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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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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).

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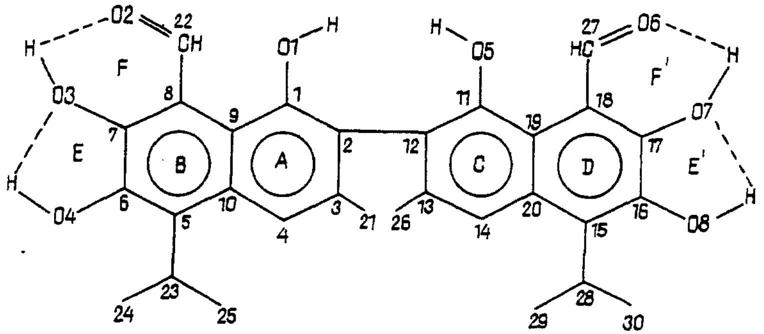

Fig. 1. Gossypol molecule.

TABLE 1. Crystallographic Parameters of the H-Clathrates of Gossypol with Lower Homologues of the Carboxylic and Monohydric Alcohol Series

Host	a	b	c	α	β	γ	V, Å³	ρ, g/cm³
	Å			deg.				
1. УКК	14,292 (2)	6,902 (1)	14,700 (2)	91,91 (1)	92,81 (1)	98,92 (1)	1430	1,35
2. МРК	14,249 (3)	6,969 (1)	14,620 (4)	90,07 (2)	92,82 (2)	99,09 (2)	1422	1,33
3. ПРК	14,669 (5)	6,929 (2)	14,774 (6)	91,33 (3)	91,96 (3)	99,73 (3)	1478	1,33
4. МСК	15,104 (9)	6,917 (7)	14,823 (9)	92,44 (4)	92,03 (5)	100,12 (5)	1521	1,32
5. АКК	14,39 (1)	6,966 (7)	14,79 (2)	91,10 (9)	90,74 (9)	99,47 (7)	1463	1,34
6. МСП	13,420 (3)	7,156 (2)	14,508 (3)	93,51 (1)	98,17 (1)	94,95 (1)	1372	1,33
7. ЭСП	14,695 (6)	7,113 (3)	15,002 (9)	93,90 (4)	112,95 (4)	88,75 (3)	1439	1,30

TABLE 2. Geometry of the Intermolecular H-Bonds in H-Clathrates of Gossypol with FA and MAlc

G*	Bond	Distance, Å			O—H...O angle, deg
		O...O	O—H	H...O	
FA	O5—H...O3^{i}	2,809	0,84	2,14	148
	O1G—H...O6	2,649	1,27	1,40	171
	O8—H...O1G^{ii}	2,918	0,99	2,12	150
	O1—H...O2G	2,768	0,99	1,84	163
	O4—H...O2G^{i}	3,188	1,05	2,42	144
MALc	O5—H...O3^{i}	2,811	0,92	2,04	152
	O1—H...OG	2,830	0,89	2,13	148
	O8—H...OG^{ii}	3,107	0,99	2,25	165
	OG—H...O6	3,111	1,06	2,07	169

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*G — guest.

Symmetry codes: (i) −x, −y, 1 − z; (ii) 1 − x, 1 − y, 2 − z.

The coplanarity of the atoms of the naphthyl nuclei AB and CD are close to ideal — in them the deviations do not exceed 0.04 Å. The lengths of the bonds and the valence angles differ little from their values in preceding structures [3-5].

The complex of gossypol obtained from solutions in formic acid of kh. ch. ["chemically pure"] grade containing 0.1% of acetic acid consisted of a double solvate with the composition gossypol·(0.82 FA)·(0.18 AA). The formation of such a solid substitution solution from the solution mentioned indicates that the tendency of the gossypol to form clathrates with acetic acid is substantially greater than that with formic acid. This phenomenon can be used for the superfine purification of formic acid from trace amounts of acetic acid with the aid of gossypol [6].

In the H-clathrate of gossypol with FA, the right and left (atropoisomeric) molecules of the host are united pairwise into the centrosymmetrical dimers that are typical for crystalline forms of gossypol with the aid of O5—H...O3 H-bonds (Table 2). The relatively small

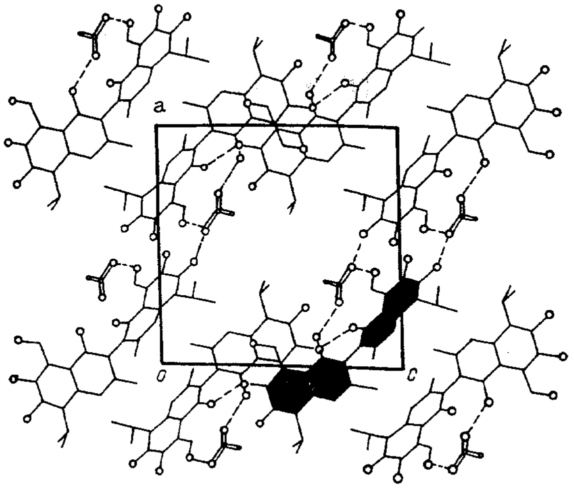

Fig. 2

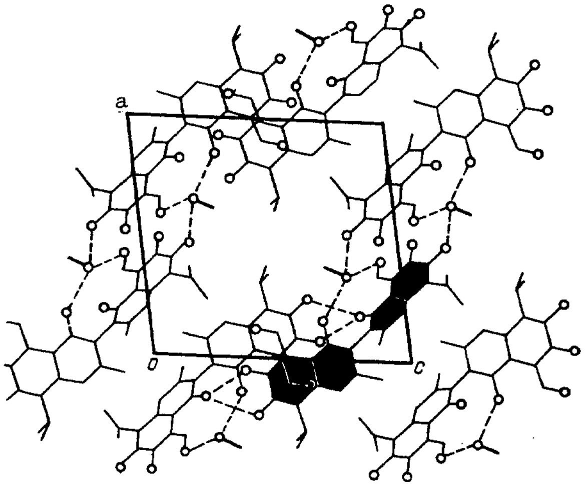

Fig. 3

Fig. 2. Crystalline structure of the H-clathrate of gossypol with FA.

Fig. 3. Crystalline structure of the H-clathrate of gossypol with MAlc.

value of the dihedral angle between the naphthyl nuclei permits the AB half of the molecule to be positioned parallel to the direction of the y axis at a distance of $\approx b/2$, i.e., it leads to the formation of stacks, in the production of which a definite role is undoubtedly played by stacking interaction. The stacks obtained by translation in the $[10\bar{1}]$ direction are located in similar planes (Fig. 2). Between the points of contact of two stacks, pockets arise that are surrounded by the polar substituents of the gossypol molecules. It is in these that the molecules of acids are located, each forming four H-bonds with the host molecules (see Table 2).

The carbonyl oxygen atom of a molecule of the acid forms O1—H...O2G and O4—H...O2G H-bonds (where G is a guest molecule – in this case, a carboxylic acid) with the gossypol molecules from two neighboring dimers in the stack, leading to a reinforcement of the stack (see Fig. 2). One of the two H-bonds of the hydroxy group of the G molecule – O1G—H...O6 – also reinforces the stack, while the other – O8—H...O1G – joins the stacks into a bilayer. In forming these H bonds, the guest molecules shield the polar groups of the host lying in the pockets, and their methyl groups (acetic acid) or hydrogen atoms (formic acid) are directed towards the interlayer space. As a result, the surface of the bilayer becomes completely hydrophobic, and the interactions between the layers have a purely Van der Waals nature.

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

Atoms	x/a	y/b	z/c	U^{eq}_{iso}
C1	1678 (3)	−0548 (5)	8528 (2)	35 (1)
C2	0973 (24)	−2123 (6)	8387 (2)	35 (1)
C3	0962 (3)	−3795 (6)	8898 (2)	36 (1)
C4	1613 (3)	−3763 (6)	9621 (2)	38 (1)
C5	2947 (3)	−2121 (6)	10653 (2)	37 (1)
C6	3691 (3)	−0644 (6)	10749 (3)	42 (1)
C7	3841 (3)	0874 (6)	10118 (3)	38 (1)
C8	3174 (3)	1079 (6)	9397 (2)	37 (1)
C9	2388 (3)	−0496 (6)	9251 (2)	34 (1)
C10	2310 (3)	−2123 (6)	9838 (2)	34 (1)
C11	0397 (3)	−2326 (5)	6712 (3)	36 (1)
C12	0214 (3)	−2013 (6)	7619 (2)	23 (1)
C13	−0692 (3)	−1663 (6)	7841 (3)	36 (1)
C14	−1398 (3)	−1719 (6)	7162 (3)	41 (1)
C15	−2011 (3)	−2183 (7)	5543 (3)	51 (1)
C16	−1800 (3)	−2420 (7)	4651 (3)	51 (1)
C17	−0878 (3)	−2519 (6)	4394 (3)	45 (1)
C18	−0115 (3)	−2506 (6)	5029 (3)	37 (1)
C19	−0311 (3)	−2297 (5)	5985 (2)	35 (1)
C20	−1232 (3)	−2081 (6)	6230 (5)	40 (1)
C21	0251 (3)	−5596 (6)	8688 (3)	38 (2)
C22	3331 (3)	2837 (6)	8862 (3)	51 (1)
C23	2754 (3)	−3663 (6)	11383 (3)	44 (1)
C24	2544 (4)	−2786 (8)	12289 (3)	76 (2)
C25	3537 (4)	−4902 (7)	11496 (4)	76 (2)
C26	−0895 (3)	−1195 (6)	8823 (3)	49 (1)
C27	0799 (3)	−2646 (7)	4669 (3)	49 (1)
C28	−3028 (3)	−2109 (10)	5792 (3)	84 (3)
C29	−3693 (4)	−3971 (12)	5541 (5)	122 (3)
C30	−3389 (5)	−0306 (12)	5407 (5)	119 (3)
O1	1724 (2)	1067 (4)	7982 (2)	50 (1)
O2	4062 (2)	4089 (4)	8993 (2)	57 (1)
O3	4635 (2)	2152 (4)	10277 (2)	47 (1)
O4	4328 (2)	−0591 (4)	11483 (2)	55 (1)
O5	1267 (2)	−2674 (4)	6477 (2)	52 (1)
O6	0906 (2)	−2837 (5)	3837 (2)	61 (1)
O7	−0760 (2)	−2650 (4)	3484 (2)	57 (1)
O8	−2504 (2)	−2532 (6)	3966 (2)	76 (1)
O9	4232 (2)	7269 (5)	7984 (2)	79 (1)
C10	2777 (2)	6091 (5)	7445 (2)	70 (1)
C31	3455 (4)	7340 (8)	7466 (2)	69 (2)
C32	3619 (24)	8902 (46)	6879 (22)	92 (13)

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

In the structure of the H-clathrate of gossypol with methanol, a slight rearrangement takes place because of the change in the nature of the host—guest H-bond. Since the guest molecule now contains a hydroxy group in place of a carboxy group, the number of intermolecular host—guest H-bonds falls from four to three (Fig. 3). In two of these bonds the alcohol molecule acts as proton-acceptor, and in the third as proton-donor (see Table 2). In contrast to the H-clathrates of gossypol with carboxylic acids, here there is no bond with the O4—H group. This bond was one of three bonds making the dimers into stacks. Yet in its absence the general pattern of H-binding remains as before: host...host H-bonds unite gossypol molecules only into dimers, while host—guest H-bonds form layers. In the case of the carboxylic acids, each of the carboxy groups gave four H bonds with the aid of the two O atoms. Here, in such cases, only the single O atom of the hydroxy group participates (it gives three H-bonds). The latter leads to an approach of the stacks, which is shown as a decrease in the parameters a and c of the crystal (see Table 1).

The H-clathrate with MAlc undergoes desolvation instantaneously after the removal of the crystal from the mother solution. EALc molecules are more strongly bound in the lattice of the complex and it decomposes at 50°C. The solid substitution solutions gossypol·x(FA)·(1 − x)(AA) decompose over a wide range depending on the value of x: at x = 1, desolvation takes place at room temperature, at x = 0 it does so at 185-187°C. As a result of the de-

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

Atoms	*x/a*	*y/b*	*z/c*	U_{iso}^{eq}
C1	3012 (9)	8332 (8)	10218 (7)	42 (4)
C2	2943 (8)	7122 (8)	10189 (7)	37 (4)
C3	3270 (9)	6636 (8)	9388 (7)	36 (3)
C4	3650 (9)	7356 (8)	8659 (7)	45 (4)
C5	4100 (9)	9376 (8)	7845 (7)	52 (4)
C6	4111 (10)	10596 (9)	7872 (7)	52 (4)
C7	3773 (9)	11152 (8)	8652 (8)	49 (4)
C8	3382 (9)	10478 (8)	9434 (7)	44 (4)
C9	3351 (9)	9167 (8)	9438 (7)	38 (3)
C10	3704 (9)	8625 (8)	8647 (7)	40 (4)
C11	3449 (9)	5744 (8)	11920 (7)	43 (3)
C12	2519 (9)	6367 (7)	11013 (7)	40 (4)
C13	1215 (9)	6263 (8)	10868 (8)	47 (4)
C14	0909 (10)	5497 (9)	11643 (7)	51 (4)
C15	1423 (11)	4017 (9)	13317 (9)	65 (5)
C16	2354 (12)	3513 (9)	14255 (9)	64 (5)
C17	3667 (10)	3645 (9)	14436 (7)	62 (5)
C18	4097 (10)	4325 (8)	13667 (8)	52 (4)
C19	3146 (10)	4948 (8)	12715 (7)	46 (4)
C20	1834 (10)	4822 (8)	12566 (7)	47 (4)
C21	3236 (11)	5251 (9)	9406 (8)	64 (5)
C22	2977 (11)	11162 (9)	10153 (9)	70 (5)
C23	4429 (12)	8855 (9)	6952 (9)	70 (5)
C24	5779 (14)	9047 (13)	6929 (11)	113 (7)
C25	3475 (16)	9310 (13)	5865 (10)	122 (8)
C26	0217 (10)	6953 (9)	9914 (9)	68 (5)
C27	5460 (11)	4296 (9)	13893 (8)	69 (5)
C28	0037 (11)	3736 (12)	13087 (9)	79 (5)
C29	—0667 (14)	4486 (17)	13659 (13)	159 (11)
C30	—0110 (16)	2389 (12)	13271 (12)	133 (8)
O1	2752 (7)	8884 (5)	11011 (5)	58 (3)
O2	3002 (7)	12307 (6)	10094 (6)	77 (3)
O3	3826 (6)	12377 (5)	8579 (5)	61 (2)
O4	4408 (7)	11375 (6)	7107 (5)	74 (3)
O5	4709 (6)	5392 (6)	12086 (5)	62 (2)
O6	6234 (8)	3781 (7)	14768 (6)	82 (3)
O7	4454 (7)	3072 (6)	15377 (5)	82 (3)
O8	2069 (8)	2794 (7)	15057 (6)	93 (2)
O9	7610 (7)	2072 (6)	17061 (6)	69 (3)
O10	8634 (7)	2697 (7)	15904 (6)	95 (4)
C31	8512 (12)	1998 (9)	16733 (8)	58 (4)
C32	9727 (11)	1107 (11)	17268 (9)	71 (5)
C33	9775 (13)	0299 (12)	18205 (9)	99 (6)
C34	10635 (13)	1026 (14)	16740 (14)	140 (9)

composition of these three types of complexes an unsolvated crystalline form — a definite polymorph — of gossypol is formed which has a melting point of 197-199°C.

EXPERIMENTAL

Single crystals were obtained from saturated solutions of gossypol in suitable solvents with slow evaporation. To determine desolvation temperatures and melting points we used a thermomicroscope of the Boëtius type [7]. The compositions of the H-clathrates and, particularly, of the solid substitution solutions gossypol·FA·AA, were monitored with the aid of an XL-200 NMR spectrometer [8]. The qualitative x-ray phase analysis of the H-clathrates and of the polymorph were carried out by recording their diffractograms on a DRON-UM1 instrument [9].

Crystallographic parameters were determined and refined on a Syntex-P2_1 automatic four-circle diffractometer (USA). The collection of experimental results — integral intensities of the reflections — was carried out on the same diffractometer. In this process we used Cu$K\alpha$ radiation monochromatized by reflection from a graphic crystal, with $\theta/2\theta$ scanning at a variable rate of 3.91-11.72 deg/min to angles of $2\theta < 120°$. After the primary treatment of the results (with allowance for polarization and Lorentz factors), 2603 and 2664 reflections with $F > 2\sigma(F)$ for the H-clathrates of gossypol with FA and MAlc, respectively, were used in the calculation. Absorption was not taken into account because of the absence of strong absorbing atoms from the structures.

The structures were interpreted by direct methods with the aid of the MULTAN-78 program [10] included with the XTLSM complex set up on an SM-4 computer [11]. The structures were refined first in the isotropic and then in the anisotropic approximation. Hydrogen atoms were found from the difference Fourier syntheses. To determine the multiplicities of the population of the sites by formic and acetic acid molecules in the solid substitution solution gossypol·0.82 FA·0.18AA we made use of the possibilities of the SHELXSM packet of programs [11]. The R factors amounted to 0.048 and 0.063 for the H-clathrates of gossypol with FA and with MAlc, respectively. The final coordinates and equivalent isotropic temperature factors are given in Tables 3 and 4.

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HUMULENOIDS FROM PLANTS OF THE FAMILY APIACEAE
SPATIAL STRUCTURE OF α-APIENES

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A conformational analysis has been made by the method of molecular mechanics of the α-apienes — natural sesquiterpenes isolated from plants of the Apiaceae family. The results of the mathematical method with the inclusion of those x-ray structural studies have shown that in the molecules under consideration it is possible to expect the predominant realization of four conformations of the 11-membered ring: $_{14}A_8{}^7$, $^{14}A_7{}^8$, $_{14}A_7{}^8$, and $^{14}A_8{}^7$. These four conformations of unsubstituted α-apiene and its natural derivatives have been characterized energetically, and the barriers to their interconversions have been evaluated.

Humulenoids with a 4(5)-cis double bond have been isolated from plants of the Apiaceae family and have therefore acquired the name of apienes [1] (by analogy with the heliangolides and germacranolids [2]). The conformation of the 11-membered ring in the apienes has not hitherto been studied, if we leave out of consideration individual x-ray structural communications [3-7], i.e., no attempt has been made to systematize the stereochemistry of the 11-

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