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Cholamide Dihydrate

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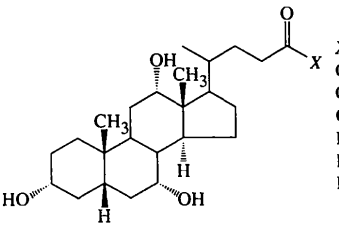
Abstract

The crystal structure of cholamide dihydrate (3α,7α,12α-trihydroxy-5β-cholan-24-amide dihydrate, $C_{24}H_{41}NO_4.2H_2O$), recrystallized from ethyl acetate by slow evaporation, has been determined. This structure is the first reported crystal structure of cholamide solvated solely with water.

Comment

Polymorphism, the ability of a compound to crystallize in different forms, is quite common (Byrn, 1982). Steroids are just one class of compounds which display polymorphic capabilities, often crystallizing into different solvated forms. One such group of steroids is cholic acid (3α,7α,12α-trihydroxy-5β-cholan-24-oic acid) and its derivatives methyl cholate (3α,7α,12α-trihydroxy-5β-cholan-24-oic acid methyl ester), sodium cholate (sodium 3α,7α,12α-trihydroxy-5β-cholan-24-oate), cholamide (3α,7α,12α-trihydroxy-5β-cholan-24-amide), *N*-methylcholamide (*N*-methyl-3α,7α,12α-trihydroxy-5β-cholan-24-amide) and *N*,*N*-dimethylcholamide (*N*,*N*-dimethyl-3α,7α,12α-trihydroxy-5β-cholan-24-amide). Many solvated structures have been reported for cholic acid (Lessinger, 1982; Lessinger & Low, 1993; Miki *et al.*, 1988; Johnson & Schaefer, 1972; Jones & Nassimbeni, 1990; Miki, Kasai, Shibakami, Takemoto & Miyata, 1991; Nakano, Sada & Miyata, 1994, 1996; Caira, Nassimbeni & Scott, 1993, 1994*a*,*b*, 1996; Shibakami & Sekiya, 1994; Scott, 1995). Recently, studies have expanded to include methyl cholate (Norton & Haner, 1965; Miyata *et al.*, 1987; Miki *et al.*, 1992; Wahle & Byrn, 1996*a*), sodium cholate (Norton & Haner, 1965; Cobbledick & Einstein, 1980; Wahle, Stowell & Byrn, 1996; Wahle & Byrn, 1996*b*), cholamide (Sada, Kondo, Miyata, Tamada & Miki, 1993; Sada, Kondo, Miyata & Miki, 1994; Wahle & Byrn, 1996*c*), *N*-methylcholamide (Sada & Miyata, 1996; Wahle & Byrn, 1997) and *N*,*N*-dimethylcholamide (Wahle & Byrn, 1997). Presently, the only crystal structures reported for cholamide are solvated with organic solvents (Sada *et al.*, 1993, 1994; Sada, Matsuura & Miyata, 1996) or a mix of organic solvent and water (Wahle & Byrn, 1996*c*). Here, we continue our examination of cholamide by reporting the first form solvated solely with water, *i.e.* cholamide dihydrate (*X* = $NH_2.2H_2O$).



X	Name
O^-Na^+	Sodium cholate
OH	Cholic acid
OMe	Methyl cholate
NH_2	Cholamide
NHMe	*N*-Methylcholamide
NMe_2	*N*,*N*-Dimethylcholamide

The *ORTEP*II (Johnson, 1976) diagram for cholamide dihydrate is presented in Fig. 1. The rings have a geometry similar to the structures of the other cholamide derivatives reported to date, with a *cis* ring juncture for the *A*/*B* rings and *trans* ring junctures for the *B*/*C* and *C*/*D* rings. When the dihydrate structure is overlaid using a least-squares fit with the 2-propanolate structure (Sada *et al.*, 1994) and the acetonitrile dihydrate structure (Wahle & Byrn, 1996*c*), the four steroid rings are quite similar, while the side chains differ considerably. Various torsion angles in the side chain differ considerably from one structure to another (Table 1). The steroid molecules pack in a twisted-layer pattern, with a tunnel of water molecules running parallel to the *b* axis. Fig. 2 presents the packing diagram drawn using *QUANTA*4.1 (Molecular Simulations Incorporated, 1995).

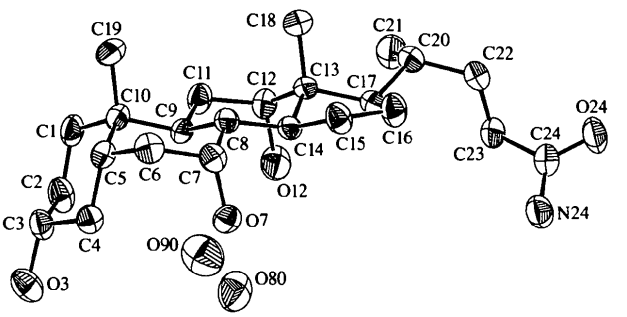


Fig. 1. *ORTEP*II (Johnson, 1976) diagram of cholamide dihydrate showing 50% probability displacement ellipsoids for non-H atoms. The water molecules are also included.

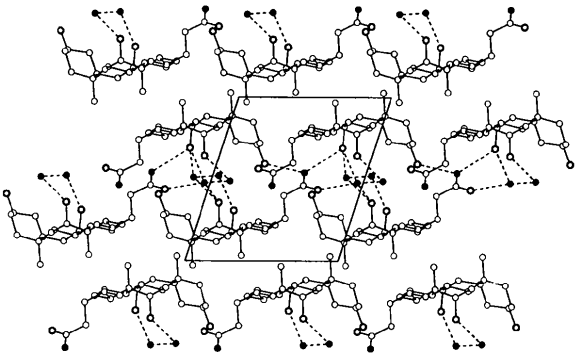


Fig. 2. Packing diagram for cholamide dihydrate viewed down the *b* axis. N atoms are represented by dark filled circles. Steroid O atoms are represented by dark open circles. Water O atoms are represented by light filled circles. Hydrogen bonds are represented by dashed lines.

The hydrogen bonding is quite complex and can be separated into three different groups: steroid–steroid, steroid–water and water–water hydrogen bonds (Table 2). Steroid–steroid hydrogen bonds exist between the O3 hydroxyl atom and the O24 amide atom, between the O3 hydroxyl atom and the N24 amide atom, and finally between the O7 hydroxyl atom and the N24 amide atom. Five steroid–water hydrogen bonds hold the water molecules in a tunnel. The O80 water atom hydrogen bonds to both the O7 and O12 hydroxyl atoms, and the O24 amide atom, while the O90 water atom hydrogen bonds to both the O7 and O12 hydroxyl atoms. Finally, one water–water hydrogen bond exists between the O80 and O90 water atoms. All of the O···O and O···N distances fall within the normally accepted ranges for hydrogen bonds. Fig. 2 presents the hydrogen-bonding patterns for cholamide dihydrate.

Experimental

Cholamide was synthesized from cholic acid (Sigma Chemical Co., St. Louis, MO, USA) using a mixed anhydride technique previously formulated (method *A*: Bellini, Quaglio, Guarneri & Cavazzini, 1983). After the cholamide precipitate was washed with ethyl acetate (Mallinckrodt Speciality Chemicals Co., Paris, KY, USA) and filtered, the ethyl acetate filtrate was preserved and allowed to evaporate to dryness, during which time the cholamide dihydrate crystals grew.

Crystal data

$C_{24}H_{41}NO_4.2H_2O$
M_r = 443.63
Monoclinic
$P2_1$
a = 10.3344 (7) Å
b = 10.8162 (7) Å
c = 11.3620 (7) Å
β = 108.730 (6)°
V = 1202.8 (3) Å^3
Z = 2
D_x = 1.22 Mg m^{-3}
D_m not measured
Cu $K\alpha$ radiation
λ = 1.54184 Å
Cell parameters from 25 reflections
θ = 40–46°
μ = 0.661 mm^{-1}
T = 296 K
Block
0.25 × 0.25 × 0.25 mm
Colorless

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: none
2717 measured reflections
2587 independent reflections
2232 reflections with $I > 2\sigma(I)$
R_{int} = 0.030
θ_{max} = 74.33°
$h = -12 \rightarrow 12$
$k = -13 \rightarrow 0$
$l = -14 \rightarrow 0$
3 standard reflections
frequency: 83 min
intensity decay: 3.35%

Refinement

Refinement on F^2
$R(F)$ = 0.042
$wR(F^2)$ = 0.130
S = 1.062
2587 reflections
302 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.0856P)^2 + 0.0664P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.003
$\Delta\rho_{max}$ = 0.16 e Å^{-3}
$\Delta\rho_{min}$ = −0.28 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)
Absolute configuration: known fragment

Table 1. *Torsion angle data (°) for three cholamide solvates: dihydrate, (I), 2-propanolate, (II), and acetonitrile dihydrate, (III)*

	(I)	(II)	(III)
C17—C20—C22—C23	67.7 (4)	−156.6†	67.9 (5)
C20—C22—C23—C24	−153.8 (3)	176.8†	−172.5 (4)
C22—C23—C24—N24	115.3 (4)	129.8†	115.9 (5)

† Measured using *QUANTA*4.1 (Molecular Simulations Incorporated, 1995).

Table 2. *Hydrogen-bonding data (Å) for (I)*

O3···O24^{i}	2.748 (3)	O12···O80^{iv}	2.760 (5)
O3···N24^{ii}	2.933 (4)	O12···O90	2.699 (4)
O7···N24^{iii}	3.052 (4)	O24···O80^{v}	2.789 (4)
O7···O80	2.813 (4)	O80···O90	2.639 (6)
O7···O90^{ii}	2.885 (4)		

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

The e.s.d.'s for the C—C bond lengths average 0.004 (4) Å (range 0.003–0.005 Å). Atoms H1N, H2N, H81O and H82O were refined isotropically, while the other H atoms were not refined ($U = 1.3U_{eq}$ of bonding atom). The O—H bond lengths for the refined H atoms average 0.9 (1) Å, while the e.s.d.'s average 0.08 Å (range 0.07–0.09 Å). The N—H bond lengths average 0.945 (7) Å, while the e.s.d.'s average 0.06 Å (range 0.05–0.07 Å).

Data collection: *CAD-4 Operations Manual* (Enraf–Nonius, 1977). Cell refinement: *CAD-4 Operations Manual*. Data reduction: *PROCESS* in *MolEN* (Fair, 1990). Program(s) used to solve structure: *SIR* (direct methods) (Altomare *et al.*, 1994). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *ORTEP*II (Johnson, 1976). Software used to prepare material for publication: *CIF VAX* in *MolEN*.

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Lists of atomic coordinates, displacement parameters, structure factors and complete geometry have been deposited with the IUCr (Reference: BK1304). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Anti-Inflammatory Drugs. V. [Tris-(2-hydroxymethyl)methyl]ammonium 2-[(2,6-Dichlorophenyl)amino]phenylacetate (TRISH.D)

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Abstract

The structure of the title compound, $C_4H_{12}NO_3^+.C_{14}H_{10}Cl_2NO_2^-$, in the solid state consists of a two-dimensional network of hydrogen-bonded TRISH$^+$ {[tris(2-hydroxymethyl)methyl]ammonium} cations and D$^-$ {2-[(2,6-dichlorophenyl)amino]phenylacetate} anions lined up along the [100] and [010] directions, respectively. Comparisons between the conformations of the TRISH$^+$ cation and the TRIS base ($C_4H_{11}NO_3$) show that the intermolecular hydrogen bonds have a major influence on determining the structures.

Comment

Diclofenac derivatives like the title compound, (I), are powerful anti-inflammatory drugs which are widely used in the form of soluble salts. Thus, as in our previous crystallographic studies on analogous derivatives, attention has been devoted to the relationship between the solid-state conformation of this diclofenac salt and its solubility. Moreover, the interaction between tris(hydroxymethyl)(amino)methane (TRIS) and drugs might be relevant to biochemical studies, since the TRIS buffer is widely used in the physiological pH range 7–9. Other structures of this class of non-steroidal anti-inflammatory drugs determined so far are those of the sodium salt tetrahydrate, NaD.4H_2O (Reck, Faust & Dietz, 1988), the free acid, HD (Moser, Sallmann & Wiesenberg, 1990; Kovala-Demertzi, Mentzafos & Terzis, 1993), the (2-hydroxyethyl)pyrrolidinium salt, EPH.D (Castellari & Sabatino, 1994; Ledwige, Draper, Wilcock & Corrigan, 1996), the (2-hydroxyethyl)-pyrrolidinium salt dihydrate, EPHD.2H_2O (Ledwige, Draper, Wilcock & Corrigan, 1996), the bis(2-hydroxyethyl)ammonium salt, NDEAH.D (Castellari & Ottani, 1995), the (2-hydroxyethyl)piperidinium, (2-hydroxyethyl)morpholinium and (2-hydroxyethyl)piperazinium salts, HEPP.D, HEM.D and HEPZ.D, respectively (Castellari & Sabatino, 1996), and the tris(2-hydroxy-