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ORIGINAL PAPER

The Crystal and Molecular Structure of Dianhydrogossypol

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Abstract Dianhydrogossypol (4,4′-dihydroxy-5,5′-diisopropyl-7,7′-dimethyl-bis(3*H*-naphtho[1,8-bc]furan-3-one)) was made by refluxing gossypol in *m*-xylene. Proton NMR spectroscopy was used to confirm that complete conversion was achieved over a time period of several hours. Single crystals of the compound were obtained by slow evaporation from dichloromethane. Diffraction studies indicate that this crystal form is tetragonal with a $I4_1/a$ space group and with cell dimensions of $a = b = 33.8265(4)$ Å, $c = 9.1497(2)$ Å, $V = 10469.4(3)$ Å^3 at 100 K. The structure was solved by direct methods and was refined to an $R1$ value of 0.0415 on 6,408 independent reflections. Dianhydrogossypol exists as a pair of enantiomers within this structure. The two fused planar ring systems are oriented at a 117° angle to each other (i.e., close to perpendicular), and the isopropyl groups are oriented with the ternary carbon hydrogen atoms pointed inward toward the center of the molecule. Repeating groups of four molecules (of the same chirality) pack to form a helical structure that is supported by intermolecular hydrogen bonds. Each helix is surrounded by four neighboring helices that are composed of molecules of the opposite chirality. The helices form the walls of empty channels that are 5–6 Å wide. As has been found for some gossypol crystal forms, the open-channel structure of dianhydrogossypol might be useful for scavenging or carrying small molecules. Additional NMR studies confirm that dianhydrogossypol can be converted directly to gossypol lactol ethers in the presence of anhydrous alcohols.

Keywords Clathrates · Cottonseed · Natural products · Solvates · Terpenes · X-ray structure · Zeolites

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Introduction

Cotton, a member of the plant family Malvaceae, differs from other oilseed plants because of the presence of lysigenous glands (commonly referred to as pigment glands) that occur throughout of the plant. Among various secondary metabolites, pigment glands contain gossypol, a disesquiterpene with an unusual binaphthalene structure and interesting chemical properties (Fig. 1). Within the cotton plant, the compound appears to act as a natural insecticide [1]. Although gossypol is removed from crude cottonseed oil during chemical refining, its presence in whole seed and cottonseed meal limits the feeding of these materials to ruminants [2]. The compound is also of current research interest because it exhibits a wide range of potentially important biological actions, including antiviral, anticancer, and antifertility effects [3–5].

Because of its biological properties, there is current interest in making gossypol derivatives. Many derivatives have been reported, including ethers, acetates, and Schiff bases complexes of the aldehydes, and a review of this work has been recently presented by Kenar [6]. Among these chemical modifications, Clark [7] noted that gossypol

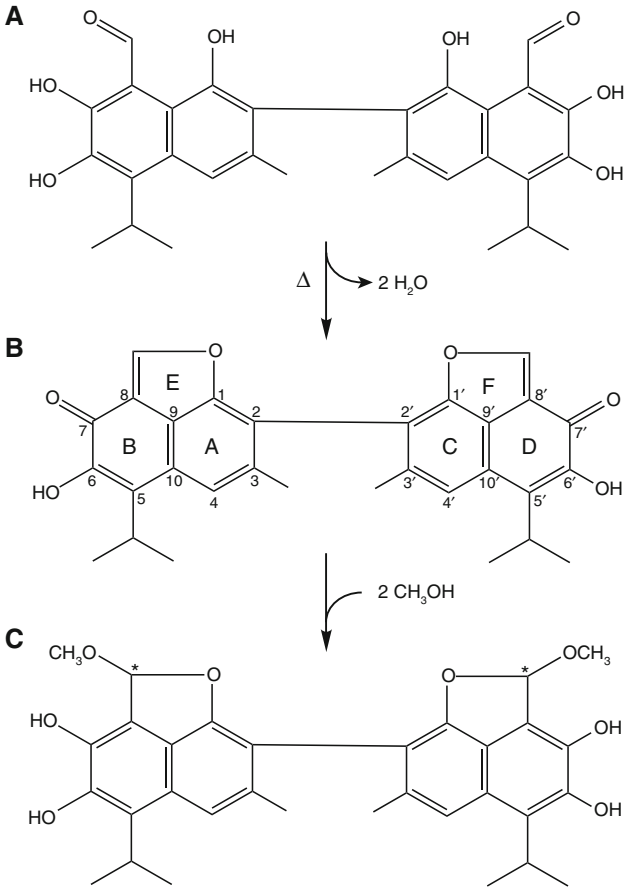

Fig. 1 Structures of gossypol (**a**), dianhydrogossypol (**b**), and the dimethyl lactol ether of gossypol (**c**). Rings of the dianhydrogossypol structure are labeled to correspond with the discussion. *Asterisks* indicate the locations of new chiral centers in the lactol ether

can lose two molecules of water to form dianhydrogossypol (6,6′-dihydroxy-5,5′-diisopropyl-3,3′-dimethyl-7,7′-dioxo-bis(3*H*-naphtho[1,8-bc]furan-3-one)) (Fig. 1).[1] Berardi and Frampton reported forming the compound from gossypol in ethyl acetate by storing the solution in the dark for prolonged periods of time or by reflux heating [8]. Jaroszewski and coworkers [9] formed the compound by heating in toluene. They also used optically pure (+)-gossypol to form (+)-dianhydrogossypol, which was then found to racemize in boiling *m*-xylene (139 °C) with a half-life of about 22 h. They reported that gossypol, when heated, tended to dehydrate rather than racemize, and they proposed that any racemization of optical gossypol would most likely occur through the formation of dianhydrogossypol.

[1] Previous reports refer to this compound as anhydrogossypol. Because many research groups are working on asymmetrical derivatives of the dimeric gossypol molecule, it is likely that reports on both mono- and dianhydrogossypol will appear in the future. Hence, we have used the term dianhydrogossypol to describe the structure that has both sides of the molecule dehydrated.

It has also been proposed that some form of dianhydrogossypol contributes to the formation of gossypurpurin, a purple colored product that has not been obtained in sufficient purity to determine its structure [10]. Recently, we have studied the chemical and physical changes that occur in isolated gland pigments stored under different conditions and have obtained HPLC evidence indicating that mono- and dianhydrogossypol are formed in glands when they are stored at elevated temperatures for extended periods of time. To help confirm this, we synthesized and isolated the compound. After purification, the compound's structure was confirmed by proton NMR spectroscopy. A single crystal was then obtained from dichloromethane, and the structure of this crystal was determined by low-temperature X-ray diffraction. Herein, we report on the results of these structural studies.

Experimental Procedures

Preparation of Dianhydrogossypol

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 methyl ethyl ketone and acetic acid to yield a fairly pure preparation of gossypol-acetic acid (1:1). Dianhydrogossypol was obtained by refluxing a solution of gossypol-acetic acid in *m*-xylene for 2–3 h. During the reaction, approximately half the solution volume was distilled away with most of the evolved water. Upon cooling, dianhydrogossypol precipitated from the solution. Single crystals were prepared by dissolving the compound in dichloromethane (20 mg/mL) and allowing the solvent to slowly evaporate over a few days at the room temperature.

NMR

Data were recorded on a "Tesla BS 567-A" NMR-spectrometer with a resonance frequency for hydrogen of 100.028 MHz (the magnetic field intensity was 2.349 kG). Chemical shifts were measured relative to the signal for tetramethylsilane or from the solvent signal. A classical two-pulse experiment S2Pul was applied. The second pulse was used for registration of a signal of free induction, and in some experiments the first pulse on the channel decoupler was used for pre-saturation of the solvent signals. The duration of the second 90° pulse was 11.2 μs. In experiments, the first pulse was applied for 7.0 μs. The duration of a pulse of pre-saturation was 5.0–6.0 s at 100–200 μW. All experiments were conducted at room temperature. In

some cases a smoothing filter was applied to increase signal sensitivity to 2.0 Hz.

Single Crystal Diffraction Study

Data were collected on a Gemini R (Oxford Diffraction Systems, UK) X-ray diffractometer equipped with an Oxford Cryosystems open-flow cryostat operated at 100 K and a graphite monochromator emitting MoK_α radiation ($\lambda = 0.71073$ Å). Data collection covered a hemisphere of the reciprocal space by combining three sets of exposures with φ angles of 0, 90 and 180° with each 60 s exposure covering 1.0° in the ω angle. The crystal-to-detector distance was 56 mm and the detector swing angle was −30°. Coverage of the expected peaks was >99%. Crystal decay was monitored by repeating the initial 426 data frames at the end of collection and was negligible. The total data collection time was 15.3 h. The 6,408 reflections (4,406 observed) that covered a range of $4.5° < \theta < 29.5°$ were used for the refinement of the unit cell.

The structure was solved by direct methods (SHELXS-97) and was refined by full-matrix least squares (SHELXL97) [11]. Non-hydrogen atoms were refined anisotropically. All hydrogen atoms attached to oxygen atoms were found from difference maps and were refined isotropically. All hydrogen atoms attached to carbons were placed at calculated positions and were unrefined. Molecular graphics were generated with XP available in SHELXTL-Plus [12]. A summary of the crystal and diffraction data and the refinement is given (Table 1).[2]

Table 1 Selected crystal, diffraction, and refinement data for anhydrogossypol

Formula	$C_{30}H_{26}O_6$ ($C_4H_4N_2$)
CCDC deposit no.	687080
Formula weight	482.51
Crystal system	Tetragonal
Space group	I41/a (No. 88)
Unit cell dimensions (Å)	
a	33.8265 (4)
b	33.8265 (4)
c	9.1497 (2)
V (Å^3)	10469.4 (3)
Z	16
Density (calc.) (g/cm^3)	1.224
μ (mm^{-1})	0.085
F(000)	4,064
Crystal size (mm)	0.20 × 0.16 × 0.12
Temperature (K)	100 (2)
Wavelength (Å)	0.71073 (MoK_α)
θ range (deg)	4.62–29.42
Index ranges	$-46 < h < 45$
	$-46 < k < 41$
	$-12 < l < 12$
Reflections collected	27,264
Independent reflections	6,408
R(int)	0.0308
*R*1	0.0435
*wR*2	0.1306
S	1.08
Residual peak density (e/Å^3)	0.39
Residual hole density (e/Å^3)	−0.30

Results and Discussion

The proton NMR spectrum of dianhydrogossypol (Fig. 2) was recorded in $CDCl_3$. The prominent feature of the spectrum is the absence of downfield signals (11–16 ppm) associated with the aldehyde proton of gossypol, and the occurrence of a new signal at 8.45 ppm corresponding to the =CH–O– proton of the newly formed five-atom ring (Fig. 1). In addition, the signals for the remaining protons were similar to those previously reported for the compound [13]. The spectrum was re-recorded over a 10-day period and was unchanged, from which we conclude that reversion to gossypol did not occur.

In the process of collecting the NMR data we noticed some differences occurred when CD_3OD was added to the solvent. The addition of deuterated methanol resulted in immediate shifts in the dianhydrogossypol spectrum. In addition to the expected signals, there were aldehyde signals at 11.3 ppm, signals related to lactol forms of gossypol (6.84 and 6.80 ppm) and also two sets of signals for the hydrogen atom at the naphthyl C4 position (7.75 and 7.32 ppm). Assuming that the signals of the isopropyl methyl groups at 1.55 ppm would be essentially the same for all of the substances present, the methyl group at the naphthyl C3 position gave ten peaks of varying intensity. These changes indicated transient conditions of multiple compounds that included gossypol tautomers and possibly other derivatives. Over the course of a day, the spectrum became more homogeneous. After 4 days, the transformation appeared to be complete, and the characteristic signals of dianhydrogossypol were not observed. There was only a small amount of aldehyde,

[2] Supplementary crystallographic data for the crystal structure have been deposited in the Cambridge Crystallographic Data Center and have reference number CCDC-687080. 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: +44-1223-336033; Email: deposit@ccdc.cam.ac.uk.

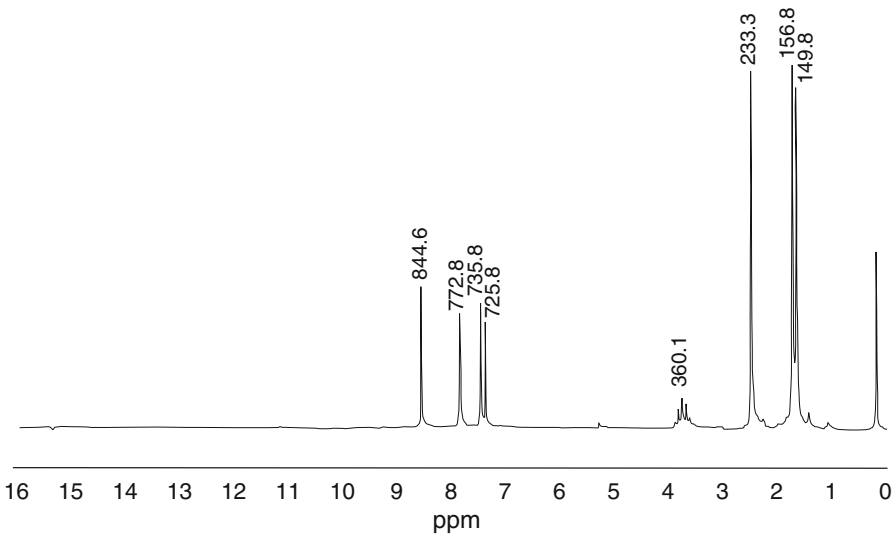

Fig. 2 ^{1}H-NMR spectrum of dianhydrogossypol in $CDCl_3$. The shift at 7.26 ppm is a $CHCl_3$ contaminant in the solvent

which suggested that the structure was present predominately as the lactol tautomer. The results indicated the formation of the dimethyl ethers of the lactol tautomer of gossypol (Fig. 1).

Abdyllaev et al. [13] have reported proton NMR spectra for gossypol, dianhydrogossypol and the dimethyl lactol ether of gossypol and have commented on the various transformations of these compounds. In this report, the dilactol was obtained by combining gossypol directly with deuterated methanol [13]. The conversion required two weeks. Hence, this dimethyl lactol can be formed either directly from gossypol or indirectly by the initial dehydration of gossypol to form dianhydrogossypol. Abdyllaev also showed that the dimethyl lactol ether in pure chloroform quickly transformed into dianhydrogossypol, i.e., the reverse of the reaction reported here. This compound, therefore, only appears to be stable in the presence of significant amounts of methanol. Because the formation of each lactol results a new chiral center, the dimethyl lactol ethers likely exist as a mixture of diastereomers.

The molecular structure of dianhydrogossypol consists of two connected planar ring systems, each containing a naphthalene ring with a fused dihydrofuran ring (Fig. 1). The two ring systems are connected by a C2–C12 bond (Fig. 3), and within the crystal structure these rings are oriented with a 117° angle between same sides of these fused rings. This near perpendicular orientation is within the range of values observed for the bridged binaphthalene orientations observed within gossypol crystal forms [14].

In gossypol compounds, the isopropyl groups are typically oriented so that the methyl moieties straddle the sides of the naphthalene rings. This occurs most frequently with the group's ternary carbon hydrogen atoms oriented inward and toward the center of the molecule, but occasionally gossypol structures are found with one the isopropyl groups rotated 180° from this position [14]. In the dianhydrogossypol structure, both of the isopropyl groups are positioned with these isopropyl hydrogen atoms pointed inward and toward the center of the molecule. One of the isopropyl groups essentially bisects the extended

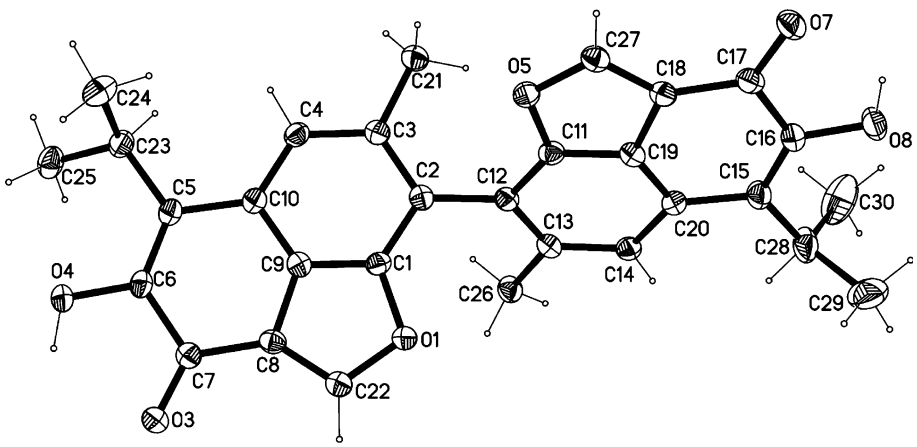

Fig. 3 ORTEP diagram (50% probability level) and atom numbering for crystalline dianhydrogossypol

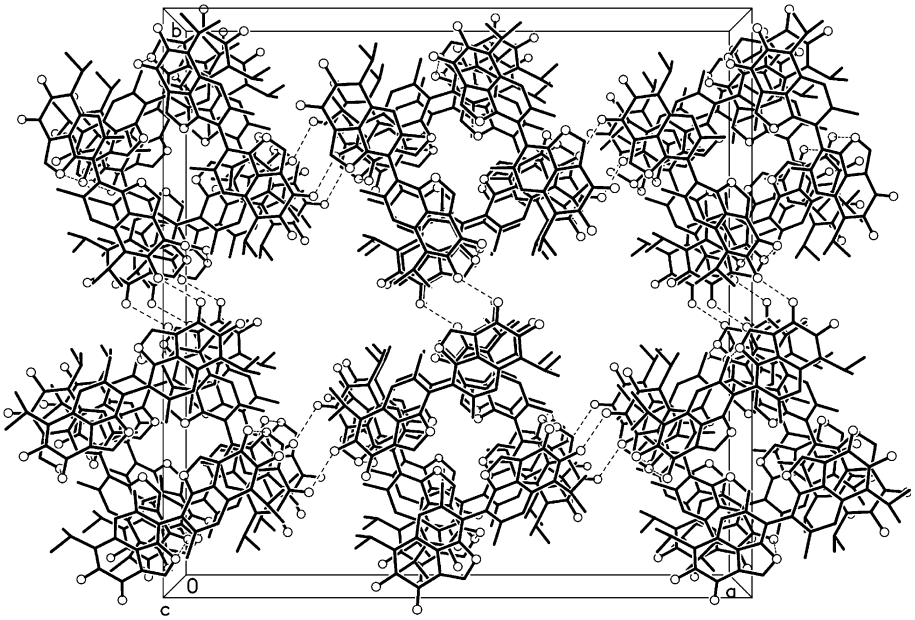

Fig. 4 The structure of the dianhydrogossypol (view along the *c*-axis). Hydrogen atoms are omitted for clarity

naphthalene ring plane, but the other group is rotated ~30° from this position. This distorted position appears to be supported by an intramolecular C25–H···O4 hydrogen bond. Although this type of interaction is substantially weaker than a typical O–H hydrogen bond, the interaction is noted as being capable of influencing molecular conformation and packing in some solid-state structures [15]. As the O4 atom in this interaction also donates to two hydrogen bonds (one intramolecular with the O3 atom and one intermolecular with the O7 atom), it may serve as a stronger than normal hydrogen bond receptor that enhances participation with the C–H group. The O8–H hydroxyl group on the other half of the dianhydrogossypol molecule does not participate in an intermolecular hydrogen bond and appears to be a less suitable acceptor for the C–H group.

Bond distances and bond angles from the two halves of the molecule are close to being equal, and most of these values were within expected values. However, there are notable differences in the lengths of some of these bonds compared with values that are typical for gossypol. Compared with the relatively short C3–C4 and C13–C14 aromatic ring bonds of gossypol molecules (~1.37 Å), the corresponding bonds in the dianhydrogossypol molecule are longer with lengths of 1.411 and 1.410 Å, respectively. In addition, the C1–C9, C11–C19, C9–C10, and C19–C20 bonds in dianhydrogossypol are shorter by 0.04 to 0.05 Å than the same bonds in gossypol. Within the B and D rings

Table 2 Hydrogen bonding within the dianhydrogossypol crystal structure

D-H···A	Symmetry	D–H (Å)	H···A (Å)	D···A (Å)	D–H···A (deg)
Intramolecular					
O4–H···O3		0.89 (2)	2.10 (2)	2.630 (2)	117
O8–H···O7		0.90 (2)	1.99 (2)	2.612 (2)	125
C25–H···O4		0.98	2.41	2.837 (2)	105
C26–H···O1		0.98	2.57	3.230 (2)	125
C29–H···O8		0.98	2.46	3.046 (2)	118
C30–H···O8		0.98	2.58	3.133 (3)	116
Intermolecular					
O4–H···O7	$3/4 + y, 3/4 - x, -1/4 + z$	0.89 (2)	2.19 (2)	2.924 (2)	140
C27–H···O4	$3/4 - y, -3/4 + x, 1/4 + z$	0.95	2.41	2.979 (2)	118
C22–H···O1	$3/4 - y, -1/4 + x, 3/4 - z$	0.95	2.48	3.323 (2)	147
C24–H···O7	$3/4 - y, -1/4 + x, 3/4 - z$	1.00	2.70	3.595 (2)	152
C27–H···O7	$1 - x, -y, 1 - z$	0.95	2.44	3.240 (2)	142
C28–H···O3	$1 - x, 1/2 - y, z$	1.00	2.53	3.450 (2)	153

(Fig. 1) of dianhydrogossypol, the lengths of the C6–C7, C16–C17, C5–C10, C15–C20, C7–C8 and C17–C18 bonds are between 1.443 and 1.492 Å, indicating that they are sigma bonds. The shortest bonds within these rings are for the C5–C6 and C15–C16 bonds each with a length of 1.371 Å. Within the F and E rings, bond lengths are within expected values. Bond angles around these five-atom fused rings, however, vary considerably. The C9–C8–C22 and C19–C18–C27 valance angles are 105.4° and 105.3° respectively, which is less than the 120° that would be expected for a standard *sp2* carbon atom and less that the angle for a regular pentagon (108°). Correspondingly, the C7–C8–C22 and C17–C18–C27 valence angles are widened to 137.3° and 137.7°, respectively. Similar but smaller variations exist on the other side of the fused rings about the C1 and C11 atoms.

Within the crystal structure, enantiomeric dianhydrogossypol molecules are associated into infinite helices (Fig. 4). These helices are supported by O4–H···O7 and C27–H···O4 intermolecular hydrogen bonds (Table 2). The molecules within these helices are related through a 4_1 symmetry operation. This association extends along the [001] direction to form open channels within the structure (Fig. 4) that are 5–6 Å wide (Fig. 5). The void volume of each channel is 1,641 $Å^3$, and the channels make up about 15.7% of the cell volume. This corresponds to a void volume of 410 $Å^3$ per dianhydrogossypol molecule and a packing factor of 0.59.

Each helical structure is interlaced with four neighboring helices that consist of molecules of the opposite chirality. Thus, the walls of a channel consist of the four molecules of one full helix and four molecules (one from each of the adjoining helices) of the opposite chirality. Within these walls there are additional intermolecular C–H hydrogen bond interactions (C22–H···O1 and C24–H···O7) (Table 2) and one short contact of 2.948(2) Å between the O3 atom and the O5 atom of a symmetry related $(3/4 - y, -1/4 + x, 3/4 - z)$ molecule of the opposite chirality. The enantiomer pairs form a centrosymmetric dimer unit that is supported by C27–H···O7 hydrogen bonds. Each dianhydrogossypol molecule also associates with a second molecule of the same chirality by a twofold axis with this interaction supported by a C28–H···O3 hydrogen bond.

The diffraction study also indicated the presence of a few partially occupied molecules within the channels. In solving the structure we considered that these areas of electron density might be chlorine atoms from retained dichloromethane, but a better fit of the data was obtained by modeling these as five partially occupied oxygen atoms (i.e., water molecules). Fitting these peaks as oxygen atoms resulted in occupancy factors of 0.2–0.3. Excluding these atoms from the model increased the *R*1 factor on the observed observations to 0.0569. Because

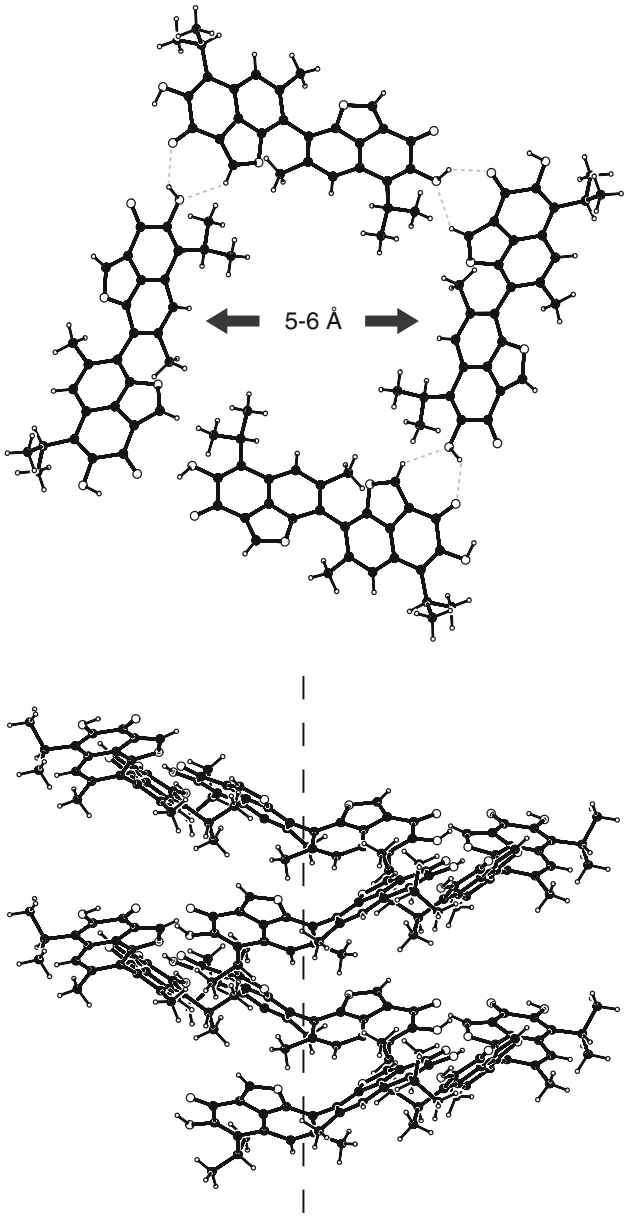

Fig. 5 Axial and longitudinal views of the channels and infinite helixes formed by the dianhydrogossypol molecules. Individual molecules are related by a symmetric 4_1 operation. The O4–H···O7 and C27–H···O4 hydrogen bond interactions are shown as *dashed lines* in the axial view

dianhydrogossypol rapidly reverts to gossypol in the presence of water at even moderate temperatures [13], it is unlikely that these water molecules were occluded during the formation of the crystal. It is more likely that they diffused into the structure during the diffraction experiment and were nonreactive because of the low temperature used for data collection. Regardless of the details, their presence suggests that these channels might readily adsorb other compounds and that the crystal form might be used as a molecular carrier.

In solid-state form, the parent gossypol compound is a surprisingly versatile host compound that forms inclusion complexes (i.e., solvates) with many organic compounds [14]. More than one hundred of these complexes have been reported with most formed by crystallization from the occluded solvent [14]. These different crystal forms can be organized into 20–25 structural families based on packing motifs. Included among these are a number of structures that have the solvent molecules residing in channels within a matrix of gossypol molecules. By varying temperature and using a vacuum, these solvent molecules can sometimes be coaxed out of the channels to leave a "pure" gossypol material. These desolvated clathrates have distinct power diffraction patterns, indicating that at least some aspects of the underlying individual crystal form are retained [16]. The 1:1 molar clathrate formed between gossypol and dichloroethane at room temperature (referred to as the α-form to distinguish it from two other known dichlorothane:gossypol complexes) readily loses its guest molecules but retains its basic structure to leave relatively large empty channels of $\sim$5.5 Å width [16–18]. This open-channel compound (referred to as the P3 gossypol polymorph) has been used to adsorb other small molecules and to effect non-symmetrical synthesis of gossypol derivatives [18, 19]. With ammonia and methylamine, the adsorption results in a Schiff base reaction between the amines and the gossypol aldehyde groups. Because only one of the two aldehyde moieties sits along the walls of the channels, the reaction permits high selectively for the asymmetrical mono Schiff base structure. With methylamine, for example, this mono Schiff base was produced in an 80% yield [18].

Dianhydrogossypol, when crystallized from dichloroethane, also forms an open-channel structure with a width about equal to the channel formed by the P3 gossypol polymorph. However because the organization of the host molecules is different between these structures, sorption properties of this crystal form would also be expected to be different.

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