

Zwitterionic 4-piperidinecarboxylic acid monohydrate

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The title compound, 4-piperidiniocarboxylate (isonipepotic acid), crystallizes as a zwitterion and incorporates one water molecule, *i.e.* $C_6H_{11}NO_2 \cdot H_2O$. The piperidine ring adopts a chair conformation and the α -carboxylate group is oriented in the equatorial position. The combination of the interactions between the α -amino and α -carboxylate groups and the water molecules builds a three-dimensional assembly of hydrogen bonds.

Comment

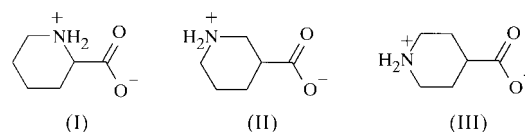
Compounds with both amino and carboxylic acid groups in their molecular structure, such as α -amino acids, can exist as zwitterions in the crystalline state as well as in aqueous solutions. In a zwitterion, both charged groups, COO^- and NH_3^+ (or NH_2^+ or NH^+), interact with each other and with the aqueous solvent by means of electrostatic, polarization and hydrogen-bonding interactions. These interactions affect their structural conformation, functionality and biological activity (Price *et al.*, 1998).

In the solid state, zwitterions often cocrystallize with solvent molecules. The role played by the solvent molecules is diverse (Görbitz & Hersleth, 2000); they might be directly involved in the formation of hydrogen bonds with themselves and with the zwitterion, or they could just fill void space. Proline, for example, crystallizes forming infinite chains of dimers linked by head-to-tail hydrogen bonds; water molecules act as bridges among chains, stabilizing the three-dimensional structure (Padmanabhan *et al.*, 1995; Janczak & Luger, 1997). Other examples of amino acids with lateral chains strictly hydrophobic, which pack in a similar way to proline, have been reported in the recent literature (Dalhus & Görbitz, 1999*a,b*).

In the gaseous phase, the amino acid exists in its neutral form, however, in the presence of solvent molecules, generally water, the amino acid rapidly ionizes forming the zwitterion (Jensen & Gordon, 1995; Tajkhorshid *et al.*, 1998). The solvation effects in the zwitterion formation have been the subject of much interest and theoretical studies using different

approaches have appeared in the recent literature, particularly concerning the simplest α -amino acids, *e.g.* glycine and alanine (Jensen & Gordon, 1995; Tajkhorshid *et al.*, 1998).

From a theoretical point of view, it is interesting to study the structural isomers 2-piperidinecarboxylic acid, (I) (pipecolic acid or homoproline), 3-piperidinecarboxylic acid, (II) (nipepotic acid), and 4-piperidinecarboxylic acid, (III) (isonipepotic acid). These compounds have a piperidinium ring, which enables the charge separation between the amino and carboxylic acid groups, and offer additional degrees of freedom due to the possibility of different conformers, keeping in mind the simplicity of the molecule to avoid costly computational calculations. Preliminary theoretical calculations (Cuervo *et al.*, 2000) at the *ab initio* and density-functional-theory levels have shown that in the absence of water the three isomers exist as the favourable neutral form, with isomer (III) being the least stable by about 20 kcal mol⁻¹. As water is introduced, the zwitterion becomes the stable form and, for instance, zwitterion (I) is stabilized when two water molecules are added in its vicinity.



The crystalline structure of (I), a potent amino acid antagonist, has been reported (Bhattacharjee & Chacko, 1979). In the solid state, this compound is a zwitterion and crystallizes with four water molecules. Compound (II) is also a zwitterion, but it is not a hydrate (Brehm *et al.*, 1976). Very little is known of 4-piperidinecarboxylic acid, (III). Our study shows this compound is zwitterionic and crystallizes in the space group $Pna2_1$, incorporating one water molecule as crystallization solvent. Fig. 1 shows the molecular diagram and labelling scheme of (III)·H₂O. The existence of the zwitterionic form of (III)·H₂O is confirmed by the presence of two H atoms bonded to the N1 atom, as was depicted in the difference Fourier map where the two H atoms were located, and the almost symmetrical α -carboxylate group, with C1—O1 and C1—O2 distances being equal within 2σ (see Table 1). The

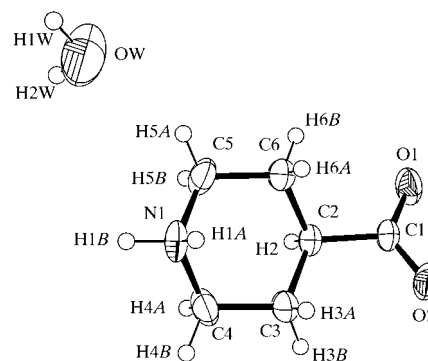


Figure 1
ORTEP (Burnett & Johnson, 1996; Farrugia, 1997) drawing of (III)·H₂O showing the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as spheres of arbitrary radii.

piperidine ring adopts the stable chair conformation, as in compounds (I) and (II), and in 12 related piperidinium rings not substituted at the amino group found in the Cambridge Structural Database (Allen & Kennard, 1993). The N—C bond lengths are in agreement with the reported value for piperidinium rings (Allen *et al.*, 1987).

The α -carboxylate group at C2 is attached to the ring in the favourable equatorial position. The orientation of the α -carboxylate group is described by the torsion angles O1—C1—C2—C6 -57.4 (2), O1—C1—C2—C3 178.6 (2), O2—C1—C2—C3 -2.2 (2) and O2—C1—C2—C6 121.8 (2) $^\circ$. O1 is 0.136 (1) \AA below and O2 is 0.946 (2) \AA above the piperidine mean plane. The asymmetric arrangement of the α -carboxylate is also observed in the solid-state CP MAS ^{13}C NMR, which shows two peaks at 25.46 and 27.83 p.p.m., corresponding to C3 and C6, respectively. These two peaks overlap at 25.61 p.p.m. in the ^{13}C NMR spectrum taken in D_2O due to free rotation about the C1—C2 bond in the liquid state.

The geometric parameters of the hydrogen bonds are given in Table 2. Two sets of head-to-tail N1—H1B \cdots O2 and N1—H1A \cdots O1 interactions form extended chains which run parallel to the c and b axes, respectively. In addition, water molecules interact with amino acid molecules through OW—H1W \cdots O2 and OW—H2W \cdots O1 hydrogen bonds, thus producing sinuous chains running parallel to the a axis. The combination of these interactions along the principal directions builds an intricate three-dimensional assembly of hydrogen bonds. Fig. 2 shows a projection of the crystal structure viewed down the c axis.

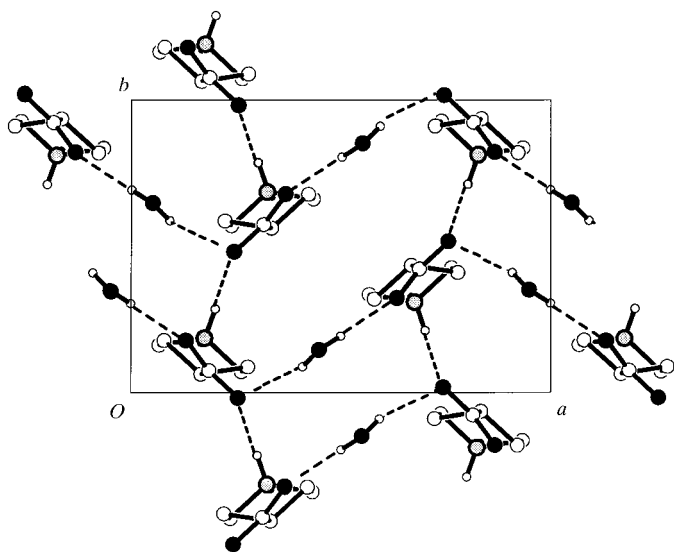


Figure 2
ORTEP (Burnett & Johnson, 1996; Farrugia, 1997) projection diagram of (III)·H₂O viewed down the c axis. The N1—H1B \cdots O2 interaction is not shown.

Experimental

A crystal suitable for X-ray diffraction analysis was obtained by slow evaporation of a saturated 1:1 water–ethanol solution of isonipicotic acid (Aldrich, I-1,800-8, 97%). CP-MAS ^{13}C NMR (400 MHz): δ 181.52 (C-1), 45.77 (C-5), 43.53 (C-4), 41.21 (C-2), 27.83 (C-6), 25.46

(C-3). ^{13}C NMR (400 MHz, D_2O): δ 182.08 (C-1), 43.74 (C-4, C-5), 41.37 (C-2), 25.61 (C-3, C-6).

Crystal data

$\text{C}_6\text{H}_{11}\text{NO}_2 \cdot \text{H}_2\text{O}$
 $M_r = 147.17$
 Orthorhombic, $Pna2_1$
 $a = 11.9647$ (11) \AA
 $b = 8.3276$ (7) \AA
 $c = 7.6054$ (7) \AA
 $V = 757.78$ (12) \AA^3
 $Z = 4$
 $D_x = 1.290$ Mg m^{-3}

Mo $K\alpha$ radiation
 Cell parameters from 4773 reflections
 $\theta = 1.5$ – 25.4 $^\circ$
 $\mu = 0.10$ mm^{-1}
 $T = 293$ (2) K
 Plate, colourless
 $0.4 \times 0.4 \times 0.3$ mm

Data collection

Siemens CCD area-detector diffractometer
 φ and ω scans
 6524 measured reflections
 754 independent reflections
 734 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.038$
 $\theta_{\text{max}} = 25.4$ $^\circ$
 $h = -14 \rightarrow 14$
 $k = -10 \rightarrow 10$
 $l = -9 \rightarrow 9$

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.037$
 $wR(F^2) = 0.101$
 $S = 1.05$
 754 reflections
 105 parameters
 H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0654P)^2 + 0.1836P]$
 where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\text{max}} = 0.012$
 $\Delta\rho_{\text{max}} = 0.29$ e \AA^{-3}
 $\Delta\rho_{\text{min}} = -0.19$ e \AA^{-3}

Table 1

Selected geometric parameters (\AA , $^\circ$).

| | | | |
|----------|-----------|----------|-----------|
| C1—O2 | 1.240 (3) | C3—C4 | 1.525 (3) |
| C1—O1 | 1.248 (3) | C4—N1 | 1.483 (4) |
| C1—C2 | 1.534 (3) | C5—N1 | 1.493 (4) |
| C2—C3 | 1.519 (3) | C5—C6 | 1.514 (4) |
| C2—C6 | 1.530 (3) | | |
| O2—C1—O1 | 123.8 (2) | N1—C4—C3 | 110.7 (2) |
| O2—C1—C2 | 119.2 (2) | N1—C5—C6 | 109.8 (2) |
| O1—C1—C2 | 116.9 (2) | C4—N1—C5 | 111.9 (2) |

Table 2

Hydrogen-bonding geometry (\AA , $^\circ$).

| $D\text{—}H\cdots A$ | $D\text{—}H$ | $H\cdots A$ | $D\cdots A$ | $D\text{—}H\cdots A$ |
|------------------------------------|--------------|-------------|-------------|----------------------|
| N1—H1A \cdots O1 ⁱ | 0.89 (4) | 1.86 (4) | 2.744 (3) | 175 (4) |
| N1—H1B \cdots O2 ⁱⁱ | 0.94 (4) | 1.85 (4) | 2.776 (3) | 169 (3) |
| OW1—H1W \cdots O2 ⁱⁱⁱ | 0.87 (8) | 1.97 (7) | 2.752 (4) | 149 (8) |
| OW1—H2W \cdots O1 ⁱⁱ | 0.85 (7) | 2.06 (6) | 2.862 (4) | 157 (7) |

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

The H atoms of the NH_2^+ moiety were located from difference Fourier maps and refined with isotropic displacement parameters. The H atoms of the water molecule were located in the final difference Fourier map, their positions were refined and their isotropic displacement parameters were set to 1.2 times the equivalent displacement parameter of the OW atom. The H atoms of the piperidine ring were placed in geometrically calculated positions and their isotropic displacement parameters were set to 1.2 times the equivalent displacement parameter of their parent atoms.

Data collection: *SMART* (Siemens, 1996); cell refinement: *SAINT* (Siemens, 1996); data reduction: *SHELXTL* (Siemens, 1996); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEPIII* (Burnett & Johnson, 1996; Farrugia, 1997); software used to prepare material for publication: *PLATON* (Spek, 2000).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: BK1590). Services for accessing these data are described at the back of the journal.

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