CRYSTAL STRUCTURES OF CYCLODEXTRIN COMPLEXES WITH CHIRAL MOLECULES

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ABSTRACT. The chiral recognition by cyclodextrins and permethylated cyclodextrins have been investigated on the basis of the X-ray data of crystalline inclusion complexes. The macrocyclic ring of α- and β-cyclodextrin shows a round and symmetrical structure. α-Cyclodextrin includes racemic 1-phenylethanol with the statistical disorder of the hydroxyl group. A pair of the R- and S-isomers of flurbiprofen are included within the cylindrical cavity formed by dimeric β-cyclodextrin molecules with a head-to-head arrangement. The macrocyclic ring of permethylated cyclodextrins is remarkably distorted from the regular polygonal symmetry and has more flexibility in the conformational change than cyclodextrins. Owing to the distorted conformation and steric hindrance involving methyl groups, permethylated cyclodextrins do not equally include both isomers, as demonstrated by the permethylated α-cyclodextrin complexes with mandelic acids. Permethylated α-cyclodextrin binds D-mandelic acid more tightly *via* a host-guest hydrogen bond and induced-fit conformational change. Permethylated β-cyclodextrin forms a hydrated crystalline complex with R-flurbiprofen, but S-flurbiprofen forms a non-hydrated crystalline complex. Significant differences between the two complexes are found in the orientation of the phenyl group and hydrogen-bond formation involving the carboxyl group.

1. INTRODUCTION

Cyclodextrins form diastereoisomers by including optically active guests within the cavity of their macrocycles. On this basis, several attempts have been made to utilize cyclodextrins as a reagent for the resolution of racemic compounds [1]. Though cyclodextrins consist of six or more optically active D-glucose units, the cavity, which accommodates guest molecules, presents a round and symmetrical feature. This may cause difficulties in recognizing the chirality of included guests, as suggested by the fact that, with few exceptions, only low optical resolution is achieved by the precipitation of racemic compounds with

Journal of Inclusion Phenomena **2**, 583–594. 0167-7861/84.15.

cyclodextrins. On the other hand, permethylated cyclodextrins are expected to have more potential to recognize the chirality of optically active guests, since our recent X-ray studies [2] have revealed that the macrocyclic conformation of permethylated cyclodextrins is remarkably distorted from the regular polygonal symmetry and has more flexibility than that of parent cyclodextrins. In the present paper, we deal with crystal structures of inclusion complexes of cyclodextrins and permethylated cyclodextrins with optically active guests, and the potential of chiral recognition of the host molecules is discussed in terms of the host-guest interaction.

2. X-RAY DATA OF CYCLODEXTRIN AND PERMETHYLATED CYCLODEXTRIN COMPLEXES

Crystal structures of cyclodextrin and permethylated cyclodextrin complexes were determined by the X-ray method. Detailed descriptions of the structures have been described elsewhere. Experimental data are given in Table I.

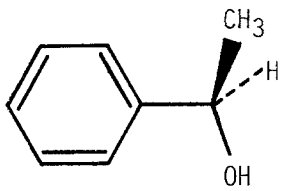
Table I. Experimental data for α-cyclodextrin–racemic 1-phenylethanol complex (I), β-cyclodextrin–S-flurbiprofen complex (II), β-cyclodextrin–racemic flurbiprofen complex (III), permethylated α-cyclodextrin–L-mandelic acid complex (IV), permethylated α-cyclodextrin–D-mandelic acid complex (V), permethylated β-cyclodextrin–R-flurbiprofen complex (VI), and permethylated β-cyclodextrin–S-flurbiprofen complex (VII)

	I	II	III	IV	V	VI	VII
Stoichiometry	1:1	2:2	2:2	1:1	1:1	1:1	1:1
Number of water	4	21	20	3	2	0	1
F. W.	1239.1	3136.8	3118.8	1431.5	1413.5	1673.8	1691.8
Space group	$P2_1$	P1	P1	$P2_1$	$P2_1$	$P2_12_12_1$	$P2_12_12_1$
a(Å)	8.176	15.446	15.420	13.123	11.624	15.271	15.092
b(Å)	23.930	15.513	15.490	23.187	23.739	21.451	21.714
c(Å)	13.853	18.107	18.033	13.113	13.786	27.895	28.269
α(°)		113.52	113.63				
β(°)	106.69	99.32	99.36	107.19	106.56		
γ(°)		102.89	103.05				
V(Å3)	2569	3772	3685	3812	3646	9137	9264
Z	2	1	1	2	2	4	4
D_x(g.cm^{-3})	1.585	1.399	1.405	1.247	1.289	1.217	1.213
Reflections	3565	9639	9472	4837	4924	5979	3525
R-Value	0.040	0.095	0.084	0.087	0.055	0.089	0.10

3. DESCRIPTION OF THE STRUCTURE

3.1. α-Cyclodextrin Complex with Racemic 1-Phenylethanol [3]

As shown in Fig. 1, α-cyclodextrin forms a 1:1 complex with racemic 1-phenylethanol. The α-cyclodextrin ring is in the round shape with diagonal distances of 8.35-8.62 Å measured between glycosidic oxygen atoms. α-Cyclodextrin molecules are stacked to form a column structure, as shown in Fig. 2. The plane through six glycosidic oxygen atoms is not perpendicular to the column axis, but inclines at an angle of 17.0°. As all primary hydroxyl groups are in a *gauche-gauche* conformation, no hydrogen bond is formed between adjacent α-cyclodextrin molecules along the column, although in typical column structures adjacent α-cyclodextrin molecules are linked by many hydrogen bonds. The guest 1-phenylethanol molecule is located within the column, being sandwiched between two α-cyclodextrin molecules. The phenyl group has a contact with the secondary hydroxyl side of α-cyclodextrin, while the methyl group is inserted into the next α-cyclo-



R-1-Phenylethanol

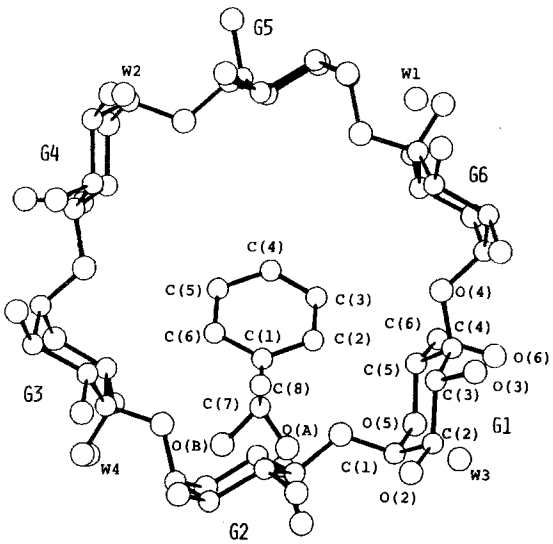


Fig. 1. α-Cyclodextrin–racemic 1-phenylethanol complex. O(A) and O(B) denote disordered hydroxyl groups, corresponding to S- and R-isomers, respectively. Water molecules are denoted by W1, W2, W3, and W4.

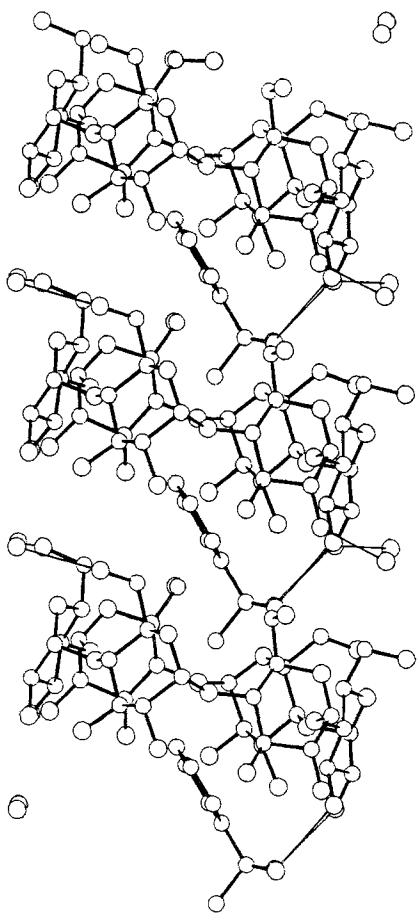
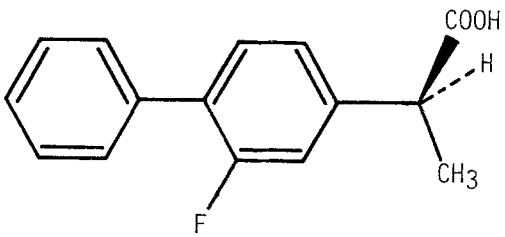


Fig. 2. Stacking feature of the complex. Hydrogen bonds are indicated by thin lines.

dextrin ring from the primary hydroxyl side. The R- and S-isomers of 1-phenylethanol occupy the same site with the occupancy factor of 0.5 each. The only difference is found in the orientation of the hydroxyl group, as denoted by O(A) and O(B) in Fig. 1. The host-guest hydrogen bond is formed between the hydroxyl group of 1-phenylethanol and the secondary hydroxyl group of α-cyclodextrin with O(A)···O(3,G2) and O(B)···O(2,G2) distances of 2.74 and 2.87 Å, respectively.

3.2. β-Cyclodextrin Complexes with Flurbiprofen

3.2.1. S-Flurbiprofen [4]. As shown in Fig. 3, two β-cyclodextrin molecules form a head-to-head dimer with the secondary hydroxyl sides facing each other. The two β-cyclodextrin molecules are linked with many hydrogen bonds, thus producing a hydrophobic and cylindrical cavity. Each β-cyclodextrin molecule includes a guest S-flurbiprofen molecule, and the two 1:1 complexes, which are related *via* a *pseudo* two-fold symmetry axis, are coupled to form a 2:2 complex. The guest S-flurbiprofen molecule fully penetrates the host ring, with the fluorophenylene group located at the center of the cavity. The phenyl groups of the guests face each other between the two β-cyclodextrin molecules. The biphenyl moiety is twisted by angles of 40.0° and 33.2°. The carboxyl group of S-flurbiprofen protrudes from the primary hydroxyl side of β-cyclodextrin and forms hydrogen bonds with water and adjacent β-cyclodextrin molecules, as shown in Fig. 5.



S-Flurbiprofen

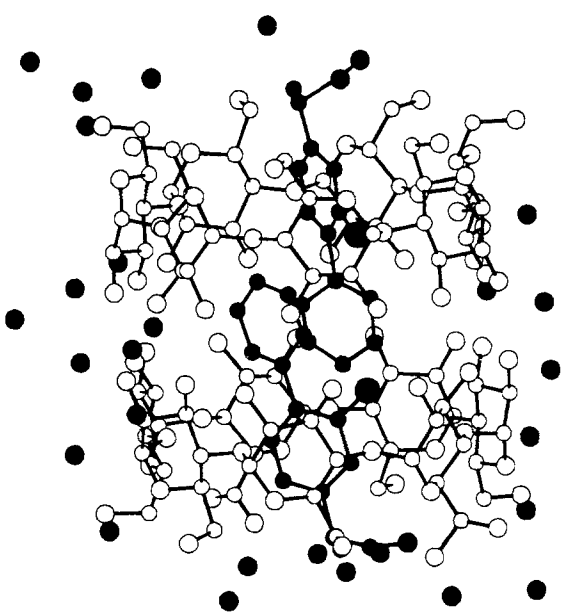


Fig. 3. Structure of the β-cyclodextrin–S-flurbiprofen complex. S-Flurbiprofen and water molecules are shown by full circles.

3.2.2. Racemic Flurbiprofen [5]. The structure of the β-cyclodextrin complex with racemic flurbiprofen is shown in Fig. 4. The crystal

is isomorphous with that of the S-flurbiprofen complex. The crystal also consists of dimeric β-cyclodextrin molecules. A pair of R- and S-flurbiprofen molecules are included within the cylindrical cavity of the β-cyclodextrin dimer. One β-cyclodextrin molecule includes the R-isomer, and the other includes the S-isomer. In spite of the different absolute configuration, the biphenyl moiety of both R- and S-isomers has the same chirality, having twist angles of 37.4° and 34.8°, respectively. The major difference between the structures of the complexes with racemic flurbiprofen and S-flurbiprofen is found around the carboxyl group of the guests, as shown in Fig. 5, as the R-isomer in the racemic flurbiprofen complex is replaced by the S-isomer in the S-

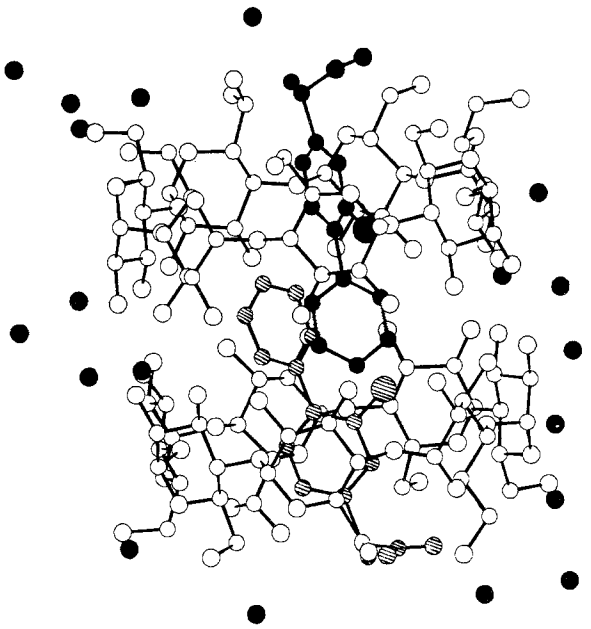


Fig. 4. Structure of the β-cyclodextrin complex with racemic flurbiprofen. The R-isomer is shown by shaded circles. The S-isomer and water molecules are shown by full circles.

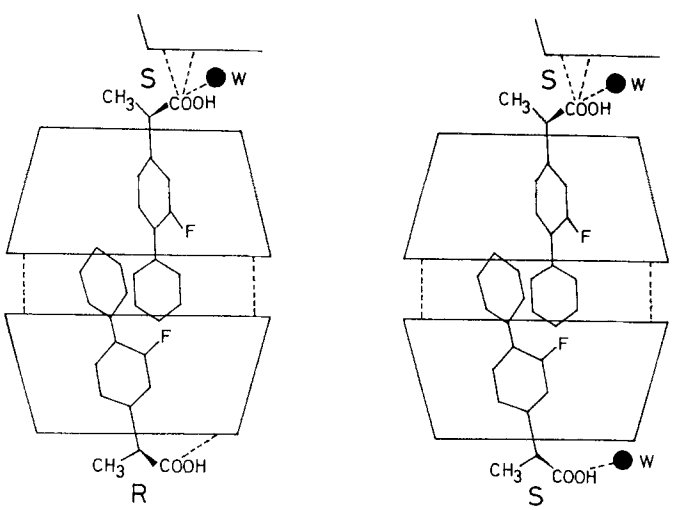
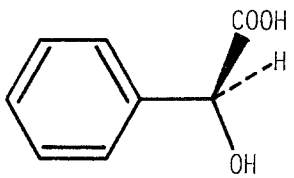


Fig. 5. Schematic representation of the inclusion features of the S-flurbiprofen (right) and racemic flurbiprofen (left) complexes.

flurbiprofen complex. The conformation and hydrogen-bond formation of the carboxyl group of the S-isomer in the racemic flurbiprofen complex are the same as those found in the S-flurbiprofen complex. The carboxyl group of the R-isomer forms a hydrogen bond with a primary hydroxyl group of the host β-cyclodextrin, which is in the *gauche-trans* conformation. On the other hand, the corresponding carboxyl group of the S-flurbiprofen is oriented in a direction unsuitable for the formation of a hydrogen bond with host hydroxyl groups, therefore forming a hydrogen bond with a water molecule.

3.3. Permethylated α-Cyclodextrin Complexes with Mandelic Acids [6]

3.3.1. L-Mandelic acid. Permethylated α-cyclodextrin has a *pseudo* two fold symmetry, as shown in Fig. 6. The six glycosidic oxygen atoms form a slightly distorted hexagon with diagonal distances 8.45-8.73 Å. The G3 and G6 residues are nearly perpendicular to the O(4) plane, but the G1 and G4 residues incline by *ca.* 35° with the O(6) side towards the center of the cavity. These G1 and G4 residues are held by the O(6)···water···O(6) hydrogen-bond bridge, which is formed by the water molecule located at the O(6) side of the host cavity. The phenyl group of L-mandelic acid is inserted into the host cavity from the O(2), O(3) side. The hydroxyl and carboxyl groups are located outside the cavity and form hydrogen bonds with water molecules (Fig. 7).



L-Mandelic acid

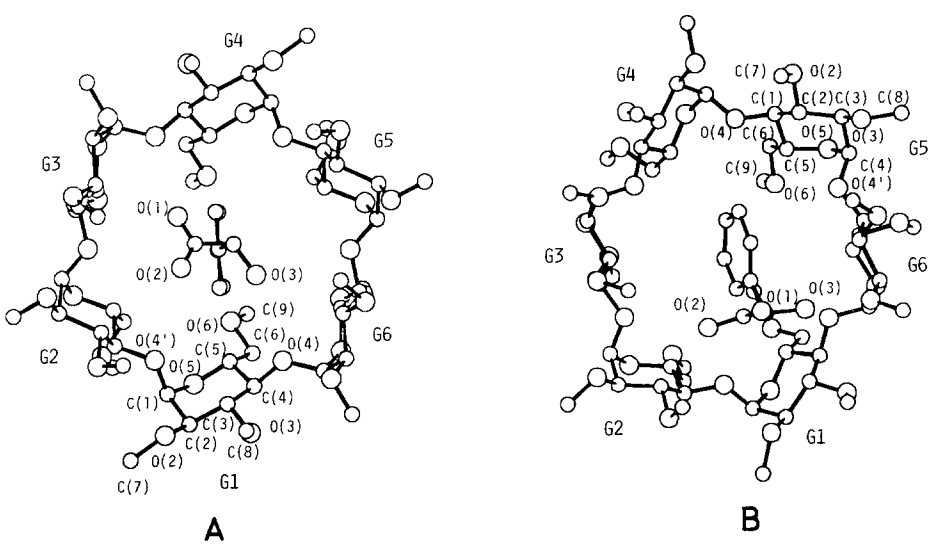


Fig. 6. Structures of permethylated α-cyclodextrin complexes with L-mandelic acid (A) and D-mandelic acid (B).

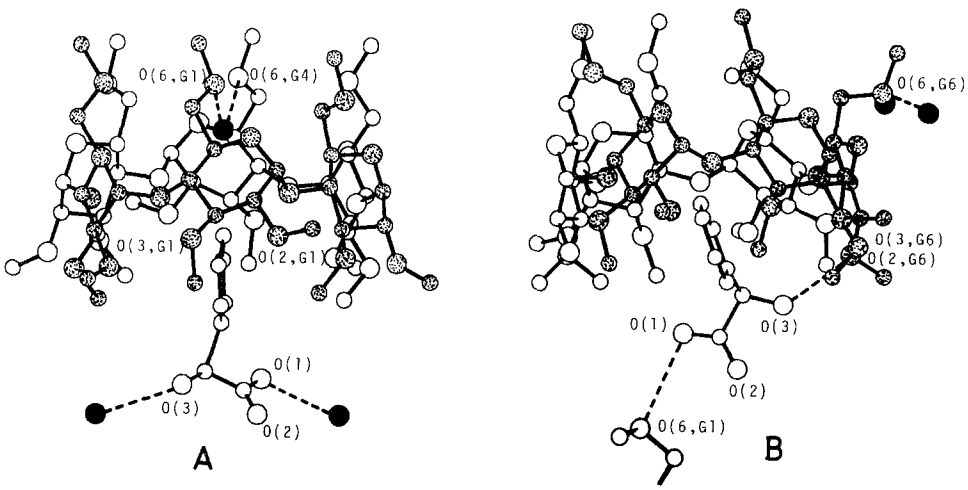


Fig. 7. Host-guest interaction in the permethylated α-cyclodextrin complexes with L-mandelic acid (A) and D-mandelic acid (B). Water molecules are shown by full circles. Broken lines indicate hydrogen bonds. The G1, G2, and G6 residues in the L-mandelic acid complex and the G4, G5, and G6 residues in the D-mandelic acid complex are shaded.

3.3.2. D-Mandelic acid. The permethylated α-cyclodextrin ring is elliptically distorted with the diagonal distances of the O(4) hexagon, 8.08-9.08 Å. The phenyl group of D-mandelic acid is inserted from the O(2), O(3) side of the guest ring more deeply than the phenyl group of L-mandelic acid. The phenyl plane is not parallel to the molecular axis of permethylated α-cyclodextrin, which is defined as the axis perpendicular to the O(4) plane and through the center of the O(4) hexagon, but makes an angle of *ca.* 20°. The empty space of the O(6) side of the cavity is filled with a methoxyl group of the host molecule. The hydroxyl group of D-mandelic acid forms a hydrogen bond with an O(2) oxygen atom of the host molecule. The carboxyl group is hydrogen-bonded to an O(6) oxygen atom of the adjacent host molecule.

3.4. Permethylated β-Cyclodextrin Complexes with Flurbiprofen [7]

3.4.1. R-Flurbiprofen. The permethylated β-cyclodextrin ring is remarkably distorted from the regular heptagonal symmetry, as shown in Fig. 8. The distortion of the host macrocyclic ring is characterized by the large tilt-angles of permethylated D-glucose residues, which are in the range from -12.9° to 43.8°. The permethylation makes the host cavity deeper, but also makes the O(6) side of the cavity narrower. Accordingly, the guest molecule can not be fully included within the host cavity. The phenyl group is located at the center of the host ring, while the other part of the guest molecule protrudes outward from the O(2), O(3) side. The carboxyl group of R-flurbiprofen forms a hydrogen bond with

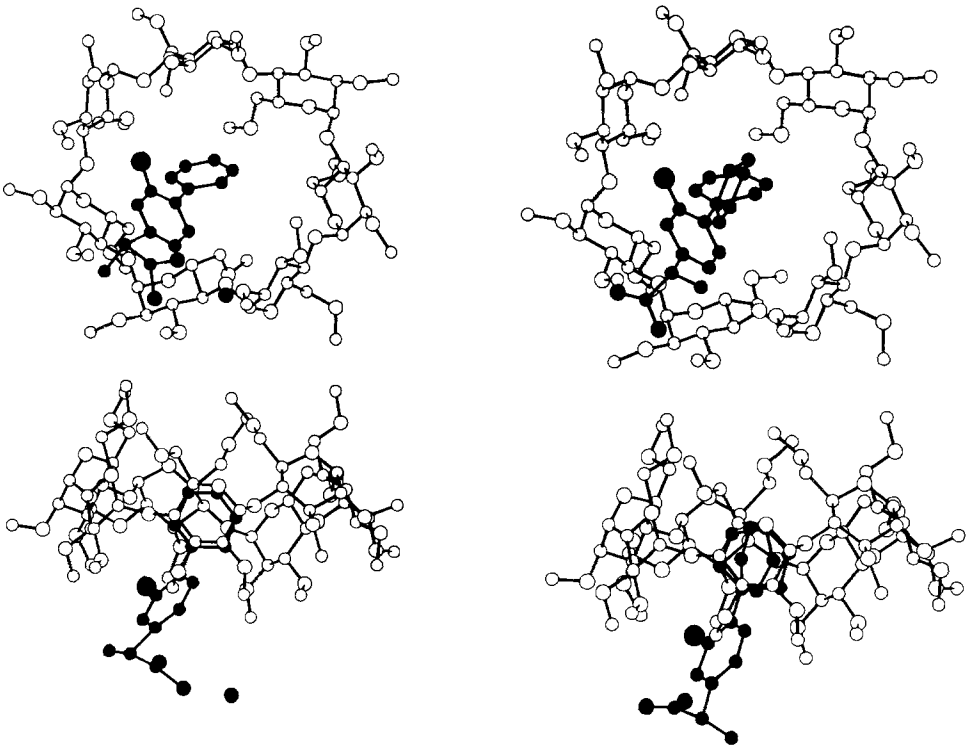


Fig. 8. Permethylated β-cyclodextrin complexes with R-flurbiprofen (left) and S-flurbiprofen (right). The guest and water molecules are shown by full circles.

a water molecule. The two phenyl planes make an angle of 54.7°, which is larger than those found in the β-cyclodextrin complexes.

3.4.2. S-Flurbiprofen. The conformation of the host molecule is nearly the same as that of the R-flurbiprofen complex, except for the orientation of a C(6)-O(6) bond: a *gauche-trans* conformation is found in the S-flurbiprofen complex, while the corresponding C(6)-O(6) bond in the S-flurbiprofen complex shows a *gauche-gauche* conformation. The phenyl group of the guest molecule is located at the same position as that found in the R-flurbiprofen complex, but its orientation is disordered two-fold, as shown in Fig. 8. One phenyl plane is in a similar orientation to that of R-flurbiprofen, while the other is rotated to the opposite side with respect to the fluorophenylene plane. The biphenyl angles of the former phenyl group and the latter are 51.1° and 60.3°, respectively. The carboxyl group of S-flurbiprofen is oriented outside the host ring and forms a hydrogen bond with an oxygen atom of an adjacent host molecule, as shown in Fig. 9.

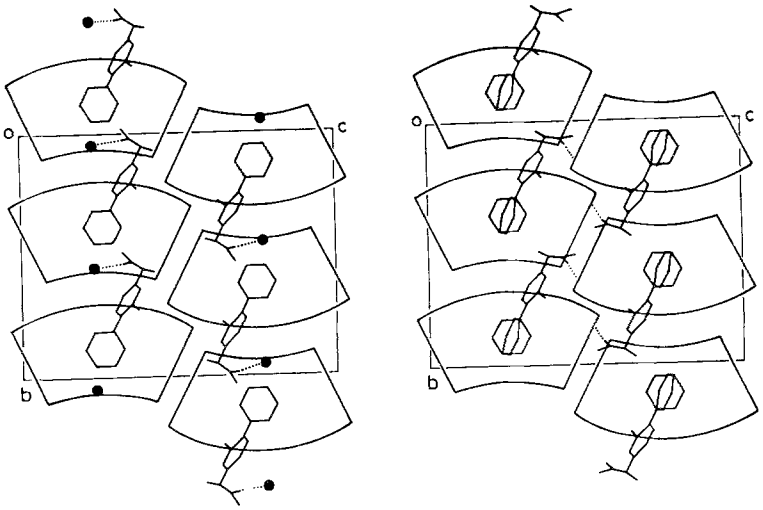


Fig. 9. Schematic drawings of the crystal packing of permethylated β-cyclodextrin complexes with R-flurbiprofen (left) and S-flurbiprofen (right). Water molecules are shown by full circles. Dotted lines indicate hydrogen bonds.

4. DISCUSSION

4.1. Conformation of Host Molecules

Table II shows geometrical data describing the macrocyclic conformation of cyclodextrins and permethylated cyclodextrins. The radius and side length of the O(4) heptagon of β-cyclodextrin, 5.0 Å and 4.38-4.39 Å, respectively, are similar to those (5.00-5.01 Å and 4.38-4.39 Å, respectively) of permethylated β-cyclodextrin. The O(4) hexagon of permethylated α-cyclodextrin is somewhat larger than that of α-cyclodextrin: the radius of the O(4) hexagon is 4.23 Å in α-cyclodextrin and 4.30 Å in permethylated α-cyclodextrin.

The permethylation markedly affects the planarity of the O(4) heptagon of β-cyclodextrin, and increases the root-mean-square deviation of O(4) atoms from their least-squares plane; 0.006-0.020 Å in β-cyclodextrin and 0.404-0.416 Å in permethylated β-cyclodextrin.

The effect of the permethylation on the macrocyclic conformation appears most clearly in the change of O(2)···O(3') distances and tilt-angles. The average O(2)···O(3') distances of permethylated cyclodextrins are about 0.6 Å larger than those of parent cyclodextrins. In α- and β-cyclodextrin, secondary hydroxyl groups form intramolecular O(2)···O(3') hydrogen bonds, as indicated by the O(2)···O(3') distances of 2.79-2.89 Å. These intramolecular hydrogen bonds may maintain the round macrocyclic

Table II. Average values of radius of the O(4) polygon (I),[a] O(4)···O(4') distance between adjacent residues (II), O(2)···O(3') distance between adjacent residues (III), root-mean-square deviation of O(4) atoms from the least-squares plane (IV), and tilt-angle.[b]

		I (Å)	II (Å)	III (Å)	IV (Å)	V (°)
α-Cyclodextrin—racemic 1-phenylethanol		4.23	4.24	2.89	0.106	9.5
β-Cyclodextrin—racemic flurbiprofen	(I)	5.05	4.39	2.80	0.015	8.5
	(II)	5.05	4.38	2.79	0.006	8.0
β-Cyclodextrin—S-flurbiprofen	(I)	5.05	4.39	2.80	0.020	9.0
	(II)	5.05	4.39	2.79	0.017	9.2
Permethylated α-cyclodextrin—L-mandelic acid		4.30	4.29	3.40	0.207	20.7
Permethylated α-cyclodextrin—D-mandelic acid		4.30	4.29	3.39	0.132	17.8
Permethylated β-cyclodextrin—R-flurbiprofen		5.00	4.39	3.44	0.416	20.3
Permethylated β-cyclodextrin—S-flurbiprofen		5.01	4.38	3.43	0.404	19.0

a) The radius was measured from the center of gravity of polygon to each individual O(4) atom.
b) Tilt-angle is defined as an angle made by the O(4) plane and the plane through C(1), C(4), O(4), and O(4') atoms of each residue.

structure. On the other hand, the permethylation makes the formation of such hydrogen bonds impossible, and also causes steric hindrance between O(2) oxygen atoms and methyl groups attached to O(3) oxygen atoms [2]. Accordingly, the O(2)···O(3') distance is enlarged to avoid the steric hindrance involving methyl groups, and as a result, permethylated glucose residues are obliged to incline with a large tilt-angle (Table II).

The tilt-angles of α- and β-cyclodextrin are distributed in the ranges 4.1-14.6° and 3.4-15.3°, respectively. Average values of the tilt-angles of permethylated cyclodextrins are about twice the corresponding values of parent cyclodextrins. Moreover, each individual tilt-angle of permethylated cyclodextrins is distributed in wider ranges; 1.9-35.9° in permethylated α-cyclodextrin and -14.3-43.8° in permethylated β-cyclodextrin. Such a macrocyclic conformation of permethylated cyclodextrins produces a cavity with a shape and size different from that of parent cyclodextrins. As most of the methyl groups are oriented outside the macrocyclic ring, the host cavity becomes deeper by the permethylation. On the other hand, the sharp inclination of permethylated glucose residues makes the O(6) side of the cavity narrower. Moreover, the incapability of forming intramolecular hydrogen bonds

makes the macrocyclic conformation more flexible. Therefore, such a distorted and flexible macrocyclic structure may be more favorable for the recognition of the chirality of included guests, since the host-guest contact may be closer for a certain isomer through the induced-fit conformational change of the host molecule.

4.2. Host-Guest Interaction and Chiral Recognition

As shown in the α-cyclodextrin complex with racemic 1-phenylethanol and the β-cyclodextrin complex with racemic flurbiprofen, α- and β-cyclodextrin equally include R- and S-isomers of the guests. In the α-cyclodextrin–1-phenylethanol complex, the hydrogen-bond energy may differ between the R- and S-isomers, since the O(A)···O(3,G2) distance is shorter than that of the O(B)···O(2,G2) distance. But, the 1:1 ratio of the included R- and S-isomer suggests that such slight structural difference is not sufficient for α-cyclodextrin to discriminate between the R- and S-isomer and to include exclusively either isomer.

In the β-cyclodextrin complex with racemic flurbiprofen, the R-isomer is included in a similar manner to that of the S-isomer in the S-flurbiprofen complex, but the hydrogen-bonding contact involving the carboxyl group is different, as shown in Fig. 5. The β-cyclodextrin molecule discriminates between R- and S-flurbiprofen through such difference in hydrogen bonds, and includes each isomer independently. It should be noted that the biphenyl moiety of both R- and S-flurbiprofen shows the R-configuration in these β-cyclodextrin complexes. This indicates that β-cyclodextrin includes the biphenyl moiety with the R-configuration more favorably than that with the S-configuration. As both the R- and S-configurations of the biphenyl moiety may be in equilibrium in solution, β-cyclodextrin induces the chirality in the included guest by fixing the biphenyl configuration so as to be the most suitable one for accommodation in the cavity.

The R-configuration of the biphenyl moiety is also observed in the permethylated β-cyclodextrin complex with R-flurbiprofen. In the permethylated β-cyclodextrin–S-flurbiprofen complex, however, the phenyl group is disordered, and both R- and S-configurations are observed. The reason may be that permethylated β-cyclodextrin loosely includes only the phenyl group. On the other hand, β-cyclodextrin tightly binds R- and S-flurbiprofen, as indicated by the fact that the angle made by the two phenyl groups of biphenyl moiety, 33.2-40.0°, is significantly smaller than the biphenyl angle, 54.4°, of uncomplexed racemic flurbiprofen [8]. The biphenyl angle of permethylated β-cyclodextrin complexes is in the range 51.1-60.3°, which is in good agreement with the angle of uncomplexed racemic flurbiprofen. Being different from β-cyclodextrin, permethylated β-cyclodextrin does not form a complex with racemic flurbiprofen. Using the X-ray method, a crystal, obtained from a solution containing racemic flurbiprofen, was found to contain only the S-isomer [9].

The geometrical structure of the host-guest interaction of the permethylated α-cyclodextrin complex with L-mandelic acid differs from that of the D-mandelic acid complex. The comparison of the two structures suggests that the complex formation with D-mandelic acid induces the conformational change of the host molecule so as to accommodate the guest

molecule more suitably within the cavity. The shallow inclusion of L-mandelic acid may be ascribed to the following: (1) the formation of such a host-guest hydrogen bond as found in the D-mandelic acid complex is sterically hindered by methyl groups, and (2) the hydrogen-bond formation with water molecules outside the cavity prevents the phenyl group from penetrating deeply into the host ring. Permethylated α-cyclodextrin does not form a crystalline complex with racemic mandelic acid, as indicated by the fact that a crystal obtained in the presence of racemic mandelic acid contains only the L-isomer [9]. The complexes with D- and L-isomers seem to crystallize separately. These results suggests a possibility of resolving racemic mandelic acid and racemic flurbiprofen by utilizing the complex formation with permethylated cyclodextrins.

REFERENCES

1. W. L. Hinze, *Separation and Purification methods*, **10**, 159-237 (1981).
2. K. Harata, K. Uekama, M. Otagiri, and F. Hirayama, *J. Incl. Phenom.*, **1**, 279-293 (1984).
3. K. Harata, *Bull. Chem. Soc. Jpn.*, **55**, 1367-1371 (1982).
4. K. Uekama, T. Imai, F. Hirayama, M. Otagiri, and K. Harata, *Chem. Pharm. Bull.*, **32**, 1662-1664 (1984).
5. K. Uekama, F. Hirayama, T. Imai, M. Otagiri, and K. Harata, *Chem. Pharm. Bull.*, **31**, 3363-3365 (1983).
6. K. Harata, K. Uekama, M. Otagiri, and F. Hirayama, *Chem. Lett.*, **1983**, 1807-1810.
7. K. Harata, F. Hirayama, T. Imai, K. Uekama, M. Otagiri, *Chem. Lett.*, **1984**, 1549-1552.
8. J. L. Flippen and R. D. Gilardi, *Acta Crystallogr., Sect. B*, **31**, 926-928 (1975).
9. K. Harata, F. Hirayama, T. Imai, M. Otagiri, and K. Uekama, unpublished work.