Dalton Transactions

RSC Publishing

PAPER

View Article Online
View Journal | View Issue

Cite this: *Dalton Trans.*, 2013, **42**, 2414

Methylene-bis[(aminomethyl)phosphinic acids]: synthesis, acid–base and coordination properties†

Tomáš David, Soňa Procházková, Jana Havlíčková, Jan Kotek, Vojtěch Kubíček,* Petr Hermann and Ivan Lukeš

Three symmetrical methylene-bis[(aminomethyl)phosphinic acids] bearing different substituents on the central carbon atom, $(NH_2CH_2)PO_2H–C(R^1)(R^2)–PO_2H(CH_2NH_2)$ where R^1 = OH, R^2 = Me ($H_2\mathbf{L^1}$), R^1 = OH, R^2 = Ph ($H_2\mathbf{L^2}$) and R^1,R^2 = H ($H_2\mathbf{L^3}$), were synthesized. Acid–base and complexing properties of the ligands were studied in solution as well as in the solid state. The ligands show unusually high basicity of the nitrogen atoms (log K_1 = 9.5–10, log K_2 = 8.5–9) if compared with simple (aminomethyl)phosphinic acids and, consequently, high stability constants of the complexes with studied divalent metal ions. The study showed the important role of the hydroxo group attached to the central carbon atom of the geminal bis(phosphinate) moiety. Deprotonation of the hydroxo group yields the alcoholate anion which tends to play the role of a bridging ligand and induces formation of polynuclear complexes. Solid-state structures of complexes $[H_2N{=}C(NH_2)_2][Cu_2(H_{-1}\mathbf{L^2})_2]CO_3{\cdot}10H_2O$ and $Li_2[Co_4(H_{-1}\mathbf{L^1})_3(OH)]{\cdot}17.5H_2O$ were determined by X-ray diffraction. The complexes show unexpected geometries forming dinuclear and cubane-like structures, respectively. The dinuclear copper(II) complex contains a bridging μ_2-alcoholate group with the $^-O–P(=O)–CH_2–NH_2$ fragments of each ligand molecule chelated to the different central ion. In the cubane cobalt(II) complex, one μ_3-hydroxide and three μ_3-alcoholate anions are located in the cube vertices and both phosphinate groups of one ligand molecule are chelating the same cobalt(II) ion while each of its amino groups are bound to different neighbouring metal ions. All such three metal ions are bridged by the alcoholate group of a given ligand.

Received 4th September 2012,
Accepted 14th November 2012

DOI: 10.1039/c2dt32045b

www.rsc.org/dalton

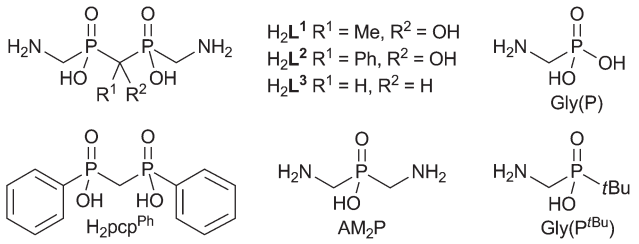
Introduction

Aminoalkylphosphonic and -phosphinic acids represent a group of organophosphorus compounds with a wide range of applications.[1–3] A specific group of compounds among aminoalkylphosphonates are those containing the geminal bis(phosphonic acid) group. The geminal bis(phosphonic acids) (BPs) exhibit high affinity to hydroxyapatite, the main inorganic component of bone tissue, and they are regularly applied as drugs for treatment of osteoporosis, Paget's disease and other disorders of calcified tissues metabolism. They are engaged not only in protection of the bone surface, but also in growth regulation of cells which are responsible for bone formation and resorption. The geminal BPs containing a nitrogen atom in the side chain attached to the bridging carbon atom inhibit farnesyl diphosphate synthase.[3] The BPs without the nitrogen atom are metabolized into non-hydrolysable methylene-containing ATP analogues, which are accumulated inside the cell and exhibit cytotoxicity.[4] Unfortunately, the BP's cytotoxicity and inhibition activity cannot be used for other than bone-associated applications due to the extremely strong affinity of BPs to calcified tissues.[5] An alternative could be found in geminal bis(phosphinates), BPis. The geminal bis(phosphinates) maintain the P–C–P fragment and show low affinity to hydroxyapatite.[6,7] Whereas geminal BPs have been widely studied, geminal BPis have attracted much less attention. Some of them have been synthesized[6–11] but there have been published only a few papers dealing with their coordination behaviour[12,13] except for two simple ligands, methylene-bis(phosphinic acid), where phosphorus is directly bound to Pt(II) or Pd(II),[14] and methylene-bis[(phenyl)phosphinic acid] H_2pcp^{Ph} (Scheme 1).[15]

However, amine-containing geminal BPis offer various coordination modes and, thus, we turned our attention to the synthesis and characterization of methylene-bis[(aminomethyl)phosphinic acids]. Here, we report on results of the study of the symmetrical ligands bearing different substituents

Department of Inorganic Chemistry, Faculty of Science, Charles University in Prague, Hlavova 2030128 40 Prague 2, Czech Republic. E-mail: kubicek@natur.cuni.cz; Fax: +420 221921253; Tel: +420 221921264

†Electronic supplementary information (ESI) available: Overall protonation constants and stability constants; distribution diagrams of $H_2\mathbf{L^2}$ and $H_2\mathbf{L^3}$; HR-MS spectra of Cu-$\mathbf{L^1}$ and Cu-$\mathbf{L^2}$ systems; geometrical parameters of the bis(phosphinate) moiety and coordination spheres in the solid state. CCDC 898276, 898277, 898278 and 898279. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2dt32045b



Scheme 1 Structures of studied methylene-bis[(aminomethyl) phosphinic acids] and other compounds discussed in the text.

on the central carbon atom (Scheme 1). The ligands can be convenient in applications where rather strong acidity and weak complexation ability of the phosphinic acid group is desired.

Experimental

Materials and methods

Commercially available chemicals had synthetic purity and were used as received. NMR spectra were recorded at 25 °C on a Varian NMR system operating at 300 MHz proton frequency with an ASW probe. Chemical shifts were referenced to TMS ($\delta_H = \delta_C = 0$ ppm) or *t*BuOH ($\delta_H = 1.25$, $\delta_C = 31.2$ ppm) and H_3PO_4 (external standard, $\delta_P = 0$ ppm) and are given in the ppm scale and the coupling constants are given in Hz. ESI-MS spectra were recorded on a Bruker Esquire 3000 spectrometer with ESI ionization and ion-trap detection. High resolution MS spectra were measured on a Bruker APEX-Q FTMS. UV-Vis spectra were measured on a Schimadzu UV-2401PC spectrometer at 25 °C in the wavelength range 200–800 nm. TLC was performed with silica gel on aluminium sheets (Merck 10554 F_{254}); the spots were detected with UV fluorescence ($\lambda = 254$ nm) or visualized by iodine vapours.

Phthalimido-methylphosphinic acid (2). Under an argon atmosphere, dry $(NH_4)H_2PO_2$ (20.0 g, 241 mmol) was suspended in hexamethyldisilazane (HMDS, 100 mL) and the mixture was heated at 110 °C under a gentle flow of argon overnight. The mixture containing $HP(OTMS)_2$ (**1**) was cooled to room temperature (RT) and dry CH_2Cl_2 (100 mL) was added. The solution of (*N*-bromomethyl)phthalimide (15.0 g, 62.5 mmol) in dry CH_2Cl_2 (300 mL) was added dropwise and the mixture was stirred at RT overnight. Then, the resulting solution was dropped into EtOH (800 mL) and the solution was evaporated to dryness under reduced pressure. Crude product was dissolved in boiling 1% aq. HCl (100 mL) and the resulting suspension was filtered on a fine glass frit while hot. The filtrate was cooled down and left standing overnight. The precipitate formed was collected on a glass frit and dissolved in boiling water until a clear solution was formed. The solution was cooled down and left overnight. The precipitate formed (containing mainly the disubstituted product) was filtered off on a glass frit and the filtrate was evaporated to dryness. The solid residue was dissolved in a minimum amount of water and left standing overnight. A white crystalline solid was collected by filtration on a glass frit, washed with cold water and dried in a desiccator over P_2O_5 to give the product (17.2 g, 31%).

NMR (dmso-d_6): ^{1}H δ 3.86 (2H, dd, $^2J_{HP}$ = 10, $^3J_{HH}$ = 2, N–CH_2–P); 7.18 (1H, dt, $^1J_{HP}$ = 558, $^3J_{HH}$ = 2, P–*H*); 7.80–7.90 (4H, m, aryl H); ^{13}C{^{1}H} δ 38.0 (d, $^1J_{CP}$ = 98, N–*C*H_2–P); 123.4, 131.5, 134.8 (aryl C); 167.3 (s, *C*=O); ^{31}P δ 17.6 (dt, $^1J_{PH}$ = 558, $^2J_{PH}$ = 10). ESI-MS(−): *m*/*z* 223.5 [(M − H)$^-$, calcd 224.1]. TLC (EtOH : aq. NH_4OH 1 : 1): R_f = 0.8. Elem. anal. (calcd for $C_9H_8NO_4P$, M_r = 225.1): C 48.0 (48.0); H 3.5 (3.2); N 6.2 (6.3). mp 202 °C (with decomposition).

1-Hydroxy-ethane-1,1-bis[(aminomethyl)phosphinic acid] (H_2L^1). Under an argon atmosphere, compound **2** (6.15 g, 27.3 mmol) was suspended in HMDS (100 mL) and the mixture was heated at 110 °C under a gentle flow of argon overnight. The mixture was cooled to RT and dry CH_2Cl_2 (200 mL) was added. A solution of acetyl chloride (1.13 g; 14.4 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise and the mixture was stirred at RT overnight. Then, the resulting solution was dropped into EtOH (500 mL) and the resulting suspension was evaporated to dryness under reduced pressure. The solid was dissolved in boiling water (50 mL) and treated with charcoal while hot. The filtrate was cooled to RT and conc. aq. HCl (10 mL) was slowly added. The mixture was left to stand for 2 h and the solid was collected on a medium-coarse glass frit, washed with water and dried over P_2O_5 in vacuum. This crude intermediate **3** (5.5 g, obtained as a yellowish powder) was dissolved in 6 M aq. HCl (100 mL) and the solution refluxed for 24 h. After cooling to RT, precipitated phthalic acid was filtered off. The filtrate was evaporated to dryness under reduced pressure and further co-evaporated three times with water (50 mL). The crude product was purified on cation-exchange resin (Dowex 50, H^+-form). Impurities were eluted off with water and water : EtOH 1 : 1 mixtures. The pure product was eluted with 5% aq. ammonia. Fractions containing product were treated with charcoal and the filtrate was evaporated to dryness. The residue was suspended in water (100 mL). The solid was collected on a glass frit, washed with EtOH and dried over P_2O_5 in vacuum to give the product as a white powder (1.74 g, 47%).

3: NMR (5% Et_3N in dmso-d_6): ^{1}H δ 1.35 (3H, t, $^3J_{HP}$ = 14, CH_3); 4.09 (4H, m, N–CH_2–P); 7.75–7.90 (8H, m, aryl H); ^{13}C{^{1}H} δ 18.3 (s, *C*H_3); 37.0 (dd, $^1J_{CP}$ = 106; $^3J_{CP}$ = 9, N–*C*H_2–P); 70.8 (t, $^1J_{CP}$ = 97 Hz, $P_2C(CH_3)$–OH); 122.7, 132.0, 134.1 (aryl C); 167.6 (s, *C*=O); ^{31}P{^{1}H} δ 28.8 (s). ESI-MS(−): *m*/*z* 490.8 [(M − H)$^-$, calcd 491.0]. TLC (MeCN : MeOH : aq. NH_4OH 3 : 1 : 2): R_f = 0.4.

H_2L^1: NMR ($NaOD/D_2O$, pD = 12): ^{1}H δ 1.47 (3H, t, $^3J_{HP}$ = 14, CH_3); 2.89 (4H, m, N–CH_2–P); ^{13}C{^{1}H} δ 20.9 (s, *C*H_3); 41.4 (dd, $^1J_{CP}$ = 98; $^3J_{CP}$ = 9, N–*C*H_2–P); 77.0 (t, $^1J_{CP}$ = 86, $P_2C(CH_3)$–OH); ^{31}P{^{1}H} δ 36.8 (s). ESI-MS(−) *m*/*z*: 230.5 [(M − H)$^-$, calcd 231.0]; ESI-MS(+) *m*/*z*: 203.7 [(M + H − CH_2NH_2)$^+$, calcd 204.1]; 232.7 [(M + H$^+$)$^+$, calcd 233.05]; 254.7 [(M + Na)$^+$, calcd 255.0]; 276.7 [(M + 2Na − H)$^+$, calcd 277.0]. TLC (EtOH : aq. NH_4OH 1 : 1): R_f = 0.4. Elem. anal. (calcd for $C_4H_{14}N_2O_5P_2 \cdot 1.5H_2O$, M_r =

259.1): C 18.5 (18.4); H 6.6 (6.8); N 10.8 (10.5). mp 276 °C (with decomposition).

(Hydroxy)(phenyl)methylene-bis[(aminomethyl)phosphinic acid] (H_2L^2). Under an argon atmosphere, the compound **2** (5.00 g, 22.2 mmol) was suspended in HMDS (30 mL) and the mixture was heated at 110 °C under a gentle flow of argon overnight. The mixture was cooled to RT and dry CHt_2Cl_2 (20 mL) was added. The solution of benzoyl chloride (1.64 g, 11.7 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise and the mixture was stirred at RT overnight. Then, the reaction mixture was dropped into EtOH (200 mL) and the resulting suspension was evaporated to dryness under reduced pressure. The solid was dissolved in boiling H_2O (50 mL) and treated with charcoal while hot. The filtrate was then cooled to RT and conc. aq. HCl was slowly added (5 mL). After 2 h, the suspension was decanted off, the solid was dissolved in a mixture of MeCN : $CHCl_3$: MeOH 1 : 1 : 1 (50 mL) and the resulting solution was left standing overnight. The precipitate was collected on a medium-coarse glass frit, washed several times with water and dried over P_2O_5 in vacuum. This crude intermediate **4** (3.93 g, obtained as a white powder) was dissolved in a mixture of 75% aq. N_2H_4 (80 mL) and EtOH (80 mL) and stirred at RT overnight. The mixture was evaporated to dryness and three times co-evaporated with EtOH. The residue was dissolved in a minimum amount of water and excess of EtOH was added. After standing overnight, the precipitate was collected on a medium-coarse glass frit. The solid was dissolved in water and purified on anion-exchange resin (Dowex 1, OH^--form). Impurities were eluted off with water, and the product was eluted with 6 M aq. HCl. The fractions containing the product were combined and evaporated to dryness. The solid was suspended in water (100 mL) and excess of EtOH was added. After standing overnight, the precipitate was collected on a medium-coarse glass frit, washed with EtOH and dried over P_2O_5 in vacuum to give the product as a white powder (1.63 g, 40%).

4: NMR (5% Et_3N in dmso-d_6): ^{1}H δ 3.74 (4H, m, N–CH_2–P); 7.10–7.20 (1H, m, aryl H); 7.20–7.30 (2H, m, aryl H); 7.82 (10H, bs, aryl H); ^{13}C{^{1}H} δ 36.0 (d, $^1J_{CP}$ = 100 Hz, N–*C*H_2–P); 77.2 (t, $^1J_{CP}$ = 80 Hz, P_2C(Ph)–OH); 122.8, 126.0, 126.2, 127.3, 131.7, 134.3, 137.3 (aryl C); 167.6 (s, *C*=O); ^{31}P{^{1}H} δ 30.4 (s). TLC (MeCN : MeOH : aq. NH_4OH 3 : 1 : 2): R_f = 0.5. ESI-MS(−) *m*/*z*: 552.8 [(M − H^+)$^-$, calcd 553.1]; ESI-MS(+) *m*/*z*: 577.0 [(M + Na^+)$^+$, calcd 577.1]; 656.1 [(M + $NHEt_3^+$)$^+$, calcd 656.2].

H_2L^2: NMR (NaOD/D_2O, pD = 6): ^{1}H δ 3.11 (4H, m, N–CH_2–P); 7.35–7.50 (3H, m, aryl H); 7.70–7.80 (2H, m, aryl H); ^{13}C{^{1}H} δ 35.6 (d, $^1J_{CP}$ = 99, N–*C*H_2–P); 81.7 (t, $^1J_{CP}$ = 96, P_2C(Ph)–OH); 126.5 (t, $^3J_{CP}$ = 4, ^{ar}*C*H–^{ar}C–C–P_2); 128.4 (s, aryl C); 129.1 (s, aryl C); 137.4 (s, aryl C); ^{31}P{^{1}H} δ 28.3 (s). ESI-MS(−) *m*/*z*: 292.5 [(M − H)$^-$, calcd 293.1]; ESI-MS(+) *m*/*z*: 294.7 [(M + H)$^+$, calcd 295.1]; 316.8 [(M + Na)$^+$, calcd 317.0]; 332.7 [(M + K)$^+$, calcd 333.0]. TLC (EtOH : aq. NH_4OH 1 : 1): R_f = 0.4. Elem. anal. (calcd for $C_9H_{16}N_2O_5P_2$·HCl·H_2O, M_r = 348.7): C 31.0 (31.0); H 5.5 (5.1); N 8.0 (7.8); Cl 11.2 (11.4). mp 225 °C (with decomposition).

Methylene-bis(phosphinic acid) (6). Under an argon atmosphere, a solution of $CH_2(PCl_2)_2$ (**5**) (20.0 g; 91.8 mmol) in dry THF (50 mL) was slowly added to a cooled mixture (5 °C) of water (150 mL) and THF (50 mL). After stirring for 1 h, volatiles were evaporated under reduced pressure. The resulting oil was dissolved in a minimum amount of MeOH and an excess of Me_2CO was added until two phases were formed. The upper phase was discarded and the resulting oil was dried in vacuum for several days. The oil solidified to a colourless mass after standing at 5 °C overnight (10.8 g, 82%).

NMR (dmso-d_6): ^{1}H δ 2.40 (2H, t, $^2J_{HP}$ = 17, CH_2); 7.10 (2H, d, $^1J_{HP}$ = 561, P–*H*); ^{13}C{^{1}H} δ 33.4 (t, $^1J_{CP}$ = 80, *C*H_2); ^{31}P δ 19.3 (dt, $^1J_{PH}$ = 561, $^2J_{PH}$ = 17). ESI-MS(−) *m*/*z*: 330.6 [(2M − 3H^+ + 2Na^+)$^-$, calcd 330.9]; ESI-MS(+) *m*/*z*: 332.8 [(2M − H^+ + 2Na^+)$^+$, calcd 332.9]. TLC (EtOH : NH_4OH 1 : 1): R_f = 0.8. Elem. anal. (calcd for $CH_6O_4P_2$·H_2O, M_r = 162.0): C 7.6 (7.4); H 4.8 (5.0).

Methylene-bis[(aminomethyl)phosphinic acid] (H_2L^3). In a 250 mL round-bottom flask, methylene-bis(phosphinic acid) **6** (3.45 g; 21.3 mmol), dibenzylamine (5.00 mL; 95.5 mmol) and paraformaldehyde (2.90 g; 96.6 mmol) were suspended in a mixture of 6 M aq. HCl (40 mL) and THF (40 mL) and stirred overnight at 50 °C. The reaction mixture was evaporated to dryness and then co-evaporated three times with CH_2Cl_2, until the residue solidified. The crude intermediate **7** (containing a large amount of dibenzylamine hydrochloride) was used for subsequent reaction without further purification. It was dissolved in MeOH (250 mL) under an argon atmosphere and ammonium formate (47.9 g; 760 mmol) and catalyst (10% w/t Pd/C; 4.00 g) were added. The reaction mixture was refluxed for 2 h. Another portion of ammonium formate (28.7 g; 455 mmol) and catalyst (2.40 g) was added and the reaction mixture was refluxed for a further 3 h. After removal of volatiles under reduced pressure, the residue was co-evaporated several times with MeOH. The black residue was treated with water and the suspension was filtered off on a fine glass frit. The filtrate was evaporated to dryness, the residue was dissolved in water and the amino acid was adsorbed on anion exchange resin (Amberlite IRA 402, OH^--form). Impurities were eluted off with water and the product was eluted with 6 M aq. HCl. Fractions containing product were treated with charcoal, the filtrate was evaporated to dryness and the residue was co-evaporated three times with water. The solid was dried in vacuum over P_2O_5 to give the product as a white powder (3.84 g, 63%).

7: NMR ($CDCl_3$): ^{1}H δ 1.99 (2H, t, $^2J_{HP}$ = 16, P–CH_2–P); 3.03 (4H, d, $^2J_{HP}$ = 10, P–CH_2–N); 4.35 (8H, m, CH_2Ph); 7.35–7.45 (12H, m, aryl H); 7.50–7.60 (8H, m, aryl H); ^{13}C{^{1}H} δ 38.5 (t, $^1J_{CP}$ = 81, P–*C*H_2–P); 51.4 (d, $^1J_{CP}$ = 90, P–*C*H_2–N); 58.1 (s, *C*H_2Ph); 129.0, 129.5, 129.9, 131.0 (s, aryl C); ^{31}P{^{1}H} δ 17.4 (s). ESI-MS(−) *m*/*z*: 560.9 [(M − H^+)$^-$, calcd 561.2]; ESI-MS(+) *m*/*z*: 563.2 [(M + H^+)$^+$, calcd 563.2]; 585.2 [(M + Na^+)$^+$, calcd 585.2]; 601.2 [(M + K^+)$^+$, calcd 601.2]. TLC (MeCN : $CHCl_3$: MeOH 1 : 1 : 1): R_f = 0.5.

H_2L^3: NMR (NaOD/D_2O, pH = 7): ^{1}H δ 2.47 (2H, t, $^2J_{HP}$ = 17, P–CH_2–P); 3.18 (4H, d, $^2J_{HP}$ = 11, P–CH_2–N); ^{13}C{^{1}H} δ 36.3 (t, $^1J_{CP}$ = 83, P–*C*H_2–P); 39.5 (d, $^1J_{CP}$ = 99, P–*C*H_2–N); ^{31}P{^{1}H} δ 18.5 (s). ESI-MS(−) *m*/*z*: 201.1 [(M − H^+)$^-$, calcd 201.0]; ESI-MS (+) *m*/*z*: 203.3 [(M + H^+)$^+$, calcd 203.0]; 225.4 [(M + Na^+)$^+$, calcd 225.0]; 241.4 [(M + K^+)$^+$, calcd 241.0]. TLC (EtOH : aq. NH_4OH

1 : 1): R_f = 0.7. Elem. anal. ($C_3H_{12}N_2O_4P_2{\cdot}0.5HCl{\cdot}H_2O$, M_r = 238.3): C 15.1 (14.8); H 6.1 (5.8); N 11.8 (11.5), Cl 7.4 (7.8). mp 310 °C (with decomposition).

Potentiometric titrations. Methodology of the potentiometric titrations and processing of the experimental data were analogous to those previously reported.[16] Titrations were carried out in a vessel thermostatted at 25 ± 0.1 °C at ionic strength I = 0.1 M KNO_3. The ligand-to-metal ratio was 1 : 1 (and 2 : 1 in some cases) with c_M = 0.004 M, the pH range was 1.7–12 (or till precipitation of metal hydroxide). Titrations were carried out at least three times, each consisting of about 40 points. The water ion product, pK_w = 13.78, and stability constants of $M^{2+} - OH^-$ systems were taken from ref. 17. The protonation constants β_n calculated are concentration constants and are defined by $\beta_n = [H_nL]/([H]^n \times [L])$ ($\log K_1 = \log \beta_1$; $\log K_n = \log \beta_n - \log \beta_{n-1}$). The stability constants are defined by $\beta_{hlm} = [M_mH_hL_l]/[M]^m \times [H]^h \times [L]^l$. The constants (with standard deviations) were calculated with the program OPIUM.[18] Throughout the paper, pH means $-\log [H^+]$.

Preparation of single crystals

$H_2L^1{\cdot}0.5H_2O$. Powdered $H_2L^1{\cdot}1.5H_2O$ (26 mg) was dissolved in a mixture of 0.1 M aq. $CuCl_2$ (1 mL) and 6 M aq. HCl (1 mL). Volatiles were removed under reduced pressure and the oily residue was dissolved in water (1 mL). Single crystals of $H_2L^1{\cdot}0.5H_2O$ were formed on standing at RT for one week.

$H_2L^3{\cdot}H_2O$. Powdered $H_2L^3{\cdot}0.5HCl{\cdot}H_2O$ (29 mg) was suspended in 0.1 M aq. $CoCl_2$ (1 mL). The 1 M aq. LiOH was added dropwise until all material dissolved and the solution reached pH 8. Diffusion of ethanol vapour at RT yielded oil which slowly crystallized. Single crystals of $H_2L^3{\cdot}H_2O$ were obtained on standing for three weeks.

$Li_2[Co_4(H_{-1}L^1)_3(OH)]{\cdot}17.5H_2O$. Powdered $H_2L^1{\cdot}1.5H_2O$ (26 mg, 0.1 mmol) was suspended in 0.1 M aq. $CoCl_2$ (1 mL, 0.1 mmol). The 1 M aq. LiOH was added dropwise until all material dissolved and the solution reached pH 8. Diffusion of ethanol vapour at RT yielded oil which slowly crystallized. Single crystals of $Li_2[Co_4(H_{-1}L^1)_3(OH)]{\cdot}17.5H_2O$ were obtained on standing for six weeks.

$(Hgua)_4[Cu_2(H_{-1}L^2)_2]CO_3{\cdot}10H_2O$. Powdered $H_2L^2{\cdot}HCl{\cdot}H_2O$ (35 mg, 0.1 mmol) was dissolved in 0.1 M aq. $CuCl_2$ (1 mL, 0.1 mmol). The 1 M aq. $(Hgua)_2CO_3$ was added dropwise to reach pH 10. Diffusion of ethanol vapour at RT yielded single crystals of $[H_2N{=}C(NH_2)_2]_4[Cu_2(H_{-1}L^2)_2]CO_3{\cdot}10H_2O$ on standing for five days.

X-ray diffraction study

The diffraction data were collected at 150 K (Cryostream Cooler, Oxford Cryosystem) using a Nonius Kappa CCD diffractometer and Mo-K_α radiation (λ = 0.71073 Å) and analyzed using the HKL DENZO program package.[19] The structures were solved by direct methods (SIR92),[20] and refined by full-matrix least-squares techniques (SHELXL97).[21] All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were located in the difference map of electron density; however, they were placed in theoretical (C–H) or original (O–H) positions with thermal parameters $U_{eq}(H) = 1.2\ U_{eq}(X)$ as their free refinement led to some unrealistic bond lengths. Table 1 contains selected crystallographic parameters for the structures reported in this paper. Data for the structures have been deposited with the Cambridge Crystallographic Data Centre with CCDC-898276 ($H_2L^1{\cdot}0.5H_2O$), 898277 ($H_2L^3{\cdot}H_2O$), 898278 ($Li_2[Co_4(H_{-1}L^1)_3$ (OH)]·17.5H_2O), and 898279 {$(Hgua)_4$-$[Cu_2(H_{-1}L^2)_2]CO_3{\cdot}10H_2O$} reference numbers.

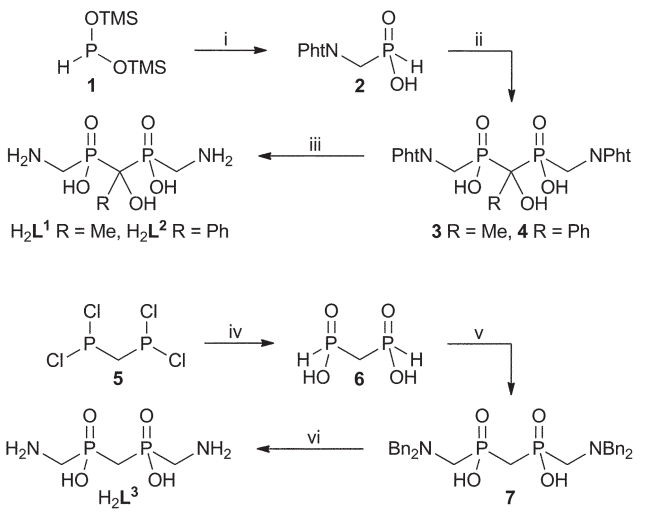
Table 1 Experimental data of reported crystal structures

Parameter	$H_2L^1{\cdot}0.5H_2O$	$H_2L^3{\cdot}H_2O$	$Li_2[Co_4(H_{-1}L^1)_3(OH)]{\cdot}17.5H_2O$	$(Hgua)_4[Cu_2(H_{-1}L^2)_2]CO_3{\cdot}10H_2O$
Formula	$C_4H_{15}N_2O_{5.5}P_2$	$C_3H_4N_2O_5P_2$	$C_{12}H_{69}Co_4Li_2N_6O_{33.5}P_6$	$C_{23}H_{70}Cu_2N_{16}O_{23}P_4$
M_w	241.12	220.10	1269.15	1189.91
Colour	Colourless	Colourless	Red	Brownish green
Shape	Plate	Prism	Plate	Plate
Dimensions (mm)	0.10 × 0.31 × 0.45	0.20 × 0.45 × 0.50	0.14 × 0.25 × 0.56	0.12 × 0.35 × 0.69
Crystal system	Monoclinic	Orthorhombic	Orthorhombic	Triclinic
Space group	*C*2/*c*	*Pbcn*	$P2_12_12_1$	*P*1
a (Å)	16.4183(4)	11.5649(4)	13.0426(3)	14.1333(4)
b (Å)	6.7200(2)	8.9009(3)	13.2471(4)	14.2073(4)
c (Å)	17.8230(4)	8.3936(3)	26.9972(7)	14.4339(4)
α (°)	—	—	—	69.875(1)
β (°)	101.253(1)	—	—	76.646(1)
γ (°)	—	—	—	65.391(1)
V (Å^3)	1928.62(9)	864.02(5)	4664.5(2)	2461.05(12)
Z	8	4	4	2
D_c (g cm^{-3})	1.661	1.692	1.807	1.606
μ (mm^{-1})	0.454	0.493	1.706	1.086
F (000)	1016	464	2620	1244
Diffractions; observed ($I_o > 2\sigma(I_o)$)	2218; 2003	993; 944	10 660; 9956	22 429; 21 349
Parameters	124	56	622	1226
G-o-f on F^2	1.077	1.127	1.038	1.027
R; *R*′ (all data)	0.0261; 0.0302	0.0232; 0.0246	0.0293; 0.0331	0.0237; 0.0262
w*R*; w*R*′ (all data)	0.0713; 0.0739	0.0690; 0.0702	0.0721; 0.0737	0.0604; 0.0618
Difference max; min (e Å^{-3})	0.489; −0.262	0.325; −0.368	0.839; −0.517	0.428; −0.338

Results and discussion

Synthesis

The studied compounds were synthesized using two different strategies (Scheme 2). Those containing a hydroxy group attached to the bridging carbon atom were prepared from Pht-protected (aminomethyl)phosphinate fragments. The reaction of bis(trimethylsilyloxy)phosphine **1** with (*N*-bromomethyl)-phthalimide followed by hydrolysis of the silylester groups gives a mixture of hypophosphorous acid, and monosubstituted and disubstituted products as previously reported.[22] To improve the procedure, we developed a simple and efficient method for separation of the mixture based on different solubility of the components in water. In the next step, the obtained phthalimido-methylphosphinic acid **2** is converted to the corresponding trimethylsilylphosphinate by reaction with hexamethyldisilazane and treated with acetyl- or benzoylchloride. The reaction is analogous to that previously reported for geminal bis(H-phosphinates)[7,23] and for cyclic amino-bis-(phosphinates)[11] and proceeds in high yield. The target ligands $H_2\mathbf{L}^1$ and $H_2\mathbf{L}^2$ were obtained after removal of the phthalimide protecting groups by hydrochloric acid or by hydrazine, respectively. Compound $H_2\mathbf{L}^3$ was prepared using a "build up" strategy starting from commercially available bis (dichlorophosphino)methane **5**. The compound was hydrolyzed yielding methylene-bis(phosphinic acid) **6** (ref. 24) that was consequently treated with paraformaldehyde and dibenzylamine. The three component Mannich-type reaction yields protected bis(phosphinate) **7** in high yield. The target ligand $H_2\mathbf{L}^3$ was obtained by hydrogenolysis of benzyl groups using Pd/C as the catalyst. This synthesis is more straightforward than the amine alkylation approach used in synthesis of similar (aminomethyl)phosphinic-phosphonic acid, $NH_2CH_2–PO_2H–CH_2–PO_3H_2$.[25] Unlike geminal bis(H-phosphinates) slowly decomposing in aqueous solution,[7] all the ligands are fully stable in aqueous solution at any pH.



Scheme 2 Synthesis of studied geminal bis(phosphinates). (i) (*N*-Bromomethyl)phthalimide in CH_2Cl_2, RT; (ii) 1. HMDS, 110 °C; 2. RCOCl in CH_2Cl_2, RT; 3. EtOH; (iii) conc. aq. HCl, reflux or N_2H_4 in EtOH, RT; (iv) H_2O in THF, RT; (v) dibenzylamine, paraformaldehyde, aq. HCl in THF, 50 °C; (vi) $NH_4(HCOO)$, Pd/C in MeOH, reflux.

Acid–base and coordination properties in solution

Solution behaviour of the title geminal bis(phosphinic acids) and their complexes was studied by potentiometry. The studied bis[(aminomethyl)phosphinates] show similar protonation constants (Table 2 and S1†). Phosphinic acid groups are strongly acidic and their protonation takes place at pH < 3 (Fig. 1A). At weakly acidic and neutral regions, the only species present in the solution is the neutral zwitterionic form, H_2L, where both protons are bound on amine nitrogen atoms. The pK_a values assigned to the amino groups are surprisingly high if compared to those of simple (aminoalkyl)phosphinic acids (Table 2). For the studied ligands, the values of the highest constants are comparable to those of carboxylic and phosphonic amino acids. Also values of the second protonation constants are noticeably high. The small differences between the first and the second constants indicate independent protonation of both distant amino groups. The high basicity of the nitrogen atoms could be ascribed to the presence of intramolecular hydrogen bonds similar to those found in the solid state (see below).

Stability constants of complexes of the title geminal bis[(aminomethyl)phosphinates] with Cu^{2+}, Zn^{2+}, Ni^{2+} and Co^{2+} ions were determined from potentiometric titrations at 1 : 1 and 2 : 1 ligand-to-metal ratios. Despite excess of the ligand used in the latter cases, no species of ML_2 stoichiometry could be identified. Experimentally determined stability constants of the complexes are summarized in Table S2† and the derived stability constants are given in Table 3. The distribution diagrams are shown in Fig. 2, S1, S2 and S3.† Similarly to protonation constants of the ligands, stability constants of their complexes, log K_{ML}, do not follow typical trends among amino acids. The presence of two highly basic nitrogen atoms and

Table 2 Protonation constants, log K_a, of the studied methylene-bis[(aminomethyl)phosphinic acids] (25 °C, I = 0.1 M) and related ligands

Constant	$H_2\mathbf{L}^1$	$H_2\mathbf{L}^2$	$H_2\mathbf{L}^3$	AM_2P[16]	Gly(P)[26]	Gly(P^{tBu})[27]	Gly[26]	H_2pcp^{Ph} [15e]
log K_a(L)	10.00	9.84	9.49	8.51	10.05	8.42	9.56	3.33[a]
log K_a(HL)	8.89	8.55	8.80	7.07	5.39	1.20	2.36	1.35[a]
log K_a(H_2L)	1.35	<1	2.09	0.77	0.40	—	—	—

[a] I = 0.5 M NMe_4Cl.

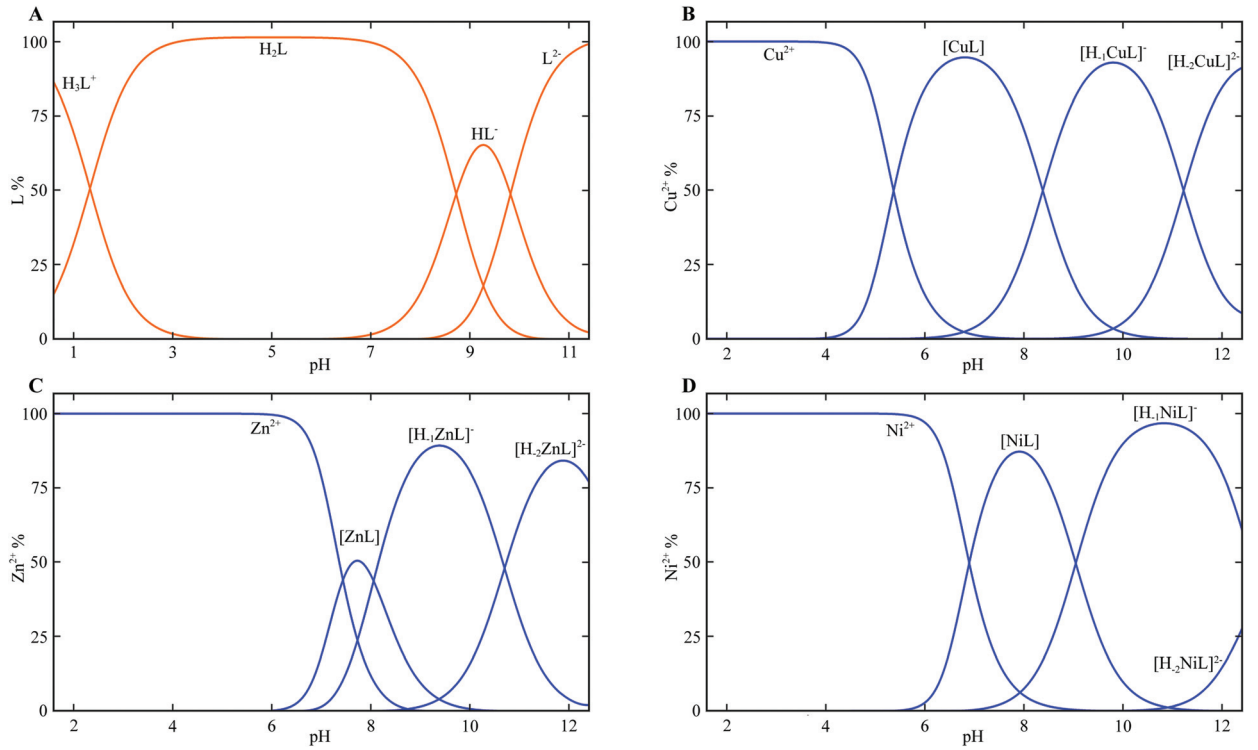


Fig. 1 Distribution diagrams of $H_2\mathbf{L^1}$ in the absence of metal ions (A) and in the presence of Cu^{2+} (B), Zn^{2+} (C) and Ni^{2+} (D) ions ($c_L = c_M = 4$ mM, $I = 0.1$ M, 25 °C).

Table 3 Equilibrium constants (log K_{ML} or pK_a) in systems containing the title ligands and some divalent metal ions

		Ligand		
Metal ion	Equilibrium[a]	$H_2\mathbf{L^1}$	$H_2\mathbf{L^2}$	$H_2\mathbf{L^3}$
Cu^{2+}	$Cu^{2+} + (L)^{2-} \rightleftharpoons [Cu(L)]$	10.76	11.13	9.87
	$[Cu(L)] \rightleftharpoons [CuH_{-1}(L)]^{-} + H^{+}$	8.41	8.07	8.82
	$[CuH_{-1}(L)] \rightleftharpoons [CuH_{-2}(L)]^{2-} + H^{+}$	11.26	12.29	10.53
Zn^{2+}	$Zn^{2+} + (L)^{2-} \rightleftharpoons [Zn(L)]$	6.78	6.51	6.29
	$[Zn(L)] \rightleftharpoons [ZnH_{-1}(L)]^{-} + H^{+}$	8.04	8.77	8.58
	$[ZnH_{-1}(L)] \rightleftharpoons [ZnH_{-2}(L)]^{2-} + H^{+}$	10.72	11.02	—
Ni^{2+}	$Ni^{2+} + (L)^{2-} \rightleftharpoons [Ni(L)]$	7.87	7.13	7.51
	$[Ni(L)] \rightleftharpoons [NiH_{-1}(L)]^{-} + H^{+}$	9.04	8.57	8.41
	$[NiH_{-1}(L)] \rightleftharpoons [NiH_{-2}(L)]^{2-} + H^{+}$	12.77	12.50	—
Co^{2+}	$Co^{2+} + (L)^{2-} \rightleftharpoons [Co(L)]$	[b]	7.28	5.79
	$[Co(L)] \rightleftharpoons [CoH_{-1}(L)]^{-} + H^{+}$	[b]	7.84	[b]
	$[CoH_{-1}(L)] \rightleftharpoons [CoH_{-2}(L)]^{2-} + H^{+}$	8.18	8.01	[b]
	$[CoH_{-2}(L)] \rightleftharpoons [CoH_{-3}(L)]^{3-} + H^{+}$	11.69	10.03	[b]

[a] Proton dissociation sites are not distinguished (see text). [b] Not determined due to the formation of precipitate.

two phosphinate groups result in higher stability constants of the complexes when compared to those found for other aminoalkylphosphonic/phosphinic acids (Table 4). Despite that, determination of several stability constants was disabled by formation of hydroxide precipitates in the alkaline region (pronounced mainly in the case of the Co^{2+} ion). The complexes with stoichiometry $H_{-1}ML$, $H_{-2}ML$ and $H_{-3}ML$ are formed at pH > 7; here, the negative stoichiometric coefficients represent (i) dissociation of a coordinated water molecule (*i.e.* formation of hydroxido complexes) and/or (ii) dissociation of a proton from the hydroxo group attached to the central carbon atom and the alcoholate coordination, as suggested in the case of the $H_2\mathbf{L^1}$ and $H_2\mathbf{L^2}$ ligands. The sites of the deprotonations cannot be distinguished by potentiometry; however, both coordination modes might be present in the solutions (see below).

Coordination modes in solution were studied more in detail for the Cu^{2+} complexes. Presence of the hydroxyl group in the molecule results in significantly different behaviour among the Cu^{2+} complexes. Ligands $H_2\mathbf{L^1}$ and $H_2\mathbf{L^2}$ form dark green water-soluble complexes at pH above 5. The electronic spectra of the complexes (Fig. 2) were measured at pH corresponding to the maximum abundance of [CuL] and $[CuH_{-1}L]$ species in the distribution diagrams. The colour of the complexes is mostly given by strong CT-bands, which are shifted to the visible region with maxima around 310 and 360 nm for $Cu\mathbf{L^1}$ and $Cu\mathbf{L^2}$, respectively. The shift of the CT-bands indicates coordination of the alcoholate groups in the solution in a similar manner as was found in the solid state (see below). Analogous behaviour of dinuclear Cu^{2+} complexes was previously reported for various ligands.[28] Similar spectra were observed for both [CuL] and $[CuH_{-1}L]$ species. In the case of the [CuL] complex, coordination of the alcoholate group indicates protonation of one nitrogen atom. Thus, the ligand is more likely coordinated in the tridentate manner by amine nitrogen, phosphinate and alcoholate oxygen atoms. For the case of coordination through the alcoholate oxygen atom, any form of tetradentate binding is not possible for geometrical

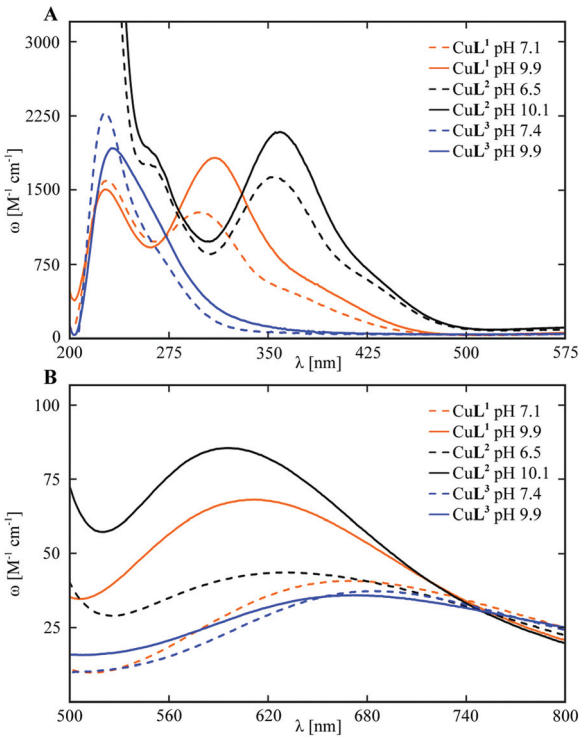


Fig. 2 UV-Vis spectra of Cu^{2+} complexes with the title bis[(aminomethyl)phosphinic acids] (25 °C, water).

Table 4 Comparison of stability constants, log K_{ML}, of complexes with the title ligands and with the related amino acids

Metal ion	H_2L^1	H_2L^2	H_2L^3	AM_2P[16]	Gly(P)[26]	Gly(P^{tBu})[27]	Gly[26]
Cu^{2+}	10.76	11.13	9.87	7.64	8.12	5.37	8.12
Zn^{2+}	6.78	6.51	6.29	4.12	5.00	—	4.96
Ni^{2+}	7.87	7.13	7.51	5.58	5.25	3.62	5.78
Co^{2+}	—	7.28	5.79	4.07	4.52	3.17	4.67

reasons. In the case of the $[MH_{-1}L]$ complex, one could expect similar dimeric species as was found in the solid state of the CuL^2 complex (see below). For both ligands L^1 and L^2 the dinuclear complexes were also identified as major signals in the high resolution MS spectra (Fig. S4†). Unfortunately, potentiometry could not easily distinguish between monomeric and oligomeric species.

In contrast, ligand H_2L^3 forms a light blue poorly soluble Cu^{2+} complex and this system could be studied in solution only due to slow kinetics of crystallization. The electronic spectra (Fig. 2) show a weak d–d transition at around 680 nm and a strong CT-band in the UV region (<300 nm) that could be expected for amine and phosphinate coordination. Colour and electronic spectra of the complex resemble those of the bis(glycinato)copper complex.[29] Thus, tetradentate coordination through both phosphinate oxygen atoms and both amine groups could be expected.

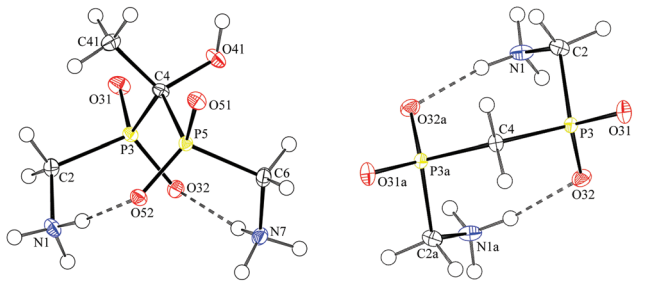


Fig. 3 Molecular structures of H_2L^1 (left) and H_2L^3 (right) found in the solid-state structures of $H_2L^1{\cdot}0.5H_2O$ and $H_2L^3{\cdot}H_2O$, showing medium–strong intramolecular hydrogen bonds.

Solid-state structure of the bis[(aminomethyl)phosphinic acids] and their complexes

The structures of two ligands and two complexes in the solid state were determined by X-ray diffraction. The ligands, H_2L^1 and H_2L^3, are practically insoluble in water and, therefore, the single-crystals suitable for the analysis were isolated only from mixtures containing metal ions. The presence of metal ions increases solubility due to metal–ligand interaction and slows down crystallization of the ligands. In both structures, the molecules are in the zwitterionic forms with protons localized on nitrogen atoms. Presence of the substituents attached to the central carbon atom of ligand H_2L^1 results in longer distances from phosphorus to the central carbon and a smaller P–C–P angle (Table S3†). Both structures are stabilized by hydrogen bonds between the amine group and the oxygen atom of the opposite phosphinate group (Fig. 3). The hydrogen bond lengths are 2.67/2.80 Å and 2.76 Å for ligands H_2L^1 and H_2L^3, respectively. These medium–strong hydrogen bonds are probably also present in solution and they could explain the high values of amine protonation constants.

Single-crystals of $[H_2N{=}C(NH_2)]_4[Cu_2(H_{-1}L^2)_2]CO_3{\cdot}10H_2O$ were obtained by slow diffusion of ethanol into the solution containing ligand H_2L^2 and Cu^{2+} ions neutralized at pH 10 with guanidinium carbonate. An independent unit contains two dinuclear complexes. Both independent complex units possess the same coordination motif and their angles and distances differ only slightly (Fig. 4 and Table S4†). All Cu^{2+} ions are coordinated in distorted octahedral geometry with two amine nitrogen atoms and two alcoholate oxygen atoms originating from two different ligand molecules coordinated in the equatorial plane. These two μ^2-alcoholate oxygen atoms form the bridge to the other Cu^{2+} ion which is also coordinated by the remaining two amine groups. The Cu···Cu separations are 3.032 and 3.047 Å in the two independent units. Axial positions of the copper coordination polyhedrons are occupied by phosphinate oxygen atoms. Due to Jahn–Teller distortion, the coordination bonds to phosphinate oxygen atoms are significantly longer (~2.4–3.1 Å) compared to the distances between the metal centre and the equatorial donor atoms (~1.9–2.0 Å), see Table S4.† The structure contains hydrate water molecules, guanidinium and carbonate ions forming a rich system of medium–strong hydrogen bonds.

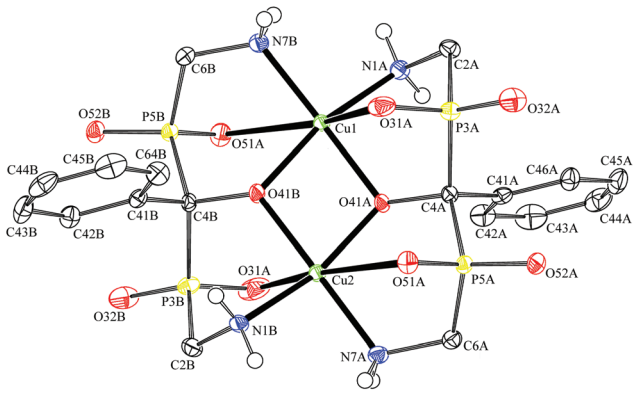


Fig. 4 One of the $[Cu_2(H_{-1}\mathbf{L^2})_2]^{2-}$ units found in the solid-state structure of $(Hgua)_4[Cu_2(H_{-1}\mathbf{L^2})_2]CO_3{\cdot}10H_2O$. Hydrogen atoms attached to carbon atoms are omitted for clarity reasons.

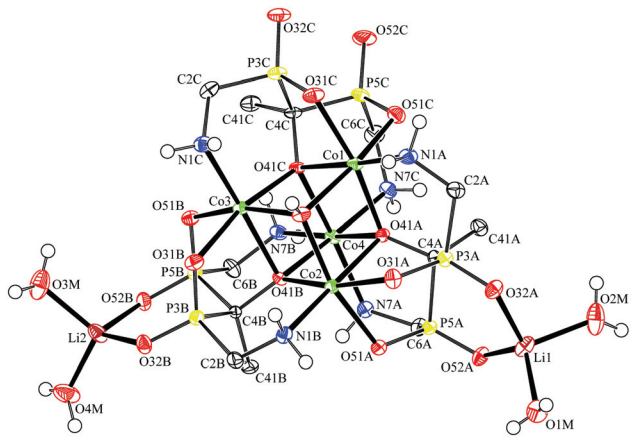


Fig. 5 Solid-state structure of the $[Co_4(OH)(H_{-1}\mathbf{L^1})_3\{Li(H_2O)_2\}_2]$ unit found in the crystal structure of $Li_2[Co_4(H_{-1}\mathbf{L^1})_3(OH)]{\cdot}17.5H_2O$. Hydrogen atoms attached to carbon atoms are omitted for clarity reasons.

Slow diffusion of ethanol into the solution containing ligand $H_2\mathbf{L^1}$ and Co^{2+} ions (at pH 8) yielded single-crystals of $Li_2[Co_4(H_{-1}\mathbf{L^1})_3(OH)]{\cdot}17.5H_2O$. The core of the complex consists of a cubane-like structure composed of four Co^{2+} ions and four oxygen atoms forming μ_3-bridges (Fig. 5). Three oxygen atoms originate from the deprotonated hydroxo group attached to the central carbon atoms of three ligand molecules. The last oxygen atom belongs to a hydroxide anion. Each of the bis(phosphinate) ligands is coordinated through two phosphinate groups and one bridging alcoholate oxygen atom to one Co^{2+} ion forming two five-membered chelate rings. Such tridentate coordination disables coordination of nitrogen atoms to the same metal ion and, thus, the amine groups of each ligand are coordinated to two different neighbouring Co^{2+} ions (those coordinated by the alcoholate in μ_3-bridging fashion). The coordination bonds, Co–O and Co–N, are in the range expected for the Co^{2+} ion (~2.1–2.2 Å). The separation of Co···Co is in the range 3.13–3.22 Å, with slightly closer separations of cobalt(II) ions bound through a μ_3-hydroxido bridge (3.13–3.16 Å) rather than those separated by an alcoholate donor (3.18–3.22 Å). The cubane-like core is slightly distorted, with Co–O–Co and O–Co–O angles in the ranges 94–99° and 81–85°, respectively. However, the geometry of the cubane-like core is very similar to those found in analogous structures bridged by polydentate ligands, like in citrato or tris(carboxylato)methoxo complexes.[30,31] The negative charge of the whole cubane is compensated by two Li^+ ions chelated by uncoordinated phosphinate oxygen atoms of the same ligand molecule. The coordination sphere of each Li^+ ion is completed by two water molecules. Selected relevant distances and angles are compiled in Tables S5 and S6.†

Conclusions

Three symmetrical methylene-bis[(aminomethyl)phosphinic acids] bearing different substituents on the central carbon atom, $(NH_2CH_2)PO_2H{-}C(R^1)(R^2){-}PO_2H(CH_2NH_2)$ where R^1 = OH, R^2 = Me ($H_2\mathbf{L^1}$), R^1 = OH, R^2 = Ph ($H_2\mathbf{L^2}$) and R^1,R^2 = H ($H_2\mathbf{L^3}$), were synthesized. The compounds exhibit high basicities of nitrogen atoms and high stabilities of the complexes with divalent metal ions that are unusual for α-aminoalkylphosphinic acids. The solution and solid state studies of the complexes have shown an important role of the hydroxo group attached to the central carbon atom of the bis(phosphinate) moiety that induces formation of dinuclear or polynuclear complexes.

Acknowledgements

Support from the Grant Agency of the Czech Republic (No. P207/10/P153), the Grant Agency of Charles University (No. 310011) and from the Long-Term Research Plan of the Ministry of Education of the Czech Republic (No. MSM0021620857) is acknowledged. This work was carried out in the framework of COST CM802 (PhoSciNet) Action. We thank Dr Ivana Císařová (Charles University in Prague) for performing X-ray measurements.

Notes and references

1 N. J. Wardle, S. W. A. Bligh and H. R. Hudson, *Curr. Org. Chem.*, 2007, **11**, 1635–1651.
2 F. Orsini, G. Sello and M. Sisti, *Curr. Med. Chem.*, 2010, **17**, 264–289.
3 A. Mucha, P. Kafarski and L. Berlicki, *J. Med. Chem.*, 2011, **54**, 5955–5980.
4 D. G. G. Russel and M. J. Rogers, *Bone*, 1999, **29**, 97–106.
5 H. Fleisch, *Bisphosphonates in Bone Disease*, Academic Press, London, 2000.
6 S. P. Luckman, F. P. Coxon, F. H. Ebetino, R. G. G. Russell and M. J. Rogers, *J. Bone Miner. Res.*, 1998, **13**, 1668–1678.
7 T. David, P. Křečková, J. Kotek, V. Kubíček and I. Lukeš, *Heteroatom Chem.*, 2012, **23**, 195–201.

8 F. H. Ebetino and L. A. Jamieson, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1990, **51**, 23–26.
9 R. Gobel, F. Richter and H. Weichman, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1992, **73**, 67–80.
10 (*a*) S. Gouault-Bironneau, S. Deprele, A. Sutor and J.-L. Montchamp, *Org. Lett.*, 2005, **7**, 5909–5912; (*b*) M. I. Antczak and J.-L. Montchamp, *Tetrahedron Lett.*, 2008, **49**, 5909–5913.
11 B. Kaboudin, F. Saadati and T. Yokomatsu, *Synlett*, 2010, 1837–1840.
12 L. P. Loginova, I. V. Levin, A. G. Matveeva, S. A. Pisareva and E. E. Nifanťev, *Russ. Chem. Bull.*, 2004, **53**, 2000–2007.
13 F. Gaizer, G. Haegele, S. Goudetsidis and H. Papadopoulos, *Z. Naturforsch., B: Chem. Sci.*, 1990, **45**, 323–328.
14 (*a*) C. King, R. A. Auerbach, F. R. Fronczek and D. M. Roundhill, *J. Am. Chem. Soc.*, 1986, **108**, 5626–5627; (*b*) C. King, D. M. Roundhill and F. R. Fronczek, *Inorg. Chem.*, 1987, **26**, 4288–4290; (*c*) C. King, D. M. Roundhill, M. K. Dickson and F. R. Fronczek, *J. Chem. Soc., Dalton Trans.*, 1987, 2769–2780; (*d*) D. M. Roundhill, Z.-P. Shen, C. King and S. J. Atherton, *J. Phys. Chem.*, 1988, **92**, 4088–4094; (*e*) C. King, Y. Yin, G. L. McPherson and D. M. Roundhill, *J. Phys. Chem.*, 1989, **93**, 3451–3455; (*f*) Q.-J. Pan, H.-G. Fu, H.-T. Yu and H.-X. Zhang, *Inorg. Chem.*, 2006, **45**, 8729–8735.
15 (*a*) E. Berti, F. Cecconi, C. A. Ghilardi, S. Midollini, A. Orlandini and E. Pitzalis, *Inorg. Chem. Commun.*, 2002, **5**, 1041–1043; (*b*) F. Cecconi, S. Dominguez, N. Masciocchi, S. Midollini, A. Sironi and A. Vacca, *Inorg. Chem.*, 2003, **42**, 2350–2356; (*c*) F. Cecconi, C. A. Ghilardi, S. Midollini and A. Orlandini, *Inorg. Chem. Commun.*, 2003, **6**, 546–548; (*d*) F. Cecconi, D. Dakternieks, A. Duthie, C. A. Ghilardi, P. Gili, P. A. Lorenzo-Luis, S. Midollini and A. Orlandini, *J. Solid State Chem.*, 2004, **177**, 786–792; (*e*) S. Ciattini, F. Costantino, P. Lorenzo-Luis, S. Midollini, A. Orlandini and A. Vacca, *Inorg. Chem.*, 2005, **44**, 4008–4016; (*f*) J. Beckmann, F. Costantino, D. Dakternieks, A. Duthie, A. Ienco, S. Midollini, C. Mitchell, A. Orlandini and L. Sorace, *Inorg. Chem.*, 2005, **44**, 9416–9423; (*g*) F. Costantino, S. Midollini, A. Orlandini and L. Sorace, *Inorg. Chem. Commun.*, 2006, **9**, 591–594; (*h*) S. Midollini, P. Lorenzo-Luis and A. Orlandini, *Inorg. Chim. Acta*, 2006, **359**, 3275–3282; (*i*) S. Midollini and A. Orlandini, *J. Coord. Chem.*, 2006, **59**, 1433–1442; (*j*) F. Costantino, S. Midollini and A. Orlandini, *Inorg. Chim. Acta*, 2008, **361**, 327–334.
16 V. Kubíček, P. Vojtíšek, J. Rudovský, P. Hermann and I. Lukeš, *Dalton Trans.*, 2003, 3927–3938.
17 C. F. Baes Jr. and R. E. Mesmer, *The Hydrolysis of Cations*, Wiley, New York, 1976.
18 M. Kývala and I. Lukeš, *International Conference, Chemometrics '95*, Pardubice, Czech Republic, 1995, p. 63; Full version of "*OPIUM*" is available (free of charge) on http://www.natur.cuni.cz/~kyvala/opium.html
19 (*a*) Z. Otwinovski and W. Minor, *HKL DENZO and Scalepack Program Package*, Nonius BV, Delft, 1997; (*b*) Z. Otwinovski and W. Minor, *Methods Enzymol.*, 1997, **276**, 307–326.
20 A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Crystallogr.*, 1994, **27**, 435.
21 G. M. Sheldrick, *SHELXL97. Program for Crystal Structure Refinement from Diffraction Data*, University of Göttingen, Göttingen, 1997.
22 S. Chen and J. K. Coward, *J. Org. Chem.*, 1998, **63**, 502–509.
23 K. Issleib, W. Moegelin and A. Balszuweit, *Z. Chem.*, 1985, **25**, 370–371.
24 C. King, D. M. Roundhill and F. R. Fronczek, *Inorg. Chem.*, 1986, **25**, 1290–1292.
25 A. Flohr, A. Aemissegger and D. Hilvert, *J. Med. Chem.*, 1999, **42**, 2633–2640.
26 A. E. Martell and R. M. Smith, *Critical Stability Constants*, Plenum Press, New York, 1974–1989, vol. 1–6; *NIST Standard Reference Database 46 (Critically Selected Stability Constants of Metal Complexes), version 5.0*, 1994.
27 J. Rohovec, I. Lukeš, P. Vojtíšek, I. Císařová and P. Hermann, *J. Chem. Soc., Dalton Trans.*, 1996, 2685–2691.
28 (*a*) T. C. Higgs, K. Spartalian, C. J. O'Connor, B. F. Matzanke and C. J. Carrano, *Inorg. Chem.*, 1998, **37**, 2263–2272; (*b*) N. A. Rey, A. Neves, A. J. Bortoluzzi, W. Haase and Z. Tomkowicz, *Dalton Trans.*, 2012, **41**, 7196–7200; (*c*) R. Prabu, A. Vijayaraj, R. Suresh, L. Jagadish, V. Kaviyarasan and V. Narayanan, *Bull. Korean Chem. Soc.*, 2011, **32**, 1669–1678.
29 H. Borsook and K. V. Thimann, *J. Biol. Chem.*, 1932, **98**, 671–705.
30 T. A. Hudson, K. J. Berry, B. Moubaraki, K. S. Murray and R. Robson, *Inorg. Chem.*, 2006, **45**, 3549–3556.
31 B. F. Abrahams, T. A. Hudson and R. Robson, *J. Am. Chem. Soc.*, 2004, **126**, 8624–8625.

