Crystal Structure of Heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin Complexes with *m*-Iodophenol and 4-Biphenylacetic Acid. Guest-induced Conformational Change of a Pyranose Ring

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Crystal structures of heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (TM-β-CDx) complexes with *m*-iodophenol (MIP) and 4-biphenylacetic acid (BPA) have been determined by X-ray analysis. The macrocylic ring of TM-β-CDx is elliptically distorted in both complexes. The 2,3,6-tri-*O*-methylglucose residues incline against the plane through seven glycosidic oxygen atoms to relieve the steric hindrance involving methyl groups at the O(2), O(3) side. In the MIP complex, one glucose residue exhibits the skew (twist boat) conformation. The MIP molecule is fully included within the TM-β-CDx cavity, both ends of which are blocked by adjacent molecules, and the hydroxy group is hydrogen-bonded to O(2) of the host TM-β-CDx. In the BPA complex, the phenyl group is located at the centre of the cavity while half a molecule protrudes from the O(2), O(3) side. The carboxy group of BPA is located in intermolecular space to form a hydrogen bond with an adjacent TM-β-CDx molecule. The complex formation induces the chiral conformation in BPA. The biphenyl group is in the *R*-configuration with an angle of 42.4° between the two benzene rings.

Cyclodextrins are cyclic oligosaccharides consisting of α-1,4-linked D-glucose residues. The torus-shaped molecules have a large cavity and form inclusion complexes with a variety of molecules or ions that have a suitable size and shape to be accommodated, even if only partially.[1,2] The round structure of cyclodextrins is maintained mainly by the intramolecular hydrogen bonds between O(2) and O(3) of the adjacent residue.[3] Chemical modification of cyclodextrins affects the conformation of the macrocycle.[4] The methylation of O(2)H and O(6)H hydroxy groups makes the cavity deeper without significant distortion of the macrocyclic ring because the O(3)H hydroxy groups can form intramolecular O(3)–H···O(2) hydrogen bonds. In contrast, the macrocyclic ring is distorted in the fully-methylated cyclodextrins and the steric hindrance involving methyl groups enlarges the O(2), O(3) end of the cavity. The full methylation affects not only the macrocyclic conformation but also the pyranose conformation of the glucose residues. In our preliminary report on the structure of hexakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (TM-β-CDx) complex with *m*-iodophenol (MIP),[5] it has been shown that one glucose residue has a twist-boat conformation.

TM-β-CDx forms a 1:1 complex with 4-biphenylacetic acid (BPA) which is a non-steroidal anti-inflammatory drug. It has been reported that the solubility and bioavailability of BPA are enhanced by complex formation with cyclodextrins.[6] In our earlier papers on the β-CDx and TM-β-CDx complex with flurbiprofen [2-(2-fluoro-4-biphenyl)propionic acid], which is also a biphenyl derivative, we have shown that β-CDx and TM-β-CDx more favourably include the biphenyl moiety with the *R*-configuration.[7–9] The structure of the BPA complex is of interest in relation to the chiral discrimination by cyclodextrins.

In this paper we present the further refined structure of the MIP complex and the structure of the BPA complex. The conformational change of the TM-β-CDx caused by the complex formation and host–guest interaction will be discussed.

Experimental

Materials and Measurements.—Crystals of TM-β-CDx complex with MIP were obtained at 50 °C by the slow evaporation of an aqueous solution containing TM-β-CDx and MIP in a 1:1 molar ratio. X-Ray diffraction data were measured on a Nicolet P3/F diffractometer with graphite-monochromated Cu-Kα radiation. A crystal of dimensions 0.4 × 0.3 × 0.3 mm was used for data collection. The unit cell parameters were refined with 25 reflections in the 2θ range from 40–43°. A total of 6245 reflections were measured up to 118° in 2θ using the θ–2θ scan mode. 4929 reflections (79%) with $|F_o| > 3\sigma(F)$ were considered as observed and used for the structure determination and refinement.

The TM-β-CDx complex with BPA was crystallized from an 18 cm^3 aqueous solution containing 143 mg TM-β-CDx and 10.6 mg BPA. The solution was allowed to stand at 40 °C. Rod-like crystals were grown in two weeks. X-Ray diffraction experiments were carried out under the same conditions as for the MIP complex. A crystal of dimensions 0.5 × 0.3 × 0.2 mm was used for data collection. A total of 6837 reflections were collected up to 118° in 2θ and 5515 reflections (81%) with $|F_o| > 3\sigma(F)$ were used for the structure determination and refinement.

Crystal Data.—(**1**) MIP complex: $C_{63}H_{112}O_{35}\cdot C_6H_5IO$, M = 1649.6, orthorhombic, space group $P2_12_12_1$, a = 15.669(3), b = 20.798(4), c = 25.486(4) Å, Z = 4, D_x = 1.319 g cm^{-3}, μ = 41.35 cm^{-1}. (**2**) BPA complex: $C_{63}H_{112}O_{35}\cdot C_{14}H_{12}O_2\cdot H_2O$, M = 1659.8, orthorhombic, space group $P2_12_12_1$, a = 14.890(3), b = 21.407(5), c = 28.540(6) Å, Z = 4, D_x = 1.212 g cm^{-3}, μ = 9.35 cm^{-1}.

Structure Determination and Refinement.—The structure of the TM-β-CDx-MIP complex was determined by the heavy atom method combined with phase refinement by the tangent formula. Because of the poor resolution of the electron-density map calculated with iodine phases, no light atoms were located on the map. Phases of 640 reflections with $|E| > 1.5$ were then refined by the tangent formula. The successive E-map revealed most of the light atoms. The structure was refined by the block-diagonal least-squares method and Fourier synthesis. A relatively large temperature factor, indicating the possibility of disorder, was observed for O(6) and C(9) atoms of the G1, G5 and G7 residues. However, each atom was observed as one

Table 1 Fractional coordinates (× 10^4) of the TM-β-CDx complex with MIP

	x	*y*	*z*		*x*	*y*	*z*
C(1,G1)	832(7)	−628(5)	658(5)	O(4,G4)	2606(5)	1833(3)	3557(3)
C(2,G1)	−46(8)	−608(6)	391(5)	O(5,G4)	1454(5)	665(3)	4351(3)
C(3,G1)	−660(7)	−162(5)	677(4)	O(6,G4)	1912(5)	−62(4)	3433(4)
C(4,G1)	−706(7)	−334(5)	1262(5)	C(1,G5)	3407(8)	2132(5)	3541(4)
C(5,G1)	188(7)	−422(6)	1480(5)	C(2,G5)	3371(8)	2622(5)	3098(4)
C(6,G1)	225(10)	−694(8)	2047(6)	C(3,G5)	4242(8)	2732(6)	2855(4)
C(7,G1)	400(9)	−883(9)	−490(6)	C(4,G5)	4649(7)	2086(6)	2680(4)
C(8,G1)	−1689(10)	226(9)	53(6)	C(5,G5)	4228(8)	1512(5)	2942(4)
C(9,G1)	140(17)	−1713(13)	2390(17)	C(6,G5)	4880(10)	952(7)	2956(6)
O(2,G1)	2(6)	−412(5)	−143(3)	C(7,G5)	1944(8)	2669(6)	2750(5)
O(3,G1)	−1500(5)	−211(4)	465(3)	C(8,G5)	4911(16)	3667(8)	3174(9)
O(4,G1)	−1104(4)	169(3)	1545(3)	C(9,G5)	5155(19)	−53(10)	3129(13)
O(5,G1)	709(5)	−843(4)	1181(3)	O(2,G5)	2806(5)	2461(3)	2682(3)
O(6,G1)	−214(7)	−1250(6)	2097(5)	O(3,G5)	4800(6)	3029(4)	3219(3)
C(1,G2)	1992(7)	139(5)	1593(4)	O(4,G5)	4564(4)	2024(4)	2122(3)
C(2,G2)	−2326(6)	814(6)	1679(4)	O(5,G5)	4061(5)	1675(4)	3475(3)
C(3,G2)	−2075(7)	1075(5)	2226(4)	O(6,G5)	4470(8)	423(6)	3084(6)
C(4,G2)	−2267(7)	578(5)	2655(4)	C(1,G6)	5332(7)	1941(5)	1842(4)
C(5,G2)	−1920(8)	−83(5)	2502(4)	C(2,G6)	5254(7)	2322(5)	1329(4)
C(6,G2)	−2156(10)	−634(5)	2889(5)	C(3,G6)	4492(6)	2095(5)	1001(4)
C(7,G2)	−2611(9)	1596(8)	994(6)	C(4,G6)	4552(6)	1369(5)	926(4)
C(8,G2)	−2015(10)	2161(6)	2487(6)	C(5,G6)	4789(7)	994(5)	1425(4)
C(9,G2)	−3241(14)	−1162(8)	3354(6)	C(6,G6)	5103(8)	316(6)	1311(5)
O(2,G2)	−2034(5)	1236(4)	1284(3)	C(7,G6)	3840(8)	2825(6)	395(5)
O(3,G2)	−2520(5)	1647(3)	2312(3)	C(8,G6)	5904(10)	3296(7)	1588(7)
O(4,G2)	−1833(4)	837(3)	3102(3)	C(9,G6)	6039(11)	−275(7)	755(7)
O(5,G2)	−2241(5)	−276(3)	2008(3)	O(2,G6)	5130(5)	2991(4)	1428(3)
O(6,G2)	−3020(6)	−642(4)	3002(4)	O(3,G6)	4510(5)	2390(3)	502(3)
C(1,G3)	−2100(7)	627(5)	3610(4)	O(4,G6)	3720(4)	1178(3)	743(3)
C(2,G3)	−2129(8)	1207(6)	3980(4)	O(5,G6)	5464(4)	1298(3)	1703(3)
C(3,G3)	−1238(7)	1490(5)	4079(4)	O(6,G6)	5788(6)	339(4)	946(4)
C(4,G3)	−617(7)	965(5)	4236(4)	C(1,G7)	3693(7)	668(5)	368(4)
C(5,G3)	−646(7)	386(5)	3856(5)	C(2,G7)	3005(7)	799(5)	−44(4)
C(6,G3)	−169(8)	−207(5)	4053(5)	C(3,G7)	2110(7)	675(5)	146(4)
C(7,G3)	−3441(10)	1728(10)	3939(10)	C(4,G7)	2040(6)	50(5)	445(4)
C(8,G3)	−1059(11)	2565(6)	4397(7)	C(5,G7)	2723(6)	48(5)	875(4)
C(9,G3)	−1024(10)	−931(7)	4569(7)	C(6,G7)	2790(11)	−515(6)	1314(6)
O(2,G3)	2652(6)	1712(4)	3759(4)	C(7,G7)	3689(11)	1577(7)	−595(6)
O(3,G3)	−1309(6)	1934(4)	4501(3)	C(8,G7)	797(9)	1078(8)	−263(6)
O(4,G3)	211(4)	1260(3)	4208(3)	C(9,G7)	2690(14)	−1624(8)	1427(10)
O(5,G3)	−1543(5)	179(3)	3824(3)	O(2,G7)	3028(5)	1439(3)	−233(3)
O(6,G3)	−368(7)	−424(4)	4550(3)	O(3,G7)	1545(5)	663(4)	−297(3)
C(1,G4)	835(7)	1082(5)	4577(4)	O(4,G7)	1192(4)	−14(3)	647(3)
C(2,G4)	1290(7)	1674(5)	4772(4)	O(5,G7)	3534(4)	69(3)	618(3)
C(3,G4)	1776(7)	2012(5)	4343(4)	O(6,G7)	2759(6)	−1056(5)	1036(4)
C(4,G4)	2345(7)	1537(5)	4043(4)	C(1,IP)	183(8)	1829(7)	1135(6)
C(5,G4)	1864(7)	936(5)	3904(4)	C(2,IP)	405(8)	1415(6)	1545(5)
C(6,G4)	2445(7)	410(5)	3673(5)	C(3,IP)	1269(10)	1465(6)	1706(5)
C(7,G4)	302(10)	1916(7)	5474(5)	C(4,IP)	1883(10)	1849(7)	1477(6)
C(8,G4)	2015(9)	3137(5)	4485(6)	C(5,IP)	1599(11)	2203(8)	1082(6)
C(9,G4)	2378(11)	−598(7)	3242(7)	C(6,IP)	755(10)	2185(7)	894(6)
O(2,G4)	749(5)	2134(4)	5005(3)	O(1,IP)	−614(6)	1799(5)	936(4)
O(3,G4)	2316(5)	2504(4)	4540(3)	I(1,IP)	1581(1)	840(1)	2358(1)

peak on the electron density map. At the final stage, the position of hydrogen atoms attached to methine and methylene groups was calculated and these atoms were included in the refinement with the isotropic temperature factor fixed to that of the attached heavier atom. The refinement converged at an *R*-value of 0.065. The quantity minimized was $\Sigma w(|F_o| - |F_c|)^2$ with unit weight for all the reflections. The maximum values for positive and negative residual electron densities were 0.38 and −0.41 e Å^{-3}, respectively. The maximum shift/esd value was 0.24.

The crystal of the BPA complex was nearly isomorphous with the crystal of the TM-β-CDx complex with *p*-iodophenol (PIP).[10] A set of TM-β-CDx coordinates of the PIP complex was used as an initial model. The structure was refined by the same procedure as that used for the MIP complex. A BPA molecule and a water molecule were found on a difference Fourier map. The O(6) atom of the G7 residue was disordered and occupied two sites, O(6) and O(6′), with respective occupancies of 0.65 and 0.35. In contrast, the C(9,G7) atom was not disordered although a relatively large temperature factor was observed. A relatively large temperature factor was also observed for the O(6) and C(9) atoms of the G2 and G6 residues. However, the electron density map indicated no disorder for those atoms. The refinement converged at an *R*-value of 0.085. The maximum values for positive and negative residual electron density were 0.32 and −0.28 e Å^{-3}, respectively, and the maximum shift/esd value was 0.33. Atomic coordinates are given in Tables 1 and 2. Tables of thermal parameters, hydrogen atom coordinates, bond distances, bond angles and torsion angles have been deposited with the Cambridge Crystallographic Data Centre (CCDC).*

* For details, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 2*, 1992, Issue 1.

Table 2 Fractional coordinates (× 10^4) for the TM-β-CDx complex with BPA[a]

	x	y	z		x	y	z
C(1,G1)	8 747(7)	4 624(5)	4 738(4)	C(3,G5)	8 721(7)	3 670(5)	439(4)
C(2,G1)	8 043(7)	4 185(5)	4 918(3)	C(4,G5)	9 035(6)	4 303(5)	595(4)
C(3,G1)	7 475(7)	3 953(5)	4 502(3)	C(5,G5)	8 381(7)	4 621(5)	932(3)
C(4,G1)	7 086(7)	4 501(4)	4 251(3)	C(6,G5)	8 613(7)	5 297(5)	1 060(4)
C(5,G1)	7 826(7)	4 954(5)	4 104(4)	C(7,G5)	6 615(9)	3 056(8)	−109(5)
C(6,G1)	7 488(8)	5 569(5)	3 881(4)	C(8,G5)	9 563(11)	2 789(7)	129(7)
C(7,G1)	8 707(8)	3 764(7)	5 620(4)	C(9,G5)	9 091(11)	6 257(6)	721(5)
C(8,G1)	6 730(9)	2 952(5)	4 475(5)	O(2,G5)	7 408(6)	3 084(4)	175(3)
C(9,G1)	6 354(11)	6 330(6)	3 928(5)	O(3,G5)	9 261(5)	3 441(4)	76(3)
O(2,G1)	8 414(5)	3 654(3)	5 149(2)	O(4,G5)	9 894(4)	4 204(3)	814(2)
O(3,G1)	6 773(5)	3 550(4)	4 674(3)	O(5,G5)	7 508(4)	4 642(3)	729(2)
O(4,G1)	6 620(5)	4 273(3)	3 846(2)	O(6,G5)	8 814(6)	5 625(4)	646(3)
O(5,G1)	8 338(5)	5 136(3)	4 513(2)	C(1,G6)	5 190(8)	3 457(8)	2 083(4)
O(6,G1)	6 786(6)	5 809(4)	4 152(3)	C(2,G6)	5 536(9)	2 855(7)	1 847(4)
C(1,G2)	11 932(7)	4 115(6)	3 972(4)	C(3,G6)	6 349(8)	2 978(7)	1 550(4)
C(2,G2)	11 631(8)	3 664(6)	4 366(4)	C(4,G6)	6 208(7)	3 549(5)	1 218(4)
C(3,G2)	10 634(7)	3 679(5)	4 417(4)	C(5,G6)	5 818(8)	4 110(6)	1 479(4)
C(4,G2)	10 290(7)	4 352(5)	4 477(3)	C(6,G6)	5 539(10)	4 673(8)	1 167(5)
C(5,G2)	10 665(7)	4 779(5)	4 104(4)	C(7,G6)	5 221(12)	1 863(7)	2 142(6)
C(6,G2)	10 474(9)	5 473(6)	4 210(6)	C(8,G6)	7 470(12)	2 249(7)	1 273(7)
C(7,G2)	12 785(9)	2 872(8)	4 388(7)	C(9,G6)	4 219(9)	4 388(10)	738(7)
C(8,G2)	9 920(9)	2 771(5)	4 744(4)	O(2,G6)	5 688(7)	2 406(5)	2 183(3)
C(9,G2)	10 325(16)	6 440(7)	3 809(10)	O(3,G6)	6 540(7)	2 446(4)	1 287(3)
O(2,G2)	11 864(6)	3 034(4)	4 273(3)	O(4,G6)	7 076(5)	3 692(3)	1 043(2)
O(3,G2)	10 400(5)	3 327(3)	4 828(2)	O(5,G6)	5 031(5)	3 941(5)	1 739(3)
O(4,G2)	9 325(4)	4 314(3)	4 430(2)	O(6,G6)	5 110(7)	4 510(6)	745(3)
O(5,G2)	11 628(5)	4 723(4)	4 089(3)	C(1,G7)	5 828(8)	4 577(5)	3 708(4)
O(6,G2)	10 578(8)	5 816(5)	3 771(5)	C(2,G7)	5 064(8)	4 100(6)	3 637(4)
C(1,G3)	12 528(7)	3 897(5)	2 157(4)	C(3,G7)	5 285(7)	3 663(5)	3 224(4)
C(2,G3)	12 479(8)	3 280(6)	2 415(4)	C(4,G7)	5 493(9)	4 052(6)	2 787(4)
C(3,G3)	11 891(8)	3 319(5)	2 861(4)	C(5,G7)	6 254(12)	4 528(8)	2 895(5)
C(4,G3)	12 190(7)	3 873(5)	3 147(4)	C(6,G7)	6 629(14)	4 944(10)	2 459(6)
C(5,G3)	12 164(7)	4 471(5)	2 851(4)	C(7,G7)	4 605(9)	4 049(7)	4 447(5)
C(6,G3)	12 429(9)	5 092(6)	3 093(4)	C(8,G7)	4 558(10)	2 653(6)	3 325(5)
C(7,G3)	12 608(17)	2 239(8)	2 143(7)	C(9,G7)	6 464(20)	5 814(11)	2 080(9)
C(8,G3)	11 136(11)	2 485(7)	3 252(5)	O(2,G7)	4 928(5)	3 716(4)	4 040(3)
C(9,G3)	13 520(12)	5 575(6)	3 556(6)	O(3,G7)	4 531(5)	3 272(4)	3 124(3)
O(2,G3)	12 174(7)	2 793(4)	2 113(3)	O(4,G7)	5 830(5)	3 658(4)	2 418(3)
O(3,G3)	11 990(7)	2 756(4)	3 114(3)	O(5,G7)	5 963(7)	4 902(4)	3 291(3)
O(4,G3)	11 583(4)	3 918(4)	3 539(2)	O(6,G7)	5 972(9)	5 228(7)	2 325(6)
O(5,G3)	12 772(5)	4 394(3)	2 463(3)	O(6′,G7)	6 688(28)	5 609(11)	2 604(9)
O(6,G3)	13 288(6)	5 012(4)	3 311(3)	C(1,BP)	7 491(10)	1 587(6)	3 608(5)
C(1,G4)	10 596(7)	4 624(5)	717(4)	C(2,BP)	8 245(10)	1 863(7)	3 775(5)
C(2,G4)	11 464(7)	4 247(6)	659(4)	C(3,BP)	8 571(9)	2 395(7)	3 557(4)
C(3,G4)	11 709(7)	3 922(5)	1 100(4)	C(4,BP)	8 152(8)	2 636(6)	3 173(4)
C(4,G4)	11 704(7)	4 362(5)	1 525(4)	C(5,BP)	7 398(10)	2 370(7)	3 001(6)
C(5,G4)	10 884(6)	4 790(5)	1 531(4)	C(6,BP)	7 078(9)	1 867(7)	3 233(6)
C(6,G4)	10 990(8)	5 348(5)	1 887(4)	C(7,BP)	8 543(9)	3 213(7)	2 930(5)
C(7,G4)	11 443(13)	4 043(9)	−179(5)	C(8,BP)	8 564(16)	3 232(7)	2 453(5)
C(8,G4)	12 665(11)	3 004(6)	935(5)	C(9,BP)	8 902(17)	3 813(9)	2 250(6)
C(9,G4)	10 230(12)	6 120(7)	2 324(6)	C(10,BP)	9 175(12)	4 296(8)	2 496(6)
O(2,G4)	11 410(6)	3 807(4)	290(3)	C(11,BP)	9 179(12)	4 251(9)	2 949(6)
O(3,G4)	12 610(5)	3 679(4)	1 079(3)	C(12,BP)	8 866(10)	3 693(8)	3 176(5)
O(4,G4)	11 685(4)	4 011(3)	1 954(2)	C(13,BP)	7 059(13)	1 016(8)	3 803(6)
O(5,G4)	10 725(5)	5 072(3)	1 082(3)	C(14,BP)	6 585(19)	1 111(8)	4 227(8)
O(6,G4)	10 150(6)	5 591(4)	1 980(3)	O(1,BP)	6 889(14)	755(8)	4 550(6)
C(1,G5)	7 129(7)	4 047(5)	629(4)	O(2,BP)	6 097(10)	1 471(6)	4 329(5)
C(2,G5)	7 749(7)	3 715(5)	283(4)	O(1,W)	4 060(13)	5 352(8)	2 175(7)

[a] The occupancy of O(6,G7) and O(6′,G7) is 0.65 and 0.35, respectively.

Results

Conformation of the 2,3,6-*Tri*-O-*methylglucose Residue.*— The numbering scheme of the molecules is shown in Fig. 1. Fig. 2 shows stereo-drawings of the structures. The TM-β-CDx molecule consists of seven 2,3,6-tri-*O*-methylglucose residues. Except for the G5 residue in the MIP complex, the pyranose ring of all residues is in the $^4C_1$ chair conformation. The average torsion angles for the pyranose ring in the chair conformation are given in Table 3. These torsion angles are in good agreement between the two TM-β-CDx molecules. The G5 residue in the MIP complex is in the $^0S_2$ skew (twist boat) conformation. The C(1), C(2), C(4) and C(5) atoms form a twist plane and the C(3) and O(5) atoms are *exo*-planar. With the change from $^4C_1$ to $^0S_2$, the equatorial C(2)–O(2), C(3)–O(3) and C(4)–O(4) bonds turn to the axial conformation while the C(1)–O(4′) bond changes from axial to equatorial. As the result, the C(3)–O(3) bond is *trans* to the C(2)–O(2) and C(4)–O(4) bonds. The C(6)–O(6) bonds show two types of conformations. Five C(6)–O(6) bonds in both molecules are *gauche* to both the C(5)–O(5) and C(4)–C(5) bonds. The other C(6)–O(6) bonds show a *gauche-trans* conformation. Methyl groups are located at the edge of the torus-shaped molecule. The O(2)–C(7)

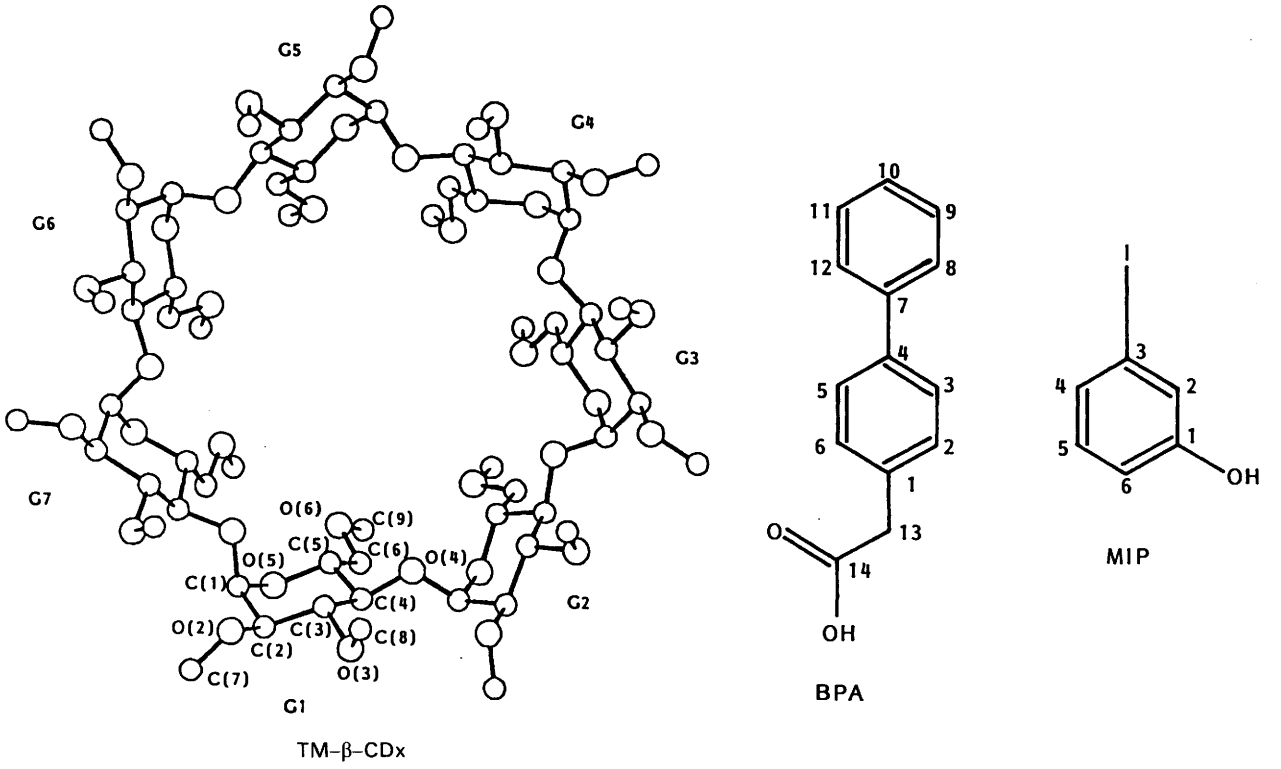

Fig. 1 Atomic numbering scheme of TM-β-CDx, BPA, and MIP

Table 3 Average torsion angles/° of the pyranose ring

	MIP Complex		BPA Complex
	$^4C_1$	$^0S_2$	$^4C_1$
C(1)–C(2)–C(3)–C(4)	−50(3)	54	−52(3)
C(2)–C(3)–C(4)–C(5)	48(3)	−18	51(4)
C(3)–C(4)–C(5)–O(5)	−53(6)	−40	−54(4)
C(4)–C(5)–O(5)–C(1)	62(4)	70	61(2)
C(5)–O(5)–C(1)–C(2)	−63(2)	−34	−62(2)
O(5)–C(1)–C(2)–C(3)	56(6)	−29	56(3)
O(4′)–C(1)–C(2)–O(2)	55(6)	−29	57(2)
O(2)–C(2)–C(3)–O(3)	66(4)	167	64(3)
O(3)–C(3)–C(4)–O(4)	−72(4)	−136	−69(4)
O(4)–C(4)–C(5)–C(6)	70(9)	85	67(7)

bonds point away from the centre of the macrocycle and mostly *gauche* to the C(1)–C(2) bond. The O(3)–C(8) bond is oriented rather parallel to the molecular axis that is perpendicular to the plane through seven O(4) atoms. The C(8)H_3 methyl groups are situated in the midst of the adjacent two O(2) atoms with a distance of 3.01–3.81 Å. Most of the O(6)–C(9) bonds are *trans* to the C(5)–C(6) bond, but the G2 residue in the BPA complex and the G3 residue in the MIP complex have a *gauche* conformer.

Conformation of the Macrocycle.—Some parameters describing the macrocyclic conformation of the TM-β-CDx molecule are shown in Fig. 3. Seven glycosidic O(4) atoms form a distorted heptagon. The calculation of the least-squares plane of seven O(4) atoms gives a root-mean-square deviation of 0.42 Å for the MIP complex and 0.45 Å for the BPA complex. The radius of the heptagon varies in the ranges 4.16–5.47 Å for the MIP complex and 4.57–5.37 Å for the BPA complex. The O(2)···O(3′) distance between adjacent residues is in the range 3.17–3.69 Å in the BPA complex. In the MIP complex, because of the skew conformation of the G5 residue, the O(2)···O(3′) distances involving the G5 residue, 4.60 and 4.80 Å, are markedly larger than those of others which are distributed between 3.32 and 3.76 Å. The pyranose ring of 2,3,6-tri-*O*-methylglucose residues is not perpendicular to the O(4) plane. The tilt-angle given in Table 4 is a good measure to use to estimate the relative degree of inclination for each residue. The five residues, G1, G3, G4, G6 and G7, incline with their O(6) side towards the inside of the macrocycle, while the other two residues are rotated in the opposite direction. Since the G1 and G2 residues are oppositely rotated to each other with respect to the O(4) plane, a large angle, 56.6° in the MIP complex and 52.4° in the BPA complex, is observed between the planes through C(1), C(4), O(4) and O(4′) of these residues. The two TM-β-CDx molecules are superimposed by the least-squares method (Fig. 4). The G5 residues and all methyl groups are not included in the least-squares calculation. The root-mean-square difference of 0.55 Å indicates that the macrocyclic conformation of the two molecules is similar in spite of the remarkable distortion of the macrocycle.

Host–Guest Interaction.—Intermolecular contacts between the host and guest molecules are shown in Fig. 5. In the MIP complex, the guest molecule is fully included within the host cavity. The iodine atom is located at the O(6) side of the cavity and further penetration is blocked by the methoxy group of the G4 residue. The iodophenyl group forms a van der Waals contact with the inside wall of the cavity. The hydroxy group of MIP is hydrogen-bonded to O(2) of the G2 residue with an O(1,IP)···O(2,G2) distance of 2.67 Å. The benzene ring makes an angle of 57.0° with the O(4) plane.

The BPA model is inserted into the host cavity from the O(2), O(3) side. The phenyl group located at the centre of the cavity is sandwiched by the G1 and G5 residues. The biphenyl group forms a van der Waals contact with the inside wall of the cavity. The phenyl group makes an angle of 55.7° with the O(4) plane. The carboxy group forms a hydrogen bond with O(3,G6) of an adjacent molecule. The biphenyl group is in the *R*-configuration and the angle made by two benzene rings is 42.4°.

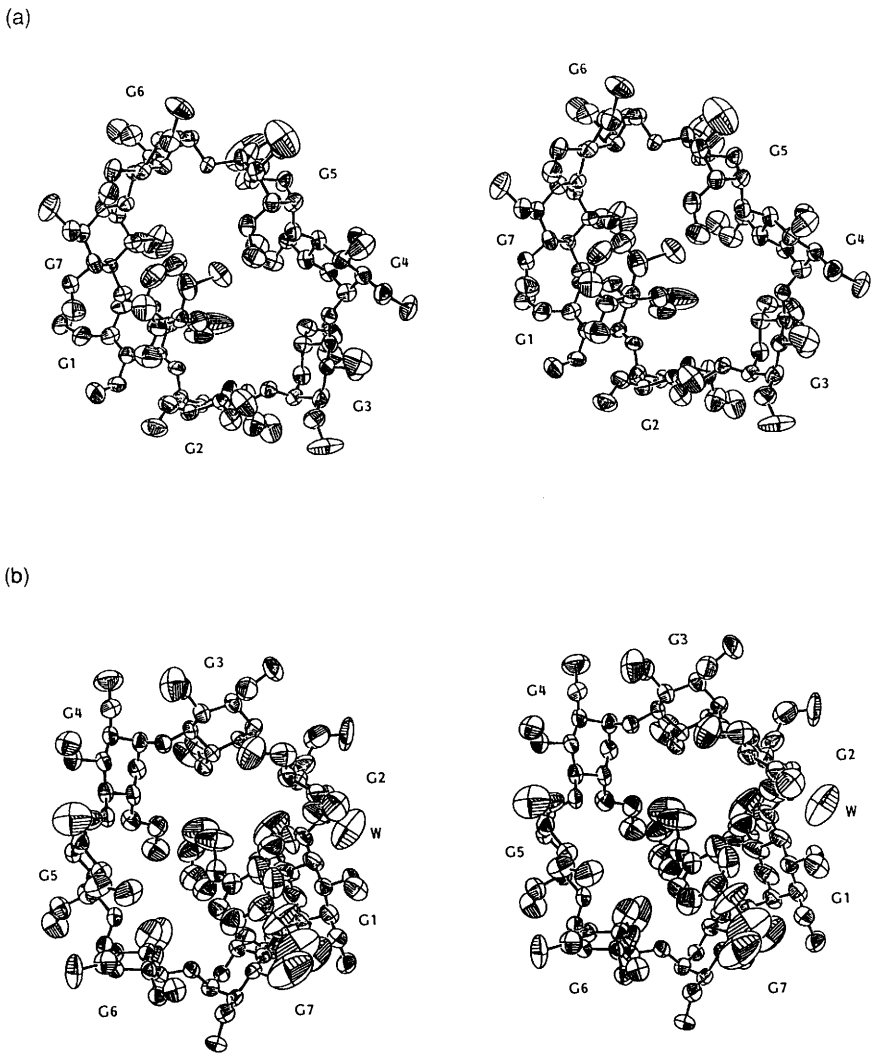

Fig. 2 Stereo-drawings of the structure: (*a*) MIP complex; (*b*) BPA complex

Table 4 Planarity of the O(4) heptagon and tilt angle

	Deviation from the plane/Å			Tilt-angle[a]/°	
	MIP Complex	BPA Complex		MIP Complex	BPA Complex
O(4,G1)	0.170	−0.506	G1	51.7	41.3
O(4,G2)	0.590	−0.271	G2	−13.6	−14.4
O(4,G3)	−0.506	0.663	G3	28.3	36.5
O(4,G4)	−0.150	−0.087	G4	45.2	43.5
O(4,G5)	0.318	−0.563	G5	−6.1	−13.8
O(4,G6)	0.224	0.276	G6	13.3	15.8
O(4,G7)	−0.647	0.488	G7	27.7	28.3

[a] The tilt angle is defined as an angle made by the O(4) plane and a plane through C(1), C(4), O(4) and O(4′) of each residue. The positive value indicates that the residue is rotated with its O(6) side toward the inside of the molecule.

Crystal Packing.—Crystal structures are shown in Fig. 6. The TM-β-CDx molecules in the MIP complex are arranged parallel to the *ac* plane to form molecular layers with a brick-work packing pattern. The O(4) planes makes an angle of 26.2° with the *ac* plane. The adjacent two molecular layers are moved, parallel to the *a* axis, such that both ends of the TM-β-CDx cavity are blocked by molecules of adjacent layers. The guest MIP molecule is therefore enclosed in the isolated 'cage' in the crystal.

In the BPA complex, the host molecules are stacked along the *b* axis in a zigzag mode to form a distorted column structure. The molecule is parallel to the *ac* plane with the angle of 4.6°. Since the centre of the molecule is laterally shifted from the two-fold screw axis, the cavity does not form a continuous channel. The O(6) side of the cavity is blocked by the next molecule. The other side of the cavity is open to the intermolecular space. Half of the BPA molecule protrudes from the O(2), O(3) side and the carboxy group is hydrogen-bonded to O(3,G6) of an adjacent column with a O(2,BP)···O(3,G6) distance of 2.66 Å. The water molecule is located in the intermolecular space and forms hydrogen bonds with the O(6,G1) and O(5,G5) atoms, which are at a distance of 2.89 and 2.93 Å, respectively, from O(1,W).

Discussion

The present X-ray structure of the MIP complex demonstrates that one of seven pyranose rings in fully methylated β-CDx has a non-chair conformation. The skew conformation is less stable than the chair conformation and has been considered as an intermediate state.[11] In the crystal structures of the cyclodextrin

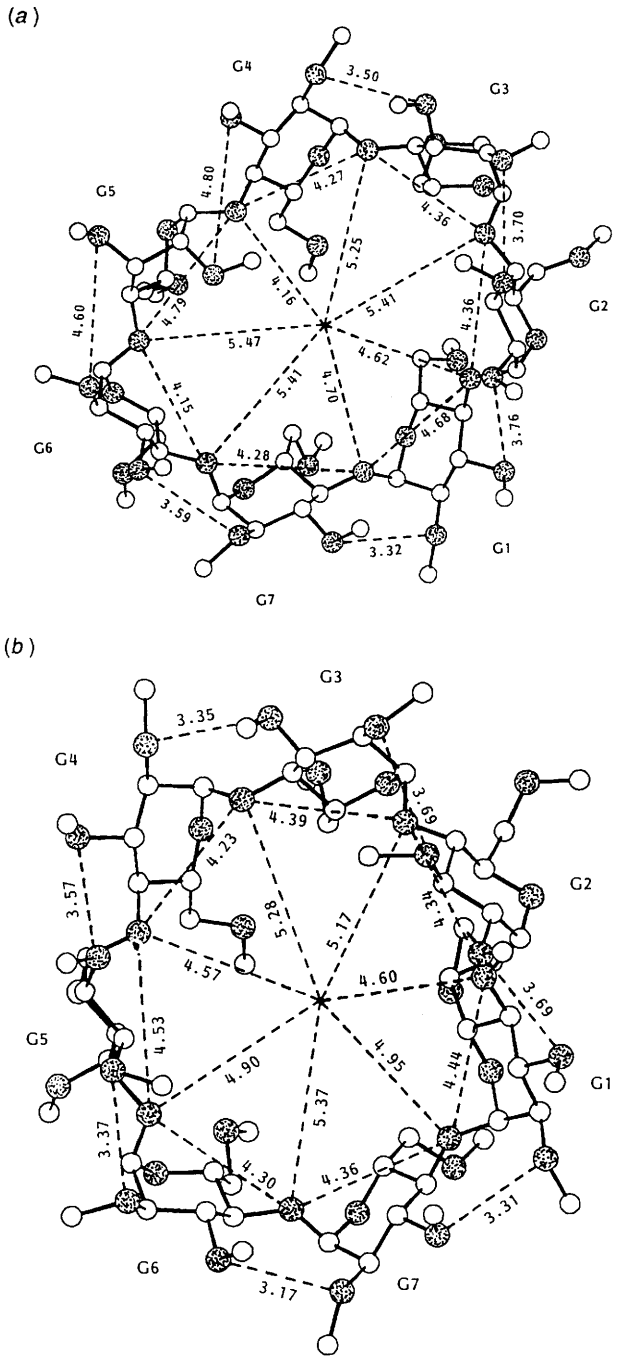

Fig. 3 Macrocyclic structure of TM-β-CDx: (*a*) MIP complex; (*b*) BPA complex

or methylated cyclodextrin complexes so far reported, the pyranose ring was always in the chair conformation. In the fully methylated cyclodextrins, the distorted macrocyclic conformation has been mainly ascribed to steric hindrance, involving methyl groups.[12] In native β-CDx, the chair conformation of the pyranose ring, as well as the macrocyclic conformation, is stabilized by the intramolecular O(2)···O(3′) hydrogen bonds.[13] The $^4C_1$ chair conformation is favourable for formation of the O(2)···O(3′) hydrogen bond. In TM-β-CDx, the molecule is free from such geometrical restraints that are imposed by the intramolecular hydrogen bonds. Therefore, not only the macrocycle but also the pyranose ring is more flexible than that of β-CDx.

The conformational change of the pyranose ring caused by full methylation has been indicated in the analysis of the torsion angle index,[14] which is defined as the function of endocyclic torsion angles of the pyranose ring: $\Phi = |\varphi[C(1)–C(2)]| + |\varphi[C(2)–C(3)]| + |\varphi[C(5)–O(5)]| + |\varphi[O(5)–C(1)]| – |\varphi[C(3)–C(4)]| – |\varphi[C(4)–C(5)]|$, where $\varphi[C(1)–C(2)]$ is the torsion angle of O(5)–C(1)–C(2)–C(3). The torsion angle index in native cyclodextrins is linearly correlated with the O(4)···O(4′) distance.[15] However, in fully methylated cyclodextrins, no such correlation has been observed.[12] The methyl group bonded to an O(3) atom is located between two O(2) atoms and causes steric hindrance with them. The steric hindrance can be relieved by the increase of the O(2), O(3) distance, which requires a large inclination of each residue. In the BPA complex, five residues, G1, G3, G4, G6 and G7, incline with their O(6) side toward the inside of the macrocyclic ring, but the other two residues incline in the opposite direction to relieve the O(6) side of the residue from steric hindrance. In contrast, in the MIP complex the steric hindrance at the O(2), O(3) side is partly relieved by the conformational change of the G5 residue to the skew form. The C(2)–O(2) and C(3)–O(3) bonds in the G5 residue are so oriented that the methoxy groups have no unfavourable short contacts with adjacent residues.

In fully methylated α-CDx complexes, two types of macrocyclic conformation have been observed although all pyranose rings are in the chair conformation.[16] One has a symmetrical structure with a pseudo two-fold axis and the other is markedly distorted. The two structures of fully methylated α-CDx have been found to be sensitive to the chirality of the guest. On the other hand, in spite of the skew conformation of the G5 residue, the shape of the TM-β-CDx molecule in the MIP complex is very similar to that of the BPA complex as shown in Fig. 4. A similar macrocyclic structure has been observed in the TM-β-CDx complexes with flurbiprofen[9] and PIP.[10] In the BPA complex, the G5 residue can not be in the skew conformation because the O(3)C(8)H_3 groups with an axial conformation will bring unfavourable short contacts with the phenyl group of BPA.

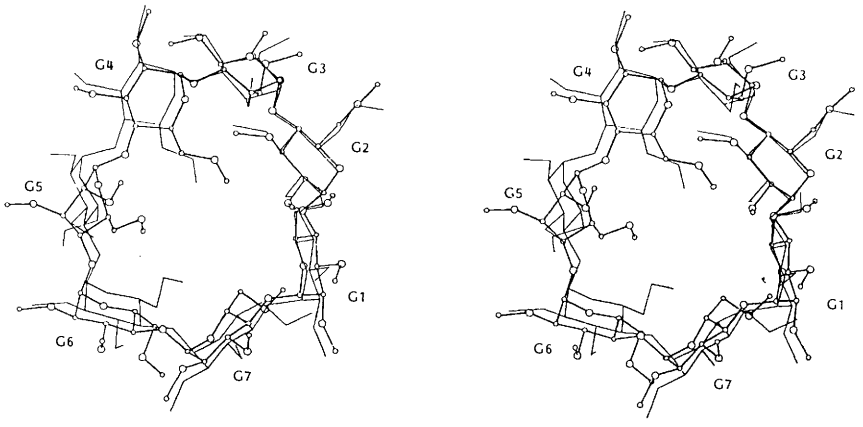

Fig. 4 Stereo-drawing of the superposition of TM-β-CDx molecules in the complexes with MIP and BPA. Atoms of the MIP complex are shown by circles and the TM-β-CDx structure of the BPA complex is shown by thin lines.

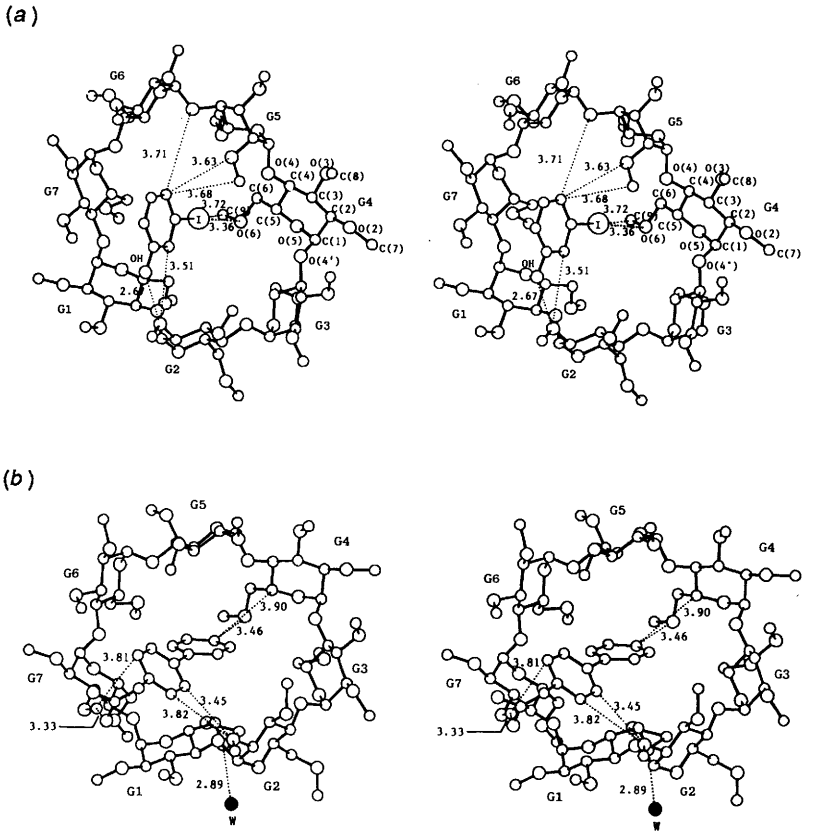

Fig. 5 Intermolecular contacts between TM-β-CDx and the guest: (*a*) MIP complex; (*b*) BPA complex

The macrocyclic structure of the TM-β-CDx molecule in the BPA complex is nearly the same as that of the PIP complex. The iodophenyl group of PIP is included in a similar manner with that of MIP. But the hydroxy group protrudes from the O(2), O(3) side and forms hydrogen bonds with two water molecules. The unit cell volume of the PIP and BPA complexes is 8.7% larger than that of the MIP complex. A hydrophilic group of PIP and BPA occupies the intermolecular space while the host cavity includes a hydrophobic portion of the guest molecule. It is of interest that the skew conformation of the G5 residue is induced by the inclusion of MIP but not PIP. The iodophenyl group in both the MIP and PIP complexes is situated at the same place with the same orientation but PIP has no short contact with the G5 residue. The comparison of the TM-β-CDx structure between the MIP and BPA complexes (Fig. 4) indicates that at least one pyranose ring in TM-β-CDx is in the boat-skew equilibrium in solution. Each of the two TM-β-CDx structures may be a snapshot of the dynamic state. The cage-type packing structure can be formed when the guest molecule is fully included in the host cavity. In the MIP complex, the O(2), O(3) side of the G5 residue is in van der Waals contact with the O(6) side of the adjacent TM-β-CDx molecule related by the two-fold screw axis. Therefore, the crystal packing found in the MIP complex is not possible if the G5 residue has a chair conformation. In the complexes with PIP, BPA or flurbiprofen, the guest molecule is too large to be fully included, and part of the guest molecule should be accommodated in the intermolecular space.

BPA also forms a 2:2 complex with β-CDx in the crystalline state.[17] The lattice dimensions which are similar to those of the flurbiprofen complex are as follows: a = 15.452(2), b = 15.546(2), c = 18.094(3) Å, α = 113.03(1)°, β = 99.35(1)° and γ = 103.47(1)°. Two β-CDx molecules form a head-to-head dimer with each O(2), O(3) side facing. Although the BPA molecule was not located on the electron-density map because of the disorder, the dimer cavity seems to include two BPA molecules in a similar manner found in the flurbiprofen complex.

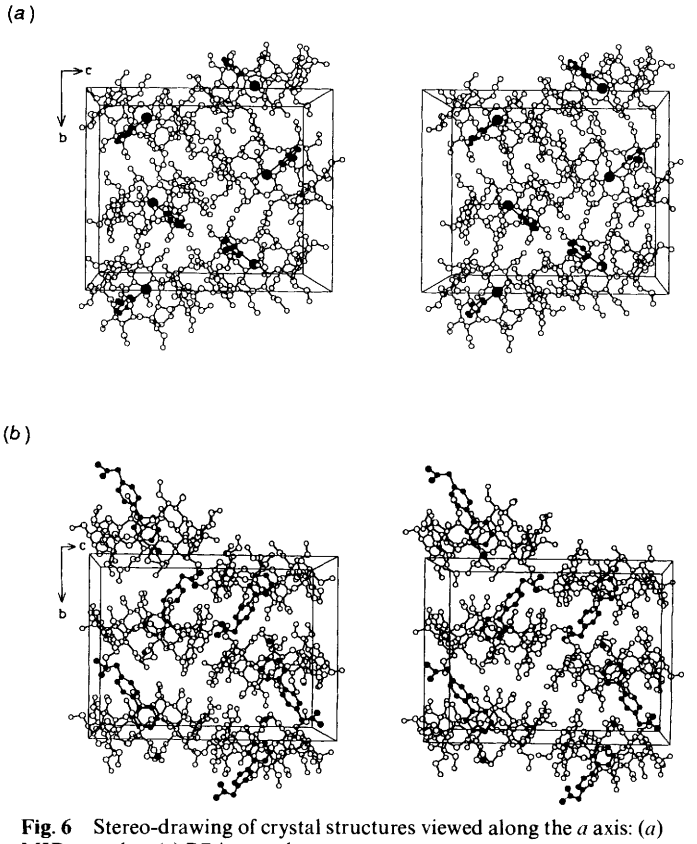

Fig. 6 Stereo-drawing of crystal structures viewed along the *a* axis: (*a*) MIP complex; (*c*) BPA complex

The complex formation with TM-β-CDx induces the chiral conformation on BPA. The biphenyl molecule itself is planar in the crystalline state.[18,19] On the other hand, flurbiprofen is an optically active molecule which has an asymmetric carbon atom. In the crystal of flurbiprofen,[20] two benzene rings make an angle of 54.4°, and two molecules with *R*- and *S*-configuration are related by the centre of symmetry. The biphenyl group of (*S*)-flurbiprofen is in the *R*-configuration. The BPA molecule in the TM-β-CDx complex is found to be in the *R*-configuration with a biphenyl angle of 42.4°. The *R*-configuration of the biphenyl group has been also observed in (*R*)- and (*S*)-flurbiprofen complexes with β-CDx and the (*R*)-flurbiprofen complex with TM-β-CDx. The biphenyl angle of flurbiprofen is 33–34° in the β-CDx complexes[7,8] and 51–60° in the TM-β-CDx complexes. The structure of the BPA and flurbiprofen complexes indicates that the TM-β-CDx cavity more favourably includes the biphenyl group with the *R*-configuration than that of the *S*-configuration. It has been reported that cyclodextrins recognize the chirality of the included guest, such as fenoprofen[21,22] and mandelic acid,[16] which have an asymmetric carbon atom. On the other hand, α-CDx equally includes *R*- and *S*-isomers of 1-phenylethanol because of the symmetrical shape of the cavity.[23] The methylated cyclodextrins provide more asymmetric cavity than native cyclodextrins and higher ability of chiral recognition can be expected.

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