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The Structure of the Cyclodextrin Complex. XI. Crystal Structure of Hexakis(2,3,6-tri-*O*-methyl)-*α*-cyclodextrin-*p*-Iodoaniline Monohydrate

Kazuaki Harata,* Kaneto Uekama,† Masaki Otagiri,† and Fumitoshi Hirayama†
Research Institute for Polymers and Textiles, 1-1-4, Yatabe-Higashi, Tsukuba, Ibaraki 305
†*Faculty of Pharmaceutical Sciences, Kumamoto University, 5-1, Oe-honmachi, Kumamoto 862*

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The crystal structure of hexakis(2,3,6-tri-*O*-methyl)-α-cyclodextrin-*p*-iodoaniline complex, $C_{54}H_{96}O_{30}\cdot C_6H_6NI\cdot H_2O$, was determined by the X-ray method. The crystal is monoclinic with the space group $P2_1$, $Z=2$, $a=11.440(4)$, $b=23.674(6)$, $c=13.531(3)$ Å, and $\beta=91.90(2)°$. The structure was solved by the heavy atom method combined with the rigid-body least-squares technique and refined by the block-diagonal least-squares method to the final *R*-value of 0.11 for 2186 reflections ($\sin\theta/\lambda<0.49$). Hexakis(2,3,6-tri-*O*-methyl)-α-cyclodextrin is in the shape of a truncated elliptical cone; these cones are stacked along the a axis to form a channel-type structure. The guest *p*-iodoaniline and water molecules are located in the channel. The iodophenyl group is inserted rather loosely from the base side of the truncated cone. The iodine atom is located at the center of the cavity, while the amino group outside the host cavity forms a hydrogen bond with the water molecule. The water molecule is also hydrogen bonded to the adjacent host molecule along the channel. The crystal is built up of columns of the host molecules, which are closely packed in the van der Waals contact.

The chemical modification of cyclodextrins has been investigated to improve complexing and catalytic abilities by introducing various groups into the macrocyclic ring.[1] Permethylation of cyclodextrins gives compounds which are quite interesting in their macrocyclic structure and complex formation, since permethylated cyclodextrins have no hydroxyl groups. Syntheses and some chemical and spectroscopic data have been recently reported,[2–5] but their structural features have not yet published. The crystal structure of hexakis(2,3,6-tri-*O*-methyl)-α-cyclodextrin(methyl-α-CDx)complex with *p*-iodoaniline has been investigated by the X-ray method. In this paper, the structure of the complex will be discussed mainly by comparison with the structure of α-cyclodextrin–*p*-indoaniline complex.[6]

Experimental

Methyl-α-CDx was added to a *p*-iodoaniline-saturated aqueous solution at 40 °C to prepare a 5% solution. The solution was cooled to 0 °C to dissolve methyl-α-CDx, then allowed to stand at 50 °C. Colorless rod-like crystals were obtained. Lattice parameters and intensities were measured on a Nicolet P3/F diffractometer with graphite-monochromated Cu *Kα* radiation. 2168 independent reflections with $|F_o|\geqq 3\sigma(F)$ were obtained up to 90° in 2θ. No corrections were made for absorption and extinction.

Crystal Data. $C_{54}H_{96}O_{30}\cdot C_6H_6NI\cdot H_2O$, $F.W.=1462.4$, monoclinic, space group $P2_1$, $Z=2$, $a=11.440(4)$, $b=23.674(6)$, $c=13.531(3)$ Å, $\beta=91.90(2)°$, $V=3662.6$ Å^3, $D_x=1.326$, $D_m=1.31$ g cm^{-3}.

Determination and Refinement of the Structure

The structure was solved by the heavy atom method. The electron-density map calculated with iodine phases revealed that the methyl-α-CDx ring is located nearly perpendicular to the a axis. But the center of symmetry which appeared in the map made it quite difficult to estimate the position of light atoms. Therefore, the rigid-body least-squares technique was adopted to determine the orientation and disposition of each 2,3,6-tri-*O*-methylglucose residue. Non-iodine atoms in *p*-iodoaniline and water molecules were found on Fourier and difference-Fourier maps. The structure was refined

Table 1. Fractional coordinates ($\times 10^3$) and isotropic temperature factors (B/Å^2) of hexakis(2,3,6-tri-*O*-methyl)-α-cyclodextrin

	x	*y*	*z*	*B*/Å^2		*x*	*y*	*z*	*B*/Å^2
C(1,G1)	56(3)	472(2)	300(3)	7.5(1.0)	C(1,G4)	110(3)	23(2)	181(3)	6.6(0.9)
C(2,G1)	138(3)	492(2)	374(3)	6.6(0.9)	C(2,G4)	190(3)	10(1)	106(2)	6.0(0.9)
C(3,G1)	189(3)	442(1)	421(2)	5.2(0.8)	C(3,G4)	232(3)	67(1)	65(2)	4.9(0.8)
C(4,G1)	96(3)	406(1)	471(2)	5.0(0.8)	C(4,G4)	130(3)	94(1)	9(2)	5.8(0.8)
C(5,G1)	-14(3)	397(1)	393(2)	6.0(0.8)	C(5,G4)	29(3)	100(1)	80(2)	5.4(0.8)
C(6,G1)	-129(4)	373(2)	432(3)	9.9(1.3)	C(6,G4)	-84(3)	110(2)	9(3)	6.8(0.9)
C(7,G1)	197(5)	579(2)	295(4)	13.9(1.8)	C(7,G4)	289(4)	-77(2)	148(3)	9.6(1.3)
C(8,G1)	373(5)	454(2)	498(4)	12.6(1.6)	C(8,G4)	432(4)	65(2)	31(3)	9.8(1.3)
C(9,G1)	-270(6)	402(3)	562(5)	18.7(2.6)	C(9,G4)	-277(4)	123(2)	18(3)	9.7(1.3)
O(2,G1)	237(2)	521(1)	335(2)	8.7(0.7)	O(2,G4)	289(2)	-16(1)	163(2)	8.2(0.7)
O(3,G1)	267(3)	459(1)	511(2)	10.2(0.8)	O(3,G4)	318(2)	54(1)	-10(2)	8.3(0.7)
O(4,G1)	145(2)	351(1)	495(1)	5.3(0.5)	O(4,G4)	172(2)	150(1)	-13(1)	4.6(0.5)
O(5,G1)	-43(2)	447(1)	345(2)	6.2(0.6)	O(5,G4)	-1(2)	47(1)	121(1)	5.1(0.5)
O(6,G1)	-144(4)	413(2)	514(3)	16.7(1.4)	O(6,G4)	-172(2)	124(1)	77(2)	8.1(0.7)
C(1,G2)	95(3)	386(2)	-62(3)	7.2(1.0)	C(1,G5)	105(3)	109(1)	541(2)	6.0(0.8)
C(2,G2)	166(3)	436(1)	-32(2)	5.4(0.8)	C(2,G5)	197(3)	63(2)	517(3)	6.9(0.9)
C(3,G2)	194(3)	438(1)	73(2)	4.6(0.7)	C(3,G5)	222(3)	67(2)	409(3)	7.4(1.0)
C(4,G2)	85(3)	443(2)	126(3)	7.5(1.0)	C(4,G5)	116(3)	57(1)	345(2)	4.1(0.7)
C(5,G2)	2(3)	393(2)	90(3)	7.1(1.0)	C(5,G5)	20(3)	96(1)	385(2)	4.8(0.7)
C(6,G2)	-126(3)	393(2)	131(3)	7.2(1.0)	C(6,G5)	-100(3)	76(2)	342(3)	7.2(1.0)
C(7,G2)	292(4)	458(2)	-172(3)	9.7(1.3)	C(7,G5)	340(5)	38(2)	642(4)	13.4(1.7)
C(8,G2)	362(4)	478(2)	151(3)	9.3(1.2)	C(8,G5)	396(4)	48(2)	342(4)	12.0(1.5)
C(9,G2)	-295(4)	438(2)	147(3)	9.5(1.2)	C(9,G5)	-298(4)	106(2)	337(4)	11.8(1.5)
O(2,G2)	280(2)	430(1)	-81(2)	7.5(0.6)	O(2,G5)	305(3)	79(1)	580(2)	9.5(0.8)
O(3,G2)	263(2)	486(1)	98(2)	6.6(0.6)	O(3,G5)	305(2)	23(1)	392(2)	8.1(0.7)
O(4,G2)	108(2)	436(1)	231(2)	5.4(0.5)	O(4,G5)	140(2)	64(1)	250(1)	4.5(0.5)
O(5,G2)	-10(2)	394(1)	-12(2)	6.7(0.6)	O(5,G5)	7(2)	96(1)	487(2)	5.6(0.5)
O(6,G2)	-177(2)	442(1)	114(2)	7.4(0.6)	O(6,G5)	-184(2)	121(1)	370(2)	9.5(0.8)
C(1,G3)	171(3)	165(1)	-109(2)	5.8(0.8)	C(1,G6)	150(3)	339(2)	593(3)	6.7(0.9)
C(2,G3)	275(3)	204(1)	-138(2)	4.4(0.7)	C(2,G6)	260(3)	300(1)	614(2)	5.7(0.8)
C(3,G3)	263(2)	259(1)	-80(2)	4.7(0.7)	C(3,G6)	266(3)	248(2)	552(2)	6.1(0.7)
C(4,G3)	147(3)	289(1)	-100(2)	4.6(0.7)	C(4,G6)	152(3)	213(1)	575(2)	5.2(0.7)
C(5,G3)	47(3)	248(2)	-87(2)	5.3(0.7)	C(5,G6)	47(2)	250(2)	559(2)	4.7(0.6)
C(6,G3)	-63(4)	274(2)	-132(3)	9.3(1.2)	C(6,G6)	-67(4)	217(2)	593(3)	8.8(1.2)
C(7,G3)	448(4)	159(2)	-186(3)	10.2(1.3)	C(7,G6)	448(4)	333(2)	664(3)	9.1(1.2)
C(8,G3)	441(4)	313(2)	-32(3)	8.1(1.1)	C(8,G6)	433(4)	200(2)	505(3)	9.8(1.3)
C(9,G3)	-249(7)	263(4)	-159(6)	24.3(3.5)	C(9,G6)	-245(6)	234(4)	524(6)	21.9(2.9)
O(2,G3)	379(2)	177(1)	-102(2)	6.2(0.6)	O(2,G6)	361(2)	335(1)	584(2)	7.2(0.6)
O(3,G3)	356(2)	294(1)	-111(2)	8.0(0.7)	O(3,G6)	360(2)	214(1)	585(2)	8.0(0.7)
O(4,G3)	150(2)	333(1)	-31(1)	4.6(0.5)	O(4,G6)	153(2)	167(1)	507(1)	5.0(0.5)
O(5,G3)	67(2)	196(1)	-144(2)	6.1(0.6)	O(5,G6)	55(2)	301(1)	616(2)	5.5(0.5)
O(6,G3)	-154(3)	245(2)	-110(3)	16.0(1.2)	O(6,G6)	-157(3)	252(2)	573(2)	12.5(0.9)

Table 2. Fractional coordinates ($\times 10^3$) and B_{eq} of *p*-iodoaniline and water

	x	*y*	*z*	B_{eq}/Å^2
C(1,IA)	557(5)	272(2)	263(4)	13.1
C(2,IA)	519(8)	227(2)	217(4)	22.3
C(3,IA)	383(5)	215(2)	209(4)	13.3
C(4,IA)	306(4)	257(4)	243(4)	15.1
C(5,IA)	352(6)	307(2)	278(5)	15.8
C(6,IA)	475(8)	314(2)	282(6)	25.5
N(IA)	669(4)	276(3)	255(6)	19.6
I(IA)	114.2(0.2)	247.8(—)	238.7(0.3)	12.4
O(W)	−190(6)	200(3)	219(5)	29.4

by the block-diagonal least-squares method. Anisotropic temperature factors were used for *p*-iodoaniline and water, isotropic ones for methyl-α-CDx. The quantity minimized was $\sum w(|F_o|-|F_c|)^2$ with $w=1.0$ for all the reflections. The final *R*-value was 0.11. The atomic scattering factors were taken from "International Tables for X-Ray Crystallography."[7] The atomic parameters are given in Tables 1 and 2. Tables of observed and calculated structure factors, anisotropic temperature factors of *p*-iodoaniline and water, bond-distances, angles, and conformation angles of methyl-α-CDx are kept at The Chemical Society of Japan (Document No. 8211).

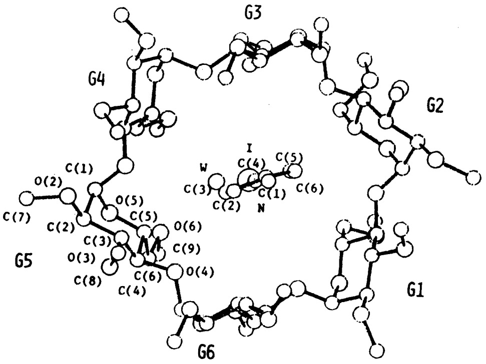

Fig. 1. Structure and numbering scheme of hexakis (2,3,6-tri-*O*-methyl)-α-cyclodextrin–*p*-iodoaniline monohydrate. The water molecule is denoted by W.

Description and Discussion of the Structure

Outline of the Structure. The structure and numbering scheme of the methyl-α-CDx–*p*-iodoaniline complex are shown in Figs. 1 and 2. Methyl-α-CDx is in the shape of a truncated elliptical cone, and is stacked along the a axis with a head-to-tail fashion to form a channel-type structure, as shown in Fig. 3. About two-thirds of the guest *p*-indoaniline molecules are inserted from the O(2), O(3) side of methyl-α-CDx. The amino group forms a hydrogen bond with the water molecule.

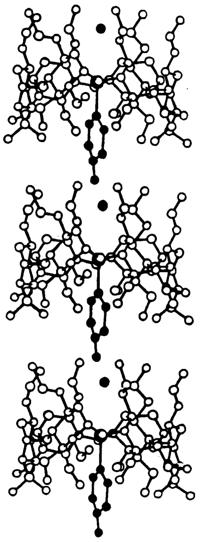

Fig. 3. A stacking feature of the complex. *p*-Iodoaniline and water are shown by black dots.

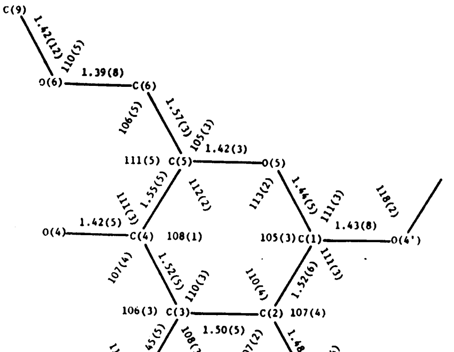

Fig. 4. Average bond distances (*l*/Å) and angles (*ϕ*/°) of hexakis(2,3,6-tri-*O*-methyl)-α-cyclodextrin over six 2,3,6-tri-*O*-methylglucose residues. Standard deviations in parentheses were estimated according to the equation, $\sigma=[\sum_{i=1}^{6}(x_i-\bar{x}^2)/5]^{1/2}$, where x_i referes to the bond distance or angle in the *i*-th residue and $\bar{x}$ is the average value.

Conformation of Methyl-α-CDx. Average bond distances and angles over six 2,3,6-tri-*O*-methylglucose residues are shown in Fig. 4. Geometrical data for the methyl-α-CDx ring are given in Tables 3—5. The C(6)–O(6) bonds of G1 and G2 residues are in the *gauche-gauche* conformation, the other four C(6)–O(6) bonds being in the *gauche-trans* conformation. All O(6)–C(9) bonds are *trans* to the C(5)–C(6) bond. The orientations of O(2)–C(7) and O(3)–C(8) bonds are different. All O(2)–C(7) bonds are oriented outside the methyl-α-CDx

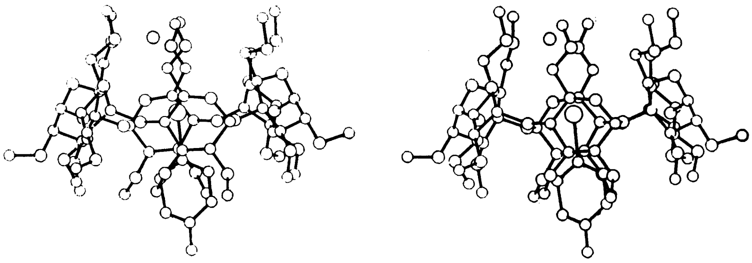

Fig. 2. A stereo-drawing of a side-view of the complex.

Table 3. Selected intramolecular distances

Distance(l/Å)		Distance(l/Å)	
I. O(4)···O(4) distances			
O(4,G1)···O(4,G2)	4.11	O(4,G5)···O(4,G6)	4.25
O(4,G1)···O(4,G6)	4.36	O(4,G1)···O(4,G4)	8.37
O(4,G2)···O(4,G3)	4.35	O(4,G2)···O(4,G5)	8.82
O(4,G3)···O(4,G4)	4.34	O(4,G3)···O(4,G6)	8.27
O(4,G4)···O(4,G5)	4.13		
II. O(2)···O(3) distances			
O(2,G1)···O(3,G2)	3.33	O(2,G3)···O(3,G4)	3.26
O(2,G6)···O(3,G1)	3.26	O(2,G4)···O(3,G5)	3.23
O(2,G2)···O(3,G3)	3.37	O(2,G5)···O(3,G6)	3.25
III. O(2)···C(8) distances			
O(2,G6)···C(8,G1)	3.04	O(2,G3)···C(8,G4)	3.25
O(2,G1)···C(8,G2)	3.08	O(2,G4)···C(8,G5)	3.07
O(2,G2)···C(8,G3)	3.38	O(2,G5)···C(8,G6)	3.39

Table 4. Least-squares plane through six O(4) atoms and deviations from the plane

The plane equation is of the $AX+BY+CZ=D$ form, where X, Y, and Z are the coordinates in Å units along the a, b, and c* axes, respectively.

$0.9979X+0.0418Y+0.0497Z=1.9499$

Deviations of atoms from the plane (l/Å)

O(4,G1)	0.16	O(4,G4)	0.15
O(4,G2)	−0.24	O(4,G5)	−0.24
O(4,G3)	0.08	O(4,G6)	0.08

Table 5. Torsion-angle indices and tilt-angles

Residue	ϕ/°	Residue	ϕ/°
I. Torsion-angle index[a)]			
G1	160	G4	491
G2	145	G5	142
G3	151	G6	134
II. Tilt-angle[b)]			
G1	24.5	G4	23.6
G2	22.6	G5	22.1
G3	3.0	G6	3.0

a) The torsion-angle index is defined as follows:
$|\phi(C(1)\text{–}C(2))|+|\phi(C(2)\text{–}C(3))|+|\phi(C(5)\text{–}O(5))|+|\phi(O(5)\text{–}C(1))|-|\phi(C(3)\text{–}C(4))|-|\phi(C(4)-C(5))|$.

b) The tilt-angle is defined as the angle made by the plane through six O(4) atoms and the plane through O(4′), C(1), C(4), and O(4) of each glucose residue.

ring; the average conformation angles of C(1)–C(2)–O(2)–C(7) and C(3)–C(2)–O(2)–C(7) are 106° and −137°, respectively. On the other hand, the O(3)–C(8) bonds turn inside the methyl-α-CDx ring, giving the average C(2)–C(3)–O(3)–C(8) and C(4)–C(3)–O(3)–C(8) angles of −120° and 123°, respectively.

Methyl-α-CDx is in the shape of an elliptically distorted and truncated cone (Fig. 2). The diagonal O(4)···O(4) distances of 8.27, 8.37, and 8.82 Å are similar to those of the α-cyclodextrin-*p*-iodoaniline complex (8.16, 8.44, and 8.88 Å). The longest diagonal is found along the plane of the included *p*-iodoaniline. The O(4)···O(4) distances between adjacent 2,3,6-tri-*O*-methylglucose residues (4.11—4.36 Å) also resemble those of the α-cyclodextrin-*p*-iodoaniline complex (4.07—4.40 Å). But the torsion angle indices (134—160°) are significantly larger than those of the α-cyclodextrin complex (115—134°), suggesting that the pyranose-ring conformation is slightly different in methyl-α-CDx and α-cyclodextrin.

The deviations of O(4) atoms from their least-squares plane (Table 4) shows that these atoms are arranged in a boat form. The boat form is also observed in the α-cyclodextrin-*p*-iodoaniline complex, although the atomic deviation in the α-cyclodextrin complex is smaller than that in the methyl-α-CDx complex. Significant conformational differences between α-cyclodextrin and methyl-α-CDx are observed in O(2)···O(3) distances between the adjacent residues and tilt-angles. The O(2)···O(3) distances in methyl-α-CDx range from 3.23 to 3.37 Å. On the other hand, the corresponding distances in α-cyclodextrin are in the range 2.68—3.00 Å, indicating hydrogen-bond formation. The relatively large O(2)···O(3) distances in methyl-α-CDx are mainly ascribed to the steric hindrance between O(2) and C(8) methyl group of adjacent residue. As seen from Table 3, relatively short distances are found between O(2) and C(8) (3.04—3.39 Å). The steric hindrance also affects the tilt-angle of the 2,3,6-tri-*O*-methylglucose residues (Table 5). The G3 and G6

Table 6. Intermolecular distances less than 3.5 Å

Distance(l/Å)		Distance(l/Å)	
O(6,G4)–O(W)	2.77	C(2,G2)–O(5,G4)	3.43(c)
O(6,G5)–O(W)	2.65	C(9,G2)–O(3,G4)	3.32(c)
N(IA)–O(W)	2.49(a)	O(6,G2)–C)2,G4)	3.38(c)
C(1,IA)–O(W)	3.43(a)	O(6,G2)–O(3,G4)	3.39(c)
C(2,IA)–O(W)	3.39(a)	C(9,G1)–O(3,G5)	2.95(d)
C(7,G3)–O(3,G6)	3.47(b)	O(6,G1)–O(3,G5)	3.46(d)
O(3,G3)–C(7,G6)	3.38(b)		

Code	Symmetry operator		
None	x,	y,	z
a	$1+x$,	y,	z
b	x,	y,	$-1+z$
c	$-x$,	$1/2+y$,	$-z$
d	$-x$,	$1/2+y$,	$1-z$

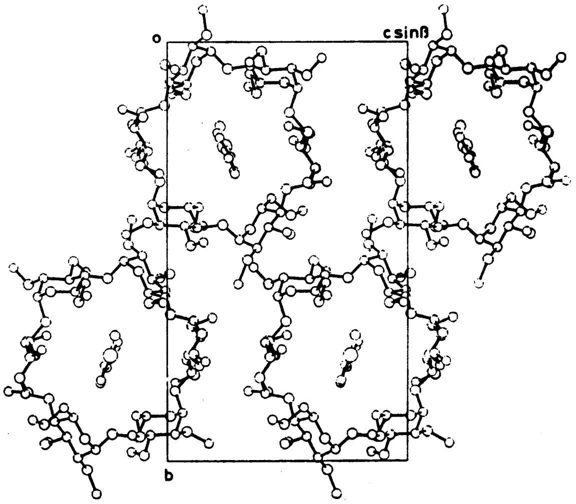

Fig. 5. Crystal structure viewed down the a axis.

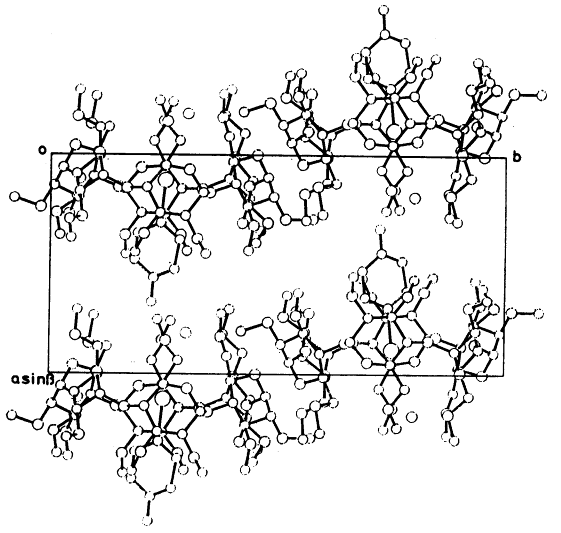

Fig. 6. Crystal structure viewed down the c axis.

residues are almost perpendicular to the O(4) plane, but the other four residues are tilted by the angles of 22.1—24.5°. In the α-cyclodextrin–*p*-iodoaniline complex, the tilt-angles are in the range from 2.1 to 15.6°, and the average value (10.8°) is smaller than that of methyl-α-CDx (16.7°). The conformation of α-cyclodextrin is held by the O(2)···O(3) hydrogen bonds. Since methyl-α-CDx forms no intramolecular hydrogen bonds, the macrocyclic conformation may be more responsible for the steric hindrance between 2,3,6-tri-*O*-methylglucose residues, host-guest interaction, and molecular packing in the crystal.

Methyl-α-CDx–Guest Interaction. *p*-Iodoaniline molecule is inserted into the methyl-α-CDx ring from the O(2), O(3) side, and about two-thirds of the molecule is included. The shortest methyl-α-CDx···guest distance is 3.87 Å, which is found between O(4,G1) and C(5,IA). Therefore, *p*-iodaniline is rather loosely bound in the methyl-α-CDx cavity. The benzene ring is nearly parallel to the C(2,G2)···C(2,G5) diagonal, along which the methyl-α-CDx is elliptically distorted. The iodine atom is located at the center of the cavity. This inclusion geometry is different from that of the α-cyclodextrin complex, in which the whole iodophenyl group is tightly included, although *p*-iodoaniline is also inserted from the O(2), O(3) side. In the methyl-α-CDx complex, the deep penetration of *p*-iodoaniline may be interrupted by the large tilt of G1, G2, G4, and G5 residues, making the O(6) side narrower. The amino group is hydrogen-bonded to a water molecule located at the O(6) side of the adjacent methyl-α-CDx. The water molecule is also hydrogen-bonded to the O(6) atoms of G4 and G5 residues, thus forming $-NH_2$··· water···O(6) hydrogen-bond bridges.

Molecular Packing. Methyl-α-CDx molecules are stacked along the a axis to form a typical channel-type structure. This packing feature resembles those of the α-cyclodextrin complexes with *m*-nitroaniline[8] and benzaldehyde.[9] But, owing to the methylation of all hydroxyl groups, no hydrogen bonds can be formed between methyl-α-CDx molecules along the channel. The O(4) plane is nearly perpendicular to the channel axis (86.3°). *p*-Iodoaniline and water molecules are alternately arranged in the channel. The α-cyclodextrin–*p*-iodoaniline complex does not form a channel-type structure because the dimension of *p*-iodoaniline is large compared with the repetition unit of the channel. In contrast, the repetition unit in the methyl-α-CDx complex is larger than the size of the guest *p*-iodoaniline; thus, a water molecule is also located in the channel to fill the vacant space.

Projections of the crystal structure are shown in Figs. 5 and 6. Since the two-fold screw axis is perpendicular to the channel axis, methyl-α-CDx in the symmetry-related column are arranged upside down. The methyl-α-CDx columns are closely packed in the crystal (Fig. 5). A somewhat short contact (2.95 Å) is found between C(9,G1) and O(3,G5), but other intermolecular distances (Table 6) indicate that the methyl-α-CDx columns are in the van der Waals contact.

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