*Journal of Inclusion Phenomena* **1**, 279–293. 0167–7861/84/0013–0279$02.25.



# Conformation of Permethylated Cyclodextrins and the Host-Guest Geometry of their Inclusion Complexes

KAZUAKI HARATA★
*Research Institute for Polymers and Textiles, 1-1-4 Yatabe-Higashi, Tsukuba, Ibaraki 305, Japan*

KANETO UEKAMA, MASAKI OTAGIRI and FUMITOSHI HIRAYAMA
*Faculty of Pharmaceutical Sciences, Kumamoto University, 5–1 Oe-honmachi, Kumamoto 862, Japan*

(Received: 17 June 1983; accepted: 30 October 1983)

**Abstract.** Macrocylic conformation of permethylated cyclodextrins and the geometry of their inclusion complexes were examined on the basis of the X-ray data of three permethylated α-cyclodextrin complexes and two permethylated β-cyclodextrin complexes. The host macrocyclic ring is remarkably distorted owing to steric hindrance involving the methyl groups and the inability to form intramolecular hydrogen bonds. The guest molecules are included within the host cavity, but their position and orientation are quite different from those found in the corresponding cyclodextrin complexes.

**Key words:** Cyclodextrins, permethylated cyclodextrins, crystal structure

## 1. Introduction

Cyclodextrins form a number of inclusion complexes with a variety of guest molecules [1,2]. In these complexes, which are formed in the solid state or in solution, the guest molecule is held within the cavity of the host macrocycle. To explain the driving force of the complex formation, several intermolecular forces and interactions such as Van der Waals forces [3], hydrophobic interaction [4,5], strain energy of the macrocyclic ring [6], dipolar interaction [7], and high-energy water within the host cavity [8], etc., have been proposed, but the major factor remains a matter of controversy. Cyclodextrins also act as catalysts in chemical reactions [1,8] such as hydrolysis and oxidation, etc., and hydroxyl groups of cyclodextrins have been proposed as active sites [9].

Modifications of cyclodextrins have been intensively investigated in order to improve their complex-forming and catalytic abilities. Some modified cyclodextrins, which are called 'capped cyclodextrins', have been synthesized to enhance the hydrophobicity of the host cavity [10,11]. The catalytic ability of cyclodextrins has also been improved by introducing more reactive groups into the macrocyclic ring [1,2,12]. The properties of such modified cyclodextrins have been discussed only in terms of their complex-forming and/or catalytic activities in relation to the introduced groups, although the substituents can be expected to affect the macrocyclic conformation and the geometry of host-guest interaction.

Recently, synthesis and certain chemical and physical properties of permethylated cyclodextrins have been reported [13–15]. Permethylated cyclodextrins also from inclusion complexes which are more stable for certain guests in aqueous solution than the corresponding

★ Author for correspondence.

complexes of unsubstituted cyclodextrins. Permethylated cyclodextrins are quite simple and favorable cyclodextrin derivatives with which to investigate the orientation of substituent groups attached to each of the O(2), O(3), and O(6) oxygen atoms, and the effect of substituents on the macrocyclic conformation. As permethylated cyclodextrins have no hydroxyl groups, it is also interesting, in comparison with unsubstituted cyclodextrins, to investigate how the macrocyclic conformation and host-guest interaction change in the absence of intramolecular hydrogen bonding. In this contribution, we will discuss the structural characteristics of permethylated cyclodextrins (methyl-CDx) on the basis of the structures of permethylated α-cyclodextrin complexes with *p*-iodoaniline (*p*-IAN), benzaldehyde (BA), and *p*-nitrophenol (*p*-NPH), and permethylated β-cyclodextrin (methyl-β-CDx) complexes with *p*-iodophenol (*p*-IPH) and (*S*)-flurbiprofen (FP), all of which were determined by X-ray diffraction techniques.

## 2. X-Ray Data of Cyclodextrin and Permethylated Cyclodextrin Complexes

Compositions of crystalline complexes of cyclodextrins and of permethylated cyclodextrins studied thus far are given in Table I. The X-ray structures of α-cyclodextrin and methyl-α-CDx complexes with *p*-IAN, *p*-NPH, and BA have already been published [16–21]. Stezowski and his co-workers have reported the crystal structure of the β-cyclodextrin – *p*-IPH complex [22]. Recently, we have determined the crystal structures of the β-cyclodextrin – FP complex and of the methyl-β–CDx complexes with *p*-IPH and FP. The crystal data are as follows: $a = 15.404(2)$, $b = 15.478(2)$, $c = 18.093(2)$ Å, $\alpha = 113.62(1)°$, $\beta = 99.29(1)°$, $\gamma = 102.99(1)°$, and space group P1 for the β-cyclodextrin – FP complex; $a = 14.997(2)$, $b = 21.368(2)$, $c = 28.205(2)$ Å, and space group $P2_12_12_1$ for the methyl-β-CDx – *p*-IPH complex; $a = 15.196(2)$, $b = 21.588(2)$, $c = 27.968(2)$ Å, and space group $P2_12_12_1$ for the methyl-β-CDx – FP complex. Detailed descriptions of these structures will be published elsewhere.

Table I. Crystalline complexes of cyclodextrins and permethylated cyclodextrins

| Host | Guest | Stoichiometry |
|---|---|---|
| α-Cyclodextrin | *p*-Iodoaniline | $C_{36}H_{60}O_{30} \cdot C_6H_6NI \cdot 3H_2O$ |
| | Benzaldehyde | $C_{36}H_{60}O_{30} \cdot C_7H_6O \cdot 6H_2O$ |
| | *p*-Nitrophenol | $C_{36}H_{60}O_{30} \cdot C_6H_5NO_3 \cdot 3H_2O$ |
| Methyl-α-CDx | *p*-Iodoaniline | $C_{54}H_{96}O_{30} \cdot C_6H_6NI \cdot H_2O$ |
| | Benzaldehyde | $C_{54}H_{96}O_{30} \cdot C_7H_6O$ |
| | *p*-Nitrophenol | $C_{54}H_{96}O_{30} \cdot C_6H_5NO_3 \cdot H_2O$ |
| β-Cyclodextrin | *p*-Iodophenol | $(C_{42}H_{70}O_{35})_2 \cdot (C_6H_5OI)_3 \cdot 24H_2O$ |
| | (*S*)-Flurbiprofen | $(C_{42}H_{70}O_{35})_2 \cdot (C_{15}H_{13}O_2F)_2 \cdot 21H_2O$ |
| Methyl-β-CDx | *p*-Iodophenol | $C_{63}H_{112}O_{35} \cdot C_6H_5OI \cdot 4H_2O$ |
| | (*S*)-Flurbiprofen | $C_{63}H_{112}O_{35} \cdot C_{15}H_{13}O_2F$ |

## 3. Conformation of the Methylglucose Residue

The conformation and numbering scheme of the 2,3,6-tri-*O*-methylglucose (methylglucose) residue are shown in Figure 1. The pyranose ring is in the $^4C_1$ chair conformation. The C(6) – O(6) bonds show two types of orientation, *gauche-gauche* and *gauche-trans*. In methyl-α-CDx complexes with *p*-IAN and BA, four C(6) – O(6) bonds are in the *gauche-trans*

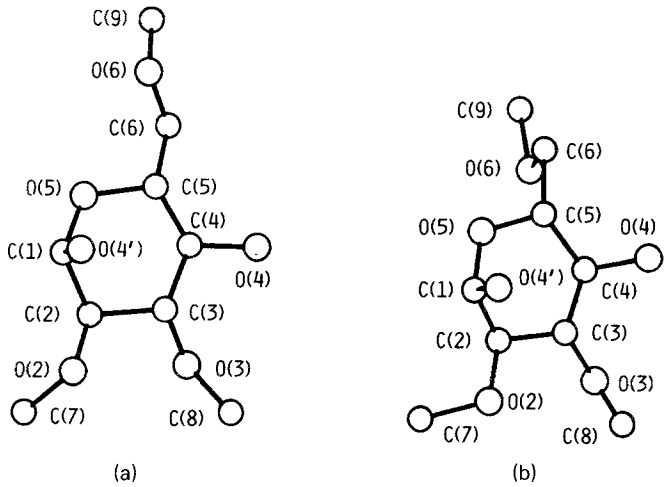


Fig. 1. Atomic numbering and conformation of methylglucose residue: the *gauche-trans* conformation of the C(6) – O(6) bond (a), and the *gauche-gauche* conformation of the C(6) – O(6) bond (b). The O(2) – C(7) bond of the methylglucose residue b is *trans* to the C(2) – C(3) bond.

conformation, while the others are in the *gauche-gauche* conformation. The methyl-α-CDx complex with *p*-NPH has three C(6) – O(6) bonds with the *gauche-trans* conformation and the other three with the *gauche-gauche* conformation. In contrast, methyl-β-CDx has more C(6) – O(6) bonds with the *gauche-gauche* conformation: five C(6) – O(6) bonds with the *gauche-gauche* conformation and two C(6) – O(6) bonds with the *gauche-trans* conformation in the *p*-IPH complex, and four bonds with the *gauche-gauche* conformation and three bonds with the *gauche-trans* conformation in the FP complex. Most of the C(9) – O(6) bonds are *trans* to the corresponding C(5) – C(6) bonds in both methyl-α-CDx and methyl-β-CDx. But, certain C(9) – O(6) bonds show an orientation which has the C(5) – C(6) – O(6) – C(9) torsion angle smaller than 120°; this causes a large standard deviation for the average value, as shown in Table II.

Table II. Average torsion angles involving methoxy groups

| | Torsion angle (°) | | | | |
|---|---|---|---|---|---|
| | Methyl-α-CDx complex | | | Methyl-β-CDx complex | |
| | *p*-IAN | BA | *p*-NPH | *p*-IPH | FP |
| C(1) – C(2) – O(2) – C(7) | 107 ± 20 | 108 ± 19 | 91 ± 30 | 94 ± 29 | 91 ± 30 |
| C(3) – C(2) – O(2) – C(7) | – 137 ± 22 | – 133 ± 20 | – 147 ± 30 | – 147 ± 26 | – 148 ± 30 |
| C(2) – C(3) – O(3) – C(8) | – 120 ± 9 | – 113 ± 12 | – 113 ± 8 | – 117 ± 16 | – 115 ± 16 |
| C(4) – C(3) – O(3) – C(8) | 123 ± 13 | 131 ± 11 | 124 ± 12 | 127 ± 18 | 128 ± 16 |
| C(5) – C(6) – O(6) – C(9) | 166 ± 19 | 163 ± 22 | 173 ± 8 | 163 ± 33 | 164 ± 30 |

The O(2) – C(7) bonds are oriented away from the center of the macrocyclic ring. The relatively large standard deviations for the torsion angles of C(1) – C(2) – O(2) – C(7) and C(3) – C(2) – O(2) – C(7) are due to two types of orientations of O(2) – C(7) bonds, which are mainly observed in the methyl-α-CDx complex with *p*-NPH and in the two methyl-β-CDx

complexes. One type of orientation is shown in Figure 1a. In this case, two torsion angles involving O(2) – C(7) bonds are close to 120°. The other type, as shown in Figure 1b, indicates that the O(2) – C(7) bond is nearly *gauche* with respect to the C(1) – C(2) bond, having C(1) – C(2) – O(2) – C(7) angles within 60–80°. In the methyl-α-CDx complexes with *p*-IAN and BA, such a difference in the O(2) – C(7) orientation is not clear, as the C(1) – C(2) – O(2) – C(7) angles fall in the range 90–130°. The O(3) – C(8) bonds are turned toward the methyl-CDx cavity. The conformation about the C(3) – O(3) bond is restricted in such a way that the two torsion angles, C(2) – C(3) – O(3) – C(8) and C(4) – C(3) – O(3) – C(8), are close to 120°, although the latter angle is somewhat larger than the former.

Table III. Glycosidic oxygen angles

| | Angle (°) | | | | |
|---|---|---|---|---|---|
| | Methyl-α-CDx complex | | | Methyl-β-CDx complex | |
| Residue | *p*-IAN | BA | *p*-NPH | *p*-IPH | FP |
| G1 | 115 | 119 | 118 | 116 | 115 |
| G2 | 121 | 115 | 118 | 120 | 119 |
| G3 | 117 | 116 | 119 | 114 | 119 |
| G4 | 116 | 117 | 118 | 113 | 114 |
| G5 | 118 | 118 | 118 | 119 | 115 |
| G6 | 119 | 117 | 117 | 120 | 116 |
| G7 | — | — | — | 115 | 113 |
| Average | 118 ± 2 (120 ± 2)[a] | 117 ± 1 (119 ± 1)[a] | 117 ± 1 (119 ± 1)[a] | 117 ± 3 | 116 ± 2 |

[a] Average values of the corresponding α-cyclodextrin complexes.

The glycosidic oxygen angles are given in Table III. The average values of methyl-α-CDx, 117–118°, are slightly smaller than the values, 119–120°, of α-cyclodextrin. On the other hand, methyl-β-CDx gives nearly the same values as those of β-cyclodextrin. The average

Table IV. Torsion-angle indices

| | Torsion-angle index (°) | | | | |
|---|---|---|---|---|---|
| | Methyl-α-CDx complex | | | Methyl-β-CDx complex | |
| Residue | *p*-IAN | BA | *p*-NPH | *p*-IPH | FP |
| G1 | 160 | 138 | 140 | 126 | 120 |
| G2 | 145 | 142 | 124 | 126 | 131 |
| G3 | 151 | 119 | 140 | 100 | 114 |
| G4 | 149 | 146 | 148 | 143 | 139 |
| G5 | 142 | 131 | 120 | 122 | 122 |
| G6 | 134 | 130 | 144 | 115 | 123 |
| G7 | — | — | — | 130 | 119 |
| Average | 147 ± 9 (127 ± 7)[a] | 134 ± 10 (128 ± 11)[a] | 144 ± 11 (131 ± 13)[a] | 123 ± 13 | 124 ± 8 |

[a] Average values of the corresponding α-cyclodextrin complexes.

values of torsion-angle indices [23] are 147°, 134°, and 136° in the methyl-α-CDx complexes (Table IV). These values are larger than those, 127, 128, and 131°, respectively, of the corresponding α-cyclodextrin complexes. The average O(4)···O(4′) distances between adjacent glucose residues, 4.26, 4.25, and 4.31 Å, are also slightly larger than those of α-cyclodextrin, 4.24, 4.29, and 4.24 Å, respectively, as shown in Table V. The average torsion-angle indices in methyl-β-CDx are smaller than those of methyl-α-CDx, while the average O(4)···O(4′) distances are larger. However, both torsion-angle indices and O(4)···O(4′) distances are close to those of β-cyclodextrin; for instance, 121° on average for the torsion-angle index and 4.36 Å on average for the O(4)···O(4′) distance in the β-cyclodextrin complex with 1,4-diazabicyclo[2.2.2]octane [24].

A plot of the O(4)···O(4′) distance against the torsion-angle index is shown in Figures 2 and 3. A linear correlation between these values has been observed in α- and β-cyclodextrin [17,24], as well as in mono- and disaccharides [23]. But, methyl-CDx shows no such

Table V. Geometrical data for O(4) polygons

*I. Distances from the center of gravity of the polygon to each individual O(4) atom*

| | Distance (Å) | | | | |
|---|---|---|---|---|---|
| | Methyl-α-CDx complex | | | Methyl-β-CDx complex | |
| Residue | *p*-IAN | BA | *p*-NPH | *p*-IPH | FP |
| G1 | 4.20 | 4.13 | 4.51 | 4.92 | 4.94 |
| G2 | 4.42 | 4.48 | 4.16 | 5.35 | 5.26 |
| G3 | 4.16 | 4.18 | 4.25 | 4.99 | 5.03 |
| G4 | 4.18 | 4.16 | 4.48 | 4.57 | 4.67 |
| G5 | 4.41 | 4.48 | 4.15 | 5.27 | 5.23 |
| G6 | 4.11 | 4.15 | 4.26 | 5.18 | 5.20 |
| G7 | — | — | — | 4.63 | 4.76 |
| Average | 4.25 ± 0.13 | 4.27 ± 0.17 | 4.30 ± 0.16 | 4.99 ± 0.30 | 5.00 ± 0.22 |
| | (4.24 ± 0.15)[a] | (4.28 ± 0.22)[a] | (4.23 ± 0.20)[a] | | |

*II.* O(4)···O(4′) *distances between adjacent residues*

| | Distance (Å) | | | | | |
|---|---|---|---|---|---|---|
| | Methyl-α-CDx complex | | | | Methyl-β-CDx complex | |
| Residue | *p*-IAN | BA | *p*-NPH | Residue | *p*-IPH | FP |
| G1–G2 | 4.11 | 4.19 | 4.29 | G1–G2 | 4.42 | 4.41 |
| G1–G6 | 4.36 | 4.19 | 4.19 | G1–G7 | 4.41 | 4.33 |
| G2–G3 | 4.35 | 4.21 | 4.44 | G2–G3 | 4.24 | 4.33 |
| G3–G4 | 4.34 | 4.51 | 4.22 | G3–G4 | 4.32 | 4.54 |
| G4–G5 | 4.13 | 4.08 | 4.16 | G4–G5 | 4.20 | 4.24 |
| G5–G6 | 4.25 | 4.32 | 4.54 | G5–G6 | 4.45 | 4.42 |
| | | | | G6–G7 | 4.29 | 4.39 |
| Average | 4.26 ± 0.11 | 4.25 ± 0.15 | 4.31 ± 0.15 | Average | 4.33 ± 0.10 | 4.38 ± 0.09 |
| | (4.24 ± 0.13)[a] | (4.29 ± 0.14)[a] | (4.23 ± 0.18)[a] | | | |

[a] Average values of the corresponding α-cyclodextrin complexes.

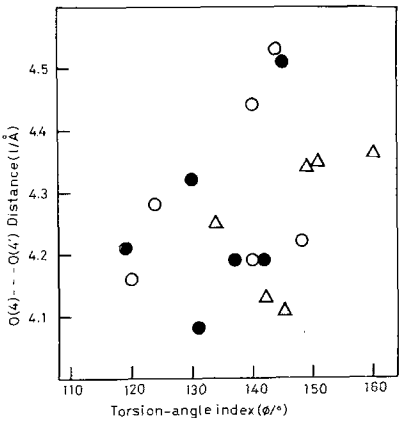


Fig. 2. Plot of O(4)···O(4′) distance against torsion-angle index in methyl-α-CDx complexes with *p*-IAN (△), BA (●), and *p*-NPH (○).

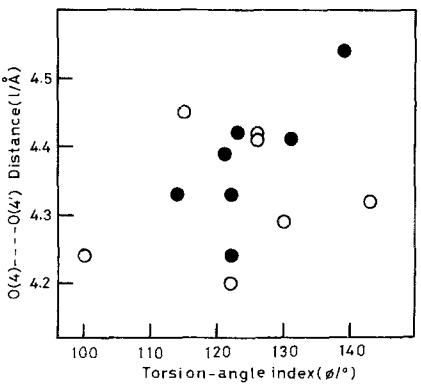


Fig. 3. Plot of O(4)···O(4′) distance against torsion-angle index in methyl-β-CDx complexes with *p*-IPH (○) and FP (●).

correlation. This indicates that the permethylation affects the conformation of the pyranose ring so as to break the linear relationship found in cyclodextrins.

## 4. Conformation of the Macrocyclic Ring

The six O(4) atoms of methyl-α-CDx form a distorted hexagon. The planarity of the hexagon is quite good, although the root-mean-square deviation of the O(4) atoms from the plane is slightly larger than that of the corresponding α-cyclodextrin (Table VI). The O(4) heptagon in methyl-β-CDx is much more distorted than that of β-cyclodextrin. The root-mean-square deviations of the O(4) atoms are 0.44 and 0.41 Å. These are more than twice the values found in methyl-α-CDx, 0.19, 0.17, and 0.16 Å.

The radius of the O(4) polygon is defined as the distance from the center of gravity of the polygon to each individual O(4) atom. The average value in methyl-α-CDx (4.25–4.30 Å) is

Table VI. Atomic deviations from the least-squares plane through the O(4) polygon

| | Deviation (Å) | | | | |
|---|---|---|---|---|---|
| | Methyl-α-CDx complex | | | Methyl-β-CDx complex | |
| | *p*-IAN | BA | *p*-NPH | *p*-IPH | FP |
| O(4,G1) | 0.16 | 0.14 | −0.04 | 0.48 | 0.47 |
| O(4,G2) | −0.24 | −0.21 | −0.14 | 0.26 | 0.22 |
| O(4,G3) | 0.08 | 0.06 | 0.15 | −0.57 | −0.52 |
| O(4,G4) | 0.15 | 0.16 | 0.02 | −0.05 | −0.04 |
| O(4,G5) | −0.24 | −0.23 | −0.19 | 0.65 | 0.60 |
| O(4,G6) | 0.08 | 0.06 | 0.20 | −0.32 | −0.30 |
| O(4,G7) | — | — | — | −0.45 | −0.43 |
| r.m.s. Deviation | 0.17 | 0.16 | 0.14 | 0.44 | 0.41 |
| | (0.09)[a] | (0.12)[a] | (0.12)[a] | | |

[a] Root-mean-square deviations of the corresponding α-cyclodextrin complexes.

about 0.7 Å smaller than that in methyl-β-CDx (4.99–5.00 Å), as shown in Table V. However, no significant difference is observed in these values between cyclodextrins and their permethylated derivatives. The average O(4)···O(4′) distances between adjacent methylglucose residues in methyl-α-CDx, 4.26, 4.25, and 4.31 Å, are shorter than those, 4.33 and 4.38 Å, in methyl-β-CDx. The comparison of O(4)···O(4′) distances between cyclodextrins and methyl-CDxs indicates that the O(4)···O(4′) distance is scarcely affected by permethylation.

In cyclodextrins, O(2) and O(3) hydroxyl groups between adjacent residues are generally linked by O(2) – H···O(3) or O(3) – H···O(2) hydrogen bonds. The distances between O(2) and O(3) of adjacent residues are largely in the range 2.6–3.0 Å; relatively long distances, such as 3.7 Å in the α-cyclodextrin – BA complex, are rarely observed. In contrast, however, permethylated cyclodextrins have no hydroxyl groups, so they cannot form such intramolecular hydrogen bonds. Most of the O(2)···O(3′) distances are in the range 3.2–3.5 Å in methyl-α-CDx and 3.2–3.7 Å in methyl-β-CDx. The average values, 3.46 and 3.43 Å, in methyl-β-CDx are larger than those, 3.28, 3.35, and 3.34 Å in methyl-α-CDx.

The C(8)$H_3$ methyl groups are located between two adjacent O(2) atoms. In methyl-α-CDx, they occupy a position that is nearly equidistant from two O(2) atoms; the average C(8)···O(2) and C(8)···O(2′) distances are in the range 3.2–3.4 Å, as shown in Table VII. A similar C(8)···O(2) distance is observed in methyl-β-CDx, but the C(8)···O(2′) distances, 3.44 and 3.46 Å in average values, are somewhat longer than those of methyl-α-CDx. This may reflect the relatively large O(2)···O(3′) distances of methyl-β-CDx.

Typical macrocyclic conformations of methyl-α-CDx and methyl-β-CDx are illustrated in

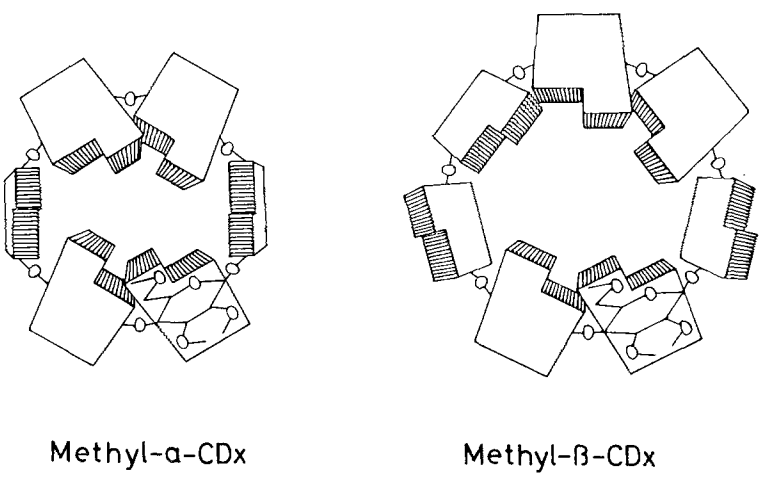


Fig. 4. Schematic representation of the macrocyclic conformation of methyl-α-CDx and methyl-β-CDx. Oxygen atoms are denoted by O.

Figure 4. These conformations are characterized by the large inclination of some methylglucose residues, when compared with the conformation of cyclodextrins. The macrocyclic conformation of cyclodextrins has been discussed in terms of the tilt-angle, which is defined as an angle made by the plane through O(4) polygon and the plane through C(1), C(4), O(4), and O(4′) of each residue, as well as the geometry of O(4) polygons. The tilt-angles of four methylglucose residues in the methyl-α-CDx complexes with *p*-IAN and BA are in the range 22–28°. These residues incline with their O(6) side toward the macrocyclic ring. The other

Table VII. O(2)···O(3′), O(2)···C(8), and O(2′)···C(8) distances

*I.* O(2)···O(3′) *distances*

| | Distance (Å) | | | | | |
|---|---|---|---|---|---|---|
| | Methyl-α-CDx complex | | | Methyl-β-CDx complex | | |
| Residues | *p*-IAN | BA | *p*-NPH | Residues | *p*-IPH | FP |
| O(2,G1) – O(3,G2) | 3.33 | 3.46 | 3.26 | O(2,G1) – O(3,G2) | 3.23 | 3.28 |
| O(2,G6) – O(3,G1) | 3.26 | 3.38 | 3.45 | O(2,G7) – O(3,G1) | 3.41 | 3.40 |
| O(2,G2) – O(3,G3) | 3.37 | 3.32 | 3.30 | O(2,G2) – O(3,G3) | 3.56 | 3.54 |
| O(2,G3) – O(3,G4) | 3.26 | 3.33 | 3.30 | O(2,G3) – O(3,G4) | 3.33 | 3.36 |
| O(2,G4) – O(3,G5) | 3.23 | 3.35 | 3.27 | O(2,G4) – O(3,G5) | 3.71 | 3.66 |
| O(2,G5) – O(3,G6) | 3.25 | 3.27 | 3.48 | O(2,G5) – O(3,G6) | 3.68 | 3.64 |
| | | | | O(2,G6) – O(3,G7) | 3.30 | 3.24 |
| Average | 3.28 ± 0.05 | 3.35 ± 0.06 | 3.34 ± 0.10 | Average | 3.46 ± 0.19 | 3.43 ± 0.19 |
| | (2.87 ± 0.13)[a] | (3.05 ± 0.32)[a] | (2.84 ± 0.14)[a] | | | |

[a] Average values of the corresponding α-cyclodextrin complexes.

*II.* C(8)···O(2) *distances*

| | Distance (Å) | | | | | |
|---|---|---|---|---|---|---|
| | Methyl-α-CDx complex | | | Methyl-β-CDx complex | | |
| Residue | *p*-IAN | BA | *p*-NPH | Residue | *p*-IPH | FP |
| G1 | 3.10 | 3.22 | 3.25 | G1 | 3.49 | 3.49 |
| G2 | 3.44 | 3.47 | 3.43 | G2 | 3.29 | 3.24 |
| G3 | 3.43 | 3.54 | 3.42 | G3 | 3.61 | 3.61 |
| G4 | 3.12 | 3.18 | 3.17 | G4 | 3.01 | 3.04 |
| G5 | 3.50 | 3.25 | 3.45 | G5 | 3.21 | 3.34 |
| G6 | 3.50 | 3.53 | 3.22 | G6 | 3.75 | 3.72 |
| | | | | G7 | 3.18 | 3.11 |
| Average | 3.35 ± 0.19 | 3.37 ± 0.12 | 3.32 ± 0.12 | Average | 3.36 ± 0.26 | 3.36 ± 0.25 |

*III.* C(8)···O(2) *distances between adjacent methylglucose residues*

| | Distance (Å) | | | | | |
|---|---|---|---|---|---|---|
| | Methyl-α-CDx complex | | | | Methyl-β-CDx complex | |
| Residues | *p*-IAN | BA | *p*-NPH | Residues | *p*-IPH | FP |
| C(8,G2) – O(2,G1) | 3.04 | 3.37 | 3.21 | C(8,G2) – O(2,G1) | 3.44 | 3.35 |
| C(8,G3) – O(2,G2) | 3.08 | 3.43 | 3.21 | C(8,G3) – O(2,G2) | 3.18 | 3.18 |
| C(8,G4) – O(2,G3) | 3.38 | 3.23 | 3.33 | C(8,G4) – O(2,G3) | 3.39 | 3.32 |
| C(8,G5) – O(2,G4) | 3.25 | 3.41 | 3.37 | C(8,G4) – O(2,G4) | 3.55 | 3.50 |
| C(8,G6) – O(2,G5) | 3.07 | 3.38 | 3.41 | C(8,G6) – O(2,G5) | 3.51 | 3.46 |
| C(8,G1) – O(2,G6) | 3.39 | 3.24 | 3.45 | C(8,G7) – O(2,G6) | 3.56 | 3.66 |
| | | | | C(8,G1) – O(2,G7) | 3.60 | 3.63 |
| Average | 3.20 ± 0.16 | 3.34 ± 0.09 | 3.33 ± 0.10 | Average | 3.46 ± 0.14 | 3.44 ± 0.17 |

two methylglucose residues, which face each other, are almost perpendicular to the O(4) plane with the tilt-angles of 2–4°. The average tilt-angles of methyl-α-CDx, 17, 18, and 19°, are larger than those of the corresponding α-cyclodextrin complexes, 11, 16, and 11°, respectively.

Table VIII. Tilt-angles of methylglucose residues

| | Angle (°) | | | | |
|---|---|---|---|---|---|
| | Methyl-α-CDx complex | | | Methyl-β-CDx complex | |
| Residue | *p*-IAN | BA | *p*-NPH | *p*-IPH | FP |
| G1 | 25 | 28 | 26 | 30 | 28 |
| G2 | 23 | 24 | 16 | 17 | 17 |
| G3 | 3 | 2 | 9 | −13 | −12 |
| G4 | 24 | 23 | 28 | 43 | 43 |
| G5 | 22 | 26 | 15 | 35 | 35 |
| G6 | 3 | 4 | 19 | −16 | −13 |
| G7 | — | — | — | 43 | 38 |
| Average | 17 ± 11 (11 ± 5)[a] | 18 ± 12 (16 ± 4)[a] | 19 ± 7 (11 ± 4)[a] | 20 ± 25 | 19 ± 24 |

[a] Average values of the corresponding α-cyclodextrin complexes.

The macrocyclic conformation of methyl-β-CDx is more remarkably distorted than that of methyl-α-CDx. The average tilt-angles in methyl-β-CDx are similar to those of methyl-α-CDx, 19–20°, as shown in Table VIII, but the individual values are distributed over a wider range, −16 to 48°. Five methylglucose residues are inclined with their O(6) side toward the macrocyclic ring, while the other two residues are inclined so that their O(2), O(3) sides are closer to each other. These two methylglucose residues display negative values of the tilt-angle. A negative tilt-angle has been also found in cyclodextrins [25], but large values such as those found in methyl-β-CDx have not been observed. Relatively large tilt-angles are also found in cyclodextrin complexes: for instance, 29° [26] and 42° [27]. But, the large tilt by the plane through the glucose residues seems to be unfavorable in forming intramolecular hydrogen bonds, as the O(2)···O(3′) distances are forced to be enlarged. In cyclodextrins, the tilt-angle is mostly in the range from 0 to 20° in α-cyclodextrin and from −5 to 28° in β-cyclodextrin. Therefore, the large tilt of the methylglucose residues in the macrocyclic ring may be ascribed to the repelling interaction between C(8)$H_3$ methyl groups and adjacent O(2) atoms, and the release of conformational restrictions imposed by intramolecular hydrogen bonds. This finding is also supported by the X-ray study of the heptakis (2,6-di-*O*-methyl)-β-cyclodextrin complex with adamantanol [28], in which the macrocyclic conformation is similar to that of β-cyclodextrin.

## 5. Host-Guest Interaction

### 5.1. METHYL-α-CDx – *p*-IAN

The iodophenyl group is included within the cavity, while the amino group protrudes outside from the O(2), O(3) side of the cavity, as shown in Figure 5a. The molecular axis of *p*-IAN is almost parallel to the molecular axis of methyl-α-CDx, which is defined as the axis normal to the O(4) plane and through the center of gravity of the O(4) hexagon. The iodine atom is located nearly at the center of the cavity. The benzene ring, being nearly parallel to the longest

diagonal to the O(4) hexagon, is surrounded by the six $O(2)C(8)H_3$ methoxy groups. A water molecule is also included within the cavity, forming hydrogen bonds with two O(6) atoms of methyl-α-CDx.

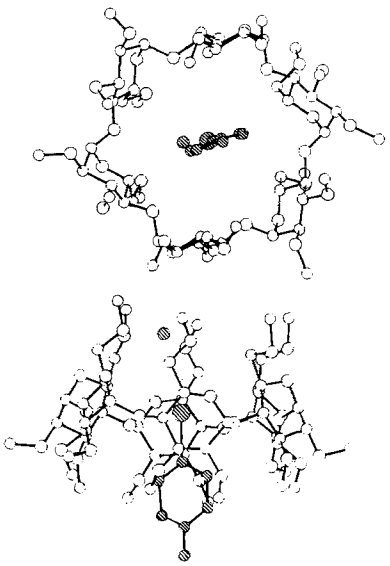

Fig. 5a

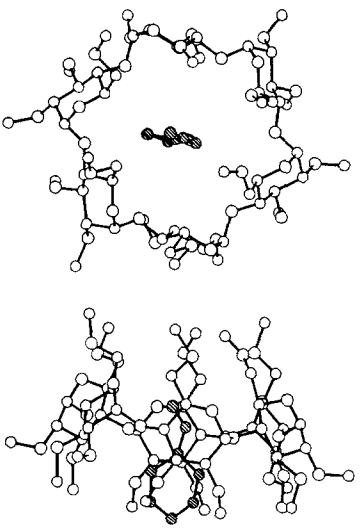

Fig. 5b

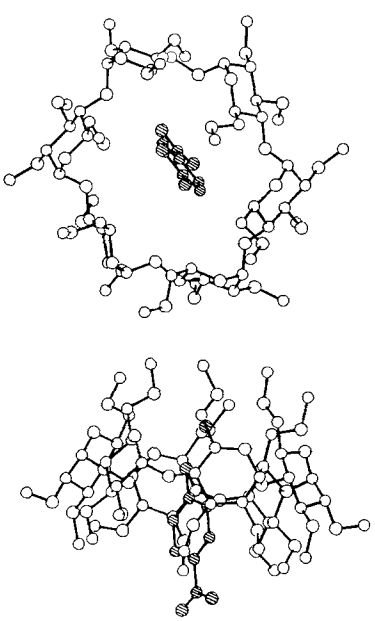

Fig. 5c

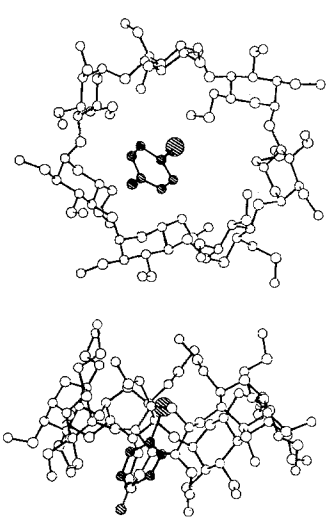

Fig. 5d

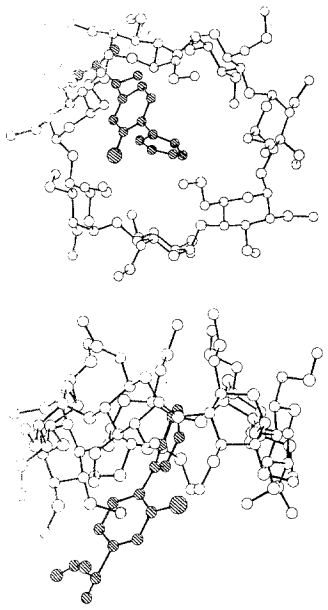

Fig. 5e

Fig. 5. Inclusion features of methyl-α-CDx complexes with *p*-IAN (a), BA (b), and *p*-NPH (c), and methyl-β-CDx complexes with *p*-IPH (d) and FP (e). Guest and water molecules are shown by shaded circles.

### 5.2. METHYL-α-CDx – BA

The BA molecule is almost fully included within the methyl-α-CDx cavity, and is sandwiched by two methylglucose residues which are almost normal to the O(4) plane (Figure 5b). The carbonyl group is located at the center of the cavity, while the benzene ring is situated nearly at the same site as that found in the *p*-IAN complex (Figure 5a).

### 5.3. METHYL-α-CDx – *p*-NPH

The hydroxyl group of *p*-NPH is inserted into the methyl-α-CDx ring, while the nitro group protrudes outside from the O(2), O(3) side of the methyl-α-CDx ring (Figure 5c). The phenolic hydroxyl group is located at the center of the cavity. Although the benzene ring is located at a position similar to those found in the complexes with *p*-IAN and BA, the *p*-NPH molecule is inclined with respect to the molecular axis of methyl-α-CDx. The water molecule, being located at the O(6) side of the cavity, forms hydrogen bonds with the phenolic hydroxyl group and two O(6) atoms, thus linking the guest molecule and methyl-α-CDx.

### 5.4. METHYL-β-CDx – *p*-IPH

The inclusion feature of *p*-IPH (Figure 5d) is similar to that of the methyl-α-CDx – *p*-IAN complex, but the molecular plane of *p*-IPH inclines so as to make an angle of 57.5° with the O(4) plane. The iodophenyl group is more deeply inserted into the methyl-β-CDx ring than that of the methyl-α-CDx – *p*-IAN complex. The phenolic hydroxyl group protrudes outside the cavity from the O(2), O(3) side.

### 5.5. METHYL-β-CDx – FP

The phenyl group is inserted from the O(2), O(3) side of the methyl-β-CDx ring (Figure 5e). The other part of the guest molecule lies outside the host ring. The FP molecule is tilted with respect to the molecular axis of methyl-β-CDx; the plane through the fluorobenzene moiety makes an angle of 58.3° with the O(4) plane. The fluorine atom is in Van der Waals contact with the two C(8) atoms; F···C(8) distances are 3.40 and 3.28 Å.

### 5.6. COMPARISON WITH CYCLODEXTRIN COMPLEXES

Schematic representations of the inclusion features of both cyclodextrin and methyl-CDx complexes are shown in Figures 6 and 7. Remarkable differences are observed in the position and orientation of the guest molecule within the host cavity. In the complexes with *p*-NPH and BA, an upside-down relationship is observed in the orientation of the guest molecule in the cyclodextrin and methyl-α-CDx complexes. The carbonyl group of BA, which is located at the center of the methyl-α-CDx cavity, protrudes from the O(2), O(3) side of the α-cyclodextrin ring, although the benzene ring is located at a similar place near the O(2), O(3) side of the cavity in both complexes. In the α-cyclodextrin – *p*-NPH complex, the host molecule includes the nitrophenyl group, which, however, is replaced by the hydroxyphenyl group in the methyl-α-CDx complex. The *p*-IAN molecule is included in a similar orientation in both α-cyclodextrin and methyl-α-CDx complexes, but, in the methyl-α-CDx complexes, the *p*-IAN molecule is relatively shifted toward the O(2), O(3) side. These differences in the inclusion geometry are ascribed to the change in shape and size of the host cavity. The permethylation enlarges the whole cavity of the host molecule, but it also makes the host molecule incapable of forming intramolecular hydrogen bonds which might otherwise participate in the stabilization of a round macrocyclic ring and prevents a large inclination of each residue. Moreover, the methyl groups introduced to the O(3) position enlarge the O(2), O(3) side of the cavity as well as making the O(6) side narrower. The effect of such conformational change on the geometry of host-guest interaction can be most clearly shown in the *p*-NPH complex. In the α-cyclodextrin complex, the nitrophenyl group is well-fitted to the cavity, and therefore, seems to be tightly bound. In the methyl-α-CDx complex, however, the O(6) side of the cavity is so narrow that the nitrophenyl group could not occupy the same site in the cavity as that found in the α-cyclodextrin complex because of steric hindrance. The guest molecule seems to be more loosely bound in the cavity of methyl-CDx than that of cyclodextrins, since the guest molecule is located at the O(2), O(3) side of the methyl-CDx cavity, which is wider than that of the cyclodextrin cavity.

The methyl-β-CDx forms a 1 : 1 complex with *p*-IPH, but a 2 : 3 stoichiometry is observed in the β-cyclodextrin-*p*-IPH complex [22]. As shown in Figure 7, two β-cyclodextrin molecules form a head-to-head dimer, and each β-cyclodextrin ring includes a *p*-IPH molecule with the iodine atom nearly at the center of the ring and the hydroxyl group at the O(6) side of the cavity. The third *p*-IPH molecule is sandwiched between the two β-cyclodextrin molecules. When compared with the methyl-β-CDx complex, the upside-down relationship is found in the orientation of the *p*-IPH molecule, although the hydrophobic iodophenyl group is included. The formation of a head-to-head dimer is also found in the β-cyclodextrin – FP complex, in which the two FP molecules are packed in the cylindrical cavity formed by the two β-cyclodextrin molecules, thus forming a 2 : 2 complex. In contrast to the methyl-β-CDx complex, each FP molecule is found deep in the host cavity, and the fluorobenzene moiety is located at the center of the cavity. The FP molecule is oriented in the opposite direction

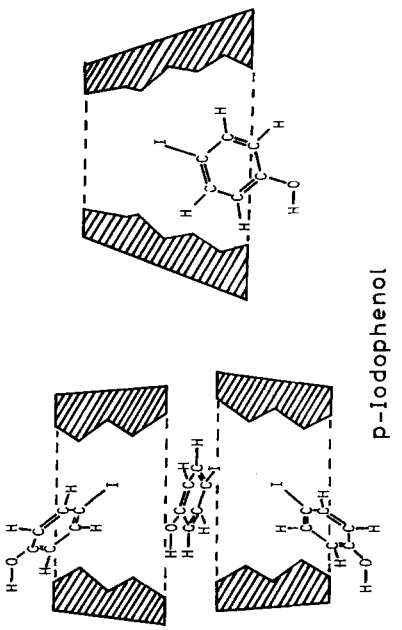


Fig. 7. Comparison of inclusion features between $\beta$-cyclodextrin and methyl-$\beta$-CDx.

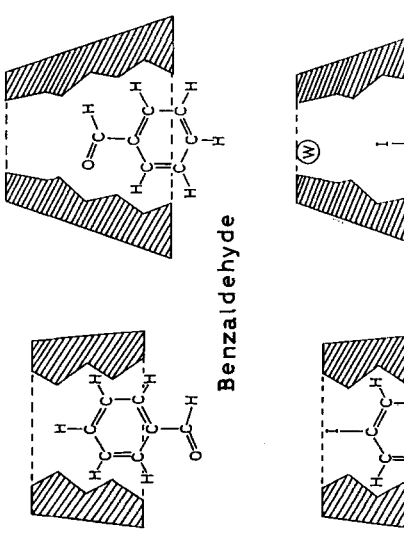


Fig. 6. Comparison of inclusion features between $\alpha$-cyclodextrin and methyl-$\alpha$-CDx complexes.

to that found in the methyl-β-CDx complex, and therefore, the propionic acid moiety protrudes from the O(6) side. In the methyl-β-CDx complex, the large inclination of methylglucose residues seems to prevent the deep penetration of the FP molecule.

## 6. Conclusions

Permethylated cyclodextrins are remarkably distorted from the regular polygonal structure. The inability to form intramolecular hydrogen bonds and the steric hindrance involving the $C(8)H_3$ methyl groups make most of the methylglucose residues sharply inclined. As a result, the O(2), O(3) side of the cavity is enlarged, and the O(6) side becomes narrower. Guest molecules are included at the O(2), O(3) side of the cavity, and the protrusion of a part of the guest molecule is observed only at the O(2), O(3) side. An upside-down relationship in the orientation of the guest molecules, *p*-NPH, BA, *p*-IPH, and FP, is found between cyclodextrin complexes and methyl-CDx complexes.

## References


1. M. L. Bender and M. Komiyama, *Cyclodextrin Chemistry*, Springer-Verlag, Berlin (1978).
2. J. Szejtli, *Cyclodextrins and their Inclusion Complexes*, Akademiai Kiado, Budapest (1982).
3. R. J. Bergeron, D. M. Pillor, G. Gibeily, and W. P. Roberts, *Bioorg. Chem.* **7**, 263–271 (1978).
4. K. Harata, *Bull. Chem. Soc. Jpn.* **49**, 2066–2072 (1976).
5. I. Tabushi, Y. Kiyosuke, T. Sugimoto, and K. Yamamura, *J. Am. Chem. Soc.* **100**, 916–919 (1978).
6. W. Saenger, M. Noltemeyer, P. C. Manor, B. Hingerty, and B. Klar, *Bioorg. Chem.* **5**, 187–195 (1976).
7. R. I. Gelb, L. M. Schwartz, B. Cardelino, H. S. Fuhrman, R. F. Johnson, and D. A. Laufer, *J. Am. Chem. Soc.* **103**, 1750–1757 (1981).
8. D. W. Griffiths and M. L. Bender, *Adv. Catal.* **23**, 209–261 (1973).
9. R. L. VanEtten, G. A. Clowes, J. S. Sebastian, and M. L. Bender, *J. Am. Chem. Soc.* **89**, 3253–3262 (1967).
10. J. Emert and R. Breslow, *J. Am. Chem. Soc.* **97**, 670–671 (1975).
11. I. Tabushi, K. Shimokawa, N. Shimizu, and K. Fujita, *J. Am. Chem. Soc.* **98**, 7855–7856 (1976).
12. I. Tabushi, *Acc. Chem. Res.* **15**, 66–72 (1982).
13. J. Boger, R. J. Corcoran, and J. M. Lehn, *Helv. Chim. Acta* **61**, 2190–2218 (1978).
14. B. Casu and M. Reggiani, *Carbohydr. Res.* **76**, 59–66 (1979).
15. J. Szejtli, A. Lipták, I. Jodál, P. Fügedi, P. Nánási, and A. Neszmélyi, *Starch/Stürke* **32**, 165–169 (1980).
16. K. Harata, *Bull. Chem. Soc. Jpn.* **48**, 2409–2413 (1975).
17. K. Harata, *Bull. Chem. Soc. Jpn.* **50**, 1416–1424 (1977).
18. K. Harata, K. Uekama, M. Otagiri, F. Hirayama, and H. Ogino, *Bull. Chem. Soc. Jpn.* **54**, 1954–1959 (1981).
19. K. Harata, K. Uekama, M. Otagiri, and F. Hirayama, *Bull. Chem. Soc. Jpn.* **55**, 407–410 (1982).
20. K. Harata, K. Uekama, M. Otagiri, F. Hirayama, and Y. Sugiyama, *Bull. Chem. Soc. Jpn.* **55**, 3386–3389 (1982).
21. K. Harata, K. Uekama, M. Otagiri, and F. Hirayama, *Bull. Chem. Soc. Jpn.* **55**, 3904–3910 (1982).
22. J. J. Stezowski, K. H. Jogun, E. Eckle, and K. Bartels, *Nature* **274**, 617–619 (1978).
23. A. D. French and V. G. Murphy, *Carbohydr. Res.* **27**, 391–406 (1973).
24. K. Harata, *Bull. Chem. Soc. Jpn.* **55**, 2315–2320 (1982).
25. K. Lindner and W. Saenger, *Carbohydr. Res.* **99**, 103–115 (1982).
26. W. Saenger, R. K. McMullan, J. Fayos, and D. Mootz, *Acta Crystallogr. Sect. B* **30**, 2019–2028 (1974).
27. P. C. Manor and W. Saenger, *J. Am. Chem. Soc.* **96**, 3630–3639 (1974).
28. M. Czugler, E. Eckle, and J. J. Stezowski, *J. Chem. Soc., Chem. Commun.*, 1981, 1291–1292.