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Disodium pamidronate

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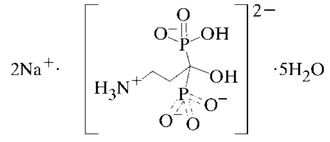
The title compound, disodium 3-ammonium-1-hydroxypropylidene-1,1-bisphosphonate pentahydrate, $2Na^+\cdot C_3H_9NO_7P_2^{2-}\cdot 5H_2O$, is used for the diagnosis and treatment of a number of bone disorders. In the solid state, disodium pamidronate shows zwitterionic character and has four different modes of chelation to sodium. The metal is octahedrally coordinated by zwitterion and water O atoms. Both coordination to sodium and hydrogen bonding determine the packing in the crystal, which comprises columns lying parallel to the crystallographic *a* axis.

Comment

Several bisphosphonates are safe and efficacious therapeutic agents widely used for the treatment of a number of bone disorders, *e.g.* osteoporosis, Paget's disease of bone and bone metastases. They have the PCP group in common, which is an analogue of inorganic pyrophosphate and has the ability to adsorb with high affinity to the mineral phase of bone, while the lateral chain attached to the central C atom operates at the cellular level affecting the activity of the macrophage cells that resorb bone tissue, the osteoclasts. The title compound, (I), belongs to the group of nitrogen-containing bisphosphonates, which act intracellularly by inducing repression of the enzymes of the mevalonate pathway, responsible for the function of key proteins involved in cellular signaling, thus leading to the selective loss of activity of the osteoclasts and then to their apoptotic death (Russell & Rogers, 1999; Rogers *et al.*, 2000; Rodan & Martin, 2000). The nitrogen-containing bisphosphonates also exhibit herbicidal and antiparasitic activities (Martin *et al.*, 1999), and could offer a novel therapeutic alternative for the treatment of American trypanosomiasis (Urbina *et al.*, 1999). In nuclear medicine, technetium-labelled pamidronate has been applied as a scanning agent in bone scintigraphy, a sensitive procedure to detect bone metastases (Degrossi *et al.*, 1985), and, according to preclinical studies, α- and β-particle emitter compounds derived from pamidronate could yield highly effective radiopharmaceuticals for the treament of bone cancer (Larsen *et al.*, 1999; Zeevaart *et al.*, 1999). Due to the importance of the subject, there has been increased interest in determining the structures, as well as in elucidating the coordination chemistry, of the bisphosphonates. The structure of the free acid of pamidronate is known, and the data, deposited in the Cambridge Structural Database (Allen *et al.*, 1983) with refcode SOPSEV (Shkol'nikova *et al.*, 1990), were retrieved and subsequently used in a comparison of both structures. As a part of an ongoing study of the molecular and crystal structures of chemical compounds that affect osseous metabolism and are used as therapeutic agents to treat bone diseases (Vega *et al.*, 1996, 1998), we report herein the single-crystal X-ray analysis of the disodium salt of pamidronate, (I).



(I)

In the title compound (see Fig. 1), the central C1 atom is substituted with $(PO_3)^{2-}$, $(PO_3H)^-$, and OH groups and an alkylamine lateral chain containing the terminal quaternary ammonium group. As with the previously studied free acid, it has zwitterionic character and possesses a monoprotonated phosphonate group. The geometry around each P atom is that of a distorted tetrahedron, as can be seen from the ranges of bond angles around P1 and P2 of 106.41 (15)–113.87 (14) and 103.46 (14)–119.49 (14)°, respectively. The P1—O bond lengths are essentially similar, and the O—P1—O bond angles deviate by less than 5° from the ideal tetrahedral angle (see Table 1); therefore, an examination of the geometry around P1 shows that all the P1—O bonds have partial double-bond

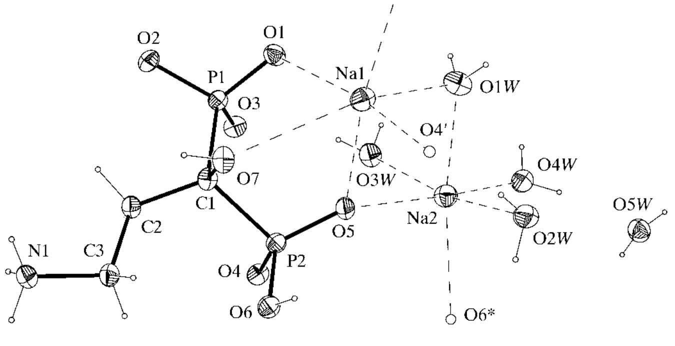


Figure 1
View of the title compound showing the atom-numbering scheme and displacement ellipsoids drawn at a 30% probability level. The sixfold coordination to sodium is depicted as dashed lines, with symmetry-related atoms represented as circles of arbitrary radii [symmetry codes: (′) 1 + *x*, *y*, *z*; (*) 1 − *x*, 2 − *y*, 1 − *z*.]

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character. The value of the O1—P1—O3 angle [113.87 (14)°] suggests that atoms O1 and O3 have slightly more negative charge than O2; the P1—O2 bond is close to 10σ larger than P1—O1 and P1—O3. In the monoprotonated phosphonate group, the P2—O bond lengths differ considerably, and, as in SOPSEV, the largest distance corresponds to the single bond of the protonated O atom. It was expected that the other two bonds would be of similar length due to electronic delocalization between the charge and the lone-pair electrons of the unprotonated O atoms. This is clearly evident in SOPSEV, where the bond lengths are 1.506 and 1.507 Å; however, in this work, P2—O4 [1.514 (2) Å] and P2—O5 [1.487 (2) Å] differ by more than 12σ. Such dissimilarity seems to be due to an unequitable electronic delocalization of the negative charge, so that, instead of spreading over both unprotonated O atoms, it could largely be associated with one of them. The O4—P2—O5 angle is close to 120°, possibly as a result of Coulombic repulsion between the negative charges; hence, it is almost 4° larger than in SOPSEV and more than 5° wider than O1—P1—O3. The influence of the intermolecular interactions on the bonds in the $(PO_3H)^-$ group (Shkol'nikova *et al.*, 1990) and the presence of an O—H···O intermolecular hydrogen bond (H···O = 1.73 Å) usually result in the P—O bond lengths of a phosphonate being similar. In the title compound, this is not the case, as the O6—H3···O2*W* hydrogen bond (H···O = 2.01 Å) is significantly larger than that in SOPSEV (Shkol'nikova *et al.*, 1990).

In disodium pamidronate, one phosphonate group is staggered with respect to the other, as can be seen from the six torsion angles along the P1···P2 direction: O1—P1—P2—O5 −20.4 (1)°, O2—P1—P2—O6 −41.2 (2)°, O3—P1—P2—O4 −26.9 (1)°, O3—P1—P2—O5 92.4 (1)°, O1—P1—P2—O6 94.5 (2)° and O2—P1—P2—O4 84.6 (2)°. As expected, the sum of the absolute values of the averages of the negative and positive torsion angles is 120°. A comparison of the O2—P1—C1—P2 and O6—P2—C1—P1 torsion angles [160.98 (15) and 171.43 (15)°, respectively, in the present work, and −162.91 and −174.46° in SOPSEV] indicates that the O atoms of the O—P—C—P—O chain, in both structures, depart slightly from a planar W configuration. Such a configuration of the O—P—C—P—O chain is related to the biological activity of the compound (Shkol'nikova *et al.*, 1990). On inspecting the orientation of one PO_3 group with respect to the other, Leroux *et al.* (1991) observed an inverse correlation between the value of the P—C—P angle (φ) and a certain 'staggering' angle among the PO_3 groups when viewed along the P···P vector (ρ). The ρ angle was calculated as the product of averaging the O*x*—P1—C1—P2 and P1—C1—P2—O*y* sum (Vega *et al.*, 1996); thus, the φ/ρ relationship (in °) found for pamidronate, 110.3/46 (5)° in this work and 110.6/45 (6)° in SOPSEV, is in agreement with that observed for related compounds and hence confirms the general trend (Vega *et al.*, 1996).

All the O atoms of the zwitterion, with the exception of O2, are engaged in the coordination to sodium, wherefore disodium pamidronate shows four different modes of chelation: (i) tridentate, involving the hydroxyl O7 atom and the phosphonyl O1 and O5 atoms; (ii) bidentate, involving the phosphonyl O3 and O4 atoms; (iii) monodentate, involving atom O6; and (iv) bridging, involving atom O5 (Fig. 1). All but one water O atom are involved in the coordination to sodium, the exception being O5*W* located near the positive end of the zwitterion, *i.e.* the quaternary ammonium. Atom O1*W* acts, together with the phosphonyl O5 atom, as a bridge between Na1 and Na2; the cations approach at a rather close Na···Na distance of 3.357 (2) Å. A sixfold coordination sphere surrounds Na1 and Na2, whereby each is approximately located at the centre of a distorted octahedron (see Table 1). The best equatorial plane of the O_6Na1 octahedron is that defined by atoms O5, O7, O1*W* and O3^{i}, the cation lying 0.113 (2) Å from this plane and forming an O1···Na1···O4^{i} angle of 160.45 (11)° with apical atoms O1 and O4^{i} [symmetry code: (i) $1 + x, y, z$]. In contrast, the main constituents of the O_6Na2 octahedron are the crystallization water O atoms. In this case, the cation lies 0.116 (2) Å from the equatorial plane defined by atoms O1*W*, O2*W*, O3*W* and O6^{ii}, and the O5···Na2···O4*W* angle is 162.87 (11)° [symmetry code: (ii) $1 - x, 2 - y, 1 - z$].

16 of the 19 available H atoms, namely the hydroxyl, phosphonyl, four alkylamine and ten water H atoms, are involved in an intricate hydrogen-bonding scheme (see Table 2). The H···O distances found in this work, ranging from 1.88 to 2.15 Å for the 14 single hydrogen bonds, are significantly longer than those in SOPSEV (H···O 1.70–1.97 Å), where the two shortest distances determine the packing of the molecules in chains. The packing in the crystal of SOPSEV is different to that of the disodium salt (see below), a fact which could be associated with the lower solubility of the free acid in comparison with that of the title compound.

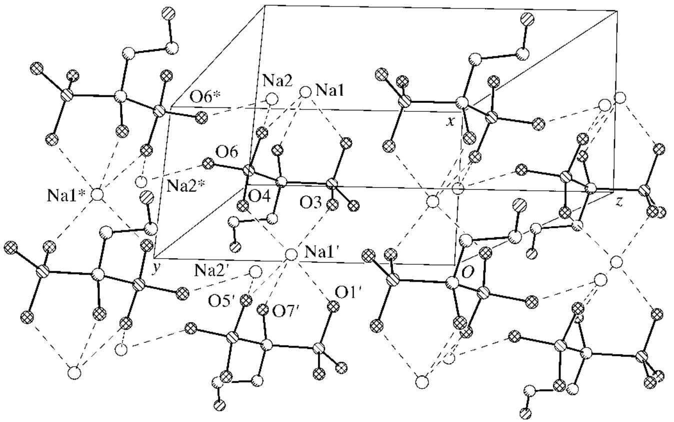

Figure 2

Packing diagram showing the coordination to sodium (dashed lines). H atoms and water molecules have been omitted for clarity. [Symmetry codes: (') $x - 1, y, z$; (*) $1 - x, 2 - y, 1 - z$.]

The coordination to the metal and the hydrogen bonding determine the packing in the crystal of disodium pamidronate. Centrosymmetrically related zwitterions, linked by monodentate ligation through O6···Na2^{ii}, form a 'dimer'. This dimer is joined to a [100]-translated dimer *via* the ligation to

Na1 (Fig. 2), so that the stacking of dimers along the crystallographic *a* axis results in the formation of a column. As is apparent in Fig. 2, the negative end of the zwitterion occupies the centre of the column, adjacent to the cations, whereas its positive end (the quaternary ammonium) projects away from the centre as far as possible. The packing is completed by the hydrogen-bond interactions, which, as only a few of them occur inside a column, appear to be the main intercolumnar cohesive forces.

Experimental

The title compound was obtained from Laboratorios Gador S.A., Buenos Aires, Argentina. Crystals suitable for X-ray diffraction were obtained by slow evaporation from a water solution.

Crystal data

$2Na^+\cdot C_3H_9NO_7P_2^{2-}\cdot 5H_2O$
$M_r = 369.11$
Triclinic, $P\overline{1}$
$a = 5.9588\ (4)$ Å
$b = 10.901\ (1)$ Å
$c = 11.290\ (1)$ Å
$\alpha = 113.700\ (5)°$
$\beta = 93.164\ (4)°$
$\gamma = 91.957\ (5)°$
$V = 669.22\ (10)$ Å^3
$Z = 2$
$D_x = 1.832$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 10 466 reflections
$\theta = 1.0$–$25.0°$
$\mu = 0.45$ mm^{-1}
$T = 293\ (2)$ K
Needle, colourless
$0.40 \times 0.04 \times 0.01$ mm

Data collection

Nonius KappaCCD diffractometer
φ scans, and ω scans with κ offsets
Absorption correction: multi-scan (*SORTAV*; Blessing, 1995)
$T_{\rm min} = 0.841$, $T_{\rm max} = 0.995$
12 361 measured reflections
2342 independent reflections
1750 reflections with $I > 2\sigma(I)$
$R_{\rm int} = 0.1$
$\theta_{\rm max} = 25.0°$
$h = -6 \rightarrow 7$
$k = -12 \rightarrow 12$
$l = -13 \rightarrow 13$
Intensity decay: negligible

Refinement

Refinement on F^2
$R(F) = 0.042$
$wR(F^2) = 0.106$
$S = 1.06$
2342 reflections
182 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0309P)^2 + 0.3970P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\rm max} < 0.001$
$\Delta\rho_{\rm max} = 0.26$ e Å^{-3}
$\Delta\rho_{\rm min} = -0.42$ e Å^{-3}

H atoms were treated as riding, at distances of 0.97 (C—H), 0.89 (N—H) and 0.82 Å (O—H), and their isotropic displacement parameters were constrained to be 1.2 times those of their hosts (1.5 for those attached to O atoms). All O*W*—H*W* distances were restrained according to a *SHELXL*97 *DFIX* instruction, with $U_{\rm iso}(HW) = 1.5U_{\rm eq}(OW)$.

Data collection: *COLLECT* (Nonius, 1997–2000); cell refinement: *HKL SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *HKL SCALEPACK* and *DENZO* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *XP* in *SHELXTL*/*PC* (Sheldrick, 1991); software used to prepare material for publication: *PARST* (Nardelli, 1995) and *WinGX* (Farrugia, 1999).

Table 1
Selected geometric parameters (Å, °).

P1—O1	1.519 (2)	Na1—O1	2.289 (3)
P1—O2	1.537 (2)	Na1—O3$^{\rm i}$	2.380 (3)
P1—O3	1.518 (2)	Na1—O4$^{\rm i}$	2.386 (3)
P2—O4	1.514 (2)	Na1—O5	2.387 (3)
P2—O5	1.487 (2)	Na1—O7	2.827 (3)
P2—O6	1.614 (2)	Na1—O1*W*	2.487 (3)
C1—O7	1.451 (4)	Na2—O5	2.274 (3)
C1—P1	1.869 (3)	Na2—O6$^{\rm ii}$	2.456 (3)
C1—P2	1.845 (4)	Na2—O1*W*	2.304 (3)
C1—C2	1.536 (5)	Na2—O2*W*	2.691 (3)
C2—C3	1.517 (5)	Na2—O3*W*	2.401 (3)
C3—N1	1.492 (4)	Na2—O4*W*	2.454 (3)
O1—P1—O3	113.87 (14)	P1—C1—P2	110.27 (17)
O2—P1—O3	111.70 (13)	O1—Na1—O4$^{\rm i}$	160.45 (11)
O1—P1—O2	109.92 (14)	O3$^{\rm i}$—Na1—O1*W*	89.51 (9)
O1—P1—C1	106.90 (14)	O5—Na1—O1*W*	84.65 (9)
O2—P1—C1	107.69 (14)	O3$^{\rm i}$—Na1—O7	117.85 (9)
O3—P1—C1	106.41 (15)	O5—Na1—O7	69.08 (8)
O4—P2—O5	119.49 (14)	O5—Na2—O4*W*	162.87 (11)
O5—P2—O6	108.88 (13)	O1*W*—Na2—O3*W*	85.99 (10)
O4—P2—O6	105.96 (13)	O3*W*—Na2—O6$^{\rm ii}$	109.56 (10)
O4—P2—C1	110.28 (14)	O1*W*—Na2—O2*W*	80.22 (9)
O5—P2—C1	107.60 (15)	O6$^{\rm ii}$—Na2—O2W	83.94 (9)
O6—P2—C1	103.46 (14)		

Symmetry codes: (i) $1 + x, y, z$; (ii) $1 - x, 2 - y, 1 - z$.

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O6—H3···O2*W*$^{\rm vi}$	0.82	2.01	2.811 (3)	165
O7—H4···O2$^{\rm v}$	0.82	1.91	2.708 (3)	165
N1—H9···O2$^{\rm iii}$	0.89	1.88	2.757 (3)	169
N1—H10···O1$^{\rm v}$	0.89	1.93	2.817 (4)	172
N1—H11···O5*W*$^{\rm ii}$	0.89	2.05	2.872 (4)	153
O1*W*—H11*W*···O3$^{\rm iv}$	0.81	2.02	2.814 (3)	166
O1*W*—H12*W*···O3*W*$^{\rm i}$	0.80	1.96	2.753 (3)	171
O2*W*—H21*W*···O4$^{\rm i}$	0.80	2.07	2.859 (4)	171
O2*W*—H22*W*···O4$^{\rm ii}$	0.82	1.90	2.717 (3)	172
O3*W*—H31*W*···O3	0.82	2.15	2.919 (4)	157
O3*W*—H32*W*···O1$^{\rm iv}$	0.82	1.89	2.703 (3)	172
O4*W*—H41*W*···O5*W*	0.81	2.03	2.816 (4)	164
O4*W*—H42*W*···O2$^{\rm iv}$	0.81	2.03	2.838 (4)	176
O5*W*—H51*W*···O4*W*$^{\rm viii}$	0.81	2.02	2.813 (4)	168
O5*W*—H52*W*···O2*W*$^{\rm vii}$	0.80	2.04	2.830 (4)	172
C2—H5···O2	0.97	2.55	2.962 (4)	106
C2—H5···O7$^{\rm v}$	0.97	2.55	3.503 (4)	167

Symmetry codes: (i) $1 + x, y, z$; (ii) $1 - x, 2 - y, 1 - z$; (iii) $-x, 1 - y, -z$; (iv) $1 - x, 1 - y, 1 - z$; (v) $1 - x, 1 - y, -z$; (vi) $2 - x, 2 - y, 1 - z$; (vii) $2 - x, 2 - y, 2 - z$; (viii) $1 - x, 2 - y, 2 - z$.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: NA1543). Services for accessing these data are described at the back of the journal.

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