

Synthesis, Characterization and Crystal Structure of Calcium-3-amino-1-hydroxypropylidene-1,1-bisphosphonic Acid

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Following the strategy of using polyfunctional phosphonic acids for the synthesis of open-framework metal phosphonates, 3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid was used in the synthesis of a new calcium phosphonate. The compound, calcium-3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid $[\text{Ca}_{0.5}\{(\text{H}_3\text{N}^+\text{CH}_2\text{CH}_2)\text{C}(\text{OH})(\text{PO}_3\text{H}^-)(\text{PO}_2\text{H}^-)\}_2]\cdot\text{H}_2\text{O}$ (**1**) is a three-dimensional framework prepared by nonhydrothermal synthesis route. The asymmetric unit contains one independent Ca atoms, two chelating and bridging phosphonic ligands and one lattice water molecule. The structure of **1** is built up from CaO_6 polyhedra forming CaO chains connected to a three-dimensional metal-oxygen-metal framework with ammonium propyl groups pointing into the space between these layers. There are empty pore within the layers along the 'c' direction.

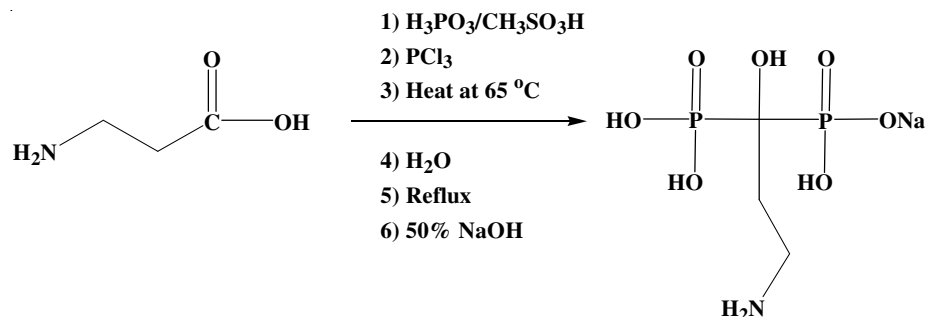
Key Words: Bisphosphonate, Crystal structure, Strands, Channels, Hydrogen bonding, Thermogravimetric analysis.

INTRODUCTION

Bisphosphonic acids are excellent antihypercalcemics and are rapidly evolving as therapeutic agents for the treatment of a number of diseases which are characterized by abnormal calcium metabolism¹⁻⁶. Such compounds have demonstrated effectiveness in arresting bone deterioration and restoring normocalcemia in patients with hypercalcemia of malignancy, metastatic bone disease, Paget's disease and osteoporosis and they have the potential for other applications as well^{7,8}. To facilitate further evaluation of bisphosphonic acid and their metal complexes as a therapeutic agent, it was essential to develop an efficient and practical synthesis to guarantee availability for its evaluation in clinical trials. Several methods have been reported for the synthesis of 1,1-bisphosphonates. One of the methods used in the preparation was by the reaction of a carboxylic acid with phosphorous acid and phosphorus trichloride (**Scheme-I**)⁹.

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Scheme-I: Synthesis of (3-amino-1-hydroxypropylidene)bisphosphonic acid as sodium salt

Due to chemical applications of the metal bisphosphonates in ion exchange, sorption and catalysis, research on the chemistry of metal phosphonates has recently focused on the properties of these solid materials¹⁰⁻¹³. Usually, the structures are polymeric in nature consisting of chains, layers, pillared layers, one-, two- or three-dimensional networks¹⁴⁻¹⁶. The dimensionality is dependent not only on the number of donor atoms of the ligand, but also on the length of the organic group between the phosphonate groups and on the degree of protonation and stability of the phosphonate group¹⁷⁻²⁰.

Previously, the structures of polymeric iron bisphosphonate complexes *via* hydrothermal syntheses have been reported^{21,22}. The synthesized structures are proved to be two-dimensional chains. In this paper we describe the syntheses and characterization of the calcium bisphosphonate [Ca_{0.5}{(H₃N⁺CH₂CH₂)C(OH)(PO₃H⁻)(PO₃H⁻)₂}·H₂O that was first obtained as a result of nonhydrothermal routes.

EXPERIMENTAL

All work involving air- and/or moisture-sensitive compounds was carried out by using standard vacuum and Schlenk techniques. Suitable single crystal of the title compound was carefully selected under a polarizing microscope. X-ray crystallographic data was collected using Bruker AXS with CCD area-detector, Mo-K_α radiation ($\lambda = 0.71073 \text{ \AA}$), graphite monochromator and double-pass method $\phi \omega$ -scan. Data were collected and refined with SMART²³, reduced with SAINT²³ and the experimental absorption corrected with SADABS²⁴.

IR spectra (KBr pellet) were measured on a Bruker Optik IFS²⁵. NMR spectra were recorded with a Bruker Advance DPX200 spectrometer at 300 K (200 MHz for ¹H, 81 MHz for ³¹P) with calibration against the solvent signal (D₂O; 4.87 ppm) or an external standard of 85 % H₃PO₄, respectively. Elemental analyses were obtained on a VarioEL from Elementaranalysensysteme GmbH. Thermogravimetric analysis was done on a simultaneous thermoanalysis apparatus STA 409 from Netzsch under nitrogen (heating rate 5 K min⁻¹).

Structure analysis and refinement: The structure was solved by direct methods (SHELXS-97)²⁵; refinement was done by full-matrix least squares on F² using the

SHELXL-97 program suite²⁵. Cambridge crystallographic data center (CCDC) contains the supplementary crystallographic data for this paper under the code CCDC 707626. These data can be obtained free of charge *via* the internet at www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK). The crystal data and structure refinement are shown in Table-1.

TABLE-1
CRYSTAL DATA AND STRUCTURE REFINEMENT FOR $\text{C}_3\text{H}_{10}\text{Ca}_{0.5}\text{NO}_8\text{P}_2$

Empirical formula	$\text{C}_3\text{H}_{10}\text{Ca}_{0.5}\text{NO}_8\text{P}_2$	γ (°)	90.00
fw	270.10	V (Å ³)	1988.2(10)
Cryst. colour	White	Z	4
Crystal dimens (mm ³)	0.25 × 0.20 × 0.10	h	-20→16
Temp. (K)	293(2)	k	-20→20
Wavelength (Å)	0.71073	l	-15→15
Cryst. syst	Triclinic	Reflections	3044
Space group	C2/c	Parameters	144
Formula unit/unit cell	8	Density (calcd.) (Mg/m ³)	1.805
a (Å)	15.370(6)	F(000)	1112
b (Å)	12.238(3)	GOF on F2	1.180
c (Å)	12.132(2)	R1/wR2	0.0495, 0.1083
α (°)	90.00	R1/w (all data)	0.0619, 0.1135
β (°)	109.20(2)	Absorption coefficient (μ)	0.718

Preparation of 3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid: A 250 mL flask was fitted with a mechanical stirrer, a thermocouple, an addition funnel and a reflux condenser through which brine was circulated (1:1 isopropanol: water) at -15 °C. The reflux condenser was connected to a 5 M NaOH trap. The system was flushed with argon and charged with 3-aminopropylidene-1,1-bisphosphonic acid, $\text{H}_2\text{N}(\text{CH}_2)_2\text{-COOH}$ (8.90 g, 0.10 mol), phosphoric acid H_3PO_3 , (8.20 g, 0.10 mol) and methanesulfonic acid $\text{CH}_3\text{SO}_3\text{H}$ (40 mL). The mixture was heated to 65 °C, trichlorophosphine, PCl_3 (15.5 mL, 0.20 mol) was added over 0.5 h and the mixture maintained at 65 °C for 16 h. The clear colourless solution was cooled to room temperature and quenched with vigorous stirring into 50 mL of 0-5 °C water. The reaction flask was rinsed with an additional 25 mL of water and the combined solution was refluxed for 5 h. The solution was then cooled to room temperature, the pH was adjusted to 4.3 with 50 % NaOH (6.5 mL) and the resulting suspension was kept for 2 h at 0-5 °C. The product was collected by filtration, washed with cold water and 95 % ethanol and dried at room temperature for over night yielding 17.0 g (57 %) as the monosodium salt monohydrate. ($\text{C}_3\text{H}_{14}\text{NO}_8\text{P}_2\text{Na}$) (277.08 g/mol) Calcd. C: 12.99, H: 5.05, N: 5.05. Found C: 12.71, H: 4.77, N: 4.82. IR (major peaks only): 3330 (br, ν_{OH}), 1647 ($\nu_{\text{C-C}}$), 1461 ($\nu_{\text{P=O}}$), 1070 ($\nu_{\text{P-O}}$). ¹H NMR (D_2O) (200 MHz) δ (ppm): 3.45 (t, CH_2 , $J = 5.52$ Hz), 2.38 (m, CH_2 , $J = 5.52$ Hz), ³¹P NMR (D_2O) δ 17.02.

Preparation of bis(3-ammonium-1-hydroxypropylidene-1,1-bisphosphonato)calcium: $\text{CaCl}_2 \cdot 6\text{H}_2\text{O}$ (0.219 g, 1.00 mmol) and 3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid sodium salt (0.277 g, 1.00 mmol) were dissolved each separately in 25 mL of distilled water. After mixing of the two solutions, the resulting slurry was left with constant stirring for 6 h and the precipitate was filtered. The supernatant was left standing for 8 days at room temperature with evaporation of some of the solvent. After this time, the white crystals of the title compound were collected by filtration (yield 130 mg, 48 %). Anal. ($\text{C}_3\text{H}_{10}\text{Ca}_{0.5}\text{NO}_8\text{P}_2$) (270.10 g/mol) calcd. C: 13.32, H 3.70, N: 5.18 %. Found C: 13.11, H: 3.89, N: 4.96 %.

RESULTS AND DISCUSSION

Crystal structure: The structure of **1** is best described as monomeric units consisting of octahedral Ca1 atoms with two symmetrically chelating $\{(\text{H}_3\text{N}^+(\text{CH}_2)_2)\text{-C}(\text{OH})(\text{PO}_3\text{H}^-)_2\}$ ligands, connected into polymeric chains in the direction of c-axis (Fig. 1). H atoms connected to C atoms were placed onto calculated positions. The crystal structure consists of columns or strands of PO_3H^- corner-sharing tetrahedra (Figs. 1 and 2). The strands are arranged as chains of corner-sharing polyhedra with the ammonium propyl groups in the bisphosphonate pointing into the space between these layers (Fig. 2). The bridging oxygen atoms are provided by the PO_3H^- groups. Within the column there exists only one crystallographically type of calcium. Each PO_3H^- group bridges between two Ca atoms with two of its oxygen atoms as Ca-O-P-O-Ca. As expected, the bonding around the Ca atom is octahedral, with angles of $112.463(81)^\circ$, $90.440(67)^\circ$, $96.394(66)^\circ$, $84.511(74)^\circ$ and $162.955(71)^\circ$ for O6-Ca1-O6', O6-Ca1-O4, O6-Ca1-O4', O6-Ca1-O1, O6-Ca1-O1', respectively. The Ca-O bond lengths of Ca1-O1; 2.3894(21) Å, Ca1-O4; 2.3055(17) Å, Ca1-O6; 2.2916(24) Å are compare well with the values previously obtained for similar crystal structures containing bisphosphonic acid ligand^{21,22,26,27}. Bond distances and angles between nonhydrogen atoms are listed in Table-2.

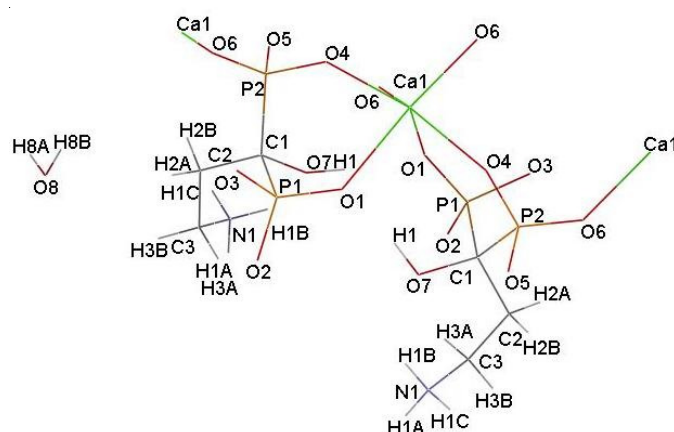


Fig. 1. Section of the structure of **1** showing the geometry around Ca atom centers

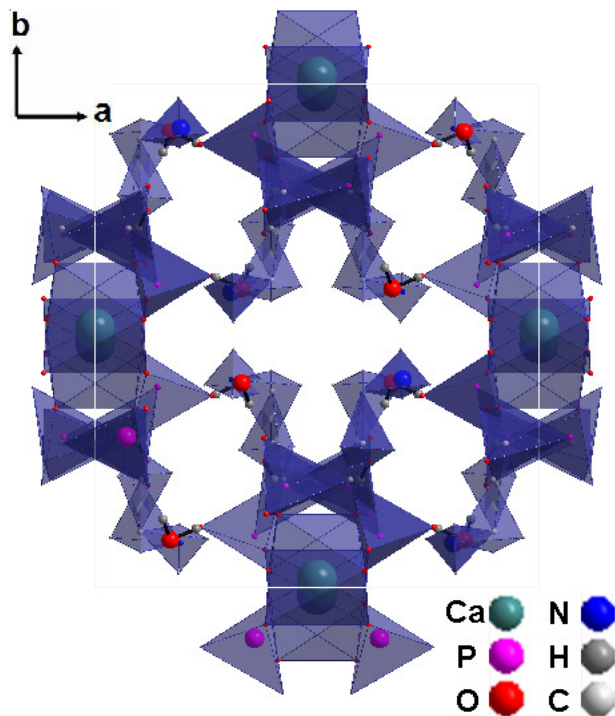


Fig. 2. Section of the structure of **1** showing the cavity formed by PO_3H^- groups and octahedral calcium atoms building blocks through *c* direction

TABLE-2
SELECTED BONDS LENGTHS (Å) AND ANGLES (°) IN **1**

Ca1–O1	2.3894(21)	Ca1–O4	2.3055(17)
Ca1–O6	2.2916(24)	P1–O1	1.5154(20)
P1–O2	1.5011(20)	P1–O3	1.5780(26)
P2–O4	1.5194(19)	P2–O5	1.5687(21)
P2–O6	1.4963(25)	P1–C1	1.8512(24)
O7–H1	0.9314(546)	O7–C1	1.4513(39)
N1–H1A	0.8902(23)	N1–H1B	0.8903(25)
N1–H1C	0.8900(18)	C1–C2	1.5397(37)
C1–O7	1.4513(39)	–	–
O6–Ca1–O6	112.463(81)	O6–Ca1–O4	90.440(67)
O6–Ca1–O4	96.394(66)	O6–Ca1–O1	84.511(74)
O6–Ca1–O1	162.955(71)	O2–P1–O1	115.445(105)
O2–P1–O3	107.463(106)	O3–P1–O1	110.209(107)

Neighboring strands arrangement gives rise to cavities along the '*c*' direction (Fig. 2) and channels in '*b*' direction (Fig. 3). The zigzag channels in the '*b*' direction contain the water molecules of crystallization which cannot be observed in any other direction.

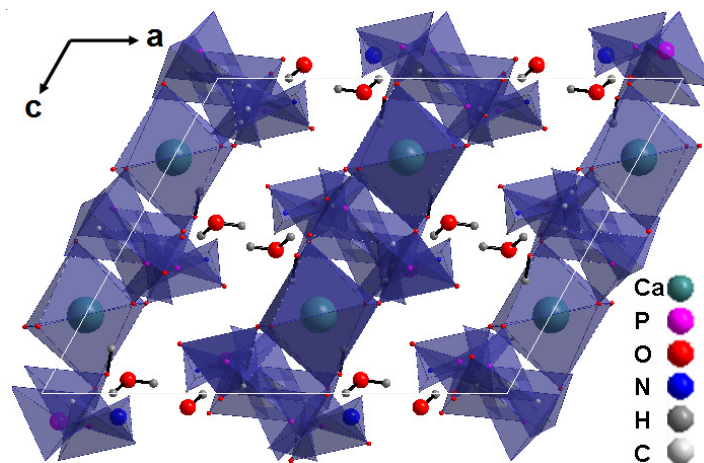


Fig. 3. Polyhedral representation of the crystal structure of compound **1** along b-axis showing zigzag channels between the strands

Neighboring strands are connected through hydrogen bonding interactions. One type of the hydrogen bonding is provided by complementary H-bonds between the PO_3H^- groups in the *ac*-plane (Fig. 4). The unprotonated O atoms from one bisphosphonate form hydrogen bonds with a neighboring bisphosphonate. This interaction is also stabilized by hydrogen bonding with a water molecule located in the bisphosphonate sheet. Water molecules provide additional hydrogen bonding to the PO_3H^- groups and thereby also connect the adjacent columns in the *ac*-plane (Fig. 4). Hydrogen bonds (the geometry and symmetry codes) are listed in Table-3.

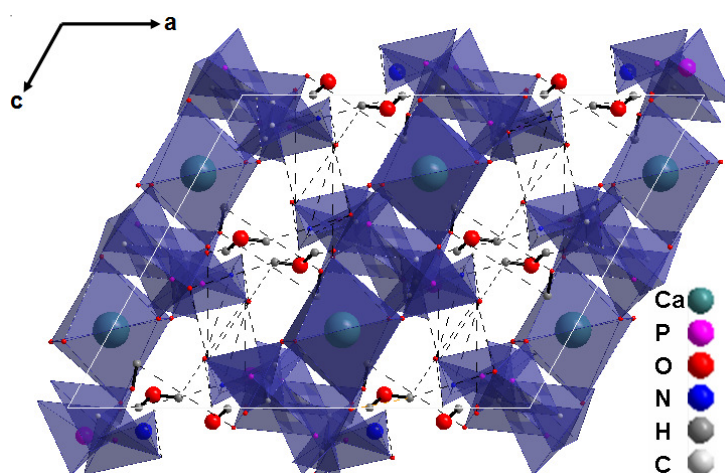


Fig. 4. Polyhedral representation of the connection of neighboring strands of **1** within the *ac*-plane showing the complementary hydrogen bonding between the PO_3H^- groups and the hydrogen bonding by water molecules of crystallization

TABLE-3
SELECTED HYDROGEN BONDING INTERACTIONS (Å, °) IN **1**

D-H...A	D-H (Å)	H...A (Å)	D...A (Å)	D-H...A (°)
N1-H1A...O8 ⁱ	0.8902(23)	1.9621(23)	2.8401(33)	7.872(109)
O8-H8B...O3 ⁱⁱ	0.8520(603)	3.0062(38)	2.1642(604)	7.467(4207)
O7iii-H1...O1 ^{iv}	0.9314(546)	2.5733(563)	2.9898(28)	55.120(3288)
O8-H8A...O2 ^v	0.8444(630)	1.8789(646)	2.7077(36)	9.187(3790)

Symmetry codes: (i) x, 1-y, 0.5+z (ii) -0.5+x, 0.5-y, -0.5+z (iii) 1-x, y, 1.5-z (iv) 1-x, y, 1.5-z (v) 1-x, y, 0.5-z.

TGA measurements: The thermogravimetric studies of **1** demonstrate two weight losses processes (Fig. 5). The first step (7.3 %) corresponds to a loss of one lattice molecule of water (theoretical value = 6.67 %). The TGA diagram shows that the dehydration begins at 85 °C. This process is complete at around 134 °C, as expected for lattice water. The burning of organic chains and transformation of phosphonic moieties occur at 355-440 °C. The observed weight loss (27.7 %) is comparable to the theoretical value of 27.0 %. The thermogravimetric process is complete with a total weight loss value of 34.7 %. The amorphous white residue (65.3 %) was suggested to be calcium pyrophosphate CaP_2O_5 . The formula weight calculated from these results is 182 which are in good agreement with the TGA result.

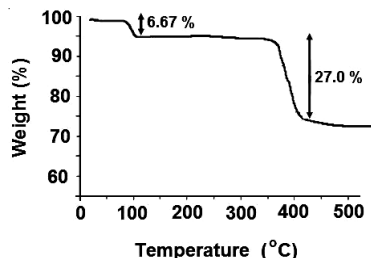


Fig. 5. Results of the TGA investigations of compound **1**

Infrared measurements: The strong band near 1210 cm^{-1} indicates the presence of the hydrogen-bonded P=O group in the bisphosphonate^{4,15,16}. A number of broad and weak bands observed in the $2790\text{--}2150\text{ cm}^{-1}$ region can be assigned to the $\nu(\text{PO-H})$ and $\delta(\text{POH})$ vibrations^{15,16,21}. Symmetrical and asymmetrical stretching vibrations of P-OH groups ($\nu(\text{P-OH})$) appear at 1012 and 951 cm^{-1} , respectively^{22,28}. The band around 1077 cm^{-1} probably belongs to the POH bending vibration $\delta(\text{POH})$ ^{22,28}. The corresponding stretching ($2927\text{--}2852\text{ cm}^{-1}$) and bending ($1456\text{--}1189\text{ cm}^{-1}$) vibrations of CH_2 groups have also been detected^{9,10,27,28}.

Conclusion

New calcium phosphonate $[\text{Ca}_{0.5}\{(\text{H}_3\text{N}^+\text{CH}_2\text{CH}_2)\text{C}(\text{OH})(\text{PO}_3\text{H}^-)(\text{PO}_3\text{H}^-)\}_2]\cdot\text{H}_2\text{O}$, **1** has been synthesized from reacting calcium chloride with 3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid sodium salt. The structure of compound **1** has

been solved using X-ray single crystal data. The new compound was characterized by TGA measurements, IR spectroscopy and chemical analysis. It has been demonstrated that the octahedrally coordinated calcium atom and the bisphosphonate ligand form a three dimensional framework. Single-crystal data are found to be in good agreement with IR and TGA studies.

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