February, 1987] © 1987 The Chemical Society of Japan Bull. Chem. Soc. Jpn., 60, 497—502 (1987) 497

The Structure of the Cyclodextrin Complex. XIX. Crystal Structures of Hexakis(2,3,6-tri-*O*-methyl)-α-cyclodextrin Complexes with (*S*)- and (*R*)-Mandelic Acid. Chiral Recognition through the Induced-Fit Conformational Change of the Macrocyclic Ring

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(Received August 23, 1986)

Hexakis(2,3,6-tri-*O*-methyl)-α-cyclodextrin (methyl-α-CDx) forms crystalline inclusion complexes with (*S*)-mandelic acid (*S*-MA) and (*R*)-mandelic acid (*R*-MA). Both crystals are monoclinic, and the space group is $P2_1$ with cell dimensions: a=13.123(2), b=23.187(4), c=13.113(2) Å, β=107.19(1)° for the *S*-MA complex, a=11.624(2), b=23.739(4), c=13.786(2) Å, β=106.56(1)° for the *R*-MA complex. The structures were solved by inspection of a Patterson map and the R-map method, and refined by the block-diagonal least-squares method to the *R*-values of 0.087 for the *S*-MA complex and 0.055 for the *R*-MA complex. In the *S*-MA complex, the methyl-α-CDx molecule, which has a *pseudo* two-fold symmetry, loosely includes the phenyl group of *S*-MA. The hydroxyl and carboxyl groups of *S*-MA protrude from the O(2), O(3) side of the methyl-α-CDx cavity and form hydrogen bonds with water molecules located outside the host cavity. The methyl-α-CDx molecule in the *R*-MA complex tightly binds the *R*-MA molecule which is deeply inserted into the host cavity. The hydroxyl group of *R*-MA is hydrogen-bonded to an O(2) oxygen atom of host methyl-α-CDx. The comparison of the two structures suggests that the complex formation induces the conformational change of the host molecule to accommodate *S*-MA or *R*-MA more suitably within the cavity.

Cyclodextrins form diastereoisomers by including optically active guests. Many attempts have been made to resolve racemic compounds by the co-precipitation with cyclodextrins.[1] Except for some cases, however, cyclodextrins are not good reagents for this purpose. Since the intramolecular cavity of cyclodextrins is round and rather symmetrical, cyclodextrins does not seem to be sensitive to the chirality of included guests, as demonstrated in our earlier reports.[2,3] α-Cyclodextrin equally includes *R* -and *S*-isomers of 1-phenylethanol although the hydroxyl group attached to the assymmetric carbon atom is disordered.[2] In the crystal of the β-cyclodextrin complex with racemic Flurbiprofen, a pair of *S*- and *R*-isomers are packed within the cavity formed by two β-cyclodextrin molecules.[3]

Recently, it has been found that the permethylation markedly changes the macrocyclic conformation of cyclodextrins.[4] Permethylated cyclodextrins also form inclusion complexes with a variety of guests, but the geometry of the host-guest interaction differs from that of the parent cyclodextrin complexes because of the different size and shape of the macrocyclic cavity. Previously, we have briefly reported that permethylated cyclodextrins recognize the chirality of mandelic acid[5] and Flurbiprofen[6,7] in the crystalline state. This paper deals with the crystal structures of hexakis(2,3,6-tri-*O*-methyl)-α-cyclodextrin (methyl-α-CDx) complexes with (*S*)-mandelic acid (*S*-MA) and (*R*)-mandelic acid (*R*-MA), and will discuss the chiral recognition through the induced-fit conformational change of methyl-α-CDx.

Experimental

Materials and Measurements. Methyl-α-CDx complexes with *S*- and *R*-MA were crystallized at 50 °C by standing aqueous solutions containing methyl-α-CDx and each isomer with ca. 1 : 1 molar ratio. Lattice parameters and diffraction intensities were measured at room temperature on a Nicolet P3/F diffractometer with graphite-monochromated Cu *K*α radiation. Lattice parameters were refined by using 25 reflections with 2θ values in the range 40—45°. By using θ—2θ scan mode, 4837 (*S*-MA complex) and 4925 (*R*-MA complex) independent reflections with $|F_o| \geqq 3\sigma(F)$ were obtained up to 118° in 2θ. No corrections were made for absorption or extinction effects..

Crystal Data: (1) *S*-MA complex, $C_{54}H_{96}O_{30} \cdot C_8H_8O_3 \cdot 3H_2O$, F.W.=1431.5, monoclinic, space group $P2_1$, Z=2, a=13.123(2), b=23.187(4), c=13.113(2) Å, β=107.19(1)°, V=3812(1) Å^3, Dx=1.247 g cm^{-3}, (2) *R*-MA complex, $C_{54}H_{96}O_{30} \cdot C_8H_8O_3 \cdot 2H_2O$, F.W.=1413.5, monoclinic, space group $P2_1$, Z=2, a=11.624(2), b=23.739(4), c=13.786(2) Å, β=106.56(1)°, V=3646(1) Å^3, Dx=1.289 g cm^{-3}.

Determination and Refinement of the Structure. The orientation of the molecular axis of methyl-α-CDx was easily deduced from a Patterson map in both structures. The rotation around the molecular axis and the position of the molecule in the unit cell were determined from an R-map, which was calculated by using a model structure of methyl-α-CDx having a six-fold molecular symmetry. The orientation and position of each residue were corrected by the rigid-body least-squares method. After the refinement of atomic parameters of methyl-α-CDx, the guest and water molecules were found on Fourier and difference-Fourier maps. The block-diagonal least-squares refinement of the structure, including 42 hydrogen atoms (*S*-MA complex) and 96 hydrogen atoms (*R*-MA complex), achieved the *R*-value of 0.087 for the *S*-MA complex and 0.055 for the *R*-MA complex. The quantity minimized was $\sum w(|F_o| - |F_c|)^2$, with w=1.0 for all the reflections. Final atomic parameters and B_{eq} values are given in Table 1. Tables of observed and calculated structure factors, anisotropic temperature factors of non-hydrogen atoms, atomic parameters of hydrogen atoms, bond dis-

Table 1. Final Atomic Coordinates (×10^4) and B_{eq} Values[a)]

I. Methyl-α-CDx–*S*-MA complex

	x	y	z	B_{eq}/Å^2		x	y	z	B_{eq}/Å^2
C(1,G1)	5459(12)	3240(6)	5644(10)	7.30	C(8,G4)	237(15)	2868(7)	-3028(12)	9.47
C(2,G1)	6553(11)	2924(6)	5841(11)	7.82	C(9,G4)	-870(23)	2856(13)	3023(19)	17.35
C(3,G1)	6389(10)	2378(5)	5162(10)	6.24	O(2,G4)	-543(9)	1705(4)	-2322(8)	9.40
C(4,G1)	5492(10)	1996(5)	5332(9)	5.69	O(3,G4)	-434(8)	2932(4)	-2348(7)	7.90
C(5,G1)	4515(10)	2345(6)	5260(9)	5.97	O(4,G4)	503(5)	3400(3)	-254(6)	4.76
C(6,G1)	3704(13)	2018(7)	5713(13)	8.10	O(5,G4)	-910(6)	2112(4)	226(8)	6.91
C(7,G1)	7686(13)	3768(7)	6199(17)	11.58	O(6,G4)	-353(10)	2662(5)	2277(9)	10.37
C(8,G1)	7989(12)	2110(7)	4708(16)	9.93	C(1,G5)	2211(9)	209(5)	1593(9)	5.14
C(9,G1)	1933(20)	2096(13)	5814(22)	17.09	C(2,G5)	1967(9)	186(5)	369(9)	5.39
O(2,G1)	7320(7)	3273(4)	5542(9)	8.79	C(3,G5)	1618(9)	789(5)	-111(9)	5.16
O(3,G1)	7352(7)	2046(4)	5441(8)	7.80	C(4,G5)	668(9)	979(5)	274(9)	5.23
O(4,G1)	5260(6)	1583(3)	4502(6)	4.80	C(5,G5)	962(9)	966(5)	1499(9)	5.27
O(5,G1)	4771(8)	2860(4)	5931(7)	7.11	C(6,G5)	53(12)	1115(7)	1960(12)	8.02
O(6,G1)	2706(9)	2326(5)	5356(10)	10.39	C(7,G5)	2801(16)	-480(9)	-541(18)	12.57
C(1,G2)	3393(9)	4753(5)	2789(9)	5.41	C(8,G5)	1859(15)	1116(8)	-1742(12)	9.65
C(2,G2)	4619(9)	4797(5)	3015(9)	5.53	C(9,G5)	-1785(15)	935(10)	1779(21)	14.40
C(3,G2)	5087(8)	4191(5)	3377(9)	4.90	O(2,G5)	2908(6)	8(4)	110(7)	7.06
C(4,G2)	4727(9)	3994(5)	4327(9)	4.99	O(3,G5)	1304(7)	739(4)	-1227(6)	6.60
C(5,G2)	3495(9)	4011(5)	4036(9)	5.33	O(4,G5)	444(6)	1569(3)	-120(6)	5.32
C(6,G2)	3057(11)	3865(7)	4961(12)	7.54	O(5,G5)	1273(6)	385(3)	1847(6)	5.12
C(7,G2)	5535(19)	5450(9)	2211(16)	13.06	O(6,G5)	-885(8)	796(5)	1414(9)	8.82
C(8,G2)	6747(13)	3876(9)	3125(16)	10.42	C(1,G6)	5430(9)	993(5)	4783(9)	5.31
C(9,G2)	3189(19)	4029(10)	6777(14)	13.38	C(2,G6)	5761(8)	667(5)	3937(9)	5.40
O(2,G2)	4877(7)	4972(4)	2076(7)	6.63	C(3,G6)	4899(8)	709(5)	2864(8)	4.91
O(3,G2)	6231(6)	4242(4)	3683(7)	6.92	C(4,G6)	3859(9)	475(5)	3001(9)	5.12
O(4,G2)	5120(6)	3418(3)	4555(6)	5.34	C(5,G6)	3581(9)	736(5)	3947(9)	5.24
O(5,G2)	3162(6)	4591(3)	3729(6)	5.11	C(6,G6)	2697(10)	390(7)	4248(9)	6.76
O(6,G2)	3588(9)	4179(5)	5888(8)	8.77	C(7,G6)	7649(10)	586(8)	4405(14)	9.22
C(1,G3)	228(9)	3983(5)	-404(9)	5.27	C(8,G6)	5232(12)	741(8)	1160(12)	8.28
C(2,G3)	1062(9)	4301(5)	-775(8)	5.37	C(9,G6)	1500(16)	424(11)	5235(15)	12.64
C(3,G3)	2137(9)	4266(5)	105(8)	5.08	O(2,G6)	6738(6)	884(4)	3804(7)	6.83
C(4,G3)	2004(9)	4514(5)	1128(9)	5.29	O(3,G6)	5201(7)	391(4)	2083(7)	6.46
C(5,G3)	1042(8)	4247(5)	1422(8)	5.02	O(4,G6)	3056(6)	602(3)	2020(6)	4.89
C(6,G3)	749(9)	4581(6)	2283(10)	6.45	O(5,G6)	4484(6)	742(3)	4890(5)	5.12
C(7,G3)	626(14)	4387(7)	-2674(10)	8.87	O(6,G6)	2274(8)	751(5)	4874(8)	9.10
C(8,G3)	3833(11)	4231(8)	-247(12)	8.43	O(W1)	1948(20)	2463(22)	3102(23)	20.76
C(9,G3)	-211(15)	4548(10)	3503(15)	11.56	O(W2)	-3107(19)	738(10)	-725(19)	22.50
O(2,G3)	1193(7)	4089(4)	-1747(6)	6.64	O(W3)	5701(18)	4195(11)	8094(18)	22.48
O(3,G3)	2918(7)	4589(4)	-199(7)	6.91	C(1,SM)	4891(18)	2491(11)	100(22)	14.76
O(4,G3)	2990(5)	4375(3)	1941(6)	4.85	C(2,SM)	5412(24)	2483(12)	1201(18)	17.17
O(5,G3)	111(5)	4239(4)	506(6)	5.29	C(3,SM)	4775(19)	2441(11)	1805(16)	14.37
O(6,G3)	127(8)	4232(5)	2748(8)	9.09	C(4,SM)	3572(22)	2506(12)	1458(23)	16.54
C(1,G4)	-643(9)	1733(6)	-476(11)	6.47	C(5,SM)	3191(15)	2504(12)	277(23)	16.88
C(2,G4)	-791(11)	2050(6)	-1555(12)	8.05	C(6,SM)	3844(18)	2537(13)	-402(21)	16.42
C(3,G4)	-149(10)	2595(6)	-1408(9)	6.01	C(7,SM)	5547(20)	2280(18)	-750(36)	33.09
C(4,G4)	-332(9)	2972(5)	-507(10)	5.69	C(8,SM)	5807(20)	2834(17)	-1046(40)	30.64
C(5,G4)	-260(10)	2624(6)	499(10)	5.98	O(1,SM)	5082(16)	3080(11)	-1464(15)	20.61
C(6,G4)	-698(12)	2955(6)	1301(12)	7.54	O(2,SM)	6659(17)	3033(10)	-895(22)	22.90
C(7,G4)	-1207(18)	1204(7)	-2694(14)	12.28	O(3,SM)	6379(15)	1961(10)	-278(22)	23.61

II. Methyl-α-CDx–*R*-MA complex

	x	y	z	B_{eq}/Å^2		x	y	z	B_{eq}/Å^2
C(1,G1)	1084(5)	4726(3)	3433(5)	3.96	C(8,G4)	4031(8)	-790(6)	2147(9)	10.15
C(2,G1)	1976(5)	4853(3)	4473(5)	4.05	C(9,G4)	-2729(7)	1135(4)	-1105(6)	6.07
C(3,G1)	2292(5)	4343(3)	5141(5)	3.81	O(2,G4)	2455(5)	-216(2)	2333(4)	5.59
C(4,G1)	1219(5)	3971(3)	5134(5)	3.76	O(3,G4)	2777(5)	470(2)	698(4)	5.88
C(5,G1)	318(5)	3915(3)	4091(5)	3.74	O(4,G4)	1504(4)	1522(2)	582(3)	3.86
C(6,G1)	-882(6)	3700(3)	4199(5)	4.52	O(5,G4)	-405(4)	506(2)	1409(4)	4.39
C(7,G1)	3034(8)	5663(4)	4149(7)	7.10	O(6,G4)	-1543(4)	970(2)	-500(4)	5.14
C(8,G1)	4009(8)	4642(4)	6491(6)	7.72	C(1,G5)	768(6)	1073(3)	5768(5)	4.16
C(9,G1)	-1495(8)	3042(4)	2850(7)	7.43	C(2,G5)	1530(6)	554(3)	5771(5)	4.31
O(2,G1)	3081(4)	5078(2)	4375(4)	5.01	C(3,G5)	1781(6)	490(3)	4767(5)	4.22
O(3,G1)	2792(4)	4504(2)	6183(3)	5.21	C(4,G5)	638(6)	510(3)	3886(5)	4.14
O(4,G1)	1659(4)	3424(2)	5477(3)	3.86	C(5,G5)	-157(6)	1011(3)	3991(5)	4.43
O(5,G1)	68(3)	4468(2)	3626(3)	3.75	C(6,G5)	-1422(6)	967(4)	3262(6)	5.72
O(6,G1)	-1717(4)	3575(2)	3231(4)	4.91	C(7,G5)	2627(9)	507(6)	7521(6)	9.42
C(1,G2)	1255(6)	3934(3)	-87(5)	4.36	C(8,G5)	3574(8)	-26(5)	4749(7)	7.89
C(2,G2)	2169(6)	4380(3)	339(5)	4.34	C(9,G5)	-3191(9)	1467(7)	2696(10)	12.31
C(3,G2)	2453(5)	4404(3)	1475(5)	3.99	O(2,G5)	2661(4)	591(2)	6528(3)	4.84
C(4,G2)	1280(5)	4503(3)	1781(4)	3.69	O(3,G5)	2302(5)	-60(2)	4728(4)	5.61
C(5,G2)	255(6)	4120(3)	1194(5)	3.97	O(4,G5)	1026(4)	576(2)	2987(3)	4.14
C(6,G2)	-957(6)	4334(3)	1223(5)	4.83	O(5,G5)	-314(4)	1013(2)	4982(3)	4.25
C(7,G2)	3459(13)	4657(7)	-616(12)	14.70	O(6,G5)	-1975(5)	1502(3)	3261(5)	8.28
C(8,G2)	4380(7)	4705(5)	2471(7)	7.76	C(1,G6)	1580(6)	3264(3)	6455(5)	4.37
C(9,G2)	-3015(7)	4138(5)	725(8)	8.02	C(2,G6)	2628(6)	2895(3)	6973(5)	4.27
O(2,G2)	3255(4)	4269(2)	69(4)	5.58	C(3,G6)	2596(6)	2312(3)	6461(5)	4.21
O(3,G2)	3220(4)	4864(2)	1861(4)	4.80	C(4,G6)	1384(5)	2038(3)	6280(5)	3.87
O(4,G2)	1601(3)	4387(2)	2843(3)	3.57	C(5,G6)	392(6)	2454(3)	5774(5)	4.08
O(5,G2)	175(4)	4094(2)	133(3)	4.03	C(6,G6)	-900(6)	2242(3)	5621(6)	4.97
O(6,G2)	-1845(4)	3947(3)	732(4)	6.20	C(7,G6)	4374(11)	3324(7)	7968(7)	12.95
C(1,G3)	1554(6)	1699(3)	-380(5)	4.66	C(8,G6)	4379(7)	1751(4)	6730(7)	7.45
C(2,G3)	2711(6)	2018(3)	-307(5)	4.98	C(9,G6)	-2186(8)	2136(4)	6659(8)	8.04
C(3,G3)	2746(6)	2578(3)	257(5)	4.40	O(2,G6)	3729(4)	3166(2)	7011(4)	5.22
C(4,G3)	1607(6)	2922(3)	-254(5)	4.34	O(3,G6)	3483(4)	1968(2)	7123(3)	4.98
C(5,G3)	501(6)	2566(3)	-308(6)	5.02	O(4,G6)	1390(4)	1568(2)	5647(3)	3.84
C(6,G3)	-644(7)	2854(3)	-920(7)	6.88	O(5,G6)	499(4)	2963(2)	6368(3)	4.16

Table 1. (Continued)

	x	y	z	$B_{eq}/Å^2$		x	y	z	$B_{eq}/Å^2$
C(7,G3)	4621(10)	1621(6)	-271(9)	11.02	O(6,G6)	-1018(4)	2069(2)	6593(4)	5.75
C(8,G3)	4571(8)	3020(5)	1173(8)	8.63	O(W1)	-457(5)	1024(3)	7824(4)	6.52
C(9,G3)	-2709(9)	2817(5)	-978(13)	13.74	O(W2)	731(13)	-1004(6)	3284(13)	22.51
O(2,G3)	3708(4)	1682(2)	229(4)	5.90	C(1,RM)	4153(7)	2892(4)	4121(6)	5.57
O(3,G3)	3786(4)	2883(2)	201(4)	5.89	C(2,RM)	4552(9)	2345(4)	4222(7)	7.78
O(4,G3)	1661(4)	3405(2)	378(3)	4.14	C(3,RM)	3813(11)	1901(5)	3754(9)	9.90
O(5,G3)	567(4)	2051(2)	-858(3)	4.87	C(4,RM)	2666(10)	2022(5)	3159(9)	10.13
O(6,G3)	-1636(5)	2533(3)	-802(6)	8.70	C(5,RM)	2259(9)	2570(6)	3016(8)	10.22
C(1,G4)	524(6)	225(3)	2137(5)	4.51	C(6,RM)	2985(8)	3001(5)	3496(7)	7.76
C(2,G4)	1498(6)	75(3)	1651(5)	4.57	C(7,RM)	4927(7)	3359(4)	4693(7)	6.47
C(3,G4)	1996(6)	606(3)	1306(5)	4.20	C(8,RM)	6147(7)	3396(4)	4428(7)	6.40
C(4,G4)	996(6)	972(3)	637(5)	4.13	O(1,RM)	6047(5)	3561(3)	3524(4)	7.25
C(5,G4)	-50(5)	1048(3)	1105(5)	3.84	O(2,RM)	7089(5)	3322(3)	5102(6)	9.21
C(6,G4)	-1156(6)	1295(3)	393(5)	4.71	O(3,RM)	5215(5)	3297(3)	5743(5)	8.59
C(7,G4)	2503(14)	-790(4)	2147(13)	17.07					

a) $B_{eq}=8\pi^2(u_1^2+u_2^2+u_3^2)/3$, where u_i is the root-mean-square deviation in the i-th principal axis of the thermal ellipsoid.

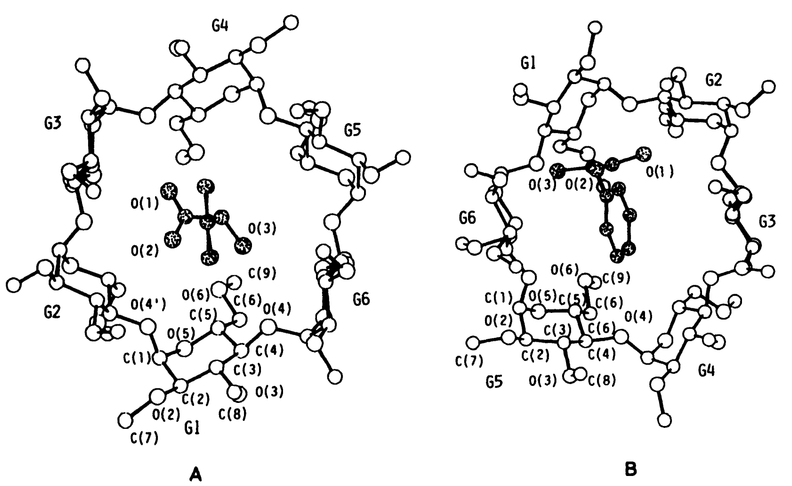

Fig. 1. The numbering scheme of the methyl-α-CDx complexes with *S*-MA (A) and *R*-MA (B). The guest molecules are shaded.

tances, angles, and conformation angles are kept at The Chemical Society of Japan (Document No. 8719). The computation was carried out on a FACOM M-380 computer at the Center of the Research Information Processing System (RIPS), Agency of Industrial Science and Technology, Tsukuba.

Description of the Structure

Conformation of Methyl-α-CDx. The numbering scheme of both complexes is shown in Fig. 1. The average bond distances and angles of 2,3,6-tri-*O*-methylglucose residues are shown in Fig. 2. Table 2 gives geometrical data describing the macrocyclic conformation of methyl-α-CDx.

Methyl-α-CDx in the *S*-MA Complex: The methyl-α-CDx molecule has a *pseudo* two-fold symmetry. The conformational difference among six 2,3,6-tri-*O*-methylglucose residues is observed in the orientation of C(6)-O(6) bonds. Two O(6)-C(6) bonds (G2 and G5 residues) are in a gauche-gauche conformation, while the others show a gauche-trans conformation. All O(6)-C(9) bonds are trans to the corresponding C(5)-C(6) bond. The O(2)-C(7) bonds point away from the center of the methyl-α-CDx ring. On the other hand, the O(3)-C(8) bonds are oriented to the opposite direction, turning to the inside of the methyl-α-CDx ring. The six glycosidic oxygen atoms form a nearly regular hexagon with the radius of 4.23—4.38 Å and the O(4)···O(4′) distance of 4.24—4.36 Å (Table 2). The O(2)···O(3′) distances are longer than those found in α-cyclodextrin complexes[2] because of the steric hindrance involving C(8)H_3 methyl groups.[4] The C(8) atoms are located at a position equidistant from O(2) and O(2′) atoms with the distance of 3.12—3.52 and 3.31—3.41 Å, respectively. The G3 and G6 residues are nearly perpendicular to the plane through the six O(4) atoms. The sharp inclination of the G1 and G4 residues (the tilt-angles of 35.9 and 34.6°, respectively) is supported by the included W1 water molecule which forms the O(6, G1)···W1···O(6, G4) hydrogen-bond bridge.

Methyl-α-CDx in the *R*-MA Complex: The methyl-α-CDx ring is less symmetrical than that of the *S*-MA complex. The C(6)-O(6) bonds show also two types of orientations. The gauche-gauche conformation is found in the G4 and G6 residues, and the C(6)-O(6) bonds in the other residues are in the gauche-trans conformation. Except for the O(6, G1)-C(9, G1) bond,

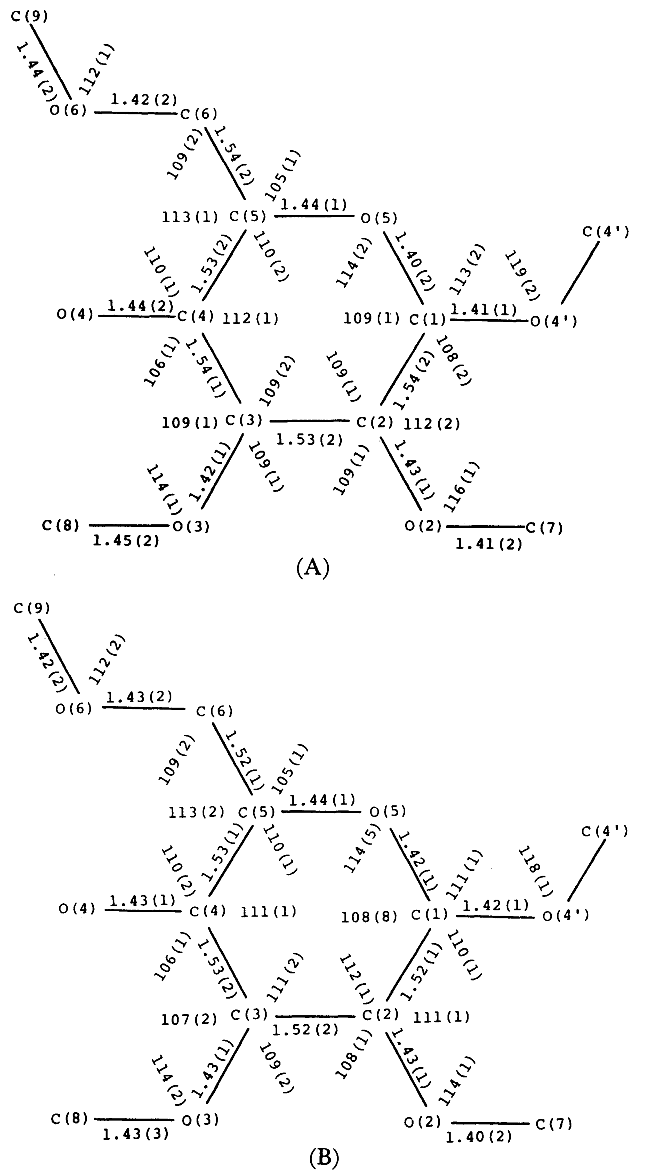

Fig. 2. Average bond distances and angles for the 2,3,6-tri-*O*-methylglucose residue in the methyl-α-CDx complexes with *S*-MA (A) and *R*-MA (B). Standard deviations given in parentheses were estimated according to $\sigma=[\sum_{i=1}^{6}(x_i-\bar{x})^2/5]^{1/2}$, where x_i is the bond distance or angle in the *i*-th residue and $\bar{x}$ is the average value.

Table 2. Geometrical Data Describing the Macrocyclic Conformation of Methyl-α-CDx

I. Distance (l/Å) from the center of gravity of six O(4) atoms to each O(4) atom

	S-MA Complex	*R*-MA Complex
O(4, G1)	4.26	4.05
O(4, G2)	4.23	4.54
O(4, G3)	4.37	4.27
O(4, G4)	4.26	4.03
O(4, G5)	4.23	4.55
O(4, G6)	4.38	4.29
Average	4.29	4.29

II. O(4)···O(4′) distance (l/Å) between adjacent residues

	S-MA Complex	*R*-MA Complex
O(4, G1)···O(4, G2)	4.25	4.27
O(4, G1)···O(4, G6)	4.31	4.43
O(4, G2)···O(4, G3)	4.34	4.14
O(4, G3)···O(4, G4)	4.30	4.49
O(4, G4)···O(4, G5)	4.24	4.17
O(4, G5)···O(4, G6)	4.36	4.28
Average	4.30	4.30

III. O(2)···O(3′) distance (l/Å) between adjacent residues

	S-MA Complex	*R*-MA Complex
O(2, G1)···O(3, G2)	3.43	3.55
O(2, G2)···O(3, G3)	3.43	3.34
O(2, G3)···O(3, G4)	3.37	3.20
O(2, G4)···O(3, G5)	3.30	3.38
O(2, G5)···O(3, G6)	3.46	3.44
O(2, G6)···O(3, G1)	3.39	3.44
Average	3.40	3.39

IV. Deviation (d/Å) of O(4) atoms from their least-squares plane

	S-MA Complex	*R*-MA Complex
O(4, G1)	0.031	0.093
O(4, G2)	0.238	−0.153
O(4, G3)	−0.271	0.033
O(4, G4)	0.034	0.150
O(4, G5)	0.235	−0.204
O(4, G6)	−0.266	0.081
R.M.S. Deviation	0.207	0.132

V. Tilt-angle[a] (ϕ/°) of each 2,3,6-tri-*O*-methylglucose residue

	S-MA Complex	*R*-MA Complex
G1	35.9	29.3
G2	19.8	23.0
G3	7.9	1.9
G4	34.6	23.2
G5	18.7	26.6
G6	7.5	2.9
Average	20.7	17.8

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

all the O(6)-C(9) bonds are trans to the corresponding C(5)-C(6) bond. The O(6, G1)-C(9, G1) bond turns to the inside of the methyl-α-CDx ring, and the C(9,G1)H_3 methyl group caps the O(6) side of the cavity. The O(2)-C(7) and O(3)-C(8) bonds show the same conformations as those in the *S*-MA complex. The macrocyclic ring is rather elliptically distorted compared with the methyl-α-CDx ring in the *S*-MA complex. The diagonal O(4, G2)···O(4, G5) distance of 9.08 Å is 1 Å longer than the O(4, G1)···O(4, G4) distance (8.08 Å). The G3 and G6 residues, which face to each other, are nearly perpendicular to the plane through six O(4) atoms. The other residues incline with their O(6) side turning to the inside of the methyl-α-CDx ring. In spite of the elliptical distortion of the methyl-α-CDx ring, the O(2)···O(3′) distances do not much differ from those of the *S*-MA complex. The

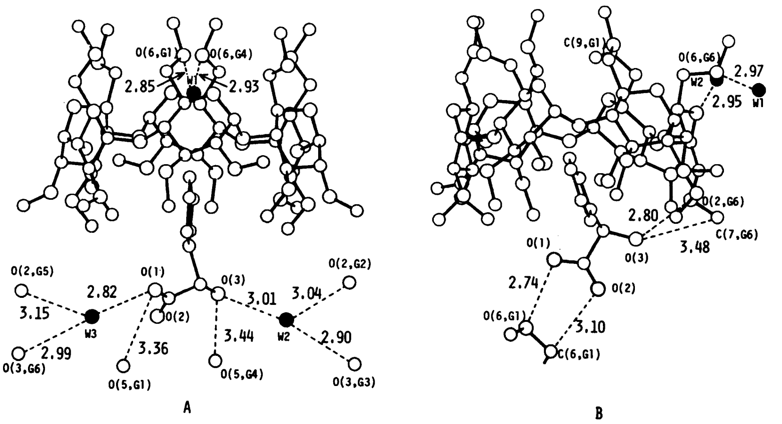

Fig. 3. The inclusion feature of the methyl-α-CDx complexes with *S*-MA (A) and *R*-MA (B). Water molecules are shown by full circles. Intermolecular contacts (Å) involving the guest and water molecules are shown by dashed lines.

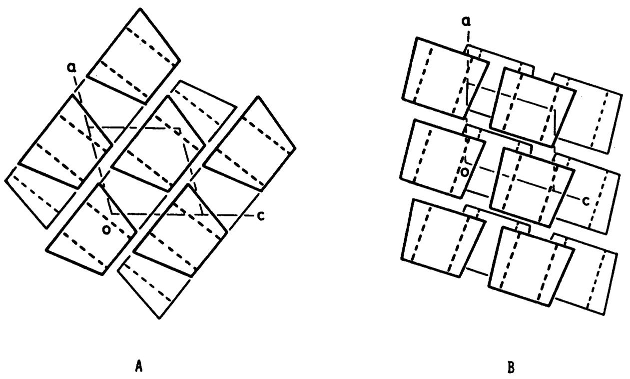

Fig. 4. Schematic drawings of the packing feature of methyl-α-CDx molecules in the crystals of the *S*-MA complex (A) and *R*-MA complex (B).

average O(2)···C(8) and O(2′)···C(8) distances (3.30 and 3.38 Å, respectively) indicate that the C(8)H_3 methyl group is located at an equidistant position from the two O(2) oxygen atoms.

Host-Guest Interaction. The inclusion feature of the complexes are shown in Fig. 3. In both complexes, the phenyl group is inserted into the methyl-α-CDx ring from the O(2), O(3) side, but the mode of the host-guest interaction differs between these complexes.

***S*-MA Complex:** The phenyl group is included within the host cavity parallel to the *pseudo* two-fold axis of methyl-α-CDx. The *S*-MA molecule is weakly bound at the O(2), O(3) side of the cavity, as indicated by the relatively large temperature factors of *S*-MA (Table 1), since the phenyl group is only partially inserted into the host cavity. The W1 water molecule is also included at the O(6) side of the cavity to fill the vacant space. The hydroxyl and carboxyl groups protrude outside the cavity, and form hydrogen bonds with the W2 and W3 water molecules, respectively. These water molecules are also hydrogen-bonded to oxygen atoms of adjacent methyl-α-CDx molecules.

***R*-MA Complex:** The host molecules are stacked along the a axis to form a channel-type structure, as shown in Fig. 4. The guest *R*-MA molecule is included within the methyl-α-CDx column. The phenyl group is more deeply inserted into the host cavity, and sandwiched between the G3 and G6 residues (Figs. 1 and 3). The phenyl plane makes an angle of 70.5° with the plane through six O(4) atoms. The hydroxyl group of *R*-MA is hydrogen-bonded to the O(2, G6) atom. The carboxyl group is located outside the host cavity, and forms hydrogen bond with the O(6, Gl) oxygen atom of the adjacent methyl-α-CDx molecule.

Crystal Structure. The crystal structure of both complexes are shown in Figs. 5 and 6. In the *S*-MA complex, methyl-α-CDx molecules are arranged to form a layer parallel to the [10$\bar{1}$] plane (Fig. 4). Two adjacent layers are shifted by about half a molecule, forming a blick-work pattern. The O(6) side of the cavity is open to the intermolecular space of the next layer, where the W2 and W3 water molecules are located.

Methyl-α-CDx molecules in the *R*-MA complex are arranged along the a axis in a head-to-tail mode to form an endless column. The methyl-α-CDx ring is not perpendicular to the column axis, but the plane through six O(4) atoms makes an angle of 72.5° with the column axis. The guest *R*-MA molecule is arranged in the methyl-α-CDx column. Two water molecules are located outside the methyl-α-CDx column. W1 forms hydrogen bonds with O(6, G4) and O(6, G6), while W2 is hydrogen-bonded to O(5, G6).

Discussion

As shown in Figs. 1 and 3, the macrocyclic conformation of methyl-α-CDx differs depending on the included isomer. When methyl-α-CDx includes *S*-MA, the macrocyclic ring becomes symmetrical and has the *pseudo* two-fold symmetry. The symmetrical

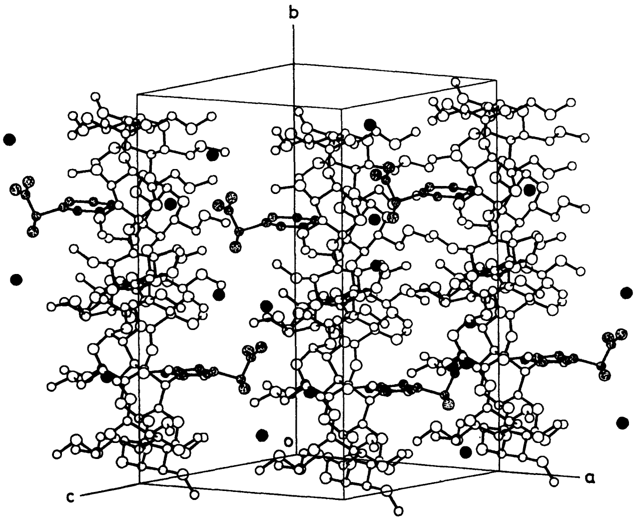

Fig. 5. The crystal structure of the methyl-α-CDx–S-MA complex.

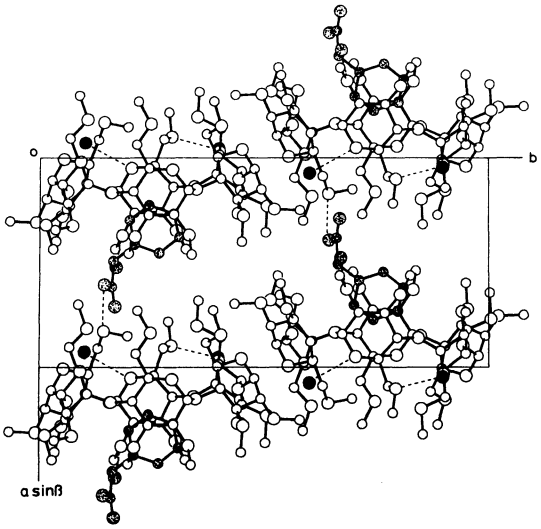

Fig. 6. The crystal structure of the methyl-α-CDx–R-MA complex viewed along the c axis.

cavity is favorable to accommodate the phenyl group which is located on the *pseudo* two-fold axis of methyl-α-CDx. The macrocyclic ring of the R-MA complex is less symmetrical and somewhat elliptically distorted. The elliptical change of the host cavity, which may be induced by the host-guest interaction, is suitable for the deep penetration of R-MA. The formation of the host-guest hydrogen bond between the hydroxyl group of R-MA and the O(2, G6) atom of methyl-α-CDx requires the inclination of R-MA towards the G1, G6 side of the methyl-α-CDx ring as well as the deep penetration. As the result, a long axis of the benzene ring becomes parallel to the O(4, G2)··· O(4, G5) diagonal, as shown in Fig. 1. The macrocyclic ring should become elliptical to include the phenyl group in such orientation. The methyl-α-CDx molecule seems to recognize the chirality of mandelic acid by the formation of the host-guest hydrogen bond. The hydrogen-bond formation with S-MA may be prevented by the steric hindrance involving methyl groups. When R-MA is replaced by S-MA, the hydroxyl group of S-MA should approach to the O(2) or O(3) atom of the G2 residue to form a hydrogen bond. But, such approach is blocked by the methyl group attached to the O(3, G2) atom. The hydrogen-bond formation of S-MA with water molecules does not require the deep penetration of S-MA into the host cavity.

The comparison of these structures with the α-cyclodextrin-1-phenylethanol complex[2] suggests the important role of methyl groups in the chiral recognition. Both isomers of 1-phenylethanol are equally included within the α-cyclodextrin cavity in the crystal except for the orientation of the hydroxyl group attached to the asymmetric carbon atom. The hydroxyl group of R- and S-isomers are hydrogen-bonded to the O(2)H and O(3)H hydroxyl groups of α-cyclodextrin, respectively. Such hydrogen bonding may be prevented by the methyl group attached to the O(3) oxygen atom when 1-phenylethanol is included in methyl-α-CDx. The induced-fit conformational change requires the flexibility of the macrocyclic ring. The macrocyclic ring of parent cyclodextrins is considerably rigid because of the intramolecular O(2)··· O(3′) hydrogen bond. The permethylation blocks the intramolecular hydrogen bond and makes the macrocyclic ring more flexible. The chiral recognition by permethylated cyclodextrins has been also observed in the permethylated β-cyclodextrin complexes with Flurbiprofen.[6]

References

1) W. L. Hinze, *Separation and Purification Methods*, **10**, 159 (1981).

2) K. Harata, *Bull. Chem. Soc. Jpn.*, **55**, 1367 (1982).

3) K. Uekama, F. Hirayama, T. Imai, M. Otagiri, and K. Harata, *Chem. Pharm. Bull.*, **31**, 3363 (1983).

4) K. Harata, K. Uekama, M. Otagiri, and F. Hirayama, *J. Inclusion Phenom.*, **1**, 279 (1984).

5) K. Harata, K. Uekama, M. Otagiri, and F. Hirayama, *Chem. Lett.*, **1983**, 1807.

6) K. Harata, F. Hirayama, T. Imai, K. Uekama, and M. Otagiri, *Chem. Lett.*, **1984**, 1549.

7) K. Harata, K. Uekama, M. Otagiri, and F. Hirayama, *J. Inclusion Phenom.*, **2**, 583 (1985).