Crystal and Molecular Structure of an Enantiomeric Gossypol-Acetic Acid Clathrate

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ABSTRACT: Single crystals of gossypol with three molecules of acetic acid (gossypol triacetic acid) were grown from solutions of gossypol acetic acid and acetone. The crystals were unstable in air but could be stabilized for X-ray diffraction analysis by coating the crystal surfaces with a thin layer of mineral oil. The gossypol triacetic acid complex ($C_{30}H_{30}O_8 \cdot 3C_2H_4O_2$) forms an orthorhombic crystal system with $P2_12_12_1$ ($Z = 4$) symmetry. Unit cell dimensions were $a = 9.0208(7)$ Å, $b = 17.4884(10)$ Å, and $c = 24.358(2)$, Å yielding a volume of 3842.7(5) Å^3 and a density of 1.2077(2) g/cm^3. As with all previously reported crystals of gossypol, the gossypol molecules were of the aldehyde tautomer, and the two planar naphthalene rings were approximately perpendicular. Acetic acid molecules were found to lie in channels within the gossypol matrix. Individual crystals contained only one gossypol enantiomer, but both enantiomers crystallized from solution. Although the crystal habit could not be used to distinguish between the gossypol enantiomers, a fragment of the crystal could be derivatized and analyzed by high-performance liquid chromatography for this purpose. The ability to grow large, nonracemic crystals leads to a simple procedure for separating small quantities of the individual gossypol enantiomers.

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KEY WORDS: Gossypol, gossypol acetic acid, gossypol enantiomers, inclusion compounds, isomers, isomer separation.

Gossypol [1,1′,6,6′,7,7′-hexahydroxyl-5,5′-diisopropyl-3,3′-dimethyl-(2,2′-binaphthalene)-8,8′-dicarboxaldehyde] is a pigmented, polyphenolic compound (Scheme 1) found in cottonseed. The compound contributes to the toxicity of cottonseed products used as animal feeds (1) but has also been shown to be active as a male antifertility agent (2,3) and to have anticancer and immunosuppressive properties (4–6).

Gossypol forms inclusion compounds with many different low molecular weight organic molecules (7), and crystal structures for 37 gossypol complexes and related structures have been deposited in the January 1998 version of the Cambridge Crystal Structure Database (8). These structures indicate that gossypol accommodates different guest molecules by packing in a variety of forms. Guest molecules occupy isolated cells, channels, and intersecting channels within the gossypol matrix. Different host/guest ratios are also found. Salicylaldehyde, for example, forms complexes with gossypol/guest ratios of 1:1 and 1:2 (9,10), and diethyl ether forms complexes in ratios of 1:1 and 2:1 (11,12). In the former case, the different forms were produced under different crystallization conditions, whereas in the latter case, the unstable monosolvate was desolventized to form the semisolvate. Polymorphism has also been observed among gossypol inclusion complexes. The best-studied example is the clathrate formed with dichloromethane, which forms both monoclinic and triclinic crystals with host/guest ratios of 1:1 as well as a triclinic crystal with a host/guest ratio of 1:2 (13). Crystal structures have also been reported for several gossypol derivatives (14–16).

Crystallization from a racemic mixture of a chiral compound generally results in a crystalline racemate (17). To our knowledge, all previously reported crystalline forms of gossypol are racemates. Essentially, all of these structures have centrosymmetric arrangements of the enantiomers. There is one curious exception: In the gossypol/diethyl ether (2:1) clathrate (12), the reported space group is $P2_1$, indicative of a noncentrosymmetric arrangement of chiral objects. The structure must, however, be a racemate because it is formed by desolventization of the racemic gossypol/diethyl ether (1:1) complex. To explain this apparent anomaly, Gdaniec *et al.* (7) proposed that the gossypol/diethyl ether (2:1) structure is a lamellar twin with alternating enantiomeric layers, which in some circumstances can give a diffraction pattern similar to that of an enantiomeric crystal. Ibragimov *et al.* (15) postulate that the tendency of gossypol to form crystalline racemates is due to favorable hydrogen-bonding interactions between the enantiomers; however, centrosymmetric gossypol structures also exist without these intermolecular hydrogen bonds (18).

We have produced a new crystallographic form of gossypol with acetic acid in a one-to-three ratio (gossypol triacetic acid) and believe that this is the first report of a nonracemic crystalline form of gossypol. The inclusion complex has an orthorhombic crystal system with a $P2_12_12_1$ space group ($Z = 4$) and is markedly different from a previously reported one-to-one gossypol acetic acid complex (19,20) that crystallizes
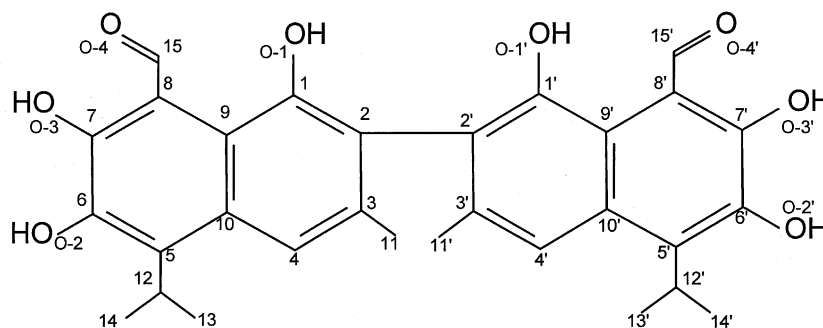
SCHEME 1

as a centrosymmetric, triclinic structure with a P$\bar{1}$ space group. Only the gossypol clathrate with 1,4-dioxane has been reported in an orthorhombic system (21), but its reported space group (Pbcn) also indicates that it is a racemate. The existence of a chiral crystalline form of gossypol suggests that it is possible to separate the individual isomers without forming diastereomers by chemical derivatization (22–24). In this report, the crystal and molecular structure of this new gossypol form is described along with evidence that the enantiomers of gossypol can be obtained by crystallization.

MATERIALS AND METHODS

Solutions were prepared by adding 0.5 g of gossypol acetic acid and ~4.0 mL (3 g) of acetone to small glass vials at room temperature. Samples were initially stored at −20°C to promote the formation of primary nuclei. After melting most of the precipitated material by gentle heating, the vials were maintained at 4°C to promote crystal growth. The increased temperature reduced the formation of primary nuclei and increased the size of the crystals.

Data collection and structure solution were conducted at the Iowa State Molecular Structure Laboratory. A single crystal with dimensions 0.7 × 0.2 mm × 0.15 mm was mounted on a glass fiber, coated with oil, and subjected to X-ray diffraction. A Siemans P4RA diffractometer (Madison, WI) was used for data collection at 213 ± 1 K. Unit cell parameters were determined from 25 reflections found from a hemispherical search in the θ range of 21.191 to 55.992°. Diffraction data was collected over a θ range of 2.11 to 56.74 using CuKα radiation (λ = 1.54178 Å) with a graphic monochromator (*h*: −1 → 9; *k*: −18 → 1; *l*: −1 → 26). No significant intensity variations were noted for the three standard reflections that were monitored every 97 reflections. The total number of reflections collected was 3,391, and the final data set consisted of 3,181 independent reflections (R_{int} = 0.0226) of which 2,984 were considered observed [$I \geq 2\sigma (I)$]. Lorentz and polarization corrections were applied to the data, but no correction for absorption was used because of the very low absorption coefficient (μ = 0.783 mm^{-1}) and relatively flat azimuthal scans. F(000) was 1480.

All nonhydrogen atoms were placed directly from the E-

map and were refined with anisotropic displacement parameters. Hydrogen atoms were treated as riding atoms with individual isotropic displacement factors. The structure was refined by the full-matrix least-squares method with SHELXL-93 (25,26). Weights were assigned as $w = 1/[\sigma^2(F_o^2) + (0.0994P)^2 + 2.0627P]$ with $P = (F_o^2 + 2 F_c^2)/3$. The refinement converged with $R = 0.0505$ and $wR = 0.1382$. Mean and largest Δ/σ values were 0.002 and −0.032, respectively, with the largest peak and hole differences being 0.435 $e/Å^{-3}$ and −0.319 $e/Å^{-3}$. Refinement calculations were performed on an IBM-compatible computer.

Single crystals were also analyzed by high-performance liquid chromatography (HPLC). Crystals were washed with 1:5 and 1:10 (vol/vol) solutions of acetone/hexane to remove amorphous gossypol from the crystal surfaces, derivatized with (R)-2-amino-1-propanol to form diastereomers, and separated by chromatography. HPLC was conducted using a reversed-phase C18 column with ultraviolet detection at 254 nm, similar to the method of Kim *et al*. (27).

RESULTS AND DISCUSSION

Crystals separated from the mother liquor and stored at room temperature turned opaque and formed a crust of noncrystalline gossypol over several hours, and vials containing the isolated crystals had a pronounced acetic acid odor. Apparently, acetic acid molecules sublime away from the crystal surfaces upon isolation. Similar instability has been reported for gossypol diethyl ether (1:1), gossypol chloroform (1:1), gossypol 1,3-dioxane (1:1), and several dianilinegossypol clathrates (9,12,28,29). In one instance, this phenomenon has been used to isolate single crystals with a different ratio of host and guest (12). In other cases, including our structure, removal of the structure from the mother liquor appeared to result in slow decomposition. Despite this instability, the gossypol triacetic acid crystals could be studied by X-ray diffraction at low temperature after application of a thin layer of mineral oil.

The gossypol triacetic acid ($C_{30}H_{30}O_8 \cdot 3C_2H_4O_2$) crystals were long yellow prisms. The crystal system was orthorhombic with a $P2_12_12_1$ space group (Z = 4). Unit cell dimensions were a = 9.0208(7) Å, b = 17.4884(10) Å, and c = 24.358(2) Å, giving a unit cell volume of 3842.7(5) Å^3. The calculated density
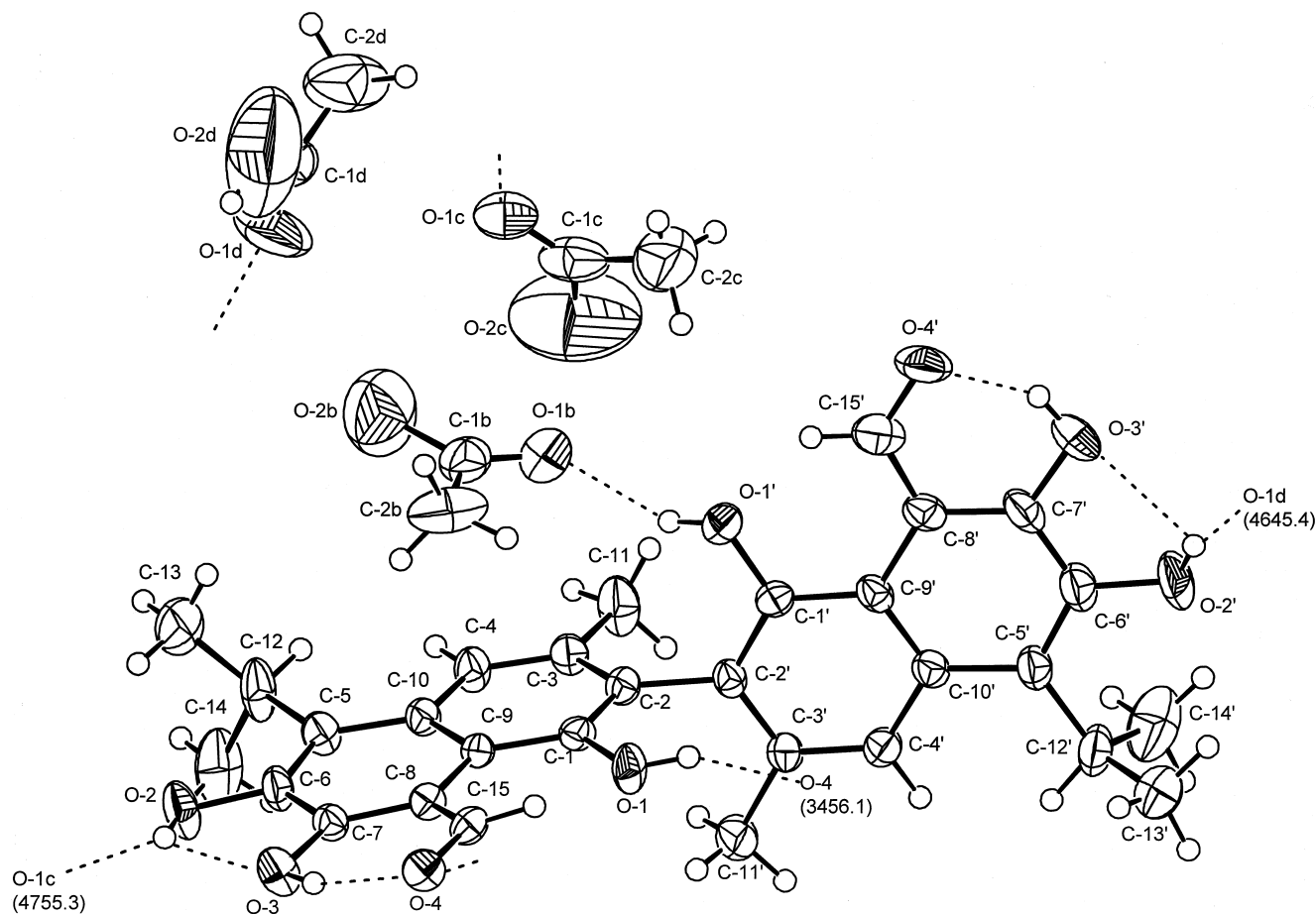
FIG. 1. Oak Ridge Thermal Ellipsoid Plot diagram of the gossypol triacetic acid assymetric unit. See Table 2 for information on symmetry codes.

was 1.2077(2) g/cm^3. This is the lowest density reported for an underivatized gossypol inclusion complex; densities of the other forms are between 1.25 and 1.60 g/cm^3 (7). The Flack parameter (30) was −0.09(30), indicating that the correct absolute molecular configuration was determined. Unfortunately, we were unable to use the diffracted crystal to determine the isomeric form of the structure. A 50% probability Oak Ridge Thermal Ellipsoid Plot of the asymmetric unit is shown in Figure 1. Fractional molecular coordinates and thermal motion parameters are given in Appendices 1 and 2.

A summary of the bond lengths for the structure is given in Table 1. Most bond lengths were similar to the average values reported by Allen *et al.* (31); however, the carbon-to-oxygen bond lengths of the acetic acid hydroxyl moieties were longer than expected. The acetic acid molecules also exhibited a large amount of thermal motion, and an area of slightly higher electron density was found near O-1d (Fig. 1). Subsequent refinement with the occupancy factors coupled showed that this oxygen position was partially occupied. It is likely that the acetic acid guests are considerably disordered at room temperature, which contributes to the observed instability of the crystals outside the crystallization solution.

The gossypol molecules within this complex are in the aldehyde form. This feature is exhibited by all gossypol-con-

taining crystal structures reported to date, but is not exhibited for gossypol derivatives (14,16). Both naphthalene moieties of the structure are close to planar with root-mean-squared atomic deviations from least-squares best-fit planes of 0.047 and 0.032 Å. The maximum displacement from these planes is 0.055 Å for atoms C-7 and C-8. The binaphthalene ring system is close to perpendicular with an 88.3(2)° angle between the least-squared best fit of these two planar moieties. This angle is toward the high end of the range of values (67.8 to 89.5°) calculated from the structures reported in the Cam-

TABLE 1
Bond Length Statistics for the Gossypol Triacetic Acid Clathrate[a]

Bond type	Minimum (Å)	Maximum (Å)	Average (Å)	Typical[b] (Å)
Csp^2–Csp^2 (aromatic)	1.364(5)	1.498(5)	1.416(5)	1.38(1)
Csp^2–Csp^3	1.442(7)	1.523(5)	1.489(6)	1.51(2)
Csp^3–Csp^3	1.513(8)	1.535(7)	1.525(7)	1.53(2)
O–Csp^2 (phenol)	1.331(5)	1.382(4)	1.358(5)	1.36(2)
O=Csp^2 (aldehyde)	1.245(5)	1.250(5)	1.248(5)	1.19(1)
O=Csp^2 (carboxylic)	1.199(7)	1.227(7)	1.213(7)	1.25(2)
O–Csp^2 (carboxylic)	1.454(12)	1.506(7)	1.489(8)	1.31(2)

[a]Estimated standard deviations are given in parentheses.
[b]Typical values reported by Allen *et al.* (31).

bridge Crystal Structural Database (8). The methyl groups of each isopropyl moiety straddle the naphthalene ring with the hydrogen atoms at C-12 and C-12′ oriented toward the hydrogen atoms at C-4 and C-4′, respectively. Although most gossypol crystals exhibit this feature, a few structures have one pair of the isopropyl methyl groups oriented in the opposite direction (9,18,32–34) or have a mixed occupancy of these two states (28).

The host gossypol molecules form channels that parallel the **a** coordinate axis (Fig. 2). Acetic acid guest molecules fill these channels and lie in close proximity. The distances between the carboxyl carbon atoms of the three guest molecules are 4.049(6) Å (C-1b…C-1c), 4.205(7) Å (C-1b…C-1d), and 5.659(8) Å (C-1c…C-1d) with the angles of 45.5(5)° (C-1b…C-1d…C-1c), 47.8(4)° C-1d…C-1c…C-1b), and 86.5(4)° (C-1c…C-1b…C-1d). Hydrogen bonds between acetic acid moieties were not distinguished, but the carbonyl groups of each acetic acid molecule accepted a hydrogen bond from a gossypol molecule (discussed below). The structure is best described as a tubulato-coordinatoclathrate (35), and although many of the features of this structure are found in other gossypol inclusion complexes, this structure is distinct from the 12 different families of gossypol complexes already identified (7).

All of the gossypol hydroxyl groups contribute to hydrogen bonds (Table 2, Fig. 1). As is common in gossypol crystals, the O-2, O-2′, O-3, and O-3′ hydrogen atoms form intramolecular hydrogen bonds resulting in pseudo five- and six-member rings (Fig. 1). In addition, the O-2 and O-2′ hydrogen atoms donate to the carbonyl oxygen atoms of two separate acetic acid molecules. The O-1′ hydroxyl hydrogen, which is often found to donate to an acceptor moiety of a hydrophilic guest molecule (36), bonds to the carbonyl oxygen of the third acetic acid molecule. One gossypol-to-gossypol intermolecular hydrogen bond is present: the O-1 hydrogen
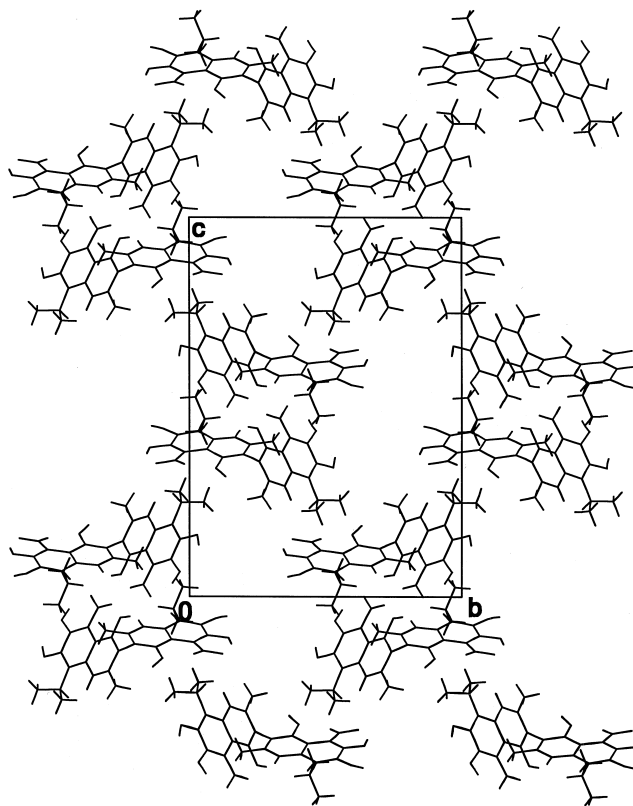

FIG. 2. Packing of gossypol molecules as viewed along the **a** axis direction in the gossypol triacetic acid clathrate (acetic acid molecules have been removed).

donates to the O-4 oxygen of an adjacent molecule. Networks of hydrogen bonds were identified (Table 2). None of these formed infinite chain or ring structures.

HPLC confirmed that individual crystals contained only one gossypol enantiomer and that both enantiomers crystal-

TABLE 2
Hydrogen Bonding in the Gossypol Triacetic Acid Clathrate

Donor–H…Acceptor	Acceptor symmetry code[a]	H…A (Å)	D…A (Å)	D–H…A (°)
Intramolecular				
O-2–H-13 … O-3	1555.1	2.145	2.625	115.4
O-2′–H-13′ … O-3′	1555.1	2.255	2.630	106.8
O-3–H-14 … O-4	1555.1	1.730	2.485	146.7
O-3′–H-14′ … O-4′	1555.1	1.705	2.466	147.6
Intermolecular				
O-1–H-1 … O-4	3456.1	2.036	2.763	143.1
O-1′–H-1′ … O-1b	1555.2	1.996	2.754	148.0
O-2–H-13 … O-1c	4755.3	1.924	2.662	144.5
O-2′–H-13′ … O-1d	4645.4	1.906	2.711	157.6

Hydrogen bond networks:
1: O-1 [1555.1] → O-4 [3456.1] ← O-3 [3456.1] ← O-2 [3456.1] → O-1c [2655.3]
2: O-4′ [1555.1] ← O-3′ [1555.1] ← O-2′ [1555.1] → O-1d [4654.4]
3: O-1′ [1555.1] → O-1b [1555.2]

[a]Symmetry codes are designated as $ni_xj_yk_z \cdot m$ where n = number of the asymmetric unit (1 = x, y, z; 2 = $\frac{1}{2} - x, -y, \frac{1}{2} + z$, 3 = $\frac{1}{2} + x, \frac{1}{2} - y, -z$, 4 = $-x, \frac{1}{2} + y, \frac{1}{2} - z$), i_x, j_y, k_z specifies a unit cell relative to a central cell of $i_x = 5$, $j_y = 5$, $k_z = 5$, and m denotes the residue within the asymmetric unit (1 = gossypol, 2 = acetic acid (B), 3 = acetic acid (C), 4 = acetic acid (D)).
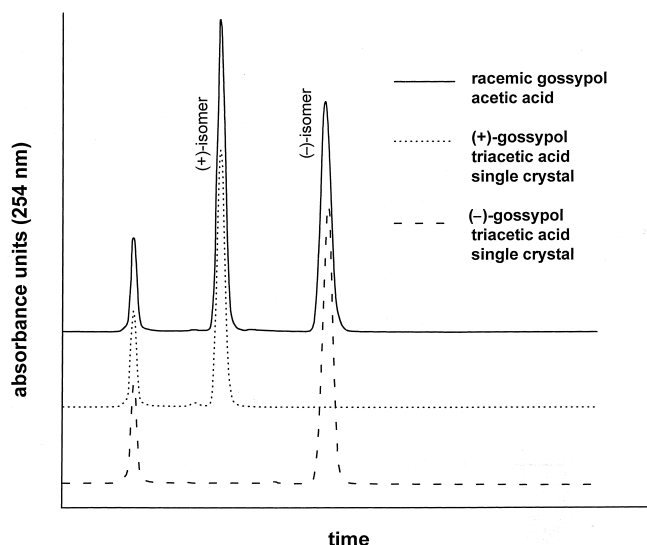
FIG. 3. High-performance liquid chromatogram of the (*R*)-2-amino-1-propanol derivatives of racemic gossypol acetic acid, a single crystal of (+)-gossypol triacetic acid, and a single crystal of (–)-gossypol triacetic acid.

lized from solution. Removing crystals from the mother liquor tended to leave a thin coating of amorphous gossypol on the crystal surfaces, but careful washing of the isolated crystals with solutions of hexane/acetone gave essentially pure preparations of the individual isomers (Fig. 3). Unfortunately, the chirality of the gossypol molecules within an individual crystal could not be determined visually from the crystal habit. However, this could be determined by polarimetry or by using a small sample for analysis by chromatography. The existence of a nonracemic crystalline form of gossypol suggests that useful amounts of the individual isomers can be prepared without resorting to chemical derivatization to form diastereomers.

ACKNOWLEDGMENT

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APPENDIX 1
Fractional Coordinates, Equivalent Isotropic Thermal Motion and Occupancy Parameters for the Gossypol Triacetic Acid Clathrate[a]

Atom	x/a	y/b	z/c	Ueq[b]	Occupancy
Gossypol					
O-1	0.8499(3)	0.74912(14)	0.94277(9)	0.0367(7)	
O-2	0.4858(4)	0.47108(15)	0.83819(11)	0.0486(9)	
O-3	0.4599(3)	0.53442(14)	0.93541(10)	0.0376(7)	
O-4	0.5079(3)	0.64109(14)	1.00040(9)	0.0333(7)	
C-1	0.8576(5)	0.71705(19)	0.89098(13)	0.0264(9)	
C-2	0.9629(5)	0.74226(19)	0.85459(14)	0.0284(10)	
C-3	0.9747(5)	0.7065(2)	0.80252(14)	0.0321(10)	
C-4	0.8767(5)	0.6497(2)	0.78991(14)	0.0347(11)	
C-5	0.6680(5)	0.5614(2)	0.81138(15)	0.0335(10)	
C-6	0.5736(5)	0.5326(2)	0.84990(15)	0.0334(11)	
C-7	0.5605(5)	0.56629(19)	0.90261(14)	0.0274(9)	
C-8	0.6448(5)	0.63036(19)	0.91740(13)	0.0253(9)	
C-9	0.7563(5)	0.65832(18)	0.87909(13)	0.0242(9)	
C-10	0.7670(5)	0.62323(19)	0.82608(13)	0.0279(9)	
C-11	1.0928(6)	0.7315(3)	0.76333(16)	0.0530(14)	
C-12	0.6647(6)	0.5284(3)	0.75352(17)	0.0525(15)	
C-13	0.5138(7)	0.5341(3)	0.72668(19)	0.075(2)	
C-14	0.7252(7)	0.4464(3)	0.7524(2)	0.0699(17)	
C-15	0.6036(5)	0.6674(2)	0.96844(14)	0.0289(10)	
H-1	0.9184	0.7822	0.9462	0.080	
H-2	0.4247	0.4644	0.8643	0.080	
H-3	0.4507	0.5611	0.9644	0.080	
H-4	0.8829	0.6266	0.7542	0.080	
H-5	1.0861	0.7016	0.7304	0.080	
H-6	0.0784	0.7846	0.7546	0.080	
H-7	1.1889	0.7247	0.7796	0.080	
H-8	0.7311	0.5588	0.7319	0.080	
H-9	0.5186	0.5127	0.6904	0.080	
H-10	0.4429	0.5062	0.7482	0.080	
H-11	0.4841	0.5867	0.7244	0.080	
H-12	0.7225	0.4271	0.7156	0.080	
H-13	0.8256	0.4461	0.7655	0.080	
H-14	0.6652	0.4147	0.7757	0.080	
H-15	0.6510	0.7147	0.9780	0.080	

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APPENDIX 1 (continued)

Atom	x/a	y/b	z/c	Ueq^b	Occupancy
O-1′	0.9248(4)	0.90179(15)	0.83613(11)	0.0417(8)	
O-2′	1.4532(4)	1.09539(16)	0.94151(14)	0.0615(10)	
O-3′	1.2142(4)	1.14341(15)	0.89019(14)	0.0578(10)	
O-4′	0.9691(4)	1.12054(15)	0.84847(12)	0.0571(10)	
C-1′	1.0464(5)	0.8783(2)	0.86489(13)	0.0287(10)	
C-2′	1.0732(5)	0.80082(19)	0.87316(14)	0.0269(10)	
C-3′	1.2032(5)	0.7777(2)	0.89958(15)	0.0317(10)	
C-4′	1.3003(5)	0.8317(2)	0.91857(15)	0.0320(10)	
C-5′	1.3784(5)	0.9660(2)	0.93475(15)	0.0345(10)	
C-6′	1.3533(6)	1.0425(2)	0.92460(17)	0.0418(11)	
C-7′	1.2246(6)	1.0672(2)	0.89694(16)	0.0404(12)	
C-8′	1.1163(5)	1.0169(2)	0.87861(15)	0.0324(10)	
C-9′	1.1420(5)	0.9351(2)	0.88582(14)	0.0292(10)	
C-10′	1.2727(5)	0.9113(2)	0.91315(14)	0.0304(10)	
C-11′	1.2342(6)	0.6939(2)	0.9077(2)	0.0489(13)	
C-12′	1.5140(6)	0.9423(2)	0.9671(2)	0.0505(13)	
C-13′	1.5165(7)	0.9764(3)	1.0246(2)	0.0678(16)	
C-14′	1.6570(7)	0.9574(4)	0.9358(3)	0.0799(19)	
C-15′	0.9834(6)	1.0505(2)	0.8563117)	0.0475(13)	
H-1′	0.8989	0.8669	0.8138	0.080	
H-2′	1.4091	1.1374	0.9480	0.080	
H-3′	1.1319	1.1538	0.8749	0.080	
H-4′	1.3905	0.8152	0.9359	0.080	
H-5′	1.3274	0.6882	0.9263	0.080	
H-6′	1.1569	0.6713	0.9294	0.080	
H-7′	1.2389	0.6688	0.8727	0.080	
H-8′	1.5070	0.8879	0.9716	0.080	
H-9′	1.4241	0.9660	1.0427	0.080	
H-10′	1.5961	0.9537	1.0451	0.080	
H-11′	1.5313	1.0306	1.0224	0.080	
H-12′	1.6511	0.9354	0.8998	0.080	
H-13′	1.6730	1.0115	0.9328	0.080	
H-14′	1.7378	0.9346	0.9555	0.080	
H-15′	0.9015	1.0177	0.8477	0.080	
Acetic acid B					
O-1b	0.7592(5)	0.8322(2)	0.75533(15)	0.0713(11)	
O-2b	0.5740(9)	0.7681(3)	0.7026(2)	0.143(2)	
C-1b	0.6375(7)	0.8009(3)	0.7547(2)	0.0550(14)	
C-2b	0.5460(9)	0.7938(4)	0.8041(2)	0.084(2)	
H-1b	0.5971	0.8156	0.8349	0.080	
H-2b	0.4541	0.8203	0.7985	0.080	
H-3b	0.5262	0.7407	0.8112	0.080	
H-4b	0.6348	0.7747	0.6764	0.080	
Acetic acid C					
O-1c	0.2628(5)	0.40239(18)	0.89006(14)	0.0557(9)	
O-2c	0.0222(10)	0.3472(6)	0.8798(4)	0.230(5)	
C-1c	0.1424(8)	0.4052(4)	0.8693(2)	0.0689(17)	
C-2c	0.1020(9)	0.4691(5)	0.8314(3)	0.115(3)	
H-1c	0.1843	0.5033	0.8270	0.080	
H-2c	0.0752	0.4482	0.7963	0.080	
H-3c	0.0192	0.4964	0.8464	0.080	
H-4c	0.0577	0.3140	0.9017	0.080	
Acetic acid D					
O-1d[c]	0.3873(9)	0.2411(3)	0.9707(3)	0.109(3)	0.814(13)
O-1d[c]	0.5215(12)	0.2390(4)	0.9255(3)	0.13(2)	0.186(13)
O-2d	0.5875(12)	0.3255(7)	0.9485(4)	0.254(6)	
C-1d	0.4511(11)	0.3019(4)	0.9753(3)	0.090(2)	
C-2d	0.3844(12)	0.3599(4)	1.0103(3)	0.122(3)	
H-1d	0.6139	0.2867	0.9298	0.080	
H-2d	0.2969	0.3373	1.0258	0.080	
H-3d	0.4507	0.3746	1.0392	0.080	
H-4d	0.3573	0.4042	0.9893	0.080	

[a]Estimated standard deviations are given in parentheses.
[b]$Ueq = 1/3 \sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j$.
[c]O-1d was found to occupy 2 sites.

APPENDIX 2
Anisotropic Thermal Motion Parameters for the Gossypol Triacetic Acid Clathrate[a]

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Gossypol						
O-1	0.045(2)	0.0406(14)	0.0244(12)	−0.0131(11)	0.0046(14)	−0.0156(14)
O-2	0.065(2)	0.0429(15)	0.0379(14)	−0.0138(12)	0.0121(16)	−0.0275(16)
O-3	0.049(2)	0.0338(13)	0.0303(13)	−0.0079(11)	0.0135(15)	−0.0087(14)
O-4	0.040(2)	0.0360(13)	0.0234(12)	−0.0034(11)	0.0057(14)	−0.0004(14)
C-1	0.035(3)	0.0253(18)	0.0188(16)	−0.0014(14)	−0.001(2)	0.0007(18)
C-2	0.032(3)	0.0280(19)	0.0250(18)	−0.0029(15)	−0.003(2)	−0.0030(18)
C-3	0.037(3)	0.036(2)	0.0240(17)	−0.0004(16)	0.004(2)	−0.008(2)
C-4	0.045(3)	0.037(2)	0.0224(17)	−0.0073(16)	0.002(2)	−0.012(2)
C-5	0.043(3)	0.0323(19)	0.0247(18)	−0.0047(16)	0.005(2)	−0.007(2)
C-6	0.038(3)	0.0273(19)	0.035(2)	−0.0065(16)	−0.002(2)	−0.0119(19)
C-7	0.030(3)	0.0269(18)	0.0249(17)	0.0006(15)	0.0013(19)	−0.0044(18)
C-8	0.027(3)	0.0253(17)	0.023717)	−0.0025(15)	0.0021(18)	0.0012(17)
C-9	0.028(3)	0.0222(17)	0.0226(16)	−0.0012(14)	−0.0023(18)	−0.0008(17)
C-10	0.035(3)	0.0259(18)	0.0226(17)	−0.0028(14)	−0.0010(19)	−0.0039(18)
C-11	0.059(4)	0.065(3)	0.035(2)	−0.010(2)	0.013(2)	−0.028(3)
C-12	0.064(4)	0.063(3)	0.031(2)	−0.020(2)	0.012(2)	−0.037(3)
C-13	0.115(6)	0.076(3)	0.034(2)	−0.003(2)	−0.019(3)	-0.036(4)
C-14	0.071(4)	0.080(4)	0.058(3)	0.044(3)	0.019(3)	−0.021(3)
C-15	0.031(3)	0.0335(19)	0.0225(17)	−0.0041(16)	−0.003(2)	0.0010(18)
O-1′	0.042(2)	0.0357(14)	0.0477(15)	0.0012(13)	−0.0164(16)	−0.0003(14)
O-2′	0.067(2)	0.0296(14)	0.088(2)	−0.0107(15)	−0.017(2)	−0.0178(16)
O-3′	0.077(3)	0.0226(14)	0.074(2)	0.0067(13)	−0.008(2)	−0.0050(15)
O-4′	0.085(3)	0.0329(16)	0.0531(17)	0.0131(13)	−0.0128(19)	0.0070(17)
C-1′	0.033(3)	0.0309(19)	0.0223(17)	0.0006(15)	−0.001(2)	−0.0011(19)
C-2′	0.032(3)	0.0264(18)	0.0221(16)	−0.0024(15)	0.002(2)	−0.0069(18)
C-3′	0.040(3)	0.0255(19)	0.0295(18)	−0.0035(15)	-0.005(2)	−0.0030(19)
C-4′	0.031(3)	0.032(2)	0.0330(19)	−0.0008(16)	−0.004(2)	0.0002(19)
C-5′	0.039(3)	0.031(2)	0.0336(19)	−0.0046(17)	−0.001(2)	−0.0089(19)
C-6′	0.049(3)	0.034(2)	0.042(2)	−0.0055(18)	−0.001(2)	−0.012(2)
C-7′	0.058(4)	0.024(2)	0.039(2)	−0.0001(16)	0.004(3)	−0.011(2)
C-8′	0.041(3)	0.031(2)	0.0256(18)	0.0030(16)	0.006(2)	−0.001(2)
C-9′	0.039(3)	0.0254(18)	0.0230(17)	0.0000(15)	0.004(2)	−0.0060(19)
C-10	0.041(3)	0.0253(19)	0.0251(17)	−0.0015(14)	-0.001(2)	−0.0039(19)
C-11′	0.051(3)	0.028(2)	0.069(3)	−0.001(2)	-0.019(3)	0.002(2)
C-12′	0.045(4)	0.036(2)	0.070(3)	−0.009(2)	-0.026(3)	−0.005(2)
C-13′	0.084(5)	0.064(3)	0.055(3)	0.002(2)	-0.025(3)	−0.018(3)
C-14′	0.052(4)	0.093(4)	0.094(4)	−0.032(4)	-0.013(4)	0.005(3)
C-15′	0.067(4)	0.038(2)	0.038(2)	0.0035(18)	−0.001(3)	0.006(2)
Acetic acid B						
O-1b	0.056(3)	0.0574(19)	0.0537(18)	−0.0078(15)	0.009(2)	−0.0206(19)
C-2b	0.096(6)	0.138(7)	0.110(6)	−0.043(5)	-0.030(5)	0.039(6)
C-1b	0.056(5)	0.083(4)	0.068(3)	−0.037(3)	0.016(4)	−0.015(4)
O-2b	0.184(8)	0.245(9)	0.262(10)	-0.061(8)	0.042(8)	−0.115(8)
Acetic acid C						
O-1c	0.076(3)	0.069(2)	0.069(2)	0.0034(18)	−0.024(2)	−0.008(2)
C-2c	0.101(6)	0.090(4)	0.062(3)	0.020(3)	−0.005(4)	0.038(4)
C-1c	0.066(4)	0.043(3)	0.056(3)	−0.002(2)	--0.017(3)	0.009(3)
O-2c	0.174(7)	0.146(5)	0.108(4)	−0.018(3)	−0.010(4)	−0.036(5)
Acetic acid D						
O-1d[b]	0.166(7)	0.043(3)	0.118(5)	−0.028(3)	−0.013(5)	−0.005(4)
O-1d[b]	0.20(4)	0.038(11)	0.16(3)	−0.011(14)	−0.10(3)	−0.046(17)
O-2d	0.216(10)	0.361(15)	0.186(8)	0.027(9)	−0.007(9)	0.164(11)
C-1d	0.136(7)	0.054(3)	0.082(4)	−0.009(3)	-0.057(5)	0.014(4)
C-2d	0.215(10)	0.085(4)	0.067(4)	0.002(3)	−0.030(6)	−0.022(6)

[a]Estimated standard deviations are given in parentheses.
[b]O-1d was found to occupy two sites.