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Research Article

Bis(ammonium) Zoledronate Dihydrate

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Neutralization of 2-(1-imidazole)-1-hydroxyl-1,1′-ethylidenediphosphonic acid (zoledronic acid) by an excess of ammonia yielded bis(ammonium) zoledronate dihydrate, $\{C_5H_8N_2O_7P_2{}^{2-}, 2(H_4N^+), 2(H_2O)\}$. The product is readily soluble in water and forms monocrystals for which the X-ray structural analysis was carried out. The zoledronic anion is of double negative charge due to deprotonation of three P–OH groups and protonation of the nitrogen in the imidazole ring. The structure is stabilized by extensive network of N–H$\cdots$O and O–H$\cdots$O hydrogen bonds expanding through the crystal in plane (002). The imidazole ring is involved in π-π stacking interactions with its symmetry equivalents related by inversion centers at (1 0 0) and (1 1/2 0), with distances between centroids (Cg–Cg) of 3.819 (2) and 3.881 (2) Å, respectively.

1. Introduction

Bisphosphonates have been subject of intensive research mainly due to their application in medicine as bone resorption inhibitors [1]. 2-(1-Imidazole)-1-hydroxyl-1,1′-ethylidenediphosphonic acid, known as zoledronic acid, is regarded as the third generation of drugs for osteoporosis. Due to its structure, imidazolyl $-CH_2-C(OH)\{O{=}P(OH)_2\}_2$, the acid may be deprotonated at all four P–OH groups and protonated at the imidazolic N atom. The kind of the ion formed should influence not only coordination mode and intermolecular interactions but also the water solubility of the product, which may alter bioavailability.

Salts of zoledronic acid in the solid state usually contain monovalent anion resulting from deprotonation of two OH groups and protonation of the imidazole nitrogen. Examples include salts of sodium $Na^+\cdot C_5H_9N_2O_7P_2{}^-\cdot 4H_2O$ [3] and a series of compounds of general formula $(C_5H_9N_2O_7P_2{}^-)_2M(H_2O)_2$ M=Mg [4], Zn [5], Mn [6], Cu [7], Co, and Ni [8]. In some cases (for Cu, Co, Mn, and Ni), polynuclear complexes or coordination polymers are formed, with potentially interesting magnetic properties (e.g., [9]). Doubly negative anion was encountered in the catena((μ_3-zoledronato)aqua calcium) [10]. Triply negative anion was found in a tris(dicyclohexylammonium) zoledronate ethanol solvate monohydrate [11]. It is one of the few structures reported with nonprotonated imidazole ring. The other two are the cobalt derivative with coordination of the ring nitrogen to a metal atom Co$\cdots$N [9] and the mentioned above calcium salt [10]. Structure of another organic ammonium salt of the acid was recently reported (albeit with mononegative anion)—cytosinium zoledronate trihydrate [12]. In this paper, we carried out neutralization of zoledronic acid with excess of ammonia to reveal whether mono-, bis-, or trisammonium salt will be formed in the solid state and to study the basic properties and the structure of the obtained product.

2. Materials and Methods

Starting material 2-(1-imidazole)-1-hydroxyl-1,1′-ethylidenediphosphonic acid monohydrate (zoledronic acid monohydrate) was supplied by Polpharma SA (Starogard Gdanski, Poland) and used as such (m.p. 239°C). Other reagents were of analytical grade and were used without further workup.

2.1. Synthesis. Preparation of $C_5H_{20}N_4O_9P_2$ is given as follows. Solution of 3 mol/dm^3 ammonia (eight-fold excess, 0.86 mL, 2.6 mmol) and solid zoledronic acid (88 mg, 0.325 mmol) were added to a mixture of water (8 mL) and ethanol (4 mL). The contents were stirred and heated to boiling. The solution was concentrated under vacuum to ca

Table 1: Crystal data, data collection, and refinement details for $C_5H_8N_2O_7P_2^{2-}\cdot 2(H_2O)\cdot 2(H_4N^+)$.

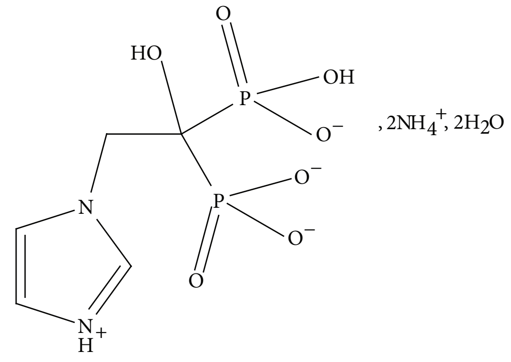
Empirical formula	$C_5H_{20}N_4O_9P_2$
Formula weight	342.19
Crystal system	Triclinic
Space group	$P\bar{1}$
Temperature	293 K
Wavelength	0.71073 Å
Unit cell dimensions	$a = 6.8415\ (4)$ Å
	$b = 7.5070\ (5)$ Å
	$c = 13.9398\ (10)$ Å
	$\alpha = 81.735\ (6)^\circ$
	$\beta = 82.922\ (5)^\circ$
	$\gamma = 82.780\ (5)^\circ$
Volume	698.84 (8) Å^3
Z	2
Density (calcd.)	1.626 Mg m^{-3}
Absorption coeff.	$\mu = 0.36$ mm^{-1}
$F(000)$	360
Crystal size	0.45 × 0.12 × 0.08 mm
Crystal color and shape	Colorless, block
θ range data collection	$\theta = 2.8$–25.1°
Limiting indices	$h = -5 \rightarrow 8$
	$k = -8 \rightarrow 8$
	$l = -16 \rightarrow 15$
Reflections collected	3930
Independent reflections	2481 ($R_{\text{int}} = 0.023$)
Refinement method	Full-matrix least-square on F^2
Data/restraints/parameters	2481/14/235
Goodness-of-fit on F^2	1.07
Final R indices $[I > 2\sigma(I)]$	$R_1 = 0.0481$
	$wR(F^2) = 0.1153$
R indices (all data)	$R_1 = 0.0586$
	$wR(F^2) = 0.1279$
Residual el. density	$\Delta\rho_{\max} = 0.49$ e Å^{-3}
	$\Delta\rho_{\min} = -0.34$ e Å^{-3}

2 mL and left to crystallize by slow evaporation, and after, a few days, colorless crystals (m.p. 260-261°C) suitable for X-ray diffraction were obtained.

Elemental analysis, CHNS, found the following (calculated for $C_5H_{20}N_4O_9P_2$): C 17.73% (17.55), H 5.75% (5.89), N 16.01% (16.37), and S 0% (0). Apparatus used is Vario El Cube CHNS (Elementar).

2.2. X-Ray Crystallography. Diffraction data were collected using KM4CCD (Kuma), Sapphire2, large Be window, 4-axis kappa diffractometer with graphite monochromator, and Mo K_α radiation, at ambient temperature. More details are given in Table 1.

Structure was refined with all heavy atoms treated as anisotropic and H-atoms as isotropic. All C–H and C–OH hydrogen atoms were refined as riding on their bonded counterpart atoms with the usual constrains. Hydrogen atoms belonging to water molecules were found in the Fourier map and refined with O–H bond length constrained to 0.82 Å. The same location method was applied to the H atoms bound to ammonium nitrogen atoms, whose N–H distances were constrained to 0.86 Å. Hydrogen atom at O6 was found in the electron density map and refined as riding on the oxygen atom.



Scheme 1

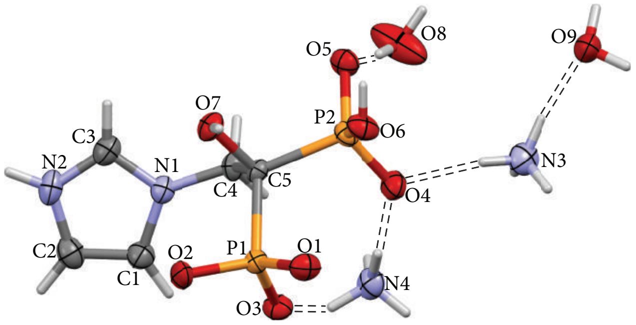


Figure 1: Molecular structure of $C_5H_{20}N_4O_9P_2$ showing atom labeling scheme. All hanging hydrogen bonds are not shown; displacement ellipsoids 50%.

Programs used are the following: for data collection, CrysAlis PRO (Agilent Technologies) [13]; for cell refinement and data reduction, CrysAlis PRO [13]; for solving structure, SUPERFLIP [14]; for refineing structure, SHELXL97 [15] and WinGX [16]; for molecular graphics, Mercury [17] and ORTEP-3 [18]; software used for preparing material for publication, PLATON [2], CSD [19], and publCIF [20].

Supplementary crystallographic data for $C_5H_{20}N_4O_9P_2$, CCDC 935170, can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, Cambridge, UK.

3. Results and Discussion

Reaction of zoledronic acid with an excess of ammonia yielded the title compound: $C_5H_8N_2O_7P_2^{2-}\cdot 2(H_4N^+)\cdot 2(H_2O)$.

Its molecular structure is shown in Scheme 1 and Figure 1, and geometric parameters are given in Table 2. The bisphosphonate anion is of double negative charge due to

Table 2: Selected geometric parameters (Å, °).

P1–O1	1.516 (2)	O7–C5	1.443 (3)
P1–O3	1.526 (2)	N2–C3	1.325 (4)
P1–O2	1.537 (2)	N2–C2	1.366 (4)
P1–C5	1.879 (3)	N1–C3	1.337 (4)
P2–O4	1.509 (2)	N1–C1	1.384 (4)
P2–O5	1.514 (2)	N1–C4	1.478 (4)
P2–O6	1.578 (2)	C1–C2	1.353 (5)
P2–C5	1.861 (3)	C5–C4	1.543 (4)
O1–P1–O3	112.51 (12)	C3–N1–C1	108.4 (3)
O1–P1–O2	111.12 (13)	C3–N1–C4	124.2 (3)
O3–P1–O2	112.06 (12)	C1–N1–C4	127.4 (2)
O1–P1–C5	109.45 (12)	C2–C1–N1	106.5 (3)
O3–P1–C5	105.41 (12)	C1–C2–N2	107.6 (3)
O2–P1–C5	105.88 (12)	O7–C5–C4	104.3 (2)
O4–P2–O5	116.33 (13)	O7–C5–P2	109.87 (18)
O4–P2–O6	109.22 (13)	C4–C5–P2	106.06 (18)
O5–P2–O6	110.01 (12)	O7–C5–P1	111.87 (18)
O4–P2–C5	107.62 (12)	C4–C5–P1	112.52 (19)
O5–P2–C5	109.04 (13)	P2–C5–P1	111.85 (14)
O6–P2–C5	103.87 (13)	N2–C3–N1	108.5 (3)
C3–N2–C2	109.0 (3)	N1–C4–C5	114.0 (2)
C3–N1–C1–C2	−0.2 (3)	O2–P1–C5–O7	34.8 (2)
C4–N1–C1–C2	178.6 (3)	O1–P1–C5–C4	157.95 (19)
N1–C1–C2–N2	0.0 (4)	O3–P1–C5–C4	36.7 (2)
C3–N2–C2–C1	0.2 (4)	O2–P1–C5–C4	−82.2 (2)
O4–P2–C5–O7	173.78 (18)	O1–P1–C5–P2	38.68 (18)
O5–P2–C5–O7	−59.2 (2)	O3–P1–C5–P2	−82.56 (16)
O6–P2–C5–O7	58.1 (2)	O2–P1–C5–P2	158.53 (14)
O4–P2–C5–C4	−74.1 (2)	C2–N2–C3–N1	−0.3 (4)
O5–P2–C5–C4	52.9 (2)	C1–N1–C3–N2	0.3 (3)
O6–P2–C5–C4	170.17 (18)	C4–N1–C3–N2	−178.6 (3)
O4–P2–C5–P1	48.92 (17)	C3–N1–C4–C5	84.1 (3)
O5–P2–C5–P1	175.92 (13)	C1–N1–C4–C5	−94.5 (3)
O6–P2–C5–P1	−66.81 (16)	O7–C5–C4–N1	−60.4 (3)
O1–P1–C5–O7	−85.1 (2)	P2–C5–C4–N1	−176.36 (19)
O3–P1–C5–O7	153.69 (18)	P1–C5–C4–N1	61.1 (3)

deprotonation of three P–OH groups and protonation of the nitrogen in the imidazole ring. The longest P–O bond is noted for the only P–OH group (at O6 atom). Contrary to tris(dicyclohexylammonium) zoledronate [11], no intramolecular P–OH$\cdots$O hydrogen bond was formed. Protonation at the ring nitrogen N2 is confirmed by location of H2N from the electron density peak in the Fourier map. Presence of a strong hydrogen bond N2–H2N$\cdots$O2$^{\mathrm{v}}$ (charge assisted, see Table 3) is an additional evidence of the protonation.

It is worthy noting that P1–O2 bond is longer than other P1–O bonds probably due to the mentioned hydrogen bond. Analysis of Table 3 reveals that it is a bond with the second smallest H$\cdots$A distance. Even stronger is the interaction O6–H6$\cdots$O3$^{\mathrm{i}}$, of the only phosphorus hydroxyl group with the negatively charged oxygen, forming a first-level chain C(6) motif passing in parallel to the *a*-axis. The hydrogen bond network is complex with most of the first-level motifs being discrete. Among the second-level graph motifs, notable is a centrosymmetric ring R2,4(8) motif with four N3–H donors and two O9 acceptors placed on the inversion center at (1/2 1/2 1/2). Packing of molecules is organized in hydrophilic and hydrophobic layers parallel to the *ab* (i.e., (001)) plane, Figure 2. The hydrogen-bonding network is present in vicinity of the planes at $z = 0.5 + n$ ($n \in Z$, the set of all integers), while close to the planes at $z = 0 + n$ dominating are the stacking interactions. The imidazole groups, involved in π-π ring stacking, interact with their symmetry equivalents related by inversion centers at (1 0 0) and (1 1/2 0), with Cg–Cg distances 3.819 (2) and 3.881 (2) Å,

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

	D–H	H···A	D···A	D–H···A
O6–H6···O3$^{\text{i}}$	0.82	1.74	2.552 (3)	170
O7–H7···O8$^{\text{ii}}$	0.82	1.95	2.699 (3)	151
O8–H8A···O5	0.81 (2)	1.95 (2)	2.751 (4)	168 (4)
O8–H8B···O2$^{\text{iii}}$	0.80 (2)	2.01 (2)	2.806 (4)	171 (5)
O9–H9A···O1$^{\text{iii}}$	0.83 (2)	1.96 (2)	2.769 (3)	166 (4)
O9–H9B···O3$^{\text{iv}}$	0.84 (2)	2.00 (2)	2.841 (3)	179 (4)
N2–H2N···O2$^{\text{v}}$	0.86 (2)	1.77 (2)	2.613 (3)	165 (4)
N3–H3A···O1$^{\text{vi}}$	0.88 (2)	1.89 (2)	2.761 (4)	168 (4)
N3–H3B···O4$^{\text{iv}}$	0.86 (2)	2.16 (3)	2.968 (4)	156 (4)
N3–H3B···O6$^{\text{iv}}$	0.86 (2)	2.61 (3)	3.315 (4)	140 (4)
N3–H3C···O4	0.88 (2)	2.14 (2)	3.003 (4)	169 (5)
N3–H3D···O9	0.86 (2)	2.16 (3)	2.909 (4)	146 (4)
N4–H4A···O9$^{\text{vii}}$	0.88 (2)	2.02 (3)	2.812 (4)	149 (3)
N4–H4B···O2$^{\text{vi}}$	0.87 (2)	2.01 (2)	2.857 (4)	165 (3)
N4–H4C···O4	0.88 (2)	2.01 (2)	2.893 (4)	179 (5)
N4–H4D···O5$^{\text{vii}}$	0.88 (2)	2.16 (2)	3.000 (4)	159 (4)

Symmetry codes: $^{\text{i}}x-1, y, z$; $^{\text{ii}}x, y-1, z$; $^{\text{iii}}x-1, y+1, z$; $^{\text{iv}}-x+1, -y+1, -z+1$; $^{\text{v}}-x+2, -y, -z$; $^{\text{vi}}x, y+1, z$; $^{\text{vii}}x+1, y, z$.

Table 4: Ring stacking interaction parameters [Å, °], calculated with PLATON program [2]. Imid = (N1–C1–C2–N2–C3); all dihedral angles between rings $\alpha = 0°$ due to symmetry.

Ring(I)	Ring(II)	Cg(I)–Cg(II)	β	γ	CgI_perp	Slippage
Imid	Imid^{a}	3.819 (2)	34.20	34.20	−3.1585 (16)	2.147
Imid	Imid^{b}	3.881 (2)	27.64	27.64	3.4376 (16)	1.800

Symmetry codes: $^{a}2-x, -y, -z$; $^{b}2-x, 1-y, -z$.

respectively; for details, see Table 4. The title compound is very readily soluble in water.

4. Conclusions

Neutralization of 2-(1-imidazole)-1-hydroxyl-1,1′-ethylidenediphosphonic acid (zoledronic acid) by an excess of ammonia gives bis(ammonium) zoledronate dehydrate: $\{C_5H_8N_2O_7P_2{}^{2-}, 2(H_4N^+), 2(H_2O)\}$. Crystals are readily soluble in water. The anion is of double negative charge due to deprotonation of three OH groups and protonation of the nitrogen atom in the imidazole ring. The structure is stabilized by extensive network of N–H···O and O–H···O hydrogen bonds and π-π stacking interactions between the imidazole rings.

Conflict of Interests

The authors have no conflict of interests with the mentioned commercial entity.

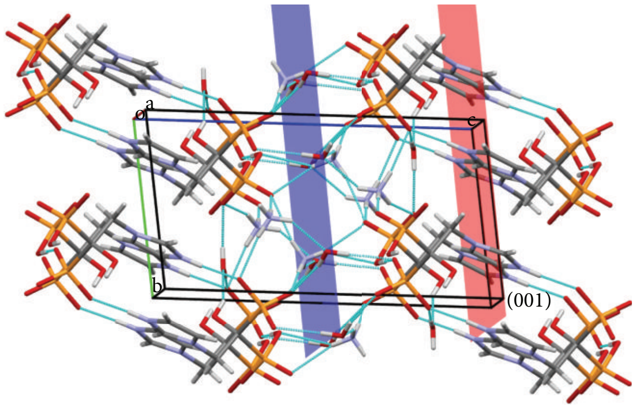


Figure 2: Layers of hydrogen bonding, about *ab* plane at $z = 1/2$ (blue) and ring stacking in vicinity of the plane at $z = 1$ (pink) in the crystals of bis(ammonium) zoledronate dehydrate.

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