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Complexing properties of [(glycylamino)methyl]phosphinic acids towards Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+} ions in aqueous solutions

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The complexing properties of the phosphinic acid analogues of glycylglycine ([(glycylamino)methyl]phosphinic acids) $NH_2CH_2C(O)–NHCH_2P(O)(R)(OH)$ [GlyGly(P^R)] (R = Ph, Me and *tert*-Bu) towards Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+} ions in aqueous solutions are investigated using potentiometry, and absorption and EPR spectroscopies. The potentiometric results indicate different properties of the Cu^{2+}–GlyGly(P^R) systems in comparison with glycylglycine and its phosphonic acid analogue $NH_2CH_2C(O)–NHCH_2P(O)(OH)_2$ [GlyGly(P)]. The phosphinic dipeptides GlyGly(P^R) readily form complexes with Cu^{2+}/ligand molar ratio 1 : 2 exhibiting the $(N_{amine}, N_{amide})_2$ coordination mode above pH 9 even in solutions with only a slight excess of the ligand. In the system with GlyGly, the Cu^{2+} complex is observed at pH 12–13 and a metal : ligand ratio of 1 : 500. The metal-induced deprotonation of the amide nitrogen and the extent of formation of the 1 : 2 complexes depend on the acidity of the phosphinic acid group which is influenced by the substituent at the phosphorus atom. The models based on potentiometry are confirmed by spectroscopic measurements. Stability constants of the phosphinic dipeptides GlyGly(P^R) with the other metal ions are the same as for glycylglycine and, therefore, the same binding pattern through the amine group and peptide oxygen is proposed. The presence of protonated complexes is assumed in all the systems studied. In the protonated complexes, the peptide is bound through the phosphinic acid group whereas the amino group remains protonated. The presence of the species in the system containing the phosphonic acid analogue of glycylglycine [GlyGly(P)] with Cu^{2+}, which was investigated by potentiometry previously, is confirmed by EPR spectroscopy.

(Aminoalkyl)phosphonic or (aminoalkyl)phosphinic acids have enjoyed much interest as phosphorus analogues of naturally occurring amino carboxylic acids due to their biological activity.[1] Because of the tetrahedral structure of both the phosphonic [$–P(O)(OH)_2$] and phosphinic [–P(O)(R)(OH), R = alkyl, aryl] acid groups, they mimic the tetrahedral intermediates of the hydrolysed esters, amides and peptides. Thus, they often act as inhibitors of esterases, peptidases and related enzymes and metalloenzymes. (Aminoalkyl)phosphinic acid derivatives exhibit pronounced biological effects and they strongly inhibit metalloenzymes,[2] such as matrix metalloproteinases and astacins, angiotensin I converting enzyme, thrombin, endothelin converting enzyme, *etc.*, or alter function of receptors, *e.g.* GABA receptors.[3] (Aminoalkyl)phosphinic acid peptides have been proposed as compounds of interest for new drug design,[4] such as analgesics, antibiotics or agents against protozoa infections.

The complexing properties of aminoalkylphosphonic/phosphinic acids are not so well understood as those of aminocarboxylic acids. Simple (aminoalkyl)phosphonic acids have been extensively studied in solution[5] and in the solid state.[6] Only few papers have dealt with the complexing properties of phosphonopeptides (*i.e.*, peptides with terminal phosphonic group). The main attention was focused[7] on the interaction of Cu^{2+} with GlyGly(P), GlyAla(P), AlaLeu(P), LeuAla(P) and LeuLeu(P), where Gly(P), Ala(P) and Leu(P) correspond to the phosphonic acid analogues of appropriate common amino acids. In our previous papers, we investigated the influence of the length of the amino acid side chain on the complexing properties of dipeptides containing Gly(P) and both enantiomers of Ala(P) towards common transition-metal ions.[8,9] In the Ala(P) series, main attention was focused on the differences in the solution properties of diastereoisomers.[9] The differences between the diastereoisomers of phosphonodipeptides are larger, probably due to a stronger interaction of the hydrophilic and/or hydrophobic parts of the molecules. Similarly to simple (aminoalkyl)phosphonic acids, phosphonodipeptides readily form protonated complexes. The pK_a dependences on the side chains correspond to those for common dipeptides but the differences in the phosphonodipeptide series are smaller than in the analogous series of common dipeptides. The observed lower acidity of the ammonium group indicates its weak interaction with phosphonate. In contrast to carboxylic dipeptides, deprotonation and simultaneous co-ordination of the peptide amide moiety was observed only in systems containing Cu^{2+} as a result of the repulsion of electron density from the double-charged phosphonate group, and, consequently, higher basicity of the peptide amide group. The formation constants of the complexes of phosphonodipeptides are higher than those observed for the carboxylic dipeptides. The relative increase in stability constants for phosphonic dipeptides in comparison with carboxylic dipeptides follows the order $Cu^{2+} > Zn^{2+} > Co^{2+} > Ni^{2+}$, like in the analogous systems with simple (aminoalkyl)phosphonic and aminocarboxylic acids. We also focused our interest on systems containing Pt(II) or Pd(II) and (aminoalkyl)phosphonic acids or their dipeptides.[10]

Little attention has also been paid to the co-ordination properties of (aminoalkyl)phosphinic acids in solution[11] as well

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as in the solid state.[12] The results indicate, compared with the aminocarboxylic acids, a stronger acidity of the phosphinic acid group and weaker basicity of the nitrogen atoms, and, consequently, lower stability constants for the complexes. The substituent on the phosphorus atom in the phosphinic acid group also significantly affects their co-ordination properties, as it was found for phosphinic acid analogues of glycine [$H_2NCH_2P(O)(R)OH$, R = H, Me, Ph, *tert*-Bu].[13] The goal of this paper was to establish whether the phosphinic acid group is able to modify complexing properties of the peptide moiety.

As a continuation of our studies on the complexing properties of metal ions towards aminophosphorus acid ligands containing the >N–C–P moiety,[8–10,13,14] we present the results on a series of simple phosphinodipeptides, analogues of GlyGly (Scheme 1). They contain phosphinic acid groups

$H_2N\text{-}CH_2\text{-}C(O)\text{-}NH\text{-}CH_2\text{-}\mathbf{COOH}$

Gly-Gly

$H_2N\text{-}CH_2\text{-}C(O)\text{-}NH\text{-}CH_2\text{-}\mathbf{P(O)(OH)_2}$

Gly-Gly(P)

$H_2N\text{-}CH_2\text{-}C(O)\text{-}NH\text{-}CH_2\text{-}\mathbf{P(O)(R)(OH)}$

Gly-Gly(P^R)

R=Me, Ph, *t*-Bu

Scheme 1

with substituents exhibiting different electronic effects (methyl, phenyl, and *tert*-butyl). This permits us to follow changes in their complexing ability similarly to our previous studies.[13]

Experimental

Chemicals and stock solutions

Dipeptides GlyGly(P^R)[15] and GlyGly(P)[16] were synthesised using a published procedure and were proved to be pure by NMR and TLC. Thermogravimetry of the phosphinodipeptides shows that GlyGly(P^{Me}) and GlyGly(P^{tBu}) are anhydrous, GlyGly(P^{Ph}) is a monohydrate (loss of water occurs over the range 100–140 °C). The anhydrous dipeptides decompose above 140 °C [GlyGly($P^{t\text{-}Bu}$)] or 200 °C [GlyGly(P^{Me}) and GlyGly(P^{Ph})]. Water was deionized using Milli-Q system (Millipore). Stock solutions of the individual metal cations were prepared by dissolving in water the appropriate nitrates recrystallised from aqueous solution. The metal content of the stock solutions was determined by titration with standard Na_2H_2edta solution. Nitric acid was prepared by passing recrystallised potassium nitrate through a Dowex 50W-8 column in the H^+ form because of traces of NO and NO_2 present in the concentrated acid. Carbonate-free potassium hydroxide solution was standardised against potassium hydrogen phthalate and HNO_3 solution against a KOH solution. Stock solutions of the ligands were prepared by dissolving appropriately dried samples in water. Analytical concentrations of the ligands were calculated from the weighted amount of the compounds, those from the joint calculation of the concentration and protonation constants were the same within experimental errors.

Potentiometric titrations

Titrations were carried out in a vessel thermostatted at 25.0 ± 0.1 °C, at an ionic strength of I (KNO_3) = 0.1 mol dm^{-3} and in the presence of extra HNO_3 in the region of $-\log[H^+] = 1.8–12$ (or until the mV reading was unstable) using a PHM 240 pH-meter, a 2 cm^3 ABU 900 automatic piston burette and a GK 2401B combined electrode (Radiometer, Denmark). The initial volume was 5.0 cm^3 and concentration of the metal ions was 0.004–0.008 mol dm^{-3}. The metal : ligand ratios were 1 : 1.1, 1 : 2 and 1 : 5. Titrations for each ratio were carried out at least three times. Each titration consisted of about 40 experimental points. Inert atmosphere was ensured by a constant flow of argon saturated with the solvent vapor during measurements. The stability constants for M^{2+}–OH^- systems included in the calculations and $pK_w = 13.78$ were taken from ref. 17. The protonation and stability constants β_{pqr} are concentration constants and are defined by $\beta_{pqr} = [M_pL_qH_r]/[M]^p[L]^q[H]^r$. The constants were calculated using the OPIUM program;[18] standard deviations are given by the program. The program minimises the criterion of the generalised least-squares method using the calibration function [eqn. (1)]: where the term E_0

$$E = E_0 + S\log[H^+] + j_a[H^+] + j_bK_w/[H^+] \qquad (1)$$

contains the standard potentials of the electrodes used and contributions of inert ions to the liquid-junction potential, S corresponds to the Nernstian slope, the value of which should be close to the theoretical value, and $j_a[H^+]$ and $j_b[OH^-]$ terms are contributions of the H^+ and OH^- ions to the liquid-junction potential. The calculation strategy was discussed in the Supplementary material of our previous paper.[14b]

Spectrophotometry

Solutions for quantitative spectrophotometric titrations in the Cu^{2+}–ligand systems were prepared under the same conditions as the potentiometric titrations at metal : ligand ratios 1 : 1.1 and 1 : 2 at two ligand concentrations, 0.004 and 0.008 mol dm^{-3} for both the ratios. About 15 points were measured through the whole pH region for each titration. The spectra were recorded in the range 400–850 nm on a Varian Cary 1/E double-beam spectrophotometer against a solution containing no Cu^{2+}. The spectrophotometric titration data were treated together with potentiometric data using OPIUM.[18] Because of the low sensitivity of spectrophotometry to minor species and species with a similar co-ordination mode, some of them had to be considered to exhibit the same spectral parameters. They are Cu^{2+} aqua complexes and $[Cu(LH)]^{2+}$ (4*O*-environment) and, despite a different number of nitrogen atoms, $[CuL]^+$ and $[CuL_2]$ [(1 or 2)N_{amine} co-ordination]. The values of parameters listed in Table 4 were calculated from the simulated spectra given by OPIUM.

EPR measurements

Anisotropic EPR spectra (9.15 GHz) of frozen solutions were recorded at 120 K using a Varian E-9 spectrometer in the presence of ethylene glycol to ensure good glass formation in frozen solutions. Analytical concentration of Cu^{2+} varied in the range 0.001–0.005 mol dm^{-3} at various Cu^{2+} : ligand ratios (from 1 : 1.1 to 1 : 10) and different pH values. At high pH values and with some metal/ligand ratios, a noticeable influence of ethylene glycol added on the species distribution was observed. In such cases, the spectra were run with no glass-forming additives.

Results and discussion

Protonation of phosphinic dipeptides

Phosphinic dipeptides GlyGly(P^R) exhibit virtually the same basicity of amino group as GlyGly,[19] and thus, no influence of phosphinic acid group on the other side of the molecule was observed (Table 1). This is different from GlyGly(P), for which a weak interaction is assumed due to a higher pK_a value of the amine.[8] In addition, the basicity of the amino group in the phosphinic dipeptides is slightly lower than that of parent (aminomethyl)phosphinic acids Gly(P^R).[13] The acidity of the phosphinic acid moiety depends on electronic properties of the phosphorus substituent in the same way as it was observed for the Gly(P^R) series.[13]

Table 1 Protonation and dissociation constants of phosphinic acid analogues of GlyGly and those of similar ligands

Ligand	$\log\beta_{011} = pK_3$ or pK_2	$\log\beta_{012}$	pK_2 or pK_1	$\log\beta_{013}$	pK_1
GlyGly(P^{Ph})[a]	8.002(3)	9.316(6)	1.31		
GlyGly(P^{Me})[a]	8.083(4)	9.795(7)	1.71		
GlyGly($P^{t\text{-}Bu}$)[a]	8.053(3)	10.128(5)	2.08		
GlyGly(P)[b]	8.18	14.30	6.22	15.51	1.22
GlyGly[c]	8.09		3.11		
Gly[c]	9.58		2.34		
$GlyNH_2$[c]	7.98				
Gly(P)[d]	10.06		5.40		0.4
Gly(P^{Ph})[e]	8.08		<0.5		
Gly(P^{Me})[e]	8.40		0.89		
Gly($P^{t\text{-}Bu}$)[e]	8.43		1.20		

[a] This work (25 °C, I = 0.1 mol dm^{-3} KNO_3). [b] Ref. 8 (25 °C, I = 0.1 mol dm^{-3} KNO_3). [c] $GlyNH_2$ = glycinamide, ref. 19 (25 °C, I = 0.1 mol dm^{-3}). [d] Ref. 10*a*, 19 (25 °C, I = 0.1 mol dm^{-3}). [e] Ref. 13 (25 °C, I = 0.1 mol dm^{-3} KNO_3).

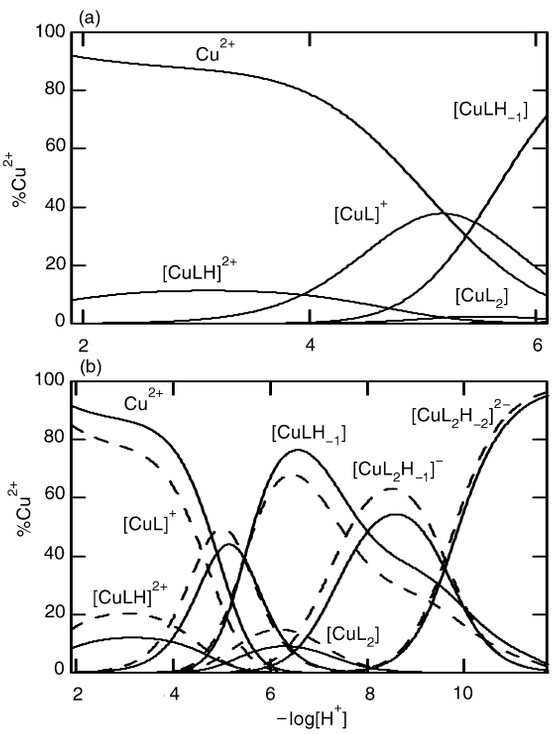


Fig. 1 Distribution diagrams for the Cu^{2+}–GlyGly(P^{Me}) system (25 °C, I = 0.1 mol dm^{-3} KNO_3) at (a) M : L = 1 : 1.1, c_{Cu} = 0.005 mol dm^{-3} and (b) M : L = 1 : 2, c_{Cu} = 0.0025 mol dm^{-3} (——); M : L = 1 : 2, c_{Cu} = 0.005 mol dm^{-3} (---).

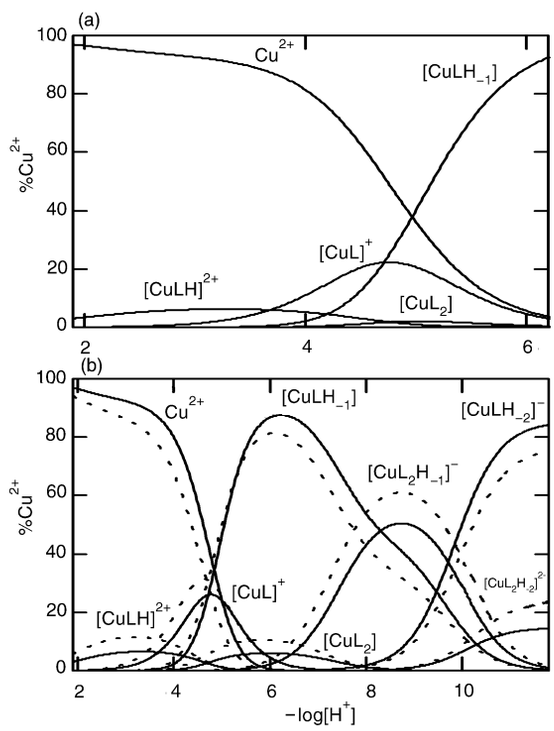


Fig. 2 Distribution diagrams of Cu^{2+}–GlyGly($P^{t\text{-}Bu}$) system (25 °C, I = 0.1 M KNO_3) at (a) M : L = 1 : 1.1, c_{Cu} = 0.005 mol dm^{-3} and (b) M : L = 1 : 2, c_{Cu} = 0.0025 mol dm^{-3} (——); M : L = 1 : 2, c_{Cu} = 0.005 mol dm^{-3} (---).

Copper(II)–phosphinodipeptide systems

(Aminomethyl)phosphinic acids [Gly(P^R)] contain [13] a less basic nitrogen atom (pK_2 = 8.1–8.4) in comparison with Gly (pK_2 = 9.58)[19] and its phosphonic acid analogue Gly(P) (pK_3 = 10.06).[19] Due to higher basicity of the amino group, the dipeptides containing Gly(P) are less prone to the metal-assisted deprotonation of the amide nitrogen than dipeptides containing C-terminal glycine.[7a,8] Therefore, we expected that dipeptides derived from Gly(P^R) would exhibit an easier deprotonation of the amide nitrogen. The assumption was tested in systems containing Cu^{2+} and GlyGly(P^R).

The systems were investigated by potentiometry at two different analytical concentrations of the metal ions, as is illustrated in distribution diagrams (Figs. 1 and 2), and a model proposed to fit the titration data was tested by spectroscopic measurements. The results from the simultaneous treatment of the potentiometric and spectrophotometric data are presented in Table 2 and compared with those for similar ligands in Table 3. The spectroscopic parameters are shown in Table 4.

In the systems with molar ratios M : L = 1 : 1, the complexation starts in slightly acidic solutions with the formation of minor protonated species $[Cu(LH)]^{2+}$ (Figs. 1 and 2). Based on EPR results and on the proton dissociation constants found for the complexes (pK_{CuLH} = 3.67–4.03) and free ligands, we suggest co-ordination mainly *via* a phosphinate oxygen atom or *via* both phosphinate and carbonyl moieties with formation of a seven-membered chelate ring; the amine group remains protonated (Scheme 2). Since the hard phosphinate group exhibits almost the same ligand field as water,[13] electronic spectra of the solutions containing the species are scarcely affected in comparison with Cu^{2+}–aqua complexes. Therefore, the protonated species cannot be confirmed in the model provided by the treatment (OPIUM) of spectrophotometric titration data only. The corresponding species with GlyGly in the same coordination mode was suggested in refs. 21 and 22.

Deprotonation of the amine group leads to $[CuL]^+$ species with co-ordinated amine group and carbonyl oxygen forming a five-membered chelate ring (Scheme 2). The EPR parameters

(Table 4 and Fig. 3) correspond to those observed for [Cu(GlyGly)]$^+$ where this binding mode is well documented.[22–24] The values of pK_{CuLH} change in the opposite direction to that of the free ligands. Such order can be explained by increasing participation of the acid groups from phenylphosphinic to *tert*-butylphosphinic acid in the co-ordination sphere, probably in an axial position. The values of logβ_{110} = logK_1 (~5.6) are the same, they are not influenced by the changes in the pK_as of the phosphinic acid group in the phosphinodipeptide series. These values are comparable with those for [Cu(GlyGly)]$^+$ (similar basicity of amine group) and lower than for [Cu(GlyGly(P))] where an additional interaction of basic phosphonate group was suggested.[7–9,10*b*] This supports the weak complexation mode *via* the phosphinic acid group mentioned above.

The loss of a proton from the amide moiety leads to [Cu(LH$_{-1}$)] species with similar spectral parameters to those in corresponding GlyGly[21–24] and GlyGly(P)[7–9] complexes where the co-ordination of amine and amide nitrogens and oxygen of the acid group is assumed. The complex is a dominant species in the pH region 5–8 in solutions with Cu^{2+} : GlyGly(P^R) = 1 : 1. However, the ligands are probably bound predominantly through amine and deprotonated amide nitrogen atoms (Scheme 2). An interaction through the phosphinate group is also assumed, becoming more important with increasing basicity of the group (see also below). Therefore, the pK_{CuL} values (see Table 3) increase in the order *tert*-Bu < Me ≈ Ph. Thus, like in the formation of [CuL], the participation of phosphinate in the coordination sphere and formation of the N_{amine}, N_{amide}, O_P-chelate is most favourable for the *tert*-butyl substituent. The binding mode is proved for [Cu(GlyGlyH$_{-1}$)] in the solid state[25] as well as in solution.[21–24] The phosphinic acid group is much more acidic than the carboxylic group and, consequently, exhibits a lower complexation ability for formation of the N_{amide}, *O*-chelate ring. As the abundance of the tricoordinated microspecies rises, the value of pK_{CuL} decreases due to the preference of the complex with two chelate rings.

Table 2 Stability constants (logβ_{pqr}) for complexes of phosphinic acid analogues of GlyGly (25 °C, I = 0.1 mol dm^{-3} KNO$_3$) with Cu^{2+}, Ni^{2+}, Zn^{2+} and Co^{2+}

Ion	Species	GlyGly(P^{Ph})	GlyGly(P^{Me})	GlyGly(P$^{t\text{-Bu}}$)
Cu^{2+}	[CuLH]$^{2+}$	9.77(3)	9.57(2)	9.23(4)
	[CuL]$^+$	5.68(1)	5.638(6)	5.60(1)
	[CuL$_2$]	9.89(2)	9.99(2)	10.1(1)
	[CuLH$_{-1}$]	0.057(7)	0.176(4)	0.874(4)
	[CuLH$_{-2}$]$^-$	−8.65(7)	—	−8.587(8)
	[CuL$_2$H$_{-1}$]$^-$	3.35(1)	3.427(9)	3.93(1)
	[CuL$_2$H$_{-2}$]$^{2-}$	−5.30(7)	−6.16(2)	−6.81(7)
Ni^{2+}	[NiLH]$^{2+}$	10.35(6)	9.32(3)	9.38(4)
	[NiL]$^+$	4.29(3)	4.087(8)	4.09(1)
	[NiL$_2$]	7.43(4)	7.27(1)	7.40(2)
Zn^{2+}	[ZnLH]$^{2+}$	10.21(5)	9.61(2)	9.89(2)
	[ZnL]$^+$	3.58(3)	3.571(8)	3.55(1)
	[ZnL$_2$]	6.40(3)	6.19(1)	6.34(2)
	[ZnLH$_{-2}$]$^-$	−13.27(4)	−13.50(2)	−13.39(2)
Co^{2+}	[CoLH]$^{2+}$	9.94(5)	9.61(2)	9.4(1)
	[CoL]$^+$	3.28(3)	3.20(2)	3.09(6)
	[CoL$_2$]	5.43(7)	5.79(7)	5.4(2)
	[CoL$_2$H$_{-1}$]$^-$	−3.64(7)	—	—

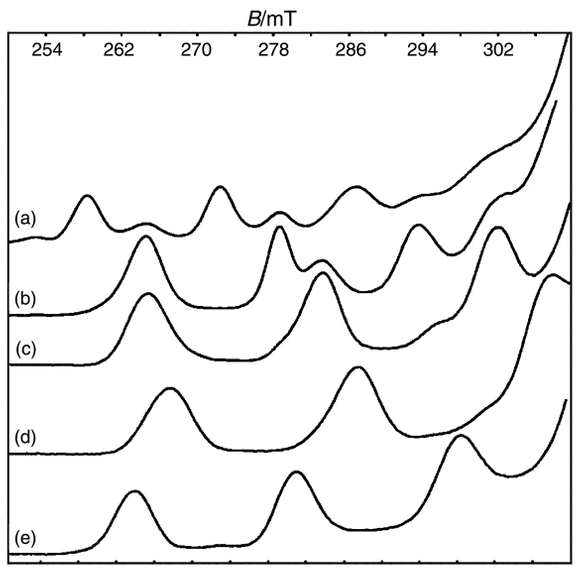


Fig. 3 EPR spectra of the Cu^{2+} and Gly–Gly(P^{Me}) system with varying pH and metal : ligand ratios [(a)–(d), 1 : 10; (e), 1 : 1.1; $c_{Cu^{2+}}$ = 0.005 mol dm^{-3}], (a) [CuL]$^+$, pH = 4.6, (NH_2, CO) co-ordination, (b) [CuL$_2$], pH = 6.0, (NH_2, CO)$_2$ co-ordination, (c) [CuL$_2$H$_{-1}$]$^-$, pH = 7.1, (NH_2, N$^{(-)}$, $PO_2CH_3^{(-)}$), (NH_2, CO) co-ordination, (d) [CuL$_2$H$_{-2}$]$^{2-}$, pH = 10.2, (NH_2, N$^{(-)}$)$_2$ co-ordination, (e) [CuLH$_{-1}$], pH = 7.2, (NH_2, N$^{(-)}$, $PO_2CH_3^{(-)}$) co-ordination.

Table 3 Comparison of stability constants and derived constants of phosphinic acid analogues of GlyGly and those of similar ligands

Ion	Constant[a]	GlyGly(P^{Ph})	GlyGly(P^{Me})	GlyGly(P$^{t\text{-Bu}}$)	GlyGly(P)[b]	GlyGly[c]	Gly[c]	GlyNH$_2$[c]	Gly(P)[c]
Cu^{2+}	pK_{CuLH}	4.09	3.93	3.63	5.18	3.76[d]	—	—	4.4
	pK_{CuL}	5.62	5.64	4.73	5.25	4.10	—	6.91	—
	pK_{CuL_2}	6.54	6.56	6.17	7.17	—	—	6.91	—
	p$K_{CuL_2H_{-1}}$	8.65	9.59	10.74	—	(12.04)[d]	—	8.12	—
	p$K_{CuLH_{-1}}$	8.71	—	9.46	9.89	9.35	—	—	8.5
	logK_1	5.68	5.64	5.60	6.86	5.55	8.15	5.35	8.10
	logK_2	4.21	4.35	4.50	4.53	—	6.85	4.20	6.55
Ni^{2+}	pK_{NiLH}	6.06	5.23	5.29	5.79	—	—	—	6.32
	logK_1	4.29	4.09	4.09	4.54	4.05	5.74	3.80	5.3
	logK_2	3.14	3.18	3.31	3.41	3.20	4.84	3.08	3.7
Zn^{2+}	pK_{ZnLH}	6.63	6.04	6.34	5.87	—	—	—	6.80
	logK_1	3.58	3.57	3.55	4.17	3.38	4.96	3.28	4.95
	logK_2	2.82	2.62	2.79	—	2.84	4.23	—	—
Co^{2+}	pK_{CoLH}	6.66	6.41	6.31	—	—	—	—	7.3
	logK_1	3.28	3.20	3.09	3.46	3.02	4.67	—	4.52
	logK_2	2.15	2.59	2.3	2.70	2.29	3.79	—	3.57

[a] pK_{MLqHr} means pK_a of the particular species; K_1 = [ML]/[M][L] and K_2 = [ML$_2$]/[ML][L]. [b] Ref. 8. [c] Ref. 19,20. [d] Ref. 21.

Table 4 EPR and electronic absorption data for systems of GlyGly(P^R) and similar ligands with Cu^{2+}

Ligand	Stoichiometry	Donor set	$g_{\|\|}$	$10^4 A_{\|\|}$/ cm^{-1}	λ_{max}[a]/ nm	ε[a]/dm^3 mol^{-1} cm^{-1}	Conditions[b] c_L/c_M; pH	Ref.
H_2O	$[Cu(H_2O)_6]^{2+}$		2.411	137	810	12		22
GlyGly(P^{Ph})	$[CuLH]^{2+}$	$(PO_2R^{(-)})$			~800	13	—	This work
	$[CuL]^+$	(NH_2, CO)	2.332	157	}	}	1.1/1; 4.6	
	$[CuL_2]$	$2(NH_2, CO)$	2.279	153	} 732	} 31	10/1; 6.0	
	$[CuLH_{-1}]$	$((NH_2, N^{(-)}, PO_2R^{(-)})$	2.250	180	647	76	1.1/1; 7.2	
	$[CuL_2H_{-1}]^-$	$(NH_2, N^{(-)}, PO_2R^{(-)}), (NH_2, CO)$	2.225	190	644	62	10/1; 8.1	
	$[CuLH_{-2}]^-$	$(NH_2, N^{(-)}, PO_2R^{(-)}), (OH^{(-)})$	—	—	637	61		
	$[CuL_2H_{-2}]^{2-}$	$2(NH_2, N^{(-)})$	2.193	208	533	57	10/1; 10.1	
GlyGly(P^{Me})	$[CuLH]^{2+}$	$(PO_2R^{(-)})$			~800	12		This work
	$[CuL]^+$	(NH_2, CO)	2.330	156	}	}	1.1/1; 5.1	
	$[CuL_2]$	$2(NH_2, CO)$	2.278	158	} 716	} 34	10/1; 6.0	
	$[CuLH_{-1}]$	$((NH_2, N^{(-)}, PO_2R^{(-)})$	2.252	184	648	71	1.1/1; 7.2	
	$[CuL_2H_{-1}]^-$	$(NH_2, N^{(-)}, PO_2R^{(-)}), (NH_2, CO)$	2.228	193	621	66	10/1; 8.1	
	$[CuLH_{-2}]^-$	$(NH_2, N^{(-)}, PO_2R^{(-)}), (OH^{(-)})$	—	—	—	—	—	
	$[CuL_2H_{-2}]^{2-}$	$2(NH_2, N^{(-)})$	2.192	208	551	40	10/1; 10.2	
GlyGly($P^{t\text{-}Bu}$)	$[CuLH]^{2+}$	$(PO_2R^{(-)})$			~800	12		This work
	$[CuL]^+$	(NH_2, CO)	2.328	157	}	}	1.1/1; 5.1	
	$[CuL_2]$	$2(NH_2, CO)$	—	—	} 693	} 48		
	$[CuLH_{-1}]$	$((NH_2, N^{(-)}, PO_2R^{(-)})$	2.25	2182	642	74	1.1/1; 6.5	
	$[CuL_2H_{-1}]^-$	$(NH_2, N^{(-)}, PO_2R^{(-)}), (NH_2, CO)$	2.229	172	611	59	2/1; 9.3	
	$[CuLH_{-2}]^-$	$(NH_2, N^{(-)}, PO_2R^{(-)}), (OH^{(-)})$	2.250	158	635	60	1.1/1; 11.2	
	$[CuL_2H_{-2}]^{2-}$	$2(NH_2, N^{(-)})$	2.190	211	537	45	2/1; 11.2	
GlyGly(P)	$[CuLH]^+$	$(PO_3H^{(-)})$	—	—	—	—	—-	This work
	$[CuL]^-$	(NH_2, CO)	2.328	157			1.1/1; 5.5	
	$[CuL_2]^{2-}$		—	—				
	$[CuLH_{-1}]^-$	$((NH_2, N^{(-)}, PO_3^{(2-)})$	2.246	187			1.1/1; 6.9	
	$[CuLH_{-2}]^{2-}$	$((NH_2, N^{(-)}, PO_3^{(2-)}) (OH^-)$	2.254	177			1.1/1; 10.3	
	$[CuL_2H_{-1}]^{3-}$	$(NH_2, N^{(-)}, PO_3^{(2-)}), (NH_2, CO)$	2.227	174			5/1; 8.3	
GlyGly	$[Cu(LH)_2]^{2+}$	$2(CO_2^{(-)})$	2.359	156			500/1; 3.80	22
	$[CuL]^+$	(NH_2, CO)	2.332	161			2/1; 4.10	
	$[CuLH_{-1}]$	$((NH_2, N^{(-)}, CO_2^{(-)})$	2.248	185	640	84	1.1/1; 6.90	
	$[CuLH_{-2}]^-$	$((NH_2, N^{(-)}, CO_2^{(-)}) (OH^{(-)})$	2.252	152	640	78	1.1/1; 10.30	
	$[CuL_2H_{-1}]^-$	$(NH_2, N^{(-)}, CO_2^{(-)}), (NH_2, CO)$	2.232	168	625	82	2/1; 8.60	
	$[CuLH_{-3}]^{2-}$	$(NH_2, N^{(-)}) 2(OH^{(-)})$	2.220	203	658	72	2/1; 12.90	
	$[CuL_2H_{-2}]^{2-}$	$2(NH_2, N^{(-)})$	2.200	206	550	44	500/1; 13.20	
$GlyNH_2$	$[CuL]^+$	(NH_2, CO)	2.331	161			3/1; 5.20	22
	$[CuL_2]^{2-}$	$2(NH_2, CO)$	2.276	171			3/1; 6.50	
	$[CuL_2H_{-1}]^+$	$(NH_2, N^{(-)}, (NH_2, CO)$	2.229	199			3/1; 7.70	
	$[CuL_2H_{-2}]^{2-}$	$2(NH_2, N^{(-)})$	2.194	203	528	52	3/1; 10.20	

[a] Values of λ_{max} and ε of phosphinic acid analogues of GlyGly are taken from calculation of stability constants using OPIUM (see Experimental section for details). [b] For EPR measurement only.

Precipitation of $Cu(OH)_2$ was observed when further increasing $-\log[H^+]$ to about 6 in the systems with the metal : ligand molar ratio 1 : 1 for GlyGly(P^{Ph}) and GlyGly(P^{Me}). EPR indicates that $[Cu(H_{-1}L)_2]^{2-}$ is the only EPR-active species (due to the increase in the ligand : metal ratio) in such alkaline solutions (pH > 9). However, for the Cu(II) GlyGly(P^{Ph}) system, the spectrophotometry indicates species $[Cu(LH_{-1})(OH)]^-$ for $-\log[H^+]$ above 10 and metal : ligand ratio 1 : 2 (Fig. 4). Therefore, the species has been included in the calculations. A different behaviour was found in the system with GlyGly($P^{t\text{-}Bu}$). Precipitation of $Cu(OH)_2$ was observed in more alkaline solution at $-\log[H^+]$ above 10, and for the metal : ligand ratio 1 : 2; the solution was blue up to very high values of $-\log[H^+]$ (see below). For GlyGly($P^{t\text{-}Bu}$), we suggest the formation of a hydroxo species $[Cu(LH_{-1})(OH)]^-$ with structure similar to the corresponding GlyGly complex[21–24] on the basis of EPR spectral parameters and $pK_{CuLH_{-1}}$. The species exhibits (N_{amine},N_{amide},O_P) tridentate dipeptide coordination with the last equatorial position occupied by the hydroxide anion. The presence of the hydroxo complex again supports the higher abundance of microspecies with tridentate coordination mode for GlyGly($P^{t\text{-}Bu}$). Such complexation stabilises Cu^{2+} ion against basic hydrolysis and, therefore, the hydroxo complex can be observed similarly in the systems with more basic ligands GlyGly[19] and GlyGly(P).[7,8]

In solutions with higher ligand : metal ratios, complexes with Cu : L = 1 : 2 are easily formed. In slightly acidic solution, complex $[CuL_2]$ is highly abundant. We suggest the (N_{amine}, $O_{peptide}$)$_2$ coordination mode (Scheme 2) on the basis of comparison of $g_{||}$ and $A_{||}$ with the $[Cu(GlyNH_2)_2]^{2+}$ complex.[22] The corresponding species was not found in the Cu^{2+}–GlyGly system; however it is present in Cu^{2+}–GlyGly(P) (see below). Values of $\log K_2$ (see Table 3) rise slightly with increasing basicity of the phosphinodipeptide. Therefore, some interaction with the phosphinate group (a seven-membered ring) is assumed, similarly to GlyGly(P). The species is present in the same $-\log[H^+]$ range as $[Cu(LH_{-1})]$. The phenomenon is more pronounced for GlyGly(P^{Ph}) and GlyGly(P^{Me}), which exhibit a lower ability of the phosphinate group to coordinate Cu^{2+}. The observation is illustrated by the difference in distribution diagrams (Figs. 1 and 2).

In neutral solution, the $[Cu(L)(LH_{-1})]^-$ species is formed. Based on similarities to the GlyGly containing system,[20–22,24] we suggest (Scheme 2) that a deprotonated ligand molecule is bound in equatorial plane through the amine and amide nitrogen atoms and, partially, through the phosphinate oxygen atom

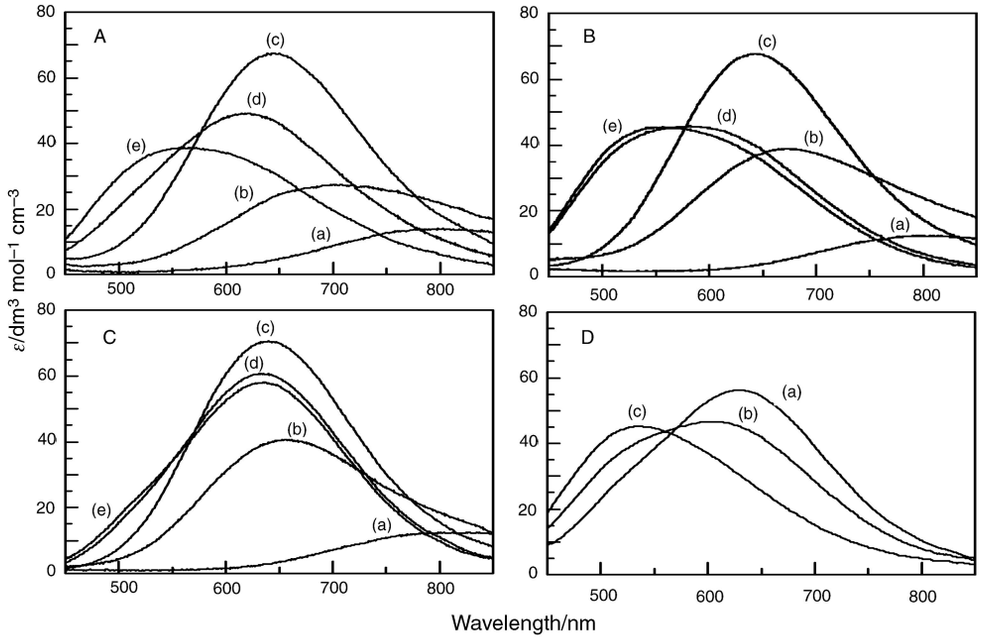
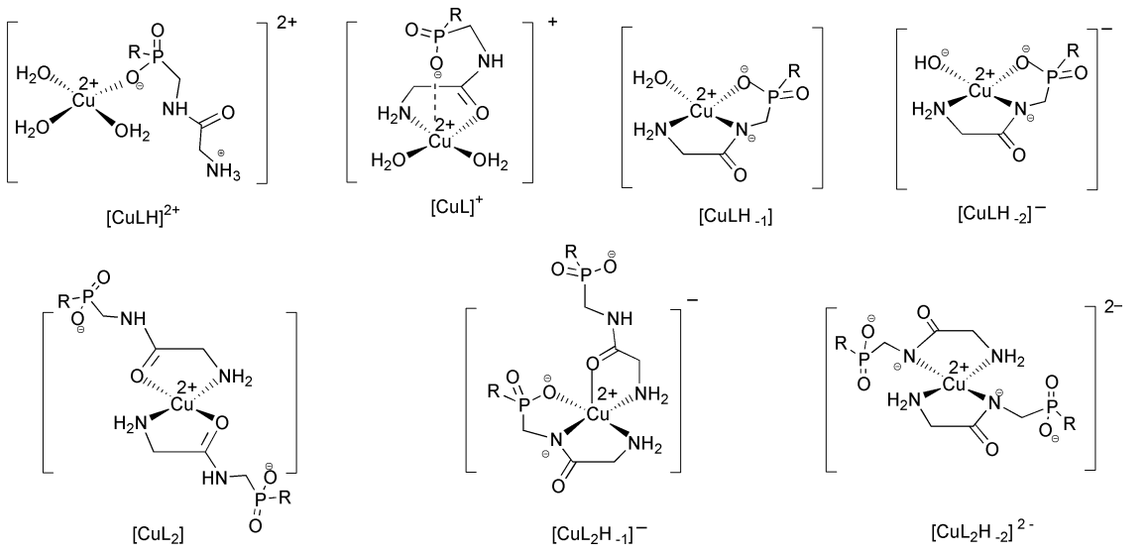


Fig. 4 A, Absorption spectra of Cu^{2+}–GlyGly(P^{Me}) system in molar ratio 1 : 2 (c_L = 0.005 mol dm^{-3}, c_{Cu} = 0.0025 mol dm^{-3}) at −log[H^+] 3.0 (a), 4.6 (b), 7.4 (c), 10.1 (d), 11 (e). B, Absorption spectra of Cu^{2+}–GlyGly(P^{Ph}) system in molar ratio 1 : 2 (c_L = 0.005 mol dm^{-3}, c_{Cu} = 0.0025 mol dm^{-3}) at −log[H^+] 2.5 (a), 5.1 (b), 7.7 (c), 10.2 (d), 11 (e). C, Absorption spectra of Cu^{2+}–GlyGly($P^{t\text{-}Bu}$) system in molar ratio 1 : 2 (c_L = 0.005 mol dm^{-3}, c_{Cu} = 0.0025 mol dm^{-3}) at −log[H^+] 2.5 (a), 4.7 (b), 7.4 (c), 10.1 (d), 11 (e). D, Absorption spectra of Cu^{2+}–GlyGly($P^{t\text{-}Bu}$) system at 1 : 2 (a), 1 : 5 (b), 1 : 10 (c) ligand to metal ratios (−log[H^+] 12.5, c_{Cu} = 0.005 mol dm^{-3}).



Scheme 2 Tentative structures of the species formed in systems Cu^{2+}–GlyGly(P^R), R = Ph, Me, *tert*-Bu, at different metal : ligand ratios and pH values.

[in the case of GlyGly($P^{t\text{-}Bu}$)]. The second ligand molecule is bound by the amine nitrogen atom in the equatorial plane and by the amide oxygen atom in axial position. The values of pK_{CuL_2} are almost the same and very close to the corresponding value for $GlyNH_2$ (see Table 2 and below).

The most surprising result is the very easy formation of purple complex $[Cu(LH_{-1})_2]^{2-}$, in which the $(N_{amine}, N_{amide})_2$ coordination is suggested. The corresponding species $[Cu(GlyGlyH_{-1})_2]^{2-}$ is formed only with the metal : ligand ratio as high as 1 : 500 and pH above 12.[21–23,26,27] In the systems with GlyGly(P^{Ph}) and GlyGly(P^{Me}), the species is formed even at the Cu^{2+}/dipeptide ratio 1 : 2 and −log[H^+] above 9. However, for GlyGly($P^{t\text{-}Bu}$), the complex is significantly present mainly at metal : ligand ratios lower than 1 : 5 and at pH above 11 (based on absorption and EPR spectra). The values of the dissociation constant $pK_{CuL_2H_{-1}}$ (Table 3) substantially increase in the order of substituents Ph < Me < *tert*-Bu, which is opposite to that observed for pK_{CuL} and can be explained in the same way. If we assume a large extent of didentate coordination in $[Cu(LH_{-1})]$ [for GlyGly(P^{Ph}) and GlyGly(P^{Me})], then, with a ligand excess, the second ligand molecule is very easily incorporated in the equatorial plane (with the same coordination mode).

Parameters of absorption spectra for the species discussed above are comparable with those for GlyGly and $GlyNH_2$. Absorption parameters (λ_{max}) of complexes of carboxylic amino acids, their oligopeptides, and similar compounds can be estimated.[28] Such estimations are based on contributions of donor atoms in equatorial positions. Using the equations published,[28] we tried to calculate λ_{max} for $[Cu(LH_{-1})_2]^{2-}$, where the coordination mode is the same for both kinds of dipeptides. The agreement is good for R = Ph and *t*-Bu ($\Delta\lambda_{max}$ = 4 and 8 nm) but poor for R = Me ($\Delta\lambda_{max}$ = 22 nm). These differences are caused by an influence of phosphinate moieties on the amide nitrogen atom. From the results, we cannot estimate coefficient(s) for phosphinate group(s) themselves and, therefore, cannot calculate λ_{max} for the other species (*e.g.* $[Cu(LH_{-1})]$). In

addition, such calculations are complicated by the partial co-ordination of phosphinate and/or by axial co-ordination as discussed above.

Cu^{2+}–GlyGly(P) system

To compare the spectral parameters of Cu^{2+} complexes, EPR spectra were measured in the Cu^{2+}–GlyGly(P) system (Table 4). The EPR measurements confirmed the model proposed previously,[8] with the exception of a higher abundance of the protonated complexes. In addition to the $[CuLH]^{2+}$ found by potentiometry, EPR spectra detected additional $[Cu(LH)_2]$ and $[Cu(L)(LH)]^-$ species. In these species the protons are bound to oxygen atoms of the phosphonate groups and the coordination sphere consists of amine nitrogen and peptide oxygen atoms (forming a five-membered chelate ring), possibly with an additional interaction through the deprotonated oxygen atom of a phosphonate moiety. The same coordination mode is suggested for [CuL] species. All other species detected in the Cu^{2+}–GlyGly(P) system have the same coordination environment as the corresponding species with GlyGly. The complex $[Cu(LH_{-1})_2]^{2-}$, characteristic of phosphinodipeptides, was not detected by EPR under the experimental conditions used (L : M = 5 : 1).

Complexation in systems with phosphinodipeptides and Co^{2+}, Ni^{2+} and Zn^{2+}

In these systems, the best model involves protonated complexes $[M(LH)]^{2+}$, $[ML]^+$and $[ML_2]$ species and, for Zn^{2+}, the hydroxo complex $[ZnL(OH)_2]^-$ (Table 2). In the protonated complexes, the ligands should be co-ordinated through phosphinate groups and, possibly, also by the oxygen atom of the carbonyl group (with formation of a seven-membered ring) as suggested by the pK_{MLH} values of the complexes slightly lower than the amine pK_2 of the free ligands. The species were not found in GlyGly systems. For Zn^{2+} systems, such an observation can explain strong binding of phosphinic oligopeptides in the active centre of some metalloenzymes[29] as the ligands are able to interact with the metal ion also only through the phosphinate group. The complexes $[ML]^+$ have comparable stability to those of GlyGly (Table 3) and we can assume a similar co-ordination sphere through the amine group and peptide oxygen atom. With higher $-\log[H^+]$, $[ML_2]$ species is formed to a low extent, followed by precipitation of metal hydroxides (Co^{2+} and Ni^{2+}). In the case of Zn^{2+}, we could titrate the systems to $-\log[H^+]$ about 11 and, thus, hydroxo species are included in the model. In contrast to the systems with GlyGly, the deprotonation and simultaneous coordination of the amide-peptide moiety were not observed in any system with Ni^{2+} or Co^{2+}, probably due to instability of the tridentate (N_{amine}, O_{amide}, O_P) coordinated species and precipitation of the hydroxide.

Conclusions

The systems containing the phosphinic acid analogues of GlyGly and biogenic transition metal ions were investigated in solution by potentiometry and spectral methods. The acidity and coordination ability of the phosphinic acid group depend on the substituents on the phosphorus atom. The *tert*-butylphosphinic acid group is the most basic in the series of phosphinodipeptides studied and thus the complexing properties of GlyGly($P^{t\text{-}Bu}$) are similar to those observed for GlyGly. However, even in this dipeptide, the deprotonation of the amide–peptide moiety was not observed in systems with Ni^{2+} or Co^{2+} due to instability of the tridentate (N_{amine}, O_{amide}, O_P) coordinated species. On the other hand, the low basicity of phenyl and methylphosphinic acid groups results in the formation of $[Cu(N_{amine}, N_{amide})_2]^{2-}$ complexes. The chemical model found for systems with Cu^{2+} was confirmed by EPR measurements.

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