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Synthesis of ammonium substituted β-cyclodextrins for enantioseparation of anionic analytes

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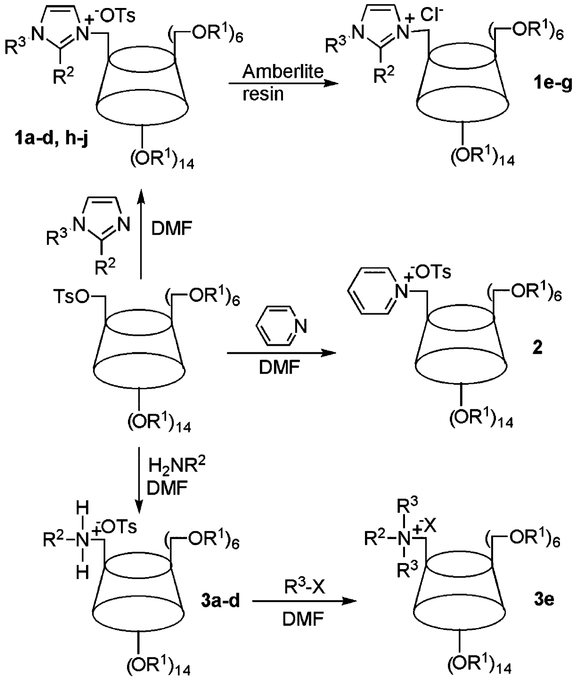
Abstract—New ammonium functionalized cyclodextrins can be prepared in excellent yields by displacement of 6-tosyl-β-cyclodextrin with alkylimidazoles, pyridine or alkylamines and achieve excellent enantioseparation of dansyl amino acids presumably due to electrostatic interactions between the cationic host and anionic guest.

There is increasing interest in developing chiral ionic liquids as solvents for enantioselective reactions and as chiral stationary phases for enantioseparation.[1–5] Several types of chiral ionic liquid have been developed involving the imidazole moiety with expensive chiral, alkylated side-chains[6] or chiral anions.[7] Other chiral ionic liquids have been derived from the chiral pool,[8] however the applications of these salts for enantioseparations remained unexplored. In an attempt to prepare cyclodextrin-based chiral ionic liquids, we have prepared several cationic β-cyclodextrins (CDs) substituted at the 6-position with imidazolium **1**, pyridinium **2** and quaternary ammonium **3** moieties (Scheme 1). While the melting points of these compounds are too high (115–267 °C) (Table 1) for ionic liquid applications, these cationic cyclodextrins proved highly successful stationary phases for the enantioseparation of aromatic carboxylic acids at low concentrations (3–10 mM). This is presumably due to the strong electrostatic interaction between cationic CD and the anionic analytes.[9–11]

β-Cyclodextrin monofunctionalized with a tosyl group at the 6-position was prepared using the previously reported procedure by Brady et al.[12] Alkylimidazolium-β-cyclodextrin tosylates **1** were prepared in excellent yields by heating mono-6-(*p*-toluenesulfonyl)-β-cyclodextrin with an alkylimidazole in DMF at 90 °C for 2 days (Scheme 1). Pyridinium-β-cyclodextrin tosylate **2** was similarly



Scheme 1.

Keywords: Cationic cyclodextrins; Enantiomeric resolution.

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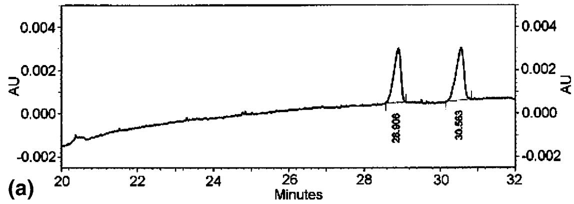
Table 1. Yields and melting point data for cationic β-cyclodextrins

Entry	Cationic cyclodextrin	R^1	R^2	R^3	X^-	Yields (%)	Melting point (°C)
1	**1a**[13]	H	H	CH_3	OTs	99	257–259 (dec)
2	**1b**	H	H	n-C_4H_9	OTs	97	254–256 (dec)
3	**1c**	H	H	n-C_8H_{17}	OTs	98	256–258 (dec)
4	**1d**	H	CH_3	CH_3	OTs	62	257–258 (dec)
5	**1e**	H	H	CH_3	Cl	93	233–235 (dec)
6	**1f**	H	H	n-C_4H_9	Cl	93	249–250 (dec)
7	**1g**	H	CH_3	CH_3	Cl	82	199–200 (dec)
8	**1h**	Ac	H	CH_3	OTs	64	129–130
9	**1I**	Ac	H	n-C_4H_9	OTs	76	115–116
10	**1j**	Ac	CH_3	CH_3	OTs	62	125–126
11	**2**[14]	H	H	—	OTs	85	239–241 (dec)
12	**3a**[15]	H	C_3H_5	—	OTs	92	249–250 (dec)
13	**3b**	H	n-C_3H_7	—	OTs	98	260–261 (dec)
14	**3c**	H	n-C_4H_9	—	OTs	97	263–264 (dec)
15	**3d**	H	n-C_5H_{11}	—	OTs	96	266–267 (dec)
16	**3e**	H	n-C_3H_7	CH_3	I^-	89	241–243 (dec)

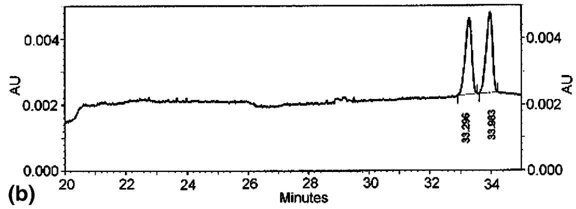
prepared by refluxing mono-6-tosyl-β-cyclodextrin with pyridine at 90 °C for 2 days in 85% yield. Allyl, and alkylammonium-β-cyclodextrin tosylates **3** were prepared by refluxing mono-6-tosyl-β-cyclodextrin with allylamine, n-propylamine, n-butylamine and n-pentylamine in DMF for only 5 h. Quaternization with an alkyl halide gave the quaternary ammonium CD salt. The tosylate anion could be exchanged with chloride by ion-exchange using Amberlite resin. The salts **1a–j**, **2** and **3a–e** have very high solubility in methanol and water.

These cationic cyclodextrins proved to be excellent chiral selectors in capillary electrophoresis. Figure 1a–c shows typical electrophoregrams for enantioseparation of three racemates that were successfully resolved using **1e** (7 mM concentration) at pH 7.52 and 15 kV at normal polarity.

DL-Dansyl Norvaline: α = 1.05; R_s = 3.75



DL-Dansyl Serine: α = 1.02; R_s = 1.67



3-Phenylbutyric acid: α = 1.01; R_s = 1.27

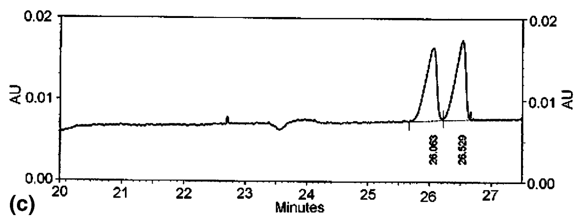


Figure 1. Capillary electrophoresis of racemates using **1e** as a chiral selector.

In summary, novel cationic cyclodextrins can be cleanly prepared in excellent yields from the corresponding tosylate. These ionic compounds provide base-line enantioseparation of appropriately sized aromatic carboxylic acids by capillary electrophoresis. We are currently investigating the fictionalization of cyclodextrin hydroxyl groups to lower the melting point of the ionic compound and thereby obtain a chiral ionic liquid.

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13. Preparation of mono-6-deoxy-6-(3-methylimidazolium)-β-cyclodextrin tosylate **1a**: A mixture of mono-6-(*p*-toluenesulfonyl)-β-cyclodextrin (12.89 g, 0.01 mol) and 1-methylimidazole (2.50 g, 0.03 mol) in DMF (25 mL) were stirred under nitrogen at 90 °C for 2 days. After cooling to room temperature, acetone (100 mL) was added to the resultant solution, which was vigorously stirred for 30 min. The solid formed was filtered, washed with acetone and finally dried under high vacuum to afford a white solid (13.50 g, 99%): mp 257–259 °C (dec). FTIR (KBr): 3399, 2927, 1638, 1155, 1080, 1033 cm^{-1}. ESI MS (*m*/*z*): 1199.60 [M^+], calcd 1199.42; 171.30 [$^-$OTs], calcd 171.17. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.30 (s, 3H, CH_{3Ts}), 2.82 (t, 1H, $J = 6.0$ Hz, H-2), 3.06 (t, 1H, $J = 6.0$ Hz, H-4), 3.23 (t, 1H, $J = 9.2$ Hz, H-5), 3.31–3.47 (m, 12H, H-2,4), 3.50–3.64 (m, 27H, H-3,5,6), 3.85 (s, 3H, CH_{3im}), 4.32 (t, 1H, $J = 9.2$ Hz, OH-6), 4.50 (t, 1H, $J = 5.6$ Hz, OH-6), 4.56 (t, 4H, $J = 5.6$ Hz, OH-6), 4.84 (d, 6H, $J = 3.2$ Hz, H-1), 4.98 (d, 1H, $J = 3.6$ Hz, H-1), 5.64–5.84 (m, 13H, OH-2,3), 5.99 (d, 1H, $J = 5.8$ Hz, OH-2), 7.13 (d, 2H, $J = 8.0$ Hz, $=CH_{meta}$), 7.49 (d, 2H, $J = 8.4$ Hz, $=CH_{ortho}$), 7.68 (s, 1H, $=CH\text{-}5_{im}$), 7.69 (s, 1H, $=CH\text{-}4_{im}$), 9.01 (s, 1H, $=CH\text{-}2_{im}$). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 20.7 (CH_{3Ts}), 35.8 (CH_{3im}), 49.8 (C6), 59.9 (C6), 69.6 (C5), 72.0 (C5), 72.3 (C3), 73.3 (C2), 81.5 (C4), 83.0 (C4), 01.8 (C1), 123.0 ($=CH_{im}$), 123.3 ($=CH_{im}$), 125.4 (C_{meta}), 128.0 (C_{ortho}), 137.0 ($=CH_{im}$), 137.7 (C_{para}), 145.4 (C_{ipso}).

14. Preparation of mono-6-deoxy-6-pyridinium-β-cyclodextrin tosylate **2**: A mixture of mono-6-(*p*-toluenesulfonyl)-β-cyclodextrin (2.58 g, 2.0 mmol) and pyridine (0.48 g, 6.0 mmol) in DMF (5 mL) was stirred under nitrogen at 90 °C for 2 days. After cooling to room temperature, acetone (25 mL) was added to the resultant solution, which was vigorously stirred for 30 min. The solid formed was separated by filtration, washed with acetone and finally dried under vacuum to give a white solid (2.33 g, 85%): mp 239–241 °C. FTIR (KBr): 3394, 2925, 1636, 1158, 1080, 1032 cm^{-1}. ESI MS (*m*/*z*) 1196.60 [M^+], calcd 1196.42; 171.30 [$^-$OTs], calcd 171.01. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.29 (s, 3H, CH_{3Ts}), 3.12–3.47 (m, 14H, H-2,4), 3.55–3.67 (m, 26H, H-3,5,6), 3.86–3.96 (m, 2H, H-6), 4.18 (t, 1H, $J = 10.0$, 10.8 Hz, OH-6), 4.28 (t, 1H, $J = 6.0$, 5.6 Hz, OH-6), 4.45 (t, 1H, $J = 5.2$, 5.6 Hz, OH-6), 4.54 (t, 2H, $J = 5.6$, 5.2 Hz, OH-6), 4.60 (t, 1H, $J = 5.6$, 7.6 Hz, OH-6), 4.77–4.88 (m, 6H, H-1), 5.02 (d, 1H, $J = 6.0$ Hz, H-1), 5.58 (d, 1H, $J = 2.0$ Hz, OH-3), 5.63–5.87 (m, 12H, OH-2,3), 6.06 (d, 1H, $J = 6.0$ Hz, OH-2), 7.10 (d, 2H, $J = 7.6$ Hz, $=CH_{metaTs}$), 7.48 (d, 2H, $J = 8.0$ Hz, $=CH_{orthoTs}$), 8.13 (t, 2H, $J = 7.2$, 6.8 Hz, $=CH\text{-}3_{pyr}$), 8.64 (t, 1H, $J = 8.0$, 7.7 Hz, $=CH\text{-}4_{pyr}$), 9.01 (d, 2H, $J = 6.0$ Hz, $=CH\text{-}2_{pyr}$). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 20.7 (CH_{3Ts}), 58.7 (C6), 59.8 (C6), 60.8 (C6), 61.6 (C6), 70.2 (C5), 71.3, 71.9, 72.1, 72.3, 73.0, 73.4 (C5, C3, C2), 80.6, 81.4, 82.9 (C4), 83.6 (C4), 100.9 (C1), 101.8, 101.9, 102.3 (C1), 125.4 (C_{metaTs}), 127.9 ($C3_{pyr}$), 128.0 ($C_{orthoTs}$), 137.5 (C_{paraTs}), 145.4 (C_{ipsoTs}), 145.5 ($C4_{pyr}$), 146.1 ($C2_{pyr}$).

15. Preparation of mono-6-(allylammonium)-6-deoxy-β-cyclodextrin tosylate **3a**: A mixture of mono-6-(*p*-toluenesulfonyl)-β-cyclodextrin (2.58 g, 2.0 mmol) and allyl amine (0.34 g, 6.0 mmol) in dimethyl formamide (5 mL) was refluxed for 5 h under nitrogen. After cooling to room temperature, acetone (25 mL) was added to the resultant solution, which was vigorously stirred for 30 min. The white solid formed was filtered, washed with acetone and dried under vacuum overnight to give the desired product (2.48 g, 92%): mp 249–250 °C (dec). FTIR (KBr): 3426, 2926, 1638, 1157, 1080, 1032 cm^{-1}. ESI MS (*m*/*z*): 1174.40 [M^+], calcd 1174.42; 171.30 [$^-$OTs], calcd 171.17. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.29 (s, 3H, CH_{3Ts}), 2.85 (t, 1H, $J = 8.8$ Hz, H-2), 3.10 (d, 1H, $J = 12.0$ Hz, H-4), 3.32–3.54 (m, 14H, H-2,4 and CH_2), 3.60–3.63 (m, 27H, H-3,5,6), 3.80 (t, 1H, $J = 8.4$ Hz, H-3), 4.50 (s br, 1H, OH-6), 4.83 (d, 6H, $J = 3.6$ Hz, H-1), 4.87 (d, 1H, $J = 3.2$ Hz, H-1), 5.16–5.38 (m, 2H, $=CH_2$), 5.67 (s br, 6H, OH-3), 5.73 (s br, 8H, OH-2,3), 5.81–5.87 (m, 1H, –CH=), 7.12 (d, 2H, $J = 8.3$ Hz, $=CH_{meta}$), 7.48 (d, 2H, $J = 7.8$ Hz, $=CH_{ortho}$). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 20.7 (CH_3), 40.9 (CH_2), 50.6 (C6), 59.9 (C6), 69.0 (C5), 72.0 (C5), 72.2 (C3), 73.0 (C2), 81.2 (C4), 83.6 (C4), 101.9 (C1), 119.8 ($=CH_2$), 125.4 (C_{meta}), 128.1 (C_{ortho}), 130.8 (–CH=), 137.9 (C_{para}), 145.1 (C_{ipso}).