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The Zn^{2+} salt of pamidronate: a role for water in the metal–cation binding properties of bisphosphonates

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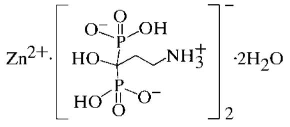
Pamidronate (3-ammonium-1-hydroxypropylidene-1,1-bisphosphonate) is used clinically in the treatment of diseases affecting bone tissue. In the salt zinc pamidronate dihydrate, $Zn^{2+}\cdot 2C_3H_{10}NO_7P_2^{-}\cdot 2H_2O$, pamidronate is a zwitterion with an overall charge of −1. The carbon chain adopts a *trans* conformation, separating maximally the positively charged N atom from the negative phosphonate groups. The Zn^{2+} ion lies on an inversion center and is surrounded by a sixfold coordination sphere provided by two bidentate chelating zwitterions and two water molecules. The bidentate O···Zn···O bond angle is 92.70 (7)°, while the O···O bite distance is 3.018 (3) Å.

Comment

Metal cations are bound strongly by bisphosphonates (alternatively named diphosphonates) through their phosphonate O atoms. This ability gives a high tropism to the bisphosphonate skeleton, and it interacts readily with calcium hydroxyapatite crystals. In clinical practice, a number of bisphosphonates are available for the treatment of diseases affecting bone tissue (Martin & Grill, 2000; Watts, 2003). Pamidronate, a potent inhibitor of osteoclast-mediated bone resorption, is indicated for hypercalcaemia, osteolytic metastases and Paget's disease of the bone (Widler *et al.*, 2002). Novel roles of bisphosphonates in other diseases have also been suggested (Wolf & Stoller, 1994; Dunn *et al.*, 1998; Reid, 2003). Additional fields where compounds of this type have found useful applications include diagnosis (Degrossi *et al.*, 1985), bone imaging (Love *et al.*, 2003), nuclear medicine (Elder *et al.*, 1997; Larsen *et al.*, 1999) and organometallic chemistry (Distler *et al.*, 1999; Stock & Bein, 2002).

Recent structural studies of pamidronate, in particular those of its sodium (Vega *et al.*, 2002) and calcium (Fernández *et al.*, 2002) salts, showed that, concomitant with its chelating behavior, its carbon chain was able to adopt different conformations. Such an observation inspired a further exploration of the conformational diversity among bisphosphonates, and so the structural determination of the zinc salt, (I), of pamidronate was undertaken. In addition, the binding of the hydration water molecule in two salts of pamidronate has been characterized by thermogravimetric analysis. The results obtained, together with the single-crystal X-ray diffraction analysis of (I), are reported in the present communication.



(I)

In the molecular anion in (I), the geminal atom C1 is substituted by the phosphonate groups, the alcohol function and the alkylamine side chain (Fig. 1). Both P atoms have tetrahedral geometry, which is defined by the bridging C atom and by three O atoms, two of which are unprotonated. The P—C and P—O bond lengths, the P—C—P, O—P—O and O—P—C bond angles, and the mutual orientation of the PO_3 groups (Table 1) are in good agreement with the values found in related structures (Fernández & Vega, 2003; Fernández *et al.*, 2003). The carbon chain adopts a different conformation with respect to that in the Ca^{2+} pamidronate salt (Fernández *et al.*, 2002), hereafter CaH_2PAM, the conformation being *trans* in (I) [C1—C2—C3—N1 = 174.2 (2)°] but close to *gauche*⁻ in the latter [−72.1 (2)°]. To illustrate this difference, the position of atom N1 relative to the least-squares mean plane defined by atoms C1, C2 and C3 is −0.144 (6) Å for (I) and 1.311 (4) Å for CaH_2PAM. Possibly, the twisting of the chain is stabilized intramolecularly in CaH_2PAM by a hydrogen bond between atom N1 and the hydroxy O atom [N···O = 2.692 (2) Å, H···O = 1.93 (4) Å and N—H···O = 132 (3)°]. In (I), atom N1 is maximally separated from atom O7 and thus no intramolecular interaction was observed. An inspection of the

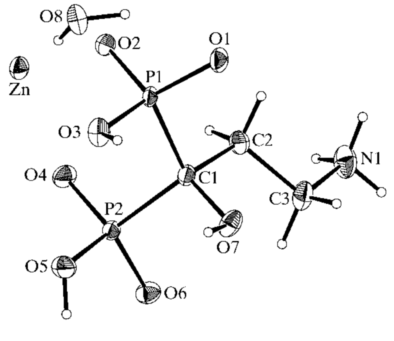


Figure 1
A view of (I), showing the atomic numbering scheme and displacement ellipsoids at the 50% probability level.

four N—H···O interactions listed in Table 2 leads to the conclusion that the hydrogen bonds involving atom N1 are weaker than those in CaH_2PAM.

As with the Ca^{2+} salt, the molecular anion has an overall charge of −1 and zwitterionic character, given by one −1 charge on each PO_3 group and a +1 charge on atom N1. A 2:1 relationship exists between pamidronate and the metal cation. The Zn^{2+} ion is located on an inversion center and the geometry defined by the coordinated atoms is octahedral (Fig. 2). In the coordination sphere around the Zn^{2+} ion there are three symmetry-independent oxygen ligands, namely two from the zwitterion (atoms O2 and O4) and one from the crystallization water molecule (O8). The Zn—O distances have a mean value of 2.100 (2)°, while the O—Zn—O bond angles are 180° or depart slightly from 90° (Table 1). The zwitterionic oxygen ligands have a *cis* geometry, sustaining an O2—Zn—O4 bond angle of 92.70 (7)°, while the O2···O4 bite distance is 3.018 (3) Å. The corresponding values found in the Ca^{2+} octahedron are 81.48 (4)° and 3.065 (2) Å, respectively. The Zn^{2+} octahedra pack along the *a* axis in a column, where the metal cation is at the center and the zwitterion disposes its negative groups towards the Zn^{2+} ion, while its positive end is elongated in the opposite direction. Inside a column, there are hydrogen bonds between zwitterions related by a center of symmetry [O8—H7···O3($-x$, $-y$, $-z$); see Table 2] and between [100]-translated ions [N1—H1···O4($1+x$, y, z), N1—H1···O2($1-x$, $-y$, $-z$) and O8—H8···O1($1-x$, $-y$, $-z$)]. This column interacts with three neighbors *via* the remaining hydrogen bonds listed in Table 2.

Pamidronate functions as a bidentate ligand in the zinc salt, while pamidronate is both mono- and bidentate in its calcium salt. This difference could originate in a number of factors, including the steric hindrance of the coordinated ligands and the energy of hydration of the particular metal cation. The volume of the Ca^{2+} coordination sphere is ~1.5 times larger than that of Zn^{2+} [the mean Ca···O distance is 2.3276 (12) Å], suggesting that, in the former, there is sufficient space for two bidentate and two monodentate zwitterions to be accommodated. In (I), as less room is available around the Zn^{2+} ion, two water molecules are placed as monodentate ligands instead of two zwitterions. The water molecule in CaH_2PAM is too far from the metal cation to form contacts with it and is hydrogen bonded to the N atom. In (I), water is retained in the coordination sphere of the metal cation, possibly because the energy of hydration of the zinc ion is higher than that of calcium, in keeping with the smaller ionic radius of the former (Gutiérrez Ríos, 1994; Pavlov *et al.*, 1998). This fact is in good agreement with the results obtained from the thermogravimetric analysis performed on samples of the Ca^{2+} and Zn^{2+} salts of pamidronate. A weight loss of 7.0%, corresponding to two water molecules per formula unit (calculated weight 6.6%), takes place at 369 K in CaH_2PAM, while for the Zn^{2+} salt, the dehydration (weight loss 7.2%, calculated 6.3%) occurred at a higher temperature (473 K).

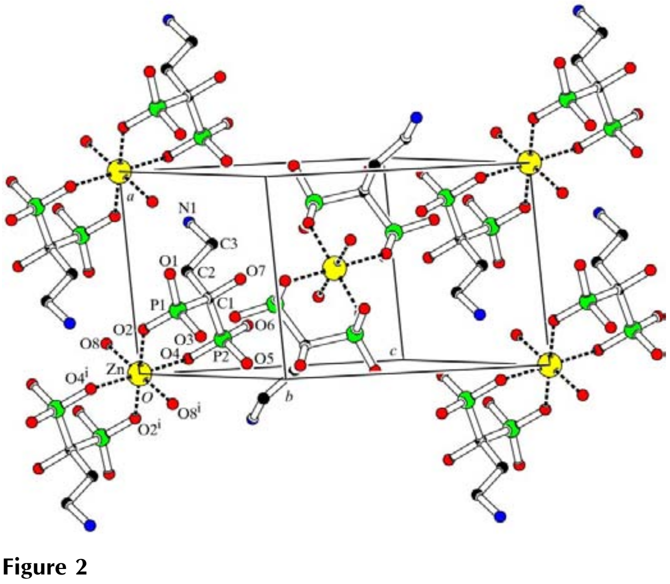


Figure 2
A portion of the packing of (I), showing the zinc coordination sphere (dashed lines). All H atoms have been omitted for clarity. [Symmetry code: (i) $-x$, $-y$, $-z$.]

Experimental

A sample of pamidronic acid was obtained from Laboratorios Gador SA, Buenos Aires, Argentina. A powdered sample of the bisphosphonate (M_r = 239.12) was added to $ZnCO_3$ in a 1:1 ratio and then dissolved in an excess of hot water. Crystals suitable for X-ray diffraction were obtained by evaporating this solution at room temperature.

Crystal data

$Zn^{2+}\cdot 2C_3H_{10}NO_7P_2^-\cdot 2H_2O$
$M_r = 569.52$
Monoclinic, $P2_1/n$
$a = 7.3531$ (2) Å
$b = 10.8223$ (2) Å
$c = 10.9197$ (2) Å
$\beta = 94.469$ (2)°
$V = 866.32$ (3) Å^3
$Z = 2$
$D_x = 2.183$ Mg m^{-3}

Cu *Kα* radiation
Cell parameters from 25 reflections
$\theta = 20$–30°
$\mu = 6.37$ mm^{-1}
$T = 293$ (2) K
Prism, colorless
0.25 × 0.22 × 0.10 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
Non-profiled $\omega/2\theta$ scans
Absorption correction: ψ scan (North *et al.*, 1968)
$T_{min} = 0.271$, $T_{max} = 0.529$
2128 measured reflections
1535 independent reflections
1434 reflections with $I > 2\sigma(I)$

$R_{int} = 0.046$
$\theta_{max} = 66.9°$
$h = -1 \rightarrow 8$
$k = -12 \rightarrow 1$
$l = -13 \rightarrow 13$
1 standard reflection frequency: 60 min
intensity decay: 5%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.037$
$wR(F^2) = 0.100$
$S = 1.06$
1535 reflections
157 parameters
H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0703P)^2 + 0.7592P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.007$
$\Delta\rho_{max} = 0.88$ e Å^{-3}
$\Delta\rho_{min} = -0.76$ e Å^{-3}

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Table 1
Selected geometric parameters (Å, °).

C1—P1	1.838 (3)	O5—P2	1.5603 (19)
C1—P2	1.849 (2)	O6—P2	1.5161 (19)
O1—P1	1.5208 (18)	O2—Zn	2.0236 (17)
O2—P1	1.5058 (19)	O4—Zn	2.1454 (19)
O3—P1	1.5433 (19)	O8—Zn	2.132 (2)
O4—P2	1.5094 (19)		
P1—C1—P2	113.25 (13)	O5—P2—C1	106.39 (11)
O1—P1—O2	114.07 (11)	O6—P2—C1	108.37 (11)
O1—P1—O3	110.93 (12)	O2—Zn—O2^{i}	180.00 (14)
O2—P1—O3	110.74 (11)	O2—Zn—O8^{i}	87.89 (8)
O1—P1—C1	105.70 (11)	O2—Zn—O8	92.11 (8)
O2—P1—C1	108.99 (12)	O8^{i}—Zn—O8	180.00 (9)
O3—P1—C1	105.94 (11)	O2—Zn—O4	92.70 (7)
O4—P2—O5	111.50 (11)	O8—Zn—O4	89.89 (8)
O4—P2—O6	114.39 (12)	O2—Zn—O4^{i}	87.30 (7)
O5—P2—O6	108.06 (11)	O8—Zn—O4^{i}	90.11 (8)
O4—P2—C1	107.79 (11)	O4—Zn—O4^{i}	180.00 (14)
P2—C1—P1—O1	178.23 (13)	P1—C1—P2—O4	55.32 (17)
P2—C1—P1—O2	−58.76 (16)	P1—C1—P2—O5	−64.39 (16)
P2—C1—P1—O3	60.44 (16)	P1—C1—P2—O6	179.62 (13)

Symmetry code: (i) $-x, -y, -z$.

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

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
O8—H7$\cdots$O3^{i}	0.84 (3)	2.38 (4)	2.919 (3)	123 (3)
O8—H7$\cdots$O7^{ii}	0.84 (3)	2.23 (3)	2.905 (3)	137 (3)
O8—H8$\cdots$O1^{iii}	0.85 (3)	1.91 (3)	2.732 (3)	161 (4)
O3—H4$\cdots$O6^{iv}	0.85 (3)	1.64 (3)	2.474 (3)	171 (4)
O7—H6$\cdots$O4^{iv}	0.84 (2)	2.12 (3)	2.845 (3)	144 (3)
O5—H5$\cdots$O1^{v}	0.84 (3)	1.67 (3)	2.513 (3)	178 (4)
N1—H1$\cdots$O2^{iii}	0.88 (3)	2.35 (3)	3.127 (3)	147 (4)
N1—H1$\cdots$O4^{vi}	0.88 (3)	2.35 (4)	3.017 (3)	133 (3)
N1—H2$\cdots$O5^{ii}	0.88 (3)	2.19 (3)	2.997 (3)	152 (4)
N1—H3$\cdots$O1^{vii}	0.85 (3)	2.41 (3)	3.106 (3)	140 (4)

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

H atoms attached to C atoms were placed 0.97 Å from their hosts and treated using a riding model, with isotropic displacement parameters fixed at $1.2U_{\rm eq}$(C). The positional parameters of H atoms attached to O- and N-atom hosts were refined with O—H and N—H distances restrained to 0.85 (3) and 0.89 (3) Å, respectively. The displacement parameters of these H atoms were fixed at 1.5 times those of their carrier atoms.

Data collection: *CAD*-4 *EXPRESS* (Enraf–Nonius, 1994); cell refinement: *CAD*-4 *EXPRESS*; data reduction: *XCAD*4 (Harms & Wocadlo, 1995); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *PLUTON* (Spek, 2003) and *ZORTEP* (Zsolnai & Pritzkow, 1995); software used to prepare material for publication: *PLATON* (Spek, 2003) and *WinGX* (Farrugia, 1999).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SQ1145). Services for accessing these data are described at the back of the journal.

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