The structure of the Cyclodextrin Complex. XIV. Crystal Structure of Hexakis(2,3,6-tri-*O*-methyl)-α-cyclodextrin–Benzaldehyde (1 : 1) Complex

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The crystal structure of the hexakis(2,3,6-tri-*O*-methyl)-α-cyclodextrin (abbreviated to methyl-α-CDx)–benzaldehyde (1:1) complex, $C_{54}H_{96}O_{30}\cdot C_7H_6O$, was investigated by the X-ray method. The crystal is monoclinic with the space group $P2_1$ and $Z=2$; the cell dimensions are $a=11.604(1)$, $b=23.832(3)$, $c=13.539(1)$ Å, and $\beta=106.11(1)°$. The structure was determined by inspection of a Patterson map and a trial-and-error method combined with the rigid-body least-squares technique, and refined by the block-diagonal least-squares method to the final R-value of 0.10 for 3597 reflections ($\sin\theta/\lambda\leqq0.49$). The methyl-α-CDx molecule is in the shape of a distorted and truncated hexagonal cone. The guest benzaldehyde molecule is fully included within the host cavity. The carbonyl group is located at the center of the cavity, while the phenyl group is located at the base-side of the host cone. Methyl-α-CDx molecules, of which *pseudo* hexagonal axis is inclined by an angle of 17.0° against the crystallographic a axis, are stacked along the a axis to form a head-to-tail channel-type structure.

The complex formation of many compounds, especially pharmaceuticals, with cyclodextrins and their derivatives has been intensively investigated as the cyclodextrins increase solubility and chemical stability of guest compounds.[1,2] These effects of cyclodextrins have been interpreted on the basis of the inclusion phenomena of various guest compounds into cyclodextrins. Previously, we reported on the crystal structure of the α-cyclodextrin–benzaldehyde complex,[3] in which the benzaldehyde molecule is included in the column formed by the stack of α-cyclodextrin rings. Permethylated α-cyclodextrin (hexakis(2,3,6-tri-*O*-methyl)-α-cyclodextrin, abbreviated to methyl-α-CDx) also forms a crystalline complex with benzaldehyde. In this paper, we deal with the crystal structure of the methyl-α-CDx–benzaldehyde (1:1) complex, which will be discussed mainly in comparison with the structure of the α-cyclodextrin–benzaldehyde complex and the methyl-α-CDx–*p*-iodoaniline complex.[4]

Experimental

Crystals of the methyl-α-CDx–benzaldehyde (1:1) complex were obtained by standing an aqueous solution at 40 °C, which contains methyl-α-CDx and benzaldehyde in a 1:1 molar ratio. Measurements of lattice parameters and reflection intensities were carried out on a Nicolet P3/F diffractometer with graphite-monochromated Cu $K\alpha$ radiation. By using the θ-2θ scan technique, 3597 independent reflections with $|F_o|\geqq3\sigma(F)$ were collected up to 100° in 2θ. No corrections were made for absorption or extinction effects.

Crystal Data: $C_{54}H_{96}O_{30}\cdot C_7H_6O$, F.W.=1331.7, monoclinic, space group $P2_1$, $Z=2$, $a=11.604(1)$, $b=23.832(3)$, $c=13.593(1)$ Å, $\beta=106.11(1)°$, $V=3597.1$ Å^3, $D_x=1.229$, $D_m=1.22$ g cm^{-3}.

Determination and Refinement of the Structure

The orientation of the *pseudo* hexagonal axis of methyl-α-CDx was deduced by inspection of a Patterson map. The rotational parameter around the molecular axis and the translational parameters along the crystallographic a and c axes were determined by the trial-and-error method. After the correction of the position and orientation of each 2,3,6-tri-*O*-methylglucose residue by the rigid-body least-squares technique, atomic parameters of methyl-α-CDx were refined by the block-diagonal least-squares method. At this stage, the benzaldehyde molecule was found on a Fourier map. Successive block-diagonal least-squares refinement of the structure converged the R-value to 0.10. The quantity minimized was $\Sigma w(|F_o|-|F_c|)^2$ with $w=1.0$ for all the reflections. The atomic scattering factors were taken from the "International Tables for X-Ray Crystallography."[5] The final atomic coordinates and B_{eq} values are given in Table 1. Tables of anisotropic temperature factors, observed and calculated structure factors, bond distances and angles, and conformation angles in methyl-α-CDx are on file with The Chemical Society of Japan (Document No. 8259). The computation was carried out on a FACOM M-200 computer at the RIPS Center, Tsukuba.

Description and Discussion of the Structure

Outline of the Structure. The structure and numbering scheme of the complex is shown in Fig. 1. Methyl-α-CDx is in the shape of a distorted and truncated hexagonal cone. The guest benzaldehyde molecule is included in the cavity of methyl-α-CDx. The carbonyl group is located at the center of the cavity, while the phenyl group is located at the O(2), O(3) side. Methyl-α-CDx molecules are stacked along the a axis to form a head-to-tail channel-type structure as shown in Fig. 3.

Conformation of Methyl-α-CDx. Average bond distances and angles over six 2,3,6-tri-*O*-methylglucose residues are shown in Fig. 2. Geometrical data of the methyl-α-CDx ring are given in Tables 2 and 3. The C(6)–O(6) bonds in the G4 and G5 residues are in a *gauche-gauche* conformation, while the others have a *gauche-trans* conformation. All O(2)–C(7) bonds are

TABLE 1. FRACTIONAL COORDINATES ($\times 10^4$) AND B_{eq} OF THE METHYL-α-CDx–BENZALDEHYDE COMPLEX

	x	y	z	B_{eq}/Å^2
C(1,G1)	1224(13)	4789(-)	3473(11)	8.0
C(2,G1)	2185(14)	4888(7)	4527(13)	9.3
C(3,G1)	2551(14)	4326(7)	5115(11)	8.3
C(4,G1)	1412(15)	4037(6)	5239(12)	8.6
C(5,G1)	436(13)	3990(6)	4233(12)	8.0
C(6,G1)	-852(14)	3837(8)	4384(15)	10.2
C(7,G1)	3327(19)	5708(7)	4418(16)	12.1
C(8,G1)	4594(16)	4404(15)	6320(21)	19.6
C(9,G1)	-2368(32)	3343(21)	3257(32)	40.9
O(2,G1)	3252(10)	5132(5)	4330(9)	10.2
O(3,G1)	3310(15)	4455(6)	6158(9)	14.5
O(4,G1)	1775(8)	3482(4)	5589(7)	7.5
O(5,G1)	245(8)	4543(4)	3725(8)	8.2
O(6,G1)	-1592(11)	3689(7)	3456(10)	13.6
C(1,G2)	1369(12)	3856(7)	-100(11)	7.8
C(2,G2)	2346(14)	4314(7)	332(12)	8.4
C(3,G2)	2619(13)	4310(7)	1576(11)	8.2
C(4,G2)	1434(11)	4460(7)	1803(10)	7.2
C(5,G2)	411(13)	4057(6)	1239(10)	7.1
C(6,G2)	-823(11)	4322(7)	1266(12)	8.2
C(7,G2)	3777(23)	4517(13)	-571(20)	18.7
C(8,G2)	4593(15)	4592(11)	2633(15)	13.3
C(9,G2)	-2893(14)	4114(9)	795(18)	12.8
O(2,G2)	3433(9)	4167(5)	102(9)	9.7
O(3,G2)	3425(9)	4781(5)	1898(8)	9.3
O(4,G2)	1716(8)	4365(4)	2900(6)	7.0
O(5,G2)	326(8)	4046(4)	185(7)	7.0
O(6,G2)	-1674(10)	3909(6)	839(10)	11.1
C(1,G3)	1427(13)	1612(7)	-460(10)	7.6
C(2,G3)	2627(12)	1930(7)	-378(11)	7.6
C(3,G3)	2725(12)	2473(7)	206(10)	7.2
C(4,G3)	1636(12)	2854(6)	-275(11)	7.0
C(5,G3)	483(13)	2514(6)	-269(11)	7.7
C(6,G3)	-618(13)	2859(7)	-892(13)	8.9
C(7,G3)	4508(19)	1499(9)	-415(18)	13.4
C(8,G3)	4660(16)	2900(10)	1055(15)	12.6
C(9,G3)	-2501(27)	2770(11)	-505(39)	33.1
O(2,G3)	3545(10)	1565(15)	107(9)	9.9
O(3,G3)	3767(9)	2761(5)	59(9)	9.5
O(4,G3)	1749(8)	3330(4)	387(6)	6.4
O(5,G3)	477(8)	2011(4)	-882(7)	7.4
O(6,G3)	-1704(10)	2537(5)	-847(11)	13.0
C(1,G4)	232(15)	259(7)	2203(12)	9.0
C(2,G4)	1197(13)	55(6)	1689(12)	8.2
C(3,G4)	1753(14)	539(6)	1325(11)	7.8
C(4,G4)	798(11)	910(6)	617(11)	6.4
C(5,G4)	-275(12)	1051(6)	1063(10)	7.2
C(6,G4)	-1346(13)	1266(6)	211(12)	8.4
C(7,G4)	1831(19)	-840(7)	2538(16)	12.5
C(8,G4)	3788(17)	363(11)	1256(16)	13.6
C(9,G4)	-2738(20)	1075(11)	-1462(16)	16.5
O(2,G4)	2101(9)	-262(4)	2397(8)	9.2
O(3,G4)	2508(9)	355(5)	722(9)	9.6
O(4,G4)	1375(7)	1450(4)	535(6)	6.5
O(5,G4)	-672(8)	549(4)	1420(7)	7.3
O(6,G4)	-1682(10)	860(5)	-601(9)	10.4
C(1,G5)	601(13)	1219(8)	5851(12)	9.1
C(2,G5)	1311(14)	660(7)	5860(11)	8.7
C(3,G5)	1567(13)	590(7)	4791(11)	8.4
C(4,G5)	405(13)	619(7)	3976(10)	7.4
C(5,G5)	-265(12)	1166(7)	4024(10)	7.8
C(6,G5)	-1548(19)	1248(9)	3241(15)	13.1
C(7,G5)	2460(18)	451(10)	7562(12)	12.7
C(8,G5)	3455(19)	55(13)	4908(19)	15.7
C(9,G5)	-3340(22)	706(15)	2518(18)	19.1
O(2,G5)	2427(10)	695(5)	6604(8)	10.1
O(3,G5)	2069(12)	58(5)	4786(9)	10.7
O(4,G5)	783(8)	639(4)	3001(7)	7.2
O(5,G5)	-471(8)	1169(5)	5011(7)	8.3
O(6,G5)	-2132(14)	745(10)	3326(12)	17.8
C(1,G6)	1813(13)	3329(8)	6612(11)	8.5
C(2,G6)	2808(13)	2936(6)	7093(12)	8.1
C(3,G6)	2635(13)	2378(7)	6435(11)	7.7
C(4,G6)	1399(13)	2141(6)	6404(11)	7.4
C(5,G6)	387(13)	2572(7)	5962(12)	9.0
C(6,G6)	-783(15)	2296(8)	6345(19)	13.5
C(7,G6)	4802(20)	3215(14)	7934(18)	18.5
C(8,G6)	4276(17)	1766(10)	6434(17)	13.1
C(9,G6)	-2663(33)	2374(22)	6294(27)	29.6
O(2,G6)	3933(10)	3181(5)	7053(8)	10.2
O(3,G6)	3527(9)	2002(5)	7028(8)	9.4
O(4,G6)	1266(8)	1687(4)	5691(7)	7.8
O(5,G6)	677(9)	3077(5)	6609(8)	8.8
O(6,G6)	-1563(19)	2705(11)	5940(18)	25.0
C(1,BA)	2389(24)	2403(24)	3262(22)	30.5
C(2,BA)	3069(24)	1883(11)	3244(16)	15.8
C(3,BA)	4302(35)	1853(18)	3531(20)	26.6
C(4,BA)	4992(44)	2269(28)	3963(26)	40.3
C(5,BA)	4360(30)	2685(18)	3765(20)	23.9
C(6,BA)	3237(27)	2811(19)	3615(21)	22.9
C(7,BA)	1323(37)	2562(21)	2968(24)	26.6
O(1,BA)	475(30)	2317(15)	2597(21)	34.1

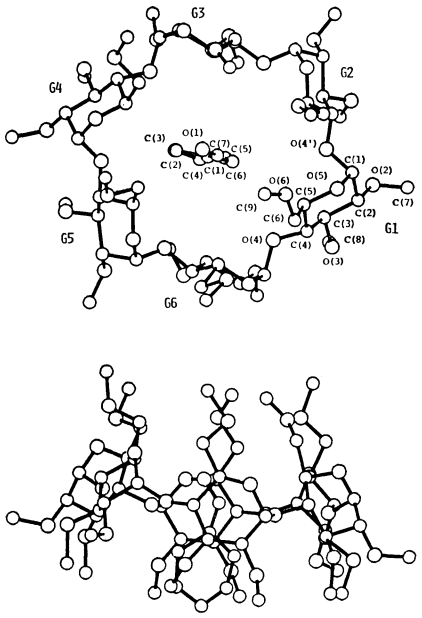

Fig. 1. Structure and numbering scheme of the methyl-α-CDx–benzaldehyde complex.

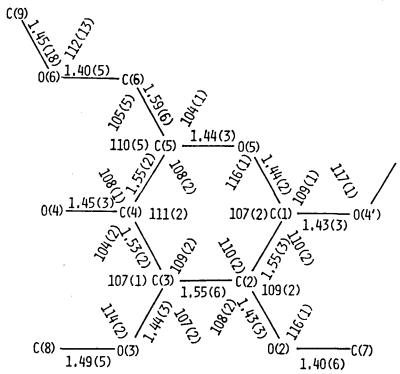

Fig. 2. Average bond distances (l/Å) and angles (ϕ/°) over six 2,3,6-tri-*O*-methylglucose residues. Standard deviations in parentheses were estimated according to the equation:

$$\sigma = [\sum_{i=1}^{6}(x_i - \bar{x})^2/5]^{1/2},$$

where x_i refers to the bond distance or angle in the i-th residue, and $\bar{x}$ is the average value.

directed outside the methyl-α-CDx ring. The O(3)–C(8) and O(6)–C(9) bonds are oriented along the molecular axis of methyl-α-CDx. Six O(4) atoms form a distorted hexagon. The longest diagonal distance (8.95 Å) is found between O(4,G2) and O(4,G5), the shortest one (8.29 Å) being found between O(4,G1) and O(4,G4). The O(4)···O(4) distances between ad-

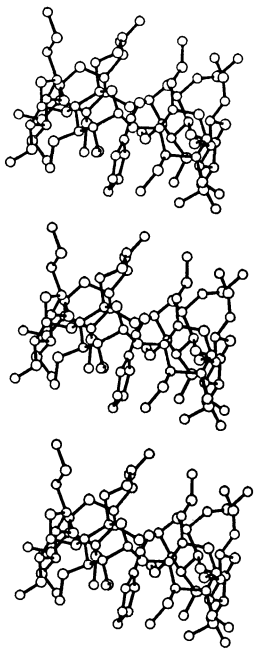

Fig. 3. Stacking feature of the methyl-α-CDx–benzaldehyde complex.

TABLE 2. GEOMETRICAL DATA FOR METHYL-α-CDx

I. O(4)···O(4) distances

Distance	*l*/Å	Distance	*l*/Å
O(4,G1)···O(4,G2)	4.19	O(4,G5)···O(4,G6)	4.32
O(4,G1)···O(4,G6)	4.19	O(4,G1)···O(4,G4)	8.29
O(4,G2)···O(4,G3)	4.21	O(4,G2)···O(4,G5)	8.95
O(4,G3)···O(4,G4)	4.51	O(4,G3)···O(4,G6)	8.33
O(4,G4)···O(4,G5)	4.08		

II. O(2)···O(3) and O(2)···C(8) distances

Distance	*l*/Å	Distance	*l*/Å
O(2,G1)···O(3,G2)	3.46	O(2,G4)···C(8,G4)	3.18
O(2,G2)···O(3,G3)	3.38	O(2,G5)···C(8,G5)	3.25
O(2,G3)···O(3,G4)	3.32	O(2,G6)···C(8,G6)	3.53
O(2,G4)···O(3,G5)	3.33	O(2,G1)···C(8,G2)	3.37
O(2,G5)···O(3,G6)	3.35	O(2,G2)···C(8,G3)	3.43
O(2,G6)···O(3,G1)	3.27	O(2,G3)···C(8,G4)	3.23
O(2,G1)···C(8,G1)	3.22	O(2,G4)···C(8,G5)	3.41
O(2,G2)···C(8,G2)	3.47	O(2,G5)···C(8,G6)	3.38
O(2,G3)···C(8,G3)	3.54	O(2,G6)···C(8,G1)	3.24

III. Tilt-angles[a)]

Residue	ϕ/°	Residue	ϕ/°
G1	27.9	G4	22.9
G2	23.7	G5	26.1
G3	1.7	G6	3.8

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

jacent residues vary in the range 4.08—4.32 Å. These O(4) atoms are roughly coplanar with a maximum deviation of 0.23 Å. The O(2)···O(3) distances (3.27—3.46 Å) between adjacent residues are significantly larger than those found in α-cyclodextrin complexes.[3)] This may be ascribed to the large tilt of the four residues (G1, G2, G4, and G5), which results from the repulsive interaction between the C(8) methyl group and the O(2) atoms of the adjacent residue. The C(8) methyl group is located at a position nearly equidistant from the two vicinal O(2) atoms; 3.18—3.53 Å between C(8) and O(2), and 3.23—3.43 Å between C(8) and O(2) of the adjacent residue.

TABLE 3. 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.

$0.9506X-0.1139Y+0.2889Z=0.9720$

Deviations of atoms from the plane

	l/Å		*l*/Å
O(4,G1)	0.14	O(4,G4)	0.16
O(4,G2)	−0.21	O(4,G5)	−0.23
O(4,G3)	0.06	O(4,G6)	0.06

TABLE 4. INTERMOLECULAR DISTANCES BETWEEN METHYL-α-CDx AND BENZALDEHYDE

Distance	*l*/Å	Distance	*l*/Å
O(4,G1)···C(6,BA)	3.89	C(5,G5)···O(1,BA)	3.59
C(5,G3)···O(1,BA)	3.91	O(4,G5)···C(2,BA)	3.93
C(5,G4)···O(1,BA)	3.63	C(8,G6)···C(4,BA)	3.86
O(4,G4)···C(2,BA)	3.79	C(8,G6)···C(3,BA)	3.94
C(5,G5)···O(1,BA)	3.82	C(6,G5)···O(1,BA)	3.73

The macrocyclic conformation of α-cyclodextrin and methyl-α-CDx has been discussed previously on the basis of the tilt-angle of each residue as well as the geometry of the O(4) hexagon.[3,4)] The tilt-angles (Table 2) were calculated as the angle made by the O(4) plane and the plane through C(1), C(4), O(4), and O(4′). The G3 and G6 residues are nearly perpendicular to the O(4) plane, while the other four residues are sharply inclined with the O(6) side nearer to the molecular axis of methyl-α-CDx. Although the average tilt-angle (17.7°) is somewhat larger than that of the *p*-iodoaniline complex (16.5°), the conformational feature of methyl-α-CDx is quite similar in both complexes.

Methyl-α-CDx-Guest Interaction. The guest benzaldehyde molecule is included within the methyl-α-CDx cavity. The carbonyl group is located at the center of the cavity, while the phenyl group is located at the O(2), O(3) side. The benzaldehyde molecule is sandwiched between the G3 and G6 residues, and the plane through benzaldehyde is nearly parallel to the longest diagonal of the methyl-α-CDx ring. The C(7,BA)–O(1,BA) bond of benzaldehyde is oriented toward the C(5,G4) atom. This inclusion geometry is similar to that of the iodophenyl group,[4)] in which iodine atom is located at the center of the cavity. Intermolecular distances between methyl-α-CDx and benzaldehyde are given in Table 4. The shortest distance of 3.59 Å is found between C(5,G5) and O(1, BA). The comparison of the inclusion geometry between the α-cyclodextrin complex[3)] and the present

complex shows that the permethylation of α-cyclodextrin remarkably affects the position and orientation of the guest molecule as well as the macrocyclic conformation of methyl-α-CDx. In the α-cyclodextrin–benzaldehyde complex, the benzaldehyde molecule is turned upside down in the cavity. Although the phenyl group is also located at the similar position, the carbonyl group protrudes from the cavity and is in contact with the next α-cyclodextrin molecule. Such orientation of the benzaldehyde molecule may be unfavorable in the methyl-α-CDx cavity. The protrusion of the carbonyl group from the O(2), O(3), side may be obstructed by the next methyl-α-CDx molecule, which partly blocks the O(2), O(3) side of the methyl-α-CDx ring. The introduction of methyl groups into the α-cyclodextrin ring enlarges the O(2), O(3) side of the cavity as indicated by the O(2)···O(3) distances, so that the guest molecule seems to be more loosely bound in the methyl-α-CDx cavity.

Molecular Packing. Methyl-α-CDx molecules are stacked along the a axis to form an endless column as shown in Fig. 3. This packing feature resembles that found in the *p*-iodoaniline complex.[4] But, the molecular axis of methyl-α-CDx, which is defined as the axis through the center of gravity of six O(4) atoms and perpendicular to the O(4) plane, is more inclined against the column axis: 3.7° in the *p*-iodoaniline complex and 17.0° in the benzaldehyde complex. Adjacent methyl-α-CDx rings along the column are shifted laterally with respect to each other within the molecular plane. Such a shift reduces the region of overlap of the molecule, and as a result, enables the close packing along the column axis. The distance between the O(4) planes of neighboring methyl-α-CDx molecules in the benzaldehyde complex is 0.32 Å shorter than the corresponding distance in the *p*-iodoaniline complex, although the repetition unit along the column differs by only 0.16 Å. In the α-cyclodextrin–benzaldehyde complex,[3] the α-cyclodextrin molecules stacked along the column axis are linked to one another *via* direct and water-mediated hydrogen bonds. Owing to the methylation of all hydroxyl groups, methyl-α-CDx forms no intermolecular hydrogen bonds, but instead, forms van der Waals contacts, most of which involve methyl groups as shown in Figs. 4 and 5.

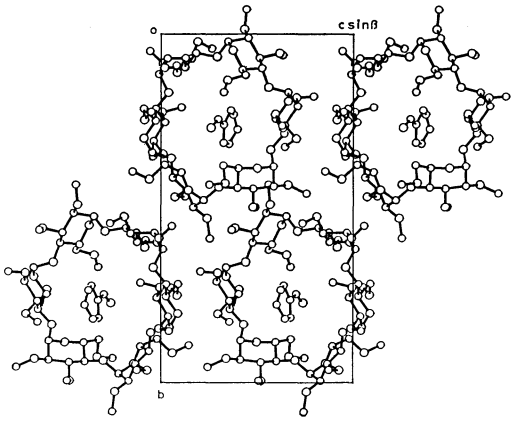

Fig. 4. Crystal structure viewed down along the a axis.

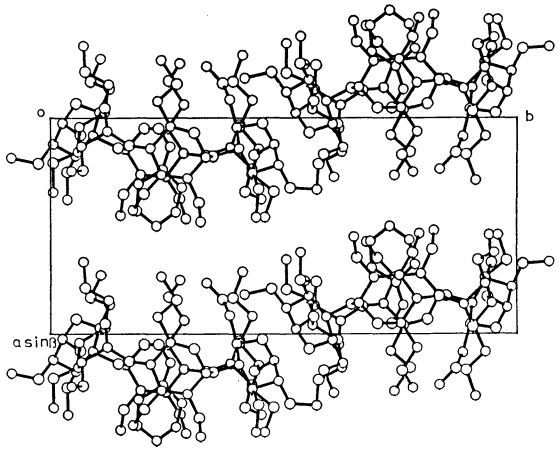

Fig. 5. Crystal structure viewed down along the c axis.

Table 5. Intermolecular distances less than 3.7 Å

Distance	*l*/Å		Distance	*l*/Å	
C(2,G1)-O(6,G5)	3.57	(f)	C(8,G2)-C(8,G5)	3.64	(g)
C(6,G1)-O(3,G5)	3.55	(f)	O(3,G2)-O(6,G4)	3.44	(e)
C(7,G1)-O(6,G5)	3.69	(f)	O(3,G2)-C(9,G4)	3.20	(e)
C(8,G1)-C(8,G5)	3.52	(g)	O(5,G2)-C(2,G4)	3.59	(e)
O(2,G1)-C(8,G5)	3.68	(g)	C(9,G3)-C(7,G6)	3.42	(d)
O(3,G1)-C(9,G5)	3.48	(f)	O(3,G3)-C(7,G6)	3.58	(c)
O(3,G1)-O(6,G5)	3.51	(f)	C(8,G4)-C(9,G5)	3.40	(a)
O(5,G1)-C(2,G5)	3.35	(f)	C(9,G6)-C(4,BA)	3.56	(b)

Code	Symmetry operator		
a	$1+x$,	y,	z
b	$-1+x$,	y,	z
c	x,	y,	$-1+z$
d	$-1+x$,	y,	$-1+z$
e	$-x$,	$1/2+y$,	$-z$
f	$-x$,	$1/2+y$,	$1-z$
g	$1-x$,	$1/2+y$,	$1-z$

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