Acta Crystallographica Section B
Structural Science
ISSN 0108-7681

Hydrogen-bonded aggregations of oxo-cholic acids

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Received 14 February 2005
Accepted 12 April 2005

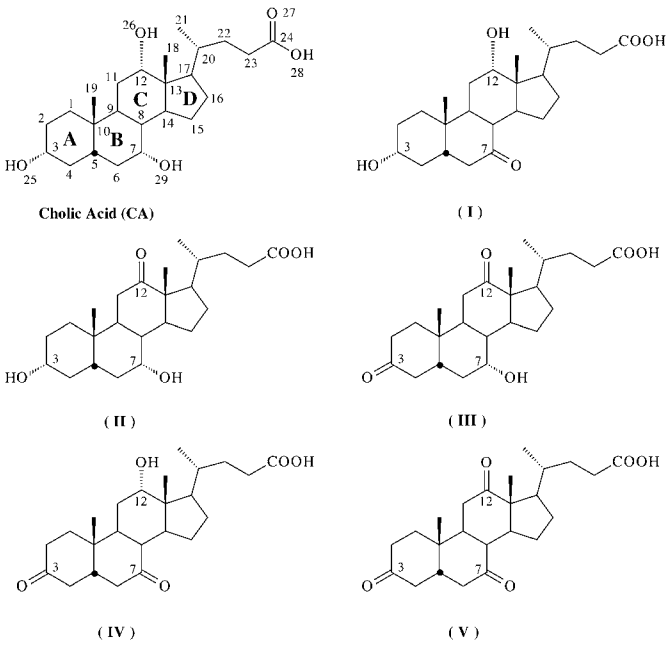
The crystal structures of six new crystals of oxo-cholic acids (oxo-CA) are reported: (I) 3α,12α-dihydroxy-7-oxo-5β-cholan-24-oic acid; (II) 3α,7α-dihydroxy-12-oxo-5β-cholan-24-oic acid; (III) 7α-hydroxy-3,12-dioxo-5β-cholan-24-oic acid; (IV-α) and (IV-β) 12α-hydroxy-3,7-dioxo-5β-cholan-24-oic acid; (V) 3,7,12-trihydroxy-5β-cholan-24-oic acid. (IV-β) is a pseudopolymorphic solvated form of (IV-α) and contains small channels which can trap disordered water molecules. In all the structures the four saturated cycles, forming the common alicyclic skeleton, have the same conformation, while the carboxylic side chain adopts flexible conformations in order to produce the most efficient crystal aggregations. The structures display a variety of supramolecular architectures dominated by networks of cooperative O—H···O hydrogen bonds forming different packing motifs often supported by weaker C—H···O interactions.

1. Introduction

Cholic acid (CA; 3α,7α,12α-trihydroxy-5β-cholan-24-oic acid) is a steroidal compound classified as a bile acid which is produced in the liver of vertebrates from cholesterol. The human bile acid pool mainly consists of approximately 90% of cholic, chenodeoxycholic and deoxycholic acids, in a ratio of approximately 2:2:1 (Hofmann, 1988).

Cholic, chenodeoxycholic and its 7-hydroxy epimer ursodeoxycholic acids have central pharmaceutical relevance in the treatment of bile acid deficiency and in the dissolution of cholesterol gallstones. In addition, there is an increasing interest in the use of these derivatives as chiral hosts for molecular recognition.

Cholic acid is one of the classical host compounds that form crystalline clathrate complexes with various organic guests (Herndon, 1967; Miki *et al.*, 1988; Caira *et al.*, 1993, 1994*a*,*b*; Shibakami *et al.*, 1995; Nowak *et al.*, 2000; Nakano *et al.*, 2001; Miyata & Sada, 1996; Miyata *et al.*, 2004) that, in most cases, have been used for enantioresolution of organic racemates (Bortolini *et al.*, 2005). In the enantioselective inclusion complexation of a racemic guest with a chiral host, in fact, one enantiomer of the former is separated as an inclusion host–guest complex crystal. From the inclusion crystal an optically active guest can be isolated by an appropriate method and the host may be recovered and used for further cycles. Using this procedure several classes of organic racemates have been successfully resolved with CA, *i.e.* lactones (Sada *et al.*, 2001), secondary alcohols (Sada *et al.*, 1995), epoxides (Fantin *et al.*, 2000*a*), amines (Sada *et al.*, 1996) and cyclic ketones (Bertolasi *et al.*, 2001).



A peculiar feature of cholic acid molecular structure is the facial amphiphilicity generated by the three hydroxy groups and the carboxylic moiety characterizing the hydrophilic face (α-face), and the two methyl groups distinguishing the lipophilic face (β-face) of the steroidal plane. X-ray crystallographic studies showed that most of the host–guest framework possesses a bilayer-type structure constructed by hydrogen bonds between the hydrophilic faces (Fig. 1) with a specific cyclic motif (Fig. 2) and van der Waals associations between the lipophilic β-faces. The guest compounds (G) are trapped by van der Waals forces and steric complementarity within the molecular channels of the lipophilic layer.

The crystal structure of cholic acid with no guest molecules (Miki *et al.*, 1990) displays a supramolecular architecture where the molecules form corrugated layers held together by hydrophilic and lipophilic interactions (Fig. 3). The hydrophilic zone consists of a system of hydrogen bonds which involve all the O atoms in the molecule forming infinite chains of σ-cooperative O—H···O hydrogen bonds (Jeffrey, 1997), also assisted by π-conjugation within the carboxyl group (Fig. 4). It may be assumed that the supramolecular arrangements of cholic acid inclusion compounds are very stable because they tend to maintain analogous hydrogen-bond systems assisted by σ-cooperativity and π-conjugation, thus forming cyclic networks (Fig. 2) rather than infinite chains.

It would be of interest to determine the crystal structures of oxo-cholic acid derivatives in order to discover new supramolecular aggregations established by a variety of hydrogen-bond architectures which are in relation to the position and number of oxidized hydroxy groups. In this paper we report the investigation of six crystal structures of cholic acid derivatives that have been selectively oxidized at C3 or/and C7 or/and C12 to the corresponding keto compounds in the order: (I): 3α,12α-dihydroxy-7-oxo-5β-cholan-24-oic acid, (II): 3α,7α-dihydroxy-12-oxo-5β-cholan-24-oic acid, (III): 7α-hydroxy-3,12-dioxo-5β-cholan-24-oic acid, (IV-α and IV-β): 12α-hydroxy-3,7-dioxo-5β-cholan-24-oic acid, (V): 3,7,12-trioxo-5β-cholan-24-oic acid.

2. Experimental

2.1. Syntheses

Compounds (I), (II) and (III) were prepared and characterized according to recently described procedures (Dean *et al.*, 1999; Bortolini *et al.*, 1996; Fantin *et al.*, 1993). Compound

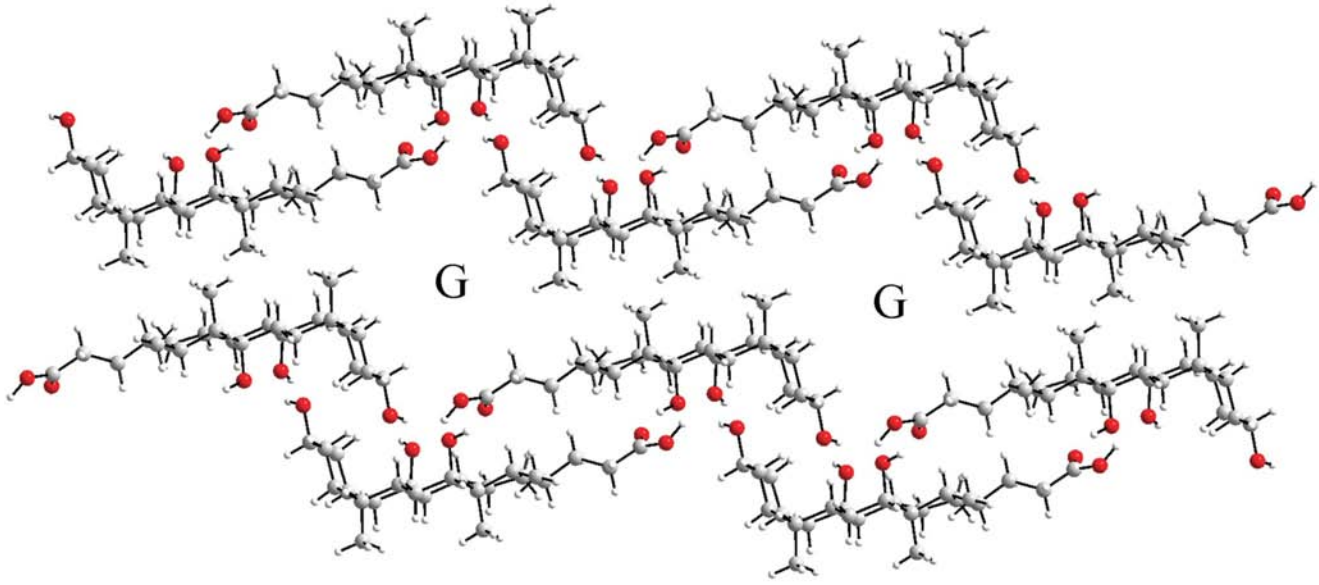


Figure 1
Molecular packing diagram of the layer structure of CA, including the guest molecules G trapped within lipophilic channels.

(IV) was obtained from the 3-keto-7,12-dihydroxy precursor by oxidation with *N*-bromosuccinimide (Fieser & Rajagopalan, 1949). Compound (V) was prepared starting from CA *via* oxidation with Jones' reagent (Bowden *et al.*, 1946).

Single crystals were grown from ethyl acetate. The solutions were allowed to evaporate slowly to obtain X-ray quality crystals. For (IV) two species of crystals, namely (IV-α) and (IV-β), with different aspects, were found within the same crystallization bulk. The two concomitant crystallizing forms were distinguishable as prismatic shaped and transparent crystals for the unsolvated pseudopolymorph (IV-α) and plated, irregular and somewhat opaque crystals for the solvated polymorph (IV-β). The term 'pseudopolymorph' has been reported by Byrn and Bernstein in their respective books (Byrn, 1982; Bernstein, 2002) and recently better defined by Desiraju (2004).

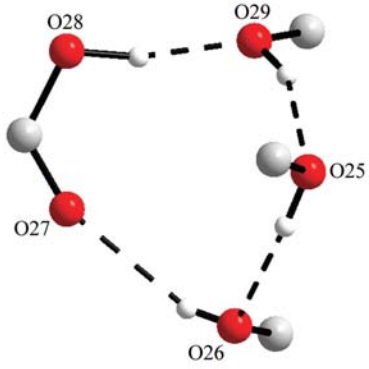


Figure 2
The cyclic $\cdots$O—H$\cdots$O$\cdots$ hydrogen-bonding arrangement formed by CA molecules in CA inclusion compounds.

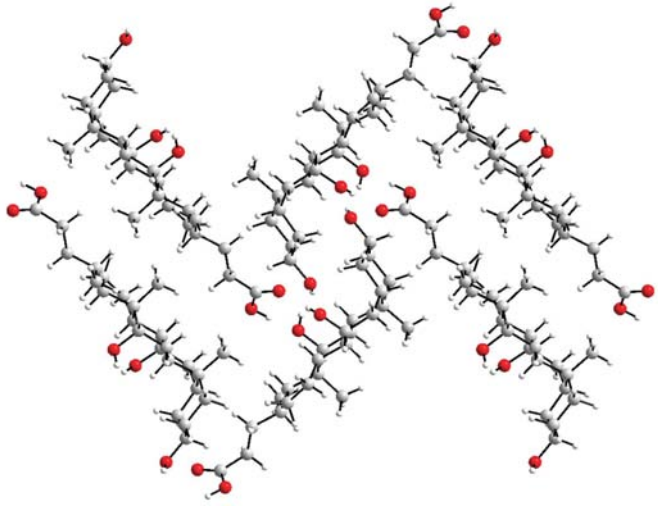


Figure 3
Molecular aggregation in corrugated layers in the structure of CA with no guest molecules (Miki *et al.*, 1990).

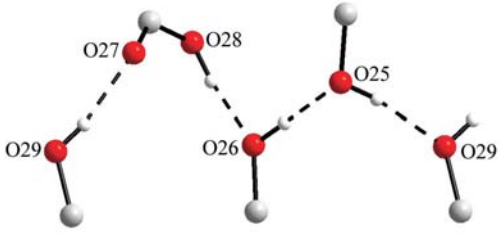


Figure 4
Infinite chain of cooperative $\cdots$O—H$\cdots$O$\cdots$ hydrogen bonds in crystals of CA with no guest molecules.

2.2. Crystal structure determinations

The diffraction data for all the compounds were collected at room temperature using a Nonius Kappa CCD diffractometer with graphite-monochromated Mo $K\alpha$ radiation (λ = 0.7107 Å). Data sets were integrated using the *DENZO-SMN* package (Otwinowski & Minor, 1997) and corrected for Lorentz and polarization effects. The structures were solved by direct methods (*SIR*97; Altomare *et al.*, 1999) and refined using full-matrix least-squares. For (I), (II) and (III) all non-H atoms were refined anisotropically and the C—H hydrogen atoms were included on calculated positions riding on their attached atoms with fixed distances of 0.96 (CH_3), 0.97 (CH_2) or 0.98 Å (CH). All O—H hydrogen atoms were refined isotropically. For (IV-α) and (V) all non-H atoms were refined anisotropically and H atoms isotropically. In (IV-β) the asymmetric unit is built up by two independent molecules displaying different conformations of the carboxylic side chain. Furthermore, molecule *B* shows disorder within the carboxylic group. From the difference-Fourier maps three different positions of the two O atoms could be identified and refined isotropically with fixed occupancies of 0.5:0.3:0.2, respectively. The carboxylic H atoms with partial occupancies were not identified. All other non-H atoms, for both molecules *A* and *B*, were refined anisotropically and C—H hydrogen atoms included on calculated positions riding on their attached atoms with fixed C—H distances, as reported above. The remaining O—H hydrogen atoms were refined isotropically. From the final difference-Fourier maps two small peaks were found within the channels: one in a general position and the other in a special position (0,*y*,0), at a distance of 2.68 Å. They were identified as O atoms of disordered water molecules and refined isotropically with partial occupancies. All calculations were performed using *SHELXL*97 (Sheldrick, 1997), *PARST* (Nardelli, 1995) and *PLATON* (Spek, 1999), as implemented in the *WINGX* (Farrugia, 1999) system of programs. The crystal data and refinement parameters are summarized in Table 1.[1] The hydrogen-bond parameters are given in Table 2, torsion angles and side-chain conformations in Table 3, and the puckering parameters of the skeleton rings in Table 4.

[1] Supplementary data for this paper are available from the IUCr electronic archives (Reference: SN5016). Services for accessing these data are described at the back of the journal.

Table 1
Experimental details.

	(I)	(II)	(III)
Crystal data			
Chemical formula	$C_{24}H_{34}O_5$	$C_{24}H_{34}O_5$	$C_{24}H_{36}O_5$
M_r	406.54	406.54	404.53
Cell setting, space group	Orthorhombic, $P2_12_12_1$	Orthorhombic, $P2_12_12_1$	Monoclinic, $P2_1$
a, b, c (Å)	8.9879 (1), 9.4028 (1), 26.4369 (4)	6.3122 (1), 10.8884 (2), 32.0624 (7)	10.2677 (4), 7.1108 (2), 15.2270 (6)
β (°)	90	90	92.340 (1)
V (Å^3)	2234.22 (5)	2203.64 (7)	1110.82 (7)
Z	4	4	2
D_x (Mg m^{-3})	1.209	1.225	1.209
Radiation type	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$
No. of reflections for cell parameters	3690	2878	2705
θ range (°)	3.8–28.0	3.7–28.0	3.4–27.5
μ (mm^{-1})	0.08	0.08	0.08
Temperature (K)	295	295	295
Crystal form, colour	Prism, colourless	Prism, colourless	Irregular, colourless
Crystal size (mm)	0.42 × 0.35 × 0.28	0.36 × 0.14 × 0.10	0.25 × 0.11 × 0.06
Data collection			
Diffractometer	Nonius Kappa CCD	Nonius Kappa CCD	Nonius Kappa CCD
Data collection method	φ and ω scans	φ and ω scans	φ and ω scans
Absorption correction	None	None	None
No. of measured, independent and observed reflections	24 241, 3049, 2385	13 705, 3006, 2415	14 953, 2721, 2236
Criterion for observed reflections	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$
R_{int}	0.041	0.076	0.039
θ_{max} (°)	28.0	28.0	27.5
Range of h, k, l	$-11 \Rightarrow h \Rightarrow 11$ $-12 \Rightarrow k \Rightarrow 12$ $-34 \Rightarrow l \Rightarrow 34$	$-8 \Rightarrow h \Rightarrow 8$ $-14 \Rightarrow k \Rightarrow 14$ $-41 \Rightarrow l \Rightarrow 42$	$-13 \Rightarrow h \Rightarrow 13$ $-8 \Rightarrow k \Rightarrow 9$ $-19 \Rightarrow l \Rightarrow 19$
Refinement			
Refinement on	F^2	F^2	F^2
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.039, 0.110, 1.04	0.044, 0.120, 1.04	0.041, 0.107, 1.05
No. of reflections	3049	3006	2721
No. of parameters	277	277	273
H-atom treatment	Mixture of independent and constrained	Mixture of independent and constrained	Mixture of independent and constrained
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0534P)^2 + 0.2792P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0556P)^2 + 0.316P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0521P)^2 + 0.1088P]$, where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	<0.0001	<0.0001	<0.0001
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.15, −0.13	0.16, −0.16	0.15, −0.14
Absolute structure	Flack (1983)	Flack (1983)	Flack (1983)
Flack parameter	−3.4 (15)	1.2 (15)	0.2 (14).

	(IV-α)	(IV-β)	(V)
Crystal data			
Chemical formula	$C_{24}H_{36}O_5$	$C_{24}H_{36}O_5{\cdot}0.5H_2O$	$C_{24}H_{36}O_5$
M_r	404.53	413.54	402.51
Cell setting, space group	Orthorhombic, $P2_12_12_1$	Monoclinic, $C2$	Monoclinic, $P2_1$
a, b, c (Å)	8.4953 (1), 12.7060 (2), 20.8011 (3)	26.6049 (4), 7.7044 (1), 22.9126 (3)	12.0863 (3), 6.8301 (2), 13.1153 (4)
β (°)	90	93.424 (1)	101.138 (1)
V (Å^3)	2245.30 (5)	4688.1 (1)	1062.28 (5)
Z	4	8	2
D_x (Mg m^{-3})	1.197	1.172	1.258
Radiation type	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$
No. of reflections for cell parameters	3622	5260	3134
θ range (°)	4.0–30.0	4.2–27.5	3.2–30.0
μ (mm^{-1})	0.08	0.08	0.09
Temperature (K)	295	295	295
Crystal form, colour	Prism, colourless	Irregular, colourless	Prism, colourless
Crystal size (mm)	0.45 × 0.35 × 0.32	0.35 × 0.12 × 0.08	0.40 × 0.26 × 0.12
Data collection			
Diffractometer	Nonius Kappa CCD	Nonius Kappa CCD	Nonius Kappa CCD
Data collection method	φ and ω scans	φ and ω scans	φ and ω scans
Absorption correction	None	None	None

Table 1 (continued)

	(IV-α)	(IV-β)	(V)
No. of measured, independent and observed reflections	26 164, 3664, 3189	26 846, 5683, 4381	16 592, 3336, 2638
Criterion for observed reflections	$I > 2\sigma(I)$	$I > 2\sigma(I)$	$I > 2\sigma(I)$
R_{int}	0.035	0.034	0.030
θ_{max} (°)	30.0	27.5	30.0
Range of h, k, l	$-11 \Rightarrow h \Rightarrow 11$ $-17 \Rightarrow k \Rightarrow 17$ $-29 \Rightarrow l \Rightarrow 29$	$-33 \Rightarrow h \Rightarrow 34$ $-9 \Rightarrow k \Rightarrow 8$ $-29 \Rightarrow l \Rightarrow 29$	$-17 \Rightarrow h \Rightarrow 17$ $-9 \Rightarrow k \Rightarrow 8$ $-18 \Rightarrow l \Rightarrow 18$
Refinement			
Refinement on	F^2	F^2	F^2
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.050, 0.146, 1.06	0.055, 0.166, 1.01	0.038, 0.101, 1.05
No. of reflections	3664	5683	3336
No. of parameters	406	567	397
H-atom treatment	Refined independently	Mixture of independent and constrained refinement	Refined independently
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0967P)^2 + 0.2322P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.1005P)^2 + 1.4815P]$, where $P = (F_o^2 + 2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2) + (0.0503P)^2 + 0.0934P]$, where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	0.009	0.004	0.008
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.45, −0.32	0.35, −0.27	0.20, −0.15
Absolute structure	Flack (1983)	Flack (1983)	Flack (1983)
Flack parameter	−0.3 (15)	1.6 (15)	−0.3 (12)

Computer programs used: *Kappa CCD Server Software* (Nonius, 1997), *DENZO SMN* (Otwinowski & Minor, 1997), *SIR*97 (Altomare *et al.*, 1999), *SHELXL*97 (Sheldrick, 1997), *ORTEP*III (Burnett & Johnson, 1996), *PARST* (Nardelli, 1995), *PLATON* (Spek, 1999).

3. Results and discussion

The structures of oxo-cholic acids display a variety of carboxylic side-chain conformations which can be described using the four torsion angles ψ_1 = C13—C17—C20—C22, ψ_2 = C17—C20—C22—C23, ψ_3 = C20—C22—C23—C24 and ψ_4 = C22—C23—C24—O28H reported in Table 3 and in Fig. 5. All the molecules have in common a similar alicyclic skeleton and, in spite of the presence of sp^2 C atoms of the keto groups, all the six-membered rings *A*, *B* and *C* adopt almost perfect chair conformations and the five-membered rings *D* display similar mixed envelope/twisted conformations (Table 4). Both the flexibility of the carboxylic side chain and the different ratio between hydroxy and oxo groups generate a variety of supramolecular aggregations which are rationalized and discussed in terms of O—H···O cooperative hydrogen-bond networks and C—H···O weaker hydrogen-bond interactions (Desiraju & Steiner, 1999; Castellano, 2004). In general, we have considered the C—H···O interactions where the H···O distance is less than 2.70 Å and C—H···O angle is greater than 130° to be significant.

For each oxo-cholic acid structure the hydrogen-bond patterns were analysed to detect their structural differences and similarities in relation to the number and position of the oxo groups. The CA molecule in the structures of CA inclusion compounds exhibits a perfect match between hydrogen-bond donors and acceptors (Fig. 6). Each hydroxy group acts, at the same time, both as a hydrogen-bond acceptor and donor, and the carboxyl group is involved in two hydrogen bonds with hydroxy groups. The hydrogen-bond pattern undergoes significant changes in crystals of oxo-CA derivatives, giving rise to a variety of three-dimensional aggregations as described over the following sections.

3.1. Structure of (I): 7-oxo-CA

An *ORTEP*III (Burnett & Johnson, 1996) view of (I) is shown in Fig. 7. The oxidation of CA at C7 induces a dramatic variation of hydrogen-bond architecture occurring in CA and its inclusion compounds. The carboxylic side chain preserves a full extended *t t t t* conformation similar to that observed in the *β-trans* host framework of CA inclusion compounds (Nakano *et al.*, 2001). The carboxyl group is still an acceptor of hydrogen bonds from the O26—H hydroxy group, but acts as a hydrogen-bond donor at a different O25—H hydroxy group owing to the oxidation and orientation changes of the oxygen O29 that, in turn, behaves as an acceptor from the O25—H hydroxy group (Fig. 8). This new type of molecular aggregation with different mutual orientations of the molecules prevents the formation of lipophilic and hydrophilic layers. The overall hydrogen-bond scheme forms finite chains, as shown in Fig. 9, rather than cycles or infinite chains. The crystal packing is stabilized by weak C—H···O interactions (Table 2) involving the carbonyl O27 oxygen.

The O28—H···O25 hydrogen bond displays a short O28···O25 distance of 2.681 (3) Å which is similar to those occurring in carboxylic acid structures when the molecules are linked in *catemers* (Leiserowitz, 1976). Accordingly, this strong hydrogen bond could play an essential role in determining the overall architecture of the crystal packing.

3.2. Structure of (II): 12-oxo-CA

An *ORTEP*III view of (II) is shown in Fig. 10. Besides the presence of the C12═O26 keto group, this oxo-CA derivative adopts the unusual *g t t t* conformation of the carboxylic side chain which determines the S-shaped molecular aspect. The

Table 2
O—H···O and C—H···O hydrogen-bond parameters (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
(I)				
O26—H26···O27^{i}	0.85 (3)	2.06 (3)	2.883 (3)	162 (3)
O28—H28···O25^{ii}	1.00 (4)	1.70 (4)	2.681 (3)	168 (4)
O25—H25···O29^{iii}	0.85 (4)	1.90 (4)	2.755 (3)	178 (3)
C2—H2*B*···O27^{i}	0.97	2.64	3.500 (3)	148
C9—H9···O27^{i}	0.98	2.51	3.462 (3)	164
(II)				
O29—H29···O27^{iv}	0.96 (4)	1.91 (4)	2.820 (3)	157 (3)
O25—H25···O29^{i}	0.92 (4)	1.90 (4)	2.780 (3)	159 (3)
O28—H28···O25^{v}	0.92 (5)	1.71 (5)	2.680 (3)	172 (5)
C15—H15*A*···O27^{vi}	0.97	2.54	3.412 (3)	150
C23—H23*B*···O26^{vii}	0.97	2.46	3.401 (3)	163
(III)				
O28—H28···O26^{viii}	0.85 (4)	1.90 (4)	2.730 (2)	168 (3)
O29—H29···O25^{i}	0.99 (4)	1.84 (4)	2.836 (3)	174 (4)
C2—H2*B*···O27^{ix}	0.97	2.36	3.310 (4)	164
C15—H15*B*···O25^{viii}	0.95	2.67	3.584 (4)	157
C23—H23*A*···O28^{x}	0.97	2.64	3.495 (4)	146
(IV-α)				
O26—H26···O29^{xi}	0.84 (4)	2.04 (4)	2.834 (3)	159 (4)
O28—H28···O26^{iv}	0.98 (4)	1.82 (4)	2.726 (3)	152 (4)
C1*A*—H1*A*···O27^{xii}	0.86 (3)	2.70 (3)	3.538 (5)	168 (3)
C19—H19*A*···O25^{ix}	0.94 (4)	2.56 (4)	3.466 (4)	162 (4)
(IV-β)				
O26*A*—H26*A*···O29*A*^{xiii}	0.80 (4)	2.17 (4)	2.927 (5)	159 (4)
O28*A*—H28*A*···O26*B*^{xiv}	1.11 (5)	1.56 (5)	2.606 (4)	154 (4)
O26*B*—H26*B*···O25*B*^{xv}	0.83 (5)	2.04 (5)	2.812 (3)	155 (5)
O28*B*···O27*B*^{xvi}			2.74 [av.]	
C23*B*—H234···O25*A*^{xvii}	0.97	2.54	3.450 (5)	156
C2*A*—H21···O25*A*^{xviii}	0.97	2.67	3.499 (6)	144
C6*A*—H61···O27*B*^{xviii}	0.97	2.36	3.315 (12)	166
C5*A*—H5*A*···O25*A*^{xix}	0.98	2.62	3.378 (6)	134
C2*B*—H24···O25*B*^{xv}	0.97	2.61	3.461 (6)	146
C2*B*—H23···O27*A*^{xx}	0.97	2.66	3.533 (7)	150
C18*B*—H185···O29*B*^{xxi}	0.96	2.44	3.230 (6)	140
C12*B*—H12*B*···O29*B*^{xxi}	0.98	2.66	3.412 (6)	134
(V)				
O28—H28···O25^{xxii}	0.86 (4)	1.90 (4)	2.737 (3)	168 (4)
C19—H19*A*···O27^{xxiii}	0.93 (3)	2.62 (3)	3.497 (3)	156
C5—H5···O27^{xxiii}	0.99 (3)	2.66 (3)	3.569 (3)	152
C2—H2*B*···O27^{xxiv}	1.08 (3)	2.62 (4)	3.614 (5)	152
C4—H4*B*···O29^{xxv}	1.06 (3)	2.55 (3)	3.560 (4)	158
C23—H23*B*···O25^{xxv}	0.88 (4)	2.58 (4)	3.299 (4)	140
C8—H8···O26^{xxi}	0.96 (2)	2.59 (3)	3.415 (4)	145
C18—H18*A*···O27^{xxvi}	1.00 (9)	2.64 (2)	3.600 (3)	162

Symmetry codes: (i) $2-x,\frac{1}{2}+y,\frac{1}{2}-z$; (ii) $2-x,\frac{1}{2}-y,\frac{1}{2}-z$; (iii) $x-\frac{1}{2},\frac{3}{2}-y,-z$; (iv) $\frac{1}{2}+x,\frac{1}{2}-y,1-z$; (v) $\frac{3}{2}-x,2-y,\frac{1}{2}+z$; (vi) $\frac{1}{2}+x,\frac{3}{2}-y,1-z$; (vii) $x-\frac{1}{2},\frac{5}{2}-y,1-z$; (viii) $x-1,y,z$; (ix) $x+1,y,z$: (x) $-x,\frac{1}{2}+y,-z$; (xi) $-x,y-\frac{1}{2},\frac{1}{2}-z$; (xii) $\frac{1}{2}-x,-y,z-\frac{1}{2}$; (xiii) $x,y-1,z$; (xiv) $\frac{1}{2}+x,\frac{1}{2}+y,z$; (xv) $\frac{3}{2}-x,\frac{1}{2}+y,2-z$; (xvi) $1-x,y,1-z$; (xvii) x,y,z; (xviii) $\frac{3}{2}-x,y-\frac{1}{2},1-z$; (xix) $\frac{3}{2}-x,\frac{1}{2}+y,1-z$; (xx) $2-x,y,2-z$; (xxi) $x,y+1,z$; (xxii) $1-x,y-\frac{1}{2},z$; (xxiii) $x,y+1,z-1$; (xxiv) $x,y,z-1$; (xxv) $1-x,y-\frac{1}{2},-z$; (xxvi) $2-x,\frac{1}{2}+y,1-z$.

molecules are still linked head-to-tail by means of strong O28—H···O25 hydrogen bonds, with the short distance of O28···O25 being 2.680 (3) Å, while the carbonyl O27 atom acts as a hydrogen-bond acceptor from the O29—H hydroxy group (Fig. 11). The carboxylic side chains form cooperative cyclic networks built up by three hydrogen bonds, including the carboxylic group as well as O25—H and O29—H hydroxy groups. Both the oxo O26 atom, which is not involved in this network of O—H···O hydrogen bonds, and the carbonyl O27 atom act as acceptors of the weaker C—H···O interactions, from C15—H and C23—H moieties, which contribute to the crystal architecture stability.

Table 3
Selected torsion angles (°) and carboxylic side-chain conformation.

ψ_1 = C13—C17—C20—C22; ψ_2 = C17—C20—C22—C23; ψ_3 = C20—C22—C23—C24; ψ_4 = C22—C23—C24—O28H.

	ψ_1	ψ_2	ψ_3	ψ_4	Conformation
(I)	169.5 (2)	177.5 (2)	169.7 (2)	140.8 (2)	*t t t t*
(II)	89.9 (2)	−162.7 (2)	−170.4 (2)	−163.1 (2)	*g t t t*
(III)	−178.6 (2)	−168.9 (2)	78.0 (3)	173.0 (2)	*t t g t*
(IV-α)	175.6 (2)	60.6 (2)	178.5 (2)	63.4 (3)	*t g t g*
(IV-β)*A*	176.5 (3)	−159.5 (4)	75. 7 (5)	4.7 (6)	*t t g c*
(IV-β)*B*	176.8 (3)	−160.4 (3)	179.3 (3)	–	*t t t* –
(V)	177.4 (2)	-70.6 (3)	161.8 (2)	155.8 (3)	*t g t t*

3.3. Structure of (III): 3,12-dioxo-CA

An *ORTEP*III view of (III) is shown in Fig. 12. The number of intermolecular O—H···O hydrogen bonds significantly decreases because of the presence of two (C3═O25 and C12═O26) keto groups. Each oxygen is involved in only one O—H···O hydrogen bond, except the carbonyl O27 oxygen which only accepts a weaker C—H···O interaction (Fig. 13). The molecules are interlinked by simple translation through a strong O28—H···O26 interaction and related by a 2_1 axis through O29—H···O25. Both these hydrogen bonds are independent and are not included in linear or cyclic networks. The carboxylic side chain adopts a *t t g t* conformation with the torsion angle ψ_3 in a *gauche* orientation. Owing to the lack of other strong hydrogen-bond donors, a better packing mode is achieved by means of further softer C—H···O interactions from C15—H, C2—H and C23—H moieties at O25, O27 and O28 O atoms, respectively.

3.4. Structure of (IV-α): 3,7-dioxo-CA

An *ORTEP*III view of (IV-α) [the unsolvated pseudopolymorphic form of (IV)] is shown in Fig. 14. The mutual exchange of oxo/hydroxy groups between the C12 and C7 sites generates a new three-dimensional hydrogen-bond network. The molecules are linked in chains by an analogous O28—H···O26 hydrogen bond, albeit around a 2_1 screw axis rather than using a simple crystallographic translation, as observed in (III). This interaction is made possible by the peculiar *t g t g* conformation of the carboxylic side chain. The oxo O29 atom acts as a hydrogen-bond acceptor from the O26—H hydroxy group through a further 2_1 axis. The hydrogen-bond scheme displayed in Fig. 15 shows that O26 is involved in two hydrogen bonds, while the O25 and O27 atoms do not participate in the O—H···O network as they are acceptors of the softer C—H···O interactions from C19—H and C1—H moieties, respectively.

3.5. Structure of (IV-β): 3,7-dioxo-CA

The asymmetric unit of (IV-β) [the solvated pseudopolymorphic form of (IV)] is built up by two independent molecules whose *ORTEP*III views are shown in Figs. 16(*a*) and (*b*). These molecules differ in their carboxylic side-chain conformation, which is folded for molecule *A* and extended for molecule *B*. The carboxyl group in molecule *A* adopts an unusual *cis* orientation, as shown by the ψ_4 torsion angle value of 4.7 (6)°, while in molecule *B* the carboxyl group is highly disordered, displaying three main conformations. The two independent molecules exhibit very different hydrogen-bond systems (Figs. 17*a* and *b*). Molecule *A* shows a somewhat similar arrangement to that of (IV-α). Nevertheless, the side chain adopts an unusual *t t g c* conformation to point the O28*A*—H hydroxy H atom at the O26*B* hydroxy O atom of molecule *B*. The O26*A*—H hydroxy and O29 oxo groups link the molecules in chains by translation along the *b* axis. The *B* molecules are connected in dimers around a twofold crystallographic axis by means of hydrogen bonds between the disordered carboxyl groups. The O26*B*—H hydroxy group is involved in two hydrogen bonds with the O28*A*—H hydroxy and O25*B* oxo groups. The O25*A* and O29*B* atoms only accept softer C—H···O hydrogen bonds. The molecules form pseudo-layers (Fig. 18) interlinked by finite chains of O28*A*—H···O26*B*—H···O25*B* hydrogen bonds.

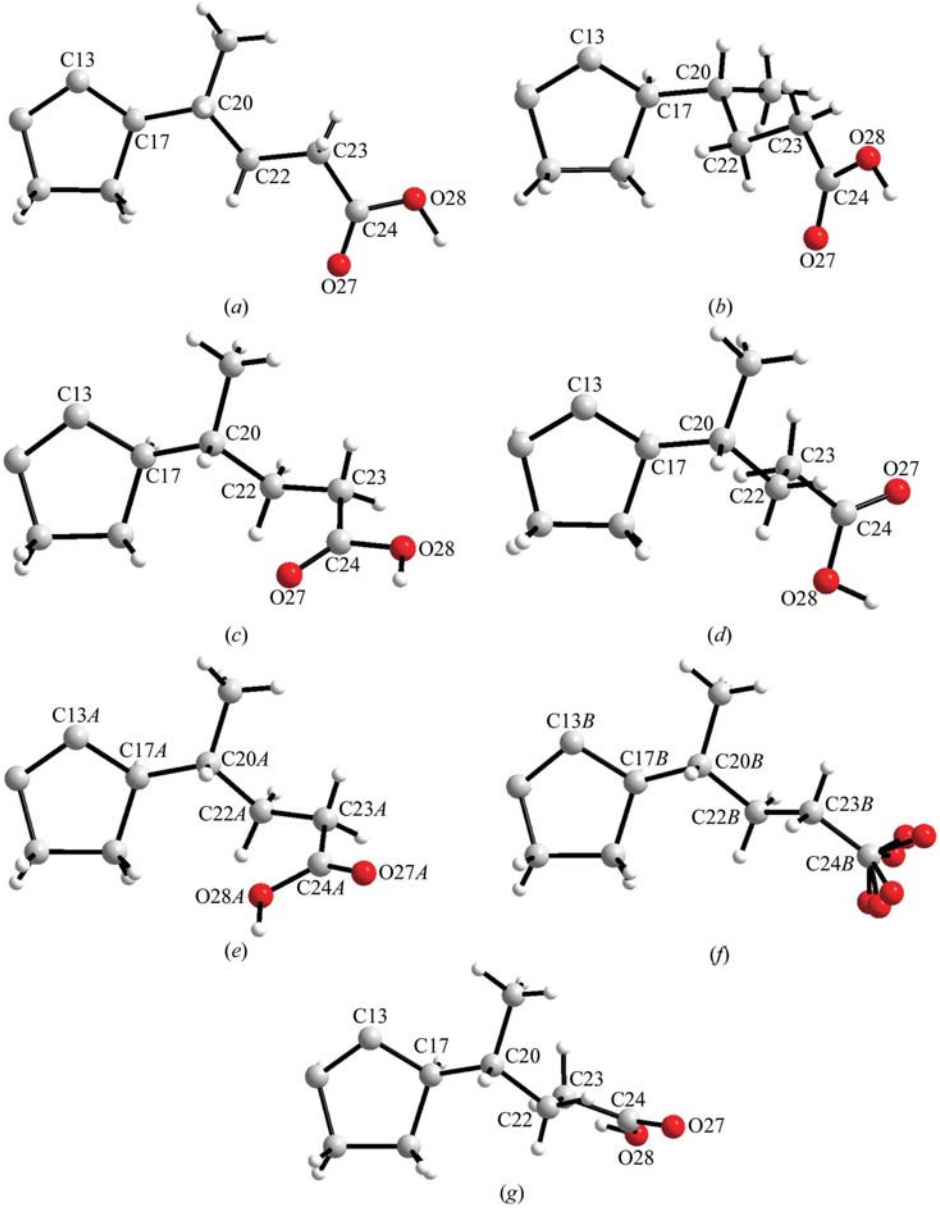


Figure 5
The carboxylic side-chain conformations for the molecules of oxo-cholic acid derivatives in the six determined structures. The fragments are projected on the mean planes of the five membered *D* rings of the alicyclic skeletons. Each side-chain conformation is defined by the four torsion angles: ψ_1 = C13—C17—C20—C22, ψ_2 = C17—C20—C22—C23, ψ_3 = C20—C22—C23—C24 and ψ_4 = C22—C23—C24—O28H and using the symbols: *t* = *trans*, *g* = *gauche* and *c* = *cis*. (*a*) (I), conformation = *t t t t*; (*b*) (II), conformation = *g t t t*; (*c*) (III), conformation = *t t g t*; (*d*) (IV-α), conformation = *t g t g*; (*e*) (IV-β)*A*, conformation = *t t g c*; (*f*) (IV-β)*B*, conformation = *t t t* – (because of the disorder, the torsion angle ψ_4 is not defined); (*g*) (V), conformation = *t g t t*.

The complete packing arrangement (Fig. 18) resembles those characterizing the CA inclusion compounds (Fig. 1). Although it is impossible to identify separated lipophilic and hydrophilic layers, however, around the 0,*y*,0 axis and the symmetrically related special positions small channels can be observed where disordered water molecules are trapped. The volume of the host cavity per unit cell has been calculated to be 467.7 Å^3, which corresponds to a volume *per* guest molecule of 116.9 Å^3, sufficient to include small solvent molecules. This volume can be compared with that of 150–200 Å^3 observed in crystals of inclusion compounds of CA with monosubstituted benzenes (Miyata *et al.*, 2004).

3.6. Structure of (V): 3,7, 12-trioxo-CA

Compound (V) is the polymorphic β form of the trioxo-cholic acid or dehydrocholic acid (DHA).

An *ORTEP*III view of (V) is shown in Fig. 19. The molecules are linked head-to-tail by means of O28—H···O25 hydrogen bonds around 2_1 axes (see Fig. 20). The carboxylic side chain adopts a folded *t g t t* conformation and the O—H bond of the carboxyl group

Table 4
Puckering parameters (Å, °; Cremer & Pople, 1975) and ring conformation.

	(I)	(II)	(III)	(IV-α)	(IV-β)*A*	(IV- β)*B*	(V)
Ring							
A = C1—C2—C3—C4—C5—C10							
Q	0.553 (2)	0.546 (3)	0.546 (3)	0.532 (2)	0.533 (3)	0.538 (4)	0.523 (3)
φ_2	150 (2)	−93 (7)	−110 (3)	132 (3)	153 (2)	143 (5)	149 (2)
θ_2	174.6 (2)	177.8 (2)	174.6 (3)	174.1 (2)	171.6 (4)	175.6 (4)	170.8 (3)
Conformation	$^4C_1$	$^4C_1$	$^4C_1$	$^4C_1$	$^4C_1$	$^4C_1$	$^4C_1$
B = C5—C6—C7—C8—C9—C10							
Q	0.581 (2)	0.566 (2)	0.577 (2)	0.587 (2)	0.547 (4)	0.573 (4)	0.574 (2)
φ_2	−42 (18)	−104 (2)	−138 (2)	142 (10)	−85 (4)	67 (8)	−130 (4)
θ_2	0.8 (2)	7.6 (3)	8.7 (3)	1.4 (2)	5.9 (4)	2.8 (4)	3.1 (2)
Conformation	$^1C_4$	$^1C_4$	$^1C_4$	$^1C_4$	$^1C_4$	$^1C_4$	$^1C_4$
C = C8—C9—C11—C12—C13—C14							
Q	0.570 (2)	0.555 (2)	0.591 (2)	0.576 (2)	0.568 (4)	0.576 (3)	0.598 (2)
φ_2	−106 (3)	−84 (1)	−104 (1)	−92 (2)	−122 (5)	−52 (5)	−102 (1)
φ_2	4.5 (2)	16.0 (2)	18.2 (2)	5.9 (2)	3.9 (4)	4.5 (4)	11.6 (2)
Conformation	$^1C_4$	$^1C_4$	$^1C_4$	$^1C_4$	$^1C_4$	$^1C_4$	$^1C_4$
D = C13—C14—C15—C16—C17							
q_2	0.474 (2)	0.445 (2)	0.430 (2)	0.462 (2)	0.476 (4)	0.464 (4)	0.450 (2)
φ_2	−173.5 (3)	−152.2 (3)	−168.3 (4)	−171.1 (3)	−169.2 (5)	−166.2 (5)	−170.6 (4)
Conformation	$^2T_1/E_1$	$^2E/^2T_1$	$^2T_1/E_1$	$^2T_1/E_1$	$^2T_1/E_1$	$^2T_1/E_1$	$^2T_1/E_1$

exhibits an unusual *antiplanar* conformation, while the other oxo-cholic derivatives adopt the more common *synplanar* conformation observed in carboxylic acid structures (Leiserowitz, 1976). Owing to the presence of many oxo groups that are potential hydrogen-bond acceptors, with respect to only one O—H donor, the crystal packing is stabilized by a number of weak C—H···O hydrogen bonds, as listed in Table 2. For instance, the carboxylic O27 atom is an acceptor of four C—H···O interactions donated by three different molecules.

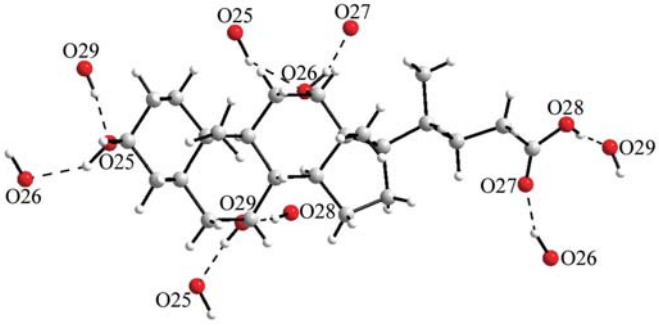


Figure 6
The O—H···O hydrogen-bond framework around the molecule of cholic acid in crystal structures of cholic acid inclusion compounds.

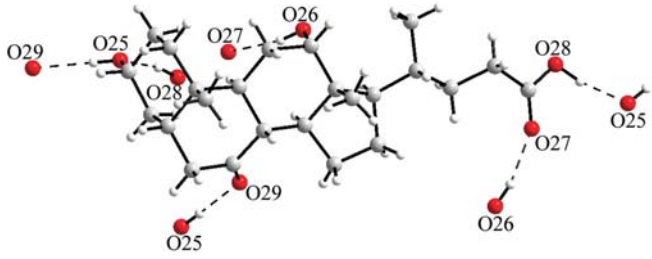


Figure 8
The O—H···O hydrogen-bond framework around the 7-oxo-cholic acid derivative in the crystal structure of (I).

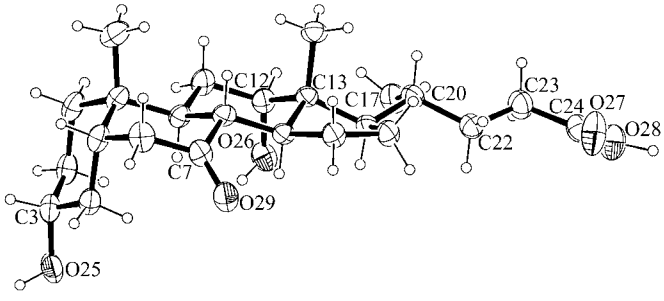


Figure 7
*ORTEP*III view of (I), 7-oxo-CA, showing the displacement ellipsoids at 30% probability.

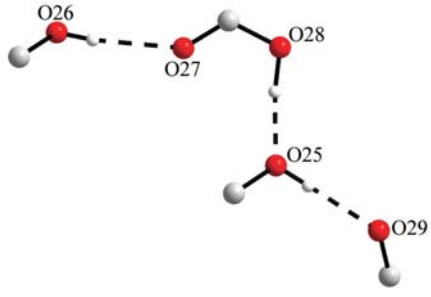


Figure 9
The hydrogen-bonding scheme which forms finite chains in the crystal packing of (I).

The structure of the polymorphic α form of (V) (recently published by Bertolasi *et al.*, 2002) displays a packing where two independent crystallographic molecules having the different side-chain conformations *t t g t* and *t t t t* are linked in dimers by means of hydrogen bonds between the carboxyl groups.

Among the compounds reported the DHA acid is the unique oxo-CA which forms inclusion compounds. We have found that this derivative is particularly efficient in the optical resolution of aryl methyl sulfoxides (Fantin *et al.*, 2000*b*) and cyclic amides (Fantin *et al.*, 2003) with enantiomeric excesses up to 98%. The crystal structure, where DHA includes the enantioselective *R*-(+)-methyl-*p*-tolyl-sulfoxide, does not display channels as in CA. The molecules of sulfoxide are accommodated in between the carboxylic groups, thus forming intercalated layers (Bertolasi *et al.*, 2002).

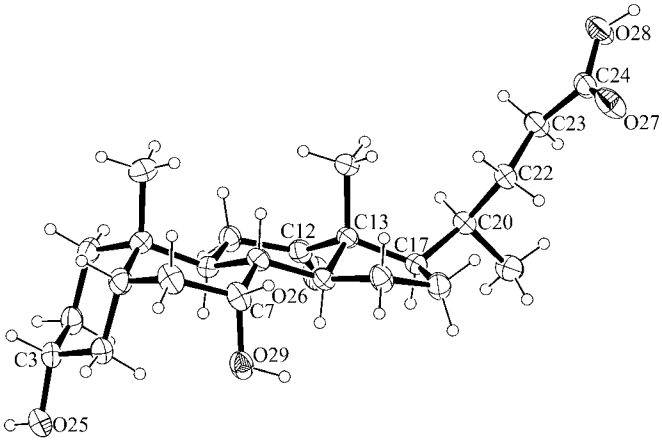


Figure 10
*ORTEP*III view of (II), 12-oxo-CA, showing the displacement ellipsoids at 30% probability.

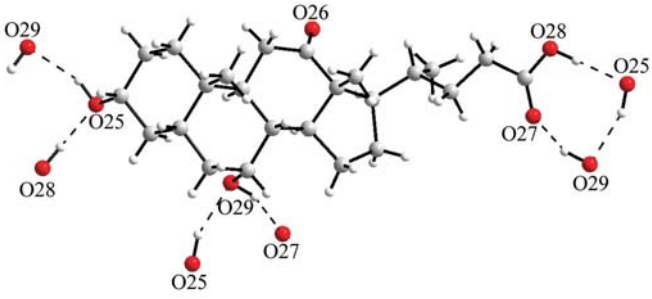


Figure 11
The O—H···O hydrogen-bond framework around 12-oxo-cholic acid in the crystal structure of (II).

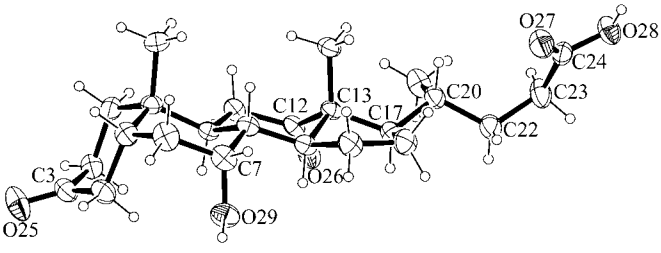


Figure 12
*ORTEP*III view of (III), 3,12-dioxo-CA, showing the displacement ellipsoids at 30% probability.

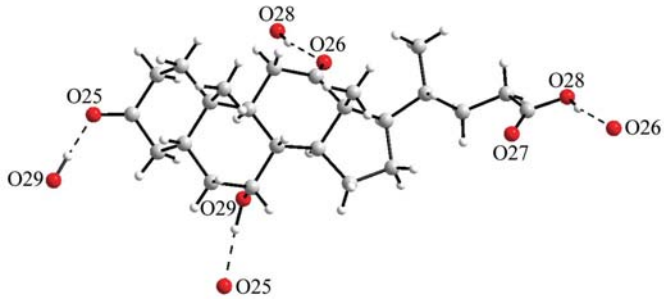


Figure 13
The O—H···O hydrogen-bond framework around 3,12-dioxo-cholic acid in the crystal structure of (III).

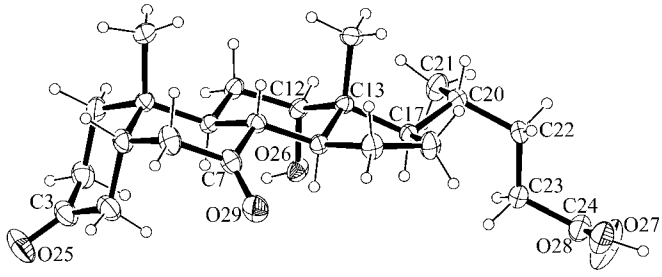


Figure 14
*ORTEP*III view of (IV-α), 3,7-dioxo-CA, showing the displacement ellipsoids at 30% probability.

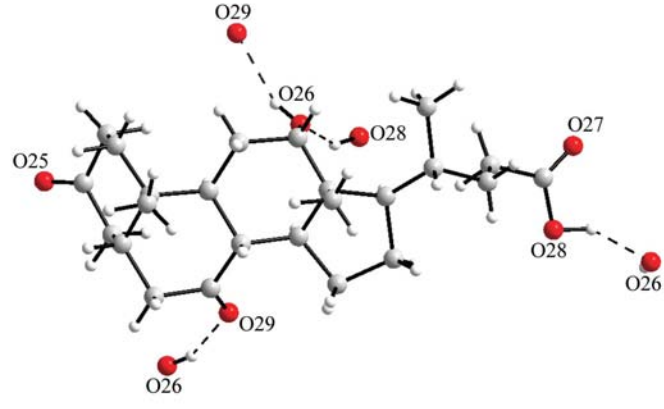


Figure 15
The O—H···O hydrogen-bond framework around 3,7-dioxo-cholic acid in the crystal structure of (IV-α).

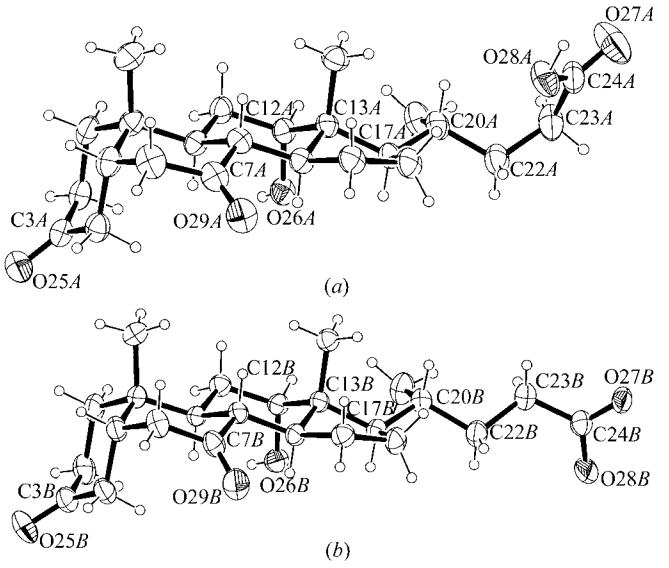


Figure 16
(*a*) *ORTEP*III view of (IV-β), 3,7-dioxo-CA (molecule *A*), showing the displacement ellipsoids at 30% probability. (*b*) *ORTEP*III view of (IV-β), 3,7-dioxo-CA (molecule *B*), showing the displacement ellipsoids at 30% probability. Among the three orientations of the carboxylic group, only the orientation with the greatest occupancy is shown.

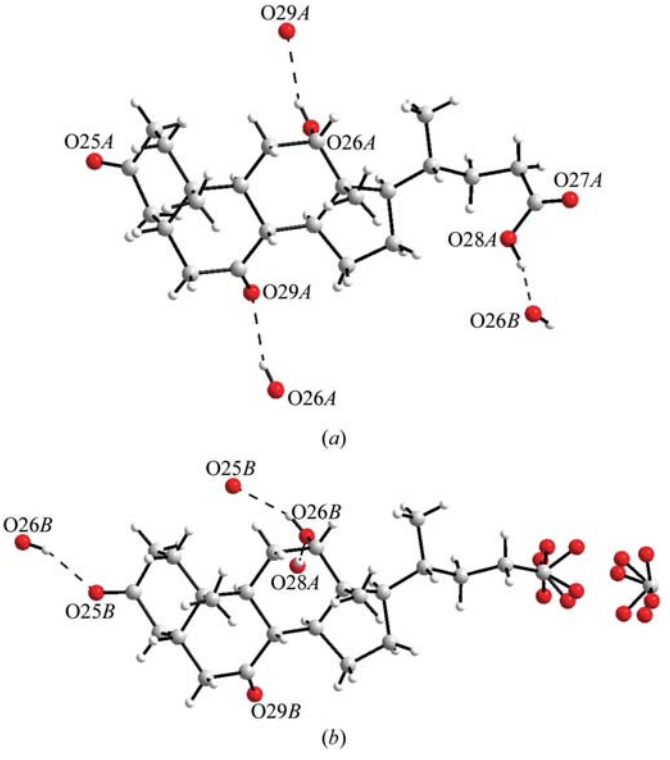


Figure 17
(*a*) The O—H···O hydrogen-bond framework around molecule *A* of 3,7-dioxo-cholic acid in the crystal structure of the solvated pseudopolymorphic form (IV-β). (*b*) The O—H···O hydrogen-bond framework around molecule *B* of 3,7-dioxo-cholic acid in the crystal structure of the solvated pseudopolymorphic form (IV-β).

4. Conclusions

The systematic structural study on the supramolecular assemblies of a series of oxo-cholic acid derivatives has been reported. The oxo groups that replace the hydroxy groups and the conformational variations of the carboxylic side chain induce dramatical changes in the donor–acceptor relationships among hydrogen-bonding groups. The flexibility of the carboxylic side chain and the ability of the O—H carboxyl group to form the strongest O—H···O hydrogen bonds are the driving forces to obtain an efficient network of hydrogen bonds which tends to involve all the available oxo, hydroxy and carbonyl groups. Accordingly, the observed structural aggregations display a large variety of hydrogen-bonding supramolecular architectures which include a number of C—H···O softer interactions useful to stabilize the structural motifs.

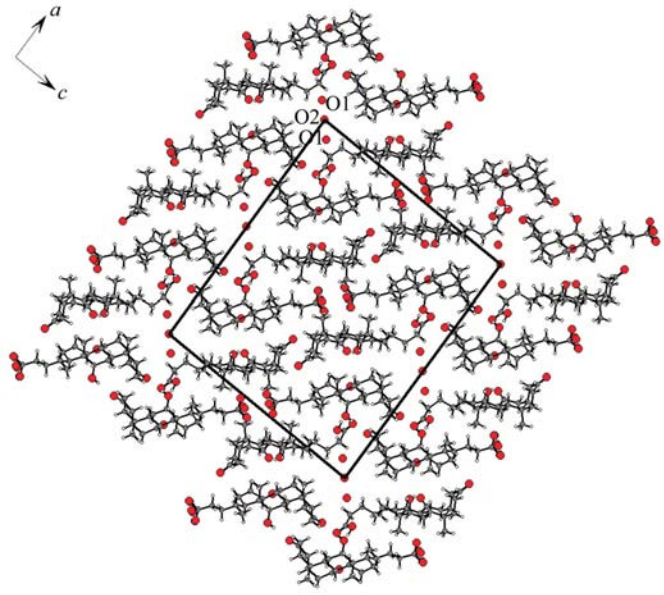


Figure 18
The unit cell of (IV-β) as viewed down the crystallographic *b* axis, showing the pseudo-layers and the channels containing disordered water molecules.

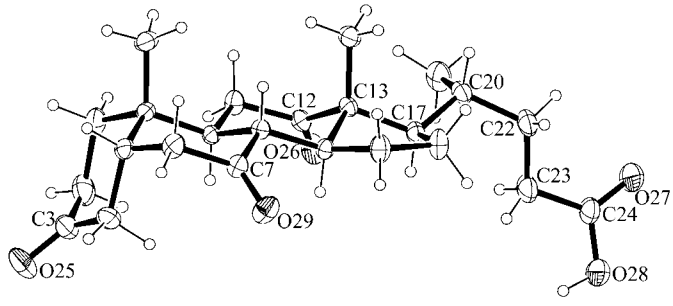


Figure 19
*ORTEP*III view of (V), 3,7, 12-trioxo-CA, showing the displacement ellipsoids at 30% probability.

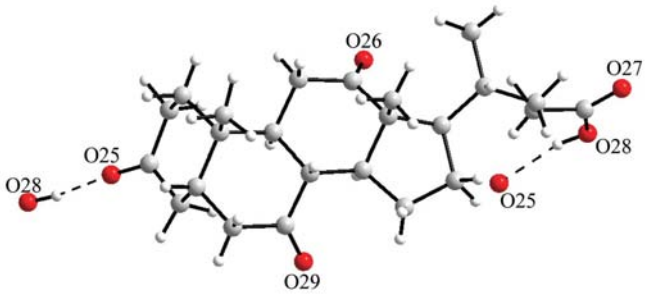


Figure 20
O—H···O hydrogen-bond framework around 3,7,12-trioxo-cholic acid in the crystal structure of (V).

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