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CRYSTAL STRUCTURE OF THE INCLUSION COMPLEX OF HEXAKIS-(2,6-DI-*O*-METHYL)CYCLOMALTOHEXAOSE WITH 3-IODOPROPIONIC ACID

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ABSTRACT

The crystal of the 1:1 complex of hexakis(2,6-di-*O*-methyl)cyclomaltohexaose with 3-iodopropionic acid is orthorhombic, space group $P2_12_12_1$, with a = 10.707(1), b = 14.564(3), c = 41.448(4) Å, and Z = 4. The round shape of the host molecule is maintained by the intramolecular O-2···HO-3′ hydrogen bonds. The guest molecule is fully included within the host cavity, with the iodine atom located on the O-6 side. The carboxyl group, located on the O-2,3 side, forms a hydrogen bond with HO-3 of the adjacent host. The host molecules are arranged in a herringbone fashion to form a typical cage-type packing structure.

INTRODUCTION

The chemical modification of cyclomalto-oligosaccharides (cyclodextrins, CDs) has been extensively studied[1–3]. Methylated CDs have unique characteristics compared with CDs. For example, they dissolve in alcohol, acetone, and chloroform, and their solubilities in water decrease rapidly with the increase in temperature.

X-Ray studies have shown that the macrocyclic conformation and host–guest interaction are affected greatly by the degree of methylation. The conformations of CDs in which all HO-2 and HO-6 are methylated are similar[4–6] to that of corresponding native CDs. On the other hand, the macrocyclic conformation in crystalline complexes of 2,3,6-tri-*O*-methyl CDs are distorted markedly[7–9], and fully methylated CDs form inclusion complexes with benzene derivatives in the crystalline state. Heptakis(2,6-di-*O*-methyl)cyclomaltoheptaose (DM-βCD) forms 1:1 crystalline complexes with disubstituted benzenes, but the guest molecules are located in intermolecular crevices[5]. Hexakis(2,6-di-*O*-methyl)cyclomaltohexaose (DM-αCD) forms inclusion complexes with iodine and 1-propanol in a manner similar to that of αCD. We now report on the crystal structure of the DM-αCD complex with 3-iodopropionic acid.

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TABLE I

ATOMIC CO-ORDINATES (× 10^4) AND TEMPERATURE FACTORS ($Å^2$)[a]

		x	y	z	B_{eq}
G1	C-1	347(19)	5906(15)	544(4)	7.3
	C-2	853(18)	6196(14)	185(4)	6.7
	C-3	1219(20)	7201(12)	173(4)	6.2
	C-4	237(19)	7828(12)	290(4)	6.0
	C-5	−190(21)	7551(12)	638(4)	6.7
	C-6	−1295(19)	8124(12)	752(4)	6.5
	C-7	1602(23)	4871(18)	−90(6)	11.3
	C-8	−2443(30)	8354(25)	1211(6)	14.7
	O-2	1844(13)	5604(9)	114(3)	7.3
	O-3	1499(13)	7408(10)	−167(3)	7.9
	O-4	742(11)	8730(9)	306(2)	6.0
	O-5	−537(12)	6605(9)	630(3)	6.4
	O-6	−1464(17)	7913(14)	1078(3)	11.8
G2	C-1	3269(20)	5134(13)	1549(4)	7.2
	C-2	3702(18)	4734(15)	1218(4)	7.1
	C-3	3190(18)	5368(13)	949(4)	6.0
	C-4	1785(18)	5381(13)	968(4)	6.1
	C-5	1384(20)	5732(11)	1312(3)	5.8
	C-6	−129(21)	5638(13)	1342(4)	7.0
	C-7	5728(21)	4047(14)	1269(6)	9.3
	C-8	−418(26)	3984(16)	1423(6)	10.8
	O-2	5024(15)	4841(7)	1221(3)	7.4
	O-3	3538(13)	4900(10)	646(3)	8.0
	O-4	1483(12)	6097(8)	746(3)	6.0
	O-5	1884(12)	5117(8)	1543(3)	6.5
	O-6	−596(13)	4763(10)	1234(3)	7.6
G3	C-1	5120(18)	7866(11)	2263(4)	5.4
	C-2	6062(20)	7087(12)	2134(4)	6.4
	C-3	5485(20)	6722(11)	1819(4)	5.9
	C-4	4188(20)	6266(13)	1898(4)	7.0
	C-5	3336(16)	7059(11)	2045(4)	4.8
	C-6	2061(18)	6685(12)	2153(4)	5.7
	C-7	8238(19)	6950(15)	2082(5)	8.3
	C-8	1078(21)	5449(18)	2404(5)	9.9
	O-2	7185(12)	7558(8)	2076(3)	6.2
	O-3	6277(13)	6017(8)	1688(3)	6.8
	O-4	3672(12)	6054(7)	1583(2)	5.7
	O-5	3957(12)	7394(7)	2331(2)	5.6
	O-6	2184(13)	5874(9)	2336(3)	7.5
G4	C-1	4481(18)	11288(11)	1866(4)	5.6
	C-2	6129(18)	10871(13)	1931(4)	6.1
	C-3	6114(17)	9830(10)	1892(4)	5.3
	C-4	5139(16)	9424(10)	2121(3)	4.5
	C-5	3871(18)	9915(11)	2061(4)	5.7
	C-6	2793(21)	9596(12)	2303(4)	6.8
	C-7	7918(36)	11717(29)	1781(7)	22.1
	C-8	2481(27)	9314(18)	2856(5)	11.3
	O-2	6947(13)	11274(10)	1695(3)	8.5

TABLE I *(continued)*

		x	y	z	B_{eq}
	O-3	7299(12)	9465(10)	1986(3)	8.2
	O-4	4977(12)	8514(7)	2035(2)	5.3
	O-5	3997(12)	10893(7)	2095(2)	5.7
	O-6	3324(14)	9725(9)	2626(3)	8.2
G5	C-1	2627(22)	12021(12)	749(5)	7.5
	C-2	4016(27)	12210(16)	767(5)	10.2
	C-3	4642(23)	11482(15)	1008(4)	8.3
	C-4	4006(19)	11736(13)	1345(4)	6.9
	C-5	2583(20)	11618(11)	1305(4)	6.7
	C-6	1865(21)	11927(14)	1619(4)	7.7
	C-7	5231(37)	12588(17)	277(6)	15.2
	C-8	1900(25)	13084(19)	2031(5)	10.5
	O-2	4593(16)	11884(9)	444(3)	8.8
	O-3	5967(14)	11685(11)	1038(3)	8.9
	O-4	4496(11)	11025(8)	1545(2)	5.5
	O-5	2196(14)	12261(8)	1061(3)	7.5
	O-6	2387(17)	12769(9)	1722(3)	9.2
G6	C-1	214(18)	9424(12)	119(5)	6.4
	C-2	1327(20)	9931(14)	−63(4)	7.6
	C-3	2226(21)	10267(11)	186(4)	6.5
	C-4	1546(21)	10980(17)	400(4)	8.4
	C-5	369(23)	10433(15)	575(5)	8.8
	C-6	−409(24)	11189(17)	744(5)	10.2
	C-7	1893(22)	9476(17)	−605(4)	9.4
	C-8	−1152(28)	12720(20)	644(6)	12.9
	O-2	1921(13)	9240(8)	−261(3)	6.5
	O-3	3191(15)	10775(10)	11(3)	8.6
	O-4	2432(13)	11103(7)	669(3)	6.3
	O-5	−372(12)	10092(10)	309(3)	7.7
	O-6	−655(16)	11954(13)	522(3)	11.4
IP	I-1	1302(2)	8880(2)	1454(1)	9.3
	C-1	3953(50)	8448(36)	812(13)	37.9
	C-2	3124(29)	8220(26)	1022(6)	10.1
	C-3	3014(28)	8840(26)	1200(6)	9.7
	O-1	4580(27)	7579(21)	668(7)	15.5
	O-2	4773(25)	8963(18)	702(7)	15.2
	I-2	4536(7)	8159(6)	688(2)	9.6

$^aB_{eq} = {}^4/_3\Sigma a_i a_j B_{ij}$, where a_i and a_j are lattice parameters and B_{ij} is the anisotropic temperature factor.

EXPERIMENTAL

X-Ray measurements. — An aqueous solution of DM-αCD and 3-iodopropionic acid (~1:1 molar ratio) was kept at 50° to give crystals of the 1:1 complex. The X-ray experiment was carried out at room temperature and the crystal was stable in air. Lattice parameters and diffraction intensities were measured on a

Nicolet P3/F diffractometer, using graphite-monochromated CuK_α radiation. By using the θ–2θ scan mode, 4994 reflections were measured in the 2θ range up to 118°, and 3243 reflections with $|F_o| \geq 3\sigma(F)$ were used for determination of the structure and refinement. No corrections were made for absorption or extinction effects.

Crystal data. — $C_{48}H_{84}O_{30} \cdot C_3H_8IO_2$, mol. wt. 1341.1. Orthorhombic, space group $P2_12_12_1$, $Z = 4$, $a = 10.707(1)$, $b = 14.564(3)$, $c = 41.448(4)$ Å, $V = 6463(2)$ Å^3, $D_x = 1.378$ g.cm^{-3}.

Structure determination and refinement. — The structure was solved by the heavy-atom method combined with phase refinement by the tangent formula. In the electron-density map phased with the contribution from iodine only, no light atoms could be located because of the poor resolution of the map. When the phases of the reflections with $|E| \geq 1.4$ were refined by the tangent formula, most of the light atoms were found on the E-map. The structure was fully determined by successive Fourier and difference-Fourier syntheses and refined by the block-diagonal least-squares method. During the refinement, the 3-iodopropionic acid molecule was found to be two-fold disordered with occupancies of 0.75 and 0.25. The occupancy factor of the molecule was estimated from the electron density of the iodine atom and not refined. The light atoms with the lower occupancy were not located because of statistical overlap of their electron densities on the molecule with the higher occupancy. The least-squares refinement minimizing $\Sigma w(|F_o| - |F_c|)^2$, with anisotropic temperature factors and unit weight for all the reflections, converged at an R value of 0.095. Final atomic co-ordinates are listed in Table I*.

DESCRIPTION OF THE STRUCTURE

The structure and numbering scheme of the complex are shown in Fig. 1. The DM-αCD molecule is round in shape and includes 3-iodopropionic acid. Each pyranose ring is in the $^4C_1$ conformation. Average bond distances and angles for the six 2,6-di-*O*-methyl-D-glucopyranose residues are given in Fig. 2, and Table II contains the torsion angles. Methyl groups attached to O-2 point away from the center of the macrocycle as indicated by the torsion angles C-1–C-2–O-2–C-7 and C-3–C-2–O-2–C-7 which are near ±120°. Except for the G1 unit, the C-6–O-6 bonds are *gauche* to the C-4–C-5 and C-5–O-5 bonds. The C-6–O-6 bond of the G1 unit is *trans* to the C-4–C-5 bond and *gauche* to the C-5–O-5 bond. The MeO-6 groups are *trans* except in the G2 unit. The torsion angles involving these methoxyl groups, C-5–C-6–O-6–C-8, are in the range −170 to −178°. The torsion angle of the C-6–O-6 bond of the G2 unit is 74°, showing a *gauche* conformation.

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*Observed and calculated structure factors and anisotropic temperature factors are deposited with, and can be obtained from, Elsevier Science Publishers B.V., BBA Data Deposition, P.O. Box 1527, Amsterdam, The Netherlands. Reference should be made to No. BBA/DD/413/*Carbohydr. Res.*, 192 (1989) 33–42.

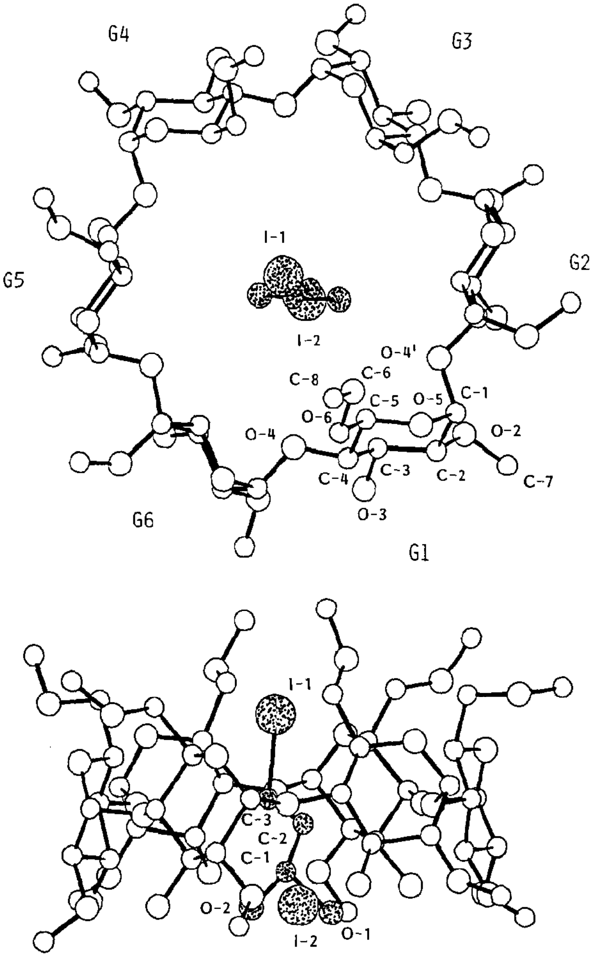

Fig. 1. The structure and numbering scheme of the complex of DM-αCD with 3-iodopropionic acid.

Some parameters describing the macrocyclic conformation of DM-αCD are given in Table III and Fig. 3. The O-4 atoms are coplanar within 0.178 Å, and these atoms form a nearly regular hexagon with the radius 4.18–4.29 Å and side length 4.19–4.32 Å. The distance between O-2 and O-3′ of the next unit is in the range 2.73–3.03 Å, indicating the formation of intramolecular O-2···HO-3′ hydrogen bonds.

Each 2,6-di-*O*-methyl-D-glucopyranose residue inclines with its O-6 side towards the inside of the macrocycle. The tilt-angles (Table III) are in the range 4.8–19.5°. Therefore, the O-6 side of the cavity of DM-αCD is somewhat narrower than the O-2,3 side.

The 3-iodopropionic acid molecule is fully included within the cavity of DM-

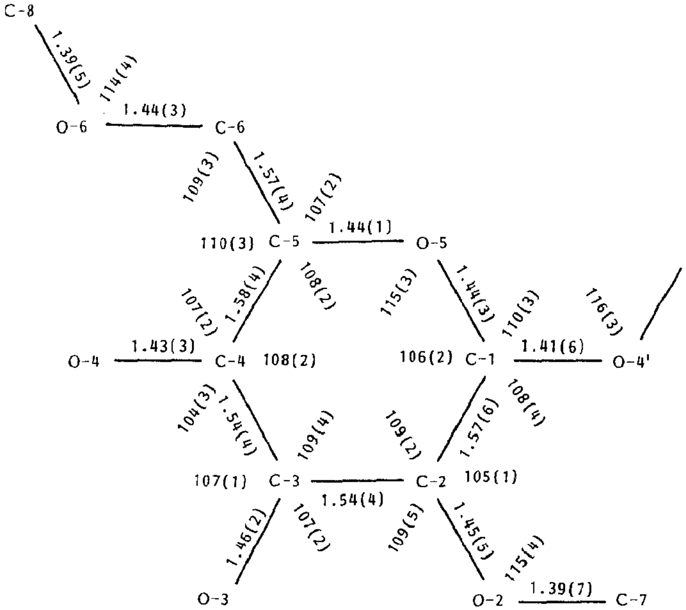

Fig. 2. Average bond distances and angles of six 2,6-di-*O*-methyl-D-glucopyranose residues. Standard deviations in parentheses were estimated according to the equation:

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

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

TABLE II

TORSION ANGLES (ϕ/°) OF DM-αCD

	G1	*G2*	*G3*	*G4*	*G5*	*G6*
C-1–C-2–C-3–C-4	−52	−60	−63	−58	−64	−63
C-2–C-3–C-4–C-5	55	56	61	53	60	61
C-3–C-4–C-5–O-5	−54	−60	−60	−55	−62	−59
C-4–C-5–O-5–C-1	61	65	67	61	70	66
C-5–O-5–C-1–C-2	−57	−67	−68	−62	−71	−68
O-5–C-1–C-2–C-3	48	63	63	60	68	63
O-4'–C-1–C-2–O-2	62	57	61	63	53	61
O-2–C-2–C-3–O-3	67	73	67	69	71	68
O-3–C-3–C-4–O-4	−69	−77	−69	−73	−71	−77
O-4–C-4–C-5–C-6	68	77	73	68	75	81
C-4–C-5–C-6–O-6	−171	47	47	54	45	49
O-5–C-5–C-6–O-6	70	−69	−70	−69	−70	−62
C-1–C-2–O-2–C-7	101	106	157	122	122	120
C-3–C-2–O-2–C-7	−136	−140	−89	−117	−125	−123
C-3–C-4–O-4–C-1'	119	141	128	125	137	134
C-5–C-4–O-4–C-1'	−121	−105	−120	−118	−109	−115
C-4–O-4–C-1'–C-2'	−130	−134	−136	−129	−132	−130
C-4–O-4–C-1'–O-5'	113	117	108	114	111	115
C-5–C-6–O-6–C-8	−178	74	−172	−171	−174	−170

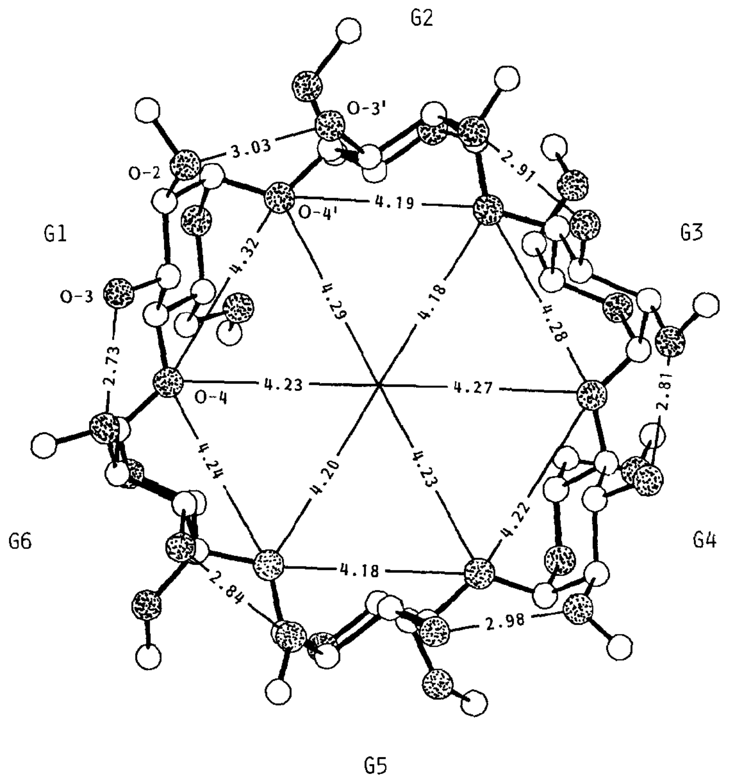

Fig. 3. O-4 · · · O-4′ distances (Å) and O-2 · · · O-3′distances (Å) in DM-αCD. Oxygen atoms are shown by shaded circles.

TABLE III

SOME PARAMETERS DESCRIBING THE CONFORMATION OF THE MACROCYCLE

Residue	*I*[a]	*II*[b]	*III*[c]	*IV*[d]
G1	119	109	19.5	−0.119
G2	114	137	4.8	0.086
G3	114	140	12.8	0.175
G4	119	133	15.9	−0.165
G5	117	151	7.9	0.025
G6	113	140	8.1	0.101

[a] Glycosidic oxygen angle (ϕ/°). [b] Torsion-angle index (ϕ/°), which is defined as: $\phi = |\phi(\text{C-1–C-2})| + |\phi(\text{C-2–C-3})| + |\phi(\text{C-5–O-5})| + |\phi(\text{O-5–C-1})| - |\phi(\text{C-3–C-4})| - |\phi(\text{C-4–C-5})|$. [c] Tilt angle (ϕ/°), which is defined as the angle made by the O-4 plane and the plane through C-1, C-4, O-4, and O-4′. [d] Deviation of O-4 atoms from the least-squares plane through six O-4 atoms (*d*/Å).

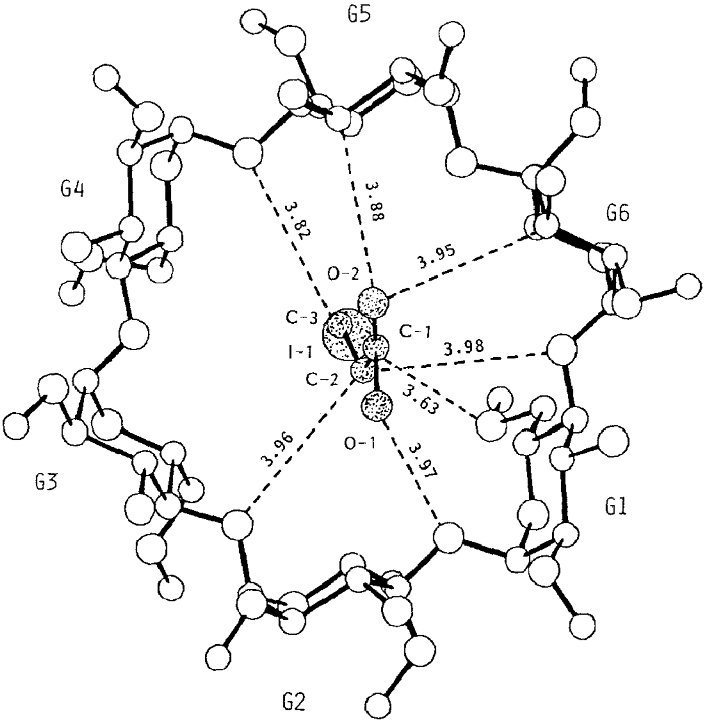

Fig. 4. Intermolecular distances <4 Å between DM-αCD and 3-iodopropionic acid.

αCD, but is disordered in the host cavity. The molecule with the higher occupancy (0.75) is included with its carboxyl group being located at the O-2,3 side. The iodine atom is situated at the center of the hexagon composed of six CH_2-6 methylene groups. The guest molecule with the lower occupancy (0.25) is expected to be included in an inverted position, although the propionic acid moiety of this

TABLE IV

COMPARISON OF THE MACROCYCLIC CONFORMATIONS OF αCD, DM-αCD, AND TM-αCD

	αCD[a]	*DM-αCD*[b]	*TM-αCD*[c]
Radius of the O-4 hexagon (*l*/Å)	4.2(0.1)[d]	4.2(0.1)	4.3(0.2)
O-4 · · · O-4′ distance (*l*/Å)	4.2(0.1)	4.2(0.1)	4.3(0.1)
O-2 · · · O-3′ distance (*l*/Å)	3.0(0.1)	2.9(0.1)	3.4(0.1)
O-4 angle (ϕ/°)	119(1)	116(3)	118(1)
Planarity of the O-4 hexagon (*d*/Å)[e]	0.102	0.123	0.132
Torsion-angle index (ϕ/°)	131(4)	135(14)	137(12)
Tilt-angle (ϕ/°)	13(10)	12(6)	18(12)

[a] αCD–1-propanol complex, see ref. 11. [b] Present work. [c] Complex of fully methylated αCD with D-mandelic acid, see ref. 8. [d] Average values are given with standard deviations. [e] The root-mean-square deviation of O-4 atoms from the least-squares plane through six O-4 atoms.

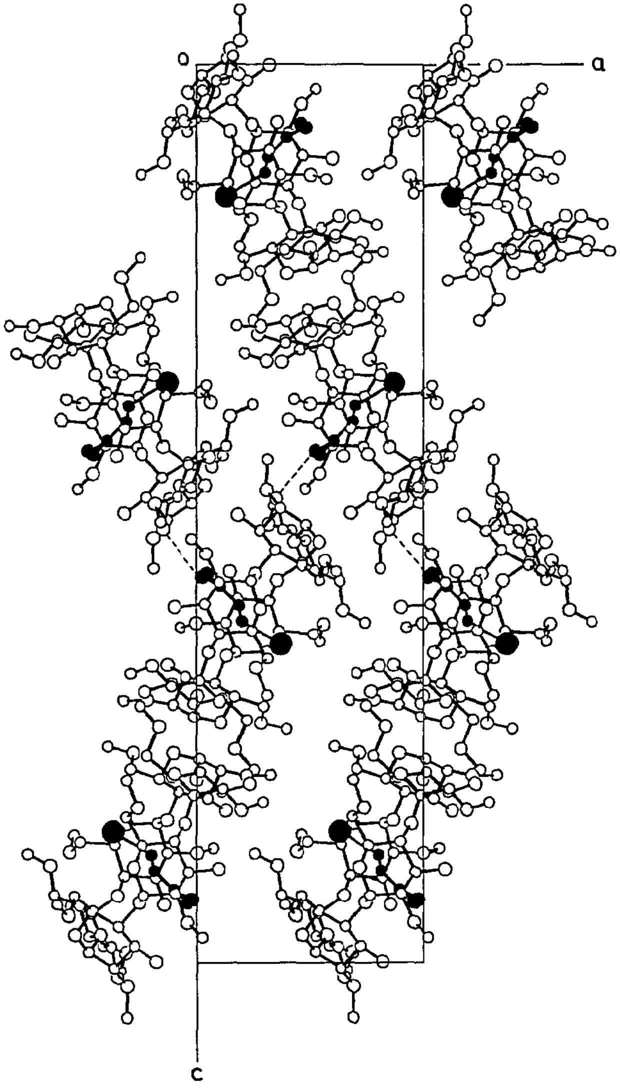

Fig. 5. Crystal structure viewed along the *b* axis. 3-Iodopropionic acid molecules are shown by full circles. For clarity, the iodine atom with the lower occupancy is not shown. Dashed lines denote hydrogen bonds.

molecule could not be determined. These disordered molecules may be overlapped in the electron density map and the light atoms with the lower occupancies are hidden. The host–guest contacts <4.0 Å are shown in Fig. 4. The shortest intermolecular distance, 3.63 Å, is observed between I-1 and O-6 of G1. The intermolecular distances indicate that the guest 3-iodopropionic acid molecule is in van der Waals contact with the host DM-αCD.

The crystal structure of DM-αCD is shown in Fig. 5. The molecules are arranged in a herring-bone fashion parallel to the *ac* plane and shows a typical cage-type packing structure. The O-2,3 side of the cavity of DM-αCD is blocked by the G1 and G6 units of adjacent molecules. The carboxyl group of the guest is hydrogen-bonded to the O-3 of G1 of the symmetry-related DM-αCD molecule ($1/2 + x$, $1/2 - y$, $-z$). The blocking of the O-6 side of the host cavity by the G3 and G4 units of adjacent hosts creates an isolated cavity in which the 3-iodopropionic acid molecule is accommodated.

DISCUSSION

The DM-αCD molecule has a macrocyclic structure similar to that[11] of αCD. This finding indicates that the methylation of HO-2 and HO-6 does not greatly affect the conformation of the macrocycle. The structure of the macrocycle is maintained by the intramolecular O-2 · · · HO-3′ hydrogen bonds between two adjacent units. In fully methylated αCD (TM-αCD), the macrocyclic ring is less symmetrical, more flexible, and free from the conformational restriction imposed by the intramolecular hydrogen bonds[8]. The O-2 · · · O-3′ distance of the TM-αCD increases to 3.4 Å (Table IV).

The conformation of the host molecule was also affected by the included guest. The 3-iodopropionic acid molecule fills the cavity of DM-αCD. On the other hand, in the DM-αCD complexes with iodine and 1-propanol[6], the guests are too small to fill the whole cavity and are located at the O-2,3 side. As a result, the 2,6-di-*O*-methyl-D-glucopyranose residues incline so as to reduce the empty space at the O-6 side. The tilt-angle found in these complexes, 8.0–21.3°, is larger than that (4.8–19.5°) in the 3-iodopropionic acid complex.

3-Iodopropionic acid also forms[10] a crystalline inclusion complex with αCD. The 3-iodopropionic acid molecule of the DM-αCD complex is included upside down, compared with the guest molecule of the αCD complex. The stabilization of the guest molecule by hydrogen-bond formation of the carboxyl group seems to be of major importance. Both orientations of the guest in the cavity may be in equilibrium in solution, but it is the complex in which the guest molecule can form hydrogen bonds that crystallizes.

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