

Inclusion Complexes of Gossypol with 2-Pentanone, 3-Pentanone, and 2-Hexanone

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Abstract

Inclusion complexes of gossypol with 2-pentanone, 3-pentanone, and 2-hexanone were prepared by crystallization from the corresponding ketone and hexane, and their structures were determined by low-temperature X-ray diffraction. All three compounds crystallize in monoclinic systems and have a 2:1 gossypol-to-solvent molar ratio. Both gossypol–pentanone complexes crystallize in $C2/c$ space groups, and the solvent cavities in these structures have C_2 symmetry. The 3-pentanone molecule, which has C_2 symmetry, sits symmetrically within the cavity, while the 2-pentanone molecule, which lacks C_2 symmetry, takes two equally probable orientations within the cavity. Both structures are similar to previously reported gossypol inclusion complexes formed with small esters and 3-hexanone. The distal positioning of the carbonyl group in 2-hexanone does not allow it to fit into the same solvent cavity that exists in the pentanone structures. In the gossypol–2-hexanone complex, the solvent cages are skewed, and the C_2 site symmetry is lost. As a result, the structure crystallizes in a Cc space group and has a larger asymmetric unit and unit cell. Although the 2-hexanone structure retains many of the features of the gossypol–pentanone complexes, this is the first report of a gossypol inclusion compound with this extended structure.

Introduction

Gossypol [1,1',6,6',7,7'-hexahydroxy-5,5'-diisopropyl-3,3'-dimethyl-(2,2'-binaphthalene)-8,8'-dicarboxaldehyde] (Figure 1) is a natural product of the cotton plant that has a number of potentially useful biological properties, including activity as an insecticide [1], contraceptive agent [2], anti-cancer agent [3–5], and anti-viral agent [6]. Gossypol also forms inclusion complexes with many low molecular weight compounds. Gdaniec and coworkers have classified these complexes into 12 families based on hydrogen-bonding patterns and packing characteristics [7]. Among these families, the Type 10 inclusion form occurs with straight chain esters between five and seven atoms in length [7, 8]. These structures crystallize in $C2/c$ space groups and have a 2:1 gossypol-to-solvent molar ratio.

Because of their structural similarities to esters, five-to-seven carbon ketones would also be expected to form Type 10 gossypol complexes. The only ketone of this size studied to date is 3-hexanone, which does form a Type 10 structure [8]. In this work, we studied the crystallization of gossypol with 2-pentanone, 3-pentanone, and 2-hexanone. Inclusion compounds were formed with all three solvents, and the structure of each

was determined by low-temperature X-ray diffraction. Both pentanone complexes form typical Type 10 structures; the gossypol–2-hexanone complex, however, forms a related structure that has not been previously observed.

Experimental

Gossypol was dissolved in each ketone until the solutions were close to saturated. Hexane was then added to induce crystallization at room temperature (20–22 °C), which yielded the inclusion compounds. Single crystals of an appropriate size were either selected or cut from larger crystals.

A Siemens diffractometer with a graphite monochromator and a SMART 1K CCD detector was used for data collection. The radiation source was $MoK\alpha$ ($\lambda = 0.71073 \text{ \AA}$), and at least two full sets of ω and ϕ scans were collected for each compound at $-123 \text{ }^\circ\text{C}$. Each set of data was integrated with the Bruker SAINT system [9] and corrected for Lorenz, polarization, and absorption effects. The Bruker SHELX NT system (version 5.1) [10] was used for structure solution and refinement. Initial solutions were obtained by direct methods (SHELXS-97), and all three structures were refined by least-squares optimization on F^2 over all

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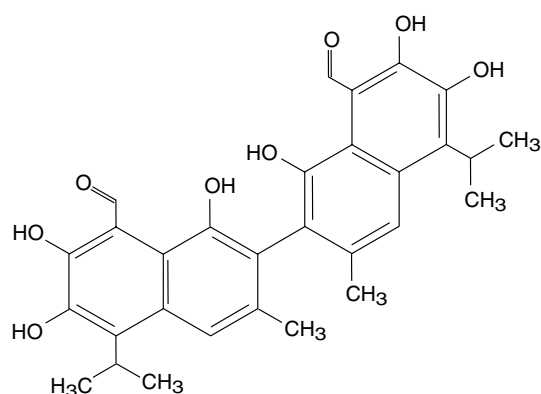


Figure 1. Structure of gossypol.

unique reflections. A full-matrix optimization approach was used for the gossypol–pentanone complexes, and a block-diagonal approach was used for the larger gossypol-2-hexanone complex. All non-hydrogen atoms were refined anisotropically. All of the hydrogen atoms for the gossypol-3-pentanone structure and most of the hydrogen atoms for the other two structures were located from difference maps and were refined isotropically. The remaining hydrogen atoms, which were all associated with disordered solvent molecules, were either placed as riding atoms or refined as rotating groups. The gossypol hydroxyl hydrogen atoms that form hydrogen bonds to the disordered solvent molecules were also problematic. In the structure containing 2-pentanone, the disordered solvent carbonyl groups were positioned very close to each other and only a

Table 1. Crystal and diffraction data for the inclusion complexes formed between gossypol and 2-pentanone, 3-pentanone and 2-hexanone

	Gossypol-2-pentanone (2:1)	Gossypol-3-pentanone (2:1)	Gossypol-2-hexanone (2:1)
<i>Crystal data</i>			
Empirical formula	2C ₃₀ H ₃₀ O ₈ · C ₅ H ₁₀ O	2C ₃₀ H ₃₀ O ₈ · C ₅ H ₁₀ O	2C ₃₀ H ₃₀ O ₈ · C ₆ H ₁₂ O
Formula weight, Z	1123.27, 4	1123.27, 4	1137.30, 12
Crystal color and habit	Yellow, rhombic prism	Yellow, rhombic prism	Yellow, rhombic prism
Crystal size, mm	0.15 × 0.15 × 0.6	0.40 × 0.60 × 1.0	0.30 × 0.35 × 0.55
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	C2/c	C2/c	Cc
Unit cell dimensions, Å	<i>a</i> = 11.0142(9) <i>b</i> = 30.625(3) <i>c</i> = 16.331(1)	<i>a</i> = 11.104(1) <i>b</i> = 30.550(3) <i>c</i> = 16.2340(2)	<i>a</i> = 11.1899(4) <i>b</i> = 91.503(3) <i>c</i> = 16.4273(6)
Unit cell angles, °	β = 91.201(1)	β = 90.808(3)	β = 90.970(1)
Cell volume, Å ³	5507.3(8)	5508(2)	16,817(1)
Cal. density, g/cm ³	1.355	1.354	1.347
<i>F</i> (0 0 0)	2384	2384	7248
<i>Data collection</i>			
2 θ range, °	3.64–50.06	2.66–66.56	3.56–53.42
Index range	–12 ≤ <i>h</i> ≤ 6 –18 ≤ <i>k</i> ≤ 34 –18 ≤ <i>l</i> ≤ 18	–17 ≤ <i>h</i> ≤ 17 –47 ≤ <i>k</i> ≤ 46 –25 ≤ <i>l</i> ≤ 24	–11 ≤ <i>h</i> ≤ 13 –113 ≤ <i>k</i> ≤ 96 –20 ≤ <i>l</i> ≤ 19
Reflections collected	10,499	53,710	50,913
Unique reflections	4368	10,602	26,185
Observed reflection (>2 σ (<i>I</i>))	1909	3805	19,435
μ , mm ^{–1}	0.098	0.098	0.097
<i>R</i> _{int}	0.0548	0.0564	0.0289
<i>R</i> _{sigma}	0.1542	0.1947	0.0477
Completeness to 2 θ , %	89.4	99.7	87.2
Absorption correction	Empirical <i>T</i> _{min} = 0.697899 <i>T</i> _{max} = 1.000000	Empirical <i>T</i> _{min} = 0.760751 <i>T</i> _{max} = 1.000000	Empirical <i>T</i> _{min} = 0.740195 <i>T</i> _{max} = 1.000000
<i>Refinement</i>			
Data/parameters/restraints	4368/538/33	10602/511/0	26185/2672/828
Weighting factor	$W = q/[\sigma^2(F_o^2) + (0.0278P)^2]$ $q = \exp[-(6.0(\sin\theta)/\lambda)^2]$ $P = (F_o^2 + 2F_c^2)/3$	$W = q/[\sigma^2(F_o^2) + (0.0339P)^2]$ $q = \exp[4.0(\sin\theta)/\lambda^2]$ $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0810P)^2]$ $P = (F_o^2 + 2F_c^2)/3$ 0.3(6)
<i>Flack parameter</i>			
<i>R</i> indices (observed data)	<i>R</i> ₁ = 0.0385, <i>wR</i> ₂ = 0.0735	<i>R</i> ₁ = 0.0368, <i>wR</i> ₂ = 0.0806	<i>R</i> ₁ = 0.0492, <i>wR</i> ₂ = 0.1198
<i>R</i> indices (all data)	<i>R</i> ₁ = 0.1009, <i>wR</i> ₂ = 0.0867	<i>R</i> ₁ = 0.0991, <i>wR</i> ₂ = 0.0882	<i>R</i> ₁ = 0.0762, <i>wR</i> ₂ = 0.1354
GOF	1.066	0.999	1.033
Largest residual peak, e/Å ³	0.174	0.305	0.387
Largest residual hole, e/Å ³	–0.232	–0.210	–0.270
RMS difference, e/Å ³	0.052	0.049	0.053

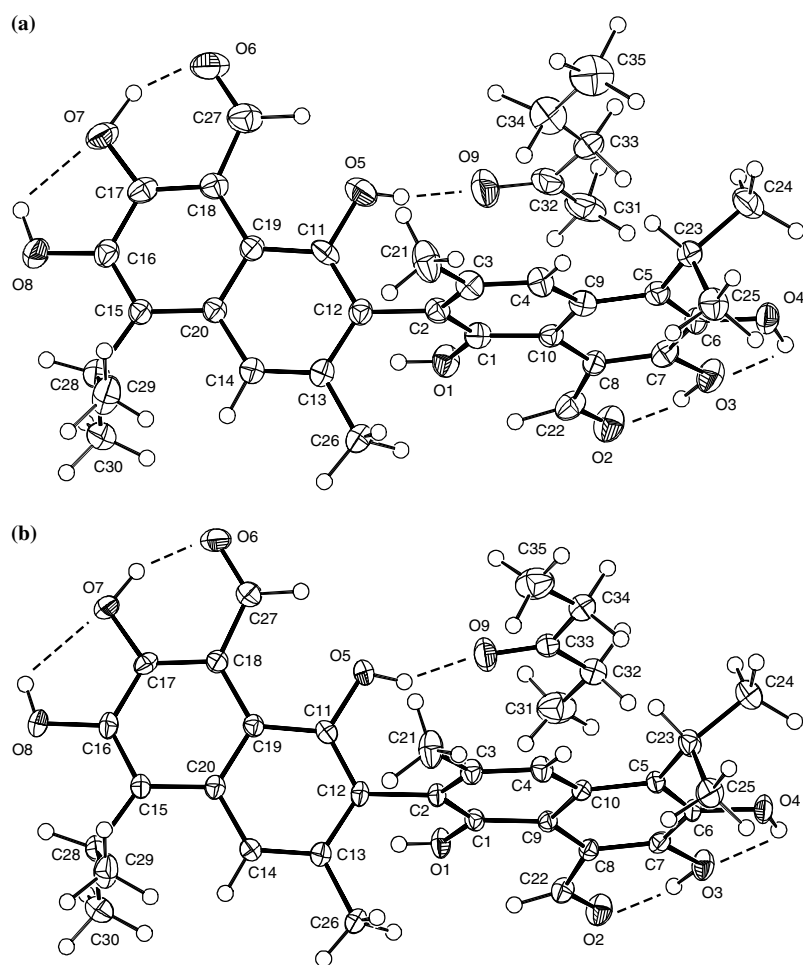


Figure 2. ORTEP diagram (50% probability level) of the gossypol-2-pentanone (2:1) (a) and gossypol-3-pentanone (2:1) (b) crystal forms. Only half of each solvent molecule is part of the asymmetric unit. For the gossypol-2-pentanone structure, only one of the two equivalent solvent orientations is shown.

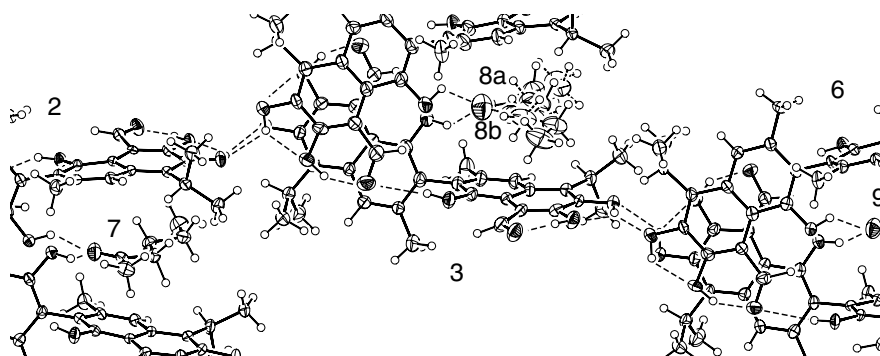


Figure 3. ORTEP diagram (50% probability level) of the gossypol-2-hexanone (2:1) crystal form. The asymmetric unit consists of six gossypol molecules (labeled 1 through 6) and three 2-hexanone molecules (labeled 7 through 9) and form three distinct di-gossypol-solvent assemblies. The disordered solvent in the middle assembly was modeled in two orientations (labeled 8a and 8b) with occupancy factors of 83% and 17%. The atom numbering of the gossypol molecules is as given in Figure 2.

single position was considered for the gossypol hydroxyl hydrogen atoms that hydrogen bond to these groups. In the structure with 2-hexanone, the disordered solvent

carbonyl groups were separated by a significant distance, and the gossypol hydroxyl hydrogen atoms that form hydrogen bonds to these carbonyl groups were

Table 2. Hydrogen bond geometries in the gossypol-2-pentanone (2:1) crystal form

Bond	$d(\text{D-H}), \text{\AA}$	$d(\text{H}\cdots\text{A}), \text{\AA}$	$d(\text{D}\cdots\text{A}), \text{\AA}$	$\langle (\text{D-H}\cdots\text{A}), ^\circ$
<i>Intramolecular</i>				
O(3)-H \cdots O(2)	0.97(3)	1.60(3)	2.491(3)	150(3)
O(4)-H \cdots O(3)	0.90(3)	2.04(3)	2.588(3)	118(2)
O(7)-H \cdots O(6)	0.93(3)	1.64(3)	2.484(3)	148(3)
O(8)-H \cdots O(7)	0.87(3)	2.13(3)	2.623(3)	115(2)
<i>Intermolecular</i>				
O(5)-H \cdots O(9)	0.78(3)	1.92(3)	2.593(5)	145(3)
O(5)-H \cdots O(9) ⁱ	0.78(3)	2.49(3)	3.135(5)	140(3)
O(4)-H \cdots O(8) ⁱⁱ	0.90(3)	2.17(3)	2.962(3)	147(3)
O(8)-H \cdots O(4) ⁱⁱⁱ	0.87(3)	2.17(3)	2.889(3)	139(3)

i = $-x + 2, y, -z + 1/2$; ii = $-x + 1/2, y + 1/2, -z + 1/2$; iii = $x + 1/2, y - 1/2, z$.

Table 3. Hydrogen bond geometries in the gossypol-3-pentanone (2:1) crystal form

Bond	$d(\text{D-H}), \text{\AA}$	$d(\text{H}\cdots\text{A}), \text{\AA}$	$d(\text{D}\cdots\text{A}), \text{\AA}$	$\langle (\text{D-H}\cdots\text{A}), ^\circ$
<i>Intramolecular</i>				
O(3)-H \cdots O(2)	0.88(2)	1.68(2)	2.488(1)	152(2)
O(4)-H \cdots O(3)	0.79(2)	2.14(2)	2.593(2)	117(2)
O(7)-H \cdots O(6)	0.84(2)	1.71(2)	2.489(2)	152(2)
O(8)-H \cdots O(7)	0.80(2)	2.17(2)	2.619(1)	116(2)
<i>Intermolecular</i>				
O(5)-H \cdots O(9)	0.79(2)	2.18(2)	2.847(2)	143(2)
O(4)-H \cdots O(8) ⁱ	0.79(2)	2.21(2)	2.932(1)	152(2)
O(8)-H \cdots O(4) ⁱⁱ	0.80(2)	2.25(2)	2.894(1)	138(2)

i = $-x + 1/2, y + 1/2, -z + 1/2$; ii = $x - 1/2, y - 1/2, z$.

expected to be similarly disordered. It was not possible, however, to extract the secondary positions from the data. Instead, each hydroxyl hydrogen atom was refined in a single orientation, resulting in a hydrogen bond forming with the closer of the carbonyl oxygen atoms. Finally, bond distance restraints were used to improve the geometry of the disordered 2-hexanone molecule with the smaller occupancy factor.

The crystallographic data related to these structures have been deposited at the Cambridge Crystallographic Data Center (gossypol-2-pentanone, CCDC no. 224392, gossypol-3-pentanone, CCDC no. 224393, and gossypol-2-hexanone, CCDC no. 224394). Copies of the data can be obtained free of charge by application to the CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK.

Results and discussion

All three structures crystallize in monoclinic systems with a gossypol-to-solvent molar ratio of 2:1. The gossypol-pentanone complexes have C2/c space groups with asymmetric units consisting of one gossypol molecule and one-half solvent molecule. The gossypol-2-hexanone complex has a Cc space group and an asymmetric unit consisting of six gossypol molecules and three solvent molecules. The

unit cell of the 2-hexanone complex is approximately three times larger than the cell of the other two structures. Densities of the three compounds are almost identical (Table 1).

The gossypol conformation in all three complexes is similar to the gossypol conformation in other Type 10 compounds [7]. In each structure, the gossypol molecule exists in the aldehyde tautomeric form (Figures 2 and 3). The naphthalene rings are approximately perpendicular with angles between the best-fit naphthalene planes of 80.0(1)° for the 2-pentanone structure, 77.6(1)° for the 3-pentanone structure, and between 77.2(1)° and 81.6(1)° for the six distinct molecules in the 2-hexanone structure. Intramolecular hydrogen bonds are formed between all of the O(3)-H \cdots O(2), O(4)-H \cdots O(3), O(7)-H \cdots O(6), and O(8)-H \cdots O(7) atoms (Tables 2-4). Unlike most gossypol inclusion complexes, but similar to other Type 10 complexes [7, 8], the gossypol isopropyl moieties are oriented with one set of the methyl groups rotated away from the center of the molecule and the other set rotated toward the center of the molecule (Figures 2 and 3). Recent DFT calculations [11] indicate that the inward orientation of the isopropyl methyl groups is higher in energy than the outward orientation, suggesting that the occurrence of this conformation in Type 10 complexes is stabilized by packing effects.

Table 4. Hydrogen bond geometries in the gossypol-2-hexanone (2:1) crystal form

Bond	$d(\text{D-H})$, Å	$d(\text{H}\cdots\text{A})$, Å	$d(\text{D}\cdots\text{A})$, Å	$\langle(\text{D-H}\cdots\text{A})\rangle$, °
<i>Intramolecular</i>				
O(3) ₁ -H \cdots O(2) ₁	0.95(2)	1.57(2)	2.495(3)	162(4)
O(4) ₁ -H \cdots O(3) ₁	0.89(2)	2.00(4)	2.595(4)	123(3)
O(7) ₁ -H \cdots O(6) ₁	0.92(2)	1.63(2)	2.505(3)	158(4)
O(8) ₁ -H \cdots O(7) ₁	0.90(2)	2.24(4)	2.626(3)	106(3)
O(3) ₂ -H \cdots O(2) ₂	0.90(2)	1.63(2)	2.487(3)	159(4)
O(4) ₂ -H \cdots O(3) ₂	0.91(2)	1.98(3)	2.588(3)	123(3)
O(7) ₂ -H \cdots O(6) ₂	0.96(2)	1.54(2)	2.465(3)	162(4)
O(8) ₂ -H \cdots O(7) ₂	0.89(2)	2.09(3)	2.620(3)	118(3)
O(3) ₃ -H \cdots O(2) ₃	0.93(2)	1.64(3)	2.497(3)	151(4)
O(4) ₃ -H \cdots O(3) ₃	0.92(2)	1.99(4)	2.591(4)	122(3)
O(7) ₃ -H \cdots O(6) ₃	0.95(2)	1.60(3)	2.472(3)	151(4)
O(8) ₃ -H \cdots O(7) ₃	0.92(2)	2.14(8)	2.608(3)	111(6)
O(3) ₄ -H \cdots O(2) ₄	0.92(2)	1.60(2)	2.488(3)	160(4)
O(4) ₄ -H \cdots O(3) ₄	0.91(2)	1.97(3)	2.589(3)	124(3)
O(7) ₄ -H \cdots O(6) ₄	0.92(2)	1.70(3)	2.513(3)	146(4)
O(8) ₄ -H \cdots O(7) ₄	0.90(2)	2.00(3)	2.637(3)	126(3)
O(3) ₅ -H \cdots O(2) ₅	0.89(2)	1.65(2)	2.483(3)	155(4)
O(4) ₅ -H \cdots O(3) ₅	0.90(2)	2.09(3)	2.599(3)	115(3)
O(7) ₅ -H \cdots O(6) ₅	0.92(2)	1.68(3)	2.484(3)	143(3)
O(8) ₅ -H \cdots O(7) ₅	0.88(2)	1.94(3)	2.609(3)	131(3)
O(3) ₆ -H \cdots O(2) ₆	0.91(2)	1.72(3)	2.498(3)	142(4)
O(4) ₆ -H \cdots O(3) ₆	0.87(2)	2.16(3)	2.583(3)	109(3)
O(7) ₆ -H \cdots O(6) ₆	0.92(2)	1.74(3)	2.507(3)	139(4)
O(8) ₆ -H \cdots O(7) ₆	0.92(2)	2.06(3)	2.639(3)	120(3)
<i>Intermolecular</i>				
O(4) ₁ -H \cdots O(8) _{4,i}	0.89(2)	2.27(3)	3.021(2)	142(4)
O(5) ₁ -H \cdots O(9) ₇	0.90(2)	2.21(3)	2.947(3)	140(3)
O(8) ₁ -H \cdots O(4) _{5,ii}	0.90(2)	2.22(3)	2.957(3)	139(3)
O(1) ₂ -H \cdots O(6) ₁	0.89(2)	2.48(7)	3.125(3)	129(7)
O(4) ₂ -H \cdots O(8) ₃	0.91(2)	2.21(3)	2.907(2)	133(3)
O(5) ₂ -H \cdots O(9) ₇	0.89(2)	1.96(3)	2.716(2)	142(3)
O(8) ₂ -H \cdots O(4) _{6,iii}	0.89(2)	2.17(3)	2.889(2)	138(3)
O(1) ₃ -H \cdots O(6) ₄	0.89(2)	2.50(2)	3.336(3)	158(3)
O(4) ₃ -H \cdots O(8) ₆	0.92(2)	2.24(3)	3.017(3)	143(4)
O(5) ₃ -H \cdots O(9) _{8a}	0.91(2)	1.88(3)	2.650(3)	141(3)
O(8) ₃ -H \cdots O(4) _{1,iv}	0.92(2)	2.05(5)	2.882(2)	150(8)
O(4) ₄ -H \cdots O(8) _{5,iv}	0.91(2)	2.13(3)	2.893(2)	141(3)
O(5) ₄ -H \cdots O(9) _{8b}	0.90(2)	1.75(4)	2.225(2)	110(3)
O(5) ₄ -H \cdots O(9) _{8a}	0.90(2)	3.07(5)	3.381(4)	103(3)
O(8) ₄ -H \cdots O(4) ₂	0.90(2)	2.39(3)	2.944(2)	120(3)
O(1) ₅ -H \cdots O(6) ₆	0.88(2)	2.46(2)	3.206(3)	143(3)
O(4) ₅ -H \cdots O(8) _{2,v}	0.90(2)	2.12(2)	2.937(2)	150(3)
O(5) ₅ -H \cdots O(9) ₉	0.88(2)	1.87(3)	2.682(3)	153(4)
O(8) ₅ -H \cdots O(4) ₃	0.88(2)	2.31(3)	2.897(2)	124(3)
O(4) ₆ -H \cdots O(8) _{1,vi}	0.87(2)	2.10(2)	2.937(2)	160(3)
O(5) ₆ -H \cdots O(9) ₉	0.88(2)	2.66(6)	3.049(3)	108(5)
O(8) ₆ -H \cdots O(4) _{4,i}	0.92(2)	2.21(3)	2.899(2)	132(3)

i = $x - 1, y, z$; ii = $x + 1/2, y - 1/2, z$; iii = $x - 1/2, y - 1/2, z$;
iv = $x + 1, y, z$; v = $x - 1/2, y + 1/2, z$; vi = $x + 1/2, y + 1/2, z$.

For all three complexes, pairs of gossypol molecules of the same chirality are orientated with one pair of naphthalene rings stacked on top of each other and the other pair separated to form the top and bottom of a solvent cavity (Figure 4). The three molecules together (two gossypol molecules and one solvent molecule) form an assembly that repeats throughout the unit cell. Within the assembly, the two gossypol O(5) hydroxyl groups are located on the same side of the solvent cage such both can form hydrogen bonds with the solvent molecule. The assembly also appears to be supported by a pair of weak gossypol-to-gossypol interactions between the O(1) hydroxyl groups and the O(6) carbonyl groups (Figure 4). These O \cdots O distances in the 2-pentanone and 3-pentanone complexes are 3.75 and 3.68 Å, respectively, and are too large to indicate significant hydrogen bonds. Nevertheless, in each of these interactions the O(1) hydroxyl hydrogen atom is directed toward the O(6) carbonyl oxygen atom of the other gossypol molecule.

For both gossypol-pentanone structures, the solvent cages have C₂ rotational symmetry. The C₂ symmetry of the 3-pentanone molecule allows it to reside symmetrically on the solvent cavity with the carbonyl bond aligned on the cavity's rotation axis and with the carbonyl oxygen atom forming equivalent hydrogen bonds with each of the gossypol O(5)-H hydrogen atoms (Table 3). In contrast, the 2-pentanone molecule, which lacks C₂ symmetry, takes two equivalent orientations within the cavity. Because these carbonyl oxygen atoms are not located on the cavity's rotation axis, each orientation forms unequal hydrogen bonds with the O(5) hydroxyl hydrogen atoms (Table 2). Similar solvent disorder is found in other Type 10 compounds [7].

Intermolecular gossypol-to-gossypol hydrogen bonds form between the O(4)-H and O(8) atoms and between the O(8)-H and O(4) atoms. Each O(4)-H and O(8)-H group, in effect, hydrogen bonds to two hydroxyl oxygen atoms (one intramolecular and one intermolecular) and one hydroxyl hydrogen atom (Tables 2 and 3). These hydrogen bonds tie the di-gossypol-solvent assemblies into enantiomorphic layers that run parallel to the *ab* plane (Figure 5). Adjacent layers are composed of gossypol molecules of the opposite enantiomer, and the layers form a van der Waals type of packing.

Although the gossypol-2-hexanone complex is similar to the gossypol-pentanone complexes and other Type 10 complexes, this structure differs in a number of features because of the distal positioning of 2-hexanone carbonyl moiety. The asymmetric unit consists of three distinct di-gossypol-solvent assemblies (Figure 3). The gossypol molecules in the assemblies reside slightly askew of each other, and the solvent cavities do not have C₂ symmetry. None of the 2-hexanone molecules are equally disordered within the structure. In two of the cavities, the 2-hexanone molecule exists in a single orientation, but are

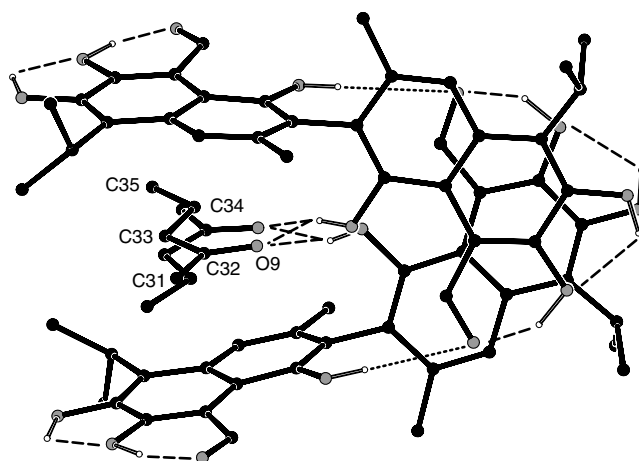


Figure 4. Packing of a pair of gossypol molecules and the disordered guest molecule in the inclusion compound with 2-pentanone. The crystallography equivalent orientations of the guest molecule are shown. Hydrogen bonds are indicated by dashes. The weak O(1)–H···O(6) interactions are shown as dotted lines.

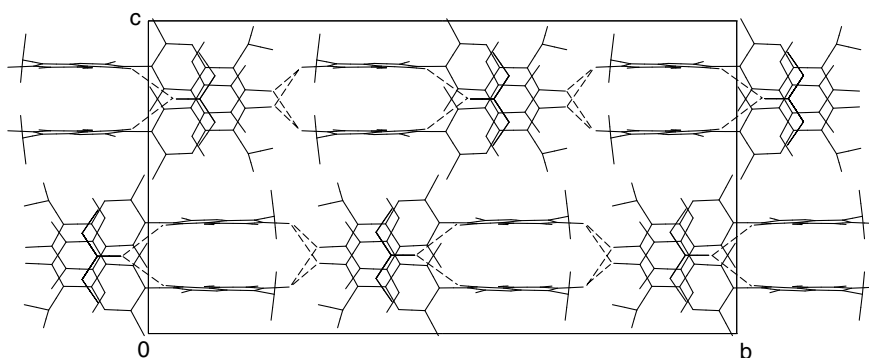


Figure 5. Packing of molecules in the gossypol-3-pentanone (2:1) crystal form. Gossypol layers (parallel to the *ab* plane) are composed of a single gossypol enantiomer with adjacent layers composed of the opposite enantiomer. Hydrogen bonds are indicated by dashes.

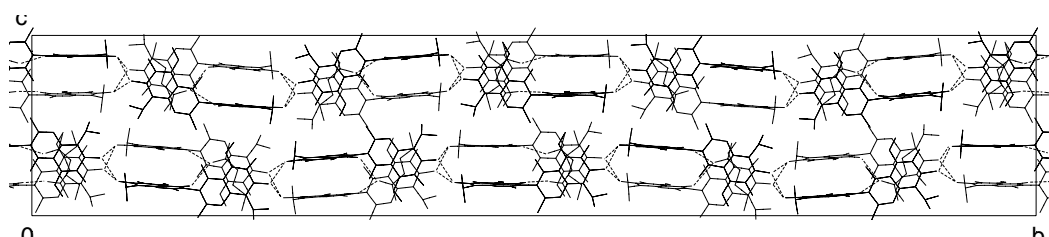


Figure 6. Packing diagram for the gossypol-2-hexanone (2:1) crystal form. As for the pentanone structures, gossypol layers (parallel to the *ab* plane) are composed of a single gossypol enantiomer with adjacent layers composed of the opposite enantiomer. Hydrogen bonds are indicated by dashes.

orientated such that the carbonyl oxygen atoms still form hydrogen bonds with both gossypol O(5) hydroxyl groups (Table 4). In the third cavity, the solvent is disordered with occupancies of 83% and 17%. The 2-hexanone carbonyl oxygen atoms in this cavity are positioned such that each tends to form a hydrogen bond with the closest gossypol O(5) hydroxyl group. Only a weak interaction is possible with the other O(5) hydroxyl group. All of the

2-hexanone molecules are oriented with their aliphatic tails extending at an angle of $\sim 30^\circ$ toward the ends of the gossypol molecules, which appears to occur so that the solvent does not extend much beyond the surrounding top and bottom naphthalene rings. The skewing of the assemblies is apparent from the geometries of the weak O(1)–H···O(6) interactions. In the gossypol–pentanone assemblies, symmetry forces these interactions to have identical geometries.

In the gossypol-2-hexanone assemblies, one of these interactions becomes stronger and the other becomes weaker. The stronger interactions have typical hydrogen-bond geometries (Table 4). The weaker interactions have O...O distances between 4.15(3) and 4.46(3) Å, which are too long to be considered hydrogen bonds. Still, the O(1) hydroxyl hydrogen atoms are directed toward the O(6) atoms in these interactions.

The packing of the assemblies within the 2-hexanone complex is similar to other Type 10 structures. Intramolecular hydrogen bonds are formed between the O(4) hydroxyl hydrogen and O(8) atoms and between the O(8) hydroxyl hydrogen and O(4) atoms, both within and between asymmetric units (Table 4). This leads a packing arrangement that is similar to the gossypol-pentanone complexes with gossypol layers formed from molecules of the same chirality that run parallel to the *ab* plane. The packing of the assemblies, however, is somewhat disrupted, which is apparent from the orientations of the pairs of naphthalene rings not involved in forming the top or bottom of the solvent cage. In typical Type 10 structures, these planar rings are aligned parallel to the *ab* plane (Figure 5). In the gossypol-2-hexanone complex, one ring pair is oriented almost parallel to the *ab* plane, the ring pair in the next assembly is tilted downward, and the ring pair in the third assembly is tilted upward (Figure 6). As for the other Type 10 structures, adjacent gossypol layers have the opposite chirality, and these layers form only van der Waals contacts with each other.

One variation of the Type 10 packing scheme has already been reported in the structure of gossypol-isobutylacetate (2:1) [12]. In this compound, the branched aliphatic side chain of the guest molecule distorts the solvent cage resulting in the loss of C₂ symmetry. In addition, the isobutylacetate molecules are not equally disordered within the cavity, but instead

have a 33% and 67% distribution. A larger asymmetric unit is formed, which contains two gossypol molecules and one solvent molecule (i.e., one assembly) and the space group becomes P2₁/n. Nevertheless, this structure has a unit cell that is the same size as the typical Type 10 structure. In the gossypol-2-hexanone (2:1) complex, the disruption of the structure is more severe. Three distinct assemblies are required to form the asymmetric unit, and the unit cell is three times longer than that of the typical Type 10 complex. The structure represents a third variation of the Type 10 family of gossypol inclusion compound.

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