

The gossypol–cyclododecanone (1/2) inclusion complex

Michael K. Dowd^{a*} and Edwin D. Stevens^b

^aCommodity Utilization Research Unit, Southern Regional Research Center, ARS, USDA, 1100 Robert E. Lee Boulevard, New Orleans, LA 70124, USA, and

^bDepartment of Chemistry, University of New Orleans, 2000 Lakeshore Drive, New Orleans, LA 70148, USA

Correspondence e-mail: mkdowd@srrc.ars.usda.gov

Received 24 April 2003

Accepted 19 May 2003

Online 30 June 2003

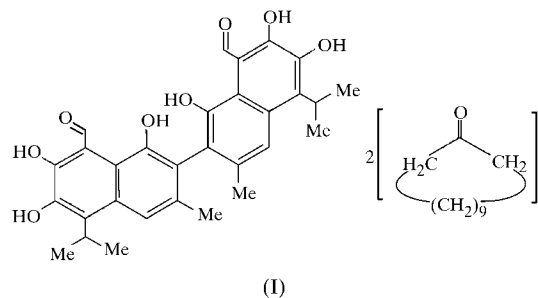
Gossypol and cyclododecanone crystallize at room temperature as an inclusion complex in a 1:2 molar ratio. This complex, *viz.* 1,1',6,6',7,7'-hexahydroxy-5,5'-diisopropyl-3,3'-dimethyl-2,2'-binaphthalene-8,8'-dicarboxaldehyde–cyclododecanone (1/2), $C_{30}H_{30}O_8 \cdot 2C_{12}H_{22}O$, is unusual in that there is limited intermolecular hydrogen bonding within the structure. Each cyclododecanone molecule accepts a hydrogen bond from a gossypol molecule, but there are no gossypol-to-gossypol hydrogen-bond interactions. The gossypol molecules form a framework structure enclosing channels, and the cyclododecanone molecules lie in these channels. In terms of the number of non-H guest atoms, this is the largest gossypol inclusion complex reported to date.

Comment

Gossypol is a biologically active disesquiterpene found in the cotton plant and other members of the Malvaceae family. The compound is known to form inclusion complexes with many small-molecular-weight organic compounds. These complexes have been grouped by Gdaniec *et al.* (1996) into 12 families on the basis of intermolecular hydrogen-bond and packing patterns. As part of a project to determine whether gossypol can form inclusion complexes with larger molecules, experiments were conducted with cyclododecanone, and a structure was identified, *viz.* the title complex, (I), that represents a new family of gossypol inclusion complex.

The title complex contains two molecules of cyclododecanone per gossypol molecule (Fig. 1), and no unusual bond lengths or valence angles were found. As is observed for most gossypol complexes, both halves of the gossypol moiety exist as aldehydes (Fig. 1*a*), and intramolecular O3–H103...O2, O4–H104...O3, O7–H107...O6 and O8–H108...O7 hydrogen bonds are formed (Fig. 2). The naphthalene rings are approximately perpendicular, with an angle of 81.9 (1)° between the least-squares best-fit naphthalene planes. Both

isopropyl moieties are oriented with the methyl groups pointing outward and away from the binaphthalene bridge.



Each cyclododecanone ring is characterized by a periodic ...*gauche-gauche-trans*... arrangement of the ring torsion angles (Table 1), which results in a 'square' conformation (Figs. 1*b* and 3). The distance between atoms along parallel sides of the square is ~4.5 Å and the distance between atoms across the diagonal is ~5.5 Å. A similar ring shape has been observed for crystalline cyclododecanone (Groth, 1979), cyclododecane (Dunitz & Shearer, 1960) and 2,12-dibromocyclododecanone (Dehli & Groth, 1969), and has been interpreted as the solution conformation of cyclododecanone from NMR data (Anet *et al.*, 1973; Rawdah, 1991).

In (I), each cyclododecanone carbonyl group accepts a hydrogen bond from either the O1–H101 or the O5–H105

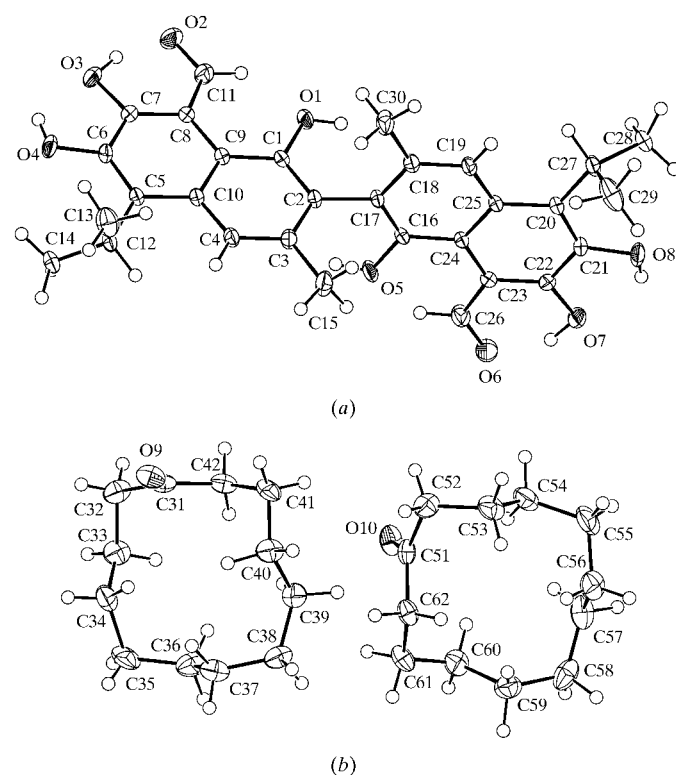


Figure 1

Views of (a) the gossypol molecule and (b) the two cyclododecanone molecules in (I). Displacement ellipsoids are shown at the 50% probability level.

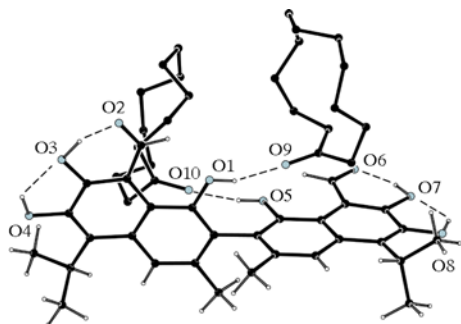


Figure 2
The association of the gossypol and cyclododecanone molecules in (I). Hydrogen bonds are shown as dashed lines, and cyclododecanone H atoms have been omitted for clarity.

hydroxyl group of the gossypol molecule (Table 2 and Fig. 2). The cyclododecanone molecules are arranged such that the face of each ring is oriented parallel to the long axis of the gossypol group (parallel to the C2–C17 bond) and perpendicular to the planes of both naphthalene rings (Fig. 3).

There are no hydrogen-bond interactions between adjacent gossypol molecules, which is unusual among known gossypol complexes. The only other gossypol complex without direct gossypol-to-gossypol hydrogen bonds is gossypol-1,4-dioxane (1/3) (Ibragimov *et al.*, 1993; Gdaniec *et al.*, 1996). In this structure, two of the three dioxane molecules accept pairs of hydrogen bonds to form bridges between adjacent gossypol molecules. The gossypol-di-1,4-dioxane assemblies pack in a two-dimensional lattice. The third dioxane molecule sits in a channel formed within this lattice and interacts with the structure through van der Waals effects.

In (I), each cyclododecanone molecule accepts a single hydrogen bond from a host gossypol molecule, and no hydrogen-bond bridges are present. The gossypol molecules form a lattice that surrounds rectangular channels which run parallel to the *c* axis (Fig. 4). The channels are occupied by the cyclododecanone molecules, which are oriented with their

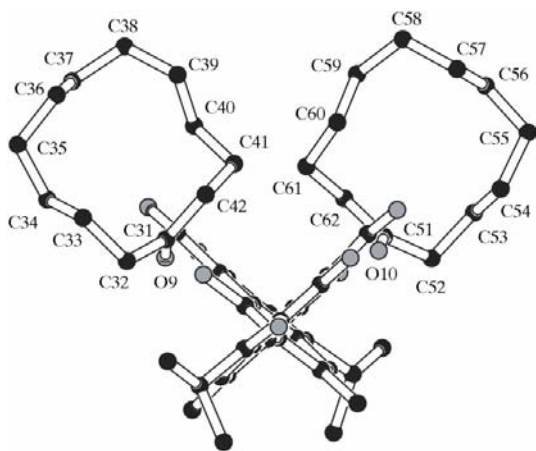


Figure 3
The conformation of the cyclododecanone rings, viewed along the C2–C17 bond.

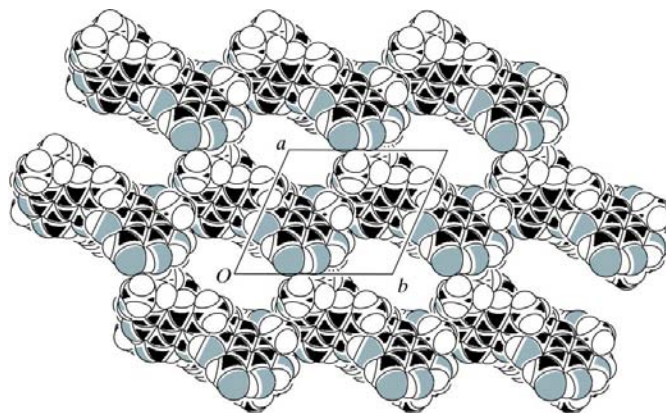


Figure 4
The packing of the gossypol molecules in (I), viewed along the *c* axis. Gossypol molecules are shown in CPK (Corey–Pauling–Koltun) space-filling format, and cyclododecanone molecules have been omitted in order to show the channels.

faces perpendicular to the channel direction. Along the *c* direction, the chiral gossypol molecules separate into alternating enantiomorphic layers (Fig. 5), which interact only through van der Waals effects. Similar layering is observed in gossypol inclusion compounds formed with small esters (Ibragimov *et al.*, 1990; Gdaniec *et al.*, 1996), although in these structures the gossypol molecules within enantiomorphic layers share hydrogen bonds.

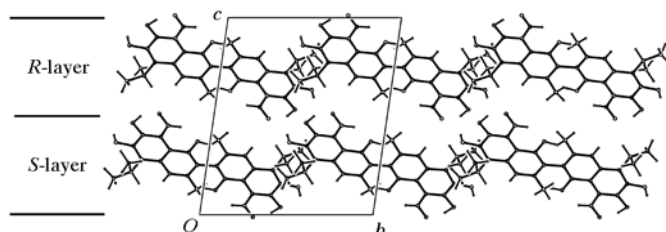


Figure 5
A view of the enantiomorphic layers associated with the packing of the gossypol molecules in (I). Cyclododecanone molecules have been omitted for clarity.

In terms of guest size, (I) is the largest gossypol inclusion complex reported to date, containing 26 non-H atoms of guest molecule per gossypol molecule. In comparison, the next highest gossypol-to-guest non-H-atom ratios are for gossypol-pyridine (1/3), gossypol-1,4-dioxane (1/3) and gossypol-tropolone (1/2), each of which contains 18 non-H atoms per gossypol molecule (Gdaniec *et al.*, 1996; Talipov *et al.*, 2002). The title complex is also the second example of gossypol forming an inclusion complex with a compound that is normally solid at room temperature.

Experimental

Cyclododecanone (m.p. 332 K) was dissolved in hexane until the solution was almost saturated. Racemic gossypol was dissolved in this solution, and additional hexane was added to induce crystallization of (I) at 298 (2) K.

Crystal data

$C_{30}H_{30}O_8 \cdot 2C_{12}H_{22}O$
 $M_r = 883.13$
 Triclinic, $P\bar{1}$
 $a = 12.2640$ (4) Å
 $b = 14.4674$ (4) Å
 $c = 15.1532$ (5) Å
 $\alpha = 82.108$ (1)°
 $\beta = 89.206$ (1)°
 $\gamma = 66.264$ (1)°
 $V = 2435.32$ (13) Å³

$Z = 2$
 $D_x = 1.204$ Mg m⁻³
 Mo $K\alpha$ radiation
 Cell parameters from 30 511 reflections
 $\theta = 2.2$ – 29.9 °
 $\mu = 0.08$ mm⁻¹
 $T = 150$ (2) K
 Irregular, yellow
 $0.6 \times 0.5 \times 0.4$ mm

Data collection

Bruker CCD area-detector diffractometer
 φ and ω scans
 Absorption correction: empirical (SADABS in SAINT; Bruker, 1998)
 $T_{\min} = 0.749$, $T_{\max} = 0.975$
 65 791 measured reflections

14 038 independent reflections
 10 049 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.053$
 $\theta_{\text{max}} = 29.9$ °
 $h = -17 \rightarrow 17$
 $k = -20 \rightarrow 20$
 $l = -21 \rightarrow 21$

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.055$
 $wR(F^2) = 0.163$
 $S = 1.04$
 14 038 reflections
 851 parameters
 H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0993P)^2 + 0.1464P]$
 where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\text{max}} = 0.003$
 $\Delta\rho_{\text{max}} = 0.39$ e Å⁻³
 $\Delta\rho_{\text{min}} = -0.29$ e Å⁻³

All H atoms were located from difference maps and most were refined with an isotropic model, giving C–H distances in the range

Table 1
 Selected torsion angles (°).

C1–C2–C17–C16	–99.92 (15)	C40–C41–C42–C31	71.40 (18)
C1–C2–C17–C18	83.58 (16)	C32–C31–C42–C41	–165.17 (13)
C3–C2–C17–C16	81.65 (15)	C62–C51–C52–C53	70.47 (18)
C3–C2–C17–C18	–94.85 (15)	C51–C52–C53–C54	61.67 (19)
C42–C31–C32–C33	69.15 (19)	C52–C53–C54–C55	–160.64 (15)
C31–C32–C33–C34	60.0 (2)	C53–C54–C55–C56	71.7 (2)
C32–C33–C34–C35	–160.62 (15)	C54–C55–C56–C57	74.4 (2)
C33–C34–C35–C36	75.7 (2)	C55–C56–C57–C58	–159.30 (15)
C34–C35–C36–C37	74.0 (2)	C56–C57–C58–C59	65.5 (2)
C35–C36–C37–C38	–160.00 (14)	C57–C58–C59–C60	65.9 (2)
C36–C37–C38–C39	64.34 (19)	C58–C59–C60–C61	–161.27 (14)
C37–C38–C39–C40	64.0 (2)	C59–C60–C61–C62	69.47 (19)
C38–C39–C40–C41	–160.31 (15)	C60–C61–C62–C51	70.70 (18)
C39–C40–C41–C42	72.10 (19)	C52–C51–C62–C61	–164.42 (13)

Table 2

Hydrogen-bonding geometry (Å, °).

$D-H \cdots A$	$D-H$	$H \cdots A$	$D \cdots A$	$D-H \cdots A$
O1–H101 \cdots O9	0.86 (2)	1.96 (2)	2.7451 (14)	150 (2)
O3–H103 \cdots O2	0.94 (3)	1.57 (3)	2.4700 (15)	158 (2)
O4–H104 \cdots O3	0.80 (3)	2.08 (2)	2.5904 (16)	121 (2)
O5–H105 \cdots O10	0.85 (2)	1.99 (2)	2.7272 (14)	145 (2)
O7–H107 \cdots O6	0.91 (3)	1.63 (3)	2.4598 (15)	149 (3)
O8–H108 \cdots O7	0.80 (2)	2.05 (2)	2.5935 (16)	125 (2)

0.93 (2)–1.05 (2) Å and O–H distances in the range 0.80 (3)–0.94 (2) Å. However, the H atoms on atoms C29 and C30 were modeled as rotating groups, with C–H distances of 0.98 Å, in order to improve the tetrahedral geometry about these C atoms.

Data collection: SMART (Bruker, 1998); cell refinement: SAINT (Bruker, 1998); data reduction: SAINT; program(s) used to solve structure: SHELXS97 (Sheldrick, 1997); program(s) used to refine structure: SHELXL97 (Sheldrick, 1997); molecular graphics: PLATON (Spek, 2003); software used to prepare material for publication: PLATON.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GD1253). Services for accessing these data are described at the back of the journal.

References

- Anet, F. A. L., Cheng, A. K. & Krane, J. (1973). *J. Am. Chem. Soc.* **95**, 7877–7878.
 Bruker (1998). SMART and SAINT. Versions 5.0. Bruker AXS Inc., Madison, Wisconsin, USA.
 Dehli, J. & Groth, P. (1969). *Acta Chem. Scand.* **23**, 587–596.
 Dunitz, J. D. & Shearer, H. M. M. (1960). *Helv. Chim. Acta*, **43**, 18–35.
 Gdaniec, M., Ibragimov, B. T. & Talipov, S. A. (1996). *Comprehensive Supramolecular Chemistry*, Vol. 6, *Solid-State Supramolecular Chemistry: Crystal Engineering*, edited by D. D. MacNicol, F. Toda & R. Bishop, pp. 117–146. Oxford: Pergamon Press.
 Groth, P. (1979). *Acta Chem. Scand. Ser. A*, **33**, 203–205.
 Ibragimov, B. T., Gdaniec, M., Talipov, S. A., Dadabaev, B. N. & Beketov, K. M. (1993). *Khim. Prir. Soedin.* pp. 801–807.
 Ibragimov, B. T., Talipov, S. A. & Gdaniec, M. (1990). *J. Inclusion Phenom. Mol. Recognit. Chem.* **8**, 409–421.
 Rawdah, T. N. (1991). *Tetrahedron*, **47**, 8579–8586.
 Sheldrick, G. M. (1997). SHELXL97 and SHELXS97. University of Göttingen, Germany.
 Spek, A. L. (2003). *J. Appl. Cryst.* **36**, 7–13.
 Talipov, S. A., Ibragimov, B. T., Ohashi, Y., Harada, J. & Saleh, M. I. (2002). *Kristallografiya*, **47**, 488–493.