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New Heterocyclic Mono- and Bis(α-hydroxymethyl)phosphinic Acids: Synthesis and Cu^{II} Binding Abilities

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A simple and efficient method for the synthesis of (α-hydroxymethyl)phosphinic acids in a pyridine and imidazole series from their corresponding aldehydes and aqueous hypophosphorous acid was developed. The same reaction carried out with an excess of aldehyde in the presence of a mineral acid led mainly to the corresponding bis(α-hydroxymethyl)phosphinic acids in moderate yields. The coordination properties of these compounds towards Cu^{II} ions were determined. Additionally, it was found that [(hydroxy)(2-pyridyl)- and (hydroxy)(4-pyridyl)methyl]phosphinic acids were easy to cleave in aqueous sulfuric acid solutions, to form phosphorus acid (H_3PO_3) and the corresponding pyridinemethanols. The kinetics of the cleavage reaction was studied. On the basis of the obtained results, a mechanism of the cleavage was formulated.

Introduction

In recent years, organophosphorus compounds have been of great interest. A wide range of application in the areas of medicinal, agricultural, and industrial chemistry have been found owing to their significant biological and physical properties, as well as their utility as synthetic intermediates.[1] Among many known phosphorus compounds (phosphane oxides, phosphonic, or phosphinic acids and their esters), α-functionalized phosphonates, that is α-amino- and α-hydroxyphosphonates particularly, have gathered considerable attention owing to their biological activity.[2] In contrast to the widely studied α-aminophosphonates, the α-hydroxyphosphonates have received less attention, although important examples have been recognized for their high inhibitory activity. The 1-hydroxyalkylphosphonic acids are active toward such essential enzymes as polymerase,[3] renin,[4] or HIV protease (human immunodeficiency virus).[5] Surprisingly, far less data is available regarding the chemistry of α-hydroxyphosphinic acids, although there is evidence that these compounds are biologically active.[6]

The most convenient synthetic route leading to α-hydroxyphosphinic acids is the addition of hypophosphorous acid (H_3PO_2) to carbonyl compounds.[7] Usually, this method requires anhydrous hypophosphorous acid in inert solvents. It gives the results upon prolonged heating of the reactants in the presence of mineral acid. Majewski reported the synthesis of bis(1-hydroxyalkyl)phosphinic acids by the addition of bis(trimethylsiloxy)phosphane to aldehydes and ketones, followed by subsequent ethanolysis of the resulting bis(1-trimethylsiloxyalkyl)phosphinates.[8] Recently, a new approach was developed based on the reactivity of elemental red P towards aldehydes in both basic and acidic media.[9] Likewise, in order to accelerate and facilitate the reaction of hypophosphorous acid with aldehydes, the application of microwave energy was reported.[10] Nevertheless, each of these methods suffers from various limitations, such as specially prepared anhydrous reactants in an oxygen-free atmosphere and using long, harsh reaction conditions. Furthermore, these reactions are usually accompanied by the formation of undesired side products; for example, the prolonged heating of hypophosphorous acid with carbonyl compounds leads to the oxidation or disproportionation of the (α-hydroxymethyl)phosphinic acid formed, giving the corresponding stable α-hydroxyphosphonic acids and other products.[11]

To the best of our knowledge, heterocyclic α-hydroxyphosphinic acids possessing a P–H bond are basically unknown. The main difficulty in the synthesis of this class of compounds is the inapplicability of the used, regular synthetic procedures. This is due to the possibility of the decomposition of some heterocyclic moieties and the occurrence of side reactions; for example, the oxidation of a P–H bond and the cleavage of a molecule in certain α-hydroxyphosphinates. For this reason, it is necessary to search

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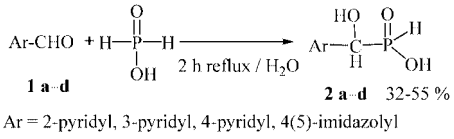
for new, simple methods, which could be more useful and efficient in the preparation of these compounds.

Our interest in the preparation of heterocyclic α-hydroxyphosphinic acids led us to investigate the reaction of hypophosphorous acid with heterocyclic aldehydes. Thus, in this paper, we wish to report the first successful synthesis of mono- and bis(α-hydroxymethyl)phosphinic acids derived from pyridine and imidazole. Additionally, the coordination properties of these compounds toward Cu^{II} cations were studied, using potentiometric and spectroscopic methods. We also wish to report the results of our studies regarding the discovery of unusual cleavage of [(hydroxy)(2-pyridyl)- and (hydroxy)(4-pyridyl)methyl]phosphinic acids, possessing a P–H bond in aqueous HCl or sulfuric acid solutions.

Results and Discussion

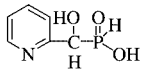
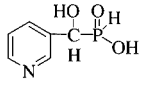
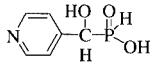
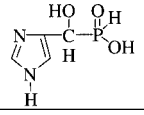
I. Synthesis of Heterocyclic (α-Hydroxymethyl)phosphinic Acids 2a–d

The synthesis of phosphinic acids **2a**–**d** is illustrated in Scheme 1. The structures and yields of the obtained products are presented in Table 1.



Scheme 1. Synthesis of (α-hydroxymethyl)phosphinic acids.

Table 1. Yields and structures of (α-hydroxymethyl)phosphinic acids **2a**–**d**.

Compd. No.	Structure	Yield[a] [%]
2a		32
2b		54
2c		45
2d		55

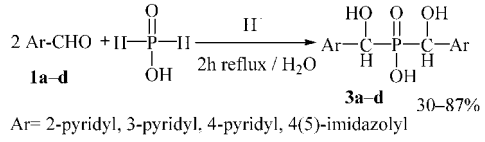
[a] Yield of isolated products after crystallization from MeOH.

Heterocyclic aldehydes **1a**–**d** reacted easily with the aqueous solution of hypophosphorous acid at elevated temperature (reflux) to afford expected hydroxymethylphosphinic acids **2a**–**d**, which were isolated in good yields and purified by crystallization from methanol. Obtained compounds **2a**–**d** were racemic mixtures owing to the presence of a chiral carbon atom attached to a pseudoasymmetric phosphorus atom. However, the latter loses its chirality by the rapid transfer of the proton between the phosphoryl (P=O) group and the acidic (P–OH) site. Hence, only one signal for phosphorus was observed on the ^{31}P NMR spectrum of **2a**–**d**.

It is worth noting in this case that equimolar amounts of reagents were used (1.0 equiv. of hypophosphorous acid treated with 1.0 equiv. of aldehyde) and the reaction was carried out in homogeneous, aqueous solution at ca. 100 °C. Monitoring of the reaction mixture by ^{31}P NMR spectroscopy revealed the total consumption of the hypophosphorous acid during 2 h of reaction time. The progress of the method compared to other ones known from literature is that it uses common solvent (water) and requires no assistance, neither microwave or ultrasound irradiation, nor prolonged heating during the formation of heterocyclic hydroxyphosphinic acids **2a**–**d**. Therefore, this method presents a real progress in the synthesis of these compounds.

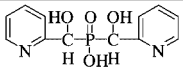
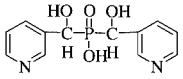
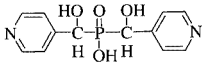
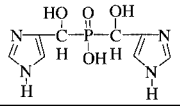
II. Synthesis of Heterocyclic Bis(α-hydroxymethyl)-phosphinic Acids 3a–d

During our studies on the preparation of (α-hydroxymethyl)phosphinic acids, we found that besides **2a**–**d** also small amounts of the corresponding bis(α-hydroxymethyl)phosphinic acids were formed. These compounds (especially the pyridine derivatives) can be viewed as good chelating agents with a wide application in biological screening and NMR imaging.[12,13] Therefore, we have modified and extended our method used for the synthesis of (α-hydroxymethyl)phosphinic acids **2a**–**d** to the synthesis of the corresponding heterocyclic bis(α-hydroxymethyl)phosphinic acids **3a**–**d**, as illustrated in Scheme 2. The structures and yields of products **3a**–**d** are given in Table 2.



Scheme 2. Synthesis of bis(α-hydroxymethyl)phosphinic acids.

Table 2. Yields and structures of (α-hydroxymethyl)phosphinic acids **3a**–**d**.

Compd. No.	Structure	Yield[a] [%]
3a		30
3b		57
3c		36
3d		87

[a] Yield of isolated products after crystallization from MeOH.

In this case, 1 equiv. of hypophosphorous acid was treated with 2 equiv. of the corresponding aldehyde in the presence of 2 equiv. of HCl. As in the preceding case, the reaction was performed in a simple way in an aqueous solution (reflux, 2 h). Formed bis(α-hydroxymethyl)phosphinic acids **3a**–**d** were easily isolated after the concentration of the reaction mixture and purified by crystallization from MeOH. Bis(α-hydroxymethyl)phosphinic acids **3a**–**d** were obtained as mixtures of two diastereomers (*meso* and *d*,*l* form) owing to the presence of two chiral carbon atoms bonded to the phosphorus atom.[8,9b] The ratios of the diastereomers found in products **3a**–**b** were easily determined by means of ^{31}P NMR spectroscopy and they were found to be 1:1 for all products.

III. Complexation of Cu^{II} Ions by Mono- and Bis-(α-hydroxymethyl)phosphinic Acids

Two obtained imidazole products, (α-hydroxymethyl)-phosphinic acid **2d** (ligand **L^2**) and bis(α-hydroxymethyl)-phosphinic acid **3d** (ligand**L^3**) were examined for their binding ability toward Cu^{II} ions. Additionally, for comparison, the coordination ability of the parent [(hydroxy)(4-imidazolyl)methyl]phosphonic acid (ligand **L^1**) was studied. Ligands **L^4** and **L^5**, being the pyridine derivatives **3b** and **3c**, respectively, were also included in the studies on metal ion binding properties. The data obtained are collected in Tables 3 and 4 and Figures 1 to 4.

Table 3. Potentiometric and spectroscopic data for ligand **L^1** and **L^2** and Cu^{2+} complexes.

Species	logβ	pK	UV/Vis		EPR	
			λ [nm]	ε [M^{-1}cm^{-1}]	$A_\parallel$ [G]	$g_\parallel$
L^1						
HL	7.66(1)	7.66				
H_2L	13.53(1)	5.87				
H_3L	≈14.58(14)	ca. 1.05				
CuL	8.57(3)		684	52.5	146	2.31
CuL_2	15.06(4)		654	65.1	156	2.30
L^2						
HL	6.39(1)	6.39				
H_2L	≈7.73(5)	ca. 1.36				
CuL	5.34(2)		718	33.4	143	2.35
CuL_2	10.16(2)		699	38.1	151	2.30
$CuH_{-1}L_2$	2.29(2)	7.87	645	44.7	183	2.25
$CuH_{-2}L_2$	–6.91(3)	9.20	614	48.6	183	2.27

Ligand **L^1** (Figure 1) exhibits three protonation constants assigned to the imidazole (pK = 7.66) and phosphonate (pK = 5.87 and ≈ 1) groups. The conversion of the phosphonic derivative into a phosphinic one results in **L^2**, (Figure 1) which is characterized by two protonation constants: one attributed to imidazole (pK = 6.39) and the second one to phosphinic groups (pK ≈ 1). The latter constant is too low to be reliably evaluated from the potentiometric data.

The presence of an additional imidazole moiety in **L^3** results in two constants, assigned to the imidazole groups, pK = 7.05 and pK = 6.09, respectively. The phosphinic protonation constant in **L^3** was again too low to be evaluated by the potentiometric data. The exchange of imidazole by β-substituted pyridine groups in **L^4** (Figure 2) results in the constants assigned to the corresponding pyridine moieties of **L^4**, pK = 5.56 and pK = 4.74.

Table 4. Potentiometric and spectroscopic data for ligand **L^3** and **L^4** and Cu^{2+} complexes.

Species	Logβ	pK	UV/Vis		EPR	
			λ [nm]	ε [M^{-1}cm^{-1}]	$A_\parallel$ [G]	$g_\parallel$
L^3						
HL	7.05(1)	7.05				
H_2L	13.14(1)	6.09				
CuH_2L_2	25.28(1)		690	39	137	2.35
$CuHL_2$	21.23(1)	4.05	674	44	147	2.31
CuL_2	15.49(1)	5.74	669	46	158	2.30
$CuH_{-1}L_2$	8.09(1)	7.40	–	–	–	–
$CuH_{-2}L_2$	–2.59(2)	10.68	–	–	–	–
L^4						
HL	5.56(1)	5.56				
H_2L	10.30(2)	4.74				
H_3L	≈11.88(9)	≈1.58				
CuHL	8.53(1)			Minor		
CuL	3.74(1)	4.79	699	43	143	2.36
CuL_2	6.59(1)		–	–	–	–
$CuH_{-2}L_2$	–5.83(2)		–	–	–	–

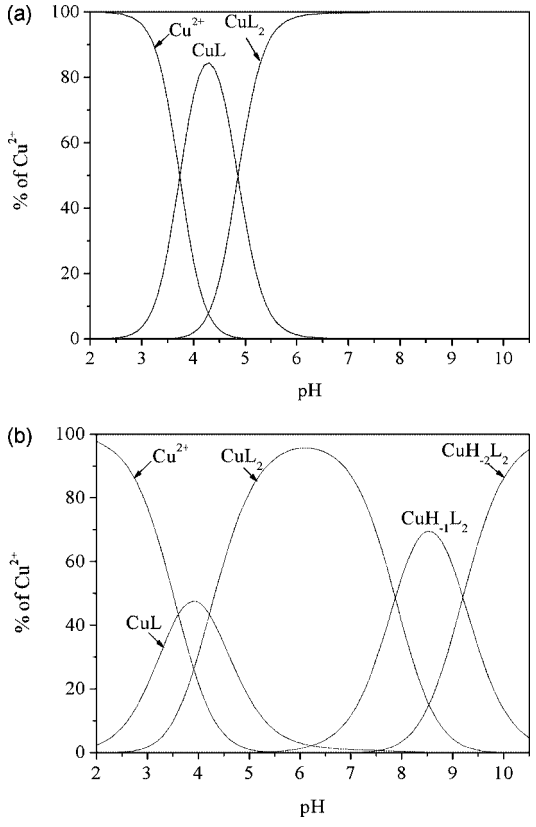


Figure 1. Species distribution curves for (a) Cu^{II}–**L^1** and (b) Cu^{II}–**L^2** as a function of pH.

All ligands have a major binding site located at a heterocyclic nitrogen, in the case of **L^1**, **L^2**, and **L^3** for imidazole and **L^4** for the pyridine moiety. In all of these molecules,

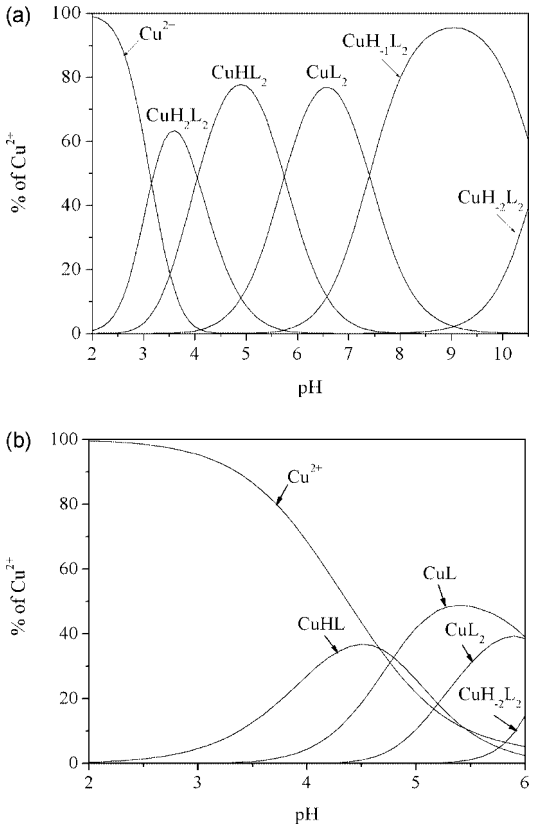


Figure 2. Species distribution curves for (a) Cu^{II}–$\mathbf{L^3}$ and (b) Cu^{II}–$\mathbf{L^4}$ as a function of pH.

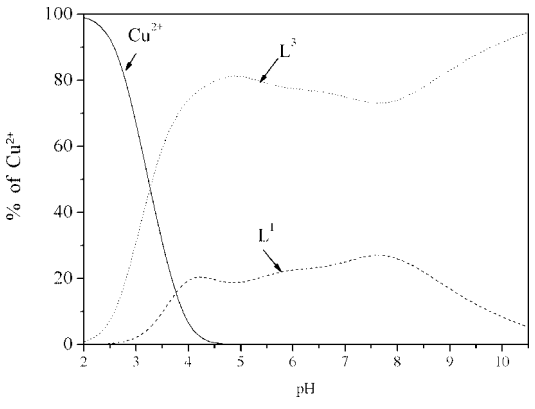


Figure 3.The competition plot for Cu^{II} complexes with $\mathbf{L^1}$ (dotted line) and $\mathbf{L^3}$ (dashed line) for Cu^{II}: $\mathbf{L^1}$:$\mathbf{L^3}$ molar ratio 1:2:2.

phosphonic or phosphinic oxygens may serve as the additional donors. The hydroxy group could also be a potential binding site at the higher pH. The calculations based on the potentiometric titrations show a similar coordination pattern to that of $\mathbf{L^1}$ and $\mathbf{L^2}$ (Figure 2). The major complexes formed: CuL and CuL_2 (Figure 2) are coordinated by $1\times$ or $2\times\{N_{imid}, PO_3^{2-}\}$donor set, respectively,[14,15] according to the spectroscopic data (Table 3). The d-d transition energy changes from around 715–680 nm, which corresponds well to one nitrogen coordination to 700–650 nm, suggesting two nitrogen donor sets (Table 3). EPR parameters obtained for mono complexes are slightly different than those of bis complexes (Table 3). In $\mathbf{L^2}$, the binding mode which involves two imidazole nitrogen atoms and two phosphinic oxygen atoms is not very stable. Above pH 7, the complex undergoes hydrolysis to $Cu(H_{-1}L)$ and then to $Cu(H_{-2}L)$, with log*K* of 7.87 and 9.20, respectively. The changes in the EPR spectra of $\mathbf{L^2}$, when compared to $\mathbf{L^1}$ (Table 3), may indicate the presence of hydroxy groups in the metal ion coordination sphere. The comparison of the binding abilities, the competition plot (Figure 3), shows that above pH 4 $\mathbf{L^1}$ becomes a much more effective chelator for Cu^{II} than $\mathbf{L^2}$.

The coordination abilities change significantly when a second unit of imidazole or pyridine appears. The coordination in ligand $\mathbf{L^3}$ starts from the formation of $Cu(H_2L_2)$ (Figure 4), which undergoes further deprotonation to form CuL_2 and then in higher (basic) pH, it hydrolyses to $Cu(H_{-1}L)$ and $Cu(H_{-2}L)$.

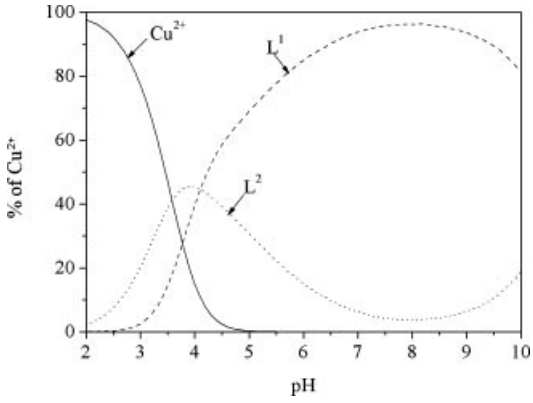


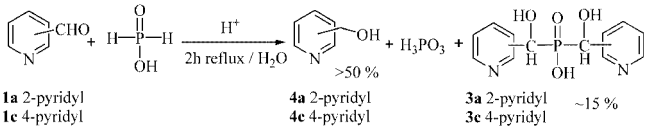
Figure 4. The competition plot for Cu^{II} complexes with $\mathbf{L^1}$ (dashed line) and $\mathbf{L^2}$ (dotted line) for Cu^{II}: $\mathbf{L^1}$:$\mathbf{L^2}$ molar ratio of 1:2:2.

The spectroscopic parameters indicate $2\times\{N_{imid}, PO_2^{2-}\}$ coordination mode in CuL_2 complex, characterized by 669 nm d–d transition band and A_{II} = 158, g_{II} = 2.30 EPR parameters (Table 4). The comparison of bisphosphinic ligand $\mathbf{L^3}$ and its phosphonic analogue $\mathbf{L^1}$ (Figure 3) reveals that $\mathbf{L^3}$ has better binding abilities. $\mathbf{L^4}$ behaves like its aforementioned phosphonic analogue[14] with $1\times N_{pyr}$ coordination in CuL and $2\times N_{pyr}$ binding in CuL_2 (Figure 4). Low stability constants indicate a monodentate coordination mode which results in easy hydrolysis beginning above pH 6. In the Cu–$\mathbf{L^5}$ system, the formation of precipitate prevents any study on this system.

IV. Cleavage of [(Hydroxy)(pyridyl)methyl]phosphinic Acids 2a and 2c

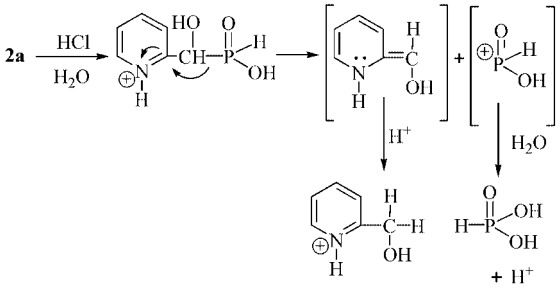
During our work on the synthesis of [(hydroxy)(pyridyl)-methyl]phosphinic acids, we unexpectedly found that an equimolar mixture of 2-pyridine-, or 4-pyridinecarboxaldehyde, and an aqueous solution of hypophosphorous acid in the presence of HCl heated at reflux leads to a mixture of the corresponding 2-pyridine- (**4a**), or 4-pyridinemeth-

anol (**4c**) and phosphorus acid (H_3PO_3). 2-Pyridine- and 4-pyridinemethanol are commercial compounds[19] and were easily identified. Expected [(hydroxy)(pyridyl)methyl]phosphinic acids **2a**,**c** were not found in this case. Besides pyridinemethanols **4a**,**c**, small amounts of bis(α-hydroxymethyl)phosphinic acids **3a**,**c** were also isolated (Scheme 3).



Scheme 3. Reaction of hypophosphorous acid with 2-pyridine- and 4-pyridinecarboxaldehyde in the presence of HCl.

The same reaction carried out without the use of hydrochloric acid (section **I**) leads exclusively to (α-hydroxymethyl)phosphinic acids **2a**,**c**. In the case of 3-pyridinecarboxaldehyde (**1b**) and imidazole-4-carboxaldehyde (**1d**), the reaction proceeds in a regular way, even in the presence of hydrochloric acid, [(hydroxy)(3-pyridyl)- and (hydroxy)(4-imidazolyl)methyl]phosphinic acids **2b**,**d** were formed. The obtained results clearly indicate **2a** and **2c** are cleaved by solutions of strong, mineral acids to form pyridinemethanols **4a**,**c** and H_3PO_3. The reaction resembles the cleavage of corresponding 2-pyridine- and 4-pyridinemethyl-α-aminophosphonic,[20] aminophosphinic[21] and aminophosphane oxides,[22] which we previously described. According to these findings,[20–22] such a kind of cleavage is an electrophilic displacement of the phosphonic or phosphinic group by a proton (H^+). In this case, formed in the first stage of the reaction, hydroxyphosphinic acids (**2a**, **2c**) undergo similar transformations, consisting on the formation of the corresponding pyridinemethanols and phosphorus acid. The strong, acidic medium and the existence of a P–H bond in **2a**,**c** additionally facilitates the cleavage, which occurred only in the case of pyridine derivatives. This observation was proved independently, by heating samples of **2a** and **2c** in aqueous 1 M HCl solution, during kinetic studies (section **V**). It is interesting that the corresponding 2- and 4-pyridine hydroxyphosphonic acids are stable in acidic conditions.[20] In turn, heterocyclic bis(hydroxy)phosphinic acids **3a**–**d** proved to be resistant toward cleavage in 1 M HCl, under the applied conditions. It is noteworthy that [(hydroxy)(3-pyridyl)methyl]phosphinic acid (**2b**) does not undergo cleavage in 1 M HCl solution. Prolonged heating of **2b** in 1 M HCl leads only to a partial oxidation of **2b** by oxygen from the atmosphere to the corresponding [(hydroxy)(3-pyridyl)methyl]phosphinic acid, which is stable.[20] Also, a similar resistance for cleavage was observed for parent [(amino)(3-pyridyl)methyl]phosphonic acids.[20] On the basis of the chemical and kinetic results, a mechanism for the cleavage of [(hydroxy)(pyridyl)methyl]-phosphinic acids **2a**,**c** was formulated and it is presented in Scheme 4.



Scheme 4. Proposed mechanism for the cleavage of [(hydroxy)(2-pyridyl)- or (hydroxy)(4-pyridyl)methyl]phosphonic acid in 1 M HCl.

V. Kinetic Measurements

For kinetic purposes, the cleavage of (α-hydroxymethyl)-phosphinic acids **2a**,**c** were run in aqueous solutions containing a definite quantity of sulfuric acid. The reactions were measured in NMR tubes by ^{31}P NMR spectroscopy and the relative quantities of the phosphorus-containing products and starting materials were estimated from the corresponding integrated ^{31}P NMR signals. In this case, the appearance of a signal due to phosphorus acid (H_3PO_3), together with the subsequent decay of a signal corresponding to **2** was observed.

On the basis of ^{31}P NMR spectroscopic data, the rate constants were calculated. The measured cleavages followed pseudofirst-order kinetics. It was found that the rate constants were strongly dependent on the concentration of the sulfuric acid (Table 5, Entry 1 and 5 for **2a**; Entry 6 and 8 for **2c**). It was also significant that 2-pyridyl derivative **2a** underwent cleavage much faster than corresponding 4-pyridyl **2c**. The runs, which were performed in deuterated solvents and with the use of deuterated reagents, proved that the cleavages were considerably faster in solutions of common, nondeuterated acids. It was possible to calculate the kinetic isotope effects (Table 5, Entry 1 and 6 for **2a** and **2c**, respectively), which was equal to 6.96 and 3.24 for the 2-pyridyl and the 4-pyridyl derivatives, respectively. The considerably high value of k_H/k_D indicates that the protons are involved in a rate-determining step of the reaction. The kinetic measurements for the cleavage of **2a** were also carried out at 85 °C and 75 °C in order to calculate the activation parameters (*Ea*, $\Delta H^{\neq}$, $\Delta S^{\neq}$, Table 5). The low value for the energy of activation (*Ea*) is significant and indicates the ease of splitting a C–P bond in **2a**. The calculated entropy of the reaction ($\Delta S^{\neq}$) is –95.67 J mol^{-1} K^{-1}, and the value may reflect unease in the protonation of oxygen[23] in a phosphinic group of **2a** before splitting. It is noteworthy that the rate constants were calculated from estimated ^{31}P NMR spectroscopic integrated signals, and therefore, these results should not be considered as exact data for mere kinetic studies. Nevertheless, these results are already very useful because they give a general picture of the cleavage mechanism (Scheme 4).

Table 5. Rate constants and kinetic parameters for the cleavage of α-hydroxymethyl phosphinic acids **2a** and **2c** at 95 °C.

Entry	Compound	Solvent	Concentration. of compound	Concentration of acid	Kinetic parameters		
			[mol L^{-1}]	[mol L^{-1}]	k_{obsd} [h^{-1}]	$t_{1/2}$ [h]	k_H/k_D
1	**2a**	H_2O	0.164	1.0 (H_2SO_4)	5.99[c]	0.11	6.96
2		H_2O	0.164	1.0 (H_2SO_4)	4.66[a,c]	0.15	
3		H_2O	0.164	1.0 (H_2SO_4)	3.05[b,c]	0.23	
4		D_2O	0.164	1.0 (D_2SO_4)	0.86	0.81	
5		H_2O	0.164	0.5 (H_2SO_4)	0.26	2.67	
6	**2c**	H_2O	0.164	1.0 (H_2SO_4)	1.65	0.42	3.24
7		D_2O	0.164	1.0 (D_2SO_4)	0.51	1.35	
8		H_2O	0.164	0.5 (H_2SO_4)	0.43	1.61	

[a] Reaction carried out at 85 °C. [b] Reaction carried out at 75 °C. [c] Calculated for **2a**; Ea = 35.99 kJ mol^{-1}, $\Delta H^{\neq}$ = 32.93 kJ mol^{-1}, $\Delta S^{\neq}$ = –95.67 J mol^{-1} K^{-1}.

Conclusions

A simple and convenient route to new pyridine and imidazole mono- and bis(α-hydroxymethyl)phosphinic acids, starting from hypophosphorous acid and the corresponding heterocyclic aldehydes was developed. In contrast to the methods known from literature, it was clearly showed that the presented method requires no external assistance, such as microwave or ultrasound irradiation, or prolonged heating, and proceeds easily in aqueous solutions to afford the desired products in good overall yields. The obtained pyridine and imidazole hydroxyphosphinic acids showed a good binding ability toward Cu^{II} ions. The equilibrium data show that 1:1 and 1:2 complexes are formed in the studied pH range for $\mathbf{L^1}$, $\mathbf{L^2}$, and $\mathbf{L^4}$. The binding site is located on the nitrogen and phosphinic oxygen atoms. Relatively, the most effective ligand is bis(α-hydroxymethyl)phosphinic acid **3d** ($\mathbf{L^3}$), which forms only 1:2 complexes where Cu^{II} is bound by two imide nitrogen atoms. It was shown that [(hydroxy)(2-pyridyl)- and (hydroxy)(4-pyridyl)methyl]-phosphonic acids are easily cleaved by 1 M HCl at elevated temperatures; this results in the formation of the corresponding pyridinemethanols and phosphorus acid (H_3PO_3). This reaction resembles the acidic cleavage of the corresponding aminophosphinic pyridine compounds.[21,22] The mechanism of this transformation is proposed by analogy to the mechanism of cleavage of pyridine aminophosphonic and aminophosphinic acids, previously described by our group.[22]

Experimental Section

General: NMR spectra were recorded with a Bruker Avance DRX 300 instrument, operating at 300.13 MHz for ^{1}H, 121.50 for ^{31}P and 75.47 MHz for ^{13}C. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (J) are reported in Hz. IR spectra were recorded with a Perkin–Elmer 1600 FTIR spectrophotometer. NMR and IR spectra were done in the Laboratory of Instrumental Analysis at the Faculty of Chemistry, Wroclaw University of Technology. Melting points were determined with an Electrothermal 9200 apparatus and a Boetius hot-stage apparatus and are uncorrected. Elemental analyses and potentiometric measurements were done in the Laboratories of Instrumental Analysis at the Faculty of Chemistry, University of Wroclaw. All reagents were purchased from the Aldrich Company and were used without further purification.

Imidazole-4(5)-methyl(hydroxy)phosphonic Acid (ligand $\mathbf{L^1}$): A solution of 4(5)-imidazolecarboxaldehyde (**1d**; 0.6 g, 6.25 mmol), diethyl phosphite (0.86 g, 6.25 mmol), and triethylamine (0.63 g, 6.25 mmol) in ethanol (30 mL) was heated at reflux for 4 h, and the solution was concentrated to give crude diethyl imidazole-4(5)-methyl(hydroxy)phosphonate as a thick oil. The crude ester was treated with 20% aqueous HCl (30 mL), and the solution was heated at reflux for 6 h. After evaporation of the solvent, crude imidazole hydroxyphosphonic acid was obtained as a yellowish semisolid. Repeated crystallization of the product from methanol, containing a small amount of diethyl ether (ca. 5%), and drying gave the analytically pure sample of $\mathbf{L^1}$. White solid, yield: 0.62 g (56%), m.p. 252–256 °C. ^{1}H NMR (300 MHz, D_2O): δ = 8.12 (s, 1 H, imidazole-2), 6.91 (s, 1 H, imidazole-5), 4.66 (d, 1 H, J = 13.8 Hz, C*H*-P) ppm.^{31}P NMR (121.5 MHz, D_2O): δ = 17.38 (s) ppm. ^{13}C NMR (75.5 MHz, D_2O): δ = 133.4 (s, C-2), 131.70 (s, C-5), 116.3 (d, $^2J_{C-P}$ = 6.1 Hz, C-4), 63.92–61.84 (d, J_{C-P} = 157.8 Hz, C-α) ppm. IR (KBr): $\tilde{\nu}$ = 3387 (OH), 3266, 3162 (P–OH), 2602, 1492, 1309, 1270 (P=O), 1195, 1064, 970, 937, 831, 736, 685, 621, 543 cm^{-1}. $C_4H_7N_2O_4P$ (178.08): calcd. C 26.98, H 3.96, N 15.73; found C 26.91, H 3.90, N 15.01.

General Procedure for the Preparation of Heterocyclic (α-Hydroxymethyl)phosphinic Acids 2a–d: Commercially available hypophosphorous acid (50% aqueous solution, 1.32 g, 20 mmol) was added to a solution of the appropriate aldehyde (20 mmol) in distilled H_2O (50 mL), and the mixture was heated at 100 °C (reflux) for 2 h. After this, the solvent was removed under reduced pressure, and the residue was dissolved in MeOH (10 mL) and refrigerated. Usually, after 24 h, the products, pyridine- or imidazole (α-hydroxymethyl)phosphinic acids **2a**–**d**, were separated as white solids and collected by filtration, washed with a small amount of cold methanol, and dried in air. In the case of **2a**, the product was additionally purified and decolorized by use of the NORIT SX2 in water, heating at reflux for 1 h, and then the mixture was filtered and evaporated to give the product, which was crystallized from methanol/diethyl ether. All products gave satisfactory spectroscopic data in accordance with the assigned structures.

[(Hydroxy)(2-pyridyl)methyl]phosphinic Acid (2a): White solid, yield: 1.1 g (32%), m.p. 140–142 °C. ^{1}H NMR (300 MHz, D_2O): δ = 8.50 (d, 1 H, J = 5.7 Hz, py-6), 8.33 (t, 1 H, J = 8.0 Hz, py-4), 7.80 (d, 1 H, J = 8.2 Hz, py-3), 7.72 (t, 1 H, J = 6.0 Hz, py-5), 7.66–5.86 (d, 1 H, J_{H-P} = 547.6 Hz, P-*H*), 5.03 (d, 1 H, J = 11.4 Hz, C*H*-P) ppm. ^{31}P NMR (121.5 MHz, D_2O): δ = 21.33 (s) ppm. ^{13}C NMR (75.5 MHz, D_2O): δ = 152.6 (s, C-2), 146.2 (s, C-6), 140.6 (s,

C-4), 125.6 (s, C-5), 124.9 (s, C-3), 71.32–70.08 (d, J_{C-P} = 94.4 Hz, C-α) ppm. IR (KBr): ṽ = 3104 (OH), 3048, 2830 (P–OH), 2691, 2515, 2319 (P–H), 1463, 1403, 1316, 1250, 1182 (P=O), 1155, 1042, 951, 804, 738, 605, 490 cm^{-1}. $C_6H_8NO_3P$ (173.11): calcd. C 41.63, H 4.66, N 8.09; found C 41.60, H 4.71, N 7.98.

[(Hydroxy)(3-pyridyl)methyl]phosphinic Acid (2b): White solid, yield: 1.87 g (54%), m.p. 149–151 °C. ^{1}H NMR (300 MHz, D_2O): δ = 8.66 (s, 1 H, py-2), 8.63 (d, 1 H, *J* = 5.1 Hz, py-6), 8.50 (d, 1 H, *J* = 7.8 Hz, py-4), 7.97 (t, 1 H, *J* = 6.3 Hz, py-5), 7.72–5.93 (d, 1 H, J_{H-P} = 534 Hz, P-*H*), 4.96 (d, 1 H, *J* = 9.2 Hz, C*H*-P) ppm. ^{31}P NMR (121.5 MHz, D_2O): δ = 24.37 (s) ppm. ^{13}C NMR (75.5 MHz, D_2O): δ = 144.5 (s, C-6), 139.8 (s, C-2), 138.7 (s, C-4), 138.6 (d, $^2J_{C-P}$ = 9.1 Hz, C-3), 126.8 (s, C-5), 70.88–69.56 (d, J_{C-P} = 89.5 Hz, C-α) ppm. IR (KBr): ṽ = 3447 (OH), 3094, 3069, 2829 (P–OH), 2674, 2333 (P–H), 1558, 1470, 1403, 1379, 1262, 1206, 1156 (P=O), 1115, 1067, 1043, 1029, 1000, 965, 837, 690 (P–C), 616, 541 cm^{-1}. $C_6H_8NO_3P$ (173.11): calcd. C 41.63, H 4.66, N 8.09; found C 41.56, H 4.79, N 8.01.

[(Hydroxy)(4-pyridyl)methyl]phosphinic Acid (2c): White solid, yield: 1.55 g (45%), m.p. 174–176 °C. ^{1}H NMR (300 MHz, D_2O): δ = 8.64 (d, 2 H, *J* = 6.6 Hz, py-2, py-6), 7.96 (d, 2 H, *J* = 6.0 Hz, py-3, py-5), 7.75–5.95 (d, 1 H, J_{H-P} = 541 Hz, P–*H*), 5.08 (d, 1 H, *J* = 12.6 Hz, C*H*–P) ppm.^{31}P NMR (121.5 MHz, D_2O): δ = 23.87 (s) ppm. ^{13}C NMR (75.5 MHz, D_2O): δ = 140.26 (s, C-2, C-6), 124.72 (d, $^2J_{C-P}$ = 2.8 Hz, C-4), 124.23 (s, C-3, C-5), 73.64–72.40 (d, J_{C-P} = 93.4 Hz, C-α) ppm. IR (KBr): ṽ = 3099 (OH), 2823 (P–OH), 2671, 2377, 2308 (P–H), 2141, 2050, 1524, 1497, 1383, 1362, 1276, 1213, 1193 (P=O), 1145, 1052, 988, 955, 842, 747, 693, 633, 544 cm^{-1}. $C_6H_8NO_3P$ (173.11): calcd. C 41.63, H 4.66, N 8.09; found C 41.61, H 4.68, N 8.03.

[(Hydroxy)(4-imidazolyl)methyl]phosphinic Acid (2d): White solid, yield: 1.78 g (55%), m.p. 119–121 °C. ^{1}H NMR (300 MHz, D_2O): δ = 8.62 (s, 1 H, imidazole-2), 7.79–5.98 (d, 1 H, J_{H-P} = 545 Hz, P–*H*), 7.37 (s, 1 H, imidazole-5), 4.82 (d, 1 H, *J* = 10.0 Hz, C*H*-P) ppm.^{31}P NMR (121.5 MHz, D_2O): δ = 23.36 (s) ppm. ^{13}C NMR (75.5 MHz, D_2O): δ = 133.83 (s, C-2), 129.61 (s, C-5), 116.33 (d, $^2J_{C-P}$ = 5.7 Hz, C-4), 65.13–63.72 (d, J_{C-P} = 106.3 Hz, C-α) ppm. IR (KBr): ṽ = 3357 (OH), 3125 (P–OH), 2853, 2614, 2375, 1313, 1271 (P=O), 1147, 1019, 967, 817, 658, 623, 547, 462 cm^{-1}. $C_4H_7N_2O_3P$ (162.08): calcd. C 29.64, H 4.35, N 17.28; found C 29.55, H 4.41, N 17.20.

General Procedure for the Preparation of Heterocyclic Bis(α-hydroxymethyl)phosphinic Acids 3a–d: Hypophosphorous acid (50% aqueous solution, 1.32 g, 20 mmol) was mixed with the appropriate heterocyclic aldehyde (40 mmol) and diluted with aqueous HCl (1 M, 40 mmol, 40 mL). The resulting homogeneous mixture was heated at reflux for 2 h. The solvent was then evaporated under reduced pressure, and the residue was dissolved in methanol (10 mL) and placed in the refrigerator for crystallization. The separated products, bis(α-hydroxymethyl)phosphinic acids **3a**–**d**, were collected by filtration, washed with cold MeOH, and dried on air. All products gave satisfactory spectroscopic data in accordance with the assigned structures.

Bis[(hydroxy)(2-pyridyl)methyl]phosphinic Acid Hydrochloride (3a): White solid, yield: 2.1 g (30%), m.p. 160 °C (dec.) (ref.[9b] 148–150 °C). All spectroscopic data are in agreement with the literature.[9b]

Bis[(hydroxy)(3-pyridyl)methyl]phosphinic Acid, Hydrochloride (3b): White solid, yield: 4.0 g (57%), m.p. 237–240 °C. ^{1}H NMR (300 MHz, D_2O): *Diastereomer 1*: δ = 8.65 (s, 2 H, py-2, py-2′), 8.55–8.45 (m, 4 H, py-4, py-6), 7.90 (m, 2 H, py-5), 5.33 (d, 2 H, C*H*-P, *J* = 9.0 Hz) ppm; *Diastereomer 2*: δ = 8.62 (s, 2 H, py-2, py-2′), 8.55–8.45 (m, 4 H, py-4, py-6), 7.92–7.88 (m, 2 H, py-5), 5.19 (d, 2 H, C*H*-P, *J* = 10.7 Hz) ppm. ^{31}P NMR (121.5 MHz, D_2O): δ = 31.53 (s) and 29.33 (s) ppm in a ratio 1:0.8. ^{13}C NMR (75.5 MHz, D_2O): *Diastereomer 1*: δ = 144.9 (s, C-2, C-2′), 139.7 (s, C-6, C-6′), 139.5 (s, C-3, C-3′), 139.0 (s, C-4, C-4′), 126.7 (s, C-5, C-5′), 68.02–66.61 (d, J_{C-P} = 106.4 Hz, C-α, C′-α) ppm; *Diastereomer 2*: δ = 144.6 (s, C-2, C-2′), 140.0 (s, C-6, C-6′), 139.5 (s, C-3, C-3′), 139.0 (s, C-4, C-4′), 126.7 (s, C-5, C-5′), 69.75–68.37 (d, J_{C-P} = 104.6 Hz, C-α, C′-α) ppm. IR (KBr): ṽ = 3375 (OH), 3111, 3094 (P–OH), 3030, 2937, 2877, 2797, 2648, 1618, 1463, 1220 (P=O), 1139, 1115, 1029, 848, 735, 688 cm^{-1}. $C_{12}H_{13}N_2O_4P$·2HCl (353.14): calcd. C 40.81, H 4.28, N 7.93; found C 40.85, H 4.32, N 7.88.

Bis[(hydroxy)(4-pyridyl)methyl]phosphinic Acid Hydrochloride (3c): White solid, yield: 2.54 g (36%), m.p. 250 °C (dec.). ^{1}H NMR (300 MHz, D_2O): *Diastereomer 1*: δ = 8.65–8.62 (d, 4 H, *J* = 9.8 Hz, py-2, py-6), 8.01–7.98 (d, 4 H, *J* = 9.9 Hz, py-3, py-5), 5.44 (d, 2 H, *J* = 9.36 Hz, C*H*-P) ppm; *Diastereomer 2*: δ = 8.70–8.67 (d, 4 H, *J* = 6.7 Hz, py-2, py-6), 7.91–7.89 (d, 4 H, *J* = 6.7 Hz, py-3, py-5), 5.34 (d, 2 H, *J* = 13.9 Hz, C*H*-P) ppm. ^{31}P NMR (121.5 MHz, D_2O): δ = 31.3 (s) and 29.4 (s) ppm in a ratio 1:0.7. ^{13}C NMR (75.5 MHz, D_2O): *Diastereomer 1*: δ = 160.8 (s, C-4, C-4′), 140.3 (s, C-2, C-2′, C-6, C-6′), 124.9 (s, C-3, C-3′, C-5, C-5′), 71.37–70.03 (d, J_{C-P} = 101.2 Hz, C-α, C′-α) ppm; *Diastereomer 2*: δ = 160.5 (s, C-4, C-4′), 141.1 (s, C-2, C-2′, C-6, C-6′), 125.7 (s, C-3, C-3′, C-5, C-5′), 74.68–73.34 (d, J_{C-P} = 100.9 Hz, C-α, C′-α) ppm. IR (KBr): ṽ = 3226 (OH), 3100, 3080, 3063 (P–OH), 2938, 2848, 1630, 1618, 1505, 1493, 1408, 1367, 1347, 1334, 1269, 1237 (P=O), 1198, 1184, 1144, 1100, 1062, 1026, 1005, 954, 834, 811, 756 cm^{-1}. $C_{12}H_{13}N_2O_4P$·2HCl (353.14): calcd. C 40.81, H 4.28, N 7.93; found C 40.70, H 4.32, N 7.91.

Bis[(hydroxy)(4-imidazolyl)methyl]phosphinic Acid Hydrochloride (3d): White solid, yield: 87%, m.p. 218–222 °C. ^{1}H NMR (300 MHz, D_2O): *Diastereomer 1*: δ = 8.55–8.52 (m, 2 H, imidazole-2), 7.31–7.28 (m, 2 H, imidazole-5), 5.16 (d, 2 H, *J* = 8.3 Hz, C*H*-P) ppm; *Diastereomer 2*: δ = 8.55–8.52 (m, 2 H, imidazole-2), 7.31–7.28 (m, 2 H, imidazole-5), 5.06 (d, 2 H, *J* = 9.6 Hz, C*H*-P) ppm. ^{31}P NMR (121.5 MHz, D_2O): δ = 30.2 (s) and 28.8 (s) ppm in a ratio 1:0.9. ^{13}C NMR (75.5 MHz, D_2O): *Diastereomer 1*: δ = 133.6 (s, C-2, C-2′), 130.6 (s, C-4, C-4′), 116.6 (s, C-5, C-5′), 63.71–62.24 (d, J_{C-P} = 110.7 Hz, C-α, C′-α) ppm. *Diastereomer 2*: δ = 133.6 (s, C-2, C-2′), 130.2 (s, C-4, C-4′), 116.5 (s, C-5, C-5′), 62.48–61.00 (d, J_{C-P} = 111.6 Hz, C-α, C′-α) ppm. IR (KBr): ṽ = 3347 (OH), 3125, 3029 (P–OH), 2855, 2616, 1312 (P=O), 1220, 1145, 1096, 1023, 818, 658, 624 cm^{-1}. $C_8H_{11}N_4O_4P$·2HCl (331.09): calcd. C 29.02, H 3.96, N 16.92; found C 28.91, H 4.00, N 16.87.

Potentiometric Studies of Cu^{II} Complexes: Both protonation and stability constants were determined by pH-metric titration of 1.8–2.0 cm^3 samples at 25 °C over the pH range 2.5–10.5. The ligand concentration in the samples was 3 × x 10^{-3} mol L^{-1} and the molar ratio of metal ion: ligand varied from 1:2 to 1:6. Initial solutions were titrated with sodium hydroxide solutions delivered by a 0.25 mL micrometer syringe previously calibrated by the weight titrations of standard materials. The purities and exact concentration of the ligand solutions were determined by the method of Gran.[16] pH-Metric titrations were performed in 0.1 M KNO_3 solutions by using MOLSPIN automatic titration system with Russell CMAW711 semi-combined electrode calibrated with H^+ concentration with the use of HNO_3.[17] The method SUPERQUAD was used for stability constants and calculation of protonation constants.[18]

Spectroscopic Studies of Cu^{II} Complexes: The absorption spectra were recorded with Beckman DU 650 spectrometer and thermo-

statted at 25 °C. Electron paramagnetic resonance (EPR) spectra were performed in ethylene glycol/water (1:2) solutions at 77 K with a Bruker ESP 300 spectrometer at the X-band frequency (9.3 GHz). The ligand concentration used in the spectroscopic samples was 6–18×10^{-3} M, and the metal concentration was 2–3×10^{-3} M.

Kinetic Measurements: Solutions of samples of the corresponding pyridine hydroxymethylphosphinic acids **2a**,**c** (c = 0.164 M L^{-1}) in distilled H_2O, containing an appropriate quantity of H_2SO_4 (the 0.5 and 1.0 M L^{-1} H_2SO_4 solutions) in NMR tubes were prepared and thermostatted at 95 °C for a determined period of time (5, 10, 15, 30, 60, 90, 120 min, respectively). The ^{31}P NMR spectra were consecutively recorded. The kinetic runs in D_2O with use of D_2SO_4 were done similarly. The use of different concentrations of H_2SO_4, (or D_2SO_4) allowed for the calculation of the pseudofirst-order rate constants (k_{obs}). The rate constants were determined by plotting the dependence of $log(a\text{-}x)$ on time (where the "a" is a relative quantity of the starting hydroxyphosphinic acid and the "a-x" represents a relative quantity of the unconsumed hydroxyphosphinic acid).

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