Diastereomeric Differences of “Pendant Type” Monosubstituted Cyclodextrins, Mono-[6-deoxy-6*N*(*N*'-formyl L- and D-phenylglycylamino)]- β -cyclodextrin in Conformation and “Induced-fit” Behavior

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ABSTRACT: Two sets of diastereomers, mono[6-deoxy-6-(L- and D-tyrosylamino)]- β -cyclodextrin (**1**, **2**) and mono[6-deoxy-6*N*(*N*'-formyl L- and D-phenylglycylamino)]- β -cyclodextrin (**3**, **4**), were prepared. Based on NMR and fluorescence spectroscopic studies, it was suggested that the aromatic group attached to **1**, **2**, **3**, and **4** was located at the outside of the cavity and that these CDs had an expanded and distorted cavity enclosed by the aromatic group and the parent CD wall. The conformation of **1** and **2** is “capped type,” whereas that of **3** and **4** is “pendant.” The difference between **3** and **4**, which is only one chiral carbon at the appended group among 36 chiral carbons comprising these total modified CDs, induced more remarkable differences than that among the “capped type” CD in (1) the conformation or hydrophobic cavity shape, (2) selectivity for guest molecules, and (3) “induced-fit” behavior. These differences seem to be caused by a combination of weak interactions. The difference between **3** and **4** having a formyl group at the middle of the arm is observed in the phenyl ring and the “flexible arm” environment, whereas that between **1** and **2** having a hydroxyl group as the hydrogen bonding point at the head of the appended group is observed in the macrocyclic ring.

KEY WORDS Cyclodextrin / Nuclear Magnetic Resonance / Flexible Arm / Diastereomer / Inclusion / Molecular Recognition / Weak Interaction / Induced-Fit /

The lock and key picture¹ is one of the most frequently invoked concepts in chemistry. According to this model, nature has developed holes in proteins that are capable of recognition by geometric fit. The concept applies to substrates in enzymes, or to effectors generally, which then stimulate biologically important activities and responses. In the early stage of host-guest chemistry, many “rigid” modifications had been reported to achieve sophisticated molecular recognition comparable to natural systems.² Molecular recognition is a dynamic process based on distinct chemical interactions, not on passive fitting of “a lock and a key.” The proposal of induced fit,³ in which a protein receptor adapts its conformation so as to achieve optimal binding with a substrate should be considered. From this point of view, we have prepared one-point aromatic amino acid-binding CDs.⁴ These modified CDs have a phenyl group used as the cavity size controlling factor, or as a “self-guest molecule” through the flexible arm of *sp*³ carbons between the parent CD cavity and the phenyl group and behave as a “flexible host.” For example, 6-deoxy-6-[(*N*-formylphenylalanyl)amino]- β -CD (f-Phe-CD) formed an “intramolecular complex” including the f-Phe-residue in the hydrophobic cavity and the intramolecular complex was released by adding the guest molecules. That phenomenon is like an induced-fit in an enzyme-substrate system. An enantioselective inclusion behavior was also observed;^{5,6} however, the “inside self-inclusion” type flexible CDs do not have sufficient binding constants because the distorted field where an enantiomer was recognized was formed by a partial interruption of the native CD cavity. To achieve both large binding ability and high enantioselectivity, the “outside type” flexible CD should be paid much attention. Mono[6-

deoxy-6-(L-tyrosylamino)]- β -cyclodextrin (**1**) is the only one outside type flexible CD with both large ability and high enantioselectivity that we had reported previously. The other type of modified CD with an aromatic group located outside the cavity is mono[6-deoxy-6*N*(*N*'-formylphenylglycyl amino)]- β -cyclodextrin (**3**, **4**). Its arm between the CD cavity and the phenyl group is shorter than that of f-Phe-CD. Because the binding constants for 1,8-anilinonaphthalene sulfonic acid (ANS) or 2,6-toluidinonaphthalene sulfonic acid (TNS) is larger than that of native CD and f-Phe-CD, **3** and **4** should have an expanded cavity and the phenyl group is like a “pendant,” whereas the Tyr group is “capped” type. However, precise characterization of **3** and **4** with NMR spectra has not been carried out. It has been known that plural weak interactions played an important role in molecular recognition with cyclodextrin derivatives.^{4,5} However, there has not been enough evidence. It is desirable that the conformation and functions are compared among minimum chemical differences except for the weak interaction group. Comparison between diastereomers is a desirable experiment. We have previously reported the comparison of binding constants for guests between diastereomers of flexible CDs, but the structural differences in diastereomers have never been reported.

In this report, to clarify the cooperative weak interactions in inclusion phenomena in aqueous solution, two diastereomers of outside intramolecular complex type flexible CDs were prepared and characterized (Scheme 1). We wish to indicate one artificial example in which one weak interaction point change the total macrocyclic conformation and functions.

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Scheme 1. Structure of monosubstituted cyclodextrin.

EXPERIMENTAL

Materials

Mono[6-deoxy-6-(L- and D-tyrosylamino)]- β -cyclodextrin (**1**, **2**), mono[6-deoxy-6*N*(*N'*-formyl L- and D-phenylglycylamino)]- β -cyclodextrin (**3**, **4**) and mono-[6-deoxy-6*N*(*N'*-formyl-L- and D-phenylalanyl)amino]- β -cyclodextrin (**5**, **6**) were prepared according to a method with DCC which we reported previously.² **1**; 22% yield; (Found: C, 43.13%; H, 6.93%; N, 2.08%; Calcd for $C_{51}H_{80}N_2O_{36} \cdot 7H_2O$: C, 43.03%; H, 6.67%; N, 1.97%). **2**; 37% yield; (Found: C, 44.02%; H, 6.45%; N, 2.06%; Calcd for $C_{51}H_{80}N_2O_{36} \cdot 5H_2O$: C, 44.12%; H, 6.61%; N, 2.02%). **3**; 35% yield; (Found: C, 44.49%; H, 6.04%; N, 2.09%; Calcd for $C_{51}H_{80}N_2O_{36} \cdot 5H_2O$: C, 44.22%; H, 6.40%; N, 2.02%). **4**; 25% yield; (Found: C, 44.26%; H, 6.34%; N, 1.99%; Calcd for $C_{51}H_{80}N_2O_{36} \cdot 5H_2O$: C, 44.22%; H, 6.40%; N, 2.02%).

Measurement

The NMR spectra were measured on a JEOL EX400WB spectrometer in D_2O using DSS as an internal reference (0.00 ppm). The fluorescence spectra were measured on a JASCO FP-770 fluorophotometer. The association constants (*K*) between the host and various guest molecules were estimated by drawing Benesi-Hildebrand plots. The *K* values were obtained from fluorescence spectra which originated from the guest molecules.

RESULTS AND DISCUSSION

Conformation of "Capped Type" CDs (**1** and **2**) and Guest-Induced Movement

NMR studies have provided important information concerning the molecular geometry of CD inclusion complexes.⁷ Our previous examination by 1H NMR measurements also clarified the structural conformation of f-Phe-CD and **1**. Direct evidence for the self-inclusion has been obtained by 2D NOE measurement, ROESY. The 1H homonuclear NOE measurement is one of the most effective techniques for obtaining information concerning through-space distances among proton nuclei

within 5 Å. Upon considering these experimental facts, the f-L-Phe-residue was concluded to form the "inside type of intramolecular inclusion complex." From the characteristic chemical shifts of the phenyl protons in the 1D NMR spectra, the location of the phenyl group, whether inside or outside of the cavity, can also be easily determined.⁶ The decision based on the large downfield shift of the *para* proton could not be applied to **1** with the hydroxyl group at the *p*-position.⁸ To clarify whether the Tyr-residue is outside or inside the cavity, the 2D ROESY method was carried out. In the ROESY spectrum, although the crosspeaks between the anomeric C1 protons and the aglyconic C4 protons were clearly observed, the protons of the Tyr-residue have the NOE crosspeak with neither protons on the macrocyclic ring nor with the H_{α} and H_{β} protons of the Tyr-residue. These results indicate that the hydroxyphenyl group of the Tyr-residue is outside the cavity of the macrocyclic ring. Compound **1** has a sufficient arm length to include the Tyr-residue in its hydrophobic cavity. Figure 1 shows the 1H NMR spectra of **1** and **2**. Without the *p*-position proton at Tyr, a characteristic chemical shift of aromatic protons was also observed. The chemical shift of the aromatic ring appended to **2** is almost the same as that of **1**, but a narrower split than native Tyr molecule is observed, which suggested that the hydroxyl group interacted with the hydroxyl group on the CD rim by hydrogen bonding. In the ROESY spectrum, the protons of the Tyr-residue also have the NOE crosspeak with neither the protons on the macrocyclic ring nor with the H_{α} and H_{β} protons of the Tyr-residue. The hydroxyphenyl group of **2** is also outside the cavity of the macrocyclic ring. There are some differences in the chemical shift originating from the glucose ring of CD. A characteristic difference is observed at 4.8–5 ppm and 2.4–3.3 ppm. The former can be assigned to an anomeric proton (C1H), reflecting distortion of the macrocyclic ring. The latter can be confirmed as glucose protons of the CD ring identified by the 2D COSY method. However, the chemical shift is too complicated to identify more precisely. The Tyr-residue show positive fluorescence. Quantum yields of both **1** and **2** at 25°C are 0.12, whereas that of native Tyr is 0.14. The above data supported

Figure 1. 400 MHz ^1H NMR spectra of Tyr (upper), **1** (middle), and **2** (bottom) in D_2O .

Figure 2. 400 MHz ^1H NMR spectra of **1** (upper) and **2** (bottom) in D_2O with excess cyclohexanol.

the belief that the Tyr-residue of **1** and **2** is almost the same environment and is not in a hydrophobic but in a hydrophilic area. Interestingly, the diastereomeric difference at the Tyr moiety, even outside the cavity and even with enough flexibility, affects mainly the macrocyclic ring.

What induced the characteristic chemical shift of the hydroxyphenyl ring? Figure 2 shows the ^1H NMR spectrum with excess cyclohexanol, which is known as a good guest molecule for CD without ring-current effect; $K=460\text{ mol}^{-1}\cdot\text{dm}^3$.⁹ The characteristic aromatic proton shift is shown to agree with that of native Tyr. Simultaneously, many well-resolved chemical shifts assigned to the macrocyclic ring change to simple sharp peaks. We have already reported that even monosubstitution can distort the symmetry of the macrocyclic ring, which is reflected in the ^{13}C NMR, especially the C1 and C4 carbons around the glucosidic bond of CD. It has also been reported that the C1 and C4 carbon atoms in oligosaccharides can be directly correlated with one of the torsion angles (Ψ°), a change in the ob-

served ^{13}C chemical shift of *ca.* 2 ppm corresponds to an average change in Ψ of *ca.* 10° .¹⁰ Figure 3 shows the ^{13}C NMR spectra of **1** without and with excess cyclohexanol. Without the guest molecule, the resonances of all carbons comprising the CD ring were observed as seven sets of signals. The lowest chemical shift of C4 was assigned as the substituted glucopyranose unit of the macrocyclic ring. The $\Delta\delta$ value of **1** is 1.51 and 2.17 ppm (except C4') for C1 and C4 respectively, which means that the difference between the narrowest and widest Ψ is *ca.* 10° . When excess cyclohexanol was added to the solution, the resonances were also changed. The $\Delta\delta$ values of **1** decreased and these were 0.75 and 0.89 ppm for C1 and C4 respectively. These results suggest that the difference between the narrowest and widest Ψ is *ca.* 4° . Interestingly, the same phenomenon has been observed in 1 M alkaline solution without cyclohexanol. In 1 M alkaline solution, because the hydroxy group at the Tyr-residue is deprotonated and 21 of the hydroxy groups on the CD ring are not deprotonated (the $\text{p}K_a$ value of the hydroxyl group at the

Figure 3. 100 MHz ^{13}C NMR spectra of A-CD (A) and 1 (B) in D_2O without (A, B) and with excess cyclohexanol (C).

Tyr-residue is pH 10.13), there is no hydrogen bonding between the CD rim and the pointed end of the appended Tyr-residue. 2 shows almost the same behavior. On adding the other guest, 1-naphthol, the ^1H and ^{13}C resonances also changed but less than with cyclohexanol. Based on the above result, (1) the characteristic chemical shift of the hydroxyphenyl protons should be due not to the hydrophobic cavity but to hydrogen bonding, and (2) diastereomeric differences among "capped" type monosubstituted CDs appear mainly in the distortion of the macrocyclic ring and little in the phenyl ring and flexible arm located outside the parent CD cavity. When a guest molecule is included, 1 and 2 adapt their conformation to achieve optimal binding with the guest, hydrogen bonding stress is released partially or completely and the distortion of the macrocyclic ring decreases. With a guest molecule, there is little difference between the diastereomers, 1 and 2.

Conformation of "Pendant" Type CDs, 3 and 4

Figure 4 shows the ^1H NMR spectra of 3, 4 and *N*-formylphenylglycine (f-pheGly) in D_2O . Compared with Tyr-appended CDs, there are many differences between the diastereomers both in the aromatic group and the macrocyclic ring. Phenyl protons of free f-pheGly are observed as one sharp peak, whereas those of 3 and 4 are well-resolved peaks in 2 groups with a 3:2 ratio, 7.38–7.20 ppm and 7.33–7.21 ppm, respectively. This characteristic chemical shift has been observed in f-Phe-CD, but compared with f-Phe-CD, the $\Delta\delta$ values between the 2 peaks of the chemical shift are small, 0.114 and 0.064 ppm for 3 and 4, respectively. On adding cyclohexanol, the $\Delta\delta$ value decreases and finally one sharp peak appears the same as without the CD ring with excess cyclohexanol (Figure 5). The $\Delta\delta$ value would reflect the hydrophobic effect from the CD cavity. To obtain space distance information, the ROESY method

Figure 4. 400 MHz ^1H NMR spectra of f-L-pheGly (upper), **3** (middle), and **4** (bottom) in D_2O .

Figure 5. 400 MHz ^1H NMR spectra of **3** (upper) and **4** (bottom) in D_2O with excess cyclohexanol.

was tried. There are cross peaks between the aromatic (C1H) and aglyconic protons (C4H) and the *ortho*-protons of the phenyl group and the α proton of the f-pheGly-residue but no cross peak between the phenyl protons and the glucoglucose protons of the CD ring. From these results, The phenyl protons are affected by the hydrophobic cavity but do not stay near the cavity within $5 \text{ \AA}$. We had previously referred to the outside phenyl group as "pendant."¹¹ The phenyl group of **3** and **4** really hangs on the narrow side rim of the CD cavity with some interaction with the CD ring. The phenyl group of **4** is farther away from the cavity than in **3**. The chemical shifts assigned to the CD ring are observed in many well-resolved sharp peaks. That of **3** is more complicated than that of **4**. For example, the anomeric protons of **3** can be observed in 7 doublet peaks (4.72–4.96 ppm), whereas those of **4** show only 4 peaks (4.76–4.93 ppm), which means that the macro-

cyclic ring of **3** is more distorted than that of **4**. The ^{13}C NMR spectra also support this hypothesis (Table I). With the phenyl group of **3** being nearer to the CD cavity than that of **4**, a greater effect seems to be produced by the phenyl group and the formyl proton (0.07 ppm upfield shift). Remarkably, the total NMR chemical shift change is small; however, the chemical shift change of α proton of **4** was observed at about 0.1 ppm upfield. Moreover, the chemical shift of **4** around 3.0 ppm, which could be assigned to the C6 proton of the modified glucopyranose unit of the CD ring by the 2D COSY method is anomalous (about 0.2 ppm downfield shift and observed overlapping on the C4 proton). Interestingly, the observed chemical shift change is separated for the two diastereomers (Figure 6). This result suggests that the formyl proton, the α proton, the phenyl protons and the C6 protons constituted a different environment between **4** and **3**. The pair of the formyl proton and

Table I. ^{13}C Chemical shifts of the monosubstituted cyclodextrin in D_2O^a

Assignment	δ/ppm					
	1 ^e	2 ^f	3 ^e	4 ^f	A-CD ^e	β -CD ^e
C1($\Delta\delta$) ^b	101.44 (1.51)	98.24 (1.89)	102.58 (0.89)	99.35 (0.83)	102.87 (0.19)	103.71
	102.20	99.45	103.03	100.00	103.06	
	102.25	100.00	103.24	100.18		
	102.47	100.13	103.42			
	102.82		103.47			
	102.85					
C4($\Delta\delta$) ^b	102.95					
	81.24 (3.97)	77.78 (2.87)	81.71 (4.01)	78.31 (2.61)	82.04 (1.96)	82.74
	81.33 (2.17) ^c	78.27 (1.84) ^c	82.06 (1.19) ^c	79.23 (0.92) ^c	82.26 (0.22) ^c	
	81.66	78.60	82.33	81.92 ^d	84.00 ^d	
	82.19	79.08	82.39			
	82.72	79.24	83.01			
	83.41	79.56	83.06			
	85.21 ^d	80.65 ^d	85.72 ^d			

^a Measured with EX 400WB (JEOL) spectrometer at 100 MHz and 27°C. ^b The variation of δ . ^c The variation of δ except the δ of C4 carbon in substituted glucopyranose unit. ^d The δ of C4 carbon in substituted glucopyranose unit. ^e Reported value (ref 8). ^f This work.

Figure 6. Structure of arm of modified CD forming outside self inclusion complex.

phenyl proton of **3** are different from that of f-pheGly without the CD ring, whereas the pair of the α proton and C6 protons of **4** are different from that. This is the first observation that only one chirality located outside the macrocyclic ring changes the total macromolecular conformation and is reflected directly in chemical shifts around the chiral center carbon.

Guest-Induced Movement of "Pendant" and Weak Interactions

Figure 5 shows the ^1H NMR spectra of **3** and **4** with excess cyclohexanol. Several changes induced by inclusion of the guest molecule can be observed. First, the complicated well-resolved peaks assigned to the macrocyclic ring change to a simple peak almost the same as that of CD without modification. Second, the $\Delta\delta$ values of the phenyl proton, which reflect the distance of the hydrophobic cavity, are decreased; these are 0.00 and 0.04 ppm for **3** and **4**, respectively. Simultaneously, shifted peaks on the arm, the α proton, the formyl proton and the C6 protons appended to the arm change. The resonance of **3** is almost the same pattern as that of f-pheGly without the CD ring and 6-amino-6-deoxy- β -CD without f-pheGly, which indicates that there is no interaction between the CD and the appended group. Compound **4**, having less total modification effect on the chemical shift than **3**, retained the characteristic chemical shift pattern even with cyclohexanol (especially, the α

Figure 7. "Induced-fit" behaviour of "capped" type CD and "pendant" type CD displayed this report.

proton indicates a upfield shift). The C4 and the C6 protons which were observed to overlap without the guest molecule can be clearly observed in separate peaks. On adding 1-naphthol, the resonances of **4** changed more than that of **3**, and the resonance of phenyl protons can be observed as strong one peak. From the above results, it is suggested that the conformational difference between **3** and **4** increases on inclusion of a guest molecule and the conformational differences depend on the kind of guest molecule. This is exactly "induced-fit" behavior (Figure 7).

Molecular Recognition Ability

Table II shows the association constants of **1**, **2**, **3** and **4** for some naphthyl derivatives; for comparison, those of the other CDs are also indicated. Large association constants were displayed by **1** and **2**. The K values for ANS was 4–5 times larger than that of the parent β -CD. The large K values for **2** suggest that **2** has a bigger cavity than the parent β -CD. Although the phenyl ring wall of **3** and **4** is also located outside the cavity and consist of an enclosed hydrophobic cavity, even a slight increase in association constants is indicated. However, the difference among the diastereomers of the "pendant" type (**3** and **4**) is the largest among the other monosubstituted CDs, the "capped" (**1** and **2**) or "inside self-inclusion" type (f-Phe-CD). When including TNS, the

Table II. Association constants^a

Host	Guest ($K/\text{mol}^{-1} \cdot \text{dm}^3$)		
	ANS ^b	TNS ^b	1-Naphthol ^c
1	365 ± 6^a	360 ± 1^a	— ^c
2	488 ± 10	283 ± 0	— ^c
K_L/K_D	0.74	1.27	
3	80 ± 19^a	$2:1^d$	129
4	137 ± 17^a	1026 ± 47^a	220
K_L/K_D	0.58		0.59
f-L-PheCD	68 ± 19^a	207 ± 29^a	$2:1^{a,d}$
f-D-PheCD	78 ± 11^a	167 ± 27^a	$2:1^d$
K_L/K_D	0.87	1.23	
L-PheCD	87 ± 1	456 ± 1	$2:1^d$
β -CD	78 ± 8^a	$2:1^d$	$2:1^{a,d}$

^aSome of K values were reported previously. ^bDetermined with fluorescence intensity at 540 nm excited at 350 nm; conditions; pH 7.0 solutions ($1/15 \text{ mol} \cdot \text{dm}^{-3}$ phosphate buffer), 25°C , $[\text{guest}] = 5.0 \times 10^{-5} \text{ mol} \cdot \text{dm}^{-3}$, $[\text{cyclodextrin}] = 0.0 - 8 \times 10^{-3} \text{ mol} \cdot \text{dm}^{-3}$.

^cDetermined with fluorescence intensity at 340 nm excited at 290 nm; conditions: pH 7.0 solutions, 25°C , $[\text{guest}] = 2.5 \times 10^{-5} \text{ mol} \cdot \text{dm}^{-3}$, $[\text{cyclodextrin}] = 0.0 - 5 \times 10^{-3} \text{ mol} \cdot \text{dm}^{-3}$. ^dTwo host-one guest complex formation.

ratio between host and guest is different, 1:1 and 1:2. These results also support that the “pendant” type monosubstituted CD displays the most conformational differences in NMR resonances.

The Differences between “Capped” and “Pendant”

Why does a “pendant” type monosubstituted CD display “induced-fit” behavior? Why are diastereomeric differences induced in the “pendant” type CDs, **3** and **4**? What is the difference between the “capped” type CD and the “pendant” type CD? Association constants (K) between native CD and L-, D-Tyr, f-L-, D-pheGly and f-L-, D-Phe were examined in pH 6.0 $1/15 \text{ mol} \cdot \text{dm}^{-3}$ phosphate buffer at 25°C . K is 13.7, $10.9 \text{ mol} \cdot \text{dm}^{-3}$ for f-L-, D-pheGly, 34.6, $46.2 \text{ mol} \cdot \text{dm}^{-3}$ for f-L-, D-Phe. Tyr is hardly included in CD cavity (K should be below 1). As is shown in Figure 6, the distance of the arm is

different. Tyr-CD has a sufficient arm length to include the phenyl ring in its cavity; whereas, an arm of f-pheGlyCD is too short to include the phenyl ring. However, the phenyl ring of Tyr is hardly included in the CD cavity; in other words Tyr prefers to stay hydrophilic area outside the CD cavity. The hydrophobic interaction between the CD cavity and the phenyl ring seems to prefer the “pendant” type. It seems that the driving force for including the phenyl ring into the CD cavity of the “pendant” type is larger than that of the “capped” type and that the factor that disturbs the self-inclusion of the “pendant” type is only the length of the arm. For the above reason, the diastereomeric difference in the f-pheGly appended CD transformed the difference in the location of the α proton or the formyl proton and affected the possibility of interaction between the hydroxy group at the rim of the CD ring and the arm; interesting behavior could then be observed.

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