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A 1:1 complex between deoxycholate and tris(hydroxymethyl)methylammonium

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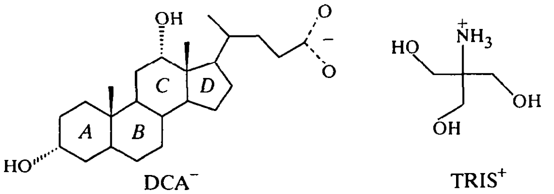
Abstract

The structure of the 1:1 complex of deoxycholate (3α, 12α-dihydroxy-5β-cholan-24-oate, $C_{24}H_{39}O_4^-$, DCA$^-$) and tris(hydroxymethyl)methylammonium [$(CH_2OH)_3CNH_3^+$ or $C_4H_{12}NO_3^+$, TRIS$^+$] has been determined. The crystal structure is one of four known where DCA exists in the monoclinic space group $P2_1$. The side-chain conformation of DCA is synclinal, which is coupled with a half-chair conformation of ring *D*. The asymmetric unit contains one DCA$^-$ anion, one TRIS$^+$ cation and three water molecules.

Comment

Deoxycholic acid (DCA) is a bile acid, which aids in the transportation and digestion of fatty acids and fat-soluble vitamins in the intestine. DCA is amphiphilic and can form micelles in aqueous solutions. We report here the crystal structure of the 1:1 complex of deoxycholate and tris(hydroxymethyl)methylammonium, (I).



DCA$^-$ TRIS$^+$

DCA is a steroid, with three six-membered rings labelled *A*, *B* and *C*, and one five-membered ring labelled *D*. Rings *A*, *B* and *C* are essentially rigid, whereas ring *D* has a flexible conformation related to the side chain. The positions of the O atoms in the carboxyl group are influenced by the formation of hydrogen bonds (Giglio & Quagliata, 1975). The molecular conformation and atom-numbering scheme for (I) are shown in Fig. 1.

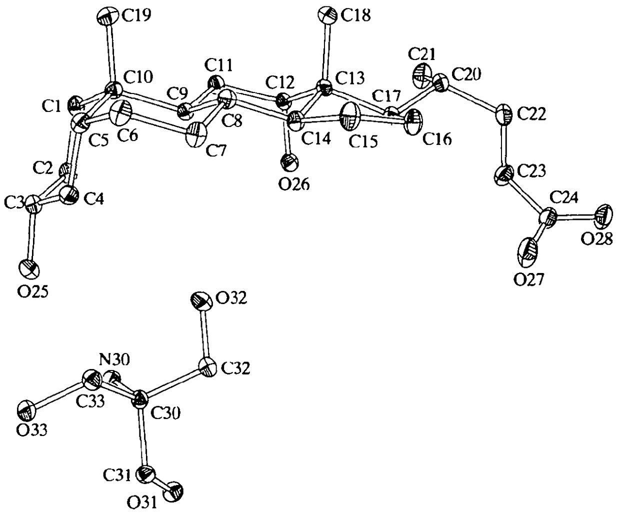


Fig. 1. The molecular conformation and atomic numbering scheme (Sheldrick, 1994) for DCA and TRIS in (I). Displacement ellipsoids are drawn at the 50% probability level and H atoms have been omitted for clarity.

A search in the Cambridge Structural Database (Allen & Kennard, 1993; Version of March 1998) reveals a total of 44 structures incorporating DCA (present work included). Orthorhombic crystals predominate in the crystallographic material, with a total of 36 reported structures. The remaining eight structures are monoclinic (4), tetragonal (2) and hexagonal (2). The first three structures of DCA in the monoclinic space group were published by Coiro *et al.* (1980), Campanelli *et al.* (1984) and Cerrini *et al.* (1993). The present complex is the fourth monoclinic structure.

The layered structure (Fig. 2) of the title complex is parallel to the *ab* plane. The thickness of the hydrophobic layer, given by the distance between planes defined by the O26 atoms on adjacent molecular layers, is 8.3 Å. The corresponding thickness of the hydrophilic layer is 6.8 Å. A DCA monolayer is composed of rows of DCA$^-$ anions linked in a 'head-to-tail' fashion through the O25—H25···O28 hydrogen bond. These DCA monolayers are connected by van der Waals interactions into bilayers, and 14 unique hydrogen bonds hold the bilayers together (Table 2).

Selected torsion angles of the side chain and ring *D* are given in Table 1, according to the convention of Klyne & Prelog (1960). The conformation of ring *D* is suitably described by the phase angle of pseudorotation (Δ) and the maximum angle of torsion (φ_m) (Altona *et al.*, 1968). The value of Δ in the DCA–TRIS complex is 4.7° (φ_m 45.6°). This value indicates a conformation very close to a half-chair for ring *D*. The five torsion angles of ring *D*, *i.e.* φ_0 (C17—C13—C14—C15), φ_1 (C14—C13—C17—C16), φ_2 (C15—C16—C17—C13), φ_3 (C14—C15—C16—C17) and φ_4 (C13—C14—C15—C16) (Table 1), are in good agreement with the postulated values of 46.7, −37.8, 14.4, 14.4 and −37.8°, respectively (Altona *et al.*, 1968).

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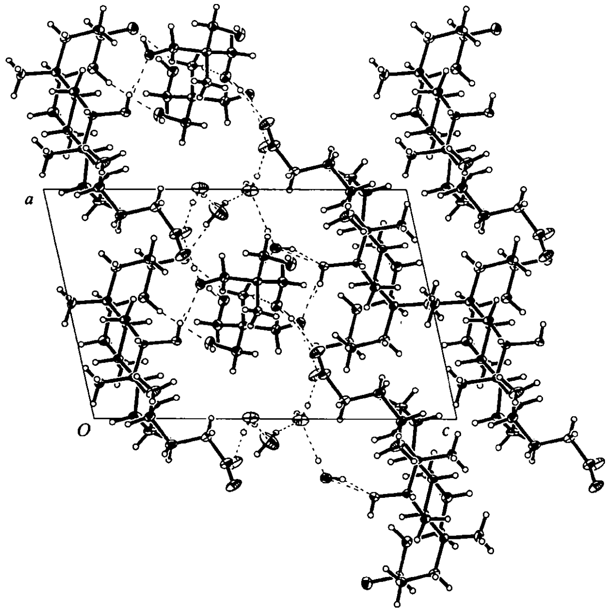

Fig. 2. The crystal packing in (I) viewed along the *b* axis.

The side-chain torsion angles, ψ_1 (C13—C17—C20—C21), ψ_2 (C17—C20—C22—C23) and ψ_3 (C20—C22—C23—C24) (Table 1), correlate well with the values calculated from a van der Waals energy map (Giglio & Quagliata, 1975), with the ψ_2 torsion angle synclinal.

Experimental

Transparent needle-shaped crystals of (I) were formed after two to three months at 277 K from a solution (5 mg ml^{-1}) of sodium deoxycholate in 50 m*M* TRIS/5 m*M* ethylenediaminetetraacetic acid buffer (pH 9.0).

Crystal data

$C_4H_{12}NO_3^+ \cdot C_{24}H_{39}O_4^- \cdot 3H_2O$
$M_r = 567.75$
Monoclinic
$P2_1$
$a = 10.16730\,(10)$ Å
$b = 10.1932\,(2)$ Å
$c = 15.4592\,(2)$ Å
$\beta = 102.048\,(1)°$
$V = 1566.86\,(4)$ Å^3
$Z = 2$
$D_x = 1.203$ Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
$\lambda = 0.71073$ Å
Cell parameters from 7716 reflections
$\theta = 1.35$–$36.33°$
$\mu = 0.090$ mm^{-1}
$T = 150\,(2)$ K
Block
$0.51 \times 0.32 \times 0.23$ mm
Colourless

Data collection

Siemens SMART CCD area-detector diffractometer
ω scans
Absorption correction: multi-scan *via SADABS* (Sheldrick, 1996)
$T_{min} = 0.955$, $T_{max} = 0.980$
24 971 measured reflections
12 833 independent reflections

11 732 reflections with $I > 2\sigma(I)$
$R_{int} = 0.022$
$\theta_{max} = 36.33°$
$h = -16 \rightarrow 16$
$k = -16 \rightarrow 16$
$l = -24 \rightarrow 25$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.035$
$wR(F^2) = 0.092$
$S = 1.057$
12 832 reflections
421 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.0396P)^2 + 0.1891P]$ where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{max} = 0.001$
$\Delta\rho_{max} = 0.379$ e Å^{-3}
$\Delta\rho_{min} = -0.238$ e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected torsion angles (°)*

C17—C13—C14—C15	45.57 (8)
C14—C13—C17—C16	−37.04 (8)
C15—C16—C17—C13	16.15 (9)
C14—C15—C16—C17	11.75 (10)
C13—C14—C15—C16	−35.68 (9)
C13—C17—C20—C21	−58.53 (11)
C17—C20—C22—C23	69.98 (11)
C20—C22—C23—C24	−146.13 (9)
C22—C23—C24—O27	88.75 (13)
C22—C23—C24—O28	−86.62 (12)

Table 2. *Hydrogen-bonding geometry (Å, °)*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O25—H25···O28^{i}	0.87 (2)	1.79 (2)	2.660 (1)	173 (2)
O26—H26···O31^{ii}	0.79 (2)	2.00 (2)	2.762 (1)	163 (2)
N30—H30*A*···O43	0.89 (2)	1.99 (2)	2.854 (1)	164 (2)
N30—H30*B*···O25	0.83 (2)	2.22 (2)	2.989 (1)	154 (2)
N30—H30*C*···O33^{ii}	0.89 (2)	1.93 (2)	2.805 (1)	168 (2)
O31—H31*C*···O27^{iii}	0.82 (2)	1.77 (2)	2.583 (1)	179 (2)
O32—H32*C*···O43^{ii}	0.75 (2)	2.06 (2)	2.802 (1)	171 (2)
O33—H33*C*···O28^{i}	0.83 (2)	1.84 (2)	2.659 (1)	168 (2)
O41—H41*A*···O25	0.86 (3)	1.96 (3)	2.812 (1)	171 (3)
O41—H41*B*···O42^{iv}	0.79 (3)	2.27 (3)	3.046 (2)	165 (3)
O42—H42*A*···O27^{iii}	0.85 (3)	1.91 (3)	2.753 (1)	170 (2)
O42—H42*B*···O41^{v}	0.80 (3)	2.02 (3)	2.824 (2)	174 (2)
O43—H43*A*···O26^{v}	0.84 (2)	1.94 (2)	2.741 (1)	160 (2)
O43—H43*B*···O42^{iv}	0.82 (2)	1.91 (2)	2.733 (1)	178 (2)

Symmetry codes: (i) $1 + x, y - 1, z$; (ii) $1 - x, \frac{1}{2} + y, 1 - z$; (iii) $-x, y - \frac{1}{2}, 1 - z$; (iv) $1 + x, y, z$; (v) $1 - x, y - \frac{1}{2}, 1 - z$.

The absolute configuration of DCA$^-$ was assigned according to the known chirality of the crystallized material. H atoms were given isotropic displacement parameters equal to 1.2 (–CH and –CH$_2$) and 1.5 (–CH$_3$ and –OH) times the equivalent isotropic displacement parameter of their parent atoms. H atoms were added at calculated positions and refined using a riding model. H atoms participating in hydrogen bonds were refined without constraints.

Data collection: *SMART* (Siemens, 1995). Cell refinement: *SAINT* (Siemens, 1995). Data reduction: *SAINT*. Program(s) used to solve structure: *SHELXTL* (Sheldrick, 1994). Program(s) used to refine structure: *SHELXTL*.

The purchase of the Siemens SMART diffractometer was made possible through financial support from The

Norwegian Council of Research (NFR). The structure was presented as a poster at the 16th Nordic Structural Chemistry Meeting in Sigtuna, Sweden, in January 1998, thanks to financial support from the conference organizers, as well as from *Acta Chemica Scandinavica*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: OS1052). Services for accessing these data are described at the back of the journal.

References

Allen, F. H. & Kennard, O. (1993). *Chem. Des. Autom. News*, **8**, 31–37.
Altona, C., Geise, H. J. & Romers, C. (1968). *Tetrahedron*, **24**, 13–32.
Campanelli, A. R., Candeloro de Sanctis, S., Giglio, E. & Petriconi, S. (1984). *Acta Cryst.* C**40**, 631–635.
Cerrini, S., Pochetti, G., Gallese, F. & Possagno, E. (1993). *Acta Cryst.* C**49**, 1087–1092.
Coiro, V. M., Giglio, E., Morosetti, S. & Palleschi, A. (1980). *Acta Cryst.* B**36**, 1478–1480.
Giglio, E. & Quagliata, C. (1975). *Acta Cryst.* B**31**, 743–746.
Klyne, W. & Prelog, V. (1960). *Experientia*, **16**, 521–523.
Sheldrick, G. M. (1994). *SHELXTL*. Version 5.03. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
Sheldrick, G. M. (1996). *SADABS. Empirical Absorption Correction Program*. University of Göttingen, Germany.
Siemens (1995). *SMART* and *SAINT*. *Area Detector Control and Integration Software*. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.

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3,5-Dichloro-4-(imidazolidin-2-ylideneammonio)benzoate dihydrate

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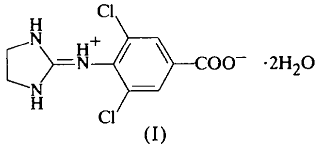
Abstract

The title compound, $C_{10}H_9Cl_2N_3O_2 \cdot 2H_2O$, exists in the zwitterionic form as a result of proton transfer from the carboxylic acid group to the bridging nitrogen. The imidazolidine ring adopts a half-chair conformation. The dihedral angle between the imidazolidine and phenyl rings is 67.29 (6)°, and the carboxyl group is twisted by 5.4 (1)° from the phenyl ring. The crystal structure is stabilized by a network of hydrogen bonds involving the two water molecules.

Comment

Clonidine, an imidazolidine derivative is one of the centrally acting antihypertensive drugs which act primarily *via* α-adrenoceptors in the brain. Quantitative structure–activity studies suggest that the antihypertensive activity of this molecule is governed by distinct steric and electronic characteristics (van Zwieten *et al.*, 1983). In recent years, a large number of imidazolidine derivatives were synthesized in an effort to obtain a more active molecule, but none of them were found to be more potent than clonidine itself.

The title compound, (I), differs from clonidine by the presence of an acid group at the *para*-position of the phenyl ring. Quantitative structure-activity studies showed that hypotensive activity is favoured when small groups are substituted at the *para*-position. Because this compound has a melting point in excess of 573 K and substantial solubility in water, it seemed possible that the compound exists as a zwitterion in the solid state. The X-ray structure determination of this compound was undertaken to evaluate this possibility and to study the molecular conformation.



(I)

The bond lengths and angles in the structure agree very well with those observed in clonidine (Byre *et al.*, 1976; Cody & DeTitta, 1979). The compound is found to be a zwitterion with protonation having occurred at the imino nitrogen. The imidazolidine ring adopts a half-chair conformation with asymmetry parameter ΔC_2(C7) = 0.0108 (8) (Nardelli, 1983); the mean plane through this ring make a dihedral angle of 67.29 (6)° with the phenyl plane. The carboxyl group is twisted by 5.4 (1)° from the phenyl ring [C3—C4—C10—O2 −5.1 (3) and C5—C4—C10—O1 −5.5 (2)°]. In the asymmetric unit, both water molecules are linked to the carboxyl group through O—H···O hydrogen bonds. In the crystal, all the N—H groups are involved in N—H···O intermolecular hydrogen bonds either with water or carboxyl O atoms to form a network structure (Table 2). The water O4 atom acquired full tetracoordination due to hydrogen bonding.

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