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

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The compounds studied in this paper, viz. (1-ammonio-1phosphonopropyl)phosphonate, $C_3H_{11}NO_6P_2$, (I), and 1-(acetylamino)propylidene-1,1-bisphosphonic acid dihydrate, C₅H₁₃- $NO_7P_2 \cdot 2H_2O_1$ (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_{PO2}- $H \cdots O_{C=0}$ 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 xaxis. 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-Pbridge 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

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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-(acetylamino)propylidene-1,1bisphosphonic 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 PO₃ 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 KISROT (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 2

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

lengths of the equivalent P–C, C–C and P–O bonds in (I) and (II) are very similar. An inspection of the latter bond lengths clearly indicated the presence of protonated and deprotonated O atoms (Vega *et al.*, 1996); the P–O bonds are in the range 1.4912 (14)–1.505 (3) Å, while the P–O(H) bonds are in the range 1.5283 (15)–1.5614 (14) Å.

The P-C-P bond angle is similar in the two structures, while the O-P-O angles reflect the electronic state of the PO₃ group. Thus, the neutral PO₃ groups have O-P-O(H)angles in the range 111.99 (8)-116.31 (8)°, while the (H)O-P-O(H) angles range from 102.72 (8) to 105.90 (18)°. By contrast, the O-P-O angle within the negatively charged PO₃ group is the largest [118.11 (16)°]. The planar 'W' shape delineated by the O-P-C-P-O sequence, which is relevant for the biological activity of the bisphosphonate (Shkol'nikova et al., 1990), is found in both structures. The O-P-C-P torsion angles that characterize the 'W' shape are -179.66 (19) and 158.2 (2)° in (I), and -164.05 (9) and -154.23 (9)° in (II) (Tables 1 and 3). The C-C-C bond angles in (I) and (II) are larger than the ideal tetrahedral value, suggesting that the sp^3 -hybridized C2 atom could be deformed because of some conformational freedom associated with thermal motion or disorder. Other bisphosphonates with an aliphatic side chain also display a larger C2 bond angle (Vega et al., 1996; Fernández et al., 2002). As shown by the values of the P-C-C-C torsion angles, the C2-C3 bond is coplanar with the C1-P1 bond but is twisted in relation to the C1-P2 bond, the P1-C1-C2-C3 and P2-C1-C2-C3 torsion angles being -175.3 (4) and 59.0 (5)°, respectively, for (I), and -175.27(14) and $-54.2(2)^{\circ}$, respectively, for (II). In addition, the C2–C3 bond is twisted towards the N atom, the C3-C2-C1-N1 torsion angles being -58.6(5) and $67.1(2)^{\circ}$ for (I) and (II), respectively.

The acetyl part of (II) shows the typical planar nature associated with the amide bond, and the bond lengths (Table 3) correspond well to those found in the peptide bond (Lehninger *et al.*, 2000). Therefore, atoms C1, N1, C4, C5 and O7 form a plane, from which atom N1 deviates the most [by

0.008 (2) Å]. Atom P1 deviates more than P2 with respect to the C1/N1/C4/C5/O7 plane [1.7277 (5) versus 1.2066 (5) Å]. Such an atomic disposition could allow an intramolecular O4-H4···O7 interaction (Table 4), thus forming a sevenmembered ring involving atoms O7, C4, N1, C1, P2, O4 and H4. In addition, as a possible cause of this interaction, the N1-C1-P2 bond angle is 5° larger than that in (I), *i.e.* 111.37 (12) versus 106.3 (2)°.

The hydrogen-bonding scheme for (I) consists of O_{PO_2} - $H \cdots O_{PO_3}$ and $N - H \cdots O_{PO_3}$ interactions (Table 2). All the possible donor atoms, namely all the H atoms of the N1 group and of the protonated atoms O3, O4 and O5, are involved in the interactions. The packing in the crystal of (I), as depicted in Fig. 3, can be described as an arrangement of the molecules, bound by $O3-H9\cdots O6^{iii}$, $O4-H10\cdots O2^{iv}$, $O5-H11\cdots O1^{v}$ and $N1 - H3 \cdots O1^{ii}$ interactions (Table 2), into planes running parallel to the crystallographic x axis. These planes are stacked along the z axis and are connected by the remaining N- $H \cdots O$ hydrogen bonds. In (II), intermolecular interactions occur between O atoms, without the participation of the N1 group (Table 4). As shown in Fig. 4, the molecules are dimerized head-to-head through the O3-H3···O1^{vi} $O_{PO_2} \cdots O_{PO_2}$ interaction; this dimer is joined to others by means of the carbonyl O7 atom and the water O9 atom, thus forming a chain running along the crystallographic x axis. The interchain cohesion is provided by interactions involving the O8 water molecule. It appears that the molecules in the crystal of (II) are less tightly packed than those in (I), possibly because of the lack of interactions of the N1 group. Hence, the interchain cohesion is weakened, preventing the chains from



Figure 3

Partial packing diagram for (I), showing the O-H···O (dotted lines) and some of the N-H···O (dashed lines) hydrogen bonds. Only the H atoms attached to O and N atoms are shown. Atoms labeled with a prime ('), a hash (#) and an ampersand (&) are at the symmetry positions $(\frac{1}{2} - x, -y, z - \frac{1}{2})$, $(x - \frac{1}{2}, \frac{1}{2} - y, -z)$ and $(\frac{1}{2} + x, \frac{1}{2} - y, -z)$, respectively.



Figure 4

Partial packing diagram for (II), showing the $O-H \cdots O$ (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) Åb = 12.937 (5) Å $c = 5.714 (3) \text{\AA}$ $V = 862.4 (6) \text{ Å}^3$ Z = 4 $D_{\rm r} = 1.687 {\rm Mg} {\rm m}^{-3}$

Data collection

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

Mo $K\alpha$ radiation Cell parameters from 20 reflections $\theta = 10-20^{\circ}$ $\mu = 0.50 \text{ mm}^{-1}$ T = 293 (2) KCube, colorless $0.20\,\times\,0.15\,\times\,0.15$ mm

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

3),

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)	$\Omega^2 - P1 - \Omega^3$	112 71 (16)
C1 - C2 - C3	112.09(19) 117.9(4)	$04 - P^2 - 05$	105.90(18)
01 - P1 - 02	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).

$D - H \cdots A$	D-H	$H \cdot \cdot \cdot A$	$D \cdot \cdot \cdot A$	$D - \mathbf{H} \cdots A$
$N1 - H1 \cdots O6^{i}$	0.89	2.01	2.814 (4)	149
$N1 - H2 \cdot \cdot \cdot O2^{i}$	0.89	1.99	2.796 (4)	149
$N1 - H3 \cdot \cdot \cdot O1^{ii}$	0.89	1.96	2.740 (4)	146
O3−H9···O6 ⁱⁱⁱ	0.82(3)	1.82(3)	2.623 (4)	169 (5)
$O4-H10\cdots O2^{iv}$	0.85 (3)	1.68 (3)	2.524 (4)	173 (6)
$O5-H11\cdotsO1^{v}$	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	
$C_5H_{13}NO_7P_2 \cdot 2H_2O$	Mo $K\alpha$ radiation
$M_r = 297.14$	Cell parameters from 19 718
Monoclinic, $P2_1/c$	reflections
$a = 11.8880 (3) \text{\AA}$	$\theta = 2.9-28.3^{\circ}$
b = 12.4715 (4) Å	$\mu = 0.41 \text{ mm}^{-1}$
c = 7.9403 (2) Å	T = 120 (2) K
$\beta = 95.4986 \ (13)^{\circ}$	Thin plate, colorless
V = 1171.82 (6) Å ³	$0.26 \times 0.11 \times 0.06 \text{ mm}$
Z = 4	
$D_{\rm u} = 1.684 {\rm Mg m}^{-3}$	

Data collection

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

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 $\theta_{\rm max} = 28.3^{\circ}$

 $h = -15 \rightarrow 15$

 $k = -16 \rightarrow 16$

 $l = -9 \rightarrow 10$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F^2) + (0.0579P)^2]$
	$w = 1/[0 (1_0) + (0.057)1)$
R(F) = 0.043	+ 0.7884P]
$wR(F^2) = 0.113$	where $P = (F_{a}^{2} + 2F_{c}^{2})/3$
S = 1.07	$(\Delta/\sigma)_{\rm max} = 0.007$
2901 reflections	$\Delta \rho_{\rm max} = 0.34 \ {\rm e} \ {\rm \AA}^{-3}$
178 parameters	$\Delta \rho_{\rm min} = -0.57 \mathrm{e} \mathrm{\AA}^{-3}$
H atoms treated by a mixture of	
independent and constrained	
refinement	

Table 3

Selected	geometric	parameters ([A, °) for ((\mathbf{H})).
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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 (Å, $^{\circ}$) for (II).

$D - H \cdots A$	$D-\mathrm{H}$	$H \cdot \cdot \cdot A$	$D \cdot \cdot \cdot A$	$D - \mathbf{H} \cdots A$
02_H209	0.85(2)	1.62 (2)	2 455 (2)	167 (3)
$O_2 - H_2 \cdots O_j^{v_i}$	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 $U_{\rm eq}$ values of their carrier atoms. The O–H distances were restrained at 0.85 (3) Å using the DFIX command implemented in *SHELXL*97 (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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