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Noboru Yoshida[a]; Kazuaki Harata[b]; Tetsuya Inoue[a]; Naohito Ito[a]; Kazuhiko Ichikawa[a]
[a] Laboratory of Molecular Functional Chemistry, Division of Material Science, Graduate School of Environmental Earth Science, Hokkaido University, Sapporo, Japan [b] National Institute of Bioscience and Human Technology, Tsukuba, Ibaraki, Japan

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Structure and Molecular Recognition of Chiral Amino-Cyclodextrin: One-dimensional Array by Self-assembly in Solid and Chiral Discrimination in Solution

NOBORU YOSHIDA[a,*], KAZUAKI HARATA[b], TETSUYA INOUE[a]
NAOHITO ITO and KAZUHIKO ICHIKAWA[a]

[a] *Laboratory of Molecular Functional Chemistry, Division of Material Science, Graduate School of Environmental Earth Science, Hokkaido University, Sapporo 060, Japan;*
[b] *National Institute of Bioscience and Human Technology, 1-1 Higashi, Tsukuba, Ibaraki 305, Japan*

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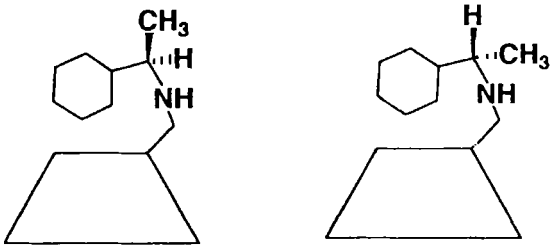
The crystal structure and molecular recognition behaviour of a new chiral-amino cyclodextrin are reported; van der Waals interaction, hydrogen bond and the electrostatic interactions play an important role in the self-assembling process and chiral recognition for (R)-(−)- and (S)-(+)-mandelic acid.

Keywords: Molecular recognition, cyclodextrin, self-assembly, chirality, x-ray structure

Recently, great interest has been focused on the chemical modification of cyclodextrins which leads to enzyme-like function [1], chiral discrimination [2], altering the macrocyclic structure [3], fluorescent sensor [4] and molecular device [5]. A principal driving force to form a regioselective cyclodextrin-guest complex both in solid [6] and in solution [7] may be the weak interactions such as van der Waals forces, dipole–dipole, hydrogen bonding, and CH$\cdots\pi$ interactions. Electrostatic interactions also contribute to the complementary recognition of some organic anions such as nucleotides [8], anthracene-2-sulfonate [9] and anilinonaphthalene-sulfonate [10] by positively charged amino-β-cyclodextrin. Furthermore, the complementary geometry between host and guest could control the rate and mechanism for the molecular recognition by α-cyclodextrin [11].

Here, we report the synthesis and structure of the chiral amino-β-cyclodextrins (Scheme 1)



SCHEME 1 Chiral amino-β-cyclodextrins.

*Corresponding author. e-mail: nyoshida@high.hokudai.ac.jp

and their chiral discrimination for (R)-(−)- and (S)-(+)-mandelic acid in aqueous solution.

β-Cyclodextrin and chemically modified β-cyclodextrin are capable of readily forming inclusion complexes with a variety of chiral guest molecules [12], but very few data on the structure and recognition behaviour in solution of purely synthesized chiral amino-β-cyclodextrins have been reported. The chiral amino-β-cyclodextrin in this communication could have both more weak chiral field in its cavity and the stronger one at the cyclohexylethylamino moiety.

Reactions of R(−)-1- and S(+)-1-cyclohexylethylamine and well-dried tosylated β−cyclodextrin at 100°C for 22 h give mono (6-(R(−)-1-cyclohexylethylamino)-6-deoxy)-β-cyclodextrin (β-$CD_{x\text{-(R)CHEA}}$) and mono (6-(S(+)-1-cyclohexylethylamino)-6-deoxy)-β-cyclodextrin (β-$CD_{x\text{-(S)CHEA}}$), respectively [10]. These compounds gave microanalytical, mass spectral (FAB^+, glycerol) and ^1H NMR (400 MHz, D_2O) data in agreement with the proposed structures (Scheme 1). It is noteworthy that the water solubility of β-$CD_{x\text{(R)CHEA}}$ is much smaller than that of β-$CD_{x\text{-(S)CHEA}}$. This would be probably due to the difference in the crystal packing. Therefore, single crystal suitable for the X-ray diffraction is obtained only for (R) derivative by recrystallization and slow evaporation from the aqueous solution.

The crystal structure[†] (Fig. 1) indicates the R(−)-cyclohexylethylamino group of β-$CD_{x\text{-(R)CHEA}}$ points away from the molecular centroid.

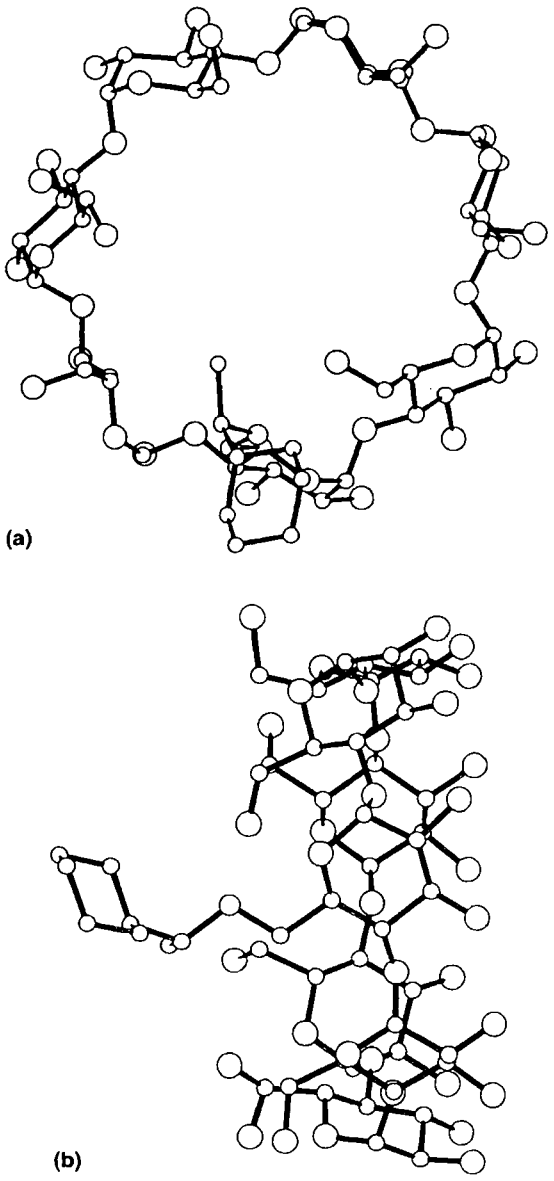


FIGURE 1 Top (a) and side (b) views of the structure β-$CD_{x\text{-(R)CHEA}} \cdot 8H_2O$.

[†]Crystal data for β-$CD_{x\text{-(R)CHEA}} \cdot 8H_2O$: $C_{42}H_{69}O_{34} \cdot C_8H_{16}N \cdot 8H_2O$, M = 1388.3, monoclinic, space group $P2_1$, $Z = 2$, a = 15.215(1), b = 15.862(1), c = 15.417(1) Å, β = 116.79(1)°, U = 3321.2 Å^3, D_c = 1.388 g·cm^{-3}. X-ray diffraction data were measured on a Nonius CAD4 diffractometer with graphite monochromated CuKa radiation. Lattice parameters were determined by using 25 reflections. Intensities of 7149 reflections were measured using θ–2θ scan mode to 150° in 2θ. Absorption and decay corrections were made by using the program incorporated in Nonius Molen software. The structure was solved molecular replacement method using a computer-generated symmetrical model of β-cyclodextrin and refined by the block-diagonal least-squares method [16]. Coordinates of hydrogen atoms attached to methine and methylene groups were calculated and incorporated in the structure factor calculation. The quality minimized was $\Sigma w(|F_0| - |F_c|)^2$ with w = 1.0. The R value was 0.071 for 4696 reflections with $F_0 > 3\sigma(F)$. The maximum shift/esd value was 0.09. The maximum values of positive and negative residual electron density in the F_0–F_c map were 0.66 and −0.36 eÅ^{-3}, respectively. Atomic coordinates, bond lengths and angles, and thermal parameters will be been deposited at the Cambridge Crystallographic Data Centre (CCDC) in the full version of this paper.

The conformation of the macrocyclic ring of the β-CD_x moiety of β-$CD_{x\text{-(R)CHEA}}$ is basically the same as that of native β-cyclodextrin. The pyranose ring of the seven glucose units is in the $^4C_1$ chair conformation. The C6 —O6 bond has gauche-gauche conformation in four glucose residues and gauche-trans conformation in one residue. One 6-O hydroxyl group is disordered and shows two alternate conformations, gauche-gauche and gauche-trans. The macrocyclic ring is a round structure, which is maintained by seven intramolecular O2···O3′ type hydrogen bonds. The cyclohexyl group is in a chair conformation. The amino group is hydrogen-bonded to a 6-O hydroxyl group of the adjacent residues.

The crystal packing along the *b* axis is shown in Figure 2. The molecules are arranged in a self-assembling helically polymeric structure along the twofold axis. The cyclohexyl group is fully included within van der Waals contact into the cavity of the adjacent molecule from the secondary hydroxyl side. The round structure of the macrocyclic ring is considered to be ascribed to the inclusion of a bulky cyclohexylethylamino group. The strong intermolecular hydrogen bond (O···O 2.81 Å) between O3(G2) and O6(G6) contributes to the one-dimensional supramolecular array. It is noteworthy that several weak C—H···O hydrogen bonds (H···O distance of 2.76 – 2.90Å)[13] are also comprised in this head-to-tail structure (Fig. 2b). Generally, monosubstituted-6-deoxycyclodexrin may tend to prefer polymeric [14] or self-encapsulated [15] geometries depending on the size and shape of the 6-substituted group.

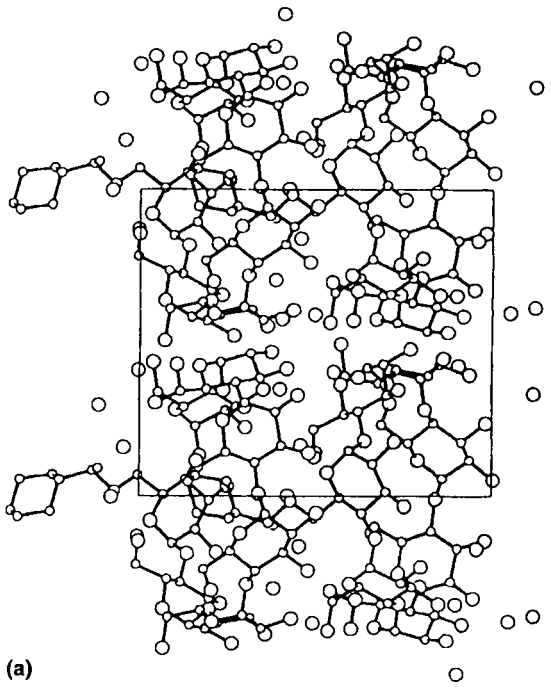


FIGURE 2(a) The packing in the crystal of β-$CD_{x\text{(R)CHEA}}\cdot 8H_2O$ viewed along the *b*-axis. The crystal packing is maintained by van der Waals and hydrogen-bonds. The H-bonding network involves the intercalated water molecules.

Amino-βCD_x has the ability to exert pH-responsive photophysical control on the fluorescent probe such as 8-anilinonaphthalene-sulfonate (1,8-ANS). Figure 3 shows the pH-responsive profile of the fluorescence intensity of the inclusion complexes of ANS with β-CD_x, β-$CD_{x\text{-(R)CHEA}}$ and β-$CD_{x\text{-(S)CHEA}}$.

The ANS/β-CD_x complex shows essentially pH independent and low fluorescence over the pH range 2 – 12. On the other hand, the fluorescent intensity in the ANS/β-CD_xCHEA system increases drastically at the lower pH region. Protonation of the amino nitrogen atom of β-CD_x-CHEA and the resultant electrostatic interaction between host and guest ($-NH_2+\cdots-O_3S-$) leads to the increase in fluorescent intensity [10]. The different pH-responsive profiles between β-$CD_{x\text{-(R)CHEA}}$ and β-$CD_{x\text{-(S)CHEA}}$ at lower pH region indicate the difference in the chiral environment with restricted conformational motions of both enantiomers in aqueous solution.

Binding ability of both chiral amino-β-CD_x for (R)-(–)- and (S)-(+)-mandelic acid was examined by the competition method [17]. The calculated formation constants (K_f) are shown in Table I.

The K_f values for the chiral amino-β-CD_x/mandelic acid complexes were in the range 40 – 60 M^{-1} which are 3 – 5 times larger than the

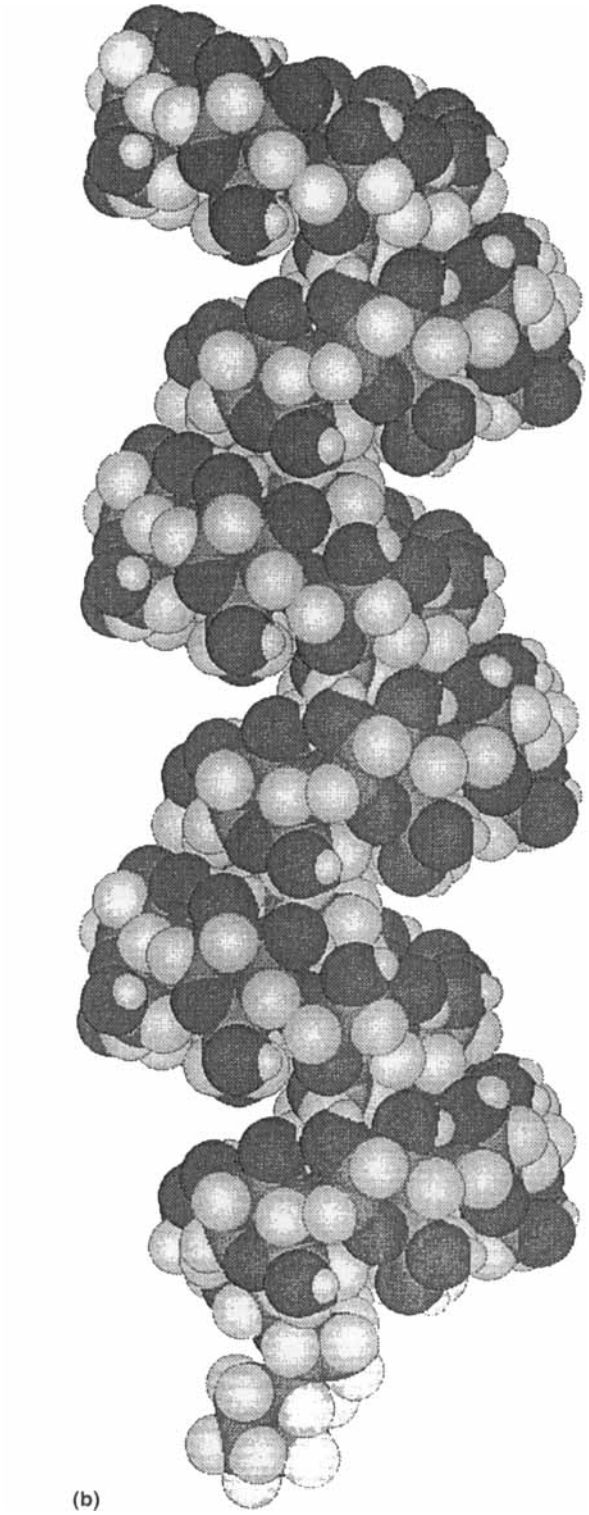


FIGURE 2(b) Space-filling model of one-dimensional supramolecular array of β-$CD_{x\cdot(R)CHEA}\cdot 8H_2O$. Water molecules are omitted for clarity.

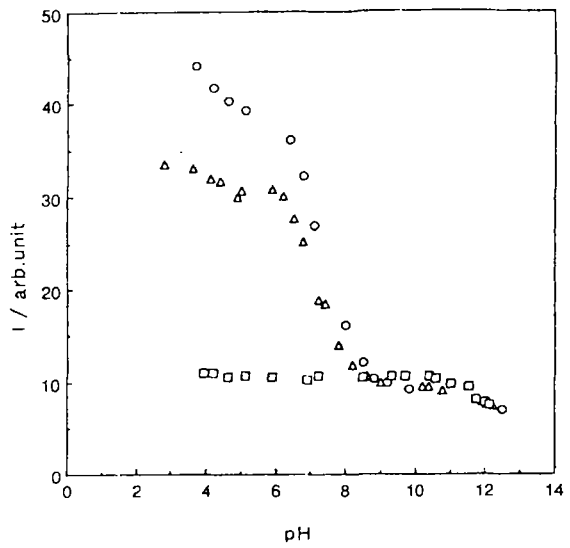


FIGURE 3 Fluorescence intensity *versus* pH for β-$CD_{x\text{-}(R)CHEA}$ (O), β-$CD_{x\text{-}(S)CHEA}$ (Δ) and β-CD_x ($\square$). [Host] = 0.5 mM, [1,8-ANS] = 12 μM. At 25°C, λ_{ex} = 350 nm and λ_{em} = 492 nm.

TABLE I Formation Constants (K_f) between chiral amino-βCD_x and mandelic acid (MA) at 25°C and pH = 4.7

Host	K_f/M^{-1} (R)-MA	K_f/M^{-1} (S)-MA	$K_f(R)/K_f(S)$
β-$CD_{x\text{-}(R)CHEA}$	63 ± 4	52 ± 2	1.2
β-$CD_{x\text{-}(S)CHEA}$	47 ± 4	36 ± 2	1.3
β-CD_x	13 ± 1	14 ± 1	0.9

corresponding β-CD_x complex. These larger K_f values as compared with those for the native β-CD_x complex would be due to the electrostatic interaction between host and guest at pH = 4.7. The hydrophobic local environment of cyclohexyl group further enhances this effect [10]. The enhancement in the chiral discrimination of amino-β-CD_x for mandelic acid anions is in the range of 1.2–1.3 (Tab. I) and larger than that of β-CD_x complexes. The ratios of $K_f(R)/K_f(S)$ could be comparable with those of 6B-amino-6-A-carboxy-β-cyclodextrin [18].

The new chiral amino-βCD_x derivatives demonstrated the self-assembled supramolecular motifs in the design and engineering of chiral solids using the weak interactions and the enhanced ability for the chiral recognition for (R)-(−)- and (S)-(+)-mandelic acids in solution. This provides a basis for the other chiral recognition in aqueous solution for the chiral guest such as amino acid anions and peptides.

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