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Polymorphism of crystalline inclusion complexes and unsolvated hosts. VII. Pseudodimorphism of the inclusion complex between gossypol and 1,4-dioxane and structure of the β-phase complex. Four different H-bonds possible in the gossypol molecule

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Abstract. A new β-phase inclusion complex between gossypol and 1,4-dioxane is obtained at 40 °C and its crystal structure determined. Crystal data are: $C_{30}H_{30}O_8.C_4H_8O_2$, triclinic, $P\bar{1}$, a = 10.905(2) Å, b = 11.055(2) Å, c = 13.772(3) Å, α = 107.07(3) °, β = 96.72(3) °, γ = 98.68(3) °, V = 1546.53 Å^3, Z = 2, R = 0.062. Two possible intramolecular hydrogen bonds of the C—H···O type along with two known H-bonds of the O—H···O type are described for the gossypol molecule for the first time. One of the two isopropyl groups of the gossypol molecule is disordered in three positions. Centrosymmetric dimers typical for many crystal modifications of gossypol are associated into infinite columns by the two H-bonds of the 1,4-dioxane molecule. The packing of these columns gives rise to the stable channel type structure of the β-phase complex.

Key words: gossypol, dioxane, inclusion complexes, crystal structure, X-ray crystallography.

Supplementary Data relating to this article are deposited with the British Library as supplementary publication No. 82239 (17 pages)

1. Introduction

Gossypol is a versatile host molecule readily giving inclusion complexes with substances relating practically to all types of organic compounds [1–3]. Moreover, it is able to form different inclusion complexes with the same guest under various conditions. For example, the gossypol host-guest complex with dichloromethane is trimorphic [4] while diethyl ether forms with gossypol two different clathrates [5]. Gossypol gives with unsymmetric (1,3-dioxane) and symmetric (1,4-dioxane) dioxanes different inclusion complexes having 1 : 1 [6] and 1 : 3 [7] host-guest ratios, respectively. The gossypol host-guest complex with 1,4-dioxane crystallizes

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in space group Pbca the highest among the known clathrates of gossypol. Two of the three 1,4-dioxane molecules incorporate gossypol molecules into layers by H-bonds in which both 1,4-dioxane oxygen atoms participate. The third solvent molecule is located without H-bonding in channels formed during stacking of these layers and is disordered. The complex is stable under ambient conditions but decomposes at 112 °C [7].

Crystallization of gossypol from solutions in 1,4-dioxane at 40 °C produces another host-guest complex with stoichiometry 1 : 1. The present paper is devoted to the structure of this new modification called the β-phase complex and to its comparative discussion with the clathrate obtained at ambient conditions (α-phase).

2. Experimental

Single crystals of the inclusion complex with 1,4-dioxane were grown by slow evaporation of the solvent from a gossypol solution at 40 °C. Unit-cell parameters were determined on a Syntex $P2_1$, diffractometer by a least-squares fitting of the setting angles of 15 reflections. Crystal data are given in Table I.

The intensities of the reflections were measured with graphite monochromatized CuK_α radiation. No significant intensity variation was observed for two standard reflections monitored after each group of 100 reflections. Data were corrected for Lorentz and polarization effects but not for absorption. The structure was solved by direct methods with the program SHELX-86 [8]. Gossypol and guest molecules were located on the “best” E map. An isopropyl group of the gossypol AB-half was found to be disordered in the three positions with site occupation factors of 0.62; 0.20 and 0.18. The structure was refined first with isotropic and then with anisotropic thermal parameters by a least-squares method using the program SHELXL93 [9]. Hydrogen atom positions were determined from the ΔF maps and their positional and isotropic thermal parameters were included in the refinement. Final atomic coordinates are listed in Table II. Hydrogen atom parameters, anisotropic thermal parameters and structure factors are in the Supplementary Data.

3. Results and Discussion

3.1. MOLECULAR STRUCTURE AND FOUR DIFFERENT H-BONDS POSSIBLE IN THE GOSSYPOL MOLECULE

The structure of the gossypol molecule has been fully described in previous papers [1–7]. Here we will discuss some other interesting features of the gossypol molecule in respect to H-bonding overlooked before. It is known that gossypol has two types of O—H···O intramolecular H-bonds (Table III) closing five- and six-membered rings (Figure 1a, rings I and II). Nevertheless two other weaker H-bonds may be considered in the gossypol molecule.

The H-bond closing six-membered ring III was not taken into account specially in our previous articles since the C—H group had to be placed relative to oxygen

Table I. Crystal data and structure refinement for the β-phase complex of gossypol with 1,4-dioxane

Empirical formula	$C_{30}H_{30}O_8 \cdot C_4H_8O_2$
Formula weight	606.64
Temperature	293(2) K
Wavelength	1.54178
Crystal system	triclinic
Space group	$P\bar{1}$
Unit cell dimensions	a = 10.905(2) Å, α = 107.01(3) °
	b = 11.055(2) Å, β = 96.72(3) °
	c = 13.772(3) Å, γ = 98.68(3) °
Volume	1546.5(5) Å^3
Z	2
Density (calculated)	1.303 Mg/m^3
Absorption coefficient	0.792 mm^{-1}
F(000)	644
Crystal size	0.2 × 0.2 × 0.5 mm^3
Theta range for data collection	3.41 to 57.35 deg.
Index ranges	$0 \Leftarrow h \leftarrow 11, -12 \leftarrow k \leftarrow 11, -15 \leftarrow l \leftarrow 14$
Reflections collected	4202
Independent reflections	4200 [R(int) = 0.1341]
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4200/1/436
Goodness-of-fit on F^2	0.976
Final R indices [I > 2(I)]	R1 = 0.0617, wR2 = 0.1386
R indices (all data)	R1 = 0.1252, wR2 = 0.1598
Largest diff. peak and hole	0.181 and −0.155 e. Å^{-3}

atom O(1) [O(5)] at a H-bonding distance due to the stereochemical peculiarities of the gossypol molecule. However, another H-bond of type IV (Figure 1a) also closing a six-membered ring was never considered. As written many times before the hydrogen atom at the atom C(23) [C(28)] of the isopropyl group may be directed towards the hydrogen at C(4) [C(14)] atom or vice versa. When an isopropyl group has the former orientation its methyl groups are situated on the left side of the C(5)—C(23) [C(15)—C(28)] bond and at least one hydrogen atom of each methyl group is found to be in a H-bonding position [10,11] relative to the O(4) [O(8)] atom. An analysis of the previously published gossypol structures shows that indeed such mutual disposition of the O and H atoms takes place.

The fifth type of possible H-bonding that may exist in the gossypol molecule is one between the H atom of the O(1)—H [O(5)—H] hydroxyl group and π-

Table II. Atomic coordinates ($\times$ 10^4) and equivalent isotropic displacement parameters ($Å^2$ $\times$ 10^3) for the β-phase complex of gossypol with 1,4-dioxane. U(eq) is defined as one third of the trace of the orthogonalized U_{ii} tensor

Atom	x/a	y/b	z/c	U(eq)
C(1)	2154(3)	−1338(3)	−190(3)	43(1)
C(2)	2212(3)	−2618(3)	−351(3)	43(1)
C(3)	1614(3)	−3274(3)	249(3)	47(1)
C(4)	986(3)	−2637(3)	977(3)	48(1)
C(5)	275(4)	−678(4)	1977(3)	51(1)
C(6)	247(4)	592(4)	2126(3)	56(1)
C(7)	821(3)	1282(3)	1535(3)	50(1)
C(8)	1455(3)	710(3)	754(3)	44(1)
C(9)	1505(3)	−651(3)	554(3)	41(1)
C(10)	910(3)	−1327(3)	1166(3)	43(1)
C(11)	2363(4)	−4025(3)	−2098(3)	51(1)
C(12)	2955(4)	−3309(3)	−1114(3)	47(1)
C(13)	4218(4)	−3319(3)	−808(3)	48(1)
C(14)	4827(4)	−4073(4)	−1490(3)	53(1)
C(15)	4917(4)	−5651(3)	−3183(3)	49(1)
C(16)	4249(4)	−6508(4)	−4078(3)	56(1)
C(17)	2962(4)	−6563(4)	−4389(3)	56(1)
C(18)	2303(4)	−5700(3)	−3820(3)	52(1)
C(19)	2947(4)	−4845(3)	−2821(3)	46(1)
C(20)	4229(4)	−4837(3)	−2500(3)	48(1)
C(21)	1707(4)	−4654(4)	117(4)	69(1)
C(22)	1979(4)	1516(4)	191(3)	63(1)
C(23)	−314(6)	−1394(6)	2651(4)	76(2)
C(24)	−1669(16)	−1610(21)	2509(21)	105(7)
C(25)	477(23)	−1042(22)	3677(14)	107(8)
C(24R)	−1351(79)	−1910(60)	2285(45)	436(82)
C(25R)	−22(49)	−669(42)	3809(32)	94(14)
C(24L)	−1643(65)	−1195(69)	2979(46)	98(21)
C(25L)	646(81)	−1428(87)	3377(79)	306(78)
C(26)	4877(4)	−2563(4)	265(3)	71(1)
C(27)	1063(5)	−5693(4)	−4315(3)	75(1)
C(28)	6311(4)	−5551(4)	−2931(3)	65(1)
C(29)	7009(5)	−5079(6)	−3686(4)	112(2)
C(30)	6659(6)	−6815(6)	−2842(4)	109(2)
O(1)	2749(3)	−668(2)	−749(2)	66(1)
O(2)	1960(3)	2692(2)	427(2)	74(1)
O(3)	714(3)	2523(2)	1766(2)	69(1)

Table II. Continued

Atom	x/a	y/b	z/c	U(eq)
O(4)	−324(3)	1260(3)	2903(2)	81(1)
O(5)	1104(3)	−4049(3)	−2393(2)	71(1)
O(6)	519(3)	−6490(3)	−5138(2)	89(1)
O(7)	2445(3)	−7464(3)	−5301(2)	74(1)
O(8)	4848(3)	−7318(3)	−4714(2)	82(1)
C(1D)	5388(5)	−1233(5)	−2243(4)	82(1)
C(2D)	6071(4)	−282(4)	−2662(3)	74(1)
C(3D)	3542(5)	−1386(5)	−3366(4)	86(2)
C(4D)	4237(5)	−427(5)	−3773(4)	82(2)
O(1D)	4081(3)	−1181(3)	−2317(3)	85(1)
O(2D)	5535(3)	−477(3)	−3699(2)	66(1)

electrons of the other half of the molecule. This type of H-bonding is possible because of the favorable arrangement of the naphthyl nucleus *peri*-situated to the ordinary C(2)–C(12) bond hydroxyl group, i.e. due to the nearly perpendicular mutual disposition of the gossypol halves [13].

The geometry of these possible H-bonds in the β-phase of the gossypol-1,4-dioxane complex is given in Table III. The first 3 types of intramolecular H-bonds are practically identical with bonds in the other gossypol clathrates [4–7]. An isopropyl group of the AB-half is disordered in three positions (Figure 1b). The main orientation of this group is the symmetric one with a site occupation factor (s.o.f.) of 0.62 whereas the s.o.f. of the "left" and "right" orientations are nearly equal (0.20 and 0.18 respectively). C—H$\cdots$O type hydrogen bonds of the symmetrically oriented isopropyl group are identical to bonds in the CD-half isopropyl group which is only symmetrically situated (Table III). In the "left" orientation methyl group $C(24)H_3$ is situated nearer to the O(4) atom while the second methyl group $C(25)H_3$ of this isopropyl group moves away from the oxygen atom. In the opposite "right" orientation methyl group $C(25)H_3$ comes close to the O(4) atom and the $C(24)H_3$ group moves away from this atom. As a result of such orientation only one strong H-bond is observed instead of two H-bonds in the symmetrical case (Table III).

The dihedral angle between naphthyl moieties is equal to 93.3°. Bond lengths and angles are practically identical to ones in the other gossypol complexes [4–7]. The conformation and geometric characteristics of the 1,4-dioxane molecule are identical to those found in other host-guest complexes of the given guest [12].

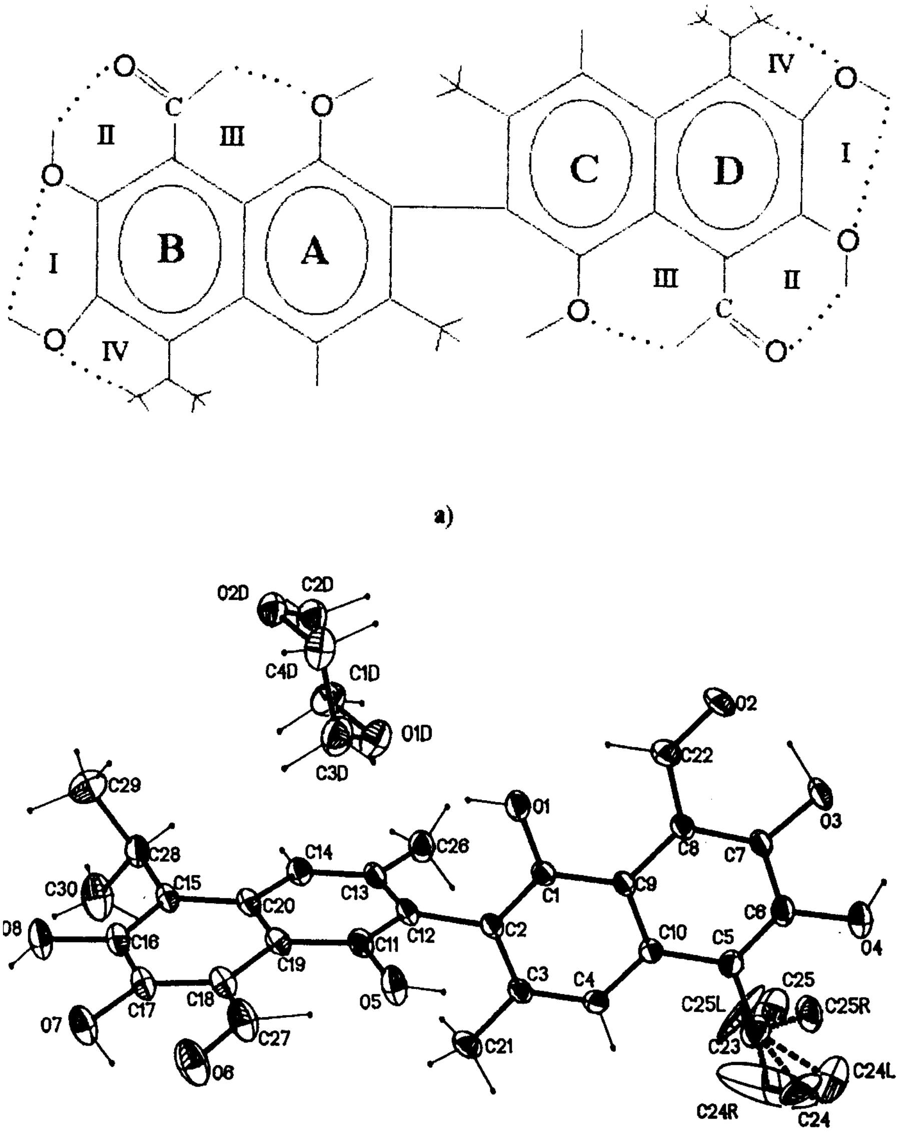

Figure 1. H-bonds (a) and the conformation (b) of the gossypol molecule. Thermal ellipsoids are drawn with 50% probability.

3.2. CRYSTAL STRUCTURE

Before solving the structure of the gossypol-1,4-dioxane β-phase complex we have considered on the basis of its unit cell parameters that it is isostructural to complexes of gossypol with acetone, cyclohexanone, isopropanol etc., i.e. it belongs to type I gossypol host-guest complexes [1]. However, results of its crystal structure

Table III. Intra- and intermolecular hydrogen bonds in the structure of the β-phase complex of gossypol with 1,4-dioxane

D—H$\cdots$A	Type	D$\cdots$A	D—H	H$\cdots$A	∠D—H$\cdots$A
	Symmetry	(Å)	(Å)	(Å)	(deg.)
Intramolecular H-bonds					
O(4)—H$\cdots$O(3)	I	2.627	0.89	2.04	122.0
O(8)—H$\cdots$O(7)		2.617	0.80	2.24	109.6
O(3)—H$\cdots$O(2)	II	2.448	1.04	1.48	152.9
O(7)—H$\cdots$O(6)		2.504	1.02	1.63	140.6
C(22)—H$\cdots$O(1)	III	2.693	1.03	1.97	125.1
C(27)—H$\cdots$O(5)		2.728	1.1	1.91	128.0
C(24)—H$\cdots$O(4)	IV	3.149	0.96	2.52	124.0
C(25)—H$\cdots$O(4)		3.228	0.96	2.75	111.0
C(25R)—H$\cdots$O(4)		2.808	0.96	2.32	111.0
C(24L)—H$\cdots$O(4)		2.910	0.96	2.18	132.0
C(29)—H$\cdots$O(8)		3.016	1.13	2.43	111.0
C(30)—H$\cdots$O(8)		2.915	0.94	2.29	123.0
Intramolecular H-bonds					
O(5)—H$\cdots$O(3)		2.843	0.84	2.19	134.7
O(1)—H$\cdots$O(1D)	$-x, -y, -z$	2.712	0.86	1.94	149.1
O(8)—H$\cdots$O(2D)	$1-x, -1-y, -1-z$	2.693	0.80	2.04	137.8

determination show that indeed a motif of structures is very similar but they are not entirely isostructural.

Two enantiomeric gossypol molecules are associated into centrosymmetric dimers by a pair of O(5)—H$\cdots$O(3) H-bonds typical for many gossypol polymorphs and host-guest complexes [1–7]. In clathrates of type I these dimers are incorporated by H-bonds O(8)—H$\cdots$O(4) (guests are acetone, tetrahydrofuran etc.) or O(4)—H$\cdots$O(7) (guests are cyclohexanone and isopropanol) into infinite columns. In the β-phase complexes of gossypol with 1,4-dioxane the dimers are joined to columns through the 1,4-dioxane molecules having H-bonds O(1)—H$\cdots$O(1D) and O(8)—H$\cdots$O(2D) (Table III). It should be noted that in the case of the α-phase complex the 1,4-dioxane molecule associates two gossypol molecules with the same chirality whereas here two enantiomeric host molecules are incorporated by the guest component (Figure 2). The columns formed are parallel to the [111] direction. The packing of these columns gives rise to the crystal structure of the β-phase complex. However, the surface of the columns of this inclusion complex has a slightly different structure. Therefore the columns contact by other parts or in the β-phase complex they are shifted relative to each other

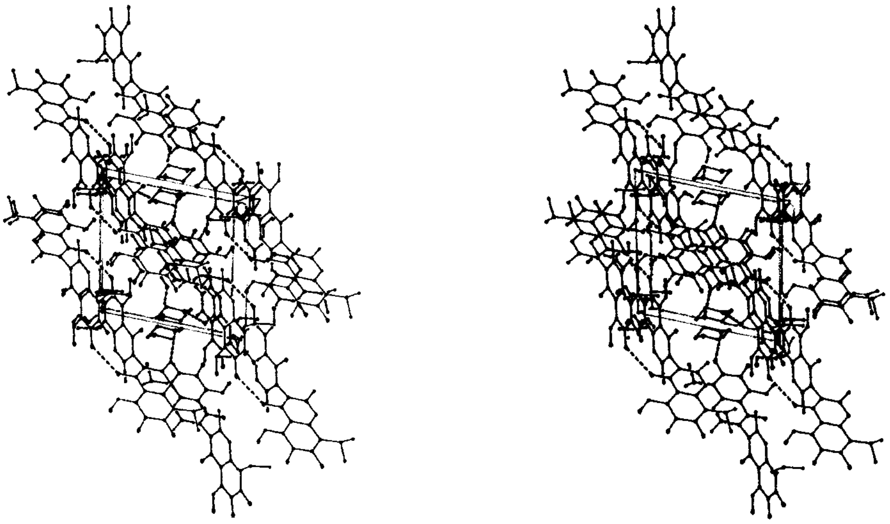

Figure 2. The structure of the β-phase complex of gossypol with 1,4-dioxane. For clarity only the major orientation of the disordered gossypol isopropyl group is shown.

before contacting than in the α-phase complex. Around the isopropyl group of the gossypol AB-half some empty space remains. It is filled as a result of disordering of the isopropyl group in the three positions. Ordered and H-bonded to the host, guest molecules are located in the channels running in the direction of the z-axis (Figure 2).

Oxygen atoms O(2) and O(6) showing strong proton acceptor properties are not involved in intermolecular H-bonds in the β-phase complex. Hydroxyl groups O(4)—H and O(7)—H also do not participate in H-bonding. However, atoms O(4) and O(6) of the two neighboring gossypol molecules of the same column are at short contact distances (3.02 Å).

4. Concluding Remarks

In addition to the traditionally discussed two types of intramolecular H-bonds two new types may be considered for the gossypol molecule. They are C—H···O type H-bonds closing six-membered rings. One more type of possible intramolecular H-bonds is one between the hydrogen of the gossypol *peri*-hydroxyl and the π-electrons of the other naphthyl moiety of the molecule. As a result of taking into account these possible H-bonds proton donor and proton acceptor abilities of all polar groups are satisfied. Now each of the six hydroxyl groups participates once as a proton donor and a second time as a proton acceptor. In spite of using the H-bonding potency of the gossypol molecule entirely gossypol may be involved in the different systems of the intermolecular H-bonds that show the unusual H-bonding ability of this compound.

The new β-phase inclusion complex between gossypol and 1,4-dioxane is obtained additionally to the known α-phase. In the $1:3$ α-phase complex one of the three 1,4-dioxane molecules is disordered and located in the channels, whereas in the case of the $1:1$ β-phase complex one of the two isopropyl groups of gossypol is disordered and ordered and H-bonded guest molecules are also placed in the channels. Unfortunately, further increase of the temperature from 40 °C in order to obtain other new modifications of the host-guest complex is impossible because of the chemical reaction of gossypol.

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