocyanate/pyridine/12 h/N$_2$; (iv) DCC/CH$_2$Cl$_2$/1 h; (v) silica/toluene/overnight; (vi) CuI(PPh$_3$)/DMF/48 h.

about 1 mg/mL and the injection volume was 3 μL. Each sample was injected in triplicate. The separation parameters such as retention factor (k), selectivity (α) and the resolution (R_s) for evaluation of enantioseparation were determined using standard formulas (based on USP standards) [13].

2.3. Preparation of the CSPs

The synthetic route for the desired CD based CSPs is shown in Scheme 1.

2.3.1. Synthesis of heptakis-N$_3$-CD **3**

Pre-dried β-CD (2 g) was added to a solution of iodine (10 g) and triphenylphosphine (10 g) in dry DMF (40 mL). The reaction mixture was stirred at 90 °C for 12 h, after which about 20 mL of DMF was removed under vacuum and the pH of the reaction system was adjusted to 9–10 with 3 M NaOMe. The precipitated product was collected by filtration and washed with acetone to give iodinated β-CD **2** with a yield of 60%. Thereafter, **2** was dissolved in 50 mL DMF and reacted with sodium azide (2.8 g) at 90 °C for 16 h. DMF was removed and the reaction mixture was poured into cold water and filtered. The obtained solid was then washed with water and vacuum dried to afford heptakis(6-deoxy-6-azido)-β-CD **3** in a yield of 80% [14]. IR (cm^{-1}): 3396 (O–H str), 2928 (C–H str), 2106 (N$_3$ str), 1051 (sym C–O–C str); ^{1}H NMR (DMSO-d_6, TMS) δ: 5.9–5.6 (14H), 5.0–4.9 (7H), 4.0–3.5 (42H); ESI-MS (m/z): 1309.2 (calcd.) and 1331.4 (found) for [M+Na$^+$].

2.3.2. Synthesis of heptakis-N$_3$-Ph-CD **4**

Phenyl isocyanate (10 mL) was added to a solution of **3** (2.0 g) in dried pyridine (30 mL, dried over CaH$_2$). The reaction mixture was heated to 90 °C under nitrogen for 12 h. The pyridine and unreacted phenyl isocyanate were then removed under vacuum and the residue dissolved in ethyl acetate (100 mL). Water (50 mL) was added with vigorous stirring. The organic layer was separated and washed with water (2× 50 mL), combined and dried with anhydrous magnesium sulphate. After the removal of the solvent, the resulting residue was purified by flash chromatography using hexane–ethyl acetate (2:1, v/v) as the eluting phase to afford 2.9 g of a light yellow solid **4** (65% yield) [15]. IR (cm^{-1}): 3395, 3313 (N–H str), 3060 (C–H str), 2106 (N$_3$ str), 1744 (C=O str), 1602, 1532, 1445

(arom str) 1054 (sym C–O–C str); ^{1}H NMR (CD$_3$Cl, TMS) δ: 7.5–6.8 (84 H); 5.6–3.8 (49 H) ESI-MS (m/z): 2975.1 (calcd.) and 2997.3 (found) for [M+Na$^+$].

2.3.3. Multiple "click" chemistry for the preparation of CSPs

3 (0.8 g) or **4** (1.5 g) was added to a suspension of alkynyl functionalized silica (2.2 g) in 15 mL DMF followed by addition of CuI(PPh$_3$)(40 mg) in a single portion (the alkynyl functionalized silica and CuI(PPh$_3$) were prepared according to a similar procedure in our previous report [16]). The reaction mixture was stirred for 2 days at 80 °C. The crude product was then filtered, washed with DMF and extracted with acetone/methanol for 24 h before being vacuum dried.

The obtained **CSP1** and **CSP2** were packed into the stainless columns (15 mm × 4.6 mm i.d.) following a conventional high-pressure slurry packing procedure using a packing pump from LabAlliance (State College, PA, USA) with methanol as the packing solvent.

3. Results and discussion

3.1. Characterization of the CSPs

CSP1 and **CSP2** were characterized by elemental analysis and FTIR. Elemental analyses showed an increase of carbon content from 5.94% for alkynyl silica to 11.3% and 13.7% for **CSP1** and **CSP2** respectively, as well as an increase in the nitrogen content from 1% for alkynyl silica to 3.9% and 3.2% for **CSP1** and **CSP2** respectively. FTIR spectra (Fig. S-1 supporting information) obtained before and after tethering of the CD to alkyne modified silica indicated that the strong alkyne absorption at 2121 cm^{-1} was greatly diminished by the multiple "click" reactions. There were no obvious absorptions at 2104 cm^{-1} in the spectrum of **CSP1** indicating most of the azido groups had been converted to triazole linkages. This absorption was seen in the post-tethering FTIR spectrum of **CSP2**, but was very weak, indicating a small percentage of unreacted azido groups. More importantly, there appeared representative absorptions associated with the modified CDs (2943 cm^{-1} for the methylene of **CSP1**; 1738 cm^{-1} and 1448 cm^{-1} for the carboxyl and aromatic rings, respectively, of **CSP2**).
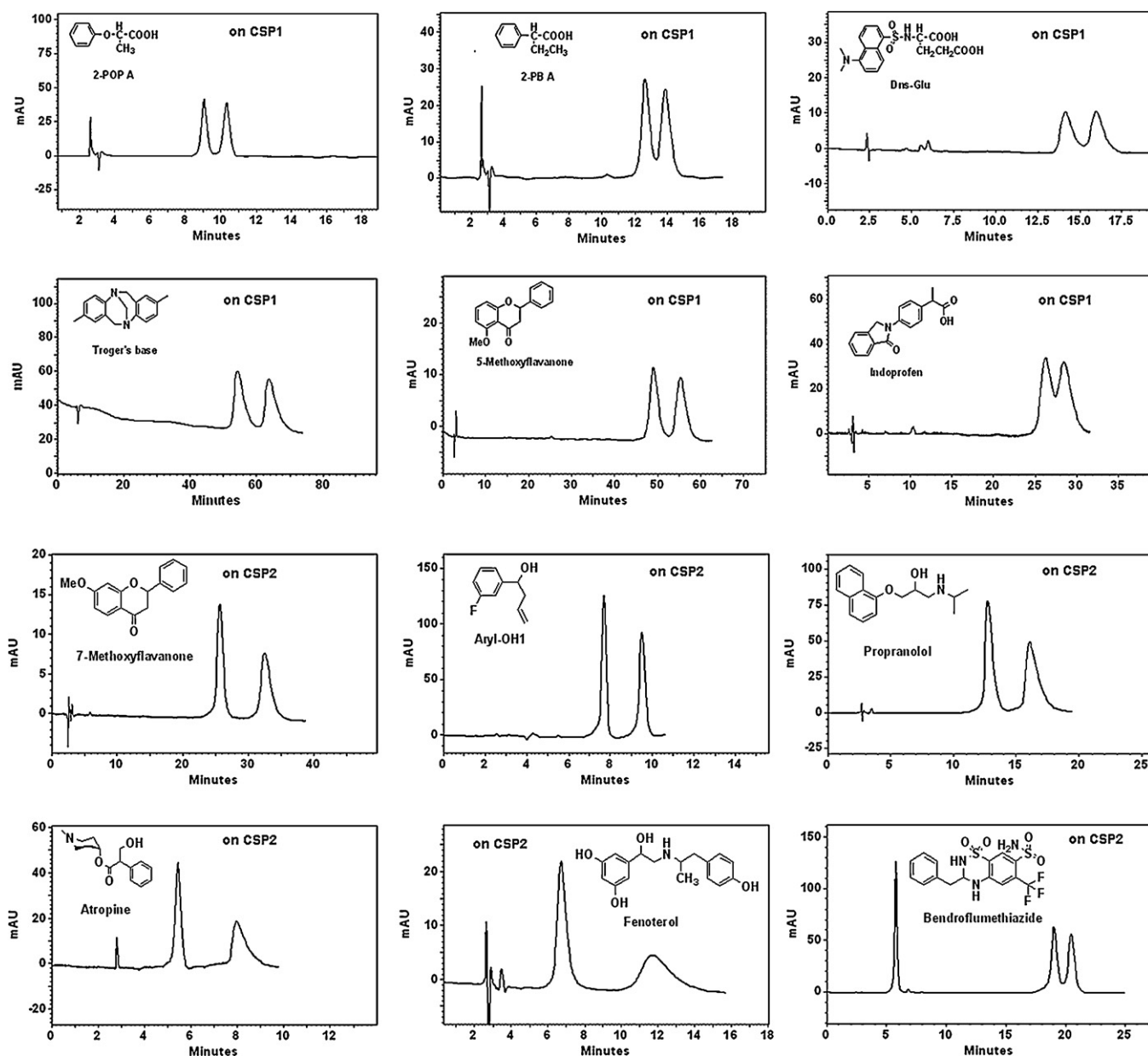
Fig. 2. Representative chromatograms on **CSP1** and **CSP2**. Refer to Tables 1 and 2 for separation conditions.

3.2. Enantioseparations on **CSP1** and **CSP2**

The enantiorecognition abilities of the two newly prepared CSPs were investigated by HPLC of various chiral compounds in reversed phase mode. Some representative chromatograms are presented in Fig. 2.

3.2.1. Chiral HPLC with **CSP1**

CSP1 afforded chiral recognition ability to flavonoid enantiomers, hydroxyl, carboxylic and dansyl amino acids, indoprofen, ketoprofen, brompheniramine, cyclothiazide and Tröger's base. The retention and resolution parameters are listed in Table 1.

Five pairs of flavonoid enantiomers including those bearing –OCH$_3$ and –OH groups on the bicyclic rings or –OH on the single phenyl ring were partially separated with MeOH and water as the eluting phase. However, the selectivities were modest with only 5′-methoxyflavanone baseline separated. The three flavonoids with –OCH$_3$ groups linked to the bicyclic rings were faster eluting but better resolved on **CSP1** and the unsubstituted flavanone

had the lowest resolution. This profile was different to the results previously obtained with **CCN-CSP** [13]. The latter demonstrated quite good chiral selectivity towards flavanone enantiomers and hydroxyl substituted flavonoid enantiomers under the same conditions while **CSP1** proved to be better at resolving methoxyl substituted flavonoid enantiomers. These results suggest that the free CD 6-OH in **CCN-CSP** plays a role in resolving flavonoids while the sterically restricted CD mouth of **CSP1** appears to be important to the host–guest inclusion of methoxy substituted flavonoids. Seven dansyl amino acids were partially resolved on **CSP1** with Dns-Phe exhibiting the longest retention time presumably due to the strong inclusion of the two aromatic moieties [17,18]. Compared with **CCN-CSP** [13], the current **CSP1** afforded much lower enantiorecognition towards all the studied dansyl amino acids but better separation of 2-POP A, 3ClPOP A and 4OHPOP A enantiomeric pairs.

Five other chiral compounds – brompheniramine, indoprofen, ketoprofen, cyclothiazide as well as Tröger's base could be at least partially resolved on CSP1. Indoprofen enantiomers and

Table 1
Enantioseparation results on **CSP1**.

Analytes	k_1	k_2	α	R_s	Conditions
Flavonoids					
Flavanone	22.4	23.1	1.03	0.41	(a)
6-Methoxyflavanone	19.2	20.8	1.08	1.09	(a)
7-Methoxyflavanone	18.7	20.4	1.09	1.15	(a)
5-Methoxyflavanone	15.3	17.5	1.14	1.65	(a)
4′-Hydroxyflavanone	24.1	25.4	1.05	0.64	(a)
6-Hydroxyflavanone	23.3	24.5	1.05	0.62	(a)
Dns amino acids					
Dns-Thr	2.92	3.46	1.18	0.91	(b)
Dns-Val	2.67	3.29	1.23	1.45	(b)
Dns-Leu	3.05	3.33	1.09	0.61	(b)
Dns-Glu	3.81	4.51	1.19	1.35	(b)
Dns-Nva	2.39	2.68	1.11	0.51	(b)
Dns-Ser	2.46	2.81	1.14	0.53	(b)
Dns-Phe	3.8	14.5	1.05	0.40	(b)
Hydroxyl and carboxylic acids					
2-POPA	2.02	2.44	1.21	2.00	(c)
2-OHPP A	2.42	2.67	1.10	0.98	(c)
2-PB A	3.21	3.62	1.13	1.33	(c)
3ClPOP A	3.52	3.82	1.09	1.06	(c)
4-NPOP A	5.50	5.83	1.06	1.17	(c)
4-OHPOP A	1.37	1.58	1.15	1.25	(c)
Other drugs					
Brompheniramine	2.38	2.56	1.07	0.42	(d)
Indoprofen	8.46	9.06	1.07	0.73	(d)
Ketoprofen	8.37	8.87	1.06	0.65	(d)
Cyclothiazide	2.12	2.78	1.31	1.05	(b)
Troger's base	16.6	19.7	1.18	1.64	(a)

Separation conditions: flow rate = 0.7 mL/min (a) MeOH/H$_2$O (v/v) = 35/65; (b) ACN/TEAA (pH = 5.2) (v/v) = 35/65; (c) MeOH/TEAA (pH = 5.2) (v/v) = 50/50; (d) ACN/TEAA (pH = 5.2) (v/v) = 25/75.

racemic ketoprofen were not resolved on **CCN-CSP**, but could be partially so on **CSP1**. In general, however, resolution was not as good with **CSP1** as with **CCN-CSP**. In particular, nimodipine, propranolol, bendroflumethiazide and chlorthalidone, could not be even partially resolved on **CSP1**. Although Tröger's base was baseline resolved on this CSP, as it was on **CCN-CSP**, the retention time was significantly longer. These results indicate the important interactions of these chiral analytes with the CD 6-OH groups.

3.2.2. Chiral HPLC with **CSP2**

Phenylcarbamoyl groups provide π–π and dipole–dipole interactions which are not available to unmodified CD CSPs [19,20]. Twenty seven chiral compounds including flavonoids, aryl alcohols, β-blockers, β-agonists, atropine, *p*-chloropheyl-pyrimidine, cyclothiazide and bendroflumethiazide were baseline or partially resolved on **CSP2** in reversed phase mode HPLC (Table 2).

CSP2 afforded better separation of most flavonoids relative to **CSP1**, presumably because of π–π interactions between the CD phenylcarbamoyl groups and the aromatic analytes. 6-Methoxyflavanone and 7-methoxyflavanone were more strongly retained because of the lipophilicity of the methoxyl groups. Long retention does not always correlate with better resolution, however, as observed for flavanone and 6-methoxyflavanone. The latter had a shorter retention time but was better resolved. Of the three methoxyl substituted flavonoids, 5-methoxyflavanone had the shortest retention time and poorest resolution. This may be due to steric hindrance of favorable H-bonding and dipole–dipole interactions between the analyte carbonyl and the CD carbamoyl groups [21].

The racemic aryl alcohols were well separated on **CSP2**, except for aryl-OH 6, indicating the importance of the favorable π–π interactions between the CSP and the alkene groups of aryl-OH 1–5 [12]. Enantioseparation of some β-blockers and β-agonists were achieved by using TEAA buffer. Alprenolol and propra-

nonol showed enhanced enantioseparation relative to similar compounds. Fenoterol and terbutaline exhibited good resolution, perhaps because the chiral center is located at the α-position and we are currently investigating this hypothesis.

The good resolving ability of **CSP2** was further investigated with atropine, brompheniramine, *p*-chlorophenyl-pyrimidine, cyclothiazide and bendroflumethiazide. Atropine was base-line resolved on **CSP2** with a high resolution value of 3.57 while brompheniramine registered the poorest separation. Cyclothiazide and bendroflumethiazide bear strongly H-bonding –NH and SO$_2$NH–groups adjacent to the chiral carbon and were relatively well resolved [22].

3.2.3. Solvent effects

The eluting phase consisted of organic modifiers (ACN and MeOH) and water or TEAA buffer. Some neutral and weakly acidic or basic chiral compounds such as alcohols, flavonoids, thiazides and Tröger's base were eluted simply with ACN/MeOH and water. However, buffer was required for the elution of ionic analytes such as hydroxyl, carboxylic and dansyl amino acids, β-blockers, β-agonists, and atropine.

In general, increasing the proportion of organic modifier reduced the retention times and resolution of the analytes due to increased competition for the CD cavity. ACN had a greater influence than MeOH, reflecting its greater affinity for the CD cavity [23]. The resolution of flavonoid enantiomers and dansyl amino acids was much better with ACN/H$_2$O than with MeOH/H$_2$O on **CSP1**. However, Tröger's base was only resolved with MeOH/H$_2$O on **CSP1** and no separation was observed with ACN/H$_2$O despite the longer retention time (Fig. S-2a supporting information). A similar situation was observed for the separation of bendroflumethiazide on **CSP2**. ACN/H$_2$O afforded fair resolution while no enantiodiscrimination was observed with MeOH/H$_2$O (Fig. S-2b supporting information). ACN is a more powerful eluting solvent than MeOH, but in some cases the H-bonding of MeOH proved to be important [24].

Table 2
Enantioseparation results on **CSP2**.

Analytes	k_1	k_2	α	R_s	Conditions
Flavanone	4.79	5.53	1.15	2.54	(a)
6-Methoxyflavanone	7.43	8.37	1.13	2.12	(a)
7-Methoxyflavanone	7.55	9.27	1.22	2.91	(a)
5-Methoxyflavanone	4.03	4.10	1.02	1.06	(a)
4′-Hydroxyflavanone	3.61	3.98	1.10	1.51	(a)
6-Hydroxyflavanone	3.81	4.07	1.07	1.34	(a)
Aryl-OH 1	1.94	2.18	1.12	1.84	(b)
Aryl-OH 2	2.76	2.93	1.06	1.24	(b)
Aryl-OH 3	1.93	2.18	1.13	1.96	(b)
Aryl-OH 4	3.19	3.64	1.14	2.41	(b)
Aryl-OH 5	1.81	2.05	1.13	1.97	(b)
Aryl-OH 6	0.99	1.03	1.04	0.42	(b)
Alprenolol	1.66	2.02	1.20	2.02	(c)
Metoprolol	0.95	0.99	1.04	0.70	(c)
Nadolol	$k1 = 0.41$		$k2 = 0.58$	$k3 = 0.99$	(c)
Pindolol	1.04	1.12	1.07	0.88	(c)
Labetalol	3.02	3.23	1.07	<0.3	(c)
Propranolol	3.24	4.10	1.27	2.20	(c)
Acebutolol	1.29	1.33	1.03	0.71	(c)
Fenoterol	1.24	2.92	2.35	2.70	(c)
Terbutaline	0.61	1.13	1.84	2.26	(d)
Dobutamine	1.09	1.80	1.84	1.86	(e)
Eltilefrine	3.03	3.28	1.08	0.77	(f)
Alprenolol	1.66	2.02	1.20	2.02	(f)
Atropine	0.81	1.44	1.78	3.57	(f)
Brompheniramine	3.10	3.21	1.03	<0.3	(f)
p-Chlorophenyl-pyrimidine	2.12	2.40	1.13	0.96	(f)
Cyclothiazide	5.31	5.83	1.10	1.08	(g)
Bendroflumethiazide	5.80	6.31	1.09	1.48	(g)

Separation conditions: flow rate = 0.7 mL/min (a) MeOH/H$_2$O (v/v) = 50/50; (b) ACN/H$_2$O (v/v) = 35/65; (c) MeOH/TEAA (pH = 4.2) (v/v) = 35/65; (d) MeOH/TEAA (pH = 4.2) (v/v) = 5/95; (e) MeOH/TEAA (pH = 4.2) (v/v) = 50/50; (f) MeOH/TEAA (pH = 4.2) (v/v) = 35/65; (g) ACN/H$_2$O (v/v) = 40/60.

4. Conclusions

Heptakis(6-deoxy-6-azido)-β-CD and heptakis(6-deoxy-6-azido-phenylcarbamoylated)-β-CD were successfully immobilized onto alkynyl functionalized silica with multiple "click" reactions to provide stable, new chiral stationary phases. Free hydroxyl CD **CSP1** could partially or baseline resolve hydroxyl, carboxylic and dansyl amino acids, Tröger's base, indoprofen and ketoprofen, which was not possible on phenylcarbamoylated CD **CSP2**. Both **CSP1** and **CSP2** could separate flavonoids with better resolution provided by the latter. Aryl alcohols, β-blockers, β-agonists, atropine and bendroflumethiazide were only separated on **CSP2**.

Acknowledgements

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.chroma.2010.10.059.

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