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BRIEF COMMUNICATIONS

GOSSYPOL CLATHRATES: STRUCTURE AND THERMAL BEHAVIOR OF THE GOSSYPOL ACRIDINE COMPLEX

© **M. T. Khonkeldieva, S. A. Talipov, L. Yu. Izotova,
Z. G. Tilyakov, B. T. Ibragimov, and É. N. Kurtaliev**

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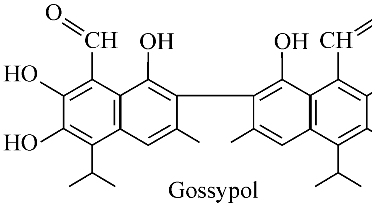
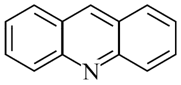
The natural compound gossypol forms a stable clathrate with acridine. The composition of the clathrate is $C_{30}H_{30}O_8 \cdot 0.5C_{13}H_9N$. The unit cell is monoclinic, $C2/c$ space group, $a = 11.3213(3)$ Å, $b = 30.5957(13)$ Å, $c = 17.0824(4)$ Å, $\gamma = 94.153(2)°$, $V = 5901.5(3)$ Å^3, $M = 1153.24$, $Z = 8$, $d_x = 1.369$ g/cm^3, and $R = 0.0413$ for 4726 reflections. The structure of the clathrate allows one to refer this compound to the ethyl acetate isomorphic host–guest group of gossypol complexes.

Key words: gossypol, acridine, clathrate formation, crystal structure.

Today, science knows only three host–guest complexes of gossypol [1] with solid compounds (found in the solid state in the usual conditions): tropolone [2], pyrazine [3], and cyclododecanone [4]. To conduct further investigation of how these complexes are formed, we made an attempt to produce gossypol clathrate with acridine, which is a solid (m.p. = 107 °C) nitrogen-containing compound known to be a biologically active coloring agent [5]. Crystallization of a gossypol acridine mix (1:1) from its solution in methylene chloride yielded a clathrate with the 2:1 host–guest mole ratio. The single crystal XRD and TG-DSC methods were used to study its crystal structure and thermal stability.



Gossypol



Acridine

Experimental. Crystals of gossypol acridine clathrate were grown at room temperature from the solution in dichloromethane with the 1:1 gossypol–guest mole ratio. The crystallographic parameters of the single crystals were determined and refined with an Xcalibur Oxford Diffraction CCD diffractometer (CuK_α radiation, graphite monochromator; at room temperature). The data collection strategy was implemented using the CrysAlisPro software [6]. The integral

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A. S. Sadykov Institute of Bioorganic Chemistry, Uzbekistan Academy of Sciences, Tashkent, Uzbekistan; samat_talipov@yahoo.com. Translated from *Zhurnal Strukturnoi Khimii*, Vol. 52, No. 1, pp. 197-200, January-February, 2011. Original article submitted April 7, 2010; revision July 9, 2010.

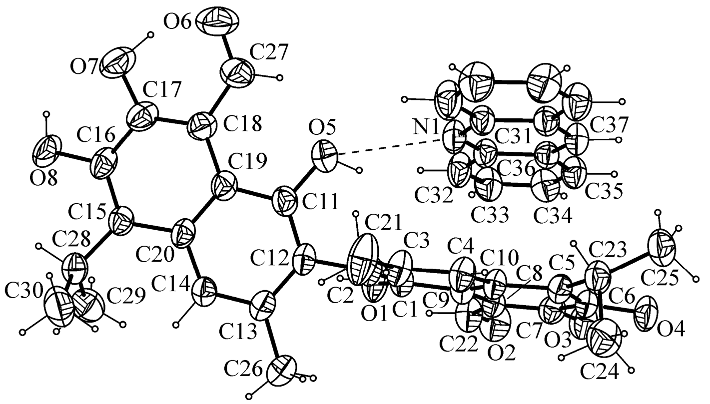

Fig. 1. Atom numbering in the gossypol and acridine molecules in the structure of gossypol acridine clathrate. The thermal ellipsoids are 50% probability.

intensities were measured by ω-scanning monochromated by reflection from a graphite crystal. After averaging the equivalent reflections and deleting the weak ones with $I < 2\sigma(I)$, we got a working set of 4726 reflections. The absorption correction was introduced by the multi-scan method in CrysAlisPro [6]. The structures were solved by the direct method using the SHELXS-97 software [7] and refined by the full-matrix least squares method using SHELXL-97 [8]. All the nonhydrogen atoms were anisotropically refined. Hydrogen atoms were determined from the difference synthesis and isotropically refined. The final value of the R factor is $R = 0.0413$, ($wR2 = 0.1298$). The molecular graphics was plotted using the XP program in the SHELXTL-Plus software package [9].

The structure has been deposited with Cambridge Crystallographic Data Center (http://www.ccdc.cam.ac.uk; e-mail: deposit@ccdc.cam.ac.uk; no. CCDC 768416).

Thermal stability of the solvates was determined on a Netzsch Simultaneous Analyzer STA 409 PG. All measurements were conducted in the inert nitrogen atmosphere at a nitrogen flow rate of 50 ml/min. The temperature range of the measurements was 25-350°C; the heating rate was 5 K/min. The amount of the sample substance per one measurement was 5-6 mg.

Results and Discussion. Crystals of gossypol acridine clathrate have the following crystallographic parameters: they are monoclinic, $C_{30}H_{30}O_8 \cdot 0.5C_{13}H_9N$ (the host–guest ratio is $m:n = 2:1$), $a = 11.3213(3)$ Å, $b = 30.5957(13)$ Å, $c = 17.0824(4)$ Å, $\gamma = 94.153(2)°$, $V = 5901.5(3)$ Å^3, $M = 1153.24$, $Z = 8$, $d_x = 1.369$ g/cm^3 and crystallize in the $C2/c$ space group. The gossypol molecule is in the general position, and the guest molecule is localized on the twofold axis. In terms of the host molecules' positions, this structure is isostructural to the so-called ethyl acetate isomorphic group [10], which comprises dozens of gossypol clathrates.

The gossypol molecules in the acridine clathrate (Fig. 1) are in the aldehyde tautomeric form. The bond angles and interatomic distances do not show any significant difference from the standard values [11]. The system of intramolecular H-bonds in the gossypol molecule has a specific property: it is nonsymmetrical. The isopropyl groups of the gossypol molecule can be in two stable states that differ from each other by rotation around the C(5)–C(23) (C(15)–C(28)) bonds by 180°. H(23)–(H(28)) can be directed towards the C(4)–(C(14)) atom or towards the closest hydroxyl group [10]. The solvates have both orientations; therefore, the C28–H…O8 hydrogen bond is present in one half of the molecule and absent in the other (Table 2).

The planarity of the naphthyl cores of gossypol molecules is identical; a deviation from the mean square plane is no greater than 0.03 Å. The dihedral angle between the mean square planes of the naphthyl cores is 103.2°.

The structure of the clathrate is characterized by the absence of typical centrosymmetric dimers, which have been observed in a large number of structures involving gossypol molecules (Fig. 2) [10-12]. Only two hydroxyl groups (O(4)–H

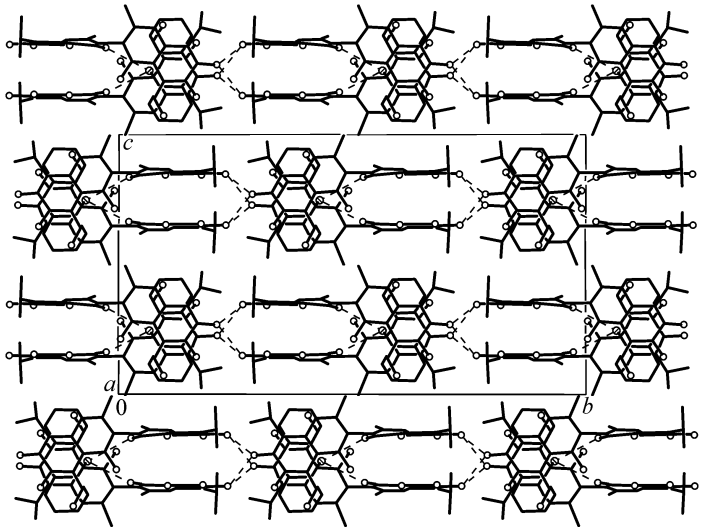

Fig. 2. Crystal structure of the gossypol acridine clathrate.

TABLE 1. Hydrogen Bonds in the Structure of the Gossypol Acridine Complex: Distances (Å) and Angles (deg)

H-Bond	D–H	H…A	D…A	D–H…A	Symmetry Operation for A Atom
Intramolecular Hydrogen Bonds					
O3–H...O2	0.99(3)	1.55(3)	2.487(2)	156(2)	
O4–H…O3	0.89(2)	2.07(2)	2.595(2)	117(2)	
O7–H…O6	0.99(3)	1.58(3)	2.501(2)	153(2)	
O8–H…O7	0.84(2)	2.07(2)	2.622(2)	123(2)	
C22–H...O1	0.98(2	2.07(2)	2.750(2)	125.0(16)	
C27–H...O5	0.96(2)	2.06(2)	2.712(2)	123.8(17)	
C28–H…O8	0.98(2)	2.19(2)	2.777(2)	117(1)	
Intermolecular Hydrogen Bonds					
O5–H…N1	0.86(3)	2.47(3)	3.175(2)	140(2)	
O4–H…O8	0.89(2)	2.16(2)	2.947(2)	148(2)	3/2–*x*, 1/2+*y*, 1/2–*z*
O8–H…O4	0.84(2)	2.39(2)	2.971(2)	127(2)	–1/2+*x*, –1/2+*y*, *z*

TABLE 2. Geometry of C–H…π Contacts Observed in the Structure of the Gossypol Acridine Complex: Distances (Å) and Angles (deg)

D–H…A Bond	Symmetry Operation	Distance		Angle
		D…A	H…A	D–H…A
C33–H…π (centroid of the cycle C11–C19)	*x*, –*y*, –1/2+*z*	3.8096(18)	2.97(2)	144.3(16)
C34–H…π (centroid of the cycle C15–C20)	*x*, –*y*, –1/2+*z*	3.4714(18)	2.65(2)	139.3(18)

and O(8)–H) out of the eight polar functional groups of the gossypol molecule, which are capable of H-bonding, participate in the intermolecular host–host H-bonds (Table 1). The gossypol molecules are packed by means of four hydrogen bonds (which form the R_4^4 (8) cycle) in bilayers parallel to the *ab* plane. The distinctive feature of these clathrates is that each bilayer consists of molecules of the same chirality (*R* or S). The layers of different chirality alternate when packed into the crystal structure.

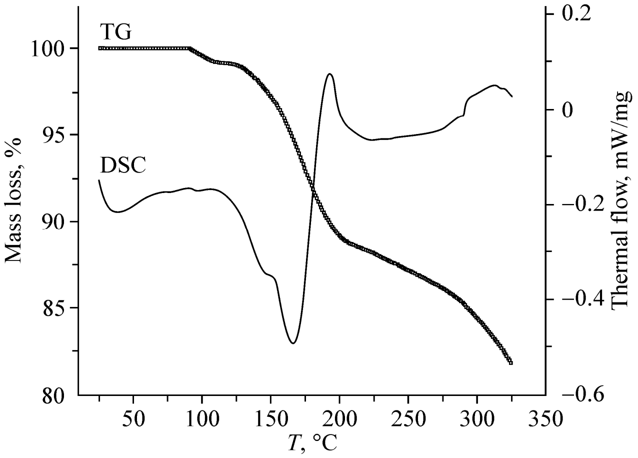

Fig. 3. TG/DSC diagram of changes in the crystals of gossypol acridine clathrate in the temperature range of 25°C to 325°C.

When the gossypol molecules are packed in bilayers, they form voids with twofold symmetry axes. The floor and ceiling of these voids are the C(1)–C(10) naphthyl cores of the A(x, y, z) and B($1 - x, y, 0.5 - z$) molecules, and the side walls are the C11–C20 naphthyl cores of the C($1 - x, y, 0.5 - z$) and D($1 - x, y, 0.5 - z$) molecules. The guest acridine molecules are located in the voids. The nitrogen atom of the guest molecule is a bifurcate (double) proton acceptor for the O(5)–H hydroxyl groups of two gossypol molecules. This hydrogen bond is rather weak (3.175(2) Å, 140(2)°); however, the guest molecule is additionally stabilized in the clathrate void by means of stacking interactions between the naphthyl cores of the gossypol and acridine molecules (the distance between the centroids of the C5–C10 and C31–C36–C37–N1 cycles is 3.670 Å) and by means of C–H…π interactions of the C33 and C34 atoms with the C11–C20 naphthyl core (Table 2). The surface of the bilayers is hydrophobic; therefore, the interaction between the neighboring bilayers is of purely van der Waals nature (Fig. 2).

An analysis of the TG-DSC curves shows that the complex is stable up to 100°C (Fig. 3). In the temperature range of 100°C to 200°C, the sample mass is observed to decrease (~12%). The endothermic peak that corresponds to this process has a shoulder at 149°C and a minimum at 166°C. It characterizes two processes: (1) two water molecules detach from the gossypol molecule to form anhydrogossypol, and (2) the guest acridine molecule is released (T_m = 110°C). The formation of anhydrogossypol is confirmed by the exothermic peak (max 192°C) typical of the DSC curve of the compound [13]. The loss of mass at temperatures higher than ~200°C is related to acridine sublimation. The computed mass loss with the release of acridine is 13.55%, and that of water is 6.21%. The sum of these values is 19.76%. Acridine is known to sublime easily, with the evaporation occurring in the temperature range of 150°C to 250°C. Thus, at the first stage (100-200°C), two water molecules detach from the gossypol molecule, and acridine begins to sublime (the mass loss is ~12%). At the second stage (200-330°C), acridine continues to evaporate; therefore, the TG curve does not reach the plateau.

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