Stereoselectivity in the Formation of Ternary Histidinatocopper(II) Complexes in the Biological pH Range

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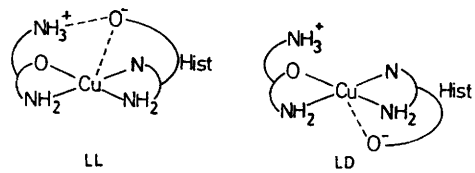
Summary In the biological pH range marked stereoselectivity is present in the formation of ternary histidinato-copper complexes containing ligands (A) with positively charged, protonated sidechains; there is preferential formation of the complex containing ligands of the same optical hand, *e.g.* Cu(L-hist)(L-HA).

IN an earlier communication we noted that stereoselectivity in the formation of bis binary complexes of Cu^{2+} with amino-acids was rare but that it was present in mixed complexes with histidine and bidentate amino-acids containing suitably orientated aromatic rings such as phenylalanine and tryptophan.[1] An extension of this study to cover mixed complexes of the type (D- or L-histidine)-Cu/Ni/Zn-(L-amino-acid, A), where A contains a third donor centre, demonstrates a particular form of stereoselectivity with copper which is strongly pH dependent and is probably of biochemical importance. Amino-acids studied include lysine, ornithine, arginine, 2,4-diaminobutyric acid, *Im*-benzylhistidine, *N*-benzyl-*Im*-benzylhistidine, aspartic acid, and glutamic acid. A selection of results is shown in the Table. The precision quoted is, in our opinion, a realistic measure of the relative values of the constants.

It has been generally accepted that there is insignificant stereoselectivity in the formation of bis-histidinato-copper(II) complexes[2,3] although Ritsma found that the species CuH(D or L-hist)$_2$ is marginally more stable than the mixed monoprotonated species CuH(L-hist)(D-hist) by $0{\cdot}050 \pm 0{\cdot}012$ log units.[4] We have confirmed this observation by studying the system: Cu^{2+} + histidine + substituted histidines, and suggest that it is a real difference. The concentration of the monoprotonated bis complex is very pH dependent and makes a maximum contribution in



FIGURE

the intermediate pH region. The other ligands studied (with the exception of glutamic and aspartic acids) can simulate this monoprotonated form of histidine in that they possess a side chain which is protonated in the intermediate pH region to give a positively charged substituent group. The presence of such a cationic group in the side chain has been found to favour the formation of the optically pure

ternary complex of formula Cu(L-hist)(L-HA)$^+$ {*i.e.* the 1111 species, where 1111 corresponds to the subscripts *wxyz* in $[Cu_w(hist)_xA_yH_z]$} when the length of the side chain exceeds three atoms. As the pH is increased the amino-acid becomes deprotonated to give the 1110 species, which does not have the positively charged side-chain. Such a species showed no detectable stereoselectivity, although in some cases a rearrangement of co-ordination centres is thought to take place. Stereoselectivity was found with side chains containing both protonated amine and imidazole groups.

groups are *cis*, and with the racemic LD complex when they are *trans*. Presumably both isomers occur in solution and microconstants for both contribute towards the measured constants but the stereoselectivity found may be explained if the species with *cis* co-ordination is favoured thermodynamically. Apart from the results reported here there is no definitive evidence to favour one particular isomer over the other. However, it is interesting to note that co-ordination is *cis* in crystalline L-histidinato-L-threoninato-copper.[6] The absence of stereoselectivity in the 1111 species with 2,4-diaminobutyric acid could result from the

TABLE. Formation constants for the species $[M_w(D/L\text{-hist})_x(L\text{-A})_yH_z$ at 25° and $I = 0{\cdot}10$M (log β_{wxyz} values, standard deviations in parentheses).

Amino-acid (L-A)	Species	Cu^{2+} D-Hist	Cu^{2+} L-Hist	$\Delta\log\beta$
Lysine	1111	27·785(10)	27·883(1)	−0·098(14)
	1110	17·13(2)	17·12(2)	0
Arginine	1111	29·126(4)	29·250(6)	−0·124(7)
Ornithine	1111	27·373(7)	27·493(9)	−0·120(12)
	1110	17·24(2)	17·26(2)	0
2,4-Diaminobutyric acid	1111	26·745(6)	26·750(4)	0
Im-Benz-hist	1111	23·993(1)	24·111(2)	−0·118(3)
	1110	18·587(1)	18·586(2)	0
N-Benz-*Im*-benz-hist	1111	22·730(10)	22·979(8)	−0·249(13)
	1110	17·41(2)	17·24(2)	0·17(3)
Aspartic acid	1112	26·40(9)	26·58(5)	−0·18(10)
	1111	22·786(10)	22·854(11)	−0·068(15)
	1110	18·266(4)	18·183(4)	0·083(6)
Glutamic acid	1112	26·68(2)	26·66(2)	0
	1111	22·697(6)	22·702(5)	0
	1110	17·864(2)	17·858(2)	0

		Ni^{2+}			Zn^{2+}		
		D-Hist	L-Hist	$\Delta\log\beta$	D-Hist	L-Hist	$\Delta\log\beta$
Im-Benz-hist	1110	16·523(3)	16·060(8)	0·457(9)	12·583(9)	12·273(11)	0·310(15)
N-benz-*Im*-benz-hist	1110	16·106(7)	15·360(10)	0·746(12)	12·282(6)	12·037(8)	0·245(10)

In the pH range at which this stereoselectivity is apparent, the histidine is probably acting as a terdentate ligand to Cu^{2+} with two nitrogen donors in the equatorial plane and the carboxy-oxygen taking up a weakly bonded apical position.[4,5] It is therefore suggested that the explanation for stereoselectivity in such mixed monoprotonated complexes lies in electronic interaction between the $\equiv NH^+$ group of the side-chain of A and the weakly co-ordinated $-CO_2^-$ group of the histidine as demonstrated in the Figure.

The ternary complex in which these charged groups are on the same side of the co-ordination plane will tend to be stabilized relative to the opposite configuration. This occurs with the LL ternary complex when the $-NH_2$ donor inability of the short side-chain to hydrogen bond effectively with the histidyl carboxy-group, in spite of its positive charge.

When the side-chain contains a negatively charged group (*e.g.* CO_2^-) the opposite effect should be found with the deprotonated form of the ligand. Weak apical co-ordination would make the second ligand partially tridentate and, assuming a predominance of *cis* co-ordination, the racemic DL ternary complex should be preferred in the 1110 species. This was found to be the case when the second ligand was aspartic acid.

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