Inclusion Complexes of the Natural Product Gossypol. Crystal Structure of the 1:1 Complex of Gossypol with Isovaleric Acid

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

B. T. IBRAGIMOV and B. N. DADABAEV
Institute of Bioorganic Chemistry of UzSSR Academy of Sciences, Tashkent, U.S.S.R.

Abstract. The crystal structure of the 1:1 lattice inclusion complex of gossypol with isovaleric acid has been determined by X-ray structure analysis. The crystals of $C_{30}H_{30}O_8 \cdot C_5H_{10}O_2$ are monoclinic, space group $C2/c$, $a = 28.835(7)$, $b = 9.063(2)$, $c = 26.880(4)$ Å, $\beta = 109.66(1)°$, $V = 6615(2)$ Å^3, $Z = 8$, $D_x = 1.25$ g cm^{-3}, μ(Cu $K\alpha$) = 7.14 cm^{-1}, $T = 295$ K. The structure was solved by direct methods and refined with isotropic thermal parameters to the final R value of 0.132 for 1114 observed reflections. Hydrogen bonded gossypol molecules form columns along the [1 0 1] direction. These columns pack into layers parallel to the (101) plane. The layers of gossypol molecules are separated by the layers of isovaleric acid. The acid molecules are connected *via* a pair of O—H⋯O hydrogen bonds forming centrosymmetric dimers. There is no hydrogen bond interaction between the carboxylic acid dimers and gossypol molecules.

Key words. Crystal structure, X-ray crystallography, gossypol, host–guest complexes.

1. Introduction

Gossypol (1,1′,6,6′,7,7′-hexahydroxy-5,5′-diisopropyl-3,3′-dimethyl [2,2′-binaphthalene]-8,8′-dicarboxaldehyde) forms lattice inclusion complexes with a large number of organic molecules [1]. Earlier we have presented data on inclusion compounds of gossypol with aromatic hydrocarbons [2], carboxylic acid esters [3–5], ketones [6, 7], aldehydes [7], cyclic and acyclic ethers [7–9]. An interesting morphotropic transition is observed for inclusion complexes of gossypol with haloderivatives of methane. Dichloromethane gives a channel-type inclusion compound, which after desolvation forms a gossypol polymorph [10]. Tetrachloromethane (CCl$_4$) forms an inclusion compound of a layer type [11]. The inclusion complex of gossypol with chloroform belongs to a new structural type of gossypol inclusion compound. The chloroform-type inclusion compound is also formed with diiodomethane, 1,2-dichloroethane, 1,2-dibromoethane and isovaleric

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* Author for correspondence.

acid as guest molecule. This article deals with this isostructural group of complexes taking as an example the 1:1 complex of gossypol with isovaleric acid.

2. Experimental

Single crystals of gossypol:isovaleric acid were obtained by slow evaporation of the solvent from a gossypol solution in isovaleric acid. The yellow crystals were prismatic and slowly decomposed when exposed to air. A specimen of approximate dimensions of $0.05 \times 0.1 \times 0.4$ mm was used for measurements on a Syntex P2$_1$ diffractometer. The lattice parameters were determined by a least-squares fitting of the setting angles of 15 reflections (2θ in range 25 to 30°).

The crystal data are as follows: $C_{30}H_{30}O_8 \cdot C_5H_{10}O_2$, monoclinic, space group $C2/c$, $a = 28.835(7)$, $b = 9.063(2)$, $c = 26.880(4)$ Å, $\beta = 109.66(1)°$, $V = 6615(2)$ Å^3, $Z = 8$, $D_x = 1.25$ g cm^{-3}, $\mu(\text{Cu } K_\alpha) = 7.14$ cm^{-1}, $T = 295$ K.

Intensities of reflections were measured with graphite monochromatized Cu K_α radiation ($\lambda = 1.54178$ Å) to $2\theta_{max} = 115°$. No significant intensity variation was observed for 2 standard reflections monitored after each group of 100 reflections. Data were corrected for Lorentz and polarization effects but not for absorption. Out of 4680 measured reflections 1114 had $I > 2\sigma(I)$. The structure was solved by direct methods with the program *MULTAN80* [12]. The gossypol molecule was located on an E map. The guest molecule was found from a ΔF synthesis. The structure was refined with isotropic thermal parameters by least-squares methods using the program *SHELX76* [13]. The refinement with anisotropic thermal parameters was not attempted due to the limited number of observed reflections. Constraints were imposed on bond lengths and bond angles in the guest molecule. Final values of R and WR are 0.132 and 0.130, respectively. Unit weights were used throughout the refinement. In the final ΔF map, calculated after the last cycle of refinement, the maximum and minimum peaks were 0.89 and -0.57 eÅ^{-3}. The scattering factors used in calculations were those included in *SHELX76* [13]. Final atomic parameters are given in Table 1. Drawings were prepared with the program *PLUTO* [14]. Lists of bond lengths, bond angles and structure factors have been deposited with the British Library Lending Division, and copies may be ordered quoting Sup. No. 82085 (9 pp.).

3. Results and Discussion

3.1. MOLECULAR STRUCTURE

The numbering scheme of the gossypol and isovaleric acid molecules is given in Figure 1. The high values of standard deviations in bond lengths and angles which are due to the limited number of diffraction data do not allow us to discuss the molecular structure in detail, but some features of the structure can be described. The gossypol molecule is in the aldehyde form as it is in the other gossypol structures. The isopropyl groups have similar orientation and are oriented towards O(4) in the ring system AB and towards O(8) in the ring system CD. The naphthalene moieties AB and CD form a dihedral angle of 94(3)°. The intramolecular distances and angles (Table 1, Supplementary Material) do not differ

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

Atom	x/a	y/b	z/c	U
C(1)	0.3430(8)	0.061(3)	0.544(1)	0.042(7)
C(2)	0.3872(8)	0.076(3)	0.5367(9)	0.035(7)
C(3)	0.3892(9)	0.092(3)	0.485(1)	0.048(8)
C(4)	0.3452(9)	0.096(3)	0.442(1)	0.047(8)
C(5)	0.2538(9)	0.082(3)	0.403(1)	0.059(9)
C(6)	0.2105(9)	0.085(3)	0.412(1)	0.049(8)
C(7)	0.2061(9)	0.061(3)	0.462(1)	0.057(8)
C(8)	0.249(1)	0.044(3)	0.507(1)	0.053(8)
C(9)	0.2968(9)	0.068(3)	0.501(1)	0.050(8)
C(10)	0.3000(8)	0.077(3)	0.4491(9)	0.038(7)
C(21)	0.4382(8)	0.106(3)	0.476(1)	0.052(8)
C(22)	0.244(1)	0.022(4)	0.555(1)	0.10(1)
C(23)	0.256(1)	0.089(4)	0.347(1)	0.07(1)
C(24)	0.248(1)	0.240(4)	0.324(1)	0.09(1)
C(25)	0.226(1)	−0.035(4)	0.314(1)	0.10(1)
O(1)	0.3404(5)	0.048(2)	0.5933(6)	0.053(5)
O(2)	0.2002(8)	0.013(3)	0.5596(8)	0.108(8)
O(3)	0.1611(6)	0.052(2)	0.4658(6)	0.063(6)
O(4)	0.1653(6)	0.092(2)	0.3713(6)	0.055(5)
C(11)	0.4514(9)	0.186(3)	0.613(1)	0.046(8)
C(12)	0.4330(8)	0.065(3)	0.5840(9)	0.039(8)
C(13)	0.4577(9)	−0.070(3)	0.599(1)	0.048(8)
C(14)	0.4990(8)	−0.080(3)	0.6434(9)	0.038(7)
C(15)	0.5624(8)	0.037(3)	0.7213(8)	0.029(7)
C(16)	0.5766(9)	0.161(3)	0.7493(9)	0.040(8)
C(17)	0.5555(9)	0.303(3)	0.736(1)	0.048(8)
C(18)	0.5158(9)	0.319(3)	0.689(1)	0.044(8)
C(19)	0.4956(8)	0.186(3)	0.6581(9)	0.037(8)
C(20)	0.5187(8)	0.047(3)	0.6738(8)	0.031(7)
C(26)	0.437(1)	−0.211(3)	0.568(1)	0.07(1)
C(27)	0.501(1)	0.467(4)	0.674(1)	0.07(1)
C(28)	0.5901(8)	−0.110(3)	0.7356(9)	0.040(7)
C(29)	0.589(1)	−0.171(4)	0.788(1)	0.10(1)
C(30)	0.642(1)	−0.096(4)	0.734(1)	0.11(1)
O(5)	0.4270(6)	0.322(2)	0.5981(6)	0.050(5)
O(6)	0.5194(7)	0.577(2)	0.7002(7)	0.076(6)
O(7)	0.5769(6)	0.417(2)	0.7664(6)	0.056(6)
O(8)	0.6164(5)	0.157(2)	0.7980(6)	0.044(5)
O(P1)	0.0655(7)	−0.012(2)	0.0119(7)	0.098(8)
O(P2)	0.0207(7)	0.060(3)	0.0608(8)	0.15(1)
C(P1)	0.0594(6)	0.021(4)	0.0540(6)	0.17(2)
C(P2)	0.1031(8)	−0.001(3)	0.1033(8)	0.20(2)
C(P3)	0.1174(8)	0.144(3)	0.1338(8)	0.14(2)
C(P4)	0.169(1)	0.131(4)	0.175(1)	0.24(3)
C(P5)	0.116(2)	0.270(3)	0.095(1)	0.23(2)

Table II.   Selected torsion angles (°) of gossypol and isovaleric acid

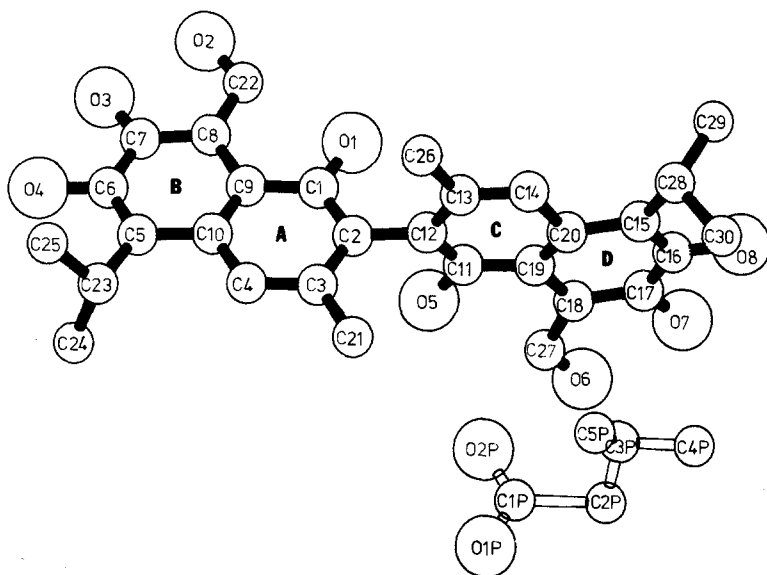| *Gossypol*	
C(1)—C(2)—C(12)—C(11)	−88(3)
isovaleric acid	
O(1P)—C(1P)—C(2P)—C(3P)	122(2)
O(2P)—C(1P)—C(2P)—C(3P)	−63(3)
C(1P)—C(2P)—C(3P)—C(4P)	−166(2)
C(1P)—C(2P)—C(3P)—C(5P)	43(2)

Fig. 1.   The atom numbering scheme of the gossypol and isovaleric acid molecules.

significantly from those observed in the other gossypol inclusion compounds. The isovaleric acid molecule was refined with constraints imposed on bond lengths and angles but with no constraints imposed on torsion angles. The torsion angles describing its conformation are given in Table II.
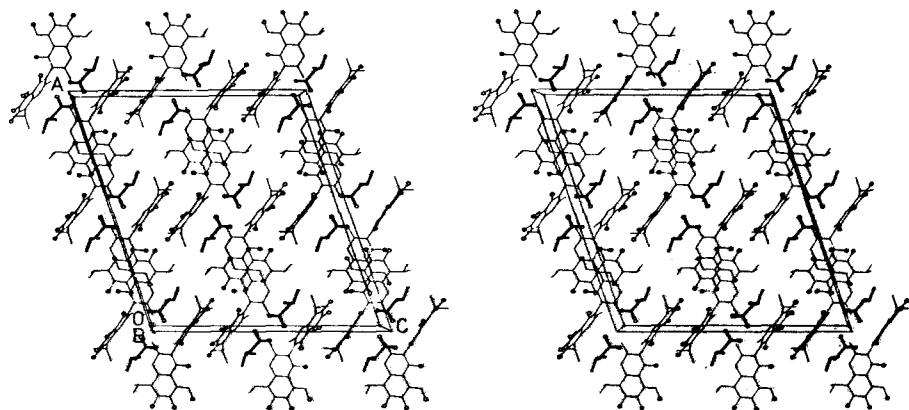
3.2. CRYSTAL PACKING

The lattice inclusion complex of gossypol with isovaleric acid belongs to a new structural type of complex formed by gossypol. It was very surprising to discover that this complex belongs to the same structural type as complexes formed with chloroform, 1,2-dichloroethane, 1,2-dibromoethane or diiodomethane. The crystal data for these complexes are given in Table III. The latter solvents are not able to form hydrogen bonds with gossypol while normally one would expect isovaleric acid to interact with the host molecule *via* hydrogen bonds. Projections of the

Table III. Crystal data for the chloroform-type lattice inclusion complexes of gossypol

	Guest molecule			
	$CHCl_3$	$CH_2Cl—CH_2Cl$	$CH_2Br—CH_2Br$	CH_2I_2
a (Å)	28.464(4)	28.25(2)	28.217(9)	28.676(8)
b (Å)	8.948(1)	8.988(4)	9.058(4)	9.164(4)
c (Å)	26.480(4)	25.80(1)	26.004(11)	26.158(6)
β (deg)	108.93(1)	107.84(4)	107.90(3)	108.21(2)
V (Å^3)	6379	6235	6325	6529
D_x(g cm^{-3})	1.33	1.27	1.43	1.54

crystal structure on the (010) plane and down the diagonal [101] are shown in Figures 2 and 3, respectively. Hydrogen bonded gossypol molecules form columns along [101]. Within the columns characteristic centrosymmetric dimers *via* hydrogen bonds between O(3) and O(5) [O(3)···O(5) distance, 2.79(2) Å] can be distinguished. The dimers related by a 2-fold axis form hydrogen bonds O(1)···O(8) [2.94(2) Å]. A fragment of the column is presented in Figure 4. The outer surface of the column is hydrophobic and there is no hydrogen bond interaction between neighbouring columns which form layers parallel to the (1 0 1) plane. The guest carboxylic acid molecules form typical centrosymmetric dimers with an O(1P)···O(2P) distance of 2.63(2) Å. As these entities are much more hydrophobic than the carboxylic acid monomer the dimers can be located in the hydrophobic space between gossypol layers. The closest contact between the host and guest layers is 3.29(4) Å [C(27)···O(2P)]. This would explain why the complex of gossypol with isovaleric acid belongs to the same structural type as the complex with chloroform. This type of packing is, however, not very efficient. The crystal density of

Fig. 2. Stereodiagram of the crystal packing viewed along the *b* axis.
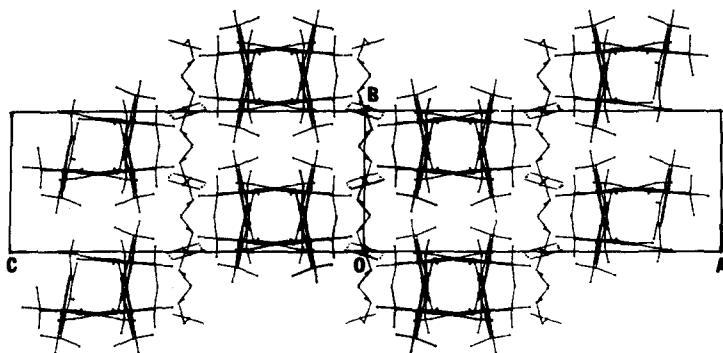
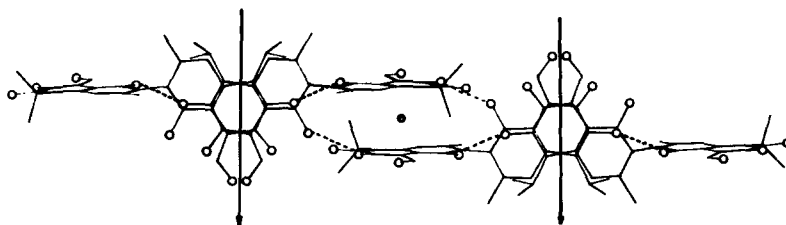Fig. 3.   Stereodiagram of the crystal packing viewed down the [101] diagonal.

Fig. 4.   Stereodiagram of the fragment of a gossypol column showing the hydrogen bond scheme.

1.25 g cm^{-3} is much lower than in the complex with acetic acid (1.35 g cm^{-3}) [15] but a little higher than in the polymorphic form of gossypol obtained from dichloromethane (1.22 g cm^{-3}) [10].

Acknowledgements

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