Crystal Structure and Multiphase Decomposition of a Novel Cholic Acid Inclusion Compound with Mixed Guests

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The crystal structure of a unique cholic acid inclusion compound with acetone and water guests exhibiting extensive hydrogen bonding is reported and the phases formed during decomposition identified by thermal analysis and X-ray powder diffraction.

Cholic acid (CA, 3α,7α,12α-trihydroxy-5β-cholan-24-oic acid), exhibits inclusion capacity for a wide range of guest molecules.[1] Single crystal structure analyses of cholic acid with small alcohol guest molecules such as methanol,[2] ethanol[3] and propanol[2] as well as those of the mono-[4] and hemi-hydrates[5] reveal extensively hydrogen-bonded structures. However, the majority of cholic acid inclusion compounds crystallise as infinite, puckered host bilayers which pack together to form channels propagating in the [010] direction in which guests are accommodated. Such channel structures are known with diverse guests such as acetophenone,[6] aniline, nitrobenzene,[7] γ-valerolactone,[8] various aliphatic esters[9] and others. These inclusion compounds typically exhibit no short range host–guest interactions with all host hydroxy groups being involved in host–host hydrogen bonding.

We now report the structure† and thermal analysis of the complex formed by CA with one acetone and three water molecules. This structure (Fig. 1) is extensively hydrogen bonded with host–host, host–guest and guest–guest hydrogen bonding resulting in a packing arrangement unique amongst CA structures. The CA•acetone•3H_2O compound collapses under heating, with partial guest loss, to a phase different from that of the host alone. XRD and thermal analysis were used to identify this phase.

The packing diagram of the compound viewed down [010] is presented as Fig. 2. Instead of the characteristic pleated bilayers packed to form channels bounded by the steroid A ring and side chain which contain guests with no short range host–guest interactions as seen in the majority of CA inclusion compound structures, this structure contains extensive host–host, host–guest and guest–guest hydrogen bonding. While there still exist infinite puckered bilayers which propagate in the *b* direction these do not pack leaving spaces between (as in the channel type structures), but instead the guest atoms form a complex hydrogen bonded network with the host and other guests.

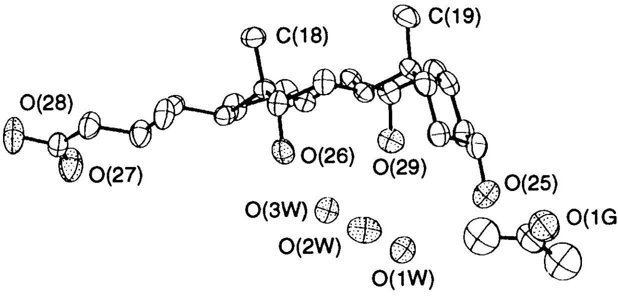

Fig. 1 Ortep plot of CA•acetone•3H_2O with 30% enclosure ellipsoids; O atoms are speckled

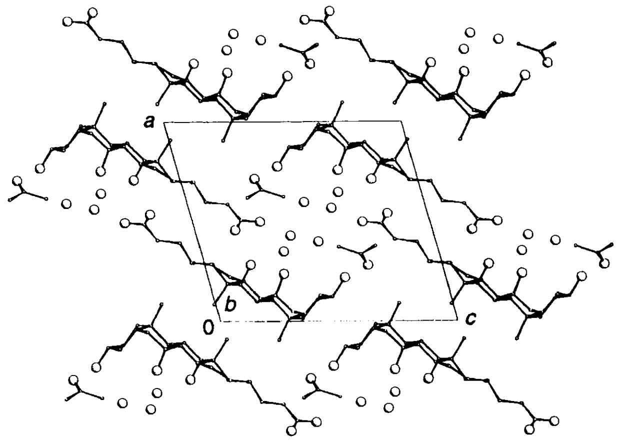

Fig. 2 Packing diagram of CA•acetone•3H_2O viewed down [010]

There are ten unique hydrogen bonds in the asymmetric unit involving all potentially hydrogen-bonded groups. These are illustrated in Fig. 3. O•••O Distances, bond lengths and hydrogen bond angles are listed in Table 1. These ten unique hydrogen bonds translated along the screw axis at $\frac{1}{2},y,\frac{1}{2}$ involve all OH groups of the steroid host molecule and all guests and so form the 'glue' which holds the bilayers together. All host hydroxy oxygen atoms except O(28) act as hydrogen bond acceptors. O(1W) and O(2W) act as donors and receptors for two hydrogen bonds each whilst O(3W) acts as a receptor for only one hydrogen bond from O(1W) but donates two. The acetone guest molecule is held in the hydrogen bond network by a hydrogen bond from O(25) of the host.

Rising temperature TG of the inclusion compound reflects changes in the rate of guest loss indicated by inflection points in the guest loss curve. These are reflected in the rising temperature DSC trace as a number of discrete endotherms. In an attempt to

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† *Crystal data.* $C_{24}H_{40}O_5{\cdot}C_3H_6O{\cdot}3H_2O$, M_r = 520.70, monoclinic, space group $P2_1$, a = 13.111(3), b = 7.759(2), c = 14.893(3) Å, β = 105.70(2)°, V = 1458(1) Å^3, Z = 2, D_c = 1.186 g cm^{-3}, crystal size = 0.45 × 0.45 × 0.35 mm. Intensity data were collected at 294 K on an Enraf–Nonius CAD4 diffractometer using Mo-Kα (λ = 0.7107 Å) radiation to θ_{max} = 25°; 2885 unique reflections were collected. The structure was solved using the program SHELX-86[10] and refined using the program SHELX-76.[11] Final R_w for 2327 reflections with $I_{rel} > 2\sigma(I_{rel})$ = 0.0576 with $w = [\sigma^2 F + 0.0041\,39|F_o|^2]^{-1}$. Residual electron density (max, min) = 0.41, −0.24 e Å^{-3}. All non-hydrogen atoms except those of the acetone methyl groups were refined anisotropically. Hydroxy and water protons were located in electron density difference maps and refined with bond length restraints, the O–H distance being inferred from O••• O distances after Olovson and Jönson[12] while all other hydrogen atoms were placed in calculated positions. Bond lengths and angles for the steroid backbone were similar to those found in other structures and the torsion angles of the side-chain indicate the extended conformation. Anisotropic displacement parameters indicate relatively large thermal motion of the side-chain and guest molecules as indicated in Fig. 1. Atomic numbering conforms to standard steroid usage. Atomic coordinates, thermal parameters, bond lengths, bond angles and torsion angles have been deposited at the Cambridge Crystallographic Data Centre (for details see 'Instructions for Authors, 1994', *J. Chem. Soc., Perkin Trans. 2*, issue 1).

Table 1 Hydrogen bonding distances and angles

	Bond	O···O/Å	O–H/Å	H···O/Å	O–H···O/°
1	O(25)–H(25)···O(1GA)	2.925(8)	0.95(3)	2.01(3)	159(2)
2	O(1W)–H(11W)···O(25)	2.894(6)	0.96(6)	2.00(6)	154(5)
3	O(3W)–H(23W)···O(1W)	2.931(8)	0.96(5)	1.99(5)	168(4)
4	O(26)–H(26)···O(27)^b	2.733(6)	0.97(7)	1.93(8)	139(6)
5	O(2W)–H(12W)···O(26)	2.676(6)	0.98(5)	1.73(5)	161(6)
6	O(28)^a–H(28)···O(2W)^c	2.740(6)	0.97(10)	1.79(9)	165(8)
7	O(1W)–H(21W)···O(3W)	2.792(6)	0.96(4)	1.84(4)	173(4)
8	O(3W)–H(13W)···O(29)	2.844(6)	0.96(5)	1.93(6)	160(5)
9	O(29)^b–H(29)^b···O(2W)^c	2.761(7)	0.96(3)	1.83(3)	163(3)
10	O(2W)–H(22W)···O(1W)	2.772(6)	0.96(5)	1.82(5)	172(5)

^{a} $x, y, z + 1$. ^{b} $-x + 1, y - \frac{1}{2}, -z + 1$. ^{c} $-x + 1, y + \frac{1}{2}, -z + 1$.

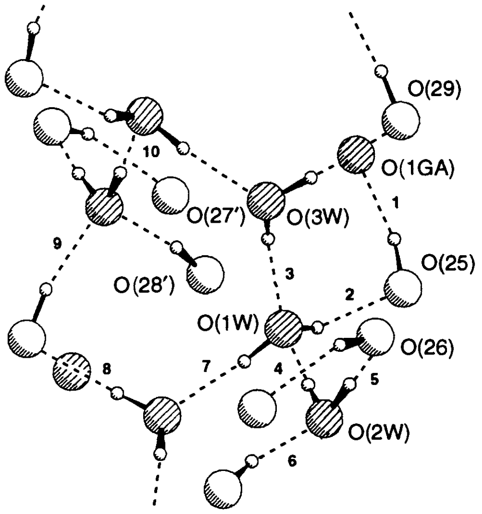

Fig. 3 Hydrogen bonding system viewed normal to [010]; unique hydrogen bonds are indicated by bold numbers and acetone and water oxygen atoms are striped

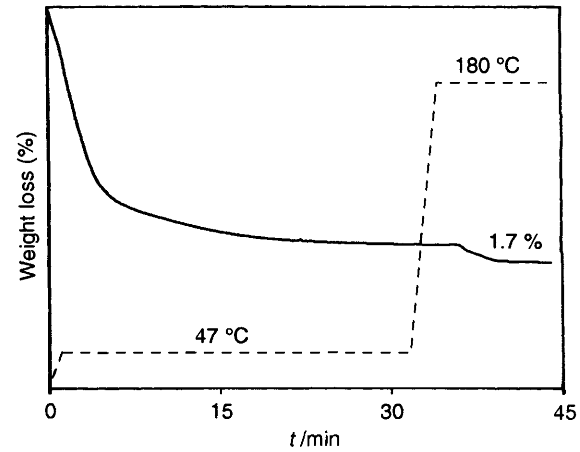

Fig. 4 Programmed TG trace with temperature profile indicated as a dashed line

elucidate the changes occurring we subjected the complex to programmed TG. From a starting temperature of 30 °C the temperature was ramped to 47 °C at 20 °C min^{-1} and held at this temperature for 30 min then ramped to 180 °C at 40 °C min^{-1} and held for 10 min. Separation of two distinct guest loss events was achieved as is illustrated in Fig. 4. Although the first step was difficult to measure, as the crushed compound begins to lose mass immediately upon removal from the mother liquor, the second loss corresponded to 1.7% of the mass of the original compound. This mass % corresponds to the loss of one water molecule per two CA•acetone•$3H_2O$ units or in other words to the existence of 2CA•H_2O units remaining after partial guest loss.

Analysis of rising temperature continuous powder XRD* photographs indicates the existence of at least one stable phase different from both the initial inclusion complex phase and from the final CA(α) phase. This stable phase produced a pattern indistinguishable from that obtained from crystals of the hemihydrate.

To test the assertion that CA•acetone•$3H_2O$ decomposes to the hemihydrate structure, XRD patterns were recorded for hemihydrate crystals (easily grown from a number of wet solvents), and for the compound remaining after heating of the inclusion compound to 47 °C for 30 min. It proved impossible to obtain the powder traces of the undesorbed CA•acetone•$3H_2O$ complex due to rapid desorption of guest during grinding and spectral measurement and the calculated pattern generated using the program LAZYPULVERIX[14] modified to produce summed Gaussian curves was used for comparison.

XRD patterns of the phase obtained after partially drying the complex and that of the hemihydrate are analogous and clearly different to those of either the CA(α) form or the inclusion complex. This, combined with the stoichiometry derived from the measured weight loss for this phase, indicates that CA•acetone•$3H_2O$ decomposes first to the hemihydrate and only then to the CA(α) form.

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* The continuous XRD pattern of the inclusion compound was recorded under heating at a constant rate using a modified Weissenberg camera after Boeyens *et al.*[13] Decoupling sample and camera movement allowed for continuous photographic recording of the XRD pattern while the sample was heated. Crushed samples were mounted with mother liquor in Lindemann tubes which were incompletely sealed to allow escape of guest vapour and prevent pressure build-up. Samples were heated over the range 27–127 °C over a period of 6 h with constant temperature monitoring and the XRD pattern recorded with lateral film movement of 0.3 mm min^{-1}.

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Paper 4/02148G
Received 11*th April* 1994
Accepted 11*th May* 1994