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Synthesis and Complexation Properties of *N,N*-Bis(phosphinomethyl)amine as a New Class of 1-Aminophosphinic Acids with Transition Metals and Lanthanide Ions in Aqueous Solution

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ABSTRACT: The treatment of aromatic aldehydes with ammonia and hypophosphorus acid gave novel C_2-symmetric *N,N*-bis(phosphinomethyl)amines as a new class of 1-aminophosphinic acid compounds. Complexation properties of *N,N*-bis(phosphinomethyl)amines with transition metals such as Co^{2+}, Ni^{2+}, Zn^{2+}, Cu^{2+}, and Cd^{2+} and lanthanide ions La^{3+} and Gd^{3+} were studied in aqueous solution by the pH-potentiometric method. Dissociation constants (p*K*) of the compound were determined by the pH-potentiometric technique. The complexation studies with compound *dl*-**2a** showed the best fit of the titration curves were obtained when the ligand−metal stoichiometric ratio was 1:1 and 2:1.

1. INTRODUCTION

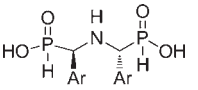
Aminophosphinic acids have attracted considerable attention because of their significant biological activity.[1] 1-Aminophosphinic acids are phosphorus analogues of natural amino acids and are expected to show strong coordination ability with metals. It has been indicated that 1-aminophosphinic acid derivatives are selective inhibitors of various proteolytic enzymes, particularly metalloproteases.[2−7] The design of potent and specific enzyme inhibitors with significant pharmacological activity and low toxicity requires the knowledge of metal binding properties to provide insight about the mechanism of their biological activity.

Over the past several years, our laboratories have reported novel methods for the synthesis of 1-amino-*H*-phosphinic acids.[8−11] In a previous communication, we reported the synthesis of *N,N*-bis(phosphinomethyl)amines as a novel 1-amino-*H*-phosphinic acid containing two phosphinic moieties with C_2-symmetry axis.[12] As an extension of previous studies,[13−18] we have now prepared a series of diastereomerically pure *N,N*-bis(phosphiomethyl)amines *dl*-**2** (Scheme 1). The dissociation constants and chelate stability of the representative analogues were examined with a number of metal ions including the transition series and lanthanide ions. In this paper, we disclose experimental details for the synthesis of *dl*-2 and results of the coordination studies.

2. EXPERIMENTAL SECTION

2.1. Instrumentation. All chemicals were commercial products and distilled or recrystallized before use. NMR spectra were taken with a 250 Bruker Avance instrument with the chemical shifts being reported as δ parts per million and couplings expressed in hertz. The chemical shift data for each signal on ^{1}H NMR are given in units of δ relative to D_2O (δ = 4.7). For ^{13}C NMR spectra, the chemical shifts in D_2O are recorded relative to the tetramethylsilane (TMS) resonance (δ = 0.0). For ^{31}P NMR spectra, the chemical shifts in D_2O are recorded to the H_3PO_4 (85 %) resonance (δ = 0.0). Silica gel column chromatography was carried out with silica gel 100 (Merck no. 10184). Merck silica gel 60 F254 plates (no. 5744) were used for the preparative thin layer chromatography (TLC). Experiments were carried out with a pH meter that were calibrated by buffer solution 2 and 9 before use. The titrant addition was performed with a Metrohm Dosimat automatic buret.

Scheme 1



dl-**2**

2.2. General Procedure for the Preparation of Compound 2. The aldehyde (3 mmol) was added to ammonium hydroxide (30 %, 15 mL), and the solution was stirred for 5 h at reflux. During this time, a white precipitate formed. The precipitate was removed by filtration and was dried. The solid was dissolved in 5 mL of ethanol and hypophosphorus acid (5 mmol, anhydrous) was added to this mixture, and the resulting solution was stirred for (2 to 12) h at reflux. The solvent was evaporated, and the mixture resolved in acetone by heating. Dropwise addition of water gave the crude product as a white solid. The crude product was washed with ethanol and dried in air at room temperature to give product **2** in (40 to 71) % yield. The solid product was washed with ethanol/water (50 mL, 9:1) and dried in air at room temperature to give a single diastereoisomer (*R**,*R**)-**2**.

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2.2.1. {[(Hydroxyphosphinoylphenylmethyl)amino]phenylmethyl}phosphinic Acid (R,R*-**2**a).* White solid; mp: 222−224 °C; ^{1}H NMR (D_2O, 250 MHz): 3.79 (2H, d, J = 13.5 Hz, −CHP), 6.83, (2H, d, J_{HP} = 552 Hz), 6.85−7.40 (10H, m); ^{13}C NMR (D_2O-NaOD, 62.9 MHz): 61 (dd, J_{CP} = 98.5 and 14.1 Hz), 127.0, 127.5, 127.7, 128.5, 128.7, 128.9, 134.9, 136.5; ^{31}P NMR (D_2O/H_3PO_4, 101.2 MHz): 17.89 ppm; IR (KBr): 3650−2120 (−OH), 1250 (P═O), 1055−710 (P−O) cm^{-1}; Anal. Calcd for $C_{14}H_{17}NO_4P_2$: C, 51.68; H, 5.27; N, 4.31. Found: C, 51.55; H, 5.20; N, 4.56; Calcd. Mass: 326.0711; Found: 326.0742.

2.2.2. {(4-Chlorophenyl)-{[(4-chlorophenyl)hydroxyphosphinoylmethyl]amino}methyl}phosphinic Acid (R,R*-**2**b).* White solid; mp: 240−242 °C; ^{1}H NMR (D_2O, 250 MHz): 3.79 (2H, d, J = 14.0 Hz, −CHP), 6.84 (2H, d, J_{HP} = 552 Hz), 6.91 (4H, d, J = 7.2 Hz), 7.21 (4H, d, J = 7.2 Hz); ^{13}C NMR (D_2O-NaOD, 62.9 MHz): 59.2−61.5 (m, CHP), 128.7, 130.1 (d, J_{CP} = 5.7 Hz), 132.8 (d, J_{CP} = 3.1 Hz), 133.4 (d, J_{CP} = 3.8 Hz); ^{31}P NMR (D_2O/H_3PO_4, 101.2 MHz): 17.37 ppm; IR (KBr): 3650−2120 (−OH), 1250 (P═O), 1080−750 (P−O) cm^{-1}; Anal. Calcd for $C_{14}H_{15}Cl_2NO_4P_2$: C, 42.75; H, 3.85; N, 3.56. Found: C, 42.56; H, 3.80; N, 3.5; Calcd. Mass: 393.9931; Found: 393.9917.

2.2.3. {(4-Fluorophenyl)-{[(4-fluorophenyl)hydroxyphosphinoylmethyl]amino}methyl}phosphinic Acid (R,R*-**2**c).* White solid; mp: 230−232 °C; ^{1}H NMR (D_2O, 250 MHz): 3.98 (2H, d, J = 13.5 Hz, −CHP), 6.99 (2H, d, J_{HP} = 552 Hz), 7.01−7.15 (m, 8H); ^{13}C NMR (D_2O-NaOD, 62.9 MHz): 60.1 (dd, J_{CP} = 98.5 and 14.1 Hz), 115.4 (d, J_{CP} = 21.4 Hz), 130.1−130.5 (m, Ar), 162.1 (d, J_{CP} = 243.2 Hz); ^{31}P NMR (D_2O/H_3PO_4, 101.2 MHz): 17.22 ppm; IR (KBr): 3650−2120 (−OH), 1240 (P═O), 1180−580 (P−O) cm^{-1}; Anal. Calcd for $C_{14}H_{15}F_2NO_4P_2$: C, 46.53; H, 4.19; N, 3.88. Found: C, 46.56; H, 4.12; N, 3.72; Calcd. Mass: 384.0342; Found: 384.0327.

2.2.4. {[(Hydroxyphosphinoyl-(4-methoxyphenyl)methyl]amino)-(4-methoxyphenyl)methyl}phosphinic Acid (R,R*-**2**d).* White solid; mp: 212−214 °C; ^{1}H NMR (D_2O, 250 MHz): 3.63 (s, 6H), 3.73 (2H, d, J = 14.5 Hz, −CHP), 6.86 (2H, d, J_{HP} = 550 Hz), 6.82 (4H, d, J = 8.0 Hz), 6.90 (4H, d, J = 8.0 Hz); ^{13}C NMR (D_2O-NaOD, 62.9 MHz): 55.3, 59.2−61.5 (m, CHP), 114.8, 120.4, 130.1 (d, J_{CP} = 5.5 Hz), 159.7; ^{31}P NMR (D_2O/H_3PO_4, 101.2 MHz): 17.81 ppm; IR (KBr): 3650−2320 (−OH), 1248 (P═O), 1150−650 (P−O) cm^{-1}. Anal. Calcd for $C_{16}H_{21}NO_6P_2$: C, 49.86; H, 5.50; N, 3.64. Found: C, 49.71; H, 5.43; N, 3.52; Calcd. Mass: 386.1004; Found: 386.0826.

2.2.5. {[(Hydroxyphosphinoyl-p-tolylmethyl)amino]-p-tolylmethyl}phosphinic Acid (R,R*-**2**e).* White solid; mp: 228−230 °C;^{1}H NMR (D_2O, 250 MHz): 2.18 (s, 6H), 3.33 (2H, d, J = 14.0 Hz, −CHP), 6.74 (2H, d, J_{HP} = 551 Hz), 6.75−7.17 (8H, m); ^{13}C NMR (D_2O-NaOD, 62.9 MHz): 20.1, 60.53 (dd, J_{CP} = 98.7, 14.2 Hz), 128.4 (d, J_{CP} = 5.7 Hz), 128.8 (d, J_{CP} = 5.7 Hz), 129.0, 129.2, 131.6, 133.3, 137.6 (d, J_{CP} = 3.1 Hz), 137.9 (d, J_{CP} = 3.1 Hz); ^{31}P NMR (D_2O/H_3PO_4, 101.2 MHz): 18.24 ppm; IR (KBr): 3650−2220 (−OH), 1251 (P═O), 1185−610 (P−O) cm^{-1}. Anal. Calcd for $C_{16}H_{21}NO_4P_2$: C, 54.38; H, 5.99; N, 3.96. Found: C, 54.30; H, 5.85; N, 4.05; Calcd. Mass: 354.1024; Found: 354.1026.

2.2.6. {(2-Fluorophenyl)-{[(2-fluorophenyl)hydroxyphosphinoylmethyl]amino}methyl}phosphinic Acid (R,R*-**2**f).* White solid; mp: 226−228 °C; ^{1}H NMR (D_2O, 250 MHz): 4.15 (2H, d, J = 14.7 Hz, −CHP), 6.90 (2H, d, J_{HP} = 557.5 Hz), 6.75−7.85 (m, 8H); ^{13}C NMR (D_2O-NaOD, 62.9 MHz): 60.1 (dd, J_{CP} = 98.5 and 14.1 Hz), 116.1 (d, J_{CP} = 21.4 Hz), 125.3−130.5 (m, Ar), 161.1 (d, J_{CP} = 242.0 Hz); ^{31}P NMR (D_2O/H_3PO_4, 101.2 MHz): 15.95 ppm; IR (KBr): 3650−2120 (−OH), 1240 (P═O), 1180−580 (P−O) cm^{-1}; Anal. Calcd for $C_{14}H_{15}F_2NO_4P_2$: C, 46.53; H, 4.19; N, 3.88. Found: C, 46.50; H, 4.15; N, 3.75.

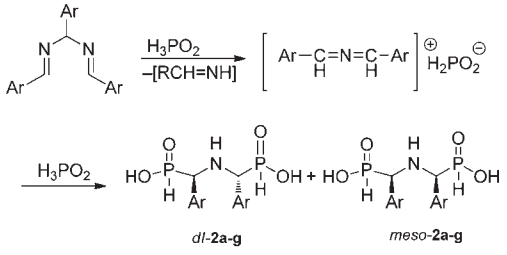
2.2.7. {[(Hydroxyphosphinoyl-naphthalen-2-yl-methyl)-amino]naphthalen-2-yl-methyl}phosphinic Acid (R,R*-**2**g).* White solid; mp: 212−214 °C; ^{1}H NMR (D_2O, 250 MHz): 4.13 (2H, d, J = 13.2 Hz, −CHP), 7.13 (2H, d, J_{HP} = 551 Hz), 6.90−7.80 (m, 14H), 6.90 (2H, d, J = 8.0 Hz); ^{13}C NMR (D_2O-NaOD, 62.9 MHz): 61.2 (dd, J_{CP} = 97.5 and 13.8 Hz), 126.1−126.5 (m, Ar) 127.6, 128.0 (d, J_{CP} = 7.0 Hz), 128.2, 132.5, 132.6 132.9; ^{31}P NMR (D_2O/H_3PO_4, 101.2 MHz): 17.80 ppm; IR (KBr): 3650−2100 (−OH), 1248 (P═O), 1050−750 (P−O) cm^{-1}; Anal. Calcd for $C_{22}H_{21}NO_4P_2$: C, 62.10; H, 4.98; N, 3.29. Found: C, 61.97; H, 5.03; N, 3.22; Calcd. Mass: 426.1024; Found: 426.1021.

2.3. Potentiometric Measurements. Titrations can be undertaken manually by preparing a series of solutions with known total concentrations; it is much more efficient and reliable to use computerized titration setups. Here a computer controls the buret and the pH meter, which provides information on the free proton concentration, $[H^+]$, at any time during the titration. After each addition, the solution is stirred, and enough time is allowed for complete equilibration before the data are acquired. The carbonate free NaOH concentration (0.5 M) was standardized against potassium hydrogen phthalate (0.5 M), and HCl solution concentration was determined with NaOH. The ionic strength was fixed by $NaNO_3$ (0.1 M). All solutions were prepared in three times distilled water. The titration processes were performed under argon atmosphere and room temperature. The stability constant, both for protons and complexes with metal ions, were determined by pH-metric titration of 50 mL samples over the pH range (2 to 11). The titrant solutions for protonation constants containing dissolved ligand (0.001 M), HCl (0.016 M) in the presence of 0.1 M $NaNO_3$, were titrated against standardized NaOH (0.5 M). Titrations were performed in triplicate, and the Newton−Raphson algorithm is the computation of all species concentrations, set of formation constants, and total component concentration.[19] For the stability constant of the metal ion complexes, the ligand-to-metal ratio was 1:1 and 2:1 without the addition of acid at the same ionic strength.

3. RESULTS AND DISCUSSION

3.1. Preparation of Diastereomerically Pure *N,N*-Bis-(phosphinomethyl)amines Having a C_2-Axis of Symmetry. In previous reports, we explained that diimines, readily prepared from aromatic aldehydes and ammonia solution, serve as masked *N*-methylene methanaminiums (Ar—CH═N$^+$═CH—Ar) and doubly react with H_3PO_2 to give 1-aminoalkylphosphinic acid derivatives **2**a−g having a C_2-axis or a symmetric face on the nitrogen atom as a mixture of diastereoisomers (Scheme 2 and Table 1). Individual diastereoisomers *dl*-**2**a−h were readily isolated by applying differences in their solubility to organic solvents. The structure of *dl*-**2**b was determined after converting it to the cyclic bisphosphinic acid **3**, through careful NMR and X-ray analyses (Scheme 3).[20] The structural determination of other analogues **2**a and **2**c−g was also done after converting these analogues to cyclic bisphosphinic acids corresponding to compound **3** based on the similarity of their NMR spectra to

Scheme 2



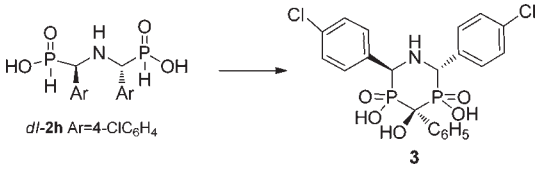
a:Ph, **b**:4-ClC$_6$H$_4$, **c**:4-FC$_6$H$_4$, **d**:4-MeOC$_6$H$_4$, **e**:4-MeC$_6$H$_4$, **f**:2-FC$_6$H$_4$, **g**:2-naphthyl

Table 1. Synthesis of 1-Aminophosphinic Acids 2 from Diimines (1)

		reaction time		yield %[b]	mp
entry	Ar	h	yield %[a]	(*R**,*R**)-**2**	°C
a	C_6H_5	10	48	20	222−224
b	*p*-ClC_6H_4	11	71	41	240−242
c	*p*-FC_6H_4	12	61	31	230−232
d	*p*-$MeOC_6H_4$	12	45	25	212−214
e	*p*-MeC_6H_4	11	64	35	228−230
f	*o*-FC_6H_4	2	42	21	226−228
g	2-naphthyl	8	40	15	212−214

[a] Isolated yields of mixtures of two diastereoisomers. [b] Isolated yields of diastereoisomer *dl*-**2** after washing with a solvent mixture of ethanol/water (9:1). Ratio of diastereoisomers of (*R**,*S**)-**2**/(*R**,*R**)-**2** in mother liquor is near 9:1 in all entries.

Scheme 3



those of **3**. The experimental details and physical constants including ^{1}H NMR and ^{31}P NMR are disclosed in the Experimental Section.

3.2. Coordination Ability of *dl*-2a with Various Transition Metals and Lanthanides. Compounds **2a**−**g** are composed from two symmetry units of the phosphorus analogues of amino acids and are soluble in water. Therefore, they are expected to combine with transition metals and lanthanide ions, similar to crown ethers. In this study, *dl*-**2a** was chosen as a model compound to demonstrate the complexing properties of *N*,*N*-bis(phosphinomethyl)amine **2** as a new class of 1-aminophosphinic acid compounds. Then, the complexation with transition metals such as Co^{2+}, Ni^{2+}, Zn^{2+}, Cu^{2+}, and Cd^{2+} and lanthanide ions La^{3+} and Gd^{3+} was studied in aqueous solution by the pH-potentiometric method.

From the structure of compound (*R**,*R**)-**2a** one can realize that three protons may be ionizable from protonated species, two from acidic phosphinic moiety and one from the nitrogen atom. According to potentiometric data calculations in the pH range

Table 2. pK_a Values of IDA and Compound (*R,*R**)-2a at 25 °C in 0.1 M KNO_3**

entry	compd	pK_{a1}	pK_{a2}
1	IDA[a]	2.54	9.12
2	IDA	2.59 ± 0.05	10.17 ± 0.10
3	(*R**,*R**)-**2a**	3.60 ± 0.09	10.26 ± 0.09

[a] pK_a values of IDA at 30 °C in 0.1 M KCl.[21]

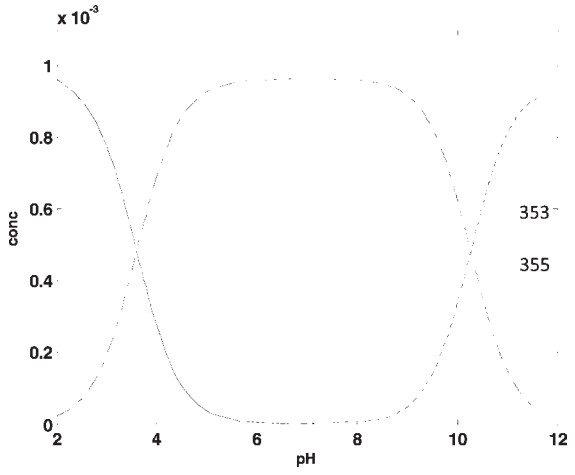


Figure 1. Species distribution of (*R**,*R**)-**2a**. The ligand concentration is 0.001 M, and HCl concentration is 0.016 M. The following lines were used for corresponding species H_2L (solid line), HL^- (long/short dashed line), L^{2-} (short dashed line).

Scheme 4

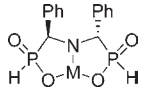


Table 3. Stability Constants for the Ligand (*R,*R**)-2a and Its Complexes with Co^{2+}, Ni^{2+}, Zn^{2+}, Cu^{2+}, Cd^{2+} La^{3+}, and Gd^{3+} at Room Temperature, in 0.1 M KNO_3**

metal	log β_{ML}	log β_{ML_2}	log β_{ML_2OH}	log $\beta_{ML_2OH_2}$
La(III)	11.86 ± 0.31	20.69 ± 0.30	11.24 ± 0.33	2.71 ± 0.31
Gd(III)	11.78 ± 0.71	21.83 ± 0.88	15.38 ± 0.66	7.59 ± 0.68
Cu(II)	10.20 ± 0.58	19.62 ± 0.57	12.45 ± 0.74	5.73 ± 0.76
Co(II)	8.84 ± 0.23	15.85 ± 0.23	5.40 ± 0.53	−2.85 ± 0.24
Ni(II)		17.98 ± 0.21	9.82 ± 0.21	0.77 ± 0.24
Zn(II)		17.78 ± 0.29	9.93 ± 0.52	3.07 ± 0.37
Cd(II)		17.22 ± 0.22	8.44 ± 0.24	−1.11 ± 0.27

studied, compound (*R**,*R**)-**2a** behaves as a H_3L acid (Table 2). Two proton formation constants of compound (*R**,*R**)-**2a** with log *K* 10.26 and 3.60 correspond to one phosphinic function and a nitrogen atom. The third log *K* value of the phosphinic group is usually well below 2 and cannot be evaluated from the potentiometric data. It is likely that the strong electron-withdrawing phosphinic functions, accompanied by the two efficient electron-withdrawing phenyl substituents, could lead to considerable lowering of the 1-amino group, basicity, and the deprotonation

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of the amine group, which was observed in the studied pH range. The concentration distribution and curves of compound (R^*,R^*)-**2a** are shown in Figure 1. To ensure the accuracy of the data, the dissociation constants of the iminodiacetic acid (IDA) were obtained by this method.[21] The favorable results obtained with the artificial IDA data clearly showed that the approach to

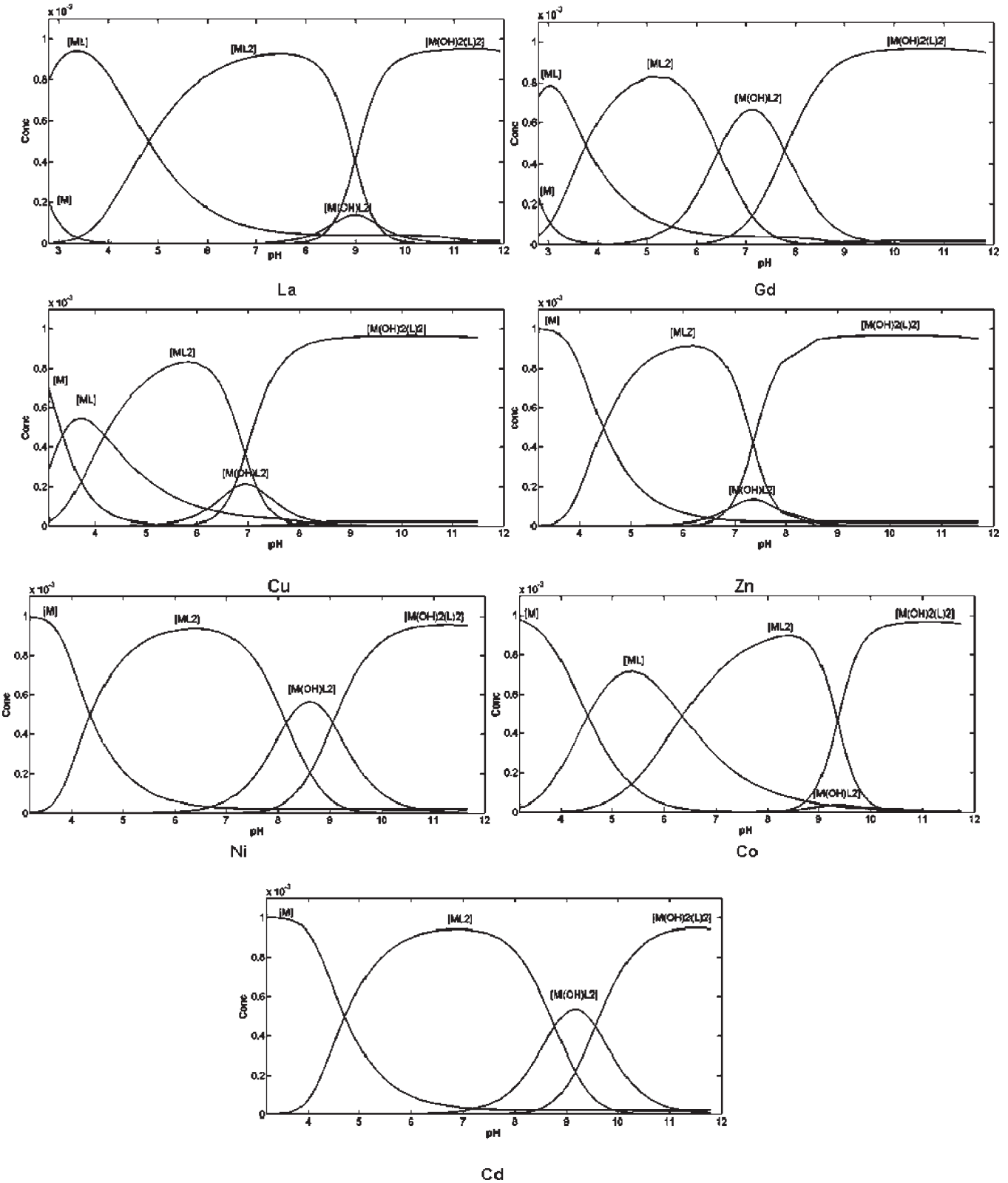
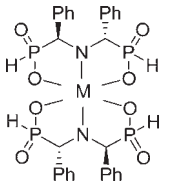


Figure 2. Species distribution diagram for the Co^{2+}, Ni^{2+}, Zn^{2+}, Cu^{2+}, Cd^{2+}, La^{3+}, and Gd^{3+}-amino bisphosphinic acid systems. The ligand concentration used in the calculation is 0.001 M and 0.002 M, and the total metal ion concentration is $1 \cdot 10^{-3}$ M (I = 0.1 M KNO_3).

dx.doi.org/10.1021/je2004897 |*J. Chem. Eng. Data* 2011, 56, 3651–3656

Scheme 5



computing the acidity constants is sufficiently accurate for analyzing the considered ligand (Table 2).

Using potentiometric titrations and calculated acidity constants by fitting the experimental data in using the Newton−Raphson algorithm, the stability constants of the interaction of metal ions with ligand (*R**,*R**)-**2**a in the range 2 < pH < 11 were studied in aqueous solution. The amino-*H*-phosphinic acid (*R**,*R**)-**2**a can behave as a tridentate ligand by binding metals at the amine nitrogen and at the oxygen of the two phosphinic groups (Scheme 4).

The complexing properties of the phosphinic acid ligand toward Co^{2+}, Ni^{2+}, Zn^{2+}, Cu^{2+}, and Cd^{2+} from transition metals and La^{3+} and Gd^{3+} of the lanthanide family were studied in two different metal ion-to-ligand molar ratios, 1:1 and 1:2. The calculations based on the potentiometric titrations suggest that Co^{2+}, Cu^{2+}, La^{3+}, and Gd^{3+} ions form four species with ligand (*R**,*R**)-**2**a: ML, $[ML_2]$, $[ML_2(OH)]$, and $[ML_2(OH)_2]$ (Table 3). Complexation starts, depending on the metal ion, from pH 3 to 8 with the formation of [ML] species. The $[ML_2]$ is present in very high concentrations in this pH region. The $[ML_2(OH)]$ and $[ML_2(OH)_2]$ species are formed at pH > 6 with low stability constants. These points are related to the formation of the hydroxo species at pH > 6 and would indicate coordination of water molecules instead of the phosphinate group.[14]

The concentration profiles of species are shown in Figure 2. The results obtained are listed in Table 3. Comparing the stability constants in Table 3 showed that the stabilities of $[ML_2]$ species are higher than other species (Scheme 5).

The interaction of metal ions Zn^{2+}, Ni^{2+}, and Cd^{2+} with the ligand (*R**,*R**)-**2**a gave the $[ML_2]$, $[ML_2(OH)]$, and $[ML_2(OH)_2]$ complexes (Table 3). The complexation of these species starts from pH 4 to 8 with the formation of $[ML_2]$ species. The hydroxo complexes, $[ML_2(OH)]$ and $[ML_2(OH)_2]$, appear at pH > 7. It is noteworthy that the dihydroxo species with lower and negative formation constants are less favored.[22] For zinc ion systems, this kind of chelation can explain binding of amino phosphinic acids in the active site of some metaloenzymes.[23] The comparison of the stability constants indicates that Gd^{3+}, La^{3+}, and Cu^{2+} have the highest tendency to make coordination with novel 1-amino-*H*-phosphinic acid. While amines are poor donors for lanthanides, with phosphinate groups they contribute to the overall stability of the complexes.[24] The addition of the phosphinate group in ligands has an extra effect on the stability of lanthanide complexes because of the two five-membered rings.[25]

4. CONCLUSIONS

In summary, we have developed a simple and practical approach for a new class of organophosphorus compounds. On the basis of the stereochemistry of the cyclic bisphosphinic acid (Scheme 2), the stereochemistry of the separable diastereoisomer of **2** was determined as a racemic pair (*S**,*S** or *R**,*R**-**2**). The pK_a values of the novel ligand (*R**,*R**)-**2**a were computed with potentiometric titration at room temperature and constant ionic strength ($NaNO_3$ = 0.1 M). Two proton formation constants of compound (*R**,*R**)-**2**a with log *K* 10.26 and 3.60 correspond to one phosphinic function and a nitrogen atom, and the third log *K* value of the phosphinic group is usually well below 2. The acidity of the amine group of this ligand is similar to the IDA due to the presence of two phosphinic acid groups. The system containing the component, ligand, and transition metal or lanthanide ions was investigated in solution by potentiometry, and the stability constants of the complexes were computed with the Newton−Raphson algorithm. The coordination of novel ligand (*R**,*R**)-**2**a to lanthanide ions shows a higher stability compared to the transition metals.

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REFERENCES

(1) Collinsova, M.; Jiracek, J. Phosphinic acid compounds in biochemistry, biology and medicine. *Curr. Med. Chem.* **2000**, *7*, 629–647.

(2) Latajka, R.; Krężel, Mucha, A.; Jewgiński, M.; Kafarski, P. Conformational investigations of bis(α-aminoalkyl)phosphinic acids and studies of the stability of their complexes with Cu(II). *J. Mol. Struct.* **2008**, *877*, 64–71.

(3) Cates, L. A.; Li, V.-S. Phosphinic Acid Analogues of Methylaspartic and Methylglutamic Acids as Antibacterials. *Pharm. Res.* **1985**, *2*, 135–136.

(4) (a) Ye, Y.; Liu, M.; Kao, J. L.-F.; Marshall, G. R. *Biopolymer* **2008**, *89*, 72–85. (b) Olszewski, T. K.; Galezowska, J.; Boduszek, B.; Kozlowski, H. *Eur. J. Org. Chem.* **2007**, 3539–3546.

(5) Kukhar, V. P.; Hudson, H. R. In *Aminophosphonic and Aminophosphinic Acids*; John Wiley & Sons, 2000.

(6) Luckman, S. P.; Coxon, F. P.; Ebetino, F. H.; Russell, G. G.; Rogers, M. J. *J. Bone Miner. Res.* **1998**, *13*, 1668–1678.

(7) Katoh, M.; Hiratake, J.; Kato, H.; Oda, J. Mechanism-based inactivation of E. coli γ-glutamylcysteine synthetase by phosphinic acid- and sulfoximine-based transition-state analogues. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1437–1442.

(8) Kaboudin, B.; As-Habei, N. Microwave-assisted synthesis of α-aminophosphinic acids from hypophosphorus acid salts under solvent free conditions. *Tetrahedron Lett.* **2003**, *44*, 4243–4245.

(9) Kaboudin, B.; Haruki, T.; Yamaghishi, T.; Yokomatsu, T. Diastereoselective addition of α-substituted α-amino-H-phosphinates to imines using Yb(OTf)3 as an efficient Lewis acid catalyst. *Tetrahedron* **2007**, *63*, 8199–8205.

(10) Kaboudin, B.; Haruki, T.; Yamagishi, T.; Yokomatsu, T. Diastereoselective Synthesis of Novel α-Amino-α′-hydroxyphosphinates by Hydrophosphinylation of α-Amino-H-phosphinates to Aldehydes. *Synthesis* **2007**, 3226–3232.

(11) Kaboudin, B.; Jafari, E. *J. Iran Chem. Soc.* **2008**, *5*, S97–S102.

(12) Kaboudin, B.; Saadati, F. A simple, novel and convenient method for the synthesis of 1-aminophosphinic acids: synthesis of a novel C2-symmetric phosphinic acid pseudodipeptide. *Tetrahedron Lett.* **2009**, *50*, 1450–1452.

(13) Kaboudin, B.; Moradi, K. TMSCl-Promoted Addition of Diethyl Phosphite to an Imine for the Synthesis of Bis[1-diethoxyphosphorylalkyl]amines. *Synthesis* **2006**, 2339–2342.

(14) Kaboudin, B.; Jafari, E. A Novel Method for the Synthesis of Bis(1-diethoxyphosphorylalkyl)amines from Diimines. *Synthesis* **2006**, 3063–3066.

(15) Kaboudin, B.; Haghighat, H.; Yokomatsu, T. A Novel Method for the Separation of Bis(α-hydroxyalkyl)phosphinic Acid Diastereoisomers via Formation of Novel Cyclic Phosphinic Acids. *J. Org. Chem.* **2006**, *71*, 6604–6606.

(16) Kaboudin, B.; Karimi, M. A new, efficient, and simple method for the one-pot synthesis of α-acetoxyphosphonates from aldehydes under solvent-free conditions. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5324–5327.

(17) Kaboudin, B.; Farjadian, F. *Beilstein J. Org. Chem.* **2006**, *2*, 4.

(18) Kaboudin, B.; Haghighat, H.; Yokomatsu, T. First resolution of (*R*,*R*)- and (*S*,*S*)-bis(1-hydroxyphenylmethyl)phosphinic acids via diastereomeric salt formation with enantiopure 1-phenylethylamines. *Tetrahedron: Asymmetry* **2008**, *19*, 862–866.

(19) Maeder, M.; Neuhold, Y. M. In *Practical Data Analysis in Chemistry*; Elsevier: Amsterdam, 2007.

(20) Kaboudin, B.; Saadati, F.; Yokomatsu, T. Reaction of 1-Amino Bisphosphinic Acids with Acid Chlorides: Synthesis of Novel Cyclic 1-Hydroxy-1′-amino-1,1-bisphosphinic Acids. *Synlett* **2010**, 1837–1840.

(21) Krasner, J.; Marinsky, J. A. The Dissociation of Iminodiacetic Acid Groups Incorporated in a Chelating Ion-Exchange Resin. *J. Phys. Chem.* **1963**, *67*, 2559–2561.

(22) Kubicek, V.; Vojtisek, P.; Rudovsky, J.; Hermann, P.; Lukes, I. Complexes of divalent transition metal ions with bis(aminomethyl)-phosphinic acid in aqueous solution and in the solid state. *J. Chem. Soc., Dalton Trans.* **2003**, 3927–3938.

(23) Grams, F.; Dive, V.; Yotakis, A.; Yiallourous, I.; Vassiliou, S.; Zwilling, R.; Bode, W.; Stöcker, W. Structure of astacin with a transition-state analogue inhibitor. *Nat. Struct. Biol.* **1996**, *3*, 671–675.

(24) Martell, A. E.; Hancock, R. D. In *Metal Complexes in Aqueous Solutions*; Plenum Press: New York, 1996.

(25) Xu, L.; Retting, S. J.; Orvig, C. Lanthanide Chemistry with Bis{[bis(carboxymethyl)amino]methyl}phosphinate: What Does an Extra Phosphinate Group Do to EDTA? *Inorg Chem.* **2001**, *40*, 3734–3738.