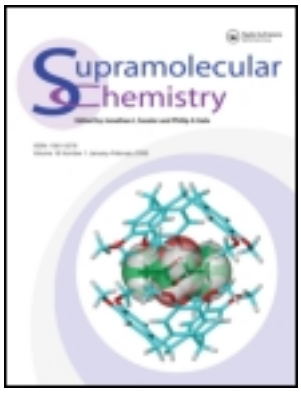

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Molecular properties of mono guest-modified cyclodextrins on the secondary site

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Novel guest-modified α- and β-cyclodextrins (CyDs) through an alkyl chain and amide bond ($\mathbf{1}_\alpha$, $\mathbf{2}_\alpha$, $\mathbf{3}_\alpha$, $\mathbf{2}_\beta$ and $\mathbf{3}_\beta$) were synthesised in satisfactory yield (81–93%) by DCC condensation between 3-monoamino-3-monodeoxy-CyD and benzoic acid, phenylpropionic acid and phenylbutylic acid, respectively. These substituted CyDs include their phenyl groups into their own cavities, forming intra-molecular host–guest complexes evidenced by varied concentration of 1D and 2D NOE NMR spectra. Compounds **1**–**3** exhibit higher water solubility than native CyD.

Keywords: secondary modification; cyclodextrin; hydrogen bonding; NMR; self-inclusion

Native cyclodextrins (CyDs) are rigid molecules that offer limited utility in terms of size, shape and availability of chemically useful functional groups. This is because the (1-4)-linked α-D-glucopyranosyl rings adapt exclusively to the energetically favoured $^4C_1$ chair form, and there is only limited rotation around the glycosidic bond. Moreover, the secondary hydroxyl groups, 2-OH and 3-OH, form a circle of consecutive inter-residue hydrogen bonds (*1*). In order to add flexibility, we have already prepared several CyDs having mono-hydrophobic substituents on the primary hydroxyl site (*2*). A phenyl group in these modified CyDs acts as the cavity-size control factor; this group is known as the 'self-guest group'. The modified CyDs also contain a flexible arm composed of sp^3 carbons between the CyD cavity and the phenyl group. The structure causes guest-induced hydrophobic wall movement to form an intra-molecular complex. Some 'guest group'-modified CyDs form an inter-molecular complex or a suprapolymer (*3*). A huge number of guest-modified CyDs on the primary site have been reported; however, very few studies on the secondary site have been reported. Secondary hydroxyl groups, present at the wide rim of the cavity, are located at a more hydrophilic region and hence play a more important role in hydrogen bonding for molecular recognition than primary hydroxyl groups present at the narrow rim. We focused on 3-monoamino-3-monodeoxy-CyD, in which the amino-substituted glucose residue has been replaced by an *altro*-pyranose unit with axial hydroxyl groups as the starting material. The investigation of mono-*altro*-β-CyD and its inclusion complex by NMR spectroscopy revealed that the hydrogen bond network in mono-*altro*-β-CyD produces an adaptable host that could be used as an induced-fit enzyme model (*4*). We prepared a series of modified CyDs having a self-guest group through the flexible short-length arm bound with amide linkage at the secondary site. In this paper, we investigate the structure and properties of novel guest-modified α- and β-CyDs on the secondary site and compare them with those of the guest-modified α- and β-CyDs on the primary site.

A series of modified CyDs (Figure 1) were prepared and purified from 3-monoamino-3-monodeoxy-α- or β-CyD and benzoic acid, phenylpropionic acid and phenylbutylic acid, respectively, according to a DCC condensation method which we had reported previously. The reaction progressed quantitatively, and $\mathbf{1}_\alpha$, $\mathbf{2}_\alpha$, $\mathbf{3}_\alpha$, $\mathbf{2}_\beta$ and $\mathbf{3}_\beta$ were obtained in yields of 91, 83, 84, 93 and 85%, respectively. Identification was carried out by NMR and MALDI-TOF-MS spectroscopy. $\mathbf{1}_\alpha$: ^{1}H NMR (500 MHz, D_2O, ppm): δ 3.37–4.01 (m, 36H, H3, H5, H6, H2, H4 of α-CyD), δ 4.87–4.92 (d, 6H, H1 of α-CyD), δ 7.48 (d, 2H, Ph), δ 7.63 (d, 3H, Ph). *m/z* calcd for $C_{43}H_{65}NO_{30}Na$: 1098.35; found 1099.57. $\mathbf{2}_\alpha$: ^{1}H NMR (500 MHz, D_2O, ppm): δ 2.47 (m, 1H, —CH_2—), δ 2.56 (m, 1H, —CH_2—) δ 2.86 (m, 2H, —CH_2—), δ 3.42–4.07 (m, 36H, H3, H5, H6, H2, H4 of α-CyD), δ 4.78–4.98 (d, 6H, H1 of α-CyD), δ 7.23 (d, 3H, Ph), δ 7.32 (t, 2H, Ph). *m/z* calcd for $C_{45}H_{69}NO_{30}Na$: 1126.38; found 1127.49. $\mathbf{2}_\beta$:^{1}H NMR (500 MHz, D_2O, ppm): δ 2.41 (t, 1H, —CH_2—), δ 2.74 (t, 1H, —CH_2—), δ 2.82 (t, 1H, —CH_2—), δ 3.03 (m, 1H, —CH_2—), δ 3.05–4.28 (m, 44H, H3, H5, H6, H2, H4 of β-CyD), δ 4.72 (s, 1H, H1 of β-CyD), δ 4.86–5.01 (d, 6H, H1 of β-CyD), δ 7.18 (d, 5H, Ph). MALDI-TOF-MS: *m/z* calcd for $C_{51}H_{79}NO_{35}Na$: 1288.43; found 1289.02. $\mathbf{3}_\alpha$:^{1}H

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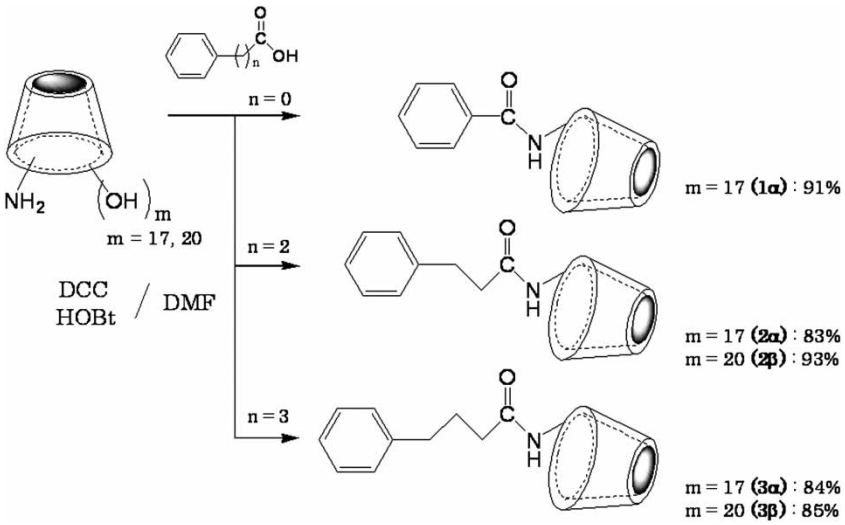

Figure 1. Synthesis of mono secondary side guest-modified CyDs.

NMR (500 MHz, D_2O, ppm): δ 1.86 (m, 2H, —CH_2—), δ 2.19 (m, 2H, —CH_2—), δ 2.59 (t, 2H, —CH_2—), δ 3.43–4.14 (m, 37H, H3, H5, H6, H2, H4 of α-CyD), δ 4.82–4.98 (d, 6H, H1 of α-CyD), δ 7.20 (d, 3H, Ph), δ 7.29 (t, 2H, Ph). MALDI-TOF-MS: *m/z* calcd for $C_{46}H_{71}NO_{30}Na$: 1140.40; found 1141.41. $\mathbf{3_\beta}$: ^{1}H NMR (500 MHz, D_2O, ppm): δ 1.78 (m, 1H, —CH_2—), δ 1.90 (m, 1H, —CH_2—), δ 2.06 (m, 1H, —CH_2—), δ 2.36 (m, 1H, —CH_2—), δ 2.48 (m, 1H, —CH_2—), δ 2.83 (m, 1H, —CH_2—), δ 3.11–4.38 (m, 53H, H3, H5, H6, H2, H4 of β-CyD), δ 4.79 (s, 1H, H1 of β-CyD), δ 4.86–5.01 (d, 6H, H1 of β-CyD), δ 7.10 (d, 2H, Ph), δ 7.16 (t, 1H, Ph), δ 7.25 (t, 2H, Ph). MALDI-TOF-MS: *m/z* calcd for $C_{52}H_{81}NO_{35}Na$: 1302.45; found 1303.15.

The representative ^{1}H NMR spectra at 303 K are shown in Figure 2. Concentration-dependent changes were not observed in the resonances of the substituted group from 10^{-5} to 10^{-2}. This is an evidence that compounds **1**–**3** form intra-molecular complexes. NMR chemical shifts of protons due to CyD components are observed as a well-split peak; this result is the same as that of the intra-molecular complex type of guest-modified CyDs (*2*). CyD resonances of $\mathbf{1_\alpha}$ are observed as broad peaks. The chemical shifts of the phenyl groups, except $\mathbf{2_\beta}$, are observed as two groups at higher field in these guest-modified CyDs than in the compound without CyD groups. CyD with the longer arm indicates the higher field shift. The resonances due to the alkyl arm can be observed as a well-split peak; each proton has a chemical shift. The resonances of β-CyD derivatives ($\mathbf{2_\beta}$, $\mathbf{3_\beta}$) are sharper and have a larger split than those of α-CyD derivatives ($\mathbf{2_\alpha}$, $\mathbf{3_\alpha}$). We examined temperature-dependent NMR resonances from 303 to 353 K in detail. It was impossible to indicate any apparent differences between the spectra at low temperature and that at high temperature. Only the protons on the arm group and H5 on the altrose group shift were

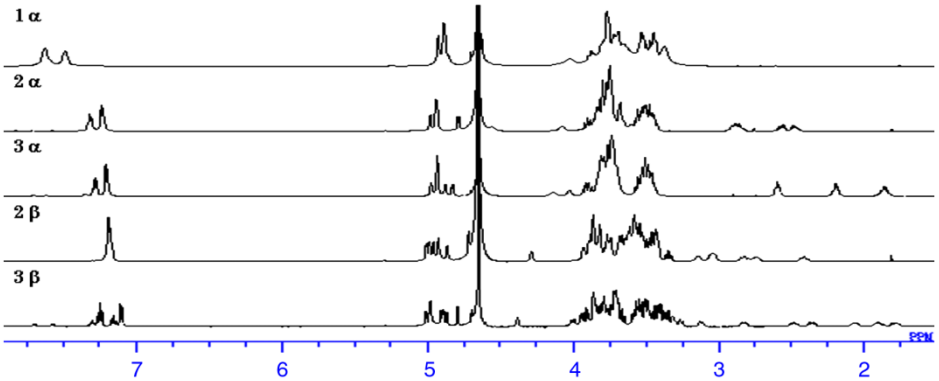

Figure 2. ^{1}H NMR spectra of **1α**, **2α**, **3α**, **2β** and **3β** in D_2O at room temperature.

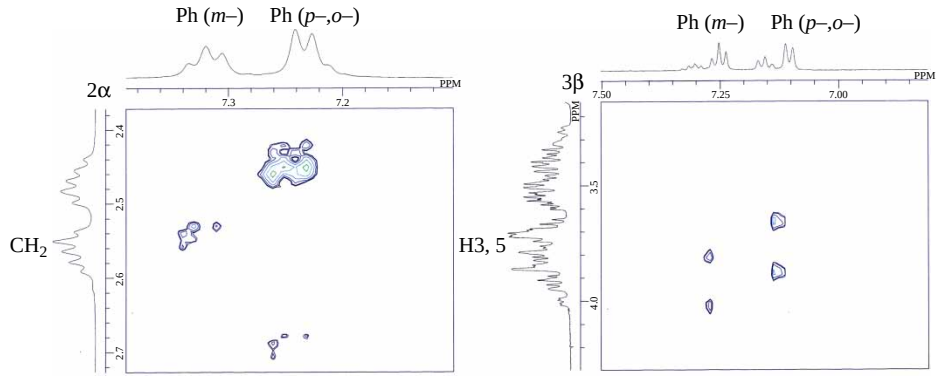

Figure 3. Part of representative NOESY spectra of secondary side guest-modified CyDs at room temperature; mixing time is 250 ms.

Table 1. Solubilities of modified α- and β-CyDs for 100 ml of water.

CyD	Modified position of the glucose unit	CyD	Solubility (g/100 ml)
α-CyD	–	α	14.5
β-CyD	–	β	1.8
6-Monoamino-6-deoxy-β-CyD	6	β	3.3
6*N*-Monophenylbutylylamino-β-CyD	6	β	0.0014
3-Monoamino-3-deoxy-β-CyD	3	β	57.2
2α	3	α	1.96
2β	3	β	2.50
3α	3	α	1.22
3β	3	β	2.04

observed over 313 K. NMR spectra of 3-monoamino-3-monodeoxy-CyDs do not depend on the temperature (303–353 K). Direct evidence for the relative orientation of the phenyl group and the macrocyclic ring has been obtained by the NOESY method (Figure 3). The cross-peaks between the H3 protons, which are inside the cavity of CyD, and the proton at the phenyl group were observed. Results confirm that modified groups of $\mathbf{1}_{\alpha}$, $\mathbf{2}_{\alpha}$, $\mathbf{3}_{\alpha}$, $\mathbf{2}_{\beta}$ and $\mathbf{3}_{\beta}$ are included in their own cavity forming intramolecular complexes. Table 1 shows the solubilities of guest-modified CyDs (6*N*-monophenylbutylylamino-β-CyD, $\mathbf{2}_{\alpha}$, $\mathbf{3}_{\alpha}$, $\mathbf{2}_{\beta}$ and $\mathbf{3}_{\beta}$) in 100 ml of water at room temperature together with data of α-, β-, 6-monoamino-6-deoxy-β- and 3-monoamino-3-deoxy-β-CyD. All secondary guest-modified CyDs are much more soluble than primary guest-modified CyD (800–1800 times). 6*N*-Monophenylbutylylamino-β-CyD (below 10 mg/100 ml) is less soluble than parent β-CyD. The solubility of $\mathbf{2}_{\beta}$ and $\mathbf{3}_{\beta}$ is more than that of $\mathbf{2}_{\alpha}$ and $\mathbf{3}_{\alpha}$, respectively, and slightly more than that for native β-CyD. The solubilities with long-armed-modified CyDs are less than those of respective shorter armed CyDs. The high water solubility should be caused by the structure of the mono-*altro*-CyD ring, the change in the circle of consecutive intramolecular hydrogen bonds.

In conclusion, novel high water-soluble and intramolecular complex-type, guest-modified α- and β-CyDs ($\mathbf{1}_{\alpha}$, $\mathbf{2}_{\alpha}$, $\mathbf{3}_{\alpha}$, $\mathbf{2}_{\beta}$ and $\mathbf{3}_{\beta}$) were synthesised in satisfactory yields. These findings will contribute to the development of supramolecular systems and hydrogen bonds in aqueous solutions. Furthermore, the conformational change induced by the formation of a host–guest complex and molecular dynamics are under investigation.

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