

Two members of the bisphosphonate class of drugs: a zwitterion and a molecular compound

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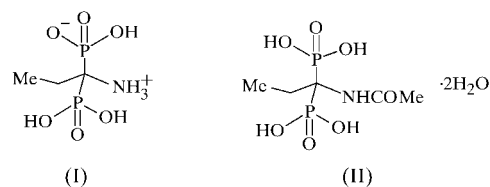
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The compounds studied in this paper, *viz.* (1-ammonio-1-phosphonopropyl)phosphonate, $C_3H_{11}NO_6P_2$, (I), and 1-(acetyl-amino)propylidene-1,1-bisphosphonic acid dihydrate, $C_5H_{13}NO_7P_2 \cdot 2H_2O$, (II), are members of a commonly used family of therapeutic agents. Compound (I) is an inner salt with separated negative (on the ionized PO_3 group) and positive (on the tetrahedral N atom) charges, while (II) possesses neutral phosphonyl groups and one amide N atom. Both structures have a C—C—C—N backbone, which has comparable geometric parameters in (I) and (II); the main difference was found in one of the N—C—P bond angles, which is lengthened in (II) because of an intramolecular $O_{PO_3} \cdots H \cdots O_{C=O}$ interaction. The hydrogen-bonding scheme in the crystal of (I) includes all possible donor atoms, namely all the H atoms of the ammonium group and the phosphonic acid functions. As a result of these interactions, the zwitterions are organized into a plane running along the crystallographic x axis. In (II), the intermolecular interactions include all possible donor atoms, except for the N atom; the packing differs from that of (I) in that the molecules are arranged in a chain running parallel to the x axis. In the chains, the molecules form head-to-head dimers, while the crystallization water molecules contribute to the intra- and interchain cohesion.

Comment

Bisphosphonate compounds are characterized by the P—C—P bond, the biologically resistant version of the P—O—P bridge of natural pyrophosphate, and have a number of practical applications in the field of human health. Because of their high tropism to bone tissue and their capacity to selectively block the action of resorbing osteoclasts, several members of this family are currently used for the treatment of

skeletal disorders (Compston, 1994; Martin & Grill, 2000; Rodan & Martin, 2000). These compounds have a potential use as drugs for the treatment of neurological disorders (Atack & Fletcher, 1994), as anti-inflammatory treatments or anti-arthritics (Schlachter *et al.*, 1998), as herbicides (Chuiko *et al.*, 1999; Cromartie *et al.*, 1999), as antiparasitics (Docampo, 2001; Urbina, 2002), and as cholesterol-lowering agents (Niesor *et al.*, 2001). Moreover, Fukuda *et al.* (1999) have reported the synthesis and therapeutic efficacy of a novel decorporating bisphosphonate to remove radioactive strontium deposited in the bone of contaminated individuals. As part of an ongoing study aimed at the determination of the structures of biologically active compounds (Vega *et al.*, 2002), single-crystal X-ray studies of (1-ammonio-1-phosphonopropyl)phosphonate, (I), and 1-(acetyl-amino)propylidene-1,1-bisphosphonic acid dihydrate, (II), have been undertaken and the results are presented here.



The bisphosphonates (I) and (II) have in common a C—C—C—N backbone and a P—C—P bridge (see Figs. 1 and 2). Compound (I), unlike (II), has a zwitterionic character, with one of the phosphonyl H atoms transferred to the N atom, leaving one of the PO_3 groups with a negative charge. The N atom in (I) possesses pyramidal sp^3 hybridization, whereas the N atom in (II) exhibits planar sp^2 hybridization. As can be seen from Tables 1 and 3, the C1—N1 bond is shorter in (II), suggesting that the electronic delocalization could be more important in this bond than in the equivalent of (I). This trend was confirmed in a search of the Cambridge Structural Database (CSD, Version 5.23; Allen, 2002), which retrieved two single-crystal X-ray studies of structures of bisphosphonates containing an acyclic N atom attached to the geminal C atom. In the compound with CSD refcode KISR0T (Lorberth *et al.*, 1991), the N atom is planar sp^2 -hybridized and the C—N distance is 1.494 Å; however, this bond is larger in SOPSAR (1.510 Å; Shkol'nikova *et al.*, 1990), where the N atom is sp^3 -hybridized (note that in both structures the N atom is dimethylated). As can be appreciated from Tables 1 and 3, the

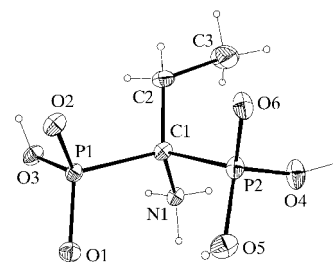


Figure 1

A view of the structure of (I), showing the atom-numbering scheme and displacement ellipsoids at the 30% probability level.

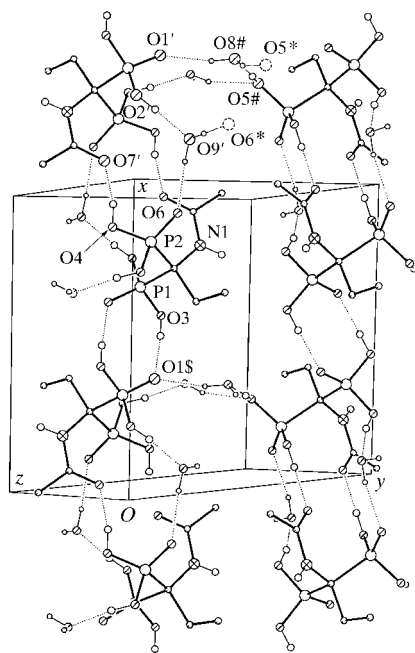


Figure 4

Partial packing diagram for (II), showing the O—H...O (dotted lines) hydrogen bonds. Only the H atoms attached to O and N atoms are shown. Atoms labeled with a dollar sign (\$), a hash (#), an asterisk (*) and a prime (') are at the symmetry positions $(1-x, -y, -z)$, $(2-x, y + \frac{1}{2}, -z - \frac{1}{2})$, $(2-x, -y, -z - 1)$ and $(2-x, -y, -z)$, respectively.

associating and forming a plane; possibly for the same reason, this effect allowed the presence of the crystallization water molecules, which could be retained in (II) but not in (I). As only (II) was used in the biological studies (Fukuda *et al.*, 1999), it could be concluded that this hydrated form of the drug showed better solubility properties than the anhydrous form.

Experimental

Crystals of (I) and (II) suitable for X-ray diffraction were obtained by slow evaporation from water solutions and were grown at 315 K for (I) and at 293 K for (II).

Compound (I)

Crystal data

$C_3H_{11}NO_6P_2$
 $M_r = 219.07$
 Orthorhombic, $P2_12_12_1$
 $a = 11.666$ (3) Å
 $b = 12.937$ (5) Å
 $c = 5.714$ (3) Å
 $V = 862.4$ (6) Å³
 $Z = 4$
 $D_x = 1.687$ Mg m⁻³

Mo $K\alpha$ radiation
 Cell parameters from 20 reflections
 $\theta = 10$ – 20°
 $\mu = 0.50$ mm⁻¹
 $T = 293$ (2) K
 Cube, colorless
 $0.20 \times 0.15 \times 0.15$ mm

Data collection

Rigaku AFC-6S diffractometer
 ω - 2θ scans
 4140 measured reflections
 1987 independent reflections
 1608 reflections with $I > 2\sigma(I)$
 $R_{int} = 0.065$
 $\theta_{max} = 27.5^\circ$

$h = 0 \rightarrow 15$
 $k = -16 \rightarrow 16$
 $l = -7 \rightarrow 7$
 3 standard reflections every 300 reflections
 intensity decay: 2%

Refinement

Refinement on F^2
 $R(F) = 0.049$
 $wR(F^2) = 0.119$
 $S = 1.02$
 1987 reflections
 118 parameters
 H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0603P)^2]$
 where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{max} = 0.003$
 $\Delta\rho_{max} = 0.33$ e Å⁻³
 $\Delta\rho_{min} = -0.24$ e Å⁻³
 Absolute structure: Flack (1983),
 807 Friedel reflections
 Flack parameter = 0.3 (2)

Table 1

Selected geometric parameters (Å, °) for (I).

O1—P1	1.498 (3)	O5—P2	1.533 (3)
O2—P1	1.505 (3)	O6—P2	1.494 (3)
O3—P1	1.561 (3)	C1—P2	1.845 (4)
C1—P1	1.852 (4)	C1—N1	1.510 (5)
O4—P2	1.536 (3)		
P1—C1—P2	112.89 (19)	O2—P1—O3	112.71 (16)
C1—C2—C3	117.9 (4)	O4—P2—O5	105.90 (18)
O1—P1—O2	118.11 (16)	O4—P2—O6	115.17 (17)
O1—P1—O3	106.74 (16)	O5—P2—O6	114.29 (18)
O1—P1—C1—P2	-67.0 (2)	O4—P2—C1—P1	158.2 (2)
O2—P1—C1—P2	61.1 (2)	O5—P2—C1—P1	47.1 (3)
O3—P1—C1—P2	-179.66 (19)	O6—P2—C1—P1	-78.6 (2)

Table 2

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

D—H...A	D—H	H...A	D...A	D—H...A
N1—H1...O6 ⁱ	0.89	2.01	2.814 (4)	149
N1—H2...O2 ⁱ	0.89	1.99	2.796 (4)	149
N1—H3...O1 ⁱⁱ	0.89	1.96	2.740 (4)	146
O3—H9...O6 ⁱⁱⁱ	0.82 (3)	1.82 (3)	2.623 (4)	169 (5)
O4—H10...O2 ^{iv}	0.85 (3)	1.68 (3)	2.524 (4)	173 (6)
O5—H11...O1 ^v	0.84 (3)	1.71 (3)	2.549 (4)	179 (6)

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

Compound (II)

Crystal data

$C_5H_{13}NO_7P_2 \cdot 2H_2O$
 $M_r = 297.14$
 Monoclinic, $P2_1/c$
 $a = 11.8880$ (3) Å
 $b = 12.4715$ (4) Å
 $c = 7.9403$ (2) Å
 $\beta = 95.4986$ (13)^o
 $V = 1171.82$ (6) Å³
 $Z = 4$
 $D_x = 1.684$ Mg m⁻³

Mo $K\alpha$ radiation
 Cell parameters from 19 718 reflections
 $\theta = 2.9$ – 28.3°
 $\mu = 0.41$ mm⁻¹
 $T = 120$ (2) K
 Thin plate, colorless
 $0.26 \times 0.11 \times 0.06$ mm

Data collection

Nonius KappaCCD diffractometer
 φ and ω scans with κ offsets
 9795 measured reflections
 2901 independent reflections
 2417 reflections with $I > 2\sigma(I)$
 $R_{int} = 0.053$

$\theta_{max} = 28.3^\circ$
 $h = -15 \rightarrow 15$
 $k = -16 \rightarrow 16$
 $l = -9 \rightarrow 10$

Refinement

Refinement on F^2

$R(F) = 0.043$

$wR(F^2) = 0.113$

$S = 1.07$

2901 reflections

178 parameters

H atoms treated by a mixture of independent and constrained refinement

$$w = 1/[\sigma^2(F_o^2) + (0.0579P)^2 + 0.7884P]$$

$$\text{where } P = (F_o^2 + 2F_c^2)/3$$

$$(\Delta/\sigma)_{\max} = 0.007$$

$$\Delta\rho_{\max} = 0.34 \text{ e } \text{\AA}^{-3}$$

$$\Delta\rho_{\min} = -0.57 \text{ e } \text{\AA}^{-3}$$

Table 3

Selected geometric parameters (\AA , $^\circ$) for (II).

O1—P1	1.4950 (14)	O6—P2	1.4912 (14)
O2—P1	1.5283 (15)	C1—P2	1.8662 (19)
O3—P1	1.5614 (14)	C1—N1	1.478 (2)
C1—P1	1.8549 (19)	C4—O7	1.242 (2)
O4—P2	1.5476 (14)	C4—N1	1.345 (2)
O5—P2	1.5546 (15)		
O1—P1—O2	116.31 (8)	O5—P2—O6	111.99 (8)
O1—P1—O3	113.48 (8)	C1—N1—C4	124.14 (16)
O2—P1—O3	102.72 (8)	P1—C1—P2	111.21 (10)
O4—P2—O5	103.79 (8)	C1—C2—C3	115.87 (15)
O4—P2—O6	115.90 (8)		
O1—P1—C1—P2	−41.50 (12)	O4—P2—C1—P1	−25.40 (12)
O2—P1—C1—P2	86.33 (11)	O5—P2—C1—P1	85.87 (11)
O3—P1—C1—P2	−164.05 (9)	O6—P2—C1—P1	−154.23 (9)

Table 4

Hydrogen-bonding geometry (\AA , $^\circ$) for (II).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
O2—H2 \cdots O9	0.85 (2)	1.62 (2)	2.455 (2)	167 (3)
O3—H3 \cdots O1 ^{vi}	0.85 (2)	1.77 (2)	2.611 (2)	174 (3)
O4—H4 \cdots O7	0.88 (2)	2.41 (3)	2.823 (2)	108 (2)
O4—H4 \cdots O7 ^{vii}	0.88 (2)	1.71 (2)	2.573 (2)	168 (3)
O5—H5 \cdots O8	0.87 (2)	1.65 (2)	2.512 (2)	170 (3)
O8—H14 \cdots O5 ^{viii}	0.86 (2)	2.19 (2)	3.022 (2)	163 (3)
O8—H15 \cdots O1 ^{ix}	0.85 (2)	1.92 (2)	2.760 (2)	167 (3)
O9—H17 \cdots O6 ^{vii}	0.83 (2)	1.95 (2)	2.768 (2)	169 (3)
O9—H16 \cdots O6 ⁱ	0.86 (2)	1.81 (2)	2.663 (2)	171 (3)

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

The H atoms of (I) and (II), except for those attached to O atoms, were refined using a riding model, with their isotropic displacement parameters constrained to 1.3 (H atoms attached to C and N atoms) or 1.5 (H atoms attached to O atoms) times the U_{eq} values of their carrier atoms. The O—H distances were restrained at 0.85 (3) \AA using the DFIX command implemented in *SHELXL97* (Sheldrick, 1991).

For compound (I), data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1993); cell refinement: *MSC/AFC Diffractometer Control Software*; data reduction: *MSC/AFC Diffractometer Control Software*. For compound (II), data collection: *COLLECT* (Nonius, 1997–2000); cell refinement: *HKL SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *HKL DENZO* (Otwinowski & Minor, 1997) and *SCALEPACK*. For

both compounds, program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *XP* in *SHELXTL/PC* (Sheldrick, 1991); 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: NA1606). Services for accessing these data are described at the back of the journal.

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