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Zoledronate complexes. I. Poly[[μ_2-aqua[μ_3-1-hydroxy-2-(1*H*,3*H*-imidazol-3-ium-1-yl)ethylidenediphosphonato]-potassium(I)] monohydrate]

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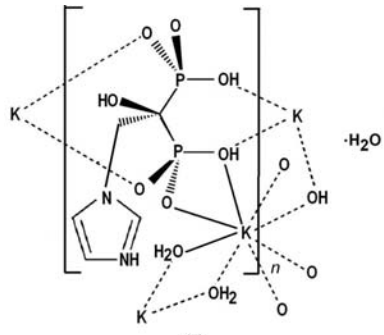
The title compound, $\{[K(C_5H_9N_2O_7P_2)(H_2O)]\cdot H_2O\}_n$, is polymeric and consists of layers parallel to (001) interconnected by hydrogen-bonding and π–π interactions. The K^+ cation is eightfold coordinated in a KO_8 environment by O atoms from three different chelating zoledronate units and two coordinated water molecules. The zoledronate group presents its usual zwitterionic character, with negative charges in the singly protonated phosphonate groups and a positive charge at the protonated imidazole N atom. The anion binds to three different K^+ cations in a (so far unreported) triply chelating manner. Intra- and interplanar interactions are enhanced by a variety of hydrogen bonds involving all available O—H and N—H donors. A strong imidazole–phosphonate C—H···O interaction is present in the structure.

Comment

Bisphosphonates (BPs) constitute an extensive family of compounds (including etidronate, pamidronate, zoledronate, *etc.*) characterized by a P—C—P backbone and which can be considered stable analogues of naturally occurring pyrophosphates. The main interest in BP-derived compounds lies in the outstanding role they play in clinical medicine due to the fact that several BPs have been established as the standard treatment for various diseases associated with excessive bone resorption, such as Paget's disease, myeloma, bone metastases, osteoporosis, *etc.* (Fleisch, 2000; Ross *et al.*, 2004; Smith, 2005; Ralston *et al.*, 1989; Reid *et al.*, 2005; Rauch & Glorieux, 2005; Chesnut *et al.*, 2004). The P—C—P base structure allows BPs to bind to many metallic cations, in particular mono- and divalent metal ions, and as a result they can adhere to bone surfaces *in vivo* (Fleisch *et al.*, 1968). Third-generation BPs are characterized by having an N-containing cyclic side chain (in the case of zoledronate, an imidazole group) which tends to make them most effective for medical treatment (Green *et al.*, 1994). Much work has been devoted to structural, magnetic and other studies of derivatives of these sorts of compounds; two arbitrarily chosen recent works on the subject are Stahl *et al.* (2006) and Zhang *et al.* (2007). In particular, a large number of metal derivatives of etidronate and pamidronate are known where the BP ligand displays a variety of coordination modes, but surprisingly, relatively few metal derivatives of zoledronic acid have been structurally characterized so far, in spite of its utmost importance as a pharmacological drug, *viz.* Co [Cambridge Structural Database (CSD; 2009 version plus updates; Allen, 2002) refcodes VIMXEV and VIMXOF; Cao *et al.*, 2007], Ni (VIMXIZ and VIMXUL; Cao *et al.*, 2007); Cu (DOGYEE, DOGYII, DOGYOO and DOGYUU; Cao *et al.*, 2008) and Zn (not yet in the CSD; Freire & Vega, 2009*a*,*b*). In particular, no such reports have been published to date for alkaline metals. In an attempt to fill this gap in the literature, and as the first report in a series on zoledronate complexes of mono- and divalent alkaline cations, we present here the crystal structure of the title potassium compound, (I).



(I)

The structure of (I) is polymeric and consists of layers parallel to (001), interconnected by hydrogen-bonding and π–π interactions. Fig. 1 shows an ellipsoid plot of the elemental unit of (I), which consists of a K^+ centre (K1), a zoledronate(1−) zwitterion, one aqua ligand (O1*W*) and one solvent water molecule (O2*W*). The K^+ cation is eight-coordinated in a KO_8 environment by O atoms from three different chelating zoledronate units and two coordinated water molecules. This eightfold coordination is the most common for the many KO_n arrangements reported in the literature, where a diversity of compounds with n as low as 3 and as high as 12 can be found.

The K—O bond distances in (I) (Table 1) fall well within the (normally broad) range observed in eight-coordinated potassium complexes, which display upper and lower limits of 2.62 and 3.52 Å, respectively, in the *ca* 350 cases reported in the 2009 version of the CSD.

The zoledronate group presents its usual zwitterionic character, with negative charges in the singly protonated phosphonate groups and a positive charge at protonated

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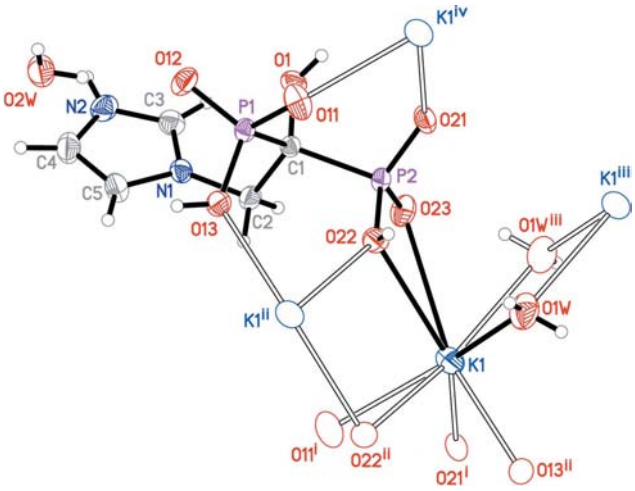

Figure 1
Displacement ellipsoid plot (40% probability) of (I), showing the atom-numbering scheme. Full lines and bonds indicate the asymmetric unit, and empty ellipsoids and bonds indicate the symmetry-related part completing the coordination polyhedron. H atoms are shown as small spheres of arbitrary radii. [Symmetry codes: (i) x, $y+1$, z; (ii) $-x+1$, $-y+2$, $-z$; (iii) $-x+2$, $-y+2$, $-z$; (iv) x, $y-1$, z.]

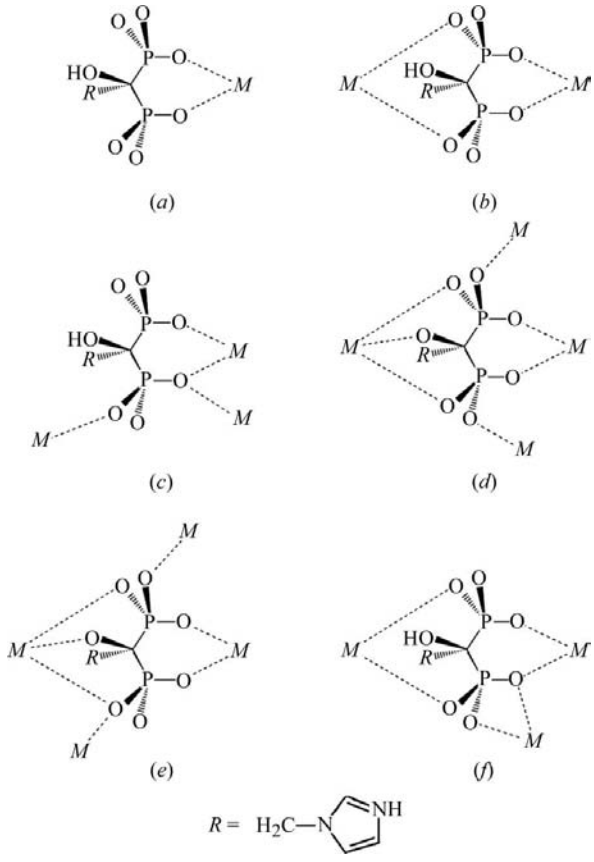

Figure 2
The reported coordination schemes found for zoledronate: (*a*) Freire & Vega (2009*a*,*b*) and Cao *et al.* (2007, 2008); (*b*), (*c*) and (*d*) Cao *et al.* (2008); (*e*) Cao *et al.* (2007); (*f*) this work.

imidazole atom N2. The resulting single negative charge provides charge balance for the cationic centre.

Bond distances in the imidazole ring suggest an approximately equal charge distribution on the two N atoms, with two short [C3—N1 = 1.330 (2) Å and C3—N2 = 1.323 (2) Å] and two long [C4—N2 = 1.373 (3) Å and C5—N1 = 1.384 (2) Å] bonds, implying partial double-bond character between atoms C3 and N1/N2, and essentially single-bond character at N1—C5 and N2—C4. The remaining double bond in the ring is found at C4—C5 [1.356 (3) Å].

Both phosphonates are singly protonated, at O13 and O22, respectively (Fig. 1), and this fact is clearly reflected in the corresponding P—O lengthening (about 0.05 Å) relative to the remaining two P—O pairs in each phosphonate [P1—O13 = 1.5567 (14) Å, P1—O11 = 1.5034 (14) Å and P1—O12 = 1.5082 (14) Å, and P2—O22 = 1.5658 (14) Å, P2—O21 = 1.5121 (14) Å and P2—O23 = 1.5030 (14) Å].

The anion binds to three different K^+ cations in a triply chelating manner, one of the bites (O22—P2—O23) being internal to one phosphonate centre and the remaining two bites involving one O atom from each phosphonate centre (O11—P1—C1—P2—O21 and O13—P1—C1—P2—O22). Even though this binding mode (entry *f* in Fig. 2) has already been observed in other related BPs (see, for instance, Stahl *et al.*, 2006), it is new for the zoledronate anion and adds to the diversity shown in the few zoledronate complexes described so far in the literature, spanning a wide range in both bridging μ values (1 to 4) and denticity (2 to 7) (Fig. 2).

Atoms O22 and O1*W* are shared by two different symmetry-related cations, resulting in a concatenated chain of centrosymmetric K_2O_2 loops running along *a* (shaded in Figs. 3 and 4). The K···K distances in these linear arrays are not particularly short: 4.5062 (15) Å in the bridge mediated by atom O1*W* and 4.7034 (19) Å in that due to atom O22, compared with the mean value of 3.85 Å in similar K_2O_2 loops in the literature. These chains are interconnected along *b* by multiple phosphonate links to form a tightly bound two-dimensional hydrophilic structure parallel to (001) (Fig. 3). The hydrophobic aromatic side chains in turn extend outwards on both sides of the plane and engage in close π–π contacts with their neighbouring counterparts (Fig. 4 and Table 2). Intra- and interplanar interactions are in turn enhanced by a variety of hydrogen bonds involving all the available O—H and N—H donors (Table 3) and where some of the phosphonate O atoms acting as acceptors receive as many as three strong interactions (*e.g.* atom O23). Incidentally, one of these contacts, a nonconventional C—H···O hydrogen bond involving an imidazole C—H group and a phosphonate O atom, appeared to be rather short for this type of usually very weak interaction (H···O = 2.36 Å; Table 3, last entry). However, data mining in the CSD showed that even if this distance is in fact short compared with those obtained for a general unrestricted C—H···O interaction [such an open search showed that less than 3% of the reported H···O values lie below the target of 2.36 Å found in (I)], it does not appear so singular when compared with values found in complexes containing similar C—H donors with enhanced acidity (due to N-atom vicinity, as in imidazole, pyridine, *etc.*) and eager O-atom acceptors (as in phosphates, phosphonates, *etc.*) which

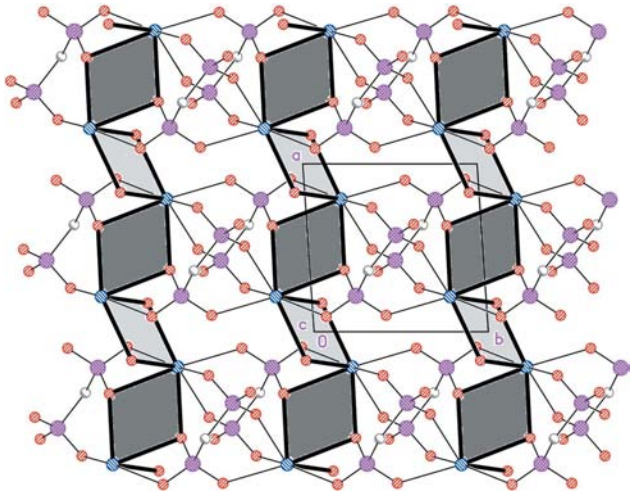

Figure 3
A packing diagram for (I), viewed along *c* and displaying the two-dimensional structure parallel to (001). Note the $\cdots$K$-$O$_2$$-K-O_2$$-K\cdots$ chains running along *a*. O22-bridged loops are shown in dark grey and O1*W*-bridged loops in light grey. Pendant imidazole and hydroxy groups, and H atoms, have been omitted for clarity.

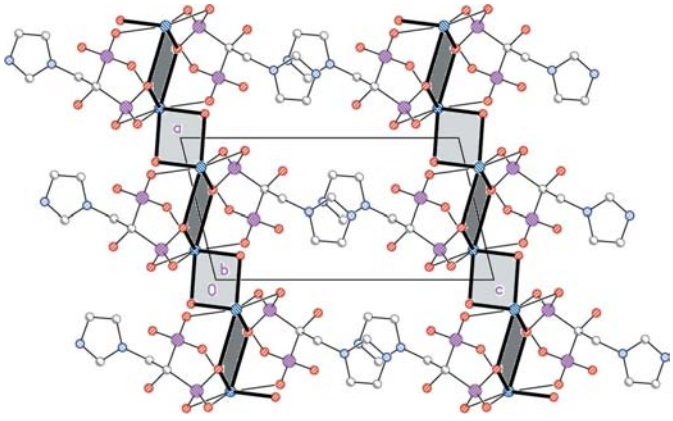

Figure 4
A packing diagram for (I), viewed along *b* and showing the planes in projection. Note the overlap of neighbouring imidazole rings.

returned a much higher rate of short C$-$H$\cdots$O contacts. In particular, a search among zoledronate complexes alone provided many occurrences comparable with those in (I) (*e.g.* for DOGYEE and DOGYUU, H$\cdots$O = 2.36 Å) and even smaller distances [VIMXIZ (2.32 Å), VIMXEV (2.30 Å) and DOGYUU (2.24 Å)], confirming that the simultaneous presence of imidazole and biphosphonate appears to be particularly favourable for the occurrence of this kind of strong C$-$H$\cdots$O interaction.

Experimental

Crystals of (I) were synthesized by neutralization of a solution of zoledronic acid (provided by GADOR ARGENTINA S.A.) with a KOH solution in a 1:1 stoichiometric ratio. The solution was left unperturbed to slowly concentrate, and after a few days large colourless blocks of (I) suitable for X-ray diffraction were obtained.

Table 1
Selected bond lengths (Å).

K1$-$O11^{i}	2.6901 (16)	K1$-$O1*W*^{iii}	2.8491 (19)
K1$-$O1*W*	2.7335 (19)	K1$-$O22^{ii}	2.9795 (16)
K1$-$O13^{ii}	2.8053 (16)	K1$-$O22	3.0576 (16)
K1$-$O21^{i}	2.8225 (16)	K1$-$O23	3.1546 (17)

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

Table 2
π–π contacts (Å, °) for (I).

*Cg*1 is the centroid of the N1/C3/N2/C4/C5 ring, CCD is the centroid–centroid distance, IPD is the interplanar distance (distance from one plane to the neighbouring centroid) and SA is the slippage angle (angle subtended by the intercentroid vector to the plane normal). For details, see Janiak (2000).

Group 1/Group 2	CCD (Å)	IPD (Å)	SA (°)
*Cg*1–*Cg*1^{i}	3.5963 (14)	3.3888 (8)	19.56

Symmetry code: (i) $1-x, 2-y, 1-z$.

Table 3
Hydrogen-bond geometry (Å, °).

D$-$H$\cdots$*A*	*D*$-$H	H$\cdots$*A*	*D*$\cdots$*A*	*D*$-$H$\cdots$*A*
O13$-$H13$\cdots$O21^{iv}	0.82	1.71	2.5124 (18)	165
O22$-$H22$\cdots$O11^{v}	0.82	1.73	2.526 (2)	164
O1$-$H1$\cdots$O2*W*^{vi}	0.82	2.00	2.744 (2)	150
N2$-$H2$\cdots$O12^{vii}	0.87	1.81	2.646 (2)	161
O1*W*$-$H1*WA*$\cdots$O23^{iii}	0.82	2.00	2.783 (2)	159
O1*W*$-$H1*WB*$\cdots$O12^{v}	0.82	2.31	3.068 (2)	152
O1*W*$-$H1*WB*$\cdots$O11^{v}	0.82	2.39	3.039 (2)	136
O2*W*$-$H2*WA*$\cdots$O12	0.82	2.00	2.817 (2)	173
O2*W*$-$H2*WB*$\cdots$O23^{viii}	0.82	1.96	2.768 (2)	170
C5$-$H5$\cdots$O23^{iv}	0.93	2.36	3.274 (3)	166

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

Crystal data

$[K(C_5H_9N_2O_7P_2)(H_2O)]\cdot H_2O$
M_r = 346.21
Triclinic, $P\overline{1}$
a = 6.9610 (14) Å
b = 7.0380 (14) Å
c = 13.322 (3) Å
α = 94.82 (2)°
β = 103.75 (3)°
γ = 92.58 (2)°
V = 630.3 (2) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 0.72 mm^{-1}
T = 295 K
0.32 × 0.30 × 0.26 mm

Data collection

Rigaku AFC-6*S* diffractometer
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.78, T_{max} = 0.83
3124 measured reflections
2482 independent reflections
2333 reflections with $I > 2\sigma(I)$
R_{int} = 0.019
3 standard reflections every 150 reflections
intensity decay: 1%

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.026
$wR(F^2)$ = 0.070
S = 1.12
2482 reflections
181 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.44 e Å^{-3}
$\Delta\rho_{min}$ = −0.31 e Å^{-3}

H atoms attached to O and N atoms were found in a difference Fourier map, further idealized (O$-$H = 0.82 Å and N$-$H = 0.87 Å) and finally allowed to ride while their isotropic displacement para-

meters were refined. H atoms attached to C atoms were placed in calculated positions (C—H = 0.93 and 0.97 Å for CH and CH_2 groups, respectively) and allowed to ride, with $U_{iso}(H) = 1.2U_{eq}(C)$.

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1988); cell refinement: *MSC/AFC Diffractometer Control Software*; data reduction: *MSC/AFC Diffractometer Control Software*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *SHELXTL* (Sheldrick, 2008); software used to prepare material for publication: *SHELXTL* and *PLATON* (Spek, 2003).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: DN3131). Services for accessing these data are described at the back of the journal.

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