X-RAY STRUCTURAL INVESTIGATION OF GOSSYPOL AND ITS DERIVATIVES*

XX. STRUCTURE OF THE SOLVATE OF GOSSYPOL WITH PYRIDINE

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UDC 547.554+548.737

The structure of the solvate of gossypol with pyridine has been determined by x-ray structural analysis. The crystalline solvate is a H-clathrate with the channel type of structure in which there are three pyridine molecules to each host molecule. On the desolvation of gossypol tripyridine, a new polymorph is formed.

In preceding communications, we have reported that gossypol is capable of forming numerous unsolvated (polymorphs) and solvated (clathrates) crystalline forms. Recently, the structures have been determined for a number of gossypol complexes – clathrates with diethyl ether [1], acetone [2], m-xylene [3], tetrahydrofuran, cyclohexanone, and butyraldehyde [4], methyl propionate and acetoacetic ester [5], isovaleric acid [6], amyl acrylate [7], acetonitrile [8], and benzene and chloroform [9]. Clathrates of gossypol with organic substances the molecules of which are capable of participating in fairly strong intermolecular

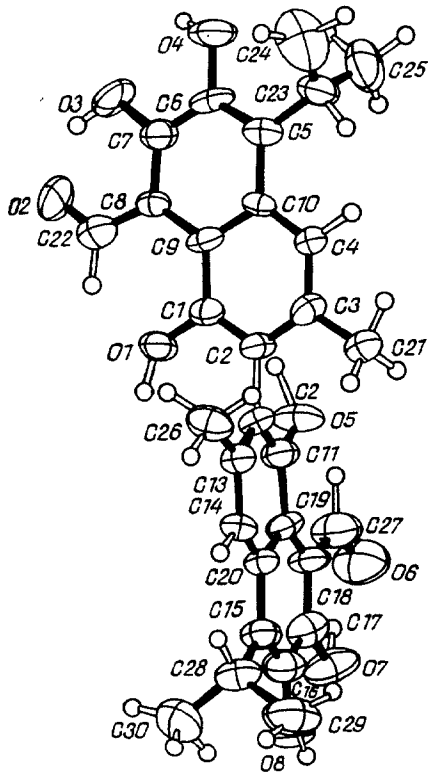

Fig. 1. Conformation of the host molecule and numbering of the atoms in the structure of the pyridine solvate of gossypol.

*Communications (XI-XIX) are represented by the publications given in the Literature Cited under Nos. 1-9.

Institute of Bioorganic Chemistry, Uzbekistan Academy of Sciences, Tashkent. Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 186-191, March-April, 1992. Original article submitted July 9, 1991; revision submitted November 21, 1991.

0009-3130/92/2802-0159$12.50

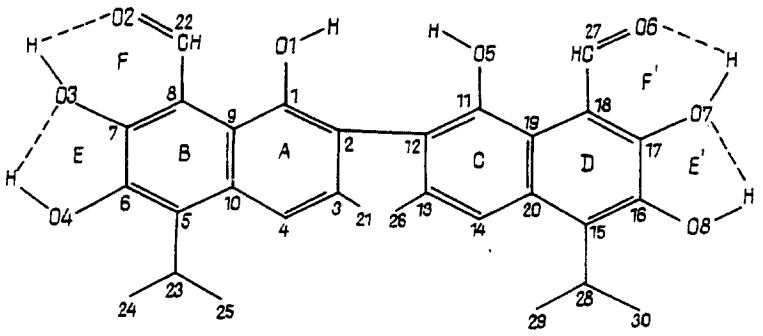

Fig. 2. H-bonds in the gossypol molecule.

TABLE 1. Geometry of the Intramolecular H-Bonds

Bond	Distance, Å			O–H... ... O, angle, deg
	O...O	O–H	H...O	
O3–H...O2	2.45	0,86	1 57	159
O4–H...O3	2,62	0,8	2 17	115
O7–H...O6	2,40	1.01	1.56	151
O8–H...O7	2,60	0,97	2,14	108

TABLE 2. Geometry of the Intermolecular H-Bonds

Bond	Distance, Å			D–H... A, angle, deg
	D...A*	D–H	H...A	
O8–H...O4	3,063	1,19	2.04	142
O1–H...N1	2.748	1.04	1.81	160
O5–H...N2	2,776	0,90	1,92	157
O4–H...O3	2,701	1,06	1,68	161

*D – donor; A – acceptor.

bonds and clathrates lacking this capacity differ substantially in structure. Clathrates in which there are specific interactions (H-bonds and electrostatic, dipole-dipole, and other interactions) between the host and guest molecules are considered as coordinatoclathrates, by analogy with Weber et al. [10]. If it is predominantly H-bonds that form these interactions, we shall call such a clathrate an H-clathrate.

Because of the capacity of the pyridine molecule for forming intermolecular H bonds, its complex with gossypol should belong to the H-clathrates. According to the results of Campbell et al. [11], gossypol forms with pyridine an organic salt in which there are two molecules of salt to each gossypol molecule. However, our preliminary physicochemical investigations have shown that this complex is not a disolvate but a trisolvate of gossypol. In order to refine the composition and type of this gossypol solvate, we have carried out a complete x-ray structural investigation of it.

In the complex of gossypol with pyridine, the gossypol:pyridine ratio is 1:3. The complex is not an organic salt but an H-clathrate of gossypol. The gossypol molecules are present in the aldehydic tautomeric form (Fig. 1). The dihedral angle between the naphthyl nuclei is 95.7°. The molecule includes H-bonds of two types. A C=O...H–O H-bond closes the six-membered rings F and F', consisting of the O2–C22–C8–C7–O3–HO3 and O6–C27–C18–C17–O7–HO7 atoms and H bonds of the O–H...O type close the five-membered rings E and E', consisting of the O3–C7–C6–O4–HO4 and O7–C17–C16–O8–HO8 atoms, respectively (Fig. 2). The characteristics of the intramolecular H-bonds (Table 1) are close to the characteristics of the H-bonds in crystalline forms of gossypol the structures of which have been determined previously [1-9]. The isopropyl groups in the two halves of the molecule have a same orientation: in the AB half the H4 and H23 atoms, and in the CD half, correspondingly, the H14 and H28 atoms are turned towards one another. The coplanarity of the naphthyl nuclei is close to ideal (the deviations do not exceed 0.03 Å). The values of the interatomic distances and the valence angles differ only slightly from the values in previous crystalline forms of gossypol.

In the trisolvate there are no centrosymmetric dimers formed by O5–H...O3 H bonds that are typical for the majority of crystalline forms of gossypol. The complex consists of an H-clathrate of the channel type, since all three pyridine molecules are located in channels, are parallel to the x axis, and have H-bonds about 2.75 Å long with the host molecules (Table 2). Since the gossypol molecules are basically surrounded by pyridine molecules, there are a few contacts between the host molecules. Among these contacts only one has the nature of an H-bond – the O8–H hydroxy group of the basis molecule forms an H-bond with the O4 atom of

TABLE 3. Coordinates ($\times 10^{-4}$) and Equivalent Isotropic Temperature Parameters ($\times 10^{-3}$) of the Atoms in the H-Clathrate of Gossypol with PRD*

Atoms	x/a	y/b	z/c	U_{iso}^{eq}
C1	0125 (4)	3803 (2)	1087 (2)	042 (1)
C2	—1102 (4)	3340 (2)	1339 (2)	043 (2)
C3	—1549 (4)	2935 (2)	1433 (2)	046 (1)
C4	—0754 (4)	2417 (2)	1255 (2)	046 (2)
C5	1388 (4)	2003 (2)	0905 (2)	048 (2)
C6	2668 (5)	2177 (3)	0789 (2)	052 (2)
C7	3150 (4)	2879 (3)	0894 (2)	051 (2)
C8	2337 (4)	3429 (2)	0732 (2)	045 (1)
C9	1405 (4)	3274 (2)	0934 (2)	040 (2)
C10	0523 (4)	2564 (2)	1021 (2)	041 (2)
C11	—2061 (4)	4427 (2)	2149 (2)	044 (1)
C12	—1970 (4)	4203 (2)	1513 (2)	043 (2)
C13	—2733 (4)	4500 (2)	1022 (2)	042 (2)
C14	—3544 (4)	5012 (2)	1189 (2)	044 (2)
C15	—4530 (4)	5789 (2)	1995 (2)	047 (2)
C16	—4654 (4)	5980 (2)	2636 (2)	048 (2)
C17	—3931 (4)	5680 (2)	3139 (2)	017 (1)
C18	—3066 (4)	5167 (2)	3016 (2)	047 (2)
C19	—2922 (4)	4943 (2)	2344 (2)	041 (1)
C20	—3660 (4)	5248 (2)	1838 (2)	042 (1)
C21	—2887 (5)	2741 (3)	1711 (3)	065 (2)
C22	2897 (5)	4109 (3)	0550 (3)	063 (2)
C23	0850 (5)	1249 (2)	0899 (3)	070 (2)
C24	1093 (7)	0882 (3)	0273 (4)	110 (3)
C25	1333 (7)	0850 (3)	1483 (4)	107 (3)
C26	—2671 (4)	4260 (3)	0322 (2)	056 (2)
C27	—2408 (6)	4905 (3)	3582 (3)	080 (2)
C28	—5271 (5)	6147 (3)	1458 (2)	076 (2)
C29	—4779 (6)	6919 (3)	1400 (3)	102 (3)
C30	—6742 (5)	6080 (3)	1535 (3)	084 (2)
O1	0588 (4)	4480 (2)	0984 (2)	057 (1)
O2	4069 (4)	4234 (2)	0389 (2)	074 (2)
O3	4425 (4)	2980 (2)	0550 (2)	069 (2)
O4	3533 (4)	1669 (2)	0773 (2)	073 (2)
O5	—1324 (4)	4156 (2)	2633 (2)	063 (1)
O6	—2522 (5)	5137 (3)	4138 (2)	092 (2)
O7	—4131 (4)	5930 (2)	3740 (2)	068 (2)
O8	—5473 (4)	6481 (2)	2826 (2)	061 (2)
N1	—0317 (4)	5760 (2)	1277 (2)	065 (2)
P11	—0488 (5)	6017 (3)	1863 (3)	076 (2)
P12	—0824 (6)	6678 (4)	1986 (3)	087 (2)
P13	—0992 (7)	7105 (3)	1462 (4)	098 (3)
P14	—0806 (6)	6850 (3)	0839 (3)	090 (2)
P15	—0481 (5)	6180 (3)	0771 (3)	074 (2)
N2	5540 (5)	1615 (3)	—0077 (2)	071 (2)
P21	6653 (7)	1972 (3)	—0096 (3)	087 (3)
P22	7708 (7)	1757 (5)	—0449 (4)	114 (4)
P23	1537 (8)	1125 (5)	—0768 (4)	123 (4)
P24	6400 (9)	0756 (4)	—0738 (4)	116 (4)
P25	5391 (7)	1011 (4)	—0391 (3)	091 (3)
N3	1214 (5)	3758 (3)	2526 (2)	076 (2)
P31	1623 (7)	3121 (4)	2525 (3)	083 (3)
P32	2869 (9)	2984 (4)	2463 (4)	105 (3)
P33	3777 (7)	3511 (6)	2402 (4)	120 (4)
P34	3379 (8)	4181 (4)	2401 (4)	108 (3)
P35	2094 (6)	4270 (3)	2459 (3)	086 (3)

*$U_{iso}^{eq} = \frac{1}{3}\sum_i\sum_j U_{ij} a_i^* a_j^* a_i a_j$.

the gossypol molecule connected with the basis molecule by the symmetry transformation x − 1, 0.5 − y, 0.5 + z. Such a comparatively weak bond 3.06 Å long forms a chain of host molecules parallel to the y axis (Fig. 3).

Thermomicroscopic, x-ray-phase, and NMR investigations have shown that the elimination of the pyridine molecules from the channels of the H-clathrates takes place at 112°C with the formation of a new gossypol polymorph. Here, because of the high content of host component (about 30% by weight), the crystals are covered with drops of liberated pyridine, but with a further rise in the temperature the drops rapidly disappear and the substance melts at 179-183°C.

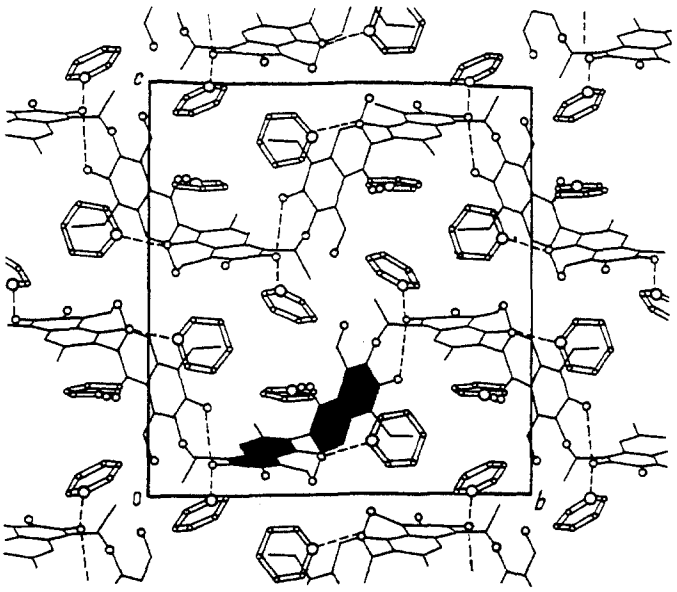

Fig. 3. Structure of the H-clathrate of gossypol with pyridine.

EXPERIMENTAL

Single crystals were isolated from solutions of gossypol in pyridine with slow evaporation of the solvent. The crystallographic parameters were determined and refined on a Syntex-$P2_1$ four-circle diffractometer (USA): a = 10.726(3), b = 20.380(4), c = 19.159(6) (Å), β = 93.95(2)°, V = 4002 Å^3; sp. gr. $P2_1/c$; ρ_{calc} = 1.25 g/cm^3; Z = 4. To measure the intensities of the reflections on the same diffractometer we used CuKα radiation monochromatized by deflection from a graphite crystal, and $\theta/2\theta$ scanning to an angle $2\theta < 120°$ at a variable rate of 3.91-11.72 deg/min. The experimental results were corrected for polarization and Lorentz factors but absorption was not taken into account in view of the absence of heavy atoms from the structure. The calculations employed 3864 reflections with $F > 2\sigma(F)$.

The structure was interpreted by the direct method with the aid of the MULTAN-78 program [12] included in the SHELXSM complex [13] and was refined by the programs of the same complex first in the isotropic and then in the anisotropic approximation. Hydrogen atoms were found from difference electron-density syntheses. The final R factor was 0.066. The coordinates and equivalent isotropic temperature parameters of the atoms corresponding to this value of the uncertainty factor are given in Table 3.

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X-RAY INVESTIGATION OF GOSSYPOL AND ITS DERIVATIVES

I. STRUCTURES OF H-CLATHRATES OF GOSSYPOL WITH LOWER HOMOLOGUES OF THE CARBOXYLIC ACID AND MONOHYDRIC ALCOHOL SERIES

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UDC 547.737

The first four homologues of the carboxylic acid series and first two homologues of the monohydric alcohol series with gossypol give equimolar H-clathrates with the channel-type structure that are isostructural with gossypol–acetic acid. Formic and acetic acids are capable of forming with gossypol a continuous series of solid substitution solutions. The desolvation of the unstable H-clathrates of carboxylic acids and monohydric alcohols form one and the same polymorph of gossypol. By x-ray structural analysis, the structures have been determined of two complexes of gossypol: an H-clathrate with methanol and a solid solution on the replacement of formic acid by acetic acid in a gossypol matrix.

In [1], R. Adams et al. reported their isolation of complexes of gossypol with the first four homologues of carboxylic acids. Of these, only the adduct with formic acid was unstable and decomposed under ordinary conditions. In 1982, Chinese authors [2] determined the structure of the gossypol complex most frequently used in chemical and medicinal investigations – gossypol–acetic acid, which is a stable equimolar "gossypol–acetic acid" adduct. However, there is no information on the crystal structures of other members of the series with carboxylic acids and monohydric alcohols. In view of this, we have made a detailed investigation of the formation of complexes by gossypol with lower homologues of the series of these two classes of organic substances. The investigations performed have shown that formic (FA), propionic (PA), butyric (BA), and acrylic (AcrA) acids and methyl (MAlc) and ethyl (EAlc) alcohols form clathrates with gossypol that are isostructural with the H-clathrate with acetic acid (AA). The crystallographic parameters of these complexes are given in Table 1. The structures of the clathrates of gossypol with FA and MAlc have been interpreted by the method of x-ray structural analysis.

The isostructural complexes are H-clathrates with the channel type of structure (with the composition host:guest = 1:1), since H-bonds act between the components and the guest molecules are located in channels. The gossypol molecules in them are present in the aldehydic tautomeric form. In the H-clathrates with BA and MAlc the dihedral angles between the naphthyl nuclei are 72.3 and 75.7°, respectively. These are the smallest values of the dihedral angle among known crystalline forms of gossypol. The isopropyl groups have the same orientation in the two halves of the molecule: they are turned in the direction of the closest hydroxy groups. Two types of H-bonds, unfailingly found in other crystalline forms of gossypol [2-5], are observed in the molecule: namely: C=O...H–O H-bonds close the six-membered rings F and F', consisting of the O2–C22–C8–C7–O3–HO3 and O6–C27–C18–C17–O7–HO7 atoms, while H bonds of the O–H...O type close the five-membered rings E and E', consisting of the O3–C7–O4–HO4 and O7–C17–C16–O8–HO8 atoms, respectively (Fig. 1).

Institute of Bioorganic Chemistry, Uzbekistan Academy of Sciences, Tashkent. Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 191-197, March-April, 1992. Original article submitted July 9, 1991; revision submitted November 21, 1991.

0009-3130/92/2802-0163$12.50