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THE MOLECULAR STRUCTURE OF 4-AMINO 1-HYDROXY BUTYLIDENE-1 BISPHOSPHONIC ACID (AHBBPA); AN UNCOMMON ANHYDROUS HYDROXYBISPHOSPHONIC ACID

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THE MOLECULAR STRUCTURE OF 4-AMINO 1-HYDROXY BUTYLIDENE-1 BISPHOSPHONIC ACID (AHBBPA); AN UNCOMMON ANHYDROUS HYDROXYBISPHOSPHONIC ACID

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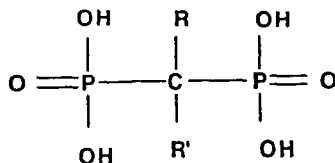
The molecular structure of an anhydrous hydroxybisphosphonic acid was determined by X-ray diffraction techniques and compared to the corresponding hydrated crystalline form. The hydrogen bond network and intermolecular interactions show that the polar bisphosphonic group undergoes a rotation to accommodate a different distribution in the hydrophobic/polar zones observed in the crystal packing, while the rest of the amino side chain connected to the functional carbon atom has identical conformation.

Keywords: Hydroxybisphosphonic acid; x-ray diffraction; Anhydrous form

INTRODUCTION

Hydroxybisphosphonic acids (HBPA-Figure 1) are very efficient compounds for complexing metallic ions and their transport in biological media.^[1] Their wide field of applications ranges from their use in bone scintigraphy^[2] to the extraction of trans actinides in nuclear industry.^[3] In addition, several substituted hydroxybisphosphonic acids are under evaluation in medicinal treatment of bone diseases as they strongly interact and regulate the biological transport of calcium.^[4] When the side chain connected to the carbon C(1) is hydrophobic, these compounds have both super acid and complexation properties.^[5] Butylidene-hydroxybisphosphonic acid, for example, is able to catalyse the intermolecular

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1, 2: R = $-(\text{CH}_2)_3\text{-NH}_2$, R' = OH; **3:** R = CH₃, R' = OH; **4:** R = R' = Cl

5: R = $-(\text{CH}_2)_5\text{-NH}_2$, R' = OH

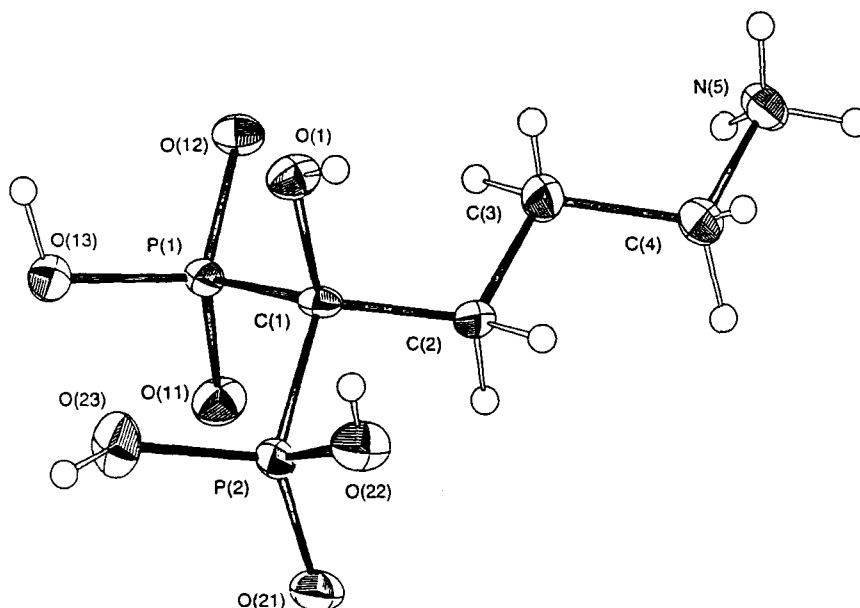


FIGURE 1 chemical formula of some HBPA with pharmaceutical activities: AHBBPA: **1, 2** (4-amino 1-hydroxybutylidene-1,1 bisphosphonic acid) R = $\text{H}_2\text{N}-(\text{CH}_2)_3-$, R' = OH. HEBPA: **3** (1-hydroxyethylidene-1,1-bisphosphonic acid) R = CH₃, R' = OH. Cl₂MDP: **4** (dichloromethylene-1,1 bisphosphonic acid) R = R' = Cl. and AHHexBPA: **5** (6-amino 1-hydroxyhexylidene-1,1 bisphosphonic acid). Below is the ORTEP representation of the title compound **1**, R = $\text{H}_2\text{N}-(\text{CH}_2)_3-$, R' = OH (ellipsoids drawn at the 50% probability level).

dehydration of methanol to dimethyl ether and simultaneously to complex the resulting protonated dimethyl oxonium cation.^[6] A number of HBPA molecular structures have been solved by X-ray diffraction,^[7,8] they all are hydrated, and/or complexed with sodium or calcium ions if no precautions are taken during the crystallisation step in water (distilled water must be used). If no cations are

available, an oxonium ion (H_3O^+) may be trapped in the structure.^[9] When the side chain carries an amino group, the internal protonation, which readily occurs, leads to the elimination of the first (strong) acidity. The compounds are less acidic but they are still strong complexing agents.^[10]

Water is always complexed in the crystal structures of HBPA acids and participates to the crystal packing stability, usually by delimiting two different 3D zones, polar and hydrophobic in character. In the present paper we describe the preparation and molecular structure of an uncommon anhydrous bisphosphonic acid: 4-amino 1-hydroxy butylidene-1 bisphosphonic acid (AHBBPA); comparison will be provided with the corresponding hydrated structure.^[11]

RESULTS AND DISCUSSION

The preparation and crystallisation of AHBBPA and the different steps of the X-ray structure determination are described in the experimental section.

The Figure 2 compares the crystal packing structures (viewed down the *b* axis) of the anhydrous structure **1** (upper) with the di-hydrated AHBBPA structure **2** (lower). As shown in this figure, the crystal structure of dehydrated AHBBPA (the title compound) is not isomorphous to the hydrated structure. The RX analysis clearly indicates that the molecule is in the zwitterionic state with the 4-amino group protonated by the first acidity of one phosphonic acid. This is also observed in the hydrated structure. The analogies of the packings are however limited because of a different cell content: one independent molecule is found in **1** and two independent molecules in **2**. In this latter case, the two molecules are related by a non-crystallographic two fold axis. However the two water molecules do not follow this rule and break the pseudo-symmetry.

Molecular description

The inter-atomic distances are given in Table I. Out of the four available acid functions, only one is ionised. The average value for the three non-ionised P-OH bonds is 1.548 Å, in good agreement with what is observed in **2** (1.551 Å) but slightly lower than the average value compiled from all the structures of hydroxybisphosphonic and tetraphosphonic acids (1.556 Å) determined in our laboratory.^[7]

At the molecular level, the two structures are very similar: the P-C, C-O and C-C distances are closely related, within the limits of the experimental errors: P-C (1.843 Å), C-OH (1.438 Å) and C-C (1.517 Å). The same observation can be

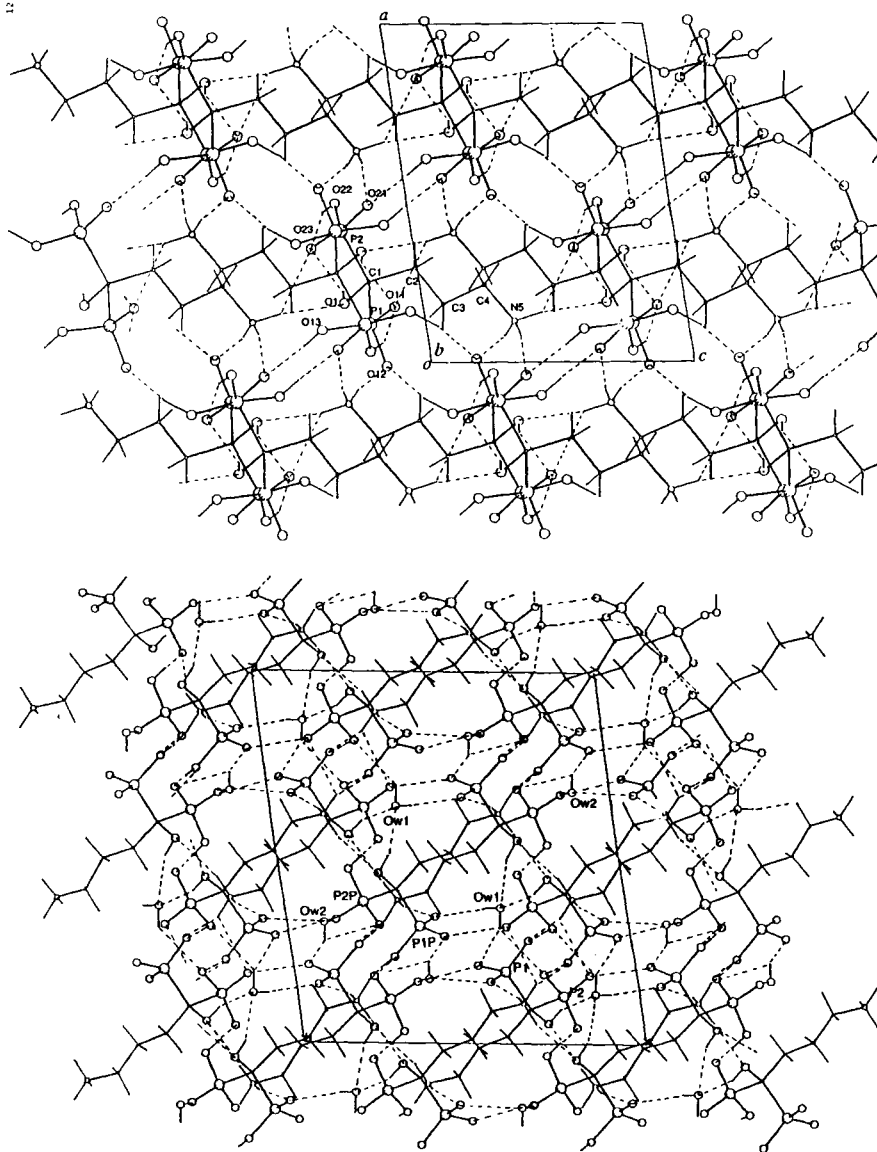


FIGURE 2 Crystal packing of the anhydrous form 1 (part a) and hydrated form 2 (part b) of 4-amino 1-hydroxy-butylidene 1,1-bis phosphonic acid (AHBBPA). The hydrophobic zones are isolated in the crystal packing by the complicated hydrogen bond networks (dashed lines).

TABLE I bond lengths and angles in the anhydrous structure of AHBBPA *1* (with e.s.d's in parentheses).

DISTANCES (Å):			
P(2)-O(21)	1.481(3)	P(1)-O(13)	1.561(3)
P(2)-O(22)	1.552(3)	C(1)-O(1)	1.438(4)
P(2)-O(23)	1.530(3)	C(1)-C(2)	1.539(5)
P(2)-C(1)	1.847(4)	C(2)-C(3)	1.518(5)
C(1)-P(1)	1.839(4)	C(3)-C(4)	1.494(6)
P(1)-O(11)	1.494(3)	C(4)-N(5)	1.491(5)
P(1)-O(12)	1.511(3)		
ANGLES (°):			
O(21)-P(2)-O(22)	108.9(2)	O(13)-P(1)-C(1)	105.8(2)
O(21)-P(2)-O(23)	116.1(2)	P(2)-C(1)-P(1)	113.5(2)
O(21)-P(2)-C(1)	110.6(2)	P(2)-C(1)-O(1)	109.3(2)
O(22)-P(2)-O(23)	107.9(2)	P(2)-C(1)-C(2)	105.9(2)
O(22)-P(2)-C(1)	106.1(2)	P(1)-C(1)-O(1)	102.5(2)
O(23)-P(2)-C(1)	106.8(2)	P(1)-C(1)-C(2)	113.5(2)
O(11)-P(1)-O(12)	116.8(1)	O(1)-C(1)-C(2)	112.2(3)
O(11)-P(1)-O(13)	107.1(1)	C(1)-C(2)-C(3)	116.6(3)
O(11)-P(1)-C(1)	109.5(2)	C(2)-C(3)-C(4)	111.0(3)
O(12)-P(1)-O(13)	109.9(1)	C(3)-C(4)-N(5)	111.2(3)
O(12)-P(1)-C(1)	107.4(2)		

drawn out from the bond angles and the dihedral angles (Table II). The similarities of the AHBBPA molecule in the two crystal structures are also evident from the chain conformation analyses. The Figure 3 shows the least-squares superimposition of the molecule in the anhydrous structure *1* over one of the two independent molecule of *2* (upper). The lower part of Figure 3 represents the least-squares fit of the two independent molecules of *2*. However, in this latter case, despite identical side chain elongation, the fit is less obvious because of a rotation of the phosphonic head. The pseudo-rotation angles that describe the rotation of the bisphosphonic groups are relevant of these discrepancies: The average value in the two independent molecules of *2* is 35° while in *1*, it is reduced to 3°6. This unique modification clearly indicates that the hydration

TABLE II The Dihedral angles (with respect to the P(1)-C(1) and P(2)-C(1) bonds) and pseudo-dihedral angles* in the anhydrous (*1*) and hydrated (*2*) crystal structures.

Molecule:	<i>1</i>	<i>2a</i>	<i>2b</i>
O(11)-P(1)-C(1)-P(2)	-61.7(2)	-82.1(2)	-78.2(2)
O(12)-P(1)-C(1)-P(2)	170.7(2)	157.2(2)	156.1(2)
O(13)-P(1)-C(1)-P(2)	53.4(2)	39.6(2)	34.7(2)
O(21)-P(2)-C(1)-P(1)	72.9(2)	47.5(2)	50.2(2)
O(22)-P(2)-C(1)-P(1)	-169.2(2)	-167.2(2)	172.7(2)
O(23)-P(2)-C(1)-P(1)	-54.3(2)	-71.1(2)	-70.4(2)
O(11)-P(1)...P(2)-O(21)	-8.6(1)	-26.2(1)	-23.9(1)
O(12)-P(1)...P(2)-O(22)	-1.8(2)	-52.6(1)	-46.3(1)
O(13)-P(1)...P(2)-O(23)	-0.3(1)	-27.8(1)	-31.9(1)
average rotation:	-3.6	-35.5	-34.0

*Dihedral angles viewed along the direction P(1)...P(2)

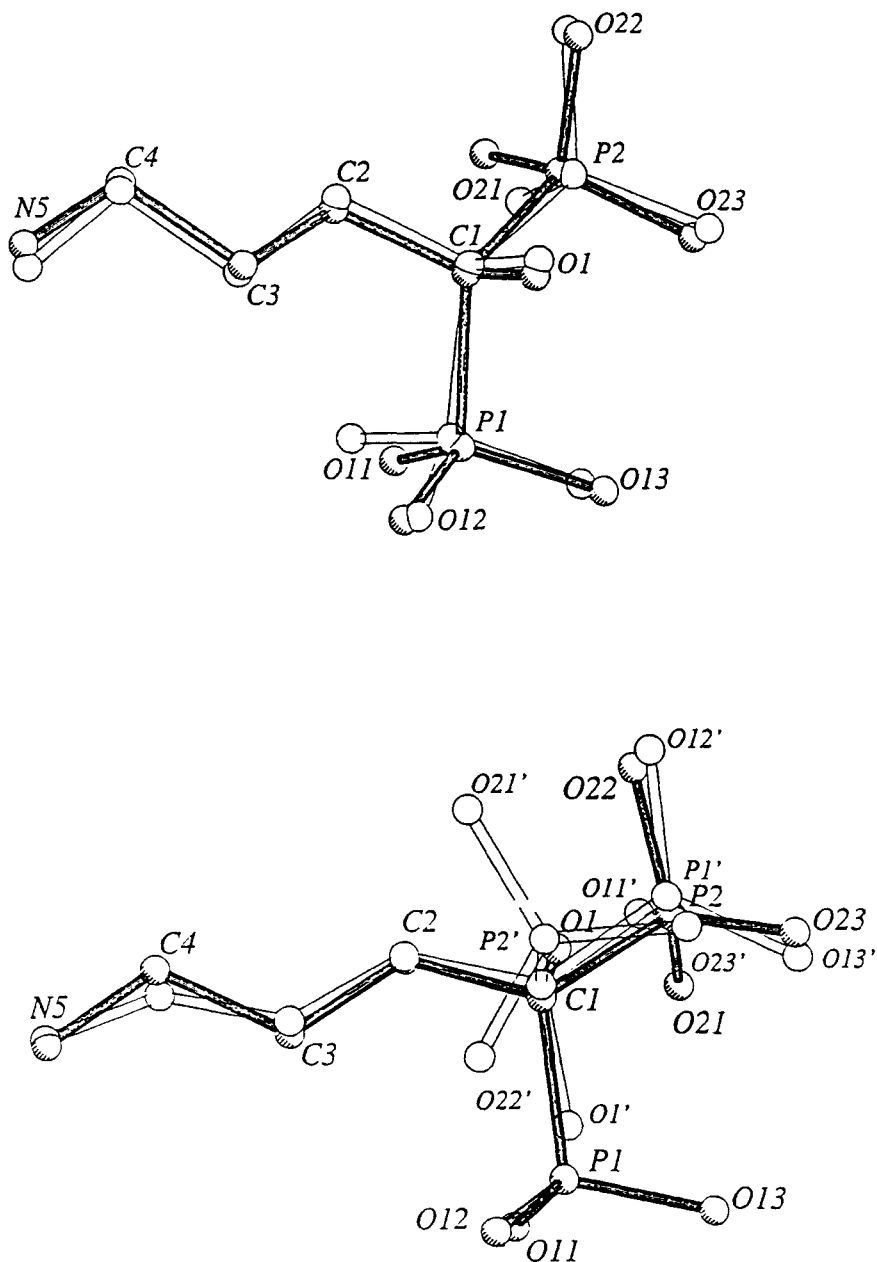


FIGURE 3 The least-squares fit of the molecular extended structures of *1* and *2a*. (upper) and *2a* over *2b* (lower) showing the different orientations observed between the two independent molecules of *2* in the crystal packing.

scheme has a strong influence on the reorientation of the phosphonic groups as to minimize the interactions in the hydrogen bond network.

The packing structures

The crystal structures of **1** and **2** are largely dominated by the polar and hydrogen bond interactions that connect the strong acidic phosphonic functions. The hydrogen bonds are involved in a very complicated network. The list of these hydrogen bond interactions in **1** is reported in Table III, (the hydrogen bond network description of **2** has already been published^[11]). In short, the molecule of the asymmetric unit is connected to 13 neighbouring copies *via* 16 polar interactions (41 contacts in **2**). These contacts can be classified in two types:

- 1) The short hydrogen bonds. These bonds connect mainly the phosphonate oxygens, with an average distance $\langle \text{OH}\cdots\text{O}=\text{P} \rangle$ (or $\langle \text{OH}\cdots\text{O}-\text{P} \rangle$) of 2.62 Å. The corresponding $\langle -\text{H}\cdots\text{O}- \rangle$ distance is 1.75 Å. The particular bond length shortening observed for the bridge O(12)-H..O(23) (2.498 Å for the O..O distance and 1.81 Å for H..O) might be the result of a tautomeric charge transfer between O(12) and O(23).
- 2) The long hydrogen bonds. This type of interaction implies the protonated N(5) amino group and the C(1) hydroxyl function. The average distances for these contacts is 2.926 Å (for the N...O and O...O distances) and 2.18 Å for the H...O distances. As they are less tightly established than the previous ones, some of these hydrogen bonds are bidentates, like the one observed in the NH_3^+ group Table III.

Moreover, the two packing views emphasize the distribution of the polar and hydrophobic zones: The hydrophobic zones are built by the stacking of the carbon side chains and delimit discrete zones, visible in Figure 2. They are in both cases similar and can be described as infinite cylinders with their axis parallel to the unique b axis. However they are located at different places in the cell: around the origin in the case of the hydrated structure **2** while they are at $x = z = 1/4$ in structure **1**.

Water inclusion/exclusion: the hydration site

The structure **2** presents two hydration sites

Water Ow(1): The single water molecule has a key role as it is deeply implicated in the hydrogen bond net through all its available ligands: the

TABLE IIIa The polar contacts and hydrogen bon network in the crystal packing of *1*. The e.s.d' are 0.003 Å for heavy-atom to heavy atom distances and 0.01 Å, for heavy-atom to hydrogen distances.

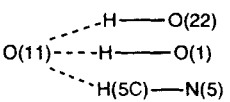
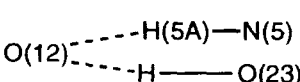
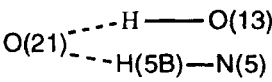
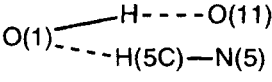
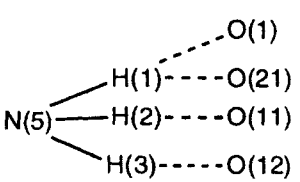
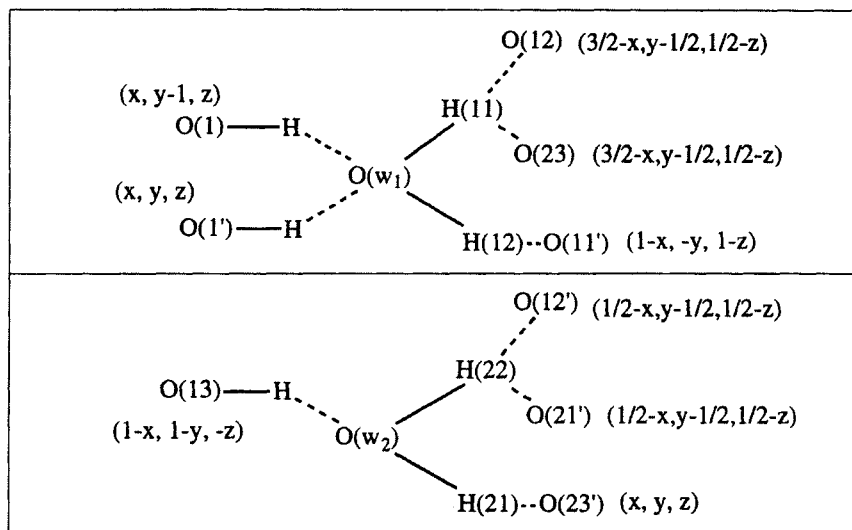
ATOMS	symmetry transformation	distance between non-H atoms (Å)	distance to H atom (Å)
	$1/2 - x, 1/2 + y, -z - 1/2$	2.661	2.02
	$1/2 - x, 1/2 + y, -z - 1/2$	2.744	2.05
	$1/2 - x, 1/2 + y, 1/2 - z$	3.002	2.22
	$-x, -2 - y, -z$	2.824	1.95
	$x - 1/2, -3/2 - y, 1/2 + z$	2.498	1.81
O(13) — H — O(21)	$x - 1/2, -3/2 - y, z - 1/2$	2.702	1.99
	$1/2 - x, -3/2 - y, 1/2 + z$	2.702	1.99
	$3/2 - x, y - 1/2, 1/2 - z$	2.965	2.08
O(22) — H — O(11)	$1/2 - x, y - 1/2, -1/2 - z$	2.661	2.02
O(23) — H — O(12)	$x + 1/2, -3/2 - y, z - 1/2$	2.498	1.81
	$1/2 - x, y - 1/2, -1/2 - z$	2.744	2.05
	$x, y, z - 1$	3.074	2.50
	$x, y, z + 1$	3.074	2.50
			
	$x - 1/2, -y - 3/2, z + 1/2$	2.965	2.08
	$1/2 - x, y - 1/2, 1/2 - z$	3.002	2.22
	$-x, -2 - y, -z$	2.824	1.95

TABLE IIIb Environment of the water molecules in 2. All the four available ligands of O(w1), and three of O(w2) are involved in a very tight hydrogen bond network, following:



two lone pairs are connected to the hydroxyl group of one molecule and the P-OH function of another molecule. On the other hand, the two hydrogens are bonded to the ionized P(1)-O⁻ groups of a third and a fourth molecule.

In the anhydrous structure, the corresponding place where the water molecule would be located corresponds to a missing cavity centered on $x = 0$; $z = 2/5$.

Water Ow(2): This site is less bonded than the first one. Only one lone pair and one hydrogen atom are implicated in the net through the P(1)-O(11) group of a first molecule and an elongated, bidentate, hydrogen bond directed towards two PO groups of two different molecules. Though weaker than Ow(1) in interactions, Ow(2) connects three different molecules in the packing instead of four.

As a result of the hydration, the compacity parameter (V/n , where n = the number of heavy atoms in the cell) for the two structures is different: 16.3 for 1 and 17.9 (the more compact) for 2.

CONCLUSION

The two molecules adopt in the two crystal structures equivalent orientations with an extended chain conformation. However, the hydration is responsible of the rotation of one phosphonic group to accommodate the additional water mol-

ecules present in **2**. Hydroxybisphosphonic acids are known to accommodate various cations and charged species.^[10] The present structure analysis shows that this concept can be achieved through two different mechanisms 1) the rotation of the bisphosphonate heads and 2) the building of a flexible hydrogen bond net. The two water molecules have a different environment thus leading to the non-equivalence of the asymmetric unit motif in **2**.

EXPERIMENTAL SECTION

Preparation of AHBBPA

To a mixture of trimethylphosphite (0.01 mole) and dimethylphosphite (0.01 mole) in chloroform (5 ml), a solution of the acid chloride (4-Phtalimido propanoyl chloride (0.01 mole) in chloroform (5 ml) was added dropwise at room temperature, with stirring under dry Nitrogen. The mixture was heated and chloroform was evaporated. The temperature was raised to 80°C during an additional period of 8 hours. After cooling the precipitate was washed with Et₂O. The bisphosphonate is redissolved in a large excess of concentrated hydrochloric acid and after a reflux of 20 hours, the corresponding acid is obtained upon standing at room temperature. The acid is purified by recrystallisation in ethanol.

I: yield > 95%; *F*_p ≅ 270° (sublim.). NMR (in D₂O) ³¹P: δ = 20 ppm (t, ³J_{PCH} = 14 Hz); ¹³C: δ C(1) = 75.2 ppm (t, J_{CP} = 153 Hz), C(2) = 30.6 ppm (s), C(3) = 26 ppm (s), C(4) = 38.2 ppm (s); ¹H: δ (-CH₂-CH₂) = 1.2–2.2 ppm (m); δ (-CH₂-N) = 2.8–3.2 (m).

Analysis of C₅H₁₃NO₇P₂ (MAHBBPA = 261):

<i>Calculated %:</i>	<i>C</i> 19.28	<i>H</i> 5.26	<i>N</i> 5.62	<i>O</i> 44.96	<i>P</i> 24.87
<i>Observed %:</i>	<i>C</i> 19.36	<i>H</i> 5.37	<i>N</i> 5.37	<i>O</i> 42.65	<i>P</i> 25.27

Crystallisations

Anhydrous form 1

The crude acid was dehydrated over P₂O₅ in a dessicator under vacuum. Crystals were grown by slow evaporation in dry air of an ethanol solution of the dehydrated acid. The crystals grow as thin colourless plates with dimensions 0.1 × 0.4 × 0.4 mm.

TABLE IV Unit cell parameters and experimental X-ray details.

Compound	1
Formula	C ₄ H ₁₃ NP ₂ O ₇
Space group	P2 ₁ /n
Cell parameters	
a =	10.503(3)
b =	10.952(3)
c =	8.028(2)
β =	98.55(3)
Z/volume =	4/913.18 Å ³
Density calc.(g.cm ⁻³)	1.812
Wavelength	CuKα (λ = 1.5418 Å)
Nb. of Measured reflections	1975
Nb. of unique reflections	1353
Final R values (all refl.):	
R	0,072
Rw (w = 1/σ ² (F))	0,065
RG = (Σw Fo-Fc ² /ΣwFo ²) ^{1/2}	0,070
Empirical Absorption corrections (Min Max) ¹⁴	0.78–1.31
Residuals in last F map (Min Max)	– 0.2; 0.3 e [–]

Hydrated form 2

Crystals are obtained by evaporation from a (1:1) water/ethanol solution at room temperature, over a period of two weeks. Their shapes are elongated rods.

X-ray Determination

X-Ray diffraction intensity data were collected on a Philips PW 1100 diffractometer, operating with the CuKα radiation (λ = 1.5418 Å) and monochromated by graphite. The structure of **1** was solved by direct methods using SHELXS86,^[12] **2** was already described.^[11] The refinements of the two structures were performed with the SHELX93^[13] computer program using anisotropic thermal factors for the non-hydrogen atoms. All hydrogen atoms were located on successive difference-Fourier maps and introduced in the calculations as fixed atoms with an isotropic thermal factor equal to that of the bonded atom. In the last steps of the refinements, hydrogens were let to refine freely. Crystallographic data[†] and final R values are listed in Table IV.

[†]Full lists of crystallographic data for compounds **1** and **2**, including tables of positional parameters, anisotropic thermal parameters, bond distances and angles are deposited with the Cambridge Crystallographic Data Center, 12, Union Road, CB2 1EZ Cambridge, UK. The corresponding cif file can be obtained by e-mail at prange@sgl1sb.univ-paris13.fr

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