Lists of structure factors, anisotropic displacement parameters, atomic coordinates and complete geometry have been deposited with the IUCr (Reference: TA1115). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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L-Histidylglycinium Dichloride

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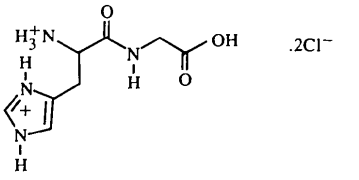
Abstract

In the title compound, $C_8H_{14}N_4O_3^{2+}.2Cl^-$, the dipeptide His–Gly crystallizes as a dication. The positively charged imidazole moiety of the histidine side chain is tightly coordinated by chloride anions and O-atom hydrogen-bond acceptors in an almost planar configuration.

Comment

The crystal structure of the dipeptide L-$^+H_2$His–Gly.2Cl$^-$, (I), was determined in order to characterize the hydrogen-bond interactions and is the fourth in a series of small peptide determinations (previous contributions: Steiner 1996*a*,*b*,*c*). Since dipeptide (I) was crystallized from 6% HCl, it was obtained as a dication, with two chloride anions balancing the charge. No water molecules are co-crystallized.



(I)

The overall conformation of (I) (Fig. 1) is conventional and need not be discussed here in detail. The same is true for most of the N—H···*A* and O—H···*A* hydrogen bonds formed by the peptide main-chain functional groups (Table 2). The O—H···Cl$^-$ hydrogen bond donated by the C-terminal C(=O)—OH group is one of the shortest of its kind [O3···Cl1$^-$ 2.932 (3) Å].

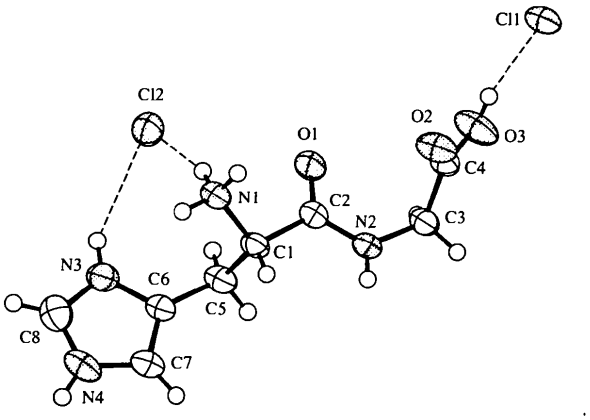


Fig. 1. The molecular structure and atom labeling of the title compound. Displacement ellipsoids are drawn at the 50% probability level. O and N atoms and Cl$^-$ anions are shaded.

The side chain of the histidine residue is oriented with the Cβ—Cγ bond (C5—C6) *trans* with respect to the Cα—C(=O) bond [torsion angle C2—C1—C5—C6 −176.2 (3)°] and the imidazole plane perpendicular to Cα—Cβ—Cγ [torsion angle C1—C5—C6—C7 −87.7 (5)°]; this is one of the common histidine conformations (Steiner, 1996*b*).

The positively charged imidazole moiety of the histidine side chain is tightly coordinated by chloride ions and O-atom hydrogen-bond acceptors in an almost planar configuration (Fig. 2). The mutual approach of the Cl1 and Cl2($x+1$, $y-1$, z) anions is quite short [3.814 (1) Å]; this is facilitated by two three-center N—H···Cl$^-$ hydrogen bonds [donated by N3—H and N1—H3N1 (Table 2)]. It is notable that O1 and Cl1 each accept an N—H···*A* and a C—H···*A* interaction of similar geometries. In particular for the O1 atom, the

two accepted contacts are geometrically almost identical. This situation is similar to the cases observed in previous studies of small peptides carrying protonated His residues.

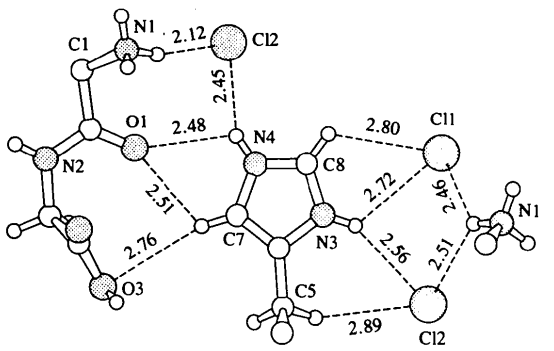


Fig. 2. The hydrogen-bond pattern around the histidine side chain projected onto the imidazole plane. O and N atoms and Cl^- ions are shaded. Numerical values of the H···*X* distances are given for normalized H-atom positions.

Experimental

L-His–Gly is commercially available (Sigma). A sample was recrystallized by slow evaporation of a solution in 6% HCl. X-ray diffraction data were measured on a specimen glued to a glass pin.

Crystal data

$C_8H_{14}N_4O_3^{2+}.2Cl^-$
M_r = 285.13
Orthorhombic
$P2_12_12_1$
a = 8.4083 (7) Å
b = 9.4040 (13) Å
c = 15.9899 (13) Å
V = 1264.3 (2) Å^3
Z = 4
D_x = 1.498 Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
λ = 1.54176 Å
Cell parameters from 25 reflections
θ = 11.1–22.7°
μ = 4.686 mm^{-1}
T = 293 (2) K
Prism
0.55 × 0.30 × 0.25 mm
Colorless

Data collection

Enraf–Nonius Turbo-CAD-4 diffractometer
ω scans
Absorption correction: ψ scan (North, Phillips & Mathews, 1968)
T_{min} = 0.25, T_{max} = 0.31
1851 measured reflections
1694 independent reflections

1619 reflections with $I > 2\sigma(I)$
R_{int} = 0.0141
θ_{max} = 59.84°
$h = 0 \rightarrow 9$
$k = -10 \rightarrow 9$
$l = 0 \rightarrow 17$
3 standard reflections
frequency: 60 min
intensity decay: 2.0%

Refinement

Refinement on F^2
$R(F)$ = 0.0324
$wR(F^2)$ = 0.0916
S = 1.094
1694 reflections
157 parameters

$\Delta\rho_{max}$ = 0.201 e Å^{-3}
$\Delta\rho_{min}$ = −0.233 e Å^{-3}
Extinction correction: *SHELXL*93
Extinction coefficient: 0.0027 (4)
H atoms not refined; rotating ammonium and OH groups, others riding
$w = 1/[\sigma^2(F_o^2) + (0.0511P)^2 + 0.7983P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
Scattering factors from *International Tables for Crystallography* (Vol. C)
Absolute configuration: Flack (1983)
Flack parameter = 0.01 (2)

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

O2—C4	1.196 (4)	N4—C8	1.301 (5)
O3—C4	1.310 (4)	N4—C7	1.364 (5)
N3—C8	1.332 (5)	C6—C7	1.342 (5)
N3—C6	1.384 (5)		
N1—C1—C2—N2	142.5 (3)	O1—C2—C1—C5	80.1 (4)
C1—C2—N2—C3	176.4 (3)	N2—C2—C1—C5	−98.3 (4)
C2—N2—C3—C4	67.5 (4)	N1—C1—C5—C6	−59.0 (4)
N2—C3—C4—O2	30.8 (5)	C2—C1—C5—C6	−176.2 (3)
N2—C3—C4—O3	−151.4 (3)	C1—C5—C6—C7	−87.7 (5)
O1—C2—N2—C3	−1.9 (5)	C1—C5—C6—N3	92.8 (4)

Table 2. *Selected hydrogen-bond parameters (Å, °)*

H···*A* and *D*—H···*A* are given for normalized H-atom positions based on bond lengths of O—H = 0.98, N—H = 1.04 and C—H = 1.09 Å.

D—H···*A*	H···*A*	*D*···*A*	*D*—H···*A*
O3—HO3···Cl1	1.97	2.932 (3)	165
N1—H1N1···O2^{i}	1.77	2.799 (4)	170
N1—H2N1···Cl2	2.12	3.123 (3)	162
N1—H3N1···Cl1^{ii}	2.46	3.195 (3)	129
N1—H3N1···Cl2^{iii}	2.51	3.244 (3)	127
N2—HN2···Cl1^{iv}	2.22	3.222 (3)	161
N3—HN3···Cl2	2.56	3.476 (3)	147
N3—HN3···Cl1^{v}	2.72	3.349 (3)	119
N4—HN4···Cl2^{iv}	2.45	3.324 (3)	141
N4—HN4···O1^{iv}	2.48	3.063 (4)	115
C1—HC1···Cl1^{iv}	2.71	3.673 (3)	147
C3—H2C3···O3^{vi}	2.45	3.093 (4)	116
C3—H2C3···Cl2^{vii}	2.80	3.597 (4)	130
C5—H1C5···Cl2	2.89	3.669 (4)	128
C7—HC7···O1^{iv}	2.51	3.072 (4)	111
C7—HC7···O3^{iv}	2.76	3.806 (5)	161
C8—HC8···Cl1^{v}	2.80	3.387 (4)	114

Symmetry codes: (i) $-x, y-\frac{1}{2}, \frac{3}{2}-z$; (ii) $-1-x, y-\frac{1}{2}, \frac{3}{2}-z$; (iii) $-x, y+\frac{1}{2}, \frac{3}{2}-z$; (iv) $x+1, y, z$; (v) $x+1, y-1, z$; (vi) $x+\frac{1}{2}, \frac{3}{2}-y, 1-z$; (vii) $x, y+1, z$.

After refinement of the non-H atoms, all H atoms were unambiguously located in difference Fourier calculations. Due to the limited number of data, the H atoms were then treated in the default riding model of *SHELXL*93 (Sheldrick, 1993), with the OH and NH_3^+ groups allowed to rotate. For the calculation of the hydrogen-bond parameters (Table 2), the H atoms of the final model were shifted along the *X*—H bonds to average neutron-determined $d(X—H)$ values, *i.e.* 'normalization'.

Data collection: *CAD*-4 *Software* (Enraf–Nonius, 1989). Cell refinement: *CAD*-4 *Software*. Data reduction: *CAD*-4 *Software*. Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1985). Program(s) used to refine structure: *SHELXL*93. Molecular graphics: *ORTEP*II (Johnson, 1976). Software used to prepare material for publication: *SHELXL*93.

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Lists of structure factors, anisotropic displacement parameters, atomic coordinates and complete geometry have been deposited with the IUCr (Reference: JZ1143). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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3-Ethoxycarbonyl-5-methoxycarbonyl-2,6-dimethyl-4-(3-nitrophenyl)pyridinium Nitrate, Dineopentyl 2,6-Dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate and Dihexyl 2,6-Dimethyl-4-(3-nitrophenyl)-pyridine-3,5-dicarboxylate

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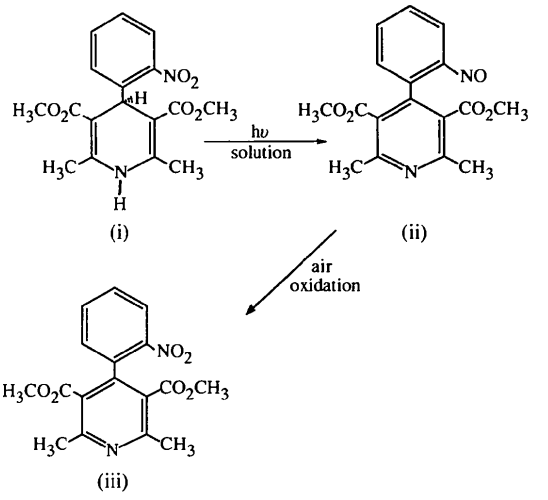
Abstract

The single-crystal X-ray structures of three oxidation products of 4-(3-nitrophenyl)-1,4-dihydropyridine, namely, 3-ethoxycarbonyl-5-methoxycarbonyl-2,6-dimethyl-4-(3-nitrophenyl)pyridinium nitrate, $C_{18}H_{19}N_2O_6^+.NO_3^-$, dineopentyl 2,6-dimethyl-4-(3-nitrophenyl)-pyridine-3,5-dicarboxylate, $C_{25}H_{32}N_2O_6$, and dihexyl 2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate, $C_{27}H_{36}N_2O_6$, suggest that their decreased calcium-blocking activity arises from incompatibility of the phenyl ring and ester conformation with the receptor site.

Comment

Derivatives of 1,4-dihydropyridine (DHP) are often prescribed as calcium-channel blockers, effective in the treatment of angina and hypertension (Triggle, Langs & Janis, 1989; Hurwitz, Partridge & Leach, 1991). Nifedipine [(i); dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate] has been shown to undergo a photodecomposition sequence (see below) forming nitrosopyridine and finally a nitropyridine product (Rowan & Holt, 1995).



This decomposition has been reported to be wavelength sensitive, with UV radiation believed to cause aromatization of the 1,4-dihydropyridine ring and reduction of the nitro group to a nitroso moiety. Daylight, followed by air oxidation, leads to re-oxidation of the nitroso group to a nitro function. The observation of this decomposition sequence has led to concern about its shelf life, packaging and potency (Núnez-Vergara, Sunkel & Squella, 1994; Sadana & Ghogare, 1991; Hayase, Itagaki, Ogawa, Akutsu, Inagaki & Abiko, 1994).

Oxidation of the 1,4-dihydropyridine ring to pyridine is reported to significantly diminish activity in some cases (Loev, Goodman, Snader, Tedeschi & Macko, 1974). The nitropyridine decomposition product has been identified as one of the major metabolites of the parent 1,4-dihydropyridine compound (Shibanuma, Iwanami, Fujimoto, Takenaka & Murakami, 1980) and has been reported to be as much as 1000 times less active (Squella, Zanocco, Perna & Núnez-Vergara, 1990). Some of the oxidized derivatives, however, do display some activity.

Structure–activity relationships (SARs) for 1,4-dihydropyridine compounds suggest that planarity of the hetero-ring correlates with increased activity, as does a perpendicular orientation of the phenyl ring with respect to the hetero-ring (Triggle, Langs & Janis, 1989). These structural features are present in the decomposition products.