Contribution of Neutron Diffraction to the Crystal Structure Determination of 1-Hydroxy-1-Phosphono-Pentyl-Phosphonic Acid Dimethyl Ammonium Salt

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The crystal structure of 1-hydroxy-1-phosphono-pentyl-phosphonic acid dimethylammonium salt has been determined by neutron diffraction measurements on single crystals at room temperature (triclinic, space group P-1, $a = 11.419(23)$ Å, $b = 10.447(18)$ Å, $c = 6.211(9)$ Å, $\alpha = 92.041(2)°$, $\beta = 95.870(3)°$, $\gamma = 110.408(2)°$, $V = 689(2)$ Å^3). Refinements of the structure using 1195 observed structure factors converged to the final $R = 0.068$. Results have put in evidence that acids of the hydroxybisphosphonic family can protonate volatile alkaline species like dimethylamine to give particularly stable crystals. The hydrogen bonds formed by the dimethylammonium cation link columns of hydroxybisphosphonate groups parallel to the [010] direction. The structure is built up by alternated hydrophobic/polar layers parallel to the (100) plane. © 2002 Elsevier Science (USA)

Key Words: bisphosphonates; neutron structure; hydrogen bonds.

INTRODUCTION

The 1-hydroxy-1-phosphono-pentyl-phosphonic acid (p-HBPA) is a member of the hydroxybisphosphonic acid family (HBPA, R–C(OH)(PO$_3$H$_2$)$_2$) which is characterized by the multiple possibilities to form complexes with metal cations and to transport them in biological media (1). Their applications cover a wide field, ranging from their use in bone scintigraphy, extraction of trans actinides in nuclear industry to effective treatments in clinical disorders as osteoporosis and Paget's disease of bone (2–4 and references therein).

Several crystalline structures of these biologically active acids and of their complex salts are known and have been compared in (5). The structures of uncomplexed acids with an extended alkyl amino chain linked to the carbon central atom are zwitterionic species like amino acids. Without the amino function linked to the central carbon, the hydroxybisphosphonic function –C(OH)(PO$_3$H$_2$)$_2$ is a tetra acid with one strong acidity (6). A precedent study of p-HBPA by X-ray diffraction has suggested the presence of dimethyloxonium cations in the crystals (7). This strange hypothesis was based on the super-acid properties of the compound, which would produce a catalytic intermolecular dehydration of methanol used in the last step of the synthesis, leading to the dimethyloxonium cation. Transfer of protons from another phosphonic acid, the 1,6-dihydroxyhexylidene-1,1,6,6-tetra phosphonic acid (DHHTP), to a water molecule has already been observed in solid state giving (DHHTP)$^{2-}$ and oxonium ions (8).

The X-ray diffraction study on single crystals of hydroxyethylidene bisphosphonic acid (HEBP), obtained from a solution containing dimethylamine, has shown the presence of dimethylammonium cation in the crystals (9). As the crystals of p-(HBPA) were obtained in a dimethylamine atmosphere, we have performed a neutron diffraction study in order to determine the nature of the cation in these crystals : dimethyloxonium or dimethylammonium cation.

The combination of the anion formation from –C(OH)(PO$_3$H$_2$)$_2$ and the ability of this anion to act as both hydrogen-bond donor and hydrogen-bond acceptor leads to the formation of a rich diversity of strong ionic hydrogen bonds. To solve some ambiguities arising from H-positions obtained from X-ray diffraction, these interesting hydrogen bond systems must be determined with precision by neutron diffraction. Only two structures of the HBPA family were solved by this technique (5).

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EXPERIMENTAL

Crystallization

The p-HBPA was obtained following the synthesis method already reported in (7). A new synthesis process for the hydroxybisphosphonic family has been recently published (10). Slow evaporation of a p-HBPA saturated ethanolic solution conducts only to an oily product. In presence of a separate dimethylamine aqueous solution (30%) and under controlled ambient conditions, large single crystals grow spontaneously.

Data Collection, Structure Solution, and Refinement

A complete neutron diffraction data set was collected at room temperature (298 K) using the four-circle diffract-

TABLE 1
Crystal Data, Data Collection, and Refinement Conditions

Crystal data	
Chemical formula	$C_7H_{21}NO_7P_2$
F_{000}	586
D_c (g cm^{-3})	1.417
Crystal system	triclinic
Space group	*P*-1
a (Å)	11.419(23)
b (v)	10.447(18)
c (Å)	6.211(9)
α (°)	92.041(2)
β (°)	95.870(3)
γ (°)	110.408(2)
V (Å^3)	689(2)
No. of reflections for lattice parameters	28 ($18 < 2\theta < 52°$)
Radiation	Orphée reactor, CEN Saclay
Wavelength (λ Å)	1.540(5), $\lambda/2$ contamination $< 10^{-3}$
Absorption coefficient (μ cm^{-1})	4.7 (calculated)
Temperature (K)	293(2)
Crystal color	Colorless
Crystal size (mm)	$3.5 \times 2.0 \times 2.0$
Crystal description (average zone faces)	$\langle 161 \rangle$, $\langle 01-3 \rangle$ and $\langle 3-10 \rangle$
Data collection	
Diffractometer	Four-circle diffractometer (6T2 channel)
Data collection range and scan mode	ω-scan for $2 < 2\theta < 50°$, ω/θ-scan for $50 < 2\theta < 80°$, $\omega/2\theta$-scan for $80 < 2\theta < 120°$, (41 steps, 2–6 s step^{-1} for $2 < 2\theta < 50°$, 4 s step^{-1} for $80 < 2\theta < 120°$) adjusted as a function of the scattering angle to match the instrument resolution $6-8 \, \text{tg} \, \theta + 18 \, \text{tg}^2 \theta$
Index range	$-12 < h < 12 \ -10 < k < 11 \ -6 < l < 6$
No. of reflections measured	2436
R_{int}	0.016
No. of independent reflections	1520
No. of reflections with $F_0 > 2\sigma(F_0)$	1195
Standard reflections, variation	(1−32) and (0−32), all the 100 measures, constant during data collection period: 7 days
Absorption correction type	numerical methods using crystal shape
Transmission factors (T_{min}, T_{max})	0.2251 0.4905
Refinement	
Refinement method	Full matrix least squares on F^2
No. of parameters refined	239
Weighting scheme	$\omega = 1/\sigma^2 \, (F^2)$
R for all and observed reflections, $R\omega$	0.089 0.068 0.085
Goodness of fit, all and observed reflections	3.998 4.591
Maxima and minima of the final Fourier map (% of the peak height of a removed oxygen atom used as a reference)	7.7 −8.6
Extinction correction method	SHELXL
Extinction coefficient	0.0198(9)
Sources of atomic scattering factors	Int. tab. of crystallography (11)

TABLE 2
Final Fractional Atomic Coordinates and Equivalent Isotropic Displacement Parameters ($U_{eq} = \frac{1}{3}\sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i \mathbf{a}_j$ Å^2) with Estimated Standard Deviations in Parentheses

| Atom	x	y	z	U_{eq}
P(1)	0.3824(5)	0.0809(5)	0.1519(7)	0.0283(13)
P(2)	0.5380(4)	0.3218(5)	−0.0697(8)	0.0287(13)
O(11)	0.5110(4)	0.0838(5)	0.2379(7)	0.0345(12)
O(12)	0.2877(4)	−0.0670(5)	0.0874(7)	0.0343(12)
O(13)	0.3235(5)	0.1492(5)	0.3177(9)	0.0374(13)
H(12)	0.3227(8)	−0.1426(9)	0.0905(12)	0.0434(21)
H(13)	0.3445(8)	0.1351(8)	0.4641(16)	0.0426(22)
O(21)	0.6390(4)	0.2663(5)	−0.1279(7)	0.0363(13)
O(22)	0.5616(4)	0.3980(5)	0.1482(7)	0.0349(12)
O(23)	0.5230(4)	0.4146(5)	−0.2576(7)	0.0336(12)
H(23)	0.4918(8)	0.4886(9)	−0.2186(12)	0.0429(20)
O(1)	0.3748(4)	0.0917(5)	−0.2836(6)	0.0292(12)
H(1)	0.4292(8)	0.0354(9)	−0.2637(12)	0.0427(21)
C(1)	0.3850(3)	0.1772(4)	−0.0927(6)	0.0252(10)
C(2)	0.2761(4)	0.2339(4)	−0.1228(7)	0.0287(11)
H(21)	0.2854(8)	0.3036(10)	0.0135(15)	0.0525(25)
H(22)	0.2873(8)	0.2878(9)	−0.2632(15)	0.0477(22)
C(3)	0.1434(4)	0.1214(5)	−0.1470(9)	0.0432(13)
H(31)	0.1407(10)	0.0435(13)	−0.2737(18)	0.0798(33)
H(32)	0.1281(10)	0.0745(11)	−0.0020(17)	0.0708(30)
C(4)	0.0396(4)	0.1763(5)	−0.2188(7)	0.0455(13)
H(41)	−0.0492(12)	0.0954(12)	−0.2474(16)	0.0780(32)
H(42)	0.0583(10)	0.2243(11)	−0.3699(18)	0.0720(29)
C(5)	0.0282(5)	0.2807(7)	−0.0529(9)	0.0636(16)
H(51)	−0.0468(16)	0.3098(15)	−0.0973(21)	0.1151(46)
H(52)	0.1135(16)	0.3721(16)	−0.0280(22)	0.1123(44)
H(53)	0.0185(16)	0.2359(17)	0.1019(30)	0.1388(57)
C(1)s	0.7958(5)	0.2693(6)	0.4047(8)	0.0492(13)
H (11)s	0.8728(15)	0.2847(14)	0.5184(22)	0.1049(41)
H(12)s	0.7436(17)	0.1693(20)	0.3655(25)	0.1305(59)
H(13)s	0.8300(15)	0.3090(16)	0.2573(27)	0.1310(55)
C(2)s	0.7890(5)	0.4914(5)	0.5270(10)	0.0551(14)
H(21)s	0.8666(16)	0.5071(15)	0.6514(23)	0.1164(47)
H(22)s	0.8266(15)	0.5343(16)	0.3904(25)	0.1204(49)
H(23)s	0.7270(14)	0.5406(15)	0.5732(21)	0.1091(43)
Ns	0.7176(3)	0.3459(3)	0.4767(6)	0.0353(9)
H(1)s	0.6814(9)	0.3071(10)	0.6087(16)	0.0555(26)
H(2)s	0.6467(10)	0.3357(10)	0.3558(16)	0.0599(26)
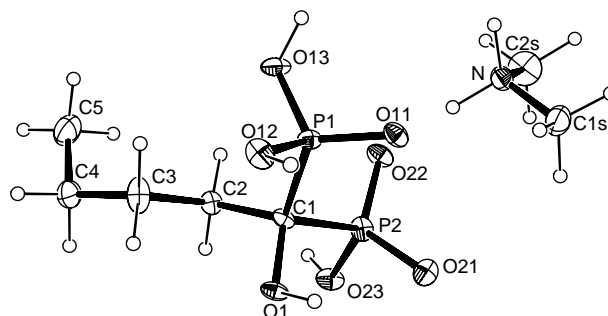
FIG. 1. Atomic labeling scheme for *p*-HBPA crystal (thermal ellipsoids at 30% probability)

ometer (6T2 channel) at the Orphée reactor of CEN Saclay. Other details concerning the crystal data, data collection and refinement conditions are given in Table 1.

Hydrogen atoms of the "unknown cation" were located from difference Fourier maps phased with positions and isotropic thermal parameters of the other atoms corresponding to the X-ray model refined using the neutron diffraction data. Attempts to refine the dimethyloxonium cation ($[(H_3C)OH(CH_3)]^+$) with the X-ray model proposed in (7) (hydroxide hydrogen splitted in two positions with a site occupation factor of 0.5) failed. Residuals peaks in difference Fourier maps suggested to increase the hydrogen occupation factor and to replace the oxygen by another atom having a higher scattering length ($b_O = 5.803$ fm, $b_{N=} 9.360$ fm). Refinements with a dimethylammonium cation ($[(H_3C)NH_2(CH_3)]^+$) were successful. All atoms, except hydrogen, were refined anisotropically. There is no orientation or occupation disorder in the structure.

Structure refinement was performed with the SHELXL93 program (12) on a Hewlett Packard Vectra VA PC. Final atomic parameters are presented in Table 2. Diagrams were prepared using ORTEP3 for Windows (13).
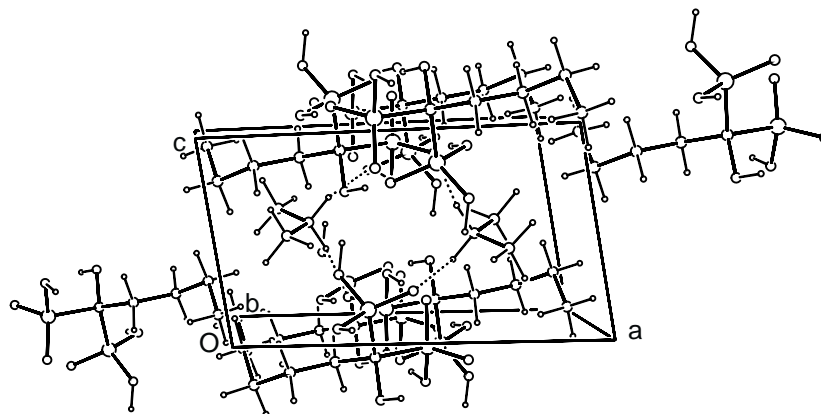

FIG. 2. Packing of *p*-HBPA crystal structure. Dotted lines indicate H-bonds concerning the dimethylammonium cation.

RESULTS AND DISCUSSION

As most of hydroxybisphosphonate compounds, *p*-HBPA crystallizes in a centrosymmetric space group of low symmetry (*P*-1). The asymmetric unit with numbering scheme and the packing of the crystal are depicted in, respectively, Figs. 1 and 2. In order to compare the structures obtained by X-ray and neutron diffraction, Table 3a presents selected bond distances and angles resulting from both structure determinations. No significative differences are observed between these values.

Hydrogen Bond Network and Packing

No hydrogen atom has appeared in disordered position. As usually found, the distances C–H, N–H and O–H (average CH in CH_3 and $CH_{2=}1.057$ and $1.068\,\text{Å}$, respectively, NH $= 1.014\,\text{Å}$ and OH $= 0.982\,\text{Å}$) are systematically longer than the corresponding distances used in X-ray riding refinements (0.96, 0.97, 0.89 and $0.82\,\text{Å}$, respectively). It can be seen that for H(1)s and H(2)s there is only one H-bond with the characteristic directionality; the other contacts (Table 3b) cannot be considered as weak

TABLE 3
Selected Bond Distances (Å), Bond Angles (°), and Torsion Angles (°) without Correction for Thermal Motion According to the Riding Model

(a) *Concerning the p-HBPA anion and the dimethylammonium cation in* **I** *(neutron model) and in* **II** *(X-ray model proposed in (7))*

$A_1 - A_2$	Distance (I)	Distance (II)	$A_1 - A_2$	Distance (I)	Distance (II)
P(1)–O(11)	1.500(7)	1.485(3)	P(2)–O(21)	1.528(7)	1.501(3)
P(1)–O(12)	1.556(7)	1.548(3)	P(2)–O(22)	1.495(7)	1.508(3)
P(1)–O(13)	1.564(7)	1.556(3)	P(2)–O(23)	1.577(7)	1.575(3)
P(1)–C(1)	1.848(6)	1.852(3)	P(2)–C(1)	1.857(7)	1.849(4)
O(1)–C(1)	1.429(6)	1.441(5)	C(1)–C(2)	1.551(6)	1.524(5)
C(2)–C(3)	1.545(6)	1.522(6)	C(3)–C(4)	1.528(6)	1.520(6)
C(4)–C(5)	1.522(7)	1.509(8)	Ns–C(1)s	1.481(6)	1.478(6)
Ns–C(2)s	1.457(6)	1.456(7)			

$A_1 - A_2 - A_3$	Angle (I)	Angle (II)	$A_1 - A_2 - A_3$	Angle (I)	Angle (II)
O(13)–P(1)–O(11)	112.7(4)	113.6(2)	O(23)–P(2)–O(21)	105.5(4)	105.9(2)
O(13)–P(1)–O(12)	107.4(4)	106.6(2)	O(23)–P(2)–O(22)	111.3(4)	111.3(2)
O(11)–P(1)–O(12)	112.6(4)	113.4(2)	O(21)–P(2)–O(22)	116.4(4)	116.4(2)
O(11)–P(1)–C(1)	112.1(4)	112.2(2)	O(21)–P(2)–C(1)	108.6(4)	109.5(2)
O(12)–P(1)–C(1)	106.6(3)	106.7(2)	O(22)–P(2)–C(1)	109.3(3)	108.0(2)
O(13)–P(1)–C(1)	104.9(4)	103.6(2)	O(23)–P(2)–C(1)	105.2(3)	105.3(2)
O(1)–C(1)–P(1)	110.6(3)	109.9(2)	O(1)–C(1)–P(2)	108.4(3)	107.8(2)
C(2)–C(1)–P(1)	113.0(3)	112.8(2)	C(2)–C(1)–P(2)	109.3(3)	111.1(3)
O(1)–C(1)–C(2)	107.3(3)	106.5(3)	C(1)–C(2)–C(3)	113.5(4)	115.8(3)
C(2)–C(3)–C(4)	112.5(4)	113.2(3)	C(3)–C(4)–C(5)	113.2(4)	113.7(4)
C(1)s–Ns–C(2)s	112.7(4)	113.5(4)			

(b) *Concerning the hydrogen atoms*

$D-H\ldots A$	Distance ($D-H$)	Distance ($H\ldots A$)	Distance ($D\ldots A$)	Angle ($D-H-A$)
O(12)–H(12)...O(21)[(i)]	1.002(13)	1.519(11)	2.511(7)	169.6(8)
O(13)–H(13)...O(1)[(ii)]	0.946(14)	1.682(11)	2.625(8)	173.8(8)
O(23)–H(23)...O(22)[(iii)]	0.989(13)	1.578(10)	2.567(7)	177.3(8)
O(1)–H(1)...O(11)[(i)]	0.996(12)	1.622(11)	2.603(7)	167.6(8)
Ns–H(1)s...O(21)[(ii)]	0.991(14)	1.778(12)	2.758(7)	169.0(9)
Ns–H(1)s...O(23)[(ii)]	0.991(14)	2.624(11)	3.155(7)	113.7(8)
Ns–H(2)s...O(22)	1.020(13)	1.809(12)	2.764(6)	154.4(9)
Ns–H(2)s...O(11)	1.020(13)	2.579(12)	3.123(7)	113.1(8)

$A_1 A_2 A_3 A_4$	Torsion angle
P(2)–C(1)–C(2)–C(3)	179.2(4)
C(1)–C(2)–C(3)–C(4)	−169.2(4)
C(2)–C(3)–C(4)–C(5)	−64.2(6)

Symmetry codes: (i) $-x + 1 - y, -z$; (ii) $x, y, z + 1$; (iii) $-x + 1, -y + 1, -z$.

H-bond as the X-ray study had suggested (7). The oxygen atom of the hydroxide group is both donor and acceptor of H-bonds. All other H-bonds are provided by the remaining hydrogen atoms of the phosphonate groups –PO$_3$ and of the nitrogen of the ammonium cation. The short donor–acceptor distances clearly indicate the strength of these bonds.

The hydroxybisphosphonate groups, related by the crystallographic center of symmetry and linked by H-bonds, are piled along the [010] direction, forming polar columns at $x = 0.5$. The H-bonds formed by the dimethylammonium cation connect these chains in the [001] direction. Hydrophobic interactions between alkyl chains and methyl groups of dimethylammonium cations contribute to hold the packing in the [100] direction. The packing of the structure can be described as formed by alternated hydrophobic and polar layers parallel to the (100) plane.

Molecular Structure of P-hydroxybisphosphonate Anion

The distance P–OH of the –PO$_3$ ionized group is smaller than those corresponding to the non-ionized group. The bond distances C–OH, P=O, P–O$^-$ and P–OH as well as the P–C–P angle agree well with the average of the analogous of bisphosphonated acids and their complex salts (5). The relative displacement between the two –PO$_3$ groups, measured by the pseudo-torsion angles (O11-P1/P2-O21 (39.9(2)), O13-P1/P2-O22 (35.4(1)) and O12-P1/P2-O23(52.6(1)), indicates that in the crystals of *p*-HBPA the hydroxybisphosphonate group presents a staggered configuration. This configuration is not usual (5), but is also observed in the crystals of HEBP (9).

The torsion angles (Table 3c) show that the alkyl chain only has an extended conformation from P(2) to C(4). The bending observed in the extremity of the chain is necessary to increase the hydrophobic interactions in the packing.

Molecular Structure of Dimethylammonium Cation

Structural values are compatible with those of the cation in the HEBP structure (9). In both structures, nitrogen is donor to two different oxygen atoms O-P, the H-bonds formed by the cation being of the same strength.

CONCLUDING COMMENTS

This neutron study has proved beyond doubt that the cation in crystals of *p*-HBPA is dimethylammonium. The presence of this cation, which has not been used as solvent in crystallizations, puts in evidence that the HBPA can trap and stabilize cationic species derived from volatile alkaline compounds like dimethylamine to give particularly stable crystals. As a consequence of the present study, the *p*-HBPA X-ray model could be correctly refined (14).

All hydrogen positions were determined. There is no disorder in the investigated *p*-HBPA crystals. Despite the contacts observed to H(1)s and H(2)s, the differences observed in bond lengths and angles prevent the classification of hydrogen bonds as bifurcated ones.

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