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Yves Leroux[a]; Alain Neuman[a]; Hélène Gillier[a]; Driss El Manouni[a]; Zahra Abkhar[a]; Thierry Prangé[a]
[a] Laboratoire de Chimie Structurale Biomoléculaire (URA 1430 CNRS) 74, Bobigny Cedex, FRANCE

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Supramolecular assembly of substituted hydroxy-bisphosphonates with cupric ion. Influence of the chain functionalization

YVES LEROUX*, ALAIN NEUMAN, HÉLÈNE GILLIER, DRISS EL MANOUNI, ZAHRA ABKHAR and THIERRY PRANGÉ

Laboratoire de Chimie Structurale Biomoléculaire (URA 1430 CNRS) 74, rue Marcel Cachin 93012 Bobigny Cedex, FRANCE

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As part of a general study of hydroxy-bisphosphonic acids (HEBP), R-C(OH)($PO_3H)_2$, three Cu (II) complexes with R=CH_3; R=-$(CH_2)_3$-NH_2 and R=-$(CH_2)_5$-NH_2, were prepared and analysed by X-Ray diffraction methods. The substitution of the methyl group in HEBP (3) by an aminopropyl (1) or by an aminopentyl (2) chain led to a drastic modification of the ionic self-assembly in the crystal and completely different polyhedral complexation networks around the Cu (II). A polymeric chain formation is observed in (3), whereas (1) and (2) display discrete tetrameric and dimeric arrangements. The results are discussed on the basis of the environment of the phosphorus atoms and the molecular geometry around the central carbon atom of the hydroxy-bisphosphonic moiety. These results are further compared to their ability for ionic transport and/or extraction.

INTRODUCTION

Bisphosphonates are part of a new class of drugs which have been developed in the past twenty years and more particularly for the treatment and investigation of various pathologies in bone, tooth and calcium metabolism.

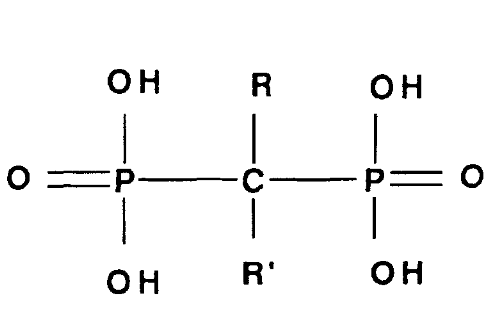
Several bisphosphonates (scheme) have been investigated in humans. Some of them are commercially developed, e.g. HEBP : 4 (1-hydroxyethylidene-1, 1-bisphosphonic acid), Cl2MDP 5 : (dichloromethylene-1,1 bisphosphonic acid), AHPrBP : 6 (3-amino 1-hydroxypropylidene-1,1 bisphosphonic acid), AHBuBP : 7 (4-amino 1-hydroxybutylidene-1,1 bisphosphonic acid) and AHHexBP : 8 (6-amino 1-hydroxyhexylidene-1,1 bisphosphonic acid).

Bisphosphonates are compounds characterised by two P-C bonds. Their appropriate name would be geminal bisphosphonates as the two P-C bonds are located on the same quaternary carbon atom. These molecules are analogs of pyrophosphates.

The basic structure P-C-P allows a great number of chemical variations, either by changing the two lateral chains on the central carbon atoms or by esterifying the phosphonic groups. A large number of bisphosphonates have been synthesised and were all considered as putative drugs in clinical tests. As indicated previously, some of them led to promising pharmaceutical developments. From these studies it has emerged that each bisphosphonate has its own characteristics, but structure-activity relationships showed that it is not possible to extrapolate a given biochemical behaviour from a compound to another.

From the chemical and biological point of view, the P-C-P bond of the acidic form of bisphosphonates has a relatively low toxicity and possess a high thermostability. Most of the chemical reagents bearing this motif are highly resistant to enzymatic degradation.

In addition to these biochemical properties, the bisphosphonic acids have a strong affinity for metal ions like calcium, magnesium, uranium and especially iron. HEBP/^{99m}Tc is a major tool for scintigraphy investigation in bone cancer imaging. The high affinity of these compounds results from the mobility of the two neigh-



4 : R = CH_3, R' = OH; 5 : R = R' = Cl; 6 : R = -$(CH_2)_2$-NH_2, R' = OH
7 : R = -$(CH_2)_3$-NH_2, R' = OH; 8 : R = -$(CH_2)_5$-NH_2, R' = OH

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*To whom correspondence should be addressed.

bouring phosphonate groups that can reorient to accommodate a large number of ionic radii.

The present study deals with their solid state to determine the effects induced by the modifications of the lateral chains on their supra-molecular associations. We report that the effect of the methyl replacement by an aminopropyl or an aminopentyl chain, led to a drastic modification of the ionic structures in the presence of cupric ions.

To our knowledge this is the first example giving direct insight into functionalization effects in the central molecular chain of bisphosphonic complexes.

EXPERIMENTAL SECTION

Synthesis of AHBuBP 7 and AHHexBP 8

These two compounds were prepared following the same procedure: To a mixture of trimethylphosphite (0.01 mol) and dimethylphosphite (0.01 mol) in chloroform (5 mL), a solution of the acid chloride (4-Phtalimido butanoyl chloride (0.01 mol) for AH Bu BP and 6-Phtalimido hexanoyl chloride for AH Hex BP) in chloroform (5 mL) was added dropwise at room temperature, with stirring under dry Nitrogen. The mixture was heated and chloroform was evaporate. Temperature was raised up to 80°C during an additional period of 8 hours. After cooling the precipitate was washed with Et_2O. The bisphosphonate is re dissolved 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 two acids are purified by recrystallisation in ethanol.

7: yield > 95%; Fp≅270° (sublim.) . NMR (in D_2O) ^{31}P:δ=20 ppm (t,$^3J_{PCCH}$=14 Hz); ^{13}C: 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 ($-CH_2-CH_2$) = 1.2-2.2 ppm (m); δ (-CH2-N) = 2.8-3.2 (m).

Analyses (obs/calc %): C: (19.36/19.28); H: (5.37/5.26); N: (5.37/5.62); O: (42.65/44.96); P: (25.27/24.87).

8: yield > 95%; Fp≅275° (sublim.) . NMR (in D_2O) ^{31}P: δ =20.01 ppm (t,$^3J_{PCCH}$=14 Hz); ^{13}C: δ C(1) = 75.0 ppm (t, J_{CP}=150 Hz), δC(2)=30.5 ppm (s), δC(3) = 24.7 ppm (s), δC(4) = 28.4 ppm (s); δC(5) = 35.0 ppm (s); δC(6) = 40.0 ppm (s); ^1H: δ ($-CH_2-CH_2)_4-$) = 1.0 - 2.5 ppm (m); δ ($-CH_2-N$) = 2.7-3.0 ppm (m).

Analyses (obs/calc %): C: (25.91/25.99); H: (6.34/6.18); N: (4.94/5.05); O: (40.89/40.84); P: (22.38/22.35).

Preparation of the Cu(II) crystal complexes 1 to 3:

To a solution of the corresponding acid (0.1 mol) in water (20 mL), a suspension of $CuCO_3$ (0.05 mol) in water (10 mL) was added dropwise. The mixture was then heated at 70°C during 4 hours and filtered. Steel-blue single crystals of complexes 1 and 2 were obtained by slow evaporation of the filtrates at room temperature over a period of several days. In all cases, yields are nearly quantitative.

X-Ray Data

The crystal structure of 3 has been described elsewhere[4].

The fresh crystals of the Cu(II) complexes 1 and 2 decompose slowly upon standing at air (dehydration). They were sealed in thin-wall glass capillaries. 2 gives very small crystals with a rather poor diffraction power. X-Ray diffraction intensity data were collected on a Philips PW 1100 diffractometer. The structures were solved by direct methods using DEVIN[5] for 1, and SHELXS86[6] for 2. The refinements were performed with the SHELX76[7] computer program. Crystallographic data* and final R values are listed in Table 1.

RESULTS AND DISCUSSION

The stoichiometries of the HEBP's Cu(II) salts were directly assigned from the X-ray analyses. The formation of 1

$$[(Cu^{2+})_2\ \{C((CH_2)_3\ NH_3^+)\ (OH)\ (PO_3H^-)_2\}_4.\ 2H_2O],\ 2H_2O$$

shows that two Cu^{2+} cations are connected through a centre of symmetry. They are associated *via* ionic coordination to four aminobutane-hydroxybisphosphonate anions and coordinated toward two additional water

Table 1 Unit cell parameters and experimental details

Compound	*1*	*2*
Formula	$Cu(P_2O_7NC_4H_{12})_2.2H_2O$	$Cu_{0,5}P_2O_7NC_6H_{16}.2H_2O$
Space group	$P2_1/c$	$P2_1/c$
Cell parameters		
a	12.622(4)	7.396(3)
b	13.524(4)	13.189(3)
c	12.521(3)	13.822(3)
β	110.82(6)	102.89(5)
Z	4	4
Density calc ($g.cm^{-3}$)	1.98	1.739
Wavelength	CuKα	CuKα
Number of reflections		
Measured	7642	4641
Unique	3655	2231
Used in refinements	3031	1796
Final R values		
R	0.077	0.105
Rw ($w=1/\sigma^2(F)$)	0.069	0.086
RG $=(\Sigma w\lvert Fo-Fc\rvert^2/\Sigma wFo^2)^{1/2}$	0.074	0.077

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*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. They can be obtained by e-mail from one of us at prange@lure.u-psud.fr molecules, implicated in the general packing framework (Fig. 1). The overall formula given above points out that the self-assembly can be described as a tetramer.

Similar arrangements occur in compound 2: discrete molecular units are also observed. The main difference resides in the Cu^{2+} cation which is now co-ordinated to two aminohexane-bisphosphonate cations and two water molecules, centrosymmetrically related. In 2 the formula of the complex becomes

2 $[Cu^{2+} \{C((CH_2)_5 NH_3{+}) (OH) (PO_3H^-)_2\}_2 . 2H_2O],$
$2H_2O$

(The previously observed tetrameric structure, simplifies as a dimer.)

In contrast to these two complexes, the structure of the HEBP/Cu(II) salt 3 does not show such arrangements of discrete base motifs, but a polymeric association through hydrogen bond network and direct O...Cu(II) coordinations[4]. The chemical formula was established as:

3 $Cu_3^{2+} ((C(CH_3) (OH) (PO_3^{2-}) (PO_3H^-))_2 . 6\ H_2O$

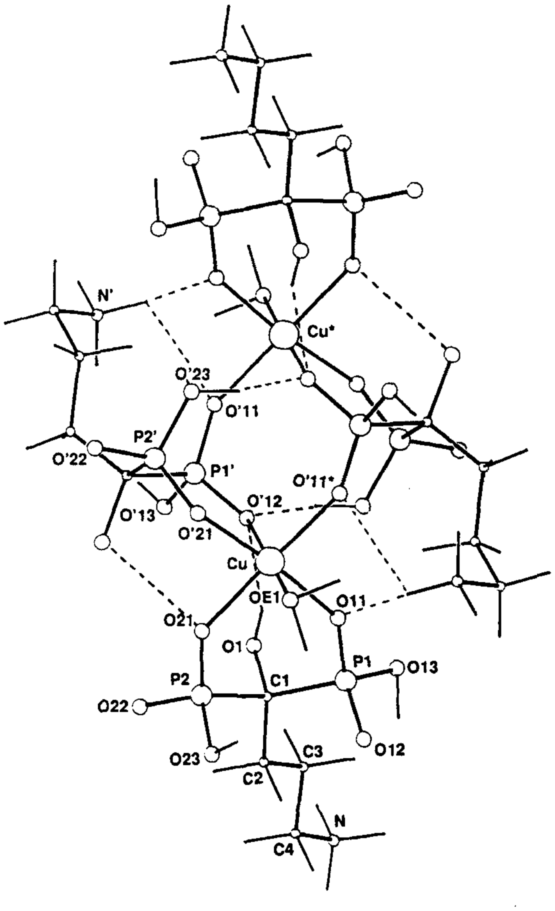

Figure 1 *ORTEP[8] representation of the Copper (II) 1-hydroxy 4-amino 1,1'-butane-bisphosphonate (1).*

In the two former structures, the Cu^{2+} cation is in the centre of an oxygen atom octahedron stretched toward one of its axis by Jahn Teller effect as shown in Table **2**. The Cu^{2+} cations lies in the base plane, rigorously for 2 but only approximately in compound 1. For these two complexes, the above mentioned axis is orthogonal to the base plane however, in compound 1, several base plane bond angles deviate more than 9° away from the ideal value of 90°.

The relevant phosphorus-oxygen bonds are reported in Table **3**.

For each phosphonate group there are two classes of bond lengths: (1) a short P-O distance, characteristic of a P=O bond, or of a single $P\text{-}O^-$ bond, (it is usually not possible to distinguish owing to the electronic delocalisation between the two oxygens); (2) a long P - O (H) bond length, relevant of a localised, non ionised, single bond.

These bond distances are in agreement with the corresponding known average values recalculated in Table **3**. The mean values for phosphorus bond angle (Table **3**) are in agreement with those from literature[1,3,4]. The high value observed for the $O = P\text{-}O^-$ angle points out the mutual repulsion of the two strongly negative oxygen atoms.

One of the relevant parameter describing the hydroxy-bisphosphonic group geometry is the dihedral angle of the average displacement of the two phosphonates groups with respect one to the other along the visual axis P(2)...P(1) (Table **4**). In the corresponding free acids[1,2] an important staggering of 27 to 44° is always observed that was previously assigned to the capacity of these strongly acid molecules to adapt to crystal field effects. In the Cu(II) salts, the reduction of the staggering is mainly due to the strong Cu-O interactions (Fig. 1 and 2). In molecule **1A** and in molecule 2, two oxygen atoms are bonded to two different phosphorus atom both coordinated to the same Cu^{2+} cation, holding in that way the two phosphonate groups in a non-staggered symmetric orientation. In **1B**, an additional interaction occurs between an oxygen atom of a phosphonate group and the second Cu^{2+} cation of the "tetramer". This type of coordination not only disturbs the symmetry of the tetramer, but also tends to distort the double coordination. Consequently, a significant shift, however limited to a mean dihedral angle of 13.4°, is observed.

The valence bond angle P(1)-C(1)-P(2) is the second characteristic parameter describing the stability of the hydroxy-bisphosphonic group. It confirms through its fluctuations the relative flexibility of this group around the central carbon atom. In structure 1, a difference of 3° is observed between the two hydroxybisphosphonates symmetrically independent (Table **3**). The carbon chains that are linked to the central C(1) also display a great flexibility. The conformation around the first bond C(1)-C(2) en-

Table 2 The Cu^{2+} octahedral coordination in the complexes 1 and 2

Compound	*1*		*2*	
Base plane	**O(11) O(21) O′(11) O′(2)** *(max.out of plane distance 0.04 Å)*		**O(12) O(21) O(12)* O(21))*** *(exactly defined))*	
Bond lengths (Å)	Cu-O(11)	1.960(5)	Cu-O(11)	1.982(7)
	Cu-O(21)	2.051(5)	Cu-O(21)	1.963(6)
	Cu-O′(11)	2.021(6)		
	Cu-O′(21)*	1.935(6)		
Bond angles (°)	O(11)-Cu-O(21)	90.1(2)	O(11)-Cu-O(21)	93.3(3)
	O(21)-Cu-O′(21)*	83.9(2)		
	O'(21)*-Cu-O′(11)	98.9(2)		
	O'(11)-Cu-O(11)	87.2(2)		
	O(11)-Cu-O′(21)*	173.8(2)		
	O(21)-Cu-O′(11)	176.0(2)		
Axis	**OE1 Cu O′12***		**OE1 Cu OE1***	
Bond lengths (Å)				
	Cu-O′(12)*	2.393(6)	Cu-O(E1)	2.397(7)
	Cu-O(E1)	2.295(7)		
Bond angles	O′(12)*-Cu-O(11)	92.0(2)	O(E1)-Cu-O(11)	90.7(3)
	O′(12)*-Cu-O(21)	87.6(2)	O(E1)-Cu-O(21)	94.0(3)
	O′(12)*-Cu-O′(21)*	89.5(2)		
	O′(12)*-Cu-O′(11)	89.5(2)		
	O(E1)-Cu-O(11)	90.2(2)		
	O(E1)-Cu-O(21)	92.5(2)		
	O(E1)-Cu-O′(21)*	88.3(2)		
	O(E1)-Cu-O′(11)	90.5(2)		
	O′(12)*-Cu-O(E1)	177.8(2)		

*symmetry related atom (1−x, −y, −z)

Table 3 Bond lengths (Å) for 1 (two molecules: **A** and **B** of the asymmetric unit) and for 2 (together with the mean values derived from published data[3] of bisphosphonic acids and bisphosphonates)

Compound	*1*		*2*
	A	**B**	
P(1)-O(11)	1.498 (6)	1.504 (6)	1.477(7)
P(1)-O(12)	1.506 (6)	1.502 (6)	1.500(7)
P(1)-O(13)	1.560 (5)	1.537 (6)	1.569(6)
P(2)-O(21)	1.508 (6)	1.503 (6)	1.498(7)
P(2)-O(22)	1.502 (6)	1.503 (6)	1.517(7)
P(2)-O(23)	1.571 (6)	1.560 (6)	1.569(7)
P(1)-C(1)	1.848 (7)	1.855 (8)	1.841(9)
P(2)-C(1)	1.837 (7)	1.838 (9)	1.849(9)
C(2)-C(3)	1.525 (11)	1.570 (13)	1.493(16)
O(1)-C1)	1.432 (9)	1.465 (10)	1.438(10)
C(1)-C2)	1.536 (11)	1.532 (12)	1.546(13)
C(3)-C4)	1.507 (11)	1.500 (14)	1.540(16)
C(4)-N	1.496 (10)	1.562 (15)	-
C(4)-C(5)			1.489(16)
C(5)-C(6)			1.466(16)
C(6)-N			1.510(14)
P(1)-C(1)-P(2)*	110.0(4)°	113.5(4)°	110.2(5)°

Bonds averages

	This work	published data	
P=O ou P-O-	1.498	1.504	(52 values)
P-O(H)	1.561	1.557	(34 values)
P-C	1.845	1.838	(32 values)

Phosphonate group bond angles mean values (this work)

O=P-O$^-$	O=P-O(H) O$^-$-P-O(H)	O=P-C(1) O$^-$-P-C(1)	(H)O-P-C(1)
114.9	109.0	108.4	106.6°

*The corresponding values in the free acids are: 110.0; 112.1 and 108.6°, respectively.

force C(3) in an approximate *trans* position with respect to one phosphorus atom. In the case of molecule 1A and 2 the dihedrals around P(1)-C(1)-C(2)-C(3) are 164.9 (7) and 156 (1)°, respectively, while in 1B this is the C(3) atom which is almost *trans* with respect to the oxygen atom 0(1). The chain is fully extended for the molecule 1A whereas 1B displays a *quasi-gauche* conformation at C(3) with an angle C(1)-C(2-)C(3)-C(4) = 141 (1)° and a

Table 4 Dihedral angles (°)

Molecule	*1*	*2*
O(11)-P(1)-O(12)	107.0 (3)	116.1 (3)
O(11)-P(1)-O(13)	114.5 (3)	111.1 (3)
O(11)-P(1)-C(1)	107.6 (3)	111.8 (3)
O(12)-P(1)-O(13)	110.9 (3)	106.0 (3)
O(12)-P(1)-C(1)	106.9 (3)	107.2 (3)
O(13)-P(1)-C(1)	109.5 (3)	103.6 (3)
O(21)-P(2)-O(22)	113.7 (3)	114.8 (3)
O(21)-P(2)-O23	110.6 (3)	111.5 (3)
O(21)-P(2)-C(1)	109.0 (3)	107.5 (4)
O(22)-P(2)-O23	108.9 (3)	106.3 (3)
O(22)-P(2)-C(1)	106.5 (3)	108.4 (4)
O23-P(2)-C(1)	107.8 (3)	108.0 (3)
P(1)-C(1)-O(1)	109.4 (5)	106.5 (5)
P(1)-C(1)-C(2)	115.1 (5)	111.8 (6)
P(2)-C(1)-O(1)	106.6 (5)	106.4 (5)
P(2)-C(1)-C(2)	107.6 (5)	111.6 (6)
O(1)-C(1)-C(2)	107.7 (6)	106.5 (6)
C(1)-C(2)-C(3)	116.6 (6)	115.3 (7)
C(2)-C(3)-C(4)	109.9 (6)	115.0 (8)
C(3)-C(4)-N	111.6 (6)	109.4 (9)
P(1)-C(1)-P(2)	110.0 (4)	113.5 (4)

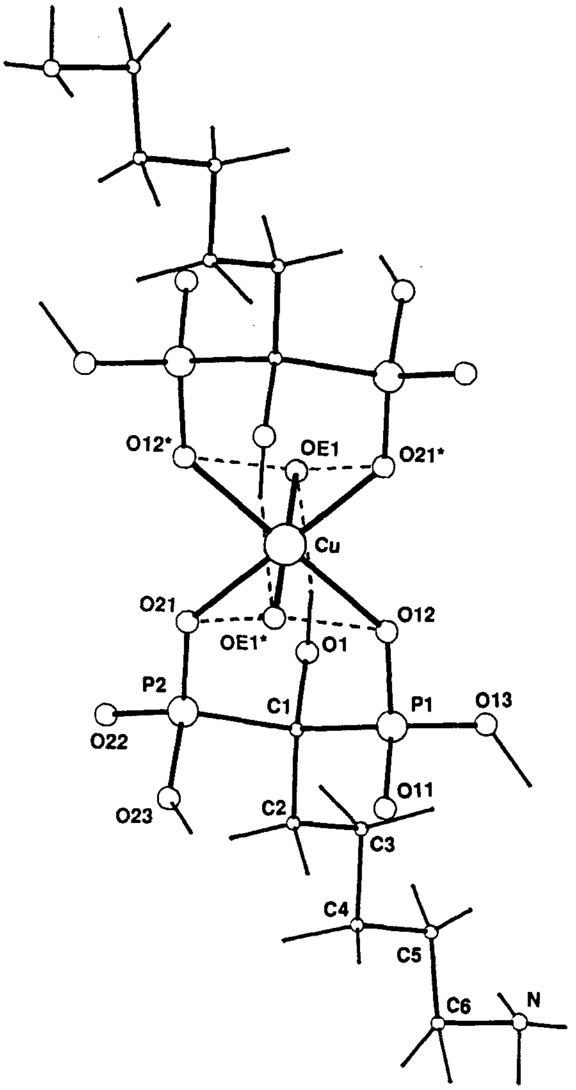

Figure 2 ORTEP[8] representation of Copper (II) 1-hydroxy 6-amino 1,1'-hexane-bisphosphonate (2).

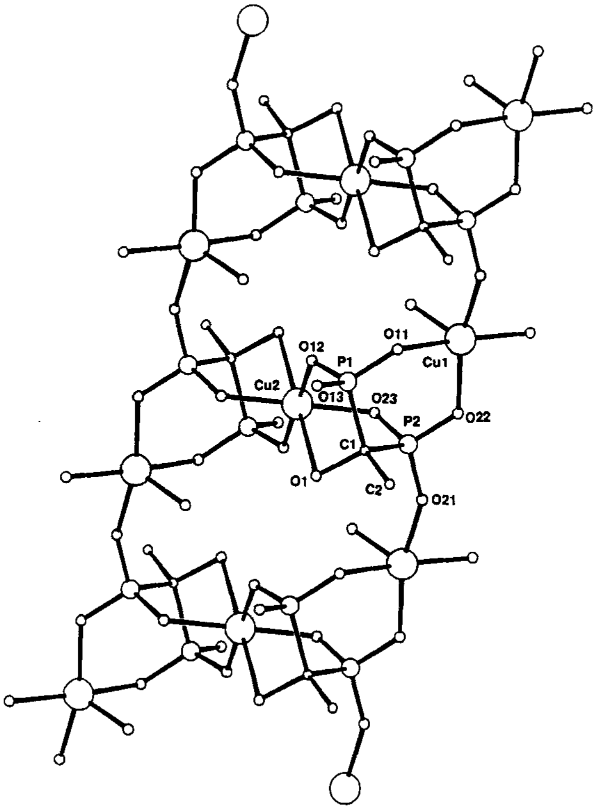

Figure 3 Copper (II) 1-hydroxy 1,1'-ethane bisphosphonate (3): representation of one of the double polymeric chains in the crystal[4].

gauche conformation at C(4) with (C(2)-C(3)-C(4)-C(5) = 69.5 (9)°, a value relevant of a chain folding up.

These differences lead one of the phosphonates groups of the same molecule to have an additional hydrogen bond towards the terminal ammonium group $-NH_3^+$ and another short contact between O'(11) and P'(1).

The chain orientations are under the dependency of the crystal field, and the important changes observed at the C(1) are greatly affected by the geometry, the length and the hydrophobicity when a methyl group (in 3) is substituted by a 3-ammonio-propyl (in 1) or by the longer hydrophobic 5-ammonio-pentyl chain (in 2). The induced changes concern:

- the stoichiometry of the complex in which the ratio Cu^{2+}/acid molecule is 3/2 for 3 and 1/2 for 1 and 2.
- the coordination polyhedron as well as the anion organisations: a double polymeric chain in 3 (Fig. 3), a binuclear tetramer in 1 (Fig. 1) and a mononuclear dimer in the case of 2 (Fig. 2).

Additional remarks can be addressed about these two points:

1. The 3-ammonio-propyl or 5-ammonio-pentyl chains induce a shield effect between the phosphonate groups and the Cu^{2+} cations located at the "outside" of the tetramers or the dimers, thus preventing additional new coordinations. Figure 1 shows the arrangement of the chains in the external part of the tetramer in 1.
In the case of 2, it is necessary to consider the relative disposition of the dimers in the crystal (Fig. 4): the parallel hydrophobic chains of the centrosymmetry related dimers together with their translated along $\vec{a}$, form hydrophobic cylinders whose axes are parallel to $\vec{a}$. Such hydrophobic zones do not allow polymer buildings in a same way it is observed in HEBP salts, particularly in the case[4] of the copper salt 3

2. For both 1 and 2, the N-termini at the end of the chains, are positively charged and lead to repulse the "outer" Cu(II) cations.

3. The ammonium groups are involved in a compact hydrogen bond network toward the phosphonate groups oxygens, another way for preventing any additional coor-

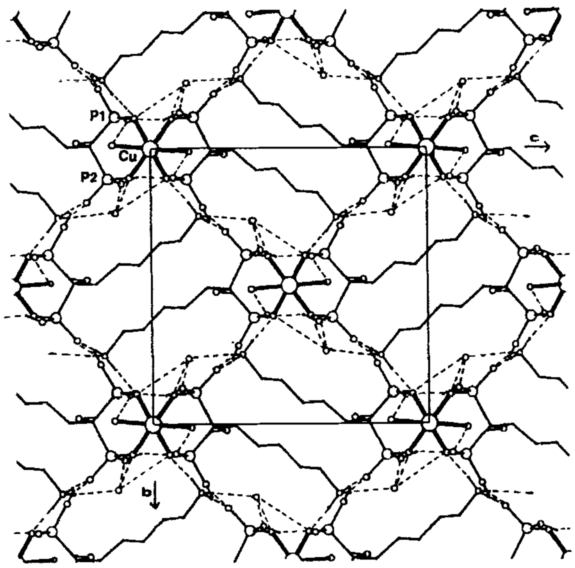

Figure 4 Copper (II) dihydrogeno 1-hydroxy 6-amino 1,1'-hexane bisphosphonate structure viewed along the **a** axis.

dination, especially toward the copper cations exterior to the oligomer (Fig. 4).

CONCLUSION

On the basis of the molecular structures, the proposed model includes: (i) the aliphatic chain elongation and (ii) the influence of the terminal ammonium group which prevents further Cu (II) coordination. These results are not only consistent within the Cu^{++} complexes but give explanations to the only partially ultrafiltrable character of other HEBP cationic complexes in aqueous solution as well as in plasma[9]. The associations obtained in the solid state are in agreement with their behaviour in aqueous media. This comparative study indicates that these closely related salts adopt completely different supramolecular assembly on the basis of a single chain elongation. The elongation of the chain and/or the increasing of its hydrophobicity tends to prevent the polymeric organisation and favours smaller tetra or di- oligimers.

REFERENCES

1 Leroux, Y.; El Manouni, D.; Safsaf, A.; Neuman, A.; Gillier, H. **1991.** *Phosphorus, Sulfur and Silicon 63*, 181–191.
2 Coiro, V.M.; Lamba, D. **1989.** *Acta Cryst.* **C45**, 446–448; Abkhar, Z. **1991** These de Doctorat de Chimie, Université Paris XIII.
3 El Messbahi, N. **1992.** Thèse de Doctorat de Chimie, Université Paris VI.
4 Neuman, A.; Safsaf, A.; Gillier, H.; Leroux, Y.; El Manouni, D. **1992.** *Phosphorus, Sulfur and Silicon 70*, 273–285.
5 Riche, C. **1973.** *Acta Cryst.* A29, 133–137; Riche, C. **1982.** DEVIN. *Abstr. seventh Eur. Crystallogr.* Meet., Jerusalem.
6 Sheldrick, G.M. **1985.** SHELXS-86, in *Crystallographic Computing*, Sheldrick, G.M.; Krüger, C.; Goddard, R. (Eds.), Oxford University Press, pp 175–189.
7 Sheldrick, G.M. **1976.** SHELX76, *Program for Crystal Structure Determination*, University of Cambridge, England.
8 Johnson, C.K. **1965.** *ORTEP, Report ORNL-3794*, Oak Ridge National Laboratory, Tennessee.
9 Wiedmer, W.H.; Zbinden, A.M.; Trechsel, U.; Fleisch, H. **1983** *Calcif. Tissue Int. 35*, 397–400.
10 Fleisch, H. **1989.** in "Recent Results in Cancer Research", Brunner, K.W., Fleisch, H.; Senn, H.J., Eds, Springer Verlag, *116*, 1–28.