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Synthesis of phenyl substituted bisphosphonates and crystal structures and characterization of Cd complexes of (dichloromethylene)bisphosphonic acid phenyl and alkyl ester derivatives†

Jonna Jokiniemi,^{*a} Jouko Vepsäläinen,^b Harri Nätikinniemi,^a Sirpa Peräniemi^b and Markku Ahlgren^a

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Two novel phenyl esters and partial phenyl esters of (dichloromethylene)bisphosphonic acid were synthesised. Three new layered Cd complexes of (dichloromethylene)bisphosphonic acid *P,P*-diphenyl, monophenyl and monoethyl esters were prepared. The complexes, $[\text{Cd}_3\{(\text{Cl}_2\text{CP}_2\text{O}_6\text{Ph})_2(\text{H}_3\text{COH})(\text{H}_2\text{O})_5\}(\text{H}_2\text{O})_2]_n$ (**7**), $[\{\text{Cd}(\text{Cl}_2\text{CP}_2\text{O}_6\text{Ph}_2)(\text{H}_2\text{O})_3\}(\text{H}_2\text{O})]_n$ (**8**) and $[\{\text{Cd}_{1.5}(\text{Cl}_2\text{CP}_2\text{O}_6\text{Et})(\text{H}_2\text{O})_2\}(\text{C}_3\text{H}_6\text{O})_{0.5}(\text{H}_2\text{O})_{4.5}]_n$ (**9**), were characterized by single crystal X-ray diffraction, IR spectroscopy, solid-state ^{31}P - and ^{113}Cd -CP/MAS NMR and elemental analysis. Also their thermal behaviour was investigated. Compound **7** consists of 1D chains with four independent octahedral Cd atoms joined by two L_1 ligands, $\text{L}_1 = (\text{Cl}_2\text{CP}_2\text{O}_6\text{Ph})^{3-}$. The chains are connected into layers by phosphonate O atoms, and the adjacent layers are held together by face-to-face π – π stacking interactions. Compound **8** shows a new type of layered structure for metal bisphosphonates, where the L_2 ligand, $\text{L}_2 = (\text{Cl}_2\text{CP}_2\text{O}_6\text{Ph}_2)^{2-}$, coordinates tridentately to three Cd^{2+} ions. Each CdO_6 octahedron is connected to three CPO_3 tetrahedra and each tetrahedron to three octahedra leading to a 2-D framework consisting of 12-membered cyclic cores. The layers are held together by edge-to-face CH/π interactions. In compound **9**, the asymmetric unit contains two independent Cd^{2+} cations connected by L_3 ligands, $\text{L}_3 = (\text{Cl}_2\text{CP}_2\text{O}_6\text{Et})^{3-}$ and aqua ligands, to form a Cd–bisphosphonate layer. The layers are further interconnected into a 3-D supramolecular network by extensive hydrogen bonds.

Introduction

Many (methylene)bisphosphonates (MBPs), the best known of which are clodronate ((dichloromethylene)bisphosphonate Cl_2MBP), are effective drugs for bone disorders such as osteoporosis.^{1–3} Bisphosphonic acids have also attracted close attention because of their utility in supramolecular chemistry and crystal engineering.^{4–6} Usually, the metal bisphosphonates form polymeric materials and microporous solids, with properties that offer a diversity of practical applications in catalysis, ion-exchange and sorption.^{6–10} Hydrogen bonds are dominant in these structures, producing one-, two- and three-dimensional networks.

The highly polar structure of clodronate, and other tetra-acidic MBPs, means that these compounds are highly hydrophilic and their oral bioavailability is poor. We have focused on the complexing properties of the less polar ester derivatives of clodronate with divalent metal cations. One stage in the mechanism of action of the non-nitrogen MBPs is rapid adsorption

onto the hydroxyapatite surface of bone through formation of a layered structure.^{11–14} Numerous metal bisphosphonate complexes where the bisphosphonic ligand is fully ionic are known, but the complexation study of their ester derivatives is limited by the lack of effective methods for their synthesis.

In an earlier work, our group studied the complexing properties of clodronate and its partially substituted symmetrical dialkyl ester derivatives.^{15–23} Also, we reported alkaline earth metal complexes of a dibenzoyl derivative of clodronic acid.²⁴ The dialkyl ester and dibenzoyl derivatives produce only molecular compounds or 1-D polymeric structures.^{19–24} More recently, we developed a synthesis method for partial amide esters of Cl_2MBP ,²⁵ and we also succeeded in preparing several metal complexes of these amide ester derivatives of clodronate in which one O atom is masked with the methyl group and the other is replaced by a cyclic amine group.^{26,27} The structures of these compounds have diverse coordination architectures: hexameric microporous material and polymeric structures with chains and layers. Now, we report the synthesis of phenyl ester derivatives of Cl_2MBP and structural studies on new Cd compounds with monophenyl, asymmetric diphenyl and monoethyl ester ligands of Cl_2MBP .

Experimental

General procedure for phenyl ester ligands

Compounds **1a**²⁸ and **1b**²⁹ were prepared from the required monophosphorus species **2** and **3** via intermediates **5a,b** and **6a,b**

^aDepartment of Chemistry, University of Joensuu, P.O. Box 111, 80101 Joensuu, Finland. E-mail: Jonna.Jokiniemi@joensuu.fi; Fax: +358 13 251 3390; Tel: +358 13 251 3386

^bLaboratory of Chemistry, Department of Biosciences, University of Kuopio, P.O. Box 1627, 70211 Kuopio, Finland

† Electronic supplementary information (ESI) available: Tables S2–S4. Thermogravimetric curves for compounds **7–9**. ^{31}P -CP/MAS NMR spectra for compounds **7–9** and ^{113}Cd -CP/MAS NMR spectrum for compound **8**. CCDC reference numbers 719961–719963. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b907874f

by known methods (see Schemes 1 and 2). Intermediates **5c**³⁰ and **5d**, prepared from tetrachloride **4**, phenol and methanol by using pyridine as a base, were chlorinated to **6c** and **6d** which are novel compounds. Compounds **1c** and **1d** were prepared from **6c** and **6d**, by using piperidine and chlorotrimethylsilane, respectively, as demethylation agent.

P,P'-dimethyl diphenyl methylenebisphosphonate **5c**: To a mixture of methylene diphosphonic dichloride **4** (6.6 g, 26 mmol) in dry toluene (40 mL) was added gradually a mixture of phenol (4.5 g, 47 mmol) and pyridine (4.0 g, 51 mmol) in dry toluene (20 mL) at 0 °C. After stirring at 0 °C for 30 min and for 1 h without cooling, a mixture of methanol (2.3 mL, 57 mmol) and pyridine (4.0 g, 51 mmol) in dry toluene (20 mL) was added within 10 min and stirred at room temperature for 2 h. The solids were collected onto filter paper and washed with toluene (20 mL). The combined toluene phases were washed twice with 1 N NaOH (2 × 10 mL), dried (MgSO₄), and evaporated to dryness *in vacuo*, and the residue was chromatographed on silica gel using ethylacetate as eluent to give **5c** (3.56 g, 38%); *R*_f 0.35. NMR chemical shifts were as reported previously.³⁰ Note: phenol is extremely toxic and must be handled carefully.

Methyl triphenyl methylenebisphosphonate **5d**: Prepared as **5c** from **4** (5.6 g, 22 mmol), phenol (5.7 g, 61 mmol), pyridine (4.8 g, 60 mmol), methanol (2.3 mL, 57 mmol) and pyridine (1.8 g, 23 mmol) to give **5d** (2.76 g, 30%); *R*_f 0.54. NMR (CDCl₃): δ_H 7.37–7.16 (15H, m), 3.90 (3H, d, ³*J*_{HP} = 11.5 Hz), 2.92 (2H, t ²*J*_{HP} = 21.2 Hz); δ_P 16.88 (d, ²*J*_{PP} = 9.3 Hz), 12.58 (d).

P,P'-dimethyl diphenyl (dichloromethylene)bisphosphonate **6c**: A mixture of benzyltriethyl ammonium chloride (0.3 g), aqueous NaOCl (8%, 15 mL) and **5c** (0.65 g, 1.8 mmol) in CCl₄ (15 mL) were stirred at room temperature for 20 min. The organic layer was separated and the water phase was extracted twice with CHCl₃ (2 × 10 mL). The combined organic layers were washed twice with water (2 × 5 mL), dried (MgSO₄) and evaporated to dryness *in vacuo* to give **6c** (0.77 g, 99%) as pale yellow liquid. NMR (CDCl₃): δ_H 7.41 – 7.18 (10H, m), 4.12 – 4.07 (6H, m); δ_P 6.25, 6.16 (due to diastereomers).

Methyl triphenyl (dichloromethylene)bisphosphonate **6d**: Prepared as **6c** from benzyltriethyl ammonium chloride (0.4 g), aqueous NaOCl (8%, 66 mL) and **5d** (2.76 g, 6.6 mmol) in CHCl₃ (66 mL) but reaction time was 1 h 20 min. **6d** (2.79 g, 87%) was obtained as pale yellow liquid. NMR (CDCl₃): δ_H 7.38 – 7.17 (15H, m), 4.08 (3H, ³*J*_{HP} = 11.1 Hz); δ_P 5.86 (d, ²*J*_{PP} = 23.6 Hz), 0.48 (d).

(Dichloromethylene)bisphosphonic acid **P,P'**-diphenyl ester dipiperidinium salt **1c**: Prepared by known method³¹ from **6c** (0.77 g, 1.8 mmol) and piperidine (5 mL) to give **1c** (1.00 g, 99%) as white solid. Anal. Found: C, 47.24; H, 6.30; N, 4.85%. Calc. for C₂₃H₃₄N₂O₆P₂Cl₂·H₂O: C, 47.19; H, 6.20; N, 4.79%. NMR (D₂O):

δ_H 7.47 – 7.12 (10H, m), 3.18 – 3.04 (8H, m), 1.82 – 1.57 (12H, m); δ_C 154.79 (t, Σ*J*_{CP} = 4.2³²), 132.35 (2C), 127.17, 124.10 (t, Σ*J*_{CP} = 2.0³²), 79.08 (t, ¹*J*_{CP} = 144.4 Hz), 47.37, 25.02, 24.30; δ_P 6.36.

[(Diphenoxyposphino)dichloromethyl]phosphinic acid monophenyl ester sodium salt **1d**: Prepared by a known method³¹ from **6d** (2.0 g, 4.1 mmol), NaI (0.61 g, 4.1 mmol) and ClSiMe₃ (0.53 g, 4.9 mmol) in dry acetonitrile (20 mL) followed by treatment with MeOH (5 mL) and H₂O (15 mL) and adjustment of pH to 10 with 1 M NaOH to give **1d** (2.00 g, 99%) as white solid. Anal. Found: C, 43.99; H, 2.96%. Calc. for C₁₉H₁₇O₇P₂Cl₂Na · H₂O: C, 44.47; H, 3.34%. NMR (D₂O/DMSO-*d*₆ 50/50): δ_H 7.54–7.22 (15H, m); δ_C 154.97 (d, ²*J*_{CP} = 8.6 Hz), 152.91 (2C, d, ²*J*_{CP} = 10.2 Hz), 133.25 (4C), 132.77 (2C), 129.45 (2C), 127.44, 123.79 (2C, d, ³*J*_{CP} = 4.0 Hz), 123.70 (4C, d, ²*J*_{CP} = 4.0 Hz), 75.81 (dd, ¹*J*_{CP} = 163.3 and 138.5 Hz); δ_P 6.52 (d, ²*J*_{PP} = 17.0 Hz), 1.48 (d).

Preparation of compounds 7–9

Synthesis and characterization of the trisodium salt of (dichloromethylene)bisphosphonic acid monoethyl ester (see Scheme 3) have been described earlier.³¹ The metal complexes **7** [{Cd₃(Cl₂CP₂O₆Ph)₂(H₃COH)(H₂O)₅}(H₂O)₂]_{*n*} and **8** [{Cd(Cl₂CP₂O₆Ph₂)(H₂O)₃}(H₂O)]_{*n*} were crystallized by slow evaporation: compound **7** from water/methanol solution and compound **8** from water/ethanol solution. Compound **9** [{Cd_{1.5}(Cl₂CP₂O₆Et)(H₂O)₂}(C₃H₆O)_{0.5}(H₂O)_{4.5}]_{*n*} was crystallized by a gel method. The crystals for X-ray diffraction analysis were separated from the gel on a watch-glass under a microscope, purified with pure precipitant and dried in air.

[{Cd₃(Cl₂CP₂O₆Ph)₂(H₃COH)(H₂O)₅}(H₂O)₂]_{*n*} (**7**)

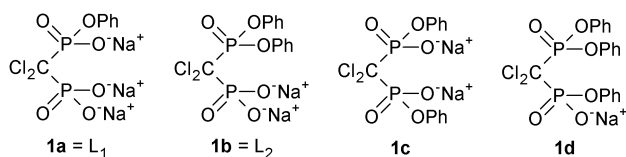
Na₃Cl₂CP₂O₆Ph (5 mg, 0.013 mmol) and Cd(NO₃)₂·4H₂O (8.66 mg, 0.029 mmol) were dissolved separately in water and mixed (2.0 mL, pH 4.8). The metal complex (**7**) was crystallized from water/methanol (1 : 1) solution by slow evaporation. About two months later, colourless crystals of **7** suitable for X-ray analysis were formed as thin needles. Anal. Found: C, 15.90; H, 2.30; Cd, 29.66%. Calc. for C₁₅H₂₈Cl₄Cd₃O₂₀P₄: C, 15.94; H, 2.41; Cd, 29.84%.

[{Cd(Cl₂CP₂O₆Ph₂)(H₂O)₃}(H₂O)]_{*n*} (**8**)

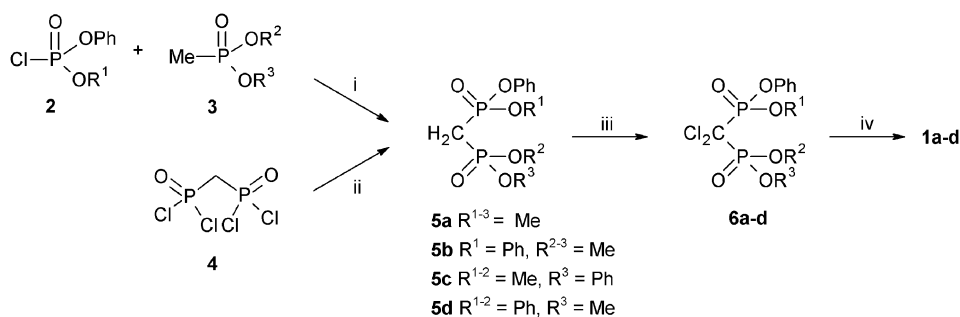
Na₂Cl₂CP₂O₆Ph₂ (1 mg, 0.0023 mmol) and Cd(NO₃)₂·4H₂O (0.71 mg, 0.0023 mmol) were dissolved separately in water and mixed (1.0 mL, pH 5.5). The metal complex (**8**) was crystallized from water/ethanol (1 : 1) solution by slow evaporation. After about two months, colourless crystals of **8** suitable for X-ray analysis were formed as thin needles. Anal. Found: C, 26.83; H, 3.11; Cd, 18.92%. Calc. for C₁₃H₁₈Cl₂CdO₁₀P₂: C, 26.94; H, 3.13; Cd, 19.40%.

[{Cd_{1.5}(Cl₂CP₂O₆Et)(H₂O)₂}(C₃H₆O)_{0.5}(H₂O)_{4.5}]_{*n*} (**9**)

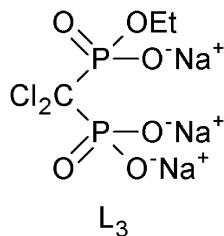
Na₃Cl₂CP₂O₆Et (10 mg, 0.030 mmol) and Cd(NO₃)₂·4H₂O (9.1 mg, 0.030 mmol) were dissolved separately in water (2.25 mL) and mixed. The solution was warmed to 40 °C in a water bath, and tetramethoxysilane (TMOS, 0.5 mL) was added. The two-phase system was shaken until homogeneous. After gel formation,



Scheme 1 Schematic representation of phenyl ester ligands of Cl₂MBP **1a–d**



Scheme 2 (i) 1. (Prⁱ)₂NH, BuLi; 2. HCl, H₂O; (ii) 1. PhOH, Pyridine; 2. MeOH, Pyridine; (iii) aq. NaOCl; (iv) 1. ClSiMe₃; 2. MeOH.



Scheme 3 Schematic representation of monoethyl ester ligand (L_3) of Cl₂MBP.

a precipitant, acetone (3 ml), was added above the gel to induce crystallization. Several months later, colourless crystals of **9** suitable for X-ray analysis were formed as thin needles. The elemental analyses were performed several times and the results were consistent indicating that the acetone molecule and 3.5 water molecules were evaporated when the crystals were dried in air. These results are supported by the IR spectrum and TG analysis. Anal. Found: C, 7.41; H, 2.44; Cd, 34.59%. Calc. for C₃H₁₁Cl₂Cd_{1.5}O₉P₂: C, 7.32; H, 2.25; Cd, 34.23%.

Materials and methods

Elemental analyses for C and H were carried out on an EA 1110 CHNS-O analyser with a gas chromatograph column and TC detector. ¹H, ¹³C and ³¹P solution-state NMR spectra were recorded on a Bruker Avance DRX 500 spectrometer operating at 500.1, 125.8 and 202.5 MHz, respectively. Cadmium was measured with a Varian 220 atomic absorption spectrometer. Thermogravimetric analyses of the compounds **7–9** were performed under a 50 ml min^{−1} flow of synthetic air at a heating rate of 5 °C min^{−1} on a Mettler Toledo TGA/SDTA851^c thermobalance. X-Ray powder diffraction data were collected on a Bruker Advance D8 diffractometer using Cu K α radiation (λ = 1.5406 Å) in the 2 θ range of 5–70° with a step size of 0.05° and a counting time of 3 s per step. Infrared spectra were recorded on a Nicolet Magna-IRTM Spectrometer 750 by the KBr pellet technique. ³¹P and ¹¹³Cd CP/MAS NMR experiments were performed at 161.97 MHz (³¹P) and 88.74 MHz (¹¹³Cd) on a Bruker AMX 400 MHz spectrometer equipped with a double-tuned Bruker MAS 400 SB-BL 4 mm probe with contact time of 5 ms and magic-angle spinning (MAS) rates of 11–12 kHz. The external standards were hydroxyapatite (2.8 ppm) and Cd(NO₃)₂·4H₂O (−100.0 ppm).

X-Ray single crystal structural characterization

Crystal data and structural refinements for the three compounds are summarized in Table 1. All measurements were carried out on a Nonius Kappa CCD diffractometer using Mo K α -radiation (λ = 0.71073 Å). Denzo and Scalepack programs were used for cell refinements and data reduction. Structures were solved by direct methods with SHELXS 97,³³ and structure refinements were carried out with SHELXL 97.³³ Hydrogen atoms were placed at calculated positions and not refined. In compound **7**, the water molecule O8 is disordered in two positions, with population parameters 0.55/0.45. Selected bond lengths and angles for compounds **7–9**, and hydrogen-bond geometry for compound **9** are given in Tables S2–S4 (see ESI†).

Results and discussion

Synthesis of phenyl ester derivatives of Cl₂MBP

The target compounds **1a–d** (Scheme 1) can be prepared *via* intermediates **5** and **6** as shown in Scheme 2 starting from selected phosphorus chlorides **2** and methylphosphonates **3**, or from methylene diphosphonic dichloride (**4**) by adding required amounts of phenol and methanol. The first approach is a selective method to prepare the required bisphosphonate intermediate **5**; *e.g.* **5b** is prepared from **2a** (R¹ = Ph) and **3** (R² = R³ = Me) without any chromatographic separations, as described earlier.³⁴ However, problems arise when mixed monophosphorus ester starting materials are needed. Compound **5c** is especially tedious to prepare from monophosphorus derivatives **2** and **3** since both **2** and **3** must be mixed methylphenyl derivatives. However, compounds **1c** and **1d** are easily obtained by using the latter approach starting from **4**.

In this work, the partially substituted phenyl dichloromethylenebisphosphonates **1a,b** were prepared from the required monophosphorus starting materials **2** and **3** by the known method *via* intermediates **5a,b** and **6a,b**.^{28,29} Compounds **1c,d**, in turn, were obtained after chromatographic separation in gram scale starting directly from commercially available **4**, phenol and methanol under basic conditions. The main problem in the latter method was the unwanted derivatives of **5**, but also the tetramethyl and tetraphenyl methylenebisphosphonates that were formed as side products were a problem. According to ³¹P NMR spectra of the reaction mixtures, maximum amounts of **5c** and **5d**, *ca.* 72 and 50%, respectively, were obtained when 1.8 and 2.7 equivalents of phenol were used. However, the separation method we developed

Table 1 Crystal data and structure refinement for compounds 7–9

	7	8	9
Formula	C ₁₅ H ₂₈ Cl ₄ Cd ₃ O ₂₀ P ₄	C ₁₃ H ₁₈ Cl ₂ CdO ₁₀ P ₂	C _{4.5} H ₂₁ Cl ₂ Cd _{1.5} O ₁₃ P ₂
<i>M_r</i>	1131.25	579.51	584.65
Crystal system	Triclinic	Monoclinic	Monoclinic
Space group	<i>P</i> -1	<i>P</i> 2 ₁	<i>C</i> 2/c
<i>a</i> /Å	6.6807(1)	5.8432(1)	31.2205(3)
<i>b</i> /Å	13.2318(2)	9.2266(2)	10.1546(1)
<i>c</i> /Å	19.3270(3)	18.6853(5)	11.6510(1)
α /°	100.308(1)	90	90
β /°	95.579(1)	91.103(1)	103.107(1)
γ /°	96.954(1)	90	90
<i>V</i> /Å ³	1656.11(4)	1007.19(4)	3597.51(6)
<i>Z</i>	2	2	8
<i>T</i> /K	120(2)	120(2)	150(2)
<i>D_c</i> /g cm ⁻³	2.269	1.911	2.159
μ (Mo K α)/mm ⁻¹	2.504	1.557	2.320
<i>F</i> (000)	1100	576	2304
θ Range/°	2.91–26.00	2.46–26.00	2.67–26.00
Reflections collected	28696	14021	27848
Independent reflections	6455	3935	4115
Data/restraints/parameters	6455/0/428	3935/0/253	4115/0/213
<i>R</i> _{int}	0.0355	0.0367	0.0383
<i>R</i> 1(<i>F</i>) [<i>I</i> > 2 σ (<i>I</i>)] ^a	0.0197	0.0198	0.0245
<i>wR</i> 2(<i>F</i> ²) [all data] ^b	0.0476	0.0502	0.0592
Goodness-of-fit on <i>F</i> ²	1.005	1.035	1.095
Flack parameter		−0.050(15)	
Largest difference map features/eÅ ⁻³	1.032, −0.581	0.445, −0.787	0.622, −1.117

$$^a R1(F) = \sum (|F_o| - |F_c|) / \sum |F_o|. \quad ^b wR2(F^2) = [\sum w(F_o^2 - F_c^2)^2 / \sum wF_o^4]^{1/2}.$$

was sufficiently effective to separate all the formed products to single compounds with >95% purity. We also tried to prepare **5a** starting from **4**, but yields of the unseparated crude products were only ca. 10%. Compound **5b** cannot be prepared from **4**, though ca. 3–4% of **5b** was isolated as a side product when **5c** and **5d** were prepared. The target partially substituted derivatives **1a–d** are obtained after chlorination with NaOCl and demethylation with chlorotrimethylsilane or piperidine.

Crystal structure of 7

Compound **7** crystallizes in the triclinic system with space group *P*-1. As shown in Fig. 1a, there are four crystallographically independent six-coordinated Cd atoms connected to infinite polymeric chains by two independent L₁ ligands (Scheme 1). The L₁ ligands are coordinated by all five unsubstituted O atoms to four Cd atoms. There is only one coordination mode; both L₁ ligands are chelated in a tetradentate fashion with two Cd atoms, forming six-membered chelate rings, and further coordinated to two other Cd atoms. The O(22) and O(42) atoms act as a monoatomic bridge between the adjacent Cd(2) and Cd(3) atoms with Cd(2)⋯Cd(3) distance of 3.5580(2) Å, which is longer than the sum of the van der Waals radii of Cd.³⁵ The remaining octahedral coordination sites around the Cd(1) and Cd(4) atoms are occupied by two aqua ligands in axial positions to form a slightly distorted octahedral geometry. The Cd(1) and Cd(4) atoms reside on the inversion centres. The Cd(4)–O bond lengths of 2.189(2)–2.338(2) Å vary more widely than those in the Cd(1)O₆ octahedra (2.256(2)–2.310(2) Å). The *cis* bond angles range from 86.49(6) to 93.51(6)° around the Cd(1) centre and vary more, from 85.04(6) to 94.96(6)°, around the Cd(4) centre (Table S3, see ESI†).

The geometry around the Cd(2) and Cd(3) atoms can be best described as a significantly distorted octahedral coordination sphere, both Cd atoms are coordinated by four phosphonate O atoms from three different L₁ ligands. Cd(2)–O distances are 2.193(2)–2.348(2) Å and Cd(3)–O distances 2.188(2)–2.371(2) Å. The coordination sphere of Cd(2) is completed by two aqua ligands with bond distances Cd(2)–O(2) 2.311(2) Å and Cd(2)–O(3) 2.402(2) Å and *trans* angle O(2)–Cd(2)–O(3) of 161.77(7)°. The aqua ligand and the methanol molecule occupy the remaining coordination sites of the Cd(3) atom with bond distances Cd(3)–O(4) 2.338(2) Å and Cd(3)–O(5)C 2.355(2) Å and *trans* angle O(4)–Cd(3)–O(5) of 162.89(7)° (Table S3†).

The 1-D infinite chains are connected by O(23) and O(43) atoms to form a layered structure. As presented in Fig. 1b, the chlorine atoms and phenyl rings point away from the layers. The interlayer distance is 12.8874(2) Å, which is the shortest in compounds 7–9. The structure can also be described as Cd(2) and Cd(3) atoms forming Cd₂O₁₀ dimers of edge-sharing CdO₆ octahedra and Cd(1) and Cd(4) atoms forming isolated CdO₆ octahedra. The octahedra are connected by corner-sharing phosphonate terahedra resulting in a (010) Cd bisphosphonate layer (Fig. 1c).

The aqua ligands and uncoordinated water molecules form only intramolecular hydrogen bonds [O⋯O 2.670(3)–3.072(3) Å, 135–175°]. Intermolecular face-to-face stacking interactions are formed between the phenyl rings of adjacent layers, with the shortest centroid–centroid distance between the parallel intermolecular phenyl rings of 3.627(1) Å and an interplane angle of 0°. In addition, there are intermolecular lone-pair – π interactions ($\delta^- \cdots \delta^+$) between the oxygen atoms and phenyl rings of adjacent layers, with O33⋯centroid distance of 3.743(2) Å.

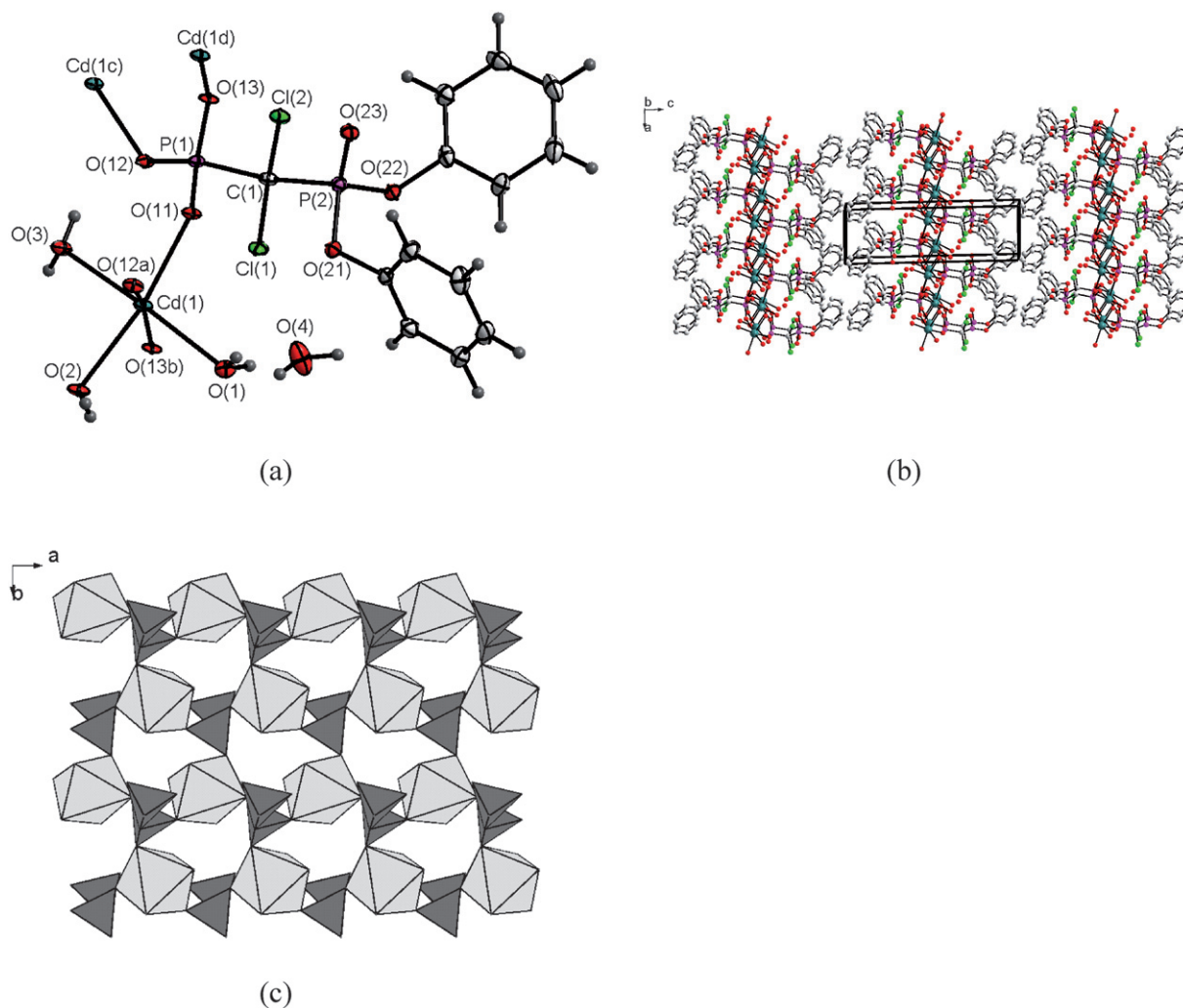


Fig. 2 (a) Structure of the asymmetric unit of compound **8** with anisotropic displacement ellipsoids (50%) and numbering scheme. Atoms labelled with suffixes a–d are at the symmetry positions $(1 - x, y - 0.5, 1 - z)$, $(1 + x, y, z)$, $(1 - x, 0.5 + y, 1 - z)$ and $(x - 1, y, z)$, respectively. (b) Packing of **8** in the direction of the *b*-axis. For clarity, hydrogen atoms are omitted. (c) One Cd-phosphonate layer viewed along the *b*-axis. CdO_6 octahedra are presented in light grey and PO_3C tetrahedra in dark grey. The lattice water molecules and phenyl substituents of the bisphosphonate ligand are omitted for clarity.

corner-sharing PO_3C tetrahedra, leading to a 12-membered ring comprising cadmium, oxygen and phosphorus atoms (Fig. 2c). The cyclic core is surrounded by (dichloromethylene)-diphenyl-phosphonate groups with $\text{Cd}\cdots\text{Cd}$ distance of 5.7354(3) Å. Similar to those in recently reported Zn pyridylphosphonate complexes,³⁶ each MO_6 octahedron corner-shares with three CPO_3 tetrahedra and *vice versa*. The arrangement leads to 12-membered M–O–P rings forming a 2-D layered construction. As far as we know, this kind of cyclic core has not previously been reported for Cd phosphonate or bisphosphonate complexes.

Crystal structure of **9**

Compound **9** crystallizes in the monoclinic system with space group $C2/c$. The complex consists of two-dimensional layers parallel to the (100) plane. The asymmetric unit contains two independent Cd^{2+} cations connected to each other by L_3 ligand and aqua ligand (see Scheme 3). The Cd(1) atom lies on the inversion centre with two symmetrically chelating L_3 ligands and

two aqua ligands in axial positions; the geometry is slightly distorted octahedron. The Cd(1)–O bond lengths are in the range of 2.266(2)–2.293(2) Å. The *cis* bond angles around the Cd(1) atom range from 86.71(6) to 93.29(6)° and deviate less than 3.3° from the expected angles for an ideal octahedral geometry (Table S3†). The aqua ligand O(1) bridges Cd(1) and the adjacent Cd(2) atom with $\text{Cd}\cdots\text{Cd}$ distance of 4.3525(2) Å. The Cd(2) atom has a highly distorted octahedral geometry and is coordinated by four phosphonate O atoms from three different L_3 ligands. The coordination sphere is completed by two aqua ligands in *cis* positions. The Cd(2)–O distances vary more widely, from 2.241(2) to 2.573(2) Å, as compared with those of Cd(1). The three *trans* angles are O(22)–Cd(2)–O(2) 162.97(6), O(13d)–Cd(2)–O(12) 155.22(6) and O(11c)–Cd(2)–O(1) 158.60(6)°. The Cd(2) atom forms its longest bond with the bridging aqua ligand, O(1). The Cd(2)–O bond lengths are comparable to those reported^{19,23} for Cd complexes of dialkyl ester derivatives of Cl_2MBP .

The L_3 anion is pentadentate; it forms two six-membered chelate rings with Cd(1) and Cd(2) atoms and is also connected

to two other Cd(2) atoms, acting as mono- and triatomic bridges between metal cations (Fig. 3a). The coordination mode of the bisphosphonate ligand in **9** is also found in compound **7**. In **9**, the cavities are formed within the layered structure. Additional acetone and lattice water molecules are located in these cavities forming extensive hydrogen bonding and connecting the layers into a 3-D supramolecular network. ($O\cdots O$ 2.668(2)–2.906(3) Å, 126.1–175.5°) with the interlayer distance of 15.2036(2) Å (Fig. 3b, Table S4†). The solvent acetone molecule and lattice water molecule O7 are located on the individual two-fold axis. As presented in Fig. 3c, the layers consist of purely corner-sharing CdO_6 octahedra and CPO_3 tetrahedra. The two phosphonate groups sharing a corner with each other are linked to the four Cd polyhedra, and thus each $Cd(1)O_6$ octahedron corner-shares with four $Cd(2)O_6$ octahedra *via* a phosphonate O atom or the O

atom of the lattice water molecule, O(1). The ethyl groups and chlorine atoms point out from the layers. Just recently, we reported the isomorphous Ca complex and the unique layered Ba complex of the same ligand.^{37,38}

Thermal analyses

The TGA diagrams of compounds **7–9** exhibit two main weight loss steps (see ESI†). In compound **7**, the water and methanol molecules are released in two steps beginning at 30 °C and completed at 220 °C. The observed weight loss of 12.6% is slightly less than the calculated value of 14.0%. For compound **8**, the first step extends from 50 to 160 °C, and corresponds to the release of aqua ligands and lattice water molecules. The observed weight loss of 11.8% is in good agreement with the calculated

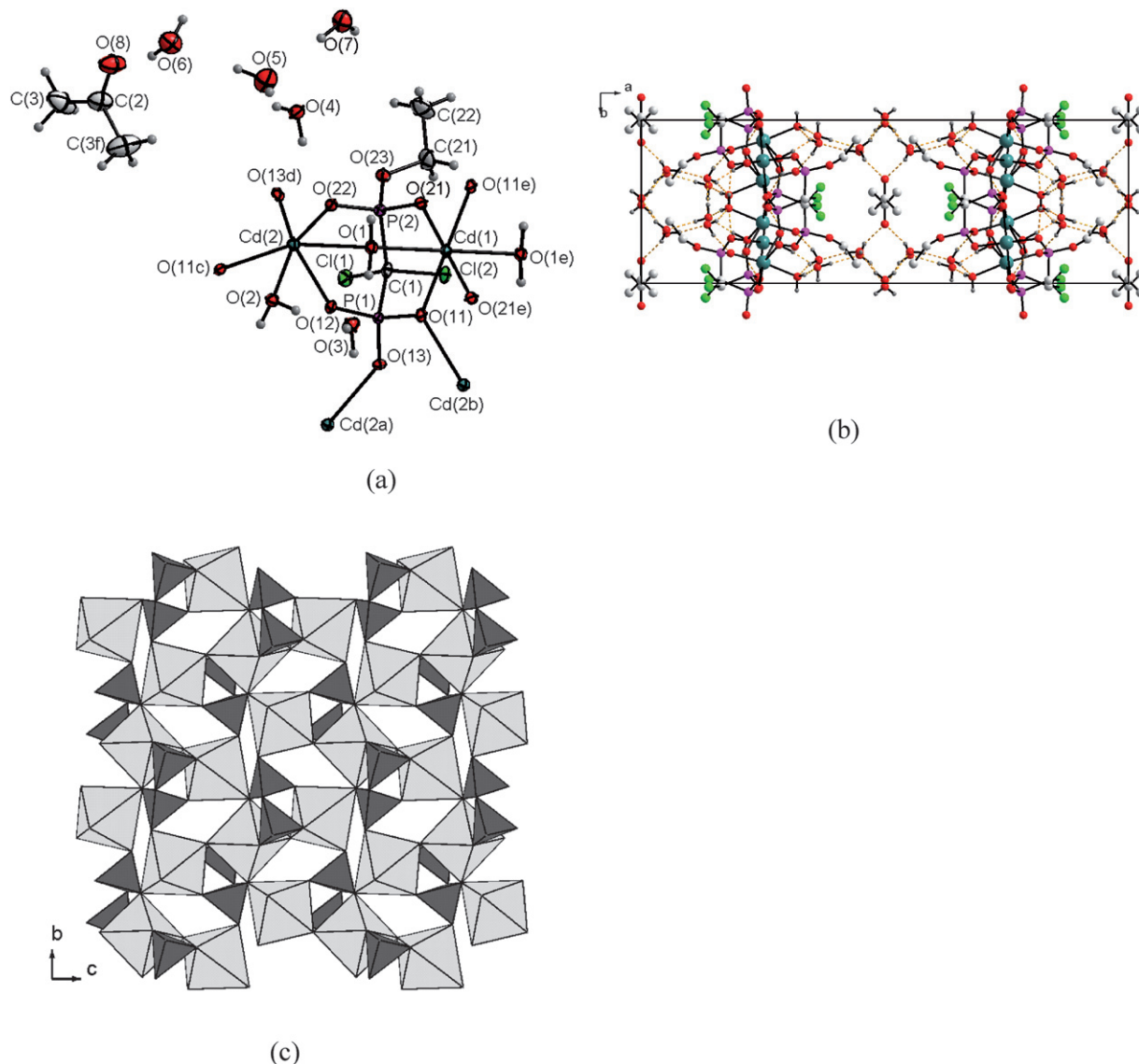


Fig. 3 (a) Structure of the asymmetric unit of compound **9** with anisotropic displacement ellipsoids (50%) and numbering scheme. Atoms labelled with suffixes a–f are at the symmetry positions $(0.5 - x, y - 0.5, 0.5 - z)$, $(x, -y, z - 0.5)$, $(x, -y, 0.5 + z)$, $(0.5 - x, 0.5 + y, 0.5 - z)$, $(0.5 - x, 0.5 - y, -z)$ and $(-x, y, 1.5 - z)$, respectively. (b) Packing of **3** in the direction of the *c*-axis showing the hydrogen bond interactions. For clarity, hydrogen atoms of the CH_2 and CH_3 groups are omitted. (c) The (100) Cd(II) bisphosphonate layer in compound **9**. CdO_6 octahedra are presented in light grey and PO_3C tetrahedra in dark grey. The lattice solvent molecules and ethyl substituents of the bisphosphonate ligand are omitted for clarity.

value of 12.4%. In the case of compound **9**, the loss of three water molecules occurred between 40 and 150 °C. The observed weight loss of 10.9% is very close to the calculated value of 11.0%. These findings are supported by elemental analyses, which indicate that the acetone molecule and 3.5 water molecules evaporated when the sample was dried in air. For compounds **7** and **9**, the second main step starts immediately after the first and is completed at 700 °C. For compound **8**, the second step occurs in the range of *ca.* 190–700 °C. The second weight loss, for all three complexes, comprises several overlapping stages, attributable to the release of organic groups, chlorine atoms and, finally, a methylene carbon atom. The dark grey residues were identified as $\text{Cd}_2\text{P}_2\text{O}_7$ and $\alpha\text{-Cd}(\text{PO}_3)_2$ for **7** and **9** (in molar ratios of 1 : 1 and 1 : 6, respectively) and $\alpha\text{-Cd}(\text{PO}_3)_2$ for **8** on the basis of their X-ray powder patterns. The observed total weight losses of 39.0% for **7** and 32.6% for **9** are close to the calculated values of 40.9% and 32.7%, respectively. For **8**, the observed total weight loss of 57.1% is somewhat more than the calculated value of 53.3%.

The XRD powder patterns measured for compounds **7–9** are in good agreement with the ones simulated from single-crystal data. Furthermore, the X-ray powder patterns of dehydrated **7–9**, after heating the compounds at 120 °C for 4 h under air atmosphere, indicate collapse of the crystal structure with the loss of the water molecules; for compound **7** also the loss of the methanol ligand. These findings can probably be explained by hydrogen bonding interactions. In the case of **9**, the layers are held together by extensive hydrogen bonds. In **7** and **8**, the hydrogen bonds are involved in the interactions of phosphonate O atoms with aqua ligands or lattice water molecules. Hence, the hydrogen bonding interactions are essential for stabilizing the crystal structures, and the removal of volatile species in **7–9** will result in the collapse of their layered architectures.

Spectroscopic properties

The ^{31}P CP/MAS NMR spectrum for compound **7** (see ESI†) contains four different chemical shifts, at 9.3, 7.8, 6.4 and 4.3 ppm, due to the presence of four P atoms in dissimilar environments. The X-ray structure shows the environments of P(1) and P(3) to be unequal since each phosphonate group is coordinated to two different metal atoms (Cd(1) and Cd(2), Cd(3) and Cd(4), respectively). In the case of P(2) and P(4), each phosphonate group is connected to four Cd atoms; one group is bound to Cd(1), Cd(3) and two Cd(2) atoms and the other to Cd(2), Cd(4) and two Cd(3) atoms. The average values of P–O bond lengths in **7** are 1.527 for P(3), 1.525 for P(1), 1.520 for P(2) and 1.514 Å for P(4). Hence, we assign the chemical shifts as follows: 9.3 for P(3), 7.8 for P(1), 6.4 for P(2) and 4.3 ppm for P(4). In the ^{31}P CP/MAS NMR spectra of compounds **8** and **9** (see ESI†), there are two distinct chemical shifts (10.0 and 7.0 ppm for **8** and 14.2 and 12.9 ppm for **9**) corresponding to two independent P atoms in different coordination environments. These findings are in good agreement with the X-ray single crystal data.

Several oxo-Cd compounds in solid state have been examined by Ellis,³⁹ who found that the chemical shifts of the peaks are related to the coordination number of Cd, and compounds with six-coordinate Cd have chemical shifts in the range 150 to –60 ppm. In the ^{113}Cd CP/MAS NMR spectrum of compound **8** (see ESI†), there is one signal with an isotropic chemical shift of

–14.2 ppm indicating the presence of one crystallographically independent Cd atom in the structure. The value agrees well with the ^{113}Cd chemical shift observed for Cd tetraphosphonate compound with Cd having octahedral geometry (–16.5 ppm).⁴⁰ The very broad signals in the ^{113}Cd CP/MAS NMR spectra of compounds **7** and **9** make detailed assignment impossible.

In the IR spectra of all three compounds **7–9**, a broad band occurs at 3400–3000 cm^{-1} showing the presence of water molecules (Fig. 4). The shape and position of the band indicate that hydrogen bond interactions are present and the water molecules are bonded loosely. This finding is supported by thermogravimetric analysis of compounds **7–9**. In the spectrum of **7**, one sharp band appears at 3590 cm^{-1} indicating the presence of a hydroxyl group that is involved in hydrogen bonding. This band can be assigned to the OH group of the methanol ligand, which interacts with phosphonate O atom, O(21) through hydrogen bonding. Similar results for IR spectra have been reported earlier.^{41,42} The bending vibration $\delta(\text{H}_2\text{O})$ is observed in all three spectra at *ca.* 1640 cm^{-1} .

The set of bands between 1250 and 940 cm^{-1} are due to the stretching vibrations of the tetrahedral CPO_3 groups.^{43,44} The strong band of the $\nu(\text{P}=\text{O})$ stretching vibration occurs in the free ligands at 1268 cm^{-1} for $\text{Na}_2\text{Cl}_2\text{C}(\text{PO}_3\text{Ph})_2$, at 1232 cm^{-1} for $\text{Na}_3\text{Cl}_2\text{CP}_2\text{O}_6\text{Et}$ and as two bands at *ca.* 1240 cm^{-1} and 1210 cm^{-1} for $\text{Na}_3\text{Cl}_2\text{CP}_2\text{O}_6\text{Ph}$. All positions are in good agreement with those reported for symmetric partial esters of MBP.³⁰

Upon complexation of the ligands, a strong, intense band appears in the spectra in the region 1260–1190 cm^{-1} . Compared with the spectra of the free ligands, the band is shifted down by *ca.* 10–30 cm^{-1} indicating reduction of the double bond character due to coordination of the phosphoryl oxygen to the metal. The set of three very strong bands of the ligands at 1210–1100 cm^{-1} corresponds to $\nu(\text{P}-\text{O})$. Upon complexation of the ligands, a new sharp band appears at *ca.* 35–60 cm^{-1} towards lower frequencies. The present findings are in good agreement with our earlier assignments of the IR spectra of Cd complexes of alkyl ester and amide ester derivatives of Cl_2MBP .^{19,23,27}

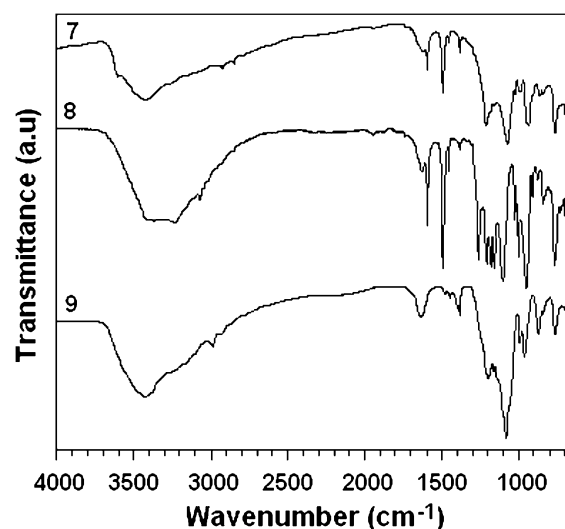


Fig. 4 IR spectra of compounds **7** [$\{\text{Cd}_3(\text{Cl}_2\text{CP}_2\text{O}_6\text{Ph})_2(\text{H}_3\text{COH})(\text{H}_2\text{O})_5\}(\text{H}_2\text{O})_2\}_n$], **8** [$\{\text{Cd}(\text{Cl}_2\text{CP}_2\text{O}_6\text{Ph})_2(\text{H}_2\text{O})_3(\text{H}_2\text{O})\}_n$] and **9** [$\{\text{Cd}_{1.5}(\text{Cl}_2\text{CP}_2\text{O}_6\text{Et})(\text{H}_2\text{O})_2\}(\text{C}_3\text{H}_6\text{O})_{0.5}(\text{H}_2\text{O})_{4.5}\}_n$].

The presence of several sharp and very strong bands in the 1250–940 cm⁻¹ region in the spectrum of compound **8** makes this spectrum more complicated than the spectra of compounds **7** and **9**. The complexity is due to the different coordination mode of the bisphosphonate ligand in compound **8**, where the fourth unsubstituted O atom of the L₂ ligand remains non-coordinated, unlike in **7** and **9** where all five unsubstituted O atoms are involved in metal coordination. We have reported similar findings for amide ester derivatives of Cl₂MBP.²⁷ There are also structural similarities in the spectra of **7** and **8**, clearly seen in the region of 1650–1400 cm⁻¹ where the $\delta(\text{CH}_2)$ bending vibrations and C–C stretching vibrations of the phenyl ring appear. The strongest band in this region, at 1490 cm⁻¹, can be assigned to the skeletal ring vibration mode. The strong bands at 761 and 688 cm⁻¹ in the spectra of **7** and **8** are characteristic of out-of-plane phenyl ring vibrations. For compound **7**, the weak bands at 2910 and 2840 cm⁻¹ can be attributed to the vibration of the CH₃ group of the methanol ligand.

In the spectrum of **9**, the bands due to the ethyl groups occur in the 3000–2820 and 1470–1370 cm⁻¹ regions. The $\nu(\text{C}=\text{O})$ stretching vibration of the acetone molecule in coordination compounds typically displays a relatively strong and sharp peak around 1700 cm⁻¹.⁴⁵ A broad band in the spectrum of **9**, is located at 1630 cm⁻¹ and a similar band at the same position is observed in the spectrum of the free ligand. This band can be assigned as the bending vibration of the water molecules. These findings indicate the absence of acetone molecule in compound **9**, and the same is supported by elemental analysis and TG studies.

Conclusions

Two novel phenyl esters (**6c** and **6d**) and partial phenyl esters (**1c** and **1d**) of clodronic acid were synthesised. We also prepared and characterized in detail three new Cd(II) complexes of ester derivatives of bisphosphonate with different layered structures. In the case of compound **8**, the L₂ ligand can adopt only bridging coordination mode due to the two large phenyl groups and the steric hindrance they cause. The structure of compound **8** is unexpected; it consists of 12-membered cyclic cores forming a Cd-phosphonate layer. We have previously reported that clodronate can produce 3-D structures when additional Na⁺ is coordinated.^{18,19} The present study shows that monoalkyl ester derivatives can form 3-D supramolecular networks, through hydrogen bonding. In compounds **7** and **9**, the number of donor atoms of the ligands, the coordination spheres of the metal and the binding mechanism of the ligands are all similar. However, the overall architectures of these compounds are different due to the differences between the organic substituents connected to the phosphonate group as well as to the preparation methods. Our results demonstrate that diverse and interesting coordination structures of metal complexes of ester derivatives of clodronic acid can be achieved through introduction of various ester substituents into the phosphonate groups.

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