Crystal Structure of the 2 : 1 Inclusion Compound Between Deoxycholic Acid and Quadricyclane

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Abstract. The 2 : 1 inclusion compound formed between deoxycholic acid ($C_{24}H_{40}O_4$, M_r = 392.58) and quadricyclane (C_7H_8, M_r = 92.14) crystallizes in space group $P2_12_12_1$ with a = 27.150(7), b = 13.359(3), c = 14.161(4) Å, Z = 4. The structure was refined to R = 0.08$_6$ and R_w = 0.08$_8$ for 2079 observed reflections with $I > 2.5\sigma(I)$. The crystal packing is very similar to that found in the norbornadiene-deoxycholic acid inclusion compound and is characterized by an assembly of antiparallel pleated bilayers, formed by molecules of deoxycholic acid held together through hydrogen bonds. Quadricyclane occupies approximately the same position of norbornadiene and its atoms give rise to good van der Waals interactions with some methyl groups of deoxycholic acid.

Key words: Inclusion compound, deoxycholic acid, quadricyclane, photoreaction.

1. Introduction

3α, 12α-Dihydroxy-5β-cholan-24-oic acid (deoxycholic acid, DCA) forms many stoichiometric crystalline complexes, termed choleic acids, of the 'channel' type with a wide variety of organic molecules [1–3]. Several crystal structures of choleic acids, belonging to orthorhombic, tetragonal and hexagonal space groups, have been solved in recent years (see [4–6] for references).

The orthorhombic system is the most commonly observed and presents the best clathrating ability. In this system, the DCA molecules give rise to adjacent antiparallel bilayers which pack together leaving empty spaces occupied by the guest molecules. Van der Waals energy calculations and the crystal structures solved so far show that two types of structures, referred to as α and β, and three packing motifs are possible in the space group $P2_12_12_1$ [7].

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One of these, corresponding to the B' minimum of the β structures, is characterized by guest molecules with a cross-section of roughly circular shape as, for example, norbornadiene (NBD), cyclohexanone and di-t-butyl diperoxycarbonate. Thus, the crystal structure of the 2 : 1 inclusion compound between DCA and NBD (DCANBD) was previously investigated in order to clarify, among other things, the nature and strength of the host-guest interactions [8]. Moreover, since the reversible valence isomerization of NBD to quadricyclo-[2.2.1.0^{2,6}.0^{3,5}]heptane (quadricyclane, QDC) in the presence of certain photosensitizers or catalysts is an attractive process for the chemical storage of solar energy [9], it was considered interesting to employ DCANBD crystals for performing the first step of a two-step process involving:

(1) Energy storage through the direct conversion of NBD to QDC by means of irradiation.
(2) Energy release through the catalyzed reconversion of QDC to NBD.

In this connection, the inclusion compound formed between DCA and QDC (DCAQDC) was prepared in order to establish whether the DCA host lattice, found in DCANBD, is nearly equal to that in DCAQDC and, hence, capable of tolerating the photoreaction NBD $\rightarrow$ QDC. Moreover, the structural information regarding the DCANBD and DCAQDC crystals can be useful for understanding a possible lattice-controlled photo-induced reaction, NBD $\rightarrow$ QDC. It can also be useful in choosing suitable photosensitizers to be included together with NBD in order to increase the quantum efficiency of the reaction and the purity of the QDC produced, as compared with the reaction in solution, using the solar radiance spectrum, which, unfortunately, does not overlap the electronic absorption spectrum of NBD. A simultaneous inclusion of two different molecules, as, for example, NBD and a photosensitizer, can occur only if the size and shape of the cavity, which is variable in the DCA orthorhombic phase, is very similar in both inclusion compounds. Therefore, van der Waals energy calculations can be very helpful in predicting which photosensitizers can be included together with NBD and QDC in the DCA channels. The results so far obtained are encouraging and have prompted us to attempt to include together NBD and a photosensitizer in the DCA channels. The work is in progress.

2. Experimental

DCAQDC was crystallized from a solution of DCA and QDC in methanol by lowering the temperature very slowly. The composition of DCAQDC was checked by gas chromatography and density measurements by flotation in an n-hexane-chloroform mixture. The observed density (1.12 g cm^{-3}) agreed with the calculated one (1.13 g cm^{-3}) for eight DCA and four QDC molecules in the unit-cell. The colourless lath-shaped crystals, elongated along c, lose QDC at 430 K and melt at 449 K, close to the melting point of pure DCA. The unit-cell parameters were obtained from a least-squares analysis of diffractometer-angle measurements for 15 reflections. The systematic absences $h00$, $0k0$ and $00l$ with h, k and l odd, respectively, identify the space group as $P2_12_12_1$.

A crystal with a maximum dimension of 0.8 mm was chosen to collect intensities up to $2\vartheta = 55°$ on a Syntex $P2_1$ diffractometer with graphite-monochromatized MoKα radiation ($\lambda = 0.71069$ Å), using the ω-scan mode. The scan rate was within the range 1.0 to 29.3° min^{-1}, depending on the peak intensity, with a scan width of 0.8°. Backgrounds were estimated by stationary counting for half the scan time. Statistical fluctuations were only observed in the intensities of four standard reflections monitored every 96 reflections. Lorentz and polarization corrections were applied, taking into account the monochromator crystal [10] but the absorption corrections were neglected.

3. Structure Determination and Refinement

The structure was solved by assuming the same atomic coordinates for DCA as those found in DCANBD, neglecting QDC. The refinement was started by means of structure factors and Fourier syntheses calculations for the two DCA molecules, belonging to the asymmetric unit. The agreement index decreased to 0.21, but would not go lower. At this stage, a difference Fourier synthesis showed some peaks, with a maximum electron density of 1.4 e Å^{-3}, three of which were attributed to the carbon atoms of QDC. A model of QDC was assumed putting all the C—C bond distances equal to 1.53 Å and the bond angles on the basis of the X-ray data of Harnisch et al. [11] concerning the molecular structure of 9,10-dihydro-9,10-(1,7-tetracyclo[$3.2.0.0.^{2,7}.0^{4,6}$]heptane)anthracene (Figure 1). The 'molecules best fitting' pro-
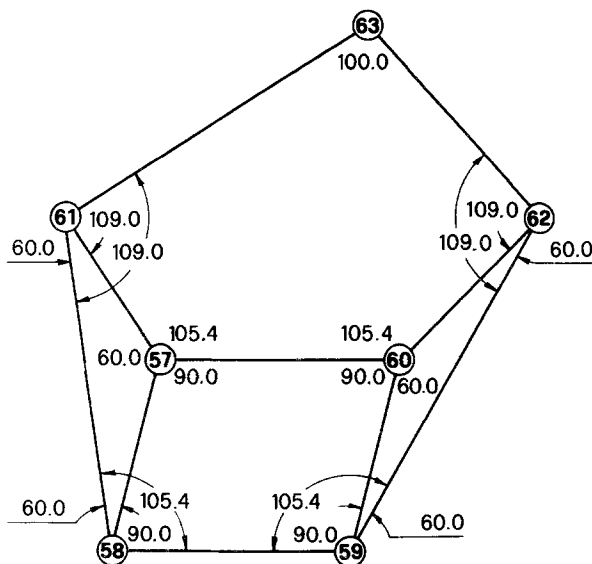

Fig. 1. Atomic numbering and bond angles of QDC.

gramme [12] was used to obtain a satisfactory overlap of three atoms of the QDC model with the three peaks of the difference synthesis. The refinement was resumed with SHELX [13], using the scattering factors of Cromer and Mann [14] and the weighting scheme $w = K_1/[\sigma^2 (F_0) + K_2 F_0^2]$, K_1 and K_2 being two constants redetermined after each cycle. The function minimized was $\Sigma w(|F_0| - |F_c|)^2$. Full-matrix least-squares cycles were carried out with the methyl carbon, oxygen and side-chain atoms of DCA only treated anisotropically. The QDC was treated isotropically as a rigid body. The hydrogen atoms of DCA were generated in each cycle at the expected positions (C—H = 1.08 Å), except those of the hydroxyl and carboxyl groups. Their positional parameters were kept fixed together with their thermal parameters approximately equal to those of the atoms to which they are attached. The refinement converged to a final R and R_w of 0.08_6 and 0.08_8, respectively. The final atomic coordinates are reported in Table I.

The bond lengths and angles of the DCA molecule are given in Figure 2. Their average e.s.d.'s are 0.017 Å and 1.1° with maximum values of 0.020 Å and 1.7°. A schematic drawing of the crystal packing and of a bilayer, viewed along c and a respectively, are shown in Figures 3 and 4.

Table I. Fractional atomic coordinates ($\times 10^4$) and thermal parameters ($\text{Å}^2 \times 10^3$) for the non-H atoms of DCAQDC with their e.s.d.'s in parentheses. For the atoms treated anisotropically U_{eq} is defined as $U_{eq} = \frac{1}{3}(U_{11} + U_{22} + U_{33})$

	x	y	z	U_{eq}/U
C(1)	1078(4)	1731(10)	−797(9)	47(4)
C(2)	570(5)	2056(10)	−446(10)	55(4)
C(3)	621(5)	2783(10)	363(9)	50(4)
C(4)	931(5)	2348(10)	1166(10)	52(4)
C(5)	1438(5)	1991(10)	819(9)	51(4)
C(6)	1748(5)	1572(10)	1609(10)	54(4)
C(7)	1559(5)	535(9)	1937(9)	48(4)
C(8)	1509(5)	−180(10)	1124(9)	48(4)
C(9)	1191(5)	270(9)	327(9)	43(4)
C(10)	1408(4)	1260(9)	−43(9)	42(3)
C(11)	1083(5)	493(9)	−457(9)	45(4)
C(12)	862(4)	−1510(9)	−110(10)	47(4)
C(13)	1185(5)	−1961(10)	698(9)	46(4)
C(14)	1257(4)	−1132(9)	1470(8)	41(3)
C(15)	1502(5)	−1713(10)	2301(10)	55(4)
C(16)	1231(5)	−2728(10)	2247(10)	56(4)
C(17)	948(5)	−2814(9)	1312(9)	46(4)
C(18)	1669(5)	−2303(9)	238(10)	47(9)
C(19)	1924(4)	1103(10)	−446(10)	55(9)
C(20)	950(5)	−3881(9)	906(10)	48(9)
C(21)	675(5)	−3998(10)	−27(11)	64(10)
C(22)	761(5)	−4641(9)	1665(11)	54(9)
C(23)	240(6)	−4486(11)	1965(11)	68(11)
C(24)	75(6)	−5277(14)	2658(13)	69(13)
O(25)	133(3)	3053(8)	685(7)	73(7)
O(26)	370(3)	−1298(6)	256(6)	52(6)
O(27)	53(5)	−6158(9)	2454(9)	105(10)
O(28)	−43(4)	−4961(7)	3496(8)	72(7)
C(29)	1198(5)	1804(10)	4339(9)	51(4)
C(30)	700(5)	2111(11)	4766(10)	57(4)
C(31)	780(5)	2860(11)	5591(10)	58(4)
C(32)	1133(5)	2398(10)	6330(9)	52(4)
C(33)	1630(4)	2058(10)	5863(9)	45(4)
C(34)	1976(5)	1602(10)	6628(10)	54(4)
C(35)	1811(5)	596(10)	6973(10)	52(4)
C(36)	1717(4)	−151(9)	6178(9)	38(3)
C(37)	1362(4)	310(9)	5424(9)	40(3)
C(38)	1559(4)	1329(9)	5024(9)	44(4)
C(39)	1230(5)	−438(9)	4668(9)	48(4)
C(40)	1006(4)	−1412(9)	5078(9)	44(4)
C(41)	1350(4)	−1885(10)	5815(9)	43(4)
C(42)	1482(4)	−1060(9)	6547(8)	41(3)
C(43)	1751(5)	−1655(10)	7327(10)	58(4)
C(44)	1468(5)	−2718(10)	7347(10)	60(4)
C(45)	1135(5)	−2732(10)	6461(9)	53(4)
C(46)	1809(5)	−2270(11)	5294(10)	58(10)
C(47)	2055(5)	1210(11)	4503(10)	59(10)
C(48)	1099(5)	−3800(10)	6055(10)	53(9)
C(49)	808(6)	−3888(11)	5135(11)	70(11)
C(50)	884(5)	−4507(9)	6810(11)	58(10)

Table I (continued)

|	x	y	z	U_{eq}/U
C(51)	356(5)	− 4326(10)	7105(11)	66(10)
C(52)	154(6)	− 5132(11)	7726(11)	61(11)
O(53)	310(3)	3056(7)	5997(7)	67(7)
O(54)	530(3)	− 1181(7)	5507(6)	53(6)
O(55)	293(4)	− 5964(8)	7762(8)	90(8)
O(56)	− 216(4)	− 4832(7)	8267(8)	76(7)
C(57)	2037(4)	5064(11)	3602(13)	258(17)
C(58)	2246(4)	4420(11)	2804(13)	264(16)
C(59)	2545(4)	5316(11)	2448(13)	250(17)
C(60)	2335(4)	5960(11)	3246(13)	322(22)
C(61)	2416(4)	4251(11)	3822(13)	227(14)
C(62)	2873(4)	5623(11)	3277(13)	269(18)
C(63)	2921(4)	4739(11)	3958(13)	285(19)
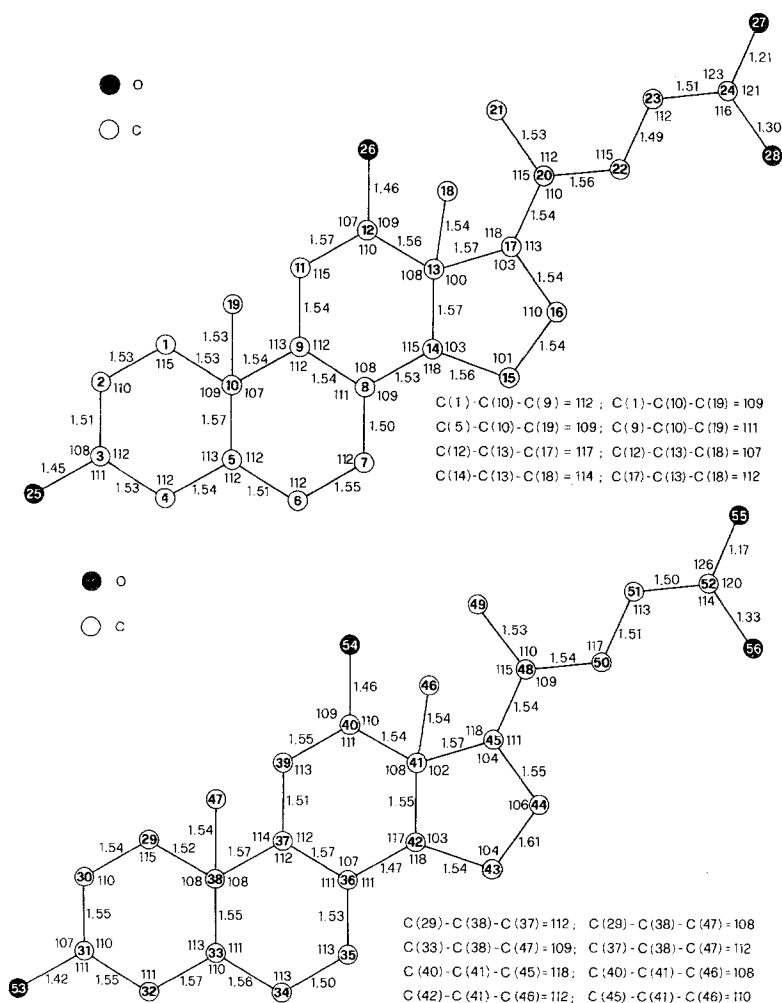
Fig. 2. Bond distances (Å) and angles (°) in the two DCA molecules of the DCAQDC asymmetric unit.
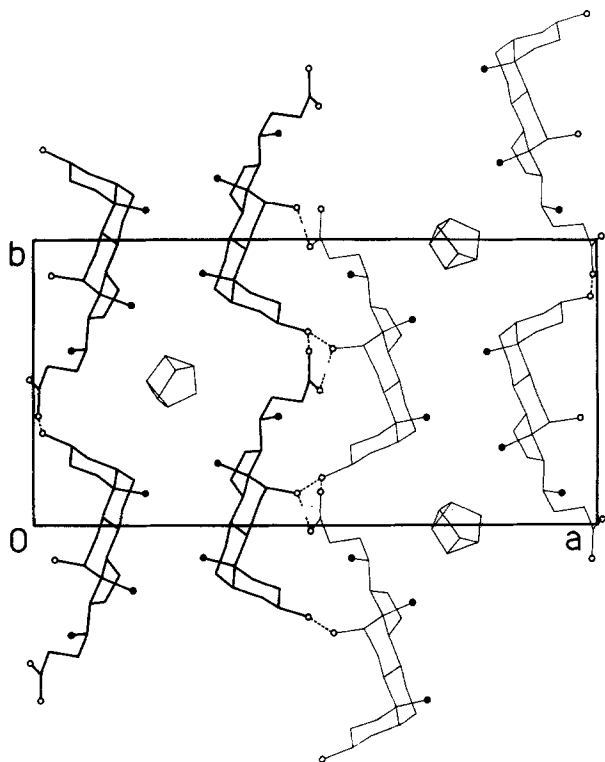
Fig. 3. DCAQDC crystal packing viewed along *c*. The filled and open circles are methyl groups and oxygen atoms, respectively. The broken lines represent hydrogen bonds.
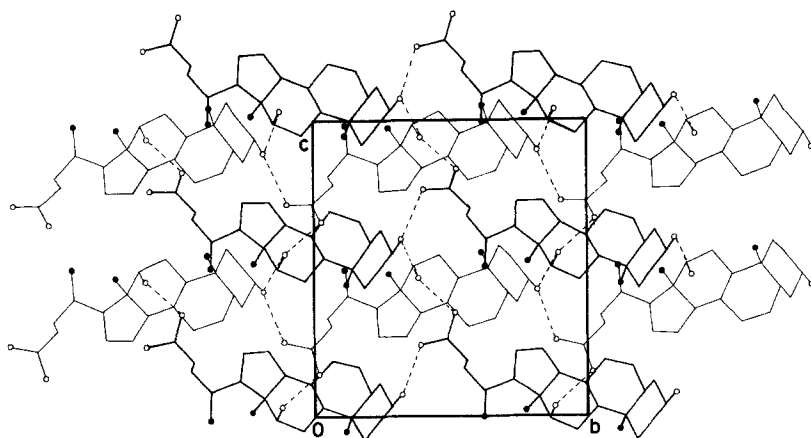

Fig. 4. Molecular packing of DCA molecules in a DCAQDC bilayer viewed along *a*. The symbols have the same meaning as in Figure 3.

4. Discussion

The low ratio (5.97) between the number of observed reflections and the number of atomic parameters did not allow us to refine all the atoms anisotropically. Thus, the rather high R and e.s.d.'s of the atomic parameters can be justified, as in the case of DCANBD.

Both the geometry and the side-chain and D-ring conformations of the two DCA molecules are similar to each other and also to those of the other orthorhombic and tetragonal crystals. The conformation of the side-chain is 'gauche' and that of the D-ring approaches the half-chair symmetry [15]. The torsion angles, together with the phase angle of pseudorotation Δ and the maximum angle of torsion φ_m [16] are listed in Table II in accordance with the convention of Klyne and Prelog [17].

Table II. Torsion angles ($°$) for the side chain and ring D of the two independent DCA molecules together with Δ and φ_m. The e.s.d.'s are within the range 1.0–2.2°

	Mol C(1) – O(28)	Mol C(29) – O(56)
C(13) – C(17) – C(20) – C(22)	173	179
C(17) – C(20) – C(22) – C(23)	63	66
C(20) – C(22) – C(23) – C(24)	177	171
C(13) – C(17) – C(20) – C(21)	– 60	– 56
C(16) – C(17) – C(20) – C(21)	180	– 176
C(21) – C(20) – C(22) – C(23)	– 65	– 61
C(22) – C(23) – C(24) – O(27)	– 63	– 24
C(22) – C(23) – C(24) – O(28)	117	156

	Mol C(1) – O(28)	Mol C(29) – O(56)
C(13) – C(14)	48	46
C(14) – C(15)	– 37	– 35
C(15) – C(16)	13	11
C(16) – C(17)	16	17
C(13) – C(17)	– 38	– 39
Δ	3	8
φ_m	48	46

The crystal packing (Figure 3) is characterized by an assembly of antiparallel pleated bilayers, extended into the bc plane, identical to that of DCANBD. The driving force which stabilizes the bilayer (Figure 4), is the hydrogen bonding. The spiralized hydrogen bonding system is described in Table III. The guest molecules fill the nonpolar channels with a cross-section of about 4.9 × 5.4 Å and with surfaces from which mainly protrude methyl groups and hydrogen atoms bonded to C(5), C(16), C(20) and C(22). The QDC molecule occupies approximately the same position as NBD, the coordinates of the centre of gravity of QDC and NBD, considering only the carbon atoms, being (0.248, 0.505, 0.331) and (0.253, 0.505, 0.331), respectively. C(57), C(58), C(60), C(62) and C(63) of QDC have atomic coordinates similar to those of C(62), C(59), C(63), C(61) and C(58) of NBD, respectively, whereas the other two pairs of carbon atoms are far from each other. The strongest DCA–QDC interactions (Table IV) involve the C(18) and C(46) methyl groups, as found in DCANBD. No intermolecular contacts of less than the sum of the van der Waals radii are observed between pairs of atoms. Thus, since the host structures are nearly identical in

Table III. O...O distances (Å) in the hydrogen bonds in a bilayer. The e.s.d.'s are within the range 0.012–0.016 Å

$O(25)...O(27^i)$	2.73	$O(26)...O(53^{iii})$	2.70
$O(25)...O(54^{ii})$	2.67	$O(53)...O(55^i)$	2.82
$O(26)...O(28^{ii})$	2.66	$O(54)...O(56^{iv})$	2.64

Symmetry code
(i) $x, 1 + y, z$ (ii) $-x, 1/2 + y, 1/2 - z$
(iii) $-x, -1/2 + y, 1/2 - z$ (iv) $-x, 1/2 + y, 3/2 - z$

Table IV. Host-guest shortest distances (Å) in DCAQDC

$C(57)...C(49^i)$	4.22	$C(61)...C(18^{ii})$	4.12
$C(60)...C(16^i)$	3.75	$C(63)...C(18^{ii})$	3.89
$C(60)...C(46^i)$	4.01	$C(63)...C(21^{ii})$	4.19
$C(61)...C(47)$	4.29	$C(63)...C(44^{iii})$	3.91

Symmetry code
(i) $x, 1 + y, z$ (ii) $1/2 - x, -y, 1/2 + z$
(iii) $1/2 - x, -y, -1/2 + z$

DCANBD and DCAQDC, and NBD and QDC can be exchanged without stressing the corresponding lattices, the photoreaction NBD → QDC can easily occur in DCANBD.

The thermal motion of the QDC heavy atoms, which have isotropic temperature factors, B's ranging within about 18–25 Å^2, is comparable with that of other guest molecules in similar choleic acids which populate the B' minimum of the β structures. If NBD in DCANBD is excluded, owing to the partial conversion of NBD to QDC by exposure to X-rays, then cyclohexanone, (S)-3-methyl cyclohexanone and di-t-butyl diperoxycarbonate present in the corresponding choleic acids have isotropic temperature factors for the heavy atoms within the ranges 15–23, 13–21 and 17–30 Å^2, respectively [18]. In contrast, the values of B_{eq} vary from 9 to 45 Å^2 for the heavy atoms of the guest molecule in the inclusion compound between DCA and (+)-camphor [19]. These very high values seem to suggest the occurrence of more than one definite orientation of the guest molecule. Potential energy calculations are in progress in order to clarify this intriguing aspect.

Acknowledgements

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