

Head-to-head dimers in the zwitterion of 1-hydroxy-3-(pyrrolidin-1-yl)-propylidene-1,1-bisphosphonic acid (EB 1053)

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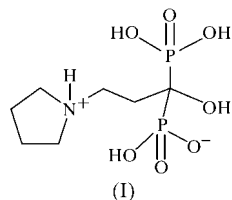
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The title compound, 1-hydroxy-1-phosphono-3-(1-pyrrolidin-yl)propylidene-1-phosphonate, $C_7H_{17}NO_7P_2$, is a member of the bisphosphonate class of drugs. As a zwitterion, it possesses a negative charge on one of the PO_3 groups and a positive charge on the pyrrolidine N atom. A zwitterion makes a contact with a neighbouring ion through the hydroxyl O atom and two phosphoryl O atoms, one each from two different PO_3 groups. Hydrogen bonding involves $O-H\cdots O$ and $N-H\cdots O$ interactions; the former are involved in the formation of head-to-head dimers, while the latter join the dimers into a chain running along the crystallographic b axis.

Comment

A number of compounds of the bisphosphonate class are used as therapeutic agents for the treatment of skeletal disorders such as osteoporosis, Paget's disease of the bone and hypercalcaemia associated with malignancy (Compston, 1994; Martin & Grill, 2000; Rodan & Martin, 2000). In this context, it has been shown that the bisphosphonate EB 1053, (I), is a potent inhibitor of bone resorption (van der Pluijm *et al.*,



1992). In other studies, (I) has been tested as a cholesterol-lowering agent (Amin *et al.*, 1992) and as an antitumour drug against breast cancer (Senaratne *et al.*, 2000). This work is part of our ongoing study of the crystal structures of chemical compounds that affect osseous metabolism and that are used

as therapeutic agents to treat bone diseases (Vega *et al.*, 1996, 1998; Fernández *et al.*, 2002). We report here the single-crystal X-ray analysis of (I).

Compound (I) consists of a P–C–P bridge with a hydroxyl group and a side chain that ends in a pyrrolidine ring (Fig. 1). Like other previously studied amine–bisphosphonates (Vega *et al.*, 2002; Van Brussel *et al.*, 2003), (I) possesses zwitterionic character. At one end of the molecule, a negative charge is located on one PO_3 group, while at the opposite end there is a positively charged N atom. This charge separation was also found for the structures of the related bisphosphonates pamidronate (anhydrous free acid; unpublished results), hereafter H_3PAM , and olpadronate [monohydrated free acid; Cambridge Structural Database (Allen, 2002) refcode FURCAW; Shkol'nikova *et al.*, 1987], hereafter H_3OLP , which possess $CH_2-CH_2-NH_3^+$ and $CH_2-CH_2-NH(CH_3)_2^+$ side chains, respectively. The P–C bond lengths (Table 1) are in good agreement with those of the related compounds. However, the P–C–P bond angle is larger in (I) [114.23 (9)° versus 110.63 (12)° in H_3PAM and 109.91 (4)° in H_3OLP]. In (I), the C2–C3 bond is *gauche* with respect to the C1–P1 and C1–P2 bonds, the P1–C1–C2–C3 and P2–C1–C2–C3 torsion angles being –43.6 (2) and 85.46 (19)°, respectively. The same trend was observed for H_3OLP but not for H_3PAM , in which the C2–C3 bond is further from C1–P2, the P2–C1–C2–C3 torsion angle being 175.46 (17)°. As atom C3 forms an intramolecular contact with atom O2 [$C3\cdots O2 = 3.028$ (2) Å, $H8\cdots O2 = 2.59$ (2) Å and $C3-H8\cdots O2 = 108$ (2)°], it is possible that C3 exerts steric hindrance on the P–C–P linkage, resulting in the lengthening of the bond. The PO_3 groups are staggered when viewed along the $P1\cdots P2$ vector, and their mutual orientation defines a 'W'-like shape for the O1–P1–C1–P2–O4 sequence. In the plane of the 'W' there is one protonated and one deprotonated O atom, as shown by the P2–C1–P1–O1 and P1–C1–P2–O4 torsion angles. This structure is similar to that observed for H_3OLP but differs from that of H_3PAM , in which both O atoms are protonated. The P–O bond lengths (Table 1) indicate the presence of single (P1–O3, P2–O4 and P2–O5) and double (P1=O1 and P2=O6) bonds, as has been observed previously for several members of this class of

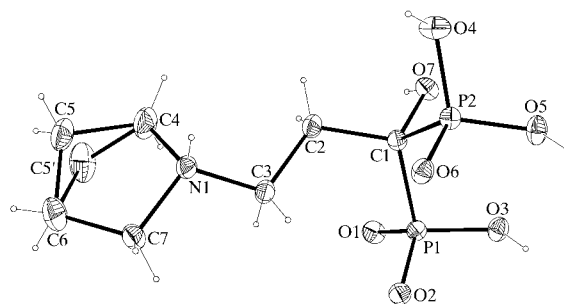


Figure 1

A view of the structure of (I), showing the atom-numbering scheme and displacement ellipsoids at the 30% probability level. H atoms of the minor-occupancy component (C5') have been omitted for clarity.

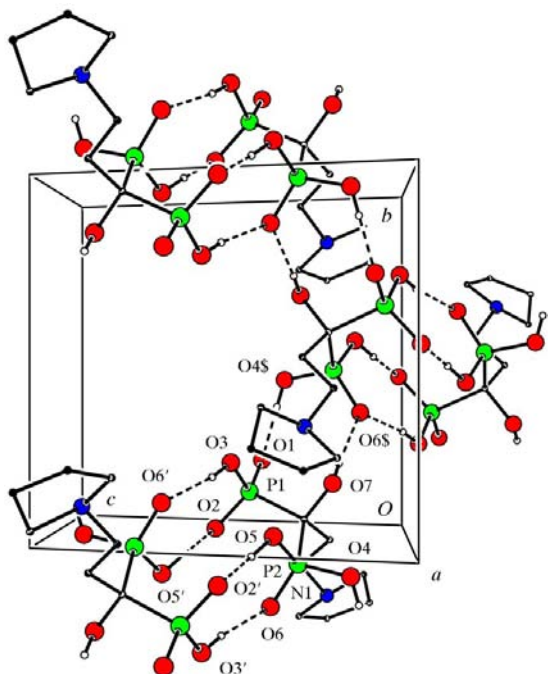


Figure 2
Partial packing diagram, showing the hydrogen bonds (dashed lines). Only H atoms attached to O atoms are shown. Atoms marked with a dollar sign (\$) or prime (') are at the symmetry positions ($\frac{3}{2} - x, y - \frac{1}{2}, \frac{1}{2} - z$) and ($2 - x, -y, 1 - z$), respectively. Only H atoms bonded to O atoms and the major conformation of the five-membered ring are shown.

compounds (Vega *et al.*, 1998). The remaining bond, P1–O2, has an intermediate length, suggesting that the negative charge could be delocalized.

Hydroxyl atom O7 is *trans* with respect to the O–C–C–C–N backbone of the molecule, the O7–C1–C2–C3 torsion angle being $-162.10(16)^\circ$. This atom is similarly orientated in H₃OLP, but it is differently disposed in H₃PAM, where the corresponding torsion angle is $-66.3(3)^\circ$. An analysis of the hydrogen bonds in which atom O7 takes part, using the *PARST* program (Nardelli, 1995), revealed that O7 acts as a donor in comparable interactions in (I) and H₃PAM. However, as an acceptor, O7 forms a stronger hydrogen bond in the latter [$D \cdots A = 2.862 \text{ \AA}$, $H \cdots A = 1.92(4) \text{ \AA}$ and $D-H \cdots A = 175^\circ$] than in (I) (Table 2). In addition, the N atom is *trans* in the three structures, the C1–C2–C3–N1 torsion angles being $-159.04(16)$ [in (I)], $174.54(6)$ (in H₃OLP) and $169.6(2)^\circ$ (in H₃PAM). Therefore, it can be reasoned that the structures in which a tertiary N atom is present have a planar O–C–C–C–N backbone in common.

In the final model, the disordered pyrrolidine ring was refined with a major component (N1–C4–C5–C6–C7) accounting for 75% of the occupancy and a minor component (25%) consisting of N1–C4–C5'–C6–C7. These rings are puckered with respect to the most symmetric conformations observed for five-membered rings (Duax *et al.*, 1976) [the Cremer & Pople (1975) ring puckering parameters are $q_2 = 0.323(3) \text{ \AA}$ and $\varphi_2 = 3.9(5)^\circ$ for the sequence C4–C5–C6–C7–N1, and $q_2 = 0.350(7) \text{ \AA}$ and $\varphi_2 = 29.5(7)^\circ$ for the

sequence C5'–C6–C7–N1–C4]. The phase values indicate that the conformations of both rings are close to envelope (Allen *et al.*, 1991), but with a tendency to be twisted (especially for the latter ring). The asymmetry parameters (Nardelli, 1983) for the C4–C5–C6–C7–N1 ring indicate a local pseudo-mirror axis, $\Delta_S(C4)$, passing through atom C4 and the mid-point of the C6–C7 bond, and a local pseudo-twofold axis, $\Delta_2(C7)$, running through atom C7 and the mid-point of the C4–C5 bond. For the C5'–C6–C7–N1–C4 ring, the local pseudo-symmetry elements, $\Delta_S(C6)$ and $\Delta_2(N1)$, run through atom C6 and the mid-point of the C4–N1 bond and through atom N1 and the mid-point of the C5'–C6 bond, respectively.

Atoms O3, O5 and O7 are all hydrogen bonded to an adjacent pyrrolidine N atom (Table 2), and their atomic dispositions are such that they define the base of a pyramid with a vertex at atom N1. An analysis using *XP* (Sheldrick, 1991) showed that N1 is 2.644 \AA from the centroid (C_g) of the triad of O atoms and forms a $N1-H1 \cdots C_g$ angle of 168° ; in addition, both P atoms are at the same distance with respect to N1 ($\sim 2 \text{ \AA}$). By comparison with H₃OLP and H₃PAM, it could be concluded that the interactions involving the N atom differ depending on the environment of the atoms involved in the interactions.

The packing in the crystal of (I) is achieved through O–H \cdots O and N–H \cdots O hydrogen bonding (Table 2). $O_{PO_3} \cdots O_{PO_3}$ hydrogen bonds pack pairs of molecules into head-to-head dimers (Fig. 2); note that atoms O2, O3, O5 and O6 are part of an eight-membered P–O–H \cdots O–P–O \cdots H–O ring. A chain running along the crystallographic *b* axis is generated by N–H \cdots O, $O_{OH} \cdots O_{PO_3}$ and $O_{PO_3} \cdots O_{PO_3}$ interactions. The latter form a nine-membered ring that includes atoms O1, O4, O6 and O7.

Experimental

A powdered sample of the title compound was donated by Dr Lise Binderup (LEO Pharmaceutical Products, Copenhagen, Denmark). Crystals suitable for X-ray diffraction were obtained by slow evaporation from an aqueous solution in an oven at 315 K.

Crystal data

$C_7H_{17}NO_7P_2$	$D_x = 1.63 \text{ Mg m}^{-3}$
$M_r = 289.16$	Mo $K\alpha$ radiation
Monoclinic, $P2_1/n$	Cell parameters from 20 reflections
$a = 9.9208(16) \text{ \AA}$	$\theta = 10\text{--}17.5^\circ$
$b = 10.7754(19) \text{ \AA}$	$\mu = 0.39 \text{ mm}^{-1}$
$c = 11.4933(17) \text{ \AA}$	$T = 293(2) \text{ K}$
$\beta = 106.439(11)^\circ$	Block, colorless
$V = 1178.4(3) \text{ \AA}^3$	$0.30 \times 0.25 \times 0.20 \text{ mm}$
$Z = 4$	

Data collection

Rigaku AFC-6S diffractometer	$R_{int} = 0.040$
ω - 2θ scans	$\theta_{max} = 28.5^\circ$
Absorption correction: ψ scan	$h = -3 \rightarrow 13$
(Molecular Structure Corporation, 1993)	$k = -14 \rightarrow 14$
$T_{min} = 0.879$, $T_{max} = 0.924$	$l = -15 \rightarrow 15$
8063 measured reflections	3 standard reflections
2992 independent reflections	every 400 reflections
2436 reflections with $I > 2\sigma(I)$	intensity decay: 1%

Table 1

Selected geometric parameters (Å, °).

C1—O7	1.438 (2)	O1—P1	1.4959 (14)
C1—P1	1.8501 (18)	O2—P1	1.5194 (13)
C1—P2	1.8348 (18)	O3—P1	1.5729 (15)
C3—N1	1.498 (2)	O4—P2	1.5482 (15)
C4—N1	1.508 (3)	O5—P2	1.5314 (14)
C7—N1	1.522 (3)	O6—P2	1.5060 (13)
P1—C1—P2	114.23 (9)	O4—P2—O5	109.12 (9)
O1—P1—O2	113.96 (8)	O4—P2—O6	112.81 (8)
O1—P1—O3	109.41 (8)	O5—P2—O6	114.02 (7)
O2—P1—O3	111.11 (8)		
P2—C1—P1—O1	−179.67 (9)	P1—C1—P2—O6	67.38 (11)
P2—C1—P1—O2	−55.95 (12)	P1—C1—P2—O5	−56.08 (11)
P2—C1—P1—O3	63.95 (11)	P1—C1—P2—O4	−170.55 (9)

Table 2

Hydrogen-bonding geometry (Å, °).

D—H...A	D—H	H...A	D...A	D—H...A
O7—H2...O6 ⁱ	0.81 (3)	1.87 (3)	2.668 (2)	167 (3)
O5—H5...O2 ⁱⁱ	0.93 (2)	1.51 (2)	2.436 (2)	170 (3)
O3—H3...O6 ⁱⁱ	0.79 (2)	1.83 (2)	2.610 (2)	171 (3)
O4—H4...O1 ⁱⁱⁱ	0.83 (2)	1.66 (2)	2.487 (2)	175 (3)
N1—H1...O3 ⁱⁱⁱ	0.85 (2)	2.51 (3)	3.268 (2)	150 (2)
N1—H1...O5 ⁱⁱⁱ	0.85 (2)	2.54 (2)	3.141 (2)	129 (2)
N1—H1...O7 ⁱⁱⁱ	0.85 (2)	2.41 (2)	3.011 (2)	129 (2)

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

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.055P)^2 + 0.191P]$
$R(F) = 0.037$	where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.103$	$(\Delta/\sigma)_{\max} = 0.004$
$S = 1.06$	$\Delta\rho_{\max} = 0.38 \text{ e } \text{Å}^{-3}$
2992 reflections	$\Delta\rho_{\min} = -0.30 \text{ e } \text{Å}^{-3}$
210 parameters	
H atoms treated by a mixture of independent and constrained refinement	

Atom C5 is disordered over two sites, and the occupancies were refined freely until the last cycles of refinement, at which point they were fixed at 0.75 for C5 and 0.25 for C5'. The displacement and positional parameters of H atoms attached to the tertiary N atom and the hydroxyl O atom were freely refined. The U_{iso} values of the remaining H atoms were kept at 1.2 (for those bonded to C atoms) and 1.5 (for those bonded to phosphoryl O atoms) times the U_{eq} value of their carriers. The positions of H atoms attached to C atoms were refined freely, except for the H atoms attached to the disordered atom, which were treated as riding, with C—H distances fixed at 0.97 Å. H atoms attached to phosphoryl O atoms were refined with a restrained O—H distance of 0.85 (3) Å using the DFIX command implemented in *SHELXL97* (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: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *XP in SHELXTL/PC* (Sheldrick, 1991); software used to prepare material for publication: *PARST* (Nardelli, 1995) and *WinGX* (Farrugia, 1999).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: NA1602). Services for accessing these data are described at the back of the journal.

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