Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 18 (2007) 1548–1553

Facile synthesis of positively charged monosubstituted α- and γ-cyclodextrins for chiral resolution of anionic racemates

Weihua Tang,[a,*] I. Wayan Muderawan,[a] Teng-Teng Ong[b] and Siu-Choon Ng[b,*]

[a]*Department of Chemistry, National University of Singapore, Singapore*
[b]*Division of Chemical and Biomolecular Engineering, College of Engineering, Nanyang Technological University, Singapore*

Received 22 May 2007; accepted 15 June 2007

Abstract—New positively charged monosubstituted α- and γ-cyclodextrins at the primary face were synthesized in good yields by displacement of the monotosylates of α- and γ-cyclodextrin with amine, alkylamines or alkylimidazoles. The influence of CD's cavity size on the resolution abilities of CD derivatives towards model analytes, that is, dansyl amino and carboxylic acids, were investigated. Results show that the formation of the inclusion complex might play an important role in chiral recognition, in that cationic γ-CD derivatives gave better resolution abilities than their α- and γ-CD analogues, presumably due to tight fit between CD hosts and the anionic guest racemates.

1. Introduction

The synthesis of structurally well-defined cyclodextrins (CDs), in which either a single or all hydroxyl groups are replaced in order to introduce desired functionalities, has become an important process over the last few decades. Strategies for selective CD modification on both the primary and secondary faces have been well reviewed.[1,2] CDs are modified for reasons ranging from improving the solubility in a desired solvent to investigating mechanistic studies of enzyme-catalyzed reactions and developing validated assays for chemical analysis.[2] For example, specific site delivery of pharmacologically active compounds is enhanced when employing monosubstituted CDs, whose water solubilities are increased in comparison with the native CDs.[3] As an important family of selectively substituted CDs, monosubstituted CDs are key precursors in the synthesis of defined di- and oligomers of CD for the strong binding effect with included guest molecules[4] and perfunctionalized CD derivatives for efficient chiral resolution capability.[5]

Native and derivatized CDs are predominant chiral selectors for the majority of enantioselective separation techniques,[6] including GC,[7] HPLC[5,8] and CE.[9] Recently, Ng et al. reported the facile synthesis of a series of positively charged monosubstituted β-CDs for enantioseparation via a CE technique.[10] By using the reported methodology, the synthesized cationic β-CD chiral selectors have achieved successful enantioseparation for a large pool of anionic and amphoteric racemates in CE.[11] However, utilization of the α- and γ-CD following this method has not been reported until now. According to the inclusion mechanism proposed for the chiral recognition with CD-based chiral selectors,[12] it is widely believed that the cavity structure of CDs plays a very important role for their enantioseparation ability,[13] since the observed stereoselectivity was due to differences in fit or inclusion of the enantiomers of the analytes in the cavities of the CDs.[12] In CD chemistry, the most critical factors influencing the stability of the inclusion complex are the size, shape, rigidity, polarity and steric hindrance of the guest analytes, as well as the cyclodextrin host molecules.[14] Hence, the dimension of the cavity may have substantive effects on the separation ability of CD-based chiral selectors.[12,13]

With the view to investigating the effect of cavity dimension on the enantioselectivity of positively charged monosubstituted CDs and expanding upon the application of Ng's methodology to α- and γ-cyclodextrin, we herein report our efforts on the preparation of three series of novel positively charged monosubstituted α- and γ-cyclodextrins. In addition, the application of newly synthesized CDs as chiral selectors in the enantioseparation of anionic and ampho-

* Corresponding authors. E-mail addresses: wh-tang@imre.a-star.edu.sg; ngsc@ntu.edu.sg

0957-4166/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2007.06.017

teric racemates in CE is illustrated. The effect of cavity size on the chiral resolution abilities of newly synthesized CDs is also discussed.

2. Results and discussion

Figure 1 depicts the synthetic routes applied, which are similar to those previously reported.[10] The starting materials, the monotosylates of α- and γ-CDs **1** were readily synthesized.[15] From the key intermediate monoazides of α- and γ-CDs **2**,[15] monoamino derivatives **3** were prepared with the aid of triphenyl phosphine in DMF at ambient temperature, followed by hydrolysis. Monoammonium CD chlorides **4** were further obtained by titration of an aqueous solution of **3** with hydrogen chloride. Monoalkylammonium α- and γ-CD tosylates **5** were prepared by refluxing compound **1** with alkylamines, such as *n*-propylamine and *n*-butylamine in DMF for 5 h. Monosubstituted alkylimidazolium α- and γ-CD tosylates **6** were prepared by heating compound **1** with alkylimidazoles in DMF at 90 °C for 2 days. Furthermore, the tosylate anion was exchanged with chloride by an ion-exchanging process via Amberlite 900 (Cl) resin. All the newly synthesized monosubstituted cationic CDs **4**–**6**, **5′** and **6′** presented very high solubilities in water and methanol, which is beneficial for chiral separation in aqueous media via CE.

It is generally known that the chiral recognition of CDs are dependent upon their ability to form enantioselective inclusion-complexes with many kinds of solutes. Several reviews[16] and papers[13a,17] have discussed general rules about the choice of CD according to the structure of analytes. In order to investigate the effect of CD cavity size on the enantioseparation ability of our newly synthesized cationic CDs, 11 model analytes including, 8 dansyl amino acids and 3 carboxylic acids, were selected, with their structure shown in Figure 2. The chiral resolution results of the model analytes are summarized in Table 1 with γ-CD-NH_3Cl and β-CD-NH_3Cl as chiral selectors. The enantioselectivity of β-CD-NH_3Cl was evaluated with a large pool of racemates.[10c] In the present study, it should be noted that improved chiral resolutions of most analytes were obtained at higher CD concentration (ca. 10 mM) for both chiral selectors. This is mainly due to the increased electrostatic interaction between CD and analytes when increasing the CD concentration. The resultant stronger binding of analytes into the CD cavity, therefore, improved the resolution of analytes. Exceptions are Dns-Aca, Dns-Nle and Dns-Val, which gave lower resolution at 5 mM.

When comparing the resolution data of dansyl amino acids and 2-NMA A, the model analytes with dansyl group or naphthyl ring, it can be seen that γ-CD-NH_3Cl provided a better chiral resolution relative to β-CD-NH_3Cl as expected. The main reason is due to the fact that the cavity size of γ-CD is larger than that of β-CD, and hence the inclusion of complex formation of the dansyl/naphthyl group into the cavity of γ-CD would be more favourable than into the cavity of β-CD. However, the chiral separation process required a longer reaction time when using γ-CD-NH_3Cl as the chiral selector. Surprisingly, Dns-Aca was resolved better by β-CD-NH_3Cl. This can be explained by the competitive inclusion model proposed by Fujimaru et al.[13a] for the enantioseparation of Dns-amino acids using β- and γ-CD-bonded chiral stationary phases. In this model, the inclusion complex can be formed between the cyclodextrin and the dansyl group, as well as the side alkyl chain adjacent to the stereogenic centre. Upon a close examination of the molecular structure of Dns-Aca, one can find

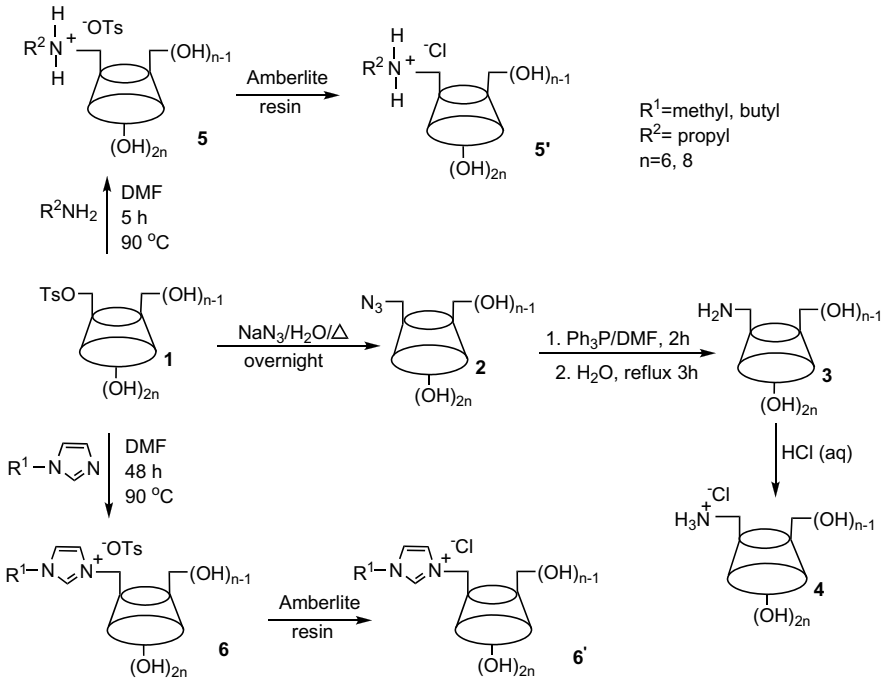

Figure 1. Scheme of synthetic approaches for positively charged monosubstituted α- and γ-cyclodextrins.

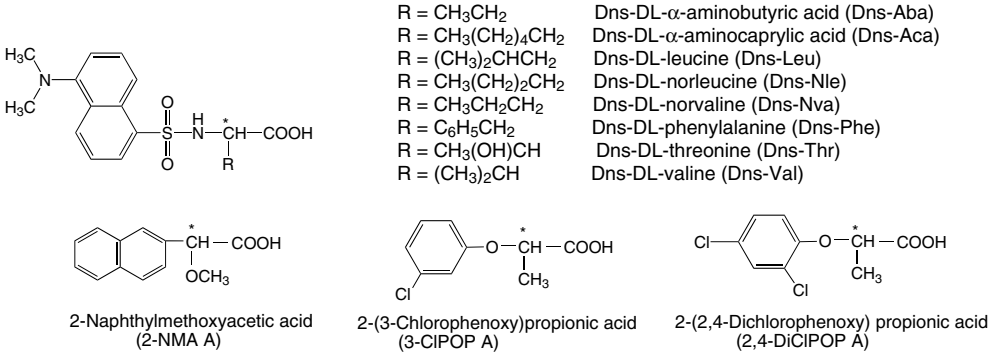

Figure 2. Structure of amphoteric analytes and carboxylic acids analytes studied.

Table 1. Migration time of the less mobile enantiomer (t_2, in min), selectivities (α) and resolutions (R_s) of racemic analytes with γ-CD-NH_3Cl and β-CD-NH_3Cl as chiral selectors at different concentrations

Entry	γ-CD-NH_3Cl						β-CD-NH_3Cl*					
	5 mM			10 mM			5 mM			10 mM		
	t_2	α	R_s	t_2	α	R_s	t_2	α	R_s	t_2	α	R_s
Dns-Aba	17.84	1.029	1.36	19.57	1.030	2.52	12.60	1.020	0.71	10.35	1.026	1.34
Dns-Aca	13.86	1.017	0.99	15.97	1.006	0.77	11.01	1.034	2.02	18.52	1.030	1.88
Dns-Nle	14.24	1.028	1.51	12.43	1.016	1.35	13.52	1.012	1.41	15.53	1.013	1.29
Dns-Nva	14.89	1.032	0.96	18.90	1.030	1.69	13.48	1.018	0.78	15.46	1.031	1.36
Dns-Phe	12.43	1.019	1.36	14.82	1.024	1.92	11.86	1.049	2.56	13.11	1.036	1.58
Dns-Thr	15.28	1.019	1.27	20.44	1.031	1.47	13.80	1.014	0.71	12.52	1.010	0.61
Dns-Val	13.25	1.023	1.35	17.68	1.026	1.13	14.17	1.012	0.79	12.08	1.010	0.74
2-NMA A	23.51	1.121	3.18	27.89	1.144	5.29	14.14	1.047	2.77	13.33	1.070	4.27
3-ClPOP A	23.26	1.006	<0.5	31.26	1.017	1.05	21.27	1.092	3.99	17.87	1.087	3.75
2,4-DiClPOP A	23.17	1.019	0.87	23.85	1.040	1.14	20.20	1.020	1.12	18.24	1.022	1.54

Conditions: 50 mM phosphate buffer, pH 6.0, uncoated capillary, +15 kV, 25 °C. *Note*: results for β-CD-NH_3Cl from Ref. 10c.

that the stereogenic centre, which is directly attached to a pendant hexyl chain, is not adjacent to the dansyl moiety. Generally, an enhanced enantioselectivity might be afforded if the analyte's stereogenic centre can easily get close to the chiral cavity of the cyclodextrins. While a bulky dansyl group cannot easily be included in the cavity of β-CD, the long hexyl pendant chain containing the stereogenic centre can. As a result, the stereogenic centre in the aliphatic pendant chain was easily exposed to the chiral environment and there was better chiral discrimination on β-CD-NH_3Cl. The moderate enantioseparation of this analyte with γ-CD-NH_3Cl may be due to the large cavity of γ-CD even when including a dansyl group as well as the pendant hexyl chain, which resulted in the stereogenic centre not getting close to the chiral environment.

The cavity dependent chiral recognition can be further observed when using 5 mM PrAM-γ-CD, PrAM-β-CD(Mono-6^A-propylammonium-6^A-deoxy-β-cyclodextrin chloride) and α-CD-NH_3Cl as chiral selectors for the enantioseparation of dansyl amino acids. As shown in Table 2, most dansyl amino acids were resolved to some extent

Table 2. Migration time of the less mobile enantiomer (t_2, in min), selectivities (α) and resolutions (R_s) of racemic analytes with 5 mM PrAM-γ-CD, PrAM-β-CD and α-CD-NH_3Cl as chiral selectors

Entry	CDs								
	PrAM-γ-CD			PrAM-β-CD			α-CD-NH_3Cl		
	t_2	α	R_s	t_2	α	R_s	t_2	α	R_s
Dns-Aba	26.23	1.031	1.11	10.7	1.018	0.86	14.67	1.00	<0.5
Dns-Aca	16.16	1.027	1.79	8.74	1.013	1.19	14.34	1.006	0.64
Dns-Leu	18.80	1.029	1.82	15.55	1.021	1.29	13.20	1.000	<0.5
Dns-Nle	20.07	1.019	1.13	10.30	1.011	0.89	13.27	1.009	0.66
Dns-Nva	21.21	1.012	0.65	11.26	1.003	<0.5	13.72	/	/
Dns-Phe	15.65	1.005	<0.5	9.40	1.008	0.79	13.85	/	/
Dns-Thr	22.46	1.012	0.89	11.43	1.005	<0.5	14.36	/	/
Dns-Val	23.67	1.015	0.76	10.86	1.003	<0.5	14.69	/	/

Conditions: 50 mM phosphate buffer, pH 6.0, uncoated capillary, +15 kV, 25 °C, /: no separation observed under the separation conditions.

when γ- and β-CD derivatives were used as chiral selectors. Conversely, α-CD derivatives can only give very poor resolution for all analytes. More importantly, better resolutions were generally obtained with a γ-CD chiral selector when compared with its β-CD analogue, due to the 'tight-fit' inclusion. A longer migration time was also observed for the resolution when using a γ-CD chiral selector. This similar phenomenon can also be explained by the inclusion model. When the dansyl group was tightly matched with the CD cavity, better recognition was obtained and shown by better resolution results. Since the dansyl group is too large to be included into the cavity of α-CD, a larger pool of analytes with different sizes in the aromatic ring or aliphatic pendant chains needs to be investigated in order to provide more useful guideline information over the choice of our synthesized CDs. A detailed enantioseparation investigation by using our monosubstituted cationic α- and γ-CDs as chiral selectors is still ongoing and the full results will be reported in the near future.

3. Conclusion

In conclusion, we have synthesized positively charged monosubstituted α- and γ-cyclodextrins which can be used for chiral separation and/or molecular recognition investigation on dansyl amino acids and anionic analytes. A study with regards to the scope of racemic analytes, chiral resolution abilities and optimization of separation conditions by using our newly synthesized CD derivatives is currently in progress.

4. Experimental

All reagents and α-, γ-cyclodextrins were purchased commercially and used directly without further purification. All racemic samples were purchased from Sigma–Aldrich (St. Louis, MO). The NMR spectra were recorded on a Bruker ACF300 (300 MHz). FT-IR spectra were obtained on a Bio-Rad (Hercules, CA) TFS156 instrument using KBr pellets. Mass spectra were obtained from a Finnigan/MAT TSQ7000. Elemental analysis was performed on a Perkin–Elmer (Norwalk, CT) 2400 CHN analyzer. All electrophoretic experiments were performed on a Beckman P/ACE MDQ CE unit (Fullerton, CA, USA) using 59.2 cm (effective length 49 cm) × 50 μm I.D. × 375 μm O.D., untreated fused-silica capillaries (Polymicro Technologies, Phoenix, AZ, USA). The cartridge coolant of the CE unit was thermostated at 25 °C. Samples were injected by 0.5 psi nitrogen (typically 10 s). The applied voltage was +15 kV. The variable-wavelength PDA detector was used for detection through three channels at 214, 254 and 280 nm.

4.1. Mono-(6^{A}-azido-6^{A}-deoxy)-α-cyclodextrin 2a, N_3-α-CD

Vacuum dried **Ts-α-CD** (5.0 g, 4.4 mmol) and excess sodium azide (5.0 g, 77.0 mmol) were dissolved in deionized water (500 mL, 27.8 mol) and refluxed overnight in a boiling water bath. The resulting solution was filtered and concentrated to 40 mL. 1,1,2,2-Tetrachloroethane (5 mL) was added and the resultant mixture was stirred for 0.5 h. The complex formed was separated from the aqueous solution by centrifugation. Removal of organic solvent afforded the crude product and the pure titled compound **2a** was obtained by recrystallization from hot water, with a yield of 70%. Melting point: 221–225 °C (lit.[15] 217 °C). ^{13}C NMR (75 MHz, D_2O): δ (ppm) 104.55 (C1), 83.80 (C4), 75.77 (C2), 74.76 (C3), 74.55 (C5), 62.93 (C6), 53.80 (C-6′-N_3). IR (cm^{-1}, KBr): 3392 (O–H str), 2930 (C–H str), 2105 (–N_3 str), 1032 (C–O str). ESI-MS (*m*/*z*): 1020.34; found for [M+Na]$^{+}$, calcd 998.32. Anal. Calcd for $C_{36}H_{59}O_{29}N_3$: C, 43.33; H, 5.96; N, 4.21. Found: C, 42.53; H, 6.10; N, 3.99.

4.2. Mono-(6^{A}-azido-6^{A}-deoxy)-γ-cyclodextrin 2b, N_3-γ-CD

By following a similar synthetic procedure as **2a**, **Ts-γ-CD** was used to synthesize the titled compound **2c** with a yield of 54%. ^{13}C NMR (75 MHz, D_2O): δ (ppm) 105.03 (C1), 83.42 (C4), 75.81 (C2), 74.79 (C3), 74.52 (C5), 62.89 (C6), 53.75 (C-6′–N_3). IR (cm^{-1}, KBr): 3392 (O–H str), 2929 (C–H str), 2106 (–N_3 str), 1028 (C–O str). ESI-MS (*m*/*z*): 1343.46 found for [M+Na]$^{+}$, calcd 1321.43. Anal. Calcd for $C_{48}H_{79}O_{39}N_3$: C, 43.61; H, 6.02; N, 3.18. Found: C, 43.13; H, 6.12; N, 3.07.

4.3. Mono-6^{A}-*N*-amino-6^{A}-deoxy-α-cyclodextrin 3a, α-CD-NH_2

A mixture of **N_3-α-CD** (4.99 g, 5.0 mmol) and triphenyl phosphine (1.443 g, 5.5 mmol) in DMF (10 mL) was stirred at room temperature for 2 h. The resultant solution was added with deionized water (1.0 mL) and refluxed for 3 h. Acetone was then added to precipitate the white solid. The solid was filtered, washed with acetone and finally dried under high vacuum overnight to give titled product **3a** with excellent yield (4.58 g, 94.4%). Melting point: 205–208 °C (lit.[15] 200 °C). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 5.68–5.43 (m, 12H, OH-2 and OH-3), 4.93–4.76 (m, 6H, H-1), 4.59–4.44 (m, 5H, OH-6), 3.82–3.54 (m, 24H, H-5$_{CD}$, H-3$_{CD}$ and H-6$_{CD}$), 3.48–3.24 (overlap with HDO, m, 12H, H-2$_{CD}$ and H-4$_{CD}$). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 101.9 (C1), 82.0 (C4), 73.2 (C3), 72.0 (C2, C5), 59.9 (C6). IR (cm^{-1}, KBr): 3383 (O–H str), 2928 (C–H str), 1080, 1028 (C–O–C str). ESI-MS (*m*/*z*): 993.37 found for [M+Na]$^{+}$, calcd 971.33. Anal. Calcd for $C_{36}H_{61}O_{29}N$: C, 44.47; H, 6.33; N, 1.44. Found: C, 44.58; H, 6.42; N, 1.46.

4.4. Mono-6^{A}-*N*-amino-6^{A}-deoxy-γ-cyclodextrin 3b, γ-CD-NH_2

By following a similar synthetic procedure as **3a**, compound **2b** was employed to afford the title product **3b** with excellent yield (90.3%). Melting point: 261–265 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 5.82–5.70 (m, 16H, OH-2 and OH-3), 4.92–4.85 (m, 8H, H-1), 4.61–4.46 (m, 7H, OH-6), 3.75–3.45 (m, 32H, H-5$_{CD}$, H-3$_{CD}$ and H-6$_{CD}$), 3.43–3.24 (overlap with HDO, m, 16H, H-2$_{CD}$ and H-4$_{CD}$); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 101.6 (C1), 80.8 (C4), 72.8 (C3), 72.5 (C2), 72.1 (C5), 59.9 (C6). IR (cm^{-1}, KBr): 3397 (O–H str), 2929 (C–H

str), 1080, 1028 (C–O–C str). ESI-MS (*m/z*): 1317.46 found for $[M+Na]^+$, calcd 1295.44. Anal. Calcd for $C_{48}H_{81}O_{39}N$: C, 44.77; H, 6.30; N, 1.08. Found: C, 44.82; H, 6.48; N, 1.13.

4.5. Mono-6^A-*N*-ammonium-6^A-deoxy-α-cyclodextrin chloride 4a, α-CD-NH$_3$Cl

To a solution of **3a** (3.89 g, 4.0 mmol) in deionized water (20 mL) was added hydrochloric acid solution (0.1 M, 10 mL). The solution was stirred for 30 min and then acetone (100 mL) was added. The precipitate that formed, was collected by suction filtration, washed with acetone (25 mL) and dried under high vacuum overnight to give the title compound **4a** with excellent yield (3.88 g, 96.2%). Melting point: 246–250 °C, accompanied by decomposition. $[\alpha]_D = +74.9$ (*c* 1.0, water). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 5.68–5.43 (m, 12H, OH-2 and OH-3), 4.93–4.76 (m, 6H, H-1), 4.59–4.44 (m, 5H, OH-6), 3.82–3.54 (m, 24H, H-5$_{CD}$, H-3$_{CD}$ and H-6$_{CD}$), 3.48–3.24 (overlap with HDO, m, 12H, H-2$_{CD}$ and H-4$_{CD}$). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 101.9 (C1), 82.0 (C4), 73.2 (C3), 72.0 (C2, C5), 59.9 (C6). ESI-MS (*m/z*): 1030.63 found for $[M+Na]^+$, calcd 1008.56. Anal. Calcd for $C_{36}H_{62}NClO_{29}\cdot 2H_2O$ (1043.33): C, 41.41; H, 6.37; N, 1.34; Cl, 3.55. Found: C, 41.52; H, 6.42; N, 1.40; Cl, 3.59.

4.6. Mono-6^A-*N*-ammonium-6^A-deoxy-γ-cyclodextrin chloride 4b, γ-CD-NH$_3$Cl

By following the similar synthetic procedure to **4a**, compound **3b** was employed to afford the title product **4b** with excellent yield (93.5%). Melting point: 254–258 °C, accompanied by decomposition. $[\alpha]_D = +102.8$ (*c* 1.0, water). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 5.82–5.70 (m, 16H, OH-2 and OH-3), 4.92–4.85 (m, 8H, H-1), 4.61–4.46 (m, 7H, OH-6), 3.75–3.45 (m, 32H, H-5$_{CD}$, H-3$_{CD}$ and H-6$_{CD}$), 3.43–3.24 (overlap with HDO, m, 16H, H-2$_{CD}$ and H-4$_{CD}$); ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 101.6 (C1), 80.8 (C4), 72.8 (C3), 72.5 (C2), 72.1 (C5), 59.9 (C6). ESI-MS (*m/z*): 1355.82 found for $[M+Na]^+$, calcd 1333.56. Anal. Calcd for $C_{48}H_{82}NClO_{39}\cdot H_2O$ (1349.43): C, 42.68; H, 6.27; N, 1.04; Cl, 2.59. Found: C, 42.78; H, 6.31; N, 1.10; Cl, 2.62.

4.7. Mono-6^A-(1-butyl-3-imidazolium)-6^A-deoxy-α-cyclodextrin tosylate 5a

Pre-dried compound **Ts-α-CD** (10.0 g, 8.8 mmol) was dissolved in an excess of 1-butylimidazole (7 mL, 88.23 mmol) and dimethyl formamide (5 mL). The suspension was allowed to stir under nitrogen for 2 days at 90 °C. The resultant solution was cooled and excess 1-butylimidazole was removed under vacuum to afford light yellow syrup. The light yellow syrup was dissolved in methanol/water (50:50 v/v) and precipitated into ethyl acetate. The precipitate was vacuum-filtered and dried further under high vacuum to afford a white solid of the final product with a yield of 80.2%. Melting point: 241–247 °C, accompanied by decomposition. $[\alpha]_D = +83.6$ (*c* 1.0, water). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 8.82 (s, 1H, =CH-2$_{im}$), 7.64 (s, 2H, =CH-4 and =CH-5$_{im}$), 7.57 (s, 2H, =CH$_{ortho}$), 7.51 (s, 2H, =CH$_{meta}$), 5.63–5.41 (m, 12H, OH-2 and OH-3), 4.83–4.76 (m, 6H, H-1), 4.68–4.46 (m, 5H, OH-6), 4.13 (*t*, 3H, $J = 5.19$ Hz, CH$_2$), 3.82–3.46 (m, 24H, H-5$_{CD}$, H-3$_{CD}$ and H-6$_{CD}$), 3.46–3.23 (overlap with HDO, m, 12H, H-2$_{CD}$ and H-4$_{CD}$), 2.07 (s, 3H, CH$_{3Ts}$), 1.75 (q, 2H, $J = 7.20$ Hz, CH$_2$), 1.22 (q, 2H, $J = 7.20$ Hz, CH$_2$), 0.88 (*t*, 3H, $J = 7.20$ Hz, CH$_3$). ESI-MS (*m/z*): 1079.47 (calcd) and 1079.60 found for $[M^+]$, 171.20 (calcd) and 170.90 found for $[^-OTs]$. Anal. Calcd for $C_{50}H_{78}S_1N_2O_{32}\cdot 2H_2O$ (1337.24): C, 44.91; H, 6.18; N, 1.05; S, 2.39. Found: C, 44.95; H, 6.21; N, 1.13; S, 2.42.

4.8. Mono-6^A-(1-methyl-3-imidazolium)-6^A-deoxy-γ-cyclodextrin tosylate 5b

By following a similar synthetic procedure to **5a**, **Ts-γ-CD** and 1-methylimidazole were employed to afford the title product **5b** with a yield of 83.5%. Melting point: 253–256 °C, accompanied by decomposition. $[\alpha]_D = +125.4$ (*c* 1.0, water). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 8.98 (s, 1H, =CH-2$_{im}$), 7.68 (s, 1H, =CH-4$_{im}$), 7.67 (s, 1H, =CH-5$_{im}$), 7.48 (d, 2H, $J = 8.04$ Hz, =CH$_{ortho}$), 7.13 (d, 2H, $J = 8.04$ Hz, =CH$_{meta}$), 5.98 (*d*, 1H, $J = 5.82$ Hz, OH-2), 5.83–5.62 (m, 16H, OH-2 and OH-3), 5.04 (*d*, 1H, $J = 3.60$ Hz, H-1), 4.92–4.84 (m, 8H, H-1), 4.78–4.54 (m, 7H, OH-6), 3.84 (s, 3H, CH$_{3im}$), 3.82–3.51 (m, 32H, H-5$_{CD}$, H-3$_{CD}$ and H-6$_{CD}$), 3.46–3.21 (overlap with HDO, m, 16H, H-2$_{CD}$ and H-4$_{CD}$), 2.29 (s, 3H, CH$_{3Ts}$). ESI-MS (*m/z*): 1362.32 (calcd) and 1362.47 found for $[M^+]$, 171.20 (calcd) and 170.91 found for $[^-OTs]$. Anal. Calcd for $C_{59}H_{92}S_1N_2O_{42}\cdot 3H_2O$ (1587.45): C, 44.64; H, 6.22; N, 1.76; S, 2.02. Found: C, 44.75; H, 6.33; N, 1.81; S, 2.11.

4.9. Mono-6^A-propylammonium-6^A-deoxy-γ-cyclodextrin tosylate 6b, PAM-γ-CD

A solution of **Ts-γ-CD** (2.90 g, 2.0 mmol) and propylamine (0.35 g, 6.0 mmol) in dimethyl formamide (5 mL) was refluxed for 5 h under nitrogen. The resulting solution was cooled to room temperature, after which acetone (25 mL) was added and stirred for 30 min. The white solid formed was filtered and dried under vacuum overnight to give the desired product (1.90 g, 62.9%). Melting point: 265–269 °C, accompanied by decomposition. $[\alpha]_D = +131.2$ (*c* 1.0, water). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 7.48 (*d*, 2H, $J = 7.62$ Hz, =CH$_{ortho}$), 7.12 (d, 2H, $J = 8.04$ Hz, =CH$_{meta}$), 5.79–5.67 (m, 16H, OH-2 and OH-3), 4.93–4.86 (m, 8H, H-1), 4.71–4.62 (m, 7H, OH-6), 3.75–3.48 (m, 32H, H-5$_{CD}$, H-3$_{CD}$ and H-6$_{CD}$), 3.42–3.24 (overlap with HDO, m, 16H, H-2$_{CD}$ and H-4$_{CD}$), 2.63 (*t*, 2H, $J = 7.23$ Hz, CH$_2$), 2.28 (s, 3H, CH$_{3Ts}$), 2.07 (s, 2H, CH$_2$), 1.47 (NH$_2$), 0.84 (*t*, 3H, $J = 7.62$ Hz, CH$_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 144.63 (C$_{ipso}$), 138.17 (C$_{para}$), 128.14 (C$_{ortho}$), 125.36 (C$_{meta}$), 101.99 (C1′), 101.56 (C1), 82.71 (C4′), 80.77 (C4), 72.76 (C2), 72.40 (C3), 72.00 (C5), 59.87 (C6), 30.61 (CH$_2$), 30.55 (CH$_2$), 20.66 (CH$_{3Ts}$), 10.98 (CH$_3$). IR (cm^{-1}, KBr): 3410 (O–H str), 2929 (C–H str), 1637 (arom C=C ring str), 1155 (S=O str), 1080, 1032 (C–O–C str), 755 (C–H arom op bend). ESI-MS (*m/z*): 1339.57 (calcd) and 1339.65 found for $[M^+]$, 171.20 (calcd) and 171.31 found for $[^-OTs]$. Anal. Calcd for $C_{58}H_{95}S_1NO_{42}\cdot 2H_2O$ (1546.41):

C, 45.05; H, 6.45; N, 0.91; S, 2.07. Found: C, 45.14; H, 6.53; N, 1.03; S, 2.15.

4.10. Ion exchange of tosylate anion into chloride

Vaccum dried compound **5** or **6** (0.8 mmol) was dissolved in 50 mL deionised water. Amberlite 900 (Cl) resin was filled in a 100 mL dropping funnel. The solution was introduced in the funnel and left for 1 h. The eluent was collected and solvent was removed to obtain a yellow crystalline solid. The desired product was obtained after being dried under vacuum overnight with excellent yield (ca. 96%). The structure of **5′** and **6′** were confirmed by ESI-MS results. After the ion exchange process, the signal at ~170.21 (for $^{-}$OTs) disappeared in the negative mode of MS spectra, while the signal for CD cations remained in the positive mode of MS spectra.

4.11. Preparation of buffer and sample solutions

Monobasic sodium phosphorate (100 mM) stock solutions were used as background electrolytes (BGEs). Running buffers were prepared by dissolving the appropriate amount of chiral selector into BGEs and titrated with sodium hydroxide or phosphoric acid to the required pH 6.0. Stock solutions (50 μg/mL) of racemic analytes were prepared and stored at 4 °C. All running buffers and sample solutions were filtrated with a 0.45 μm syringe type Millipore membrane and sonicated prior to use.

Acknowledgements

Financial support for this work was provided by the National University of Singapore (NUS). W.T. thanks the NUS for awarding the research scholarship.

References

1. Easton, C. J.; Lincoln, S. F. *Modified Cyclodextrins: Scaffolds and Templates for Supramolecular Chemistry*; Imperial College Press: River Edge, NJ, 1999.
2. Khan, A. R.; Forgo, P.; Stine, K. J.; D'Souza, V. T. *Chem. Rev.* **1998**, *98*, 1977.
3. (a) García Fernández, J. M.; Ortiz Mellet, C.; Maciejewski, S.; Defaye, J. *Chem. Commun.* **1996**, 2741; (b) Galaverna, G.; Corradini, R.; Dossena, A.; Marchelli, R. *Electrophoresis* **1999**, *20*, 2619.
4. (a) Charbonnier, F.; Humbert, T.; Marsura, A. *Tetrahedron Lett.* **1998**, *39*, 3481; (b) Aoyagi, T.; Ueno, A.; Fukushima, M.; Osa, T. *Macromol. Rapid Commun.* **1998**, *19*, 103; (c) Ishimaru, Y.; Masuda, T.; Iida, T. *Tetrahedron Lett.* **1997**, *38*, 3743; (d) Breslow, R.; Halfon, S.; Zhang, B. *Tetrahedron* **1995**, *51*, 377; (e) Venema, F.; Rowan, A. E.; Nolte, R. J. M. *J. Am. Chem. Soc.* **1996**, *118*, 257; (f) Breslow, R.; Zhang, B. *J. Am. Chem. Soc.* **1996**, *118*, 8495; (g) Jiang, T.; Sukumaran, D. K.; Soni, S.-D.; Lawrence, D. S. *J. Org. Chem.* **1994**, *59*, 5149.
5. (a) Muderawan, I. W.; Ong, T. T.; Ng, S. C. *J. Sep. Sci.* **2006**, *29*, 1849; (b) Dittmann, H.; Scharwachter, K.; Konig, W. A. *Carbohyd. Res.* **2000**, *324*, 75.
6. (a) Ward, T. J.; Hamburg, D.-M. *Anal. Chem.* **2004**, *76*, 4635; (b) Juvancz, Z.; Szejtli, J. *Trends Anal. Chem.* **2002**, *21*, 379–388.
7. Schurig, V. *Trends Anal. Chem.* **2002**, *21*, 647–661.
8. Chankvetadze, B. *J. Sep. Sci.* **2001**, *24*, 691.
9. (a) Gübitz, G.; Schmid, M. G. *Electrophoresis* **2007**, *28*, 114; (b) Eeckhaut, A. V.; Michotte, Y. *Electrophoresis* **2006**, *27*, 2880; (c) De Boer, T.; De Zeeuw, R. A.; Ensing, K. *Elelectrophoresis* **2000**, *21*, 3220–3239.
10. (a) Muderawan, I. W.; Ong, T. T.; Tang, W. H.; Young, D. J.; Ching, C. B.; Ng, S. C. *Tetrahedron Lett.* **2005**, *46*, 1747; (b) Tang, W. H.; Ong, T. T.; Muderawan, I. W.; Ng, S. C.; Chan, H. S. O. *Electrophoresis* **2005**, *26*, 3839; (c) Tang, W. H.; Muderawan, I. W.; Ong, T. T.; Ng, S. C.; Chan, H. S. O. *J. Chromatogr. A* **2005**, *1094*, 187.
11. (a) Tang, W. H.; Muderawan, I. W.; Ng, S. C.; Chan, H. S. O. *Anal. Chim. Acta* **2005**, *554*, 156; (b) Tang, W. H.; Muderawan, I. W.; Ong, T. T.; Ng, S. C. *Electrophoresis* **2005**, *26*, 3125; (c) Tang, W. H.; Ong, T. T.; Muderawan, I. W.; Ng, S. C. *Anal. Chim. Acta* **2007**, *585*, 227.
12. Armstrong, D. W.; DeMond, W. *J. Chromatogr. Sci.* **1984**, *22*, 411.
13. (a) Fujimura, K.; Suzuki, S.; Hayashi, K. *Anal. Chem.* **1990**, *62*, 2198; (b) Rekharshy, M.; Inoue, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4418; (c) Armstrong, D. W.; Stalcup, A. M.; Hilton, M. *Anal. Chem.* **1990**, *62*, 1610.
14. Szejtli, J.; Osa, T. *Comprehensive Supramolecular Chemistry, Vol. 3. Cyclodextrins*; Elsevier: Oxford, 1996.
15. Melton, L. D.; Slessor, K. N. *Carbohyd. Res.* **1971**, *18*, 29.
16. (a) Rekharsky, M. V.; Inoue, Y. *Chem. Rev.* **1998**, *98*, 1875; (b) Fanali, S. *J. Chromatogr. A* **1997**, *792*, 227.
17. (a) Fanali, S. *J. Chromatogr.* **1989**, *474*, 441; (b) Chankvetadze, B.; Endresz, G.; Blaschke, G. *J. Chromatogr. A.* **1995**, *700*, 43–49.