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X-Ray Structure and Thermal Analysis of a 1 : 1 Complex between Sulfathiazole and β-Cyclodextrin

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Abstract. An inclusion complex with the formula (β-cyclodextrin) (sulfathiazole) $8.3H_2O$ has been crystallized and characterized by physicochemical methods including single crystal X-ray analysis. The complex crystallizes in the monoclinic system, space group $P2_1$, with $a = 15.264(4)$, $b = 16.500(6)$, $c = 15.559(5)$ Å, $\beta = 117.29(3)°$ and $Z = 2$. The structure was solved using published co-ordinates for β-cyclodextrin in an isomorphous complex. Refinement by block-diagonal least-squares yielded $R = 0.061$ for 4706 unique observed reflections. Inclusion of sulfathiazole produces a slight ellipticity in the host conformation, but the guest adopts a conformation similar to that observed in its polymorphs. The guest is held in the macrocyclic cavity predominantly by hydrophobic forces, with the phenyl ring near the host primary hydroxyl side and the thiazole ring near the secondary hydroxyl side. The complex packs in layers parallel to the *ac*-plane. Layers are linked by hydrogen bonding to water molecules which are located outside the cyclodextrin cavity. An extensive network of hydrogen bonds mediated chiefly by water molecules stabilizes the crystal structure.

Key words: β-Cyclodextrin, sulfathiazole, inclusion complex, crystal structure, thermal analysis.

1. Introduction

The antibacterial sulfonamide, sulfathiazole (*N*-(2-thiazolyl)sulfanilamide), is a sparingly water-soluble drug which has been investigated on account of its ability to crystallize in a number of polymorphic forms [1, 2, 3]. Many drugs containing hydrophobic moieties have been complexed with β-cyclodextrin in an effort to increase their aqueous solubility [4, 5] and various studies have been carried out on the inclusion of sulfathiazole by β-cyclodextrin in aqueous media [6, 7, 8, 9]. These studies have reported proposals on the mode of inclusion, values of the stability constants as well as the stoichiometry in solution [7, 8, 9]. The stability constant for the β-cyclodextrin-sulfathiazole complex in solution is higher than those of other sulfonamide-β-cyclodextrin complexes [7, 8]. In view of the lack of structural data for such complexes [10], the aim of this work was to prepare a

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solid state complex between sulfathiazole and β-cyclodextrin, to characterize the complex by physicochemical methods and ultimately to determine the mode of inclusion by crystal structure solution.

2. Experimental

2.1. Materials

β-Cyclodextrin (Chinoin-Reanal, Budapest, Hungary) and sulfathiazole (Aldrich Chemical Company, Wisconsin, U.S.A.) were used as received.

2.2. Thermogravimetry and Differential Scanning Calorimetry

Thermogravimetric analysis (TGA) and differential scanning calorimetric traces (DSC) were recorded on a Perkin-Elmer PC7-series thermal analysis system in the range 30–300°C at a scanning rate of 5°C/min under N_2 gas. Sample masses were 10–11 mg. Samples were placed in vented pans.

2.3. Preparation of the Sulfathiazole-β-Cyclodextrin Complex

Crystals of the complex, which are prismatic and colorless, were prepared by stirring equimolar amounts of sulfathiazole and β-cyclodextrin in distilled water at 70°C and leaving at room temperature for 24 to 48 hours.

2.4. Crystal Structure Solution

Data were collected from a crystal of dimensions $0.28 \times 0.31 \times 0.41$ mm on an Enraf-Nonius CAD-4 diffractometer using graphite-monochromated Mo Kα radiation ($\lambda = 0.71069$ Å). Accurate cell dimensions were obtained by least-squares analysis of the setting angles of 24 reflections in the range $16 \leq \vartheta \leq 17°$. A final intensity acceptance limit of 20σ at 20° min^{-1} in ω was used with a maximum recording time of 40s per reflection. Data were collected to $(\sin \vartheta/\lambda)_{max} = 0.595$ $Å^{-1}$. Three standard reflections (−11,6,7 −5,1,12 −6,10,7), which were monitored every hour, showed no significant decrease in intensity during data collection. Orientation control was performed every 200 reflections. Data were corrected for Lp effects and for absorption. Azimuthal scans for nine reflections with χ near 90° were used for the latter and absorption corrections were from program EAC [11]. Crystal data collection and refinement details are listed in Table I. The structure was solved using published co-ordinates for the non-hydrogen cyclodextrin atoms (excluding the primary hydroxyl oxygens) of the isomorphous β-cyclodextrin-1,4-diazabicyclo[2.2.2]octane complex [12]. The y co-ordinate of atom C(1G1) was fixed and the resulting difference Fourier map revealed all but one of the non-hydrogen atoms of the guest and some of the primary hydroxyl oxygen atoms. The remaining non-hydrogen atoms, including those of eight water molecules,

TABLE I. Crystal data, experimental and refinement parameters for the title compound.

Molecular formula	$C_{42}H_{70}O_{35}.C_9H_9N_3S_2O_2.8.3H_2O$
M_r/g mol^{-1}	3080.9
Crystal system	Monoclinic
Space Group	$P2_1$
Z	2
a (Å)	15.264(4)
b (Å)	16.500(6)
c (Å)	15.559(5)
β (°)	117.29(3)
V (Å^3)	3483(2)
D_m	1.46(1) g cm^{-3}
D_x	1.469 g cm^{-3}
Crystal dimensions (mm)	0.28 × 0.31 × 0.41
Range scanned ϑ (°)	$1 \leq \vartheta \leq 25$
Index range	h 0,18; k 0,19; l −18,18
Scan width (°)	0.8 + 0.35 tan ϑ
Aperture width (mm)	1.12 + 1.05 tan ϑ
No. of reflections collected	6603
No. of unique reflections	5690
R_{int}	0.0813
No. of reflections with I > 2σ(I)	4706
No. of L.S. parameters	980
R	0.061
wR	0.061
w	$[\sigma^2(F_o) + 2.20 \times 10^{-4} F_o^2]^{-1}$
S	6.34
Shift/e.s.d. max., average	0.451, 0.003
$(\Delta\rho)_{max}$ final (eÅ^{-3})	0.38
$(\Delta\rho)_{min}$ final (eÅ^{-3})	−0.41
Absorption correction factor range	0.8903–0.9992

were located on subsequent difference Fourier maps during refinement by full-matrix least-squares techniques [13]. Many cyclodextrin hydrogen atoms were found and therefore all cyclodextrin hydrogen atoms linked to carbon atoms were inserted at idealized positions with C-H = 1.00 Å. All the hydrogen atoms of each glucose residue were assigned common isotropic temperature factors. At this stage all non-hydrogen atoms were assigned anisotropic temperature factors and further refinement was carried out by the block-diagonal least-squares method, ensuring adequate simultaneous refinement of different parts of the model. All of the cyclodextrin hydroxyl hydrogens except one were found and allowed to

TABLE II. Fractional atomic coordinates ($\times 10^4$) and equivalent isotropic thermal parameters ($Å^2 \times 10^3$) with e.s.d.s. in parentheses for the title compound.

	$U_{eq} = (1/3)\,\Sigma_i\,\Sigma_j\,U_{ij}a_i^*a_j^*a_i.a_j$			
Atom	x/a	y/b	z/c	U_{eq}
C(1G1)	3224(5)	2895(0)	−249(5)	28(3)
C(2G1)	2609(5)	3640(5)	−479(5)	29(3)
C(3G1)	1771(6)	3547(5)	−222(5)	29(3)
C(4G1)	1234(5)	2746(5)	−597(5)	26(3)
C(5G1)	1919(5)	2046(5)	−381(5)	26(3)
C(6G1)	1418(6)	1254(5)	−841(6)	37(4)
O(2G1)	3193(4)	4323(4)	13(4)	41(2)
O(3G1)	1139(4)	4215(4)	−546(5)	46(3)
O(4G1)	633(3)	2644(3)	−121(3)	30(2)
O(5G1)	2654(4)	2194(3)	−688(4)	29(2)
O(6G1)	840(4)	1333(4)	−1859(4)	45(3)
C(1G2)	6468(5)	2334(5)	3036(5)	31(3)
C(2G2)	6276(5)	3184(5)	2592(5)	31(3)
C(3G2)	5181(5)	3336(5)	2015(5)	32(3)
C(4G2)	4754(5)	2672(5)	1261(5)	27(3)
C(5G2)	4984(5)	1846(5)	1720(6)	34(3)
C(6G2)	4643(6)	1143(5)	1003(6)	41(4)
O(2G2)	6760(4)	3766(3)	3345(4)	37(2)
O(3G2)	5014(4)	4114(3)	1590(4)	42(2)
O(4G2)	3709(3)	2796(3)	769(3)	29(2)
O(5G2)	6030(4)	1755(3)	2294(3)	32(2)
O(6G2)	4985(4)	1211(4)	313(4)	45(3)
C(1G3)	6904(6)	1596(6)	6521(6)	42(4)
C(2G3)	7524(6)	2240(6)	6376(5)	39(4)
C(3G3)	7027(6)	2613(6)	5363(5)	35(3)
C(4G3)	6662(5)	1935(5)	4609(5)	32(3)
C(5G3)	6013(6)	1348(5)	4814(6)	39(4)
C(6G3)	5639(8)	648(6)	4134(7)	54(5)
O(2G3)	7781(4)	2859(5)	7079(4)	56(3)
O(3G3)	7729(4)	3106(4)	5256(4)	53(3)
O(4G3)	6066(4)	2295(3)	3693(3)	31(2)
O(5G3)	6600(4)	1018(4)	5766(4)	40(2)
O(6G3)	6399(7)	199(4)	4082(5)	72(5)
C(1G4)	4334(5)	1771(5)	7916(5)	28(3)
C(2G4)	5177(6)	2351(6)	8345(6)	39(4)
C(3G4)	5599(6)	2518(5)	7652(6)	37(4)
C(4G4)	5835(6)	1727(5)	7298(5)	33(3)
C(5G4)	4968(6)	1159(6)	6942(6)	39(4)
C(6G4)	5204(7)	325(6)	6727(8)	51(5)
O(2G4)	4851(4)	3078(4)	8597(4)	44(3)
O(3G4)	6455(4)	3001(4)	8120(5)	53(3)

TABLE II. Continued.

	$U_{eq} = (1/3)\,\Sigma_i\,\Sigma_j\,U_{ij}a_i^*a_j^*a_i.a_j$			
Atom	x/a	y/b	z/c	U_{eq}
O(4G4)	6095(4)	1961(4)	6562(4)	41(2)
O(5G4)	4629(4)	1049(4)	7639(4)	37(2)
O(6G4)	4324(6)	−143(4)	6190(5)	66(4)
C(1G5)	550(6)	2433(5)	5899(6)	28(3)
C(2G5)	1178(6)	3080(5)	6625(5)	29(3)
C(3G5)	2221(5)	3022(5)	6771(5)	26(3)
C(4G5)	2604(5)	2171(5)	7088(5)	24(3)
C(5G5)	1931(5)	1539(5)	6354(5)	26(3)
C(6G5)	2194(6)	672(5)	6657(6)	33(4)
O(2G5)	766(4)	3870(4)	6337(4)	38(2)
O(3G5)	2842(4)	3565(3)	7512(4)	34(2)
O(4G5)	3558(3)	2137(3)	7109(4)	26(2)
O(5G5)	932(4)	1650(3)	6227(4)	28(2)
O(6G5)	2148(4)	505(4)	7539(4)	35(2)
C(1G6)	−1392(5)	2794(5)	2089(5)	26(3)
C(2G6)	−1209(6)	3556(6)	2728(6)	34(3)
C(3G6)	−295(6)	3468(5)	3675(6)	32(3)
C(4G6)	−339(5)	2683(5)	4157(5)	29(3)
C(5G6)	−477(6)	1976(5)	3463(5)	31(3)
C(6G6)	−505(6)	1150(5)	3859(6)	30(3)
O(2G6)	−1136(4)	4245(4)	2200(4)	39(3)
O(3G6)	−228(5)	4114(4)	4313(4)	39(3)
O(4G6)	573(4)	2605(4)	5011(4)	32(2)
O(5G6)	−1386(4)	2098(3)	2603(4)	32(2)
O(6G6)	−1249(5)	1098(4)	4187(5)	49(3)
C(1G7)	−363(5)	2384(6)	−649(5)	35(3)
C(2G7)	−1020(6)	3078(6)	−705(6)	38(3)
C(3G7)	−832(6)	3321(5)	312(5)	31(3)
C(4G7)	−944(6)	2549(5)	804(6)	31(3)
C(5G7)	−294(6)	1864(5)	798(5)	33(3)
C(6G7)	−451(7)	1073(6)	1185(7)	48(5)
O(2G7)	−834(4)	3777(4)	−1155(4)	43(3)
O(3G7)	−1495(4)	3925(3)	287(4)	37(2)
O(4G7)	−649(3)	2760(3)	1793(3)	25(2)
O(5G7)	−510(4)	1710(3)	−201(4)	35(2)
O(6G7)	−1467(5)	832(4)	710(6)	61(4)
C(1)	3251(7)	2541(6)	3938(7)	45(4)
C(2)	2832(10)	2073(7)	4372(9)	71(7)
C(3)	2448(11)	1329(8)	4017(11)	85(9)
C(4)	2453(8)	1018(6)	3179(8)	54(5)
C(5)	2897(9)	1502(7)	2743(8)	65(6)
C(6)	3279(9)	2246(7)	3134(9)	63(6)

TABLE II. Continued.

Atom	$U_{eq} = (1/3)\,\Sigma_i\,\Sigma_j\,U_{ij}a_i^*a_j^*a_i.a_j$			
	x/a	y/b	z/c	U_{eq}
N(7)	2117(9)	271(6)	2825(9)	86(6)
S(8)	3744(2)	3490(2)	4406(2)	52(1)
O(9)	4323(5)	3723(5)	3932(6)	72(4)
O(10)	4265(7)	3446(5)	5422(6)	91(4)
N(11)	2836(6)	4082(5)	4168(5)	48(4)
C(12)	2317(7)	4374(6)	3323(6)	43(4)
N(13)	1531(6)	4863(5)	3065(5)	42(4)
C(14)	1052(7)	5143(7)	2142(7)	54(4)
C(15)	1449(8)	4886(9)	1599(7)	68(5)
S(16)	2465(2)	4256(2)	2264(2)	63(1)
O(1W)	3860(4)	50(4)	8974(4)	41(3)
O(2W)	9422(5)	530(4)	5965(5)	47(3)
O(3W)	7288(5)	185(4)	2927(5)	50(3)
O(4W)	6912(5)	669(4)	1065(5)	53(3)
O(5W)	3533(6)	−1262(7)	−85(7)	91(5)
O(6W)	823(7)	−944(8)	3145(8)	119(6)
O(7W)	2637(10)	46(8)	1188(8)	124(7)
O(8W)[a]	3765(12)	−951(10)	3345(15)	126(10)
O(9WA)[b]	4431(38)	−564(18)	2515(23)	162(26)
O(9WB)[b]	3818(30)	−659(31)	4245(35)	141(28)

[a] Site occupancy 0.7.
[b] Site occupancy 0.3.

refine subject to a distance constraint (O-H = 1.00 Å, σ = 0.05 Å). All the hydrogens attached to carbons on the guest were inserted at idealized positions and the hydrogens on the nitrogens were located and allowed to refine with a distance constraint (N-H = 1.00 Å, σ = 0.05 Å). All the hydrogen atoms of the guest were assigned a common temperature factor. Hydrogens on all the water molecules except O(8W) were also found and refined in a similar manner with a common fixed temperature factor (U_{iso} = 0.1 Å^2). Thermogravimetric analysis of the complex consistently gave a weight loss which corresponded to 8.3 water molecules. The isotropic temperature factor of O(8W) had been rather high prior to anisotropic refinement, indicating possible disorder and there were two additional peaks on the difference Fourier map of significantly higher electron density than the rest. These were therefore inserted as water molecules O(9WA) and O(9WB) and their site occupancy factors were refined along with that of O(8W). The site occupancy factors were 0.7, 0.3 and 0.3 for atoms O(8W), O(9WA) and O(9WB) respectively, giving a total of 8.3 water molecules in good agreement with the TGA results. Hydrogen atoms for these three water molecules of fractional site occupancy could not be located. Final fractional co-ordinates are given in Table II.

TABLE III. Average bond lengths (Å) and angles (°) with mean deviations for the seven glucose residues of β-cyclodextrin.

C(1)-C(2)	1.52±0.02	C(1)-C(2)-O(2)	110.2±1.3
C(1)-O(5)	1.41±0.01	C(1)-C(2)-C(3)	111.0±0.9
C(1)-O(4′)	1.41±0.01	C(3)-C(2)-O(2)	110.7±1.5
C(2)-C(3)	1.51±0.01	C(2)-C(3)-O(3)	110.0±0.8
C(2)-O(2)	1.43±0.01	C(2)-C(3)-C(4)	109.2±1.0
C(3)-C(4)	1.52±0.01	C(4)-C(3)-O(3)	110.3±1.5
C(3)-O(3)	1.41±0.01	C(3)-C(4)-O(4)	106.3±0.8
C(4)-C(5)	1.51±0.01	C(3)-C(4)-C(5)	111.2±1.0
C(4)-O(4)	1.43±0.01	C(5)-C(4)-O(4)	109.7±0.6
C(5)-C(6)	1.51±0.01	C(4)-C(5)-O(5)	109.3±1.5
C(5)-O(5)	1.44±0.01	C(4)-C(5)-C(6)	114.5±0.5
C(6)-O(6)	1.43±0.01	C(6)-C(5)-O(5)	106.6±0.8
O(5)-C(1)-O(4′)	110.5±0.8	C(5)-C(6)-O(6)	111.8±0.4
C(2)-C(1)-O(4′)	108.1±0.6	C(4)-O(4)-C(1′)	118.6±1.1
C(2)-C(1)-O(5)	110.8±0.9	C(1)-O(5)-C(5)	113.6±0.5

Bond lengths (Å) and angles (°) with e.s.d.s. for sulfathiazole.

C(1)-C(2)	1.36 (2)	C(1)-C(2)-C(3)	121 (1)
C(1)-C(6)	1.36 (2)	C(2)-C(3)-C(4)	122 (1)
C(1)-S(8)	1.75 (1)	C(3)-C(4)-N(7)	123 (1)
C(2)-C(3)	1.36 (2)	C(3)-C(4)-C(5)	117 (1)
C(3)-C(4)	1.40 (2)	C(5)-C(4)-N(7)	120 (1)
C(4)-C(5)	1.40 (2)	C(4)-C(5)-C(6)	119 (1)
C(4)-N(7)	1.35 (1)	C(1)-C(6)-C(5)	123 (1)
C(5)-C(6)	1.38 (2)	C(1)-S(8)-N(11)	107.0 (5)
S(8)-O(9)	1.44 (1)	C(1)-S(8)-O(10)	109.5 (5)
S(8)-O(10)	1.409(9)	C(1)-S(8)-O(9)	105.9 (5)
S(8)-N(11)	1.594(9)	O(10)-S(8)-N(11)	106.0 (5)
N(11)-C(12)	1.27 (1)	O(9)-S(8)-N(11)	112.8 (5)
C(12)-N(13)	1.35 (1)	O(9)-S(8)-O(10)	115.3 (6)
C(12)-S(16)	1.77 (1)	S(8)-N(11)-C(12)	122.2 (8)
N(13)-C(14)	1.36 (1)	N(11)-C(12)-S(16)	129.4 (8)
C(14)-C(15)	1.32 (2)	N(11)-C(12)-N(13)	125.4 (9)
C(15)-S(16)	1.76 (1)	N(13)-C(12)-S(16)	105.2 (7)
C(6)-C(1)-S(8)	121.0(9)	C(12)-N(13)-C(14)	119.5 (9)
C(2)-C(1)-S(8)	120.7(9)	N(13)-C(14)-C(15)	113 (1)
C(2)-C(1)-C(6)	118 (1)	C(14)-C(15)-S(16)	110.7 (8)
		C(12)-S(16)-C(15)	91.8 (6)

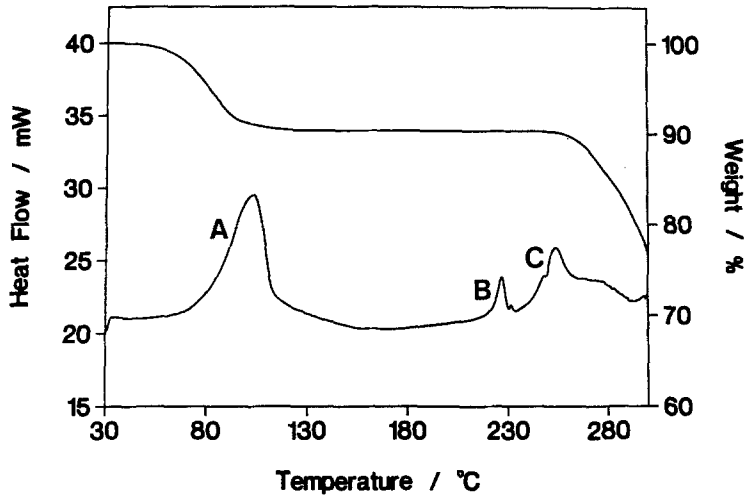

Fig. 1. TGA (upper) and DSC (lower) traces of the title compound.

3. Results and Discussion

3.1. Characterization of the Complex

TGA (Figure 1) of the complex shows a loss of 9.74 weight % from 35 to 120°C, corresponding to loss of 8.3 water molecules of crystallization for a 1 : 1 β-cyclodextrin-sulfathiazole complex, followed by onset of decomposition at about 250°C. The DSC trace (Figure 1) shows three endothermic peaks labelled A, B and C with onset temperatures of 82, 223 and 249°C respectively. A is associated with loss of water (385–412 kJ/mol for three scans) while B and C correspond to a phase change of the dehydrated complex followed by melting with concomitant decomposition.

3.2. Crystal Structure Solution

Numbering schemes for the host and guest are given in Figures 2(a) and 2(b) respectively. The sulfathiazole molecule, present as the imido tautomer (with atom N(13) protonated, rather than N(11)), is almost completely included in the cyclodextrin cavity with the phenyl ring near the primary hydroxyl side and the thiazole ring near the wider secondary hydroxyl side as shown in the stereo view (Figure 3). All seven α-D-glucose moieties of the β-cyclodextrin are in the $^4C_1$ chair conformation. Average bond lengths and angles are given in Table III. The primary hydroxyl groups are in the (−)-gauche conformation [16] except for that of the G4 residue which is in the (+)-gauche conformation, owing to hydrogen bonding from O(2G2) to O(6G4). Furthermore, O(6G4) is within hydrogen bonding distance of O(9WB).

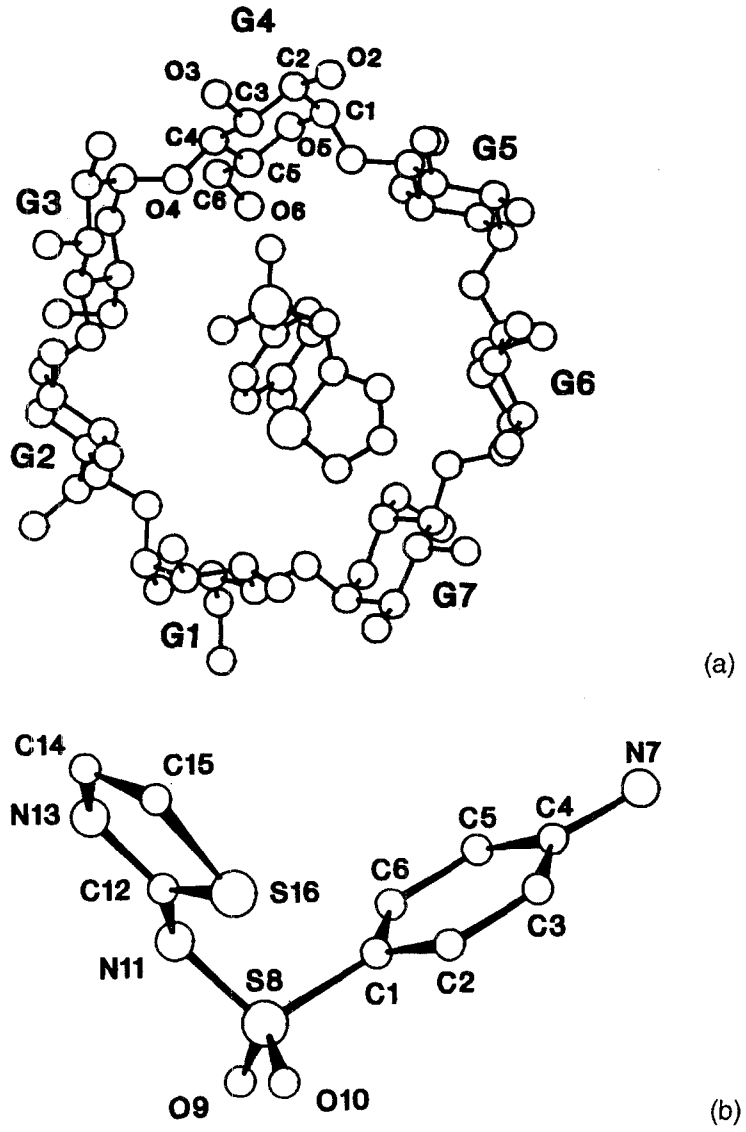

Fig. 2. Numbering schemes for (a) the host, and (b) the guest.

The conformation of the macrocycle is maintained by intramolecular O(2)-H...O(3) and O(3)-H...O(2) hydrogen bonds as in β-cyclodextrin undecahydrate [17] and other β-cyclodextrin complexes [16]. However, O(2G3) and O(3G4) are 3.1 Å apart compared with a range of 2.75–2.85 Å for all the other O(2)...O(3) distances. This is due to the relatively large tilt angles of G3 and G4 with their secondary hydroxyl groups inclined away from the cavity. The G7 residue also has a relatively large tilt angle with its secondary hydroxyl groups inclined away

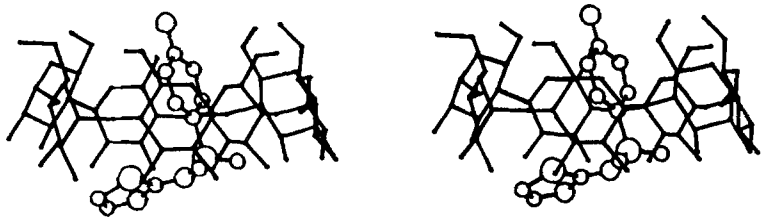

Fig. 3. Stereo drawing of the title compound viewed perpendicular to the *b*-axis (water molecules omitted).

from the cavity. The large tilt angles of these glucose residues are explained by the elliptical distortion of the cyclodextrin induced by complexation with sulfathiazole.

Table IV lists values for the O(4)...O(4′)...O(4″) angles of the O(4) heptagon, radii of the O(4) heptagon, O(4)...O(4′) distances, tilt angles and torsion angle indices. The maximum deviation from the least-squares plane through the O(4) atoms is 0.300(5) Å. Comparison of radii, O4...O4′ distances and tilt angles of the β-cyclodextrin-sulfathiazole complex with those of the isomorphous β-cyclodextrin-1,4-diazabicyclo[2.2.2]octane complex [12] shows that the β-cyclodextrin is relatively more distorted by sulfathiazole as guest because the radii and O(4)...O(4′) distances are spread over larger ranges and the tilt angles are larger.

The sulfathiazole molecule is held in the cavity primarily by hydrophobic forces, but also by a weak C-H...O interaction between C(15) and O(3G1). This type of C-H...O interaction has also been reported in a sulfathiazole-crown ether-acetonitrile complex [18]. There is another C-H...O interaction between C(14) and O(6G1) of a neighbouring cyclodextrin molecule as well as an O-H...N hydrogen bond between O(6G3) of another neighbouring cyclodextrin molecule and N(11). The latter two interactions thus contribute to the stabilization of the crystal packing rather than to the stability of the complex. A third C-H...O hydrogen bond is present between C(5) and O(7W). This particular type of hydrogen bond occurs frequently and its significance has been discussed by Steiner and Saenger [19]. The remaining two nitrogen atoms of the guest are also hydrogen bonded to water molecules. These interactions between guest and host/water molecules are listed in Table V.

The conformation of the sulfathiazole molecule is defined completely by three torsion angles, namely C(6)-C(1)-S(8)-N(11), C(1)-S(8)-N(11)-C(12) and S(8)-N(11)-C(12)-S(16). The values for these torsion angles are 108(1)°, −76(1)° and −3(1.5)° respectively and they have been compared with the corresponding torsion angles in sulfathiazole polymorphs I, II and III as well as in the sulfathiazole-crown ether-acetonitrile complex [1, 2, 18]. The conformation of the sulfathiazole molecule in the title compound is closest to that observed in the sulfathiazole-crown ether-acetonitrile complex for which the corresponding torsion angles are 122°, −85° and −5° (e.s.d.s. ≤ 1°). From the comparison of these torsion angles in all of the above structures, there appears to be a preferred narrow range for each torsion

TABLE IV. Geometrical data for β-cyclodextrin.

(i) O(4)...O(4′)...O(4″) angle (°) and radii (Å) of the O(4) heptagon (measured from the centre of gravity of seven O(4) atoms to each O(4) atom).

O(4G7)...O(4G1)...O(4G2)	124.3	G1	5.14
O(4G1)...O(4G2)...O(4G3)	125.8	G2	5.08
O(4G2)...O(4G3)...O(4G4)	133.1	G3	4.81
O(4G3)...O(4G4)...O(4G5)	125.9	G4	5.09
O(4G4)...O(4G5)...O(4G6)	126.5	G5	5.17
O(4G5)...O(4G6)...O(4G7)	127.9	G6	4.97
O(4G6)...O(4G7)...O(4G1)	133.8	G7	4.79
Average	128.2	Average	5.01

O(4)...O(4′) distances (Å).

O(4G1)...O(4G2)	4.25	O(4G5)...O(4G6)	4.29
O(4G2)...O(4G3)	4.40	O(4G6)...O(4G7)	4.48
O(4G3)...O(4G4)	4.48	O(4G7)...O(4G1)	4.25
O(4G4)...O(4G5)	4.34	Average	4.36

Tilt angles (°) and torsion angle indices (°).

Residue	Tilt-angle	Torsion-angle index
G1	8.3	122.5
G2	3.9	119.7
G3	25.7	112.9
G4	19.6	125.1
G5	7.0	114.1
G6	3.0	110.7
G7	26.1	121.6
Average	13.4	118.1

[a] The tilt angle is defined as the angle between the O(4) plane and the plane through C(1), C(4), O(4) and O(4′) of each glucose residue [14].

[b] The torsion-angle index is defined as: $|\varphi(C(1)\text{-}C(2))| + |\varphi(C(2)\text{-}C(3))| - |\varphi(C(3)\text{-}C(4))| - |\varphi(C(4)\text{-}C(5))| + |\varphi C(5)\text{-}O(5))| + |\varphi(O(5)\text{-}C(1))|$, where $\varphi(C(1)\text{-}C(2))$ is the torsion angle O(5)-C(1)-C(2)-C(3) [15].

angle. Therefore, the conformation adopted by the sulfathiazole is presumably one of relatively low energy which must contribute to the high stability constant of the complex.

TABLE V. Guest-host/water interactions.

			Distance (Å)			Angle (°)
X[a]---H	X		X-H	H...X	X...X	X-H...X
C(15)-H(15)	O(3G1)	(a)	1.00	2.58	3.34(1)	132
C(5)-H(5)	O(7W)	(a)	1.00	2.48	3.30(2)	139
N(7)-H(72)	O(6W)	(a)	1.02	2.04	3.01(2)	157
N(7)-H(71)	O(7W)	(a)	1.01	2.09	3.02(2)	152
N(13)-H(13)	O(2W)	(b)	1.00	1.81	2.76(1)	158
O(6G3)-H(63O)	N(11)	(c)	1.00	2.14	3.04(1)	150
C(14)-H(14)	O(6G1)	(d)	1.00	2.39	3.35(1)	162
O(8W)	N(7)	(a)			3.03(2)	
O(9WB)	N(7)	(a)			2.95(4)	
O(8W)	O(10)	(c)			2.91(2)	

Equivalent positions

(a) x,	y,	z	
(b) $-x+1$,	$y+1/2$,	$-z+1$	
(c) $-x+1$,	$y-1/2$,	$-z+1$	
(d) $-x$,	$y+1/2$,	$-z$	

[a] X = C, O, or N.

All 8.3 water molecules are located outside the cyclodextrin cavity. Crystal stabilization is achieved by extensive hydrogen bonding mediated chiefly by these water molecules. There are also intramolecular and intermolecular hydrogen bonds involving the hydroxyl groups of the cyclodextrin moieties (Table VI). Seven water molecules are ordered and the remaining 1.3 water molecules are disordered over three sites with fractional occupancies of 0.7, 0.3 and 0.3.

The complex packs in layers parallel to the *ac* plane and the layers are linked by water molecules. Packing diagrams are shown in Figures 4(a) and 4(b). The molecular axis of the β-cyclodextrin makes an angle of 7° with the *b*-axis and therefore molecules in successive layers, related by the twofold screw axis, are not in parallel orientation. This is an unusual packing arrangement for a β-cyclodextrin complex. Only one other similar structure is known, namely that of the β-cyclodextrin-1,4-diazabicyclo[2.2.2]octane complex [12].

Uekama *et al.* concluded from their circular dichroism, U.V. and N.M.R. studies [6, 7] that the interaction between sulfathiazole and β-cyclodextrin is predominantly hydrophobic, that the phenyl ring is inserted in the cyclodextrin cavity and that the stoichiometry is 1 : 1. Furthermore, they proposed that there may be hydrogen bonding between the amino group of sulfathiazole and some part of the cyclodextrin molecule. Their results are consistent with what is reported here. However, in the solid state the amino group of the sulfathiazole is hydrogen bonded to water

TABLE VI. Hydrogen bonding data.

			Distance (Å)			Angle (°)
O---H	O		O-H	H...O	O...O	O-H...O
O(3G1)-H(31O)	O(2G7)	(a)	1.00	1.85	2.806(8)	158
O(3G2)-H(32O)	O(2G1)	(a)	1.00	1.77	2.758(7)	171
O(6G2)-H(62O)	O(4W)	(a)	1.00	1.77	2.770(9)	173
O(3G3)-H(33O)	O(2G2)	(a)	0.99	1.99	2.862(8)	146
O(2G4)-H(24O)	O(3G5)	(a)	0.99	1.91	2.856(7)	158
O(2G5)-H(25O)	O(3G6)	(a)	1.00	1.87	2.828(8)	159
O(6G5)-H(65O)	O(1W)	(a)	1.00	1.66	2.651(7)	170
O(3G7)-H(37O)	O(2G6)	(a)	1.00	2.12	2.818(9)	126
O(3W)-H(1W3)	O(4W)	(a)	1.00	1.84	2.80 (1)	161
O(3W)-H(2W3)	O(6G3)	(a)	1.00	1.8	2.70 (1)	142
O(7W)-H(2W7)	O(9WA)	(a)	1.00	2.0	2.76 (4)	133
O(6G1)-H(61O)	O(6G5)	(b)	1.00	2.07	2.91 (1)	140
O(2G3)-H(23O)	O(8W)	(c)	1.00	2.26	2.90 (2)	121
O(3G6)-H(36O)	O(2W)	(c)	0.99	1.82	2.77 (1)	159
O(3G4)-H(34O)	O(8W)	(c)	1.00	2.08	2.76 (2)	123
O(3G4)-H(34O)	O(9WA)	(c)	1.00	1.73	2.68 (3)	157
O(2G2)-H(22O)	O(6G4)	(c)	1.00	1.85	2.76 (1)	148
O(3G5)-H(35O)	O(3W)	(c)	0.99	1.77	2.742(8)	165
O(6W)-H(2W6)	O(3G3)	(d)	1.00	2.01	2.91 (1)	149
O(6G6)-H(66O)	O(3W)	(e)	1.00	1.66	2.662(9)	178
O(2G7)-H(27O)	O(2G3)	(f)	1.00	2.15	2.998(8)	141
O(7W)-H(1W7)	O(3G7)	(g)	1.00	2.00	2.84 (1)	140
O(6G7)-H(67O)	O(3G1)	(g)	1.00	1.80	2.75 (1)	157
O(5W)-H(1W5)	O(3G7)	(g)	1.00	2.14	3.00 (1)	143
O(1W)-H(2W1)	O(5W)	(h)	1.00	2.1	2.78 (1)	124
O(4W)-H(1W4)	O(6G7)	(i)	1.00	1.9	2.78 (1)	153
O(9WB)	O(6G4)	(a)			2.89 (5)	
O(2G6)	O(6G5)	(j)			2.73 (1)	

Equivalent positions

(a) x,	y,	z
(b) $-x+1$,	$y+1/2$,	$-z+1$
(c) $-x+1$,	$y-1/2$,	$-z+1$
(d) $x+1$,	y,	z
(e) $x-1$,	y,	z
(f) $x-1$,	y,	$z-1$
(g) $-x$,	$y-1/2$,	$-z$
(h) x,	y,	$z+1$
(i) $x+1$,	y,	z
(j) $-x$,	$y+1/2$,	$-z+1$

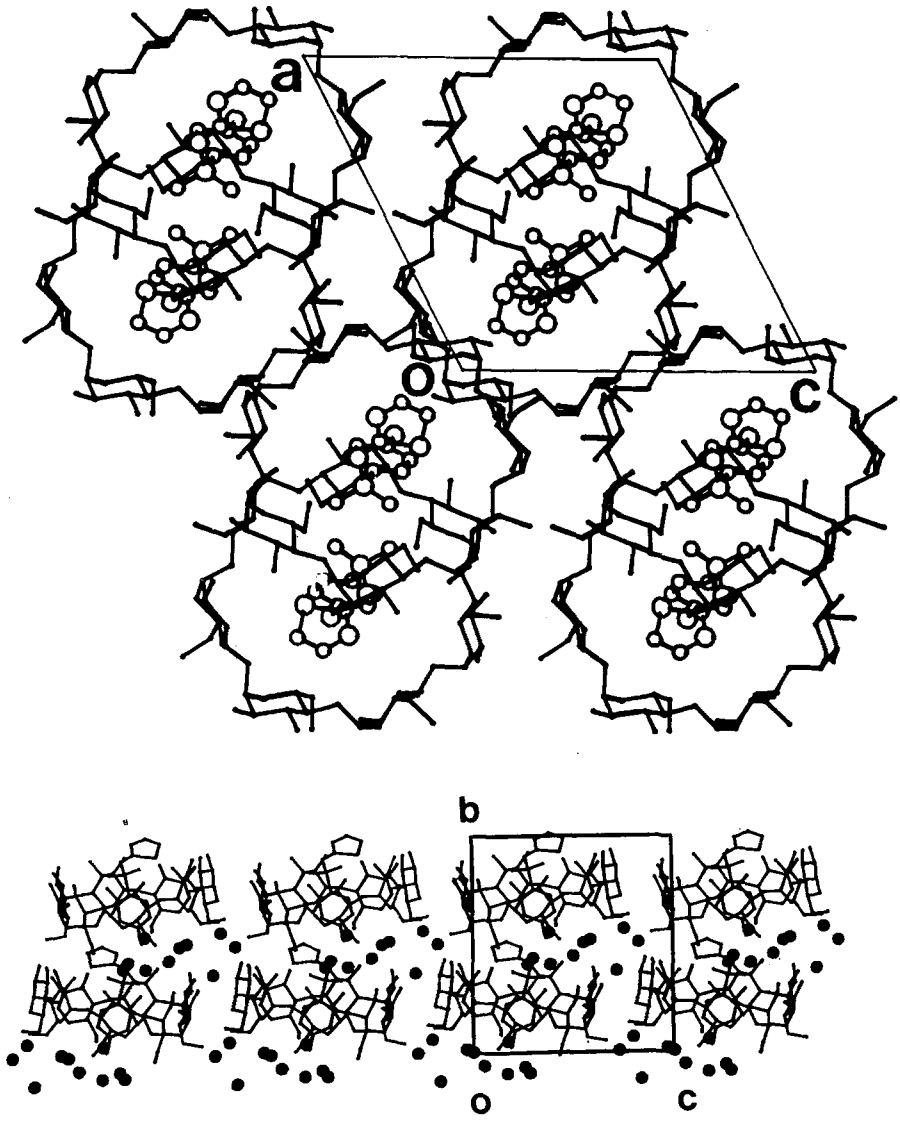

Fig. 4. Packing diagram of the title compound (a) viewed along [010] (water molecules omitted), and (b) viewed perpendicular to the *bc*-plane.

molecules and there are also some guest-host/water hydrogen bonds which may either be too transient or not present in solution.

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