

The Crystal Structure of the Inclusion Complex of Cyclomaltoheptaose (β -Cyclodextrin) with 3,5-Dimethylbenzoic Acid

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Abstract. The crystal of the β CD–3,5-dimethylbenzoic acid inclusion complex is triclinic $P1$ with $a = 15.707(3)$, $b = 15.694(3)$, $c = 15.999(3)$ Å, $\alpha = 101.502(5)$, $\beta = 101.557(5)$, $\gamma = 103.805(4)^\circ$, $V = 3624$ Å³, and $Z = 1$. Two crystallographically independent β CD molecules form a dimer by means of hydrogen bonds between secondary hydroxyl groups in which disordered guest molecules in six orientations are accommodated. In two of them the guest molecules are situated at the dimer interface, their carboxyl groups interacting with the carboxyl groups of two other guest orientations that are found on either side of the monomer cavity. In the two last orientations the guest molecules enter the monomer cavities in an opposite sense with the carboxyl groups protruding from the primary side and are stabilized by cyclodextrin hydroxyl groups. A dense water network is formed in the interdimer space consisted of 18.2 water molecules distributed over 24 sites.

Key words: Inclusion complex, β -cyclodextrin, 3,5-dimethylbenzoic acid.

Supplementary Data relating to this article are deposited with the British Library as Supplementary Publication No. SUP 82175 (61 pages).

1. Introduction

Cyclomaltoheptaose or β -cyclodextrin (β CD) is a cyclic oligosaccharide consisting of seven α -1,4-linked glucopyranose residues. It has the shape of a truncated cone with a mean inner diameter of approximately 6 Å and its ability to form inclusion complexes with a variety of guest molecules has been extensively documented [1]. In many inclusion complexes β CD molecules form dimers which are packed relative to each other in only four different modes [2]. In order to understand how the nature of the guest molecule determines the crystal packing we have been carrying out an investigation of a series of benzo derivatives as guest molecules. The title compound is the fourth in the series, the other three being the complexes with 4-*tert*-butylbenzyl alcohol [2], 4-*tert*-butyltoluene [3] and 4-*tert*-butylbenzoic acid [4].

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** Dedicated to Professor József Szejtli.

TABLE I. Crystal data for the complex of β CD with 3,5-dimethylbenzoic acid

Formula	$2(\text{C}_{42}\text{H}_{70}\text{O}_{35}) \cdot 18.2 \text{H}_2\text{O} \cdot 1.88(\text{C}_9\text{H}_{13}\text{O}_2)$
lattice type	triclinic
T (K)	293
cell dimensions	
a (Å)	15.707(3)
b (Å)	15.694(3)
c (Å)	15.999(3)
α (°)	101.502(5)
β (°)	101.557(5)
γ (°)	103.805(4)
V (Å ³)	3624
Z	1
d_{calc} (gcm ⁻³)	1.280
2θ range (°)	2.7–43.0
No. of unique reflections	8341
No. of reflections	
with $F > 4\sigma(F)$	4738
Final No. of variables	1104
Final R	0.1136

2. Experimental

2.1. PREPARATION AND CRYSTALLIZATION OF THE COMPLEX

An aqueous solution of β CD was mixed with an ethanolic solution of 3,5-dimethylbenzoic acid. The host–guest ratio was 1 : 2. The mixture was stirred at room temperature and a white precipitate was readily formed which was dissolved with the addition of some drops of EtOH. The solution was cooled slowly over a five-day period, by the end of which colorless crystals were formed. A crystal of dimensions $0.7 \times 0.5 \times 0.2$ mm, sealed in a glass capillary to prevent loss of water of crystallization, was selected for data collection.

2.2. DATA COLLECTION AND STRUCTURE REFINEMENT

Crystal data were collected on a Syntex P2₁ diffractometer with Nb-filtered $\text{MoK}\alpha$ radiation. Final lattice parameters determined from 15 reflections with $15 < 2\theta < 20^\circ$ are given in Table I along with other information of data collection and refinement. A hemisphere of data was collected by $\theta - 2\theta$ scan rates in the range $1.0 - 10^\circ/\text{min}$ and a scan width of 1.8° plus $\alpha_1 - \alpha_2$ divergence.

The structure was solved by using the coordinates of the skeleton atoms of the isomorphous β CD complex with 4-*tert*-butyltoluene [3]. All C(6) and O(6) atoms (three of which are disordered) and 24 water positions were located in

subsequent difference Fourier maps. The structure was refined isotropically up to $R = 0.1625$ by SHELX-76 [5] (function minimized $\sum w(|F_o| - |F_c|)^2$, $w = 1$). The occupation factors (K) of the water molecules were also refined, except for those that gave a value higher than one during the refinement. For those K was set to 1 and was not refined further. Anisotropic thermal parameters were then assigned to atoms O(2), O(3) and O(6) and all but two water oxygen atoms. Hydrogen atoms were introduced at ideal positions for all carbon atoms except for C(6) to which disordered oxygen atoms were bonded. At this stage of the refinement several atoms belonging to guest molecules were found. The model of the guest molecules was formed as follows: only five atoms from the phenyl rings were found and the position of the sixth atom for all three guest molecules was calculated. The phenyl rings were subsequently considered as ideal and all substituent atoms were then clearly located. One guest molecule was at the middle of the dimer almost perpendicular to the β CD 7-fold axis and the two others were included in the cavities, one with the carboxyl group buried inside and the other situated in the opposite sense with the carboxyl at the primary side. However, the resulting geometries were poor, mainly because the atoms directly bonded to the phenyl rings were out of the ring planes. Refinement of the guest by imposing constraints on all substituent atoms did not improve the geometry. Optimum results were obtained if the guest molecules were refined as rigid bodies except for the methyl carbons that were refined independently by imposing constraints on them. The final R factor was $R = 0.1124$ for reflections with $F_o > 3\sigma(F_o)$.

The poor geometry, with atoms out of the ring planes, indicates that the guest molecules are disordered and the geometry determined is an average of more than one neighboring sites. Therefore, we attempted to fit partially occupied guest molecules with conventional geometries (Table V) and different orientations into the difference electron density. The latter comprises a thick ring in the interdimer region and it extends symmetrically on either side of it. Thus, it was assumed that the orientations of the guests inside the monomer cavities would be symmetrical rather than asymmetrical, as the previous refinement with the distorted geometry had indicated. The 3,5-dimethylbenzoic acid molecule in two orientations, one with the carboxyl group pointing inside the two monomer cavities (1C and 5C, Figure 3a and b) and one with the carboxyl group pointing outside (2C and 4C, Figure 3c and d) fitted well in the electron density (Figure 2) and accounts for most of it. The central molecule is also found in two orientations (3C and 6C). The fitting was done on a Crimson Silicon Graphics workstation using the program O [6].

Subsequently, the refinement continued with the program SHELXL-93 [7] to $R = 0.1136$ for reflections with $F_o > 4\sigma(F_o)$. For the guest molecules only the occupation factors were refined independently for every orientation. The total occupancy of the guest is 1.88 molecules in the asymmetric unit. Maximum and minimum residual density in the final difference electron density map are $1.17 \text{ e}\text{\AA}^{-3}$ and $-0.65 \text{ e}\text{\AA}^{-3}$, respectively.

TABLE II. Fractional parameters ($\times 10^4$) of the β CD and the water molecules with esds in parentheses. Fractional parameters of the guest molecules ($\times 10^3$). The site occupation factors of disordered hydroxyl oxygens, water and guest molecules are also listed

Atom	x	y	z	K
1C(11)	4384(14)	8156(13)	7339(12)	
1C(21)	4712(11)	8596(12)	6621(11)	
1C(31)	5640(11)	8505(12)	6624(11)	
1C(41)	6266(11)	8898(12)	7590(11)	
1C(51)	5894(12)	8385(12)	8194(11)	
1C(61)	6448(15)	8724(14)	9154(13)	
1O(41)	7162(8)	8767(7)	7512(7)	
1O(51)	5002(8)	8469(8)	8158(8)	
1O(21)	4103(9)	8198(8)	5821(8)	
1O(31)	6012(8)	9019(8)	6047(7)	
1O(61)	6503(10)	9607(11)	9521(10)	
1C(12)	7959(12)	9508(12)	7909(11)	
1C(22)	8466(14)	9592(13)	7224(12)	
1C(32)	8836(13)	8763(13)	7004(12)	
1C(42)	9359(13)	8699(13)	7833(12)	
1C(52)	8836(13)	8631(13)	8527(12)	
1C(62)	9293(16)	8572(15)	9382(14)	
1O(42)	9609(8)	7829(8)	7634(7)	
1O(52)	8504(8)	9418(8)	8664(8)	
1O(22)	7938(9)	9713(9)	6449(9)	
1O(32)	9376(8)	8871(9)	6395(8)	
1O(62)	10064(13)	9284(15)	9774(13)	
1C(13)	10561(11)	7871(11)	7870(10)	
1C(23)	10776(12)	7384(11)	7081(11)	
1C(33)	10210(13)	6380(11)	6815(11)	
1C(43)	10400(11)	5980(10)	7595(10)	
1C(53)	10263(12)	6577(11)	8422(11)	
1C(63)	10548(13)	6296(13)	9245(12)	
1O(43)	9738(8)	5085(7)	7340(7)	
1O(53)	10737(8)	7483(8)	8581(8)	
1O(23)	10620(8)	7800(8)	6378(8)	
1O(33)	10435(8)	5889(8)	6123(7)	
1O(63)	11536(9)	6382(9)	9452(8)	
1C(14)	10059(13)	4386(12)	7513(12)	
1C(24)	9773(12)	3651(12)	6645(11)	
1C(34)	8766(11)	3231(10)	6343(10)	
1C(44)	8419(12)	2907(12)	7098(11)	
1C(54)	8730(14)	3672(14)	7924(13)	
1C(64)	8448(22)	3374(21)	8717(21)	

TABLE II. (continued)

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>K</i>
1O(44)	7447(8)	2559(8)	6806(8)	
1O(54)	9701(9)	4042(8)	8191(8)	
1O(24)	10147(8)	3977(9)	6014(8)	
1O(34)	8525(9)	2461(8)	5572(8)	
1O(64A)	8766(23)	2827(28)	8865(18)	0.86(2)
1O(64B)	8630(30)	4201(30)	9326(29)	0.14(2)
1C(15)	7028(12)	1647(12)	6834(11)	
1C(25)	6363(12)	1140(13)	5960(12)	
1C(35)	5609(12)	1616(12)	5803(11)	
1C(45)	5168(11)	1659(12)	6567(11)	
1C(55)	5895(12)	2077(13)	7451(11)	
1C(65)	5512(18)	1968(19)	8238(17)	
1O(45)	4567(8)	2176(8)	6444(7)	
1O(55)	6605(9)	1683(8)	7517(8)	
1O(25)	6818(8)	1154(8)	5250(7)	
1O(35)	4944(8)	1137(8)	5017(7)	
1O(65A)	5206(20)	1088(26)	8181(20)	0.51(3)
1O(65B)	6112(25)	2342(37)	9049(21)	0.49(3)
1C(16)	3657(12)	1806(13)	6523(12)	
1C(26)	3019(15)	1863(14)	5710(13)	
1C(36)	3034(13)	2804(12)	5657(11)	
1C(46)	2928(13)	3318(12)	6549(11)	
1C(56)	3620(15)	3269(14)	7343(13)	
1C(66)	3338(21)	3568(22)	8150(19)	
1O(46)	3113(8)	4299(7)	6546(7)	
1O(56)	3514(8)	2298(8)	7282(8)	
1O(26)	3123(9)	1367(8)	4876(9)	
1O(36)	2421(9)	2889(8)	4954(8)	
1O(66)	4132(26)	3816(20)	8868(22)	
1C(17)	2442(11)	4716(11)	6674(10)	
1C(27)	2270(11)	5147(11)	5908(10)	
1C(37)	3096(12)	5881(11)	5989(11)	
1C(47)	3376(11)	6528(10)	6909(10)	
1C(57)	3457(12)	6066(11)	7635(11)	
1C(67)	3564(13)	6639(12)	8516(11)	
1O(47)	4261(8)	7164(7)	6998(7)	
1O(57)	2634(8)	5315(8)	7465(7)	
1O(27)	1959(8)	4532(8)	5096(7)	
1O(37)	2968(9)	6385(8)	5338(7)	
1O(67)	2936(10)	7085(9)	8584(9)	
2C(11)	3248(12)	7032(12)	2252(11)	
2C(21)	2782(12)	6679(11)	2909(11)	
2C(31)	2907(12)	5735(11)	2939(11)	

TABLE II. (continued)

Atom	x	y	z	K
2C(41)	2493(12)	5138(11)	1984(10)	
2C(51)	3011(12)	5495(11)	1376(11)	
2C(61)	2649(15)	4937(15)	387(14)	
2O(41)	2641(8)	4243(8)	20646(8)	
2O(51)	2946(8)	6398(8)	1401(8)	
2O(21)	3223(8)	7312(8)	3766(8)	
2O(31)	2377(8)	5389(8)	3523(7)	
2O(61)	1785(12)	4922(10)	74(10)	
2C(12)	1864(12)	3439(11)	1649(11)	
2C(22)	1802(14)	2929(13)	2355(12)	
2C(32)	2640(14)	2579(13)	2554(12)	
2C(420)	2702(13)	2020(12)	1719(12)	
2C(52)	2790(13)	2573(13)	1060(12)	
2C(62)	2844(15)	2108(15)	178(13)	
2O(42)	3557(8)	1781(8)	1949(7)	
2O(52)	1983(8)	2911(8)	909(8)	
2O(22)	1684(9)	3460(9)	3134(9)	
2O(32)	2525(9)	2023(8)	3175(8)	
2O(62)	2106(16)	1344(12)	-229(13)	
2C(13)	3506(12)	831(11)	1707(11)	
2C(23)	4001(12)	618(12)	2476(11)	
2C(33)	5003(12)	1172(13)	2730(12)	
2C(43)	5403(12)	1008(12)	1957(11)	
2C(53)	4838(11)	1159(12)	1149(10)	
2C(63)	5128(13)	850(12)	317(12)	
2O(43)	6319(8)	1656(7)	2222(7)	
2O(53)	3720(9)	653(8)	990(8)	
2O(23)	3598(8)	788(8)	3182(7)	
2O(33)	5509(8)	954(8)	3456(7)	
2O(63)	5021(9)	-117(9)	124(8)	
2C(14)	7024(12)	1331(12)	2039(11)	
2C(24)	7759(12)	1629(12)	2918(11)	
2C(34)	8156(11)	2622(11)	3221(10)	
2C(44)	8495(12)	2983(12)	2493(11)	
2C(54)	7758(15)	2676(14)	1650(13)	
2C(64)	7989(19)	2952(20)	890(19)	
2O(44)	8853(8)	3953(8)	2770(8)	
2O(54)	7365(9)	1714(9)	1406(9)	
2O(24)	7435(8)	1261(8)	3556(8)	
2O(34)	8929(8)	2880(8)	4007(8)	
2O(64)	8579(27)	2601(22)	687(17)	
2C(15)	9745(11)	4357(11)	2750(11)	
2C(25)	10231(12)	5018(11)	3593(11)	

TABLE II. (continued)

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>K</i>
2C(35)	9770(13)	5795(12)	3773(11)	
2C(45)	9740(12)	6224(11)	3014(10)	
2C(55)	9315(13)	5496(12)	2105(11)	
2C(65)	9393(19)	5884(18)	1341(17)	
2O(45)	9231(8)	6837(8)	3112(7)	
2O(55)	9733(8)	4802(8)	2046(8)	
2O(25)	10252(8)	4573(8)	4330(7)	
2O(35)	10272(9)	6474(8)	4558(7)	
2O(65A)	10330(26)	6177(17)	1347(15)	0.55(3)
2O(65B)	9165(45)	5214(24)	471(22)	0.45(3)
2C(16)	9592(13)	7741(12)	3058(12)	
2C(26)	9542(14)	8372(14)	3824(13)	
2C(36)	8560(12)	8345(12)	3890(1)	
2C(46)	8073(11)	8457(12)	3006(11)	
2C(56)	8159(14)	7822(15)	2239(13)	
2C(66)	7893(25)	8199(23)	1443(21)	
2O(46)	7115(8)	8297(8)	3027(7)	
2O(56)	9104(9)	7890(9)	2283(9)	
2O(26)	10029(9)	8263(9)	4684(9)	
2O(36)	8524(8)	9000(9)	4614(8)	
2O(66)	7577(22)	7460(28)	919(32)	
2C(17)	6716(11)	8963(12)	2925(11)	
2C(27)	6245(11)	9132(11)	3650(11)	
3C(37)	5512(12)	8300(12)	3582(11)	
2C(47)	4852(11)	8023(11)	2647(10)	
2C(57)	5327(11)	7958(11)	1937(10)	
2C(67)	4784(13)	7812(13)	1061(12)	
2O(47)	4237(8)	7145(8)	2567(7)	
2O(57)	6088(8)	8769(8)	2103(8)	
2O(27)	6870(8)	9437(8)	4473(8)	
2O(37)	5018(9)	8431(9)	4233(7)	
2O(67)	4307(10)	8468(10)	993(9)	
1W(61A)	7299(20)	1243(19)	9175(19)	0.57
1W(61B)	8254(31)	275(44)	644(41)	0.63
1W(62)	487(32)	-777(30)	1479(22)	0.71
W(62A)	10233(24)	11199(21)	9764(27)	0.75
W(62B)	1921(10)	9469(10)	9797(11)	1.00
1W(63)	2375(10)	8106(10)	554(9)	1.00
1W(65)	3448(16)	19(15)	7814(12)	1.00
1W(21)	3659(13)	9486(12)	5008(15)	1.00
1W(22)	9161(21)	1014(17)	6000(27)	0.82
1W(23)	2243(24)	8693(38)	6220(27)	0.57
1W(24)	615(15)	2404(17)	5288(19)	0.62

TABLE II. (continued)

Atom	x	y	z	K
W(26)	1680(30)	-250(32)	4618(55)	0.50
1W(26)	1155(38)	527(28)	3410(50)	0.67
2W(61)	1102(48)	3194(30)	8986(35)	0.46
2W(62)	2184(25)	992(28)	8079(21)	0.73
2W(63)	3290(10)	9028(10)	9000(10)	1.00
2W(65A)	1353(15)	7960(15)	1753(12)	1.00
2W(65B)	139(17)	4107(28)	413(16)	0.58
2W(21)	1916(12)	7716(14)	4560(16)	0.98
2W(22)	370(15)	2200(16)	3452(18)	0.73
2W(23)	2726(43)	9133(23)	3306(22)	0.80
2W(24)	9015(18)	795(15)	4282(23)	0.77
2W(26)	969(37)	10175(36)	6079(34)	0.77
W(1)	397(71)	2056(55)	7887(81)	0.51
1C(1)	642	534	769	0.30
1C(2)	573	557	800	0.30
1C(3)	574	560	890	0.30
1C(4)	646	544	945	0.30
1C(5)	714	519	912	0.30
1C(6)	712	515	821	0.30
1C(7)	637	525	673	0.30
1C(8)	501	585	930	0.30
1C(9)	795	506	972	0.30
1O(1)	559	514	622	0.30
1O(2)	706	521	643	0.30
2C(1)	626	463	47	0.34
2C(2)	647	470	139	0.34
2C(3)	607	520	193	0.34
2C(4)	546	563	155	0.34
2C(5)	527	558	65	0.34
2C(6)	567	507	13	0.34
2C(7)	669	410	-11	0.34
2C(8)	628	528	289	0.34
2C(9)	461	604	26	0.34
2O(1)	661	337	-9	0.34
2O(2)	728	451	-46	0.34
3C(1)	596	498	452	0.44
3C(2)	672	575	474	0.44
3C(3)	759	565	485	0.44
3C(4)	773	480	473	0.44
3C(5)	698	404	454	0.44
3C(6)	610	413	441	0.44
3C(7)	507	510	441	0.44
3C(8)	839	649	507	0.44

TABLE II. (continued)

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>K</i>
3C(9)	716	316	443	0.44
3O(1)	493	583	429	0.44
3O(2)	448	456	468	0.44
4C(1)	620	581	916	0.21
4C(2)	602	558	824	0.21
4C(3)	672	544	786	0.21
4C(4)	757	551	835	0.21
4C(5)	774	575	928	0.21
4C(6)	704	589	967	0.21
4C(7)	550	602	961	0.21
4C(8)	655	517	684	0.21
4C(9)	864	578	985	0.21
4O(1)	502	540	988	0.21
4O(2)	564	684	1002	0.21
5C(1)	638	528	211	0.18
5C(2)	652	457	150	0.18
5C(3)	610	435	62	0.18
5C(4)	551	483	33	0.18
5C(5)	535	553	90	0.18
5C(6)	580	574	180	0.18
5C(7)	683	553	306	0.18
5C(8)	624	360	0	0.18
5C(9)	474	606	56	0.18
5O(1)	741	518	333	0.18
5O(2)	654	604	353	0.18
6C(1)	629	528	505	0.41
6C(2)	724	545	519	0.41
6C(3)	761	473	505	0.41
6C(4)	707	385	480	0.41
6C(5)	614	367	470	0.41
6C(6)	574	438	481	0.41
6C(7)	593	607	518	0.41
6C(8)	863	495	519	0.41
6C(9)	561	272	443	0.41
6O(1)	594	648	595	0.41
6O(2)	554	632	453	0.41

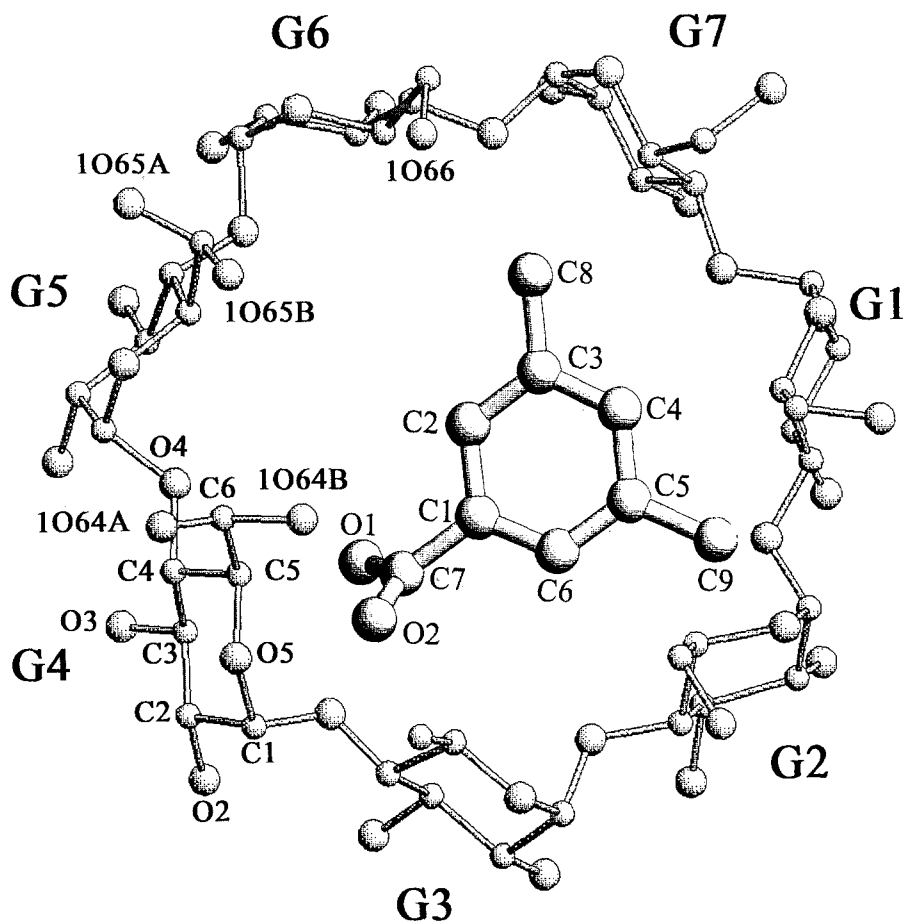


Fig. 1. The structure and the numbering scheme of molecule 1 of β CD and of 3,5-dimethylbenzoic acid [8]. Disordered hydroxyl oxygens and oxygen 1O66 pointing inside are indicated.

3. Results and Discussion

Final atomic coordinates are given in Table II. C_{mn} or O_{mn} denote the m th atom within the n th glucosidic residue (G_n) of β CD. The numbers 1–6 preceding the atom names denotes the independent molecules 1 and 2 of β CD and 1–6 of the guest. The numbering scheme of the complex is shown in Figure 1.

3.1. CRYSTAL PACKING AND HYDROGEN BONDING NETWORK

Two crystallographically independent molecules of β CD per unit cell form head-to-head dimers by means of hydrogen bonds between their 1O(3) n and 2O(3)(8 – n) atoms. Table III shows the intradimer H-bond distances and the corresponding

TABLE III. Intermolecular hydrogen bonds of the β CD - 3,5-dimethylbenzoic acid complex

Residue	Distance (Å)	Angle (°)	
	1O(3) n ...2O(3)(8 - n)	1C(3) n -1O(3) n ... 2O(3)(8 - n)	1O(3) n ...2O(3)(8 - n)- 2C(3)(8 - n)
<i>a. Intradimer</i>			
G1	2.85	116	116
G2	2.96	119	119
G3	2.83	117	118
G4	2.87	116	116
G5	2.81	116	115
G6	2.94	116	117
G7	2.86	118	118
<i>b. βCD with guest molecules</i>			
Molecule 1	Distance (Å)		
1O(64B*)...2O(2)	2.38		
1O(65B*)...2O(1)	1.81		
1O(66) ...4O(1)	2.54		
2O(65B) ...2O(2)	2.78		
2O(66*) ...4O(2)	2.98		
<i>c. Among guest molecules</i>			
1O(1)...3O(2)	2.56		
5O(2)...6O(2)	2.50		

* Translated along c axis.

angles. Although the distances 1O(2) n ...2O(3)(8 - n), 1O(3) n ...2O(2)(8 - n) and 1O(2) n ...2O(2)(9 - n), are in the range (2.97-3.33 Å) of weak H-bonds, their geometry does not indicate H-bonding formation. The angles 1O(2) n ...2O(3)(8 - n)-2C(3)(8 - n), 1O(3) n ...2O(2)(8 - n)-2C(2)(8 - n), 1C(2) n -1O(2) n ...2O(2)(9 - n) and 1O(2) n ...2O(2)(9 - n)-C(2)(9 - n) have high average values (158(3), 158(2), 165(3) and 165(3)°, respectively).

The dimers are aligned along the c axis to form channels. The angle between the axis of the dimer and the crystallographic c axis is 8.6°. The centre of each dimer projected on the O(4) n plane of the neighboring dimer along the channel is displaced by 2.4 Å. There are direct H-bonds between primary hydroxyl groups of adjacent dimers in the same channel (2O(64)...1O(64A) 3.10 Å) and in adjacent channels (1O(63)...2O(61), 1O(63)...1O(67), 2.76 and 2.94 Å, respectively and 2O(63)...1O(61), 2O(63)...2O(67), 2.77 and 2.94 Å, respectively), as well as between secondary hydroxyl groups (1O(25)...2O(27) 2.75 Å). There are 18.2 water molecules distributed over 24 sites (denoted by W) and are within H-bonding

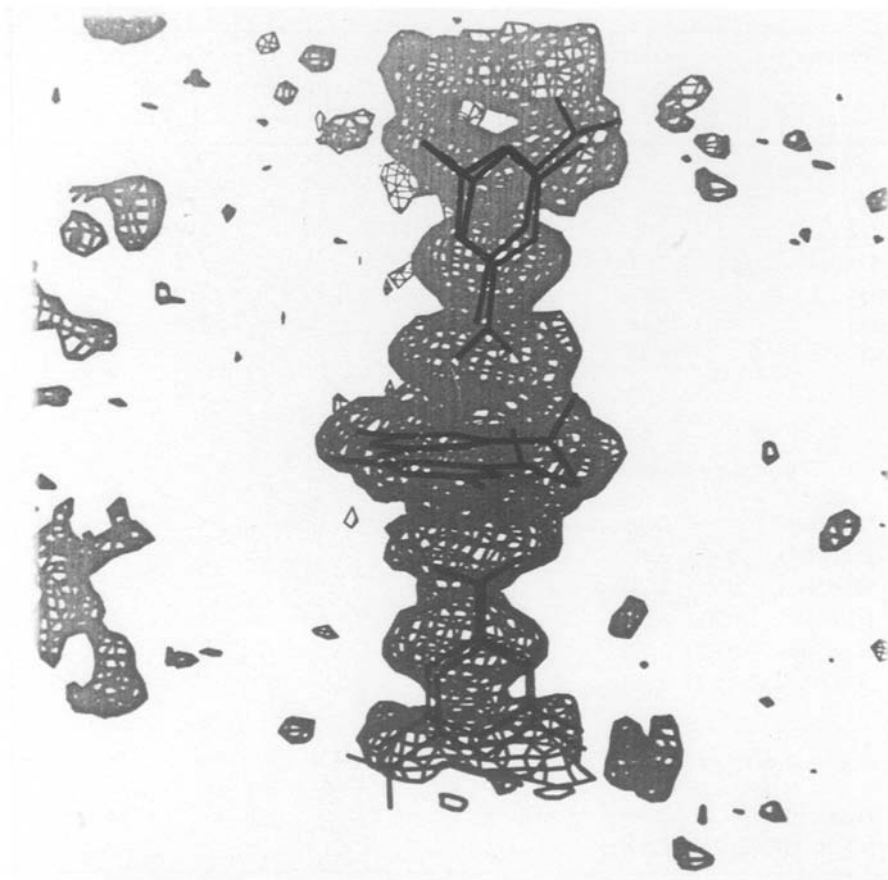


Fig. 2. Electron density distribution for 3,5-dimethylbenzoic acid. The six model orientations fitting inside the density are indicated (O program [6], minimum density contour level $0.57 \text{ e}\text{\AA}^{-3}$).

distances from the oxygen atoms of the β CD hydroxyl groups (Table IV). The water sites have been labelled by the number of the closest oxygen atoms to which they are H-bonded. It is assumed that distances O...W of 2.5–3.14 Å and angles C–O...W of 90–130° indicate H-bonding. Table IV indicates that the pseudo-twofold symmetry of the dimer is extended to the H-bonding with water molecules fairly well.

3.2. THE β CD MOLECULES

Average bond lengths and angles of the two independent β CD molecules (Table V) show that the monomers have similar geometry which compares well with other β CD complexes [2,4]. The pyranose rings have the 4C_1 conformation. Most of

TABLE IV. Hydrogen bonds of the β CD dimer with water molecules and among water molecules

Molecule 1	Distance (Å)	Molecule 2	Distance (Å)
<i>βCD with water molecules</i>			
1O(61) ... 1W(61A)	2.79	2O(61) ... 2W(65B)	2.79
... 1W(61B)	2.78	... 2W(61)	2.77
1O(62) ... 1W(62)	2.69	2O(62) ... 2W(62)	2.72
... W(62A)	2.95	... W(62A)	2.92
... W(62B)	2.86	... W(62B)	2.90
1O(63) ... 1W(63)	2.76	2O(63) ... 2W(63)	2.79
1O(64A) ... 1W(61A)	3.13	2O(64) ... 1W(61A)	2.89
... 2W(65B)	2.92	... 2W(65B)	3.17
1O(64B) ... 2W(65B)	2.69		
1O(65A) ... 1W(65A)	2.76	2O(65A) ... 2W(65A)	2.76
1O(65B) ... 1W(61A)	2.74	2O(65B) ... 2W(65B)	2.64
1O(67) ... 2W(63)	2.88	2O(67) ... 1W(63)	2.86
1O(21) ... 1W(21)	2.76	2O(21) ... 2W(21)	2.75
1O(22) ... 1W(22)	2.78	2O(22) ... 2W(22)	2.72
1O(23) ... 1W(23)	2.72	2O(23) ... 2W(23)	2.67
1O(24) ... 1W(24)	2.84	2O(24) ... 2W(24)	2.86
1O(26) ... W(26)	2.93	2O(26) ... W(26)	2.98
... 1W(26)	3.29	... 2W(26)	3.14
1O(32) ... 2W(26)	3.06	2O(32) ... 1W(26)	2.96
1O(34) ... 1W(22)	2.85	2O(34) ... 2W(22)	2.93
1O(35) ... 1W(21)	2.88	2O(35) ... 2W(21)	2.82
1O(36) ... 1W(24)	2.93	2O(36) ... 2W(24)	2.95
<i>Among water molecules</i>			
1W(62) ... 2W(65A)	2.71		
W(62B) ... 1W(63)	2.83	1W(22) ... 2W(24)	2.73
... 2W(63)	2.86	1W(23) ... 2W(21)	2.68
1W(63) ... 2W(65A)	2.73	1W(24) ... 2W(22)	2.82
... W(62B)	2.83	... 2W(24)	3.01
1W(65A) ... 2W(63)	2.66	1W(26) ... W(26)	2.76
... 1W(23)	2.89	2W(65A) ... 2W(63)	2.74
... 2W(62)	2.77	2W(26) ... W(26)	2.57
1W(21) ... 2W(23)	2.65		

the primary hydroxyl groups have the *gauche-gauche* orientation (mean torsional angles C(4)-C(5)-C(6)-O(6) and O(5)-C(5)-C(6)-O(6) 58 and -63° , respectively) and point out of the cavity. However, the primary atoms 1O(64), 1O(65) and 2O(65) exhibit disorder having, besides the *gauche-gauche* major orientation

TABLE V. Average bond distances and angles (with e.s.d.'s in parentheses) of the β CD dimer and the 3,5-dimethylbenzoic acid molecules

Distances (Å) ^a	Molecule 1	Molecule 2	Angles (°)	Molecule 1	Molecule 2
C(1)–C(2)	1.52(4)	1.49(3)	C(1)–C(2)–C(3)	110(3)	110(2)
C(1)–O(5)	1.40(2)	1.42(2)	C(2)–C(3)–C(4)	108(1)	108(3)
C(2)–C(3)	1.50(4)	1.54(4)	C(3)–C(4)–C(5)	112(2)	111(1)
C(2)–O(2)	1.42(4)	1.43(6)	C(4)–C(5)–O(5)	109(2)	110(1)
C(3)–C(4)	1.52(4)	1.51(3)	C(5)–O(5)–C(1)	115(1)	115(1)
C(3)–O(3)	1.42(4)	1.44(3)	O(5)–C(1)–C(2)	111(1)	110(1)
C(4)–C(5)	1.51(2)	1.51(3)	C(1)–C(2)–O(2)	111(2)	111(2)
C(4)–O(4)	1.46(3)	1.44(4)	C(3)–C(2)–O(2)	111(2)	110(2)
C(5)–C(6)	1.50(4)	1.50(5)	C(2)–C(3)–O(3)	111(2)	110(3)
C(5)–O(5)	1.44(4)	1.44(2)	C(4)–C(3)–O(3)	110(1)	109(1)
O(4)–C(1'')	1.42(3)	1.42(4)	C(4)–C(5)–C(6)	114(3)	113(4)
C(6)–O(6)	1.36(10)	1.36(9)	O(5)–C(5)–C(6)	106(2)	106(2)
			C(3)–C(4)–O(4)	107(2)	107(3)
			C(5)–C(4)–O(4)	109(2)	110(1)
			C(2)–C(1)–O(4')	107(2)	108(2)
			O(5)–C(1)–O(4')	111(2)	110(2)
			C(4)–O(4)–C(1'')	118(1)	118(1)
			C(5)–C(6)–O(6)	110(5)	109(6)

Distances (Å)	Angles (°) ^b
C(1)–C(2)	1.40(2)
C(2)–C(3)	1.39(2)
C(3)–C(4)	1.38(1)
C(4)–C(5)	1.39(1)
C(5)–C(6)	1.40(2)
C(1)–C(6)	1.38(1)
C(1)–C(7)	1.47(2)
C(3)–C(8)	1.51(3)
C(5)–C(9)	1.49(2)
C(7)–O(1)	1.24(6)
C(7)–O(2)	1.27(3)

^a Single primes denote the $n - 1$ residues; double primes denote the $n + 1$ residues.

^b The mean values of the remaining angles are 120° .

(A), a minor one *gauche-trans* (B) pointing inwards (torsional angles C(4)–C(5)–C(6)–O(6) -169 , -178 , -172° and O(5)–C(5)–C(6)–O(6) 68 , 55 , 50° , respectively). 1O(66) and 2O(66) also point inwards (torsional angles C(46)–C(56)–C(66)–O(66) -159 , -153° and O(56)–C(56)–C(66)–O(66) 88 , 92° , respectively, Figure 1). Both monomers show 7-fold symmetry. The mean value for the

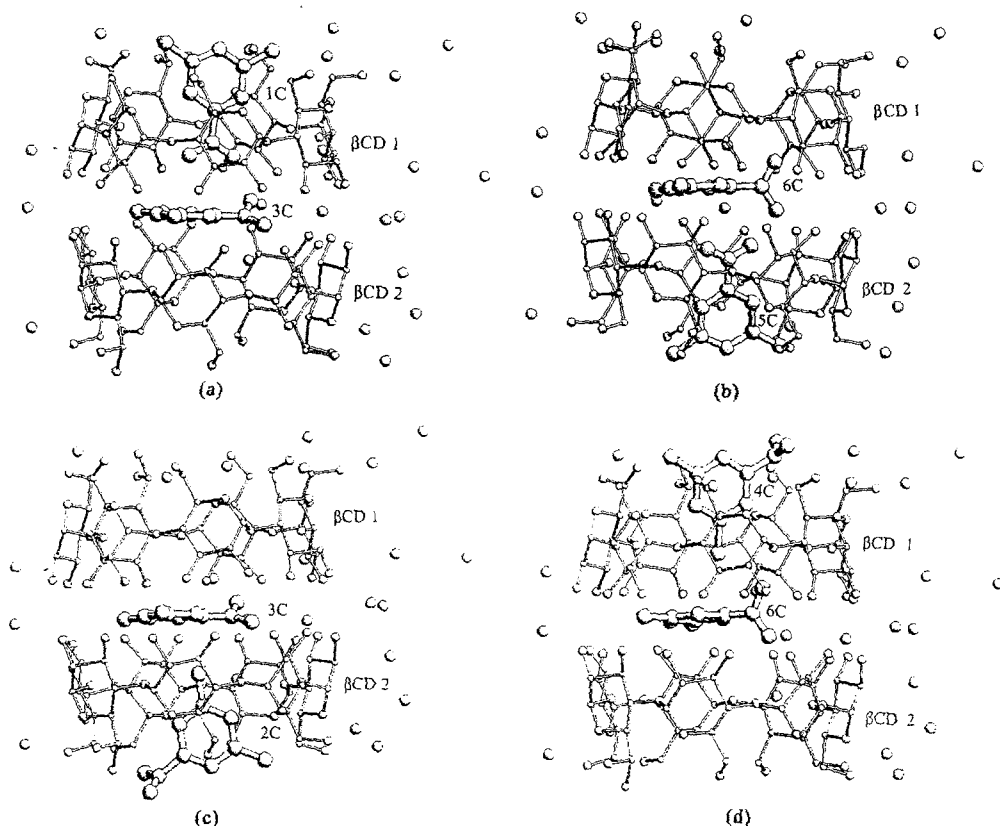


Fig. 3. Positioning of the guest molecules in the dimer: (a) central molecule 3C with guest orientation 1C (carboxylic group pointing inside); (b) central molecule 6C with guest orientation 5C (carboxylic group pointing inside); (c) central molecule 3C with guest orientation 2C (carboxylic group at the rim of β CD 2); and (d) central molecule 6C with guest orientation 4C (carboxylic group at the rim of β CD 1).

$O(4)_n \dots O(4)_{(n+1)}$ distances is 4.39 Å (range 4.27–4.48 Å) and for the angles $O(4)_{(n-1)} \dots O(4)_n \dots O(4)_{(n+1)}$ 128.6° (range 126.3–130.5°). The latter is equal to the angle of the regular heptagon. The deviations of the glucosidic O(4) atoms from their optimum plane are less than 0.04 Å. The strong intramolecular H-bonds among neighboring glucosidic units (mean value 2.87 Å, range 2.81–2.96 Å) contribute to the stabilization of the β CD macrocycle. The dihedral angles between the $O(4)_n$ plane and the planes through the atoms C(2), C(3), C(5) and O(5) have a mean value of 81° (range 78–85°), indicating that the primary hydroxyl group side of the β CD cavity is a little narrower than the corresponding secondary side.

3.3. THE GUEST MOLECULE

3,5-Dimethylbenzoic acid molecules in two orientations, 3C and 6C, with occupation factors 0.44 and 0.41, respectively, are found in the middle of the dimer almost perpendicular to its 7-fold axis. Their carboxylic groups interact with the carboxylic group of another guest molecule found in the cavity of either β CD monomer (1C, occupation factor 0.30, or 5C, occupation factor 0.18) as shown in Figure 3a and b, respectively. The guest enters the cavity of each monomer in a quite different orientation as well: 2C (occupation factor 0.34) or 4C (occupation factor 0.21) (Figure 3c and d, respectively). In the latter case the carboxylic oxygens of 2C situated at the primary rim of β CD 2 interact with the disordered oxygens 1O(64B), 1O(65B) and 2O(65B) that are pointing inside the cavity, while those of 4C situated at the primary rim of β CD 1 interact with oxygens 1O(66) and 2O(66) also pointing inside the cavity. Due to the bulkiness of the guest and the close proximity of the dimers observed in the channel packing, steric considerations forbid both cyclodextrin cavities being occupied simultaneously. Therefore, the overall picture in the crystal will be the average of Figures 3 (a–d). The refinement of the occupation factors of the six orientations without any constraints imposed on them (Table II) agrees very well with the above picture. The central position is almost fully occupied while β CD 1 and β CD 2 are almost 50% occupied.

Table III reports the O–O distances of the interacting carboxylic oxygens. Because of the disorder of the guest and the low occupancy of the individual sites, the guest atoms were not refined individually and consequently the exact positions of the carboxylic oxygens are not known. Thus, Table IIIb and c is intended to show the proximity of the oxygens and their mutual arrangement rather than exact H-bonding distances.

The residual density of the final difference electron density Fourier map indicates that the model of the disorder might be more complicated than described. However, the resolution of the present structure due to the poor quality of the crystals is beyond a more detailed description.

The complex association of the molecules in the present structure permits some thoughts about the effect of the nature and interactions of the guest molecules to the packing of the complex. Channel packing [2], by excluding water molecules from the primary faces where the dimers come close to form the channel, protects hydrophobic parts of guests located at those faces. In the present structure this is partially true. The polar guest (3C and 6C) located in the hydrophobic dimer interface region forces, even partially, another guest molecule to enter the β CD cavity with its polar group buried inside. Indirectly, this implies that a dimer-to-monomer equilibrium occurs in solution before nucleation and precipitation. Such a dimer, with the hydrophobic groups of the guest situated at the primary side, possibly directs crystallization towards the channel mode. However, the β CD system possesses sufficient flexibility to also accommodate the independent orientations of the guest 2C and 4C (Figure 3c and d, respectively) which have the polar car-

boxyl groups at the primary sides, as is common in complexes of β CD with polar guests. Those orientations are stabilized by the H-bond formation with all the β CD hydroxyl groups pointing inside the cavity, thus justifying their conformation.

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