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Alendronate zwitterions bind to calcium cations arranged in columns

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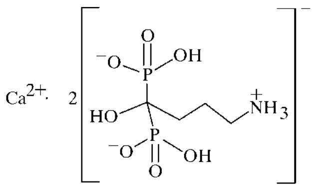
Alendronate is used clinically in the treatment of skeletal disorders, the mode of action depending on the adsorption to calcium hydroxyapatite crystals (bone). In the title compound, calcium 4-ammonium-1-hydroxybutylidene-1,1-bisphosphonate, $Ca^{2+}\cdot 2C_4H_{12}NO_7P_2^-$, alendronate is a zwitterion, possessing one negative charge on each PO_3 group and a protonated N atom. The zwitterion is disposed with its negative end facing the Ca^{2+} ion, while its positive end is stretched in the opposite direction. The geometry of the carbon chain is all-*trans*, while the hydroxy group is approximately *gauche*. The Ca^{2+} ion lies on a twofold axis parallel to *b*. The coordination sphere around the metal cation is octahedral and is determined by monodentate- and bidentate-coordinated alendronate zwitterions. The O···O bite distance is 3.080 (2) Å. Coordinated Ca^{2+} metal cations are arranged at the centre of a column running along *c*.

Comment

Bisphosphonates are a class of compounds in which the P—C—P bridge replaces the P—O—P group of naturally occurring pyrophosphate. Such a characteristic confers on bisphosphonates the capacity to interact avidly with the mineral phase of bone tissue (calcium hydroxyapatite crystals; Compston, 1994; Martin & Grill, 2000). Bisphosphonates containing an N atom in their structure, including alendronate, are potent inhibitors of osteoclast-mediated bone resorption (Shinkai & Ohta, 1996; Widler *et al.*, 2002). At sites of bone resorption, the compound is taken up by osteoclasts, which undergo a series of intracellular events (*e.g.* inhibition of the enzymes in the mevalonate pathway) that finally lead to their loss of activity and death by apoptosis (van Beek *et al.*, 2002). Clinical uses of alendronate include the treatment of bone disorders, such as osteoporosis and Paget's disease (Dyer, 2003).

Interest in studying the title compound comes from the fact that, despite their biomedical importance, only a few structures of calcium salts of bisphosphonates are known. The first crystal structures determined were those of etidronate [calcium dihydrogen 1-hydroxyethane-1,1-diphosphonate dihydrate; Cambridge Structural Database (Allen, 2002) refcode CAEHDP (Uchtman, 1972)] and clodronate [calcium dichloromethylene-1,1-diphosphonate pentahydrate; refcode CAVKUF (Nardelli *et al.*, 1983)], while of the more potent aminobisphosphonates, the structure of pamidronate [calcium 3-ammonium-1-hydroxypropylidene-1,1-bisphosphonate monohydrate; refcode XUGGEL (Fernández *et al.*, 2002)] has only recently been described. In the latter work, the structures of the free acid and of the monovalent (Na^+) and divalent (Ca^{2+}) metal cation salts of pamidronate were studied and their features compared. Using structural data from the free acid [4-ammonium-1-hydroxybutylidene-1,1-bisphosphonic acid; refcode GOWZEX (Ohanessian *et al.*, 1997)], the monosodium salt of alendronate [4-ammonium-1-hydroxybutylidene-1,1-bisphosphonate trihydrate; refcode TEHWOS (Vega *et al.*, 1996)] and the Ca^{2+} salt, (I), a similar study was carried out, the results of which are reported here.



(I)

The structure of the molecular anion in (I), hereafter CaH_2ALN, is composed of the P1—C1—P2 bridge, a hydroxy group and an alkylamine side chain attached to the geminal C atom (C1; Fig. 1). Like the previously studied free acid, H_3ALN (Ohanessian *et al.*, 1997), and the trihydrated sodium salt, NaH_2ALN (Vega *et al.*, 1996), (I) has zwitterionic character, with atom N1 bearing the positive charge. In their salts, the overall charge of the zwitterions is −1, so alendronate forms 1:1 and 2:1 complexes with Na^+ and Ca^{2+} ions, respectively. The geometry around the P atoms is tetrahedral (Table 1), and the lengths of the P—O bonds are close to 1.51 and 1.57 Å for the P—O(unprotonated) and P—O(protonated) distances, respectively. In each PO_3 group, the largest bond angle is that between the pair of unprotonated O atoms.

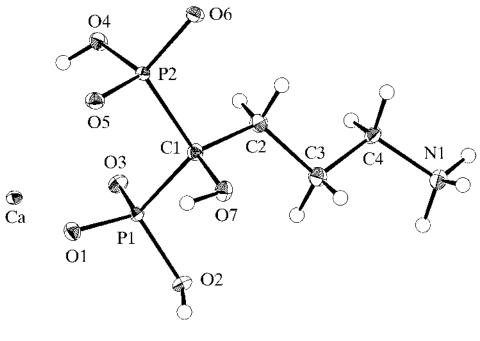


Figure 1
A view of (I), showing the atom-numbering scheme and displacement ellipsoids drawn at the 50% probability level.

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The P—C bond distances and the P—C—P bond angle are in good agreement with the values found in H_3ALN [1.847 (4) and 1839 (4) Å, and 113.5 (2)°] and NaH_2ALN [1.860 (3) and 1.854 (3) Å, and 110.0 (1)°].

Viewed along the P···P vector, the mutual orientation of the PO_3 groups defines a planar 'W'-like arrangement of the O2—P1—C1—P2—O6 chain. The relevant torsion angles are 170.7 (2) and −169.2 (2), 154.04 (12) and 156.04 (12), and −162.74 (10) and −170.15 (10)° for H_3ALN, NaH_2ALN and CaH_2ALN, respectively. The sp^3-hybridized C2 atom has a distorted-tetrahedral geometry, as indicated by the value of the C1—C2—C3 bond angle [117.7 (2)°]. An explanation for this distortion can be found when considering the intramolecular interactions in which these atoms are involved, where the H···O distance is less than the sum of the van der Waals radii (H4···O6 = 2.48 Å, H7···O2 = 2.53 Å and H6···O7 = 2.69 Å). The same geometry was observed for atom C2 in H_3ALN and NaH_2ALN, the C1—C2—C3 bond angles being 116.6 (3) and 113.9 (2)°, respectively. The disposition of the C2—C3 bond is also similar in the three structures, the values of the P1—C1—C2—C3 and P2—C1—C2—C3 torsion angles being 60.5 (6) and −174.5 (4), 57.3 (3) and −179.5 (2), and −67.3 (2) and 169.04 (16)° for H_3ALN, NaH_2ALN and CaH_2ALN, respectively.

For the related compound pamidronate (3-ammonium-1-hydroxypropylidene-1,1-bisphosphonate), a comparison of the structures of the free acid, the monovalent (Na^+) salt and the divalent (Ca^{2+}) salt revealed a different conformation of the carbon chain in the Ca^{2+} complex (Fernández *et al.*, 2002). In this structure, the conformation of the C—C—C—N chain is close to *gauche*, as shown by the value of the torsion angle [−72.1 (2)°], while in the free acid [−168.9 (2)°] and the disodium salt [153.6 (3)°], the conformation is *trans*. The hydroxy group is *gauche* in the calcium salt of pamidronate, which enables the formation of an intramolecular N—H···O(hydroxy) hydrogen bond [$D\cdots A$ = 2.692 (2) Å, $H\cdots A$ = 1.93 (4) Å and $D—H\cdots A$ = 132 (3)°]. For alendronate, a comparison of the geometric data for the structures of H_3ALN, NaH_2ALN and CaH_2ALN showed no dissimilarities. In each, the conformation of the C—C—C—C—N backbone is all-*trans*, while the hydroxy group is *gauche*. For (I), the relevant torsion angles are 52.6 (2) (O7—C1—C2—C3), 178.61 (18) (C1—C2—C3—C4) and 170.91 (17)° (C2—C3—C4—N1).

The Ca^{2+} ion lies on a twofold axis parallel to *b*. The environment around the Ca^{2+} ion (Fig. 2) is a somewhat distorted octahedron and consists of three symmetry-independent bonds provided by one monodentate and one bidentate chelator. The Ca^{2+} ion is situated on a local pseudo-mirror plane, which is defined by atoms O3($-x + 1$, $-y$, $-z + 1$), O3(x, $-y$, $z + \frac{1}{2}$), O5 and O5($-x + 1$, y, $-z + \frac{3}{2}$) (the r.m.s. deviation from the least-squares mean plane of the fitted atoms is 0.146 Å). Apical atoms O1 and O1($-x + 1$, y, $-z + \frac{3}{2}$) lie 2.283 (2) Å above and below this plane, forming an O1···Ca···O1($-x + 1$, y, $-z + \frac{3}{2}$) angle of 160.02 (12)°. The Ca···O contact distances range from 2.3037 (15) to 2.3444 (15) Å (Table 1). The O1···O5 bite distance is 3.080 (2) Å, well within the range found for the O atoms in crystals of calcium hydroxyapatite, which are bound more tightly to the Ca^{2+} ion (Nardelli *et al.*, 1983), thus explaining the biological activity of (I). The remaining phosphonyl O atoms, namely the unprotonated O6 atom, and the protonated O2 and O4 atoms, are not coordinated, and there are no other contacts below 3.2 Å to indicate additional coordination to the Ca^{2+} ion. Hydroxy atom O7 is separated by *ca* 4 Å from the metal cation, and hence the zwitterion cannot function as a tridentate ligand. This coordination is the main difference observed between the zwitterions in their Na^+ and Ca^{2+} salts, since NaH_2ALN uses two phosphonyl O atoms and the hydroxy O atom to coordinate as a tridentate ligand (Vega *et al.*, 1996). The same trend was observed for etidronate and pamidronate (Fernández *et al.*, 2002).

The Ca^{2+} ions are arranged in a columnar fashion along *c* (Fig. 2). As expected, the negatively charged part of the zwitterion is directed towards the cations close to the centre of the column, while its positive end is stretched, in the opposite direction, to its maximum possible length. Zwitterions inside the column are hydrogen bonded *via* O—H···O interactions (Table 2), while N—H···O interactions occur between adjacent columns.

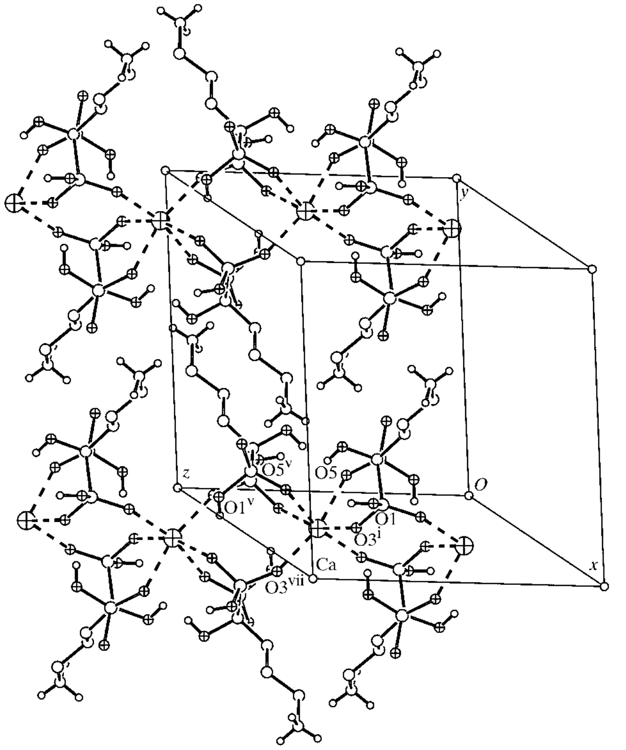

Figure 2
A simplified packing diagram, showing the calcium coordination sphere (dashed lines). Only H atoms attached to non-C-atom carriers are shown. [Symmetry codes: (i) $1 - x$, $-y$, $1 - z$; (v) $1 - x$, y, $\frac{3}{2} - z$; (vii) x, $-y$, $z + \frac{1}{2}$.]

Experimental

A sample of monosodium alendronate trihydrate was obtained from Laboratorios Gador SA, Buenos Aires, Argentina. The calcium salt was prepared as described by Uchtman (1972). A powdered sample of the bisphosphonate (M_r = 325.12) was added to $Ca(NO_3)_2{\cdot}4H_2O$ (M_r = 236.15, Fluka, Switzerland) and the mixture was placed in an excess of water. Crystals suitable for X-ray diffraction were obtained by evaporation of this solution in an oven at 315 K.

Crystal data

$Ca^{2+}{\cdot}2C_4H_{12}NO_7P_2^-$
M_r = 536.26
Monoclinic, $C2/c$
a = 15.9236 (7) Å
b = 12.4044 (6) Å
c = 11.4378 (5) Å
β = 123.516 (2)°
V = 1883.59 (15) Å^3
Z = 4

D_x = 1.891 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 971 reflections
θ = 3.9–26.0°
μ = 0.75 mm^{-1}
T = 120 (2) K
Prism, colourless
0.26 × 0.10 × 0.06 mm

Data collection

Bruker SMART6000 CCD diffractometer
ω scans
10 660 measured reflections
2342 independent reflections
2172 reflections with $I > 2\sigma(I)$

$R_{\rm int}$ = 0.092
$\theta_{\rm max}$ = 28.3°
$h = -21 \rightarrow 21$
$k = -16 \rightarrow 16$
$l = -14 \rightarrow 15$

Refinement

Refinement on F^2
$R(F)$ = 0.036
$wR(F^2)$ = 0.094
S = 1.22
2342 reflections
150 parameters
H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0227P)^2 + 3.8283P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\rm max}$ = 0.002
$\Delta\rho_{\rm max}$ = 0.69 e Å^{-3}
$\Delta\rho_{\rm min}$ = −0.41 e Å^{-3}

H atoms attached to C atoms were placed 0.97 Å from their hosts and treated using a riding model, with isotropic displacement parameters constrained to $1.2U_{\rm eq}$ of the carrier atoms. The positional parameters of the H atoms attached to atom N1 were refined freely, while for H atoms bonded to O atoms, the O—H distances were restrained to 0.85 (3) Å using the DFIX command in *SHELXL*97 (Sheldrick, 1997). The displacement parameters of these H atoms were set at $1.5U_{\rm eq}$ of their carrier atoms.

Data collection: *SMART-NT* (Bruker, 1998); cell refinement: *SMART-NT*; data reduction: *SAINT-NT* (Bruker, 1998); 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: *PARST* (Nardelli, 1995) and *WinGX* (Farrugia, 1999).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SQ1139). Services for accessing these data are described at the back of the journal.

Table 1
Selected geometric parameters (Å, °).

C1—P1	1.858 (2)	O5—P2	1.5116 (16)
C1—P2	1.869 (2)	O6—P2	1.5141 (15)
O1—P1	1.5250 (15)	Ca—O1	2.3344 (15)
O2—P1	1.5672 (14)	Ca—O5	2.3444 (15)
O3—P1	1.5089 (16)	Ca—O3$^{\rm i}$	2.3037 (15)
O4—P2	1.5710 (16)		
O3—P1—O1	115.02 (9)	O5—P2—O6	114.85 (9)
O3—P1—O2	105.75 (8)	O5—P2—O4	112.55 (9)
O1—P1—O2	110.49 (8)	O6—P2—O4	105.11 (8)
O3—P1—C1	111.95 (9)	O5—P2—C1	107.58 (9)
O1—P1—C1	106.26 (9)	O6—P2—C1	109.10 (9)
O2—P1—C1	107.16 (9)	O4—P2—C1	107.40 (9)
P2—C1—P1—O3	74.34 (13)	P1—C1—P2—O5	72.07 (12)
P2—C1—P1—O1	−52.00 (12)	P1—C1—P2—O6	−162.74 (10)
P2—C1—P1—O2	−170.15 (10)	P1—C1—P2—O4	−49.31 (13)

Symmetry code: (i) $1 - x, -y, 1 - z$.

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H10···O3$^{\rm ii}$	0.93 (3)	2.13 (3)	3.057 (2)	170 (3)
N1—H11···O6$^{\rm iii}$	0.92 (3)	1.88 (3)	2.720 (2)	150 (2)
N1—H12···O7$^{\rm iv}$	0.88 (3)	2.30 (3)	3.046 (2)	143 (2)
O7—H1···O5$^{\rm v}$	0.86 (2)	2.01 (2)	2.848 (2)	167 (3)
O2—H2···O6$^{\rm vi}$	0.85 (2)	1.76 (2)	2.574 (2)	162 (3)
O4—H3···O1$^{\rm i}$	0.82 (2)	1.78 (2)	2.572 (2)	164 (3)
O7—H1···O5	0.86 (2)	2.56 (3)	2.983 (2)	112 (2)

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

References

Allen, F. H. (2002). *Acta Cryst.* B**58**, 380–388.

Beek, E. R. van, Löwik, C. W. G. M. & Papapoulos, S. E. (2002). *Bone*, **30**, 64–70.

Bruker (1998). *SMART-NT* (Version 5.0) and *SAINT-NT* (Version 5.0). Bruker AXS Inc., Madison, Wisconsin, USA.

Compston, J. E. (1994). *Br. Med. J.* **309**, 711–715.

Dyer, O. (2003). *Br. Med. J.* **326**, 243.

Farrugia, L. J. (1999). *J. Appl. Cryst.* **32**, 837–838.

Fernández, D., Vega, D. & Goeta, A. (2002). *Acta Cryst.* C**58**, m494–m497.

Martin, T. J. & Grill, V. (2000). *Aust. Prescr.* **23**, 130–132.

Nardelli, M. (1995). *J. Appl. Cryst.* **28**, 659.

Nardelli, M., Pelizzi, G., Staibano, G. & Zucchi, E. (1983). *Inorg. Chim. Acta*, **80**, 259–271.

Ohanessian, J., Avenel, D., El Manouni, D. & Benramdane, M. (1997). *Phosphorus Sulfur Silicon*, **129**, 99–110.

Sheldrick, G. M. (1997). *SHELXS*97 and *SHELXL*97. University of Göttingen, Germany.

Shinkai, I. & Ohta, Y. (1996). *Bioorg. Med. Chem.* **4**, 3–4.

Uchtman, V. A. (1972). *J. Phys. Chem.* **76**, 1304–1310.

Vega, D., Baggio, R. & Garland, M. T. (1996). *Acta Cryst.* C**52**, 2198–2201.

Widler, L., Jaeggi, K. A., Glatt, M., Muller, K., Bachmann, R., Bisping, M., Born, A. R., Cortesi, R., Guiglia, G., Jeker, H., Klein, R., Ramseier, U., Schmid, J., Schreiber, G., Seltenmeyer, Y. & Green, J. R. (2002). *J. Med. Chem.* **45**, 3721–3738.

Zsolnai, L. & Pritzkow, H. (1995). *ZORTEP*. University of Heidelberg, Germany.