SUMMARY

The existence of a new class of ICs based on DAGP has been established. Single crystals have been obtained and the crystallographic characteristics of 15 ICs of this GP derivative have been determined.

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X-RAY STRUCTURAL INVESTIGATION OF GOSSYPOL AND ITS DERIVATIVES.

IX. SEMICLATHRATES OF GOSSYPOL WITH ESTERS OF ACETIC ACID

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UDC 547.554+548.737

Inclusion compounds of gossypol with a number of acetic acid esters have been obtained and have been identified by derivatography and NMR spectroscopy. An x-ray structural investigation of the structures of crystalline complexes of gossypol with ethyl acetate and butyl acetate has shown that these complexes are isostructural semiclathrates. On the basis of the structures of these two semiclathrates of gossypol, it has been concluded that esters and ketone with chain lengths of from five to seven atoms form inclusion compounds isomorphous with the semiclathrates of ethyl and butyl acetates. If the chain length is shorter or longer than that given, inclusion compounds with a different crystal structure are formed.

At the present time, inclusion compounds are being widely used in analytical chemistry and chromatography and in the fractionation of compounds of closely similar structure [1, 2]. No few compounds are known that give crystalline complexes with the inclusion of a number of comparatively small molecules [1-3]. Nevertheless, chemists continue to synthesize new substances that may prove to be "hosts" in the structure of inclusion compounds [4].

As a result of investigations performed by the methods of x-radiography, derivatography, and thermomicroscopy, we have established that gossypol, a physiologically active substance

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TABLE 1. Crystallographic Parameters of Complexes of Gossypol with Some Esters

Solvent	a	b	c	α	β	γ	V, Å³	Space group
	Å			degrees				
EA	11,130	16,472	30 892	90	90	89,69	5650	B2/b
BA	11,221	17,023	30,538	90	90	89 32	5833	B2/b
MA*	6.976	14.727	14.945	87,07	71,20	91,70	1452	$P\bar{1}$
AA1	14:478	14,602	16,019	77,52	115,49	112,21	3012	$P\bar{1}$
AA2	14.433	15,547	16.413	81,98	117,90	112,97	2992	$P\bar{1}$

*MA – methyl acetate; AA1 – amyl acetate; AA2 – amyl acrylate.

TABLE 2. Geometry of Hydrogen Bonds in Semiclathrates of Gossypol with EA and BA (each second line corresponds to the parameters of the H-bond in the structure of the semiclathrate of gossypol with BA)

Bond	Position of the bound molecule	O...O	O–H	H...O	O–H...O angle, deg
		Å			
O3 – H...O2		2,50	1,18	1,75	115,3
		2,50	1,08	1,58	139.6
O4 – H...O3		2,59	0,93	1,89	130,2
		2,59	1,02	1,94	119,2
O7 – H...O6		2,49	0,99	1,59	149,2
		2,48	0,83	1,81	137,0
O8 – H...O7		2,59	0,92	2,12	104,1
		2,62	1,10	2,13	103,7
O5 – H...O9	x, y, z	2.83	1,08	2,21	114,2
		2,80	0,88	2,17	128,2
O4 – H...O8	$0,5-x$; $0,5-y$; $z-0,5$	3.01	0,92	2,29	133,1
		3,00	1,02	2.17	138,0
O8 – H...O4	$x-0,5$; y; $0,5+z$	2,96	0,92	2,26	132,8
		2,92	1,10	2,05	133,0

from the cotton plant [5, 6] possesses the property of forming complexes with many organic molecules [7]. We have already obtained inclusion compounds of gossypol with ethers, ketones, aldehydes, monocarboxylic acids, alcohols, etc. In the present work we consider the structure of semiclathrates of gossypol with esters of acetic acid.

A derivatographic investigation and the NMR spectra of samples of gossypol obtained by recrystallization from solutions in ethyl acetate (EA) showed that the composition of these specimens were characterized by a gossypol:ethyl acetate ratio of 2:1. To determine the structure of this complex by x-ray structural analysis, single crystals were grown and their crystallographic parameters were determined. Subsequently, single crystals were obtained from solution in butyl acetate (BA), and their crystallographic parameters were determined, which indicated the isostructural nature of the two gossypol complexes (Table 1). This result could indicate the formation of inclusion compounds by gossypol, and a comparison of their structures is of definite interest. We therefore decided to decipher the structures of the complexes of gossypol EA and BA.

The results of the decipherment showed that in both complexes the gossypol had the aldehydic tautomeric form [8]. The dihedral angle between the mean square planes of the naphthyl nuclei of the gossypol molecule was 101.1° in both cases. In these crystal structures, the two types of intramolecular hydrogen bonds characterizing the isolated gossypol molecule [9, 10] were retained (Table 2). The numbering of the atoms in the gossypol molecule is given in Fig. 1, which shows the packing of the molecules in the crystal structures of the complexes under consideration.

In layers parallel to the xz plane, the gossypol molecules of the same chirality are linked with one another by two types of intermolecular H-bonds (Fig. 1). The hydrogen atoms of the O4–H and O8–H hydroxy groups take part simultaneously both in intermolecular and intramolecular H-bonds, these hydroxy groups playing the parts both of proton acceptors and proton

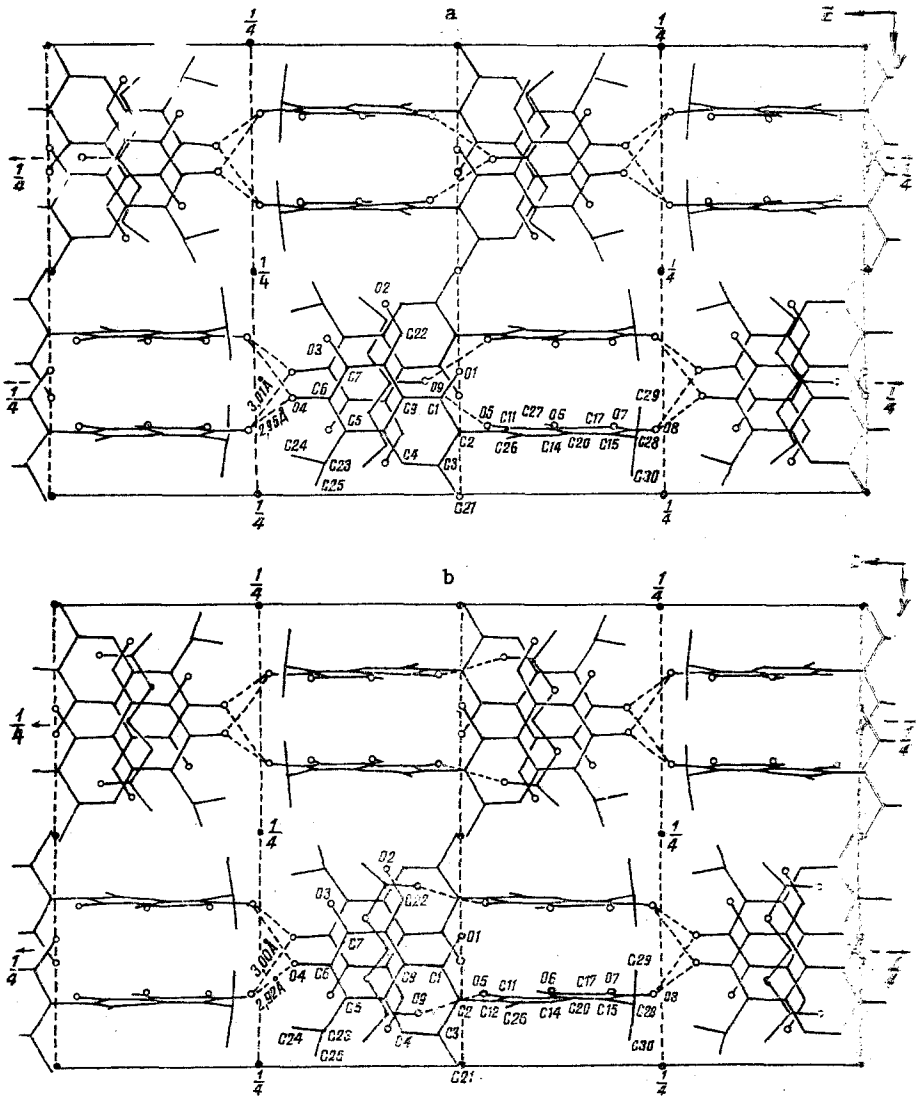

Fig. 1. Structure of the semiclathrates of gossypol with EA (a) and BA (b) (projections on the yz plane).

donors. The crystal structures have the following interesting feature – within the crystal there is, as it were, a resolution of racemic gossypol into optical antipodes arranged in alternating layers. The lengths of the O4–H...O8 hydrogen bonds are 3.01 and 3.00 Å and those of the O8–H...O4 hydrogen bonds 2.96 and 2.92 Å, respectively, in the structures of the semiclathrates gossypol with EA and with BA. The O1–H proton-donating group is not involved in intermolecular H-bonds.

The value of the dipole moment of one half of the gossypol molecule calculated by the CNDO/2 method using a program of I. A. Abronin (Institute of Organic Chemistry of the USSR Academy of Sciences) is 4.96 D. In the crystal structures of the complexes under consideration, the basic (selected) molecule is in contact with a molecule obtained from it by transformation through a twofold axis. Here, dipole-dipole interaction takes place between the "second" halves (the C11-C20 naphthyl nuclei) of these molecules, which are practically antiparallel to one another. The dihedral angle between the interacting naphthyl nuclei is 8°. The molecule obtained from the basic molecule with the aid of the twofold-axis transformation and subsequent translation along the x-axis interacts with it by their "first" halves (the C1–C10 naphthyl nuclei). Here the dihedral angle between the mean square planes of the naphthyl nuclei of these halves is 26°.

With this packing, a cavity is formed between the "first" halves of the basic gossypol molecule and of the molecule connected with it by a twofold axis. This cavity is filled by a solvent molecule, the carbonyl atom of which forms a H-bond with the two gossypol molecules

TABLE 3. Coordinates of the Atoms in the Structure of the Semiclathrates of Gossypol with EA and BA*

Atom	Semiclathrate with EA			Semiclathrate with BA		
	x/a	y/b	z/c	x/a	y/b	z/c
C1	2919 (10)	2868 (8)	4762 (4)	2984 (8)	2892 (6)	4754 (3)
C2	2579 (10)	3575 (8)	4975 (4)	2699 (9)	3598 (6)	4957 (3)
C3	2425 (11)	4305 (8)	4734 (4)	2604 (9)	4306 (6)	4711 (3)
C4	2569 (11)	4283 (8)	4287 (4)	2728 (9)	4264 (6)	4265 (3)
C5	2911 (10)	3524 (7)	3580 (4)	2999 (9)	3533 (7)	3563 (3)
C6	3284 (10)	2845 (8)	3389 (4)	3358 (9)	2846 (7)	3373 (3)
C7	3568 (10)	2146 (7)	3626 (4)	3576 (9)	2161 (7)	3608 (3)
C8	3492 (9)	2102 (7)	4078 (4)	3512 (9)	2128 (6)	4067 (3)
C9	3113 (9)	2839 (7)	4307 (3)	3178 (8)	2843 (6)	4293 (3)
C10	2839 (9)	3544 (7)	4064 (4)	2959 (9)	3542 (6)	4042 (3)
C11	1215 (9)	3528 (7)	5622 (4)	1315 (9)	3537 (6)	5588 (3)
C12	2387 (10)	3579 (7)	5445 (4)	2474 (9)	3598 (6)	5443 (3)
C13	3351 (9)	3652 (7)	5751 (4)	3425 (9)	3654 (7)	5742 (3)
C14	3122 (10)	3659 (7)	6189 (4)	3155 (8)	3631 (7)	6181 (3)
C15	1746 (10)	3637 (7)	6817 (4)	1764 (9)	3593 (7)	6814 (3)
C16	602 (10)	3556 (7)	6977 (4)	621 (9)	3526 (7)	6950 (3)
C17	—420 (9)	3513 (7)	6690 (4)	—354 (9)	3494 (7)	6662 (4)
C18	—267 (9)	3524 (7)	6236 (4)	—197 (8)	3495 (6)	6212 (4)
C19	953 (9)	3552 (7)	6063 (4)	1015 (9)	3536 (7)	6044 (3)
C20	1934 (12)	3618 (7)	6357 (4)	1996 (9)	3585 (6)	6348 (3)
C21	2141 (14)	5080 (8)	4961 (5)	2374 (11)	5073 (7)	4943 (4)
C22	3946 (13)	1376 (8)	4283 (5)	3883 (10)	1419 (7)	4280 (4)
C23	2528 (11)	4283 (9)	3337 (4)	2646 (11)	4267 (7)	3309 (4)
C24	1750 (14)	4104 (12)	2931 (5)	1859 (11)	4137 (7)	2907 (4)
C25	3624 (12)	4790 (9)	3221 (5)	3732 (11)	4787 (7)	3218 (4)
C26	4635 (10)	3728 (9)	5589 (4)	4683 (9)	3741 (7)	5587 (3)
C27	—1359 (11)	3478 (9)	5998 (4)	1258 (10)	3448 (8)	5937 (4)
C28	2740 (10)	3748 (9)	7152 (4)	2841 (9)	3701 (8)	7157 (3)
C29	3437 (13)	4539 (9)	7095 (6)	3407 (10)	4491 (7)	7110 (4)
C30	3634 (12)	3012 (9)	7187 (5)	3673 (11)	2988 (7)	7190 (4)
O1	3055 (7)	2175 (4)	5001 (2)	3065 (6)	2223 (4)	4990 (4)
O2	4201 (8)	743 (5)	4086 (3)	4096 (7)	794 (4)	4075 (2)
O3	3900 (7)	1493 (5)	3392 (2)	3852 (6)	1522 (4)	3371 (2)
O4	3444 (6)	2794 (5)	2951 (2)	3486 (6)	2794 (4)	2923 (2)
O5	275 (6)	3474 (5)	5336 (3)	396 (7)	3493 (5)	5297 (2)
O6	—2349 (7)	3455 (6)	6155 (3)	—2273 (7)	3456 (6)	6097 (3)
O7	—145 (6)	3476 (5)	6893 (2)	—1438 (6)	3457 (5)	6848 (2)
O8	375 (8)	3506 (6)	7413 (3)	365 (6)	3487 (4)	7392 (2)
HO1	311 (11)	235 (7)	527 (4)	310 (7)	229 (5)	530 (3)
HO3	428 (11)	87 (8)	353 (4)	413 (7)	104 (5)	358 (3)
HO4	372 (11)	226 (8)	294 (4)	396 (7)	228 (5)	290 (3)
HO5	62 (11)	350 (8)	501 (4)	68 (7)	356 (5)	503 (3)
HO7	189 (11)	373 (8)	662 (4)	—198 (7)	553 (5)	667 (3)
HO8	—43 (11)	350 (7)	747 (4)	—56 (7)	346 (5)	747 (3)
H4	245 (11)	482 (8)	412 (4)	260 (7)	482 (5)	410 (3)
H14	389 (11)	371 (8)	631 (4)	389 (7)	362 (5)	636 (3)
H22	422 (11)	138 (8)	465 (4)	384 (7)	140 (5)	461 (3)
H23	195 (11)	456 (8)	351 (4)	191 (7)	467 (5)	347 (3)
H27	—107 (11)	329 (8)	559 (4)	—129 (7)	342 (5)	359 (3)
H28	240 (11)	371 (8)	744 (4)	227 (7)	372 (5)	747 (3)
$H21_1$	248 (11)	511 (8)	527 (4)	254 (7)	555 (5)	474 (3)
$H21_2$	231 (11)	539 (8)	482 (4)	272 (8)	520 (5)	528 (3)
$H21_3$	134 (11)	509 (8)	498 (4)	154 (7)	512 (5)	504 (3)
$H26_1$	449 (11)	334 (8)	544 (4)	528 (7)	383 (5)	581 (3)
$H26_2$	436 (11)	429 (8)	544 (4)	475 (7)	439 (5)	540 (3)
$H26_3$	504 (11)	369 (8)	576 (4)	478 (7)	338 (5)	534 (3)
$H24_1$	116 (8)	386 (8)	305 (4)	125 (7)	463 (5)	279 (3)
$H24_2$	213 (12)	404 (8)	273 (4)	135 (7)	369 (5)	295 (3)
$H24_3$	150 (12)	469 (8)	281 (4)	256 (7)	405 (5)	261 (3)

connected with one another with the aid of the twofold axis. We have not succeeded in localizing all the atoms of the EA molecule, since it is subject to orientation disorder: the C=O group lies on the twofold axis, and the ethoxy and methyl groups are directed to one side and the other alternately. The EA molecule remains "squeezed" between the two naphthyl nuclei, being arranged almost parallel to them. This conclusion was confirmed after the localization of all the nonhydrogen atoms of the BA molecule in the complex of gossypol with this ester. In this structure, the solvent molecule likewise occupies two positions statistically, and in one cell it is bound by hydrogen bonds with the basic gossypol molecule and in the other to the gossypol molecule connected with the basic molecule by the second-order axis and translation along the X axis. Because of this, precisely half the O5—H proton-donating groups in the crystal remain unbound.

TABLE 3 (continued)

Atom	Semiclathrate with EA			Semiclathrate with BA		
	x/a	y/b	z/c	x/a	y/b	z/c
$H25_1$	407(11)	492(8)	350(4)	409(7)	498(5)	351(3)
$H26_2$	318(12)	530(8)	318(4)	409(7)	448(5)	300(3)
$H25_3$	382(11)	470(8)	302(4)	371(7)	521(5)	301(3)
$H29_1$	412(11)	464(8)	749(4)	276(7)	500(5)	706(3)
$H29_2$	278(11)	501(8)	708(4)	387(7)	452(5)	680(3)
$H29_3$	394(11)	450(8)	680(4)	414(7)	455(5)	735(3)
$H30_1$	320(12)	260(8)	725(4)	405(7)	283(5)	692(3)
$H30_2$	419(11)	292(18)	693(4)	316(8)	247(5)	723(3)
$H30_3$	426(12)	300(8)	742(4)	411(8)	310(5)	744(3)
O9	0	2500	4179(8)	281(14)	3888(10)	4444(5)
O10				256(14)	4670(10)	3856(5)
C32	0	2500	4588(10)	828(16)	4000(12)	4099(6)
C33				388(17)	3170(12)	3823(6)
C34				0	2500	4136(5)
C35				—316(18)	1335(13)	4053(7)
C36				—825(18)	745(13)	3827(7)

*The coordinates of the non-hydrogen atoms are multiplied by 10^4, and those of the H atoms by 10^3.

It follows from what has been said above that in the two structures the carbonyl atom of the solvent molecule occupies different positions (Fig. 1). The length of the O5—H...O9 hydrogen bond in the semiclathrate of gossypol with EA is 2.83 Å, while in that with BA it is 2.80 Å. In both semiclathrates the ratio of gossypol and solvent molecules is 2:1, which confirms the results of derivatography and NMR spectroscopy obtained before the structural analysis was performed.

Thus, the solvent molecules are located in cells that are closed on all sides. In this sense, the complexes under consideration are clathrates [2, 4]. The guest molecule occupying the cavity presented to it is bound to the wall of the cell by hydrogen bonds, which is a fairly rare case in clathrate formation [11]. Such complexes are usually called semiclathrates [12].

The cavities in the semiclathrates of gossypol with EA and BA molecules have a definite size and shape. It is known from the crystal chemistry of clathrates that because of the flexibility of the crystal structure the size of the cavity may increase to a certain limit [13-15]. Inclusion compounds are either not formed at all with the molecule the size of which exceeds this limit or a complex with a structure of a different type is formed. We were therefore interested in finding the maximum length of the hydrocarbon chain of an ester at which semiclathrates of the given type are still formed, and what is its minimum length. It was found that EA forms the lower limit for the length of the guest molecule and BA the upper limit for the semiclathrates of gossypol under consideration. Table 1 gives the crystallographic parameters of complexes of gossypol with MA, AA1, and AA2. MA forms with gossypol triclinic crystals with a host:guest ratio of 1:1. The isostructural crystals of the complexes of gossypol with AA1 and AA2 are also triclinic and are characterized by a gossypol: solvent composition of 2:1.

On the basis of these results, it can be predicted that esters and ketones with hydrocarbon chains having from five to seven nonhydrogen atoms will form semiclathrates of the ester series. If the length of the chain is less than five atoms, the strength of the Van der Waals interaction between the guest molecule proves to be insufficient to retain the guest in the cell. If the chain contains more than seven nonhydrogen atoms, this guest molecule cannot insert itself into the clathrate cavity. The strongest complexes are formed by a guest molecule with a length of seven atoms and the weakest by one with five atoms. The results of a thermographic and thermomicroscopic investigation of the complexes lead to the same conclusion. These facts can be used to separate esters and ketones having lengths of from four to eight nonhydrogen atoms.

EXPERIMENTAL

Single crystals were grown from solutions of gossypol in the corresponding esters. The parameters of the elementary cells and the space groups of the crystals were determined and

refined on a Syntex $P2_1$ automatic four-circle diffractometer. To measure the intensities of the reflections CuK_α radiation monochromatized by reflection from a graphite crystal was used. Scanning was carried out by the $\theta/2\theta$ method to an angle of $2\theta \leq 120°$ at a variable rate of 4.8-11.2 deg/min. The primary treatment of the experimental group for polarization and Lorentz factors was carried out, but absorption was not taken into account because the absence of heavy atoms in the structure. The calculations involved reflections with $I \geq 3\sigma$ (1). For the semiclathrate of gossypol with EA the final group consisted of 2465 reflections, and for the semiclathrate of gossypol with BA it consisted of 2388 reflections.

The crystal structure of the semiclathrate of gossypol with EA was interpreted by the direct method using the program of the Rentgen-75 group [16], and that of the semiclathrate of gossypol with BA was interpreted by the method of molecular substitution on the basis of the known isomorphous structure of the semiclathrate of gossypol with EA. The structures were refined by the programs of the SHELX-76 complex [17] first in the isotropic and then in the anisotropic approximation. Hydrogen atoms were found by difference electron-density syntheses. The final R-factor for the complex of gossypol with EA was 9.3%, and for the complex of gossypol with BA 8.9%. The coordinates of the atoms of the structure corresponding to these values of the divergence factor are given in Table 3.

SUMMARY

The crystal structures of the complexes of gossypol with ethyl and butyl acetates have been interpreted by x-ray structural analysis. It has been shown that these complexes are semiclathrates of gossypol.

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