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ORIGINAL PAPER

Hydroxy-bisphosphinic acids: synthesis and complexation properties with transition metals and lanthanide ions in aqueous solution

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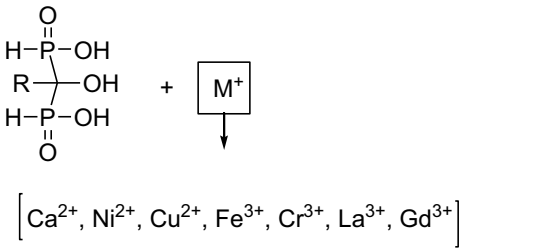
Abstract Treatment of acyl chlorides with a mixture of ammonium hypophosphite and hexamethyl disilazene gave 1-hydroxy-1,1-bisphosphinic acids. Acid dissociation constants (p*K*a) of 1-hydroxy-1,1-bisphosphinic acids were determined by the pH-potentiometric technique. Complexation properties of 1-hydroxy-1-phenylmethyl-1,1-bis(H-phosphinic acid) (HBPA 1) with Ca^{2+} as well as transition metals Fe^{2+}, Ni^{2+}, Cu^{2+}, Cr^{3+} and lanthanide ions La^{3+}, Gd^{3+} were studied in aqueous solution. The stabilizing ability of complexes of HBPA 1 with these ions in aqueous solutions was determined to show a significant difference in the complex stability due to the transition metals.

Graphical abstract The coordination of 1-hydroxy-1,1-bis(H-phosphinic acid) to metals.



Keywords Hydroxyphosphinic acids · Dissociation constant · Coordination ability · Transition metals · Lanthanide ions

Introduction

Organophosphinic acids, organic derivatives of phosphinic acid, have found a wide range of application in the areas of industrial, agricultural, and medical chemistry owing to their biological and physical properties as well as their utility as synthetic intermediates [1–3]. Among organophosphinic acids, 1-hydroxyphosphinic acids are an important class of compounds that exhibit a variety of interesting and useful properties [4]. For example, though complexation properties of 1-hydoxyphosphinic acids are similar to those natural 2-hydroxy acids in many respects, the stability constants of metal–phosphinic acids complexes are lower than those of carboxylic acids due to less basic properties of a phosphinate group than carboxylate group [5–9]. It is known that multidentate ligands containing two or three phosphinic acid groups strongly form complexes with transition metals and lanthanide ions to exhibit biological activity [10–15]. The Gd^{3+} complexes of multidentate phosphinic acid ligands have been used as contrast enhancing agents in magnetic resonance imaging [16, 17].

1-Hydroxy-1,1-bisphosphonic acids are also broadly used in medicinal chemistry as important regulators of calcium metabolism in living organisms by affecting the functioning of bone cells, such as osteoclasts and osteocytes [18]. These cells are responsible for bone formation and desorption and 1-hydroxy-1,1-bisphosphonic acids, such as alendronate and pamidronate (Fig. 1) can be used in the treatment of osteoporosis and Paget disease [19]. In contrast to the widely studied 1-hydroxy-1,1-bisphosphonic

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acid derivatives in medicinal chemistry [20–24], relatively few papers have reported on the chemistry of 1-hydroxy-1,1-bisphosphinic acids, although there is evidence that bisphosphinic acids are pharmaceutically active [12, 20, 25–27].

Recently, our laboratories reported novel and convenient methods for the synthesis of a variety of phosphinic acid derivatives [28–35]. We also reported the synthesis and complexation properties of *N,N*-bis(phosphinomethyl) amines, as a novel aminophosphinic acids, containing C_2-axis of symmetry with two phosphinic moieties [36, 37]. As part of our efforts to introduce novel structures of phosphinic acids, we have now synthesized and characterized a series of 1-hydroxy-1,1-bisphosphinic acids (Scheme 1). The complexation properties and stability constants for complexes of 1-hydroxy-1,1-bisphosphinic acids with some metal ions are studied by the UV–Vis spectroscopy.

Experimental

Instrumentation

The chemicals were obtained from commercial sources and purified by distillation or recrystallization before use. ^{1}H–NMR, ^{13}C–NMR and ^{31}P–NMR spectra were recorded on a 400 Bruker Avance instrument. Chemical shifts are reported in δ unit and expressed in ppm. High-resolution mass spectra (HRMS) were recorded on a Waters LCT ESI-TOF mass spectrometer using electrospray ionization (ESI) techniques. Merck Silica-gel 60 F254 plates (No. 5744) were used for the analytical TLC. All solution studies were carried out with a pH meter that calibrates by buffer solution 2 and 9 before using. In all potentiometric titrations, titrant additions were performed with the use of a digital burette (Metrohm Dosimat automatic burette). Spectrophotometric titrations were carried out on a Pharmacia Biotech Ultrospec 4000 instrument.

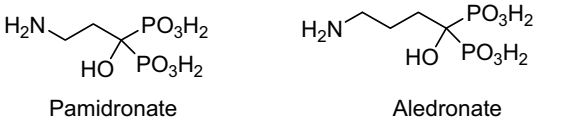
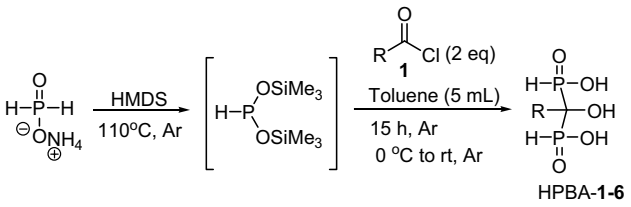


Fig. 1 Structures of the pamidronate and aledronate



R: C_6H_5-(HPBA **1**), 2-FC_6H_4-(HPBA **2**), 2-ClC_6H_4-(HPBA **3**), $C_6H_5CH_2$-(HPBA **4**), $CH_3CH_2CH_2$-(HPBA **5**), *t*-Bu-(HPBA **6**)

Scheme 1 Synthesis route of HPBAs **1–6**

General procedure for the preparation of 1-hydroxy-1,1-bisphosphinic acids

Bis[(trimethylsilyl)oxy]phosphine $(Me_3SiO)_2PH$ was prepared under an argon atmosphere using the literature procedure [38]. Ammonium hypophosphite (0.83 g, 10 mmol) was suspended in $(Me_3Si)_2NH$ (2 mL, 10 mmol) and the mixture was heated overnight at 110 °C (bath temperature) under a flow of argon. The mixture containing $(Me_3SiO)_2PH$ was cooled to 0 °C. To this mixture, the solution of acyl chloride (5 mmol) in dry toluene (5 mL) was added dropwise, and the resulting mixture was stirred overnight at RT. Methanol (5 mL) was added to the reaction mixture and the mixture was stirred for 30 min. During removal of volatiles under reduced pressure, a white precipitate was formed. The precipitate was collected and was washed with acetone (50 mL) and methanol (50 mL) to give 1-hydroxy-1,1-bis(H-phosphinic acid) as a fine, white powder after being dried in air at room temperature (Yields: 47–61 %).

1-Hydroxy-1-phenylmethyl-1,1-bis(H-phosphinic acid) (HPBA 1)

White solid; mp: 210–212 °C; ^{1}H NMR(D_2O, 400 MHz): 6.97 (2H, dt, $^1J_{HP}$ = 537.6 Hz, $^3J_{HP}$ = 12 Hz,), 7.27 (1H, d, J = 7.2 Hz), 7.36 (2H, t, J = 7.6 Hz), 7.47 (2H, d, J = 7.2 Hz); ^{13}C NMR (D_2O-100.6 MHz): 77.2 (t, $^1J_{CP}$ = 91.5 Hz), 125.2, 127.1, 128.3, 136.0; ^{31}P NMR (D_2O/H_3PO_4,162.0 MHz): 30.44 ppm; HRMS calcd for $C_7H_{11}O_5P_2$ (MH^+): 237.0082; Found: 237.0083.

1-Hydroxy-1-(2-fluorophenyl)methyl-1,1-bis(H-phosphinic acid) (HPBA 2)

White solid; mp: 199–201 °C; ^{1}H NMR(D_2O, 400 MHz): 7.08 (2H, ddt, $^1J_{HP}$ = 540.0 Hz, J_{HF} = 5.6 Hz, $^3J_{HP}$ = 18.4 Hz), 7.02–7.07 (1H, m), 7.15 (1H, t, J = 7.2 Hz), 7.22–7.27 (1H, m), 7.45–7.50 (1H, m); ^{13}C NMR (D_2O-100.6 MHz): 77.3 (dt, $^1J_{CP}$ = 86.5 Hz, J_{CF} = 6.0 Hz), 115.6, 123.6, 124.3, 128.0, 131.8, 159.1 (d, J_{CF} = 244.5); ^{31}P NMR (D_2O/H_3PO_4,162.0 MHz): 22.55 ppm; HRMS calcd for $C_7H_{10}FO_5P_2$ (MH^+): 254.9988; Found: 254.9992.

1-Hydroxy-1-(2-chlorophenyl)methyl-1,1-bis(H-phosphinic acid) (HPBA 3)

White solid; mp: 230–232 °C; ^{1}H NMR(D_2O, 400 MHz): 7.30 (2H, dt, $^{1}J_{HP} = 555.6$ Hz, $^{3}J_{HP} = 14.4$ Hz,), 7.20–7.36 (3H, m), 7.62 (1H, d, $J = 6.8$ Hz); ^{13}C NMR (D_2O-100.6 MHz78.9 (t, $^{1}J_{CP} = 84.5$ Hz), 127.0, 128.2, 128.5, 130.6, 135.7; ^{31}P NMR (D_2O/H_3PO_4,162.0 MHz): 21.56 ppm; HRMS calcd for $C_7H_{10}ClO_5P_2$ (MH^+): 270.9692; Found: 270.9689.

1-Hydroxy-2-phenylethyl-1,1-bis(H-phosphinic acid) (HPBA 4)

White solid; mp: 203–205 °C; ^{1}H NMR(D_2O, 400 MHz): 3.08 (2H, t, $J_{HP} = 12.4$ Hz), 6.75 (2H, dt, $^{1}J_{HP} = 532.0$ Hz, $^{3}J_{HP} = 10.4$ Hz), 7.19–7.36 (5H, m); ^{13}C NMR (D_2O-100.6 MHz): 48.9, 73.7 (t, $^{1}J_{CP} = 94.6$ Hz), 126.7, 128.0, 131.3, 135.4; ^{31}P NMR (D_2O/H_3PO_4,162.0 MHz): 23.82 ppm; HRMS calcd for $C_7H_{12}O_5P_2Na$: 273.0085; Found: 273.0053.

1-Hydroxy-1-butyl-1,1-bis(H-phosphinic acid) (HPBA 5)

White solid; mp: 194–196 °C; ^{1}H NMR(D_2O, 400 MHz): 0.78 (3H, t, $J = 7.2$ Hz), 1.38–1.43 (2H, m), 1.59–1.70 (2H, m), 6.80 (2H, dt, $^{1}J_{HP} = 525.2$ Hz, $^{3}J_{HP} = 17.2$ Hz); ^{13}C NMR (D_2O-100.6 MHz): 14.2, 16.2, 32.8, 74.1 (t, $^{1}J_{CP} = 94.6$ Hz); ^{31}P NMR (D_2O/H_3PO_4,162.0 MHz): 25.00 ppm; HRMS calcd for $C_4H_{13}O_5P_2$(MH^+): 203.0238; Found: 203.0238.

1-Hydroxy-2,2-dimethylpropyl-1,1-bis(H-phosphinic acid) (HPBA 6)

White solid; mp: 210–212 °C; ^{1}H NMR(D_2O, 400 MHz): 1.09 (9H, s), 6.95 (2H, dt, $^{1}J_{HP} = 530.4$ Hz, $^{3}J_{HP} = 17.2$ Hz); ^{13}C NMR (D_2O-100.6 MHz): 26.4, 36.7, 78.8 (t, $^{1}J_{CP} = 89.5$ Hz); ^{31}P NMR (D_2O/H_3PO_4,162.0 MHz): 25.65 ppm; HRMS calcd for $C_5H_{15}O_5P_2$(MH^+): 217.0395; found: 217.0386.

Potentiometric measurements

The titrations can be done manually by a burette under computer controls and the pH meter which provides information about the total concentrations of protons, [H^+], at any time during a titration. Before the data are acquired, the solution is stirred and enough time is allowed for complete equilibration after each addition. Sodium hydroxide solution (0.2 M) was standardized against potassium hydrogen phthalate (0.1 M) and HCl solution concentration was determined with NaOH. All the aqueous solutions are prepared in three times distilled water. The titration experiments were performed under Argon atmosphere at room temperature. The dissociation and protonation constants are determined by pH-metric titration of 50 ml aqueous solutions containing 2×10^{-3} M of ligand and a require volume of HCl at a fixed ionic strength of 0.05 M $NaNO_3$ over the pH range of 1.86–12.50 with standardized NaOH (0.2 M). A nonlinear least-square curve-fitting program such as the Newton–Gauss–Levenberg/Marquardt (NGL/M) method with the Newton–Raphson algorithm is used to compute the equilibrium concentrations of all species for the calculation of equilibrium constants and total component concentration [39].

Spectrophotometric titrations

Metallic ion solutions (0.001 M) were prepared in deionized water and adjusted in pH = 7 using phosphate buffer. The ionic strength was fixed with $NaNO_3$ (0.05 M). The UV–Vis titrations were performed with two different procedures, considering either metal ions or ligand as titrant by adding specific volumes of metallic ions solutions (or HBPA **1** ligand solution) to a 3 mL of aqueous solution of $1–5 \times 10^{-5}$ M HBPA **1** ligand (or metal ions). Before the data are acquired, the solution is stirred, and enough time is allowed for complete equilibration before the data are acquired. The absorbance intensities are measured at 25 °C. The stability constants of the complexes were calculated by fitting the experimental data to the desire complexation model using the NGL/M method.

Results and discussion

Synthesis of ligands HPBA1-6

Six derivatives of 1-hydroxy-1,1-bis(*H*-phosphinic acids) (HPBAs **1–6**) were synthesized via a two-step reaction sequence which is described in Scheme 1. According to Scheme 1, in the first step, bis(trimethylsilyl)hypophosphite was generated in situ from ammonium hypophosphite and hexamethyldisilazane. Then, in the second step, it was treated with an acid chloride (**1a–f**) to yield the corresponding 1-hydroxy-1,1-bis(H-phosphinic acid) (HPBAs **1–6**) in good yields. All HPBAs **1–6** were isolated as white stable solids and the structures were confirmed by ^{1}H NMR, ^{31}P NMR, ^{13}C NMR and HRMS. In the ^{1}H NMR spectra of HPBAs **1–6**, the chemically equivalent protons connected to phosphorus atoms should display a doublets, which is due to coupling of protons with the phosphorus atom. However, these chemically equivalent protons were found not to be magnetically equivalent and ^{1}H NMR spectrum is quite different from a simple doublet expected for the protons

connected to phosphorus atoms. For example, in the case of compound HPBA **3**, the ^{1}H-NMR spectrum exhibited one doublet with unexpected side peaks in each peak at δ 6.60 and 7.99 ppm indicative of H–P coupling ($^{1}J_{HP} = 556$ Hz and $^{3}J_{HP} = 40$ Hz) that shows two chemically equivalent protons are not magnetically equivalent because H_a and H_b do not couple to P_a with the same coupling constant (Fig. 2). The ^{13}C-NMR spectrum exhibited one triplet peak at δ 78.8 ppm indicative of P–C–P coupling ($^{1}J_{CP} = 84$ Hz). The 2D H–H COSY showed a strong coupling between H and P with cross peaks at 6.60 and 7.99 ppm. The 2D hetero nuclear H–C HSQC shows correlations between protons directly attached to heteronuclei carbon (see supporting information).

Dissociation constants of HPBAs 1–6

The dissociation constants of the six ligands were obtained using a potentiometric method. All ligands possess two dissociation constants. The dissociation constants, defined as $Ka_i = [H_{(n-i)}L][H^+]/[H_{(n-i+1)}L]$ where n is the number of protons, were determined in the pH range of about 1.86–12.5 in the presence of 0.05 M $NaNO_3$ at 25.0 ± 0.1 °C. The pK_a values and log β values (protonation constants, defined as $\beta_i = [H_iL]/[H^+]^i[L]$) are calculated and summarized in Table 1. The standard deviation of constants, obtained from fitting the algorithm are also shown in Table 1. Theoretically, two dissociation constants are predicted for the ligands of HPBAs **1–6** since they have two phosphinic acid groups.

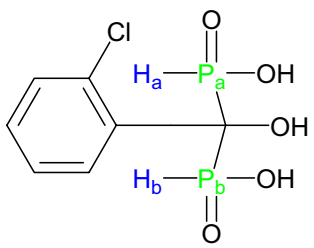


Fig. 2 Two chemically equivalent protons H_a and H_b are not magnetically equivalent

Table 1 Dissociation and protonation constants of 1-hydroxy-1,1-bis(H-phosphinic acids) (HPBAs **1–6**) at 25 °C

HPBA	pK_{a1}	pK_{a2}	Logβ_1	Logβ_2
1	8.6 ± 0.6	11.9 ± 0.4	11.9 ± 0.4	20.6 ± 0.4
2	8.3 ± 0.1	9.65 ± 0.08	9.65 ± 0.08	17.96 ± 0.07
3	8.65 ± 0.07	9.71 ± 0.05	9.71 ± 0.05	18.36 ± 0.05
4	8.1 ± 0.7	9.86 ± 0.07	9.86 ± 0.07	17.9 ± 0.7
5	8.3 ± 0.1	9.33 ± 0.07	9.33 ± 0.07	17.63 ± 0.08
6	8.63 ± 0.07	9.33 ± 0.05	9.33 ± 0.05	17.96 ± 0.05

Stability constants for the complexes of ligand HPBA 1

HPBAs **1–6** are composed of one hydroxyl group and two symmetrical phosphinate units that might combine with transition metals and lanthanide ions in 1:1 or 2:1 of the ligand to metal ratio. In this study, HPBA **1** was chosen as a model compound to demonstrate the complexing properties of 1-hydroxy-1,1-bisphosphinic acids with metal ions. The formation of equilibria between the ligand (HPBA **1**) and metal ions Ca^{2+}, Ni^{2+}, Cu^{2+}, Fe^{3+}, Cr^{3+} as well as lanthanide ions La^{3+}, Gd^{3+} were studied by UV–Vis spectroscopy. The stability constants of interaction of ligand HPBA **1** with metal ions in aqueous solution of pH = 7 were studied at an ambient temperature. The titrations were performed with two different procedures, considering either metal ions or ligand as titrant. For the calculation of the stability constants of the complexes, formation of ML_2 complex for all systems was expected based on the quality and number of donor atoms in the ligand and the properties of metal ions. However, the stoichiometry of the resulting complexes was determined from the absorbance mole-ratio plots as well as continuous variation method at the wavelength of corresponding complexes. According to the results, the formation of the complex ML_2 was considered for all studied systems (see supporting information).

As a sample of the experimental spectra, Fig. 3a shows UV–Vis titration spectra curves of Fe^{3+} on stepwise addition of aqueous solutions of HPBA **1**. This plot revealed two isosbestic points formed at 284 and 354 nm, respectively. The presence of isosbestic point during a chemical change (complex formation of the ligand with Fe^{3+}) is good evidence that only two principal species are present, and that they have a constant total concentration [40].

As mentioned, the stoichiometry of the complexes metal–ligand HPBA **1** was studied by spectrophotometric titrations using absorbance mole-ratio plots and continuous variation method. As a typical example, Fig. 3b shows the absorption intensity changes as a function of the [HPBA **1**]/[Fe^{3+}] molar ratio. The molar ratios of the ligand HPBA **1** varied from 0 to 4 and absorbance values were plotted at the wavelength of 450 nm. These changes could be pointed to the ratio of ligand HPBA **1** and Fe^{3+} ion. The formation curve of the [HPBA **1**]/[Fe^{3+}] complex would extrapolate to a coordination number of 2, and strongly supports the formation of ML_2-type complex, in which one metal ion is coordinated by two ligands of HPBA **1**. In addition, continuous variation method was used to show a distinct maximum point in the corresponding plots at mole fraction of about 0.33, which strongly emphasized the formation of 1:2 complex between Fe^{3+} and HPBA **1** ligand. This

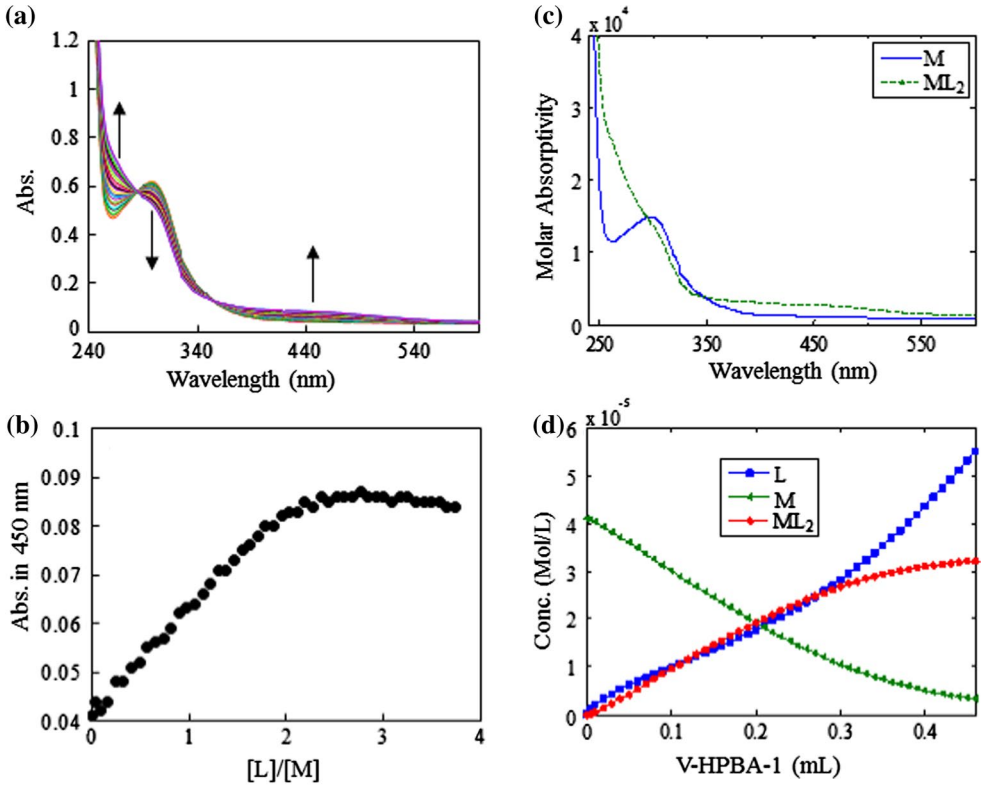


Fig. 3 **a** UV–Vis spectra for titration of Fe^{3+} (4.2×10^{-5} M) with stepwise addition of HPBA **1** (0.001 M), **b** molar ratio plot ([HPBA 1]/[Fe^{3+}]) for the investigated complexation at 450 nm, **c** respective molar absorptivity spectra and **d** calculated concentration profiles of the components

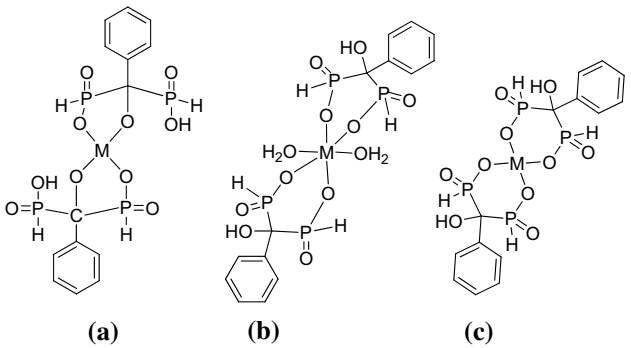


Fig. 4 Hypothetical structures for ML_2 complexes of M^{n+}

coordination number was a common characteristic of all mole-ratio plots related to the other metal ions complexation with ligand HPBA **1**. It is more likely that the formation of two six-membered (ML_2) chelating rings around metal ions leads to a more stable square-planar arrangement (Fig. 4) [41]. Stability constants of the resulting ML_2 complexes were determined by fitting the experimental data using a NGL/M method. Figure 3c, d shows concentration profiles and molar absorptivities of the present chemical components of titration of Fe^{3+} with HPBA **1** obtained by fitting the spectroscopic data.

The stability constants of ML_2 complexes of the ligand HPBA **1** and metal ions Ca^{2+}, Ni^{2+}, Cu^{2+}, Fe^{3+}, Cr^{3+} as well as lanthanide ions La^{3+}, Gd^{3+} are shown in Table 2. The data given in Table 2 revealed that the stability of the complexes of the ligand HPBA **1** with different metal ions decreases in the order $La^{3+} > Gd^{3+} > Ni^{2+} > Ca^{2+} > Fe^{3+} > Cu^{2+} \gg Cr^{3+}$. The comparison of the stability constants indicates that Gd^{3+}, La^{3+}, Ni^{2+} have the highest tendency to make coordination with the ligand HPBA **1**. Since alcohols are known to be poor donors for the lanthanides, the results suggest us that the phosphinate groups contribute to increase the overall stability of the complexes [42]. The presence of two phosphinic acids in the ligand has an extra

Table 2 Stability constants for the ligand HPBA-**1** and metal ions Ca^{2+}, Ni^{2+}, Cu^{2+}, Fe^{3+}, Cr^{3+} and lanthanide ions La^{3+}, Gd^{3+} at room temperature, in concentration of 0.05 M $NaNO_3$

Metal	$\log\beta_{ML2}$
Ca (II)	10.8 ± 0.1
Ni (II)	10.80 ± 0.09
Cu (II)	9.88 ± 0.09
Fe (III)	10.55 ± 0.06
Cr (III)[a]	–
La (III)	12.6 ± 1.4
Gd (III)[a]	11.6 ± 0.2

[a] The complexation constant between the ligand (HPBA-**1**) and Cr^{3+} could not be calculated, due to no interaction of Cr^{3+} with the ligand

effect on the stability of the lanthanide complexes by the formation of two five- or six-membered rings as shown in Fig. 4.

It should be noted that among the studied metal ion, no change in the UV–Vis titration spectra of HPBA **1** on stepwise addition of aqueous solution of Cr^{3+} was observed. Spectroscopic results showed no interaction of Cr^{3+} with the ligand of HPBA **1**.

Conclusions

In summary, in this paper, six derivatives of 1-hydroxy-1,1-bis(H-phosphinic acid) (HPBA **1–6**) have been synthesized and characterized. The pH-potentiometric technique was used for determining the acid dissociation constants (p*K*a) of the ligands. The formation equilibria between the ligand HPBA **1** and metal ions Ca^{2+}, Ni^{2+}, Cu^{2+}, Fe^{3+}, Cr^{3+} and lanthanide ions La^{3+}, Gd^{3+} were studied by UV–Vis spectroscopy. The stability constants of interaction of ligand HPBA **1** with metal ions in the pH = 7 were obtained in aqueous solution at an ambient temperature. The stability constants of the complexes of the ligand HPBA **1** with different cations decrease in the order $La^{3+} > Gd^{3+} > Ni^{2+} > Ca^{2+} > Fe^{3+} > Cu^{2+} \gg Cr^{3+}$ for ML_2 complexes. The results of absorbance mole-ratio plots and continuous variation method strongly support the formation of ML_2 between metal ions and HPBA **1**.

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