Monoclinic
$P2_1/a$
a = 12.928 (5) Å
b = 5.546 (5) Å
c = 16.445 (5) Å
β = 92.392 (5)°
V = 1178.1 (12) Å^3
Z = 4
D_x = 1.385 Mg m^{-3}
D_m not measured

Cell parameters from 250 reflections
θ = 2.48–24.91°
μ = 0.305 mm^{-1}
T = 150 (2) K
Lozenge
0.22 × 0.16 × 0.10 mm
Yellow

Data collection

Delft Instruments FAST diffractometer
Area detector scans
Absorption correction: none
4719 measured reflections
1783 independent reflections

1152 reflections with $I > 2\sigma(I)$
R_{int} = 0.0628
θ_{max} = 24.91°
$h = -14 \rightarrow 11$
$k = -5 \rightarrow 6$
$l = -16 \rightarrow 18$

Refinement

Refinement on F^2
$R(F)$ = 0.033
$wR(F^2)$ = 0.0708
S = 0.736
1780 reflections
156 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.0221P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{max}$ = 0.04
$\Delta\rho_{max}$ = 0.18 e Å^{-3}
$\Delta\rho_{min}$ = −0.15 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °)*

Cl—C5	1.745 (2)	C1—C2	1.437 (3)
O—C7	1.237 (2)	C1—C7	1.466 (3)
N—C2	1.362 (3)	C7—C8	1.501 (3)
N—C14	1.441 (3)		
C2—N—C14	124.1 (2)	O—C7—C8	116.9 (2)
O—C7—C1	122.0 (2)	C1—C7—C8	121.2 (2)
C6—C1—C7—O	−163.8 (2)	O—C7—C8—C13	41.3 (3)
C2—C1—C7—O	13.6 (3)	C1—C7—C8—C13	−138.8 (2)
C6—C1—C7—C8	16.3 (3)	O—C7—C8—C9	−133.3 (2)
C2—C1—C7—C8	−166.3 (2)	C1—C7—C8—C9	46.6 (3)

The unit cell and intensity data were collected on a Delft Instruments FAST diffractometer using the routines *ENDEX*, *REFINE* and *MADONL* in the *MADNES* software (Pflugrath & Messerschmidt, 1989), and processed using *ABSMAD* (Karaulov, 1992); detailed procedures are described by Darr, Drake, Hursthouse & Malik (1993). The H atoms were initially placed in calculated positions and thereafter allowed to ride on their attached C atoms, with common isotropic displacement parameters of 0.024 (9) (for non-methyl H atoms) and 0.044 (1) Å^2 (for methyl H atoms).

Program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994). Program(s) used to refine structure: *SHELXL93* (Sheldrick, 1993). Molecular graphics: *ZORTEP* (Zsolnai, 1996).

The use of the EPSRC X-ray Crystallographic Service at the University of Wales, Cardiff, and the assistance of Neil S. Stewart of the Cambridge Crystallographic Data Centre are gratefully acknowledged.

Lists of atomic coordinates, displacement parameters, structure factors and complete geometry have been deposited with the IUCr (Reference: BM1125). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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The Dipeptide pGlu–Pro-NH_2

JOHAN WOUTERS, BERNADETTE NORBERG AND GUY EVRARD

Laboratoire de Chimie Moleculaire Structurale, Facultes Universitaires Notre-Dame de la Paix, 61 Rue de Bruxelles, B-5000 Namur, Belgium. E-mail: wouters@scf.fundp.ac.be

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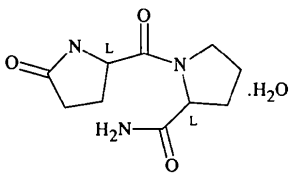
Abstract

The crystal structure of the pGlu–Pro-NH_2 dipeptide, *cis*-1-(5-oxo-L-prolyl)-L-prolinamide hydrate [*cis*-1-(5-oxo-L-prolyl)pyrrolidine-2-carboxamide hydrate], $C_{10}H_{15}N_3O_3.H_2O$, has been determined in order to establish

the conformation of the pyrrolidine ring both in natural (L) proline (Pro) and in pyroglutamic acid (pGlu), a cyclic analogue of the the natural L-glutamate amino acid. The structure was solved by direct methods and refined by least-squares calculations to a final R value of 0.026. While the pyrrolidine ring of the Pro residue adopts a twisted conformation, this ring is planar in the pGlu amino acid. The proline residue is in a *cis* orientation with respect to the peptide bond. Molecular cohesion is stabilized by a dense network of hydrogen bonds involving the free amine group of pGlu, the three O atoms of the carbonyl groups, the terminal carboxy-protective NH_2 group and a water molecule.

Comment

pGlu–Pro-NH_2, (I), where pGlu stands for α-amino-glutaric acid lactam [p(yro)Glu, glutim(in)ic acid] crystallizes in space group $P2_1$ with one molecule of dipeptide and one water molecule in the asymmetric unit. Its absolute configuration was assigned as L-pGlu and L-Pro. An analogue of the title compound, where Pro-NH_2 is replaced by L-thiazolidine-4-carboxylic acid, which displays immunomodulant drug activity on CD4 and T-lymphocyte functions has been reported recently (Ayala, Bombieri, Perosino & Stradi, 1995).



(I)

The molecular structure of (I) with the atom-numbering scheme is illustrated in Fig. 1. The three amide C—N bond distances [C2—N6 1.335 (3), C7—N9 1.330 (2) and C14—N16 1.327 (4) Å] have double-bond character indicating electronic delocalization with the adjacent carbonyl function. The C—O bonds [C2—O1 1.226 (3), C7—O8 1.233 (3) and C14—O15 1.228 (2) Å] show a more marked double-bond character (Allen *et al.*, 1987). The pyrrolidone ring adopts a quasi-planar conformation (r.m.s. deviation from the best plane through the atoms of the ring is 0.054 Å, with a maximum deviation of −0.046 Å for atom C2). The prolyl ring has puckering parameters $\varphi(2)$ of 236.3 (20)° and $Q(2)$ of 0.076 (3) Å (Cremer & Pople, 1975), indicative of a 'twisted' conformation.

The acute angle between the planes defined by the prolyl and pyrrolidone rings is 62.4 (2)°. The molecular structure of pGlu–Pro-NH_2 is characterized by a *cisoid* geometry around the peptide bond for the terminal residue (Table 1).

The structure of the title compound is in good agreement with the structure reported recently by Ayala *et al.* (1995), the r.m.s. deviation calculated on all 16 non-H atoms being 0.45 Å. Differences are mainly located at the pGlu ring, which is planar in the title structure and 'twisted' in the related one.

Molecular cohesion (Fig. 2) is achieved by intermolecular hydrogen-bonding interactions involving the free amine group of pGlu, the three O atoms of the carbonyl functions, the terminal carboxy-protective NH_2 group and a water molecule (Table 2).

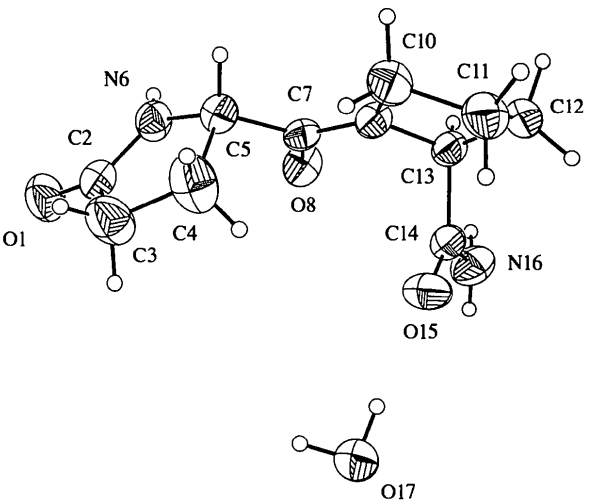


Fig. 1. The molecular structure and conformation of (I), together with the atomic numbering. Non-H atoms are represented by displacement ellipsoids at the 50% probability level.

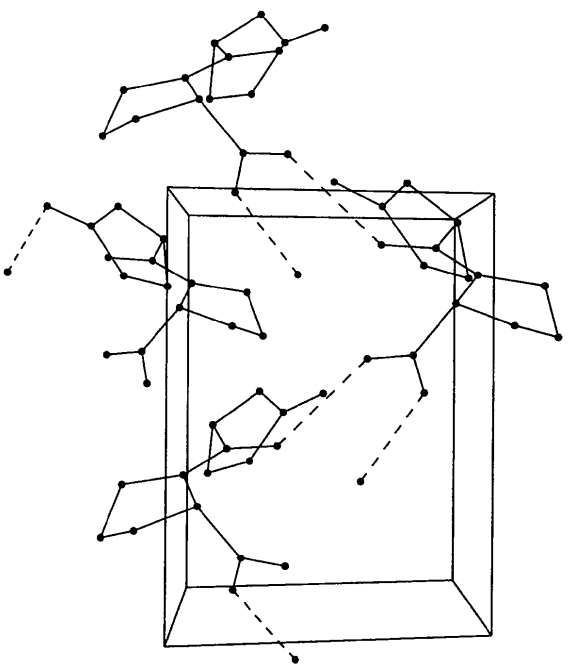


Fig. 2. Crystal-packing diagram (dotted lines indicate hydrogen-bond interactions). H atoms have been omitted.

Experimental

A sample of the title compound was obtained from Bioproduct, Peptide Department, UCB s.a., 68 rue Berkendael, Bruxelles, Belgium.

Crystal data

$C_{10}H_{15}N_3O_3.H_2O$
$M_r = 243.3$
Monoclinic
$P2_1$
$a = 10.154\ (2)$ Å
$b = 8.968\ (2)$ Å
$c = 6.749\ (2)$ Å
$\beta = 104.0\ (2)°$
$V = 596.3\ (3)$ Å^3
$Z = 2$
$D_x = 1.355$ Mg m^{-3}
D_m not measured
Cu $K\alpha$ radiation
$\lambda = 1.54178$ Å
Cell parameters from 25 reflections
$\theta = 30–40°$
$\mu = 0.887$ mm^{-1}
$T = 293\ (2)$ K
Prism
0.2 × 0.2 × 0.1 mm
Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: none
1249 measured reflections
1247 independent reflections
1202 reflections with $I > 2\sigma(I)$
$R_{int} = 0.0525$
$\theta_{max} = 71.87°$
$h = -12 \rightarrow 12$
$k = -7 \rightarrow 11$
$l = -8 \rightarrow 8$
3 standard reflections
every 60 reflections
intensity decay: none

Refinement

Refinement on F^2
$R(F) = 0.0256$
$wR(F^2) = 0.0764$
$S = 1.084$
1247 reflections
159 parameters
H atoms riding
$w = 1/[\sigma^2(F_o^2) + (0.0496P)^2 + 0.0593P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.003$
$\Delta\rho_{max} = 0.123$ e Å^{-3}
$\Delta\rho_{min} = -0.143$ e Å^{-3}
Extinction correction: *SHELXL*93
Extinction coefficient: 0.040 (3)
Scattering factors from *International Tables for Crystallography* (Vol. C)
Absolute configuration: Flack (1983)
Flack parameter = −0.0 (2)

Table 1. *Selected geometric parameters (Å, °)*

O1—C2	1.226 (3)	N9—C13	1.466 (2)
C2—N6	1.335 (3)	N9—C10	1.476 (3)
C2—C3	1.511 (3)	C10—C11	1.522 (3)
C3—C4	1.482 (4)	C11—C12	1.521 (4)
C4—C5	1.554 (3)	C12—C13	1.542 (2)
C5—N6	1.447 (2)	C13—C14	1.522 (2)
C5—C7	1.520 (3)	C14—O15	1.228 (2)
C7—O8	1.233 (3)	C14—N16	1.327 (4)
C7—N9	1.330 (2)		
O1—C2—N6	125.6 (2)	C7—N9—C13	118.5 (2)
O1—C2—C3	126.2 (2)	C7—N9—C10	128.5 (1)
N6—C2—C3	108.2 (2)	C13—N9—C10	112.6 (2)
C4—C3—C2	106.3 (2)	N9—C10—C11	102.9 (2)
C3—C4—C5	106.3 (2)	C12—C11—C10	103.8 (2)
N6—C5—C7	110.8 (2)	C11—C12—C13	103.8 (2)
N6—C5—C4	103.4 (2)	N9—C13—C14	110.2 (2)
C7—C5—C4	110.8 (2)	N9—C13—C12	103.1 (2)
C2—N6—C5	115.1 (2)	C14—C13—C12	111.7 (1)
O8—C7—N9	121.0 (2)	O15—C14—N16	124.2 (2)
O8—C7—C5	121.0 (2)	O15—C14—C13	120.6 (2)
N9—C7—C5	118.0 (2)	N16—C14—C13	115.1 (2)
O1—C2—C3—C4	173.5 (2)	C5—C7—N9—C10	0.9 (3)
N6—C2—C3—C4	−8.5 (3)	C7—N9—C10—C11	157.7 (2)
C2—C3—C4—C5	6.6 (3)	C13—N9—C10—C11	−14.7 (2)
C3—C4—C5—N6	−2.7 (3)	N9—C10—C11—C12	31.9 (2)
C3—C4—C5—C7	−121.5 (2)	C10—C11—C12—C13	−37.5 (2)
O1—C2—N6—C5	−174.7 (2)	C7—N9—C13—C14	−62.2 (2)
C3—C2—N6—C5	7.2 (2)	C10—N9—C13—C14	111.1 (2)
C7—C5—N6—C2	115.8 (2)	C7—N9—C13—C12	178.44 (15)
C4—C5—N6—C2	−2.9 (2)	C10—N9—C13—C12	−8.3 (2)
N6—C5—C7—O8	−11.3 (2)	C11—C12—C13—N9	28.0 (2)
C4—C5—C7—O8	102.9 (2)	C11—C12—C13—C14	−90.3 (2)
N6—C5—C7—N9	170.6 (2)	N9—C13—C14—O15	−43.7 (2)
C4—C5—C7—N9	−75.2 (2)	C12—C13—C14—O15	70.3 (2)
O8—C7—N9—C13	−5.0 (3)	N9—C13—C14—N16	139.9 (2)
C5—C7—N9—C13	173.2 (1)	C12—C13—C14—N16	−106.1 (2)
O8—C7—N9—C10	−177.1 (2)		

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N6—H6···O17^{i}	0.763	2.365	3.126 (4)	175.3
N16—H16A···O8^{ii}	0.795	2.102	2.866 (3)	161.2
N16—H16B···O17^{iii}	0.943	2.089	2.985 (5)	158.0
O17—H17A···O1^{iv}	0.927	1.920	2.840 (3)	172.1
O17—H17B···O15	0.888	1.972	2.859 (3)	177.2

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

Correction for background, decay, Lorentz and polarization factors were included in the data reduction. The structure was solved by direct methods using *SHELXS*86 (Sheldrick, 1990) and resulted in reliable positions for all non-H atoms. The initial model was refined by least-squares techniques with *SHELXL*93 (Sheldrick, 1993). Non-H atoms were refined with anisotropic displacement factors. H atoms potentially involved in hydrogen bonding (*i.e.* those on N6, N16 and O17) were located by Fourier difference synthesis while the others were calculated. The positions of all the H atoms were refined using the riding model method. *PLATON*94 (Spek, 1994) was used for the geometry analysis of the structure. Most machine calculations were conducted on an IBM RISC6000. The coordinates of 3-(5-oxo-L-prolyl)-L-thiazolidine-4-carboxylic acid (Ayala *et al.*, 1995) were inverted in order to generate the right absolute configuration. Comparison of the structures was performed using the in-house *KEMIT* program (Vanderveken & Vercauteren, 1991).

Data collection: *CAD*-4 *Software* (Enraf–Nonius, 1989). Cell refinement: *CAD*-4 *Software*. Molecular graphics: *ORTEP*II (Johnson, 1976). Software used to prepare material for publication: *PLATON*94.

JW thanks the National Fundation for Scientific Research (FNRS Belgium) for his Senior Research Assistant position.

Lists of atomic coordinates, displacement parameters, structure factors and complete geometry have been deposited with the IUCr (Reference: DU1169). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Cholamide Dihydrate

MARK C. WAHLE,[a] PHILLIP E. FANWICK[b] AND STEPHEN R. BYRN[a]

[a]*Department of Medicinal Chemistry and Molecular Pharmacology, Purdue University, W. Lafayette, IN 47907-1333, USA, and* [b]*Department of Chemistry, Purdue University, W. Lafayette, IN 47907, USA. E-mail: spike@sparky.pharmacy.purdue.edu*

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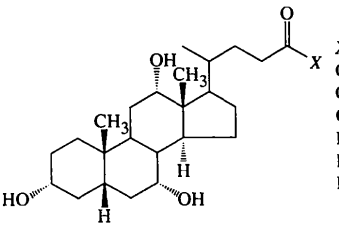
Abstract

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).

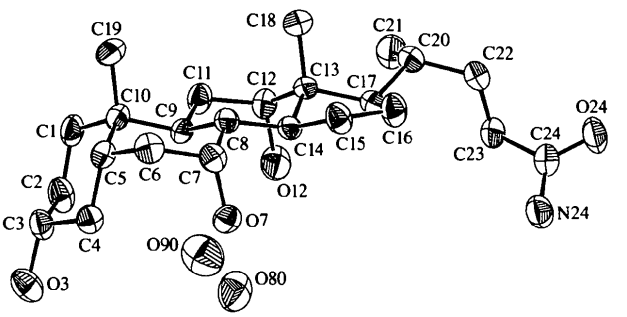


Fig. 1. *ORTEP*II (Johnson, 1976) diagram of cholamide dihydrate showing 50% probability displacement ellipsoids for non-H atoms. The water molecules are also included.