Crystal structures of 6-deoxy-6-monosubstituted β-cyclodextrins. Substituent-regulated one-dimensional arrays of macrocycles †

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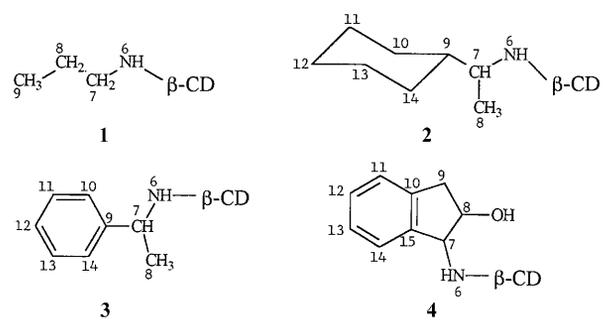
Crystal structures of four 6-monosubstituted β-cyclodextrins, 6-deoxy-6-(1-propyl)amino-β-cyclodextrin (**1**), 6-deoxy-6-[(*R*)-1-cyclohexylethyl]amino-β-cyclodextrin (**2**), 6-deoxy-6-[(*R*)-1-phenylethyl]amino-β-cyclodextrin (**3**), and 6-deoxy-6-[(1*R*,2*S*)-2-hydroxyindan-1-yl]amino-β-cyclodextrin (**4**) were determined by X-ray analysis. In each crystal, the substituent group is inserted into the adjacent β-cyclodextrin ring from the secondary hydroxy side. This donor–acceptor type self-association through intermolecular inclusion generates a one-dimensional polymeric chain. Two types of arrangement of the β-cyclodextrin rings, a helical form and a linear form, were observed. Compounds **1** and **2** form a helically extended chain along a crystallographic twofold screw axis. In contrast the β-cyclodextrin rings are linearly stacked in the crystals of **3** and **4**. The crystal packing of **3** is similar to that of a channel-type structure, while the arrangement of the β-cyclodextrin ring of **4** belongs to the cage-type. These crystal structures suggest that the self-assembly of the 6-monosubstituted β-cyclodextrins is regulated by the physical and chemical properties of the substituent group included in the adjacent β-cyclodextrin ring. A β-cyclodextrin ring with a linear and/or flexible substituent group tends to produce twofold helical packing. The inclusion of a planar and rigid group imposes restrictions on the relative orientation of the macrocycle and this causes variation in the one-dimensional arrangement depending on the shape, size, and orientation of the substituent group.

Introduction

The crystal structures of cyclodextrins and their inclusion complexes have been classified largely into three categories: cage-, channel-, and layer-type.[1] Such variety in the crystal packing has been interpreted to be caused by differences in the spatial relationship between the host and included guest molecules. In other words, the chemical and physical properties of the guest molecule control the assembly of the cyclodextrin macrocycles. On the other hand, cyclodextrins modified by the introduction of a substituent group tend to form one-dimensional arrays by the inclusion of the substituent group in the adjacent cyclodextrin ring. These modified cyclodextrins behave not only as a donor of the guest group but also as an acceptor. The molecules are arranged to form an extended polymeric chain along a twofold screw axis[2–8] or a fourfold screw axis.[3] The variety of crystal packing could be ascribed to differences in the interactions of the substituent group with the adjacent cyclodextrin moiety. However, no structure-based systematic approach has been adopted to elucidate the mechanism of controlling the formation of one-dimensional arrays as mediated by intermolecular inclusion. In this paper, we present the crystal structures of four 6-monosubstituted β-cyclodextrins (Fig. 1), 6-deoxy-6-(1-propyl)amino-β-cyclodextrin (**1**), 6-deoxy-6-[(*R*)-1-cyclohexylethyl]amino-β-cyclodextrin (**2**), 6-deoxy-6-[(*R*)-1-phenylethyl]amino-β-cyclodextrin (**3**), and 6-deoxy-6-[(1*R*,2*S*)-2-hydroxyindan-1-yl]amino-β-cyclodextrin (**4**), and discuss the relationship between crystal packing and the inclusion of the substituent group.



1 **2** **3** **4**

Fig. 1 Chemical structures of 6-monosubstituted β-cyclodextrins.

Experimental

Preparation

Compound **2** was prepared by a previously reported method.[9] Reaction of mono-tosylated β-cyclodextrin (β-CD_{ots}, 0.82 g, 0.63 mM) with (*R*)-(−)-cyclohexylethylamine (4.0 ml) at 100 °C for 22 h was carried out under nitrogen atmosphere. After cooling, the reaction mixture was poured into 150 ml of acetone. The resulting white precipitate was filtered by suction and dried *in vacuo*. The crude product was recrystallized several times from water to give pure compound **2** (0.35 g, 44.2%). The same procedure was applied for the preparation of **1**, **3**, and **4**.

Structure determination ‡

Crystals of **1**, **2**, and **4** were obtained from water. Compound **3**

† Electronic supplementary information (ESI) available: intermolecular contacts of the substituent group and hydrogen bonds (Table S1). See http://www.rsc.org/suppdata/p2/b1/b101521o/

‡ CCDC reference numbers 159690–159693. See http://www.rsc.org/suppdata/p2/b1/b101521o/ for crystallographic files in .cif or other electronic format.

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Table 1 Crystallographic data

Compound	**1**	**2**	**3**	**4**
Formula	$C_{45}H_{77}NO_{34}\cdot 10H_2O$	$C_{50}H_{85}NO_{34}\cdot 8H_2O$	$C_{50}H_{79}NO_{34}\cdot 4CH_4O\cdot 5H_2O$	$C_{51}H_{78}NO_{35}\cdot 15H_2O$
Formula weight	1356.2	1388.3	1456.4	1535.4
Space group	$P2_12_12_1$	$P2_1$	$P2_1$	$P2_1$
Cell constants *a*/Å	13.412(1)	15.215(1)	15.018(2)	15.519(1)
b/Å	19.382(2)	15.862(1)	9.114(1)	10.124(2)
c/Å	26.993(2)	15.417(1)	25.990(5)	23.519(4)
β/°		116.79(1)	101.96(1)	102.67(1)
Number of reflections	5611	5850	5721	7499
Number of parameters	894	878	993	1005
R value for all data	0.114	0.082	0.080	0.069
Max. shift/esd	0.074	0.029	0.39	0.61
Max. residual electron density (e Å^{-3})				
Positive	0.43	0.59	0.63	0.61
Negative	−0.30	−0.23	−0.39	−0.37

was crystallized from 95% aqueous methanol solution. X-Ray experiments were carried out on a Nonius CAD4 diffractometer at room temperature. Graphite-monochromated Cu-Kα radiation was used for the collection of intensity data. Crystal structures were solved by direct methods (SnB program)[10] and refined by full-matrix least-squares methods (SHELX97 program).[11] The coordinates of hydrogen atoms attached to carbon atoms were calculated and included in the structure factor calculation. Crystallographic data are shown in Table 1.

Results

Molecular structure

The structures of **1**, **2**, **3**, and **4** are shown in Fig. 2 and the parameters describing the macrocyclic conformation are listed in Table 2. The β-cyclodextrin ring in these four compounds has a round structure that is characterized by a heptagon composed of seven O4 atoms with an average diameter of 5.05 Å and a side length of 4.38 Å. These O4 atoms are coplanar within 0.087 (**1**), 0.244 (**2**), 0.119 (**3**), and 0.165 Å (**4**). The round macrocyclic structure is maintained mainly by intramolecular hydrogen bonds between the O2H hydroxy group and the O3H hydroxy group of the adjacent glucose unit (G). The $O2(G_n)\cdots O3(G_{n+1})$ distances are in the range from 2.7 to 3.2 Å and their average value for each compound is 2.90 (**1**), 2.81 (**2**), 2.87 (**3**), and 2.80 Å (**4**). As shown in Figs. 3–6, the substituent groups extend outside the β-cyclodextrin ring and are inserted into the cavity of the next molecule.

In compound **1**, the propyl group attached to the G3 unit extends into the next β-cyclodextrin ring. The C6–N6 bond is (+)-*gauche* to the C5–O5 bond and the terminal methyl group is in the *gauche* conformation. The primary hydroxy groups of the G2, G5, and G7 units are in the (−)-*gauche* conformation while the C6–O6 bond in the G1 unit is (+)-*gauche*. The primary hydroxy group in the G4 and G6 units is disordered and shows (+)-*gauche* and (−)-*gauche* conformations.

The β-cyclodextrin ring of compound **2** is the most round of the four compounds because of the inclusion of a bulky cyclohexyl group of the adjacent molecule. The cyclohexyl group with a normal chair conformation extends in a direction perpendicular to the macrocyclic ring. The primary hydroxy group in the G5 unit is disordered and has two conformers with (+)-*gauche* and (−)-*gauche* conformations. Except for the G1 unit, the five glucose units have the primary hydroxy group with a (−)-*gauche* conformation.

The G3 unit of compound **3** is disordered and shows two different orientations with tilt angles of 5.6 and 24.2°. Therefore, one pyranose ring is rotated by 18.6° with respect to the other around the axis passing through the two glycosidic oxygen atoms, O4(G3) and O4(G4). Such rotation changes the distance between O2 and O3 of the adjacent glucose unit. However, the change is so small as not to break the hydrogen bonds. The primary hydroxy group of this glucose unit is in the (+)-*gauche* conformation while the C6–O6 bond in the other glucose units has the (−)-*gauche* conformation. In contrast

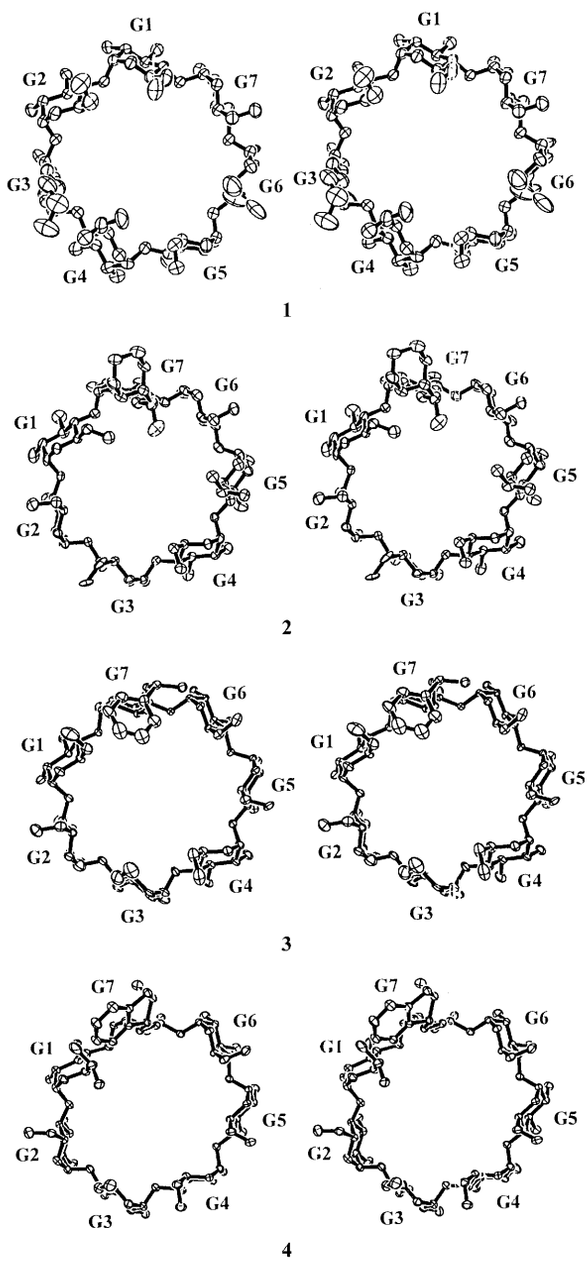
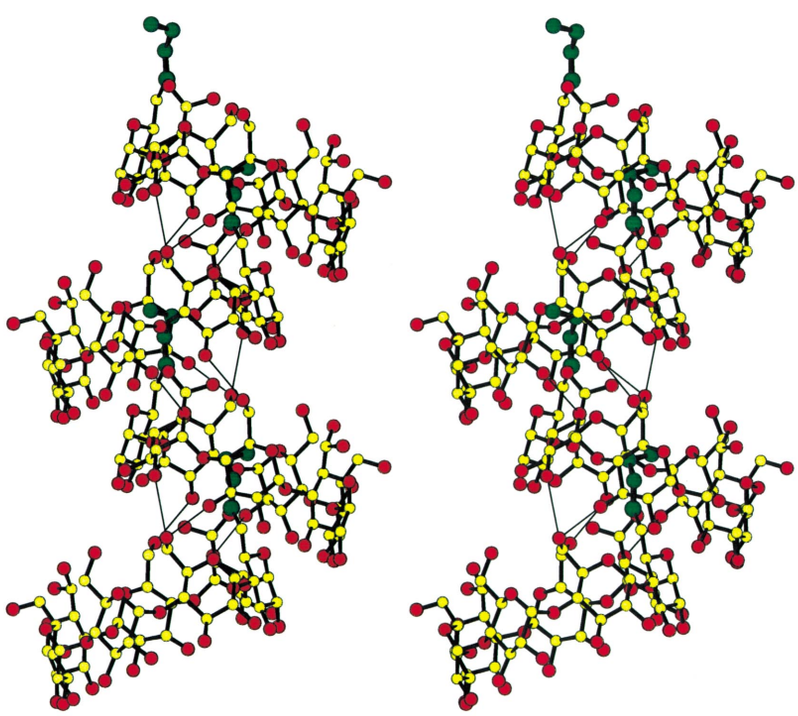


Fig. 2 Stereo-views of the molecular structure. The thermal ellipsoids are drawn at 30% probability. The 1-propylamino group is linked to the G3 unit of **1**. The other substituent groups are appended to the G7 unit.

Table 2 Parameters describing the macrocyclic conformation

	O4 · · · center distance/Å[a]					O4(G$_n$) · · · O4(G$_{n+1}$) distance/Å			
	1	2	3	4		1	2	3	4
G1	4.94	5.05	4.97	4.74	G1 · · · G2	4.41	4.42	4.32	4.39
G2	5.12	5.03	5.09	5.06	G2 · · · G3	4.33	4.36	4.30	4.32
G3	5.21	5.06	5.08	5.32	G3 · · · G4	4.43	4.34	4.39	4.29
G4	4.84	5.03	4.92	4.93	G4 · · · G5	4.43	4.42	4.42	4.57
G5	5.14	5.01	5.06	4.79	G5 · · · G6	4.41	4.35	4.34	4.35
G6	5.16	5.08	5.15	5.31	G6 · · · G7	4.37	4.39	4.36	4.21
G7	5.07	5.03	5.00	5.17	G7 · · · G1	4.46	4.37	4.48	4.54
Average	5.07	5.04	5.04	5.05	Average	4.41	4.38	4.37	4.36
	O2(G$_n$) · · · O3(G$_{n+1}$) distance/Å					Tilt angle/°[b]			
G1 · · · G2	2.84	2.84	2.83	2.86	G1	17.5	23.5	19.4	18.0
G2 · · · G3	2.92	2.76	2.98	2.85	G2	18.4	5.5	2.8	3.6
			2.76		G3	0.6	3.1	24.2	14.0
G3 · · · G4	2.86	2.73	2.83	2.73				5.6	
			2.86		G4	29.7	19.0	21.2	8.7
G4 · · · G5	3.19	2.74	2.83	2.75	G5	14.5	17.3	10.5	10.1
G5 · · · G6	2.84	2.93	2.93	2.86	G6	16.4	3.5	17.1	10.2
G6 · · · G7	2.83	2.85	2.93	2.80	G7	6.4	16.6	11.4	2.7
G7 · · · G1	2.83	2.84	2.83	2.73					
Average	2.90	2.81	2.87	2.80	Average	14.8	12.6	12.5	9.6

[a] The distance from the center of the O4 heptagon to each O4 atom. [b] The tilt angle is defined as the angle made by the plane through the seven O4 atoms and the plane through C1, C4, O4, and O4′ of each glucose unit.



1

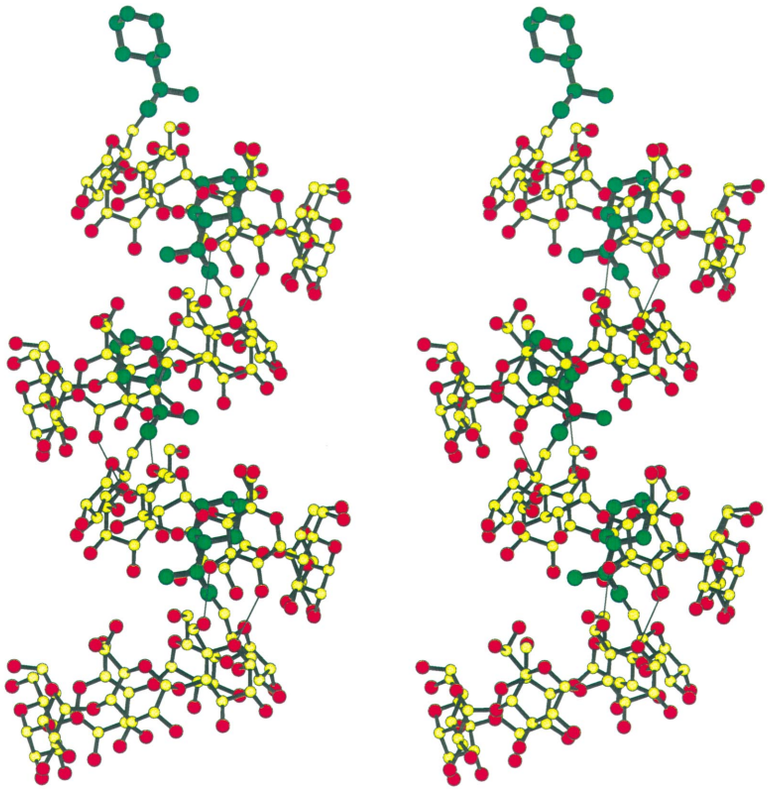
Fig. 3 Stereo-view of the one-dimensional arrangement of 6-monosubstituted β-cyclodextrin **1**. Carbon and oxygen atoms are shown in red and yellow respectively. The substituent groups are drawn in green. The thin lines denote intermolecular hydrogen bonds with a length of less than 3.2 Å.

to the other three compounds, the C6–N6 bond with the (−)-*gauche* conformation points away from the center of the macrocycle. However, the phenyl group is turned toward the β-cyclodextrin ring because of its *gauche* orientation to the C6–N6 bond with a torsion angle of −55.3°.

The inclusion of the 2-hydroxyindanyl group makes the β-cyclodextrin ring elliptical. The largest diameter is 0.6 Å larger than the shortest diameter as shown in Table 2. The average tilt angle of 9.6° is the smallest of the four compounds and this reduced inclination makes the intramolecular hydrogen bonds stronger because of the shortening of the distance between the secondary hydroxy groups. The indane moiety is directed somewhat perpendicular to the β-cyclodextrin ring while the hydroxy group points away from the macrocyclic ring. The primary hydroxy group of the G1 unit is disordered and, with the exception of the G3 unit having a (+)-*gauche* C6–O6 bond, the primary hydroxy group of the G2, G4, G5, and G6 units is in the (−)-*gauche* conformation.

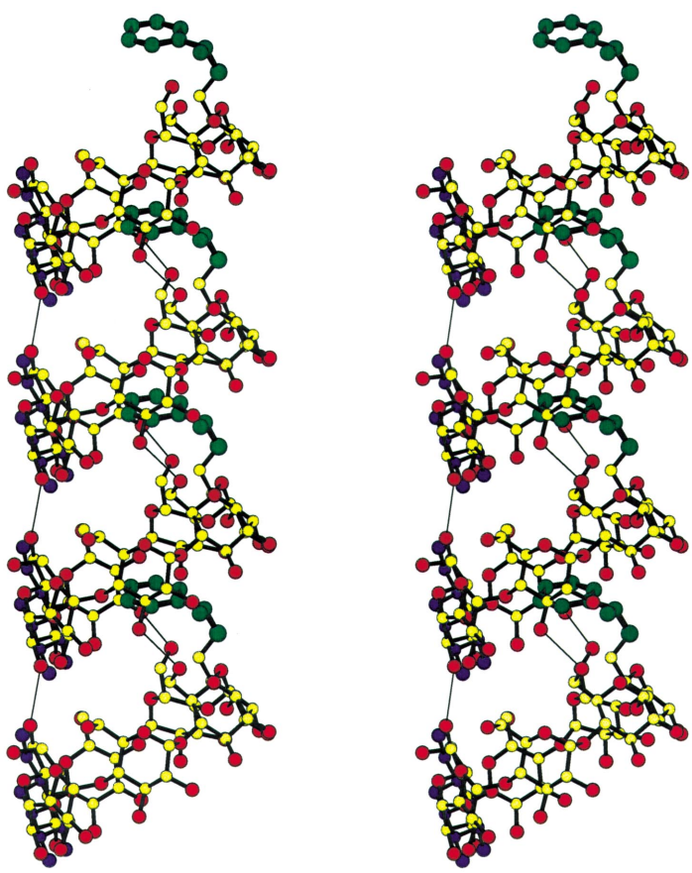
Crystal packing

The crystal structures are shown in Fig. 7 and intermolecular contacts are listed in the ESI (Table S1). The molecular arrangement in the crystal can be classified into two types. One



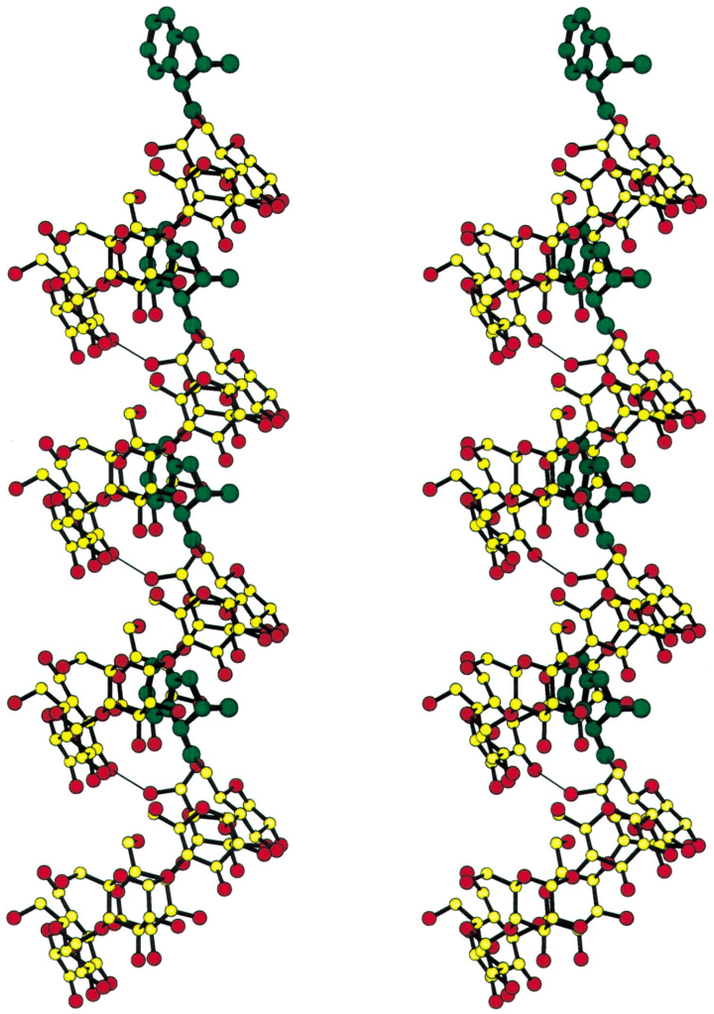
2

Fig. 4 Stereo-view of the one-dimensional arrangement of 6-monosubstituted β-cyclodextrin **2**. Carbon and oxygen atoms are shown in red and yellow, respectively. The substituent groups are drawn in green. The thin lines denote intermolecular hydrogen bonds with less than 3.2 Å.



3

Fig. 5 Stereo-view of the one-dimensional arrangement of 6-monosubstituted β-cyclodextrin **3**. Carbon and oxygen atoms are shown in red and yellow, respectively. The substituent groups are drawn in green. One mate of the disordered G3 unit with a tilt angle of 5.6° in **3** is drawn in dark blue. The tilt angle of the other mate is 24.2°. The thin lines denote intermolecular hydrogen bonds with a length of less than 3.2 Å.



4

Fig. 6 Stereo-view of the one-dimensional arrangement of 6-monosubstituted β-cyclodextrin **4**. Carbon and oxygen atoms are shown in red and yellow, respectively. The substituent groups are drawn in green. The thin lines denote intermolecular hydrogen bonds with a length of less than 3.2 Å.

is the twofold helical arrangement observed in the crystals of **1** and **2**. The molecules are aligned on a twofold screw axis and the inclusion of the substituent group of the symmetry-related mate forms a helically extended polymeric chain. The cyclodextrin ring of both **1** and **2** is not perpendicular to the screw axis but inclined to make an angle of 20.6 and 18.6°, respectively. In the crystal of **1**, molecules are arranged on the twofold screw axis parallel to the *a* axis. Because the crystal has three twofold screw axes, the adjacent helical chain that is symmetry-related by another twofold screw axis is extended in the inverse direction. The propyl group, the smallest substituent group of the four, is deeply inserted into the β-cyclodextrin ring from the secondary hydroxy side, but is loosely bound to the cavity as indicated by the relatively large temperature factors, 0.16–0.25 Å^2. The shortest contact of the propyl group is 3.94 Å found between C8(G3) and O4(G4) of the next β-cyclodextrin ring and no other contacts have been observed within 4.0 Å. The disordered primary hydroxy group of the G4 unit is also inserted into the adjacent β-cyclodextrin ring and the conformer with the (+)-*gauche* conformation is hydrogen-bonded to the amino group.

The cyclohexyl group of **2** is located at the center of the adjacent β-cyclodextrin ring and fully occupies the cavity. The methyl group protrudes from the secondary hydroxy side and is in van der Waals contact with the cyclohexyl group of the adjacent molecule. The shortest contact of the cyclohexyl group is 3.68 Å with O4(G3) of the β-cyclodextrin ring and other interatomic distances are greater than 3.8 Å. The helical arrangement is stabilized not only by the contact of the substituent group with the β-cyclodextrin ring but also by the hydrogen bonds between adjacent β-cyclodextrin rings. In the crystal of compound **2**, the O2H and O3H hydroxy groups of the G2 unit are hydrogen-bonded to O5 and O6H of the G6 unit of the next molecule, respectively. Because of the small substituent group, the β-cyclodextrin rings in the crystal of **1** have much more close contact, and four intermolecular hydrogen bonds are formed between the secondary hydroxy and the primary hydroxy sides of the adjacent molecule. The O2H(G4) and O3H(G5) hydroxy groups are hydrogen-bonded to O6H(G2) of the next molecule. In addition, the O2H(G1) and O3H(G2) hydroxy groups form hydrogen bonds with O5(G4) and O6H(G5), respectively.

In the crystal of **3**, the β-cyclodextrin rings are stacked along the *b* axis to form a structure similar to the head-to-tail channel-type packing structure. The substituent group is inserted into the next β-cyclodextrin ring from the secondary hydroxy side. The phenyl ring of **3** is so tilted in the β-cyclodextrin cavity that it only occupies the secondary hydroxy side of the cavity and a methanol molecule is included to fill the vacant space at the primary hydroxy side. The phenyl group is in van der Waals contact with the inside wall of the β-cyclodextrin cavity with the shortest distance of 3.58 Å between C8(G7) and C3(G6) of the β-cyclodextrin ring. The molecular arrangement is similar to the channel-type structure found in the α-cyclodextrin complex.[12] The head-to-tail channel type packing structure is generally maintained by six or more

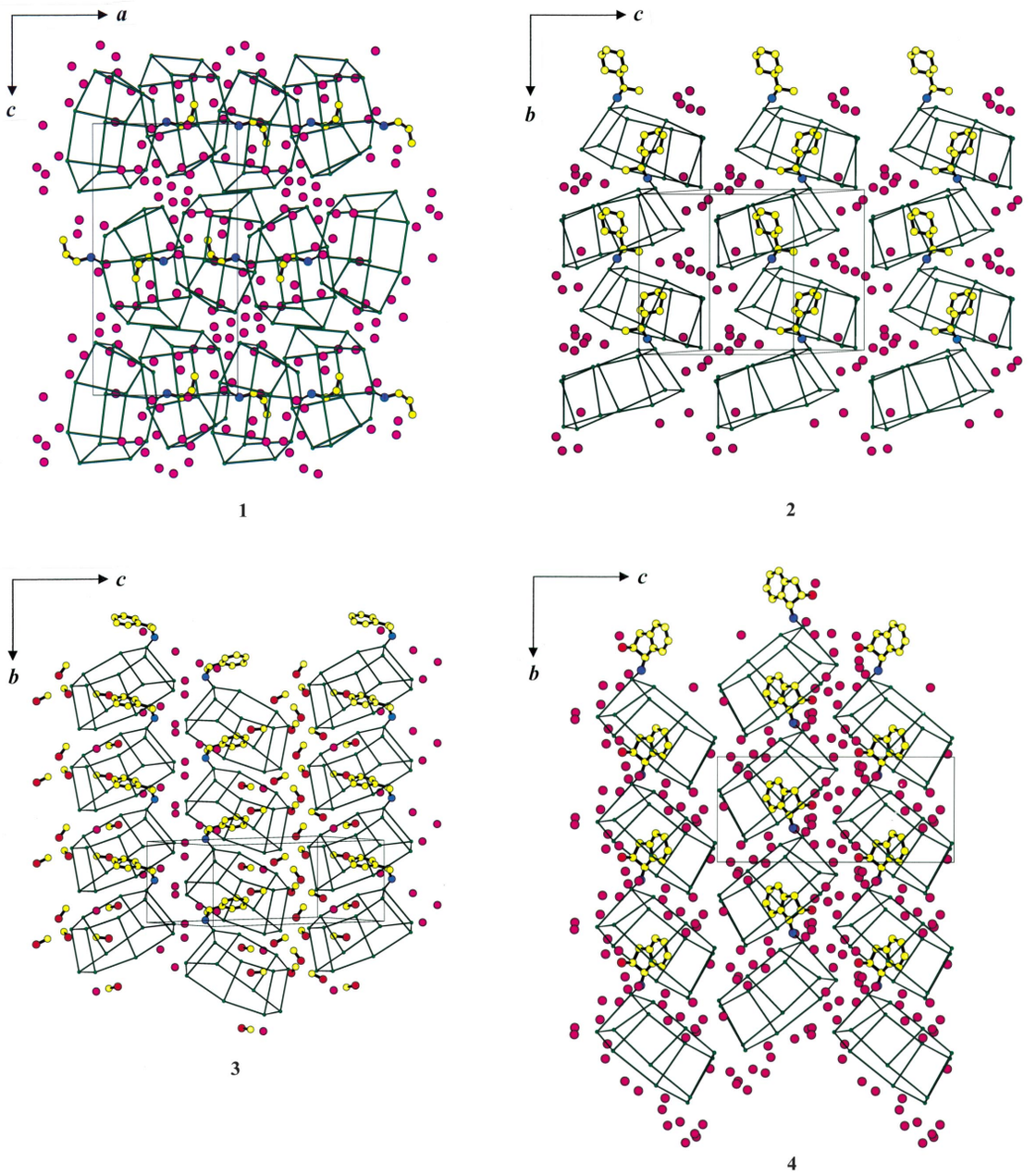


Fig. 7 Crystal structures of the four compounds, **1**–**4**. The β-cyclodextrin ring is drawn with a truncated heptagonal cone. The carbon, nitrogen, and oxygen atoms are shown in yellow, blue, and red, respectively. Water molecules are denoted by magenta circles.

hydrogen bonds between the primary hydroxy groups (O6H) and the secondary hydroxy groups (O2H/O3H) of the adjacent molecule. In contrast, compound **3** forms only three such intermolecular hydrogen bonds between the secondary hydroxy groups of O2(G1)H, O2(G3)H, and O3(G5)H and the primary hydroxy groups of O6(G4)H, O6(G3)H, and O6(G6)H, respectively, of the next molecule. Therefore, unlike the channel-type structure of cyclodextrin inclusion complexes, the column structure of **3** is mainly supported by the interaction between the substituent group and the β-cyclodextrin ring. Solvent channels are created between the β-cyclodextrin columns that are related by the twofold screw axis. Water molecules are located in the solvent channel that has contact with the G7 unit that possesses the substituent group. In contrast, the other channel is filled with methanol molecules as shown in Fig. 7. The crystal contains four methanol molecules, one of which is disordered and occupies two sites.

The 2-hydroxyindanyl group is rather laterally inserted into the β-cyclodextrin ring of the next molecule and occupies the most space of the secondary hydroxy side of the cavity. Water molecules are also located at the primary hydroxy end. The β-cyclodextrin ring is more tilted (39.2°) than that of **3** (30.4°). The adjacent β-cyclodextrin ring is half a molecule shifted parallel to the ring plane. Therefore, both ends of the β-cyclodextrin cavity are open to the intermolecular space. The crystal packing is similar to the typical cage-type packing structure that is observed in crystals of β-cyclodextrin hydrate.[13] Because of the inclusion of the bulky substituent group, adjacent β-cyclodextrin rings are so distant from each other that only one hydrogen bond is formed between O3(G3)H and one conformer of the disordered O6(G1) hydroxy group.

Discussion

Since the X-ray structure of 6-deoxy-6-(*tert*-butylthio)-β-cyclodextrin[2] was reported in 1982, several structures of monosubstituted β-cyclodextrin derivatives have been investigated by the X-ray method.[3–7] Crystal structures of monosubstituted cyclodextrins are classified into three types according to the mode of interaction of the substituent group with cyclo-

dextrin.[1] One is the self-inclusion type that is observed in the crystal structure of 6-deoxy-6-[4-(*N*-*tert*-butoxycarbonyl-2-aminoethyl)]imidazolyl-β-cyclodextrin.[9] The *N*-*tert*-butoxycarbonyl-2-aminoethyl group is bent into the β-cyclodextrin ring and the structure has been called "sleeping swan". Another type of the structure has been observed in the ternary complex of 6-deoxy-6-[2-(imidazol-4-yl)ethyl]amino-β-cyclodextrin with tryptophan and copper(II) nitrate.[14] The molecule is arranged in a layer-type packing structure. The substituent group is not included in the β-cyclodextrin ring but is located in the intermolecular space; instead, a nitrate ion is included in the primary hydroxy side of the β-cyclodextrin cavity.

The third and most frequently observed structure is that attained by one-dimensional self-assembly.[2–7] The molecules are arranged to form an extended polymeric chain associated by the intermolecular inclusion of the substituent group. Crystal structures of 2-*O*-monosubstituted and 6-*O*-monosubstituted cyclodextrins have been reported. The crystal of 2-*O*-[(*S*)-2-hydroxypropyl]-β-cyclodextrin has a nearly isomorphous structure with the native β-cyclodextrin crystal.[5] The molecules are arranged along the twofold screw axis and the substituent group is inserted into the next β-cyclodextrin ring from its secondary hydroxy side. Such 6-monosubstituted β-cyclodextrins as those having 4-*tert*-butylthio,[2] phenylsulfinyl,[3] α-D-glucosyl,[4] 2-hydroxypropyl,[6] or 6-aminohexylamino[7] groups adopt the twofold helical packing structure. In contrast, the fourfold helical structure has been observed in crystals of 6-deoxy-6-phenylthio-β-cyclodextrin.[3] In the present structures of **3** and **4**, we found a linear but non-helical array of the β-cyclodextrin macrocycles.

The crystal structures of monosubstituted β-cyclodextrins have revealed that the formation of linear polymeric structures occurs by self-assembly regulated by the substituent group. The three types of arrangement (a linear chain, a twofold helical chain, and a fourfold helical chain) observed for the 6-monosubstituted β-cyclodextrins suggest that the structural and chemical properties of the substituent group should control the crystal packing. The substituent group is always inserted from the secondary hydroxy side of the β-cyclodextrin ring. The most stable disposition of the substituent group in the β-cyclodextrin cavity not only is determined by the mechanism for attaining the best fit to the inside wall of the cavity, but also is affected by the conformational stability of the linkage connecting the substituent group to the β-cyclodextrin ring. Substituted β-cyclodextrins with aliphatic substituent groups, propylamino and 1-cyclohexylethylamino, adopt the twofold helical arrangement. This is also true for reported structures having 2-hydroxypropyl[6] or 6-aminohexylamino[7] groups. These aliphatic groups are in van der Waals contact with the atoms constructing the inside wall of the β-cyclodextrin ring. On the other hand, an aromatic substituent group causes variation in the packing structure depending on the host–guest interaction because the geometry of intermolecular inclusion is mainly regulated by the shape and size of the rigid planar group. As is observed in the structure of **4**, a bulky and planar group induces elliptical distortion of the β-cyclodextrin ring. The short interatomic distance of 3.34 Å between C13 of the indane moiety and O4(G3) indicates the stabilization of the included group by the C–H $\cdots$ O hydrogen bond because the C13-H group points to the O4(G3) oxygen atom.

The crystal of compound **3** contains four methanol molecules distributed over five sites. Interestingly, these methanol molecules fill the intermolecular channel and have contact with the disordered G3 unit. The macrocyclic structure of β-cyclodextrin is stabilized not only by the intramolecular hydrogen bonds between the secondary hydroxy groups but also by intermolecular hydrogen bonds. There are two types of intermolecular channels running parallel to the twofold screw axis. One channel is filled with water molecules that participate in the formation of the hydrogen-bond network. The other channel accommodates four methanol molecules. The hydroxy group of the methanol is hydrogen-bonded to the hydroxy group of β-cyclodextrin, but the methyl group is in van der Waals contact. Therefore, the replacement of water by methanol blocks the formation of the hydrogen-bond network in the channel. This may increase the flexibility of the glucose units, resulting in the disorder of the G3 unit. The hydrophobic cavity favors the inclusion of a methanol molecule rather than a water molecule. One methanol molecule is accommodated in the intramolecular channel and is sandwiched by phenyl groups. In the crystal of compound **1**, the propyl group is too small to fill the cavity. Two water molecules are located at the primary hydroxy side of the cavity and form hydrogen bonds with the secondary hydroxy groups of the symmetry-related adjacent β-cyclodextrin ring. In contrast, the 1-cyclohexylethyl and 2-hydroxyindanyl groups of compounds **2** and **4** fill the β-cyclodextrin cavity and no space is left for the inclusion of water molecules.

Compounds **2**, **3**, and **4** have an optically active substituent. Cyclodextrin itself is optically active and exhibits chiral discrimination properties in the complex formation. The introduction of a chiral substituent was expected to enhance chiral selectivity in complex formation. Previously we reported that compound **2** has higher chiral recognition ability than native β-cyclodextrin.[8] We have tried to crystallize the (*S*)-isomers of **2** and **3** but obtained only powder or very thin fibrous crystals unsuitable for X-ray analysis. As we demonstrated in an earlier report, the crystals of (*R*)- and (*S*)-2-hydroxypropyl-β-cyclodextrin are isomorphous and the chirality of the methine group that links the β-cyclodextrin moiety regulates the orientation of the guest group. The change in the interaction of the cyclodextrin ring with the substituent group between (*R*)- and (*S*)-hydroxypropyl-β-cyclodextrin affects the stability of the crystals, and as a result, causes the difference in their solubility.

The control of the arrangement of cyclodextrin derivatives depends not only on the intermolecular host–guest interaction but also on the packing of the host macrocycle. Most of monosubstituted cyclodextrins crystallize with the helically periodic structure or the structure similar to either the classical channel-type or cage-type. It is plausible that the stability of the packing of cyclodextrin rings dominates the formation of a polymeric structure. Therefore, the substituent group should regulate the choice of packing mode so as to attain the most stable intermolecular inclusion.

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