The Crystal and Molecular Structure of the β-Cyclodextrin Inclusion Complex with Aspirin and Salicylic Acid

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Abstract

The crystal structure of the β-cyclodextrin (β-CyD) molecular complex with aspirin (acetylsalicylic acid), salicylic acid, and water, $(C_{42}H_{70}O_{35})_2$ $(C_9H_8O_4)_2$ $(C_7H_6O_3)$ $23.3H_2O$, was determined by X-ray structure analysis. The crystal data is space group P1, a = 19.777(5), b = 15.247(3), c = 15.475(4) Å, α = 102.63(2)°, β = 116.96(2)°, γ = 104.12(2)°, V = 3729(2) Å^3, D_m = 1.409(2) g/cm^3, D_x = 1.419 g/cm^3, and Z = 1. The two β-CyDs form a dimer unit with hydrogen bond networks among the secondary hydroxyl groups of both β-CyDs. This β-CyD dimer includes three guest molecules of two different types in its hydrophobic cavity. Two of them are aspirin, which are separately included in each cavity of the β-CyD unit, with their hydrophobic benzene rings protruding into the hydrophobic cavities of the host β-CyDs.The remaining guest molecule is the hydrolyzed product of an aspirin, that is salicylic acid, which is sandwiched in the space constructed by the β-CyD dimer formation, and is statistically disordered at three sites.

Introduction

As one of the many interesting properties of the host-guest molecular complexes, CyDs have an ability to protect unstable substances from light, heat and the atmosphere. Aspirin, which is widely used as an analgesic and antipyretic and in the treatment of rheumatism, is highly unstable and easily hydrolyzed in aqueous solution. But it is reported that the hydrolysis is inhibited in the presence of β-CyD [1]. So in order to investigate the host-guest interactions of β-CyD and aspirin at the atomic level, we carried out the X-ray structure analysis of the complex. It is very interesting and important to know how the guest aspirin is included in the hydrophobic cavity of β-CyD, because aspirin has both the hydrophobic benzene ring, and the hydrophilic carboxyl group and acetyl group.

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Experimental

Colorless and prismatic crystals of the title compound were obtained by heating a 1:1 aqueous solution of β-CyD and aspirin at pH=2.3 up to 60°C and by cooling the mixture slowly to room temperature. The content of salicylic acid in the crystals was determined by dissolving them in distilled water, adding 1% of $Fe_2(SO_4)_3$ aqueous solution, and measuring the absorption at 510 nm [1]. From a crystal of 0.35x0.20x0.30 mm sealed in a glass capillary with mother liquor, X-ray intensity data were collected on a Rigaku automated four-circle diffractometer, AFC-5 with graphite-monochromatized Cu-Kα radiation. The structure of the host β-CyD was determined by using the atomic coordinates of isomorphous β-CyD: 3,4-xylidine molecular complex [2]. The initial R factor for the 154 atoms of the dimeric β-CyD molecules was 0.43 for 2126 selected strong reflections. After the refinement by the block-diagonal least-squares method, three guest molecules and many water molecules could be assigned on a difference Fourier map. One of the guest molecules lying in the center of the dimeric β-CyD unit, was disordered but it was assigned to be a salicylic acid by orienting at three different positions. Some of the water molecules were also disordered. The following refinement was done by the full-matrix least-squares method [3] with restraints to the bond lengths and angles of the host β-CyD and guest molecules. The final refinement was performed by the block-diagonal least-squares method without any restraints. Anisotropic temperature factors were applied for all the host, guest and water molecules except for the disordered guest molecules. The final R value is 0.107 for 8733 reflections with $F_o > 3\sigma F_o$. The final atomic parameters are listed in TABLE I. The atomic scattering factors used in the calculations were those taken from International Tables for X-ray Crystallography [4]. All the numerical computations were done on an ACOS-850S computer at the Crystallographic Research Center, Institute for Protein Research, Osaka Univesity, using the programs UNICS [5].

Results and Discussion

Two β-CyDs form a dimer and include three guest molecules as shown in Fig.1. All the fourteen glucopyranose moieties composing the β-CyD dimer unit take the $^4C_1$ conformation and form the two round β-CyD macrocycles. The average bond lengths and angles of the seven glucopyranose units in each β-CyD moiety are listed in TABLE II. The seven glucosyl oxygen O4 atoms of each β-CyD moiety make a good plane with maximum deviations of 0.05 and 0.04 Å for β-CyD(1) and (2), respectively. All of the C6-O6 bonds in the β-CyD dimer take gauche-gauche conformation to the C5-O5 and C4-C5 bonds i.e. O6 atoms are towards the outside of the β-CyD cavity with only one O6 atom which is disordered and takes both gauche-gauche and gauche-trans conformations. But the overall structural feature of the host molecule is very similar to that of the β-CyD·3,4-xylidine complex [2]. Fig. 2 shows the hydrogen bond networks among the secondary hydroxyl groups of each β-CyD moiety, together with the hydrogen bonds to the crystalline water molecules.

TABLE I. Final atomic coordinates and isotropic temperature factors with e.s.d.'s in parentheses of $(\beta\text{-CyD})_2(\text{Aspirin})_2(\text{Salicylic acid})23.3H_2O$

$$B_{eq} = (4/3)\sum_i\sum_j B_{ij}\mathbf{a}_i.\mathbf{a}_j \ .$$

Atom names are composed by four digits of character and numeric, starting with atomic name; atomic position,glucopyranose unit, and CyD unit for β-CyD; atomic position, then A1 to A2 for aspirin(1) and (2), A3 to A5 for disordered salicylic acids; W01 to W28 for water molecules.

ATOM	Ocup	x	y	z	B_{eq}
C111	1.00	0.0641(11)	0.2250(12)	0.3197(13)	3.02
C211	1.00	0.1358(10)	0.2909(11)	0.3299(13)	2.63
O211	1.00	0.2092(8)	0.3011(10)	0.4192(10)	4.01
C311	1.00	0.1338(10)	0.3933(12)	0.3418(14)	2.87
O311	1.00	0.2061(7)	0.4542(9)	0.3477(11)	4.00
C411	1.00	0.0560(10)	0.3799(10)	0.2410(13)	2.31
O411	1.00	0.0465(6)	0.4713(7)	0.2558(7)	1.76
C511	1.00	-0.0200(11)	0.3069(11)	0.2297(14)	2.85
O511	1.00	-0.0105(8)	0.2173(8)	0.2285(9)	3.85
C611	1.00	-0.1003(13)	0.2822(16)	0.1247(17)	5.36
O611	1.00	-0.0890(12)	0.2450(13)	0.0433(13)	8.44
C121	1.00	0.0407(9)	0.5099(10)	0.1784(11)	1.68
C221	1.00	0.1094(9)	0.6114(11)	0.2308(11)	1.83
O221	1.00	0.1878(6)	0.6024(8)	0.2792(9)	2.62
C321	1.00	0.1018(8)	0.6767(10)	0.3133(12)	1.67
O321	1.00	0.1662(6)	0.7707(7)	0.3604(9)	2.95
C421	1.00	0.0182(8)	0.6827(9)	0.2566(11)	1.33
O421	1.00	0.0089(6)	0.7357(6)	0.3355(7)	1.47
C521	1.00	-0.0509(9)	0.5791(10)	0.1980(12)	1.96
O521	1.00	-0.0375(6)	0.5170(7)	0.1278(8)	1.93
C621	1.00	-0.1373(10)	0.5823(12)	0.1251(13)	2.54
O621	1.00	-0.1369(7)	0.6260(8)	0.0551(9)	3.36
C131	1.00	-0.0138(9)	0.8172(11)	0.3214(12)	2.04
C231	1.00	0.0535(9)	0.9092(10)	0.4209(12)	1.91
O231	1.00	0.1311(6)	0.9239(7)	0.4327(9)	2.65
C331	1.00	0.0526(8)	0.8968(9)	0.5150(11)	1.29
O331	1.00	0.1125(6)	0.9841(7)	0.6064(7)	1.85
C431	1.00	-0.0332(8)	0.8846(10)	0.4934(10)	1.29
O431	1.00	-0.0341(6)	0.8681(7)	0.5824(8)	1.73
C531	1.00	-0.0980(10)	0.7899(14)	0.3946(14)	3.50
O531	1.00	-0.0905(6)	0.8023(7)	0.3081(8)	2.03
C631	1.00	-0.1857(10)	0.7823(14)	0.3639(15)	3.77
O631	1.00	-0.2010(7)	0.8643(9)	0.3393(10)	4.15
C141	1.00	-0.0605(9)	0.9271(10)	0.6338(12)	1.93
C241	1.00	0.0079(9)	0.9777(12)	0.7504(12)	2.39
O241	1.00	0.0792(6)	1.0388(7)	0.7610(8)	2.55
C341	1.00	0.0200(9)	0.9019(11)	0.7974(11)	2.06
O341	1.00	0.0803(7)	0.9507(8)	0.9057(8)	3.07
C441	1.00	-0.0606(9)	0.8409(11)	0.7807(11)	1.74
O441	1.00	-0.0505(6)	0.7632(7)	0.8137(8)	2.02

TABLE I. continued

C541	1.00	-0.1275(10)	0.7947(12)	0.6642(13)	2.72
O541	1.00	-0.1341(6)	0.8708(8)	0.6214(8)	2.34
C641	1.00	-0.2134(10)	0.7426(14)	0.6455(15)	3.69
O641	1.00	-0.2346(8)	0.8101(12)	0.6958(12)	5.58
C151	1.00	-0.0690(9)	0.7499(11)	0.8899(12)	1.98
C251	1.00	0.0076(9)	0.7517(10)	0.9834(11)	1.83
O251	1.00	0.0748(7)	0.8456(8)	1.0285(8)	2.81
C351	1.00	0.0308(8)	0.6713(10)	0.9420(11)	1.83
O351	1.00	0.1002(7)	0.6696(8)	1.0294(8)	2.72
C451	1.00	-0.0429(8)	0.5734(10)	0.8997(12)	1.98
O451	1.00	-0.0240(6)	0.5007(7)	0.8492(8)	2.30
C551	1.00	-0.1213(9)	0.5750(11)	0.8104(12)	2.23
O551	1.00	-0.1349(6)	0.6612(7)	0.8514(8)	2.35
C651	1.00	-0.1998(9)	0.4875(12)	0.7737(12)	2.58
O651	1.00	-0.2061(7)	0.4795(9)	0.8587(10)	3.78
C161	1.00	-0.0327(10)	0.4155(10)	0.8781(13)	2.35
C261	1.00	0.0489(10)	0.4049(11)	0.9234(12)	2.48
O261	1.00	0.1088(7)	0.4885(7)	1.0186(8)	2.65
C361	1.00	0.0761(8)	0.3887(10)	0.8450(11)	1.64
O361	1.00	0.1498(7)	0.3732(8)	0.8916(8)	2.90
C461	1.00	0.0062(9)	0.2960(11)	0.7474(13)	2.44
O461	1.00	0.0282(6)	0.2822(7)	0.6732(8)	2.21
C561	1.00	-0.0723(11)	0.3166(14)	0.7041(15)	4.07
O561	1.00	-0.0955(7)	0.3318(9)	0.7820(10)	3.96
C661	1.00	-0.1489(14)	0.2208(18)	0.6074(20)	6.68
O661	1.00	-0.1521(12)	0.1403(14)	0.6306(18)	9.77
C171	1.00	0.0312(9)	0.1897(9)	0.6358(11)	1.55
C271	1.00	0.1148(9)	0.2110(10)	0.6476(11)	1.80
O271	1.00	0.1790(6)	0.2608(8)	0.7563(8)	2.43
C371	1.00	0.1248(8)	0.2638(10)	0.5816(11)	1.74
O371	1.00	0.2003(6)	0.2767(8)	0.5892(9)	2.88
C471	1.00	0.0541(9)	0.2057(10)	0.4696(11)	1.65
O471	1.00	0.0584(6)	0.2654(7)	0.4109(8)	2.01
C571	1.00	-0.0277(10)	0.1841(11)	0.4604(12)	2.54
O571	1.00	-0.0321(6)	0.1363(7)	0.5309(8)	2.21
C671	1.00	-0.1032(10)	0.1121(13)	0.3477(13)	3.27
O671	1.00	-0.0892(7)	0.0267(8)	0.3163(9)	3.30
C112	1.00	0.4733(9)	0.4969(10)	1.0675(11)	1.85
C212	1.00	0.3944(9)	0.4669(10)	1.0602(12)	2.04
O212	1.00	0.3332(7)	0.3878(7)	0.9648(8)	2.74
C312	1.00	0.3675(8)	0.5530(10)	1.0725(12)	1.94
O312	1.00	0.2927(6)	0.5236(7)	1.0741(8)	2.32
C412	1.00	0.4359(9)	0.6346(11)	1.1793(11)	2.04
O412	1.00	0.4144(6)	0.7163(6)	1.1904(7)	1.66
C512	1.00	0.5155(9)	0.6639(11)	1.1780(13)	2.49
O512	1.00	0.5374(6)	0.5815(7)	1.1643(8)	2.32
C612	1.00	0.5894(10)	0.7421(13)	1.2843(15)	3.78
O612	1.00	0.5967(8)	0.7105(10)	1.3673(10)	5.11
C122	1.00	0.4108(8)	0.7524(10)	1.2809(11)	1.62
C222	1.00	0.3294(8)	0.7606(10)	1.2465(11)	1.59

TABLE I. continued

O222	1.00	0.2639(6)	0.6659(7)	1.1807(8)	2.29
C322	1.00	0.3191(8)	0.8291(10)	1.1863(12)	1.71
O322	1.00	0.2417(6)	0.8388(7)	1.1596(9)	2.63
C422	1.00	0.3888(8)	0.9270(10)	1.2595(11)	1.52
O422	1.00	0.3864(6)	0.9850(7)	1.1971(7)	1.72
C522	1.00	0.4734(9)	0.9193(10)	1.3025(12)	2.25
O522	1.00	0.4754(6)	0.8468(7)	1.3495(8)	2.02
C622	1.00	0.5454(9)	1.0152(10)	1.3913(12)	2.36
O622	1.00	0.5301(7)	1.0466(8)	1.4740(9)	3.31
C132	1.00	0.3857(10)	1.0805(11)	1.2341(13)	2.71
C232	1.00	0.3093(10)	1.0825(11)	1.1486(13)	2.45
O232	1.00	0.2357(7)	1.0103(8)	1.1269(9)	2.90
C332	1.00	0.3091(9)	1.0664(11)	1.0485(12)	2.23
O332	1.00	0.2402(6)	1.0770(9)	0.9718(9)	3.18
C432	1.00	0.3864(9)	1.1501(11)	1.0744(11)	1.98
O432	1.00	0.3943(6)	1.1295(6)	0.9857(7)	1.70
C532	1.00	0.4633(10)	1.1436(12)	1.1610(12)	2.96
O532	1.00	0.4554(7)	1.1527(8)	1.2540(8)	2.77
C632	1.00	0.5475(15)	1.2348(23)	1.2043(21)	7.82
O632	1.00	0.5282(13)	1.3192(13)	1.2271(15)	9.40
C142	1.00	0.4035(9)	1.2074(10)	0.9488(11)	1.58
C242	1.00	0.3331(9)	1.1681(12)	0.8331(11)	2.35
O242	1.00	0.2546(6)	1.1385(7)	0.8209(8)	1.77
C342	1.00	0.3412(8)	1.0855(9)	0.7713(11)	1.40
O342	1.00	0.2773(6)	1.0515(8)	0.6618(8)	2.62
C442	1.00	0.4266(8)	1.1221(10)	0.7839(11)	1.60
O442	1.00	0.4367(6)	1.0419(6)	0.7325(7)	1.46
C542	1.00	0.4941(8)	1.1664(10)	0.9006(11)	1.63
O542	1.00	0.4796(6)	1.2383(6)	0.9578(8)	1.76
C642	1.00	0.5790(9)	1.2192(11)	0.9182(13)	2.28
O642	1.00	0.5795(6)	1.2931(8)	0.8783(9)	2.74
C152	1.00	0.4535(9)	1.0536(11)	0.6544(12)	1.95
C252	1.00	0.3870(9)	0.9617(12)	0.5491(12)	2.39
O252	1.00	0.3074(6)	0.9611(8)	0.5210(8)	2.72
C352	1.00	0.3928(9)	0.8710(10)	0.5671(11)	1.80
O352	1.00	0.3325(7)	0.7880(8)	0.4675(9)	3.00
C452	1.00	0.4767(8)	0.8733(9)	0.5933(10)	1.26
O452	1.00	0.4855(6)	0.7885(7)	0.6184(8)	1.82
C552	1.00	0.5434(9)	0.9649(10)	0.6960(12)	2.02
O552	1.00	0.5305(6)	1.0512(7)	0.6804(8)	2.09
C652	1.00	0.6309(10)	0.9848(13)	0.7220(14)	3.18
O652	1.00	0.6390(7)	1.0000(9)	0.6372(9)	3.29
C162	1.00	0.5119(8)	0.7323(11)	0.5651(12)	1.91
C262	1.00	0.4460(9)	0.6271(11)	0.5005(12)	2.41
O262	1.00	0.3703(7)	0.6306(8)	0.4195(8)	2.65
C362	1.00	0.4287(8)	0.5839(10)	0.5715(11)	1.64
O362	1.00	0.3689(7)	0.4850(8)	0.5116(9)	3.10
C462	1.00	0.5096(8)	0.5833(10)	0.6523(12)	1.78
O462	1.00	0.4959(6)	0.5524(7)	0.7266(8)	1.93
C562	1.00	0.5801(9)	0.6850(10)	0.7144(12)	1.81

TABLE I. continued

O562	1.00	0.5853(6)	0.7259(8)	0.6405(9)	2.56
C662	1.00	0.6607(10)	0.6808(13)	0.7815(16)	3.71
O662	0.70	0.7244(8)	0.7687(10)	0.8312(11)	2.11
O762	0.30	0.6850(21)	0.6402(26)	0.7396(30)	2.67
C172	1.00	0.5119(9)	0.4684(11)	0.7437(12)	2.08
C272	1.00	0.4331(9)	0.3963(11)	0.7274(12)	2.22
O272	1.00	0.3687(7)	0.3617(8)	0.6195(9)	3.14
C372	1.00	0.4123(9)	0.4436(11)	0.7993(12)	2.16
O372	1.00	0.3378(6)	0.3748(8)	0.7839(9)	2.90
C472	1.00	0.4831(8)	0.4740(10)	0.9130(11)	1.53
O472	1.00	0.4644(6)	0.5267(7)	0.9814(8)	1.80
C572	1.00	0.5646(8)	0.5435(10)	0.9293(12)	1.88
O572	1.00	0.5776(6)	0.4985(7)	0.8499(8)	2.05
C672	1.00	0.6392(9)	0.5592(12)	1.0326(13)	2.57
O672	1.00	0.6425(7)	0.4713(8)	1.0424(9)	3.16
OW01	1.00	0.818(1)	0.780(1)	0.035(1)	5.4
OW02	1.00	0.170(2)	0.366(4)	0.119(3)	20.1
OW03	1.00	0.659(1)	0.313(1)	0.772(1)	7.8
OW04	1.00	0.684(1)	0.878(1)	0.544(1)	4.3
OW05	1.00	0.940(1)	0.965(1)	0.159(1)	6.3
OW06	1.00	0.245(1)	0.969(2)	0.329(1)	7.9
OW07	1.00	0.326(2)	0.469(2)	0.256(2)	16.5
OW08	1.00	0.727(1)	0.809(1)	0.131(2)	8.4
OW09	1.00	0.755(1)	0.978(1)	0.454(1)	5.8
OW10	1.00	0.655(2)	0.462(2)	0.219(2)	11.8
OW11	1.00	0.541(2)	0.230(2)	0.555(2)	10.5
OW12	1.00	0.071(2)	0.944(2)	0.195(2)	13.4
OW13	1.00	0.209(2)	0.112(2)	0.469(2)	11.2
OW14	1.00	0.382(2)	0.205(2)	0.513(3)	16.6
OW15	1.00	0.949(2)	0.067(2)	0.022(2)	14.0
OW16	1.00	0.120(2)	0.124(2)	0.098(3)	18.8
OW17	1.00	0.252(2)	0.278(2)	0.032(3)	15.9
OW18	1.00	0.642(3)	0.564(3)	0.385(3)	26.4
OW19	1.00	0.341(3)	0.319(3)	0.346(3)	21.8
OW20	1.00	0.849(2)	0.026(3)	0.814(3)	21.8
OW21	0.45	0.197(8)	0.123(7)	0.252(11)	26.6
OW22	0.55	0.256(4)	0.174(5)	0.307(5)	18.0
OW23	0.45	0.667(7)	0.500(9)	0.563(7)	25.4
OW24	0.55	0.614(4)	0.518(6)	0.519(5)	18.9
OW25	0.30	0.804(4)	0.289(5)	0.894(7)	10.0
OW26	0.30	0.798(5)	0.137(4)	0.750(7)	11.2
OW27	0.35	0.781(3)	0.210(4)	0.819(4)	7.9
OW28	0.35	0.724(5)	0.212(5)	0.704(6)	11.3
C1A1	1.00	-0.126(2)	0.484(3)	0.499(3)	9.7
C2A1	1.00	-0.102(4)	0.429(4)	0.439(5)	19.1
C3A1	1.00	-0.023(5)	0.470(6)	0.457(6)	25.9
C4A1	1.00	0.018(4)	0.572(4)	0.505(6)	21.9
C5A1	1.00	0.003(5)	0.623(4)	0.576(7)	24.9
C6A1	1.00	-0.067(3)	0.577(4)	0.575(4)	15.9
C7A1	1.00	-0.202(4)	0.443(6)	0.501(5)	23.5

TABLE I. continued

C8A1	1.00	-0.211(6)	0.308(5)	0.272(6)	29.1
C9A1	1.00	-0.258(3)	0.199(4)	0.206(4)	19.1
O1A1	1.00	-0.226(3)	0.501(4)	0.537(3)	29.0
O2A1	1.00	-0.242(4)	0.350(6)	0.460(6)	35.7
O3A1	1.00	-0.151(2)	0.326(2)	0.372(3)	17.6
O4A1	1.00	-0.219(5)	0.369(5)	0.240(5)	31.6
C1A2	1.00	0.546(2)	0.908(3)	1.045(3)	8.7
C2A2	1.00	0.551(2)	0.878(3)	0.956(2)	8.3
C3A2	1.00	0.481(2)	0.824(4)	0.857(3)	13.5
C4A2	1.00	0.404(4)	0.803(7)	0.845(5)	27.4
C5A2	1.00	0.397(4)	0.827(8)	0.932(5)	31.2
C6A2	1.00	0.467(2)	0.888(3)	1.029(3)	12.0
C7A2	1.00	0.618(2)	0.957(3)	1.155(3)	11.3
C8A2	1.00	0.674(2)	0.981(2)	0.978(3)	7.8
C9A2	1.00	0.763(2)	0.992(2)	1.014(3)	9.0
O1A2	1.00	0.607(3)	0.984(3)	1.227(3)	25.3
O2A2	1.00	0.690(1)	0.967(2)	1.174(1)	8.6
O3A2	1.00	0.627(1)	0.890(1)	0.966(1)	6.5
O4A2	1.00	0.648(2)	1.046(2)	0.981(2)	12.6
C1A3	0.33	0.222(7)	0.658(8)	0.712(9)	9.9
C2A3	0.33	0.216(6)	0.750(6)	0.732(7)	7.7
C3A3	0.33	0.210(8)	0.793(9)	0.820(10)	11.9
C4A3	0.33	0.196(5)	0.739(5)	0.877(6)	6.0
C5A3	0.33	0.193(5)	0.644(6)	0.850(7)	7.4
C6A3	0.33	0.209(5)	0.605(6)	0.771(7)	7.4
C7A3	0.33	0.238(5)	0.606(6)	0.623(6)	6.6
O1A3	0.33	0.254(3)	0.532(3)	0.625(4)	5.7
O2A3	0.33	0.234(3)	0.641(3)	0.548(4)	5.4
O3A3	0.33	0.234(4)	0.527(5)	0.777(5)	9.9
C1A4	0.33	0.210(5)	0.665(6)	0.743(6)	6.8
C2A4	0.33	0.198(6)	0.756(7)	0.768(7)	8.0
C3A4	0.33	0.202(5)	0.819(6)	0.713(6)	6.9
C4A4	0.33	0.215(4)	0.788(5)	0.627(5)	5.3
C5A4	0.33	0.226(5)	0.699(6)	0.602(6)	6.2
C6A4	0.33	0.215(6)	0.635(7)	0.653(7)	8.3
C7A4	0.33	0.211(6)	0.595(7)	0.802(7)	8.4
O1A4	0.33	0.235(4)	0.529(5)	0.785(5)	9.0
O2A4	0.33	0.198(3)	0.618(4)	0.879(4)	7.4
O3A4	0.33	0.184(3)	0.788(4)	0.850(4)	7.1
C1A5	0.33	0.208(5)	0.688(6)	0.772(7)	7.0
C2A5	0.33	0.221(6)	0.629(7)	0.832(7)	8.5
C3A5	0.33	0.234(8)	0.543(10)	0.800(11)	13.1
C4A5	0.33	0.239(6)	0.515(7)	0.710(7)	8.0
C5A5	0.33	0.236(5)	0.577(6)	0.655(7)	7.1
C6A5	0.33	0.215(8)	0.660(10)	0.681(10)	12.5
C7A5	0.33	0.186(7)	0.783(8)	0.806(9)	10.5
O1A5	0.33	0.180(3)	0.797(4)	0.888(4)	6.4
O2A5	0.33	0.201(3)	0.859(3)	0.776(3)	5.3
O3A5	0.33	0.203(3)	0.642(4)	0.912(4)	6.7

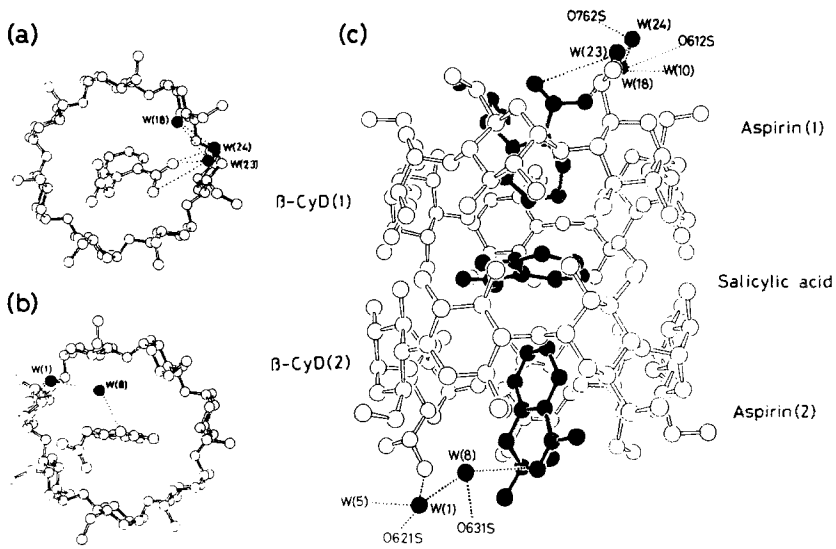


Fig. 1 (a),(b) The structure of β-CyD·aspirin complex (1) and (2), viewed from the primary hydroxyl side of each β-CyD, respectively. (c) The molecular structure of $(\beta\text{-CyD})_2(\text{aspirin})_2$ salicylic acid complex. Aspirin and salicylic acid are drawn by full lines and circles. One of the statistically disordered salicylic acid at three sites is shown in the center of β-CyD dimer.

TABLE II. The bond lengths and angles and their mean values of the host β-CyD(1) and (2).

CYCLODEXTRIN NO. 1									
BOND	D-GLUCOSYL RESIDUE								
LENGTH(Å)	1	2	3	4	5	6	7	MEAN	RMS
C1-C2	1.44	1.53	1.55	1.53	1.54	1.51	1.52	1.52	0.04
C1-O5	1.46	1.43	1.39	1.40	1.40	1.45	1.40	1.42	0.03
C2-O2	1.42	1.44	1.41	1.40	1.45	1.43	1.43	1.43	0.02
C2-C3	1.54	1.53	1.52	1.51	1.52	1.53	1.48	1.52	0.02
C3-O3	1.45	1.42	1.44	1.41	1.44	1.41	1.40	1.42	0.02
C3-C4	1.54	1.52	1.53	1.51	1.56	1.55	1.51	1.53	0.02
C4-O4	1.43	1.42	1.46	1.41	1.44	1.39	1.43	1.43	0.02
C4-C5	1.55	1.54	1.56	1.53	1.55	1.53	1.50	1.54	0.02
O4-C1	1.42	1.45	1.42	1.42	1.46	1.43	1.48	1.44	0.02
C5-O5	1.42	1.44	1.46	1.46	1.47	1.47	1.46	1.45	0.02
C5-C6	1.55	1.58	1.54	1.55	1.54	1.61	1.57	1.56	0.02
C6-O6	1.40	1.39	1.45	1.41	1.41	1.35	1.43	1.40	0.03
ANGLE(°)									
O5-C1-C2	109	109	110	110	108	110	110	110	1
O4-C1-C2	110	109	107	108	109	108	107	108	1
O4-C1-O5	106	109	111	111	113	106	111	110	3
C1-C2-O2	111	109	110	109	109	108	110	109	1

TABLE II. continued

C1-C2-C3	111	109	109	110	108	113	112	110	2
O2-C2-C3	108	110	112	114	109	113	113	111	2
C2-C3-O3	108	108	109	108	108	109	111	109	1
C2-C3-C4	107	107	107	109	106	107	109	107	1
O3-C3-C4	109	110	109	110	106	110	110	109	2
C3-C4-O4	108	106	106	108	104	108	107	107	1
C3-C4-C5	108	110	109	110	108	107	111	109	1
O4-C4-C5	106	108	107	107	105	110	107	107	1
C4-O4-C1	116	116	117	119	114	117	118	117	2
C4-C5-O5	110	110	107	110	109	110	111	109	1
C4-C5-C6	111	111	109	111	112	110	113	111	1
O5-C5-C6	107	105	105	106	104	103	105	105	1
C5-O5-C1	115	114	116	114	113	112	114	114	1
C5-C6-O6	108	113	112	110	111	111	109	111	2

CYCLODEXTRIN NO. 2

BOND	D-GLUCOSYL RESIDUE								
LENGTH	1	2	3	4	5	6	7	MEAN	RMS
C1-C2	1.46	1.50	1.50	1.54	1.58	1.54	1.54	1.52	0.04
C1-O5	1.47	1.43	1.39	1.39	1.40	1.44	1.43	1.42	0.03
C2-O2	1.41	1.43	1.43	1.42	1.43	1.48	1.43	1.43	0.02
C2-C3	1.54	1.54	1.51	1.50	1.49	1.52	1.46	1.51	0.03
C3-O3	1.45	1.45	1.42	1.45	1.46	1.43	1.47	1.45	0.02
C3-C4	1.54	1.50	1.55	1.55	1.51	1.52	1.54	1.53	0.02
C4-O4	1.41	1.44	1.43	1.42	1.46	1.44	1.43	1.43	0.02
C4-C5	1.54	1.54	1.55	1.53	1.56	1.53	1.57	1.55	0.02
O4-C1	1.43	1.45	1.43	1.43	1.41	1.44	1.45	1.43	0.01
C5-O5	1.43	1.45	1.50	1.42	1.45	1.45	1.43	1.45	0.02
C5-C6	1.54	1.54	1.61	1.54	1.52	1.48	1.52	1.54	0.04
C6-O6	1.43	1.45	1.45	1.40	1.45	1.35	1.39	1.42	0.04
ANGLE									
O5-C1-C2	112	109	110	110	106	107	108	109	2
O4-C1-C2	109	109	107	108	107	109	107	108	1
O4-C1-O5	107	110	110	110	111	109	109	109	1
C1-C2-O2	111	110	112	112	108	108	108	110	2
C1-C2-C3	111	110	112	109	109	110	110	110	1
O2-C2-C3	111	110	109	111	110	110	113	111	1
C2-C3-O3	110	108	111	109	108	110	110	109	1
C2-C3-C4	108	107	107	109	108	107	110	108	1
O3-C3-C4	108	109	106	109	106	109	108	108	1
C3-C4-O4	109	106	108	109	109	107	108	108	1
C3-C4-C5	107	112	108	109	108	113	108	109	2
O4-C4-C5	108	106	104	109	106	107	109	107	2
C4-O4-C1	117	117	115	114	116	119	116	116	1
C4-C5-O5	109	110	108	111	109	108	110	109	1
C4-C5-C6	111	113	112	111	113	112	111	112	1
O5-C5-C6	105	105	104	106	104	109	105	106	1
C5-O5-C1	114	114	114	116	117	117	116	116	1
C5-C6-O6	110	110	104	112	111	113	112	110	3

This rigid hydrogen bond network plays an important role to stabilize the β-CyD dimeric structure. Two guest aspirin molecules are included in each dimeric β-CyD, with their hydrophobic benzene ring protruding into the hydrophobic β-CyD cavities and leaving their hydrophilic groups outside the cavities and at the primary hydroxyl O6 sides. The aromatic rings of aspirin(1) and (2) are stabilized mainly by van der Waals contacts with the inner surface of β-CyD(1) and (2), respectively, and the carboxyl groups are linked to the primary hydroxyl groups of β-CyDs via water molecules by hydrogen bonding. The bond lengths and angles of the guest aspirins (Asp(1) and (2)) included in the β-CyD dimer are not significantly different from those obtained by the structure analysis of a free aspirin crystal [6]. Judging from the bond lengths and angles about the carboxyl group for both Asp(1) and (2); C-O = 1.29 and 1.24 Å, C-C-O = 118°,118° for Asp(1) and C-O = 1.26 and 1.24 Å, C-C-O = 119° and 120° for Asp(2), respectively, the carboxyl group of the aspirin may be deprotonated into a carboxylate anion of aspirin (Asp^-). The existence of Asp^- is not abnormal, because neutral or anionic guests can be included in the host CyD. Comparing the included aspirins with free aspirin, interesting differences are found in two dihedral angles i.e. 1) the dihedral angle between a plane formed by the benzene ring and that by the carboxylgroup (DA1), 2) the dihedral angle between the benzene plane and the plane of the acetyl group (DA2): DA1 = 18.8°, 9.6°, and 2.0°; DA2 = 88.1°,107.0°, and 84.7° for Asp(1), Asp(2), and aspirin free, respectively. For DA1, the carbonyl group and the benzene ring are not parallel but rotated about ten to twenty degrees to one another in the included aspirins. On the other hand, DA2 is nearly equal with Asp(1) and free aspirin, but is different between Asp(1) and (2), and also Asp(2) and free aspirin. In conclusion, these differences can not be uniquely reduced to the effect of the inclusion or by the packing force which is mainly hydrogen bonding in this case, but we can point out that the guest molecule changes their conformation to make a best fit to its host structure. On the other hand the acetyl groups of the guest aspirin do not take part in hydrogen bonding. Further the remaining guest molecule is included in the center of the β-CyD dimer. We found it to be hydrolyzed aspirin, that is salicylic acid. Because of the disorder in the salicylic acid, at the initial stage we could not assign it unambiguously. But by putting it to three different positions statistically, our assignment was comfortably completed as shown in Fig. 3. As we only used aspirins as the guest ligand in the preparation of the complex crystals, the resultant salicylic acid must have been produced by the hydrolysis of the aspirin molecules. As the hydrolysis of aspirin occurs only in aqueous solution, it is not certain whether the secondary hydroxyl groups of β-CyD have catalyzed the reaction or not. It seems to be the reason why a salicylic acid was selectively included, because the sandwiched area of the β-CyD cavity is too narrow for an aspirin molecule to be included. But this area is nearly round and too wide to fix a salicylic acid in one position, and it takes three positions statistically so as to increase van der Waals contacts between the host and guest molecules.

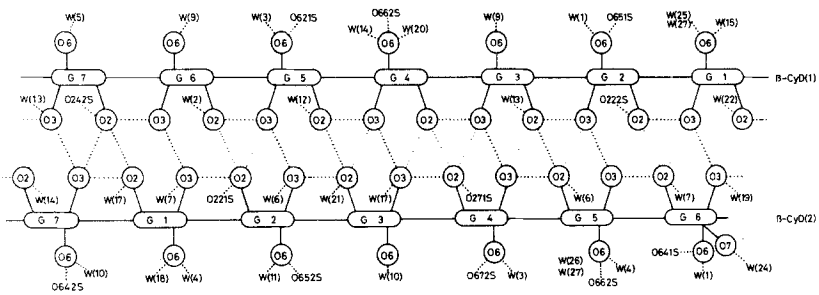
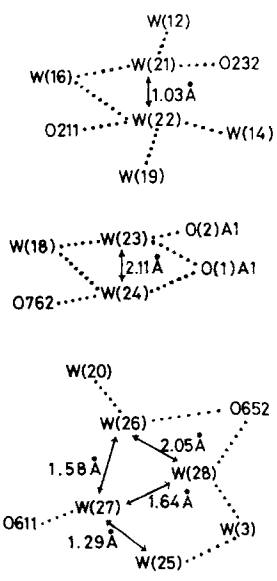


Fig. 2. Hydrogen bond networks among the secondary hydroxyl groups of β-CyD(1) and (2), together with the hydrogen bonds to the crystalline water molecules. Thick dotted lines mean hydrogen bonding in the range from 2.4 to 3.0 Å and thin dotted lines, which are used only for the bondings among the secondary hydroxyl groups, are in the range from 3.0 to 3.2 Å.

TABLE III. The connection table for the hydrogen bondings about water molecules in the range from 2.4 to 3.0 Å.

From	To
W(1)	-- W(5), W(8), 0621, 0662
W(2)	-- W(7), W(17),0261
W(3)	-- W(11),W(25),W(28),0651,0642
W(4)	-- W(9), 0641, 0612, 0652
W(5)	-- W(1), W(12),W(15),0671
W(6)	-- W(12),0322, 0252
W(7)	-- W(2), W(19),0312, 0262
W(8)	-- W(1), 0631, O(2)A2
W(9)	-- W(4), 0631, 0661
W(10)	-- W(18),0632, 0672
W(11)	-- W(3), W(14),0622
W(12)	-- W(5), W(6), W(21),0251
W(13)	-- 0231, 0371
W(14)	-- W(11),W(22),0272
W(15)	-- W(5), W(16),W(20),0611
W(16)	-- W(21),W(22),W(15)
W(17)	-- W(2), 0212, 0332
W(18)	-- W(10),W(23),W(24),0612
W(19)	-- W(7), W(22),0362
W(20)	-- W(15),W(26),0641



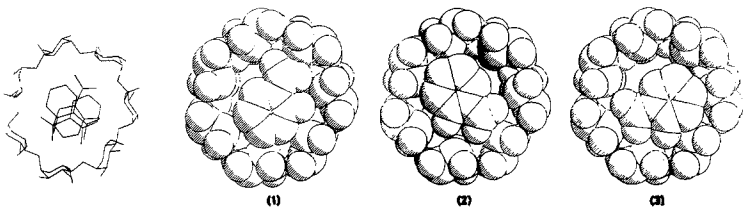


Fig. 3. Space-filling drawings of disordered salicylic acid at three positions in β-CyD moiety of the dimeric β-CyD. Each salicylic acid has the occupancy of 0.33.

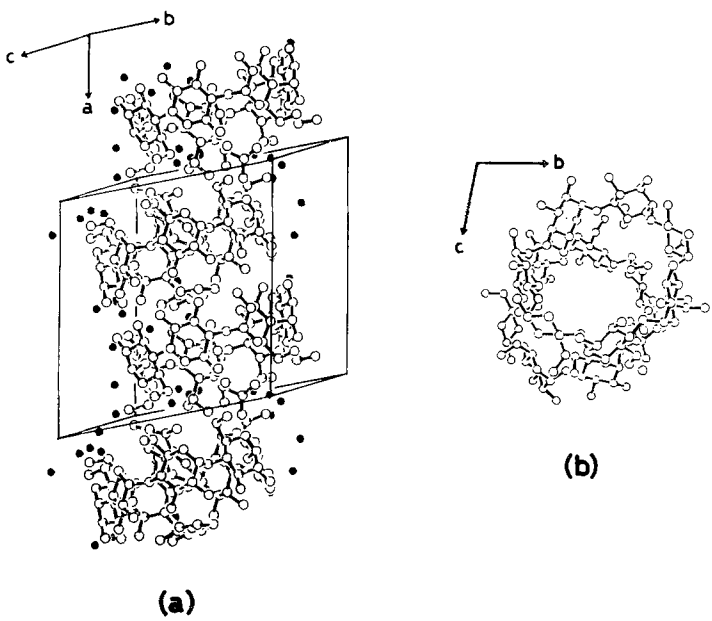


Fig. 4. Packing of β-CyD dimers (a) A projection of the packing of β-CyD dimers along the c^*-axis. (b) A projection of β-CyD(2) in the original and β-CyD(1) in the next unit cell along the a^*-axis.

This sandwiched area formed by OH--O hydrogen bonds among the secondary hydroxyl groups of the dimeric β-CyD, may be rather hydrophobic, because there are no hydrogen bondings between the hydroxyl groups of salicylic acid and those of β-CyDs. To ensure the existence of the salicylic acid, we performed a quantitative analysis of the salicylic acid content of the complex crystals. The resultant content of salicylic acid was 47% of all of the guest molecules, which was much larger than 1/3, but this deviation may be attributed to the experimental error, because aspirin could be hydrolyzed rapidly in aqueous solution. In an asymmetric unit, there exist one of the host-guest molecular complex and substantially 23.3 water molecules, which are disordered at 28 positions, are surrounding it. These water molecules play the important roles of the mediators which construct the host matrix structure or connect the host and guest molecules, and also the spacer which fills the packing spaces among the β-CyD dimeric units as shown in Figs. 1 and 4. The networks of the water molecules are shown in TABLE III. The packing of the structure is shown in Fig. 4. A channel type structure is constructed by two β-CyDs forming a dimer and this channel is closed by the dimer unit of the next unit cell just to enclose the guest molecules into their host dimeric β-CyDs.

On the basis of our structure analysis of the β-CyD·aspirin complex crystal, we now want to discuss here how the host β-CyD plays an important role to prevent the guest aspirin from the hydrolysis reaction. On the mechanism of the hydrolysis of aspirin, the classical general base catalysis of the attack by water which is activated by the carboxylate anion is generally accepted [7]. On the basis of this mechanism, the protectional function of hydrolysis of aspirin by β-CyD can be related to the following structural features: 1) As shown in Fig.1 and also as mentioned above, the guest aspirin is included in the host β-CyD with its benzene ring protruding into the hydrophobic β-CyD cavity. The carboxyl group is at the primary hydroxyl group side of β-CyD and is deprotonated into the carboxylate anion which is connected to the neighbouring upper or lower β-CyD unit by hydrogen bonds through water molecules, for example, $Asp(1)^{-}\cdots W(23)\cdots W(18)\cdots O6$ of upper β-CyD and $Asp(2)^{-}\cdots W(8)\cdots O6$ of lower β-CyD. Probably, the negative charge of the carboxylate anion is compensated by protonation of the neighbouring water molecules into H_3O^+ such as $W(23)^+$ or $W(24)^+$ and $W(8)^+$ in the crystalline state. The existence of H_3O^+ is supported by the following strong hydrogen bonds of $COO^{-}\cdots W(23)$=2.41, 2.62 Å, $COO^{-}\cdots W(8)$=2.77 Å. If this crystal structure persists in solution, the classical general base catalysis of the attack by water activated by the carboxyl anion can not be possible. 2) When the crystalline waters are removed but the same type of inclusion as mentioned in 1) is maintained even in solution, the hydrolysis of aspirin will be performed on the proposed mechanism but must proceed much slower than that without β-CyD, because of the difficulty in movement of the aspirin included by β-CyD.

On the contrary, β-CyD catalyzes the hydrolysis of phenylesters in alkaline solution [8,9]. In this case, the catalysis is thought to be caused by the anionized secondary hydroxyl groups of β-CyD and the guest phenylesters are included in the host β-CyD with their functional groups at the host secondary hydroxyl side. Our study is not for this case because of crystallization at pH=2.3, but we suppose that there may be the following two great changes in inclusion phenomena in alkaline solution: 1) aspirin can be included in β-CyD with its benzene ring protruding from the secondary hydroxyl side. 2) the head-to-head dimeric structure of β-CyD will not be formed because of lack of hydrogen bonds among the hydroxyl groups of each β-CyD and this results in producing a lot of anionized secondary hydroxyl groups of β-CyD.

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