

Inclusion Complexes of the Natural Product Gossypol. Clathrate Type Inclusion Complexes of Gossypol with Carbonyl Group Containing Guests

B. T. IBRAGIMOV and S. A. TALIPOV

Institute of Bioorganic Chemistry of Uz.S.S.R. Academy of Sciences, Tashkent, U.S.S.R.

M. GDANIEC*

Faculty of Chemistry, A. Mickiewicz University, 60–780 Poznań, Poland.

(Received: 6 February 1989; in final form: 25 May 1989)

Abstract. The crystal structures of 2:1 inclusion complexes of gossypol with methyl propionate (GPMEP) and ethyl acetoacetate (GPEAA) have been determined by X-ray structure analysis. The crystals of GPMEP, $C_{30}H_{30}O_8 \cdot 1/2 C_4H_8O_2$, are monoclinic, space group $C2/c$, $a = 11.079(3)$, $b = 30.724(7)$, $c = 16.515(5)$ Å, $\beta = 90.46(2)^\circ$, $V = 5621(3)$ Å³, $Z = 8$, $D_x = 1.33$ g cm⁻³. The structure has been refined to the final R value of 0.059 for 1899 observed reflections. The crystals of GPEAA, $C_{30}H_{30}O_8 \cdot 1/2 C_6H_{10}O_3$, are monoclinic, space group $C2/c$, $a = 11.095(2)$, $b = 30.604(9)$, $c = 16.955(5)$ Å, $\beta = 88.27(2)^\circ$, $V = 5754(3)$ Å³, $Z = 8$, $D_x = 1.35$ g cm⁻³. The structure has been refined to the final R value of 0.056 for 2502 observed reflections.

In contrast to previously investigated inclusion complexes of gossypol the host molecules do not form centrosymmetric dimers *via* hydrogen bonds. In the crystal structures the racemic gossypol is separated into enantiomers forming alternating bimolecular layers. Nearly perpendicular to these chiral bilayers run elongated cavities enclosed on each side by layers of opposite chirality. The surface of these layers is hydrophobic, the polar groups are hidden inside the layer. Guest molecules which are hydrogen bonded to the host are included in cylindrically shaped cavities. Possible hydrogen bonds between host and guest are analysed for this isostructural class of complexes.

Key words. Crystal structure, X-ray crystallography, gossypol, inclusion complexes.

Supplementary Data relevant to this article have been deposited with the British Library as Supplementary Publication No. SUP 82084 (32 pages).

1. Introduction

Gossypol, a substance isolated from the cotton plant, shows a broad spectrum of physiological activity [1–3]. Another property which makes this substance very interesting is its ability to form lattice inclusion complexes with practically all, small or medium size, organic solvent molecules [4–6]. More than 100 inclusion complexes of gossypol have been obtained and identified, and for 70 of them, for which single crystals have been grown, unit-cell parameters have been determined [6]. Complexes of gossypol with some molecules comprising a carbonyl group belong to a separate isostructural class of host : guest complexes of a clathrate type. Recently two crystal structures of such a clathrate formed by gossypol with carboxylic acid

* Author for correspondence.

esters, i.e. ethyl acetate and butyl acetate, have been reported [7, 8]. This article presents two more crystal structures belonging to this structural type, complexes of gossypol with methyl propionate and ethyl acetoacetate, and gives a detailed description of this class of clathrates. The following abbreviations are used throughout the text: gossypol:ethyl acetate, GPEEA; gossypol:butyl acetate, GPBEA; gossypol:methyl propionate, GPMEP; and gossypol:ethyl acetoacetate, GPEAA.

2. Experimental

Single crystals of inclusion complexes of gossypol with methyl propionate and ethyl acetoacetate were obtained by slow diffusion of a nonpolar solvent such as benzene, *n*-hexane or isooctane into a gossypol solution in the appropriate ester. The yellow crystals were stable when exposed to air. Unit-cell parameters were determined on a Syntex P2₁ diffractometer by a least-squares fitting of the setting angles of 15 reflections. Crystal data and some details concerning data collection and structure refinement are given in Table I. Intensities of reflections were measured with graphite monochromatized radiation. No significant intensity variation was observed for 2 standard reflections monitored after each group of 100 reflections. Integrated intensities were obtained by peak profile analysis according to Lehmann and Larsen [9]. Data were corrected for Lorentz and polarization

Table 1. Crystal data for GPMEP and GPEAA

	GPMEP	GPEAA
Formula	C ₃₂ H ₃₄ O ₉	C ₃₃ H ₃₅ O _{9.5}
Crystal system	monoclinic	monoclinic
Space group	<i>C</i> 2/ <i>c</i>	<i>C</i> 2/ <i>c</i>
<i>a</i> (Å)	11.079(3)	11.095(2)
<i>b</i> (Å)	30.724(7)	30.604(9)
<i>c</i> (Å)	16.515(5)	16.955(5)
β (deg)	90.46(2)	88.27(2)
<i>V</i> (Å ³)	5621(3)	5755(3)
ρ (g cm ⁻³)	1.33	1.35
<i>Z</i>	8	8
Radiation	Mo <i>K</i> α	Cu <i>K</i> α
μ (λ) (cm ⁻¹)	0.96	7.76
$2\theta_{\max}$	48	115
Crystal dimensions (mm)	0.7 × 0.4 × 0.4	0.3 × 0.2 × 0.05
Measured data	4703	4074
Observed data	1899	2502
σ criterion		
for observed data	$I > 2\sigma(I)$	$I > 2\sigma(I)$
Weighting scheme	$1/[\sigma^2 + 0.0002^2]$	$1/[\sigma^2 + 0.0001F^2]$
<i>R</i>	0.059	0.056
<i>R_w</i>	0.066	0.062
Goodness-of-fit	2.47	2.85

effects but not for absorption. The structures of GPMEP and GPEAA were solved by direct methods using the program *MULTAN80* [10] and refined by a full-matrix least-squares method with the program *SHELX76* [11]. The positions of hydrogen atoms bonded to C were calculated while the hydrogen atoms from hydroxyl groups were localized on ΔF maps. In GPMEP the positional and temperature parameters of hydrogen atoms were not refined. In GPEAA only the O—H hydrogen atom parameters were included in the final refinement cycles. Hydrogen atoms of the guest molecules were not determined. An empirical extinction parameter x was applied to correct F_c according to $F'_c = F_c(1 - xF_c^2/\sin \theta)$. Atomic scattering factors used in calculations were those included in *SHELX76* [11].

3. Results and Discussion

The atomic parameters are given in Table II. Tables of distances, angles, intramolecular hydrogen bond geometries, hydrogen atom parameters, anisotropic thermal parameters and structure factors are in the Supplementary Material. The numbering scheme of gossypol and the guest molecules is shown in Figure 1.

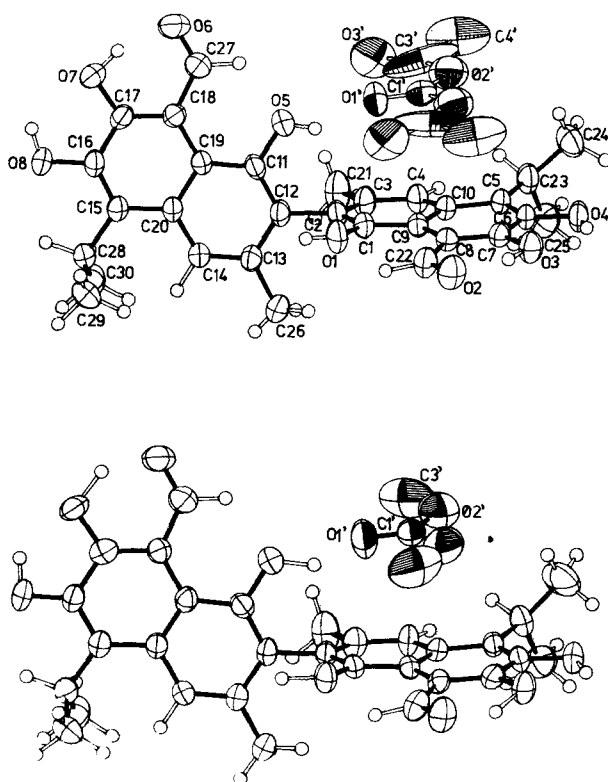


Fig. 1. ORTEP [12] drawing of the host and guest molecules of GPMEP (top) and GPEAA (bottom). Ellipsoids are drawn at the 50% probability level.

Table II. Fractional atomic coordinates and equivalent isotropic thermal parameters with e.s.d.'s in parentheses

$$U_{\text{eq}} = \frac{1}{3} \sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j$$

Atom	<i>x</i> / <i>b</i>	<i>y</i> / <i>b</i>	<i>z</i> / <i>c</i>	<i>U</i> _{eq}
<i>a. GPMEP</i>				
C(1)	0.7937(5)	0.0265(2)	0.7131(4)	0.041(3)
C(2)	0.7625(5)	0.0051(2)	0.6428(4)	0.043(3)
C(3)	0.7510(6)	0.0296(2)	0.5713(4)	0.053(3)
C(4)	0.7620(5)	0.0740(2)	0.5737(4)	0.052(3)
C(5)	0.7924(5)	0.1437(2)	0.6482(4)	0.042(3)
C(6)	0.8287(5)	0.1636(2)	0.7168(4)	0.045(3)
C(7)	0.8561(5)	0.1400(2)	0.7885(4)	0.048(3)
C(8)	0.8499(5)	0.0948(2)	0.7902(4)	0.039(3)
C(9)	0.8131(5)	0.0721(2)	0.7177(4)	0.039(3)
C(10)	0.7878(5)	0.0966(2)	0.6466(4)	0.041(3)
C(11)	0.6244(6)	−0.0584(2)	0.6471(4)	0.047(3)
C(12)	0.7410(6)	−0.0430(2)	0.6423(3)	0.045(3)
C(13)	0.8373(6)	−0.0729(2)	0.6356(4)	0.050(3)
C(14)	0.8123(5)	−0.1165(2)	0.6337(3)	0.047(3)
C(15)	0.6725(6)	−0.1798(2)	0.6364(4)	0.046(3)
C(16)	0.5579(6)	−0.1943(2)	0.6446(4)	0.049(3)
C(17)	0.4584(6)	−0.1658(2)	0.6488(4)	0.051(3)
C(18)	0.4737(5)	−0.1203(2)	0.6477(4)	0.048(3)
C(19)	0.5948(6)	−0.1038(2)	0.6440(3)	0.045(3)
C(20)	0.6933(5)	−0.1330(2)	0.6374(3)	0.044(3)
C(21)	0.7245(7)	0.0068(2)	0.4914(4)	0.079(4)
C(22)	0.8917(6)	0.0742(2)	0.8643(4)	0.057(3)
C(23)	0.7542(6)	0.1692(2)	0.5727(4)	0.060(3)
C(24)	0.8597(6)	0.1802(2)	0.5189(4)	0.076(3)
C(25)	0.6687(7)	0.2065(2)	0.5870(5)	0.104(4)
C(26)	0.9647(5)	−0.0567(2)	0.6275(4)	0.063(4)
C(27)	0.3643(6)	−0.0949(2)	0.6528(4)	0.066(4)
C(28)	0.7734(6)	−0.2130(2)	0.6243(4)	0.056(3)
C(29)	0.8605(6)	−0.2162(2)	0.6960(5)	0.077(4)
C(30)	0.8379(7)	−0.2075(2)	0.5434(4)	0.080(4)
O(1)	0.8055(4)	0.0024(1)	0.7841(2)	0.055(2)
O(2)	0.9168(4)	0.0946(1)	0.9277(3)	0.071(3)
O(3)	0.8863(4)	0.1643(1)	0.8527(3)	0.063(2)
O(4)	0.8430(4)	0.2081(1)	0.7213(2)	0.060(2)
O(5)	0.5298(4)	−0.0299(1)	0.6530(3)	0.064(2)
O(6)	0.2614(4)	−0.1104(2)	0.6553(3)	0.081(3)
O(7)	0.3498(4)	−0.1849(1)	0.6535(3)	0.065(2)
O(8)	0.5345(4)	−0.2381(1)	0.6486(3)	0.066(2)
O(1')	0.0000(0)	0.4507(3)	0.2500(0)	0.148(6)
C(1')	0.0000(0)	0.4116(4)	0.2500(0)	0.107(8)
O(2')	−0.0344(6)	0.3863(2)	0.1774(6)	0.153(4)
C(3')	−0.0667(9)	0.45115(4)	0.1013(7)	0.165(6)
<i>b. GPEAA</i>				
C(1)	0.7941(3)	0.0250(1)	0.7139(2)	0.004(2)
C(2)	0.7636(4)	0.0043(1)	0.6455(3)	0.046(2)
C(3)	0.7496(4)	0.0293(1)	0.5765(3)	0.054(2)

Table II. (Continued)

Atom	x/a	y/b	z/c	U_{eq}
C(4)	0.7597(4)	0.0740(1)	0.5809(3)	0.052(2)
C(5)	0.7896(3)	0.1435(1)	0.6535(2)	0.045(2)
C(6)	0.8286(4)	0.1628(1)	0.7202(3)	0.045(2)
C(7)	0.8564(3)	0.1383(1)	0.7882(2)	0.045(2)
C(8)	0.8497(3)	0.0931(1)	0.7904(2)	0.042(2)
C(9)	0.8114(3)	0.0707(1)	0.7195(2)	0.040(2)
C(10)	0.7862(3)	0.0962(1)	0.6511(2)	0.044(2)
C(11)	0.6263(4)	-0.0598(1)	0.6506(2)	0.045(2)
C(12)	0.7433(4)	-0.0438(1)	0.6444(2)	0.046(2)
C(13)	0.8398(4)	-0.0736(1)	0.6367(2)	0.050(2)
C(14)	0.8151(4)	-0.1174(1)	0.6355(2)	0.049(2)
C(15)	0.6772(4)	-0.1810(1)	0.6392(2)	0.042(2)
C(16)	0.5617(4)	-0.1958(1)	0.6474(2)	0.047(2)
C(17)	0.4617(4)	-0.1671(1)	0.6515(2)	0.047(2)
C(18)	0.4761(3)	-0.1222(1)	0.6510(2)	0.044(2)
C(19)	0.5978(3)	-0.1048(1)	0.6481(2)	0.040(2)
C(20)	0.6972(4)	-0.1344(1)	0.6408(2)	0.041(2)
C(21)	0.7232(6)	0.0079(2)	0.4992(3)	0.081(3)
C(22)	0.8902(4)	0.0719(1)	0.8612(3)	0.058(2)
C(23)	0.7497(4)	0.1693(1)	0.5821(3)	0.058(2)
C(24)	0.8572(4)	0.1795(2)	0.5272(3)	0.077(2)
C(25)	0.6742(5)	0.2096(1)	0.6015(3)	0.084(3)
C(26)	0.9669(5)	-0.0574(2)	0.6261(4)	0.074(3)
C(27)	0.3673(4)	-0.0963(1)	0.6523(3)	0.065(2)
C(28)	0.7782(4)	-0.2146(1)	0.6267(3)	0.054(2)
C(29)	0.8641(4)	-0.2177(1)	0.6952(3)	0.075(3)
C(30)	0.8446(5)	-0.2103(1)	0.5473(3)	0.074(3)
O(1)	0.8065(3)	0.0006(1)	0.7816(2)	0.060(1)
O(2)	0.9176(3)	0.0924(1)	0.9215(2)	0.072(2)
O(3)	0.8903(3)	0.1625(1)	0.8498(2)	0.062(1)
O(4)	0.8438(3)	0.2074(1)	0.7245(2)	0.060(2)
O(5)	0.5311(3)	-0.0311(1)	0.6579(2)	0.066(2)
O(6)	0.2642(3)	-0.1120(1)	0.6548(2)	0.084(2)
O(7)	0.3532(3)	-0.1868(1)	0.6544(2)	0.065(2)
O(8)	0.5385(3)	-0.2401(1)	0.6504(2)	0.062(2)
O(1')	0.0000(0)	0.4504(1)	0.2500(0)	0.090(3)
C(1')	0.0000(0)	0.4108(2)	0.2500(0)	0.065(3)
O(2')	0.0328(3)	0.3854(1)	0.3164(3)	0.111(2)
C(3')	0.0658(8)	0.4072(5)	0.3839(5)	0.198(7)
O(3')	0.0870(10)	0.4470(4)	0.3754(8)	0.146(6)
C(4')	0.1053(6)	0.3725(3)	0.4459(3)	0.161(4)

3.1. MOLECULAR STRUCTURE

Gossypol can exist in one of the following tautomeric forms: aldehyde, quinoid and lactol [14]. In most solvents it is found in the aldehyde form; however, there are some reports that gossypol also exists in a pure lactol form [15] or as a dynamic equilibrium mixture of aldehyde and lactol forms in some highly polar solvents [16]. In the structures described here gossypol is in the aldehyde form (Figure 1), the only

one found for gossypol in the crystalline state up to now. The dihedral angle between the least-squares planes of the naphthyl moieties equals 100 and 102° in GPMEP and GPEAA, respectively.

The highest symmetry which the gossypol molecule can possess is C_2 (2-fold axis perpendicular to the C(2)—C(12) bond); however, in the clathrate presented here this symmetry is not preserved due to different orientations of the isopropyl group in the two equivalent halves of the molecule: in one half the hydrogen atoms at C(4) and C(23) face each other while in the other the hydrogen atom at C(28) is oriented toward O(8).

Two types of intramolecular hydrogen bonds are observed in the gossypol molecule. Hydrogen bond O(3)—H...O(2) closes a six-membered ring formed by C(7), C(8), C(22), O(2), O(3) and H while hydrogen bond O(4)—H...O(3) closes a five-membered ring composed of C(6), C(7), O(3), O(4) and H. Two analogous types of hydrogen bonds are formed in the other half of the molecule.

The intramolecular hydrogen bond geometries, bond lengths and bond angles (Table I and II, supplementary material) do not differ significantly from those observed in similar clathrates, i.e. GPEEA and GPBEA [7, 8].

3.2. CRYSTAL STRUCTURE

Out of the eight polar functional groups of gossypol which are potential hydrogen bond acceptors and/or donors only 3 hydroxyl groups are involved in hydrogen bonding. Hydrogen bonds between hydroxyl groups O(4)—H and O(8)—H, which correspond to each other in the symmetrically related halves of the gossypol molecule, join the host molecules into layers parallel to the 'ac' plane (Figure 2). The geometry of the intermolecular hydrogen bonds O(4)—H...O(8) [$1.5 - x, 0.5 + y, 1.5 - z$] and O(8)—H...O(4) [$-0.5 + x, -0.5 + y, z$] is given in Table III. As a consequence, each of the above mentioned hydroxyl groups takes part in three hydrogen bonds. It acts as a donor in the intramolecular hydrogen bond and as a donor and acceptor in the intermolecular hydrogen bonds.

The most striking feature of the crystal packing of the inclusion complexes presented here is the separation of the host molecules into layers comprising molecules of the same chirality. Thus, crystals of racemic gossypol are constructed of alternate bimolecular layers of a different chirality. In these chiral layers naphthyl rings C(11)—C(20) of the basic molecule (x, y, z) and that related to it by the 2-fold axis ($1 - x, y, 1.5 - z$) are nearly parallel, the dihedral angle between their least-squares planes being 8°. The gossypol molecule has a large dipole moment* and a dipole-dipole interaction between these two halves of the gossypol molecules probably plays an important role in their mutual orientation. Dipole-dipole interactions should also influence the orientation of the naphthyl rings C(1)—C(10) of the basic molecule (x, y, z) and the molecule ($2 - x, y, 1.5 - z$). The dihedral angle between their least-squares planes is 26°.

Gossypol molecules which pack into one chiral layer form a symmetrical cage of an approximate size $5.5 \times 6.5 \times 10.5$ Å with the naphthyl moieties C(1)—C(10) of

* According to our calculations using the CNDO/2 method the dipole moment of one half of the gossypol molecule is 4.96 D.

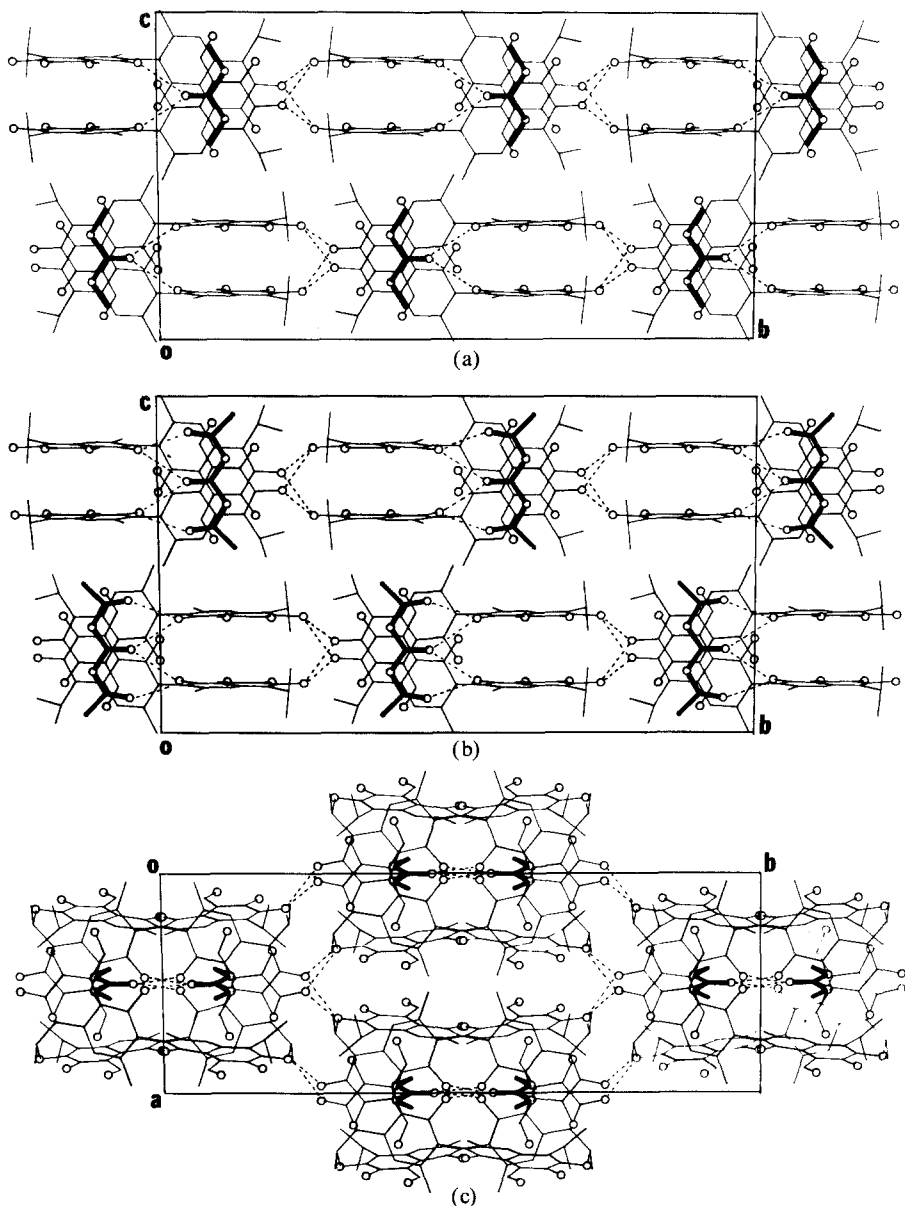


Fig. 2. Projections of the crystal structures: (a) projection of the GPMEP structure down the a axis, (b) projection of the GPEAA structure down the a axis, (c) projection of the GPMEP structure down the c axis. Hydrogen atoms have been omitted for clarity.

molecules (x, y, z) and $(1 - x, y, 1.5 - z)$ being the 'floor and ceiling' of a cage. Only one wall of the cage is hydrophilic, the others are hydrophobic. Guest molecules of an appropriate chemical nature, size and shape can be placed in this cage. The surface of the chiral layers is covered with hydrophobic groups. Intermolecular contacts indicate that there are only van der Waals interactions between these layers.

Table III. Intermolecular hydrogen bonds in GPMEP AND GPEAA

H-bond	O(5)—H...O(1')	O(5)—H...O(3')	O(4)—H...O(8)	O(8)—H...O(4)
O...O (Å)	2.933(6)		3.023(6)	2.952(6)
GPMEP O—H (Å)	1.13		1.10	0.97
O...H (Å)	2.01		2.05	2.54
<O—H...O (°)	137		146	106
symm. code	0.5 - x, 0.5 - y, 1 - z		1.5 - x, 0.5 + y, 1.5 - z	-0.5 + x, -0.5 + y, z
O...O (Å)	2.939(4)	2.95(1)	2.991(4)	2.942(4)
GPEAA O—H (Å)	0.87(4)	0.87(4)	0.83(5)	0.94(5)
O...H (Å)	2.24(5)	2.5(1)	2.25(5)	2.18(4)
<O—H...O(°)	137(3)	114(8)	150(3)	138(4)
symm. code	0.5 + x, 0.5 - y, 0.5 + z	0.5 + x, 0.5 - y, 0.5 + z	1.5 - x, 0.5 + y, 1.5 - z	-0.5 + x, -0.5 + y, z

3.3. HOST-GUEST INTERACTION

Even though the cage formed by gossypol molecules in clathrates has the symmetry of a 2-fold axis it accommodates non-symmetrical molecules. These molecules are statistically disordered around the 2-fold axis in the crystals. This explains why a guest:host molecular ratio of 1:2 is possible in these complexes where the guest molecule is non-symmetrical.

The carbonyl oxygen atoms of the guest molecules are hydrogen bonded to the hydroxyl groups O(5)—H of the two gossypol molecules whose naphthyl rings form the 'floor and ceiling' of the cage (Figure 2). In this class of clathrate inclusion complexes of gossypol to which GPMEP and GPEAA belong, the carbonyl oxygen atom forms hydrogen bonds which are located in different positions of the cage. In general, the carbonyl group-containing guest molecules which lie on a 2-fold axis are arranged so that the number of non-hydrogen atoms in a non-branched chain lying on one side of the axis does not exceed three. Molecules whose carbon-oxygen chain has more than seven or less than five atoms do not form this type of complex.

Three positions in which carbonyl oxygen atoms can form hydrogen bonds with O(5)—H of the host can be distinguished. Let them be numbered sequentially as 0, 1 and 2 (Figure 3). GPMEP represents an example in which position 0 is occupied while in GPEAA positions 0 and 2 are occupied. The term 'occupied position' refers to the case in which a carbonyl oxygen atom located in a given position will form a hydrogen bond with the host molecule.

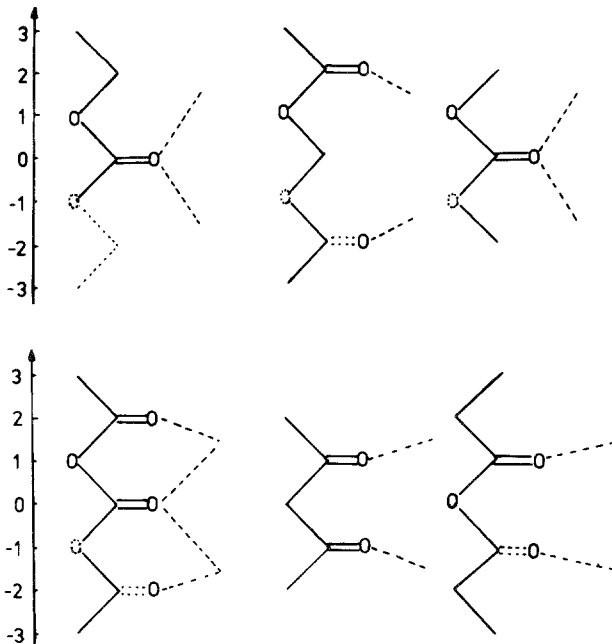


Fig. 3. Possible hydrogen bonds between hydroxyl group O(5)—H of the host and carbonyl groups of the guest.

Table IV. Crystal data of the inclusion complexes of gossypol with some carbonyl group-containing compounds

compound	$a(\text{\AA})$	$b(\text{\AA})$	$c(\text{\AA})$	$\alpha(^{\circ})$	$\beta(^{\circ})$	$\gamma(^{\circ})$	$V(\text{\AA}^3)$	space group	Z	host: guest ratio
1. GPEEA	11.125(3)	30.689(9)	16.469(4)	90.00	90.31	90.00	5622	C2/c	8	2:1
2. GPBEA	11.221(2)	30.538(9)	17.023(2)	90.00	90.48(4)	90.00	5833	C2/c	8	2:1
3. GPMEP	11.079(2)	30.724(11)	16.515(5)	90.00	90.46(2)	90.00	5621	C2/c	8	2:1
4. GPEAA	11.095(2)	30.604(9)	16.955(5)	90.00	88.27(2)	90.00	5755	C2/c	8	2:1
5. GPACA	11.011(5)	30.74(2)	16.638(6)	90.00	91.91(3)	90.00	5630	C2/c	8	2:1
6. GPMER	11.011(3)	30.747(8)	16.545(5)	90.00	90.26(2)	90.00	5601	C2/c	8	2:1
7. GPBEB	11.158(6)	30.67(3)	16.645(3)	90.00	90.50(3)	90.00	5696	C2/c	8	2:1
8. GPBEE	11.165(3)	30.70(1)	16.646(4)	90.00	90.27(3)	90.00	5698	C2/c	8	2:1
9. GPAEA	14.425(2)	15.519(1)	16.409(2)	97.89(1)	117.80(1)	67.01(1)	2986	PI	4	2:1
10. GPMEA	6.976(4)	14.727(6)	14.945(9)	87.07(4)	71.21(5)	88.30(4)	1451	PI	2	1:1
11. GPPTA	10.343(5)	11.643(3)	14.928(8)	108.83(3)	73.53(4)	84.70(3)	1598	PI	2	1:1
12. GPIEA	11.445(2)	30.724(5)	16.552(2)	90.00	91.83(3)	90.00	5806	$P2_1/n$	8	2:1

GP – gossypol, EEA – ethyl acetate, BEA – butyl propionate, EAA – ethyl propanoate, EAA – ethyl propanoate, ACA – acetylacetone, MER – methyl acrylate, EEB – ethyl bromoacetate, GPBEE – single crystals grown from equimolar mixture of BEA and BEA, AEA – amyl acrylate, MEA – methyl acetate, PTA – 1-pentanal, IEA – isobutyl acetate

The following experiments have been carried out to show that position number 1 can be occupied. If propyl propionate (PEP) is able to form complexes with gossypol then its carbonyl group has to occupy position 1. The powder diffractograms of a sample obtained by precipitation of gossypol from its solution in PEP was very similar to the diffractograms of GPEAA and GPBEA. The guest: host molecular ratio of nearly 1:2 has been determined by an NMR technique. Thus, we have shown that the GPPEP complex is formed and hence position 1 has to be occupied in the crystal structure. Moreover, we have grown single crystals of the inclusion complex of gossypol with acetylacetone (GPACA) and determined its unit-cell parameters (Table IV). In this case, the guest molecule can adopt two different arrangements in the clathrate cage: a symmetrical arrangement with positions -1 and 1 occupied and a non-symmetrical one with the carbonyl groups located in positions 0 and 2 . An analysis of the unit-cell parameters of the complexes of gossypol belonging to this structural type points to a symmetrical arrangement of the guest molecule in a cage.

Guest molecules having a carbonyl group and 5 to 7 atoms in the chain form isostructural inclusion complexes where the guest molecule is hydrogen bonded to the host. When there are more than 7 atoms in the chain a host: guest complex of another type is formed – its symmetry is lowered to triclinic (Table IV, GPAEA). A morphotropic transition is also observed when the chain is shorter than 5 atoms (Table IV, GPMEA). An exception to this rule is presented by 1-pentanal. It does not form a clathrate of the above type even though its carbon chain has 5 atoms. The inclusion complex of gossypol with pentanal belongs to a new structural type (Table III, GPPTA). The limit on the shortest length of the guest molecule points to the fact that the formation of a clathrate depends on the overall energy of hydrogen bonds and van der Waals interactions between host and guest. Hydrogen bonds, however, play a determining role in the orientation of a guest in the clathrate.

The shape and size of a cage limit the length of the guest molecule in the direction perpendicular to the plane of the chiral layer. The dimensions of the guest molecule are also restricted in two other directions. This was proved by studying inclusion compounds of gossypol with the following guests whose dimension perpendicular to the chain was gradually increased: methyl acrylate, ethyl bromoacetate and isobutyl acetate. The first two guests form clathrates of the type described in this paper while the inclusion of isobutyl acetate into the crystal lattice leads to a lower crystal symmetry (Table IV, GPIEA). In the latter case the dimensions of the unit cell are preserved but the space group changes from $C2/c$ to $P2_1/n$. Even though the symmetry of the 2-fold axis is lost it seems that the structural motif will be retained.

4. Final remarks

In the inclusion complexes described here guest molecules fit in a cage which is closed on each side by host molecules. In this sense the inclusion compounds presented here are clathrates closely related to β -hydroquinone inclusion compounds or Dianin's compounds [17]. However, in the case of gossypol clathrates the hydrogen bond between host and guest plays an important role in clathrate

formation and therefore nonpolar molecules of an appropriate length such as *n*-hexane, *n*-pentane and their haloderivatives do not form this type of structure.

Clathrate-type inclusion compounds of gossypol are formed by non-branched saturated and unsaturated carboxylic acid esters, ketones and their derivatives with a carbonyl group in the β -position. Using already existing data it is possible to predict the arrangement of the guest molecule in the cage and to describe host-guest hydrogen bonds. In most cases the hydrogen bond scheme can be predicted unequivocally. For example, all guest species with one carbonyl group in a 5-membered chain (with the exception of 1-pentanal) should form hydrogen bonds as in GPPEA. Guests with 7 atoms in a chain are arranged in the cage in only one possible way. In the other cases when there are two possible variants of a molecular arrangement one should choose the one in which carbonyl groups are symmetrically located on each side of the two fold axis. Up to now, the only case for which a proper structure cannot be predicted are monocarbonyl guest molecules with six-membered chains. In clathrates where the carbonyl group of the guest is located at position 1 or 2 the guest molecule is hydrogen bonded to one molecule of the host. In clathrate inclusion compounds which have the guest carbonyl group at position 0, or in the case of polycarbonyl compounds where the carbonyl groups are located on both sides of the 2-fold axis the guest molecule is connected with two molecules of gossypol. In this case, the stability of the bilayer of the host molecules is increased due to the additional interaction with the guest molecules. Weber [18] has suggested that the inclusion compounds, where host molecules are connected through guest molecules *via* hydrogen bonds should be classified as 'coordinatoclathrates'. According to this terminology the latter inclusion compounds are coordinatoclathrates. They are preferred to normal clathrates from the energetical point of view and this is the reason why, all other conditions being the same, the guest molecule will tend to form a coordinatoclathrate. This agrees well with the above preference criterion for a proper structure.

This property of inclusion compounds of gossypol can be used for the separation of a mixture of some carbonyl-group containing compounds. For example, it can be employed for the separation of clathrate- and coordinatoclathrate-forming molecules. According to NMR studies of crystals grown from a solution of gossypol in an equimolar mixture of ethyl acetate and butyl acetate the crystal contains 90% of ethyl acetate and 10% of butyl acetate as confirmed by the crystal data (Table IV, GPBEE).

Acknowledgements

The authors wish to thank Professor Z. Kosturkiewicz and Dr T. F. Aripov for helpful discussions and for their interest in the work. MG thanks MEN project RP.II.13.2.13 for financial support.

References

1. E. M. Vermel and S. A. Krouglyak: *Voprosy onkologii* **12**, 39 (1963).
2. S. A. Vichkanova and L. V. Goryunova: *Atibiotiki* **9**, 828 (1968).
3. National Coordinating Group on Male Antifertility Agents: *Chinese Med. J.* **4**, 417 (1978).

4. S. A. Talipov, B. T. Ibragimov, G. B. Nazarov, T. F. Aripov and A. I. Ismailov: *Khimiya prir. soed.*, 663 (1984); *Chem. Abstr.* **102**, 42891w (1985).
5. B. T. Ibragimov, S. A. Talipov, G. B. Nazarov and B. N. Dadabaev: *Tezisy dokladov V Vsesoyuznogo soveshchaniya po organicheskoi kristalokhimiye*. Chernogolovka, p. 87 (1987).
6. B. T. Ibragimov, S. A. Talipov, B. N. Dadabaev, G. B. Nazarov and T. F. Aripov: *Khimiya prir. soed.*, 675 (1988).
7. B. T. Ibragimov, S. A. Talipov, G. B. Nazarov, T. F. Aripov, Z. Shukurov and A. I. Ismailov: *Khimiya prir. soed.*, 664 (1981). *Chem. Abstr.* **96**, 85303f (1982).
8. B. T. Ibragimov, S. A. Talipov and B. N. Dadabaev: *Khimiya prir. soed.*, 669 (1988).
9. M. S. Lehmann and F. K. Larsen: *Acta Crystallogr.* **A30**, 580 (1974).
10. P. Main, S. J. Fiske, S. E. Hull, L. Lessinger, G. Germain, J.-P. Declercq and M. M. Woolfson: *MULTAN80*. A system for the Automatic Solution of Crystal Structures from X-ray Diffraction Data. Universities of York, England, and Louvain, Belgium (1980).
11. G. M. Sheldrick: *SHELX76*. Program for crystal structure determination. University of Cambridge, England (1976).
12. C. K. Johnson: *ORTEP*. Report ORNL-5138, Oak-Ridge National Laboratory, Tennessee (1976).
13. W. D. S. Motherwell and W. Clegg: *PLUTO*. Program for drawing crystal and molecular structures. University of Cambridge, England.
14. R. Adams, R. C. Morris, T. A. Geissman, D. J. Butterbaugh and E. C. Kirkpatrick: *J. Am. Chem. Soc.* **60**, 2193 (1938).
15. J. Reyes, S. D. Wyrick, L. Borriero and D. J. Benas: *Biochem. Biophys Acta* **863**, 101 (1986).
16. F. G. Kamaev, N. I. Baram, A. I. Ismailov, V. B. Leontyev and A. S. Sadykov: *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1003 (1979); *Chem. Abstr.* **91**, 55761h (1979).
17. D. D. MacNicol: in *Inclusion Compounds*, Vol. 2 (Eds. J. L. Atwood, J. E. D. Davies, and D. D. MacNicol), pp. 1-45, Academic Press, London (1984).
18. E. Weber and H.-P. Josel: *J. Incl. Phenom.* **1**, 79 (1983).