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FULL PAPER

A structural study of bisphosphonate metal complexes. Alkaline earth metal complexes of (dichloromethylene)bisphosphonic acid *P*,*P*′-diethyl ester

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The complexation properties of an ester derivative of clodronate with divalent metal cations Mg^{2+}, Ca^{2+}, Sr^{2+} and Ba^{2+} has been studied using the methods of structural chemistry and spectroscopy. A dipiperidinium salt and four alkaline earth metal complexes of the (dichloromethylene)bisphosphonic acid *P*,*P*′-diethyl ester: $(C_5H_{10}NH_2)_2Cl_2C(PO_3Et)_2$ (**1**), $[MgCl_2C(PO_3Et)_2(H_2O)_3]_n$ (**2**), $[(H_2O)_3Ca\{Cl_2C(PO_3Et)_2\}_2Ca(H_2O)_3]$ (**3**), $[(H_2O)_3Sr\{Cl_2C(PO_3Et)_2\}_2Sr(H_2O)_3]$ (**4**) and $[(H_2O)_2Ba\{Cl_2C(PO_3Et)_2\}_2Ba(H_2O)_2]_n$ (**5**) were prepared and characterised. The crystal structures were determined with the single crystal X-ray diffraction technique. The asymmetric unit of compound **1** contains two piperidinium cations and one (dichloromethylene)bisphosphonic acid *P*,*P*′-diethyl ester anion, which are bound to each other by hydrogen bonding *via* amine-N^+H_2. Compound **2** is polymeric, having two independent magnesium atoms with octahedral geometry. Calcium and strontium complexes **3** and **4** are isomorphous and dimeric with seven coordinated metal atoms connected by two $Cl_2C(PO_3Et)_2^{2-}$ ligands. In the asymmetric unit of complex **5**, two adjacent barium atoms are joined by two $Cl_2C(PO_3Et)_2^{2-}$ ligands. The dimeric units are bridged through the oxygen atoms of $Cl_2C(PO_3Et)_2^{2-}$ and aqua ligands, forming polymeric chains. The compounds were characterised by infrared spectroscopy and ^{31}P NMR spectroscopy. The aqueous solubility of the diethyl ester was defined in the presence of Ca^{2+} cations.

Introduction

Methylenebisphosphonates (MBP), which contain a stable P–C–P bridge against enzymatic hydrolysis, are commonly used to inhibit the mineralisation of soft tissues and also of bone formation and resorption disorders, *e.g.*, in Paget's disease, hypercalcemia of malignancy, and osteoporosis. The MBPs adsorb on the bone mineral by forming metal complexes with calcium, and their complexation properties are an important aspect for gaining an understanding of their mechanism of action. The structure activities and bone affinities of the MBPs are directly associated with the substituents connected both to the middle carbon and to the phosphorus atoms.[1,2] In particular, the number of the donor atoms of the ligand and its connections with the metal atoms affect the bone affinity. For example, the bone affinity of risedronate and etidronate is much greater than that of clodronate owing to their tridentate adsorption *versus* the bidentate adsorption of clodronate on the bone mineral surface. The divergence between the bone affinities of BPs is also due to their different calcium complex solubilities. The drugs encounter calcium ions both in solution and on the bone mineral surface, and the less soluble calcium complexes may actually precipitate rather than adsorb on the bone mineral.[1]

The oral bioavailability of all MBPs is low owing to high ionisation at physiological pH values, which makes them very polar and poorly absorbed from the gastro-intestinal tract. Furthermore, complexation with divalent cations, such as Ca^{2+}, hinder absorption.[3,4] Recently, an attempt has been made to improve the bioavailability of clodronate (Cl_2MBP), which is one of the best-documented MBP derivatives, by masking one or more ionizable groups to form ester derivatives, for example with the alkyl[5] or amide[6] groups. However, a more effective improvement has been found using the prodrug method.† Unfortunately, the prepared prodrug derivatives of Cl_2MBP are chemically rather too unstable for their complexation properties to be studied.

The aim of this study was to investigate the complexation properties of an ester derivative of clodronate with the divalent metal cations Mg^{2+}, Ca^{2+} and Sr^{2+}, which are presented on the bone mineral surfaces.[1] The symmetrical diethyl ester derivative is an ideal model compound for prodrugs since it is chemically stable, easy to prepare, and the complexes form easily. In addition, the aqueous solubility of the calcium complex of the diethyl ester was determined and referred to the solubility of the Ca complex of clodronate to determine the effect of the ester groups on the solubility.

The structures of the complexes of the divalent metal cations, $[MgCl_2C(PO_3Et)_2(H_2O)_3]_n$ (**2**), $[(H_2O)_3Ca\{Cl_2C(PO_3Et)_2\}_2Ca(H_2O)_3]$ (**3**) and $[(H_2O)_3Sr\{Cl_2C(PO_3Et)_2\}_2Sr(H_2O)_3]$ (**4**), have been determined together with the structures of the Cl_2MBP *P*,*P*′-diethyl ester ligand $(C_5H_{10}NH_2)_2Cl_2C(PO_3Et)_2$ (**1**) and its heavy-metal complex $[(H_2O)_2Ba\{Cl_2C(PO_3Et)_2\}_2Ba(H_2O)_2]_n$ (**5**). The structures of the complex crystals were determined using single-crystal X-ray diffraction methods, and the purity and the spectroscopic properties of the complexes were analysed by means of infrared spectroscopy (IR) and ^{31}P CP/MAS NMR spectroscopy.

† In the prodrug method one or more ionizable groups are masked with active substituents, *e.g.*, acyloxyalkyl, $-CH_2OCOR$ groups,[7] to form prodrug derivatives. The active parent drug needs to be released in the body after absorption by enzymatic and/or chemical hydrolysis.[6–9]

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Results and discussion

Description of the structures

Dipiperidinium salt of *P*,*P*′-diethyl ester of Cl_2MBP **1**, $(C_5H_{10}NH_2)_2Cl_2C(PO_3Et)_2$, crystallises in the triclinic crystal system. The asymmetric unit contains two piperidinium cations and one Cl_2MBP *P*,*P*′-diethyl ester anion, which are bound together by hydrogen bonding *via* amine-N^+H_2 [N ··· O 2.731(2)–3.010(2) Å] as shown in Fig. 1(a). The $Cl_2C(PO_3Et)_2^{2-}$

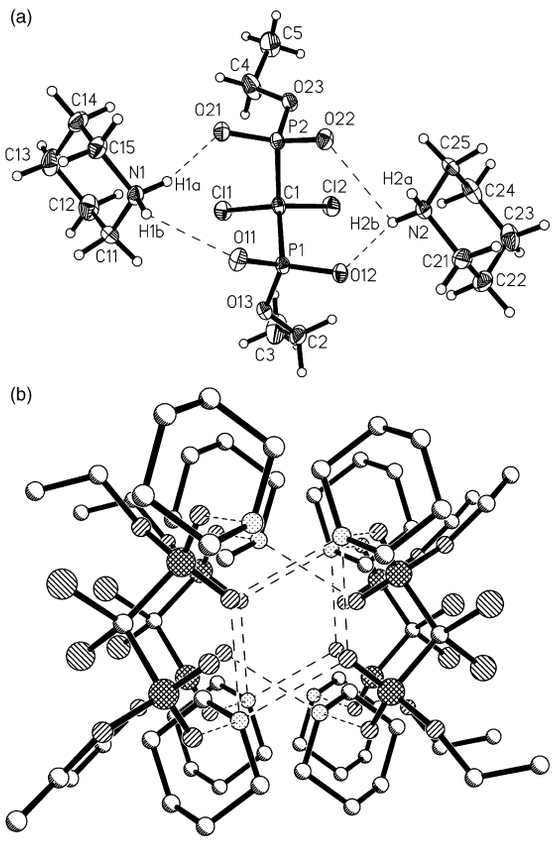

Fig. 1 (a) The structure and numbering scheme and (b) packing of compound **1**. The hydrogen atoms are omitted for clarity. 50% thermal ellipsoids are shown for all non-hydrogen atoms.

anion possesses approximate C_2 symmetry and the piperidinium cations are in chair conformation. Two additional hydrogen bonds [N ··· O 2.743(2) and 2.749(2) Å] connect the cations and anions to ribbons along the *a*-axis [Fig. 1(b)]. There are only normal van der Waals interactions between the ribbons.

The polymeric magnesium complex $[MgCl_2C(PO_3Et)_2(H_2O)_3]_n$ **2** crystallises in the triclinic crystal system. There are two independent six coordinated magnesium atoms in the centres of symmetry. Two symmetrically related $Cl_2C(PO_3Et)_2^{2-}$ ligands are chelated to Mg1 [Mg1–O11 2.083(2) and Mg1–O21 2.045(2) Å], and they connect Mg1 to adjacent Mg2 atoms [Mg2–O22 2.019(2)Å] [Fig. 2(a)]. The remainder of the octahedral coordination sites around both the Mg atoms are occupied by aqua ligands with Mg1–O1 2.134(2) Å, Mg2–O2 2.101(2) Å and Mg2–O3 2.081(2) Å. The aqua ligands form only intramolecular hydrogen bonds with each other [O1 ··· O2 = 2.969(2) Å] and with oxygen atoms O11, O12 and O23 [O ··· O 2.702(2)–3.043(3) Å].

The calcium and strontium complexes $[(H_2O)_3M\{Cl_2C(PO_3Et)_2\}_2M(H_2O)_3]$ (M = Ca in **3** and Sr in **4**), both crystallise in the orthorhombic crystal system, and the structures are isomorphous and dimeric (Fig. 3). The dimer possesses a two-fold rotation axis through the central carbon atoms of the $Cl_2C(PO_3Et)_2^{2-}$ ligands, and the metal atoms lie on a mirror plane. The $Cl_2C(PO_3Et)_2^{2-}$ ligands are chelated to both metal atoms

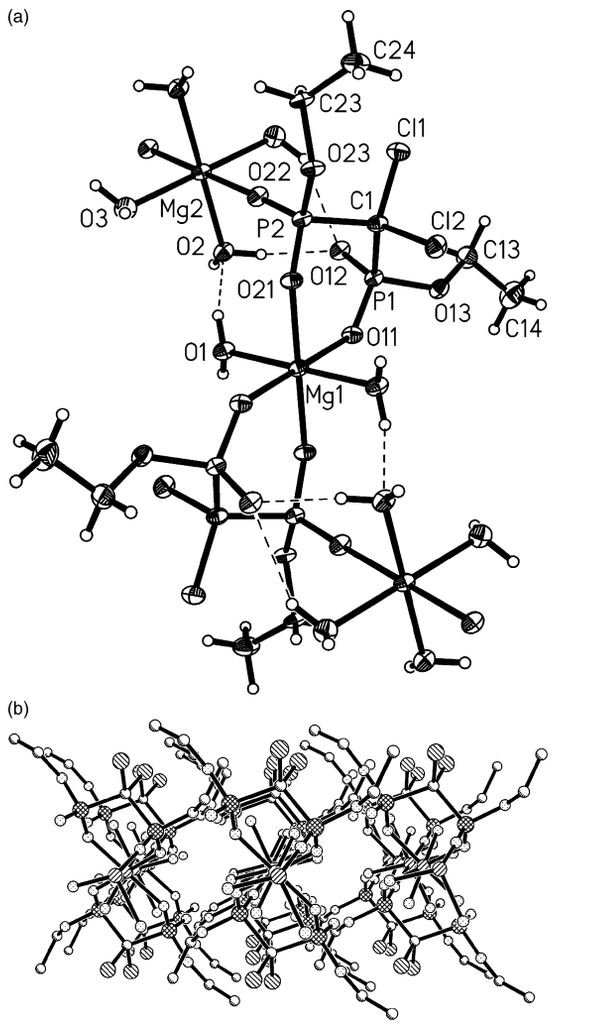

Fig. 2 (a) A part of the polymeric structure of **2** with numbering scheme and thermal ellipsoids (50%); (b) a top view of the polymeric structure of **2**.

having M–O distances of 2.406(1) Å in **3** and 2.518(2)–2.532(2) Å in **4**. The remainder of the coordination sites are occupied by disordered aqua ligands, and the M–OH_2 distances are of 2.404(2)–2.423(2) Å in **3** and 2.531(4)–2.550(4) Å in **4**. The aqua ligand O2 is disordered (66/34 in **3** and 65/35 in **4**) and no allowance for the H atoms of the disordered waters was made.

The complex $[(H_2O)_2Ba(Cl_2C(PO_3Et)_2)_2Ba(H_2O)_2]_n$ **5** crystallises in the monoclinic crystal system. The asymmetric unit contains two independent barium atoms with a coordination number of eight, joined together by two $Cl_2C(PO_3Et)_2^{2-}$ ligands. The $Cl_2C(PO_3Et)_2^{2-}$ ligands form both four- and six-membered chelate rings with Ba atoms, having Ba–O distances of 2.678(5)–2.809(5) Å [Fig. 4(a)]. Oxygen atoms containing the ethyl groups are also involved in metal coordination [Ba1–O13 3.020(5) and Ba2–O43 2.886(5) Å]. The remainder of the coordination sites are occupied by aqua ligands, having Ba–OH_2 distances of 2.736(6)–2.910(6) Å. The dimeric asymmetric units are connected through oxygen atoms of $Cl_2C(PO_3Et)_2^{2-}$ and aqua ligands, forming polymeric chains along the *b*-axis [Fig. 4(b)].

Selected bond distances and angles of the $Cl_2C(PO_3Et)_2^{2-}$ ligands in compounds **1**–**5** are presented in Table 1. The oxygen atoms not bonded to a metal atom or an ethyl group form the shortest P–O bonds: 1.488(1)–1.495(2) Å. The P–O bonds connected to metal atoms have distances very close to those above, 1.478(6)–1.499(6) Å. The longest P–O bond distances belong to the oxygen atoms bonded to the ethyl groups, or to both the ethyl group and the metal atom, 1.569(2)–1.596(1) Å. The P–C bond distances [1.842(2)–1.870(9) Å] and the P–C–P angles

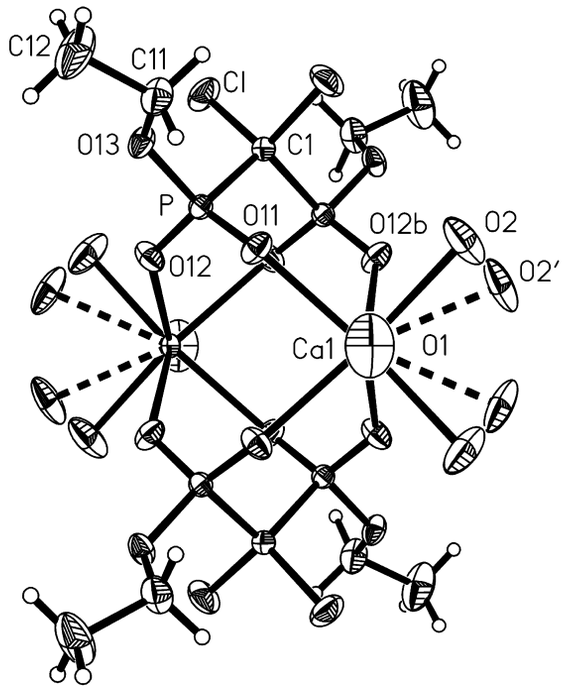

Fig. 3 The thermal ellipsoid plot (50%) with numbering scheme of compound **3**. Selected bond lengths (Å) for **3**: Ca1–O1 2.404(2), Ca1–O2 2.423(2), Ca1–O2′ 2.416(5), Ca1–O11 2.406(1), Ca1–O12b 2.406(1). Selected bond lengths (Å) for isomorphous compound **4**: Sr–O1 2.531(4), Sr–O2 2.550(4), Sr–O2′ 2.536(6), Sr–O11 2.532(2), Sr–O12b 2.518(2). In the figure, b refers to atom at (x, $-y + 1$, $-z$), and (′) refers to the disordered position of the aqua ligand.

[110.16(11)–113.90(7)°] agree well with previously reported distances and angles of clodronate[10] and its derivatives.[5] In all compounds, M–O(P) distances are, on the average, slightly shorter than M–OH_2 bonds, as found in the calcium complex of clodronate.[10]

Characterisation

The diethyl ester derivative of clodronate forms an interesting class of complexes with alkaline earth metals. The Mg and Ba complexes **2** and **5** crystallise as one-dimensional polymers, while the Ca and Sr complexes **3** and **4** are dimeric. These structural differences are easily observed with IR and ^{31}P NMR analyses.

The characteristic absorption region and characteristic absorption bands of the compounds were determined by IR spectroscopy. Band assignments were based on published values for similar compounds.[11,12] The characteristic absorption region appeared to be 1300–750 cm^{-1}. A very strong, broad band attributed to ν(P=O) appeared at *ca.* 1260–1220 cm^{-1}. The symmetric stretching vibration of the monoanionic, fully ionised PO_2^- group appeared at *ca.* 1090 cm^{-1}. Bands at 1166–1108 cm^{-1} were assigned to C–O–(P) and bands at 1063–946 cm^{-1} to P–O–(C) vibrations. Additional features of all the spectra were the bands at *ca.* 870 and 760 cm^{-1}, which were assigned to the asymmetric and symmetric P–C–P vibrations, respectively. In addition, the metal complexes **2**–**5** exhibited bands demonstrating the presence of water molecules: $\nu(H_2O)$ at *ca.* 3400 cm^{-1}, δ(H–O–H) at *ca.* 1656–1633 cm^{-1}, and in all spectra there were bands demonstrating ethyl groups (bands in the 3030–2850, 1485–1442 and 1390–1362 cm^{-1} regions). Asymmetric and symmetric stretching vibrations of CCl_2 groups were evident at *ca.* 750–740 cm^{-1}. In the case of compound **1**, there are strong bands in the 3000–2330 cm^{-1} region, attributed to the piperidinium cations.

^{31}P NMR spectra were measured for all the compounds studied. In the CP/MAS phosphorus spectra there is one (**3** and **4**), two (**1** and **2**) or four lines (**5**) which can be explained based on the X-ray crystal structures of the compounds. For compounds **3** and **4**, the environment of each phosphorus atom is equivalent. In compounds **1** and **2**, there are two phosphorus atoms in different environments, and the barium complex **5** is formed of a dimer containing four phosphorus atoms in unequal environments. In practice, the chemical shifts correlate with mean P–O bond lengths. Normally, the high field shifts belong to phosphorus, in which the P–O bond lengths are shortest: *e.g.* mean values of P–O bonds in Ba complex are 1.527 (P4), 1.522 (P1), 1.519 (P3) and 1.516 Å (P2) and the chemical shifts are 8.55, 7.67, 6.06 and 3.51 ppm, respectively.

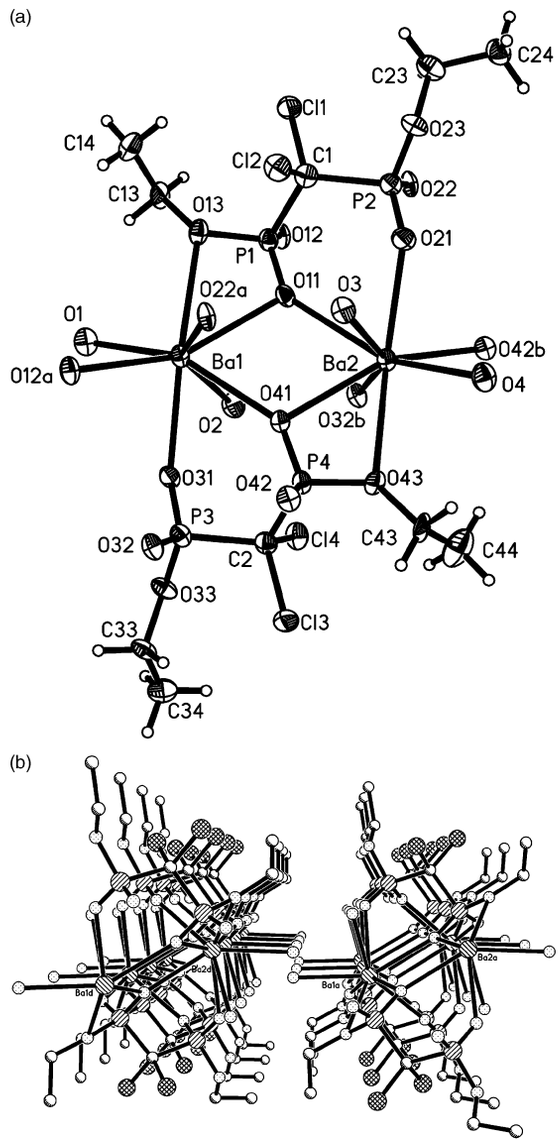

Fig. 4 (a) The structure and numbering scheme and (b) packing of compound **5** with thermal ellipsoids (50%). Selected bond lengths (Å): Ba1–O1 2.736(6), Ba1–O2 2.910(6), Ba1–O11 2.767(5), Ba1–O12a 2.694(5), Ba1–O13 3.020(5), Ba1–O22a 2.715(6), Ba1–O31 2.718(5), Ba1–O41 2.695(5), Ba2–O3 2.861(5), Ba2–O4 2.765(6), Ba2–O11 2.707(5), Ba2–O21 2.678(5), Ba2–O32b 2.716(5), Ba2–O41 2.809(5), Ba2–O42b 2.698(5), Ba2–O43 2.886(5) [a refers to atom at (x, $1 + y$, z) and b at (x, $y - 1$, z)].

Aqueous solubility

The aqueous solubility of the diethyl ester was defined in the presence of Ca^{2+} cations and referred to the solubility of clodronate under the same conditions. The formation of the solid metal complex reduced the solubility, resulting in both cases in precipitation. The aqueous solubilities of the calcium complexes were determined from the remaining solution. The aqueous solubility of **3** is approximately 133.4 mg ml^{-1}, while for calcium clodronate it is much less, as low as only 24.3

Table 1 Selected bond distances (Å) and angles (°) for **1**–**5**

	1	2	3	4	5
P1–O11	1.488(1)	1.494(2)	1.491(1)	1.482(2)	1.499(6)
P1–O12	1.490(1)	1.495(2)	1.494(1)	1.485(2)	1.478(6)
P1–O13	1.595(1)	1.577(2)	1.579(1)	1.569(2)	1.590(6)
P2–O21	1.490(1)	1.489(2)			1.478(6)
P2–O22	1.493(1)	1.489(2)			1.492(6)
P2–O23	1.596(1)	1.581(2)			1.577(6)
P3–O31					1.480(6)
P3–O32					1.493(6)
P3–O33					1.583(6)
P4–O41					1.493(6)
P4–O42					1.496(6)
P4–O43					1.593(6)
Cl(1)–C	1.793(1)	1.793(2)	1.788(1)	1.780(2)	1.804(8)
Cl(2)–C	1.799(1)	1.791(2)			1.782(8)
P1–C	1.865(2)	1.852(2)	1.851(1)	1.842(2)	1.847(9)
P2–C	1.869(2)	1.866(3)			1.870(9)
O–P1–C1	105.81(6)	105.16(10)	106.85(6)	107.20(9)	108.2(4)
	108.45(6)	107.61(10)	106.29(6)	106.50(9)	106.5(3)
	103.98(6)	106.13(10)	105.37(8)	104.98(12)	106.0(3)
O–P2–C1	108.22(6)	106.30(10)			106.0(4)
	106.46(6)	107.58(10)			106.2(3)
	104.08(6)	103.72(10)			104.0(4)
O–P3–C2					106.6(3)
					106.9(4)
					102.9(4)
O–P4–C2					106.1(4)
					107.7(3)
					106.3(3)
Cl(1)–C1–Cl(2)	107.38(7)	107.98(12)	108.34(12)	108.12(18)	108.6(4)
Cl(3)–C2–Cl(4)					107.9(4)
P1–C1–P2	113.90(7)	110.98(12)	110.16(11)	112.05(17)	113.5(4)
P3–C2–P4					112.3(4)

mg ml^{-1}. The results reveal that the masking of the ionizable groups of clodronate with the ethyl groups increases the solubility in the presence of the Ca^{2+} cations.

Experimental

General

Reagents used for the synthesis and characterisation of compounds **1**–**5** were analytical reagent grade. Infrared spectra were recorded on a Nicolet Magna-IR™ Spectrometer 750 with the KBr pellet technique. ^{31}P-CP/MAS NMR experiments were performed at 161.98 MHz on a Bruker AMX 400 spectrometer equipped with a double-tuned Bruker MAS 400 SB-BL 7 probe. For analysis of the X-ray structure, intensities were collected with a Nonius KappaCCD diffractometer.

Synthesis and crystallisation of compound 1

(Dichloromethylene)bisphosphonic acid tetraethyl ester, $Cl_2C(PO_3Et_2)_2$, was used as a starting material; its synthesis and characterisation have been reported earlier.[13] The yield of the synthesis was 82% and selectivity 100%, calculated from ^{31}P NMR spectra before isolation. NMR (D_2O): δ_H 4.14 (4H, m), 3.16 (8H, m), 1.78 (8H, m), 1.68 (4H, m), 1.28 (6H, t, J = 7.0). δ_P 8.86. δ_C 80.03 (t, $^1J_{CP}$ = 136.7), 67.15 (t + qv, ΣJ_{CP} = 6.9), 47.4 (t, $^+NCH_2$), 25.0 (t), 24.3 (t), 19.19 (q + qv, ΣJ_{CP} = 5.2).[5]

Compound **1** was recrystallised from an ethanol-water solution by slow evaporation. Crystals formed on the bottom of the test tube, but had no common shape. Found: C, 38.0; H, 7.2; N, 6.0. $C_{15}H_{34}Cl_2N_2O_6P_2$ requires C, 38.2; H, 7.3; N, 5.9%. IR/cm^{-1} (characteristic region): 1232vs, br, 1162m, 1108vs, 1090vs, 1057vs, br, 946vs, 861vs, 743vs. ^{31}P NMR: δ_P 6.32, 6.94.

Preparation of compounds 2–5

The metal complexes **2**–**5** were crystallised using a gel method. Carefully weighed amounts of dipiperidinium salt of *P*,*P*′-diethyl ester of Cl_2MBP and the metal salt were dissolved separately in water and warmed to 40 °C in a water-bath. The solutions were then mixed together, TMOS (tetramethoxysilane) was added (10%), and the two-phase system shaken until homogenous. The emulsion was left to transform to a gel after which a precipitant, in which the complex was insoluble, was added above the gel. Crystals for X-ray measurements and characterisation were purified with acetone.

The molar ligand to metal ratio used for the crystallisation of the magnesium complex **2** was 1 : 2, and ethanol was used as the precipitant. The magnesium complex crystallised as very small, plate-like crystals above the gel. Found: C, 16.3; H, 4.4; Mg, 6.3. $C_5H_{16}Cl_2MgO_9P_2$ requires C, 15.9; H, 4.3; Mg, 6.4%. IR/cm^{-1}: 1259vs, br, 1220vs, br, 1166m, 1141vs, br, 1082vs, 1063vs, br, 1026vs, 962vs, 867vs, 763s. ^{31}P NMR: δ_P 5.83, −1.19.

The molar ligand to metal ratio was 1 : 1 for the crystallisation of calcium and strontium complexes **3** and **4**. Acetone proved to be the most suitable precipitant for these complexes. Quite large crystals formed in and above the gel. The colourless crystals were cubic shaped, but they consisted of thin plates. (**3**) Found: C, 15.3; H, 4.0; Ca, 10.0. $C_{10}H_{32}Ca_2Cl_4O_{18}P_4$ requires C, 15.3; H, 4.1; Ca, 10.2%. IR/cm^{-1}: 1245vs, br, 1160m, 1117vs, br, 1095vs, 1041vs, br, 962vs, 867vs, 763s, 752s. ^{31}P NMR: δ_P 5.51. (**4**) Found: C, 13.5; H, 3.4; Sr, 19.8. $C_{10}H_{32}Cl_4O_{18}P_4Sr_2$ requires C, 13.6; H, 3.7; Sr, 19.9%. IR/cm^{-1}: 1241vs, br, 1163m, 1113vs, 1093vs, 1040vs, br, 958s, 868s, 760m, 750m. ^{31}P-NMR: δ_P 6.20.

The molar ligand to metal ratio used for crystallisation of the barium complex **5** was 1 : 1. An isopropyl alcohol–acetone mixture was used as the precipitant. The complex crystallised as very thin and long, needle-like crystals above the gel. Found: C, 12.3; H, 2.8; Ba, 29.6. $C_{10}H_{28}Ba_2Cl_4O_{16}P_4$ requires C, 12.7; H, 3.0; Ba, 29.1%. IR/cm^{-1}: 1245vs, br, 1164m, 1111vs, br, 1091vs, 1047vs, br, 954s, 861m, 759m, 743m. ^{31}P NMR: δ_P 8.55, 7.67, 6.06, 3.51.

Table 2 Experimental data for the crystallographic analyses (Kappa CCD): $(C_5H_{10}NH_2)_2Cl_2C(PO_3Et)_2$ **1**, $[MgCl_2C(PO_3Et)_2(H_2O)_3]_n$ **2**, $[(H_2O)_3Ca\{Cl_2C(PO_3Et)_2\}_2Ca(H_2O)_3]$ **3**, $[(H_2O)_3Sr\{Cl_2C(PO_3Et)_2\}_2Sr(H_2O)_3]$ **4**, $[(H_2O)_2Ba(Cl_2C(PO_3Et)_2)_2Ba(H_2O)_2]_n$ **5**

	1	**2**	**3**	**4**	**5**
Empirical formula	$C_{15}H_{34}Cl_2N_2O_6P_2$	$C_5H_{16}Cl_2MgO_9P_2$	$C_{10}H_{32}Ca_2Cl_4O_{18}P_4$	$C_{10}H_{32}Cl_4O_{18}P_4Sr_2$	$C_{10}H_{28}Ba_2Cl_4O_{16}P_4$
M_r	471.28	377.33	786.20	881.28	944.68
Crystal system	Triclinic	Triclinic	Orthorhombic	Orthorhombic	Monoclinic
Space group	$P\bar{1}$	$P\bar{1}$	*Cmca*	*Cmca*	$P2_1/c$
a/Å	9.4317(2)	7.3862(7)	24.0044(4)	24.0676(9)	25.0009(10)
b/Å	11.2372(3)	8.3578(7)	15.5269(2)	15.7465(6)	6.9490(4)
c/Å	11.9292(4)	11.8701(11)	7.9701(1)	8.0360(2)	17.3764(15)
α/°	105.774(1)	94.151(6)	90	90	90
β/°	98.221(2)	97.755(5)	90	90	93.297(4)
γ/°	106.067(2)	93.418(7)	90	90	90
V/Å^3	1136.17(5)	722.38(11)	2970.57(7)	3045.49(18)	3013.8(3)
Z	2	2	4	4	4
D_m/g cm^{-3} [a]	1.36 ± 0.01	1.70 ± 0.01	1.70 ± 0.01	1.86 ± 0.01	2.07 ± 0.07
D_c/g cm^{-3}	1.38	1.73	1.76	1.92	2.08
F(000)	500	388	1616	1712	1824
μ(Mo-Kα)/mm^{-1}	0.458	0.748	1.030	4.133	3.226
Crystal size/mm	0.40 × 0.20 × 0.10	0.25 × 0.20 × 0.03	0.20 × 0.20 × 0.20	0.20 × 0.10 × 0.10	0.20 × 0.08 × 0.08
θ Range/°	3.12–29.10	2.79–27.48	3.00–29.10	3.62–27.65	2.45–25.00
Temperature/K	120(2)	120(2)	223(2)	223(2)	120(2)
No. of unique data	5368	3041	2020	1733	5229
No. of obs. reflections	4663	2631	1803	1624	4017
No. of parameters	247	178	101	100	330
R_1 (F_o) > 4σ(F_o)	0.0314	0.0392	0.0317	0.0273	0.0533
wR_2(all data)	0.0752	0.0872	0.0831	0.0708	0.1127
Goodness-of-fit	1.054	1.174	1.050	1.086	1.351
Largest diff. peak, hole/e Å^{-3}	0.413, −0.352	0.491, −0.446	0.931, −0.496	0.846, −0.457	2.031, −1.028

[a] Measured at room temperature.

X-Ray crystallography

X-Ray diffraction data were collected with a Nonius Kappa CCD diffractometer using Mo-Kα-radiation (λ = 0.71073 Å). Denzo and Scalepack[14] programs were used for cell refinements and data reduction. The structures were solved using direct methods with SHELXS 97.[15] Structure refinements were carried out with SHELXL 97.[16] The hydrogen atoms were placed in calculated positions and not refined, except those of H_2O ligands, which were located from a Fourier difference map in **2** only. In **3** and **4**, one water ligand was disordered in two positions, with population parameters 0.66/0.34 in **3** and 0.65/0.35 in **4**. Crystallographic data are summarised in Table 2.

CCDC reference numbers 163497–163501.

See http://www.rsc.org/suppdata/dt/b2/b201124g/ for crystallographic data in CIF or other electronic format.

Aqueous solubility

The aqueous solubility of the diethyl ester was defined in the presence of the Ca^{2+} cations and referred to the solubility of clodronate under the same conditions. The aqueous solubilities were determined in a sodium acetate buffer (50 mM, pH 6.0) in various concentrations (200–400 mmol L^{-1}). The aqueous solutions of ligand and calcium salt were mixed in a molar ratio of 1 : 1 and stirred for 10 min. After one day, the supernatant solution was analysed using AAS to determine the amount of calcium compound in the solution.

Conclusions

The symmetrical diester derivative of Cl_2MBP acts both as a chelating and as a bridging ligand with the divalent metal cations that are present on the bone mineral surface. For the Mg complex, it is chelated to one Mg atom, and a third oxygen atom connects it to the other Mg atom. In the case of the Ca and Sr complexes, it is chelated to two adjacent metal atoms *via* four oxygen atoms. In contrast, unsubstituted Cl_2MBP is reported to be connected to only one Ca atom *via* two oxygen atoms.[10] It was also noted that the solubility of the Ca complex of the diethyl ester derivative was much better than the solubility of the calcium clodronate. On the basis of these findings, it can be expected that the bone affinity of the symmetrical diester derivative is likely to be better than that with the Cl_2MBP.

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