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A Structural Study on Metal Binding of *gem*-Diphosphonates, Bone Growth Regulators

M. NARDELLI, G. PELIZZI

Istituto di Chimica Generale ed Inorganica della Università di Parma, Centro di Studio per la Strutturistica Diffrattometrica del C.N.R., Via M. D'Azeglio 85, 43100 Parma, Italy

G. STAIBANO and E. ZUCCHI

Istituto Gentili S.p.A., Via Mazzini 112, 56100 Pisa, Italy

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*The crystal structures of sodium dichloromethylenediphosphonate tetrahydrate and calcium dichloromethylenediphosphonate pentahydrate, determined from single crystal X-ray diffractometer data, are compared with those of other bone growth regulators (*gem*-diphosphonates and pyrophosphates).* $Na_2CCl_2(PO_3H)_2 \cdot 4H_2O$ *crystallizes triclinic (*$P\bar{1}$*) with* Z = *2 formula units in a cell of constants:* a = *11.27(2),* b = *9.18(2),* c = *5.91(1) Å,* α = *88.57(2)°,* β = *92.69(2)°,* γ = *90.58(2)°; final* R = *0.0359 and* R_w = *0.0453. The two crystallographically independent sodium ions both show octahedral coordination, but, while one of them is coordinated by two couples of oxygens from two chelating diphosphonate anions plus a chlorine atom and a water molecule, the other is surrounded by three oxygen atoms from three different diphosphonate anions and three water molecules. Two couples of these octahedra, sharing edges, form tetrameric clusters joined together by diphosphonate bridges.* $CaCCl_2(PO_3H)_2 \cdot 5H_2O$ *crystallizes orthorhombic (*Pnma*) with unit cell dimensions:* a = *10.278(2),* b = *10.872(2),* c = *11.899(2) Å,* Z = *4; final* R = *0.0389 and* R_w = *0.0449. Calcium is heptacoordinated by two oxygen atoms from a diphosphonate anion acting as a bidentate chelating agent, and five water molecules. The coordination polyhedron can be described as a distorted monocapped trigonal prism. Chlorine is not involved in coordination to the metal. In both compounds the diphosphonate anion interacts with the cation through deprotonated oxygen atoms and assumes a nearly eclipsed conformation which gives a* $O \cdots O$ *bite distance as short as 3.06–3.27 Å which seems particularly suitable for a bidentate chelation to calcium and is characteristic of this class of calcium phosphate metabolism regulators.*

Introduction

It is well known that crystal growth of calcium hydroxyapatite, the major inorganic constituent of bone, is inhibited by polyphosphates and polyphosphonates [1, 2]. Pyrophosphate and *gem*-diphosphonates, like 1-hydroxyethylidenediphosphonate and dichloromethylenediphosphonate, are particularly effective inhibitors, but, while pyrophosphate and polyphosphates are readily hydrolyzed in the presence of pyrophosphatase* and lose their ability to inhibit hydroxyapatite crystal growth, the phosphonates do not hydrolyze and so retain their activity in conditions in which polyphosphates would be destroyed [3]. For this reason *gem*-polyphosphonates (the P–C–P bond system is essential for activity) are considered with increasing interest for medical application as regulators of calcium phosphate metabolism.

The mechanism of inhibition of hydroxyapatite crystal growth is connected with the calcium complexation by these diphosphonates, hence the interest in the structural aspects of their coordination to metal. In the present paper the results of the crystal structure analyses of the sodium and calcium dichloromethylenediphosphonates

$Na_2CCl_2(PO_3H)_2 \cdot 4H_2O$	$NaCl_2MDP$
$CaCCl_2(PO_3H)_2 \cdot 5H_2O$	$CaCl_2MDP$

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*It has been suggested [1] that pyrophosphate might be one of the physiological regulators of calcification, with hydroxyapatite deposition only taking place after the destruction of the pyrophosphate by pyrophosphatase, an enzyme present in large concentration in calcifying tissues.

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TABLE I. Experimental Data for the Crystallographic Analyses.

Compound		$Na_2CCl_2(PO_3H)_2\cdot4H_2O$	$CaCCl_2(PO_3H)_2\cdot5H_2O$
F.W.		360.9	373.0
Space Group		$P\bar{1}$	*Pnma*
a/Å		11.27(2)	10.278(2)
b/Å		9.18(2)	10.872(2)
c/Å		5.91(1)	11.899(2)
α/°		88.57(2)	90
β/°		92.69(2)	90
γ/°		90.58(2)	90
V/Å^3		611(2)	1329.6(4)
Z		2	4
D_m/Mg m^{-3} (flotation)		–	1.92
D_c/Mg m^{-3}		1.963	1.864
reflections for lattice parameters	number	22	30
	θ-range	15.3–44.4	17.5–28.5°
crystal data	radiation	Cu-Kα_1	Mo-Kα_1
	wavelength/Å	1.540562	0.709300
intensity data	radiation	Mo-K$\bar{\alpha}$	Mo-K$\bar{\alpha}$
	wavelength/Å	0.7107	0.7107
F(000)		364	760
temperature/°C		20	20
crystal size/mm^3		0.06 × 0.16 × 0.46	0.39 × 0.46 × 0.74
diffractometer		Philips PW 1100	Philips PW 1100
μ/mm^{-1}		0.893	1.143
absorption correction [37] (min–max)		–	1.001–1.087
max. (sin θ/λ)		0.68	0.70
h-range		−15/15	0/14
k-range		−12/12	0/13
l-range		0/8	0/12
standard reflection		410	080
intensity variation		none	none
no. of measured reflections		3241	2230
condition for observed reflections		$I > 2\sigma(I)$	$I > 3\sigma(I)$
no. of unique reflections		2789	1213
method for solving the structure		direct	direct
anisotropic least-squares on F		full matrix	full matrix
maximum least-squares shift to error ratio		1.50	0.64
no. of refined parameters		194	111
R		0.0359	0.0389
R_w		0.0453	0.0449
k, g ($w = k/[\sigma^2(F_o) + gF_o^2]$)		0.2901, 0.008974	0.4873, 0.005032

are reported and their relevant structural features are compared with those of the following related compounds:

$C(CH_3)(OH)(PO_3H_2)_2\cdot H_2O$	EHDP	[4]
$Na_2C(CH_3)(OH)(PO_3H)_2\cdot4H_2O$	NaEHDP	[5]
$CaC(CH_3)(OH)(PO_3H)_2\cdot2H_2O$	CaEHDP	[6]
$CH_2(PO_3H_2)_2$	PCP	[7]
$(CH_2)_2(PO_3H_2)_2$	PC$_2$P	[7].
$(CH_2)_3(PO_3H_2)_2$	PC$_3$P	[8]
$Ca_2P_2O_7\cdot2H_2O$	CaPP·2H$_2$O	[9]
α-$Ca_2P_2O_7$	α-CaPP	[10]
β-$Ca_2P_2O_7$	β-CaPP	[11]

TABLE II. Fractional Atomic Coordinates ($\times 10^5$ for Non-Hydrogen Atoms, $\times 10^3$ for Hydrogens), Principal Axes of Thermal Ellipsoids ($r_1, r_2, r_3, \times 10^4$ Å^2), U_{eq} ($\times 10^4$ Å^2) and Ratios r_{max}/r_{min}.

Atom	x	y	z	r_1	r_2	r_3	U_{eq}	r_{max}/r_{min}
$NaCl_2MDP$								
Na1	35851(8)	25658(9)	−15744(13)	133(4)	323(5)	257(4)	238(3)	2.43
Na2	59373(8)	11137(9)	15858(14)	222(6)	310(6)	258(10)	263(2)	1.40
Cl1	12288(5)	19438(6)	824(8)	99(2)	332(4)	305(5)	245(2)	3.36
Cl2	6826(5)	17928(6)	48043(8)	151(3)	392(3)	258(4)	267(2)	2.59
P1	29995(5)	6221(5)	33701(8)	100(2)	262(3)	173(2)	179(1)	2.63
P2	24439(4)	39631(5)	32194(8)	100(2)	214(3)	179(2)	164(1)	2.15
C	18619(17)	20768(21)	29205(30)	107(8)	230(10)	187(10)	174(5)	2.16
O1	34796(15)	7502(17)	57387(23)	109(6)	443(9)	249(8)	267(5)	4.08
O2	38159(13)	7638(16)	14418(23)	142(6)	275(8)	221(9)	213(4)	1.94
O3	22284(16)	−8177(17)	32079(29)	184(7)	475(9)	234(9)	298(5)	2.59
O4	13463(16)	49517(18)	25089(27)	153(7)	359(9)	225(9)	246(4)	2.35
O5	27459(13)	41891(16)	56806(23)	105(6)	297(7)	242(8)	215(4)	2.81
O6	34134(13)	41535(16)	15894(24)	174(7)	286(8)	215(9)	225(4)	1.64
O7	−11821(16)	43733(27)	18478(27)	187(8)	364(10)	257(9)	269(5)	1.95
O8	57052(18)	33430(19)	35450(29)	227(9)	380(24)	365(27)	324(5)	1.68
O9	56310(16)	28995(19)	−16221(29)	226(11)	423(10)	281(15)	310(4)	1.87
O10	80339(18)	15348(24)	12269(34)	244(11)	458(12)	357(11)	353(6)	1.88
H3	215(4)	−108(4)	207(6)	–	–	–	497(112)	–
H4	133(4)	518(6)	148(6)	–	–	–	614(122)	–
H71	−58(3)	450(4)	235(6)	–	–	–	339(94)	–
H72	−169(3)	489(3)	264(5)	–	–	–	326(72)	–
H81	505(4)	367(4)	311(7)	–	–	–	715(123)	–
H82	618(3)	404(4)	374(6)	–	–	–	523(106)	–
H91	594(3)	371(6)	−122(6)	–	–	–	493(100)	–
H92	585(4)	286(5)	−308(7)	–	–	–	807(131)	–
H101	830(3)	227(4)	165(6)	–	–	–	518(145)	–
H102	835(4)	110(5)	199(7)	–	–	–	707(145)	–
$CaCl_2MDP$								
Ca	1858(9)	25000(–)	42527(8)	129(4)	216(6)	197(8)	181(2)	1.67
Cl1	51904(14)	25000(–)	62319(14)	104(8)	571(21)	559(19)	411(5)	5.52
Cl2	24474(16)	25000(–)	68699(13)	142(7)	545(12)	502(10)	397(4)	3.83
P	32877(8)	10665(8)	49055(8)	106(4)	248(4)	161(4)	172(2)	2.35
C	35645(47)	25000(–)	57081(41)	149(23)	338(26)	173(21)	220(13)	2.27
O1	43236(24)	10051(24)	40187(20)	152(14)	288(12)	195(13)	212(7)	1.89
O2	34460(27)	119(26)	57910(27)	130(16)	586(16)	157(15)	291(8)	4.50
O3	19104(23)	10943(23)	45185(26)	114(11)	444(15)	218(12)	259(8)	3.89
O4	−7077(40)	12163(34)	57331(30)	222(21)	814(23)	342(18)	459(11)	3.66
O5	11009(42)	25000(–)	23803(35)	201(19)	411(24)	250(21)	287(12)	2.05
O6	−11776(43)	10489(50)	32574(31)	212(32)	1448(35)	227(18)	629(15)	6.84
H2	410(5)	−11(5)	593(5)	–	–	–	550(175)	–
H41	−122(8)	30(8)	573(7)	–	–	–	1165(286)	–
H42	−103(10)	159(9)	619(9)	–	–	–	1629(462)	–
H51	203(9)	250(–)	203(8)	–	–	–	742(292)	–
H52	67(6)	250(–)	185(6)	–	–	–	258(169)	–
H61	−95(6)	96(6)	276(5)	–	–	–	499(200)	–
H62	−158(9)	5(8)	326(8)	–	–	–	1542(365)	–

Experimental

All the intermediate and final products have been identified and checked for purity by means of GLC, elemental microanalysis and ^{31}P-NMR spectroscopy.

Dichloromethylenediphosphonic acid was prepared by a three step synthesis: (i) the Michaelis–Arbuzov reaction of triisopropylphosphite and methylene iodide to give tetraisopropylmethylenediphosphonate [12], (ii) chlorination of this compound by sodium ipochloride in aqueous solution [13], (iii) hydrolysis to free the acid by conc. HCl.

Disodium dihydrogenCl_2MDP was prepared by treating a concentrated aqueous solution of the acid with the stoichiometric quantity of NaOH and precipitating by methanol. Crystals suitable for X-ray analysis were obtained by slow evaporation of the aqueous solution. The calcium salt was prepared from calcium monohydrogenphosphate and disodium dihydrogenCl_2MDP following the methods described by Uchtman [6] to obtain crystals suitable for X-ray analysis.

The relevant data concerning the crystal structure analyses are summarized in Table I. Both structures were solved using the *MULTAN-74* program [14] and refined by full-matrix least-squares using the *SHELX-76* program [15]. All of the hydrogen atoms were located from difference Fourier syntheses and refined isotropically. The atomic scattering factors were from [16].

The final atomic coordinates with the mean-square displacements along the principal axes of the thermal ellipsoids [17], the equivalent isotropic thermal parameters, U_{eq}, and the ratios of the maximum and minimum principal axes of the thermal ellipsoids are quoted in Table II. Observed and calculated structure factors and anisotropic thermal parameters have been deposited with the Editor. The calculations were carried out on the CYBER 76 computer of 'Consorzio per la Gestione del Centro di Calcolo Elettronico Interuniversitario dell'Italia Nord-Orientale' (CINECA, Casalecchio, Bologna) with the financial support of the University of Parma, and the GOULD–S.E.L. 32/77 computer of the 'Centro di Studio per la Strutturistica Diffrattometrica del CNR (Parma)'. In addition to the quoted programs, *LQPARM* [18], *PARST* [19] and *PLUTO* [20] programs have been used.

Throughout the paper an averaged value, $\langle x \rangle$, is a weighted mean and the corresponding e.s.d., σ, is the larger of the values of σ_e and σ_i [21] given by the formulae:

$$\langle x \rangle = \Sigma_s w_s x_s / \Sigma_s w_s$$

$$\sigma_e = \left\{ \left(\frac{\Sigma_s w_s x_s^2}{\Sigma_s w_s} - \langle x \rangle^2 \right) / (N-1) \right\}^{1/2}$$

$$\sigma_i = (\Sigma_s w_s)^{-1/2}$$

$$w_s = 1/\sigma_s^2$$

When two values, x_1 and x_2, are compared, the ratio $\Delta/\sigma = |x_1 - x_2| / (\sigma_1^2 + \sigma_2^2)^{1/2}$ is considered, where σ_1 and σ_2 are the e.s.d.s of x_1 and x_2 respectively.

In comparing the results of the present analyses with those from the literature, all the relevant structural parameters were recalculated from the atomic coordinates quoted in the original papers, using the same program *PARST* as was used for our compounds.

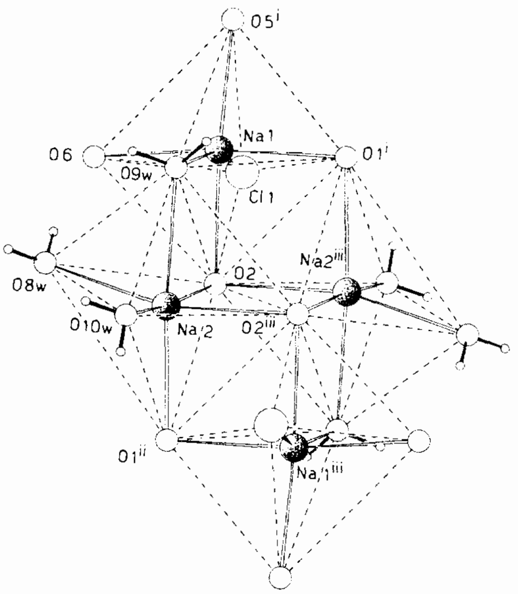


Fig. 1. A cluster of coordination octahedra in NaCl_2MDP. Equivalent positions: i = $x, y, z - 1$; ii = $1 - x, \bar{y}, 1 - z$; iii = $1 - x, \bar{y}, \bar{z}$.

Description of the Structures

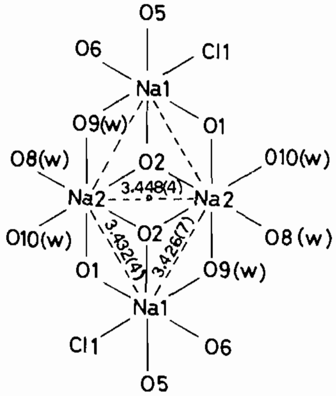
Thermal motion

Both analyses are accurate enough to justify some description of thermal motion. From the data quoted in Table II it can be inferred that thermal motion is lower in the crystals of the sodium salt, where the mean-square displacements are in the range 0.01–0.05 Å^2, than in the calcium salt where these displacements range from 0.01 to 0.14 Å^2. In the first compound motion is maximum for the water molecules and the protonated O3 oxygen atom, minimum for carbon and phosphorus, and intermediate for sodium and chlorine. In the crystals of the calcium salt motion is maximum for the O6 and O4 water molecules and for the chlorine atoms and mimimum for calcium, phosphorus, carbon and the unprotonated oxygen atoms of the phosphonyl groups.

The anisotropy, which of course is related to the environments of the atoms, is maximum for O1, intermediate for Cl1 and O5, and minimum for Na2 in the case of the sodium salt. In the case of the calcium salt anisotropy is maximum for the O6 water molecule, quite relevant for Cl1 and O2, and minimum for the calcium ion.

Metal coordination in $NaCl_2MDP$

Both Na1 and Na2 ions have octahedral coordination which involves deprotonated oxygen atoms of the phosphonyl groups, water molecules and, in the case of Na1, also one of the two chlorine atoms, Cl1. Four such octahedra, sharing edges, are arranged in tetranuclear clusters as depicted in Fig. 1 and diagrammatically indicated by the following scheme (w means a water molecule):



These clusters are joined together, in a three-dimensional network, by the phosphonate anions which bridge adjacent couples of Na1 ions, acting at the same time as bidentate chelating ligands through O1 and O5 (bite distance O1···O5 = 3.271(7) Å) and as tridentate chelating ligands through O2, O6 and Cl1 (bite distances: O2···O6 = 3.153(7), O6···Cl1 = 3.279(5), O2···Cl1 = 3.181(5) Å). As indicated by the angular values quoted in Table III, the coordination octahedra are relatively undistorted.

The coordination octahedron of Na1 involves: O2, O6 and Cl1 of the anion at (x, y, z), the O9 water molecule and the O1 and O5 oxygen atoms of an anion at (x, y, $z - 1$). Coordination about Na2 involves: the O2 oxygen atom at (x, y, z) and that of an anion at ($1 - x$, $\bar{y}$, $\bar{z}$), the O1 oxygen atom of an anion at ($1 - x$, $\bar{y}$, $1 - z$) and the three O8, O9, O10 water molecules at (x, y, z).

The coordinative interactions involving the Na^+ ions can be classified as follows:

(i) with chlorine: Na1–Cl1,

(ii) with phosphonate oxygens each interacting with only one sodium ion: Na1–O6, Na1–O5^{i},

TABLE III. Selected Bond Distances (Å) and Angles (°) in $NaCl_2MDP$ and $CaCl_2MDP$ (w Means that the Oxygen Belongs to a Water Molecule).

$NaCl_2MDP$ (i = x, y, $z - 1$; ii = $1 - x$, $\bar{y}$, $1 - z$; iii = $1 - x$, $\bar{y}$, $\bar{z}$)

Na1 environment

Na1–Cl1	2.919(5)	O6–Na1–O9(w)	92.8(2)	O1^{i}–Na1–O5^{i}	88.7(1)
Na1–O1^{i}	2.329(4)	O5^{i}–Na1–O9(w)	106.5(2)	O1^{i}–Na1–O2	90.8(1)
Na1–O2	2.408(4)	O5^{i}–Na1–O6	95.9(2)	Cl1–Na1–O6	75.2(1)
Na1–O5^{i}	2.348(3)	O2–Na1–O9(w)	91.0(2)	Cl1–Na1–O5^{i}	89.9(2)
Na1–O6	2.415(4)	O2–Na1–O6	81.6(1)	Cl1–Na1–O2	72.6(1)
Na1–O9(w)	2.324(5)	O1^{i}–Na1–O9(w)	95.7(2)	Cl1–Na1–O1^{i}	94.6(2)

Na2 environment

Na2–O1^{ii}	2.377(4)	O9–Na2–O10	86.5(2)	O2–Na2–O1^{ii}	100.3(2)
Na2–O2	2.407(5)	O9–Na2–O8	78.3(1)	O8–Na2–O10	92.5(2)
Na2–O2^{iii}	2.542(4)	O9–Na2–O2^{iii}	85.8(1)	O8–Na2–O1^{ii}	108.9(1)
Na2–O8(w)	2.399(5)	O2–Na2–O9	87.2(2)	O10–Na2–O2^{iii}	84.3(2)
Na2–O9(w)	2.489(4)	O2–Na2–O2^{iii}	91.7(2)	O10–Na2–O1^{ii}	85.5(2)
Na2–O10(w)	2.409(5)	O2–Na2–O8	89.7(2)	O2^{iii}–Na2–O1^{ii}	86.6(1)

diphosphonate anion

C–Cl1	1.798(3)	Cl1–C–Cl2	107.2(2)	O1–P1–O2	120.0(3)
C–Cl2	1.786(3)	Cl1–C–P1	108.1(2)	O1–P1–O3(H)	108.4(2)
C–P1	1.866(3)	Cl1–C–P2	107.1(2)	O2–P1–O3(H)	111.2(2)
C–P2	1.855(4)	Cl2–C–P1	110.4(2)	C–P2–O4(H)	104.1(3)
P1–O1	1.484(3)	Cl2–C–P2	109.0(2)	C–P2–O5	107.8(2)
P1–O2	1.500(2)	P1–C–P2	114.8(3)	C–P2–O6	106.9(2)
P1–O3(H)	1.577(3)	C–P1–O1	106.3(2)	O5–P2–O4(H)	107.8(3)
P2–O4(H)	1.576(3)	C–P1–O2	106.8(2)	O6–P2–O4(H)	111.2(2)

(continued overleaf)

TABLE III. *(continued)*

P2–O5	1.497(3)	C–P1–O3(H)	102.6(3)	O5–P2–O6	118.1(3)
P2–O6	1.496(2)				
$CaCl_2MDP$ (i = x, ½ − y, z)					
Ca environment					
Ca–O3	2.362(3) Å	O3–Ca–O4	79.3(1)	O3–Ca–O3^{i}	80.7(1)
Ca–O4	2.428(4)	O3–Ca–O6	94.5(1)	O3–Ca–O4^{i}	124.0(1)
Ca–O5	2.418(4)	O4–Ca–O6	76.2(2)	O3–Ca–O6^{i}	157.2(1)
Ca–O6	2.420(5)	O3–Ca–O5	80.3(1)	O4–Ca–O4^{i}	70.2(1)
		O4–Ca–O5	144.6(1)	O4–Ca–O6^{i}	120.7(1)
		O6–Ca–O5	77.0(1)	O6–Ca–O6^{i}	81.4(2)
diphosphonate anion					
C–Cl1	1.784(5)	Cl1–C–Cl2	109.3(3)	C–P–O2(H)	104.7(1)
C–Cl2	1.797(5)	Cl1–C–P	108.9(1)	C–P–O3	106.8(1)
C–P	1.850(3)	Cl2–C–P	107.4(1)	O1–P–O2(H)	111.5(2)
P–O1	1.501(3)	P–C–P^{i}	114.8(1)	O1–P–O3	117.3(2)
P–O2(H)	1.566(3)	C–P–O1	106.9(1)	O3–P–O2(H)	108.8(2)
P–O3	1.489(3)				

(iii) with phosphonate oxygens each interacting with two sodium ions: Na1–O1^{i}, Na2–O1^{ii},

(iv) with phosphonate oxygens each interacting with three sodium ions: Na1–O2, Na2–O2, Na2–O2^{iii},

(v) with water oxygens interacting with only one sodium ion: Na2–O8, Na2–O10.

(vi) with water oxygens bridging two sodium ions: Na1–O9, Na2–O9.

The variations observed in the corresponding Na–O distances, which are in the range 2.324(5)–2.542(4) Å, do not show regularities or correlations with the kind of oxygen (from phosphonate or from water), or with the number of interactions. Nevertheless, comparing the situation of the two Na^+ ions, it appears that the distances Na1–O (av. 2.37(2), min. 2.324(5), max. 2.415(4) Å) show a tendency to be shorter than Na2–O (av. 2.44(3), min. 2.377(4), max. 2.542(4) Å). This observation, which cannot be justified by steric effects due to the chlorine atom, Cl1 being far enough from Na1, may be due to the fact that there are more phosphonate oxygens coordinating to Na1 than to Na2, so the anionic charge interacts to a larger extent with Na1 than with Na2.

The protonated phosphonyl oxygen atoms, O3 and O4, are not involved in coordination to metal, but form hydrogen bonds with water molecules.

The sodium ions of the cluster of octahedra form a diamond shaped centrosymmetric metallic cluster with nearly equal Na···Na distances (av. 3.438(6) Å).

It is interesting to compare the present structure with that of NaEHDP [5]. In both compounds there are two crystallographically independent sodium ions and coordination about Na1 is in a sense similar, being octahedral with tridentate chelating behaviour of the diphosphonate anion. In the hydroxyethylidene derivative this chelating behaviour is achieved through the central hydroxyl group with O···O bite distances of 3.029(4), 3.026(4) and 2.871(5) Å. A remarkable difference between the chlorine and the hydroxy derivatives is that in this last compound a protonated oxygen atom of one phosphonyl group is involved in coordination to metal, while in the chlorine derivative only the deprotonated oxygens of the anion coordinate to sodium. Another difference involves the Na2 coordination which is approximately square pyramidal in NaEHDP, with a long O···Na = 2.857(4) Å contact. If this distance is not considered, the average value of the O–Na distance, 2.39(2), min. 2.302(4), max. 2.454(3) Å, compares quite well with the averages found for $NaCl_2MDP$. Also in NaEHDP there are four Na···Na contacts, but now their distribution and the values of the distances (av. 3.7(1), min. 3.501(1), max. 3.991(3) Å) are rather irregular.

Metal coordination in $CaCl_2MDP$

There is only one crystallographically independent calcium ion, which lies on a mirror and is surrounded by two oxygens from a bidentate chelating anion and five water oxygen atoms in a monocapped tri-

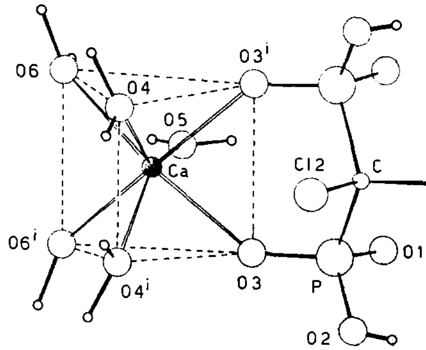


Fig. 2. Coordination of Ca in $CaCl_2MDP$. Equivalent position: i = x, ½ − y, z.

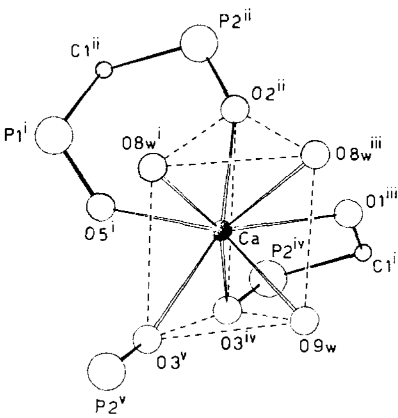


Fig. 3. Coordination of Ca in CaEHDP. The equivalent positions are referred to the coordinates published in the paper [6]: i = $x, y, z + 1$; ii = $\bar{x}, 1 - y, 2 - z$; iii = $\bar{x}, 1 - y, 1 - z$; iv = $x, y - 1, z$; v = $1 - x, 1 - y, 2 - z$.

gonal prismatic environment as shown in Fig. 2. Chlorine is not involved in coordination and the phosphonyl oxygens involved in coordination are the unprotonated ones. The interaction of metal with these oxygens is considerably stronger than with water oxygens, as indicated by the distance which is shorter for Ca–O(ph) = 2.362(3) Å than for Ca–O(w) = 2.422(3) Å av., and the difference is highly significant: $\Delta/\sigma = 14.4$.

The structural situation is quite different from that found in CaEHDP [6] where coordination of Ca^{2+} is 8 and involves two deprotonated oxygens from a diphosphonate anion, a deprotonated oxygen and an alcoholic hydroxyl of a second diphosphonate anion, a deprotonated oxygen of a third anion and three water molecules (Fig. 3), at distances ranging from 2.352(4) to 2.608(3) Å, the longest being that involving the alcoholic oxygen. Comparing these distances with those found in the calcium salt of the Cl-derivative, it appears that: (i) the shortest one is not significantly different ($\Delta/\sigma = 2.0$) from the Ca–O3 = 2.362(3) Å one of the Cl-derivative, (ii) the other distances involving the phosphonyl oxygens (av. 2.430(9) Å are very similar ($\Delta/\sigma = 0.8$) to those involving water (av. 2.422(3) Å) in the Cl-derivative, (iii) the distances involving water are much longer than in the Cl-derivative, their range being 2.484(3)–2.578(3) Å.

It is worth noting that in both calcium salts the phosphonate ligands are not chelate tridentate, as found in the sodium salts, but chelate bidentate, and for the Cl-derivative there is a tendency to coordinate more water to reach the required coordination number, rather than to involve the chlorine atoms in coordination to calcium.

TABLE IV. Calcium Coordination in *gem*-diphosphonates, Pyrophosphates and Hydroxyapatite. Distances in Å.

Compound	coord. number	(Ca–O)min	(Ca–O)max	(Ca–O)av.	geometry	Reference
$CaCl_2MDP$	7	2.362(3)	2.428(4)	2.39(1)	monocapped trigonal prism	present study
CaEHDP	8	2.352(4)	2.608(4)	2.47(3)	bicapped trigonal prism or Archimedean antiprism	[6]
$Ca_2P_2O_7 \cdot 2H_2O$	7	2.363(2)	2.642(2)	2.43(4)	monocapped octahedron	[9]
	7	2.286(2)	2.668(2)	2.42(5)	distorted pentagonal bipyramid	
α-$Ca_2P_2O_7$	8	2.360(8)	2.806(8)	2.54(6)	pseudo-cube	[10]
	8	2.250(8)	2.689(9)	2.50(5)	distorted cube	
β-$Ca_2P_2O_7$	7	2.340(10)	2.781(11)	2.44(6)	distorted pentagonal bipyramid	[11]
	9	2.342(13)	2.855(11)	2.59(5)	pentagonal bipyramid with an apical atom replaced by three atoms	
	7	2.318(10)	2.692(11)	2.43(5)	distorted pentagonal bipyramid	
	8	2.370(11)	2.927(11)	2.53(7)	octahedron with two oxygens jammed into edges	

(continued overleaf)

TABLE IV. *(continued)*

Compound	coord. number	(Ca–O)min	(Ca–O)max	(Ca–O)av.	geometry	Reference
$Ca_{10}(PO_4)_6(OH)_2$	9	2.408(8)	2.808(12)	2.43(2)*	distorted tricapped trigonal prism	[29]
	7	2.346(10)	2.708(15)	2.43(4)	pentagonal bipyramid	
	av.	2.335(12)	2.644(25)	2.414(12)		

*Excluding the longest distances.

In Table IV relevant data on calcium coordination in *gem*-diphosphonates, pyrophosphates and hydroxyapatite are compared. From them it appears that the coordination number of the metal is equal to or greater than seven with Ca–O distances ranging from 2.250(8) to 2.927(11) Å with an average value of 2.335(12) Å for the strongest interactions.

Structure and conformation of the diphosphonate anion

The dichloromethylenediphosponate anion shows a C_s symmetry with the Cl–C–Cl group lying in the mirror. In the case of the calcium salt this symmetry is a crystallographic requirement, while for the sodium salt it is only local, but a comparison of the coordinates of the two pseudo-mirror related parts of the anion shows no significant departures from the ideal symmetry, the largest Δ/σ being 0.85. From the data collected in Table III it appears that:

(i) the C–Cl distances are not significantly different in the two compounds and the average, 1.791(4) Å, is significantly ($\Delta/\sigma = 5.37$) longer than the value, 1.767(2) Å, quoted in the literature [22, 23] for the $C(sp^3)$–Cl bond,

(ii) the C–P distance in the calcium salt is a little shorter than the corresponding ones in the sodium salt, but the difference is not very significant ($\Delta/\sigma = 2.1$),

(iii) the differences between the P–O bonds when oxygen is or is not protonated are highly significant ((Δ/σ) av. = 17.2),

(iv) the O–H distances (av. 0.69(3) Å) and the P–O–H angles (av. 114(2)°) are not significantly different in the anions of the two compounds.

In Table V the averaged values of bond distances and angles in different diphosphonates and diphosphonic acids are compared. The following observations on bond lengths can be made:

(i) the C–P distances are approximately equal in the C-substituted *gem*-diphosphonates (the average 1.848(5) Å approaches the value for a $C(sp^3)$–P single bond), and systematically longer than in PCP, PC_2P, PC_3P (av. 1.789(2) Å). The difference between the two averages is significant ($\Delta/\sigma = 5.9$), indicating some influence of the substituents at the bridging carbon atom on the bonding of this atom with the phosphonyl groups,

(ii) the P–O (unprotonated) distances are in the range 1.484(3)–1.511(3) Å and the difference ($\Delta = 0.027(4)$ Å) between these values is significant ($\Delta/\sigma = 6.4$). It is possible that the interactions with metals or hydrogen bonding have some influence on them,

(iii) the P–OH distances are in the range 1.530(3)–1.556(4) Å and the difference ($\Delta = 0.026(5)$ Å) between these limits is significant ($\Delta/\sigma = 5.2$). On these distances too hydrogen bonding may have some influence. Probably it is not coincidental that the value of the range, Δ, is equal for the two kinds of P–O bonds.

Concerning the bond angles the following points deserve to be considered:

(i) the average of all the C–P–O(unprotonated) angles, 109.2(5)°, is very near to the theoretical tetrahedral value. Nevertheless, as found for the bond distances, there are systematic differences between the C-substituted *gem*-diphosphonates (av. 107.9(3)°) and the PCP, PC_2P, PC_3P acids (av. 111.7(7)°), the difference between the two averaged values being significant ($\Delta/\sigma = 5.0$).

(ii) The C–P–OH angles are systematically narrower than the theoretical tetrahedral angle and the same trend is observed for the HO–P–OH angles, while all the other angles are systematically and significantly larger.

(iii) The values of the P–C–P angles are in the range 113.7(3)–117.2(1)° and so are larger than the tetrahedral value, but much narrower than the corresponding P–O_B–P (O_B = bridging oxygen) angle in pyrophosphates which is in the range 123.0(6)–180.0(–)°. The observed values of the P–C bonds and the corresponding P–C–P angles fit well the extrapolated curve showing the relationship between the phosphorus-bridging oxygen bond length and the bridging angles in pyrophosphates [9], as shown in Fig. 4 where the continuous curve has been calculated by a least-squares fitting of the data from which the points referring to P–O_B–P angles of 180° were excluded, and this value, observed in thortveitite-type structures, probably results from disorder of two or more slightly non-linear structures [24, 25]. This correlation is a result of many effects: *i.e.* electronic effects related to the nature of the interaction

TABLE V. Averaged Bond Distances (Å) and Angles (°) in Anions of Diphosphonates and Diphosphonic Acids.

	C–P	P–O	P–OH	C–P–O	C–P–OH	O–P–O	O–P–OH	HO–P–OH	P–C–P
$NaCl_2MDP$	1.862(5)	1.496(3)	1.577(2)	106.9(3)	103.4(8)	119.1(10)	109.7(9)	–	114.8(3)
NaEHDP	1.841(3)	1.506(2)	1.580(4)	109.3(3)	103.4(6)	115.5(2)	109.3(8)	–	113.9(2)
$CaCl_2MDP$	1.850(3)	1.495(6)	1.566(3)	106.9(1)	104.7(1)	117.3(2)	110.2(14)	–	114.8(1)
CaEHDP	1.844(19)	1.504(3)	1.558(19)*	107.5(12)	106.5(9)	116.6(2)	111.0(14)*	110.5(2)*	113.7(3)
EHDP	1.836(4)	1.506(2)	1.544(4)	108.9(5)	106.4(3)	–	113.0(9)	108.5(19)	115.1(2)
PCP	1.792(2)	1.498(5)	1.548(1)	111.3(20)	106.6(14)	–	113.7(4)	104.5(22)	117.2(1)
PC_2P	1.786(2)	1.501(2)	1.548(5)	112.4(1)	105.8(35)	–	112.5(9)	107.5(1)	–
PC_3P	1.781(5)	1.497(2)	1.548(2)	112.6(4)	105.4(9)	–	109.8(7)	109.7(4)	–
av.	1.818(8)	1.500(1)	1.552(3)	109.2(5)	105.9(5)	116.7(6)	112.1(4)	107.0(9)	115.6(6)

*The H atom of a phosphonyl group is distributed in a disorderly fashion into two positions such that half the anions have the proton bonded to one oxygen and the other half to another oxygen of the same phosphonyl group.

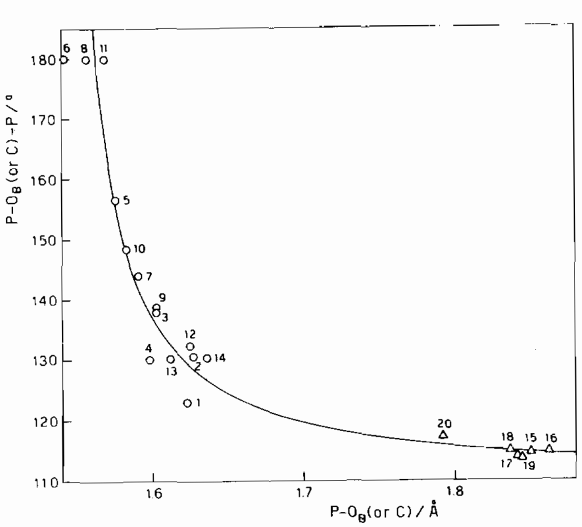


Fig. 4. Correlation between phosphorus-bridging atom bond length, x = P–O_B (or C) (Å), and bridging angle y = P–O_B (or C)–P (°). Equation of the curve: $y = (109.37x - 166.77)/(x - 1.54)$; coefficient of determination $R^2 = 0.9415$. Circles for pyrophosphates, triangles for *gem*-diphosphonates: (1) $Ca_2P_2O_7 \cdot 2H_2O$ [9], (2) and (3) β-$Ca_2P_2O_7$ [11], (4) α-$Ca_2P_2O_7$ [10], (5) α-$Cu_2P_2O_7$ [30], (6) β-$Cu_2P_2O_7$ [31], (7) α-$Mg_2P_2O_7$ [32], (8) β-$Mg_2P_2O_7$ [24], (9) and (10) α-$Zn_2P_2O_7$ [33], (11) β-$Zn_2P_2O_7$ [24], (12) $Cd_2P_2O_7$ [34], (13) $Na_4P_2O_7 \cdot 10H_2O$ [35], (14) $K_4P_2O_7 \cdot 3H_2O$ [36], (15) $CaCl_2MDP$ (present study), (16) $NaCl_2MDP$ (present study), (17) NaEHDP [5], (18) EHDP [4], (19) CaEHDP [6], (20) PCP [7].

between phosphorus and the bridging atom, repulsion between non-bonding and bonding electron pairs [26] in the valence shell of the bridging atom, repulsion between the phosphorus atoms whose distances range from 2.854(2) Å in $CaPP \cdot 2H_2O$ to 3.135(7) Å in $NaCl_2MDP$.

Considering the O–P···P–O torsion angles quoted in Table VI it appears that there is a tendency for the two phosphonyl or phosphate groups to assume a nearly eclipsed conformation (exactly eclipsed by symmetry requirements in $CaCl_2MDP$), indicating that there are no repulsive effects between the oxygen atoms of these groups influencing their mutual orientation which is essentially determined by the interactions the groups attached to the bridging carbon exert on the terminal oxygen in the case of the diphosphonates (Cl1···O4 = 3.142(6), Cl2···O3 = 3.165(5) Å in $NaCl_2MDP$ and Cl1···O1 = 3.220(3), Cl2···O2 = 3.165(3) Å in $CaCl_2MDP$) and by the interactions with the metal ions in the case of the pyrophosphates. These interactions are also responsible for the tendency all these anions show to assume a planar 'W' arrangement for the O–P–C(or O)–P–O chain of atoms as indicated by the values of the τ_1 = O1–P1–C_B(or O_B)–P2 and τ_2 = O2–P2–C_B (or O_B)–P1 torsion angles quoted in Table VI.

TABLE VI. Torsion Angles (°) in the Anions of *gem*-Diphosphonates and Pyrophosphates.

	O–P···P–O			τ_1	τ_2
$NaCl_2MDP$	−7.3(3)	−9.4(3)	−14.4(5)	175.5(3)	174.2(3)
NaEHDP	−4.9(4)	−7.1(2)	−13.5(2)	178.8(2)	177.9(2)
$CaCl_2MDP$	0	0	0	174.5(2)	−174.5(2)
CaEHDP	−23.1(2)	−20.8(3)	−31.2(5)	176.6(3)	161.5(3)
EDHP	2.8(3)	−3.2(2)	−7.6(1)	178.9(2)	−177.0(2)
PCP	22.3(1)	34.4(2)	34.9(1)	−160.0(2)	−176.1(2)
$Ca_2P_2O_7 \cdot 2H_2O$	17.0(1)	23.4(1)	34.7(2)	−165.8(1)	−167.7(1)
α-$Ca_2P_2O_7$	13.2(5)	13.8(5)	27.2(7)	−177.1(7)	−161.3(6)
β-$Ca_2P_2O_7$	6.9(6)	8.8(5)	11.7(8)	−169.4(8)	179.1(8)
	−10.9(6)	−16.9(6)	−22.1(8)	−179.6(9)	161.3(10)

Coordination to metal of the diphosphonate anions

In coordinating to Na^+ or Ca^{2+} the dihydrogen-*gem*-diphosphonate anions show different behaviours, but in every case puckered six-membered chelate rings, involving oxygens of the geminal phosphonyl groups, are formed. Only in the case of the sodium salts does an additional interaction involving the alcoholic hydroxyl group or a chlorine atom attached to the bridging carbon atom make the behaviour of these anions tridentate. In the crystals of $CaCl_2$-MDP each anion chelates only one metal ion, while in CaEHDP the calcium ion is chelated by two bidentate anions, one forming a six-membered ring through two oxygens of the geminal phosphonyl groups, the second forming a five-membered chelate ring involving the alcoholic hydroxyl group and a phosphonyl oxygen which also coordinates to an adjacent calcium ion as shown in Fig. 3.

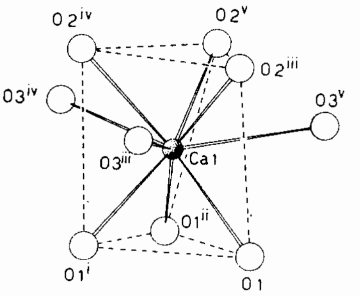


Fig. 5. Coordination of Ca1 in calcium hydroxyapatite. The equivalent positions are referred to the coordinates published in the paper [29]: $i = 1 - y, x - y + 1, z$; $ii = y - x, 1 - x, z$; $iii = 1 - x, 1 - y, \bar{z}$; $iv = y, y - x + 1, \bar{z}$; $v = x - y, x, \bar{z}$.

Chelating bidentate behaviour with formation of puckered six-membered rings is also observed in the crystals of all calcium pyrophosphates whose structure is known, and in none of these compounds is the bridging oxygen atom involved in a chelating tridentate coordination of the anion. In Table VII the data relevant for the description of the conformations of the six-membered chelate rings, observed in the crystal structures of these sodium and calcium salts, are collected. The total puckering amplitude, Q, is calculated following Cremer & Pople [27] and the asymmetry parameters following Nardelli [28]. From these data it appears that the rings are always considerably puckered (av. Q = 0.86(5) Å) and in the case of the diphosphonates the conformations of the rings are always boat with the pseudo-mirror through the metal atom, while in the case of the pyrophosphates more or less relevant distortions from this conformation are also observed.

The O···O bite distances are in the range 2.93–3.40 Å (av. 3.03(3) Å). It is important to note that non bonding distances very similar to these are present in calcium hydroxyapatite, between the oxygen atoms more strongly bound to the calcium ions. In the crystals of this compound [29] there are two kinds of calcium ions with different coordination: Ca1 (Fig. 5) is hexacoordinated in a distorted trigonal prismatic arrangement with Ca–O = 2.408(8) and 2.454(8) Å; the faces of the prism are capped by oxygens at 2.808(11) Å and the O···O non-bonding distances between the oxygen atoms more strongly bound to calcium are 2.934(15) and 3.015(15) Å; Ca2 (Fig. 6) shows a distorted penta-

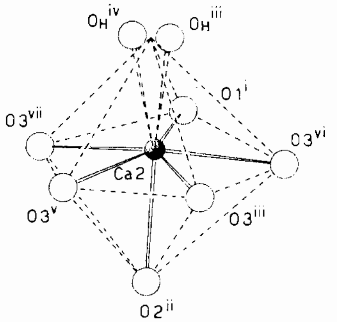


Fig. 6. Coordination of Ca2 in calcium hydroxyapatite. Equivalent positions: $i = y - x, 1 - x, z$; $ii = 1 - y, x - y + 1, z$; $iii = x, 1 + y, z$; $iv = y - x, 1 - x, \frac{1}{2} - z$; $v = x, 1 + y, \frac{1}{2} - z$; $vi = y, y - x + 1, \bar{z}$; $vii = y, y - x + 1, z + \frac{1}{2}$.

TABLE VII. Conformations of Chelate Rings. Out-of-plane Atomic Displacements (Å), Total Puckering Amplitudes, Q (Å), Displacement Asymmetry Parameters, Δ, and O···O Bite Distances (Å), (M = Metal Ion).

	M	O	P	C (or O)	P′	O′	*Q*	Δ		O···O
$NaCl_2MDP$	−0.737(3)	0.339(3)	0.336(3)	−0.612(3)	0.214(3)	0.461(3)	1.185(7)	Δ_S(Na1)	= 0.0726(17)	3.153(7)
	−0.225(3)	0.095(3)	0.258(4)	−0.480(3)	0.350(3)	0.003(3)	0.692(4)	Δ_S(Na1′)	= 0.0550(18)	3.271(7)
NaEHDP	−0.915(2)	0.477(2)	0.312(3)	−0.662(3)	0.224(2)	0.565(2)	1.404(8)	Δ_S(Na1)	= 0.0465(13)	3.026(4)
$CaCl_2MDP$	−0.318(3)	0.119(2)	0.278(1)	−0.477(3)	0.278(2)	0.119(2)	0.208(8)	Δ_S(Ca)	= 0	3.057(4)
CaEHDP	−0.044(3)	−0.045(3)	−0.078(2)	0.290(3)	−0.380(3)	0.257(3)	0.551(4)	Δ_S(O2)	= 0.0170(12)	2.928(4)
$Ca_2P_2O_7·2H_2O$	0.558(2)	−0.192(2)	−0.321(2)	0.468(1)	−0.102(2)	−0.411(1)	0.922(2)	Δ_2(O2)	= 0.0794(5)	3.014(2)
	0.542(1)	−0.447(1)	−0.042(1)	0.436(1)	−0.341(1)	−0.148(1)	0.908(1)	Δ_2(P)	= 0.0502(4)	2.990(2)
α-$Ca_2P_2O_7$	0.070(6)	0.107(6)	−0.300(5)	0.317(5)	−0.141(5)	−0.053(5)	0.479(7)	Δ_2(Ca1′ – O5)	= 0.0321(27)	3.36(1)
β-$Ca_2P_2O_7$	−0.558(7)	0.427(6)	0.049(6)	−0.393(6)	0.262(6)	0.214(6)	0.874(10)	Δ_2(P3)	= 0.0958(24)	3.40(1)
	−0.634(6)	0.314(6)	0.186(5)	−0.367(6)	0.047(6)	0.454(6)	0.937(9)	Δ_S(Ca2)	= 0.0864(34)	3.16(1)
	−0.644(7)	0.419(5)	0.119(5)	−0.432(7)	0.207(5)	0.331(6)	0.972(10)	Δ_S(Ca3′)	= 0.0468(3)	3.18(1)
	−0.550(7)	0.250(6)	0.237(5)	−0.425(7)	0.125(6)	0.363(5)	0.866(9)	Δ_S(Ca4′)	= 0.0654(32)	3.21(1)
							av. 0.862(53)			av. 3.030(26)

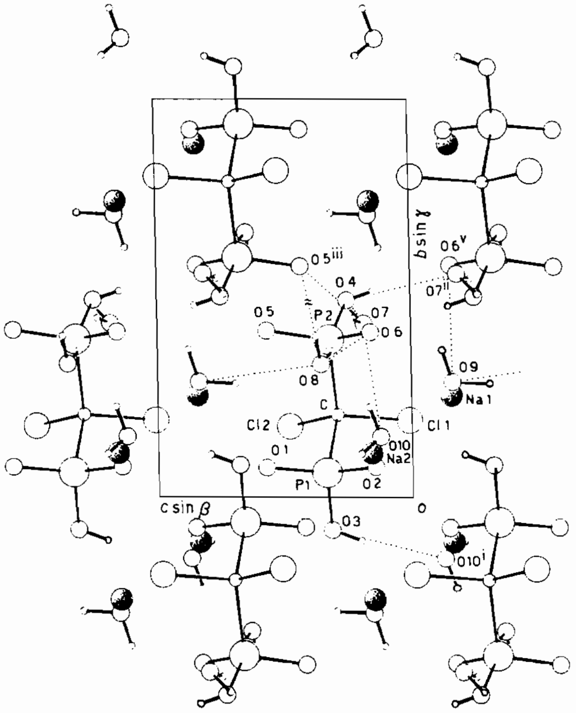


Fig. 7. Packing and hydrogen bonding in $NaCl_2MDP$.

gonal bipyramidal heptacoordination with Ca–O distances ranging from 2.346(10) to 2.708(15) Å, and the shortest non-bonding O···O contacts are 2.955(10), 3.054(12), 3.077(15) Å.

Water molecules and hydrogen bonding

The average O–H distance (0.83(3), min. 0.64(6), max. 1.16(11) Å) and H–O–H angle (104(2), min. 90(8), max. 130(3)) agree well with the corresponding values generally found for water by X-ray diffraction. If an exception is made for O9, which bridges two sodium ions, and for O7, not coordinating to any metal ion, all the other water molecules in both dichloromethylenediphosphonates behave as terminal ligands each directing an electron lone pair towards the acceptor cation with the exception of O5 in the calcium salt, where both cation and water lie on a crystallographic mirror bisecting the angle formed by the two water lone pairs both involved in coordination.

In both salts the crystal building is essentially determined by hydrogen bonds in which the water molecules and the protonated phosphonyl oxygens are involved. From Fig. 7 and from the data of Table VIII it appears that in the sodium salt, of the two protonated phosphonyl oxygens, O3 is donor to the O10(1 − *x*, $\bar{y}$, $\bar{z}$) water molecule, while O4 is donor to O7($\bar{x}$, *1* − *y*, $\bar{z}$) and acceptor from O7 water molecules. Of the four water molecules present in the

TABLE VIII. Hydrogen Bonding in $NaCl_2MDP$ and $CaCl_2MDP$.

Donor–H		Donor···Acceptor		H···Acceptor		Donor–H···Acceptor	
$NaCl_2MDP$							
O3–H3	= 0.72(4) Å	O3···O10^{i}	= 2.720(5)°	H3···O10^{i}	= 2.00(4) Å	O3–H3···O10^{i}	= 172(4)°
O4–H4	= 0.64(4)	O4···O7^{ii}	= 2.632(5)	H4···O7^{ii}	= 2.00(4)	O4–H4···O7^{ii}	= 172(5)
O7–H71	= 0.74(4)	O7···O4	= 2.903(6)	H71···O4	= 2.20(4)	O7–H71···O4	= 159(4)
O7–H72	= 0.90(3)	O7···O5^{iii}	= 2.714(4)	H72···O5^{iii}	= 1.81(3)	O7–H72···O5^{iii}	= 176(3)
O8–H81	= 0.82(4)	O8···O6	= 2.877(5)	H81···O6	= 2.07(4)	O8–H81···O6	= 169(4)
O8–H82	= 0.84(4)	O8···O5^{iv}	= 2.879(5)	H82···O5^{iv}	= 2.05(4)	O8–H82···O5^{iv}	= 176(4)
O9–H91	= 0.85(4)	O9···O6^{v}	= 2.902(6)	H91···O6^{v}	= 2.09(4)	O9–H91···O6^{v}	= 158(3)
O9–H92	= 0.91(4)	O9···O8^{vi}	= 2.880(5)	H92···O8^{vi}	= 2.03(4)	O9–H92···O8^{vi}	= 155(4)
O10–H101	= 0.78(4)	O10···O7^{vii}	= 2.771(6)	H101···O7^{vii}	= 2.02(4)	O10–H101···O7^{vii}	= 163(4)

i = $1 - x, \bar{y}, \bar{z}$ ii = $\bar{x}, 1 - y, \bar{z}$ iii = $\bar{x}, 1 - y, 1 - z$ iv = $1 - x, 1 - y, 1 - z$ v = $1 - x, 1 - y, \bar{z}$ vi = $x, y, z - 1$
vii = $1 + x, y, z$

Donor–H		Donor···Acceptor		H···Acceptor		Donor–H···Acceptor	
$CaCl_2MDP$							
O2–H2	= 0.71(6)	O2···O1^{i}	= 2.555(4)	H2···O1^{i}	= 1.89(6)	O2–H2···O1^{i}	= 157(6)
O4–H41	= 1.12(9)	O4···O3^{ii}	= 2.816(5)	H41···O3^{ii}	= 1.70(9)	O4–H41···O3^{ii}	= 170(7)
O5–H51	= 1.04(10)	O5···O6^{iii}	= 3.300(6)	H51···O6^{iii}	= 2.45(8)	O5–H51···O6^{iii}	= 138(1)
O5–H52	= 0.77(7)	O5···O1^{iv}	= 2.958(4)	H52···O1^{iv}	= 2.37(5)	O5–H52···O1^{iv}	= 134(1)
O6–H61	= 0.64(6)	O6···O1^{v}	= 2.757(4)	H61···O1^{v}	= 2.14(6)	O6–H61···O1^{v}	= 163(7)

i = $1 - x, \bar{y}, 1 - z$ ii = $\bar{x}, \bar{y}, 1 - z$ iii = $\frac{1}{2} + x, \frac{1}{2} - y, \frac{1}{2} - z$ iv = $x - \frac{1}{2}, \frac{1}{2} - y, \frac{1}{2} - z$ v = $x - \frac{1}{2}, y, \frac{1}{2} - z$

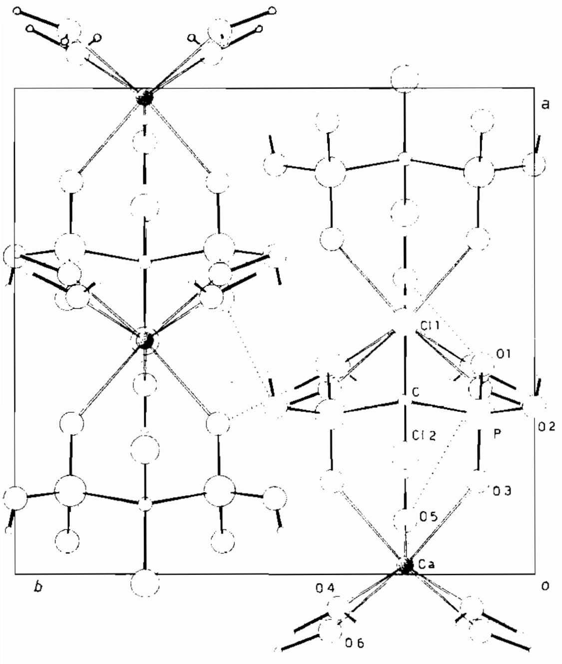


Fig. 8. Packing and hydrogen bonding in $CaCl_2MDP$.

crystal structure, three (O8, O9, O10) are involved in coordination to metal, the fourth (O7) is a hydrogen bonding donor to O4 and O5($\bar{x}$, $1 - y$, $1 - z$), and acceptor from O4($\bar{x}$, $1 - y$, $\bar{z}$) and O10($x - 1, y, z$).

In the calcium salt (Fig. 8) four hydrogen bonds are present: one formed by the protonated phosphonyl oxygen O2 which is donor to the O1 atom of an adjacent anion, the other three involve the O6, O4 and O5 water molecules which are donors to the O1, O3 and O1 phosphonyl oxygens respectively, the last one being bifurcated by crystallographic symmetry requirements.

Conclusions

In both $CaCl_2MDP$ and CaEDHP salts the *gem*-diphosphonate ligands are chelating bidentate and not tridentate as in $NaCl_2MDP$ and NaEHDP. So the hypothesis that the biological activity, which is based on their interactions with Ca^{2+}, is determined by the chelating tridentate character of these ligands [5] seems not to be valid. On the contrary it appears quite probable that the activity of *gem*-diphosphonates is due to their chelating bidentate behaviour towards the calcium ions which is strictly related to the conformation of these anions, in particular to the bite O···O distance which is in the same range, 2.9–3.1 Å, as the non-bonding distances of the oxygens more strongly bound to Ca^{2+} in calcium hydroxyapatite. This bite distance is a consequence of the reciprocal orientation of the geminal phosphonyl residues which have a tendency to be eclipsed and form a nearly planar O–P–C–P–O atomic system.

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