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X-RAY STRUCTURAL INVESTIGATION OF GOSSYPOL AND ITS DERIVATIVES XXIII AUTOCLATHRATES BASED ON A MIXED GOSSYPOL–1,4-DIOXANE MATRIX

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Gossypol forms various complexes with the isomeric dioxanes. The clathrate with 1,4-dioxane is the only complex of gossypol in which the intrinsic symmetry of the gossypol molecule — the symmetry of a twofold axis — is retained. In this complex, two out of the three 1,4-dioxane molecules belonging to each gossypol molecule participate in the construction of a mixed H-bound gossypol–dioxane matrix, while the third molecule plays the part of guest, the guest molecules having no H-bonds with the host matrix and undergoing desolvation at 108-110°C.

As already reported in preceding papers of the present series, gossypol readily forms clathrates with all the 110 organic substances tested [1, 2]. These substances are representatives of acids, alcohols, ketones, ethers, esters, etc. [3] We have shown that gossypol strictly distinguishes hydrophilic guest molecules from hydrophobic ones, forming with them H-clathrates and ordinary clathrates, respectively [4]. In ordinary clathrates, the structure is very sensitive to the geometry (form and dimensions) of the guest molecules — slight changes in the geometry of the guest molecule may cause a morphotropic transition. In the H-clathrates of gossypol, the structure is determined primarily by the chemical nature of the hydrophilic guest molecule (by the localization of the proton-donating and proton-accepting groups in the molecule and their type) and only after this by geometry. In view of this, we were interested in constructing clathrates of two isomers of dioxane, since the 1,3- and 1,4-dioxane molecules have very close geometries but differ by the mutual positions of the two oxygen atoms, which act as proton-acceptors in intermolecular hydrogen bonds.

The results of the investigations performed showed that with the dioxane isomers gossypol forms clathrates differing substantially in composition and in crystal structure In the H-clathrates with the symmetrical dioxane isomer, the crystals of which belong to the rhombic system and space group Pbcn (this is the only example of this type), there is 0.5 of a gossypol molecule in the independent part of the unit cell (Table 1). This means that the intrinsic symmetry of the host molecule — the symmetry of a twofold axis — is retained in the crystal. In the complex, to each molecule of gossypol there are three molecules of 1,4-dioxane While the clathrate of gossypol with the symmetrical dioxane isomer is the most symmetrical among gossypol clathrates, the unsymmetrical isomer gives with gossypol clathrates belonging to the lowest symmetry group — triclinic. In the independent part of the unit cell there are two gossypol molecules The ratio of gossypol and 1,3-dioxane is 1:1.

Of the two clathrates of gossypol, with the symmetrical and unsymmetrical dioxanes, the complex with 1,4-dioxane has been interpreted completely by x-ray structural analysis In it the dihedral angle between two naphthyl nuclei of the gossypol molecule is 88.8°. The geometry of the intramolecular H-bonds forming five-membered (C6C7O3HO4) and six-membered (C7C8C22O2HO3) rings differ little from the geometry in gossypol complexes interpreted previously (Fig. 1).

The values of the bond lengths and valence angles (Table 2) also agree within the 3σ limits with those found in preceding gossypol clathrates [2-7].

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TABLE 1. Crystallographic Characteristics of Clathrates of Gossypol with Dioxane Isomers

Parameters	Guest	
	1,4-dioxane	1,3-dioxane
a]	25.459(9)	12.149(4)
b } Å	11.923(3)	14.310(3)
c]	13.608(2)	18.687(3)
α]	90	91.08(2)
β } deg	90	94.16(2)
γ]	90	94.94(2)
V, Å^3	4130	3227
sp.gr.	Pbcn	$P\bar{1}$
Z*	4	4
ρ, g/cm^3	1.26	1.25

*Z — No. of molecules of gossypol in the cell.

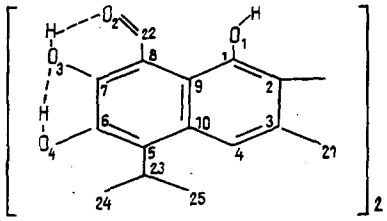

Fig. 1. The gossypol molecule.

In the structure, one of the two crystallographically independent 1,4-dioxane molecules occupies a common system of equivalent positions, while the other is located on a twofold axis As already mentioned, the gossypol molecule is located on the same symmetry element (Fig. 2) Two thirds of the 1,4-dioxane molecules participate in the construction of the gossypol–dioxane matrix. With the aid of H-bonds, in which they act as fairly strong proton-acceptors (Table 3), these molecules unite the gossypol molecule into a two-dimensional subsystem parallel to the *ac* plane. In this system, each gossypol molecule has H-bonds with four 1,4-dioxane molecules, and each dioxane molecule has H-bonds with two gosypol molecules In the packing of such subsystems bonds are formed between them which are joined into channels extending in the direction of the *z* axis. The narrowest part is formed between two 1,4-dioxane molecules and two aldehyde groups of gossypol molecules, which are linked by the twofold axis. The widest section of the channel is located between the isopropyl and methyl groups of a gossypol molecule also linked by a twofold axis. It is just here that the 1,4-dioxane molecules acting as guests are located

Thus, the 1,4-dioxane molecules take part both in the construction of the host matrix and also as guests. This gossypol complex is therefore an autoclathrate based on a mixed host matrix Gossypol behaves similarly to trimesic acid, giving, together with ordinary clathrate compounds, inclusions [8], autoclathrates [9], and autoclathrates based on a mixed host matrix [10]

The 1,4-dioxane molecules are located in channels and have a hydrophobic environment, as a result of which the formation of host–guest H-bonds is impossible. The 1,4-dioxane molecules therefore have no rigidly fixed orientation. It has been possible to find the two orientations shown in Fig. 2. The channel structure of this clathrate agrees well with the results of thermomicroscopic investigations, according to which voluminous drops of liquid are formed on two opposite faces of the crystals at 108-110°C that disappear (evaporate) with a further rise in the temperature.

The positions of the 1,4-dioxane molecules in the channels can be occupied by other molecules of suitable size and shape. We have obtained clathrates based on a gossypol–dioxane matrix containing as host components cyclohexane with a small amount of 1,4-dioxane. This permits the statement that a gossypol–dioxane matrix forms the basis of a new family of clathrates based on it.

TABLE 2. Interatomic Distances (r, Å) and Valence Angles (ω, degrees) in the Structure of the Complex of Gossypol with 1,4-Dioxane

Bond	r	Bond	r
C(1)—C(2)	1.353(7)	C(6)—C(7)	1.42(2)
C(1)—C(9)	1.43(2)	C(6)—O(4)	1.35(1)
C(1)—O(1)	1.36(1)	C(7)—C(8)	1.39(2)
C(2)—C(3)	1.41(2)	C(7)—O(3)	1.35(2)
C(3)—C(4)	1.35(2)	C(8)—C(9)	1.46(2)
C(3)—C(21)	1.50(2)	C(8)—C(22)	1.44(2)
C(4)—C(10)	1.42(2)	C(9)—C(10)	1.42(2)
C(5)—C(6)	1.37(2)	C(22)—O(2)	1.22(2)
C(5)—C(10)	1.46(2)	C(23)—C(24)	1.53(2)
C(5)—C(23)	1.49(2)	C(23)—C(25)	1.48(2)
C(1A)—C(2A)	1.437(12)	C(1B)—O(2B)	1.483(31)
C(1A)—O(6A)	1.441(11)	C(1B)—C(6B)	1.483(33)
C(2A)—O(3A)	1.420(11)	O(2B)—C(3B)	1.480(33)
O(3A)—C(4A)	1.419(10)	C(3B)—C(4B)	1.481(31)
C(4A)—C(5A)	1.425(12)	C(4B)—O(5B)	1.477(27)
C(5A)—O(6A)	1.404(12)	C(6B)—O(5B)	1.478(27)

Angle	ω	Angle	ω
C(2)—C(1)—C(9)	123.0(5)	C(2)—C(1)—O(1)	120.3(9)
C(9)—C(1)—O(1)	115.4(5)	C(1)—C(2)—C(3)	119.3(6)
C(1)—C(2)—C(12)	117.9(10)	C(3)—C(2)—C(12)	122.4(10)
C(2)—C(3)—C(4)	119.4(5)	C(2)—C(3)—C(21)	119.9(6)
C(4)—C(3)—C(21)	120.7(6)	C(3)—C(4)—C(10)	122.6(6)
C(6)—C(5)—C(10)	118.6(5)	C(6)—C(5)—C(23)	120.3(6)
C(10)—C(5)—C(23)	121.2(5)	C(5)—C(6)—C(7)	121.5(6)
C(5)—C(6)—O(4)	120.7(5)	C(7)—C(6)—O(4)	117.8(5)
C(6)—C(7)—C(8)	121.9(5)	C(6)—C(7)—O(3)	115.7(6)
C(8)—C(7)—O(3)	122.3(6)	C(7)—C(8)—C(9)	117.1(6)
C(7)—C(8)—C(22)	117.6(6)	C(9)—C(8)—C(22)	125.1(6)
C(1)—C(9)—C(8)	123.5(6)	C(1)—C(9)—C(10)	116.6(5)
C(8)—C(9)—C(10)	119.6(6)	C(4)—C(10)—C(5)	120.6(5)
C(4)—C(10)—C(9)	119.0(6)	C(5)—C(10)—C(9)	120.4(5)
C(12)—C(11)—C(19)	124.0(10)		
C(8)—C(22)—O(2)	122.8(7)	C(5)—C(23)—C(24)	113.9(5)
C(5)—C(23)—C(25)	111.6(6)	C(24)—C(23)—C(25)	111.6(7)
C(2A)—C(1A)—O(6A)	107.3(8)	O(2B)—C(1B)—C(6B)	108.5(6)
C(1A)—C(2A)—O(3A)	110.2(8)	C(1B)—O(2B)—C(3B)	108.9(5)
C(2A)—O(3A)—C(4A)	107.5(7)	O(2B)—C(3B)—C(4B)	108.7(6)
O(3A)—C(4A)—C(5A)	109.4(8)	C(3B)—C(4B)—O(5B)	108.8(7)
C(4A)—C(5A)—O(6A)	111.0(8)	C(1B)—C(6B)—O(5B)	108.9(7)
C(1A)—O(6A)—C(5A)	108.9(7)	C(4B)—O(5B)—C(6B)	109.6(5)

TABLE 3. Intermolecular H-Bonds in the Complex of Gossypol with 1,4-Dioxane*

Bond	Distance, Å			O-H...O angle, deg.
	O...O	O-H	H...O	
O1—H...O1D[i]	2.721	0.87	2.09	129
O4—H...O2D[ii]	2.721	0.86	1.96	147

*D — symbol for a 1,4-dioxane molecule.
Symmetry codes: i) −x; y; 0.5 −z; ii) 0.5 −x; 0.5−y; z−0.5.

TABLE 4. Coordinates ($\times 10^4$) and Equivalent Isotropic Thermal Parameters U of the Atoms of the Complex of Gossypol 1,4-Dioxane

Atom	*x*	*y*	*z*	*U*
C 1	0544(1)	3900(4)	1844(3)	042(1)
C 2	0296(1)	4602(4)	2473(4)	044(1)
C 3	0593(2)	5355(4)	3034(4)	051(1)
C 4	1127(1)	5369(4)	2935(4)	047(2)
C 5	1957(1)	4716(4)	2200(3)	044(1)
C 6	2192(1)	4132(4)	1462(4)	050(2)
C 7	1906(2)	3372(4)	0867(4)	053(2)
C 8	1372(1)	3170(4)	1015(3)	044(1)
C 9	1103(1)	3874(4)	1731(3)	040(1)
C 10	1394(1)	4657(4)	2292(3)	039(1)
C 21	0321(2)	6136(6)	3745(5)	089(2)
C 22	1143(2)	2234(5)	0519(5)	069(2)
C 23	2289(2)	5395(4)	2928(4)	060(2)
C 24	2712(2)	4717(6)	3435(6)	091(3)
C 25	2513(3)	6455(5)	2453(8)	112(4)
O 1	0267(1)	3174(3)	1245(2)	061(1)
O 2	1378(1)	1700(4)	-0137(3)	095(2)
O 3	2188(1)	2812(3)	0196(3)	075(1)
O 4	2717(1)	4241(3)	1289(3)	071(1)
C 1A	1191(3)	1428(7)	4722(8)	140(4)
C 2A	0700(2)	1976(7)	4925(8)	143(5)
O 3A	0709(1)	3093(4)	4562(4)	107(2)
C 4A	1109(3)	3679(7)	5077(6)	110(3)
C 5A	1602(2)	3148(8)	4909(7)	124(4)
O 6A	1595(1)	2034(5)	5242(4)	122(2)
C 1B	5256(6)	4325(21)	2791(17)	461(33)
O 2B	4803(11)	4389(14)	3472(9)	286(10)
C 3B	4315(8)	4172(15)	2913(17)	252(12)
C 4B	4254(5)	5058(16)	2159(18)	250(12)
C 5B	4707(8)	5011(12)	1481(9)	223(7)
C 6B	5197(6)	5213(19)	2035(16)	329(21)
O 5B	4707(8)	5011(12)	1481(9)	223(7)
H 4	1351(8)	5960(8)	3367(7)	045(31)
H 211	0234(8)	5798(8)	4239(7)	178(30)
H 212	0471(8)	6891(7)	3089(6)	151(25)

TABLE 4. (Continued)

Atom	x	y	z	U
H 213	0076(7)	6572(7)	3405(6)	180(24)
H 22	0751(8)	1972(7)	0747(6)	030(28)
H 23	2020(8)	5650(7)	3497(6)	103(26)
H 241	2847(8)	5349(8)	4051(7)	036(29)
H 242	3047(12)	4649(12)	2990(10)	025(52)
H 243	2575(11)	3838(11)	3686(9)	022(46)
H 251	2180(9)	6981(9)	2285(8)	152(37)
H 252	2665(8)	6476(7)	1720(6)	146(26)
H 253	2677(9)	7011(9)	3141(7)	187(34)
H 10	-0052(7)	3419(6)	1310(5)	129(22)
H 30	1499(8)	2518(8)	-0959(7)	055(31)
H 40	2839(13)	3647(12)	1012(11)	044(58)
H 11A	1171(11)	5581(10)	4960(9)	163(43)
H 12A	1268(13)	1467(12)	3938(10)	157(56)
H 21A	0634(12)	1997(12)	5700(10)	145(52)
H 22A	0387(11)	1528(11)	4562(9)	112(46)
H 41A	1121(13)	4528(12)	4826(10)	100(55)
H 42A	1016(14)	3656(12)	5854(11)	097(60)
H 51A	1903(17)	3599(17)	5295(16)	107(24)
H 52A	1684(17)	3144(17)	4131(17)	153(26)
H 11B	5271(18)	3596(17)	2479(16)	188(24)
H 12B	5580(13)	4409(12)	3163(11)	221(56)
H 31B	4018(10)	4171(10)	3323(8)	217(41)
H 32B	4337(13)	3451(11)	2578(10)	139(49)
H 41B	4248(17)	5784(17)	2466(17)	093(26)
H 42B	3947(12)	4961(13)	1780(12)	215(32)
H 51B	5507(13)	5215(14)	1625(13)	106(27)
H 52B	5192(16)	5935(15)	2375(16)	117(29)

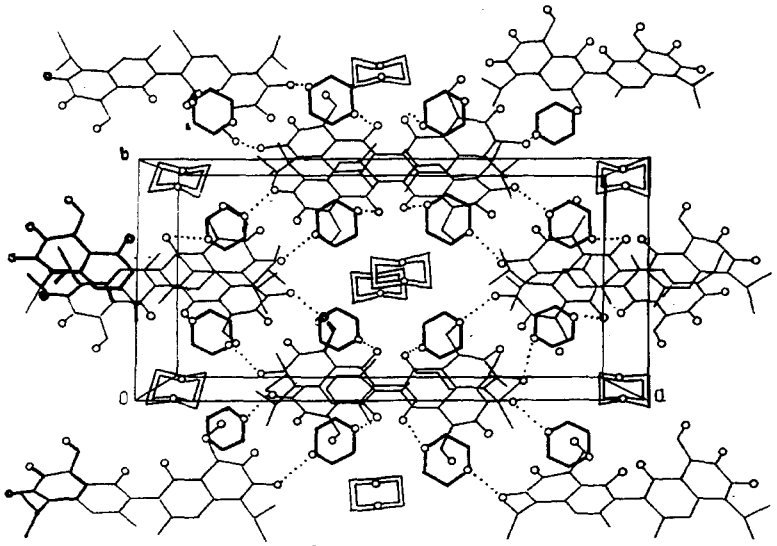

Fig. 2. Crystal structure of the complex of gossypol with 1,4-dioxane.

EXPERIMENTAL

Single crystals were grown from solutions of gossypol in the corresponding dioxane isomers. The parameters of the unit cells and the space groups were determined and refined on a Syntex $P2_1$ automatic four-circle diffractometer To measure the intensities of the reflections from a crystal of the complex of gossypol with 1,4-dioxane we used CuK_α radiation monochromatized by reflection from a graphite crystal $\theta/2\theta$ scanning up to an angle $2\theta \leq 110°$ was used with a variable rate of 4.8-12.2 deg/min. A primary treatment of the experimental group was carried out for polarization and Lorentz factors, but absorption was not taken into account in view of the absence of heavy atoms from the structure. The calculations made use of 1610 reflections.

The crystal structure was interpreted by the direct method of the MULTAN-80 programm [11] and was refined by the programs of the SHELX-76 group [12] first in the isotropic and then in the anisotropic approximation. Hydrogen atoms were found by electron-density difference syntheses. The final R factor was 0.068. The coordinates of the atoms corresponding to this value of the discrepancy factor are given in Table 4 The thermomicroscopic investigations were carried on a Boetius instrument [13]

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