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Head-to-head dimers in the zwitterion of 1-hydroxy-1-phosphono-3-(1-piperidino)propylidene-1-phosphonate (PHPBP)

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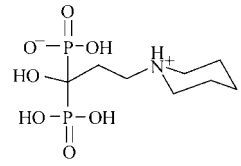
The title compound, $C_8H_{19}NO_7P_2$, is a member of the bisphosphonate family of therapeutic compounds. PHPBP has inner-salt character, consisting of a negatively charged PO_3 group and a positively charged N atom. The six-membered piperidine ring adopts an almost-perfect chair conformation. The hydroxyl group and the N atom have *gauche* and *trans* conformations in relation to the O—C—C—C—N backbone, respectively. Hydrogen bonding is the main contributor to the packing in the crystal, which consists of head-to-head dimers formed through phosphonyl–phosphonyl hydrogen bonds, while O—H···O and N—H···O interactions join the dimers into a plane parallel to crystallographic *b* and *c* axes.

Comment

Bisphosphonates are important bone-remodelling mediators, commonly used as antiresorptive agents. In this context, they are indicated for the treatment of osteoporosis, hypercalcaemia and osteolytic metastases (Compston, 1994; Martin & Grill, 2000). Compounds of this class have proved their usefulness in a wide range of applications, such as herbicides (Chuiko *et al.*, 1999; Gordon-Weeks *et al.*, 1999), antiparasitics (Docampo, 2001; Martin *et al.*, 2001), cholesterol-lowering agents (Hiyoshi *et al.*, 2000; Niesor *et al.*, 2001), drugs for the treatment of manic-depressive disorders (Atack *et al.*, 1993; Fauroux & Freeman, 1999), anti-inflammatories and anti-arthritics (Schlachter *et al.*, 1998), and heavy-metal decorporating agents (Fukuda *et al.*, 1999). As observed for several nitrogen-containing bisphosphonates, PHPBP is a potent antiresorptive agent, with a potency comparable with that of the commonly used medications alendronate, olpadronate and pamidronate (Widler *et al.*, 2002). The results from another study demonstrated that PHPBP is as potent as related amine–bisphosphonates when tested as a cholesterol-lowering agent (Amin *et al.*, 1992).

Our interest in studying PHPBP, (I), by single-crystal X-ray crystallography arose from our previous observations concerning the conformation of the alkylamino backbone (Vega *et al.*, 2002; Fernández & Vega, 2003). Thus, the structural determination of (I) has been carried out and the results are presented here.



(I)

Compound (I) (Fig. 1) is a zwitterion; the phosphonate atom O1 is ionized and the H atom is transferred to atom N1, which adopts a tetrahedral geometry (Table 1). This behaviour is a not uncommon feature of amine–bisphosphonates, as has been observed previously for related compounds (Vega *et al.*, 2002; Van Brussel *et al.*, 2003; Fernández & Vega, 2003). The geometry of atoms P1 and P2 is tetrahedral, and is defined by atoms O1/O2/O3 and O4/O5/O6, respectively. In the former group, the O—P—O and O—P—C bond angles range from 106.28 (8) to 114.70 (9)°, while for the second group, the values lie between 104.62 (9) and 113.39 (8)°. The largest angle is O1—P1—O3, which is formed by the unprotonated atoms O1 and O3. The P—O bond distances (Table 1) are close to 1.50 Å for P═O bonds (P1═O3 and P2═O5), and are approximately 1.55 Å for protonated atoms (P1—O2 and P2—O4). With respect to these values, the P1—O1 and P2—O6 bond distances are intermediate, suggesting that the order of these bonds lies between single and double. An explanation for this fact can be found when considering the intermolecular interactions in which these atoms are involved, as they form a hydrogen bond (Table 2).

The P—C bond distances in (I) are in good agreement with those of related compounds. In addition, the P—C—P bond angle (Table 1) has a value well within the range observed for other bis-phosphonates containing the C—C—C—N chain (109.91–114.23°; Fernández & Vega, 2003). The sp^3-hybridized atom C2 has a distorted tetrahedral geometry, as indicated by the value of 115.84 (16)° for the C1—C2—C3 bond angle. This fact could be attributed to a repulsive interaction between

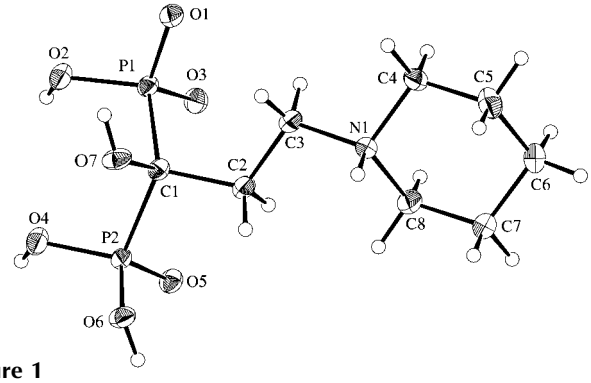


Figure 1
A view of the structure of (I), showing the atom-numbering scheme and displacement ellipsoids at the 50% probability level. H atoms are shown as small spheres of arbitrary radii.

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atoms C2 and C3 and some of the phosphonyl O atoms, namely C2—H9···O5 [$D\cdots A$ = 3.051 (3) Å, H···A = 2.58 Å and D—H···A = 110°] and C3—H10···O1 [$D\cdots A$ = 3.019 (3) Å, H···A = 2.59 Å and D—H···A = 108°].

The conformation of the C—C—C—N chain is close to *trans*, the C1—C2—C3—N1 torsion angle being 167.02 (16)°. Such a conformation is commonly found in related amine–bisphosphonates, *e.g.* in 1-hydroxy-3-(1-pyrrolidinyl)propylidene-1,1-bisphosphonic acid (EB 1053; Fernández & Vega, 2003). In spite of the molecular resemblance between (I) and this pyrrolidinyl bisphosphonate, the C2—C3 bond is disposed differently in relation to the P—C—P bridge. In (I), the C2—C3 bond is *trans* with respect to the C1—P2 bond [P2—C1—C2—C3 = 176.44 (16)°], while it is *gauche* with respect to the C1—P1 bond [P1—C1—C2—C3 = 54.7 (2)°]. For the pyrrolidinyl bisphosphonate, the C2—C3 bond is *gauche* with respect to both bonds, the corresponding torsion angles being −43.6 (2) and 85.46 (19)°, respectively.

As shown by the value of the O7—C1—C2—C3 torsion angle [−70.3 (2)°], the orientation of hydroxyl atom O7 with respect to the C—C—C—N chain is *gauche*. This indicates that the conformation around the O—C—C—C—N backbone in (I) is similar to that in disodium 3-ammonium-1-hydroxypropylidene-1,1-bisphosphonate pentahydrate (pamidronate), but it is different with respect to that of the pyrrolidinyl bisphosphonate, where the backbone is planar (Fernández & Vega, 2003). As noted earlier, this could be an effect of the intermolecular interactions in which the hydroxyl O atom is engaged. Although atom O7 forms comparable interactions as a donor in both (I) and the pyrrolidinyl bisphosphonate, it is a weaker acceptor in the latter [$D\cdots A$ = 3.011 (2) Å, H···A = 2.41 Å and D—H···A = 129°] than in (I) (see Table 2). On the limited amount of evidence available, it was stated in a previous paper that the conformation of the backbone is defined by the pattern of atomic substitution of the N atom (Fernández & Vega, 2003). In the light of the results presented here, it becomes clear that this does not constitute the major contributor to the stability of the O—C—C—C—N backbone, which comes instead from the hydrogen bonding.

The piperidinyl ring in (I) is puckered with respect to the most symmetric conformation of a six-membered ring (Duax *et al.*, 1976). The ring-puckering parameters (Cremer & Pople, 1975) for the atom sequence N1/C4/C5/C6/C7/C8 are q_2 = 0.011 (2) Å, q_3 = 0.577 (2) Å and φ_2 = 45 (12)°. The value of the phase indicates that the conformation of the ring is an almost-perfect chair (Allen *et al.*, 1991). Atoms N1 and C6 are located 0.678 (3) and −0.672 (4) Å, respectively, from the least-squares plane defined by C4/C5/C7/C8 (r.m.s. deviation of fitted atoms = 0.005 Å).

The hydrogen-bonding scheme for (I) consists of O—H···O and N—H···O interactions (Table 2). The hydrogen bonds between phosphonyl O atoms pack a pair of zwitterions into a head-to-head dimer (Fig. 2). The O atoms involved in these interactions, namely atoms O2, O3, O4 and O5, form an eight-membered P—O—H···O—P—O···H—O ring. The interactions between the phosphonyl atoms O1, O5 and O6, and the hydroxyl group, associate the dimers within a plane parallel to the crystallographic *b* and *c* axes. The N atom of the piperidine ring acts as a bifurcated donor of hydrogen bonds to the phosphonyl and hydroxyl O atoms of a neighbouring zwitterion.

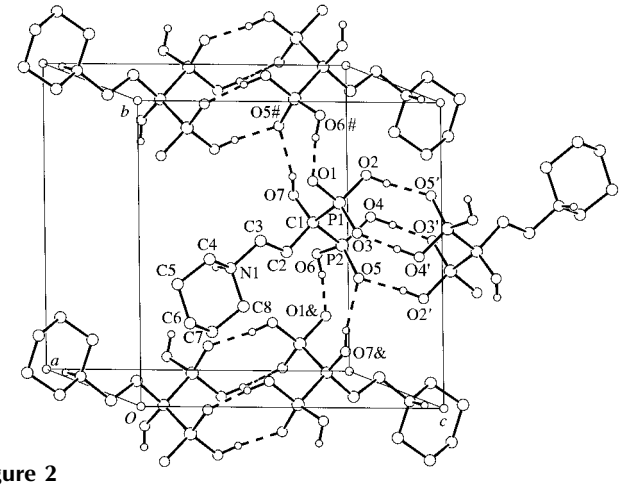

Figure 2
A partial packing diagram for (I), showing the hydrogen bonds (dashed lines). Only H atoms attached to O and N atoms are shown. Atoms marked with an ampersand (&), prime (′) or hash (#) are at the symmetry positions $(1-x,\ y-\frac{1}{2},\ \frac{3}{2}-z)$, $(1-x,\ 1-y,\ 2-z)$ and $(1-x,\ y+\frac{1}{2},\ \frac{3}{2}-z)$, respectively.

Experimental

A sample of the title compound was donated by Dr Lise Binderup (LEO Pharmaceutical Products, Copenhagen, Denmark; LEO code name SL 2333). Crystals of (I) suitable for X-ray diffraction were obtained by slow evaporation of a water solution in an oven at 315 K.

Crystal data

$C_8H_{19}NO_7P_2$
M_r = 303.18
Monoclinic, $P2_1/c$
a = 10.590 (4) Å
b = 11.490 (3) Å
c = 11.344 (5) Å
β = 116.58 (3)°
V = 1234.4 (8) Å^3
Z = 4
D_x = 1.631 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 20 reflections
θ = 4–12.5°
μ = 0.38 mm^{-1}
T = 293 (2) K
Block, colourless
0.45 × 0.35 × 0.30 mm

Data collection

Rigaku AFC-6*S* diffractometer
$\omega/2\theta$ scans
Absorption correction: ψ scan (*MSC/AFC Diffractometer Control Software*; Molecular Structure Corporation, 1993)
T_{min} = 0.786, T_{max} = 0.893
5614 measured reflections
2184 independent reflections
1938 reflections with $I > 2\sigma(I)$
R_{int} = 0.033
θ_{max} = 25.0°
$h = -12 \rightarrow 7$
$k = -13 \rightarrow 13$
$l = -13 \rightarrow 13$
3 standard reflections
every 400 reflections
intensity decay: 4.9%

Refinement

Refinement on F^2
$R(F)$ = 0.034
$wR(F^2)$ = 0.092
S = 1.04
2184 reflections
179 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0479P)^2 + 0.8012P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.007
$\Delta\rho_{max}$ = 0.37 e Å^{-3}
$\Delta\rho_{min}$ = −0.31 e Å^{-3}
Extinction correction: *SHELXL97* (Sheldrick, 1997)
Extinction coefficient: 0.0279 (19)

Table 1
Selected geometric parameters (Å, °).

P1—O1	1.5269 (15)	P2—O6	1.5309 (16)
P1—O2	1.5576 (15)	P2—C1	1.851 (2)
P1—O3	1.4979 (15)	N1—C8	1.504 (3)
P1—C1	1.850 (2)	N1—C3	1.507 (3)
P2—O4	1.5504 (15)	N1—C4	1.508 (3)
P2—O5	1.5071 (14)		
O1—P1—O2	106.28 (8)	O5—P2—O6	113.39 (8)
O1—P1—O3	114.70 (9)	O4—P2—C1	106.20 (9)
O2—P1—O3	113.89 (9)	O5—P2—C1	109.41 (9)
O1—P1—C1	106.36 (9)	O6—P2—C1	104.62 (9)
O2—P1—C1	107.46 (9)	C3—N1—C4	109.81 (15)
O3—P1—C1	107.69 (9)	C3—N1—C8	114.08 (16)
O4—P2—O5	112.98 (9)	C4—N1—C8	109.82 (16)
O4—P2—O6	109.65 (9)	P1—C1—P2	111.96 (10)
O1—P1—C1—P2	173.02 (9)	O4—P2—C1—P1	−54.69 (12)
O2—P1—C1—P2	59.53 (12)	O5—P2—C1—P1	67.55 (11)
O3—P1—C1—P2	−63.55 (12)	O6—P2—C1—P1	−170.65 (9)

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O2—H2···O5^{i}	0.83 (2)	1.72 (2)	2.547 (2)	172 (3)
O4—H4···O3^{i}	0.88 (2)	1.66 (2)	2.531 (2)	173 (3)
O6—H6···O1^{ii}	0.85 (2)	1.62 (2)	2.466 (2)	172 (3)
O7—H7···O5^{iii}	0.81 (2)	2.01 (2)	2.777 (2)	160 (3)
N1—H1···O7^{iv}	0.90 (3)	2.08 (3)	2.943 (3)	162 (2)
N1—H1···O6^{iv}	0.90 (3)	2.51 (3)	3.068 (2)	121 (2)

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

H atoms attached to O and N atoms had their positional parameters refined freely, while those attached to C atoms were treated as riding. All H atoms had their displacement parameters constrained to 1.2 (for those bonded to C atoms) or 1.5 (for those bonded to O and N atoms) times that of their hosts. O—H distances were refined with a restrained bond distance of 0.85 (3) Å using the DFIX command implemented in *SHELXL*97 (Sheldrick, 1997).

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1993); cell refinement: *MSC/AFC Diffractometer Control Software*; data reduction: *MSC/AFC Diffractometer Control Software*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ZORTEP* (Zsolnai & Pritzkow, 1995); software used to prepare material for publication: Cambridge Structural Database (Version 5.24, and updates; Allen, 2002), *PLATON* (Spek, 2003) and *WinGX* (Farrugia, 1999).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1672). Services for accessing these data are described at the back of the journal.

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