

Gossypol inclusion compound with pyrazine: crystal structure and thermal behavior

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Received: 11 August 2014 / Accepted: 13 October 2015 / Published online: 20 October 2015
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Abstract Single crystals of gossypol complex with pyrazine (1:4) have been obtained in two ways: (I) in the pyrazine solution of gossypol ($T = 56\text{ }^{\circ}\text{C}$) and (II) in the dichloromethane solution of dianhydrogossypol/pyrazine mixture (room temperature). The crystals were characterized by X-ray crystallography. Crystal data: (I), $\text{C}_{30}\text{H}_{30}\text{O}_8 \cdot 4(\text{C}_4\text{H}_4\text{N}_2)$, $M = 838.91$, $T = 130$ (2) K, $\text{MoK}\alpha = 0.71073\text{ \AA}$, $a = 7.5230$ (3), $b = 13.9185$ (6), $c = 19.8328$ (8) \AA , $\alpha = 88.789$ (4), $\beta = 87.255$ (3), $\gamma = 86.683$ (4) $^{\circ}$, $V = 2070.46$ (15) \AA^3 , $Z = 2$, $D_{\text{calc}} = 1.346\text{ g/cm}^3$, crystal system: triclinic, space group: $P\bar{1}$, $R = 0.0393$ for 7218 observed reflections; (II), $\text{C}_{30}\text{H}_{29.56}\text{O}_{7.85} \cdot 4(\text{C}_4\text{H}_4\text{N}_2)$, $M = 836.11$, $T = 100$ (2) K, $\text{CuK}\alpha$, 1.54184 \AA , $a = 7.5010$ (4), $b = 13.9425$ (6), $c = 19.7848$ (9) \AA , $\alpha = 88.618$ (4), $\beta = 87.442$ (4), $\gamma = 86.898$ (4) $^{\circ}$, $V = 2063.57$ (17) \AA^3 , $Z = 2$, $D_{\text{calc}} = 1.345\text{ g/cm}^3$, crystal system: triclinic, space group: $P\bar{1}$, $R = 0.0509$ for 7215 observed reflections. Pair of gossypol and pyrazine molecules are formed the centrosymmetric tetramers untypical for gossypol type structures. Crystal structures are characterized with the presence of wide channels for guest molecules. TG-DSC curves of gossypol with pyrazine complex (1:4) showed that decomposition of crystals occurs in four steps. Formation of new gossypol:pyrazine host:guest complexes with ratios of 2:3 and 1:1 were observed in TG-DSC curves.

Keywords Gossypol · Pyrazine · Inclusion compound · Thermal analysis · X-ray structure analysis

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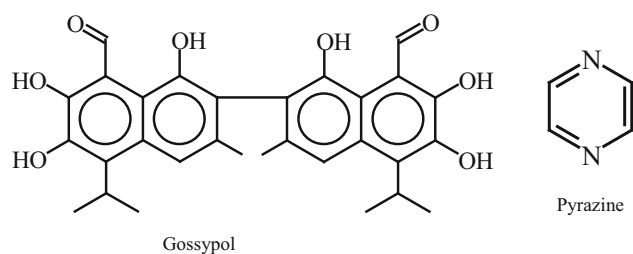
Introduction

Gossypol, a yellow polyphenolic pigment of the cotton plant [1], has a wide range of biological action, including anti-HIV, anticancer, and antifertile effects [2–8]. Gossypol is a surprisingly versatile host compound that forms inclusion complexes with many classes of compounds. Among the guest molecules included are ketones, ethers, esters, organic and mineral acids, water, various aryl compounds and halogenoalkanes. The structures of more than one hundred complexes with different guest molecules have been reported so far [9–19]. Previous studies outline the structure aspects of crystalline inclusion complexes on the basis of a mixed “gossypol-pyrazine” host [20]. Pyrazine incorporates gossypol molecules to robust supramolecular associates giving rise to a family of solvates on the basis of mixed “gossypol-pyrazine host”. Here we report the preparation and structure of gossypol inclusion complex with pyrazine (1:4) obtained in two ways and their thermal behaviors (Scheme 1).

Materials and methods

Materials

Gossypol samples were obtained from the Experimental Plant Facility of the Institute of Bioorganic Chemistry, Academy of Sciences of Uzbekistan, where it is produced from by-products of the cottonseed processing industry. The gossypol was re-crystallized from solutions of butan-2-one and acetic acid to yield fairly pure gossypol-acetic acid (1:1) clathrate [21]. The obtained powder sample of gossypol-acetic acid clathrate was dissolved in diethyl ether and acetic acid was removed from the solution by



Scheme 1 Structure of gossypol and pyrazine

washing with distilled water. Then the solution was concentrated and hot hexane was added until the volume ratio of 1:2 was obtained. The precipitate of pure gossypol was separated by filtration and its purity was determined by HPLC analysis. Pyrazine was purchased from Sigma.

Single crystal experiments

Single crystals of the **(I)** gossypol-pyrazine (1:4) were prepared from a mixture of 50 mg gossypol and 1 g

pyrazine which was heated up to the melting point of pyrazine (56 °C), where gossypol is dissolved in liquid pyrazine and kept in an open vial for 24 h, until pyrazine was evaporated. Formed large light-brown crystals were stable at room temperature and suitable for the X-ray structural analysis. To prepare the single crystals of **(II)** 0.40 mg dianhydrogossypol and 0.26 mg pyrazine were dissolved in 3 ml of dichloromethane. Then the solution was kept for 72 h at room temperature with slow evaporation of the solvent until the clear crystals appeared.

The diffraction data of the **(I)** was collected at 130 K with a KumaCCD single-crystal diffractometer (MoK α) equipped with an oxford cryostream device. The diffraction data of the **(II)** was collected at 100 K with a Xcalibur® single-crystal diffractometer (CuK α) equipped with an oxford instruments cryostream device. Data collection and reduction were performed with CrysAlis CCD [22] and CrysAlis RED [22], respectively. The structures were solved by direct methods with the SHELXS-97 program [23] and refined by full-matrix least-squares method on F² with SHELXL-97 [24]. Hydrogen atoms bound to carbons

Table 1 Crystal data and some details of data collection and structure refinement for gossypol:pyrazine (1:4) crystals

Crystal	(I)	(II)
Empirical formula	C ₃₀ H ₃₀ O ₈ ·4 (C ₄ H ₄ N ₂)	C ₃₀ H _{29.56} O _{7.85} ·4 (C ₄ H ₄ N ₂)
Formula weight	838.91	836.11
Temperature (K)	130 (2)	100 (2)
Wavelength (Å)	0.71073	1.54184
Crystal system	Triclinic	Triclinic
Space group	<i>P</i> –1	<i>P</i> –1
Unit cell dimensions:		
<i>a</i> (Å)	7.5230 (3)	7.5010 (4)
<i>b</i> (Å)	13.9185 (6)	13.9425 (6)
<i>c</i> (Å)	19.8328 (8)	19.7848 (9)
α (°)	88.789 (4)	88.618 (4)
β (°)	87.255 (3)	87.442 (4)
γ (°)	86.683 (4)	86.898 (4)
Volume (Å ³)	2070.46 (15)	2063.57 (17)
<i>Z</i>	2	2
Density calculated (g/cm ³)	1.346	1.345
F(000)	884	881
Crystal size (mm)	0.45 × 0.4 × 0.2	0.40 × 0.35 × 0.25
Range for data collection (°)	4.89–25.03	10.59–66.57
Limiting indices	–8 ≤ <i>h</i> ≤ 8, –16 ≤ <i>k</i> ≤ 16, –11 ≤ <i>l</i> ≤ 23	–8 ≤ <i>h</i> ≤ 8, –16 ≤ <i>k</i> ≤ 16, –17 ≤ <i>l</i> ≤ 23
Reflection collected/unique	15851/7218	16016/7215
Data/restraints/parameters	5004/0/589	4754/0/611
Completeness	98.9 %	97.0 %
Goodness-of-fit on F ²	0.925	0.945
Final <i>R</i> indices [<i>I</i> > 2 (<i>I</i>)]	<i>R</i> ₁ = 0.0393, <i>wR</i> ₂ = 0.0810	<i>R</i> ₁ = 0.0509, <i>wR</i> ₂ = 0.1265
<i>R</i> indices (all data)	<i>R</i> ₁ = 0.0671, <i>wR</i> ₂ = 0.0901	<i>R</i> ₁ = 0.0810, <i>wR</i> ₂ = 0.1371
$\Delta\rho_{\max}$ and $\Delta\rho_{\min}$ (eÅ ^{–3})	0.21 and –0.24	–0.20 and –0.27

were generated geometrically in idealized positions. Their displacement parameters were set equal to $1.5U_{eq}(C)$ for the methyl groups and $1.2U_{eq}(C)$ for the remaining hydrogen atoms. Hydrogen atoms of the hydroxyl groups were located in difference fourier maps and freely refined. Further analysis of the Fourier map of the **(II)** indicated that some of dianhydrogossypol molecules have turned into monoanhydrogossypol molecules and the refinement with new correction was applied to obtain lower *R*-factor. In this case site occupancies of disordered atoms were also refined. The crystal data and some details of data collection and structure refinement are given in Table 1. CCDC 1041932 and CCDC 1041980 contain the supplementary crystallographic data for this paper.

The thermal investigation of the crystals was performed on a TG-DSC STA-409 PC LUXX^o system using an open Al₂O₃ crucible with the samples weighing about 4–5 mg. A linear heating rate of 5 K/min was applied by using nitrogen gas flow of 1 l/h.

Results and discussion

It is known that gossypol forms mixed clathrates based on gossypol-pyrazine matrix with chloroform, dichloromethane and ethyl acetate where the ratio of gossypol:pyrazine is 2:1 [20]. The new gossypol complex with pyrazine with a ratio of 1:4 was obtained by two ways:

- First, the crystals were obtained from the solution of gossypol in pyrazine at 56 °C by slow evaporation of pyrazine;
- In the second case, dianhydrogossypol was dissolved in dichloromethane, then to the solution was added a solution of pyrazine until the ratio of dianhydrogossypol:pyrazine was 1:5. The single crystals were

obtained by slow evaporation of dichloromethane. In dichloromethane solution dianhydrogossypol turns to monoanhydrogossypol and gossypol as a result of reaction with water molecules. We assume that the source of water is an adsorbed water in pyrazine and moisture in air. These crystals were not identical with crystals obtained from solution of gossypol and pyrazine in dichloromethane [20], crystallographic parameters of the **(II)** were similar to the parameters of the **(I)**. Scheme 2 schematically shows the reaction pathways of dianhydrogossypol with water in **(II)**.

X-ray structure analysis

Molecular structure

Both in previously studied crystals [14, 16] and in the present clathrate gossypol molecules are in the aldehyde tautomeric form (Fig. 1). It is known that several O–H···O and C–H···O type intramolecular H-bonds are characteristic for this form (Table 2); [17, 18]. Formation of the H-bond at C24–H···O4 (C29–H···O8) favors an orientation of the isopropyl group hydrogen atom H23 (H28) towards H4 (H14) atom. Opposite orientation of hydrogen atom H23 (H28) has been observed in the work [5]. H-bonds at O4–H···O3 (O8–H···O7) and O3–H···O(2) (O7–H···O6) form five- and six-membered rings. Naphthyl fragments C1–C10 (C5 0.07 Å) and C11–C20 (C15 –0.11Å) C17 (0.12 Å) are planar and dihedral angle between those planes are equal to 88.75(3)° (**(I)**) and 88.40(4)° (**(II)**). Geometrical parameters of the pyrazine molecule are close to ideal.

Refinement of site occupancies of disordered atoms in **(II)** shows that the gossypol moiety consists of gossypol (~85 %) and monoanhydrogossypol (~15 %). In this case one part of the gossypol molecule (C1–C10) is

Scheme 2 Schematic reaction pathways of dianhydrogossypol with water in **(II)**

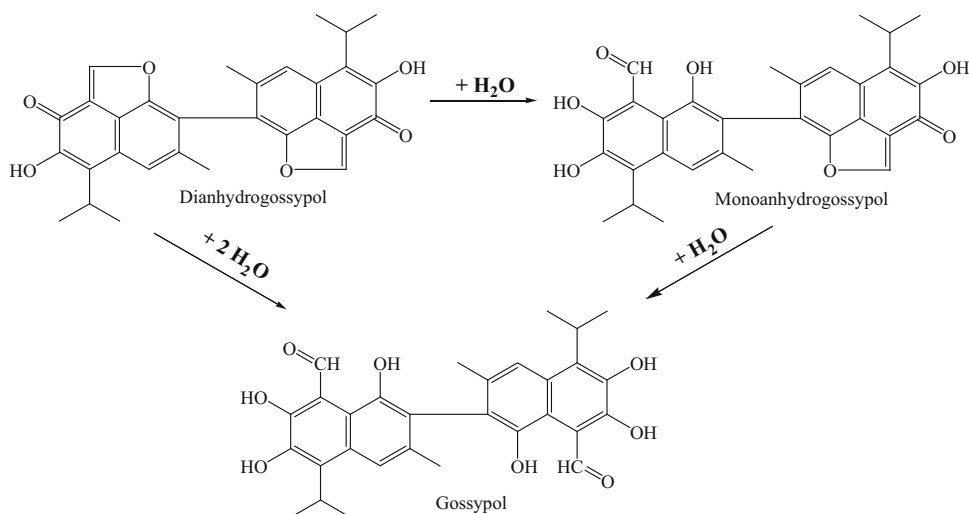


Fig. 1 ORTEP representation of the asymmetric unit cell in gossypol:pyrazine (1:4) crystal in **(I)**. Displacement ellipsoids are shown at the 50 % probability level and dashed lines show H-bonds

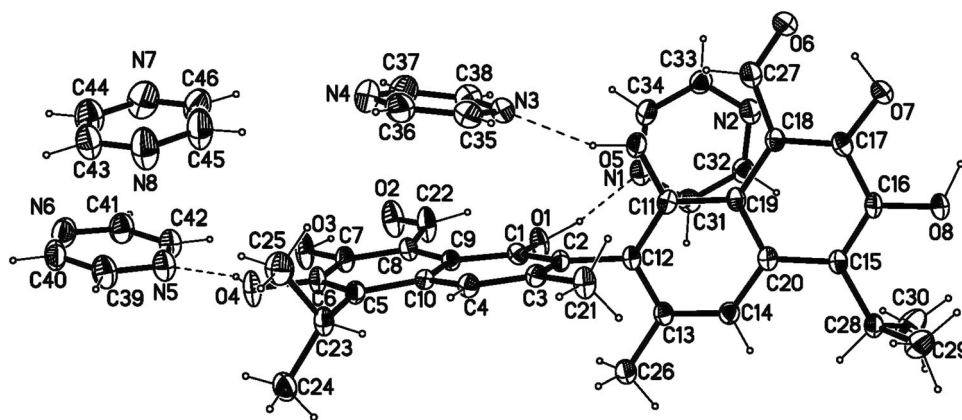


Table 2 Hydrogen bonds (Å, °) for gossypol:pyrazine (1:4) crystal structures

D-H...A	Symmetry	D-H (Å)	H...A (Å)	D...A (Å)	∠ D-H...A°
Crystal I					
Intramolecular					
O3-H...O2		1.03 (2)	1.58 (2)	2.510 (2)	149 (2)
O4-H...O3		0.94 (2)	2.11 (2)	2.640 (2)	114 (2)
O7-H...O6		0.93 (2)	1.63 (2)	2.480 (2)	152 (2)
O8-H...O7		0.97 (3)	2.18 (3)	2.637 (2)	107 (2)
Intermolecular					
O1-H...N1		0.99 (2)	1.79 (2)	2.750 (2)	164 (2)
O8-H...N4A	1-x, -y, 1-z	0.95 (3)	1.84 (3)	2.699 (2)	149 (2)
O5-H...N3		0.91 (2)	2.00 (2)	2.861 (2)	158 (2)
O4-H...N5		0.94 (2)	1.97 (2)	2.816 (2)	149 (2)
O3-H...O2	-x, 1-y, -z	1.03 (2)	2.36 (2)	3.045 (2)	123 (2)
Crystal II					
Intramolecular					
O3-H...O2		0.79 (3)	1.81 (3)	2.512 (2)	148 (3)
O4-H...O3		0.85 (3)	2.19 (3)	2.634 (2)	112 (3)
O7-H...O6		0.97 (4)	1.55 (4)	2.481 (3)	158 (4)
O8-H...O7		0.89 (4)	2.07 (3)	2.610 (3)	118 (3)
Intermolecular					
O1-H...N1		1.12 (5)	1.73 (5)	2.7773 (3)	152 (4)
O8-H...N2	1-x, -y, 1-z	0.89 (4)	1.97 (4)	2.709 (3)	139 (3)
O5-H...N3		0.91 (4)	2.00 (4)	2.861 (4)	158 (4)
O4-H...N5		0.85 (3)	2.03 (3)	2.807 (3)	153 (3)
O3-H...O2	-x, 1-y, -z	0.79 (4)	2.47 (3)	3.052 (3)	132 (3)

D donor, A acceptor

observed as a fragment of gossypol while the second part (C11–C20) consists of fragments of gossypol and monoanhydrogossypol (Fig. 2). Geometric parameters of monoanhydrogossypol's fragment are still distort, but furan ring and other atoms of this fragment is very well visible.

Crystal structure

The inclusion complex **(I)** is crystallized with one gossypol molecule and four pyrazine molecules in the asymmetric

unit. It is known that in most crystal structures of gossypol, typical centrosymmetric dimers are formed through a pair of H-bonds O5-H...O3 and π - π stacking interactions between C1 and C10 naphthyl moieties [16]. In the considered crystal structure centrosymmetric dimers are not formed, instead they are generated from two molecules of gossypol and two molecules of pyrazine via H-bonds O1-H...N1 and O8-H...N2 [graph set $R_4^4(26)$]. The second type of pyrazine molecules is bonded via H-bond at O5-H...N3, while the third type of pyrazine molecules H-bonded by

Fig. 2 Molecule of nonsymmetrical monoanhydrogossypol with labeled atoms

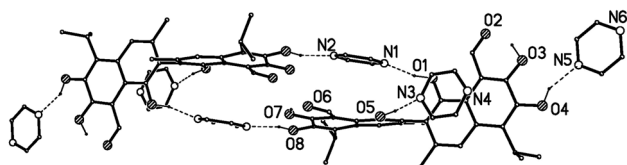
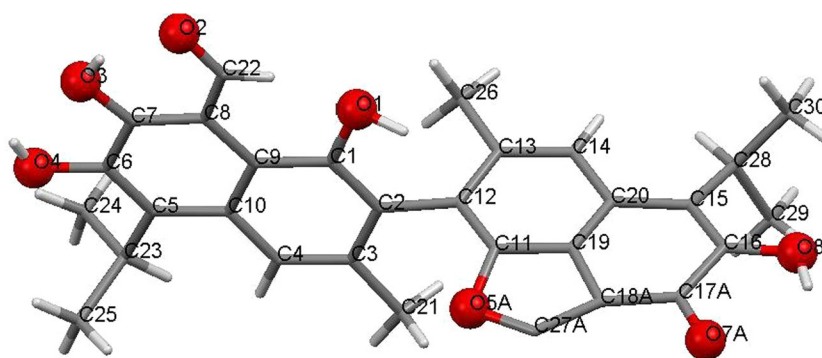
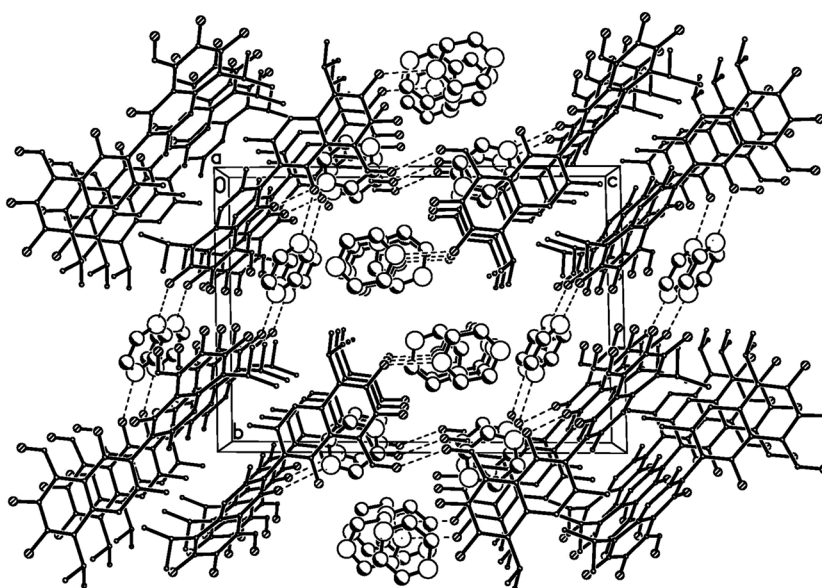


Fig. 3 Gossypol:pyrazine associate (2:6) in gossypol:pyrazine (1:4) crystal

O4-H \cdots N5. So, an associated unit via H-bond consists of two gossypol and six pyrazine molecules (Fig. 3). These associates form chains at the direction [101] by centrosymmetric H-bonds O3-H \cdots O2. Packing of chains creates cavities with the diameter of about 4–5 Å along *ab* plane and these cavities are filled with fourth type of pyrazine molecules (these molecules have no H-bonds with gossypol molecules) (Fig. 4).

Thus, the packing of the forming host molecule's H-bonded dimers leads to the formation of grid layers lying parallel to (010) with weak Van der Waals interactions. The further packing of the grid layers results in formation poor three dimensional networkwide channels along [100]

Fig. 4 Packing diagram of gossypol:pyrazine (1:4) along the *c* direction. For clarity hydrogen atoms are omitted



and also twice much narrower channels along [010]. Pyrazine molecules are located within these channels. However, host–host intermolecular interactions in both crystal structures very insignificantly. The crystal structure of (II) is isostructural with crystal structure of (I) and in the (II) monoanhydrogossypol molecules (~15 %) isomorphously replace gossypol molecules that results in the formation of a complex host–guest system with mixed host framework. So, in the crystal structure of (II) gossypol molecules are partly replaced by monoanhydrogossypol molecules.

Thermal investigations

The composition of the clathrate obtained by X-ray data (Gossypol(Gp): pyrazine 1:4) is agreed with one found by TG-DSC (Fig. 5). The TG-curve of the complex showed four step process: in the first step (75–135 °C) the Gp:pyrazine 1:4 complex turns in Gp:pyrazine 1:1.5 complex, in the second step (135–150 °C) the Gp:pyrazine 1:1.5 complex turns in Gp:pyrazine 1:1 complex, in the third step (150–190 °C) the Gp:pyrazine 1:1 complex turns

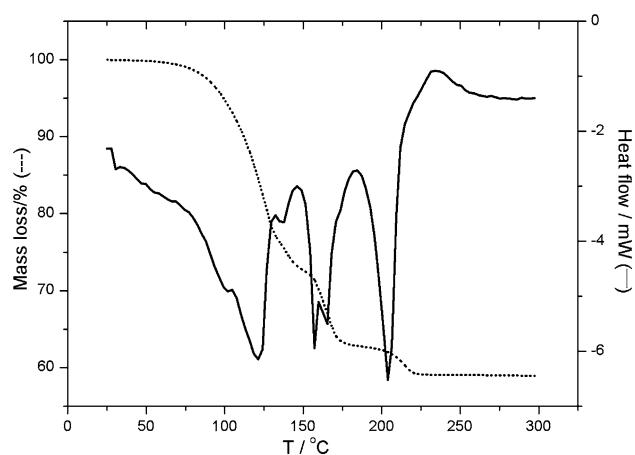


Fig. 5 TG-DSC patterns of gossypol:pyrazine (1:4) crystal

in a free gossypol, only in the fourth step (190–230 °C) gossypol molecule lost two molecules of water and turned in anhydrogossypol (Fig. 5).

Calculations of TG data are in a good agreement with the theoretical mass loss percent: 41.077 % for loss of water and pyrazine (calculated ~ 42.48 %). But on the DSC curve in the temperature range of 75–135 °C two endothermic peaks are observed: the first one (~100.99 °C) is related to phase transition to another form, where Gp:pyrazine 1:3; other peak (123.56 °C) is corresponding to the phase transition to form of Gp:pyrazine 1:1.5 complex. Third peak (136.79 °C) in the temperature range of 135–155 °C is related to the formation of Gp:pyrazine 1:1 complex, other peak (156.40 °C) in the temperature range of 155–190 °C is related to the formation of unsolvated gossypol phase (polymorph). Last peak (204.95 °C) in the temperature range of 190–215 °C is related to the loss of water molecules and gossypol turns to dianhydrogossypol. A dissymmetry of the peak (204.95 °C) also indicates that a shape of the peak is a superposition of two of these processes. Therefore, decomposition of crystals occurs in the following steps:

Step 1	Step 2	Step 3	Step 4
$2HG_4 \rightarrow H_2G_3 + 5G;$	$H_2G_3 \rightarrow 2HG + G;$	$HG \rightarrow H + G;$	$Gp \rightarrow DianhydroGp + 2H_2O.$

Conclusions

Inclusion complexes of gossypol with pyrazine (1:4) have been obtained by 2 different ways: in the pyrazine solution of gossypol ($t = 56$ °C) (**I**) and in the dichloromethane solution of the mixture of dianhydrogossypol/pyrazine (room temperature) (**II**). In the case of the (**I**) the crystal structure consists of gossypol and pyrazine while in the (**II**)

the crystal structure consists of gossypol (~85 %), monoanhydrogossypol (~15 %) and pyrazine molecules where dissolved dianhydrogossypol turns into gossypol and monoanhydrogossypol, as a result of reaction with water molecules. In the crystal structure pair of gossypol and pyrazine molecules form centrosymmetric tetramers untypical for other gossypol type structures. Crystal structures are characterized with the presence of wide channels for guest molecules. TG-DSC curves of gossypol with pyrazine complex (1:4) shows that decomposition of crystals occur in four steps. Two of these steps is explained by the formation new gossypol:pyrazine host:guest complexes in ratios of 2:3 and 1:1. By using X-ray structural analysis and TG-DSC we have observed three types of gossypol: pyrazine host:guest complexes.

Supplemental data

The supplementary crystallographic data for the crystal structures have been deposited in the Cambridge Crystallographic Data Center and have reference number CCDC-1041932 and 1041980. These data can be obtained free of charge at <http://www.ccdc.cam.ac.uk/conts/retrieving.html> or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033; email: deposit@ccdc.cam.ac.uk.

Acknowledgments We thank Professor Maria Gdaniec for support with the X-ray single crystal data collection and for assistance in the preparation of this manuscript.

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