

Inclusion Complexes of the Natural Product Gossypol. Crystal Structure of the 2:1 Complex of Gossypol with Amyl Acrylate

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

Abstract. The crystal structure of the 2:1 inclusion complex of gossypol with amyl acrylate has been determined by X-ray structure analysis. The crystals of $(C_{30}H_{30}O_8)_2 \cdot C_8H_{14}O_2$ are triclinic, space group $P\bar{1}$, $a = 14.425(2)$, $b = 15.519(1)$, $c = 16.409(2)$ Å, $\alpha = 97.89(1)$, $\beta = 117.80(1)$, $\gamma = 67.01(1)^\circ$ [reduced cell: $a = 14.425(2)$, $b = 15.519(2)$, $c = 16.017(2)$ Å, $\alpha = 92.19(1)$, $\beta = 115.01(1)$, $\gamma = 67.01(1)^\circ$], $V = 2986.7(5)$ Å³, $Z = 2$, $D_x = 1.31$ g cm⁻³, $\mu(\text{Cu } K\alpha) = 7.40$ cm⁻¹, $T = 292$ K. The structure has been solved by direct methods and refined to the final R value of 0.059 for 5155 observed reflections. The gossypol molecules bonded via several hydrogen bonds form centrosymmetric tetramers. The two independent gossypol molecules, A and B, are related within the tetramer by a local noncrystallographic 2-fold axis. The host molecules in the crystal form cavities in which two guest molecules are placed. The ester molecule interacts via a pair of $C=O \cdots H-O$ hydrogen bonds with two gossypol molecules of the same chirality and belonging to the same tetramer unit. The amyloxy group of the ester molecule shows a very large thermal motion. It adopts a non-extended conformation in which it can be fitted into the cavity formed by the host molecules.

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 82083 (42 pages)

1. Introduction

In a series of previous publications we have reported that gossypol (Figure 1) is a very versatile host forming lattice inclusion compounds with a large number of organic guest molecules [1]. For example, it forms isostructural clathrate-type inclusion compounds with carbonyl group-containing guest molecules if they comprise a chain of five to seven nonhydrogen atoms. These clathrates crystallize in the monoclinic system, space group $C2/c$ [2–4]. When the guest molecule has a chain shorter than five atoms then channel-type host: guest complexes are formed and the crystal symmetry is lowered to triclinic [5]. For guest molecules with chains longer than seven atoms a new type of host: guest complex is obtained with a host: guest molecular ratio of 2:1. Isostructural inclusion compounds of this type are formed

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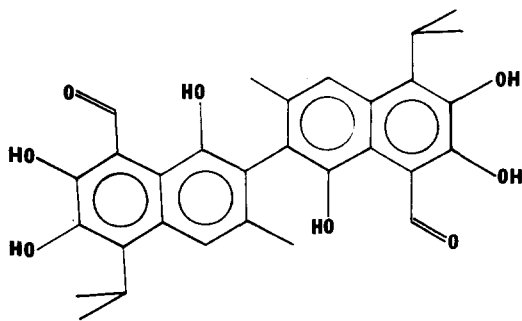


Fig. 1. Chemical formula of gossypol.

by amyl acetate and amyl acrylate. This article presents the crystal structure of a 2:1 inclusion complex of gossypol with amyl acrylate.

2. Experimental

Single crystals of gossypol:0.5 amyl acrylate were obtained by slow diffusion of nonpolar solvents such as *n*-hexane, benzene or isooctane into a gossypol solution in amyl acrylate. The yellow crystals were plate shaped and stable when exposed to the air. A specimen cut to approximate dimensions of $0.08 \times 0.2 \times 0.4$ mm was used for measurements on a Syntex P2₁ diffractometer. Lattice parameters were determined by a least-squares fitting of the setting angles of 15 reflections (2θ in the range $18\text{--}24^\circ$).

The crystal data are as follows: $(C_{30}H_{30}O_8)_2 \cdot C_8H_{14}O_2$, triclinic, space group $P\bar{1}$, $a = 14.425(2)$, $b = 15.519(1)$, $c = 16.409(2)$ Å, $\alpha = 97.89(1)$, $\beta = 117.80(1)$, $\gamma = 67.01(1)^\circ$ [reduced cell: $a = 14.425(2)$, $b = 15.519(2)$, $c = 16.017(2)$ Å, $\alpha = 92.19(1)$, $\beta = 115.01(1)$, $\gamma = 67.01(1)^\circ$], $V = 2986.7(5)$ Å³, $Z = 2$, $D_x = 1.31$ g cm⁻³, $\mu(\text{Cu } K_\alpha) = 7.40$ cm⁻¹, $T = 292$ K.

Intensities of reflections were measured with graphite monochromatized Cu K_α radiation ($\lambda = 1.514178$ Å) to $2\theta_{\text{max}} = 115^\circ$. 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 [6]. Data were corrected for Lorentz and polarization effects but not for absorption. Out of 7667 measured reflections 5155 had $I > 2\sigma(I)$. The structure was solved by direct methods using the program MULTAN80 [7]. The atoms from the naphthalene skeleton of the gossypol molecules were located on an E map. The remaining atoms were found from subsequent ΔF syntheses. The carbon atoms from the amyl group of the guest molecule were identified as very low peaks on Fourier maps. The structure was refined first with isotropic and then with anisotropic temperature factors by least-squares methods using the program SHELX76 [8]. The hydrogen atoms of the hydroxyl groups, acryl group and methyl groups at C(3) and C(13) were located on a ΔF map. The remaining hydrogen atoms were placed in calculated positions [$d(\text{C—H}) = 1.08$ Å]. The hydrogen atoms of the amyl group were not localized. Hydrogen atoms of the hydroxyl groups were allowed to vary during the refinement. An empirical isotropic extinction parameter

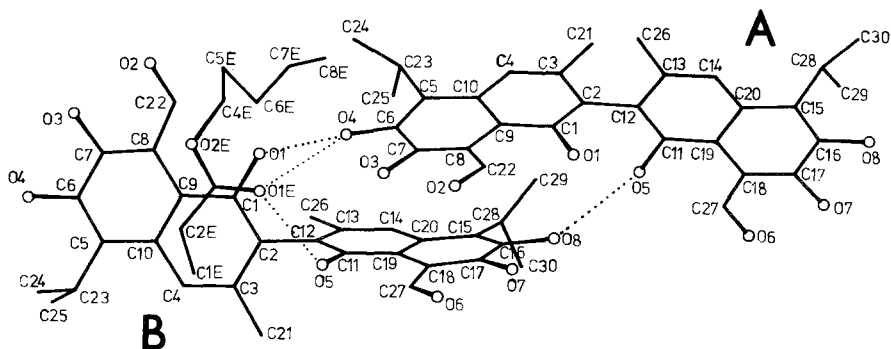


Fig. 2. The atom numbering scheme of the gossypol molecules and amyl acrylate.

χ was used to correct F_c according to $F' = F_c(1 - \chi F_c^2 / \sin \theta)$; χ converged at $46(4) \times 10^{-8}$. Final values of R and WR are 0.059 and 0.067, respectively. The weighting scheme used was $W^{-1} = k[\sigma^2(F_0) + 0.0001F_0^2]$. In the final ΔF map, calculated after the last cycle of refinement, the maximum and minimum peaks were 0.29 and $-0.30 \text{ e } \text{\AA}^{-3}$, respectively. The scattering factors used in calculations were those included in SHELX76 [8]. Drawings were prepared with the program PLUTO [9]. Final atomic parameters are given in Table I. Lists of bond lengths and angles, deviations of atoms from least-squares planes, anisotropic thermal parameters of non-hydrogen atoms, parameters of hydrogen atoms and structure factors have been deposited with the British Library Lending Division, and copies may be ordered quoting Sup. No. 82083. The numbering scheme of atoms is shown in Fig. 2.

3. Results and Discussion

3.1. MOLECULAR STRUCTURE

The gossypol used for our studies was isolated from cotton seed and was racemic while that obtained from the other source [10] is optically active. The reason for the optical activity of gossypol lies in a restricted rotation around the C(2)—C(12) bond. The presence of bulky substituents in 1,1', 3,3' positions makes a coplanar conformation of binaphthyl units energetically strongly unfavourable. The dihedral angles between naphthyl groups, as found in the crystal structures of gossypol, are centered around the value of 90° and range from 70° in the gossypol:acetic acid complex [9] to 105.5° in molecule B of gossypol:0.5 amyl acrylate. Values larger than 100° were observed when gossypol did not form centrosymmetric dimers through a pair of O(5)—H \cdots O(3) hydrogen bonds, i.e. in ethyl acetate type complexes [2–4]. The dihedral angle between naphthyl nuclei in molecule A of the present complex is $97.6(1)^\circ$.

Those naphthyl rings of molecules A and B which overlap when the molecules are transformed through the local 2-fold axis show appreciable nonplanarity of the aromatic ring systems, the maximum deviation being $0.137(4) \text{ \AA}$ for C(6) of

Table I. 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	x/a	y/b	z/c	U_{eq}
C(1A)	0.8983(3)	0.2879(3)	0.4646(3)	0.053(2)
C(2A)	0.8348(3)	0.2405(3)	0.4645(3)	0.055(2)
C(3A)	0.8472(4)	0.1524(3)	0.4234(3)	0.070(3)
C(4A)	0.9169(4)	0.1197(3)	0.3828(3)	0.071(3)
C(5A)	1.0449(3)	0.1348(3)	0.3282(3)	0.058(3)
C(6A)	1.0936(3)	0.1910(3)	0.3200(3)	0.058(3)
C(7A)	1.0972(3)	0.2712(3)	0.3715(3)	0.057(3)
C(8A)	1.0426(3)	0.3028(3)	0.4262(3)	0.052(2)
C(9A)	0.9741(3)	0.2542(3)	0.4253(3)	0.052(2)
C(10A)	0.9798(3)	0.1687(3)	0.3798(3)	0.057(2)
C(21A)	0.7848(6)	0.0954(5)	0.4269(6)	0.120(6)
C(22A)	1.0664(4)	0.3762(3)	0.4874(3)	0.068(3)
C(23A)	1.0572(4)	0.0403(3)	0.2847(3)	0.073(3)
C(24A)	1.1753(4)	-0.0197(3)	0.2983(4)	0.099(4)
C(25A)	0.9691(5)	0.0505(4)	0.1855(4)	0.105(4)
O(1A)	0.8894(3)	0.3729(2)	0.5038(2)	0.069(2)
O(2A)	1.1283(3)	0.4142(2)	0.4883(2)	0.086(2)
O(3A)	1.1606(3)	0.3122(2)	0.3647(2)	0.075(2)
O(4A)	1.1464(3)	0.1685(2)	0.2642(2)	0.074(2)
C(11A)	0.6443(4)	0.3268(3)	0.4562(3)	0.054(3)
C(12A)	0.7569(3)	0.2789(3)	0.5079(3)	0.053(3)
C(13A)	0.7980(3)	0.2638(3)	0.6032(3)	0.059(3)
C(14A)	0.7238(4)	0.2944(3)	0.6406(3)	0.061(3)
C(15A)	0.5302(4)	0.3662(3)	0.6288(3)	0.059(3)
C(16A)	0.4179(4)	0.4160(3)	0.5745(3)	0.057(3)
C(17A)	0.3743(3)	0.4372(3)	0.4797(3)	0.052(3)
C(18A)	0.4425(3)	0.4068(3)	0.4354(3)	0.050(2)
C(19A)	0.5627(3)	0.3589(3)	0.4903(3)	0.049(2)
C(20A)	0.6066(3)	0.3395(3)	0.5871(3)	0.053(3)
C(26A)	0.9222(5)	0.2135(5)	0.6643(4)	0.089(4)
C(27A)	0.3864(4)	0.4220(4)	0.3374(3)	0.079(3)
C(28A)	0.5741(4)	0.3370(4)	0.7287(3)	0.080(3)
C(29A)	0.5986(5)	0.4133(4)	0.7928(4)	0.109(4)
C(30A)	0.5166(6)	0.2909(6)	0.7481(5)	0.167(7)
O(5A)	0.6014(3)	0.3473(3)	0.3634(2)	0.078(2)
O(6A)	0.2824(2)	0.4659(2)	0.2919(2)	0.090(2)
O(7A)	0.2629(3)	0.4852(2)	0.4353(3)	0.068(2)
O(8A)	0.3425(3)	0.4459(2)	0.6110(3)	0.075(2)
C(1B)	-0.1264(3)	0.8442(3)	0.9922(3)	0.052(2)
C(2B)	-0.0410(3)	0.7561(3)	1.0147(3)	0.050(2)
C(3B)	-0.0270(3)	0.6970(3)	1.0807(3)	0.054(2)
C(4B)	-0.0968(3)	0.7285(3)	1.1219(3)	0.055(2)
C(5B)	-0.2503(3)	0.8513(3)	1.1513(3)	0.055(2)
C(6B)	-0.3346(4)	0.9378(3)	1.1269(3)	0.062(3)
C(7B)	-0.3524(3)	0.9972(3)	1.0594(3)	0.056(2)
C(8B)	-0.2855(3)	0.9724(3)	1.0142(3)	0.054(2)
C(9B)	-0.1976(3)	0.8802(3)	1.0358(3)	0.050(2)
C(10B)	-0.1816(3)	0.8199(3)	1.1031(3)	0.052(2)

Table I. (Continued)

Atom	x/a	y/b	z/c	U_{eq}
C(21B)	0.0645(5)	0.6013(4)	1.1073(4)	0.077(4)
C(22B)	-0.3044(4)	1.0442(3)	0.9551(3)	0.075(3)
C(23B)	-0.2318(4)	0.7885(3)	1.2251(3)	0.075(3)
C(24B)	-0.2230(5)	0.8353(5)	1.3150(4)	0.126(5)
C(25B)	-0.3203(5)	0.7446(4)	1.1866(5)	0.126(5)
O(1B)	-0.1436(3)	0.9004(2)	0.9248(2)	0.070(2)
O(2B)	-0.3813(3)	1.1231(2)	0.9380(2)	0.087(2)
O(3B)	-0.4393(3)	1.0809(2)	1.0424(2)	0.074(2)
O(4B)	-0.4062(3)	0.9699(3)	1.1670(2)	0.084(2)
C(11B)	0.0367(3)	0.6636(3)	0.9075(3)	0.051(2)
C(12B)	0.0399(3)	0.7289(3)	0.9741(3)	0.052(2)
C(13B)	0.1250(3)	0.7666(3)	1.0070(3)	0.056(3)
C(14B)	0.2000(3)	0.7396(3)	0.9713(3)	0.060(3)
C(15B)	0.2708(3)	0.6555(3)	0.8598(3)	0.064(3)
C(16B)	0.2594(4)	0.5965(3)	0.7891(3)	0.065(3)
C(17B)	0.1827(4)	0.5506(3)	0.7601(3)	0.060(3)
C(18B)	0.1110(3)	0.5655(3)	0.7997(3)	0.056(3)
C(19B)	0.1137(3)	0.6331(3)	0.8694(3)	0.052(2)
C(20B)	0.1958(3)	0.6752(3)	0.9009(3)	0.056(2)
C(26B)	0.1330(5)	0.8368(4)	1.0816(4)	0.074(3)
C(27B)	0.0445(4)	0.5079(3)	0.7695(3)	0.080(4)
C(28B)	0.3593(5)	0.6991(4)	0.8941(4)	0.094(4)
C(29B)	0.3580(6)	0.7492(5)	0.8224(4)	0.128(5)
C(30B)	0.4719(5)	0.6344(6)	0.9587(5)	0.165(6)
O(5B)	-0.0442(3)	0.6247(2)	0.8753(2)	0.070(2)
O(6B)	0.0431(3)	0.4505(2)	0.7088(2)	0.089(2)
O(7B)	0.1860(3)	0.4909(2)	0.6933(2)	0.078(2)
O(8B)	0.3260(3)	0.5772(3)	0.7449(2)	0.088(2)
O(1E)	0.2606(3)	0.2437(2)	0.1963(2)	0.097(3)
O(2E)	0.4200(3)	0.1335(3)	0.2023(3)	0.129(3)
C(1E)	0.2814(5)	0.3529(5)	0.0835(4)	0.114(4)
C(2E)	0.3399(4)	0.2658(5)	0.1071(4)	0.103(4)
C(3E)	0.3349(4)	0.2157(4)	0.1724(4)	0.093(4)
C(4E)	0.4168(7)	0.0740(7)	0.2639(7)	0.178(8)
C(5E)	0.506(1)	0.048(1)	0.347(1)	0.31(2)
C(6E)	0.4675(9)	0.1485(7)	0.3860(9)	0.22(1)
C(7E)	0.481(2)	0.117(1)	0.466(2)	0.43(3)
C(8E)	0.479(3)	0.143(2)	0.540(2)	0.72(3)

molecule A. The substituents are also significantly out of the ring planes. The puckering scheme of these two ring systems is similar but the degree of ring puckering is larger in molecule A than in molecule B (Table V, Supplementary Material). Even though the naphthyl rings of gossypol are abundantly substituted, giving rise to serious steric repulsions within the molecule, the nonplanarity of the ring systems is not a characteristic feature of the gossypol molecule, as one would expect. When the gossypol molecules form centrosymmetric dimers the naphthyl rings which overlap are usually planar or nearly planar. The question remains whether the planarity or nonplanarity of the naphthyl rings of gossypol is induced by crystal forces.

Table II. Selected torsion angles in gossypol and amyl acrylate

	Molecule A	Molecule B
<i>Gossypol</i>		
C(1)—C(2)—C(12)—C(11)	97.9(6)	-108.7(5)
<i>Amyl acrylate</i>		
C(1E)—C(2E)—C(3E)—O(2E)	-165.4(7)	
C(2E)—C(3E)—O(2E)—C(4E)	-175.4(7)	
C(3E)—O(2E)—C(4E)—C(5E)	-123(1)	
O(2E)—C(4E)—C(5E)—C(6E)	76(1)	
C(4E)—C(5E)—C(6E)—C(7E)	132(2)	
C(5E)—C(6E)—C(7E)—C(8E)	174(4)	

3.2. CRYSTAL PACKING

Gossypol containing six hydroxyl and two aldehyde groups per molecule may form a very rich hydrogen bond network in the crystalline state. The hydrogen atoms of the hydroxyl groups are of very different nature. The H atoms bonded to O(3) and O(7) are involved in strong intramolecular hydrogen bonds which are a part of six-membered conjugated ring systems. The H atoms at O(4) and O(8) usually take part in a bifurcated hydrogen bond, one component being an intramolecular hydrogen bond closing a five-membered ring, the other being an intermolecular bond. The hydroxyl groups O(1)—H and O(5)—H are in most cases the donors of intermolecular hydrogen bonds. As observed in other gossypol inclusion complexes, these groups act as "sensors" which recognize the guest molecule when it is able to accept a hydrogen bond.

The geometry of the intramolecular, as well as of the intermolecular hydrogen bonds found in the crystal structure of the investigated complex is given in Table III. The crystal packing is shown in Figure 3. As has been observed in almost all gossypol lattice inclusion complexes investigated so far, centrosymmetric dimers are formed through pairs of O(1)—H···O(7) hydrogen bonds by molecules of type A. Molecules of type B join to this dimer *via* three hydrogen bonds to form a centrosymmetric tetramer unit with a local noncrystallographic 2-fold axis relating molecules A and B (Figure 4). This molecular arrangement is closely related to the packing motif observed in the complex of gossypol with isovaleric acid [11] where centrosymmetric gossypol dimers related by a crystallographic 2-fold axis form a similar hydrogen bond network. However, while in that complex the host molecules are packed into infinite columns, in the complex with amyl acrylate the column formation is stopped due to hydrogen bond interaction between gossypol and the guest molecules. When the gossypol tetramer units pack into the crystal they form voids in which two ester molecules are enclosed. The acryloxy group of the guest molecule is nearly parallel to one of the naphthyl rings of molecule B (the dihedral angle between these planes is 9.8°). The carbonyl oxygen atom is an acceptor of two hydrogen bonds, one strong bond formed with O(5) of molecule B and one weak bond formed with O(4) of molecule A. The molecules of type A and B which

Table III. Geometry of hydrogen bonds

D—H...A	D...A (Å)	D—H (Å)	H...A (Å)	D—H...A (°)
<i>a. intramolecular hydrogen bonds</i>				
O(3A)—H(30A)...O(2A)	2.501(5)	0.96(6)	1.61(6)	152(6)
O(7A)—H(70A)...O(6A)	2.462(6)	0.81(5)	1.72(6)	150(5)
O(3B)—H(30B)...O(2B)	2.477(7)	1.08(8)	1.48(9)	151(6)
O(7B)—H(70B)...O(6B)	2.500(7)	0.88(7)	1.71(7)	147(5)
O(4A)—H(40A)...O(3A)	2.602(5)	0.94(6)	2.07(5)	114(4)
O(8A)—H(80A)...O(7A)	2.617(6)	0.85(5)	2.23(7)	108(6)
O(4B)—H(40B)...O(3B)	2.605(6)	0.90(5)	2.08(9)	117(5)
O(8B)—H(80B)...O(7B)	2.606(6)	1.00(6)	2.06(8)	112(4)
<i>b. intermolecular hydrogen bonds</i>				
O(1A)—H(10A)...O(7A ⁱ)	2.887(5)	0.89(6)	2.16(5)	140(5)
O(5A)—H(50A)...O(8B ⁱ)	2.983(7)	0.72(6)	2.52(7)	124(5)
O(1B)—H(10B)...O(4A ⁱ)	3.125(5)	0.88(6)	2.51(5)	135(5)
O(8B)—H(80B)...O(8A)	2.813(5)	1.00(6)	1.89(6)	151(6)
O(8A)—H(80A)...O(2A ⁱⁱ)	2.993(5)	0.85(5)	2.21(7)	153(5)
O(5B)—H(50B)...O(1E ⁱⁱⁱ)	2.748(4)	0.92(4)	1.89(3)	156(5)
O(4A)—H(40A)...O(1E ^{iv})	2.979(7)	0.94(6)	2.23(7)	135(4)
O(4B)—H(40B)...O(2E ^v)	3.008(6)	0.90(5)	2.41(8)	124(5)

Symmetry codes:

- (i) $1 - x, 1 - y, 1 - z$
- (ii) $-1 + x, y, z$
- (iii) $-x, 1 - y, 1 - z$
- (iv) $1 + x, y, z$
- (v) $-1 + x, 1 + y, 1 + z$

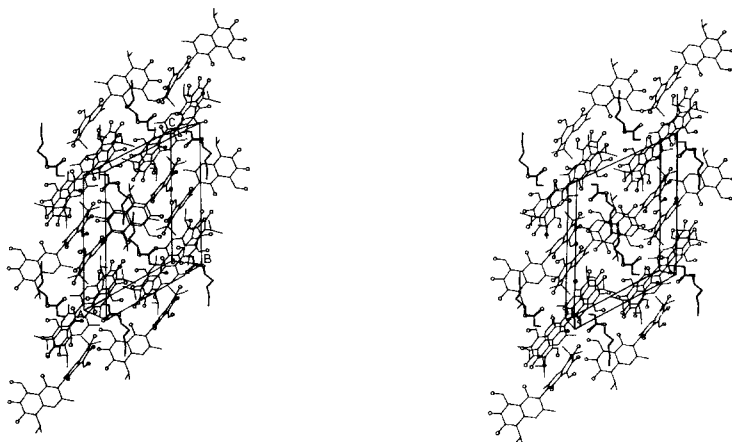


Fig. 3. Stereoview of the crystal packing (PLUTO [9]). The oxygen atoms are marked with circles, hydrogen atoms are omitted for clarity.

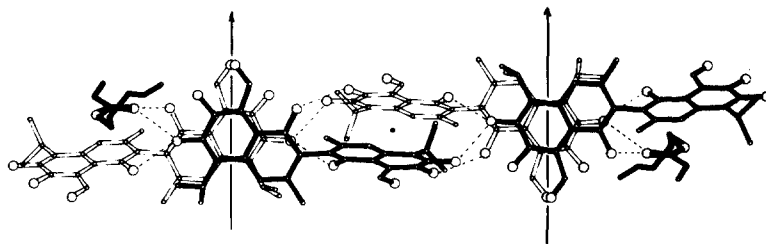


Fig. 4. The gossypol tetramer unit with two ester molecules attached by hydrogen bonds. A local non-crystallographic 2-fold axis is shown.

interact with the ester molecule belong to the same tetramer unit and are of the same chirality. The ether oxygen atom of the ester group, which is normally a very weak hydrogen bond acceptor, forms a hydrogen bond with O(4) of molecule B. While the acryloxy group of the guest molecule was easily found from the Fourier maps the location of the amyl group caused some problems. As the final refinement has shown this group has very large thermal parameters, however, all efforts to find the alternate conformation of this group have failed. The conformation adopted by the amyl residue in the crystal allows it to fit into a void formed by the hydrophobic groups of gossypol. The torsion angles describing the amyl group conformation are given in Table II.

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.

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