

X-RAY STRUCTURAL INVESTIGATION OF GOSSYPOL AND ITS DERIVATIVES

XXV. STRUCTURE OF THE CLATHRATE OF GOSSYPOL WITH ISOPROPYL ALCOHOL

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With isopropyl alcohol, gossypol forms a clathrate isostructural with the complexes of gossypol formed by ketones (acetone), aldehydes (butyraldehyde), or alcohols (propyl alcohol). The hydroxy group of isopropyl alcohol acts as the proton acceptor in a hydrogen bond of the host-guest type.

Gossypol gives clathrates with organic substances belonging to various classes [1-5]. The formation of clathrates with the members of a definite homologous series of solvents is of practical interest since, in principle, this opens up the possibility of the separation and purification of solvents by the formation of inclusion compounds [6-8]. The results of a determination of the structures of clathrates of gossypol with lower members of monohydric unbranched alcohols were given in a report [9], while the present paper is devoted to the x-ray structural analysis of inclusion compounds of gossypol with a representative of the monohydric branched alcohols — isopropyl alcohol.

Gossypol and isopropyl alcohol form complexes with an equimolar composition. In this structure, with the aid of $O5-H \cdots O3$ H-bonds the host molecule forms the centrosymmetric dimers that are typical for many crystalline forms of gossypol [1-5, 9, 10]. No such associates can arise if the gossypol molecules are in the lactol tautomeric form. In this tautomeric form, there is no $O1-H$ group acting as the proton donor for the H-bond of the dimer. The energetic suitability of dimerization is apparently due to the fixation of the aldehydic tautomeric form of gossypol in the solid state.

The isopropyl groups in the two halves of the gossypol molecule have the same orientation, namely: in the C1-C10 half the H4 and H23 atoms, and in the C11-C20 half the H14 and H28 atoms, are turned towards one another (Fig. 1). The dihedral angle between the mean square planes (the coplanarity of the atoms is close to ideal, deviations not exceeding 0.04 Å) of the atoms of the naphthyl nuclei of the gossypol molecule is 87.5°. In the gossypol molecule there are hydrogen bonds of two types (Table 1). $C=O \cdots H-O$ H-bonds close six-membered rings consisting of the atoms $O2-C22-C8-C7-O3-H$ and $O6-C27-C18-C17-O7-H$, and H-bonds of the $O-H \cdots O$ type close five-membered rings consisting of the atoms $O3-C7-C6-O4-H$ and $O7-C17-C16-O8-H$. The lengths of the bonds and the valence angles agree well with those found in clathrates of gossypol with acetone, tetrahydrofuran, and other solvents [1-5].

In this H-clathrate, in which the host and guest molecules are linked by H-bonds, the $O1-H$ hydroxy group of the host molecule exerts a proton-donating function, supplying a proton for an H-bond with the guest molecule. The latter strives to use its remaining, unused, proton for an H-bond with the $O6$ oxygen atom of another gossypol molecule.

In the crystal, dimers from enantiomeric gossypol molecules form columns in which they are united by $O8-H \cdots O4$ H-bonds (Fig. 2). The columns are parallel to the $[O \bar{1} 1]$ direction. In the direction perpendicular to the C1-C10 naphthyl nuclei, hydrophobic parts of the gossypol molecule are located on the surface of the columns. In the direction perpendicular to the C11-C20 naphthyl nuclei, the surface of the columns is coated with both hydrophobic and hydrophilic parts of the host molecule.

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TABLE 1. Geometry of the Intermolecular H-Bonds in the Crystal Structure of the Clathrate of Gossypol with Isopropyl Alcohol

Bond	Distances, Å			O—H...O angle,
	O...C	O...H	H...O	degrees
O5—H...O3 [#]	2.834	0.77	2.17	145
O6—H...O4 [#]	2.902	0.86	1.89	157
O4—H...O7 [#]	2.818	0.87	2.78	
O1—H...O3	2.789	0.70	2.03	157
O5—H...O5 [#]	3.227	1.02	2.47	132

Symmetry codes: (i) $-x, -y, 1-z$
(ii) $x, 1-y, 1-z$
(iii) $-x, 1-y, 2-z$

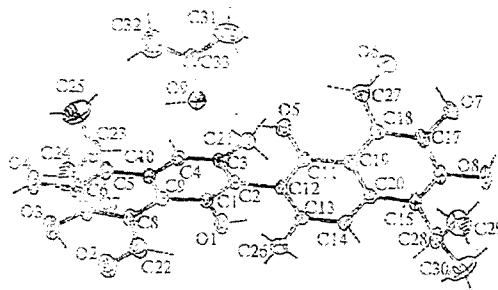


Fig. 1. Conformation of the molecules in the structure of the clathrate of gossypol with isopropyl alcohol.

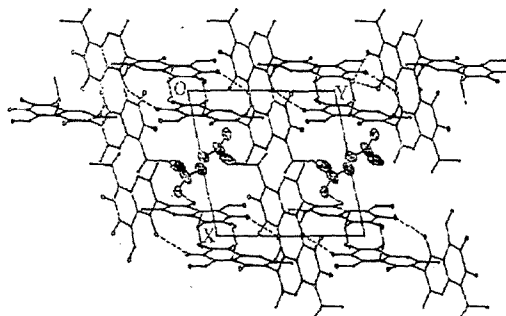


Fig. 2. Crystal structure of the clathrate of gossypol with isopropyl alcohol (xy projection; H-bonds are shown by dotted lines).

On translation in the direction of the y axis, the hydrophobic part of the C1-C10 naphthyl nucleus comes into contact with the hydrophilic part of the same nucleus. Then a cavity is formed between the parallel C11-C20 naphthyl nuclei. On translation of the columns in the direction of the x axis, the C1-C10 naphthyl nuclei form another two parallel walls of the cavity. In this direction, moreover, van der Waals interaction is realized between the columns on the contact of the hydrophilic parts of the gossypol molecule with the hydrophobic parts; for example: the C26 methyl group proves to be opposite the O2 oxygen atom. Thus, a characteristic feature of the structure is the absence of purely hydrophobic—hydrophobic or hydrophilic—hydrophilic contacts between the gossypol molecules.

In the direction of the z axis the cavities are arranged one above the other, forming centrosymmetric channels between parallel nuclei of both types. Both hydrophilic and hydrophobic parts of the gossypol molecule are present on the surface of the channels. The isopropyl and methyl groups of the C11-C20 halves in both naphthyl nuclei form a hydrophobic part of the wall of the channel, while the O1—H and O4—H groups and the O6 atom form a hydrophilic part.

The guest molecules, having a single polar group, are included in these channels and form H-bonds with the O1—H hydroxy groups. These groups are the most sensitive for host-guest H-bonding among the above-mentioned three polar groups included in the channel. Thus, the H-clathrate of gossypol with isopropyl alcohol is a H-tubulate or clathrate of the channel type and is isostructural with the H-clathrates of gossypol with acetone, tetrahydrofuran, cyclohexane, and butyraldehyde [2, 3].

TABLE 2. Crystallographic Characteristics of H-Tubulates of Gossypol with Homologous Monohydric Alcohols

Guest molecule	Å						degrees			V, Å ³	ρ, g/cm ³
	a	b	c	α	β	γ					
Isopropyl alcohol	10.585(1)	11.152(1)	14.017(2)	78.47(1)	108.80(1)	82.36(1)	1500	1.28			
Propyl alcohol	10.841(4)	11.073(2)	14.205(4)	77.68(2)	109.87(3)	78.87(2)	1500	1.28			
Butyl alcohol	11.09(2)	11.09(2)	14.51(2)	77.4(1)	110.9(1)	78.9(1)	1554	1.27			
Allyl alcohol	10.861(5)	11.035(3)	14.142(7)	78.40(3)	170.49(3)	79.55(3)	1496	1.28			
Isobutyl alcohol	10.780(3)	11.204(5)	14.399(3)	76.61(3)	107.53(2)	78.39(3)	1545	1.27			
Isoamyl alcohol	10.048(4)	11.677(5)	15.426(9)	69.92(4)	107.64(4)	85.31(3)	1585	1.27			
Methyl alcohol	13.420(3)	7.156(2)	14.508(3)	93.51(1)	98.17(1)	94.95(1)	1372	1.33			
Ethyl alcohol	13.695(6)	7.113(3)	15.002(9)	93.90(4)	112.95(4)	88.75(3)	1439	1.30			

TABLE 3. Coordinates of the Atoms ($\times 10^4$; for H atoms, $\times 10^3$) and Equivalent Isothermal Temperature Factors ($\text{\AA}^2 \times 10^3$; for H atoms, $\text{\AA}^2 \times 10^2$)

Atoms	x/a	y/b	z/c	U^*
C1	8587(5)	5691(4)	6983(4)	48(2)
C2	7589(5)	6316(4)	6051(4)	45(2)
C3	6238(5)	6188(4)	5874(4)	51(2)
C4	5954(5)	5438(5)	6648(4)	55(3)
C5	6596(6)	4009(5)	8401(4)	62(3)
C6	7603(6)	3466(5)	9348(5)	64(3)
C7	8973(6)	3579(5)	9554(4)	65(3)
C8	9378(6)	4250(5)	8799(4)	55(3)
C9	8347(5)	4895(4)	7812(4)	49(2)
C10	6966(6)	4771(5)	7616(4)	52(3)
C11	7973(5)	8346(4)	5181(4)	46(2)
C12	7959(5)	7106(4)	5220(4)	45(2)
C13	8226(5)	6600(4)	4438(4)	46(2)
C14	8572(5)	7341(5)	3709(4)	50(2)
C15	9027(5)	9349(5)	2888(4)	57(3)
C16	9033(6)	10571(5)	2870(4)	61(3)
C17	8682(5)	11126(5)	3588(4)	58(3)
C18	8303(5)	10450(5)	4362(4)	50(2)
C19	8301(5)	9142(4)	4424(4)	46(2)
C20	8625(5)	8615(5)	3667(4)	49(2)
C21	5106(5)	6907(5)	4856(5)	70(3)
C22	10825(6)	4217(5)	9084(5)	77(3)
C23	5172(6)	3775(7)	8190(5)	87(4)
C24	5099(8)	2406(9)	8407(7)	142(6)
C25	4385(9)	4474(11)	8676(9)	181(8)
C26	8175(5)	5245(5)	4448(5)	63(3)
C27	7922(6)	11144(5)	5029(5)	72(3)
C28	9423(7)	8787(6)	2085(5)	78(3)
C29	8393(10)	9286(8)	1010(7)	142(6)
C30	10822(9)	8834(9)	2114(8)	154(7)
O1	9910(3)	5832(3)	7172(3)	68(2)
O2	11691(4)	3655(4)	9959(3)	92(2)
O3	9841(4)	2961(4)	10514(3)	90(2)
O4	7312(4)	2781(4)	10142(3)	91(2)
O5	7745(4)	8839(3)	5947(3)	75(2)
O6	7922(4)	12261(3)	4939(3)	88(2)
O7	8705(3)	12343(3)	3477(3)	71(2)
O8	9369(4)	11335(3)	2121(3)	82(2)
O9	6984(5)	7928(4)	7618(3)	99(2)
C31	5424(9)	9843(9)	6983(8)	178(8)
C32	5205(9)	8201(12)	8295(9)	219(8)
C33	5935(10)	8666(8)	7713(8)	175(7)
H31a	522(1)	942(1)	644(1)	9
H31b	617(1)	1024(1)	698(1)	9
H31c	464(1)	1046(1)	687(1)	9
H32a	449(1)	794(1)	781(1)	9
H32b	481(1)	884(1)	854(1)	9
H32c	573(1)	750(1)	887(1)	9
H33	645(1)	876(1)	849(1)	9
H4	506(4)	546(4)	658(3)	6(1)
H21a	506(5)	787(5)	478(4)	11(2)
H21b	534(5)	677(5)	429(4)	12(2)
H21c	423(5)	663(5)	483(4)	10(2)
H22	1111(4)	468(4)	850(4)	9(2)
H23	463(6)	405(6)	734(5)	15(2)
H24a	531(6)	214(5)	906(5)	19(2)
H24b	561(6)	211(5)	807(5)	15(2)
H24c	405(6)	244(5)	805(5)	18(2)
H25a	497(5)	423(5)	948(4)	15(2)
H25b	349(6)	430(5)	849(5)	15(2)
H25c	437(5)	538(5)	844(4)	12(2)
H14	874(4)	703(4)	317(3)	5(1)
H27	764(4)	1070(4)	559(4)	9(2)
H28	948(6)	781(5)	226(5)	14(2)
H26a	736(5)	499(4)	446(4)	9(2)
H26b	817(7)	515(6)	386(6)	17(3)
H26c	896(4)	485(4)	502(4)	9(2)
H29a	814(6)	1020(6)	78(5)	19(2)
H29b	755(6)	904(6)	107(5)	21(2)
H29c	858(5)	890(5)	55(4)	15(2)
H30a	1073(5)	979(5)	192(5)	18(2)
H30b	1113(5)	840(5)	169(4)	13(2)
H30c	1147(5)	836(5)	286(4)	16(2)

TABLE 3 (continued)

Atoms	x/a	y/b	z/c	U [*]
H1o	996(5)	636(4)	676(4)	11(2)
H3o	1072(6)	307(5)	1047(5)	14(2)
H4o	806(4)	250(4)	1078(4)	9(2)
H5o	750(6)	838(5)	633(4)	15(2)
H7o	841(4)	1261(4)	392(4)	9(2)
H8o	935(4)	1205(4)	232(4)	7(2)
H9o	689(7)	728(7)	816(6)	20(3)

*The equivalent isothermal temperature factor U is defined as one third of the trace of the orthogonal tensor $U(i,j)$.

Isostructural with the gossypol—propyl alcohol clathrate are clathrates formed by propyl, butyl, isobutyl, allyl, and isoallyl alcohols, the crystallographic parameters of which, reduced to the same frame of reference are given in Table 2. The lower representatives of the homologous series of monohydric alcohols — methyl and ethyl alcohols — form H-tubulates of a different type, isostructural with the H-tubulates of gossypolacetic acid [9, 10]. Consequently, an increase in the length of monohydric alcohols (up to propyl) or their branching (isopropyl alcohol) leads to a morphotropic transition — the place of one H-tubulate is occupied by another H-tubulate.

EXPERIMENTAL

Single crystals of the H-clathrate of gossypol with isopropyl alcohol were grown from a solution of gossypol in isopropyl alcohol by slow evaporation. The determination and refinement of the crystallographic parameters and the collection of experimental results (integral intensities of reflections) were carried out on a Syntex-P2₁ automatic diffractometer. CuK α radiation monochromatized by reflection from a graphite crystal was used. The $\theta/2\theta$ method was employed at a rate of scanning of 5.9-19.2 deg/min to angles of $2\theta < 120^\circ$, with the rejection of weak reflections. No correction was made for absorption. After the correction of the experimental group for Lorentz and polarization factors, the number of reflections with $F > 4\sigma(F)$ amounted to 2449.

The structure was interpreted by the direct method with the aid of the SHELXS-86 program [12]. Refinement was carried out by the programs of the SHELX-76 package [13], beginning in the isotropic and then in the anisotropic approximations. Hydrogen atoms were localized from difference Fourier syntheses. The final R factor amounted to 0.061. The coordinates of the atoms and their equivalent isotropic temperature factors are given in Table 3.

REFERENCES

1. S. A. Talipov, B. T. Ibragimov, G. N. Tishchenko, T. F. Aripov, G. B. Nazarov, B. V. Strokopytov, and K. M. Polyakov, *Kristallografiya*, **33**, 384 (1988).
2. S. A. Talipov, B. T. Ibragimov, G. N. Tishchenko, and T. F. Aripov, *Kristallografiya*, **34**, 27 (1989).
3. B. Y. Ibragimov, M. Gdaniec, and B. N. Dadabaev, *J. Inclusion Phen. Molec. Recognition*, **8**, 333 (1990).
4. B. T. Ibragimov, S. A. Talipov, T. F. Aripov, and A. S. Sadykov, *J. Inclusion Phen. Molec. Recognition*, **8**, 323 (1990).
5. M. Gdaniec, B. T. Ibragimov, and S. A. Talipov, *J. Inclusion Phen. Molec. Recognition*, **9**, 231 (1990).
6. M. M. Hagan, *Clathrate Inclusion Compounds*, Reinhold, New York (1962).
7. D. D. MacNicol, J. McKendrick, and D. R. Wilson, *Chem. Soc. Rev.*, **7**, 65 (1978).
8. J. E. D. Davies, W. Kemula, H. M. Powell, and N. O. Smith, *J. Inclusion Phen. Molec. Recognition*, **1**, 4 (1983).
9. B. T. Ibragimov, S. A. Talipov, B. N. Dadabaev, and A. A. Abduvakhobov, *Khim. Prir. Soedin.*, 191 (1992).
10. B. T. Ibragimov, S. A. Talipov, B. N. Dadabaev, and A. A. Abduvakhobov, *Khim. Prir. Soedin.*, 330 (1992).
11. B. T. Ibragimov, S. A. Talipov, and P. M. Zorky, *Supramolecular Chemistry*, **3**, 147 (1994).
12. G. M. Sheldrick, *Acta Crystallogr.*, **A46**, 467 (1990).
13. G. M. Sheldrick, *SHELX-76, Program for Crystal Structure Determination*, University of Cambridge, England (1976).