Copper(II) Complexes of Ligands containing both Aminocarboxylate and Aminophosphinate Moieties

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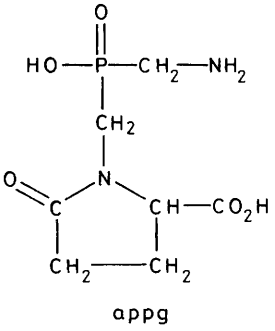
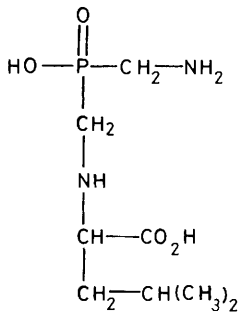
Spectroscopic (visible, e.s.r., and n.m.r.) and pH-metric studies were made of the proton and copper(II) complexes of *N*-[(aminomethyl)hydroxophosphorylmethyl]-pyroglutamic acid (-5-oxo-L-proline) and -leucine at 25 °C and I = 0.2 mol dm^{-3} (KCl). It was found that both ligands have an ambidentate character; complex formation starts at the amino acid end of the molecules then, at higher pH, the aminophosphinate moiety also takes part in co-ordination. The bidentate co-ordination ability of the leucine residue, and the monodentate co-ordination of the pyroglutamate residue, make the former ligand much more able to bind the metal ion.

Phosphonic and phosphinic acid analogues of essential amino acids are of considerable interest because of their biological activity.[1,2] In many cases, this is related to their effective inhibitory effect on various (metallo)enzymes having amino acid substrates.

In this work, the complex-forming properties of two compounds containing both aminocarboxylate and aminophosphinate moieties were studied: *N*-[(aminomethyl)hydroxophosphorylmethyl]-pyroglutamic acid (-5-oxo-L-proline) (appg) and -leucine (apl). The stoicheiometries and stabilities of the proton and copper(II) complexes of the two ligands, and the proton and metal binding sites in the complexes, were determined *via* potentiometric and spectral measurements.



appg



apl

Experimental

The ligands were prepared from (*N*-benzyloxycarbonyl)-methane(chloromethyl)phosphinic acid[3] and the ethyl ester of the respective amino acid by a condensation reaction in the presence of base, then by standard deprotection of the blocking groups. The exact concentrations of the solutions were measured by the Gran method.[4]

The stability constants of the proton and copper (II) complexes of the ligands were determined by pH-metric titration of 5-cm^3 samples in the range pH 3—10. The ligand concentration was 4 × 10^{-3} mol dm^{-3}, the metal ion:ligand ratios were 0:1, 1:1, 1:2, or 1:4, and the ionic strength was adjusted to 0.2 mol dm^{-3} with KCl. Titrations were performed with a KOH solution of known concentration (*ca.* 0.2 mol dm^{-3}). These measurements were made on a Radiometer pHM 64 instrument with a GK2301 combined electrode. The electrode system was calibrated by the method of Irving *et al.*[5]

The proton dissociation microconstants of apl were determined by pD–n.m.r. titration in D_2O with a Brucker WP 200 SY impulse FT spectrometer, as described earlier.[6]

Visible absorption spectra were recorded with a Beckman UV5240 spectrophotometer, while e.s.r. spectral measurements were carried out on a RADIOPAN SE/X spectrometer in *X*-band (9.3 GHz) at 120 K.

The concentration stability constants were calculated from the pH-metric titration curves by means of the PSEQUAD computer program.[7]

Results and Discussion

The acid dissociation macroconstants of the ligands are listed in Table 1. In the pH range studied (2—10) appg contains two (CO_2H and NH_3^+), while apl contains three (CO_2H, NH_2^+, and NH_3^+) dissociable protons (A^{2-} refers to the fully deprotonated form of the ligand in both cases). The pK, which can be attributed to the dissociation of the PO(OH) group, is < 1.0.

Similarly to other diamines,[8] the dissociation processes of the primary and secondary ammonium groups of apl overlap one another and thus the values of pk_2 and pk_3 cannot be ascribed unambiguously to one or the other process. The dissociation microconstants characteristic of the acidities of the individual groups were determined by selective monitoring of the dissociation of the secondary ammonium group *via* the pH dependence of the chemical shift of the α-CH proton of the ligand. This proton is distant enough from the other ammonium group to be used as a probe for the dissociation of the secondary ammonium group. The microconstants obtained in D_2O were converted into pk values valid for aqueous solution by taking

into account the isotope effect as described earlier.[6,9] It can be seen from Table 1 that for apl the secondary ammonium group is more acidic than the primary one, due to the electron-withdrawing effect of the aminophosphinate moiety. However, the overlap between the two dissociation processes is relatively small (see k_1/k_2 values in Table 1).

The titration curves for the copper(II)–ligand systems were evaluated by assuming various speciation models. The best fits between the measured and calculated titration curves were obtained by assuming the species given in Table 2. The fitting parameter[6] was 0.0033 cm^3 for the copper(II)–appg system (139 titration points) and 0.0042 cm^3 for the copper(II)–apl system (120 points). When the less 'important' species $[CuA_2]^{2-}$ was omitted the goodness of fit worsened by about 40% to 0.0048 and 0.0060 cm^3, respectively. Other species, such as $[CuAH_{-2}]^{2-}$ and $[CuA_2H]^-$, were rejected by the computer program.

The Figure shows the concentration distribution curves for the complexes formed in the systems studied. The main difference in the complex-forming abilities of the two ligands comes from the fact that pyroglutamic acid does not contain a secondary amino group which could be involved in the metal ion binding, *i.e.* no N,N co-ordinated complexes can be formed with appg. Both ligands form a protonated complex $[Cu(HA)]^+$ by co-ordinating to metal ion at the amino acid moiety, while the terminal NH_3^+ group is protonated. In the case of apl, this results in the formation of a five-membered chelate ring with a N,O bonding mode, while in the case of appg only monodentate co-ordination of the carboxylate is possible at the pyroglutamate moiety. Visible and e.s.r. spectral data confirm the formation of these species. The very low *d–d* transition energy and the e.s.r. parameters (small $A_{\parallel}$ and large $g_{\parallel}$) obtained for the $[Cu(HA)]^+$ complex for appg, when compared with the respective values for apl (see Table 2) clearly indicate the co-ordination of one nitrogen in the latter case and only oxygen(s) involvement in the metal ion binding in the former case.[10] The deprotonation of $[Cu(HA)]^+$ in the range pH 3–6 is definitely accompanied by a structural rearrangement. In the species [CuA], appg binds to copper(II) at the aminophosphinate moiety, forming a five-membered N,O chelate ring. This bonding mode is about three orders of magnitude less stable than that involving aminophosphonate,[11] due to the much lower basicity of the phosphinate group as compared with that of phosphonate. By

Table 1. Dissociation macro- (pK) and micro-constants (pk) of the ligands at 25 °C and I = 0.2 mol dm^{-3} (KCl)

appg	In H_2O	In D_2O
pK_{CO_2H}	2.79 ± 0.02	
$pK_{NH_3^+}$	8.19 ± 0.01	
apl		
pK_{CO_2H}	1.98 ± 0.05	
$pK_{NH_2^+}$	6.55 ± 0.01	6.97 ± 0.02
$pK_{NH_3^+}$	8.82 ± 0.01	9.32 ± 0.02
$pk_1(NH_2^+)$	6.62 ± 0.04	7.04 ± 0.03
$pk_2(NH_3^+)$	7.39 ± 0.04	7.82 ± 0.04
pk_{21}	7.98 ± 0.04	8.47 ± 0.03
pk_{12}	8.75 ± 0.04	9.25 ± 0.03
k_1/k_2	5.89	6.03

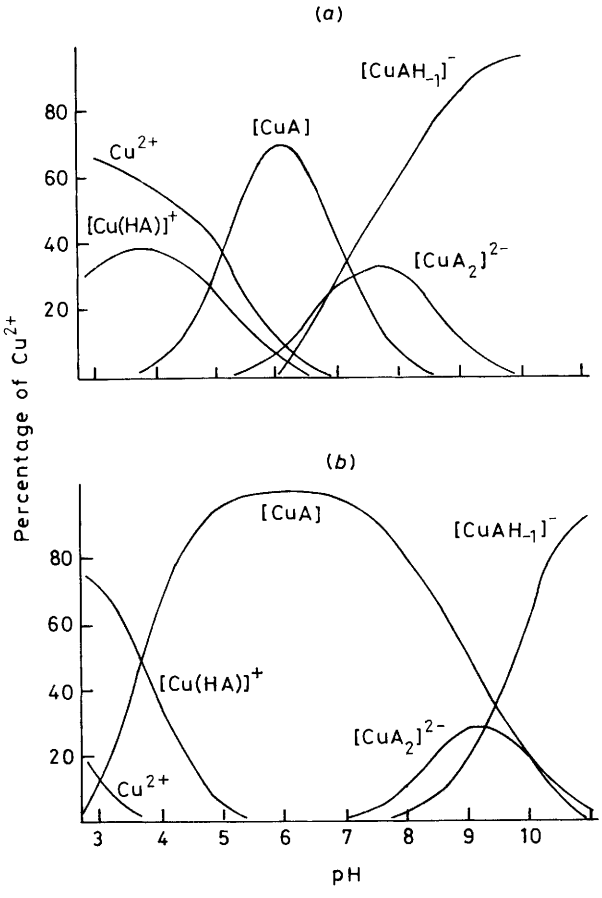


Figure. Concentration distribution of the complexes formed in the copper(II)-appg (*a*) and -apl (*b*) systems as a function of pH; c_{Cu} = 0.002, c_{ligand} = 0.004 mol dm^{-3}

Table 2. Stability constants (log β_{pqr}) and spectral data for copper(II) complexes of the ligands at 25 °C and I = 0.2 mol dm^{-3} (KCl), $\beta_{pqr} = [M_pA_qH_r]/[M]^p[A]^q[H]^r$

	appg					apl				
Complex	log β	$\lambda_{max.}$	ε	$g_{\parallel}$	$A_{\parallel}$	log β	$\lambda_{max.}$	ε	$g_{\parallel}$	$A_{\parallel}$
$[Cu(HA)]^+$	10.55 ± 0.03	750	25	2.348	134	15.79 ± 0.02	720	50	2.273	166
[CuA]	5.66 ± 0.02	720	30	2.330	134	12.08 ± 0.02	667	61	2.248	181
$[CuAH_{-1}]^-$	−1.46 ± 0.03	683	39	2.295	136	2.60 ± 0.03	650	74	2.244	181
$[CuA_2]^{2-}$	9.55 ± 0.06					14.91 ± 0.07				

	log β[a]		log β[a]
$Cu^{2+} + HA^- \rightleftharpoons [Cu(HA)]^+$	2.36(6.97)	$[Cu(HA)]^+ \rightleftharpoons [CuA] + H^+$	−4.89(−3.71)
$[CuA] \rightleftharpoons [CuAH_{-1}]^- + H^+$	−7.12(−9.48)	$[CuA] + A^{2-} \rightleftharpoons [CuA_2]^{2-}$	3.89(2.83)[b]

[a] Values in parentheses are for the complexes containing apl. [b] Log(K_{CuA}/K_{CuA_2}) 1.77(appg), 4.14(apl).

deprotonation of the terminal NH_3^+, apl can co-ordinate in a tridentate manner *via* the phosphinate and the two amino groups, forming a (5,5)-membered joined chelate system. Quadridentate co-ordination of the ligand including the simultaneous binding of the carboxylate can be assumed. This preferred bonding mode is reflected in the enhanced stability of the complex [$\log \beta_{CuA}$ is even higher than that of 2,3-diaminopropionic acid (10.62)[12] where two five-membered joined chelate rings are formed with N,N,O co-ordination]. The e.s.r. parameters and *d–d* transition energy obtained for the [CuA] complex for apl (see Table 2) indicate very clearly the involvement of two nitrogens in the co-ordination. The spectroscopic data ($\lambda_{max.}$ and $g_{\parallel}$ values) for [CuA] for appg support the co-ordination of one nitrogen only. The lower value of $A_{\parallel}$ may suggest some distortion of the tetragonal symmetry around the metal ion.[13] As the pH is raised, the dissociation of a co-ordinated water molecule or (in the case of an excess of ligand) the N,O co-ordination of a second ligand molecule takes place, with the formation of complexes $[CuAH_{-1}]^-$ {or more precisely $[CuA(OH)]^-$} and $[CuA_2]^{2-}$, respectively. These processes, however, are strongly hindered for apl, because of the tri- or quadri-dentate equatorial co-ordination of the ligand in the complex [CuA]. This is reflected in the higher pK_{CuA} and $\log (K_{CuA}/K_{CuA_2})$ values as compared with those for appg. Accordingly, the spectral data show only minor changes for the copper(II)–apl system.

Acknowledgements

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