A Structural Study of Bisphosphonate Metal Complexes − Three New Polymeric Structures of the Calcium Complex of Clodronic Acid

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Three novel calcium complexes of clodronic acid were prepared and their structures determined by single-crystal X-ray diffractometry. Previously, a monomeric structure, $[Ca\{Cl_2C(PO_3H)_2\}(H_2O)_5]$ (**1**), has been determined, but the new structures are polymeric: $[\{Ca_2[Cl_2C(PO_3)_2](H_2O)_6\}\cdot 4.5H_2O]_n$ (**2**), $[\{Ca_2Na_{0.5}[Cl_2C(PO_3)_2](H_2O)_8\}Cl_{0.5}\cdot 4H_2O]_n$ (**3**) and $[\{Ca_5[Cl_2C(PO_3)_2]_2(H_2O)_{15}\}(NO_3)_2\cdot 1.5H_2O]_n$ (**4**); and they provide new, important information about the binding abilities of clodronic acid. Compounds **2**–**4** crystallise in the triclinic crystal system, the space group being $P\bar{1}$ with $Z = 2$. Compound **2** consists of Ca atoms and Cl_2MBP ligands connected to one-dimensional chains. The chains are held together by hydrogen bonds formed by aqua ligands and lattice water molecules. The structure of **3** consists of similar calcium clodronate chains forming two-dimensional layers through additional, six-coordinate Na atoms. Compound **4** consists of two-dimensional calcium clodronate layers, the calcium atoms are connected by Cl_2MBP– and aqua ligands. The nitrate groups and lattice water molecules lie between the layers and hold them together. The layered compounds **3** and **4** reveal substantial porosity.
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Introduction

Bisphosphonates, BP, are an interesting class of compounds due to their pharmaceutical applications,[1−4] and also due to their potential chemical applications in ion exchange, sorption, catalysis, and so forth.[5−8] Typically, bisphosphonates are used to inhibit the mineralization of soft tissues and as a therapy for bone-formation and resorption disorders.[1−4] It has been proposed that one stage of the mechanism of action of the non-nitrous methylenebisphosphonates (MBP) is that they are rapidly adsorbed onto the hydroxyapatite surface of bone by forming a layered structure.[4,9−11] Recently, new insights have been reported concerning the molecular mechanism of action of MBPs.[12]

The use of BPs in ion exchange, sorption and catalysis is based on their ability to form porous materials when complexing with metal atoms and their effectiveness is related to the degree of porosity. The structures of these materials consist of chains, layers or pillared layers; dimensionality depends on the number of donor atoms of the ligands, but also on the size of the organic group between the phosphonate groups and on the degree of protonation of the phosphonate group.[5−8]

Clodronate, disodium dichloromethylenebisphosphonate tetrahydrate, is one of the best-documented MBP derivatives that is used effectively in medical applications.[13] However, there are no studies on how clodronate can form a layered structure on the hydroxyapatite surface of bone. Clodronate has six possible O-donor atoms, and therefore we can presume that it also forms polymeric structures to be utilized in chemical applications. The previously reported crystal structure of calcium clodronate, $[Ca\{Cl_2C(PO_3H)_2\}(H_2O)_5]$ (**1**), revealed that Cl_2MBP itself acted only as a bidentate chelating ligand with Ca, forming a monomeric complex.[14] However, we have reported structures of alkaline earth metal complexes of a symmetrical diethyl ester derivative of clodronic acid in which one O atom of each of the two phosphonate groups is masked by an ethyl group, and the results showed that this ligand provides 3−5 donor O atoms, producing dimeric and polymeric structures.[15] In the present study, three new polymeric structures of the calcium complex of clodronic acid, $[\{Ca_2[Cl_2C(PO_3)_2](H_2O)_6\}\cdot 4.5H_2O]_n$ (**2**), $[\{Ca_2Na_{0.5}[Cl_2C(PO_3)_2](H_2O)_8\}Cl_{0.5}\cdot 4H_2O]_n$ (**3**) and $[\{Ca_5[Cl_2C(PO_3)_2]_2(H_2O)_{15}\}(NO_3)_2\cdot 1.5H_2O]_n$ (**4**), are depicted.

Results and Discussion

The previously-published calcium clodronate **1** was prepared from calcium monohydrogenphosphate and the disodium salt of clodronic acid by slow evaporation at 60 °C.[14,16] We prepared this monomeric structure and the new polymeric calcium clodronate compounds from the disodium salt of clodronic acid (clodronate) and calcium nitrate (compounds **1**, **2** and **4**) or from clodronate and calcium

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chloride (compound **3**) using a gel method. The gel-crystallisation tests revealed that concentrated solutions of the starting materials always produced calcium complex **1**. On the other hand, the new polymeric compounds were prepared under carefully controlled conditions; the effective factors are the pH of the ligand solution, the metal concentration and the rate of the diffusion and precipitation processes. In the preparation of **1**, clodronate (0.069 mmol) was used in the gel (pH 4.2, 1 mL), and the metal salt was offered as a concentrated $Ca(NO_3)_2{\cdot}4H_2O$ solution (3.34 M, 1 mL), which was placed above the gel and after one week was replaced by an acetone/ethanol (1:1) solution. Compound **4** was prepared under similar conditions, but using only a quarter of the amount of clodronate (0.017 mmol) in pH 5.0 and by placing a pure tetramethoxysilane (TMOS)-gel layer between the original gel and the precipitants. Compound **2** was also prepared from clodronate (0.017 mmol) but in pH 6.2. A pure TMOS-gel layer was placed above the native gel, and the concentration of the Ca solution was 1/75 of the former. No organic precipitant was needed to obtain the crystals of **2**. Compound **3** was prepared using the same amount of clodronate as in **1** and $CaCl_2$ (0.14 mmol), both of which were in the gel (pH 3.2, 1 mL), and acetone was placed above the gel immediately after gelation.

The calcium clodronate compound **1** consists of monomeric units,[14] while calcium compounds **2**−**4** are polymeric. The density increases with the dimensionality: it is lowest for **1** (1.86 g/cm^3) and highest for **4** (2.04 g/cm^3). Compound **2**, $[\{Ca_2[Cl_2C(PO_3)_2](H_2O)_6\}{\cdot}4.5H_2O]_n$, consists of infinite chains, the asymmetric unit containing two independent Ca atoms and one Cl_2MBP ligand (see Figure 1, left). Compound **3**, $[\{Ca_2Na_{0.5}[Cl_2C(PO_3)_2](H_2O)_8\}\text{-}Cl_{0.5}{\cdot}4H_2O]_n$ (see Figure 2, left), consists of chains similar to those in **2**, the chains being connected to a two-dimensional layered structure by six-coordinate Na centres. Compound **4**, $[\{Ca_5[Cl_2C(PO_3)_2]_2(H_2O)_{15}\}(NO_3)_2{\cdot}1.5H_2O]_n$, consists of two-dimensional layers of calcium clodronate, the asymmetric unit containing five independent calcium atoms connected to each other by Cl_2MBP- and aqua ligands (see Figure 3, left).

In compounds **1**−**4**, the calcium atoms are hepta-coordinated, the geometry around the metal atom is a distorted, monocapped trigonal prism, and the average Ca−O bond length is 2.41(6) Å. In **2** and **3** there are two crystallographically independent Ca atoms in the asymmetric unit (see Figure 1, right, and Figure 2, right). Four of the O atoms around the two Ca atoms are from the chelating Cl_2MBP ligands, and the coordination sphere is completed by three aqua ligands. The coordinated Cl_2MBP ligands form both four- and six-membered chelate rings with the metal atoms. In **3** one aqua ligand of Ca1 also acts as a bridge between Ca1 and an additional, six-coordinate Na atom [Na−O 2.44(2) Å], which lies in the centre of symmetry. The rest of the coordination sites around Na are occupied by aqua ligands.

In **4** there are five crystallographically independent Ca atoms (see Figure 3, left). The coordination sphere of calcium atoms 1, 2, 4 and 5 consists of four oxygen atoms from two chelating ligands, forming both four- and six-membered chelate rings. The coordination spheres of the Ca atoms are completed with three aqua ligands. The coor-

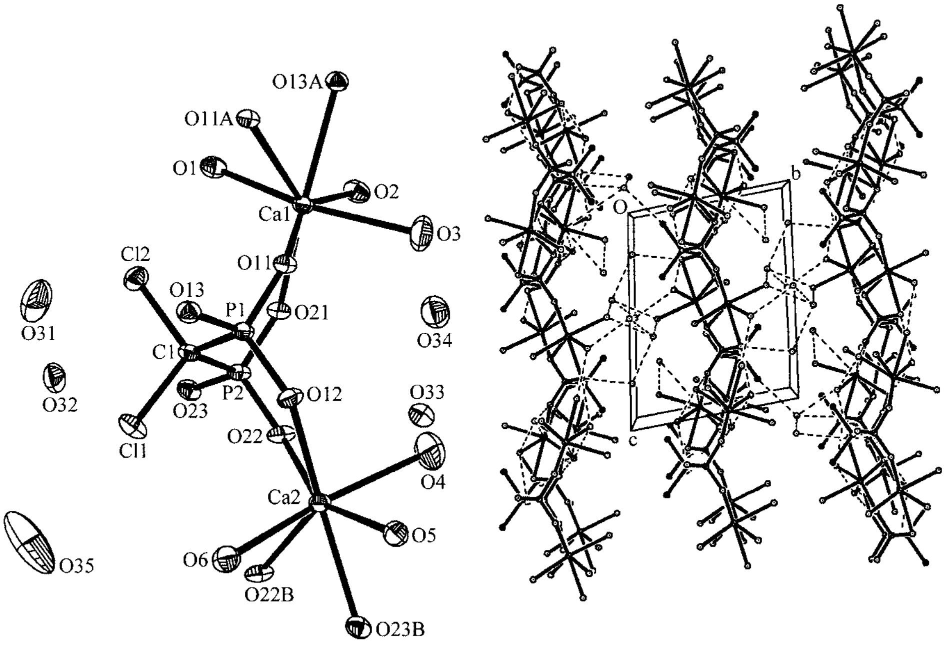

Figure 1. The structure of the asymmetric unit of **2** with numbering scheme and thermal ellipsoids (50 %; left) and packing of **2** (right); hydrogen atoms and water molecules O33′, O34′ and O35′ are omitted for clarity; selected bond lengths (Å): Ca1−O11 2.380(2), Ca1−O21 2.332(2), Ca1−O11A 2.482(2), Ca1−O13A 2.502(2), Ca1−O1 2.426(3), Ca1−O2 2.421(3), Ca1−O3 2.390(3), Ca2−O12 2.334(2), Ca2−O22 2.360(2), Ca2−O22B 2.481(2), Ca2−O23B 2.492(2), Ca2−O4 2.392(3), Ca2−O5 2.435(2), Ca2−O6 2.435(2) [A refers to atom at (−*x*, 1 − *y*, −*z*) and B at (1 − *x*, 1 − *y*, 1 − *z*)]

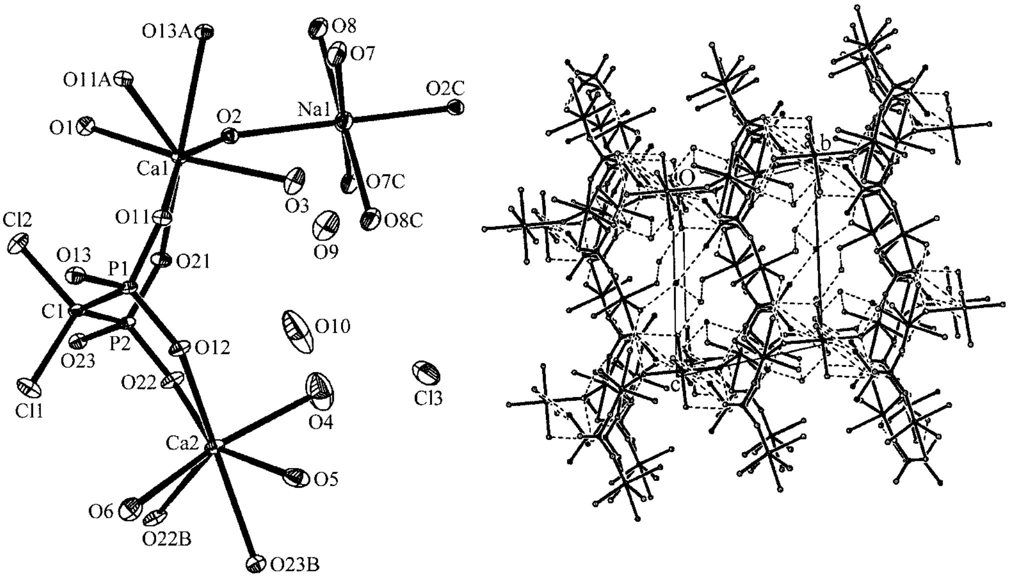

Figure 2. The structure of the asymmetric unit of **3** with numbering scheme and thermal ellipsoids (50 %; left) and packing of **3** in the direction of the *a* axis (right); hydrogen atoms are omitted for clarity; selected bond lengths (Å): Ca1−O11 2.339(1), Ca1−O21 2.340(1), Ca1−O11A 2.435(1), Ca1−O13A 2.545(1), Ca1−O1 2.445(1), Ca1−O2 2.458(1), Ca1−O3 2.407(2), Ca2−O12 2.335(1), Ca2−O22 2.357(1), Ca2−O22B 2.519(1), Ca2−O23B 2.471(1), Ca2−O4 2.395(1), Ca2−O5 2.408(1), Ca2−O6 2.419(2), Na1−O2 2.448(1), Na1−O7 2.454(2), Na1−O8 2.393(2) [A refers to atom at (−*x*, 1 − *y*, −*z*), B at (1 − *x*, 1 − *y*, 1 − *z*) and C at (1 − *x*, 2 − *y*, −*z*)]

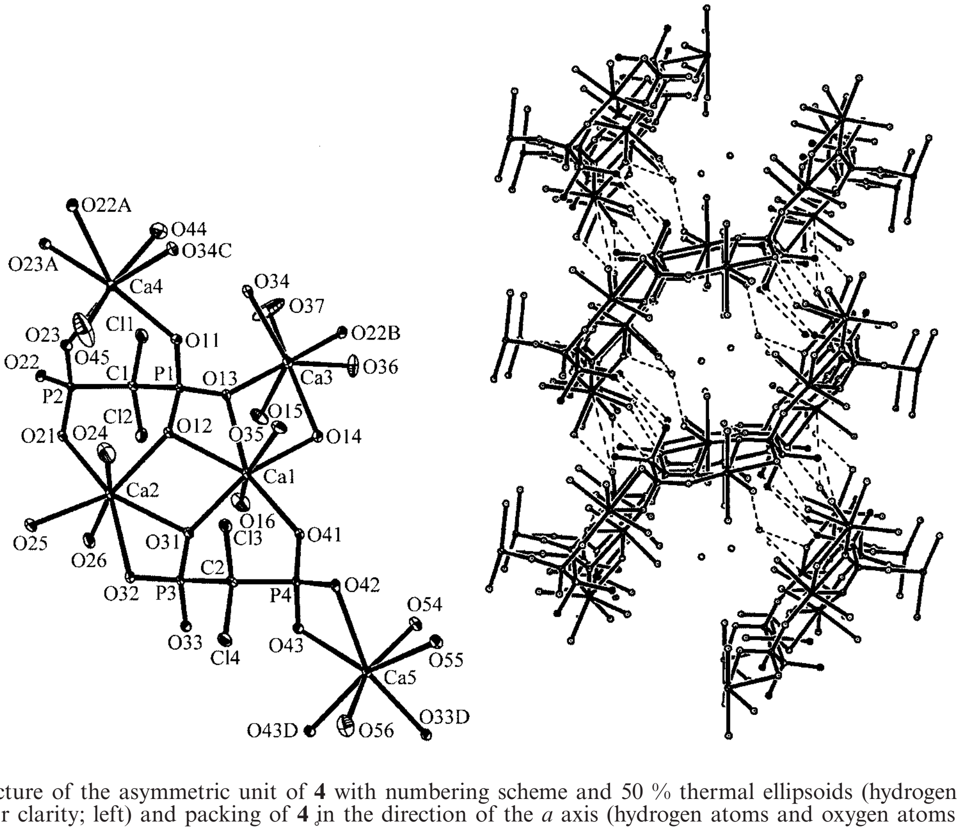

Figure 3. The structure of the asymmetric unit of **4** with numbering scheme and 50 % thermal ellipsoids (hydrogen atoms and nitrate ions are omitted for clarity; left) and packing of **4** in the direction of the *a* axis (hydrogen atoms and oxygen atoms of nitrate ions are omitted for clarity; right); selected bond lengths (Å): Ca1−O12 2.494(3), Ca1−O13 2.491(3), Ca1−O31 2.313(3), Ca1−O41 2.336(3), Ca1−O14 2.483(3), Ca1−O15 2.414(3), Ca1−O16 2.354(3); Ca2−O12 2.321(3), Ca2−O21 2.369(3), Ca2−O31 2.425(3), Ca2−O32 2.532(3), Ca2−O24 2.420(4), Ca2−O25 2.399(3), Ca2−O26 2.408(3); Ca3−O13 2.292(3), Ca3−O22B 2.310(2), Ca3−O14 2.532(3), Ca3−O34 2.576(3), Ca3−O35 2.408(3), Ca3−O36 2.392(3), Ca3−O37 2.370(3); Ca4−O11 2.349(3), Ca4−O22A 2.499(3), Ca4−O23 2.310(3), Ca4−O23A 2.456(3), Ca4−O34C 2.450(3), Ca4−O44 2.381(3), Ca4−O45 2.370(4); Ca5−O33D 2.338(3), Ca5−O42 2.528(3), Ca5−O43 2.440(3), Ca5−O43D 2.356(3), Ca5−O54 2.451(3), Ca5−O55 2.425(3), Ca5−O56 2.435(3) [A refers to atom at (1 − *x*, 1 − *y*, −*z*), B at (*x* − 1, *y*, *z*), C at (−*x*, 1 − *y*, −*z*) and D at (−*x*, −*y*, 1 − *z*)]

dination sphere of calcium atom 3 consists of only two phosphonate oxygen atoms originating from two different Cl_2MBP ligands and the rest of the sites are occupied by five aqua ligands.

In the monomeric compound **1**, one of the oxygen atoms of both phosphonate groups of Cl_2MBP is coordinated to the Ca atom, the second oxygen atom being unbound and the third protonated.[14] In the case of the polymeric compounds **2**−**4**, there are neither unbound nor protonated oxygen atoms: the Cl_2MBP ligands are coordinated to the ambient calcium atoms through all six oxygen atoms, acting as chelating and bridging ligands. In **2** and **3** all Cl_2MBP ligands form two six-membered and two four-membered chelate rings simultaneously and are coordinated to four metal atoms. In **4** one ligand acts similarly to these, while the other one is connected to six Ca atoms. The bond lengths and angles of the Cl_2MBP ligand in compounds **2**−**4** are all typical.

Some porosity was found in all compounds. In **2** the chains are connected to each other by intermolecular hydrogen bonds, forming layers parallel to the (010) plane. The chlorine atoms and aqua ligands point towards the interlayer section, and the space is filled with lattice water molecules (Figure 1, right). Between the infinite chains there are intermolecular hydrogen bonds involving the aqua ligands and phosphonate O atoms [O···O distances 2.603(12)−3.051(8) Å and angles 118−179°]. In **3** the layers are parallel to the (−111) plane. The structure reveals substantial porosity in the packing diagram, as seen in Figure 2, right. Along the *a* axis, the layers are packed one on top of the other, forming pillars where two Na and four Ca atoms in a 24-membered ring define a cavity on the plane. The aqua ligands of each metal atom point into the cavity, and the Cl3 ions sit in the middle of the opening surrounded by lattice water molecules. There are also smaller pores between the layers. Intramolecular hydrogen bonds are formed between the aqua ligands, and the intermolecular hydrogen bonds involve both water molecules and chlorine Cl3 atoms [O···O/Cl distances 2.718(2)−3.339(4) Å and angles 119−170°] holding the layers together. In compound **4**, the layers are parallel to the (011) plane, and tunnels are formed between the layers along the *a* axis. The tunnels are filled with nitrate molecules and lattice water molecules (see Figure 3, right). Both inter- and intramolecular hydrogen bonds are found, the O···O distances being 2.457(12)−3.084(4) Å and the angles 117−177°. The intermolecular hydrogen bonds hold the adjacent calcium clodronate layers together, and involve water molecules and the O atoms of nitrate.

Conclusion

The previously-published structure and the present ones clearly differ: in compound **1**, the Cl_2MBP ligand provides only two donor O atoms, being chelated to one Ca atom;[14] while in the new polymeric compounds **2**−**4**, all Cl_2MBP ligands provide six donor O atoms, forming two six-membered and two four-membered chelate rings and acting as mono- and polyatomic bridges between the Ca atoms. As a result, the Cl_2MBP ligands in **2**−**4** are tightly bound to several Ca atoms through all O atoms, resulting in one-dimensional chains or two-dimensional layers, connected to a three-dimensional open network through hydrogen bonds. In compound **3**, the porosity is marked. These new findings concerning the coordination abilities of clodronic acid may explain its activity in forming a layered structure on the hydroxyapatite surface of bone and also provide new information about the ability of clodronic acid to form porous materials that can be used in chemical applications.

Experimental Section

General Remarks: All reagents used for the synthesis and characterisation of compounds **2**−**4** were of analytical reagent grade. The synthesis and characterisation of clodronic acid and its disodium salt $Na_2[CCl_2(PO_3H_2)]\cdot 4H_2O$ have been reported earlier.[14] The metal complexes were crystallised using gel methods **A** (**3**) and **C** (**1**, **2**, and **4**). In method **A**, a carefully weighed amount of $Na_2[CCl_2(PO_3H)_2]\cdot 4H_2O$ and metal salt were dissolved in water (2 × 0.45 mL) and warmed to 40 °C in a water bath. The solutions were then mixed together, and the TMOS (0.1 mL) was added. The two-phase system was shaken until homogeneous, and the emulsion was left to form a gel. Crystallisation was induced by adding an organic precipitant (1 mL) above the gel. In method **C**, $Na_2[CCl_2(PO_3H)_2]\cdot 4H_2O$ was dissolved in water (0.9 mL); and if necessary, the pH was adjusted with NaOH (0.02−1.0 M). TMOS (0.1 mL) was added; and the two-phase system was shaken until homogeneous. The emulsion was left to form a gel. In the preparation of **2** and **4**, after gelation a pure TMOS-gel layer (0.5 mL, 20 % v/v) was added above the native gel. The metal salt was dissolved in water (1.0 mL), added above the gel, and after 1−2 weeks replaced with organic precipitant (1.0 mL).

$[Ca\{Cl_2C(PO_3H)_2\}(H_2O)_5]$ (1): Preparation of **1** by slow evaporation at 60 °C has been described previously.[14,16] In this investigation, **1** was prepared with method **C** by placing clodronate (0.069 mmol, pH 4.5) in TMOS-gel and adding a water solution of $Ca(NO_3)_2\cdot 4H_2O$ (3.34 M, pH 4.2) above the gel. After one week the metal salt solution was replaced with a 1:1 acetone/ethanol solution. In a few weeks the crystals formed in the shape of cubes. The measured cell dimensions and results of elemental analysis agree with the earlier results.[14]

$[\{Ca_2[Cl_2C(PO_3)_2](H_2O)_6\}\cdot 4.5H_2O]_n$ (2): In the preparation of **2** with method **C**, clodronate (0.017 mmol) was dissolved in water and the pH was adjusted to 6.2. A water solution of $Ca(NO_3)_2\cdot 4H_2O$ (0.043 M, pH 4.5) was added above a pure TMOS-gel layer. Two days later the colourless, plank-like crystals were formed above the gel. $CH_{21}Ca_2Cl_2O_{16.5}P_2$ (510.18): calcd. C 2.35, H 4.15; Ca, 15.7; found C 2.11, H 3.90; Ca, 15.6.

$[\{Ca_2Na_{0.5}[Cl_2C(PO_3)_2](H_2O)_8\}Cl_{0.5}\cdot 2H_2O]_n$ (3): In the preparation of **3** with method **A**, both clodronate (0.069 mmol) and calcium chloride (0.14 mmol) were dissolved in water (pH 3.2) and TMOS was added. After gelation, acetone was placed above the gel, and in six months thin crystals were formed above the gel. $CH_{20}Ca_2Cl_{2.5}Na_{0.5}O_{16}P_2$ (530.39): calcd. C 2.26, H 3.80; found C 2.04, H 4.12.

$[\{Ca_5[Cl_2C(PO_3)_2]_2(H_2O)_{15}\}(NO_3)_2\cdot 1.5H_2O]_n$ (4): In the preparation of **4** with method **C**, clodronate (0.017 mmol) was dissolved

Table 1. Crystal data of compounds **2**, **3** and **4**

	2	**3**	**4**
Empirical formula	$CH_{21}Ca_2Cl_2O_{16.5}P_2$	$CH_{20}Ca_2Cl_{2.5}Na_{0.5}O_{16}P_2$	$C_2H_{33}Ca_5Cl_4N_2O_{34.5}P_4$
M_r	510.18	530.39	1103.38
Crystal system	Triclinic	Triclinic	Triclinic
Space group	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
a (Å)	8.8019(3)	8.7689(3)	8.7757(3)
b (Å)	8.8977(3)	9.2561(3)	10.4116(5)
c (Å)	11.9694(4)	11.9222(4)	20.2680(9)
α (°)	98.640(2)	97.976(2)	89.337(2)
β (°)	106.681(2)	106.357(2)	88.556(3)
γ (°)	92.886(2)	97.496(2)	75.815(3)
V (Å^3)	883.43(5)	904.77(5)	1794.8(1)
Z	2	2	2
D_m (g cm^{-3})[a]	1.89(4)	–	2.00(8)
D_c (g cm^{-3})	1.92	1.95	2.04
F (000)	526	544	1126
μ(Mo-K_α) (mm^{-1})	1.204	1.259	1.338
Crystal size (mm^3)	0.20 × 0.20 × 0.10	0.20 × 0.20 × 0.10	0.20 × 0.20 × 0.20
θ Range (°)	3.70–26.00	2.57–26.00	2.25–25.00
Temperature (K)	120(2)	120(2)	120(2)
No. of unique data	3399	3561	5782
No. of obs. reflections	2999	3249	5206
No. of parameters	235	223	466
R_1 (Fo) $> 4\sigma(Fo)$	0.0428	0.0253	0.0447
ωR_2 (all data)	0.1169	0.0660	0.1040
Goodness-of-fit	1.087	1.043	1.010
Largest diff. peak and hole (e·Å^{-3})	0.606 and −0.612	0.587 and −0.433	1.723 and −0.909

Measured at room temperature.

in water and the pH adjusted to 5.0. A water solution of $Ca(NO_3)_2 \cdot 4H_2O$ (3.34 M, pH 4.2) was placed above a pure TMOS-gel layer. After two weeks the metal salt solution was replaced with a 1:1 acetone/ethanol solution. About two months later colourless crystals were formed as thin plates in and above the gel. $C_2H_{33}Ca_5Cl_4N_2O_{34.5}P_4$ (1103.38): calcd. C 2.18, H 3.01, N 2.54, Ca, 18.2; found C 2.20, H 3.13, N 2.48, Ca, 18.1.

X-ray Crystallographic Study: Single-crystal x-ray diffraction studies were performed on a Nonius Kappa CCD diffractometer using Mo-K_α radiation (λ = 0.71073 Å). Denzo and Scalepack[17] programs were used for cell refinements and data reduction. The structures were solved by direct methods with SHELXS 97.[18] Structural refinements were carried out with SHELXL 97.[19] The hydrogen atoms were placed in calculated positions and not refined. In **2** two water molecules, O33 and O34 are disordered over two positions with population parameters 50/50 and water molecule O35 is disordered around a centre of symmetry. The hydrogen atoms of the disordered water molecules were omitted in the calculations. In **3** the Cl3 atom is disordered around a centre of symmetry. Crystallographic data of compounds **2–4** are summarised in Table 1.
CCDC-233048 (compound **2**), -233049 (compound **3**), -233050 (compound **4**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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