

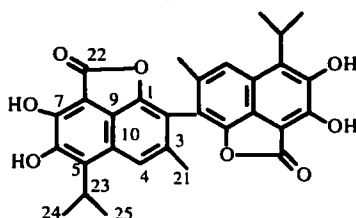
X-RAY STRUCTURAL INVESTIGATION OF GOSSYPOL AND ITS DERIVATIVES XXIX. MOLECULAR AND CRYSTAL STRUCTURE OF A COMPLEX OF GOSSYPOLIC ACID LACTONE WITH ACETIC ACID

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*The lactone of gossypolic acid, obtained by the demethylation of the tetramethyl ether of gossypolic acid, forms with acetic acid a stable complex having the 1:4 composition. The crystallographic parameters of single crystals are as follows: $a = 20.251(2) \text{ \AA}$, $b = 12.028(3) \text{ \AA}$, $c = 15.934(4) \text{ \AA}$, $V = 3881.2(2.3) \text{ \AA}^3$, $Z = 4$, $D_{\text{calc}} = 1.32 \text{ g/cm}^3$, sp. gr. *Pbcn*. The molecule is characterized by considerable strain because of the formation of the five-membered lactone ring the atoms of which are coplanar with the atoms of the naphthyl fragment. Unlike the clathrates of racemic gossypol and dianilinegossypol, the gossypolic acid lactone—acetic acid complex does not belong to the type of clathrate inclusion compounds.*

In all the crystals that have been studied, racemic gossypol exists in the aldehydic tautomeric form [1—5]. Gossypol derivatives of the Schiff base type, such as dianilinegossypol, have the quinoid form in crystals [6—9], while the lactol tautomeric form is found in crystals of gossypol hexamethyl ether [10]. In this form, in each half of the gossypol hexamethyl ether molecule exhibits an asymmetric carbon atom which, allowing for atropoisomerism, leads to the appearance of six diastereoisomers [11, 12]. In [10], the task of separating a complex mixture of these diastereoisomers in the form of three racemic pairs was successfully solved and the structure of each individual stereoisomer was determined. However, it is desirable to carry out a detailed study of the clathrate-forming capacity of gossypol derivatives in the lactol form with the use of some other derivative not characterized by a rich variety of stereoisomeric forms. With this aim, we have studied the molecular and crystal structures of gossypolic acid lactone, which has no asymmetric carbon atom in its molecule.



The product for investigation precipitated in the form of a 1:4 complex with acetic acid from a solution of gossypolic acid lactone in aqueous acetone containing acetic acid. The crystals of the complex belong to the rhombic system and have the space group *Pbcn*. In the crystals the molecules of the gossypolic acid lactone retain their intrinsic symmetry and are arranged on a second-order axis of rotation; i.e., a crystallographic twinning axis passes perpendicularly through the center of the C(2)—C(2') bond linking the two halves of the molecule.

It can be seen from the valence angles and interatomic distances of the molecule (Tables 1 and 2) that some of their values differ markedly from the standard magnitudes [13]. This is particularly appreciable for the valence angles at the C(1), C(8), and C(22) atoms if they are compared with the corresponding values for molecules of gossypol [1—5] and its derivatives in the quinoid form [7—9]. These deviations are easily explained by the sufficiently close approach of O(1) and C(22) to one

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TABLE 1. Interatomic Distances (d , Å) in the Molecule of the Complex of Gossypolic Acid Lactone with Acetic Acid

Atoms	d	Atoms'	d	Atoms	d
C(1)-C(2)	1.367(8)	C(1)-C(9)	1.369(7)	C(1)-O(1)	1.391(7)
C(2)-C(3)	1.452(8)	C(2)-C(2')	1.51(1)	C(3)-C(4)	1.382(8)
C(3)-C(21)	1.508(9)	C(4)-C(10)	1.411(8)	C(5)-C(6)	1.359(8)
C(5)-C(10)	1.438(8)	C(5)-C(23)	1.532(9)	C(6)-C(7)	1.451(8)
C(6)-O(4)	1.378(7)	C(7)-C(8)	1.385(8)	C(7)-O(3)	1.344(7)
C(8)-C(9)	1.394(8)	C(8)-C(22)	1.451(8)	C(9)-C(10)	1.397(7)
C(22)-O(1)	1.399(7)	C(22)-O(2)	1.208(7)	C(23)-C(24)	1.41(2)
C(23)-C(25)	1.40(3)	C(23)-C(24A)	1.44(3)	C(23)-C(25A)	1.43(6)
C(1sa)-C(2sa)	1.48(1)	C(1sa)-O(1sa)	1.195(9)	C(1sa)-O(2sa)	1.311(9)
C(1sb)-C(2sb)	1.48(2)	C(1sb)-O(1sb)	1.26(2)	C(1sb)-O(2sb)	1.27(2)

TABLE 2. Valence Angles (φ , deg) in the Molecule of the Complex of Gossypolic Acid Lactone with Acetic Acid

Angles	φ	Angles	φ
C(2)-C(1)-C(9)	123.4(5)	C(2)-C(1)-O(1)	126.5(5)
C(9)-C(1)-O(1)	110.1(5)	C(1)-C(2)-C(3)	114.6(5)
C(1)-C(2)-C(2')	123.2(5)	C(3)-C(2)-C(2')	122.0(5)
C(2)-C(3)-C(4)	121.2(5)	C(2)-C(3)-C(21)	119.7(5)
C(4)-C(3)-C(21)	119.0(5)	C(3)-C(4)-C(10)	122.9(5)
C(6)-C(5)-C(10)	118.9(5)	C(6)-C(5)-C(23)	121.4(5)
C(10)-C(5)-C(23)	119.7(5)	C(5)-C(6)-C(7)	124.6(5)
C(5)-C(6)-O(4)	119.1(5)	C(7)-C(6)-O(4)	116.3(5)
C(6)-C(7)-C(8)	117.0(5)	C(6)-C(7)-O(3)	114.3(5)
C(8)-C(7)-O(3)	128.6(5)	C(7)-C(8)-C(9)	117.3(5)
C(7)-C(8)-C(22)	136.1(5)	C(9)-C(8)-C(22)	106.6(5)
C(1)-C(9)-C(8)	108.7(5)	C(1)-C(9)-C(10)	124.0(5)
C(8)-C(9)-C(10)	127.3(5)	C(4)-C(10)-C(5)	131.2(5)
C(4)-C(10)-C(9)	113.9(5)	C(5)-C(10)-C(9)	114.9(5)
C(8)-C(22)-O(1)	107.2(5)	C(8)-C(22)-O(2)	133.4(6)
O(1)-C(22)-O(2)	119.5(5)	C(5)-C(23)-C(24)	116.7(8)
C(5)-C(23)-C(25)	116.4(13)	C(24)-C(23)-C(25)	117.3(17)
C(5)-C(23)-C(24A)	116.4(11)	C(5)-C(23)-C(25A)	111.7(22)
C(24A)-C(23)-C(25A)	131.0(25)	C(1)-O(1)-C(22)	107.4(4)
C(2sa)-C(1sa)-O(1sa)	124.6(7)	C(2sa)-C(1sa)-O(2sa)	113.8(6)
O(1sa)-C(1sa)-O(2sa)	121.6(7)	C(2sb)-C(1sb)-O(1sb)	120.7(11)
C(2sb)-C(1sb)-O(2sb)	113.9(11)	O(1sb)-C(1sb)-O(2sb)	125.2(11)

another for the formation of a chemical bond in the closure of the five-membered ring. Since in the production of the lactone form the exocyclic angles at the C(1) and C(8) atoms automatically increase, this leads to the moving away of the O(2) atom from O(3) to a distance of 3.46 Å and to the opening of the C(7)—C(8)—C(22)—O(2)···H—O(3) six-membered ring, which exists in the quinoid form in gossypol itself and its derivatives. The molecule of gossypolic acid lactone is therefore characterized by intramolecular H-bonds of only one type — namely the O(4)—H···O(3) bonds closing the five-membered C(6)—C(7)—O(3)···H—O(4) rings (Table 3).

TABLE 3. Intramolecular and Intermolecular H-Bonds in the Complex of Gossypolic Acid Lactone with Acetic Acid

H-Bond	Symmetry	O...O, Å	O-H, Å	O...H, Å	Angle (°)
O(4)-H...O(3)		2.616	0.77	2.08	127.4
O(2sa)-H...O(2)		2.673	0.83	1.87	162.1
O(3)-H...O(1sa)		2.612	0.90	1.79	151.8
O(1sb)-H...O(2sb)	-x, 1-y, 1-z	2.645	1.04	1.61	176.5

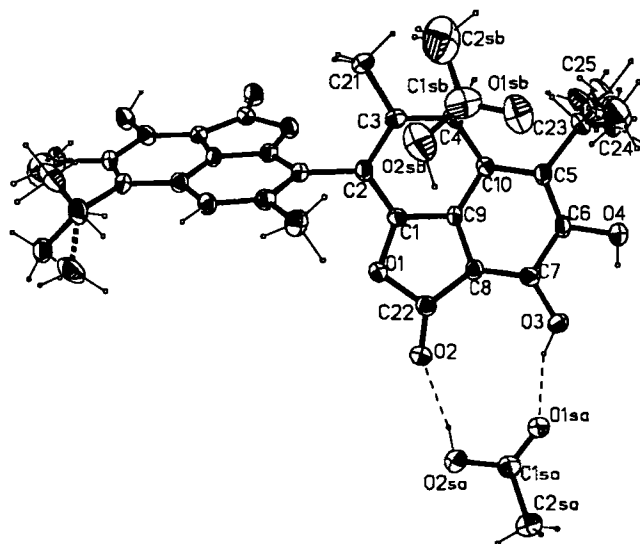


Fig. 1. Conformation of the molecules in the complex of gossypolic acid lactone with acetic acid.

The increase in the exocyclic angles at the C(1) and (C8) atoms is connected with the pronounced decrease of the exocyclic angles at the same atoms of the five-membered ring. The exocyclic angle at the C(22) atom has decreased to 107°, in place of the usual 120°. A consequence of this is an appreciable difference in the distribution of the angles at C(9) and C(10) in gossypol and, in particular, naphthalene [14]. This shows that the molecule of gossypolic acid lactone is somewhat strained.

The isopropyl groups of the gossypol molecule may exist in two stable states differing by 180° in rotation about the C(5)—C(23) bond [1—5]: H(23) may be turned towards the C(4) atom or towards the nearest hydroxy group. In gossypolic acid lactone a new possibility is realized: the H(23) atom is turned towards the C(4) atom, but this orientation is randomized over two states differing in rotation from one another by about 30°.

The naphthyl nuclei of the gossypolic acid lactone molecule are almost planar, since the maximum deviation of the atoms from the corresponding mean-square planes does not exceed 0.015 Å. The atoms of the lactone ring and the O(3), O(4), C(21), and C(23) atoms deviate differently, but on the whole they lie well within the plane of the naphthyl nucleus. Because of the absence of hydrogen atoms at the O(1) atom, which is turned in the direction of the C(2)—C(2') bond, the dihedral angle between the mean square planes of the naphthyl nuclei has decreased to 60.7°.

In the crystal, each molecule of gossypolic acid lactone is linked to two molecules of acetic acid through O(3)—H...O(1sa) and O(2sa)—H...O(2) bonds, closing the 10-membered ring C(7)—(C8)—C(22)—O(2)...H—O(2sa)—C(1sa)—O(1sa)...H—O(3) (Table 3). These bonds greatly recall to mind the centrosymmetric dimer-forming bonds frequently encountered in H-bound dimers of carboxylic acids. The possibility of the appearance of such a bond can explain the ease of formation of the crystalline complexes of gossypolic acid lactone with acetic acid (Fig. 2).

TABLE 4. Coordinates ($\times 10^4$) and Temperature Factors ($\text{\AA}^2 \times 10^3$) of the Nonhydrogen Atoms in the Complex of Gossypolic Acid Lactone with Acetic Acid

Atoms	x/a	y/b	z/c	U_{iso}
C(1)	-1(3)	2229(5)	6379(3)	50(2)
C(2)	-202(3)	2734(5)	7103(3)	51(2)
C(3)	-856(3)	3225(5)	7064(4)	57(2)
C(4)	-1235(3)	3160(5)	6344(4)	57(2)
C(5)	-1335(3)	2455(5)	4811(4)	55(2)
C(6)	-1005(3)	1903(5)	4198(4)	56(2)
C(7)	-341(3)	1462(5)	4283(4)	57(2)
C(8)	-35(3)	1598(5)	5053(4)	52(2)
C(9)	-382(3)	2175(5)	5670(3)	47(2)
C(10)	-1016(3)	2624(5)	5607(3)	51(2)
C(21)	-1121(3)	3858(6)	7809(4)	71(2)
C(22)	597(3)	1298(5)	5418(4)	54(2)
C(23)	-2034(3)	2907(6)	4668(4)	71(3)
C(24)	-2507(7)	2148(13)	4357(18)	69(7)
C(25)	-2080(15)	4014(19)	4394(27)	107(13)
C(24A)	-2571(9)	2219(20)	4958(28)	107(11)
C(25A)	-2030(26)	3870(50)	4144(37)	165(23)
O(1)	599(2)	1694(3)	6244(2)	57(1)
O(2)	1076(2)	816(4)	5152(3)	70(2)
O(3)	-120(2)	918(4)	3602(3)	73(2)
O(4)	-1305(2)	1755(4)	3429(3)	80(2)
C(1sa)	1581(4)	-50(6)	3218(4)	73(3)
C(2sa)	1984(4)	-597(7)	2563(5)	102(3)
O(1sa)	1069(3)	415(5)	3092(3)	101(2)
O(2sa)	1838(3)	-109(5)	3972(3)	106(2)
C(1sb)	-515(6)	5832(8)	5772(8)	112(5)
C(2sb)	-892(6)	6451(9)	6413(8)	168(7)
O(1sb)	-727(4)	5751(6)	5033(5)	137(3)
O(2sb)	41(4)	5488(6)	6025(5)	147(4)

$$*U_{iso} = (1/3) \sum_i \sum_j U_{ij} a_i^* a_j^*$$

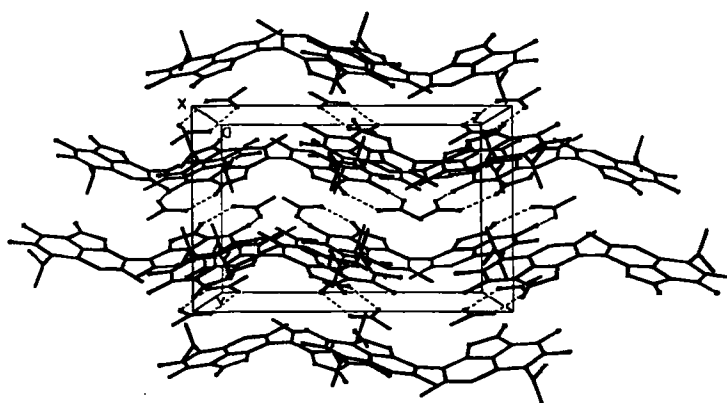


Fig. 2. Crystal structure of the complex of gossypolic acid lactone with acetic acid.

Incidentally, other acetic acid molecules form precisely such dimers. Neither these dimers nor associates of gossypolic acid—acetic acid lactones are further linked with one another. The dimers are arranged in planes formed between the associates. The planes of the naphthyl nucleus of the gossypolic acid lactone and the acetic acid of this dimer are almost parallel and the distance between them is approximately 3.60 Å. An analysis of intermolecular contacts and crystal packing shows that the complex of gossypolic acid lactone and acetic acid, unlike clathrates of racemic gossypol and of dianilinegossypol, do not belong to the type of clathrate inclusion compounds.

EXPERIMENTAL

The tetramethyl ether of gossypolic acid was obtained by R. Adams' method [15] from gossypol hexamethyl ether. The resulting crude product was demethylated without preliminary purification [16]. By repeated column-chromatographic fractionation of the demethylation products (with chloroform—benzene as eluent) we isolated in small yield a fraction which by evaporation of the eluent gave a colorless crystalline product with mp 296—298°C (decomp.). UV spectra of this product were taken on a SF-26 spectrophotometer (λ_{max} (CHCl₃), nm): 265 (lg ϵ 4.68), 366 (lg ϵ 4.26). The following signals were observed in the PMR spectra taken in deuteriochloroform solution on a XL-200 instrument (Varian, USA) (ppm): 9.20 (1H, s, OH-7), 7.66 (1H, s, H-4), 6.14 (1H, s, OH-6), 3.84 (1H, m, H-13), 2.24 (3H, s, CH₃-3), 1.48 (3H, d, J = 7.1 Hz, CH₃-13).

Single crystals of the gossypolic acid lactone—acetic acid complex were grown from solution in acetone containing CH₃COOH at room temperature and with slow evaporation for 6—7 days.

The crystallographic parameters of single crystals were determined and were refined for 15 reflections on a Syntex-P2₁ automatic four-circle diffractometer: $a = 20.251(2)$ Å, $b = 12.028(3)$ Å, $c = 15.934(4)$ Å, $V = 3881.2(2.3)$ Å³, $M = 514$, $Z = 4$, $D_{\text{calc}} = 1.32$ g/cm³, sp. gr. Pbcn.

Integral intensities were measured by the $\theta/2\theta$ scanning method using CuK α radiation monochromatized by reflection from a graphite crystal. After allowing for Lorentz and polarization factors and discarding weak reflections with $I < 2\sigma(I)$, the working group consisted of 1879 reflections. The structure was interpreted by the direct method with the aid of the SHELXS-86 program packet adapted for an IBM-386 PC [17].

The structure was refined by the SHELX-76 program packet [18] set up for the same PC. The hydrogen atoms of the molecules were localized with the aid of difference Fourier syntheses. The structure factor after the final stage of refinement of the positional and anisotropic temperature factors was $R = 0.091$. The coordinates of the atoms are given in Table 4.

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