# Structure and van der Waals Energy Study of the Palmitic Acid–Choleic Acid Complex

By V. M. Coiro

*Laboratorio di Strutturistica Chimica 'Giordano Giacomello' CNR, Area della Ricerca, CP 10,*
*00016 Monterotondo Stazione, Roma, Italy*

and A. D'Andrea and E. Giglio

*Istituto di Chimica-fisica, Università di Roma, 00185 Roma, Italy*

## Abstract

The crystals are orthorhombic, space group $P2_12_12_1$, $a = 26.020$ (4), $b = 13.543$ (2), $c = 7.268$ (1) Å and the structure has been refined to an $R$ of 0.11 and $R_w$ of 0.16 for 2352 observed data with $I > \sigma(I)$. The packing is characterized by an assembly of bilayers similar to that of other orthorhombic phases. The shape of the canals, in which the palmitic acid is accommodated, differs slightly from that in the acetic acid–choleic acid complex. The guest molecules, which are probably arranged in four statistical orientations, run along $c$ in a *trans*-planar conformation and occupy approximately three unit cells. Potential-energy calculations allowed the location of the occluded molecules and suggest a deoxycholic acid:palmitic acid:ethanol ratio of 8:1:1.

## Introduction

$3\alpha,12\alpha$-Dihydroxy-$5\beta$-cholan-24-oic acid (deoxycholic acid, DCA) crystallizes in orthorhombic, hexagonal and tetragonal phases (Candeloro De Sanctis & Giglio, 1979, and references therein) forming canal complexes with a great variety of molecules. The orthorhombic phases, which are the most important as clathrating agents, are characterized by pleated antiparallel bilayers of DCA stabilized by an efficient scheme of hydrogen bonding which is nearly the same in all the choleic acids so far studied. The mutual positions along $b$ of the bilayers, running perpendicular to $a$, and their separation along $a$ control the size and shape of the canals, which have hydrophobic interior surfaces and in which guest molecules (preferably non-polar) can be accommodated.

Since the DCA inclusion compounds may be suitable for many applications, including polymerization and photochemical reactions as well as the transport of drugs (which may become gastric-juice resistant and may have a delayed-release action), we are interested in establishing the shapes and sizes of the obtainable cavities and the nature and the strength of the interactions between host and guest molecules in order to predict which molecules can be occluded.

One of the most intensely investigated series of choleic acids is that formed by DCA combined with fatty acids. The stoichiometries of these compounds are a puzzle. In other channel-type compounds the cavities are continuously filled with guest molecules and the ratios of host to guest molecules can assume non-integral values. In contrast, in the choleic acids the ratio DCA/guest has been found to be 1, 2, 4, 6 or 8 (Wieland & Sorge, 1916; Sobotka & Goldberg, 1932; Rheinboldt, Pieper & Zervas, 1927; Rheinboldt, Flume & König, 1929). Thus, this stoichiometry implies in many cases canals with empty spaces and does not explain how fatty acids with more than 20 C atoms can satisfy a DCA/guest ratio of 8.

In order to throw light on this area we have undertaken a structural study of the palmitic acid–choleic acid complex (DCAPAL) for which a DCA/guest ratio of 8 was determined. Since the palmitic acid can completely occupy three cells and a small portion of a fourth one along $c$, it was considered interesting to verify the findings of Giacomello & Bianchi (1943) who recognized the occurrence of ethanol molecules in some choleic acids when crystallized from this solvent.

## Experimental

The title compound was crystallized at room temperature firstly from absolute ethanol and subsequently from acetone by slow evaporation. Crystal data are collected in Table 1.

A colourless prism elongated along $c$, with a maximum dimension of 0.8 mm, was chosen to determine the cell constants from a least-squares refinement performed on 14 reflections and to collect

Table 1. *Crystal data of DCAPAL for a DCA:palmitic acid:ethanol ratio of* 8:1:1

$3\alpha,12\alpha$-Dihydroxy-$5\beta$-cholan-24-oic acid, $C_{24}H_{40}O_4$, FW 392·58
Palmitic acid, $C_{16}H_{32}O_2$, FW 256·43
Ethanol, $C_2H_6O$, FW 46·07
Systematic absences: $h00$, $h$ odd; $0k0$, $k$ odd; $00l$, $l$ odd
Orthorhombic, space group $P2_12_12_1$
$Z = 4$, $F(000) = 1077$
$a = 26\cdot020$ (4), $b = 13\cdot543$ (2), $c = 7\cdot268$ (1) Å
$V = 2561\cdot2$ Å$^3$, $\lambda$(Mo $K\alpha$) $= 0\cdot71069$ Å
$D_m = 1\cdot12$, $D_x = 1\cdot12$ Mg m$^{-3}$
$\mu$(Mo $K\alpha$) $= 4\cdot8$ mm$^{-1}$
M.p. $= 456$ K

intensities up to $2\theta = 55°$ on a Syntex $P2_1$ automated diffractometer with graphite-monochromatized Mo $K\alpha$ radiation. The data were recorded by the $\omega$-scan mode at a scan rate within the range 0·5 to 29·3° min$^{-1}$, depending on the peak intensity, with a scan width of 0·8°. Three reflections, selected for orientation control and measured every 100 reflections, remained essentially constant throughout the run. Backgrounds were estimated by stationary counting for half the scan time. Lorentz and polarization corrections were applied taking into account the monochromator crystal (Azaroff, 1955) but no absorption corrections were made.

## Structure determination and refinement

The structure was solved by assuming the same atomic coordinates for DCA as those found in the acetic acid–choleic acid (DCAACA) complex (Craven & De Titta, 1972). $R$ was computed as a function of the DCA translational and rotational degrees of freedom, neglecting the contribution of the palmitic acid, for reflections with $\sin\theta/\lambda \le 0\cdot25$ Å$^{-1}$. The DCA molecule, treated as a rigid body, gave the best $R$ with the orientation assumed in DCAACA and with $-0\cdot5$ and $0\cdot2$ Å translations along $b$ and $c$ respectively. It was clear that the contribution of the palmitic acid is negligible except for the $hk0$ reflections. Isotropic block-diagonal least-squares refinement was performed with programs of Domenicano, Spagna & Vaciago (1969) and scattering factors taken from *International Tables for X-ray Crystallography* (1974), the function minimized being $\sum w(|F_o| - |F_c|)^2$ with $w = (a + |F_o| + b|F_o|^2)^{-1}$. At this stage a difference synthesis showed three peaks which were higher than all the others, and could be attributed to three C atoms of the fatty acid. After further cycles, including these three atoms, $R$ was markedly improved. Another difference synthesis showed few peaks, the three highest of which corresponded in good approximation to the previous C atoms rotated by 180° around the axis passing through $(a/4, b/2)$. Hence, the refinement was continued by

Table 2. *Fractional coordinates* $(\times 10^4)$ *with e.s.d.'s in parentheses*

| | $x$ | $y$ | $z$ |
|---|---|---|---|
| C(1) | 1170 (3) | 2588 (6) | 1514 (11) |
| C(2) | 623 (3) | 2868 (6) | 2109 (12) |
| C(3) | 651 (4) | 3609 (6) | 3681 (12) |
| C(4) | 952 (3) | 3176 (5) | 5282 (11) |
| C(5) | 1506 (3) | 2878 (5) | 4701 (12) |
| C(6) | 1809 (3) | 2481 (6) | 6357 (13) |
| C(7) | 1621 (3) | 1424 (6) | 6958 (12) |
| C(8) | 1607 (3) | 703 (5) | 5324 (11) |
| C(9) | 1298 (3) | 1124 (5) | 3709 (10) |
| C(10) | 1501 (2) | 2133 (5) | 3049 (10) |
| C(11) | 1237 (3) | 360 (5) | 2168 (10) |
| C(12) | 1016 (3) | −631 (5) | 2857 (10) |
| C(13) | 1324 (2) | −1058 (5) | 4428 (10) |
| C(14) | 1368 (3) | −267 (5) | 5938 (10) |
| C(15) | 1599 (4) | −810 (7) | 7579 (13) |
| C(16) | 1373 (4) | −1863 (6) | 7458 (13) |
| C(17) | 1082 (3) | −1929 (5) | 5553 (11) |
| C(18) | 1864 (3) | −1372 (6) | 3642 (12) |
| C(19) | 2057 (3) | 2037 (7) | 2279 (16) |
| C(20) | 1093 (3) | −2999 (5) | 4787 (12) |
| C(21) | 839 (4) | −3080 (7) | 2888 (14) |
| C(22) | 874 (4) | −3739 (6) | 6175 (13) |
| C(23) | 362 (4) | −3549 (7) | 6709 (18) |
| C(24) | 113 (4) | −4368 (6) | 7923 (14) |
| O(25) | 131 (2) | 3819 (5) | 4239 (10) |
| O(26) | 480 (2) | −476 (4) | 3400 (7) |
| O(27) | 80 (4) | −5227 (5) | 7475 (13) |
| O(28) | −45 (2) | −4107 (4) | 9522 (10) |
| C(29) | 2651 | 4795 | 817 |
| C(30) | 2351 | 5220 | 2563 |
| C(31) | 2686 | 4795 | 4209 |
| C(32) | 2335 | 5154 | 747 |
| C(33) | 2646 | 4887 | 2194 |
| C(34) | 2393 | 5166 | 3973 |

treating the DCA atoms anisotropically and the C(29)–C(34) palmitic acid atoms, with occupancy factors of 0·5, isotropically. The H atoms were generated at the expected positions (Candeloro De Sanctis, Coiro, Giglio, Pagliuca, Pavel & Quagliata, 1978), except those of the hydroxyl and carboxyl groups and the fatty acid. Their $B$'s (5 Å$^2$) and positional parameters were kept fixed. The coordinates of C(29)–C(34) did not converge and so those obtained from the difference synthesis were included and kept fixed during the last refinement. The final $R$ and $R_w$ were 0·11 and 0·16 respectively. The final atomic coordinates are reported in Table 2.*

The bond lengths and angles of DCAPAL are given in Figs. 1 and 2. Schematic drawings of the crystal packing and of a bilayer viewed along $c$ and $a$ respectively are shown in Figs. 3 and 4.
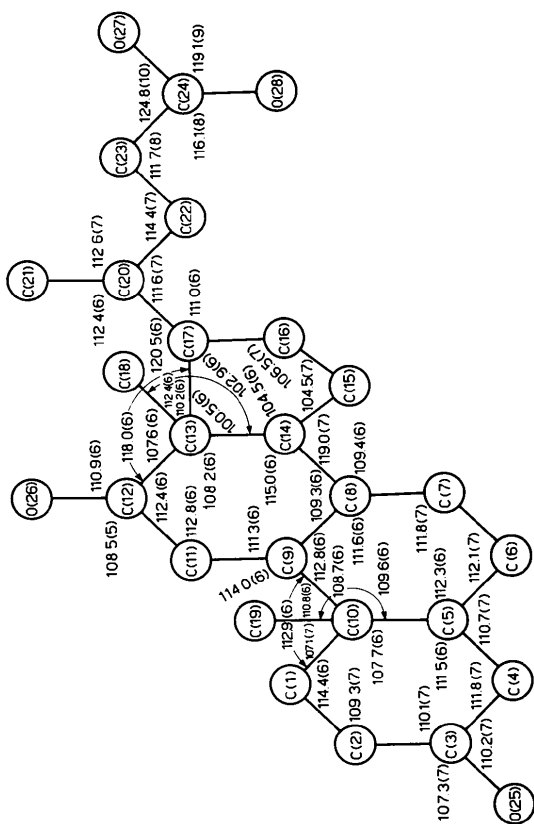
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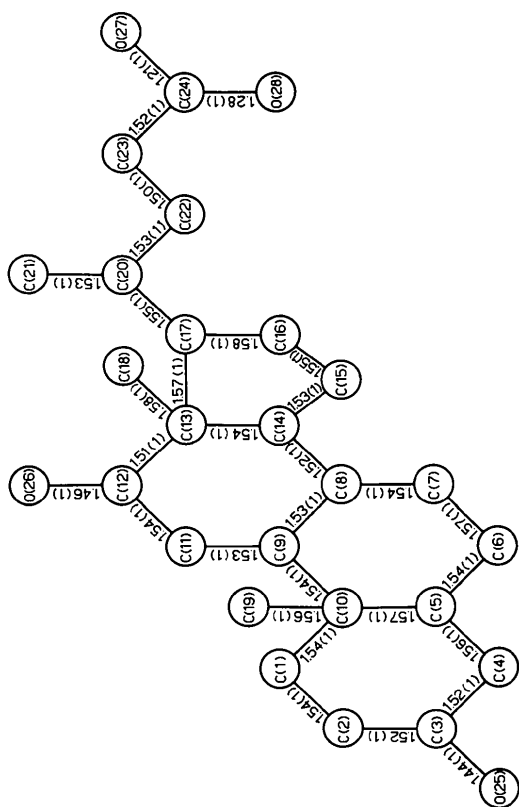Fig. 2. Bond angles (°) of DCA with e.s.d.'s in parentheses.

Fig. 1. Bond distances (Å) of DCA with e.s.d.'s in parentheses.

## Potential-energy calculations

Contemporaneously, it was decided to resort to van der Waals energy calculations in order to verify if the positions of the palmitic acid were energetically stable and if other arrangements were possible. The geometry adopted for the palmitic acid was C—C = 1·53, C—H = 1·08 Å, C—C—C = 112·00 and H—C—C = 109·47°. That of DCA was obtained during the refinement, $R$ being 0·12. The H atoms of DCA were generated as described above. The coefficients of the potentials concerning H, C, O and the methyl groups have been reported previously (Pavel, Quagliata & Scarcelli, 1976). The energy was computed (assuming a cut-off distance of 7 Å) as a function of $\varphi$, the counterclockwise rotation angle around the axis at $(a/4, b/2)$, and $t_z$ (the translation along $c$), with increments of 5° and 0·1 Å. $\varphi = 0°$ and $t_z = 0$ Å correspond to the C atoms of the fatty acid lying in a plane parallel to $bc$, with the C atom of the methyl group at $y < b/2$ and $z = 0$ Å. The other atoms of the palmitic acid have greater $z$'s and, except for the O atoms, are placed at the same distance from the axis at $(a/4, b/2)$. 28 DCA molecules, belonging to two facing monolayers of two adjacent bilayers which frame a canal in seven cells along $c$, were taken into account and kept fixed. The results of the calculations are given in Fig. 5.
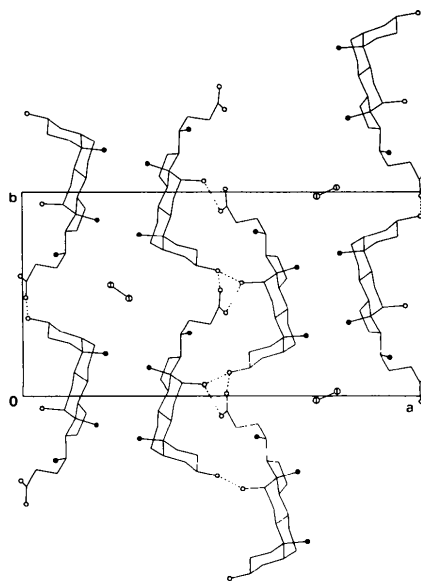
Fig. 3. A view of the DCAPAL crystal structure along $c$. The filled, open and crossed circles represent methyl groups, oxygen and palmitic acid carbon atoms respectively. The broken lines indicate hydrogen bonds.
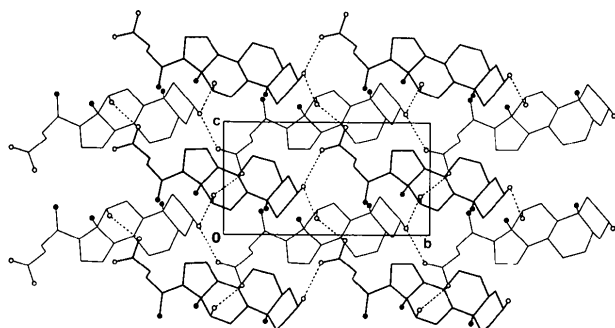
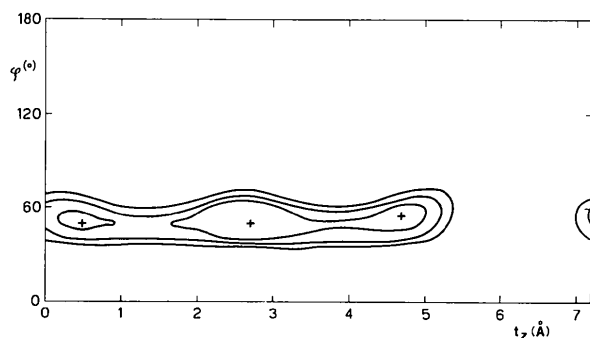Fig. 4. Molecular packing of a DCAPAL bilayer viewed along $a$. The symbols have the same meaning as in Fig. 3.



Fig. 6. Van der Waals energy $vs$ $y$ for $a = 25 \cdot 6$ and $26 \cdot 0$ Å computed with the atomic coordinates of DCA in the acetone–choleic acid complex. The arrows indicate the positions of the experimental crystal structures.



Fig. 5. Contour lines of the van der Waals energy as a function of $t_z$ and $\varphi$ for the palmitic acid in the DCAPAL crystal. The crosses indicate the locations of the minima.

## Discussion

The rather high $R$ reflects the approximation in locating the fatty acid molecules, owing to the possible head-to-tail, head-to-head and tail-to-tail sequences which can be generated by the palmitic acid with the carboxyl group pointing up or down along $c$. The angular orientation of the palmitic acid is constrained in a narrow region around $\varphi = 50°$, coinciding with that of the acetic acid in DCAACA. Three positions along $c$, marked by crosses in Fig. 5, are allowed. That at $t_z = 0 \cdot 5$ Å satisfactorily corresponds to the arrangement deduced from the difference syntheses. The same minima occur at $\varphi + \pi$ and $t_z + c/2$ for the presence of the twofold screw axis parallel to $c$, so that four statistical orientations, which may coexist in the same canal, are permitted. Moreover, the canals cannot be continuously filled, since the palmitic acid cannot start at every $z$, and this supports the hypothesis that one ethanol molecule is present between every two palmitic acid molecules. Thus a DCA:palmitic acid:ethanol ratio of 8:1:1 seems reasonable and gives
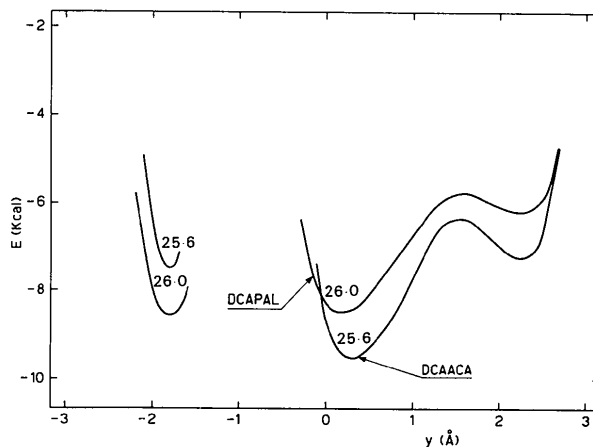
rise to a density of $1 \cdot 12$ Mg m$^{-3}$, which agrees with the measured one.

Another point deserves some attention. Van der Waals energy calculations were performed, neglecting the guest molecules, for the orthorhombic phases of DCA by moving the bilayers along $b$ for different values of $a$ (Candeloro De Sanctis & Giglio, 1979). By indicating the translation along $b$ of a bilayer by $y$ and putting $y = 0$ Å in correspondence with the bilayer position in the acetone–choleic acid complex (Tang, 1979), two regions of minimum energy, $A$ and $B$, were found, centred at $y \simeq 0 \cdot 2$ and $1 \cdot 8$ Å respectively (Fig. 6) and populated by the crystal structures so far known, which correspond to two types of cavities. Guest molecules which are small in size or thread-like can be occluded in canals of type $A$ for $a \leq 26$ Å, whereas aromatic molecules consisting of, for example, benzene rings with bulky substituents such as Br and I, can be accommodated in canals of type $B$ for $a > 26$ Å.

The $A$ region is more or less stable than the $B$ region for values of $a$ less than or greater than 26 Å respectively. At about 26 Å, which coincides with the value for DCAPAL, the two regions have the same energy (Fig. 6). Therefore the van der Waals energy of the palmitic acid in the $B$ region was computed in the same way as described above with the cell parameters of DCAPAL, in order to establish if energetical factors may explain why DCAPAL crystallizes in the $A$ region. From the calculations it clearly resulted that the energy in $B$ is much higher than that in $A$ since the shape of the $B$ cavity is suitable only for flat molecules when $a$ is 26 Å.

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# Crystals Exhibiting Disorder – The Monoclinic Polymorph of 9-Bromo-10-methylanthracene

By Raymond D. G. Jones and T. R. Welberry

Research School of Chemistry, Australian National University, PO Box 4, Canberra, ACT, Australia 2600

## Abstract

The crystal structure of $C_{15}H_{11}Br$ has been determined from X-ray (Mo $K\alpha$ radiation) and neutron ($\lambda = 0.988$ Å) diffraction data. The compound crystallizes in the monoclinic space group $P2_1/c$ with $a = 8.307$ (1), $b = 9.844$ (1), $c = 13.815$ (2) Å, $\beta = 95.96$ (1)°, $Z = 4$. Refinement led to $R$ and $wR$ values of 0.101 and 0.045 for 2197 X-ray reflexions (0.047 and 0.042 for reflexions with $I > 2.3\sigma_i$) and 0.167 and 0.056 for 2299 neutron reflexions (0.059 and 0.046). The 9,10-substituents show disorder of Br and $CH_3$, the 9-substituent occupied on average by 0.643 Br and 0.357 C and vice versa for the 10-substituent. Additionally, the neutron data show two orientations for the H atoms of the $CH_3$.

## Introduction

For some time in this laboratory, models for describing the way in which disorder may be introduced into binary mixed crystals at growth have been studied from a theoretical aspect (Welberry, 1977a,b; Welberry & Miller, 1977, 1978; Miller & Welberry, 1979). As a parallel study, we decided to examine some molecular crystal systems which might exhibit growth-disorder.

To reduce the problem to one of site occupancy at one or two atomic positions, the compounds selected had to be reasonably rigid and, once incorporated in the crystal lattice, not undergo large molecular rotations or translations, i.e. the molecules would not rearrange to some equilibrium configuration. We wished to determine the average structure by conventional Bragg scattering. Details of disorder would be studied by X-ray diffuse scattering. To ensure pronounced diffuse-scattering effects in the scattering patterns, the components of the binary solid should have a large difference in scattering power.

Polycyclic aromatic ring systems were considered to be suitable basic units. Because of their ease of synthesis, anthracene derivatives were used. Kitaigorodsky (1973) has deduced that the volumes occupied by $CH_3$, Cl, Br, $NO_2$, COOH and $NH_2$ groups in a crystal are similar. On volume considerations alone, one might conclude that binary mixed crystals could be crystallized from similarly substituted anthracenes containing the above groups. Others in our group are undertaking thermodynamic calculations of lattice energies. To enable use of the best published parameters for these calculations, we did not consider substituents containing oxygen or which could participate in hydrogen bonding. Finally, we decided that the properties of a binary mixed solid