Boldine hydrochloride	26.8 (3)	*g*
Cataline (free base)	27.9 (1)	*h*
Bulbocapnine methiodide	30.1 (3)	*i*
Isocorydine methiodide	30.6 (6)	*j*
Bulbocapnine (free base)	31.3 (5)	*k*
Isocorydine (free base)	31.8 (3)	*l*

References: (*a*) Brown & Hall (1977); (*b*) Roques, Declerq & Germain (1978); (*c*) Giesecke (1973); (*d*) Ribár, Mészáros, Engel *et al.* (1991); (*e*) Roques, Djakouré & Rossi (1978); (*f*) Zabel *et al.* (1979); (*g*) This work; (*h*) Fonseca & García-Blanco (1984); (*i*) Wei *et al.* (1984); (*j*) Touré *et al.* (1985); (*k*) Ribár, Mészáros, Gasic *et al.* (1991); (*l*) Ribár *et al.* (1992).

Data collection: *P3/P4–PC Diffractometer Program* (Siemens, 1991). Cell refinement: *P3/P4–PC Diffractometer Program*. Data reduction: *XDISK* in *SHELXTL-Plus* (Sheldrick, 1992). Program(s) used to solve structure: *XS* in *SHELXTL-Plus*. Program(s) used to refine structure: *XLS* in *SHELXTL-Plus*. Molecular graphics: *XP* in *SHELXTL-Plus*. Software used to prepare material for publication: *XPUBL* in *SHELXTL-Plus*.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry, including contact distances, have been deposited with the IUCr (Reference: PT1029). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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[D-Ala^2,D-Leu^5]-Enkephalin Hydrochloride

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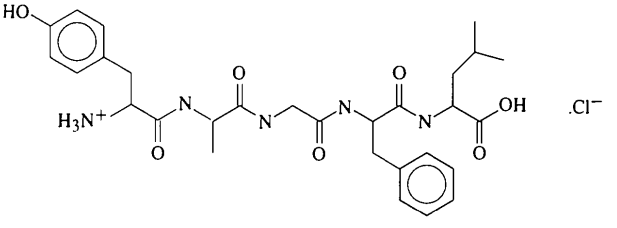
Abstract

The title compound, L-tyrosyl-D-alanyl-glycyl-L-phenylalanyl-D-leucine hydrochloride ($C_{29}H_{40}N_5O_7^+.Cl^-$), co-crystallizes with 2-butanone (C_4H_8O). The structure determination reveals a slightly distorted type I′ β-bend conformation stabilized by one intramolecular hydrogen bond. This conformation is similar to that observed for other [Leu]-enkephalin analogues.

Comment

[D-Ala^2,D-Leu^5]-enkephalin (DADLE) is a linear opioid peptide agonist which has slightly improved δ-receptor selectivity when compared with [Leu]-enkephalin (Schiller, 1991). DADLE is an important opioid peptide often used as a standard in activity studies.



DADLE.HCl

The crystal structure of DADLE is shown in Fig. 1. The bond distances and angles observed in this structure were within accepted limits. Except for the disordered Leu side-chain, the e.s.d.s for the bond lengths ranged from 0.009 to 0.020 Å in the peptide, and from 0.014 to 0.020 Å in the solvent; the e.s.d.s for the bond angles ranged from 0.6 to 1.4° in the peptide, and 1.2 to 1.7° in the solvent. The Leu^5 side-chain is disordered with approximately equal occupancy for the two positions. The respective conformation of the disorder may be described by the χ^1 torsion angles N5—C5*A*—C5*B*—C5*G* of 68.6 (8)° and N5—C5*A*—C5*B*′—C5*G*′ of 159.5 (7)°.

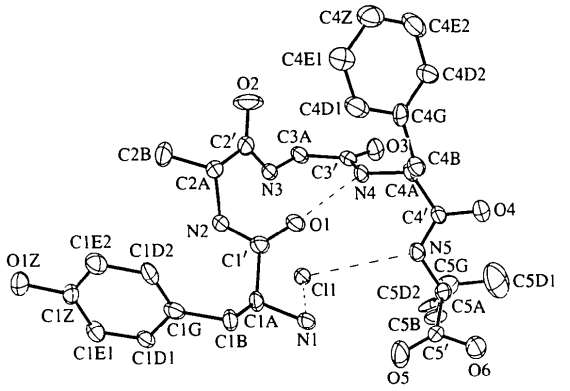


Fig. 1. View of DADLE.HCl showing the labelling of the non-H atoms. Displacement ellipsoids are shown at 20% probability levels; H atoms and solvent have been omitted for clarity; hydrogen bonds which stabilize the conformation are shown as dashed lines.

The peptide backbone has a slightly distorted type I′ β-bend folded conformation as evidenced by the φ and ψ torsion angles for residues 2 and 3, which are 75.3 (12), 7.8 (13), 98.1 (11) and −5.2 (12)° (ideal values are 60, 30, 90 and 0°) (Venkatachalam, 1968). The substitution of a D-Ala residue for Gly[2] does not appear to have caused any major changes in the peptide backbone conformation when compared with the single bend conformation observed in [Leu]-enkephalin (Smith & Griffin, 1978). However, the D-Leu[5] substitution causes a rotation of approximately 180° around φ_5 [*i.e.* 111° as opposed to values ranging from −79 to −141° for the folded [Leu]-enkephalins (Deschamps, George & Flippen-Anderson, 1995)] such that O4 faces the outside of the backbone (Fig. 1 and Table 2).

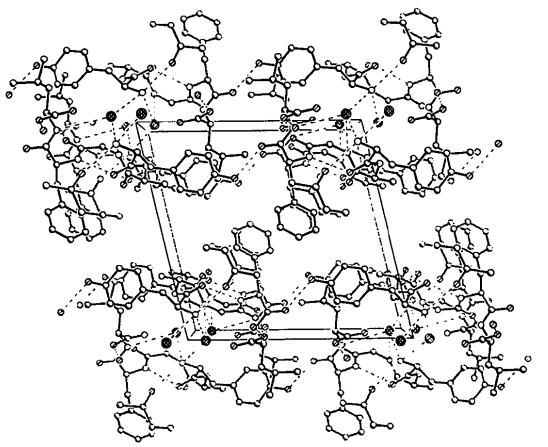


Fig. 2. Packing diagram of DADLE.HCl.C_4H_8O looking down the *b* axis. H atoms have been omitted for clarity; hydrogen bonds are shown as dashed lines.

The type I′ β-bend found in many [Leu]-enkephalins is stabilized by two intramolecular hydrogen bonds (*i.e.* N1—H···O4 and N4—H···O1). The structure of DADLE has only one intramolecular hydrogen bond, between O1 and N4. The second intramolecular hydrogen bond normally formed between residues N1 and O4 is absent due to the change in the orientation of O4. The backbone conformation is stabilized instead *via* a hydrogen bridge through Cl^- which links N1 and N5 (N1—H···Cl···H—N5), as shown in Fig. 1.

The hydrogen bonding (Table 3) also strongly influences the packing (Fig. 2). The molecules are linked into infinite sheets in the *yz* plane by O1Z···O4 hydrogen bonds along the *z* direction and O6···O3 hydrogen bonds along the *y* direction. On one side these sheets are linked through hydrogen bonding to the Cl^- ion, while on the other side of the sheet there are only hydrophobic interactions between the Phe[4] side chains and the saturated hydrocarbon chain of the solvent molecule.

Experimental

DADLE.HCl (2 mg) was dissolved in 300 µl of 2-butanone; crystals were prepared by slow evaporation of this solution at 295 K over a period of approximately 5 d.

Crystal data

$C_{29}H_{40}N_5O_7^+.Cl^-.C_4H_8O$
M_r = 678.22
Monoclinic
$P2_1$
a = 14.498 (5) Å
b = 9.263 (3) Å
c = 14.703 (4) Å
β = 103.16 (2)°
V = 1922.7 (9) Å^3
Z = 2
D_x = 1.171 Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
λ = 1.54178 Å
Cell parameters from 25 reflections
θ = 30.57–49.87°
μ = 1.304 mm^{-1}
T = 293 (2) K
Rod-shaped
0.44 × 0.22 × 0.08 mm
Colorless

Data collection

Siemens *R3m/V* diffractometer
$\theta/2\theta$ scans
Absorption correction: none
2806 measured reflections
2611 independent reflections
1657 observed reflections [$I > 2\sigma(I)$]
R_{int} = 0.0200

θ_{max} = 55.05°
$h = -15 \rightarrow 15$
$k = 0 \rightarrow 9$
$l = 0 \rightarrow 15$
3 standard reflections monitored every 97 reflections
intensity decay: 12% (linear)

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.0811
$wR(F^2)$ = 0.2138
S = 1.094
2611 reflections

Extinction correction: *SHELXL* (Sheldrick & Schneider, 1996)
Extinction coefficient: 0.0027 (5)

450 parameters
H atoms riding
$w = 1/[\sigma^2(F_o^2) + (0.1054P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.400$
$\Delta\rho_{max} = 0.261$ e Å^{-3}
$\Delta\rho_{min} = -0.197$ e Å^{-3}
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)
Absolute configuration: Flack (1983) parameter = 0.03 (6)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)*

$U_{eq} = (1/3)\sum_i\sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
Cl1	0.0082 (2)	0.3878 (3)	0.92339 (13)	0.0693 (7)
N1	−0.1244 (5)	0.6554 (7)	0.9318 (4)	0.066 (2)
C1*A*	−0.1572 (6)	0.5737 (10)	1.0052 (5)	0.059 (2)
O1	−0.2500 (4)	0.4397 (6)	0.8779 (4)	0.076 (2)
C1*B*	−0.2242 (6)	0.6676 (10)	1.0511 (5)	0.069 (3)
C1*G*	−0.2370 (6)	0.5992 (10)	1.1405 (6)	0.069 (3)
C1*D*1	−0.1640 (6)	0.5986 (10)	1.2197 (5)	0.061 (3)
C1*E*1	−0.1736 (6)	0.5358 (11)	1.3013 (6)	0.068 (3)
C1*Z*	−0.2545 (7)	0.4698 (10)	1.3064 (6)	0.065 (3)
C1*E*2	−0.3325 (7)	0.4719 (13)	1.2284 (6)	0.083 (3)
C1*D*2	−0.3189 (7)	0.5374 (12)	1.1468 (5)	0.079 (3)
O1*Z*	−0.2709 (4)	0.4046 (9)	1.3854 (4)	0.094 (2)
N2	−0.2090 (6)	0.3282 (8)	1.0172 (4)	0.074 (2)
C2*A*	−0.2724 (8)	0.2009 (11)	0.9871 (6)	0.095 (4)
C2′	−0.2373 (9)	0.1080 (12)	0.9197 (6)	0.100 (4)
O2	−0.2839 (7)	0.0037 (11)	0.8822 (6)	0.184 (4)
C1′	−0.2103 (7)	0.4411 (10)	0.9592 (6)	0.073 (3)
C2*B*	−0.2865 (9)	0.1138 (13)	1.0688 (6)	0.127 (5)
N3	−0.1515 (6)	0.1317 (8)	0.9003 (4)	0.072 (2)
C3*A*	−0.1123 (7)	0.0579 (10)	0.8332 (5)	0.073 (3)
C3′	−0.1225 (7)	0.1329 (11)	0.7420 (6)	0.070 (3)
O3	−0.0840 (5)	0.0870 (7)	0.6819 (4)	0.084 (2)
N4	−0.1731 (5)	0.2551 (7)	0.7279 (4)	0.062 (2)
C4*A*	−0.1986 (6)	0.3254 (10)	0.6354 (5)	0.063 (3)
C4′	−0.1234 (7)	0.4290 (10)	0.6162 (5)	0.069 (3)
O4	−0.1324 (5)	0.4663 (9)	0.5353 (4)	0.102 (2)
C4*B*	−0.2905 (6)	0.4054 (12)	0.6249 (6)	0.072 (3)
C4*G*	−0.3764 (7)	0.3073 (11)	0.6162 (6)	0.068 (3)
C4*D*1	−0.4221 (8)	0.2922 (13)	0.6877 (7)	0.098 (4)
C4*E*1	−0.4989 (8)	0.2050 (15)	0.6797 (8)	0.111 (4)
C4*Z*	−0.5307 (9)	0.1259 (15)	0.6019 (8)	0.122 (5)
C4*E*2	−0.4853 (9)	0.1381 (16)	0.5305 (7)	0.116 (5)
C4*D*2	−0.4070 (8)	0.2262 (11)	0.5390 (7)	0.086 (3)
N5	−0.0552 (6)	0.4757 (8)	0.6835 (5)	0.071 (2)
C5*A*	0.0156 (2)	0.5770 (7)	0.6663 (5)	0.066 (3)
C5′	−0.0020 (8)	0.7213 (11)	0.7126 (6)	0.092 (4)
O6	−0.0279 (6)	0.8220 (8)	0.6508 (4)	0.102 (3)
O5	0.0147 (9)	0.7402 (9)	0.7941 (5)	0.179 (5)
C5*B*†	0.1227 (2)	0.5688 (6)	0.7000 (6)	0.088 (7)
C5*G*†	0.1564 (3)	0.4433 (7)	0.6493 (3)	0.098 (8)
C5*D*1†	0.151 (2)	0.481 (3)	0.5476 (6)	0.23 (2)
C5*D*2†	0.2594 (4)	0.413 (2)	0.6955 (14)	0.112 (9)
C5*B*′‡	0.1081 (2)	0.4952 (8)	0.6990 (6)	0.047 (6)
C5*G*′‡	0.1928 (3)	0.5451 (10)	0.6624 (3)	0.119 (10)
C5*D*3‡	0.2872 (6)	0.4701 (18)	0.6987 (18)	0.116 (11)
C5*D*4‡	0.1629 (6)	0.5667 (8)	0.5574 (3)	0.116 (11)
O1*S*	−0.2514 (6)	0.7352 (8)	0.7659 (3)	0.145 (4)
C1*S*	−0.3032 (6)	0.8623 (8)	0.6185 (3)	0.246 (11)
C2*S*	−0.3198 (10)	0.7835 (17)	0.7117 (10)	0.138 (6)
C3*S*	−0.4149 (12)	0.783 (2)	0.7315 (12)	0.185 (8)
C4*S*	−0.4264 (18)	0.710 (2)	0.8103 (12)	0.263 (13)

† Occupancy = 0.526 (11). ‡ Occupancy = 0.474 (11).

Table 2. *Selected torsion angles (°)*

N1—C1*A*—C1′—N2	152.8 (8)	C3*A*—C3′—N4—C4*A*	−171.0 (8)
C1*A*—C1′—N2—C2*A*	168.7 (8)	C3′—N4—C4*A*—C4′	−86.7 (10)
C1′—N2—C2*A*—C2′	75.3 (12)	N4—C4*A*—C4′—N5	−15.5 (12)
N2—C2*A*—C2′—N3	7.8 (13)	C4*A*—C4′—N5—C5*A*	−178.6 (7)
C2*A*—C2′—N3—C3*A*	−175.5 (8)	C4′—N5—C5*A*—C5′	111.4 (9)
C2′—N3—C3*A*—C3′	98.1 (11)	N1—C1*A*—C1*B*—C1*G*	−165.7 (7)
N3—C3*A*—C3′—N4	−5.2 (12)	N4—C4*A*—C4*B*—C4*G*	−69.9 (9)

Table 3. *Hydrogen-bonding geometry (Å, °)*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1*A*···Cl1^{i}	0.89	2.381 (7)	3.221 (2)	157.4 (2)
N1—H1*B*···O1*S*	0.89	1.943 (7)	2.799 (3)	161.0 (3)
N1—H1C···Cl1	0.89	2.375 (7)	3.156 (2)	146.5 (2)
N3—H3···Cl1	0.86	2.549 (8)	3.277 (2)	143.0 (2)
N4—H4···O1	0.86	2.340 (9)	3.186 (2)	167.9 (2)
N5—H5···Cl1	0.86	2.699 (7)	3.531 (2)	163.3 (2)
O1*Z*—H1*Z*···O4^{ii}	0.82	1.879 (8)	2.681 (3)	166.4 (3)
O6—H6···O3^{iii}	0.82	1.894 (9)	2.659 (3)	154.6 (3)

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

The crystal used for this study was the only 'diffraction quality' crystal obtained from extensive crystallization trials. Efforts to produce better crystals have not been successful. The crystal growth conditions used in this study appear to be very sensitive to the presence of water, and it is likely that a disordered water molecule was present in the crystal structure. This would account for both the larger volume and the $(\Delta/\sigma)_{max}$ value of 0.40. However, attempts to refine on this water molecule were not successful. The crystal did degrade during data collection and therefore it was not possible to perform an absorption correction after the completion of data collection. For refinement, the C—C distances for the disordered atoms were constrained to be 1.520 (3) Å. The donor hydrogen-bond distance was fixed. All other values were calculated in the final cycles of refinement.

Data collection: *SHELXTL-Plus* (Sheldrick, 1991). Cell refinement: *SHELXTL-Plus*. Data reduction: *SHELXTL-Plus*. Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL* (Sheldrick & Schneider, 1996). Molecular graphics: *SHELXTL-Plus*. Software used to prepare material for publication: *SHELXTL-Plus*.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: BK1199). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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