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A facile synthesis of novel cyclodextrin derivatives incorporating one β-(1,4)-glucosidic bond and their unique inclusion ability†

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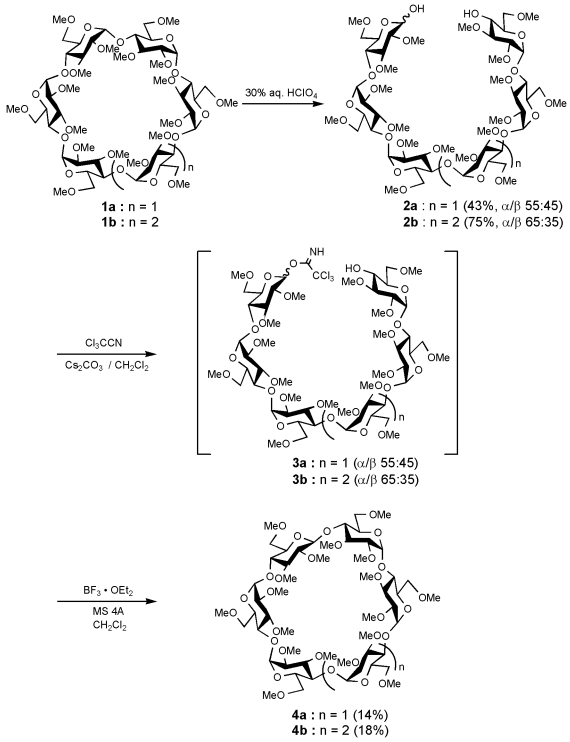
Novel cyclodextrin derivatives incorporating one β-(1,4)-glucosidic bond are easily synthesized in three steps from permethylated α- and β-cyclodextrins, and such host molecules show inclusion selectivity for sodium *m*-nitrobenzoate over the corresponding *p*-isomer, in contrast to the cases of the parent permethylated α- and β-cyclodextrins.

Cyclodextrins (CDs) are a class of cyclic oligosaccharides consisting of several α-(1,4)-linked D-glucopyranose units and have a hydrophobic cavity into which a guest molecule of appropriate size and shape is incorporated in aqueous media. Much effort has been devoted to the chemical modification of CDs in order to improve and control their inclusion ability.[1] Most of such work, however, has been limited to the modification of the hydroxyl groups on the upper and/or lower rims of CDs.[2] Recently, the modification of the CD ring skeleton as another methodology has attracted increasing attention,[3] because such modification is believed to cause a more significant change in the cavity size and/or shape of CDs, thus altering more remarkably the original inclusion ability and selectivity, compared with the modification of the CD hydroxyl groups. Conversion of the α-(1,4)-glucosidic bonds of CDs into other types of interglucosidic linkages, such as β-(1,3)-[4] and β-(1,6)-glucosidic bonds,[5] is one of the most effective methods to modify the CD ring skeleton.[3e] These synthetic processes, however, have required considerably more reaction steps in comparison with the modification of the CD hydroxyl groups. For example, Ogawa *et al.* reported the synthesis of an interesting cyclodextrin analog consisting of one α-(1,6)-glucosidic bond and five α-(1,4)-glucosidic bonds, but the synthetic approach required more than 15 reaction steps from D-maltose.[6] Although these CD derivatives with different interglucosidic linkages are expected to show unique complexation behavior, the binding ability of such host molecules has not yet been described except for the case of β-(1,6)-linked cycloglucotetraose peracetate which exhibits metal cation-binding ability.[7] Therefore, the development of an alternative methodology for facile synthesis of CD derivatives incorporating different interglucosidic bonds from that of the native CDs and the elucidation of their binding properties are strongly desired. In this communication, we report a facile synthesis of novel CD derivatives incorporating one β-(1,4)-glucosidic bond and their unique inclusion ability toward *m*- and *p*-nitrobenzoates.

The skeleton-modified CD derivatives **4a** and **4b**, in which one α-(1,4)-glucosidic bond of permethylated α- and β-CDs is replaced by a β-(1,4)-glucosidic bond, were chosen as the target molecules. Scheme 1 shows the synthetic route to **4a** and **4b**. According to the previously reported method, α- and β-CDs were converted into the corresponding permethylated derivatives **1a** and **1b**, respectively.[8] Conversion of one α-(1,4)-glucosidic bond into a β-(1,4)-glucosidic bond was carried out in three reaction steps: the ring-opening of the permethylated CD **1** by cleavage of one α-(1,4)-glucosidic bond, the reaction of the C-1 hydroxyl group on acyclic maltooligosaccharide derivatives **2** with trichloroacetonitrile, and the intramolecular glucosidation of the resulting trichloroacetimidates **3**. Recently, we developed an efficient method for the selective cleavage of one glucosidic bond of permethylated α-CD **1a** by treatment with 30% aq. $HClO_4$ at room temperature.[3h] This method was also successfully applied to the cleavage of one glucosidic bond of the permethylated β-CD **1b** to give the desired maltoheptaose derivative in 75% isolated yield. ^{1}H NMR spectra in $CDCl_3$ show that **2a** and **2b** are obtained as 55 : 45 and 65 : 35 mixtures of the α- and β-anomers, respectively. Reactions of **2a** and **2b** with trichloroacetonitrile in the presence of Cs_2CO_3 in CH_2Cl_2 at room temperature[9] almost quantitatively afforded the corresponding trichloroacetimidates **3a** and **3b**, respectively. Under such reaction conditions, the C-4 hydroxyl groups on the terminal glucose units in **2a** and **2b** did not react with trichloroacetonitrile, possibly due to the larger steric hindrance. Without further purification of these trichloroacetimidates, the BF_3·OEt_2-promoted intramolecular glucosidation in the presence of powdered molecular sieves 4A in CH_2Cl_2 at room temperature[10] was carried out to give the desired cyclic compounds **4a** and **4b** bearing one β-(1,4)-glucosidic bond in 14% and 18% yields, respectively. Here the corresponding permethylated CDs **1a** and **1b** were also isolated as by-products in 4% and 5% yields, respectively. The separation of **4a** and **4b** from the corresponding α/β anomeric mixtures was success-



Scheme 1

† Electronic supplementary information (ESI) available: ^{1}H NMR spectra of **4a** and **4b**; NMR chemical shifts of the carbohydrate protons of **4a** and **4b**; HPLC chromatograms of **4a** and **4b**. See http://www.rsc.org/suppdata/cc/b3/b309261e/

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fully carried out by reversed-phase column chromatography with acetonitrile as an eluent. The use of trimethylsilyl triflate (TMSOTf) instead of $BF_3{\cdot}OEt_2$ in these cycloglucosidations somewhat lowered the yields of **4a** and **4b** to 7% and 10% yields, respectively. The structures of these CD derivatives were confirmed by NMR and mass spectra.‡ Intense molecular ion signals at *m*/*z* 1248 (M+Na) and 1452 (M+Na) were observed in MALDI-TOF mass spectra of **4a** and **4b**, respectively. In the ^{1}H NMR spectrum of **4a**, the anomeric proton signals were observed in the range of 4.5 to 5.7 ppm. Among them, a signal present at 4.56 ppm as a doublet can be assigned to the anomeric proton with β-D-configuration by the larger coupling constant ($J_{1,2}$ = 7.7 Hz). In the case of **4b**, the anomeric protons were clearly separated into seven signals and the one at 4.70 ppm ($J_{1,2}$ = 7.0 Hz) is assigned to the proton with β-D-configuration. These NMR results suggest that both **4a** and **4b** have unsymmetrical structures, in contrast to the cases of the permethylated α- and β-CDs.

We determined the stability constants of the complexes of these host molecules **4a** and **4b** with sodium *m*-nitrobenzoate (MNB) and sodium *p*-nitrobenzoate (PNB) by the ^{1}H NMR titration method in D_2O including 132 mM NaOD and 50 mM KCl (Table 1). The upfield shift of the signals of the anomeric protons of these host molecules was observed upon addition of the *m*- and *p*-isomers of sodium nitrobenzoate, suggesting that the aromatic parts of these guest molecules are incorporated into the cavity of **4a** and **4b**. The inclusion ability of host **4a** toward both guest molecules was lower than that of the parent permethylated α-CD **1a**. On the other hand, host **4b** exhibited higher inclusion ability toward the *m*-isomer than the parent permethylated β-CD **1b**, while these hosts showed almost the same inclusion ability toward the *p*-isomer. There was little difference in the inclusion ability toward either guest between **4a** and **4b**, in contrast to the cases of **1a** and **1b** where the former host formed a more stable complex with either guest than the latter. These results clearly indicate that the hosts **4a** and **4b** possess different cavity shapes from those of the corresponding permethylated CDs. Interestingly, hosts **4a** and **4b** showed inclusion selectivity for the *m*-isomer over the *p*-isomer (K_{MNB}/K_{PNB} = 1.8 ± 0.5 for **4a**, K_{MNB}/K_{PNB} = 1.8 ± 0.6 for **4b**), in contrast to the cases of the permethylated CDs with the *p*-isomer selectivity (K_{PNB}/K_{MNB} = 2.1 ± 0.4 for **1a**, K_{PNB}/K_{MNB} = 2.6 ± 1.0 for **1b**). This finding demonstrates that the conversion of one α-(1,4)-glucosidic bond of permethylated α- and β-CDs into a β-(1,4)-glucosidic bond causes a reversal of the original inclusion selectivity. To the best of our knowledge, this is the first example of CD derivatives exhibiting clear inclusion selectivity for *m*-substituted benzoate over the corresponding *p*-isomer.

Table 1 Stability constants (M^{-1}) of complexes of CD derivatives **4a** and **4b** with MNB[a] and PNB[a] in D_2O[b] at 25 °C

	Guest	
Host	MNB	PNB
4a	50 ± 10	28 ± 2
4b	40 ± 10	23 ± 2
1a	200 ± 30	410 ± 20
1b	9 ± 2	21 ± 4

[a] MNB = sodium *m*-nitrobenzoate; PNB = sodium *p*-nitrobenzoate. [b] Including 132 mM NaOD and 50 mM KCl.

In conclusion, we have successfully developed a facile synthetic route to novel CD derivatives incorporating one β-(1,4)-glucosidic bond and demonstrated that such CD derivatives show different inclusion ability and selectivity from those of the parent permethylated α- and β-CDs. Work on elucidation of the structures of the CD derivatives and their complexes with MNB and PNB is now in progress in our laboratory.

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Notes and references

‡ Spectroscopic data for **4a**: mp 88–90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62 (d, 1H, *J* = 3.3 Hz), 5.08 (m, 2H), 5.04 (d, 1H, *J* = 3.3 Hz), 5.02 (d, 1H, *J* = 3.3 Hz), 4.56 (d, 1H, *J* = 7.7 Hz), 4.15 (m, 1H), 3.44–3.91 (m, 65H), 3.37–3.40 (m, 15H), 3.33 (s, 3H), 3.25 (m, 1H), 3.15–3.18 (m, 4H), 3.09 (t, 1H, *J* = 8 Hz); MALDI-TOF *m*/*z*: 1248 $[M+Na]^+$, 1264 $[M+K]^+$; Anal. Calcd for $C_{54}H_{96}O_{30}$: C, 52.93; H, 7.90. Found: C, 52.74; H, 7.64%.

For **4b**: mp 92–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63 (d, 1H, *J* = 3.7 Hz), 5.33 (d, 1H, *J* = 3.7 Hz), 5.28 (d, 1H, *J* = 3.3 Hz), 5.23 (d, 1H, *J* = 3.7 Hz), 5.09 (d, 1H, *J* = 3.3 Hz), 5.06 (d, 1H, *J* = 3.3 Hz), 4.70 (d, 1H, *J* = 7.0 Hz), 4.01 (m, 1H), 3.40–3.95 (m, 75H), 3.31–3.39 (m, 22H), 3.16–3.28 (m, 6H), 3.10 (t, 1H, *J* = 7.3 Hz); MALDI-TOF *m*/*z*: 1452 $[M+Na]^+$, 1468 $[M+K]^+$; Anal. Calcd for $C_{63}H_{112}O_{35}$: C, 52.93; H, 7.90. Found: C, 52.58; H, 7.56%.

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