

Ammonium 1-hydroxy-2-(2-pyridinio)ethane-1,1-diyl-diphosphonate dihydrate and potassium 1-hydroxy-2-(2-pyridinio)ethane-1,1-diyl-diphosphonate dihydrate

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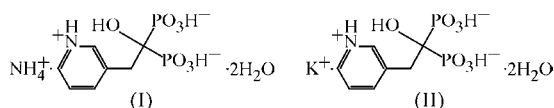
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The crystal structures of the title compounds, ammonium risedronate dihydrate, $\text{NH}_4^+\cdot\text{C}_7\text{H}_{10}\text{NO}_7\text{P}_2\cdot 2\text{H}_2\text{O}$, (I), and potassium risedronate dihydrate, $\text{K}^+\cdot\text{C}_7\text{H}_{10}\text{NO}_7\text{P}_2\cdot 2\text{H}_2\text{O}$, (II), have been determined from single-crystal X-ray data collected at 120 K. Compound (I) forms a three-dimensional hydrogen-bonded network which connects the ammonium and risedronate ions and the water molecules. In compound (II), the K^+ ions are seven-coordinated in a capped distorted trigonal prism. The coordination polyhedra form chains by corner-sharing, and these chains are connected by phosphonate groups into layers in the *ac* plane. The layers are stacked and connected by hydrogen bonds in the *b* direction. The risedronate conformation is determined by intramolecular interactions fine-tuned by crystal packing effects. All H-atom donors in both structures are involved in hydrogen bonding, with *D*...*A* distances between 2.510 (2) and 3.009 (2) Å.

Comment

Many bisphosphonates are effective drugs for a number of bone disorders, for example, osteoporosis (Rodan & Martin, 2000). In addition, bisphosphonates have shown promising antiparasitic activity (Martin *et al.*, 2001). In a search for stable salts suitable for pharmaceutical preparations, the title compounds, (I) and (II), were synthesized and their crystal structures are presented here.



The bond distances and angles of the risedronate anions in (I) and (II) are very similar and also compare well with the

values previously obtained for other crystal structures containing risedronate (risedronate monohydrate, sodium risedronate dihydrate and sodium risedronate 2.5-hydrate; Barbey & Lecouvey, 2002; Gossman *et al.*, 2003). As noted earlier (Gossman *et al.*, 2003), the P1–O3 and P2–O6 bonds are significantly longer [1.5614 (15)–1.5839 (15) Å] than the remaining P–O distances [1.4967 (13)–1.5168 (13) Å] because of the H atoms bonded to O3 and O6. A comparison of the O7–C1–C2–C3 and C1–C2–C3–C4 torsion angles gives additional information on the risedronate conformations (Table 5). In all the so far known structures, the ring plane is oriented approximately perpendicular to the phosphonate group ($\text{C1–C2–C3–C4} \approx \pm 90^\circ$). This suggests that this general conformation is independent of crystal packing forces, although if the pyridinium ring is rotated by 180° , atom N1 can still be positioned in the direction most favourable for hydrogen bonding. In the structure of (I) and risedronate monohydrate, this rotation is opposite to what is observed in the structures containing alkali metal ions. The O7–C1–C2–C3 torsion angles also fall into two distinct groups, with values of $\pm 60^\circ$. In this conformation, one of the bulky phosphonate groups will always be opposite to the pyridinium ring. The sign of O7–C1–C2–C3 is probably governed by

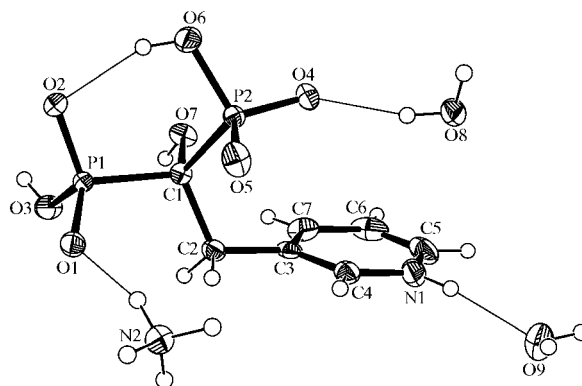


Figure 1
A view of ammonium risedronate dihydrate, (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 75% probability level.

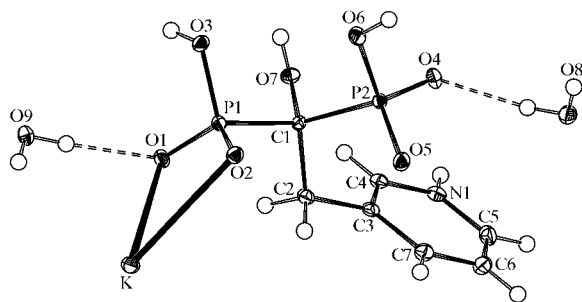


Figure 2
A view of potassium risedronate dihydrate, (II), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 75% probability level.

the hydrogen-bonding pattern in the crystal, as suggested for C1–C2–C3–C4, but there is no obvious correlation between them.

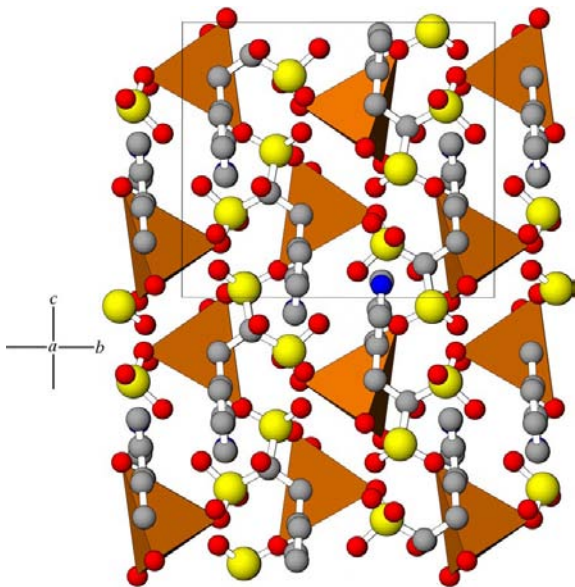


Figure 3
The crystal packing of (I), viewed along the *a* axis, showing the ammonium coordination tetrahedra. H atoms have been omitted for clarity.

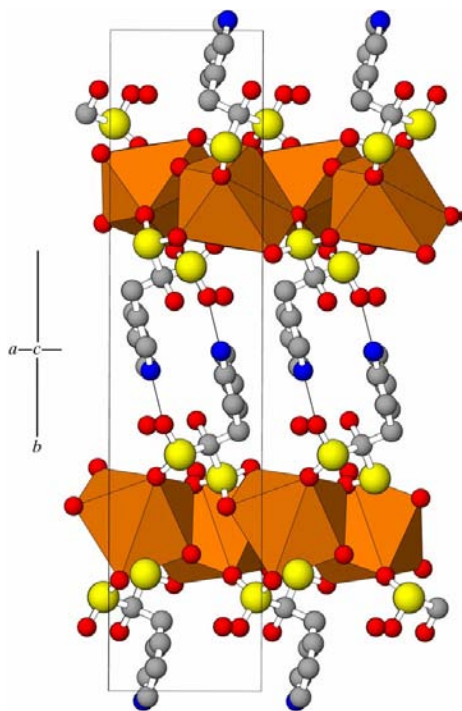


Figure 4
The crystal packing of (II), viewed along the *c* diagonal, showing the layers of K^+ coordination polyhedra connected by N1–H11...O4 hydrogen bonds (single lines). H atoms have been omitted for clarity.

In both structures, the hydrogen bonds formed by the H atoms of the phosphonate groups and H1 (bonded to pyridinium atom N1) are much stronger [$D\cdots A = 2.510(2)$ – $2.690(2)$ Å] than the remaining O–H...O bonds [$D\cdots A = 2.6454(19)$ – $2.867(2)$ Å]. The N–H...O bonds formed by the ammonium ion in (I) are even weaker [$D\cdots A = 2.768(2)$ – $3.009(2)$ Å]. While all H-atom donors are involved in hydrogen bonds, the potential acceptors O3, O6 and O7 are not. This can be understood from the lack of H-atom donors and the fact that forming few shorter bonds is, in general, energetically more favourable than forming more bonds of average length.

In (I), the ammonium ions are connected *via* hydrogen bonds to water and phosphonate O atoms (Table 2). The ammonium coordination tetrahedra are connected through the phosphonate groups into a three-dimensional network (Fig. 3). The intramolecular O6–H6A...O2 hydrogen bond found in (I) is not present in any of the known risedronate structures. This interaction locks the relative rotation of the two phosphonate groups without affecting the overall conformation. Although atom O7 is not an acceptor in conventional hydrogen bonds, it takes part in three very weak interactions [$D\cdots A = 2.997(2)$ – $3.077(2)$ Å and D –H... $A = 113(2)$ – 118°]. The C2–H2B...O3^{vii} [symmetry code: (vii) $-x, 2-y, -z$] interaction, with $H\cdots A = 2.27$ Å and D –H... $A = 161^\circ$, is potentially an interesting weak hydrogen bond.

In (II), the K^+ cation is seven-coordinated (Table 3) by water and phosphonate O atoms in a distorted capped trigonal prism. The coordination polyhedra are corner-sharing through O2, forming chains in the [101] direction. The chains are further connected through the phosphonate groups and hydrogen bonding into layers in the *ac* plane. Both water molecules are coordinated by K^+ and involved in hydrogen bonding within and between the polyhedral chains. The layers are separated by the protruding pyridinium groups, which also connect the layers *via* N1–H11...O4ⁱ [symmetry code: (i) $-x, -y, 1-z$] hydrogen bonds (Fig. 4). As observed for (I), no conventional hydrogen bonds are found involving atom O3. However, this atom forms a very weak intramolecular O7–H7A...O3 hydrogen bond [$D\cdots A = 2.9725(18)$ Å and D –H... $A = 111.5(17)^\circ$].

Experimental

For the preparation of compound (I), risedronic acid (602.26 g) was stirred in water (1200 ml) and ammonia was added (600 ml, 16 M). The mixture was heated under reflux until all the material had dissolved. Ethanol (1000 ml) and water (750 ml) were added, and the mixture was stirred overnight at room temperature. The precipitate which formed was recovered by filtration, rinsed with water–ethanol (1:1 v/v) and dried at 333 K under a vacuum. For the preparation of compound (II), risedronic acid (6 g) was stirred in water (12 ml) at approximately 333 K. KOH (19.5 ml, 1 N) was added and the mixture was refluxed until a clear solution was obtained. The solution was cooled to room temperature with stirring and finally cooled to 273 K. The precipitate which formed was recovered by filtration and rinsed with water–ethanol (1:1 v/v) and ethanol, and dried at 333 K under a vacuum. Compounds (I) or (II) (1 g) was dissolved separately in

sterilized water (15 ml) and heated under reflux until dissolved. Slow cooling yielded small crystals which were then used to nucleate a repeated recrystallization. The crystals obtained were dried in a vacuum at 313 K for 24 h and were suitable for data collection.

Compound (I)

Crystal data

$\text{NH}_4^+\cdot\text{C}_7\text{H}_{10}\text{NO}_7\text{P}_2\cdot 2\text{H}_2\text{O}$
 $M_r = 336.17$
 Monoclinic, $P2_1/n$
 $a = 10.0911$ (6) Å
 $b = 12.2790$ (7) Å
 $c = 11.1598$ (7) Å
 $\beta = 104.2400$ (10)°
 $V = 1340.31$ (14) Å³
 $Z = 4$

$D_x = 1.666$ Mg m⁻³
 Mo $K\alpha$ radiation
 Cell parameters from 5685 reflections
 $\theta = 2.4\text{--}30.8^\circ$
 $\mu = 0.37$ mm⁻¹
 $T = 118$ (2) K
 Plate, colourless
 $0.28 \times 0.14 \times 0.04$ mm

Data collection

Bruker SMART APEX diffractometer
 ω scan, frame data integration
 17561 measured reflections
 3965 independent reflections
 3279 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.076$
 $\theta_{\text{max}} = 31.0^\circ$
 $h = -14 \rightarrow 14$
 $k = -17 \rightarrow 16$
 $l = -15 \rightarrow 15$

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.048$
 $wR(F^2) = 0.111$
 $S = 1.10$
 3965 reflections
 214 parameters
 H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.05P)^2 + 0.1262P]$
 where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\text{max}} < 0.001$
 $\Delta\rho_{\text{max}} = 0.69$ e Å⁻³
 $\Delta\rho_{\text{min}} = -0.33$ e Å⁻³

Table 1

Selected bond lengths (Å) for (I).

P1—O1	1.5105 (14)	C1—C2	1.552 (3)
P1—O2	1.5150 (15)	C2—C3	1.508 (3)
P1—O3	1.5614 (15)	C3—C4	1.383 (3)
P2—O4	1.5086 (14)	C4—N1	1.348 (3)
P2—O5	1.5036 (14)	N1—C5	1.339 (3)
P2—O6	1.5839 (15)	C5—C6	1.369 (3)
P1—C1	1.8554 (19)	C6—C7	1.396 (3)
P2—C1	1.8378 (19)	C3—C7	1.391 (3)
O7—C1	1.434 (2)		

Table 2

Hydrogen-bond geometry (Å, °) for (I).

$D\text{---}H\cdots A$	$D\text{---}H$	$H\cdots A$	$D\cdots A$	$D\text{---}H\cdots A$
O3—H3 [⋯] ·O5 ⁱ	0.827 (16)	1.684 (17)	2.510 (2)	177 (3)
O6—H6A [⋯] ·O2	0.816 (16)	1.887 (19)	2.656 (2)	157 (3)
O7—H7A [⋯] ·O8 ⁱ	0.830 (16)	2.031 (18)	2.819 (2)	158 (2)
N1—H1 [⋯] ·O9	0.86	1.88	2.690 (2)	157
N2—H2C [⋯] ·O1	0.906 (16)	1.976 (17)	2.854 (2)	163 (2)
N2—H2D [⋯] ·O8 ⁱⁱ	0.885 (16)	2.124 (16)	3.009 (2)	178 (2)
N2—H2E [⋯] ·O4 ⁱⁱⁱ	0.895 (16)	2.036 (17)	2.923 (2)	171 (2)
N2—H2F [⋯] ·O2 ^{iv}	0.948 (16)	1.830 (17)	2.768 (2)	170 (2)
O8—H8A [⋯] ·O1 ^v	0.815 (16)	2.069 (17)	2.867 (2)	166 (3)
O8—H8B [⋯] ·O4	0.824 (16)	1.880 (18)	2.684 (2)	164 (3)
O9—H9A [⋯] ·O4 ^{iv}	0.810 (17)	2.012 (19)	2.785 (2)	159 (3)
O9—H9B [⋯] ·O1 ^{vi}	0.841 (17)	1.907 (18)	2.738 (2)	169 (3)

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

Compound (II)

Crystal data

$\text{K}^+\cdot\text{C}_7\text{H}_{10}\text{NO}_7\text{P}_2\cdot 2\text{H}_2\text{O}$
 $M_r = 357.23$
 Monoclinic, $P2_1/n$
 $a = 6.5356$ (4) Å
 $b = 28.1606$ (17) Å
 $c = 6.9636$ (4) Å
 $\beta = 95.9930$ (10)°
 $V = 1274.62$ (13) Å³
 $Z = 4$
 $D_x = 1.862$ Mg m⁻³

Mo $K\alpha$ radiation
 Cell parameters from 4900 reflections
 $\theta = 2.9\text{--}28.0^\circ$
 $\mu = 0.71$ mm⁻¹
 $T = 118$ (2) K
 Tabular, colourless
 $0.18 \times 0.12 \times 0.10$ mm

Data collection

Bruker SMART APEX diffractometer
 ω scan, frame data integration
 9075 measured reflections
 3052 independent reflections
 2644 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.064$
 $\theta_{\text{max}} = 28.0^\circ$
 $h = -8 \rightarrow 8$
 $k = -34 \rightarrow 37$
 $l = -8 \rightarrow 9$

Table 3

Selected bond lengths (Å) for (II).

K—O5 ⁱ	2.7283 (13)	P2—O6	1.5785 (14)
K—O2 ⁱ	2.7598 (13)	P1—C1	1.8522 (17)
K—O9 ⁱⁱⁱ	2.7599 (14)	P2—C1	1.8447 (16)
K—O3 ⁱⁱⁱ	2.8311 (13)	C1—O7	1.434 (2)
K—O6 ⁱⁱⁱ	2.8627 (14)	C1—C2	1.542 (2)
K—O2	2.8996 (13)	C2—C3	1.508 (2)
K—O1	2.9588 (13)	C3—C4	1.384 (3)
P1—O1	1.5048 (12)	C4—N1	1.339 (2)
P1—O2	1.4989 (13)	N1—C5	1.338 (2)
P1—O3	1.5747 (13)	C5—C6	1.378 (3)
P2—O4	1.5168 (13)	C6—C7	1.386 (3)
P2—O5	1.4967 (13)	C3—C7	1.391 (2)

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

Table 4

Hydrogen-bond geometry (Å, °) for (II).

$D\text{---}H\cdots A$	$D\text{---}H$	$H\cdots A$	$D\cdots A$	$D\text{---}H\cdots A$
N1—H1 [⋯] ·O4 ^{iv}	0.86	1.74	2.599 (2)	173
O3—H3 [⋯] ·O5 ^v	0.792 (15)	1.805 (17)	2.5633 (17)	160 (2)
O6—H6A [⋯] ·O9 ^{vi}	0.803 (16)	1.770 (16)	2.5631 (17)	169 (2)
O7—H7A [⋯] ·O8 ^v	0.810 (15)	1.955 (17)	2.712 (2)	155 (2)
O8—H8A [⋯] ·O1 ^{vi}	0.813 (16)	1.960 (17)	2.7725 (18)	176 (2)
O8—H8B [⋯] ·O4	0.817 (16)	1.952 (16)	2.7638 (18)	173 (2)
O9—H9A [⋯] ·O2 ⁱ	0.824 (16)	1.825 (17)	2.6454 (19)	174 (2)
O9—H9B [⋯] ·O1	0.825 (16)	1.887 (16)	2.7074 (17)	172 (2)

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

Table 5

Comparison of torsion angles (°) in (I), (II) and related compounds.

	O7—C1—C2—C3	C1—C2—C3—C4
(I)	58.1 (2)	109.7 (2)
(II)	66.90 (18)	-73.4 (2)
$\text{C}_7\text{H}_{11}\text{NO}_7\text{P}_2\cdot\text{H}_2\text{O}^a$	-59.3 (5)	83.2 (5)
$\text{C}_7\text{H}_{11}\text{NO}_7\text{P}_2\cdot\text{H}_2\text{O}^b$	-59.8 (4)	82.9 (4)
$[\text{Na}(\text{C}_7\text{H}_{10}\text{NO}_7\text{P}_2)]\cdot 2\text{H}_2\text{O}^b$	-53.9 (3)	-97.2 (3)
$[\text{Na}(\text{C}_7\text{H}_{10}\text{NO}_7\text{P}_2)]\cdot 2.5\text{H}_2\text{O}^b$	67.23 (8)	-68.20 (10)

References: (a) Barbey & Lecouvey (2002) [113 (2) K]; (b) Gossman *et al.* (2003) [193 (2) K].

*Refinement*Refinement on F^2 $R[F^2 > 2\sigma(F^2)] = 0.034$ $wR(F^2) = 0.088$ $S = 1.00$

3052 reflections

202 parameters

H atoms treated by a mixture of independent and constrained refinement

 $w = 1/[\sigma^2(F_o^2) + (0.0496P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$ $(\Delta/\sigma)_{\max} < 0.001$ $\Delta\rho_{\max} = 0.76 \text{ e } \text{\AA}^{-3}$ $\Delta\rho_{\min} = -0.47 \text{ e } \text{\AA}^{-3}$

The N atoms in the pyridinium rings were initially assigned based on displacement parameters and later confirmed by the C–N bond lengths and hydrogen bonding. All H-atom parameters were initially refined freely. In the final cycles, the H atoms of CH₂, CH and NH groups were placed in calculated positions, with C–H = 0.98 (CH₂) or 0.93 Å (CH) and N–H = 0.86 Å, and refined as riding atoms. For the OH groups and water molecules, the O–H distances were restrained to 0.82 (2) Å, and for the NH₄⁺ cation, the N–H distances were restrained to 0.89 (2) Å. The displacement parameters were set at 1.2 (CH₂, CH and NH) or 1.5 (OH and NH₄) times U_{eq} of the parent C, O or N atoms.

For both compounds, data collection: *SMART* (Bruker, 1999); cell refinement: *SAINT-Plus* (Bruker, 1999); data reduction: *SAINT-Plus*; program(s) used to solve structure: *SHELXS97* (Sheldrick,

1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3* (Farrugia, 1997) and *ATOMS* (Dowty, 2000); software used to prepare material for publication: *SHELXL97*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GZ1022). Services for accessing these data are described at the back of the journal.

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