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Crystal Structures of Heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin Complexes with (*R*)- and (*S*)-Flurbiprofen

KAZUAKI HARATA*
Research Institute for Polymers and Textiles, 1-1-4 Yatabe-Higashi, Tsukuba, Ibaraki 305, Japan

KANETO UEKAMA, TERUKO IMAI, FUMITOSHI HIRAYAMA, and MASAKI OTAGIRI
Faculty of Pharmaceutical Sciences, Kumamoto University, 5-1 Oe-honmachi, Kumamoto 862, Japan

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Abstract. Heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (TM-β-CDx) forms crystalline complexes with (*R*)-Flurbiprofen (*R*-FP), $C_{63}H_{112}O_{35}\cdot C_{15}H_{13}O_2F\cdot H_2O$, and (*S*)-Flurbiprofen (*S*-FP), $C_{63}H_{112}O_{35}\cdot C_{15}H_{13}O_2F$. The crystal structures were determined by X-ray analysis. Crystals of both compounds are orthorhombic and the space group is $P2_12_12_1$ with cell dimensions: $a = 15.092(2)$, $b = 21.714(3)$, and $c = 28.269(4)$ Å for the *R*-FP complex, and $a = 15.271(2)$, $b = 21.451(3)$, and $c = 27.895(3)$ Å for the *S*-FP complex. The macrocyclic ring of TM-β-CDx is markedly distorted because of the inability to form intramolecular hydrogen bonds and the steric hindrance involving methyl groups. In both complexes, the phenyl group is inserted into the host cavity from the O(2), O(3) side, which is wider than the O(6) side. The biphenyl moiety of *R*-FP is fixed in the *R*-configuration within the host cavity. The phenyl group of *S*-FP is disordered, and *R*- and *S*-configurations are statistically distributed with equal probability. TM-β-CDx molecules are stacked along the *b* axis to form a column structure. The TM-β-CDx molecule is laterally shifted with respect to the column axis, and a half of the guest molecule protrudes outside from the crevis of the column. The carboxyl group of *R*-FP forms a hydrogen bond with water located outside the host cavity, while the carboxyl group of *S*-FP is hydrogen-bonded to an oxygen atom of an adjacent TM-β-CDx.

Key words. Methylated cyclodextrin, inclusion complex, host-guest interaction, chiral recognition, crystal structure, Flurbiprofen.

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1. Introduction

It has been shown that the macrocyclic conformation and host-guest interaction of cyclodextrins are greatly affected by methylation. Methylation at the O(2) and O(6) hydroxyl groups extends the intramolecular cavity, whereas the round structure of the macrocyclic ring is still maintained by intramolecular O(2)---H—O(3) hydrogen bonds [1–3]. Hexakis(2,6-di-*O*-methyl)-α-cyclodextrin includes guest molecules in a similar manner to that found in the α-cyclodextrin complexes in the crystalline state [1]. On the other hand, in some heptakis(2,6-di-*O*-methyl)-β-cyclodextrin complexes with disubstituted benzenes, guest molecules are excluded from the host cavity in which some water molecules are included [3]. The macrocyclic conformation of cyclodextrins is markedly distorted by permethylation [4, 5]. Since the permethylation increases the flexibility of the macrocyclic ring, the induced-fit chiral recognition of the guest molecule is observed in the

* Author for correspondence.

hexakis(2,3,6-tri-*O*-methyl)-α-cyclodextrin (TM-α-CDx) complexes with D- and L-mandelic acid [4]. The chiral recognition ability of the parent cyclodextrins is rather low because of the round and symmetrical structure [6]. β-Cyclodextrin forms a crystalline complex with racemic Flurbiprofen, in which a pair of *R*- and *S*-isomers are included within the cylindrical cavity of the head-to-head dimer of two β-cyclodextrin molecules [7]. Recently we have found that heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (TM-β-CDx) does not form a crystalline complex with racemic Flurbiprofen but separately crystallizes with each isomer. A short communication on these structures has already been published [8]. In this paper, we report the detailed host-guest interaction of TM-β-CDx with (*R*)-Flurbiprofen and (*S*)-Flurbiprofen (*R*-FP and *S*-FP) in the crystalline state.

2. Experimental

TM-β-CDx complexes with *R*-FP and *S*-FP were crystallized at 50°C from aqueous solutions containing each TM-β-CDx and FP-isomer in ca. 1 : 1 molar ratio. Colorless crystals with a rod-like shape were stable in air. Lattice parameters and diffraction intensities were measured on a Nicolet P3/F diffractometer with graphite-monochromated Cu$K\alpha$ radiation. The refinement of the lattice parameters was done by using 25 reflections with 2θ values in the range from 35° to 40°. By using the θ-2θ scan mode, 5282 (*R*-FP complex, $2\theta \leqslant 100°$) and 6853 (*S*-FP complex, $2\theta \leqslant 118°$) independent reflections were collected, and 3525 (*R*-FP complex) and 5419 (*S*-FP complex) reflections with $|F_o| \geqq 3\sigma(F)$ were used for the structure determination and refinement. No corrections were made for absorption or extinction effects.

The crystal structures of both complexes were determined by using a set of coordinates of TM-β-CDx of the isomorphous *p*-iodophenol complex [5], and refined by the block-diagonal least-squares method with anisotropic temperature factors to the *R*-value of 0.10 (*R*-FP complex) and 0.089 (*S*-FP complex). The quantity minimized was $\Sigma\, w(|F_o| - |F_c|)^2$, with $w = 1.0$ for all the reflections used: the number of parameters were 1055 (*R*-FP complex) and 1082 (*S*-FP complex). Hydrogen atoms were not included in the structure factor calculation. In the course of the refinement, the phenyl group of *S*-FP was found to be disordered. Atomic parameters of disordered atoms were refined independently. The occupancy factor was estimated from the electron-density map, but was not refined. Atomic parameters are given in Tables I and II.

2.1 CRYSTAL DATA

(1) *R*-FP complex, $C_{63}H_{112}O_{35}\cdot C_{15}H_{13}O_2F\cdot H_2O$, formula weight = 1691.8, orthorhombic, space group $P2_12_12_1$, $Z = 4$, $a = 15.092(2)$, $b = 21.714(3)$, $c = 28.269(4)$ Å, $V = 9264(2)$ Å^3, $D_x = 1.213$ g cm^{-3}. (2) *S*-FP complex, $C_{63}H_{112}O_{35}\cdot C_{15}H_{13}O_2F$, formula weight = 1673.8, orthorhombic, space group $P2_12_12_1$, $Z = 4$, $a = 15.271(2)$, $b = 21.451(3)$, $c = 27.895(3)$ Å, $V = 9137(2)$ Å^3, $D_x = 1.217$ g cm^{-3}.

3. Description of the Structure

The atomic numbering of the TM-β-CDx complexes with *R*-FP and *S*-FP are given in Figures 1 and 2, respectively. The inclusion features of the complexes are shown in Figures 3 and 4. Average bond distances and angles of TM-β-CDx and geometrical

Table I. Atomic coordinates ($\times 10^4$) and isotropic temperature factors (Å^2) of the TM-β-CDx complex with *R*-FP[a]

	x	*y*	*z*	B_{eq}
C(1, G1)	7687(12)	4600(9)	4788(6)	5.88
C(2, G1)	7997(11)	4153(9)	4961(6)	5.86
C(3, G1)	7516(12)	3929(8)	4526(6)	5.29
C(4, G1)	7081(11)	4493(8)	4292(6)	5.49
C(5, G1)	7809(12)	4914(7)	4130(6)	5.29
C(6, G1)	7493(16)	5505(9)	3870(7)	8.09
C(7, G1)	8631(18)	3767(10)	5665(7)	9.37
C(8, G1)	6771(14)	2948(9)	4491(8)	7.32
C(9, G1)	6389(20)	6274(11)	3927(8)	11.37
O(2, G1)	8392(9)	3666(6)	5206(5)	7.22
O(3, G1)	6807(8)	3532(6)	4706(4)	6.96
O(4, G1)	6638(8)	4246(6)	3879(4)	6.80
O(5, G1)	8299(8)	5097(5)	4544(4)	5.52
O(6, G1)	6833(10)	5759(6)	4151(4)	7.46
C(1, G2)	11934(13)	4090(8)	4060(7)	6.32
C(2, G2)	11615(13)	3653(9)	4436(6)	6.54
C(3, G2)	10593(11)	3655(8)	4479(6)	5.37
C(4, G2)	10240(10)	4300(9)	4528(6)	5.58
C(5, G2)	10622(13)	4746(9)	4149(7)	6.79
C(6, G2)	10456(17)	5430(11)	4292(8)	10.39
C(7, G2)	12748(15)	2899(11)	4428(10)	10.13
C(8, G2)	9878(16)	2744(8)	4764(8)	8.50
C(9, G2)	10409(32)	6411(13)	3906(17)	23.12
O(2, G2)	11810(9)	3035(7)	4337(5)	8.14
O(3, G2)	10321(8)	3277(6)	4871(4)	6.53
O(4, G2)	9310(7)	4275(6)	4481(4)	6.11
O(5, G2)	11596(9)	4681(6)	4157(4)	7.51
O(6, G2)	10555(14)	5765(9)	3862(7)	14.25
C(1, G3)	12601(12)	3947(8)	2220(6)	5.51
C(2, G3)	12652(14)	3327(9)	2490(6)	6.47
C(3, G3)	12003(14)	3351(8)	2903(6)	6.55
C(4, G3)	12251(13)	3879(9)	3206(5)	5.92
C(5, G3)	12202(12)	4482(9)	2919(6)	6.42
C(6, G3)	12408(13)	5101(10)	3174(7)	6.67
C(7, G3)	12799(22)	2300(12)	2197(10)	13.92
C(8, G3)	11332(22)	2474(13)	3266(11)	14.45
C(9, G3)	13470(20)	5577(11)	3673(9)	11.49
O(2, G3)	12319(10)	2837(7)	2170(4)	8.05
O(3, G3)	12116(11)	2771(6)	3174(5)	8.75
O(4, G3)	11613(8)	3911(7)	3600(4)	5.75
O(5, G3)	12781(8)	4428(5)	2536(4)	5.36
O(6, G3)	13257(9)	5039(6)	3385(4)	7.32
C(1, G4)	10639(12)	4643(9)	742(6)	6.62
C(2, G4)	11532(12)	4244(11)	687(6)	7.19
C(3, G4)	11725(12)	3920(10)	1167(7)	7.07
C(4, G4)	11768(12)	4390(8)	1568(7)	5.65
C(5, G4)	10963(12)	4774(9)	1571(6)	5.57
C(6, G4)	11079(13)	5334(9)	1897(8)	7.41
C(7, G4)	11545(22)	3978(15)	−163(7)	13.80
C(8, G4)	12690(16)	3017(11)	999(8)	9.13
C(9, G4)	10268(23)	6134(12)	2317(9)	13.11
O(2, G4)	11458(11)	3761(10)	334(5)	11.37

Table I. (*Continued*)

	x	*y*	*z*	B_{eq}
O(3, G4)	12604(9)	3638(7)	1124(5)	7.79
O(4, G4)	11754(8)	4031(6)	2003(4)	6.00
O(5, G4)	10821(9)	5039(6)	1112(4)	7.28
O(6, G4)	10251(10)	5597(7)	1998(5)	8.70
C(1, G5)	7238(12)	4053(7)	634(7)	6.20
C(2, G5)	7843(13)	3743(8)	271(7)	6.32
C(3, G5)	8808(12)	3664(10)	466(6)	6.49
C(4, G5)	9115(11)	4307(8)	603(6)	5.55
C(5, G5)	8458(11)	4601(7)	952(6)	5.14
C(6, G5)	8697(12)	5267(9)	1072(6)	6.22
C(7, G5)	6706(17)	3072(13)	−99(9)	11.40
C(8, G5)	9590(18)	2820(12)	164(12)	13.29
C(9, G5)	9205(19)	6234(10)	738(8)	10.46
O(2, G5)	7510(10)	3108(7)	174(6)	9.38
O(3, G5)	9352(9)	3443(7)	101(5)	8.61
O(4, G5)	9946(8)	4209(7)	846(4)	7.29
O(5, G5)	7599(8)	4629(5)	741(4)	5.88
O(6, G5)	8909(9)	5612(6)	667(5)	7.67
C(1, G6)	5240(15)	3423(11)	2053(6)	8.21
C(2, G6)	5598(17)	2862(10)	1823(7)	8.95
C(3, G6)	6468(15)	2980(11)	1563(8)	9.13
C(4, G6)	6330(13)	3566(8)	1227(7)	6.49
C(5, G6)	5912(13)	4107(10)	1481(7)	7.24
C(6, G6)	5655(14)	4662(10)	1190(7)	7.48
C(7, G6)	5327(23)	1851(11)	2102(12)	14.39
C(8, G6)	7596(20)	2264(13)	1333(13)	15.93
C(9, G6)	4307(15)	4363(14)	759(9)	11.40
O(2, G6)	5690(12)	2398(8)	2152(6)	12.04
O(3, G6)	6657(13)	2485(7)	1271(6)	11.05
O(4, G6)	7176(8)	3696(6)	1045(4)	6.93
O(5, G6)	5115(9)	3933(6)	1739(4)	7.16
O(6, G6)	5198(10)	4460(8)	753(5)	10.20
C(1, G7)	5847(15)	4533(9)	3747(6)	7.55
C(2, G7)	5069(14)	4100(10)	3627(7)	8.01
C(3, G7)	5360(14)	3635(11)	3229(7)	7.83
C(4, G7)	5530(15)	4046(12)	2767(7)	9.66
C(5, G7)	6439(18)	4400(13)	2922(8)	10.78
C(6, G7)	6714(26)	4848(14)	2495(10)	16.16
C(7, G7)	4611(16)	4042(13)	4472(9)	10.84
C(8, G7)	4563(14)	2664(9)	3330(7)	7.27
C(9, G7)	6546(19)	5731(11)	2089(10)	12.08
O(2, G7)	4940(9)	3700(7)	4036(5)	7.97
O(3, G7)	4575(9)	3257(7)	3133(5)	7.88
O(4, G7)	5894(11)	3607(7)	2413(5)	9.09
O(5, G7)	6025(11)	4840(7)	3282(6)	10.33
O(6, G7)	6156(13)	5232(10)	2371(8)	15.44
C(1, RFP)	7366(15)	1695(9)	3543(8)	8.07
C(2, RFP)	8149(15)	1852(11)	3726(10)	10.58
C(3, RFP)	8512(15)	2322(10)	3520(9)	9.71
C(4, RFP)	8193(13)	2711(9)	3152(8)	7.83
C(5, RFP)	7384(16)	2559(12)	2961(12)	13.47
C(6, RFP)	6990(14)	2039(12)	3174(10)	10.66
C(7, RFP)	8576(16)	3256(10)	2961(8)	8.59

Table I. (*Continued*)

	x	*y*	*z*	B_{eq}
C(8, RFP)	8732(26)	3237(15)	2454(10)	16.41
C(9, RFP)	9073(24)	3798(17)	2284(8)	15.82
C(10, RFP)	9364(21)	4292(15)	2561(10)	13.99
C(11, RFP)	9208(22)	4311(15)	2994(9)	14.17
C(12, RFP)	8898(18)	3687(15)	3208(10)	12.96
C(13, RFP)	7050(38)	1205(17)	3929(15)	25.68
C(14, RFP)	6312(24)	1276(20)	4246(8)	19.76
C(15, RFP)	6475(26)	936(14)	3551(14)	21.58
F(RFP)	9350(13)	2499(8)	3663(7)	15.72
O(1, RFP)	6586(12)	509(9)	3138(6)	12.11
O(2, RFP)	5520(19)	1020(12)	3496(10)	21.61
O(W)	5587(14)	354(10)	2416(8)	15.27

[a] $B_{eq} = \frac{4}{3} \Sigma\, a_i a_j B_{ij}$, where a_i and a_j are cell parameters.

Table II. Atomic coordinates ($\times 10^4$) and isotropic temperature factors (Å^2) of the TM-β-CDx complex with *S*-FP.[a,b]

	x	*y*	*z*	B_{eq}
C(1, G1)	8613(7)	4617(5)	4747(4)	6.00
C(2, G1)	7884(7)	4153(5)	4885(4)	5.67
C(3, G1)	7377(6)	3926(5)	4444(3)	5.21
C(4, G1)	6991(6)	4513(4)	4220(3)	4.83
C(5, G1)	7744(7)	4956(5)	4061(4)	5.49
C(6, G1)	7453(8)	5554(5)	3831(4)	6.89
C(7, G1)	8481(9)	3709(6)	5601(4)	7.99
C(8, G1)	6685(9)	2933(5)	4381(5)	8.13
C(9, G1)	6373(11)	6354(6)	3889(6)	10.27
O(2, G1)	8272(5)	3612(3)	5106(3)	6.30
O(3, G1)	6694(5)	3533(4)	4598(3)	6.36
O(4, G1)	6531(4)	4320(3)	3795(2)	5.47
O(5, G1)	8216(5)	5130(3)	4502(3)	5.81
O(6, G1)	6763(6)	5805(3)	4119(3)	7.85
C(1, G2)	11830(7)	4186(6)	4041(4)	6.33
C(2, G2)	11548(7)	3763(5)	4447(4)	6.52
C(3, G2)	10530(6)	3736(5)	4463(4)	5.25
C(4, G2)	10159(6)	4394(5)	4497(4)	5.39
C(5, G2)	10503(7)	4800(5)	4097(4)	6.21
C(6, G2)	10270(8)	5500(6)	4196(5)	8.29
C(7, G2)	12713(9)	2981(9)	4506(7)	13.41
C(8, G2)	9920(8)	2800(5)	4795(5)	7.49
C(9, G2)	10253(14)	6463(7)	3825(9)	16.25
O(2, G2)	11802(6)	3133(4)	4377(3)	8.46
O(3, G2)	10299(4)	3396(3)	4892(2)	5.84
O(4, G2)	9206(4)	4301(3)	4422(2)	5.51
O(5, G2)	11468(5)	4780(4)	4127(3)	6.59
O(6, G2)	10445(7)	5804(4)	3754(4)	11.16
C(1, G3)	12538(6)	3933(5)	2189(4)	5.72
C(2, G3)	12525(7)	3326(5)	2475(4)	5.71
C(3, G3)	11940(8)	3360(5)	2906(4)	6.23
C(4, G3)	12192(7)	3913(5)	3200(4)	5.64

Table II. (*Continued*)

	x	*y*	*z*	B_{eq}
C(5, G3)	12141(7)	4496(5)	2898(4)	5.94
C(6, G3)	12359(8)	5125(6)	3127(4)	6.78
C(7, G3)	12592(19)	2296(9)	2169(7)	18.66
C(8, G3)	11352(13)	2481(7)	3331(6)	12.80
C(9, G3)	13473(12)	5651(7)	3538(7)	12.36
O(2, G3)	12221(7)	2832(4)	2151(3)	9.25
O(3, G3)	12102(6)	2800(4)	3179(3)	7.75
O(4, G3)	11556(4)	3957(4)	3597(2)	6.02
O(5, G3)	12728(4)	4435(3)	2505(2)	5.70
O(6, G3)	13190(6)	5071(4)	3354(3)	8.04
C(1, G4)	10629(7)	4621(5)	689(4)	5.57
C(2, G4)	11528(7)	4266(6)	657(4)	6.66
C(3, G4)	11735(7)	3933(6)	1123(4)	5.89
C(4, G4)	11723(7)	4391(5)	1532(3)	5.04
C(5, G4)	10895(7)	4789(5)	1541(4)	5.42
C(6, G4)	10994(7)	5329(5)	1895(4)	6.79
C(7, G4)	11478(12)	4917(9)	−206(4)	12.70
C(8, G4)	12716(10)	3057(6)	947(4)	9.30
C(9, G4)	10230(11)	6097(7)	2306(5)	10.92
O(2, G4)	11454(5)	3779(5)	291(3)	8.89
O(3, G4)	12625(5)	3702(4)	1092(3)	6.74
O(4, G4)	11703(4)	4040(3)	1969(2)	5.36
O(5, G4)	10772(4)	5068(3)	1072(3)	6.08
O(6, G4)	10190(5)	5622(4)	1952(3)	7.26
C(1, G5)	7244(7)	4071(5)	577(4)	5.78
C(2, G5)	7834(6)	3725(5)	240(4)	6.00
C(3, G5)	8806(7)	3649(5)	455(4)	6.32
C(4, G5)	9116(6)	4312(5)	564(4)	5.54
C(5, G5)	8482(6)	4625(5)	913(4)	5.63
C(6, G5)	8724(7)	5286(5)	1036(4)	5.49
C(7, G5)	6761(8)	3059(8)	−124(6)	11.80
C(8, G5)	9639(10)	2783(6)	145(8)	13.07
C(9, G5)	9234(10)	6251(5)	701(5)	8.83
O(2, G5)	7514(6)	3086(4)	167(3)	8.59
O(3, G5)	9332(5)	3408(4)	76(3)	8.13
O(4, G5)	9949(4)	4206(3)	806(2)	5.60
O(5, G5)	7627(4)	4652(3)	681(3)	5.46
O(6, G5)	8947(5)	5619(3)	612(3)	6.83
C(1, G6)	5142(8)	3585(5)	2023(4)	6.60
C(2, G6)	5475(8)	2988(6)	1791(4)	6.80
C(3, G6)	6357(7)	3091(5)	1542(4)	6.36
C(4, G6)	6262(6)	3604(5)	1181(4)	5.86
C(5, G6)	5885(7)	4206(5)	1425(4)	6.09
C(6, G6)	5675(7)	4742(6)	1092(4)	6.59
C(7, G6)	5167(10)	1954(6)	2071(6)	10.23
C(8, G6)	7462(10)	2333(7)	1330(7)	12.86
C(9, G6)	4297(8)	4436(8)	668(5)	10.48
O(2, G6)	5552(6)	2519(4)	2158(3)	8.74
O(3, G6)	6568(6)	2534(4)	1296(4)	9.34
O(4, G6)	7149(4)	3732(3)	1020(3)	6.11
O(5, G6)	5057(4)	4037(4)	1657(2)	6.27
O(6, G6)	5247(5)	4524(4)	636(3)	7.49
C(1, G7)	5693(9)	4621(6)	3704(4)	7.60

Table II. (*Continued*)

	x	*y*	*z*	B_{eq}
C(2, G7)	4975(7)	4145(6)	3622(4)	7.20
C(3, G7)	5207(8)	3736(5)	3206(4)	6.71
C(4, G7)	5319(10)	4161(6)	2769(4)	8.12
C(5, G7)	6032(13)	4643(6)	2826(4)	11.48
C(6, G7)	5853(12)	5191(8)	2418(7)	14.36
C(7, G7)	4587(10)	4079(8)	4492(5)	10.68
C(8, G7)	4505(9)	2719(6)	3310(5)	8.08
C(9, G7)	6553(16)	5918(9)	2064(7)	16.49
O(2, G7)	4869(5)	3734(4)	4036(3)	7.85
O(3, G7)	4470(5)	3338(4)	3093(3)	7.40
O(4, G7)	5701(5)	3776(4)	2395(3)	7.69
O(5, G7)	5766(7)	4998(4)	3298(3)	9.57
O(6, G7)	6546(10)	5512(7)	2475(5)	17.45
C(1, SFP)	7249(7)	1612(6)	3435(4)	6.49
C(2, SFP)	8029(8)	1783(6)	3636(5)	7.63
C(3, SFP)	8406(8)	2341(6)	3445(5)	8.06
C(4, SFP)	8052(7)	2700(6)	3100(4)	6.41
C(5, SFP)	7254(8)	2520(6)	2914(5)	8.42
C(6, SFP)	6878(9)	1975(7)	3070(5)	9.00
C(7, SFP)	8499(8)	3291(6)	2913(4)	6.99
C(8A, SFP)	8695(25)	3265(17)	2367(10)	12.65
C(8B, SFP)	9323(22)	3233(16)	2706(13)	12.41
C(9A, SFP)	8932(26)	3883(19)	2204(12)	14.16
C(9B, SFP)	9579(23)	3767(20)	2435(15)	14.85
C(10, SFP)	9235(12)	4366(9)	2515(7)	13.08
C(11A, SFP)	9183(19)	4299(15)	2999(10)	10.13
C(11B, SFP)	8398(26)	4395(16)	2732(13)	14.03
C(12A, SFP)	8865(19)	3732(13)	3203(10)	8.97
C(12B, SFP)	8024(24)	3830(12)	2891(15)	15.04
C(13, SFP)	6785(8)	989(6)	3602(4)	7.56
C(14, SFP)	6381(9)	605(6)	3200(5)	8.09
C(15, SFP)	6128(8)	1216(7)	3988(6)	9.58
F(SFP)	9220(6)	2495(4)	3638(3)	12.43
O(1, SFP)	6358(7)	1276(6)	4385(3)	11.24
O(2, SFP)	5354(7)	1322(6)	3833(4)	12.66

[a] $B_{eq} = \frac{4}{3} \Sigma\, a_i a_j B_{ij}$, where a_i and a_j are cell parameters.
[b] The occupancy for the disordered phenyl group of *S*-FP is 0.5 for A and B.

parameters describing the macrocyclic conformation of TM-β-CDx are given in Figures 5–8. The TM-β-CDx molecule shows a non-symmetrical and collapsed structure. When compared with parent β-cyclodextrin [9], no significant differences are observed in the average bond distances and angles (Figure 5). The seven glycosidic oxygen atoms (O(4)) form a distorted heptagon. The radius of the heptagon, which is measured from the center of gravity of seven O(4) atoms to each O(4) atom, is in the range 4.63–5.36 Å (*R*-FP complex) and 4.70–5.23 Å (*S*-FP complex). The side length of the heptagon, defined as the O(4)—(O(4′) distance between adjacent residues, varies in the range 4.27–4.53 Å (*R*-FP complex) and 4.22–4.55 Å (*S*-FP complex). Because of the distortion of the macrocyclic ring, the seven O(4) atoms are no longer arranged in a plane. The maximum deviation of each O(4) atom from the least-squares plane through the seven O(4) atoms is 0.66 Å in the *R*-FP complex and 0.60 Å in the *S*-FP complex (Figure 8).

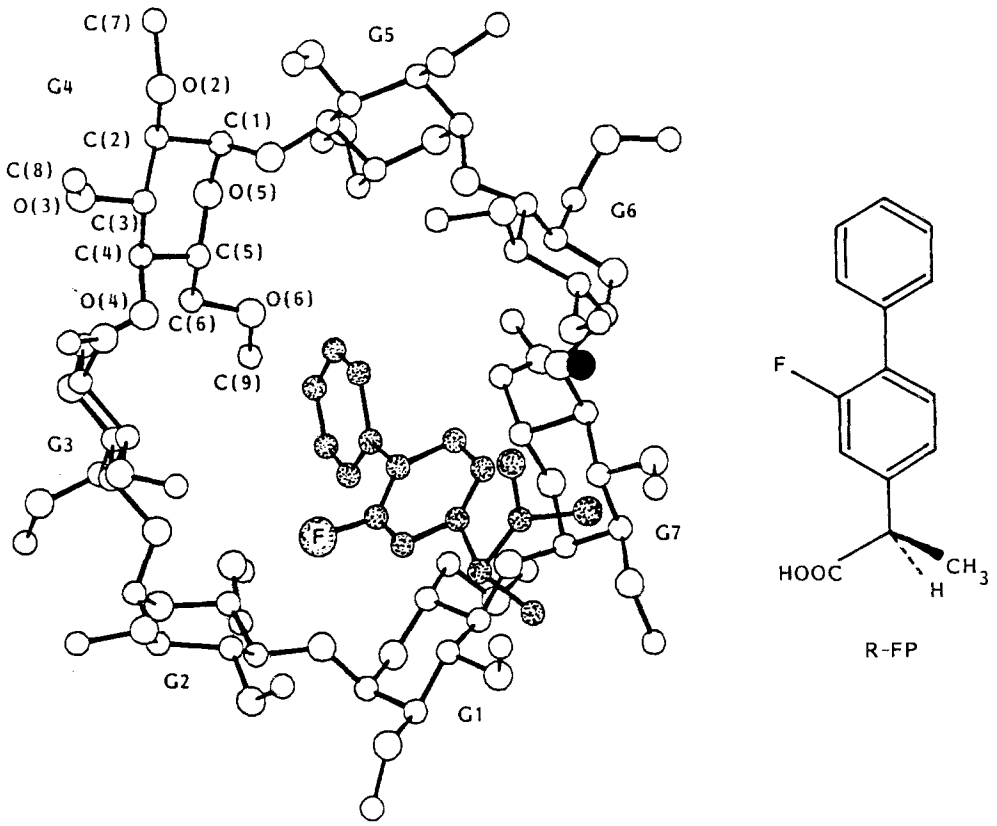

Fig. 1. Structure and numbering of the TM-β-CDx complex with *R*-FP. The *R*-FP molecule is shaded. The water molecule is shown by the full circle.

Five 2,3,6-tri-*O*-methylglucose residues in both complexes incline against the normal to the O(4) plane with their O(6) side turning to the inside of the macrocyclic ring, and give positive values of the tilt-angle which is defined as the angle made by the O(4) plane and a plane through C(1), C(4), O(4), and O(4′) of each residue (Figure 8). The G4 residue is most sharply tilted with the tilt-angles of 43.8° (*R*-FP complex) and 43.3° (*S*-FP complex). The two residues, G3 and G6, incline to the opposite side of the macrocyclic ring and give negative values of the tilt-angle. Such inclination makes the O(2), O(3) side of the macrocyclic ring wider, as shown by the distance between O(2) and O(3) of the adjacent residue, 3.18–3.74 Å (*R*-FP complex) and 3.19–3.66 Å (*S*-FP complex). Since the G3 and G4 residues in both complexes are rotated in the opposite direction to each other with respect to the glycosidic linkage, these two residues make a large angle, 56.3° (*R*-FP complex) and 55.5° (*S*-FP complex), between the planes through C(1), C(4), O(4), and O(4′) of each residue. A similar twisted conformation is observed between the G6 and G7 residues.

The conformation of TM-β-CDx is almost the same in the two complexes. The only significant difference is observed in the orientation of the O(6)CH_3 methoxyl group of the G7 residue. The C(6, G7)—O(6, G7) bond in the *R*-FP complex shows a *gauche-gauche* (to the O(5)—C(5) and C(4)—C(5) bonds, respectively) conformation, while the C(6, G7)—O(6, G7) bond in the *S*-FP complex has a *gauche-trans* conformation. The

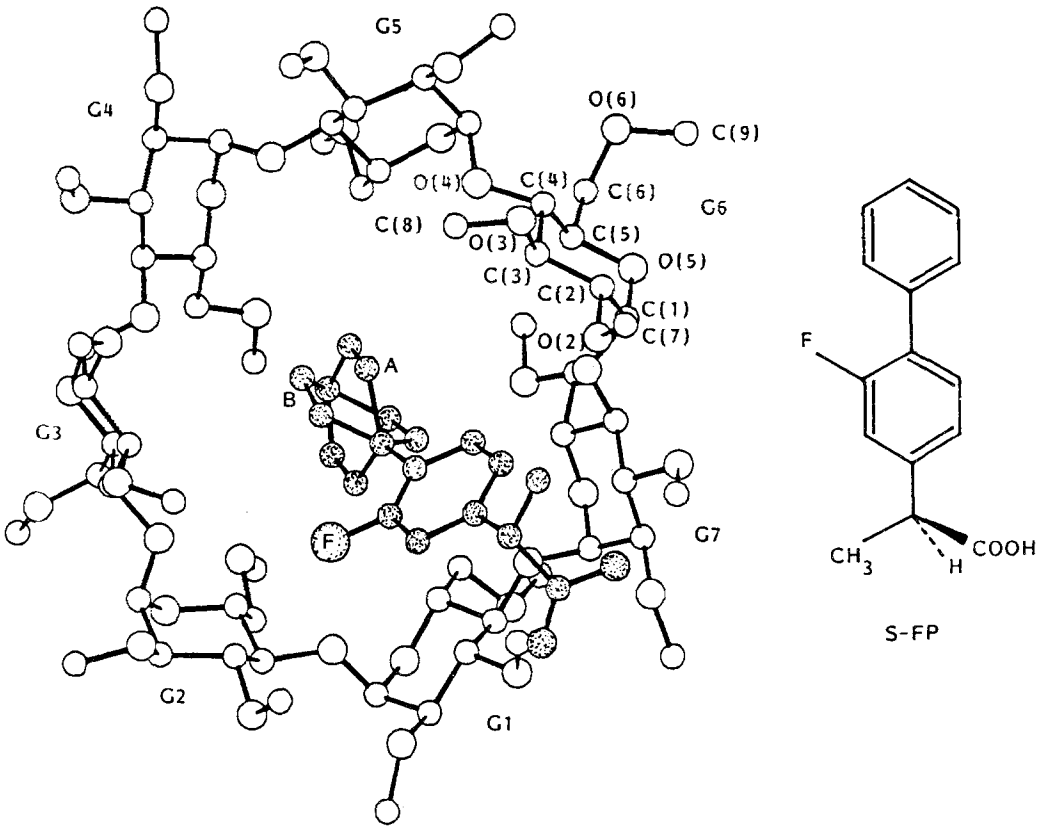

Fig. 2. Structure and numbering of the TM-β-CDx complex with *S*-FP. The *S*-FP molecule is shaded. The disordered phenyl group is indicated by A and B.

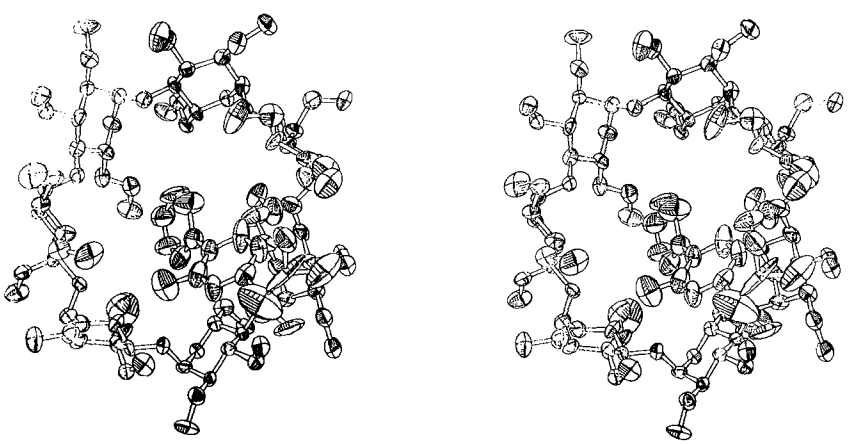

Fig. 3. A stereo-view of the TM-β-CDx – *R*-FP complex. Thermal ellipsoids are drawn with 30% probability.

Fig. 4. A stereo-view of the TM-β-CDx – *S*-FP complex. Thermal ellipsoids are drawn with 30% probability. Only the phenyl group with the *S*-configuration is shown for clarity.

O(6, G7) oxygen atom in the *R*-FP complex forms a hydrogen bond with a water molecule, but the O(6, G7) atom in the *S*-FP complex has no hydrogen-bonding contact.

As shown in Figures 3 and 4, the phenyl group of the guest is inserted into the host macrocycle from the O(2), O(3) side in both complexes, and half a molecule is accommodated within the host cavity. The fluorobiphenyl moiety is held in the host cavity by van der Waals contacts. The shortest intermolecular distance (3.20 Å) is found between C(8, G3) and the fluorine atom of *R*-FP, as shown in Figures 9 and 10. The phenyl group of *S*-FP is two-fold disordered with half occupancy. The biphenyl moiety with the phenyl group A (see Figure 2) has the *R*-configuration with an angle of 51.1°, while the phenyl group B makes an angle of 60.3° showing the *S*-configuration. The biphenyl moiety of *R*-FP shows the *R*-configuration with an angle of 54.7°. The carboxyl group of *R*-FP forms a hydrogen bond with the water molecule which is also hydrogen-bonded to O(6, G3) and O(6, G7) of adjacent TM-β-CDx molecules. In the *S*-FP complex, the carboxyl group is hydrogen-bonded to the O(3, G2) atom of adjacent TM-β-CDx.

Figure 11 shows the stacking feature of the *R*-FP complex along the two-fold screw axis. The TM-β-CDx molecules are stacked in a head-to-tail mode to form a column structure. The TM-β-CDx molecules are laterally shifted with respect to the column axis, and half of the guest molecule protrudes outside from the crevice of the column. These columns are arranged parallel to the *b* axis in the crystal as shown in Figure 12.

4. Discussion

The *R*-Flurbiprofen complex crystallizes as a monohydrate, while the crystal of the *S*-Flurbiprofen complex contains no water. Both crystals are nearly isomorphous to each other, and the fluorobiphenyl group is bound to the host TM-β-CDx in the same way. A structural difference is found in the orientation of the methyl and carboxyl groups. The carboxyl group of the *S*-isomer is hydrogen-bonded to the O(2) oxygen atom of the adjacent TM-β-CDx molecule, while the carboxyl group of the *R*-isomer is linked to the adjacent TM-β-CDx by the —COOH---water---O(6) hydrogen-bond bridge. The hydrogen bonding with water causes the conformational change of the O(6, G7)CH_3 methoxyl

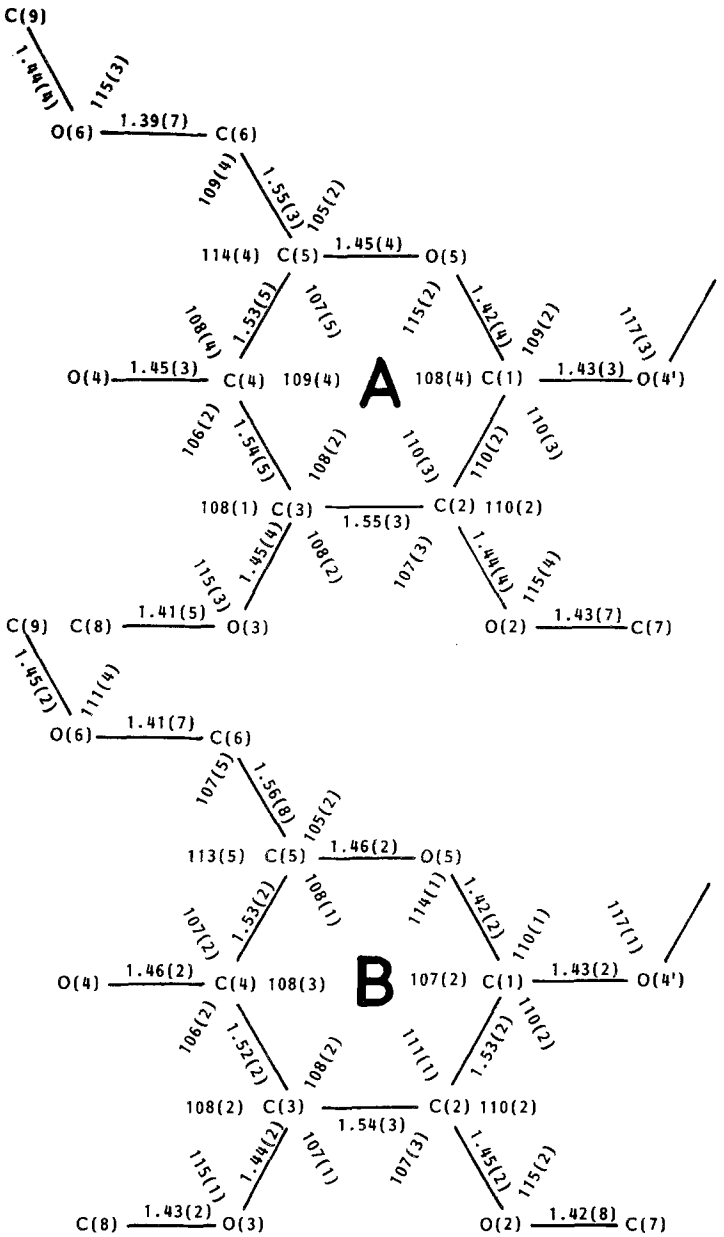

Fig. 5. Average bond distances and angles of seven 2,3,6-tri-*O*-methylglucose residues in the complexes with *R*-FP(A) and *S*-FP(B).

group. The conformation of the C(6, G7)—O(6, G7) bond is *gauche-gauche* in the *R*-FP complex and *gauche-trans* in the *S*-FP complex.

We have shown in earlier papers that β-cyclodextrin forms crystalline complexes with Flurbiprofen [7, 10], but the host-guest interaction is quite different from the present results. When β-cyclodextrin crystallizes in the presence of racemic Flurbiprofen, a pair of *R*- and *S*-isomers is included within the cylindrical cavity of the head-to-head dimer in

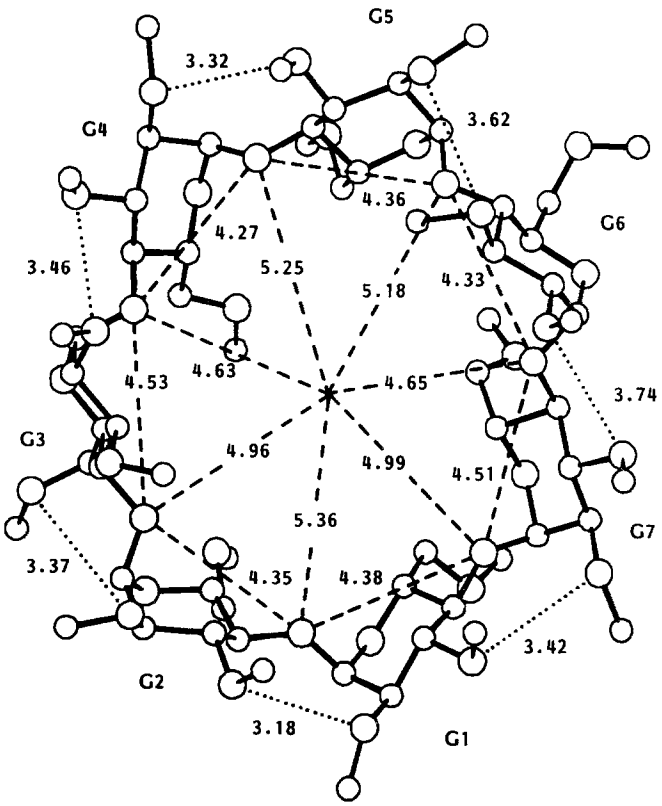

Fig. 6. Geometrical parameters describing the macrocyclic conformation of TM-β-CDx in the R-FP complex. Radius and side-length of the O(4) heptagon are denoted by dashed lines. O(2)---O(3) distances are shown by dotted lines.

which the O(2), O(3) sides of the two β-cyclodextrin molecules face each other [7]. On the other hand, in the presence of only the S-isomer, the 2 : 2 complex crystallizes with an isomorphous structure, in which the R-isomer of the racemic Flurbiprofen complex is replaced by the S-isomer [10]. The guest molecules are so closely packed within the dimer cavity that the conformation of the guest is considerably affected. The biphenyl angle of 33–44° is significantly smaller than the corresponding angle, 54.4°, in the uncomplexed racemic Flurbiprofen [11]. Since the biphenyl angle in the TM-β-CDx complexes is 51.1–60.3°, the conformation of the guest does not seem to be much affected by the complexation with TM-β-CDx. It should also be noted that the biphenyl moiety adopts the R-configuration in the β-cyclodextrin complexes, indicating that the β-cyclodextrin cavity more favorably includes the biphenyl group with the R-configuration. The R-configuration is also observed in the TM-β-CDx complex with R-FP. In the S-FP complex, however, the phenyl group is disordered, and the R- and S-configurations (A and B, respectively, in Figure 2) are statistically distributed in the crystal. The selection of the R-configuration of the biphenyl moiety in the R-FP complex may be ascribed to the difference in the macrocyclic conformation of TM-β-CDx, which is affected by the hydrogen-bond formation. The tilt-angle of the G7 residue of the R-FP complex is greater by 5.6° than the corresponding tilt-angle of the S-FP complex, and the O(6) side of the G7 residue comes nearer

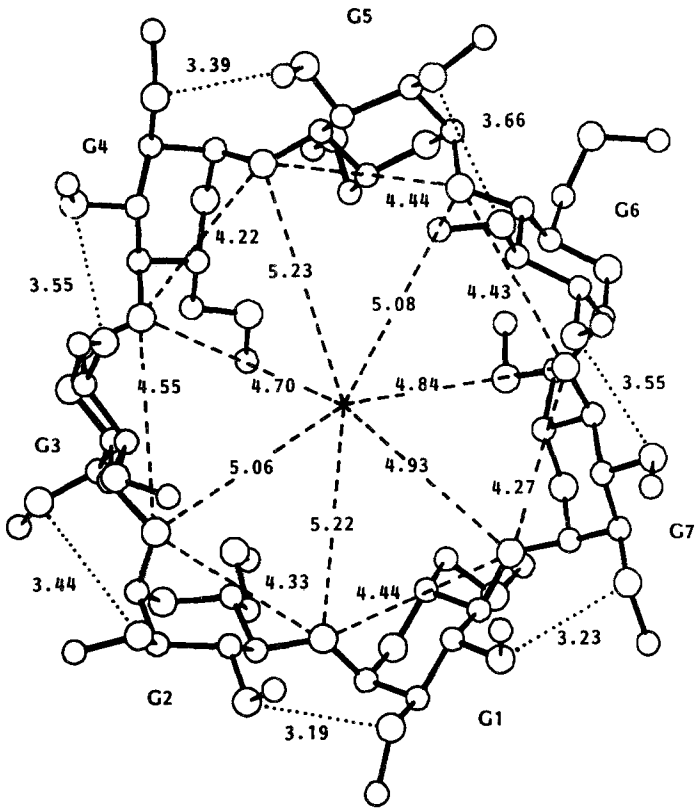

Fig. 7. Geometrical parameters describing the macrocyclic conformation of TM-β-CDx in the *S*-FP complex. Radius and side-length of the O(4) heptagon are denoted by dashed lines. O(2)---O(3) distances are shown by dotted lines.

to the center of the phenyl group. If the biphenyl moiety of the *S*-configuration is inserted into the cavity in the same manner as found in the *S*-FP complex, the phenyl group is expected to reside less than 3.0 Å from the C(5, G7)H methine group and C(6, G7)H_2 methylene group. Since the inclination of the G7 residue is held by the O(6, G7)---water hydrogen bond, the accommodation of *R*-FP with the *S*-configuration may be prevented by steric hindrance with the G7 residue.

The macrocyclic ring of TM-β-CDx is considerably distorted from the round structure of parent β-cyclodextrin. Clearly, the distortion is due to the methylation at the O(3) position, since heptakis(2,6-di-*O*-methyl)-β-cyclodextrin, in which all O(2) and O(6) hydroxyl groups are methylated, still maintains the round structure [2, 3]. The methylation of the O(6) hydroxyl group does not affect the macrocyclic conformation. The methylation of the O(2) and O(3) hydroxyl groups breaks the intramolecular O(2)---O(3′) hydrogen bonds and makes the macrocyclic conformation less symmetrical. The O(2)CH_3 methoxyl groups point away from the center of the TM-β-CDx ring. On the other hand, the O(3)CH_3 methoxyl groups are rather oriented to the inside of the macrocyclic ring, and cause steric hindrance with the adjacent two O(2) oxygen atoms, as indicated by the average C(8)---O(2) distances, 3.34 Å (*R*-FP complex) and 3.35 Å (*S*-FP complex), and the average C(8)---O(2′) distances, 3.50 Å (*R*-FP complex) and 3.45 Å (*S*-FP complex). In

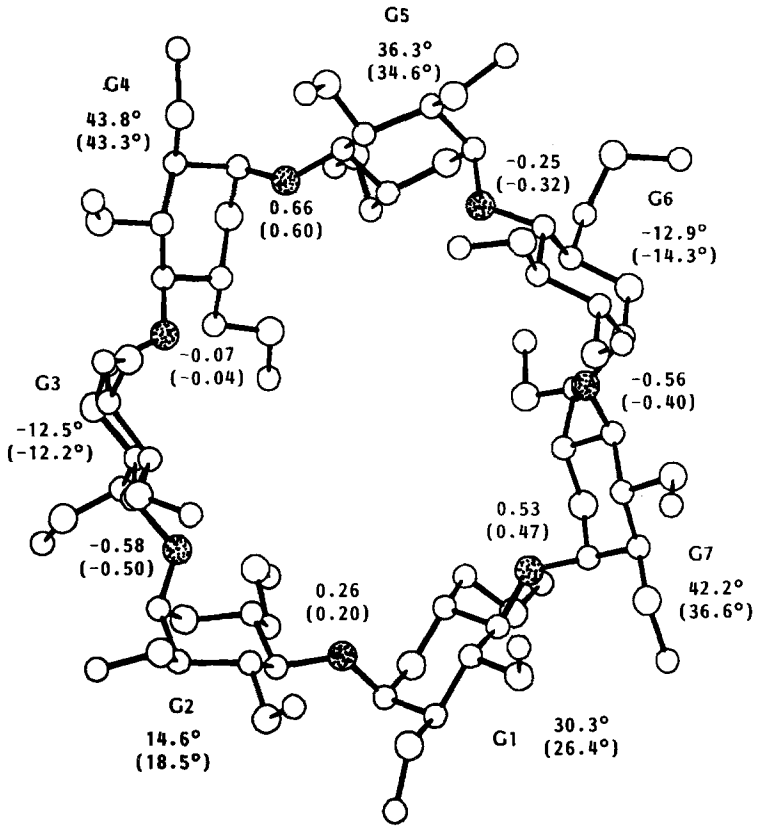

Fig. 8. Tilt-angles and deviations (in Å unit) of each O(4) atom from the least-squares plane through seven O(4) atoms in the TM-β-CDx complex with *R*-FP. The corresponding values of the *S*-FP complex are given in parentheses. O(4) atoms are shown by shaded circles.

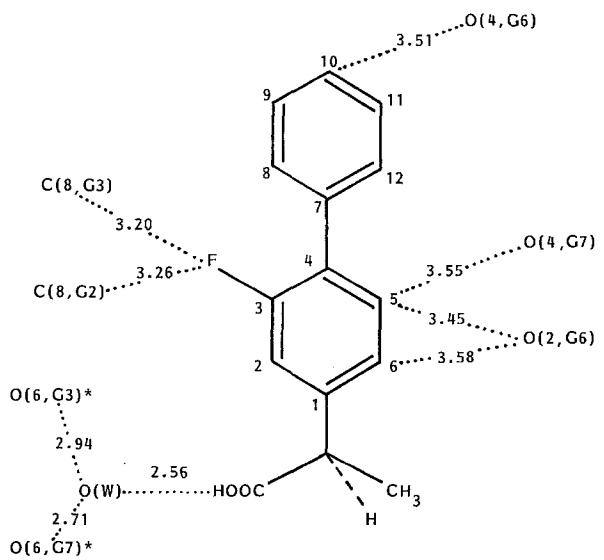

Fig. 9. Intermolecular distances less than 3.6 Å in the *R*-FP complex. Atoms in symmetry-related molecules are denoted by an asterisk.

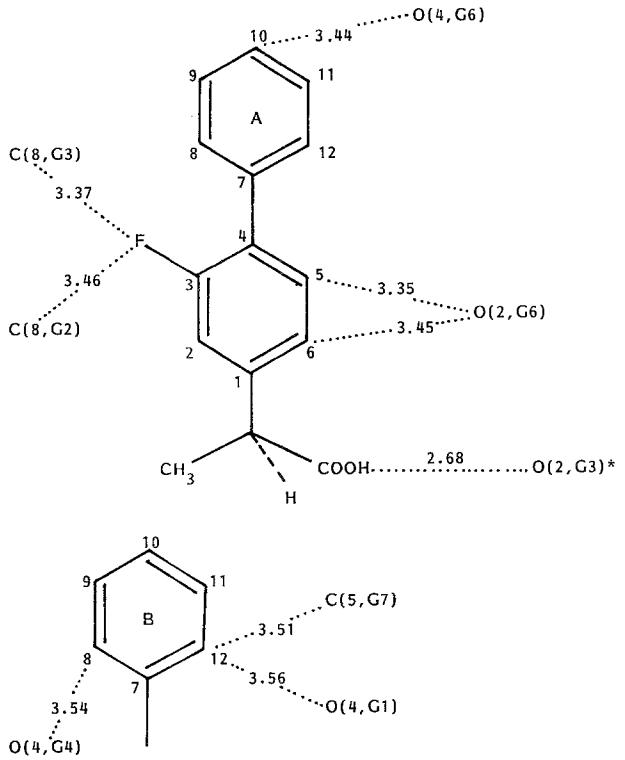

Fig. 10. Intermolecular distances less than 3.6 Å in the *S*-FP complex. Atoms in symmetry-related molecules are denoted by an asterisk.

order to relieve the repulsive interactions between O(2) and C(8)H_3 methyl groups, five 2,3,6-tri-*O*-methylglucose residues incline with their O(6) side toward the inside of the macrocyclic ring and the other two residues incline in the opposite direction.

The permethylation affects not only the macrocyclic conformation but also the conformation of the pyranose ring of each residue. As shown in Figure 5, the effect is not obvious in bond distances and angles, but can be detected by plotting the O(4)—O(4′) distance between adjacent residues against the torsion-angle index defined as follows [12]: $\Phi = |\phi(C(1)—C(2))| + |\phi(C(2)—C(3))| + |\phi(C(5)—O(5))| + |\phi(O(5)—C(1))| - |\phi(C(3)—C(4))| - |\phi(C(4)—C(5))|$, where $\phi(C(1)—C(2))$ is the endocyclic torsion angle of O(5)—C(1)—C(2)—C(3). It has been shown that cyclodextrins [13, 14], as well as mono- and oligosaccharides [12], exhibit a linear correlation between the O(4)—O(4′) distance and the torsion-angle index. In Figure 13, however, TM-β-CDx shows no such linear correlation, because the permethylation affects the endocyclic torsion angle of the pyranose ring and breaks the linear relationship between these two parameters.

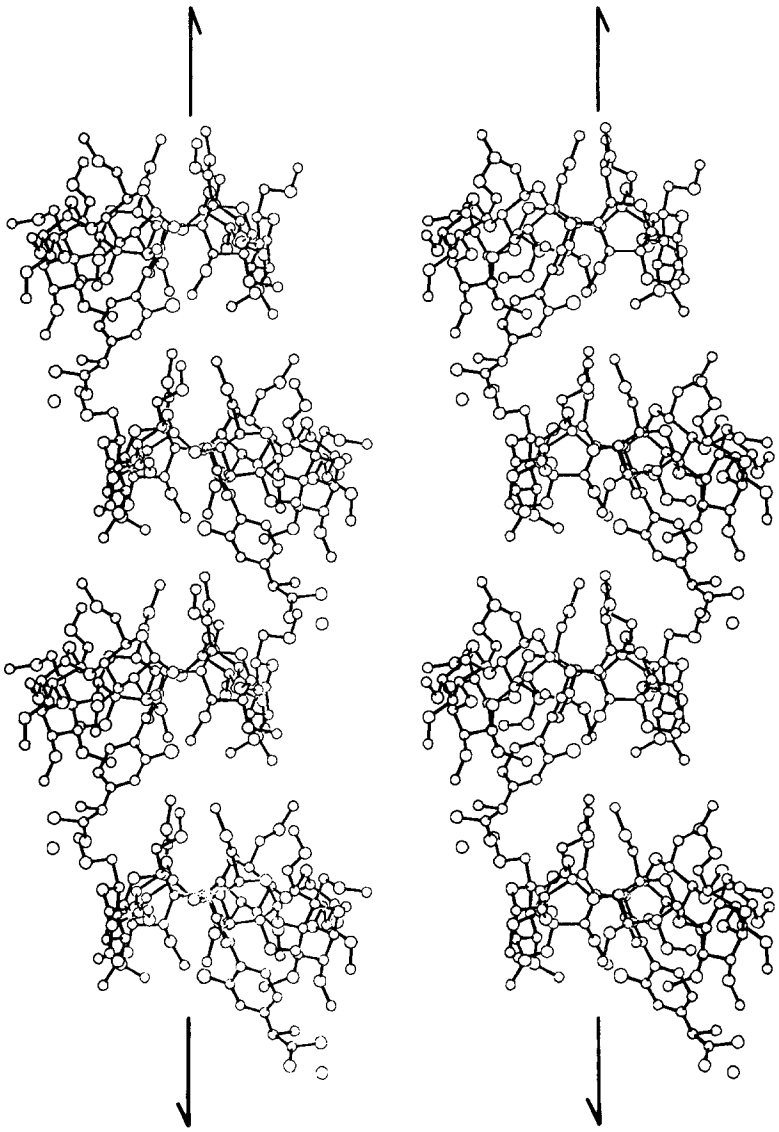

Fig. 11. A stereo-drawing of the stacking feature of the *R*-FP complex along the two-fold screw axis.

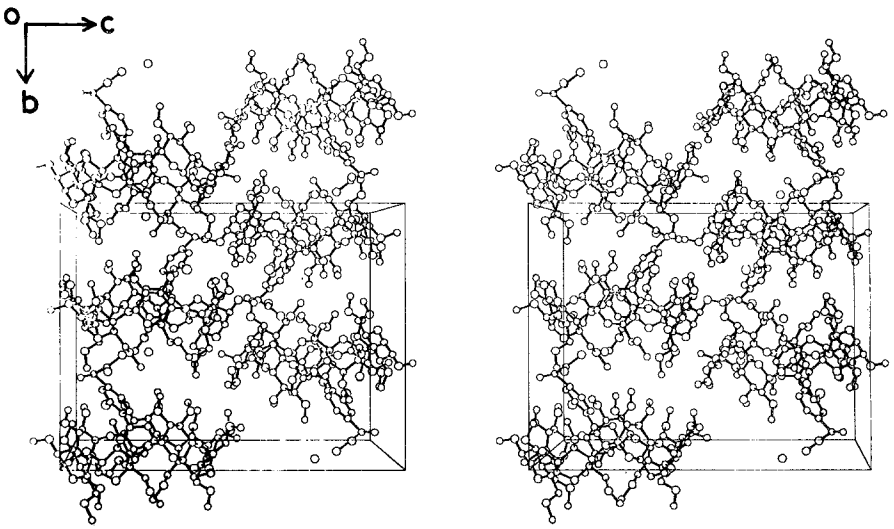

Fig. 12. A stereo-drawing of the crystal structure of the *R*-FP complex viewed along the *a* axis.

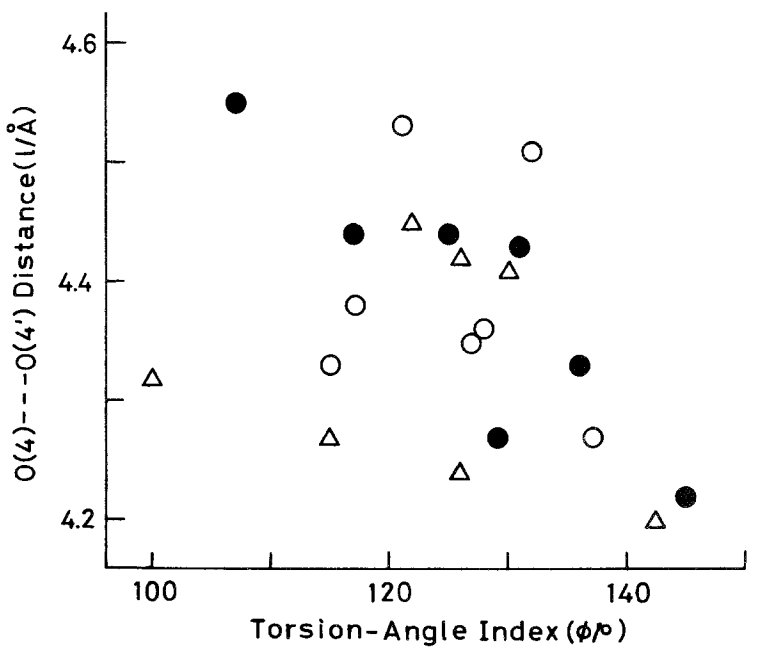

Fig. 13. Plot of O(4)—O(4′) distances against the torsion-angle index for the TM-β-CDx complexes with *R*-FP (○), *S*-FP (●), and *p*-iodophenol (△, see Ref. 5).

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