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The Crystal Structure of Heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin with Methylcyclohexane

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Abstract. The structure of the complex of the permethylated cyclodextrin, heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin (TM-βCD) with methylcyclohexane, space group $P2_12_12_1$, a = 11.149(2), b = 25.664(2) and c = 29.427(5) Å has been determined at room temperature. The structure has been solved using Patterson vector search methods and Fourier recycling and refined to a final R-value of 0.0957 for 2961 observed reflections. One methylcyclohexane molecule, disordered over two positions, is completely enclosed in the (TM-βCD) host, the latter exhibiting induced fit towards the guest. The complex molecules are stacked in a head-to-tail herringbone mode along the shortest axis a. This kind of packing allows for a large number of short contacts between the host molecules.

Key words: permethylated β-cyclodextrin, inclusion complex, methylcyclohexane.

Supplementary Data relating to this article are deposited with the British Library as Supplementary Publication No. 82240 [16 pages (15 computer printout + 1)]

1. Introduction

Methylated cyclodextrins, unlike their parent homologues, can be utilized in cases where the use of water as solvent is not allowed due to guest hydrolysis. Of course there is always the risk that the solvent may be preferentially encapsulated. This is the case in the present structure, that of the TM-βCD methylcyclohexane 1 : 1 complex. Initially, the preparation of the complex of TM-βCD with the thermochromic Schiff base (anil) 5-bromosalicylidenepyridine was intended by using methylcyclohexane as solvent. There were indications that in the solid state, thermochromic anils become photochromic when complexed by cyclodextrins, while the photochromic ones change their behavior towards fluorescence [1]. The structure of such an inclusion complex would clearly show how the topology of the cavity

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would influence the structure of the anil and hence its behavior. Unfortunately, we have not been successful in growing crystals of an anil inside a cyclodextrin so far, although several anils, cyclodextrins and solvents have been used.

2. Experimental

2.1. Preparation and crystallization of the complex

Equimolar quantities of the Schiff base and TM-βCD were dissolved in methylcyclohexane and the solution was allowed to evaporate slowly at room temperature. A few days later, pale yellow prismatic crystals were formed. A crystal of dimensions $0.7 \times 0.6 \times 0.3$ mm was selected for data collection and mounted on a glass fiber with epoxy resin.

2.2. Data collection and structure refinement

Crystal data were collected on a Syntex $P2_1$ diffractometer with Nb-filtered Mo$K\alpha$ radiation. Final lattice parameters determined from 25 reflections ($11 < 2\theta < 23°$) are given in Table I along with other information regarding data collection and refinement. One octant of data was collected by $\theta - 2\theta$ scan rates in the range 1.0–10°/min and a scan width of 1.8° plus $\alpha_1 - \alpha_2$ divergence. Three standard reflections monitored every 67 reflections with a frequency of 95 min showed no decay of the crystal during data collection.

Routine application of direct methods for phase determination did not lead to the solution of the structure. The structure was solved by using Patterson vector search methods and Fourier recycling with DIRDIF94 [2]. When we studied the initial Patterson results, it was evident that the structure did not contain a heavy atom of sufficient weight, such as the expected bromine atom of the guest, to enable successive structure expansion. Therefore, in the following experiments the bromine atoms were not counted in the cell contents. Suitable models (molecular fragments) for searching in the Patterson space were obtained from two published structures [3 and 4]. From each large ring of seven glucosidic residues seven different models were generated, each consisting of three sequential glucosidic residues. The 14 models were fed to the automated vector search procedures and one of the models led to the solution of the structure. Because of the uncertainty of the cell contents, the final structure expansion was done manually. Subsequent difference Fourier maps revealed all the missing atoms of the TM-βCD structure and some atoms of the guest molecule. Isotropic refinement was carried out by SHELXL93 [5] up to R = 0.1529. Then, anisotropic displacement parameters were assigned to all non disordered C(6), O(6), C(7), C(8) and C(9) atoms of TM-βCD. Hydrogen atoms were calculated for all the non disordered C atoms of TM-βCD using a riding model with Ueq(H) equal to 1.2 Ueq or 1.5 Ueq of the parent primary and secondary or tertiary C atoms respectively. Inspection of the difference electron density that corresponds to the guest at this stage unequivocally

Table I. Crystal data and structure refinement for the TM-βCD/methylcyclohexane complex

Formula	$C_{63}H_{112}O_{35}\cdot C_7H_{14}$
Formula weight	1527.71
Temperature (K)	293
Wavelength (Å)	0.71070
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	
a (Å)	11.149(2)
b (Å)	25.664(2)
c (Å)	29.427(5)
V (Å^3)	8420(2)
Z	4
d_{calc}(g cm^{-3})	1.205
2θ range for data collection (°)	$2.1 < 2\theta < 40.0$
Index ranges	$0 < h < 10$, $0 < k < 23$, $0 < l < 26$
Reflections collected	4085
Independent reflections	4081 [R(int) = 0.0146]
Refinement method	Full-matrix-block least-squares on F^2
Data/restraints/parameters	4073/2/578
Goodness-of-fit on F^2	1.019
Final R indices [I > 2sigma(I)]	R = 0.0957, wR^2 = 0.2530
R indices (all data)	R = 0.1342, wR^2 = 0.3113
Largest diff. peak and hole	0.404 and −0.309 e Å^{-3}

showed that it could not be assigned to 5-bromosalicylidenepyridine but to a much smaller molecule comprised of one ring. Therefore, it was concluded that the guest molecule was methylcyclohexane. All atoms of methylcyclohexane were revealed from difference Fourier maps. The resulting model (A) was fitted into the density by graphical methods using the program O [6]. At that point it was apparent that the guest was disordered at least over two sites because taking into account only model A into structure factor calculations, additional residual density around the guest atomic positions was revealed. Thus, in order to account best for that observation, model A was translated into the remaining electron density and another site, B, was assumed. The geometry of the two models was then optimized graphically to near ideal and it was not refined further. Uniform temperature factors were assigned to methylcyclohexane atoms for sites A and B which were refined along with their sof.

Table II. Fractional coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) of TM-βCD and methylcyclohexane molecules

Atom	*x*	*y*	*z*	U(eq)
C(11)	10790(16)	3605(7)	2163(6)	83(5)
C(21)	11715(16)	3538(7)	1773(6)	85(5)
O(21)	12789(14)	3838(5)	1879(5)	114(4)
C(31)	11227(15)	3710(7)	1342(5)	74(5)
O(31)	12147(13)	3597(5)	993(5)	114(4)
C(41)	10119(15)	3399(7)	1237(5)	76(5)
O(41)	9668(10)	3610(4)	801(4)	85(3)
C(51)	9228(14)	3485(6)	1619(5)	65(4)
O(51)	9783(9)	3304(4)	2028(3)	72(3)
C(61)	8073(17)	3186(8)	1569(6)	96(6)
O(61)	8312(14)	2672(6)	1454(4)	107(4)
C(71)	13607(25)	3611(10)	2171(8)	152(10)
C(81)	12304(29)	4064(11)	672(8)	179(13)
C(91)	7229(23)	2392(11)	1352(9)	147(9)
C(12)	9354(13)	5181(5)	3217(5)	58(4)
C(22)	10646(16)	5156(7)	3097(6)	83(5)
O(22)	11201(12)	5670(5)	3092(4)	103(4)
C(32)	10946(15)	4861(6)	2687(6)	77(5)
O(32)	12249(13)	4799(5)	2639(5)	106(4)
C(42)	10361(14)	4339(6)	2679(5)	69(4)
O(42)	10518(9)	4133(4)	2225(3)	69(3)
C(52)	9062(14)	4366(6)	2797(5)	69(4)
O(52)	8894(9)	4666(4)	3221(3)	69(3)
C(62)	8443(16)	3859(7)	2892(7)	91(6)
O(62)	7186(14)	3924(5)	2862(5)	111(4)
C(72)	12158(29)	5782(9)	3389(12)	228(20)
C(82)	12826(25)	5062(8)	2323(11)	171(13)
C(92)	6492(21)	3513(8)	3014(8)	129(8)
C(13)	5956(14)	6538(5)	2848(5)	59(4)
C(23)	6800(14)	6572(6)	3258(5)	70(4)
O(23)	7028(10)	7114(4)	3345(4)	78(3)
C(33)	7935(13)	6292(5)	3183(5)	55(4)
O(33)	8653(10)	6281(4)	3584(3)	79(3)
C(43)	7678(13)	5744(6)	3027(5)	63(4)
O(43)	8784(9)	5498(4)	2870(3)	69(3)
C(53)	6810(14)	5719(6)	2632(5)	62(4)
O(53)	5732(9)	6004(4)	2757(3)	69(3)
C(63)	6397(18)	5172(7)	2522(6)	91(6)
O(63A)	5910(26)	5173(10)	2084(9)	113(8)
O(63B)	6744(33)	5065(13)	2065(11)	108(10)
C(73)	6443(23)	7329(8)	3738(7)	135(9)

Table II. Continued

Atom	*x*	*y*	*z*	U(eq)
C(83)	9563(20)	6649(7)	3605(8)	130(8)
C(93A)	5802(65)	4625(27)	1934(22)	182(26)
C(93B)	6407(44)	4599(18)	1849(16)	82(13)
C(14)	5290(14)	7477(6)	1282(5)	65(4)
C(24)	6340(14)	7739(6)	1562(5)	64(4)
O(24)	7205(12)	7922(5)	1243(4)	101(4)
C(34)	6869(13)	7366(6)	1883(5)	57(4)
O(34)	7721(10)	7638(4)	2154(3)	71(3)
C(44)	5894(13)	7141(6)	2196(5)	60(4)
O(44)	6520(10)	6763(4)	2468(3)	73(3)
C(54)	4907(12)	6886(5)	1904(5)	54(4)
O(54)	4469(10)	7273(4)	1601(3)	73(3)
C(64)	3857(15)	6678(7)	2146(6)	77(5)
O(64)	3336(11)	7039(5)	2441(4)	95(4)
C(74)	7527(31)	8462(8)	1315(10)	198(15)
C(84)	8851(17)	7384(7)	2200(7)	103(6)
C(94)	2112(19)	7010(10)	2477(8)	129(8)
C(15)	5274(17)	6425(7)	−257(6)	86(5)
C(25)	5553(18)	6990(7)	−266(6)	88(5)
O(25)	6492(12)	7122(5)	−564(5)	97(4)
C(35)	5982(15)	7182(6)	206(5)	71(4)
O(35)	5950(10)	7738(4)	220(4)	79(3)
C(45)	5179(15)	6992(6)	573(5)	72(5)
O(45)	5792(8)	7082(3)	1005(3)	61(3)
C(55)	4891(16)	6419(6)	531(5)	78(5)
O(55)	4417(11)	6317(4)	79(4)	87(3)
C(65)	3932(21)	6229(8)	855(7)	115(7)
O(65)	3814(21)	5675(7)	841(5)	170(8)
C(75)	6086(28)	7154(14)	−1020(8)	185(13)
C(85)	7037(22)	7990(8)	116(6)	123(8)
C(95)	4361(48)	5421(10)	1165(10)	267(28)
C(16)	7436(12)	4646(6)	−651(5)	57(4)
C(26)	8053(14)	5119(6)	−843(6)	69(4)
O(26)	9324(10)	5041(4)	−888(4)	82(3)
C(36)	7803(12)	5598(5)	−561(5)	53(4)
O(36)	8283(11)	6049(5)	−785(4)	87(3)
C(46)	6438(13)	5670(6)	−505(5)	62(4)
O(46)	6293(10)	6106(4)	−193(3)	77(3)
C(56)	5931(14)	5164(6)	−316(5)	60(4)
O(56)	6199(9)	4744(4)	−607(3)	67(3)
C(66)	4655(19)	5154(8)	−241(6)	97(6)
O(66)	4025(13)	5325(5)	−633(5)	113(4)
C(76)	9817(18)	5221(9)	−1274(6)	118(7)

Table II. Continued

Atom	*x*	*y*	*z*	U(eq)
C(86)	9032(23)	6361(8)	−525(6)	121(8)
C(96)	2689(22)	5336(11)	−544(14)	216(18)
C(17)	9041(15)	3262(7)	530(5)	75(5)
C(27)	9581(15)	3273(6)	58(5)	74(5)
O(27)	10826(13)	3181(5)	41(5)	116(4)
C(37)	9341(14)	3817(6)	−173(5)	69(4)
O(37)	9616(11)	3780(4)	−644(4)	84(3)
C(47)	8072(14)	3954(6)	−131(5)	67(4)
O(47)	7983(9)	4513(4)	−240(3)	70(3)
C(57)	7557(16)	3868(7)	317(5)	77(5)
O(57)	7846(11)	3350(5)	495(4)	92(3)
C(67)	6172(23)	3902(8)	322(8)	122(8)
O(67A)	5579(32)	3504(13)	7(11)	122(10)
O(67B)	6002(30)	3938(12)	863(10)	148(10)
C(77)	1236(32)	2654(9)	80(12)	212(16)
C(87)	0783(19)	3949(7)	−779(8)	119(7)
C(97A)	4477(74)	3558(27)	−230(24)	182(26)
C(97B)	4952(46)	3693(20)	1003(18)	165(19)
C(A1)	9020	6100	1220	420(42)
C(A2)	10190	5790	1340	420(42)
C(A3)	9740	5250	1480	420(42)
C(A4)	9210	4980	1050	420(42)
C(A5)	8000	5230	930	420(42)
C(A6)	8350	5790	830	420(42)
C(A7)	9260	6640	1020	420(42)
C(B1)	9590	6010	860	509(50)
C(B2)	10220	5760	1280	509(50)
C(B3)	10080	5160	1290	509(50)
C(B4)	8750	5000	1200	509(50)
C(B5)	8350	5170	730	509(50)
C(B6)	8320	5770	780	509(50)
C(B7)	9450	6600	930	509(50)

Further evidence for the constitution of the inclusion complex came from the ^{1}H-NMR spectrum of the crystals of the complex dissolved in DMSO-d_6. Integration of the H-1 doublet of TM-βCD and the methyl group doublet of methylcyclohexane gave a host : guest ratio of 1 : 1.

In addition, crystals grown by dissolving TM-βCD into cyclohexane as determined by photographic methods were isomorphous to the present ones.

3. Results and Discussion

The numbering scheme for the host and guest molecules is given in Figure 1. The seven glucosidic residues have been assigned the Gn notation. Cm or Om denote the mth atom within the nth glucosidic residue of TM-βCD (Cmn or Omn in the Tables). The two positions of the disordered methylcyclohexane are designated as A and B respectively (Figure 2).

The guest molecule enters the host cavity from the secondary wider side and although it is accommodated below its center, with its methyl group pointing outwards, it is completely enclosed by the methoxyl groups (Figure 3a). All glucose residues have the $^4C_1$ conformation. The extensive distortion of the symmetrical shape of the parent β-cyclodextrin due to methylation is reflected in the geometrical parameters of the glycosidic O(4) heptagonal ring. The O(4n)$\cdots$O(4(n + 1)) distances range from 4.28 to 4.50 Å and the O(4(n $-$ 1))$\cdots$O(4n)$\cdots$O(4(n + 1)) angles vary from 120.9 to 137.7°. The deviations of the O(4) atoms from their mean plane range from 0.02 to 0.36 Å, while the corresponding deviations for the βCD dimeric structures are less than 0.02 Å [7]. The tilt angles, defined as the dihedral angles between the O(4) mean plane and the planes through atoms C(1n), C(4n), O(4n) and O(4(n + 1)) are all positive (the primary side inclines towards the cavity). The range of their values indicates a very uneven tilting (Table III). The same structural characteristic appears also in the case of the complex of TM-βCD with ethyl laurate [3]. This is in contrast to all the other TM-βCD complex structures determined so far where the rule is that two residues have negative tilt angles and hence they are inclined in the opposite direction (Table III).

Oxygen atoms O(63) and O(67) and consequently methyl carbon atoms C(93) and C(97) are disordered over two positions A and B (occupancy factors for O(63A), C(93A) 0.56 and for O(67A), C(97A) 0.45). Four primary methoxyl groups (including position A of the disordered G7 glucose) have the *gauche-gauche* orientation pointing outward of the TM-βCD cavity. In the glucosidic residues G2, G3 (both orientations), G5 and G7 (orientation B) the C(6)—O(6) bond has the *gauche-trans* orientation and points inward. All O(6)—C(9) bonds are *trans* to the corresponding C(5)—C(6) bonds except for the G5 residue where the relationship is *gauche*. The positive tilt angles along with the conformation of the primary methoxyl groups mentioned above results in the formation of 18 interglucosidic contacts involving atoms C(6), O(6) and C(9) as they are listed in Table IV. Therefore, the primary methoxyl side appears closed and inaccessible (Figure 3b).

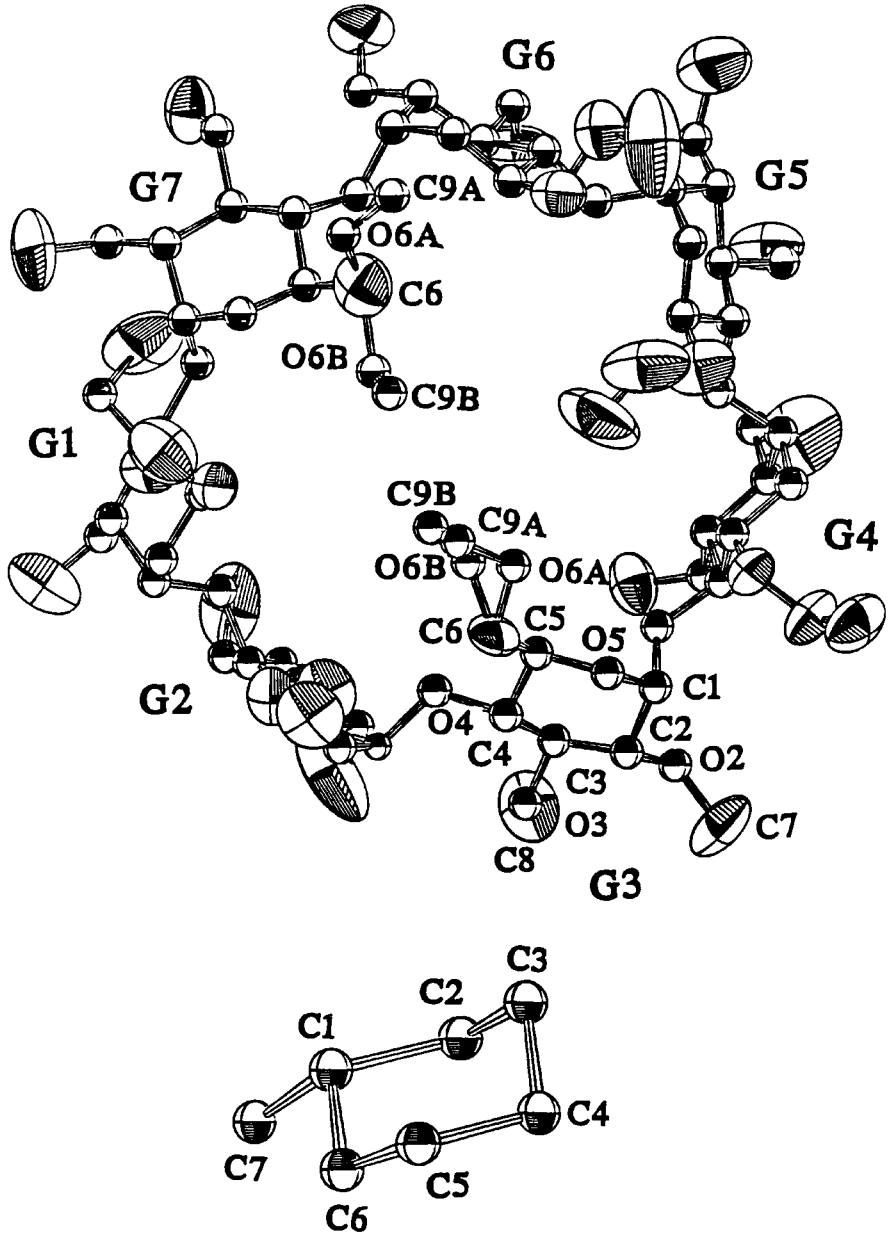

Figure 1. The host and guest molecules with the atomic numbering scheme. Displacement ellipsoids (where applicable) are plotted at the 50% level.

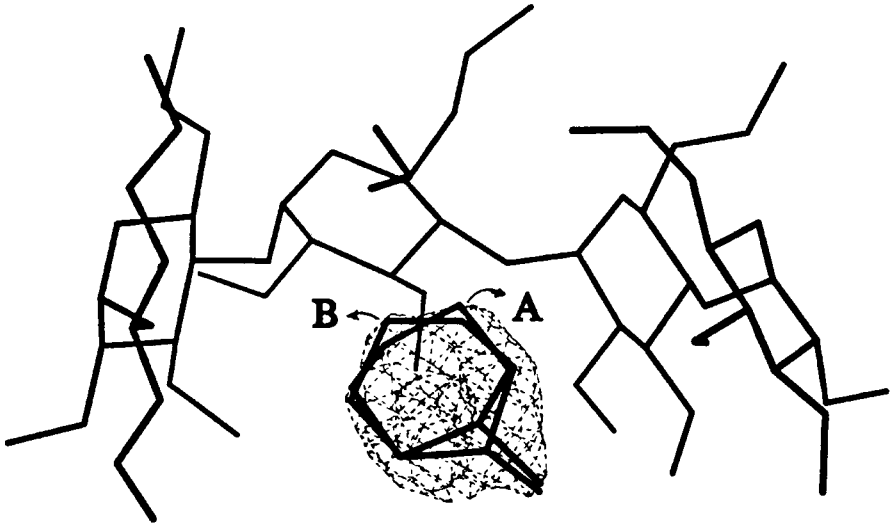

Figure 2. The fitting of the guest models A and B into the difference electron density. The front atoms of the TM-βCD molecule have been omitted for clarity.

Table III. Tilt angles (°) of the complexes of TM-βCD with methylcyclohexane (CYCL), ethyl laurate (ETLA) [3], L-menthol (MENTH) [8], S-naproxen (NAPR) [12] and m-iodophenol (MIP) [4]

	CYCL	ETLA	MENTH	NAPR	MIP
G1	15.8	33	26.5	27.0	27.7
G2	5.8	14	10.2	20.8	13.3
G3	51.5	13	−7.4	−9.4	−6.1
G4	8.8	31	47.7	44.3	45.2
G5	24.8	27	25.1	34.3	28.3
G6	8.5	17	−9.3	−14.4	−13.6
G7	40.2	30	46.5	34.4	51.7

As far as the orientation of secondary methoxyl groups is concerned, all O(2)—C(7) bonds point outward from the cyclodextrin cavity, while the O(3)—O(8) bonds point slightly inwards. The O(2n)···O(3(n + 1)) distances range from 3.33 to 3.55 Å for all residues except for G3 which is the most tilted where the distance O(23)···O(34) is 3.83 Å.

The methylcyclohexane molecule has the chair conformation with the methyl group in an equatorial position. It exhibits disorder which is roughly described by a two position model (site-occupancy factors 0.48 and 0.52) along with high

Table IV. Contacts (< 4 Å) in the TM-βCD/methylcyclohexane complex

a. Host-guest (sites A and B)

Guest A-Host	Distance (Å)	Guest B-Host	Distance (Å)
C(3)···O(42)	3.71	C(3)···O(42)	3.84
C(3)···O(63B)	3.79	C(3)···C(31)	3.94
C(3)···C(32)	3.93	C(4)···C(93B)	3.39
C(4)···O(41)	3.63	C(4)···O(63B)	3.39
C(5)···C(93B)	3.61	C(4)···O(41)	3.89
C(5)···O(63B)	3.65	C(5)···O(47)	3.34
C(5)···O(47)	3.90	C(5)···C(57)	3.66
C(5)···C(57)	3.96	C(6)···O(46)	3.75
C(6)···O(46)	3.87	C(7)···C(75)[a]	3.69
C(7)···C(75)[a]	3.71		
C(7)···C(84)	3.99		

b. In primary side of host

Host-host	Distance (Å)
C(61)···O(67B)	3.66
O(61)···C(94)	3.61
C(91)···C(94)	3.66
···O(64)	3.72
O(62)···C(63)	3.47
···C(93B)	3.55
···C(93A)	3.62
···O(63B)	3.78
O(63A)···C(95)	3.27
O(63B)···C(95)	3.86
C(93A)···C(95)	3.44
···O(67B)	3.62
···C(97B)	3.76
C(93B)···O(67B)	3.39
···C(95)	3.70
···C(97B)	3.77
C(64)···C(65)	3.97
O(65)···C(66)	3.58

Table IV. Continued

c. C—H···O hydrogen bonds[b] in TM-βCD

		Distance (Å)			Angle (°)
C H	O	C···O	C—H	H···O	C—H···O
C(61)—H(61B)	O(57)	3.19	0.97	2.49	130.0
C(62)—H(62A)	O(51)	3.27	0.97	2.37	154.2
C(63)	O(52)	3.69			
C(64)—H(64B)	O(53)	3.25	0.97	2.43	143.2
C(65)—H(65A)	O(54)	3.51	0.97	2.76	135.6
C(66)—H(66B)	O(55)	3.13	0.97	2.41	131.1
C(67)	O(56)	3.48			

[a] Symmetry operated: 0.5 + X, 1.5 − Y, −Z.
[b] Hydrogen atoms were not calculated for the atoms C(63) and C(67) due to the disorder of the corresponding methoxyl groups.

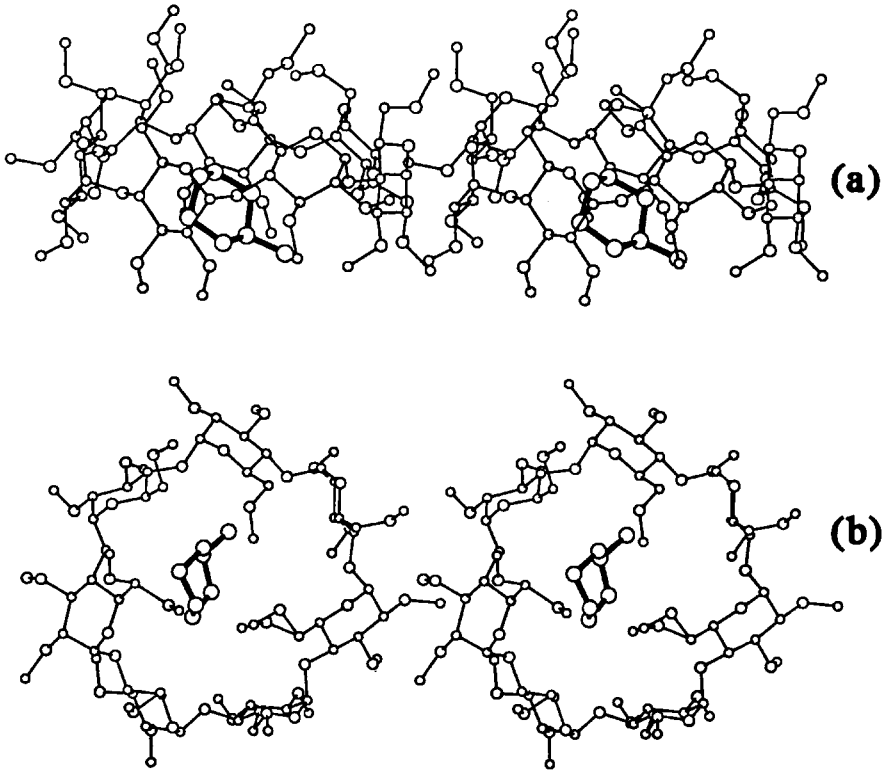

Figure 3. Stereo diagram of the TM-βCD/methylcyclohexane complex (a) as viewed from the side (b) as viewed from the primary hydroxyl side.

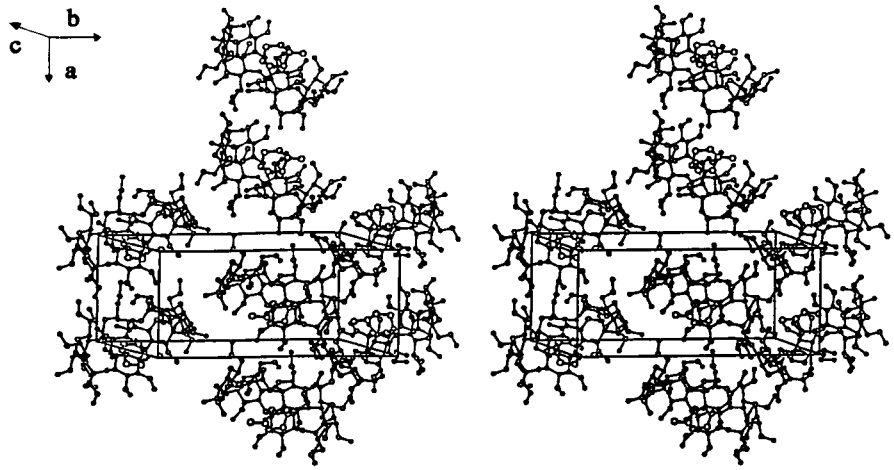

Figure 4. Stereo diagram of the packing. Four symmetry related molecules with their equivalent translated along the *a* axis are shown.

temperature factors. The guest molecule (both orientations) makes 20 contacts with the host ranging from 3.3 to 4.0 Å (Table IVa).

The structure is isomorphous to that of TM-βCD with L-menthol (MENTH) (a = 11.060(3), b = 26.138(6) and c = 29.669(6) Å) [8]. The complexes are stacked along the shortest axis a (Figure 4). The O(4n) mean planes make an angle of 31.3° with the bc plane. The packing mode resembles the cage-type packing with a herring-bone fashion of the βCD monomeric structures [9]. The secondary methoxyl side of TM-βCD is mostly closed from the primary side of a TM-βCD translated along the a axis and partly from the side wall of a related cyclodextrin molecule with the symmetry operation 0.5 + X, 0.5 − Y, −Z.

The other eight TM-βCD inclusion complexes in the literature so far, belong to the space group $P2_12_12_1$. Seven of them [3, 4, 10–13] are isomorphous (mean unit cell dimensions a = 15.1(2), b = 21.6(4) and c = 27.9(4) Å) with the macrocycles arranged along the b axis in a zigzag mode forming a distorted column structure. Their cell volumes range from 8965 [13] to 9264 Å^3 [11] compared to 8420 Å^3 of the present one, which is approximately 8% less than their mean value, indicating a closer packing which allows for numerous intermolecular contacts between host molecules. It is significant that in the present structure there are 16 contacts ranging from 3.0 to 3.6 Å with 4 between 3.0 to 3.2 Å while in the case of the TM-βCD/R-flurbiprofen complex [11] there are only 9 contacts, all at distances greater than 3.2 Å.

The TM-βCD/*m*-iodophenol complex [4] is a different case, where the molecules are arranged almost parallel to the ac plane (the O(4n) mean planes making an angle of 26.2° with it) to form molecular layers with brick-work pattern. The unit cell volume is 8305 Å^3, considerably smaller also than the volumes mentioned above.

Although the present structure and MENTH are isomorphous the conformation of the macrocycles differ significantly. The tilt angles in MENTH (Table III) are completely different from those reported here. By comparing the tilt angles of the complexes of TM-βCD with *p*-iodophenol [10], *m*-iodophenol [4] L-menthol [8] and also that of the TM-βCD monohydrate [14] the authors of MENTH claim that the conformation of the TM-βCD observed in those complexes is the preferred one and that this is independent of the guest and the crystal packing. They attribute that to the C(6n)—H$\cdots$O(5(n-1)) hydrogen bonding present in those TM-βCD complexes which plays an important role in stabilizing the conformation of the host, in much the same way as O(2n)$\cdots$O(3((n+1)) hydrogen bonding does in the parent β-cyclodextrin complexes. Actually, in MENTH there exist six close contacts C(6n)—H$\cdots$O(5(n-1)) with C$\cdots$O distances ranging from 3.06 to 3.22 Å. In the present structure there exist six contacts in the range 3.13–3.69 Å (Table IVc).

The present structure and that of the TM-βCD/ethyl laurate inclusion complex do not support the above conclusion. Ethyl laurate is a linear guest while methylcyclohexane is a small, rather symmetrical molecule. In these cases TM-βCD adopts a conformation so as to best "embrace" the guest molecule. In the cases of bulkier guest molecules such as 4-biphenylacetic acid [4], R- and S-flurbiprofen [11], naproxen [12], and ibuprofen [13], steric reasons seem to induce the negative tilting of two glucosidic residues. The same reasoning may apply in the cases of *m*- and *p*-iodophenol [4, 10] and L-menthol [8]. Therefore, we believe that the TM-βCD macrocycle exhibits sufficient flexibility to change its conformation depending on the guest molecule, in other words it exhibits induced fit.

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