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Structural Aspects of Stereodifferentiation in the Solid State

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I. Introduction

Cyclodextrins, a family of macrocyclic oligosaccharides, form crystalline inclusion complexes with a variety of guest materials.[1] The molecules have a large intramolecular cavity with a cylindrical shape, which is a major source of their complexing ability. Therefore, to be a guest, a molecule should fit into the cavity, even if only partially. It is generally recognized that the inclusion phenomena involve weak interactions, such as hydrogen bonds, electrostatic interactions, van der Waals forces, etc., instead of chemical bonding. Despite the large number of investigations which have been attempted to elucidate the nature of the complex formation, the mechanisms of molecular recognition and inclusion are still controversial. However, stereoselective discrimination during complex formation arises from the guest molecule's differing abilities to fit within the cavities of the cyclodextrins, and it is this spatial fit that is considered to be the most important factor regulating the complexation reaction.

Kazuaki Harata was born in Nagano, Japan, in 1948. He studied chemistry at the Nagoya University and received his M.S. degree in chemistry in 1972 and his Ph.D. degree in 1979 in the domain of crystallographic study of cyclodextrin complexes. From 1972 to 1992, he was a research chemist in the field of structural study of cyclodexytrin inclusion complexes in the Research Institute of Polymers and Textiles. In 1993, he moved to the National Institute of Bioscience and Human-Technology. Since 1994, he has been a Chief of the Biophysical Chemistry Laboratory in the Biomolecules Department. His scientific interests are X-ray diffraction analysis in relation to structural biology and biomimetic chemistry.

It is well-known that cyclodextrins catalyze chemical reactions[2] such as hydrolysis, oxidation, and substitution. Stereoselective acceleration is observed in these chemical reactions and has been investigated intensively in the cyclodextrin-catalyzed hydrolysis of phenyl esters. α-Cyclodextrin (α-CD) accelerates the hydrolysis of the *meta* isomer of disubstituted phenyl esters more than 100 times compared to the hydrolysis of the *para* isomers or *ortho* isomers for example.[3] This stereospecific catalysis has been attributed to differences in the binding modes of phenyl esters to α-CD, a hypothesis that has been supported by crystallographic studies.[4] A secondary hydroxyl group on α-CD is proposed to act as the catalytic center. Thus, regulation of the catalytic reaction has been suggested to depend on the inclusion geometry, such that the reaction is favored when the ester group of the substrate is at a distance where it is capable of being attacked by the secondary hydroxyl group.

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Table 1. Recent Crystallographic Studies on Cyclodextrin Inclusion Complexes

host	guest	ref
α-CD	hydroquinone (1:1) $6H_2O$	41
β-CD	ethylene glycol (1:2) $8H_2O$	51
	glycerol (1:2) $7.2H_2O$	51
	sulfathiazole (1:1) $8.3H_2O$	74
	Diclofenac sodium (1:1) $11H_2O$	58
	but-2-yne-1,4-diol (1:1) $7H_2O$	128
	calcium chloride (1:2) $11.25H_2O$	77
	menthol (2:2) $29H_2O$	125
	nonanic acid (2:1.6) $23.9H_2O$	129
ϵ-CD	$26.3H_2O$	26
ι-CD	$9H_2O$	27
dimethyl-α-CD	none	88
	H_2O	88
trimethyl-α-CD	none	94
dimethyl-β-CD	none	91
trimethyl-β-CD	H_2O	101
	ethyl laurate (1:1) $1.92H_2O$	109
	(*S*)-naproxen (1:1)	107
	menthol (1:1) $2H_2O$	126
	ibuprofen (1:1)	108
mono-6-azido-6-deoxy-α-CD	$6H_2O$	111
mono-2-*O*-allyl-α-CD	$4.36H_2O$	111
mono-(3-amino-3-deoxy)-α-CD	$5.5H_2O$	122
6-*O*-[(R)-2-hydroxypropyl]-β-CD	$10.3H_2O$	113
6-*O*-[(S)-2-hydroxypropyl]-β-CD	$12.0H_2O$	113
6^{A}-Boc-L-phenylalanylamino-6^{A}-deoxy-β-CD	nH_2O	118
6-deoxy-6-{4-[N-*tert*-butoxycarbonyl-2-aminoethyl]imidazolyl}-β-CD	$12H_2O$	119
6-deoxy-6-[(2-(4-imidazolyl)ethyl)amino-β-CD	Cu(II)(NO3)(L-tryptophanate (1:1) $15H_2O$	78
6^{I}-(6-aminohexyl)amino-6^{I}-deoxy-β-CD	$9.68H_2O$	115
6^{I},6^{II}-diamino-6^{I},6^{II}-dideoxy-β-CD	$16H_2O$	129
octakis(3,6-anhydro)-γ-CD	$14H_2O$	124
α-cycloaltrin	$21H_2O$	123

The stereoselective complex formation of cyclodextrins has been applied to various separation and purification procedures.[5] Cyclodextrins consisting of optically active D-glucose units are expected to be useful in the resolution of racemic compounds. Recently, a cyclodextrin-bonded silica gel column was used for chiral separations using HPLC.[6] Several investigations have also explored the selective precipitation of optically active compounds with cyclodextrins, and it has been found that precipitation with cyclodextrins effectively separates some racemic compounds. The optical purity of chiral sulfinyl compounds coprecipitated with β-cyclodextrin (β-CD) was generally less than 10%, but a high yield of 68.2% was achieved with isopropyl methanesulfinate.[7] Chiral recognition in the solid state depends not only on the host−guest interactions but also on the accommodation of the guest molecule in the chiral environment in the crystal.

X-ray crystallography has been a major source of information about the three-dimensional structure of the host−guest interactions. Single-crystal X-ray diffraction was first applied to α-CD and β-CD in 1942 by French and Rundle in order to determine their molecular weights.[8] James et al.[9] obtained crystallographic data for several α-CD complexes, and their low-resolution structural analysis of the iodine complex revealed the inclusion of iodine in the host macrocyclic ring. However, we had to wait until 1965 for a full X-ray structure, when Hybl et al. reported the structure of the α-CD complex with potassium acetate.[10] Since then, numerous crystal structures of cyclodextrins and their inclusion complexes have been determined, as summarized in several previous review articles.[11−14] Saenger[11] reviewed the crystallographic studies of cyclodextrin complexes reported prior to 1983. In a recent review by Harata,[14] crystal structures published before 1993 were compiled. These review articles outline the general features of crystallographic studies of cyclodextrin inclusion complexes. Here, we examine the crystal structures of cyclodextrin complexes for insight into their stereodifferentiation in the solid state. Table 1 lists structures reported in the last five years.

II. Characteristics of the Cyclodextrin Macrocyclic Structure

The shape and size of the cyclodextrin cavity are major determinants in stereoselective complex formation. Cyclodextrins consist of glucose unit building blocks which form the macrocycle and which are generally in the $^4C_1$ chair conformation, as shown in Figure 1. The structures of native cyclodextrins are fairly rigid due to intramolecular hydrogen bonds between the O-2H and the O-3H of adjacent glucose units. The cyclodextrin cavity has a hydrophobic character because the inside wall of the cavity is composed of many hydrogen atoms from the C-3H and C-5H methine groups and the C-$6H_2$ methylene groups. The cavity width of the macrocyclic structure is defined by a polygon composed of glycosidic O-4 atoms (Figure 1). The average radii of the O-4 polygons, which are the average values of the distances from the center of the polygons to each O-4, are 4.3, 5.0, and 5.9 Å in α-CD, β-CD, and γ-CD, respectively, while the side lengths fall in the range of 4.2−4.6 Å (Table 2). The macrocyclic ring is

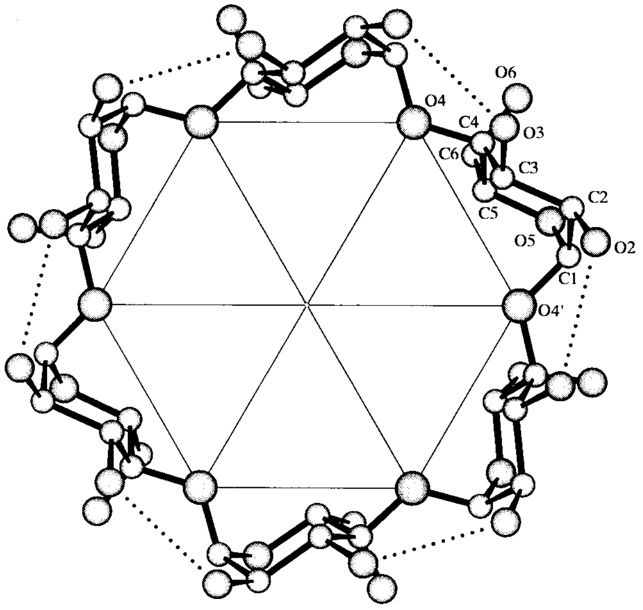


Figure 1. Structure of α-CD. The hexagon composed of the six glycosidic oxygen atoms is shown with thin lines. Dotted lines denote possible hydrogen bonds between the O-2H and O-3H of adjacent glucose units. Oxygen atoms are shaded.

distorted from an ideal *n*-fold symmetry in the crystalline state. The deviations from perfect symmetry are most easily seen as differences in inclinations of each glucose unit. To evaluate the relative inclination, the tilt-angle is defined as the angle made by the O-4 plane and a plane through the C-1, C-4, O-4, and O-4′ of each glucose unit. The average tilt-angle tends to increase as the number of glucose units increases. The inclusion of guest molecules by cyclodextrins is largely limited by their cavity size, but crystal packing is also important in creating the cavity in the solid state. This crystal packing is classified according to three categories: cage-type, channel-type, and layer-type.[14]

α-CD exhibits considerable distortion of its macrocyclic ring in the hexahydrate complex.[15] This is due to the large inclination of two glucose units which have their O-6 side toward the inside of the macrocycle. This large inclination allows these glucose units to form hydrogen bonds with included water molecules but interrupts the formation of intramolecular, interresidue hydrogen bonds. A related cyclomaltopentaose derivative has been synthesized,[16] but no structural data have been reported. The macrocyclic ring of α-CD is fairly symmetrical in the compexed state,[17] especially when the guest is bulky.[18] In the symmetrical structure of α-CD, six intramolecular hydrogen bonds are formed between adjacent glucose units but strain is imposed on the glycosidic angles (C1−O4′−C4′) as indicated by their relatively large values of 118−120°. In α-CD, the conformation of the pyranose ring is also affected by the cyclization, such that the distance between the O-4 and the O-4′ of the adjacent glucose unit is considerably shorter in the cyclic hexameric structures than in the average of corresponding noncyclic glucose oligomers.[19] This change reflects the accumulation of small changes in the endocyclic torsion angles of the pyranose ring, which are not accompanied by changes in the bond distances or angles. In the hydrated and distorted α-CD, the O-4···O-4′ distance increases, which relieves the strain at the O-4 linkage. However, in the complexed state, host−guest interactions compensate for the unfavorable increase in the strain energy.[20]

Table 2. Geometrical Data of Cyclodextrin Macrocycles

1. α-CD and Methylated α-CD

parameter	α-CD[a]	dimethyl-α-CD[b]	trimethyl-α-CD[c]
radius of the O-4 polygon (Å)	4.2 (0.1)	4.3 (0.1)	4.3 (0.2)
O-4···O4′ distance (Å)	4.2 (0.1)	4.3 (0.1)	4.3 (0.1)
O-2···O-3′ distance (Å)	3.0 (0.1)	3.0 (0.1)	3.4 (0.1)
planarity of the O-4 polygon (Å)[d]	0.10	0.11	0.13
glycosidic O-4 angle (deg)	119 (1)	119 (1)	118 (1)
tilt angle (deg)	13 (10)	15 (5)	18 (12)

2. *β*-CD and Methylated *β*-CD

parameter	*β*-CD[e]	dimethyl-*β*-CD[f]	trimethyl-*β*-CD[g]
radius of the O-4 polygon (Å)	5.0 (0.2)	5.1 (0.2)	5.0 (0.3)
O-4···O-4′ distance (Å)	4.3 (0.1)	4.4 (0.1)	4.3 (0.1)
O-2···O-3′ distance (Å)	2.9 (0.1)	2.9 (0.1)	3.5 (0.2)
planarity of the O-4 polygon (Å)[d]	0.16	0.09	0.44
glycosidic O-4 angle (deg)	118 (1)	117 (1)	117 (2)
tilt angle (deg)	14 (10)	14 (8)	20 (25)

3. *γ*-CD, *ϵ*-CD, and *ι*-CD

parameter	*γ*-CD[h]	*ϵ*-CD[i]	*ι*-CD[j]
radius of the O-4 polygon (Å)	5.9 (0.1)	6.9 (0.4)	8.4 (1.0)
O-4···O-4′ distance (Å)	4.5 (0.1)	4.5 (0.10)	4.5 (0.1)
O-2···O-3′ distance (Å)	2.8 (0.1)	3.2 (0.2)	2.9 (0.2)
planarity of the O-4 polygon (Å)[d]	0.11		
glycosidic O-4 angle (deg)	117 (1)	117 (1)	118 (1)
tilt angle (deg)	19 (9)		

[a] Reference 15. [b] Reference 89. [c] Reference 98. [d] Root-mean-square deviation of O-4 from their least-squares plane. [e] Reference 21. [f] Reference 93. [g] Reference 104. [h] Reference 22. [i] Reference 24. [j] Reference 25.

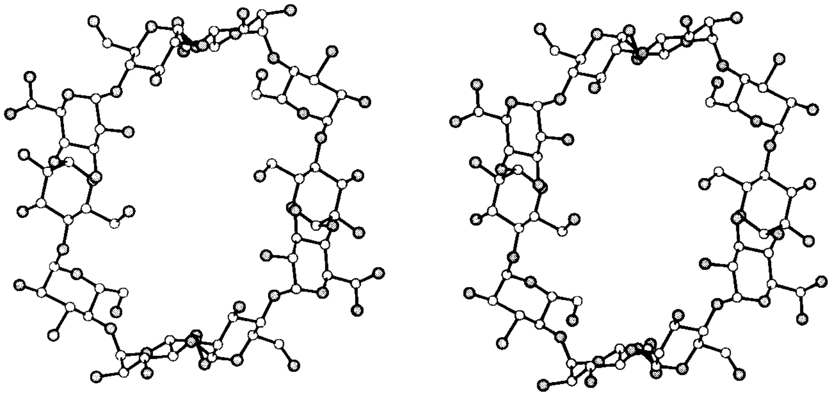


Figure 2. Stereodrawing of the structure of ϵ-CD. Oxygen atoms are shaded. The molecule, which consists of 10 glucose units, has a crystallographic 2-fold symmetry axis perpendicular to the plane.

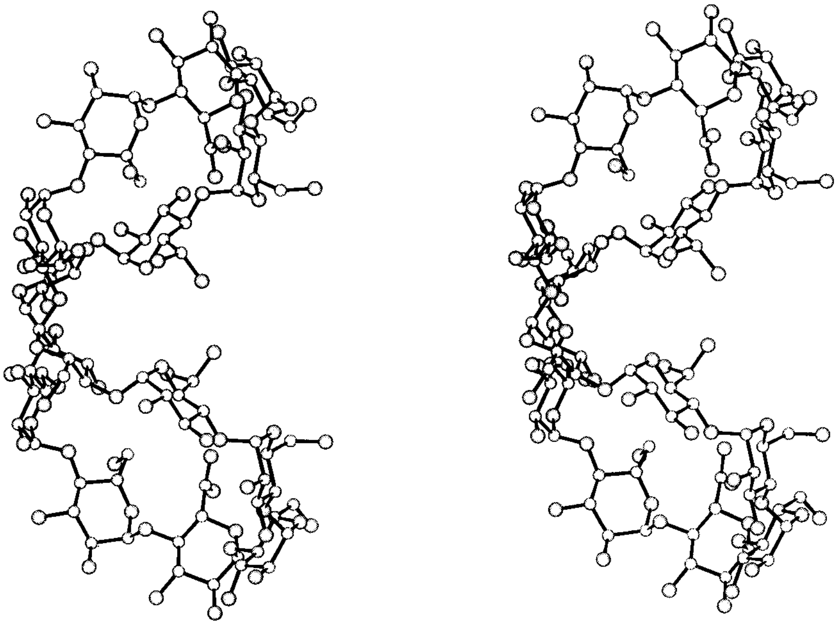


Figure 3. Stereodrawing of the structure of ι-CD. Oxygen atoms are shaded. The molecule consists of 14 glucose units and has a 2-fold crystallographic symmetry axis.

The macrocyclic rings of β-CD, with seven glucose residues, are more likely to approach *n*-fold rotational symmetry than are the rings of α-CD.[21] Its round structure is maintained by seven intramolecular hydrogen bonds between the O-2H and O-3′H of adjacent glucose units. Such hydrogen bonds impose restrictions on the inclination of the glucose units and maintain the tilt-angle at about 13°. The macrocyclic conformation of β-CD is not significantly affected by complex formation. However, the formation of a head-to-head dimeric structure has been frequently observed.[22] In the β-CD dimer, the secondary hydroxyl sides face each other and are linked by many hydrogen bonds to form a barrel-like structure. The dimer cavity has more than twice the volume of the monomer cavity and, thus, is able to include bulky guest molecules.

γ-CD, with eight residues, also forms a round structure which is maintained by intramolecular O-2⋯O-3′ hydrogen bonds.[23] The O-2⋯O-3′ distance between adjacent glucose units becomes shorter in the order α-, β-, and γ-CD, while the average tilt-angle of 14° is similar to that of β-CD. The average glycosidic O-4 angle of 117° is in good agreement with that of maltoside. In the crystalline complex, guest molecules in the γ-CD cavity tend to be disordered,[24] and only a few crystal structures have been reported.

Crystal structures of δ-, ϵ-, and ι-CD with 9, 10, and 14 glucose residues, respectively, have been determined. In these cyclodextrins, the macrocyclic ring is not round, despite the formation of intramolecular hydrogen bonds. The δ-CD's elliptical structure is warped to relieve the steric hindrance and distortion of the glycosidic linkage.[25] The more closely elliptical ring of ϵ-CD[24] is still twisted (Figure 2), and the ι-CD[27] molecule is folded into a saddle-like shape (Figure 3). These cyclodextrins have large cavities but show no evidence of the formation of inclusion complexes. ϵ-CD and ι-CD have 2-fold symmetry in the crystalline state. It is noteworthy that two glycosidic linkages in ϵ-CD and ι-CD connect glucose units with a trans-type arrangement not found in the other cyclodextrins or in noncyclic glucose oligomers. Usually adjacent glucose units form a cis-type arrangement where a hydrogen bond is formed between their O-2H and O-3H hydroxyl groups. In contrast, the adjacent glucose units in the trans-type arrangement form a hydrogen bond between their O-3H and O-6H hydroxyl groups. The cis-type arrangement is energetically more favorable;[28,29] however, the structures of ϵ-CD and ι-CD suggest that the trans-type arrangement is required to stabilize their macrocyclic conformation. Recently, cyclodextrins consisting of 17 or more glucose units have been produced by the action of potato D-enzyme.[30] No crystallographic study has been reported, but a molecular dynamic simulation suggests that it has a helically folded structure.[31]

III. Selective Inclusion by Native Cyclodextrins

A. α-Cyclodextrin

1. Cage-Type Packing Structure

In α-CD hexahydrate crystals, two of the water molecules are included in the cyclodextrin cavity.[14] α-CD forms stable crystalline complexes with 1-propanol,[17] methanol,[32] iodine,[33] krypton,[34] and other small molecules. When the guest is small enough to be fully included in the cavity, the α-CD molecules crystallize in a herringbone fashion (Figure 4), where both ends of the α-CD cavity are blocked by adjacent molecules. Because the guest molecule is enclosed within an isolated cavity, this type of packing is called “cage-type”. The secondary hydroxyl side of each α-CD is occluded by two additional α-CD molecules. Two pyranose rings from one of the α-CD molecules are related by a 2-fold screw symmetry parallel to the *b* axis, while the primary hydroxyl groups from another molecule are related by a *c* translation. The primary hydroxyl side of the α-CD contacts the primary hydroxyl groups of another molecule which is related to it by a screw axis perpendicular to the *bc* plane. It also contacts secondary hydroxyl groups related to it by a *c* translation.

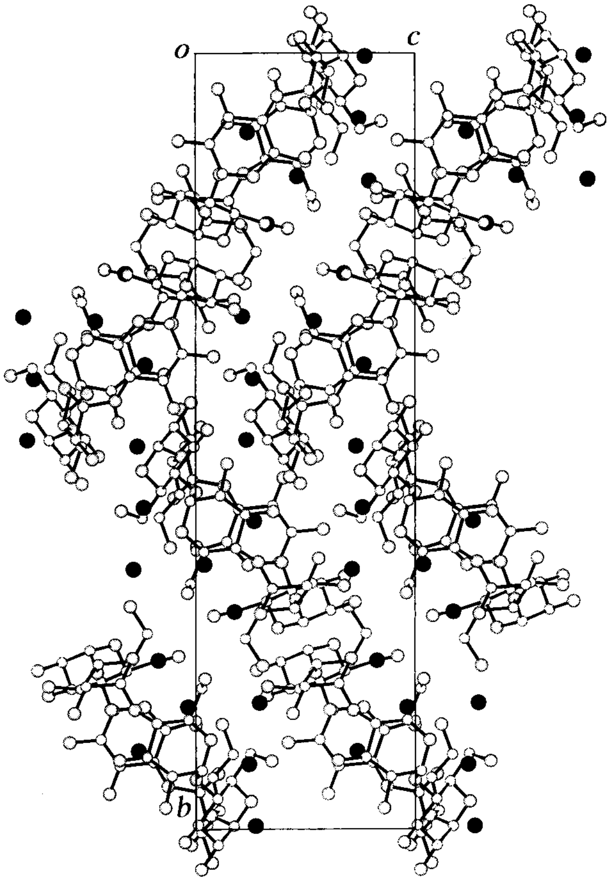


Figure 4. Crystal structure of α-CD hexahydrate viewed along the *a* axis. The space group is $P2_12_12_1$. The molecules are arranged in a herringbone fashion, forming a typical cage-type packing structure. The asymmetric unit contains six water molecules, drawn with filled circles, of which two water molecules are included in the α-CD cavity.

The largest guest which has been observed thus far is 3-iodopropionic acid.[35] The length of the 3-iodopropionic acid molecule coincides with the depth of the α-CD cavity. The carboxyl group located at the primary hydroxyl side of the α-CD forms hydrogen bonds with an adjacent α-CD host molecule. In contrast, the hydroxyl group of 1-propanol hydrogen bonds to a primary hydroxyl group on the host α-CD and to secondary hydroxyl groups on an adjacent α-CD.[17] These structures indicate that host−guest hydrogen bonding plays a crucial role in determining the orientation of a guest molecule in the cavity. Although iodine is smaller than 3-iodopropionic acid, its dumbbell shape allows it to be coaxially included and to fit snugly into the neck region of the cavity bearing the six C-5H methine groups. On the other hand, methanol and krypton are too small to occupy the entire space of the cavity. In the crystal structure, the methanol molecule is statistically disordered and alternately occupies two sites. The complex with krypton was crystallized from water at krypton pressures of 43 and 200 psi. At the higher pressure, the total occupancy of the krypton in the crystal reached 0.74. Krypton alternately occupies four sites in the α-CD cavity.

2. Channel-Type Packing Structure

In complexes of α-CD with ionic guests, channel-type packing is frequently observed. The α-CD molecules are stacked to form infinite columns in which guest molecules are linearly arranged. Because there are two possible arrangements of α-CD molecules, the column structure is classified into two types called “head-to-head” and “head-to-tail”. In the head-to-head structures, the secondary hydroxyl sides of both molecules are linked by many hydrogen bonds. The iodine−iodide ($I_2 \cdot I_3^-$) complex[36] forms a typical crystal, the structure of which is shown in Figure 5. This iodine−iodide complex crystallizes in four different forms, depending on the cation: one triclinic, one tetragonal, and two hexagonal. Structures of the triclinic and tetragonal crystals have been determined. In both the triclinic and tetragonal crystals, iodine and iodide alternate in the host channel to form a polyiodide chain, and the cations are located outside the column. In the tetragonal crystal, the α-CD ring is perpendicular to the channel axis, while it is inclined by about 7° in the triclinic crystal. The metallic luster of these crystals has been interpreted in terms of charge-transfer interactions along the polyiodide chain, and the complexes have been proposed as models for the blue starch−iodine complex.

The larger α-CD dimer cavity can include bulky molecules which cannot be accommodated in a single

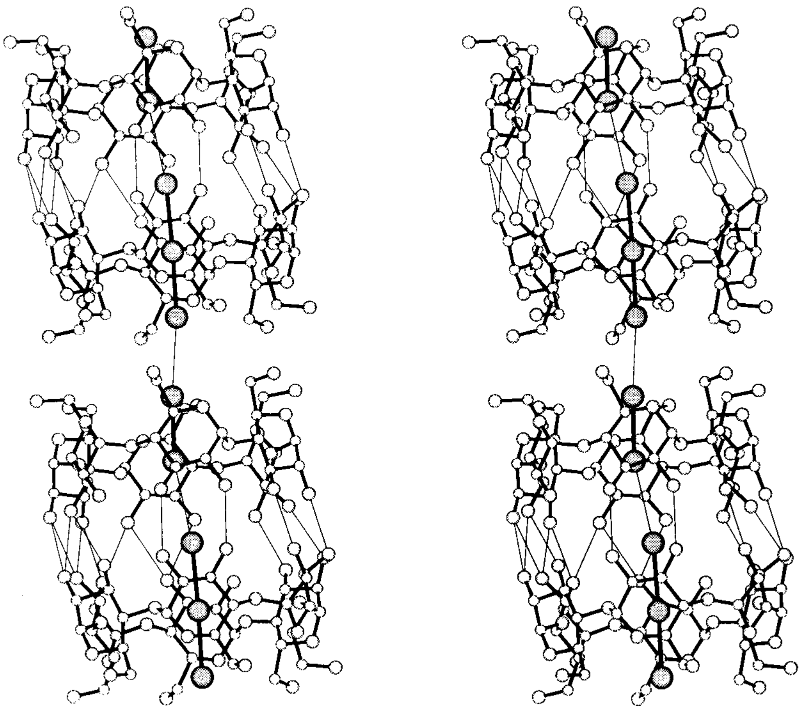


Figure 5. Stereodrawing of the structure of α-CD complexed with an iodine–iodide lithium salt. The α-CD molecules form head-to-head dimers having a barrel-like shape. Two α-CD molecules are linked by numerous hydrogen bonds between secondary hydroxyl groups, which are shown with thin lines. The dimer units are stacked to form a head-to-head channel-type structure. Iodine and I_3^- ions, which are shaded, are alternately arranged in the channel to form a linear polyiodide chain.

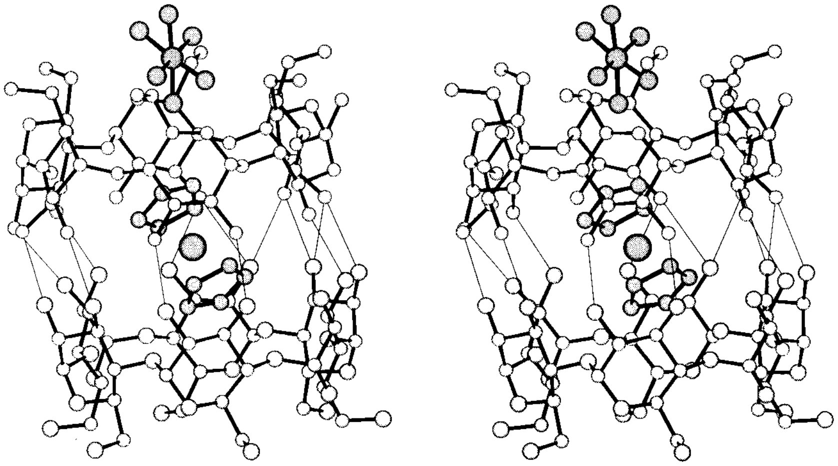


Figure 6. Stereodrawing of the structure of α-CD complexed with $[Rh(cp)_2]PF_6$. The guest molecule is shaded. Two α-CD molecules are linked by numerous hydrogen bonds (thin lines) between their secondary hydroxyl sides to form a head-to-head dimer. The $[Rh(cp)_2]^+$ ion is included in the barrel-like cavity. The PF_6^- ion is located on the primary hydroxyl side of one α-CD molecule.

α-CD cavity. Figure 6 shows the complex of α-CD with a metallocene,[37] in which the metal ion is located at the center of the dimer cavity and each of the two planar ligands is aligned with the secondary hydroxyl sides of their corresponding α-CD's. Details of the structure will be discussed in section D.

In the head-to-tail column structure, the repetition unit is a single α-CD molecule, and these are linked by hydrogen bonds between the primary hydroxyl groups on one molecule and the secondary hydroxyl groups on a neighboring molecule. This α-CD column can include a benzene ring which is aligned with its long axis parallel to the α-CD axis. Both monosubstituted and disubstituted benzenes are typical guest molecules in the channel-type structure, and the head-to-tail column accommodates benzaldehyde,[38] 1-phenylethanol,[39] *o*-fluorophenol,[40] *p*-fluorophenol,[40] hydroquinone,[41] *m*-nitrophenol,[4] and *m*-nitroaniline.[42] A comparison of these guest molecules indicates that the repetition unit coincides with the length of *p*-fluorophenol and hydroquinone. *p*-Disubstituted benzenes with larger substitutent groups do not form the head-to-tail channel-type structure. Except for 1-phenylethanol, the benzene ring of the guest molecules is located on the wider secondary hydroxyl side, while the polar groups of the guest form hydrogen bonds with primary hydroxyl groups on the next α-CD molecule. The *m*-nitroaniline complex shows that the nitrophenyl group can be fully included (Figure 7), but only partial inclusion is

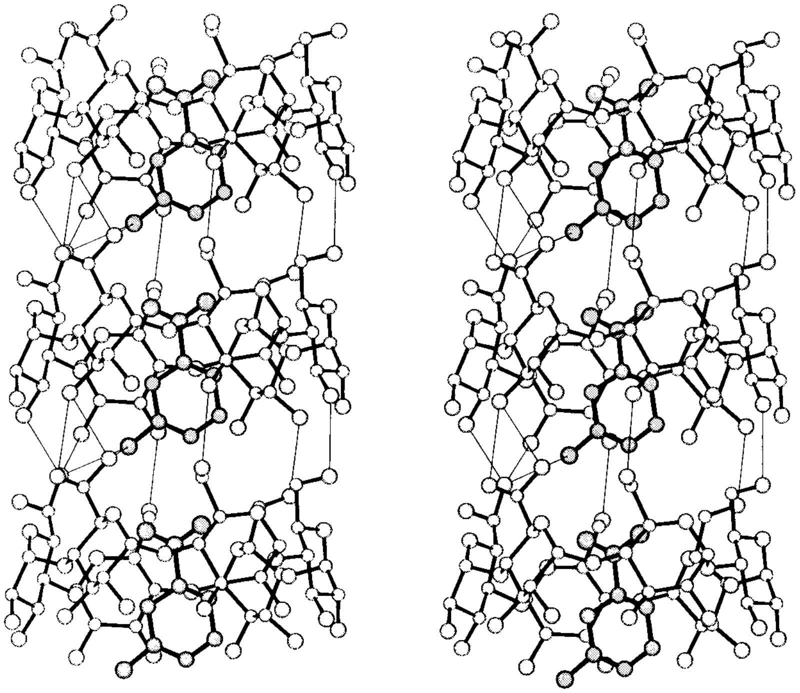


Figure 7. Stereodrawing of the structure of the α-CD−*m*-nitroaniline complex. The α-CD molecules are stacked to form a head-to-tail channel-type structure. Adjacent α-CD molecules are linked by hydrogen bonds (thin lines) between the primary hydroxyl groups and the secondary hydroxyl groups. The guest molecules are arranged in a head-to-tail mode in the channel. The nitrophenyl group is fully included in the α-CD ring. The amino group protrudes outside the ring and forms hydrogen bonds with primary hydroxyl groups on an adjacent α-CD molecule.

observed in the complex of α-CD with *m*-nitrophenol. This partial inclusion occurs such that the nitro group is inserted from the secondary hydroxyl side, while the nitro group of *m*-nitroaniline resides at the primary hydroxyl side with the C−N bond fitted to the neck of the cavity. The amino group is not included and protrudes from the secondary hydroxyl side where it hydrogen bonds with a primary hydroxyl group of the next α-CD molecule. In contrast, the carbonyl group of benzaldehyde protrudes from the secondary hydroxyl side even though it might be expected to be included in the same manner as the nitrophenyl group. The guest molecules that are *ortho* isomers are too bulky to penetrate the α-CD ring. For example, only half of the benzene ring of *o*-fluorophenol is accommodated through the secondary hydroxyl side. A comparison of the structures of *o*- and *p*-fluorophenol complexes suggests that the guest is oriented so that the fluorine atom can form a hydrogen bond with a primary hydroxyl group on a neighboring α-CD molecule.

The head-to-tail channel-type structure also has been found in complexes with ionic guests. In the potassium acetate complex,[10] an acetate ion is included at the primary hydroxyl side in such a way as to form hydrogen bonds with two primary hydroxyl groups. The vacant space of the cavity is filled by two water molecules. In complexes with benzenesulfonate[43] and 1-propanesulfonate,[44] the phenyl and propyl groups are inserted into the α-CD ring from the secondary hydroxyl side. The sulfonato groups form hydrogen bonds with primary hydroxyl groups on the next α-CD molecule. The mode of hydrogen bonding of the sulfonato group differs between these complexes because the conformation of the α-CD ring is changed by its interaction with the guest molecule. The sulfonato group of 1-propanesulfonate forms three symmetrical hydrogen bonds. In contrast, the α-CD ring of the benezenesulfonate complex is elliptical due to its inclusion of the planar ring on the benzenesulfonate. The sulfonato group also hydrogen bonds with four primary hydroxyl groups on the α-CD. The column structure can accommodate a long molecule which contacts two or more α-CD molecules. Methyl orange (sodium 4-[(4-(dimethylamino)phenyl)azo]benzenesulfonate) forms a 2:1 complex with α-CD, in which the organic anion penetrates through three α-CD rings.[45] The benzenesulfonate moiety is included in a manner similar to that observed with benzenesulfonate. The azo group fits into the neck of the α-CD cavity while the (dimethylamino)phenyl group is located at the same position as the nitrophenyl group in the *m*-nitrophenol complex.

3. Layer-Type Packing Structure

p-Disubstituted benzenes do not form the channel-type structure with α-CD because the length of the guest molecules does not match the length of the repetition unit in the host channel. *p*-Fluorophenol and hydroquinone are exceptions because they bear small substituent groups. As shown in Figure 8, α-CD molecules complexed to *p*-nitrophenol[46] are arranged in a brickwork pattern to form a “layer” structure. Adjacent layers are shifted by half a molecule. As a result, both ends of the cavity are open to the intermolecular space of the adjacent layer. The guest molecule is too large to be fully included in a single cavity but does fit in this expanded space. In the α-CD *p*-disubstituted benzene complexes, the benzene ring and one of the substituent groups are accommodated in the α-CD cavity. Generally, the substituent group (iodo,[18]

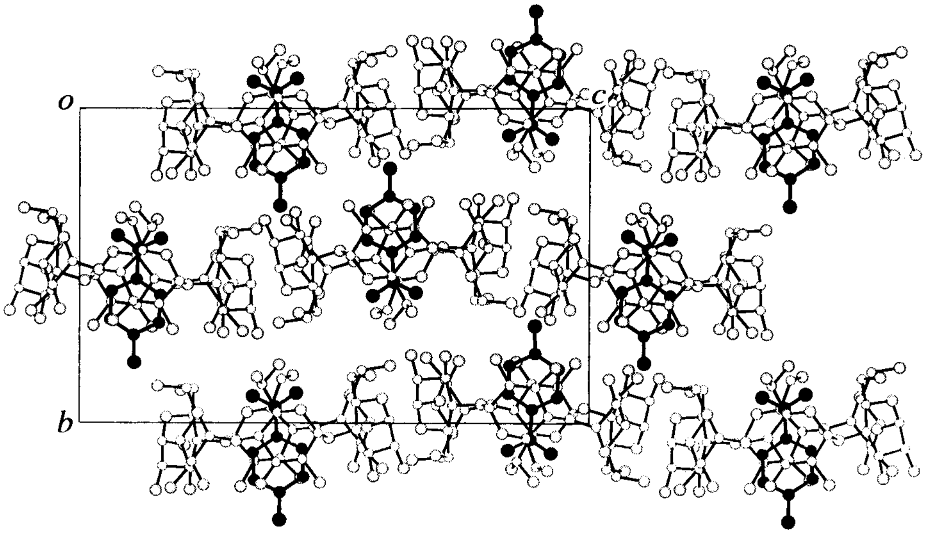


Figure 8. Crystal structure of α-CD complexed with *p*-nitrophenol, as viewed along the *a* axis. The space group is $P2_12_12_1$, and the molecules are arranged in a brickwork pattern which forms a layer-type structure. The guest molecules are shown with filled circles. The nitrophenyl group is included in the host cavity. The phenolic hydroxyl group protrudes from the secondary hydroxyl side of the CD where it contacts an adjacent layer.

nitro,[46] or carboxyl[46]) that produces the better spatial fit is included, but electrostatic forces and intermolecular hydrogen bonds also play important roles in the selection. In the *p*-nitrophenol complex, there are two possible inclusion geometries: one is inclusion of the nitrophenyl group and the other is inclusion of the hydroxyphenyl group. The crystal structure of the α-CD−*p*-nitrophenol complex has demonstrated that the nitrophenyl group is accommodated in the same manner as that of *m*-nitroaniline in its α-CD complex. It is clear that this selection produces the best spatial fit between the host and guest molecules. In α-CD, a circle composed of six C-5H methine groups forms a neck in the cylindrical cavity. The resulting cavity shape accommodates the nitrophenyl group better than the hydroxyphenyl group and the phenolic hydroxyl group protrudes from the secondary hydroxyl side where it hydrogen bonds with hydroxyl groups on the α-CD. A related structure has been observed for the complex of α-CD with hydroxybenzoic acid,[46] where the carboxyphenyl group is included in the host cavity.

N,*N*-Dimethylformamide[47] and 2-pyrrolidone,[47] which are both smaller than *p*-disubstituted benzenes, also form α-CD complexes having the layer-type structure. These guest molecules are almost fully included in the host cavity, and the intermolecular vacant space is filled with water molecules. The guest molecules are located at the secondary hydroxyl side and prevent cage-type packing by the host molecule. It is noteworthy that the layer-type structure is also formed when other small guest molecules are included. When the complex is crystallized in the presence of methanol and dimethyl sulfoxide, these molecules are simultaneously included.[48] This new complex crystallizes in the space group $P2_1$, not $P2_12_12_1$ as for the above complexes. The host cavity does not have enough space to fully accommodate methanol and dimethyl sulfoxide molecules; therefore, the methanol molecule is located at the primary hydroxyl side where it occupies the same position as in the α-CD−methanol complex. A methyl group of dimethyl sulfoxide protrudes from the secondary hydroxyl side, precluding cage-type packing.

B. β-Cyclodextrin

1. Cage-Type Packing Structure

In crystalline β-CD dodecahydrate, the water molecules included in the cavity are disordered.[21] The inside wall of the cavity is coated with hydrogen atoms which prohibit the water molecules from forming full hydrogen bonds. The β-CD cavity accommodates 6.5 water molecules distributed over 8 sites. Like α-CD, β-CD forms “cage-type” packing structures with small guest molecules such as hydrogen iodide,[49] methanol,[49] ethanol,[50] and ethylene glycol,[51] although their crystals have the $P2_1$ space group instead of $P2_12_12_1$. β-CD molecules are stacked along the 2-fold screw axis to form a herringbone pattern. One end of the cavity is occluded by an adjacent β-CD molecule which is related by screw symmetry, and the other end is blocked by a β-CD molecule which is related by a *b* translation. β-CD forms a 1:2 complex with hydrogen iodide. One I^- ion is included in the cavity but the other is located outside the cavity. In the 1:1 complex of β-CD with methanol, the guest molecule is too small to fill the cavity and water molecules are co-included. The stoichiometry of the β-CD−ethanol complex is 1:1, but the ethanol molecule is disordered in the cavity and alternately occupies two sites.

As shown in Figure 9, the β-CD complex with nicotinamide[52] also crystallizes in the cage-type structure. The β-CD cage is large enough to fully accommodate monosubstituted benzene or pyridine since its diameter is comparable to the length of the long axis of the benzene ring. In the β-CD cavity, the pyridyl group is included with its long axis perpendicular to the β-CD axis. The amido group is located at the primary hydroxyl side, forming hydrogen bonds with adjacent β-CD molecules. Although the β-CD complexed with benzyl alcohol has the same

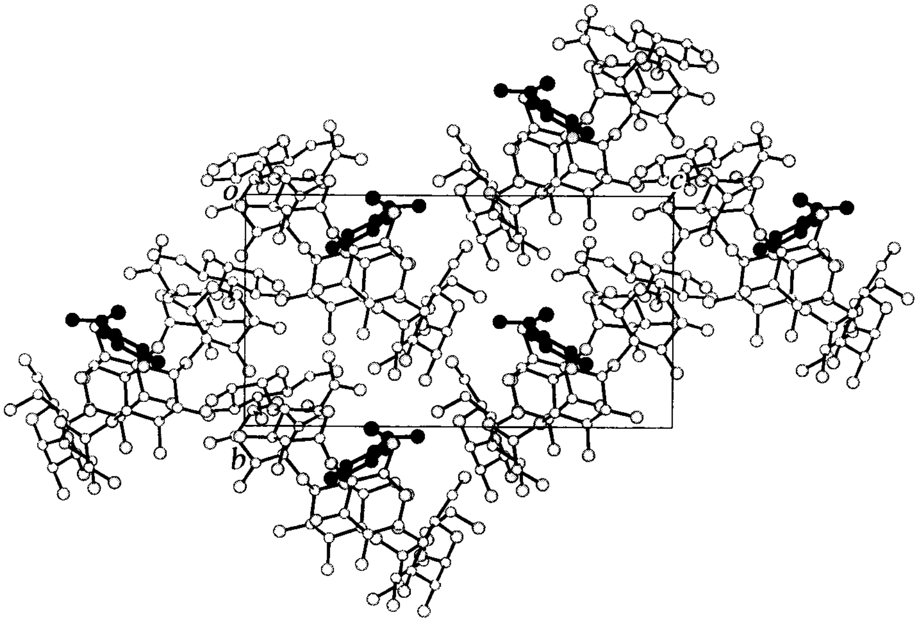


Figure 9. Crystal structure of β-CD complexed with nicotinamide, as viewed along the *a* axis. The space group is $P2_1$, and the β-CD molecules are arranged in a zigzag fashion to form a cage-type packing structure. The guest molecule, shown with filled circles, is fully included in the host cavity.

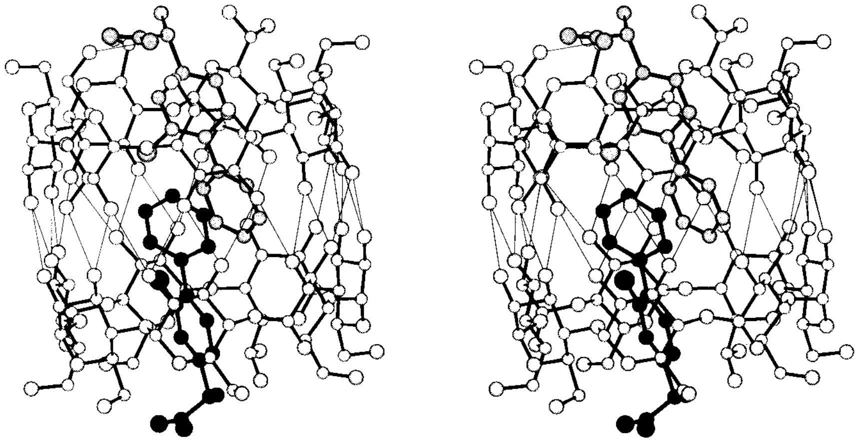
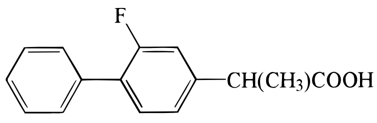


Figure 10. Stereodrawing of the structure of β-CD complexed with racemic flurbiprofen. The (*R*)-isomer of the guest is shaded, and the (*S*)-isomer is shown with filled circles. The β-CD molecules form head-to-head dimers, in which their secondary hydroxyl sides are linked by multiple hydrogen bonds (thin lines). A pair of (*R*)- and (*S*)-isomers of flurbiprofen is included in the barrel-like dimer cavity.

crystal packing as the β-CD−nicotinamide complex and the benzene ring is located at the same position as the pyridyl group, the substituent group of benzyl alcohol is located at the secondary hydroxyl side and forms hydrogen bonds with symmetry-related β-CD molecules.[53] The reason for this difference in the inclusion geometry is not clear, but a comparison of the crystal structures suggests that it results from differing host−guest hydrogen bonding as well as spatial fitting. The β-CD macrocycle is elliptically distorted in the benzyl alcohol complex. Conversely, the inclusion of a spherical hexamethylenetetramine molecule makes the host molecule symmetrical. This guest molecule is also fully accommodated in the cavity, since it is well suited to the round macrocycle.[54]

A head-to-head dimer structure is frequently observed for β-CD in crystalline complexes.[22] The dimeric structure is formed by face-to-face contact of the secondary hydroxyl sides of the β-CDs, which are linked by many hydrogen bonds in the same manner as in the α-CD dimer. An isolated dimer cage with a barrel-like shape is formed when the head-to-head dimer is arranged in a planar brickwork pattern. Each adjacent dimer layer is shifted by about half of a molecule such that both primary hydroxyl ends of the barrel are blocked by the primary hydroxyl groups of adjacent layers. The dimer cavity is more than twice as large as the cavity of a single molecule and can accommodate two or more guest molecules. β-CD forms 2:3 complexes with *p*-iodophenol[55] and 1-propanol[55] while flurbiprofen,[56,57] benzocaine,[58] ethyl cinnamate,[59] and 1-adamantanecarboxylic acid[60] form 2:2 complexes. In the 2:3 complexes, each β-CD molecule accommodates a guest molecule at its primary hydroxyl side, while the third guest molecule is sandwiched between the β-CD macrocycles. The β-CD dimer cavity can include two biphenyl moieties as demonstrated by the structure of the flurbiprofen (2-(2-fluoro-4-biphenylyl)propionic acid, Chart 1) complexes as shown in Figure 10. The 2-fluorobiphenyl

Chart 1



Flurbiprofen

moiety is longer than the depth of a single β-CD cavity, but in the dimer barrel, two fluorobiphenyl moieties pack head-to-head with the two phenyl groups facing each other at the center of the dimer cavity.[56] This arrangement allows the hydrophobic portions of the guest molecules to be enclosed in the cavity. The carboxyl groups located at the primary hydroxyl sides of the β-CDs form hydrogen bonds with those primary hydroxyl groups and/or with water molecules.

2. Channel-Type Packing Structure

Channel-type packing is formed in complexes of β-CD with a variety of guest molecules. However, except for the complex with diclofenac sodium (sodium 2-[(2,6-dichlorophenyl)amino]benzeneacetate),[61] only a head-to-head arrangement has been reported. In the crystal of the β-CD–diclofenac sodium complex, β-CD molecules are stacked head-to-tail along the 6-fold screw axis to form a helically extended tube. The guest molecule is situated between β-CD molecules rather than at the center of the β-CD molecule. The phenylene group is almost fully included at the primary hydroxyl side, and the carboxyl group is hydrogen-bonded to a primary hydroxyl group on the β-CD. Since the β-CD cavity is too small to admit the dichlorophenyl group, formation of the head-to-head dimer is not favored.

In crystals with a space group of *P*1 or *C*2, the dimer units of β-CD are stacked nearly linearly along the channel, but in crystals with a space group of $P2_1$, the β-CD dimer is arranged along a zigzag line. The guest molecules, iodine–iodide,[62] *m*-iodobenzoic acid,[63] *p*-nitroacetanilide,[64] benzocaine,[65] 4-*tert*-butyltoluene,[66] and 3,3-dimethylbutylamine,[67] form crystalline complexes with the former space groups, while *p*-iodoaniline,[68] *p*-ethylaniline,[68] benzil,[69] carmofur,[70] and fenoprofen[71,72] form crystals with the latter space group. Figure 11 shows the structure of the iodine–iodide ($I_2{\cdot}I_2{\cdot}I_3^-$) complex.[62] The iodine–iodide unit is included in the channel, but in contrast to the α-CD complex, the iodine–iodide chain is broken to form a zigzag arrangement of two iodine molecules and one iodide ion. This arrangement is necessary to fill the large diameter channel cavity. The *m*-diiodobenzoic acid complex[60] crystallizes in the same packing structure, but the guest molecules are disordered and only some iodine sites are observed in the channel. Disordered guest molecule have also been observed in complexes of β-CD with benzocaine and *tert*-butyltoluene. In 2:2 complexes of β-CD with substituted benzenes, the guest molecules are arranged head-to-head in the cavity of the dimer unit. The arrangement of guest molecules in the crystals with space group *C*2 does not exhibit 2-fold symmetry due to their disorder. The lattice framework is formed by the β-CD, and the guest molecule occupies two or more possible sites in the host column.

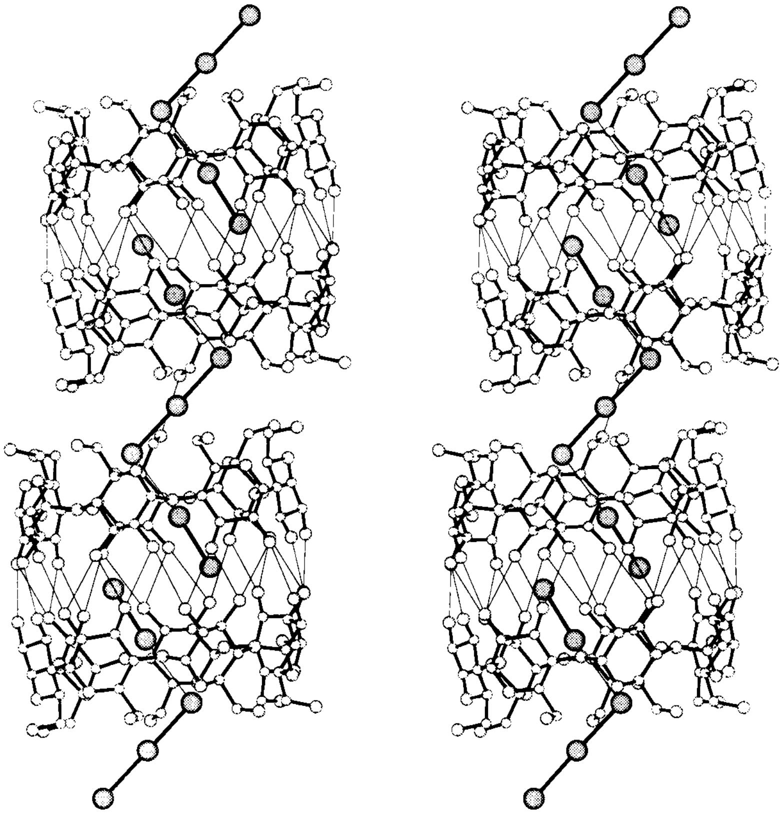


Figure 11. Stereodrawing of the structure of β-CD complexed with $I_2{\cdot}I_2{\cdot}I_3^-$. The β-CD molecules form head-to-head dimers, which stack to form a channel-type structure. The guest I_7^- ion is arranged in a zigzag fashion.

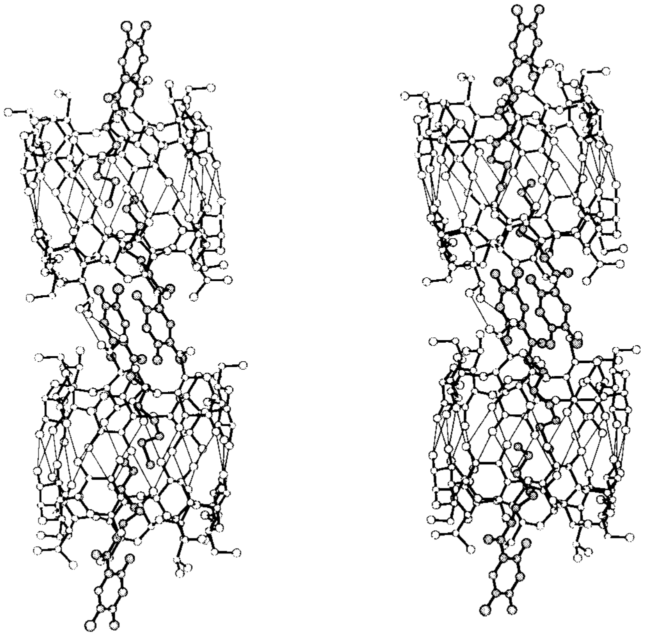
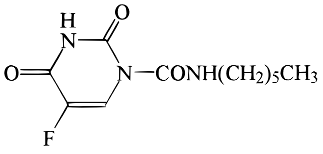


Figure 12. Stereodrawing of the structure of β-CD complexed with carmofur. The β-CD molecules form dimers which are held together by multiple hydrogen bonds (thin lines) between their secondary hydroxyl sides. The dimers are arranged in a zigzagged, channel-type structure. Only one direct hydrogen bond is formed between adjacent dimer units. The guest molecules are shaded. The hexyl group of the guest penetrates into the β-CD cavity from the primary hydroxyl side. The fluorouracil moiety is located outside of the β-CD ring where it is face-to-face with another fluorouracil moiety related to it by pseudo 2-fold symmetry.

Figure 12 shows the structure of the β-CD complex with carmofur (1-(*n*-hexylcarbamoyl)-5-fluorouracil, Chart 2). The β-CD dimer is arranged to form a zigzagged channel. The space group is $P2_1$, but the crystal has pseudo $C222_1$ symmetry. The guest molecule is too large to be accommodated, even by the dimer cavity. The hexyl group penetrates the β-CD cavity from the primary hydroxyl side, while the 5-fluorouracil moiety is located outside the dimer cavity where it is stacked face-to-face with each pair related by pseudo 2-fold symmetry. The location of the fluorouracil moiety at the primary hydroxyl side extends between the dimer units. These units are directly linked by a hydrogen bond between the primary hydroxyl groups. In their complexes with β-CD, the guest molecules iodoaniline, ethylaniline, and fenoprofen are almost fully included in the dimer cavity. Therefore, the dimer units in these complexes are more closely stacked than in the carmofur complex, resulting in a 32 Å cell dimension along the channel in the fenoprofen complex, compared to 35 Å in the carmofur complex.

Chart 2

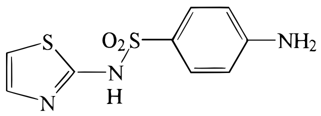


Carmofur

3. Layer-Type Packing Structure

A layer structure similar to that of α-CD is observed in complexes of β-CD with triethylenediamine[70] and sulfathiazole (*N*-(2-thiazolyl)sulfanilamide, Chart 3) as shown in Figure 13.[74] The space group of the crystals is $P2_1$, and their β-CD packing is different than that observed in the α-CD complexes with space group $P2_12_12_1$. The β-CD ring is slightly inclined against the layer plane, which is perpendicular to the screw axis, and the triethylenediamine molecule is fully enclosed in the cavity. The interlayer space of the crystals is filled with water molecules. In the sulfathiazole complex, the aminophenyl group penetrates from the secondary hydroxyl side through to the other end of the cavity. The thiazole moiety, which protrudes from the secondary hydroxyl side, is sandwiched between the two layers. Both ends of the β-CD cavity are nearly closed by the β-CD molecules in the adjacent layer which is different from the layer structure observed for α-CD. Part of the guest molecule is accommodated in the interlayer space rather than being included in the cavity.

Chart 3



Sulfathiazole

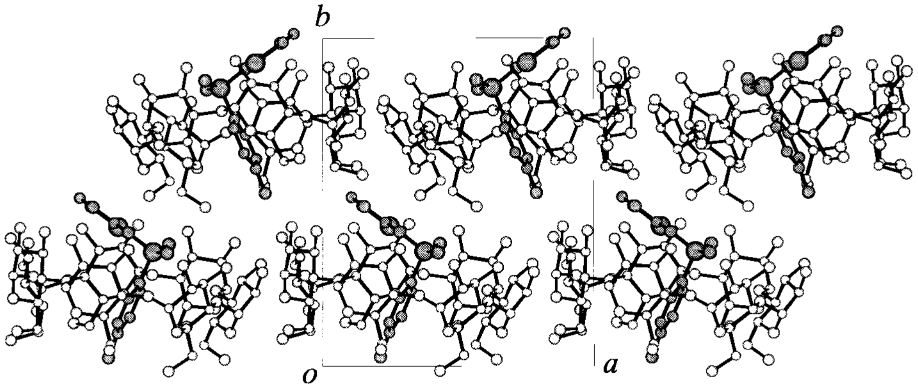


Figure 13. Crystal structure of β-CD complexed with sulfathiazole, as viewed along the *c* axis. The β-CD molecules are arranged parallel to the *ac* plane and form a layer-type structure.

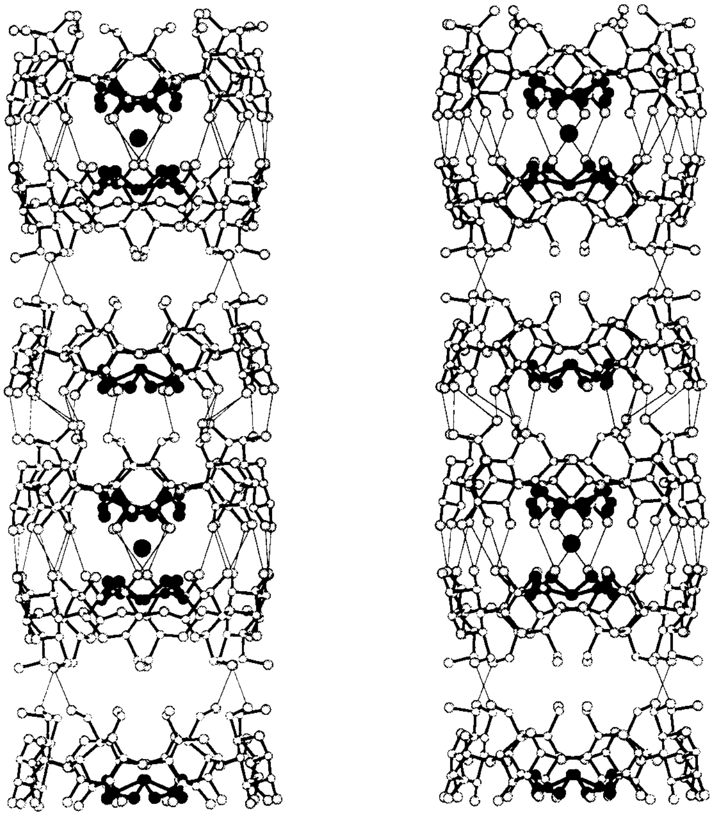


Figure 14. Stereodrawing of the structure of γ-CD complexed with potassium 12-crown-4. The γ-CD molecules are stacked to form a channel-type structure. The repetition unit in the column consists of three γ-CD molecules. Two γ-CD molecules form a head-to-head dimer, which includes the potassium 12-crown-4 (1:2) complex as shown by the filled circles. The third γ-CD molecule, which includes a metal-free 12-crown-4 molecule, is attached to the dimer in a head-to-tail mode.

A layer structure composed of head-to-head dimer units of β-CD is observed in its complex with 4-*tert*-butylbenzyl alcohol.[22] Adjacent layers are shifted so that the primary hydroxyl ends of the dimer cavity are open to the intermolecular space. The space group is $C222_1$, and the dimer unit has 2-fold crystallographic symmetry. The bulky *tert*-butylphenyl group is fully accommodated in the barrel-like cavity, where the *tert*-butyl groups related by 2-fold symmetry face each other at the center. The hydroxymethyl group of the guest protrudes from the primary hydroxyl end and forms hydrogen bonds with the β-CD in the next layer. The area sandwiched between the two β-CD molecules in the dimer is fairly hydrophobic. The secondary hydroxyl groups hydrogen bond between adjacent glucose units and/or between β-CD molecules to form a dimer, but hydrogen bonds with an included guest have not been observed. On the other hand, the primary hydroxyl group has conformational flexibility and hydrogen bonds with the included guest as well as with adjacent β-CD and water molecules. These hydrogen-bonding characteristics exhibited by the host hydroxyl groups seem to be a crucial factor in determining the guest orientation. When the primary hydroxyl groups form hydrogen bonds between the dimer units as seen in the channel-type structure, they point away from the center of the cavity. As a result, the guest molecule has more freedom in the channel-type structure than in the cage-type or layer-type structure and is disordered within the channel.

C. γ-Cyclodextrin

γ-CD complexes crystallize in two crystal forms: cage-type and channel-type. The cage-type structure is only observed in the hydrate crystal.[23] The γ-CD cavity is so large that two glucose units from an adjacent molecule are partly inserted from the secondary hydroxyl side, making the cavity space narrower than expected for the size of the macrocycle. In the cavity, 7.1 water molecules are distributed over 14 sites. When it is complexed, γ-CD forms a channel-type structure in which it has 4-fold symmetry. The inside cavity of the column is so large that an included 1-propanol molecule could not be detected because of its statistical disorder or diffusive motion.[24] This disorder or motion was indicated by the low occupancy factors in the range of 0.15−0.61 which were obtained for water molecules. In the asymmetric part of the cavity, 3.1 water molecules occupy 8 sites. The crown ether complexes of γ-CD (Figure 14) also form isomorphous crystals, in which 12-crown-4 and its lithium and potassium complexes are included within the γ-CD column.[75] The structures of these complexes are discussed in the next section.

D. Complex with Metals and Organometals

1. First Sphere Coordination

Cyclodextrins form crystalline complexes with metal ions. When β-CD is crystallized in the presence of KOH[76] or $CaCl_2$,[77] metal cations are incorporated in

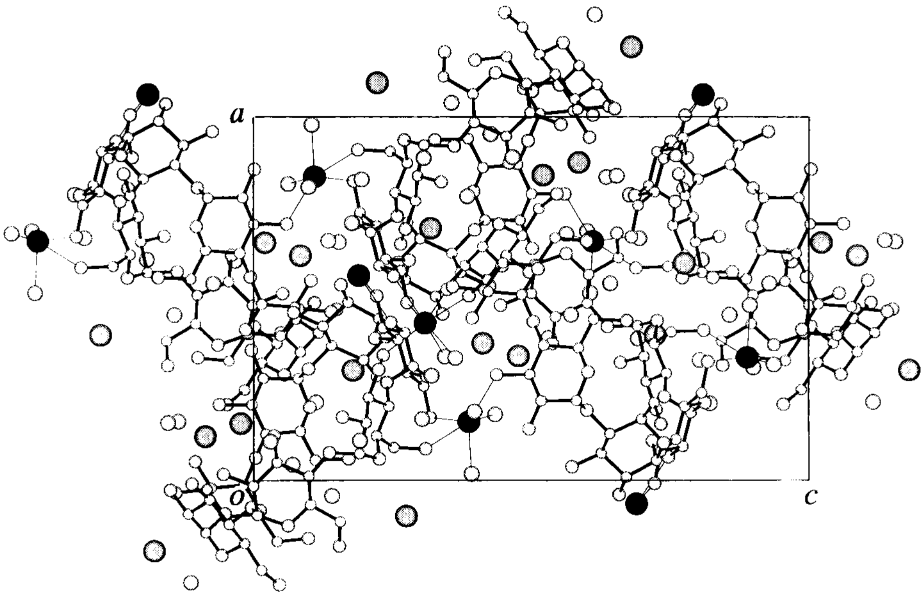


Figure 15. Crystal structure of β-CD complexed with $CaCl_2$, as viewed along the *b* axis. The space group is $P2_12_12_1$. The calcium ions are shown by filled circles, and the chloride ions are shaded. The thin lines denote short contact distances to involving the calcium ion.

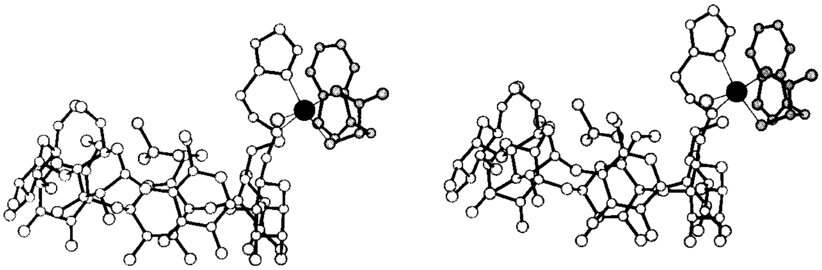


Figure 16. Stereodrawing of the structure of 6-deoxy-6-[(2-(4-imidazolyl)ethyl)amino]-β-CD complexed with $[Cu(II)NO_3]^-$ and L-tryptophanate. The copper ion is shown with a filled circle. L-Tryptophanate, the nitrate, and a coordinated water molecule are shaded. The thin lines denote short contact distances to the copper ion.

the crystal and directly contact hydroxyl oxygens on β-CD. Therefore, the structure has "first sphere" coordination. The β-CD complex with potassium hydroxide (1:1) crystallizes in a form which is isomorphous with the dodecahydrate crystal. The potassium ion is incorporated in an interstitial site and is coordinated to six oxygen atoms which belong to four different β-CD molecules. The packing of the β-CD molecules is not significantly affected by the potassium coordination. The distance of 2.7−3.0 Å between the potassium ion and the coordinated oxygen atoms is similar to the hydrogen-bonding distance between hydroxyl groups or water molecules. Therefore, a water molecule can be replaced by a potassium ion in the complex.

It is well-known that sugars form crystalline complexes with calcium ions. β-CD forms a 1:2 complex with $CaCl_2$, in which Ca^{2+} and Cl^- ions are distributed outside of the β-CD cavity. Two water molecules are accommodated within the β-CD cavity (Figure 15). The complex crystallizes in the space group $P2_12_12_1$, and the β-CD molecules are arranged in a zigzag mode along a 2-fold screw axis. Compared to the potassium hydroxide complex, the β-CD molecules in the calcium chloride complex are loosely packed. Eight oxygen atoms from various water and hydroxyl groups are coordinated to each calcium ion, while the chloride anions form three or four hydrogen bonds with hydroxyl groups and water molecules. The presence of divalent cationic salts in the crystal leads to an absence of disorder, particularly in the population and position of water sites. The divalent cation and the chloride anions directly interact with β-CD, but there is no direct contact between the ions.

The introduction of an ionic substitutent on a cyclodextrin enhances its metal binding ability. The imidazole-appended β-CD forms a ternary complex with a copper(II) ion and L-tryptophanate[78] as shown in Figure 16. The Cu(II) ion is located outside of the β-CD near its primary hydroxyl side. The 6-amino and imidazolyl groups of the host molecule and the carboxyl and amino groups of L-tryptophanate are coordinated to the metal cation. The four coordinated atoms form a square plane which is parallel to the indolyl moiety of L-tryptophanate. In addition, a water molecule is coordinated from the other side of the indolyl group to form a square pyramid. The imidazole and indole rings are directed into the cavity of an adjacent β-CD moiety from its secondary hydroxyl side, forming a polymeric structure which extends along a screw axis. A nitrate anion is located at the primary hydroxyl side of the cavity and hydrogen bonds to hydroxyl groups on adjacent β-CD moieties.

The metal ions Li^+, Na^+, K^+, and Cd^{2+} are also observed in the crystal structures of α-CD complexes with anionic guests such as iodine−iodide, methyl orange, benzenesulfonate, and propanesulfonate. They are located in the intermolecular space between cyclodextrin molecules and are coordinated to the hydroxyl groups of cyclodextrin and/or water molecules.

2. Second Sphere Coordination

In complexes of cyclodextrins with organometallic guests, the organic ligands are included in the cyclodextrin cavity. This phenomenon is demonstrated by Rh compounds[79] in α-CD complexes and Pt compounds[80] in β-CD complexes. The metal ion has no direct contact with the cyclodextrins, and the interaction therefore is called "second sphere" coordination. Some earlier work in this area has been reviewed by Stoddart et al.[81] A 1,5-cyclooctadiene molecule which is coordinated to Rh is partly inserted into the α-CD cavity from the secondary hydroxyl side. Additional stabilization is derived from hydrogen-bonding interactions between the amine ligands on Rh and secondary hydroxyl groups on the α-CD. A similar structure has been observed in the α-CD complex with carboplatin (cyclobutene-1,1′-dicarboxylatodiammineplatinum(II)),[82] where the cyclobutene ring is inserted into the α-CD cavity and the two amine ligands form hydrogen bonds with the secondary hydroxyl groups on the α-CD.

Crown compounds and metallocenes are also typical guest molecules in cyclodextrins. In α-CD complexes with metallocenes,[37,83] two α-CD molecules form a head-to-head dimer. Klingert and Rihs have reported many crystalline complexes of α-CD and β-CD with metallocenes.[84,85] α-CD complexes crystallize in either the $P1$ or $P3_2$ space group. In complexes with the $P1$ space group, the α-CD dimers are linearly stacked to form a head-to-head channel-type structure. The metal ion is sandwiched between the two ligands in the dimer cavity and has no direct contact with the α-CD. The metallocene axis does not coincide with the α-CD dimer axis but instead, the cyclopentadienyl groups are rotated around the metal ion (Figure 6). The PF_6^- ion is partly inserted into the α-CD from its primary hydroxyl side. In crystals with the space group $P3_2$, the α-CD dimers are arranged along a 3-fold screw axis to form a helically extended channel-type structure. The host−guest interaction is basically the same as in the $P1$ crystal. The metallocene is located at the center of the dimer cavity, and the PF_6^- anion is sandwiched between the α-CD dimer units at their primary hydroxyl side. However, the repetition unit length of 16.8 Å in the $P3_2$ crystal is longer than 15.6 Å observed in the $P1$ crystal. Because they are farther apart from each other, adjacent α-CD molecules are loosely stacked along the channel.

In the γ-CD complex with potassium 12-crown-4 (Figure 14),[72] the crown ring has direct contact with the γ-CD while the potassium cation is sandwiched between two 12-crown-4 molecules. The guest molecule has 4-fold symmetry, and the metal cation is located on the symmetry axis. The repetition unit of the column consists of three γ-CD molecules, two of which form a head-to-head dimer, while the third is attached to the O-6 side of the dimer in a head-to-tail mode. The dimer cavity accommodates a 2:1 complex of the 12-crown-4 and the metal cation, while the third γ-CD includes a metal-free 12-crown-4 molecule. Changing the cation from K^+ to Li^+ does not affect the crystal packing. However, the 12-crown-4 molecule in the potassium complex is more deeply included in the γ-CD cavity because of the longer distance between the 12-crown-4 molecule and the potassium ion.

IV. Modified Cyclodextrins

A. Methylated Cyclodextrins

A large number of modified cyclodextrins have been synthesized in an attempt to alter or improve their inclusion properties and also to induce biomimetic functioning.[86] Methylation is the simplest modification, and the inclusion properties of methylated cyclodextrins have been extensively investigated. Because of the differences in reactivity between O-2H, O-3H, and O-6H hydroxyl groups, two types of methylated cyclodextrins have been prepared.[87] In per(2,6-di-*O*-methyl)cyclodextrins (dimethyl-CD), all O-2H and O-6H hydroxyl groups are methylated. Further methylation of all of the O-3H hydroxyl groups produces per(2,3,6-tri-*O*-methyl)cyclodextrins (trimethyl-CD). The macrocyclic structure of dimethyl-CD is round due to its intramolecular O-3H···O-2 hydrogen bonds. The attached methyl groups are aligned in rings at both ends of the molecular cavity, thus increasing the depth of the cavity by ca. 2 Å. Because of this change in cavity size, guest molecules are included differently than in complexes of native cyclodextrins.

1. Hexakis(2,6-di-O-methyl)-α-cyclodextrin

Dimethyl-α-CD crystallizes in two forms from water.[88] One form is obtained at room temperature and has a "cage"-type packing structure similar to that of β-CD. The other crystal is prepared near the boiling temperature of water. The macrocyclic conformation of dimethyl-α-CD is nearly the same in both crystals and is also similar to the conformation of native α-CD, except for the methyl groups. The former, "cage", crystal contains one water molecule in the α-CD cavity, while the latter crystal contains no water. Instead, the crystal formed at high temperature has a methoxyl group from an adjacent molecule inserted into the α-CD cavity from its secondary hydroxyl side. Dimethyl-α-CD forms 1:1 complexes with 1-propanol and with iodine.[89] These crystals have a space group of $P2_1$, with the dimethyl-α-CD molecules arranged in a herringbone fashion similar to the packing in the β-CD cage-type structure (Figure 17). Because the cavity is deeper than that of α-CD, guest molecules within the dimethyl-α-CD are shifted to the secondary hydroxyl side of the cavity relative to their position in the α-CD complexes. Both the dark brown color of the crystalline dimethyl-α-CD−iodine complex and the short contact distance between the iodine molecule and a

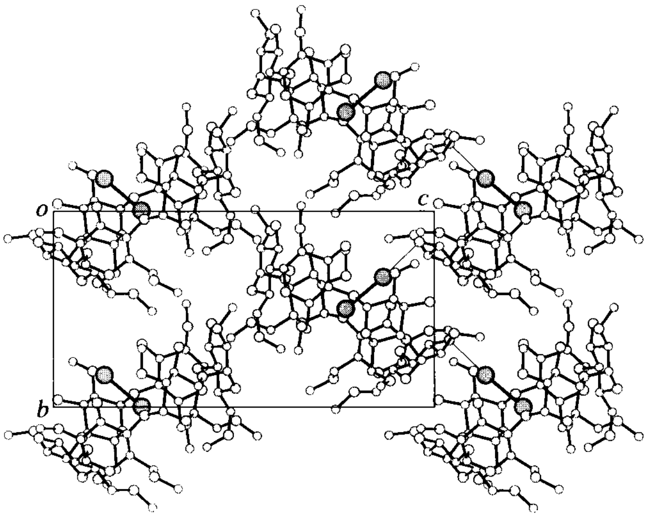


Figure 17. Crystal structure of dimethyl-α-CD complexed with iodine, as viewed along the *a* axis. The space group is $P2_1$. The dimethyl-α-CD molecules are arranged in a zigzag fashion to form a cage-type packing structure. The iodine molecules are shaded. The thin lines denote a short contact distance between the iodine atom and an O-3H hydroxyl group on an adjacent dimethyl-α-CD molecule.

hydroxyl group on an adjacent dimethyl-α-CD suggest the formation of a crystalline charge-transfer complex. The complex of dimethyl-α-CD with 3-iodopropionic acid crystallizes in the same space group, $P2_12_12_1$, as the α-CD complex and, therefore, in the same cage-type packing structure. However, 3-iodopropionic acid is included upside down in the dimethyl-α-CD cavity relative to its position in the α-CD cavity.[90] The carboxyl group which is located at the secondary hydroxyl side is hydrogen bonded to a hydroxyl group on an adjacent dimethyl-α-CD molecule. This hydrogen bond is possible because the secondary hydroxyl side is blocked by the side of the dimethyl-α-CD ring. In contrast, the primary hydroxyl side of the cavity is occluded by many methyl groups from two symmetry-related dimethyl-α-CD molecules. These factors cause the guest molecule to be oriented so that the carboxyl group can form a hydrogen bond with an adjacent dimethyl-α-CD molecule.

2. Heptakis(2,6-di-O-methyl)-β-cyclodextrin

Dimethyl-β-CD crystallizes from water with a packing structure similar to that of the dimethyl-α-CD crystal that is formed at high temperature.[91] The round macrocyclic conformation of dimethyl-β-CD is maintained by intramolecular O-3H- - -O-2 hydrogen bonds. The three O-6CH$_3$ methyl groups are directed toward the molecular axis such that the cavity is closed at the O-6 end. No water molecules have been identified in the cavity; instead, the remaining volume of the bowl-shaped cavity is occupied by an O-6 methoxyl group from an adjacent molecule, which is related to the first by a 2-fold screw symmetry. Therefore, even if water molecules occupy the cavity when the compound is in solution, they should be repelled by this methoxyl group during the course of crystallization.

The dimethyl-β-CD cavity accommodates 2-naphthoic acid within the O-6 side of the cavity (Figure 18).[89] The naphthyl group is inserted lengthwise and makes an angle of about 30° with the dimethyl-β-CD axis. The carboxyl group protrudes from the O-6 side of the dimethyl-β-CD and forms a hydrogen bond with a water molecule. The crystal packing is similar to that of uncomplexed dimethyl-β-CD. Two methoxyl groups of an adjacent dimethyl-β-CD are inserted from the secondary hydroxyl side of the cavity, thus, occupying its vacant space. Conversely, dimethyl-β-CD molecules in the complex with carmofur[70] are arranged to form a layer similar to that found in the β-CD complex with triethylenediamine. The guest molecule is 2-fold disordered and exhibits different conformations and dispositions. The hexyl group of carmofur having the higher occupancy penetrates the host cavity from the secondary hydroxyl side, while the fluorouracil moiety is located in the intermolecular space between the molecular layer. The hexyl group with the lower occupancy is excluded from the dimethyl-β-CD cavity and resides as a U-shaped molecule in the interlayer space. In both β-CD and dimethyl-β-CD complexes of carmofur, only the hexyl group is included in the host cavity. The slender, hydrophobic hexyl group fits in the cavity better than the bulky fluorouracil moiety.

In dimethyl-β-CD complexes with *p*-iodophenol and *p*-nitrophenol,[93] the guest molecule is found not in the host cavity, but in the intermolecular space as shown in Figure 19. The host cavity includes water molecules and a methoxyl group from an adjacent molecule. A chain of hydrogen bonds involving water molecules passes through the host cavity. The intermolecular space in the dimethyl-β-CD crystal is hydrophobic unlike that of native β-CD, because of the many methyl groups of dimethyl-β-CD. Therefore, a guest molecule can be favorably accommodated in the interstitial site when its shape and

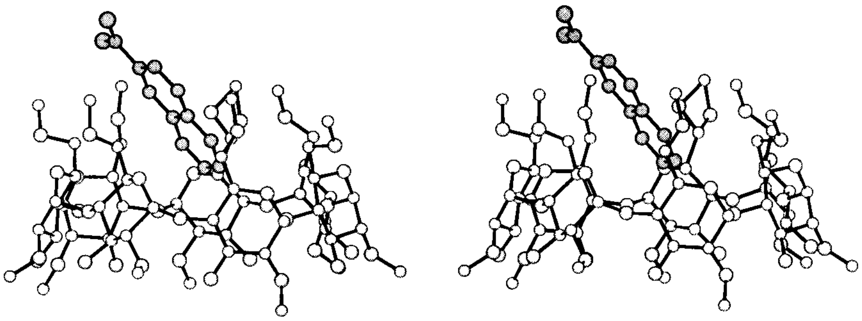


Figure 18. Stereodrawing of the structure of dimethyl-β-CD complexed with 2-naphthoic acid. The guest molecule is shaded. The naphthyl group is inserted lengthwise from the O-6 side of the dimethyl-β-CD cavity.

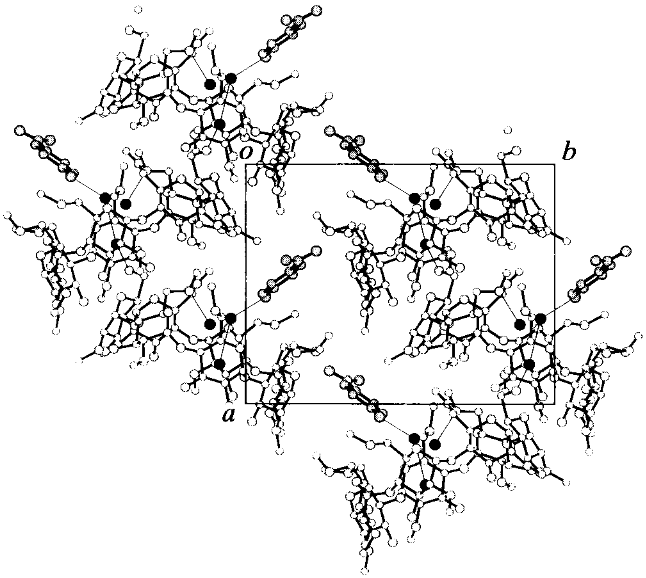


Figure 19. Crystal structure of dimethyl-β-CD complexed with *p*-nitrophenol. The space group is $P2_12_12_1$. The dimethyl-β-CD molecules are arranged along a screw axis parallel to the *a* axis. An O-6 methoxyl group of one dimethyl-β-CD molecule is inserted into the next dimethyl-β-CD ring to form a helically extended polymeric chain. The *p*-nitrophenol molecule (shaded) is located in the intermolecular space. Water molecules (filled circle) are included in the host cavity and form a hydrogen-bond chain which passes through the cavity as shown by the thin lines.

size are well suited to the space. In these structures, the dimethyl-β-CD molecules are arranged along the screw axis to form a polymeric chain with the inclusion of a symmetry-related methoxyl group. During crystallization, this methoxyl group obviously competes with the guest molecule for occupation of the host cavity.

3. Hexakis(2,3,6-tri-O-methyl)-α-cyclodextrin

Methylation of all the hydroxyl groups on α-CD blocks the formation of intramolecular hydrogen bonds. Furthermore, the resulting methyl group attached to the O-3 causes steric hindrance with the O-2 of the adjacent glucose unit. As a result, the conformation of the macrocycle is considerably distorted compared to that of native cyclodextrins. In hexakis(2,3,6-tri-O-methyl)-α-cyclodextrin (trimethyl-α-CD), trimethylglucose units incline their O-6 side toward the inside of the macrocycle to a much greater degree than the glucose units of α-CD.[94] This large inclination increases the distance between the O-2 and O-3 of adjacent trimethylglucose units, thus relieving their associated steric strain. Trimethyl-α-CD forms inclusion complexes with substituted benzenes such as benzaldehyde,[95] *p*-iodoaniline,[96] *p*-nitrophenol,[97] mandelic acid,[98] and 1-phenylethanol.[99] In their uncomplexed state, trimethyl-α-CD molecules are arranged in a herringbone pattern.[100] An O-6 methoxyl group from one trimethyl-α-CD is inserted into the cavity of an adjacent molecule from its O-2, O-3 side, while the O-6 side of the cavity is capped by an O-6 methoxyl group.

Two types of packing structures, the channel-type and the layer-type, have been observed for trimethyl-α-CD complexes. In the channel-type packing structure, trimethyl-α-CD molecules are stacked head-to-tail. The macrocyclic ring is inclined against the channel axis, and the methyl groups on adjacent molecules are in van der Waals contact. Methylation elongates the repetition unit of the channel until it is ca. 2 Å longer than that of the α-CD column, and as a result, *p*-disubstituted benzenes can be included in the channel. In the *p*-nitrophenol complex[97] (Figure 20), the guest's hydroxyphenyl group is inserted into the trimethyl-α-CD from the O-2,O-3 side, while the nitro group is located outside the cavity. The guest molecule is included upside down in trimethyl-α-CD, relative to its position in the corresponding α-CD complex. Because of the large inclination of the trimethylglucose units in trimethyl-α-CD, the O-6 side of the cavity is too narrow to accommodate the nitro group, although it does favorably adopt the smaller hydroxyl group. A water molecule is also included in the cavity and links the phenolic hydroxyl group and two O-6 atoms on the host molecule by hydrogen bonds. A similar packing structure is observed in complexes of trimethyl-α-CD with *p*-iodoaniline and benzaldehyde. The *p*-iodoaniline molecule is in the same orientation as it is in the α-CD complex, but the benzaldehyde molecule is included upside down relative to its orientation in the trimethyl-α-CD complex.

In the layer structure, the trimethyl-α-CD rings are arranged on a plane in an alternating upside down orientation.[91] The ends of the host cavity are open to the intermolecular space of the adjacent layer, and a substituent group on the included guest molecule protrudes into this space from the host cavity. The structure of the (S)-mandelic acid complex of trimethyl-α-CD will be discussed in section V.B.

4. Heptakis(2,3,6-tri-O-methyl)-β-cyclodextrin

The full methylation of β-CD markedly affects not only its macrocyclic ring but also the conformation of its glucose units. When the trimethyl-β-CD is not complexed, one of its trimethylglucose units is converted from a $^4C_1$ chair conformation into a $^1C_4$ conformation with axial C-2−O-2, C-3−O-3, and C-5−C-6 bonds.[101] This unusual conformation of the trimethylglucose unit distorts the macrocyclic ring and reduces the vacant space in the molecular cavity. It has been suggested that intramolecular C-6H··· O-5′ hydrogen bonds which form between adjacent methylglucose units are what stabilize this macrocyclic structure.[101] Another unusual conformation of a trimethylglucose unit is observed in the complex of trimethyl-β-CD with *m*-iodophenol (Figure 21), in which one trimethylglucose unit adopts an $^0S_2$ skew-boat conformation. This conformation is a high-energy intermediate state between the $^4C_1$ and $^1C_4$ conformation[102] but in this case it is stabilized by the inclusion of *m*-iodophenol.[103] The iodine atom of the *m*-iodophenol is located at the O-6 side of the macrocycle, while the hydroxyl group is hydrogen bonded to O-3. The axial O-2 methoxyl group of the methylglucose unit with the boat conformation points at the *m*-iodophenol molecule and holds down its benzene ring. It is quite different from the conformation observed in the *p*-iodophenol complex, in which all

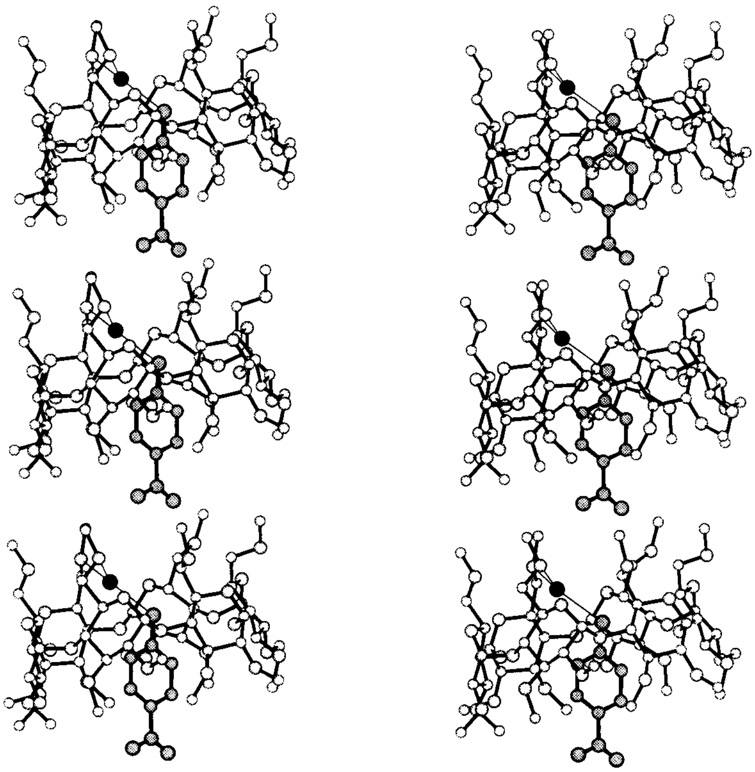


Figure 20. Stereodrawing of the structure of trimethyl-α-CD complexed with *p*-nitrophenol. The trimethyl-α-CD molecules are stacked to form a head-to-tail channel-type structure. The hydroxylphenyl group of the guest (shaded) is inserted into the host cavity and forms a hydrogen bond (thin lines) with a water molecule (filled circle).

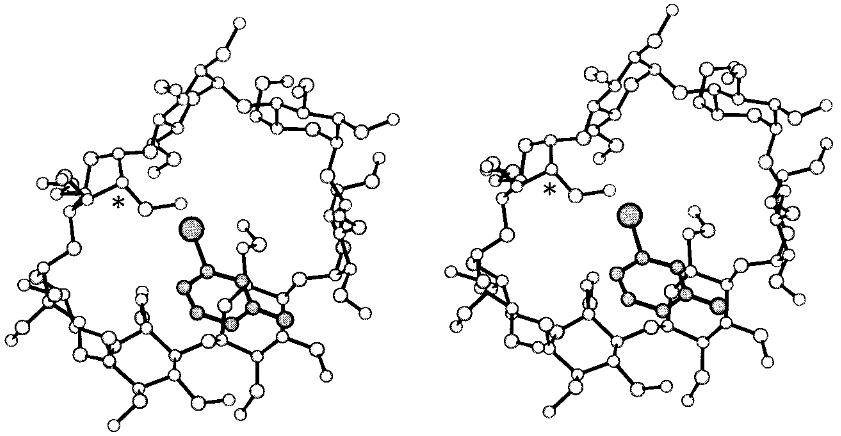
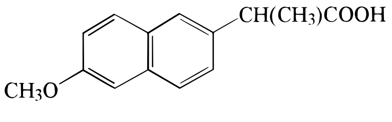


Figure 21. Stereodrawing of the structure of trimethyl-*β*-CD complexed with *m*-iodophenol. An asterisk indicates the trimethylglucose unit which is in the $^{0}S_2$ boat conformation. The *m*-iodophenol molecule is shaded.

trimethylglucose units are in the $^{4}C_1$ chair conformation.[104] The iodophenyl group is inserted into the host cavity from the O-2, O-3 side, while the phenolic hydroxyl group hydrogen bonds with water molecules located outside of the cavity.

When they are complexed, the trimethyl-*β*-CD molecules are arranged to form a head-to-tail channel-type structure. The molecules are stacked along a 2-fold screw axis in a zigzag fashion. Relatively large guest molecules such as biphenylacetic acid[105] and flurbiprofen[106] form 1:1 complexes with the trimethyl-*β*-CD, but part of the guest molecule protrudes from a distortion-induced crevice in the column. Due to a large inclination by the trimethylglucose units, the O-6 side of the cavity is narrow and the guest molecule is shifted to the O-2, O-3 side. Unlike naphthoic acid, when naproxen ((*S*)-6-methoxy-α-methyl-2-naphthaleneacetic acid, Chart 4) is complexed by dimethyl-*β*-CD, one-half of the naphthyl moiety protrudes outside of the macrocycle on the O-2, O-3 side (Figure 22).[107] The complexes of trimethyl-*β*-CD with ibuprofen (2-(4-isobutylphenyl)-propionic acid)[108] and ethyl laurate[109] also crystallize in isomorphous forms. In the former complex, isobutyl group of ibuprofen penetrates into the host cavity, while the 2-phenylpropionic acid moiety protrudes from the cavity in the same manner as the 2-(2-

Chart 4



Naproxen

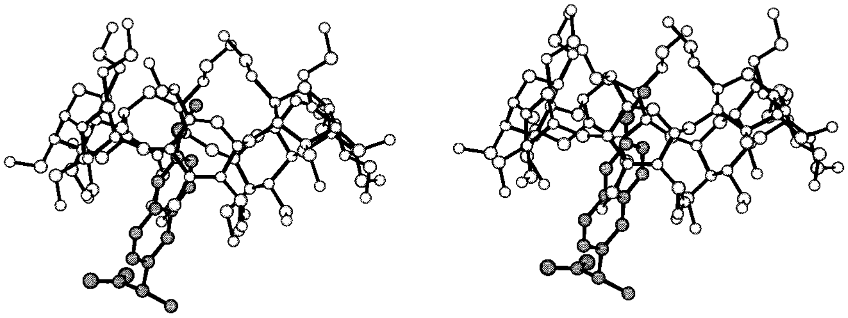


Figure 22. Stereodrawing of the structure of trimethyl-β-CD complexed with naproxen. The methoxyl group is inserted into the host cavity from its O-2, O-3 side.

fluorophenyl)propionic acid moiety of flurbiprofen. On the other hand, the ethyl laurate is fully accommodated in the host channel. Its dodecanoyl group penetrates from the O-2, O-3 side, and its terminal methyl group is inserted into the next host molecule. The ethyl group protrudes from the O-2, O-3 side of the cavity toward the O-6 side of another symmetry-related host molecule and the ester group hydrogen bonds with two water molecules. The O-2, O-3 side of the host molecule is so wide that it can accommodate both the ester group and the alkyl chain of yet another guest molecule.

B. Monosubstituted Cyclodextrins

Numerous monosubstituted cyclodextrins, especially those with appended functional groups, have been synthesized to improve the inclusion selectivity of the host or to introduce catalytic activity. The introduction of an alkyl or a hydroxyalkyl group generally decreases the solubility of the β-CD, although its solubility increases again in the presence of guest molecules.[110] The decreased solubility has been attributed to its formation of crystals which are more stable than the crystal of native β-CD. This stabilization arises from the inclusion by one molecule of a substitutent group of an adjacent molecule. In the structure of 2-hydroxypropyl-β-CD, the molecules are arranged along a screw axis and the 2-hydroxypropyl group is inserted into the cavity of the next β-CD to form a helically extended polymeric structure. A similar packing has been observed in several other monosubstituted cyclodextrins.[111−117] Such self-assembled helical structures strengthen the intermolecular contacts and better stabilize the crystal packing. The packing structure differs depending on the position of the 2-hydroxypropyl group. In the crystals of 2-*O*-(2-hydroxypropyl)-β-CD,[112] the molecules are arranged in a cage-type packing mode and are closely stacked along the 2-fold screw axis (Figure 23). In contrast, 6-*O*-(2-hydroxypropyl)-β-CD molecules do not stack due to their long, flexible side chains but are arranged helically along the 2-fold screw axis (Figure 24).[113] A similar packing structure has been observed in the crystals of 6-azido-6-deoxy-α-CD,[111] 6-deoxy-6-(*tert*-butylthio)-β-CD,[114] and 6-(6-aminohexyl)amino-6-deoxy-β-CD.[115]

A helical arrangement of molecules is also formed in the crystals of β-CD molecules which carry a bulky substitutent group. The phenyl group of 6-deoxy-6-(phenylsulfinyl)-β-CD is inserted into the cavity of adjacent β-CD from the secondary hydroxyl side, and the molecules are arranged along a 2-fold screw axis.[116] 6-Deoxy-6-(phenylthio)-β-CD molecules are stacked along a 4-fold screw axis (Figure 25) even though the phenyl group is included in the β-CD cavity in a manner similar to that of the phenylsulfinyl derivative.[116] 6-*O*-α-Glucopyranosyl-α-CD has an α-glucosyl group appended to the α-CD by an α-1,6-

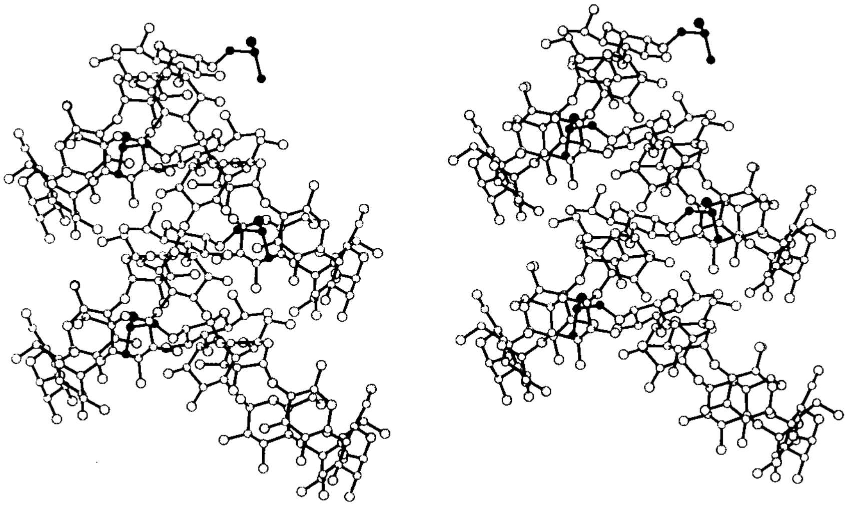


Figure 23. Stereodrawing of the stacking structure of 2-*O*-[(*S*)-2-hydroxypropyl]-β-CD. The 2-hydroxypropyl group is shown with filled circles. The molecules are stacked along a 2-fold screw axis and the 2-hydroxypropyl group is inserted into the cavity of an adjacent molecule from its secondary hydroxyl side.

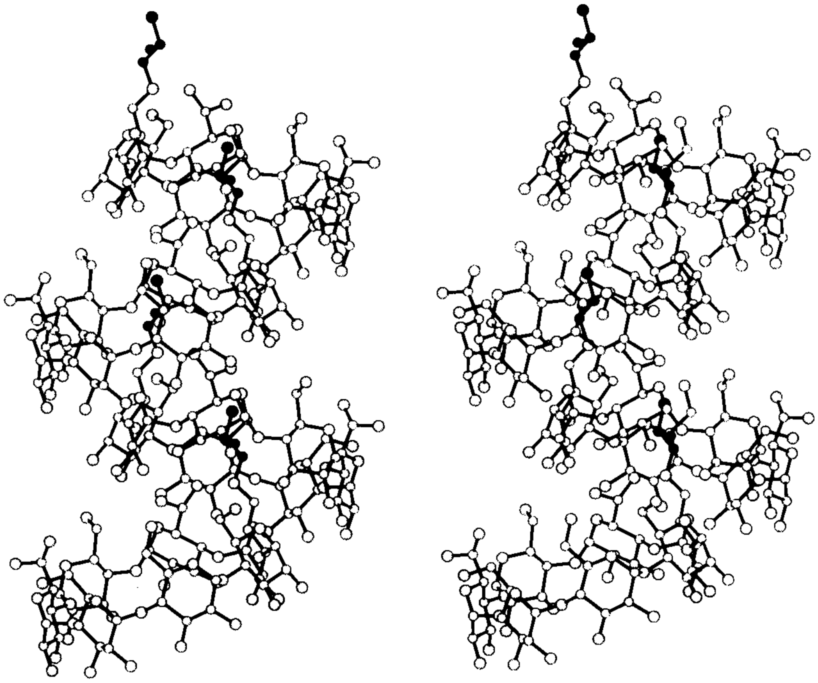


Figure 24. Stereodrawing of the stacking structure of 6-*O*-[(*S*)-2-hydroxypropyl]-*β*-CD. The 2-hydroxypropyl group is shown with filled circles. The molecules are stacked along the 2-fold screw axis, and the 2-hydroxypropyl group is inserted into the cavity of a symmetry related molecule from its secondary hydroxyl side.

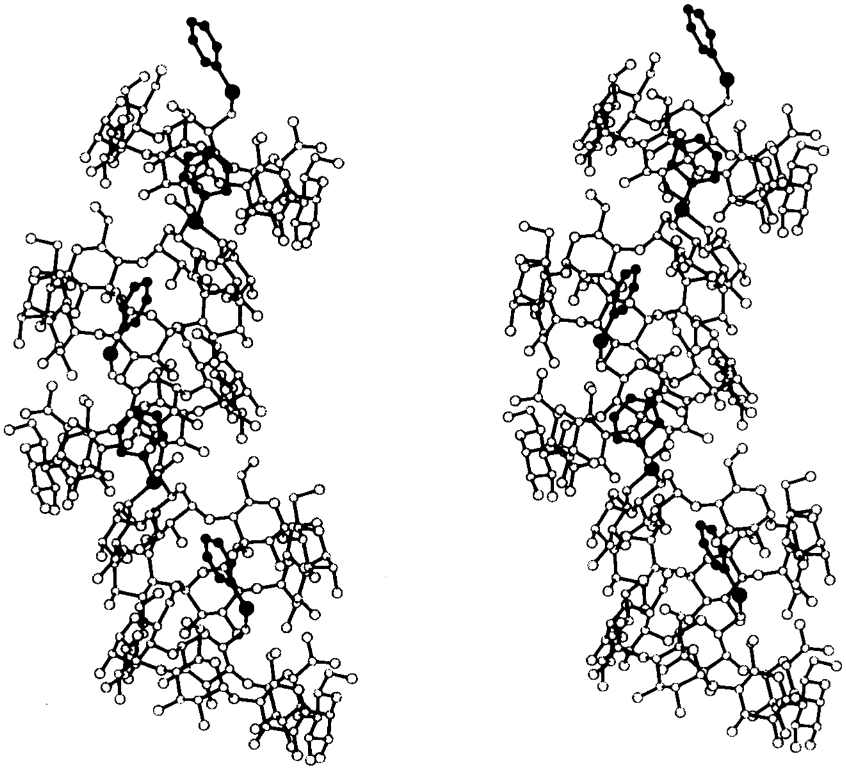


Figure 25. Stereodrawing of the stacking structure of 6-deoxy-6-(phenylthio)-*β*-CD. The phenyl group is shown with filled circles. The molecules are arranged along a 4-fold screw axis, and the phenyl group is inserted into the cavity of an adjacent *β*-CD from its secondary hydroxyl side.

linkage,[117] and this substitutent is too large to be fully accommodated in the α-CD cavity. Instead, the primary hydroxyl group of the α-glucosyl moiety penetrates into the cavity of an adjacent α-CD where it is linked to the O-2H hydroxyl group of a symmetry-related substituent via a water-mediated hydrogen-bond bridge.

β-CD derivatives with covalently linked amino acids have been investigated. In the crystal of 6-(Boc-L-phenylalanylamino)-6-deoxy-*β*-CD,[118] the molecules are arranged along a 2-fold screw axis in a manner similar to that observed for 6-*O*-monosubstituted-*β*-CD. The *tert*-butyl group of one molecule is included within a neighboring molecule, while the phenyl

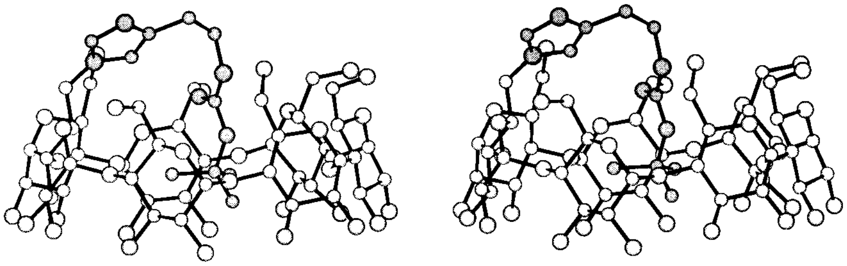


Figure 26. Stereodrawing of the structure of 6-deoxy-6-[4-(*N*-*tert*-butoxycarbonyl)imidazolyl]-*β*-CD. The substituent group is shaded. The *tert*-butoxycarbonyl group is bent so that it inserts into the *β*-CD cavity, thus demonstrating self-inclusion of a substituent.

group is sandwiched between two *β*-CDs. On the other hand, self-inclusion of a substituent group is observed with 6-deoxy-6-{4-[*N*-*tert*-butoxycarbonyl-2-aminoethyl]imidazolyl}-*β*-CD[119] and 6-deoxy-6-cyclo(L-histidyl-L-leucyl)-*β*-CD.[120] In these crystals, the molecule shows a "sleeping-swan"-like shape (Figure 26). The substituent group is bent and the butoxycarbonyl or isobutyl group is inserted into the *β*-CD ring from the primary hydroxyl side. The formation of complexes of these derivatives with guest molecules has not yet been reported, perhaps because the substituent group successfully competes with potential guest molecules during complex formation.

C. Other Modified Cyclodextrins

Modification of the secondary hydroxyl side of a cyclodextrin sometimes changes the stereochemistry of its pyranose ring. When the modification reaction involves a 2,3-epoxide intermediate, the subsequent hydrolysis or aminolysis reaction converts the glucose to altrose or altrosamine,[121] respectively. Such structural changes affect the macrocycle's conformation and also its complex formation. In the structure of 3-deoxy-3-amino-α-CD, the altrosamine residue was a ^{3,0}B boat conformation and the macrocyclic ring is elliptically distorted.[122] Cyclo-α-1,4-D-altrohexaoside derived from α-CD has a unique macrocyclic conformation in which altrose units having alternating $^1C_4$ and $^4C_1$ chair conformations are linked.[123] As a result, the structure has 3-fold symmetry. Although the structures of inclusion complexes of these modified cyclodextrins have not yet been reported, the stereoselectivity of the cyclodextrins is expected to change because of the different shapes and sizes of their macrocyclic cavities.

Octakis(3,6-anhydro)-*γ*-CD consists of anhydroglucose units in a $^1C_4$ conformation.[124] Because of its lack of intramolecular hydrogen bonds, the molecule is highly flexible and the macrocyclic ring folds to form a saddle-like shape with 2-fold symmetry. The eight axial O-2H hydroxyl groups point to the inside of the molecule, suggesting that the cavity is hydrophilic. This molecule forms complexes with metal cations, but no crystal structures have been reported.

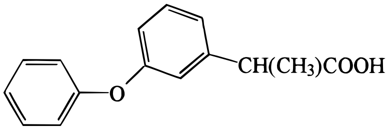
V. Chiral Recognition

A. Native Cyclodextrins

The first crystal structure determined for a cyclodextrin complex with a chiral guest was of an α-CD complex with racemic 1-phenylethanol.[39] The host α-CD molecules are stacked head-to-tail in the crystal to form a channel-type structure. The phenyl group of the guest molecule is partially included at the secondary hydroxyl side of the α-CD, while the methyl group is inserted into an adjacent α-CD cavity from its primary hydroxyl side. The hydroxyl group is 2-fold disordered, which reflects the equal amounts of the (*R*)- and (*S*)-isomer that are present. The hydroxyl groups of the (*R*)- and (*S*)-isomers are hydrogen bonded to O-3H and O-2H hydroxyl groups, respectively. Although α-CD is a chiral molecule, the internal cavity has pseudo 6-fold symmetry. Moreover, the 12 secondary hydroxyl groups form a circle. This symmetrical host cavity can accommodate both the (*R*)- and (*S*)-isomers equally.

β-CD, which forms a head-to-head dimer, can include a pair of (*R*)- and (*S*)-isomers of flurbiprofen in its dimer cavity (Figure 10).[56] The guest molecules are arranged head-to-head with the phenyl groups of both isomers in face-to-face contact at the center of the *β*-CD dimer cavity. The carboxyl group of the (*R*)-isomer is hydrogen bonded to a primary hydroxyl group on *β*-CD which points to the inside of the macrocycle. When *β*-CD is crystallized in the presence of only the (*S*)-isomer, the dimer cavity includes two (*S*)-isomer molecules arranged in the same manner as that of the racemic guest.[57] Since the (*R*)-isomer of the racemic guest is replaced by the (*S*)-isomer, a change is observed in the hydrogen-bonding contact of the carboxyl group. The carboxyl group of the (*S*)-isomer is oriented differently and therefore is hydrogen bonded to a water molecule. Attempts at resolution of the isomers by cocrystallization have produced low optical yields, due to *β*-CD's inclusion of the racemic pair. The crystal structure of a fenoprofen−*β*-CD complex (Chart 5) is similar to the flurbiprofen−*β*-CD complex. However, the *β*-CD dimer cavity includes an excess of (*S*)-fenoprofen with an *S*:*R* ratio of 3:1 when the complex is crystallized in the presence of the racemic guest.[71] Individual (*R*)- and (*S*)-fenoprofen complexes of *β*-CD form isomor-

Chart 5



Fenoprofen

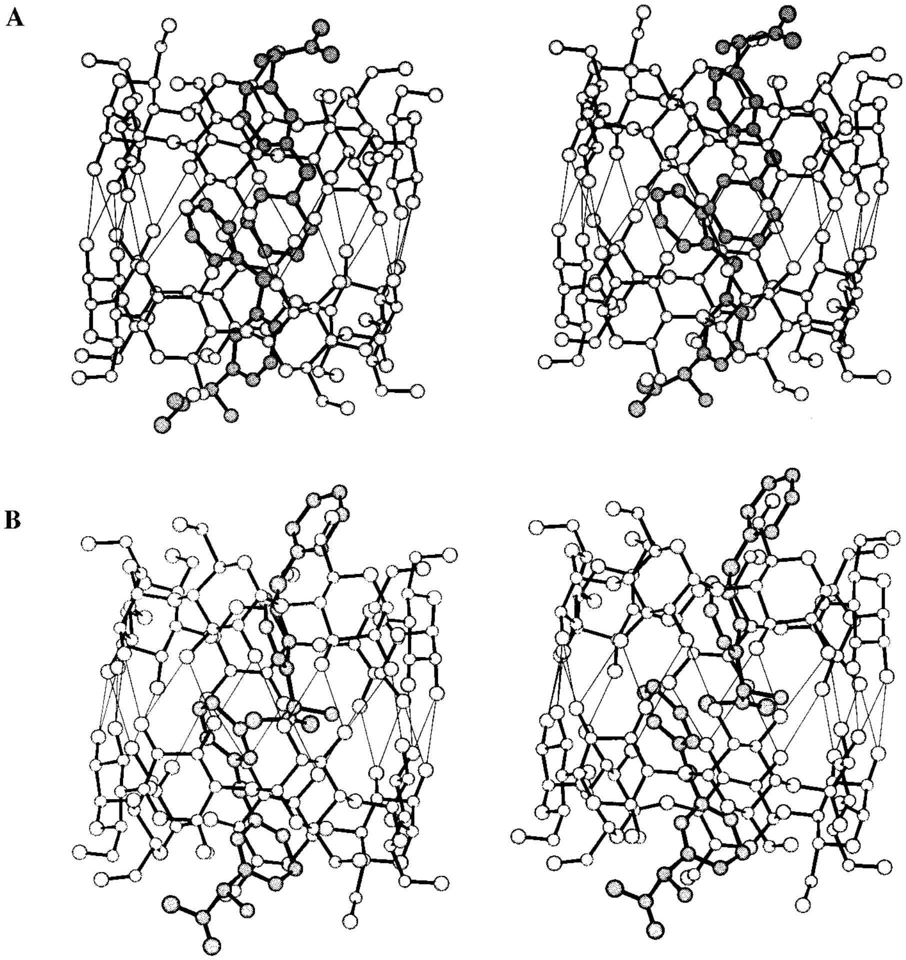


Figure 27. Stereodrawings of the structures of β-CD complexed with (*R*)-fenoprofen (A) and (*S*)-fenoprofen (B). Two β-CD molecules form a head-to-head dimer with multiple hydrogen bonds (thin lines) extending between their secondary hydroxyl sides. The (*R*)-fenoprofen molecules (shaded) are arranged in a head-to-head mode within the barrel-like cavity, while the (*S*)-isomer molecules (shaded) are arranged in a head-to-tail mode.

phous crystals. The packing structure of the crystals is the same whether the complex includes the racemic or the pure compounds, although the arrangement of the two guest molecules in the dimer cavity is different. Molecules of the (*R*)-isomer are arranged head-to-head with the two phenyl groups facing each other at the center of the dimer cavity as shown in Figure 27A. On the other hand, the (*S*)-isomers are arranged head-to-tail with the phenyl group of one guest molecule facing the phenylene group of the other guest molecule (Figure 27B).[72] Crystalline complexes of β-CD with (*S*)- and racemic methyl *p*-tolylsulfoxide[125] and L-menthol[126] also have been reported.

B. Methylated Cyclodextrins

Several crystal structures of trimethyl-α-CD complexes with optically active guests have been reported. This host molecule forms a 1:1 crystalline complex with both (*R*)- and (*S*)-1-phenylethanol.[99] The crystals are isomorphous, and the guest isomers are included in the same manner. The hydroxyl groups of both guests are hydrogen bonded to the same methoxyl oxygen atom of the host. Superposition of the two structures revealed that the guest molecules are related by a 12° rotation which maintains the host−guest hydrogen bond. In contrast, the complexes of (*R*)- and (*S*)-mandelic acid, where the methyl group of 1-phenylethanol is replaced by a carboxyl group, crystallize with different packing structures.[98] The crystal of the (*R*)-isomer complex has a channel-type packing structure which is the same as that found in crystals of the 1-phenylethanol complex. The phenyl group is inserted into the distorted macrocyclic ring, and the hydroxyl group forms a hydrogen bond with a methoxyl oxygen atom on the host (Figure 28A). On the other hand, the host molecule in the (*S*)-isomer complex has a pseudo 2-fold symmetry and is arranged in a layer-type structure. The phenyl group of the (*S*)-isomer is only partially inserted into the host cavity from the O-2, O-3 side. The hydroxyl and carboxyl groups of the mandelic acid protrude into the intermolecular space, where they form hydrogen bonds with water molecules (Figure 28B). The chiral discrimination between the crystalline forms of the mandelic acid−trimethyl-α-CD complexes has been interpreted in terms of an induced-fit conformational change in the host molecule. The macrocyclic structure of trimethyl-α-CD is more flexible than that of native α-CD, and it can change its conformation to attain a better fit for the guest molecule. The role of the hydrogen bond in chiral recognition has been examined by comparing complexes of trimethyl-α-CD with

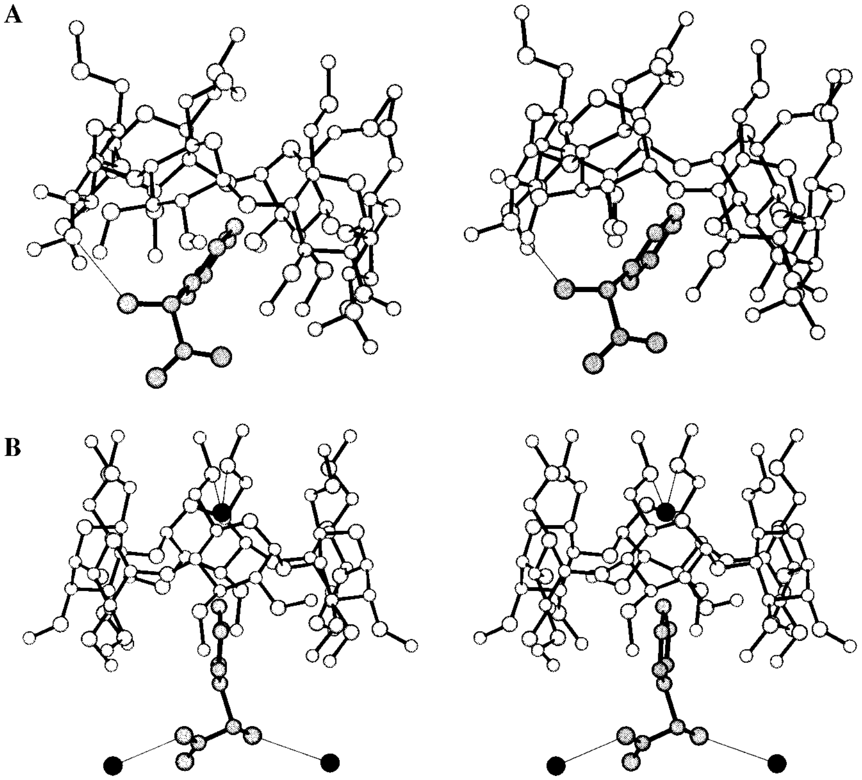


Figure 28. Stereodrawings of the structures of trimethyl-α-CD complexed with (*R*)-mandelic acid (A) and (*S*)-mandelic acid (B). The mandelic acid is shaded, and the water molecules are shown by filled circles. The thin lines denote hydrogen bonds. The hydroxyl group of (*R*)-mandelic acid is hydrogen bonded to an O-3 oxygen atom on trimethyl-α-CD. In the (*S*)-mandelic acid complex, the hydroxyl and carboxyl groups on the guest form hydrogen bonds with water molecules. A water molecule is located at the O-6 side of the host cavity and forms hydrogen bonds with two O-6 oxygen atoms.

2-phenylpropionic acid and 2-phenylbutyric acid.[127] (*R*)-2-Phenylpropionic acid is included in the same manner as (*R*)-mandelic acid. However, because the hydroxyl group of mandelic acid is replaced by a methyl group in 2-phenylpropionic acid, (*R*)-2-phenylpropionic acid does not hydrogen bond with the trimethyl-α-CD. The (*S*)-2-phenylpropionic acid also forms a crystalline complex with trimethyl-α-CD, which has the same structure as the (*S*)-mandelic acid complex. These structures suggest that a host−guest hydrogen bond is not essential for chiral recognition. The (*R*)- and (*S*)-isomers of 2-phenylbutyric acid form trimethyl-α-CD complexes which have the same crystal structure as the (*S*)-mandelic acid complex. Because of its bulky ethyl group, the (*R*)-isomer cannot deeply penetrate into the host cavity, and the complex crystallizes with the same packing structure as that of the (*S*)-isomer. Therefore, the shape and size of the guest molecule is of primary importance in chiral recognition. Since the host molecule must recognize three groups on the guest for chiral discrimination to occur, the guest molecule is required to have a suitable size and shape to accommodate this recognition by the host.

Crystals of the trimethyl-β-CD complexes of both (*R*)- and (*S*)-flurbiprofen are nearly isomorphous, although the (*R*)-isomer complex crystallizes as a monohydrate.[106] In the (*S*)-isomer complex, the phenyl group is disordered and two conformers, corresponding to the (*R*)- and (*S*)-configurations, alternately occupy the cavity (Figure 29). In contrast, only the (*R*)-configuration of the biphenyl moiety is observed in crystals of the (*R*)-flurbiprofen and 4-biphenylacetic acid complex.[101] In the β-CD complexes of flurbiprofen, the biphenyl moiety is also in the (*R*)-configuration. These structures suggest that the β-CD cavity prefers to include a biphenyl group with an (*R*)-configuration. Trimethyl-β-CD forms a crystalline complex with L-menthol. The crystal packing of this complex is similar to that of the flurbiprofen complex, but the guest molecule is almost fully accommodated in the host cavity.[126]

C. Cyclodextrins Carrying an Optically Active Group

Monosubstituted cyclodextrin molecules are arranged helically in their crystals, with the substituent group on one β-CD inserted into the cavity of an adjacent molecule from its secondary hydroxyl side. Thus, placing optically active substituents on the β-CD provides information about its interaction with chiral groups. β-CD derivatives having an optically active 2-hydroxypropyl group have been crystallized, and their X-ray structures have been reported.[112,113] However, the packing geometry of these molecules is not sensitive to the chirality of the substituent group, and the crystals of β-CD bearing either an (*R*)- or (*S*)-2-hydroxypropyl group are nearly isomorphous. This has been demonstrated by 6-*O*-substituted β-CD derivatives and indicates that the packing requirements of the β-CD macrocycle ensure that both chiral groups are included in the same manner. The crystal structure did reveal that the (*S*)-2-hydroxypropyl

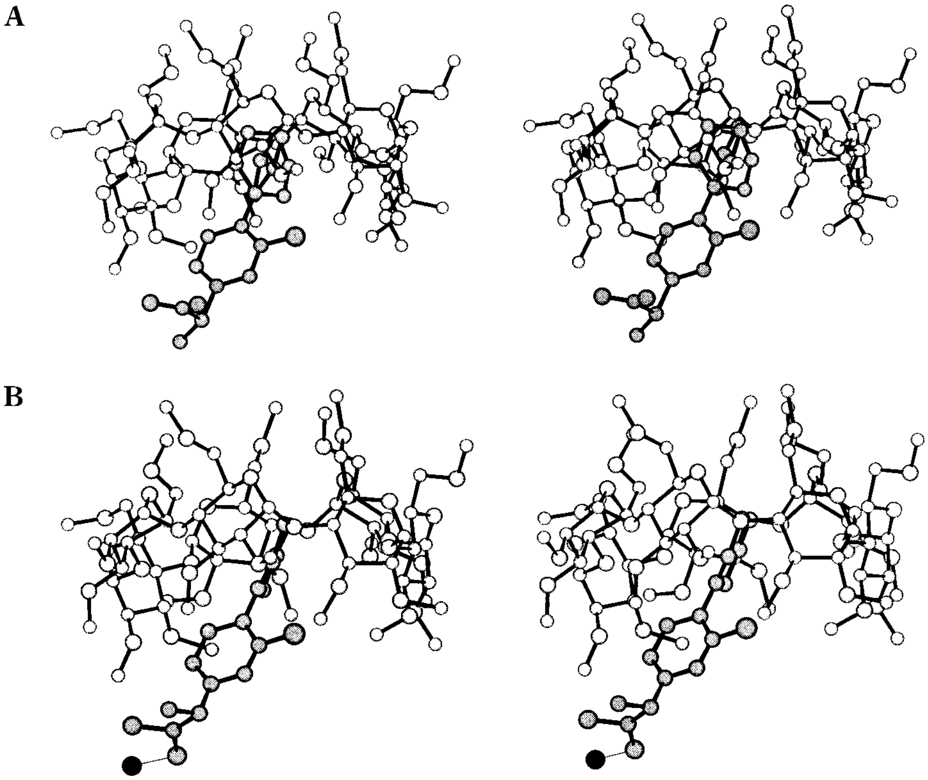


Figure 29. Stereodrawing of the structure of trimethyl-β-CD complexed with (*R*)-flurbiprofen (A) and (*S*)-flurbiprofen (B). The guest molecules are shaded, and the water molecule is identified by a filled circle. The carboxyl group on (*R*)-flurbiprofen forms a hydrogen bond (thin line) with a water molecule. The phenyl group on the (*S*)-isomer is disordered, showing both the (*R*)- and (*S*)-configuration of the biphenyl moiety.

group is better fitted to the host cavity than the (*R*)-2-hydroxypropyl group,[112] which explains the difference in the solution properties of these complexes.[113]

VI. Summary and Outlook

The structures of cyclodextrin complexes in the crystalline state are largely controlled by two factors: (i) the intrinsic characteristics of the macrocycle and (ii) crystal packing considerations. The former factors include the geometrical characteristics and physical properties of the cyclodextrin cavity. The depth of the cavity is about 8 Å, while the width depends on the number of constituent glucose units that form the internal, glycosidic oxygen polygon defining the cavity. To form inclusion complexes, guest molecules should have a size and shape which will allow them to be at least partially accommodated in the cyclodextrin cavity. For example, a phenyl group inserts lengthwise into the α-CD cavity[18,42,43,46] while β-CD includes a benzene ring sideways.[53] The α-CD cavity is too narrow to include a naphthalene ring, but naphthalene can be accommodated in the β-CD cavity.[92] Therefore, the geometry of the cavity is of primary importance in determining the host's selective inclusion of guest molecules and the structure of the host−guest interaction. Both ends of the cavity of an isolated cyclodextrin molecule are open, such that guest molecules can penetrate into the cyclodextrin ring from either side. In crystalline complexes, however, the cavity space which is available for the guest accommodation is limited by the complex's arrangement, although it is controversial whether the host−guest geometry is regulated by the crystal packing or if the structure of the complex dictates the molecular arrangement.

In crystals with a cage-type packing structure,[15,21,32−35,49−54] where the cyclodextrin molecules are arranged in a herringbone fashion, guest molecules are enclosed in an isolated cavity. In contrast, when stacks of cyclodextrin rings form a channel-type structure,[24,36−45,61−72,75] the guest molecules are arranged in infinite columns, and molecules longer than the depth of a single cavity can be included by two or more cyclodextrin molecules. The layer-type structure is intermediate between the cage-type and channel-type structures and is comprised of cyclodextrin molecules with both ends of their cavities open to intermolecular space. A part of the guest molecule is accommodated in that intermolecular space.[18,45−47,73,74]

The cyclodextrin cavity is characterized by its highly hydrophobic nature. Moreover, the cavity is positively charged, since the inside wall of the cavity is coated with hydrogen atoms from methine and methylene groups. As a result, an anion is readily accommodated within the cyclodextrin cavity when it is complexed with ionic guests. In the complexes of cyclodextrins with organometals, only the organic ligands directly contact the cyclodextrin ring.[72,79−82] This second sphere coordination is common in complexes of cyclodextrins with metallocenes.[37,83−85] In contrast, first sphere coordination is observed for metal ions which are located outside the cyclodextrin ring.[76–78] Because of the many hydroxyl groups attached to the rims of the cyclodextrin macrocycle, its intermolecular space is hydrophilic and forms a hydrogen-bond network with water molecules. In the complexes of cyclodextrin with metal ions, the metal cation replaces the water molecules in the network.

X-ray structures demonstrate that monosubstitution of cyclodextrins does not affect their macrocyclic shape. On the other hand, methylation of the O-2, O-3, or O-6 hydroxyl groups of the cyclodextrin changes the physical properties of the cavity and greatly affects complex formation. Replacement of these hydroxyl groups with methoxyl groups causes both ends of the cavity to change hydrophobic from hydrophilic. The methylation also extends the depth of the cavity by ca. 2 Å. The complex of α-CD with *m*-nitroaniline crystallizes with a channel-type structure;[42] however, dimethyl-α-CD fully includes *m*-nitroaniline to form a cage-type structure.[131] Methylating the 2-O and 6-O positions does not greatly affect the macrocyclic conformation of the cyclodextrin because intramolecular O-3H···O-2 hydrogen bonds keep the structure round. Surprisingly, *p*-iodophenol and *p*-nitrophenol are not included in the dimethyl-*β*-CD cavity[93] but instead are found in the hydrophobic intermolecular space. In fact, the guest molecules are not necessarily included in the host cavity, even if the host−guest molar ratio is 1:1 in the crystal.

Full methylation causes marked distortion of the cyclodextrin ring because it destroys the intramolecular hydrogen bonds.[94] The resulting change in the shape of the host cavity subsequently affects the geometry of the host−guest interaction. For example, trimethyl-α-CD includes the hydroxyphenyl group of *p*-nitrophenol, while α-CD includes its nitrophenyl group. The macrocyclic ring of trimethyl-CD is so flexible that it can change its conformation upon includsion of a guest. This induced-fit conformational change plays an important role in the molecular recognition ability of trimethyl-CD. Cyclodextrins are optically active molecules, but X-ray analysis of cyclodextrin complexes suggests that native cyclodextrins have little chiral recognition ability.[39,56] In contrast, trimethyl-α-CD changes its conformation in response to the chirality of mandelic acid.[98] In order for chiral recognition to occur, the host molecule should make contact with three groups on the guest. This also requires the guest molecule to have three groups of a suitable size and shape to be recognized.[127]

Cyclodextrins were the first macrocyclic compounds to be studied as hosts for molecular inclusion. Although a number of other macrocyclic compounds have been synthesized in the course of developing host−guest chemistry, cyclodextrins have been continued to be a highly important material both for scientific research and industrial application. Because of their nontoxity, cyclodextrins have been widely utilized in the chemical, pharmaceutical, and food industries. A prominent characteristic of cyclodextrins is their stereoselective inclusion of guest materials, as has been emphasized by a number of investigations. Crystal structures have been a major source of three-dimensional structural information on cyclodextrin host−guest complexes. At present, crystallographic studies are still aimed at determining the structures of individual cyclodextrin complexes. The accumulation of crystallographic data, although progressing very slowly, promises to elucidate the origin of stereodifferentiation during complex formation. With that knowledge in hand, we can design cyclodextrin derivatives to have specific inclusion properties for use as chiral separation reagents, biomimetic catalysts, etc.

VII. References

(1) Szejtli, J. *Cyclodextrins and Their Inclusion Complexes*; Akadémiai Kiadó: Budapest, 1982.
(2) Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer Verlag: Berlin, 1978.
(3) VanEtten, R. L.; Sebastian, J. F.; Clowes, G. A.; Bender, M. L. *J. Am Chem. Soc.* **1967**, *89*, 3242.
(4) Harata, K.; Uedaira, H.; Tanaka, J. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1627.
(5) Hinze, W. L. *Sep. Purif. Methods* **1981**, *10*, 159.
(6) Hilton, M. L.; Armstrong, D. W. *New Trends in Cyclodextrins and Derivatives*; Duchéne, D., Ed.; Editions de Santé: Paris, 1991; Chapter 15.
(7) Mikolajczyk, M.; Drabowicz, J. *J. Am. Chem. Soc.* **1978**, *100*, 2510.
(8) French, D.; Rundle, R. E. *J. Am. Chem. Soc.* **1942**, *64*, 1651.
(9) James, W. J.; French, D.; Rundle, R. E. *Acta Crystallogr.* **1959**, *12*, 385.
(10) Hybl, A.; Rundle, R. E.; Williams, D. E. *J. Am. Chem. Soc.* **1965**, *87*, 2779.
(11) Saenger, W. *Inclusion Compounds*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Eds.; Academic Press: London, 1984; Vol. 2, Chapter 8.
(12) Le Bas, G.; Rysanek, N. *Cyclodextrins and their industrial uses*; Duchéne, D., Ed.; Editions de Santé: Paris, 1987; Chapter 3.
(13) Harata, K. *Inclusion Compounds*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Eds.; Oxford University Press: New York, 1991; Vol. 5, Chapter 9.
(14) Harata, K. *Comprehensive Supramolecular Chemistry, Vol. 3, Cyclodextrins*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Eds.; Pergamon: Oxford, 1996; Chapter 9.
(15) Manor, P. C.; Saenger, W. *J. Am. Chem. Soc.* **1974**, *96*, 3630.
(16) Nakagawa, T.; Ueno, K.; Kashiwa, M.; Watanabe, J. *Tetrahedron Lett.* **1994**, *35*, 1921.
(17) Saenger, W.; McMullan, K.; Fayos, J.; Mootz, D. *Acta Crystallogr. Sect. B* **1974**, *30*, 2019.
(18) Harata, K. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2409.
(19) French, A. D.; Murphy, V. G. *Carbohydr. Res.* **1973**, *27*, 391.
(20) Tabushi, I.; Kiyosuke, Y.; Sugimoto, T.; Yamamura, K. *J. Am. Chem. Soc.* **1978**, *100*, 916.
(21) Lindner, K.; Saenger, W. *Carbohydr. Res.* **1982**, *99*, 103.
(22) Mentzafos, D.; Mavridis, I. M.; Le Bas, G.; Tsoucaris, G. *Acta Crystallogr. Sect. B* **1991**, *47*, 746.
(23) Harata, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2763.
(24) Ding, J.; Steiner, T.; Saenger, W. *Acta Crystallogr. Sect. B* **1991**, *47*, 731.
(25) Fujiwara, T.; Tanaka, N.; Kobayashi, S. *Chem. Lett.* **1990**, 739.
(26) Ueda, H.; Endo, T.; Nagase, H.; Kobayashi, S.; Nagai, T. *J. Incl. Phenom.* **1996**, *25*, 17.
(27) Harata, K.; Endo, T.; Ueda, H.; Nagai, T. *Supramol. Chem.* In press.
(28) Goebel, C. V.; Dimpfl, W. L.; Brant, D. A. *Macromolecules* **1970**, *3*, 664.
(29) French, A. D.; Dowd, M. K. *J. Mol. Struct. (THEOCHEM)* **1993**, *286*, 183.
(30) Takata, T.; Yamane, M.; Takata, H.; Okada, S.; Smith, S. M. *J. Biol. Chem.* **1996**, *271*, 2902.
(31) Shimada, J.; Handa, S.; Kaneko, H.; Takada, T. *Macromolecules* **1996**, *29*, 6408.
(32) Hingerty, B.; Saenger, W. *J. Am. Chem. Soc.* **1976**, *98*, 3357.
(33) McMullan, R. K.; Saenger, W.; Fayos, J.; Mootz, D. *Carbohydr. Res.* **1973**, *31*, 211.
(34) Saenger, W.; Noltemeyer, M. *Chem. Ber.* **1976**, *109*, 503.
(35) Harata, K.; Uekama, K.; Otagiri, M.; Hirayama, F. *Nihon Kagaku Kaishi* **1983**, 173.
(36) Noltemeyer, M.; Saenger, W. *J. Am. Chem. Soc.* **1980**, *102*, 2710.
(37) Klingert, B.; Rihs, G. *J. Incl. Phenom.* **1991**, *10*, 255.
(38) Harata, K.; Uekama, K.; Otagiri, M.; Hirayama, F.; Ogino, H. *Bull. Chem. Soc. Jpn.* **1878**, *51*, 1627.
(39) Harata, K. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1367.

(40) Shibakami, M.; Sekiya, A. *J. Chem. Soc., Chem. Commun.* **1992**, 1742.
(41) Steiner, T.; Saenger, W. *Carbohydr. Lett.* **1994**, *1*, 143.
(42) Harata, K. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2782.
(43) Harata, K. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2066.
(44) Harata, K. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1259.
(45) Harata, K. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1493.
(46) Harata, K. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1416.
(47) Harata, K. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2451.
(48) Harata, K. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1644.
(49) Lindner, K.; Saenger, W. *Carbohydr. Res.* **1982**, *107*, 7.
(50) Tokuoka, R.; Abe, M.; Fujiwara, T.; Tomita, K.; Saenger, W. *Chem. Lett.* **1980**, 491.
(51) Gessler, K.; Steiner, T.; Saenger, W. *Carbohydr. Res.* **1993**, *249*, 327.
(52) Harata, K.; Kawano, K.; Fukunaga, K.; Ohtani, Y. *Chem. Pharm. Bull.* **1983**, *31*, 1428.
(53) Harata, K.; Uekama, K.; Otagiri, M.; Hirayama, F.; Ohtani, Y. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1234.
(54) Harata, K. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2596.
(55) Stezowski, J. J.; Jogun, K. H.; Eckle, E.; Bartels, K. *Nature* **1978**, *274*, 617.
(56) Uekama, K.; Imai, T.; Hirayama, F.; Otagiri, M.; Harata, K. *Chem. Pharm. Bull.* **1984**, *32*, 1662.
(57) Uekama, K.; Imai, T.; Hirayama, F.; Otagiri, M.; Harata, K. *Chem. Pharm. Bull.* **1983**, *31*, 3363.
(58) Hamilton, J. A.; Sabesan, M. N. *Carbohydr. Res.* **1982**, *102*, 31.
(59) Hursthouse, M. B.; Smith, C. Z.; Thornton-Pett, M.; Utley, J. H. P. *J. Chem. Soc., Chem.* Commun. **1982**, 881.
(60) Hamilton, J. A.; Sabesan, M. N. *Acta Crystallogr. Sect. B* **1982**, *38*, 3063.
(61) Caira, M. R.; Griffith, V. J.; Nassimbeni, L. R.; van Oudtshoorn, B. *J. Chem. Soc., Chem. Commun.* **1994**, 1061.
(62) Betzel, C.; Hingerty, B.; Noltemeyer, M.; Weber, G.; Saenger, W. *J. Incl. Phenom.* **1984**, *1*, 181.
(63) Hamilton, J. A.; Sabesan, M. N.; Steinrauf, L. *Carbohydr. Res.* **1981**, *89*, 33.
(64) Harding, M. N.; Maclennan, J. M.; Paton, R. M. *Nature* **1978**, *274*, 621.
(65) Hamilton. J. A.; Sabesan, M. N. *Carbohydr. Res.* **1982**, *102*, 31.
(66) Mavridis, I. M.; Hadjoudis, E. *Carbohydr. Res.* **1992**, *229*, 1.
(67) Mavridis, I. M.; Hadjoudis, E.; Tsoucaris, G. *Carbohydr. Res.* **1991**, *220*, 11.
(68) Tokuoka, R.; Fujiwara, T.; Tomita, K. *Acta Crystallogr. Sect. B*, **1981**, *37*, 1158.
(69) Le. Bas, G.; De Lango, C.; Rysanek, N.; Toucaris, G. *J. Incl. Phenom.* **1985**, *2*, 861.
(70) Harata, K.; Hirayama, F.; Tsoucaris, G. *Chem. Lett.* **1988**, 1585.
(71) Hamilton, J. A.; Chen, L. *J. Am. Chem. Soc.* **1988**, *110*, 5833.
(72) Hamilton, J. A.; Chen, L. *J. Am. Chem. Soc.* **1988**, *110*, 4379.
(73) Harata, K. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2315.
(74) Caira, M. R.; Griffith, V. J.; Naasimbeni, L. R. *J. Incl. Phenom.* **1994**, *17*, 187.
(75) Kamitori, S.; Hirotsu, K.; Higuchi, T. *J. Am. Chem. Soc.* **1987**, *109*, 2409.
(76) Charpin, P.; Nicolis, I.; Villain, F.; De Rango, C.; Coleman, A. W. *Acta Crystallogr. Sect. C* **1991**, *47*, 1829.
(77) Nicolis, I.; Coleman, A. W.; Charpin, P.; De Rango, C. *Acta Crystallogr. Sect. B* **1996**, *52*, 122.
(78) Bonomo, R. P.; Di Blasio, B.; Maccarrone, G.; Pavone, V.; Pedone, C.; Rizzalleri, E.; Saviano, M.; Vecchio, G. *Inorg. Chem.* **1996**, *35*, 4497.
(79) Alston, D. R.; Slawin, A. M. Z.; Stoddart, J. F.; Williams, D. J. *Angew. Chem., Int. Ed. Engl.* **1985**, *19*, 786.
(80) Alston, D. R.; Slawin, A. M. Z.; Stoddart, J. F.; Williams, D. J.; Zarzycki, R. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1184.
(81) Stoddart, J. F.; Zarzycki, R. *Recl. Trav. Chim. Pays-Bas* **1988**, *107*, 515.
(82) Alston, D. R.; Slawin, A. M. Z.; Stoddart, J. F.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1602.
(83) Odagaki, Y.; Hirotsu, K.; Higuchi, T.; Harada, A.; Takahashi, S. *J. Chem. Soc., Chem. Perkin Trans. 1* **1990**, 1231.
(84) Klingert, B.; Rihs, G. *Organometallics* **1990**, *9*, 1135.
(85) Klingert, B.; Rihs, G. *J. Chem. Soc., Dalton Trans.* **1991**, 2749.
(86) Jicsinszky, L.; Fenyvesi, É. *Comprehensive Supramolecular Chemistry, Vol. 3, Cyclodextrins*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Eds.; Pergamon: Oxford, 1996; Chapter 4.
(87) Casu, B.; Reggiani, M.; Sanderson, G. R. *Carbohydr. Res.* **1979**, *76*, 59.
(88) Harata, K. *Supramol. Chem.* **1995**, *5*, 231.
(89) Harata, K. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2481.
(90) Harata, K. *Carbohydr. Res.* **1989**, *192*, 33.
(91) Steiner, T.; Saenger, W. *Carbohydr. Res.* **1995**, *275*, 73.
(92) Harata, K. *J. Chem. Soc. Chem. Commun.* **1993**, 546.
(93) Harata, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1939.
(94) Harata, K.; Uekama, K.; Otagiri, M.; Hirayama, F. *J. Incl. Phenom.* **1984**, *1*, 279.
(95) Harata, K.; Uekama, K.; Odagiri, M.; Hirayama, F. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3386.
(96) Harata, K.; Uekama, K.; Odagiri, M.; Hirayama, F. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 407.
(97) Harata, K.; Uekama, K.; Odagiri, M.; Hirayama, F. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3904.
(98) Harata, K.; Uekama, K.; Odagiri, M.; Hirayama, F. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 497.
(99) Harata, K. *J. Chem. Soc., Perkin Trans. 2* **1990**, 799.
(100) Steiner, T.; Saenger, W. *Carbohydr. Res.* **1996**, *282*, 53.
(101) Caira, M. R.; Griffith, V. J.; Nassimbeni, L. R.; van Oudtshoorn, B. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2071.
(102) Dowd, M. K.; French, A. D.; Reilly, P. J. *Carbohydr. Res.* **1994**, *264*, 1.
(103) Harata, K. *J. Chem. Soc., Chem. Commun.* **1988**, 928.
(104) Harata, K.; Uekama, K.; Otagiri, M.; Hirayama, F. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1732.
(105) Harata, K.; Hirayama, F.; Arima, H.; Uekama, K. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1159.
(106) Harata, K.; Uekama, K.; Hirayama, F.; Otagiri, M. *J. Incl. Phenom.* **1988**, *6*, 443.
(107) Caira, M. R.; Griffith, V. J.; Nassimbeni, L. R.; van Oudtshoorn, B. *J. Incl. Phenom.* **1995**, *20*, 277.
(108) Brown, G.; Caira, M. R.; V. J.; Nassimbeni, L. R.; van Oudtshoorn, B. *J. Incl. Phenom.* **1996**, *26*, 281.
(109) Mentzafos, D.; Mavridis, I. M.; Schenk, H. *Carbohydr. Res.* **1994**, *253*, 39.
(110) Lindberg, B.; Lindberg, J.; Pitha, J.; Rao, C. T.; Harata, K. *Carbohydr. Res.* **1991**, *222*, 113.
(111) Hanesian, S.; Benalil, A.; Simard, M.; Bélanger-Gariépy, F. *Tetrahedron* **1995**, *51*, 10149.
(112) Harata, K.; Rao, C. T.; Pitha, J.; Fukunaga, K.; Uekama, K. *Carbohydr. Res.* **1991**, *222*, 37.
(113) Harata, K.; Rao, C. T.; Pitha, J. *Carbohydr. Res.* **1993**, *247*, 83.
(114) Hirotsu, K.; Higuchi, T.; Fujita, K.; Ueda, T.; Shinoda, A.; Tabushi, I. *J. Org. Chem.* **1982**, *47*, 1143.
(115) Mentzafos, D.; Terzis, A.; Coleman, A. W.; de Rango, C. *Carbohydr. Res.* **1996**, *282*, 125.
(116) Kamitori, S.; Hirotsu, K.; Higuchi, T. *J. Chem. Soc., Perkin Trans. 2* **1987**, *7*.
(117) Fujiwara, T.; Tanaka, N.; Hamada, K.; Kobayashi, S. *Chem. Lett.* **1989**, *1131*.
(118) Selkti, M.; Lopez, H. P.; Navaza, J.; Villain, F.; de Rango, C. *Supramol. Chem.* **1995**, *5*, 255.
(119) Di Blasio, B.; Galdiero, S.; Saviano, M.; de Simone, G.; Benedetti, E.; Pedone, C.; Gibbons, G. A.; Deschenaux, R.; Rizzarelli, E.; Vecchio, G. *Supramol Chem.* **1996**, *7*, 47.
(120) Di Blasion, B.; Pavone, V.; Nastri, F.; Isernia, C.; Saviano, M.; Pedone, C.; Cucinotta, V.; Impellizzeri, G.; Rizzarelli, E.; Vecchio, G. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 7218.
(121) Murakami, T.; Harata, K.; Morimoto, S. *Chem. Lett.* **1988**, 553.
(122) Harata, K.; Nagano, Y.; Ikeda, H.; Ikeda, T.; Ueno, A.; Toda, F. *J. Chem. Soc., Chem. Commun.* **1996**, 2347.
(123) Nogami, Y.; Nasu, K.; Koga, T.; Ohta, K.; Fujita, K.; Immel, S.; Lindner, H. J.; Schumitt, G. E.; Lichtenthaler, F. W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1899.
(124) Yamamura, H.; Masuda, H.; Kawase, Y.; Kawai, M.; Butsugan, Y.; Einaga, H. *J. Chem. Soc., Chem. Commun.* **1996**, 1069.
(125) Vicens, J.; Fujiwara, T.; Tomita, K. *J. Incl. Phenom.* **1988**, *6*, 577.
(126) Caira, M. R.; Griffith, V. J.; Nassimbeni, L. R.; van Oudtshoorn, B. *Supramol. Chem.* **1996**, *7*, 119.
(127) Harata, K. *Proceedings of the fifth International Symposium on Cyclodextrins*; Duchéne, D., Ed.; Editions de Santó: Paris, 1990; p 676.
(128) Steiner, T.; Saenger, W. *J. Chem. Soc., Chem. Commun.* **1995**, 2087.
(129) Rontoyianni, A.; Mavridis, I. M. *Acta Crystallogr. Sect. C* **1996**, *52*, 2277.
(130) Di Blasio, B.; Galdiero, S.; Saviano, M.; Pedone, C.; Benedetti, E.; Rizzarelli, E.; Pedotti, S.; Vecchio, G.; Gibbons, W. A. *Carbohydr. Res.* **1996**, *282*, 41.
(131) Harata, K. Unpublished work.

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