

Inclusion Complexes of the Natural Product Gossypol. Recognition by Gossypol of Halogeno Methanes. Structure of the Dichloromethane Complex of Gossypol and Single Crystal Conservation after Decomposition

B. T. IBRAGIMOV, S. A. TALIPOV and T. F. ARIPOV

Institute of Bioorganic Chemistry, Uzbekistan Academy of Sciences, H. Abdullaev Str. 83, Tashkent 700143, Uzbekistan.

(Received: 29 April 1993; in final form: 21 March 1994)

Abstract. The structures of gossypol complexes are extremely sensitive to the halogenomethane present as the guest; e.g. changing the number of Cl atoms in chloromethane derivatives changes the structure of the gossypol complex. The crystals of $C_{30}H_{30}O_8 \cdot CH_2Cl_2$ are monoclinic, space group $C2/c$, $a = 21.320(4)$, $b = 19.199(6)$, $c = 15.765(2)$ Å, $\beta = 113.05(2)^\circ$, $V = 5916(2)$ Å³, $Z = 8$, $D_x = 1.35$ g/cm³, $T = 295$ K. The structure has been solved by direct methods and refined to the final R value of 0.084 for 1828 reflections. In the structure H-bonded gossypol molecules form columns, generating channels in the structure which are filled by guest molecules. After decomposition (desolvation) monocrystals of the complexes are conserved without destruction, in which there are rather wide and empty channels though slightly smaller than in the complex. An attempt is made to explain some peculiarities of the behavior of the gossypol polymorph formed on the basis of its structure with empty channels.

Key words: Gossypol, complex, crystal structure, single crystal, desolvation, polymorph.

Supplementary data relevant to this article have been deposited with the British Library Publication No. SUP 82165 (17 pages).

1. Introduction

Gossypol is an extremely versatile host. We have tested the complex formation with gossypol of over 100 organic substances and found that all of them give complexes [1]. Molecular complexes of gossypol are mainly inclusion compounds. Gossypol strictly recognizes molecules by their chemical nature (polarity) and geometry (dimensions and shape). First of all gossypol classifies the guests into two large families by their polarity (hydrophobicity and hydrophilicity) or their ability to form H-bonds with molecules of the host. Complexes of these families represent common clathrates and coordinatoclathrates [2, 3]. In gossypol coordinatoclathrates H-bonds are formed between host and guest molecules. We proposed the term H-clathrates for such kinds of coordinatoclathrates [4]. Both in common

and in coordinatoclathrates gossypol strictly distinguishes guest molecules by their shape and size. All types of gossypol complexes: cage, channel (tubulate) and layer have been observed [5]. The total number of various gossypol clathrate isostructural groups discovered by us to date is 20. We demonstrate the extreme sensitivity of gossypol clathrates to the geometry of guest molecules using the example of halogenoderivatives of methane. Special attention is paid here to one homologous series, i.e. the chloromethane derivatives.

2. Experimental

Single crystals of the gossypol complex with CH_2Cl_2 were obtained by slow evaporation at room temperature. A crystal of approximate dimensions $0.3 \times 0.3 \times 0.6$ mm mounted into a quartz capillary was used. The lattice parameters were determined by a least-squares method of the setting angles of 15 reflections (2θ in the range 25 to 30°) using a Syntex-P2₁ diffractometer. The crystal data are as follows: $\text{C}_{30}\text{H}_{30}\text{O}_8 \cdot \text{CH}_2\text{Cl}_2$, monoclinic, space group $C2/c$, $a = 21.320(4)$, $b = 19.199(6)$, $c = 15.765(2)$ Å; $\beta = 113.05(2)^\circ$; $V = 5916(2)$ Å³, $Z = 8$, $D_x = 1.35$ g/cm³, $T = 295$ K.

Intensities of reflections were measured with graphite monochromatized $\text{CuK}\alpha$ radiation to $2\theta = 116^\circ$ using the $\theta/2\theta$ scan technique. No significant intensity variations were revealed for two control reflections measured after each array of 100 reflections. Data were corrected for Lorentz and polarization effects but not for absorption. Out of 4215 measured intensities 1828 had $F > 3\sigma(F)$ and were used for further calculations. The structure was solved by direct methods using the program MULTAN-80 [6] and refined first with isotropic and then with anisotropic temperature factors by least-squares methods using the program SHELX-76 [7]. The hydrogen atoms were placed in calculated positions. Final values of R and WR are 0.084 and 0.087, respectively. The weighting scheme was not used. In the final δF map, calculated after the last cycle of refinement, the maximum and minimum peaks were 0.52 and $-0.43\text{e} \text{ \AA}^{-3}$ respectively.

3. Results and Discussion

3.1. RECOGNITION BY GOSSYPOL OF THE HALOGEN CONTAINING DERIVATIVES OF METHANE

Gossypol forms a clathrate with CCl_4 [8], in which the guest molecules are situated in closed cages (cryptate). Decreasing the number of Cl atoms by one (chloroform) gives an intercalate [9], in which the layers of guest molecules are localized between the layers of host molecules (Figure 1 and Table I). A further decrease of the number of Cl atoms (dichloromethane) gives compounds of the channel type, i.e. tubulates.

Substitution of the Cl atoms in dichloromethane by Br atoms does not change the crystal structure. However, diiodomethane cannot be accommodated in the channels and a morphotropic transition to an intercalate type structure occurs

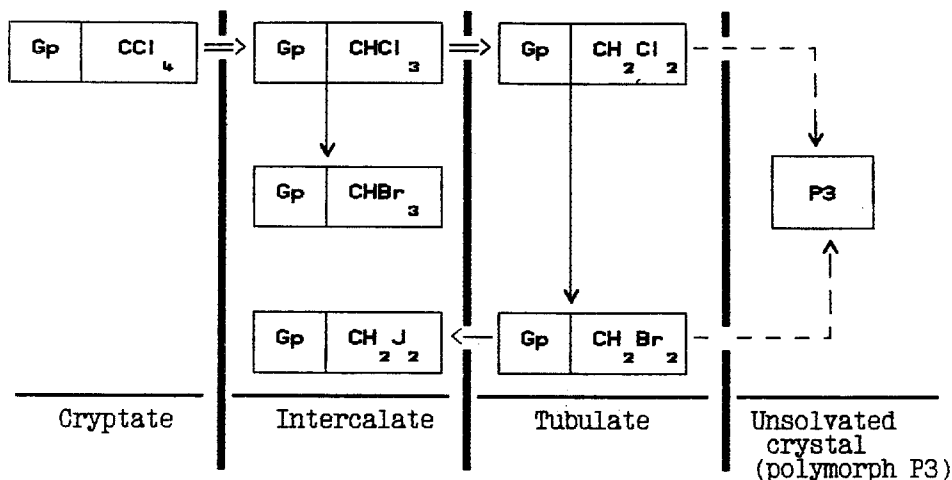


Fig. 1. Morphotropic transitions and desolvation (--->) of gossypol clathrates with halogen-derivatives of methane during the change of the number (⇒) and type (→) of the halogen atom in the guest molecule.

TABLE I. Crystallographic parameters of complexes of gossypol with halogeno methane derivatives.

Type	Cryptates	Intercalates		Tubulates			P3	
Parameters	Guest	CCl ₄	CHCl ₃	CHBr ₃	CH ₂ I ₂	CH ₂ Cl ₂	CH ₂ Br ₂	Polymorph
								-
$a(\text{\AA})$		8.847(2)	28.464(4)	28.544(3)	28.676(8)	21.320(4)	21.439(9)	21.208(8)
$b(\text{\AA})$		14.304(6)	8.948(1)	8.987(2)	9.164(4)	19.199(6)	19.087(8)	19.079(4)
$c(\text{\AA})$		13.395(5)	26.480(4)	26.759(6)	26.158(6)	15.765(2)	16.049(8)	15.267(2)
$\alpha(^{\circ})$		102.54(3)	90	90	90	90	90	90
$\beta(^{\circ})$		69.53(3)	108.93(2)	109.42(2)	108.21(2)	113.05(2)	113.68(4)	113.19(2)
$\gamma(^{\circ})$		91.12(3)	90	90	90	90	90	90
$V(\text{\AA}^3)$		1547	6380	6474	6529	5916	6015	5678
Sp.gr.		$P\bar{1}$	$C2/c$	$C2/c$	$C2/c$	$C2/c$	$C2/c$	$C2/c$
H:G*		1:1	1:1	1:1	1:1	1:1	1:1	-
Z*		2	8	8	8	8	8	8
$D_x(\text{g/cm}^3)$		1.66	1.33	1.58	1.60	1.35	1.53	1.22
Ref.		[8]	[9]					[12]

* H:G = host: guest ratio, Z – the number of gossypol molecules in the unit cell.

(Figure 1). Substitution of the Cl atoms in chloroform by Br atoms also does not lead to any structure change. Gossypol compounds with the remaining halomethane derivatives have not been studied to date.

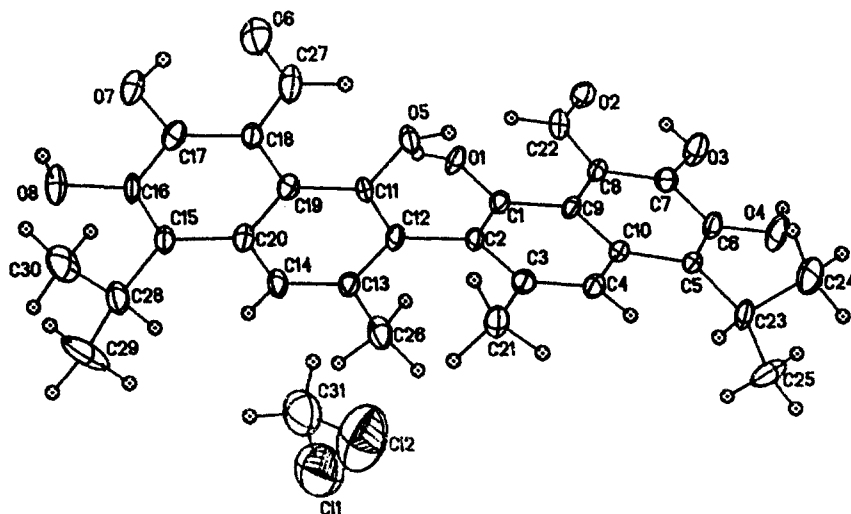


Fig. 2. Thermal ellipsoid representation and the labelling scheme of gossypol and guest molecules.

3.2. STRUCTURE OF THE DICHLOROMETHANE COMPLEX OF GOSSYPOL AND SINGLE CRYSTAL CONSERVATION AFTER DECOMPOSITION

The atomic parameters are given in Table II. Bond lengths, bond angles, the geometry of intramolecular hydrogen bonds, hydrogen atom parameters, anisotropic thermal parameters and structure factors are in the Supplementary Material. The conformation of host and guest molecules and the numbering scheme of gossypol and dichloromethane are shown in Figure 2.

3.2.1. Molecular structure

In the structure gossypol is in the aldehyde form, the only one found to date for gossypol in its crystalline state (Figure 2). The naphthyl moieties of the gossypol molecule are planar and the dihedral angle between their least-squares planes is $97.8(2)^\circ$. The isopropyl groups have identical orientations: the hydrogen atoms at C(23) and C(28) are oriented towards C(4) and C(14), respectively. There are four intramolecular hydrogen bonds in the gossypol molecule. The H-atoms of the hydroxyl groups O(3)–H and O(7)–H are involved in strong intramolecular hydrogen bonds which are part of a six-membered conjugated ring system. Hydrogen bonds O(4)–H...O(3) and O(8)–H...O(7) close five membered rings, and are much weaker [4, 8, 9]. Bond lengths, bond angles and values of intramolecular hydrogen bonds of the host are in good agreement with those observed in other gossypol host–guest complexes.

TABLE II. Atom coordinates ($\times 10^4$) and temperature factors ($\text{\AA}^2 \times 10^3$) of the gossypol complex with CH_2Cl_2 .

Atom	x	y	z	U^*
C(1)	905(5)	2625(5)	-934(8)	40(5)
C(2)	964(5)	2558(5)	-33(8)	36(5)
C(3)	1015(6)	3162(6)	502(7)	45(5)
C(4)	1016(6)	3800(6)	128(8)	43(5)
C(5)	1048(5)	4593(5)	-1105(7)	38(5)
C(6)	977(6)	4654(5)	-2005(8)	50(6)
C(7)	875(6)	4061(6)	-2589(8)	47(5)
C(8)	853(5)	3384(5)	-2291(7)	34(5)
C(9)	916(5)	3291(5)	-1344(7)	35(5)
C(10)	994(5)	3893(5)	-780(8)	38(5)
C(11)	463(5)	1517(5)	454(7)	39(5)
C(12)	1026(6)	1839(5)	358(7)	39(5)
C(13)	1646(5)	1478(6)	686(8)	44(5)
C(14)	1683(6)	835(6)	1062(8)	49(6)
C(15)	1218(6)	-190(5)	1582(8)	45(5)
C(16)	651(6)	-504(5)	1604(8)	47(6)
C(17)	11(6)	-178(6)	1281(8)	46(6)
C(18)	-78(6)	498(5)	945(7)	40(5)
C(19)	486(6)	851(5)	847(7)	37(5)
C(20)	1137(6)	502(6)	1172(8)	46(5)
C(21)	1053(7)	3086(6)	1469(7)	60(6)
C(22)	760(6)	2843(6)	-2969(8)	56(6)
C(23)	1183(6)	5226(5)	-508(8)	54(6)
C(24)	594(8)	5748(7)	-806(10)	91(8)
C(25)	1823(8)	5593(7)	-388(10)	106(9)
C(26)	2259(6)	1809(6)	606(9)	72(7)
C(27)	-747(7)	798(7)	730(10)	72(7)
C(28)	1914(6)	-543(6)	2036(9)	67(7)
C(29)	2130(8)	-583(10)	3057(10)	135(10)
C(30)	1958(7)	-1234(7)	1622(11)	95(9)
O(1)	828(4)	2048(3)	-1471(5)	50(4)
O(2)	678(4)	2945(4)	-3767(5)	56(4)
O(3)	815(5)	4225(4)	-3452(5)	72(4)
O(4)	1021(5)	5282(4)	-2369(6)	87(5)
O(5)	-157(3)	1852(4)	135(5)	48(3)
O(6)	-1225(4)	473(5)	789(7)	78(5)
O(7)	-492(4)	-555(4)	1373(5)	57(4)
O(8)	688(4)	-1161(4)	1961(6)	67(4)
Cl(1)	2622(4)	1843(4)	3281(5)	222(5)
Cl(2)	1583(5)	2339(4)	3821(5)	237(6)
C(31)	1873(10)	1643(10)	3284(15)	155(14)

* Equivalent isotropic U defined as one third of the trace of the orthogonalised $U(i, j)$ tensor.

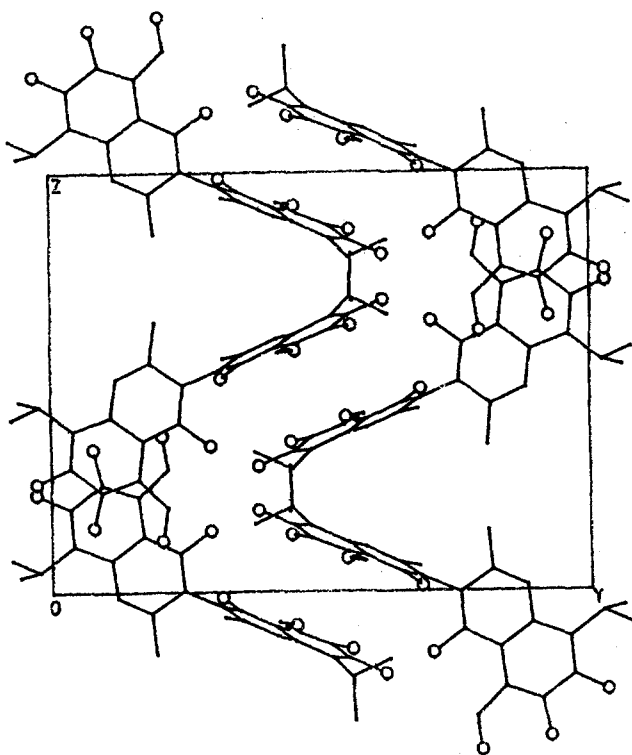


Fig. 3. The wavy chains of the host molecules in the structure of the dichloromethane complex of gossypol.

3.2.2. Crystal structure

H-bonding between O(5)–H...O(3) with a length of 2.94 Å results in right and left (athropisomeric) host molecules being combined into centrosymmetric dimers, typical of many gossypol crystal structures. The O(1)–H...O(6) H-bond (2.87 Å) of these dimers form wavy chains directed along the *z* axis (Figure 3). The packing of such chains in the crystal leads to the formation of channels, parallel to the *ac* diagonal (Figure 4). The channel walls are made from hydrophobic and hydrophilic zones of gossypol molecules. Dichloromethane molecules are situated in these channels. The latter form normal van der Waals contacts with atoms O(2), O(6), C(22), C(27), C(28) and C(30). The shortest distance between Cl atoms of dichloromethane molecules, situated in the channels, is 4.49 Å. The complex under consideration represents a common clathrate not a coordinatoclathrate [3, 4], because H-bonds are not observed between host and guest molecules.

The absence of H-bonds between the host and guest molecules evidently affects the tubulate stability, as immediate decomposition begins after removing crystals

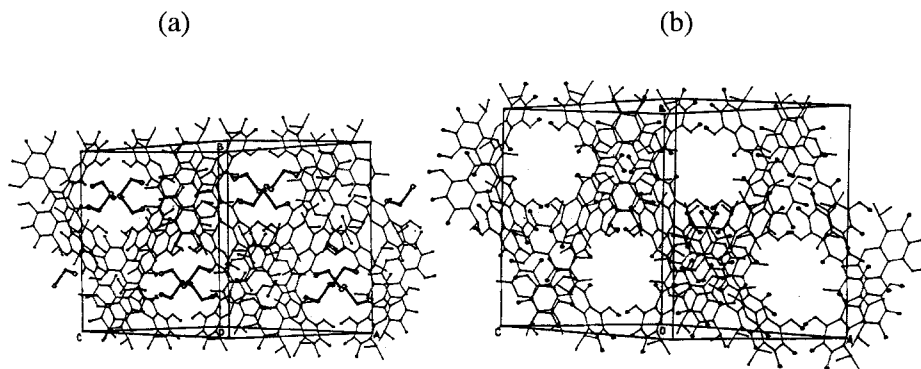


Fig. 4. The structure of the dichloromethane complex of gossypol (a) and unsolvated product (b).

of the complex from the mother solution. Surprisingly, the monocrystals are not destroyed but their volumes are only reduced by 4% in the case of CH_2Cl_2 and 9.4% in the case of CH_2Br_2 , i.e. after desolvation the channels do not collapse but slightly decrease their sizes (Figure 4). These channels are still rather large (diameter $\sim 5.5 \text{ \AA}$ without accounting for the van der Waals radii of atoms) and molecules of the atmospheric gases may freely move through them. In other words the gossypol complex with dichloromethane behaves like organic zeolites.

Taking advantage of this peculiarity of clathrate desolvation it is possible from one and the same monocrystal to obtain two sets of experiment and solve two structures – first the structure of the crystalline complex, mounted into the glass capillary and then the structure of the polymorph (nonsolvated form) from the same crystal, having carefully broken the capillary and repeating the experiment after a few hours.

In order to estimate the purity of gossypol samples the value of the extinction coefficient is used when absorbing light of wave length 366 nm [10]. Gossypol samples, obtained by recrystallization from a gossypol solution in dichloromethane, have rather low extinction coefficients compared with other polymorphs. The reason for this phenomenon is explained by finding the large channels in the structure of the P3 polymorph, obtained by desolvation of the gossypol complex with CH_2Cl_2 . The remaining gossypol polymorphs are discussed in [11]. For determination of purity a certain mass of the sample is used; the P3 polymorph contains both gossypol and included molecules (N_2 , O_2 , CO_2 etc.) in the channels. There is consequently less gossypol (in the unit mass of the P3 polymorph) compared to other nonsolvated forms and the calculated extinction coefficient value is less than the actual value. The P3 polymorph also possesses the lowest chemical stability – it changes its colour rapidly (darkens) due to oxidation products. This is, evidently, also connected with the channel structure of the given polymorph. Since the channels are filled with air, gossypol oxidation takes place quicker. If ammonia or

small amines are present in the environment, they accelerate the gossypol change, as these substances add to the aldehyde group and form derivatives of the Schiff base type.

References

1. B.T. Ibragimov and M. Gdaniec: 7th International Symposium on Molecular Recognition and Inclusion, 1992, Kyoto, *Abstracts*, 145.
2. E. Weber and H.P. Josel: *J. Incl. Phenom.* **1**, 79 (1983).
3. E. Weber: *J. Mol. Graphics* **7**, 12 (1989).
4. B.T. Ibragimov, S.A. Talipov, B.M. Dadabaev, and A.A. Abduvakhobov: *Khimiya Prir. Soed.*, 186 (1992).
5. B.T. Ibragimov, S.A. Talipov, B.M. Dadabaev, G.B. Nazarov, and T.F. Aripov: *Khimiya prir. soed.*, 675 (1988); *Chem. Abstr.* **111**, 58080c (1989).
6. P. Main, S.J. Fiske, S.E. Hull, L. Lessinger, G. Germain, J.-P. Declercq and M.M. Woolfson: MULTAN-80. *A System for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*. Universities of York, England and Louvain, Belgium (1980).
7. G.M. Sheldrick: SHELX-76. *Program for Crystal Structure Determination*. University of Cambridge, England (1976).
8. B.T. Ibragimov, S.A. Talipov, G.B. Nasarov, R.G. Mardanov, T.F. Aripov, A.I. Ismailov, and A.S. Sadykov: *Khimiya prir. soed.*, 113 (1986); *Chem. Abstr.* **105**, 227069q (1986).
9. M. Gdaniec, B.T. Ibragimov, and B.M. Dadabaev: *J. Incl. Phenom.* **9**, 231 (1990).
10. A.L. Markman and V.P. Rjekhin: *Gossypol and its Derivatives*, Moscow, 1965, 242 pp.
11. B.T. Ibragimov and S.A. Talipov: *J. Incl. Phenom.* **17**, 325 (1994).
12. S.A. Talipov, B.T. Ibragimov, G.B. Nasarov, T.F. Aripov, and A.S. Sadykov: *Khimiya prir. soed.*, 835 (1985); *Chem. Abstr.* **104**, 139743d (1986).