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THE EFFECT OF SIDE CHAIN DONOR GROUPS ON THE COORDINATION ABILITY OF THE BIS(IMIDAZOL-2-YL) LIGANDS

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ABSTRACT

The results on the copper(II) complexes of amino acid derivatives containing the chelating bis(imidazol-2-yl) residues are summarized. The stoichiometries, stability constants and structures of complexes were determined by potentiometric, UV-VIS and EPR spectroscopic methods. The data reveal, that the bis(imidazol-2-yl) group is the main binding site in very acidic solution in all systems studied. This coordination mode changes in higher pH only in case, if the ligand has free terminal amino group in chelatable position with amide and imidazole nitrogen atoms and behaving as an anchor induces the deprotonation and coordination of amide nitrogen. For amino acids derivatives this process results in formation of dimeric complexes via imidazole bridge. The deprotonation of the imidazole N(1)H group at higher pH leads to the formation of di- or polynuclear species with negatively charged imidazolato groups.

INTRODUCTION

The N(3) donor atom of imidazole rings is specially preferable binding sites of metalloenzymes. Metal ions in the active centre of enzymes are bound very often by two or more imidazole rings [1-3] and in these cases the tree-dimensional structures of the macromolecules make possible the coordination of the different side chain donor atoms to same metal ion. The active centre of these metalloenzymes can be mimicked by ligands containing two imidazole rings linked via methylene group.

On the other hand various metalloenzymes contain the imidazole moiety as a bridging ligand, e.g. in CuZn-superoxide dismutase, where both nitrogen atoms of the negatively charged imidazolato residue take part in metal bridging [4].

In our group the 3d metal ion (first of all copper(II)) complexes of numerous ligands containing bis(imidazol-2-yl) residues were studied by potentiometric, UV-VIS and EPR spectroscopic techniques in the last ten years [5-9]. The investigations of the

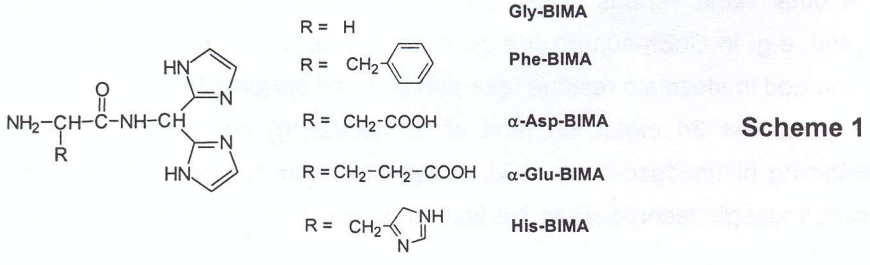
simplest ligands of this group (bis(imidazol-2-yl)methane, bis(imidazol-2-yl)methylamine, bis(imidazol-2-yl)propionic acid) [5] and some tripeptide derivatives with protected terminal amino group [7] reveal that the two imidazole nitrogen atoms forming a six-membered chelate is a stable binding site for the metal ions studied (Cu(II), Zn(II), Ni(II)). The potential donor atoms of the amino acid or peptide chain connected to the bis(imidazol-2-yl) groups, however, is able to change this coordination mode in the case, if the ligand has free terminal amino group in chelatable position with amide and imidazole nitrogen atoms and the formation of various mono- and polynuclear complexes is characteristic of basic solution [6,8,9]. The effect of the different side chain donor atoms of the amino acids chain in the bis(imidazol-2-yl) ligands are summarized in this paper.

EXPERIMENTAL

The procedure for the preparation of bis(imidazol-2-yl) ligands (Scheme 1) has already been reported elsewhere [10]. The purity of the ligands was checked by chromatographic, ^{1}H NMR and potentiometric measurements. The stability constants of the proton and copper(II) complexes of the ligands (log β_{pqr} for $[Cu_pH_qL_r]$) were determined by potentiometric titrations in aqueous solution (I = 0.2 mol dm^{-3} KCl, T = 298 K). Experimental details of the pH-metric measurements and calculation of the equilibrium parameters have been reported previously [5-9]. The structures of the various species formed in solution and the metal binding sites of the ligands were proved by UV-VIS (Hewlett Packard HP 8453 spectrophotometer) and EPR (Varian E-9 spectrometer) spectroscopic techniques [5-9].

RESULTS AND DISCUSSION

The studied five amino acid derivatives were Gly-BIMA, Phe-BIMA, α-Asp-BIMA, α-Glu-BIMA and His-BIMA (Scheme 1), in which the terminal amino group, amide- and bis(imidazol-2-yl) nitrogen atoms are in chelatable position. For α-Asp-BIMA and His-BIMA the amino nitrogen atom and carboxylate or histidine imidazole group, respectively, also make possible the coordination of metal ion.



Scheme 1

Table 1. Stability constants of proton and copper(II) complexes of amino acid derivatives (I = 0.2 mol dm^3 KCl, T = 298 K)

Species	Gly-BIMA	Phe-BIMA	α-Glu-BIMA	α-Asp-BIMA	His-BIMA
HL	7.95(1)	7.17(1)	7.53(1)	7.48(1)	7.28(1)
H_2L	13.46(1)	12.45(1)	13.05(2)	12.97(2)	13.09(2)
H_3L	16.68(1)	15.54(1)	16.79(3)	16.29(3)	17.62(2)
H_4L	—	—	19.48(4)	18.61(5)	20.23(4)
$[CuH_4L_2]$	—	—	37.46(7)	—	37.20(5)
$[CuH_3L_2]$	—	—	34.01(8)	—	33.12(9)
$[CuH_2L_2]$	31.64(9)	28.89(8)	29.84(5)	29.04(9)	28.51(9)
$[CuHL_2]$	—	—	—	23.1(4)	22.71(1)
$[CuL_2]$	18.97(3)	—	—	—	16.1(1)
$[CuH_{-1}L_2]$	11.12(6)	—	—	8.7(9)	8.8(1)
$[CuH_2L]$	—	—	19.97(2)	—	19.29(9)
[CuHL]	17.11(9)	15.44(8)	16.38	15.63(3)	—
$[CuH_{-2}L]$	–0.92(4)	–2.41(8)	—	—	-3.52(10)
$[Cu_2L_2]$	—	—	—	25.3(2)	25.68(4)
$[Cu_2H_{-1}L_2]$	—	—	—	—	19.7(1)
$[Cu_2H_{-2}L_2]$	18.43(2)		16.70(3)	15.5(1)	13.58(8)
$[Cu_2H_{-3}L_2]$	—	14.9(2)	8.26(12)	—	5.4(2)
$[Cu_2H_{-4}L_2]$	—	—	–0.71(7)	–2.3(2)	–3.5(1)
$[Cu_3L_2H_{-4}]$	—	—	8.0(1)	9.3(1)	8.53(8)
$[Cu_2L]$	—	—	—	—	15.36(4)
$[Cu_2H_{-1}L]$	—	—	10.06(5)	9.92(7)	—

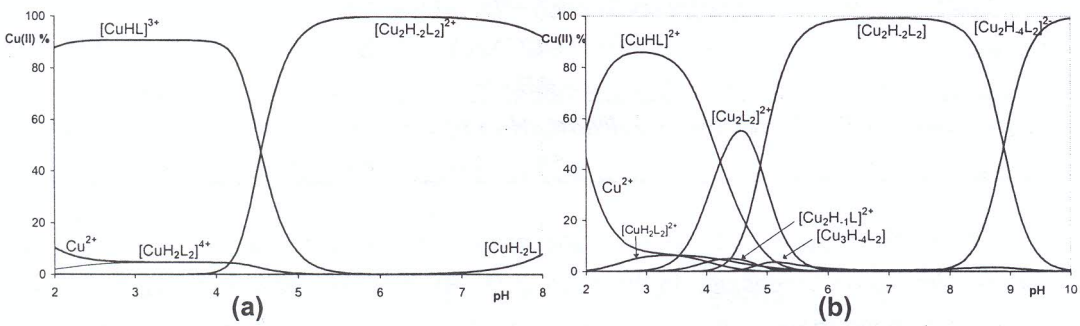


Figure 1. Species distribution of complexes formed in the copper(II)–Gly-BIMA **(a)** and α-Asp-BIMA **(b)** as a function of pH ($c_{Cu(II)} = c_L = 4 \cdot 10^{-3}$ mol dm^{-3})

It is clear from the Table 1 that the highest p*K* value belongs to the deprotonation of the ammonium group and the protonation of the bis(imidazol-2-yl) residues always

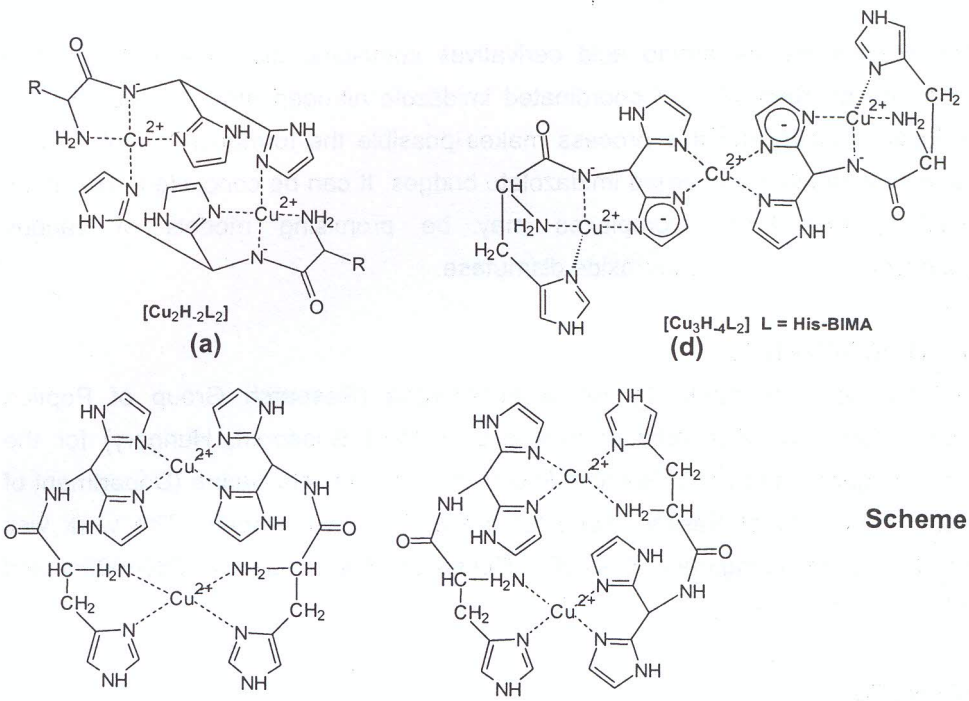
takes place in the acidic pH range. In the case of ligands containing side chain donor group the protonation equilibria of bis(imidazol-2-yl) nitrogen atoms and the carboxylate or histidine group significantly overlaps.

The stoichiometry of copper(II) complexes and the distribution curves depicted on Figure 1 show that the complex formation processes are very similar in all five cases in acidic pH range. Mono- and bis-(ligand) complexes are formed, in which two or four imidazole nitrogen are coordinated, respectively, and the terminal amino and carboxylate or histidine groups are protonated. The spectroscopic parameters support these structures (Table 2).

Table 2 The UV-VIS and EPR spectroscopic parameters of copper(II) complexes (λ_{max} [nm] (ϵ [dm^3 mol^{-1} cm^{-1}]; $A_{\parallel}$ [10^{-4} cm^{-1}], d_{Cu-Cu} [pm])

	Gly-BIMA	Phe-BIMA	α-Glu-BIMA	α-Asp-BIMA	His-BIMA
[CuHL]/ [CuH_2L], [N(Im), N(Im)] coordination					
λ_{max}	690 (31)	679 (29)	695 (27)	690 (29)	683 (32)
$g_{\parallel}$	2.299	2.303	2.297	2.298	2.298
$A_{\parallel}$	175·	166·	169	171	176
[CuH_2L_2], 2x[N(Im), N(Im)] coordination					
λ_{max}	590 (34)	588 (27)	596 (65)	601 (42)	605 (50)
$g_{\parallel}$	2.236	2.235	2.232	2.234	2.234
$A_{\parallel}$	201	192	193	193	197
[$Cu_2H_{-2}L_2$], [NH_2, N^-, N(Im)] coordination + Im bridge					
λ_{max}	595 (91)	588 (99)	589 (104)	592 (98)	592 (111)
d_{Cu-Cu}	390	393	397	393	397
[$Cu_2H_{-4}L_2$], [NH_2, N^-, N(Im)] coordination + Im bridge					
λ_{max}	—	—	562 (100)	567 (95)	565 (117)
d_{Cu-Cu}	—	—	385	386	384
[$Cu_3L_2H_{-4}$], [NH_2, N^-, N(Im)] or 2x[N(Im), N^-(Im)] coordination					
λ_{max}	—	—	592 (124)	615 (46)	580 (84)

The deprotonation of terminal amino group, however, is accompanied by new complex formation processes. In the case of Gy-BIMA, Phe-BIMA and α-Glu-BIMA is parallel with deprotonation and coordination of amide nitrogen, resulting in a dinuclear species [$Cu_2H_{-2}L_2$] (Scheme 2a). It is supported by the line broading of EPR spectra obtained above pH 6 in equimolar solution. For α-Asp-BIMA and His-BIMA the line broading of EPR spectra of equimolar solution appears at lower pH (pH > 4.5). It corresponds the formation of isomeric [Cu_2L_2] species, in which both end of the ligands are coordinated resulting in ligand bridged dimeric structures (Scheme 2b, c).



Scheme 2

These structures cannot prevent the deprotonation of amide nitrogen and formation of $[Cu_2H_{-2}L_2]$.The Cu–Cu distances calculated from the perpendicular region of the EPR spectra are very similar for the $[Cu_2H_{-2}L_2]$ of all five ligands suggesting the same structure with imidazole bridging. In basic solution the dimeric complex are broken by hydrolysis and $[CuH_{-2}L]$ mixed hydroxo complexes are formed in the Cu(II)–Gly-BIMA and –Phe-BIMA systems (Figure 1a). In the case of *α*-Glu-BIMA, *α*-Asp-BIMA and His-BIMA, however, dinuclear species are present in the whole alkali pH range (Figure 1b) and new extra base consuming processes take place in equimolar solution above pH 10. The potentiometric data can be fitted by assumption of $[Cu_2H_{-3}L_2]$ and/or $[Cu_2H_{-4}L_2]$ complexes. A slight blue shift of absorption band and a small decrease of calculated Cu–Cu distances suggest the deprotonation of the pyrrole type N(1)H group. Moreover, the deprotonated imidazole N(1) donor atoms create a new chelating site for copper(II) ion. In agreement with this expectation, there is an extra base consuming process between pH 5 and 6 in the solution containing copper(II)-ligand in 3:2 ratio resulting in the trinuclear species $[Cu_3H_{-4}L_2]$ (Scheme 2d).

The differences between the reaction of the three ligands (*α*-Glu-BIMA, *α*-Asp-BIMA, His-BIMA) and the other two ligands (Gly-BIMA, Phe-BIMA) can probably be explained by the weak axial interaction of the side chain carboxylate or histidine imidizole groups, respectively.

The studies on the amino acid derivatives containing bis(imidazol-2-yl) group show that the deprotonation of coordinated imidazole nitrogen atoms takes place in slightly basic solution and this process makes possible the formation of polynuclear complexes via negatively charged imidazolato bridges. It can be concluded from these observations, that these complexes may be promising models of various metalloenzymes, e.g. CuZn superoxide dismutase.

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REFERENCES

1. I. Bertini, C. Luchinat and A. Scozzafava, *Struct. Bonding*, Springer-Verlag, New York, 48 (1982) 45.
2. F. A. Qyichio and W. N. Lipscomb, *Adv. Protein Chem.*, 25 (1971) 1.
3. P. M. Collman, H. C. Freeman, J. M. Guss, M. Murata, V. A. Norris, J. A. M. Ramshwa and M. P. Venkatapp, *Nature*, 272 (1978) 319.
4. J. A. Tainer, E. D. Getzoff, K. M. Beem, J. S. Richardson and D. C. Richardson, *J. Mol. Biol.*, 160 (1982) 181.
5. K. Várnagy, I. Sóvágó, K. Ágoston, Z. Likó, H. Süli-Vargha, D. Sanna and G. Micera, *J. Chem. Soc., Dalton Trans.*, (1994) 2939.
6. K. Várnagy, I. Sóvágó, W. Goll, H. Süli-Vargha, G. Micera and D. Sanna, *Inorg. Chim. Acta,* 283 (1998) 233.
7. K. Várnagy, I. Sóvágó, H. Süli-Vargha, D. Sanna and G. Micera, *J. Inorg. Biochem.,* 81 (2000) 35.
8. K. Ősz, K. Várnagy, H. Süli-Vargha, D. Sanna, G. Micera and I. Sóvágó, *Inorg. Chim. Acta,* 339 (2002) 373.
9. K. Ősz, K. Várnagy, H. Süli-Vargha, D. Sanna, G. Micera and I. Sóvágó, *J. Chem. Soc., Dalton Trans* (in press).
10. Zs. Likó and H. Süli-Vargha, *Tetrahedron Lett.*, 34 (1993) 1673.