Complex Formation and Stereoselectivity in the Ternary Systems Copper(II)–D/L-Histidine–L-Amino-acids †

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Formation constants of the parent and ternary complexes of general formula [Cu^{II}(D/L-HisO)(L-A)] (HisO = histidinate; HA = phenylalanine, tryptophan, valine, proline, methionine, leucine, serine, threonine, 2,4-diaminobutyric acid, ornithine, lysine, arginine, glutamic acid, aspartic acid, glycylvaline, glycylphenylalanine, or valyl-L-valine) have been measured potentiometrically at 25.0 °C and I = 0.10 mol dm^{-3} ($K[NO_3]$). The ternary systems of Cu^{II} and the substituted histidines N^3-benzyl-L-histidine and $N^{\alpha}N^3$-dibenzyl-L-histidine with D- and L-tryptophan, phenylalanine, valine, and glutamic acid have also been studied. The ternary complexes containing tryptophan and phenylalanine are unusually stable, complexes containing ligands of opposite chirality being significantly more stable than those with ligands of the same chirality. With ornithine, lysine, and arginine, stereoselectivity is significant in monoprotonated ternary complexes, those with ligands of the same chirality being more stable. This stereoselectivity is at a maximum at *ca.* pH 6 and vanishes when the proton is ionized. With aspartic acid, stereoselectivity is significant in the non-protonated ternary complex, that with ligands of opposite chirality being more stable. The stereoselectivity found may be explained by simple electrostatic interactions.

THE formation of ternary complexes between copper(II) and various amino-acids has received intermittent attention over a number of years. Early workers were unable to obtain reliable results for the formation constants of ternary complexes as a result of computational difficulties, but the advent of more advanced computer programs enabled a body of reliable data to be built up. This has resulted in some recent reviews of the factors influencing the stability of ternary complexes, particularly with Cu^{II}.[1,2] Martin and Paris[3] made some of the earliest studies of ternary copper(II)-amino-acid complexes and Heureux and Martell[4] first detected the general tendency for ternary complex formation to be favoured when the ligands are dissimilar, one containing nitrogen-donor centres and the other oxygen. This concept, and a quantitative measure of the stabilization of ternary complexes, has been developed by Sigel and his co-workers.[1,5] Stabilization of ternary complexes of amino-acids relative to the parent complexes has also been reported by Perrin and Sharma[6] and Petit-Ramel and Paris.[7] From studies of both formation constants and enthalpy changes for the formation of ternary complexes. Gergely and his co-workers[8,9] demonstrated that, while the stabilities of ternary copper(II)–aliphatic amino-acid complexes corresponded approximately to those expected statistically, ternary copper(II)–aliphatic–aromatic amino-acid complexes were more stable than expected, suggesting copper(II)–aromatic ring interactions. This has been supported by circular dichroism (c.d.) studies.[10] Potential-energy calculations have demonstrated that stabilization of ternary complexes is to be expected as a result of enthalpy changes[11] as well as statistical factors.[12] Nagypal *et al.*[13] showed that the formation of ternary complexes is influenced by changes in ionic strength when it involves a change in charge.

Stereoselectivity in the formation of ternary complexes has received much less attention, although some results have been reported. Thin-layer chromatography has demonstrated the importance of the ternary complex [Cu(HisO)(ThrO)] ([HisO]$^-$ = histidinate, [ThrO]$^-$ = threoninate) and the system has been studied in detail by Freeman and Martin.[14] They also determined the structure of crystals of the complex by *X*-ray diffraction[15] and reported that formation of the ternary complex was not stereoselective.

Leach and Angelici[16] measured the formation constants of a number of mixed-ligand complexes of Cu^{II} containing synthetic substituted amino-acids when seeking evidence for stereoselectivity. They found that (*N*-carboxymethyl-L-valinato)copper(II) generally formed more stable complexes with L-amino-acids than with the D-antiomers. This observation was used to partially resolve racemic mixtures of amino-acids by column chromatography.[17] The work was extended to show that complexes of Cu^{II} with *N*-carboxymethyl-L-valine, -L-isoleucine, -L-serine, *N*-benzyl-*N*-carboxy-

† No reprints available.

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methyl-L-alanine, and -L-leucine all showed a preference for L-amino-acids.[18] The origin of this stereoselectivity was thought to be terdentate co-ordination by the substituted amino-acids, the effects being greatest for the *N*-benzyl-substituted ligands. Stereoselectivity was also found in the ternary copper(II) complexes of *N*-(2-pyridylmethyl)-L-aspartic acid and *N*-[(6-methyl-2-pyridyl)methyl]-L-aspartic acid with alanine (Ala), phenylalanine (Phe), tryptophan (Trp), threonine (Thr), leucine (Leu), and valine (Val), favouring the L-isomer.[19] The largest effects were observed with Phe and Trp.

Davankov and Rogozhin [20] showed that a chromatographic column incorporating L-proline (Pro) has a higher affinity for D-amino-acids in the presence of Cu^{II} than the L-isomers, and that [Cu(PhCH$_2$-L-ProO)-(PhCH$_2$-D-ProO)] is more stable than [Cu(PhCH$_2$-L-ProO)$_2$]. This work was extended to demonstrate considerable stereoselectivity in the ternary complexes [Cu(PhCH$_2$-L-ProO)(D/L-ValO)] and [Cu(PhCH$_2$-L-ProO)(D/L-ProO)].[21]

Stereoselectivity has been detected in the parent and mixed complexes of a small number of amino-acids, particularly histidine [22] and substituted histidines.[23] With Co^{II}, Ni^{II}, and Zn^{II}, stereoselectivity was found in the neutral bis complexes, the *meso*-complex [M(L-HisO)(D-HisO)] being favoured in all cases. With copper, however, the neutral bis complex did not show any stereoselectivity in its formation constants although it was detected in the protonated species such as [Cu-(HisO)$_2$H]$^+$. This absence of stereoselectivity was found to be the result of coincidental cancelling between effects of the enthalpy and entropy changes.

In this work we report the results of a study of the formation constants of the ternary complexes of a range of amino-acids with Cu^{II}. In particular we have studied the ternary complexes of D-and L-histidine (His) and a number of L-amino-acids with Cu^{II} in order to detect stereoselectivity in ternary complexes containing naturally occurring amino-acids and their D-enantiomers rather than synthetic ligands containing bulky substituents such as the benzyl group.

EXPERIMENTAL

Amino-acids were obtained from the Sigma Chemical Co. (SIGMA grade).

Complex-formation constants were calculated from potentiometric-titration curves obtained as described previously.[24] The glass electrode was calibrated in terms of hydrogen-ion concentrations and titrations were carried out at 25 °C with an ionic background of 0.10 mol dm^{-3} K[NO$_3$]. Calculations were made with the aid of the MINIQUAD computer program.[25]

RESULTS AND DISCUSSION

When a metal ion is in equilibrium with two different ligands, A and B, both of which can form bis complexes with the metal, equilibria (1)—(4) forming simple non-protonated bis complexes will be present. Following

$$[MA] + A \rightleftharpoons [MA_2] \quad (1)$$

$$[MA] + B \rightleftharpoons [MAB] \quad (2)$$

$$[MB] + A \rightleftharpoons [MAB] \quad (3)$$

$$[MB] + B \rightleftharpoons [MB_2] \quad (4)$$

Sigel,[1] two equilibrium constants involving ternary complexes can be defined, $\Delta \log K$ [equation (5)] which

$$\Delta \log K = \log K_{MAB}{}^{MA} - \log K_{MB}{}^{M} = \log K_{MAB}{}^{MB} - \log K_{MA}{}^{M} \quad (5)$$

refers to reaction (6) and $\log X$ [equation (7)] which

$$[MA] + [MB] \rightleftharpoons [MAB] + M \quad (6)$$

$$\log X = 2\log\beta_{MAB} - \log\beta_{MA_2} - \log\beta_{MB_2} \quad (7)$$

refers to reaction (8). Thus $\Delta \log K$ is a measure of the

$$[MA_2] + [MB_2] \rightleftharpoons 2[MAB] \quad (8)$$

affinity that B has for bonding to the aquated metal ion and to the complex [MA]. Since more co-ordination sites are available for bonding the first ligand to a metal ion than for the second ligand, $\Delta \log K$ should, in general, be negative. With Cu^{II} usually having a co-ordination number of four, the expected value for $\Delta \log K$ would be -0.6, values markedly greater than this demonstrating a stabilization of the ternary complex. In fact, positive values mean that B prefers to bond to the complex [MA] rather than to the solvated metal ion. $\text{Log}X$ is really a disproportionation constant. Statistically, a value of log4 (0.6) is to be expected so that values for $\log X$ of >0.6 suggest stabilization of the ternary complexes. The value of $\log X$ is clearly dependent on the stabilities of the binary bis complexes and, since these bis complexes are not intermediates in the formation of the ternary complexes, the value of $\log X$ may not truly reflect the stability of the mixed complex. However, $\log X$ will tend to be less dependent than $\Delta \log K$ on differences in the charges of the ligands A and B. Hence the choice between using $\Delta \log K$ and $\log X$ to give a measure of the stabilization of ternary complexes will depend on the particular comparisons being made.[1]

Stereoselective effects may be expressed quantitatively by comparing the formation constants of ternary complexes which are identical apart from the optical hand of one of the two ligands, *e.g.* a direct comparison of logβ[Cu(L-HisO)(L-ValO)] and logβ[Cu(D-HisO)(L-ValO)] such that equation (9) applies, *i.e.* a positive

$$\Delta \log\beta = \log\beta(\text{D-HisO}) - \log\beta(\text{L-HisO}) \quad (9)$$

[18] R. V. Snyder and R. J. Angelici, *J. Inorg. Nuclear Chem.*, 1973, **35**, 523.
[19] R. Nakon, R. R. Rechani, and R. J. Angelici, *Inorg. Chem.*, 1973, **12**, 2431.
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[25] P. Gans, A. Sabatini, and A. Vacca, *Inorg. Chim. Acta*, 1976, **18**, 237.

value for $\Delta\log\beta$ indicates that the ternary complex containing ligands of opposite chirality is the more stable.

Metal-complex-formation constants for the parent complexes studied in this work are reported in Table 1 and measured values for the formation constants of the ternary complexes are in Table 2. In each case the subscripts to the formation constants refer to w, x, y, and z in the complexes $[M_wA_xB_yH_z]$, $[M_wA_xH_z]$, and $[M_wB_yH_z]$.

TABLE 1

Complex-formation constants ($\log\beta_{xyz}$) for the parent binary complexes of amino-acids with Cu^{II} at 25.0 °C and I = 0.10 mol dm^{-3} ($K[NO_3]$). Standard deviations are given in parentheses

	Amino-acids					
xyz	His	bzh	dbzh	Asp	Glu	
011	9.128(1)	9.206(1)	8.471(4)	9.832(4)	9.746(3)	
012	15.180(3)	14.731(3)	13.98(1)	13.596(9)	13.988(7)	
013	16.76(2)	16.67(2)	15.95(3)	15.69(1)	16.27(1)	
111	14.089(5)	13.740(3)	12.46(4)	12.82(1)	12.73(1)	
122	27.56(1)	27.05(1)	25.34(6)	25.15(5)	25.18(3)	
121	23.883(2)	23.635(1)	21.02(6)	21.21(1)	20.57(2)	
110	10.111(1)	10.194(1)	8.958(3)	9.079(3)	8.545(2)	
120	18.078(3)	18.519(1)	16.76(1)	16.249(5)	15.222(7)	
	Phe	Trp	Val	Pro	Met	Leu
011	9.194(1)	9.312(1)	9.573(1)	10.515(2)	9.058(4)	9.703(1)
012	11.452(1)				11.21(1)	11.989(4)
110	7.931(1)	8.020(4)	8.049(5)	8.816(2)	7.849(3)	8.276(1)
120	14.834(1)	15.562(5)	14.913(7)	16.319(3)	14.529(4)	15.174(1)
	Ser	Thr	bipy	$H_2C_2O_4$	en	
011	9.073(3)	8.974(3)	4.503(1)	3.880(2)	9.976(1)	
012	11.024(8)	10.953(8)			17.148(2)	
110	7.858(3)	7.946(3)	8.10(2)	6.67(4)	10.523(1)	
120	14.428(3)	14.612(4)	13.44(2)	10.50(4)	19.505(2)	

For other amino-acids studied see: G. Brookes and L. D. Pettit, *J.C.S. Dalton*, 1976, 42.

TABLE 2

Complex-formation constants for the ternary complexes of D/L-histidinatocopper(II) with some normally bidentate amino-acids at 25.0 °C and I = 0.10 mol dm^{-3} ($K[NO_3]$). Standard deviations are given in parentheses

	L-Phe	L-Trp	L-Val	L-Leu
D-His				
$\log\beta_{1111}$	21.45(1)			22.2(2)
$\log\beta_{1110}$	17.699(8)	18.475(4)	17.546(3)	17.662(4)
$\log X$	2.49	3.31	2.10	2.07
$\Delta\log K$	−0.34	+0.34	−0.61	−0.72
L-His				
$\log\beta_{1111}$	21.44(1)			22.19(2)
$\log\beta_{1110}$	17.504(1)	18.003(4)	17.603(3)	17.692(4)
$\log X$	2.10	2.37	2.22	2.13
$\Delta\log K$	−0.54	−0.12	−0.55	−0.69
$\Delta\log\beta$	0.20	0.47	−0.06	−0.03

D (or L)-His (differences insignificant)

	L-Thr	L-Ser	L-Met	L-Pro
$\log\beta_{1111}$	21.43(4)			
$\log\beta_{1110}$	17.464(4)	17.20(1)	17.271(4)	18.105(6
$\log X$	2.24	1.90	1.94	1.81
$\Delta\log K$	−0.59	−0.77	−0.69	−0.82

The standard deviations quoted in the Tables do not include systematic errors and must not be taken, therefore, as being realistic estimates of the absolute accuracy of the constants. They do, however, indicate the relative precision of the results, and the importance of the particular species. This is because large calculated standard deviations usually apply to complexes which never contribute to a major extent to the equilibrium under the experimental conditions used.

Formation constants for the parent complexes (Table 1) were measured under identical experimental conditions to the constants for the ternary complexes to permit the reliable calculation of $\log X$ and $\Delta\log K$ values. No attempt was made to detect stereoselectivity in the parent bis complexes since, in all the systems, this aspect has been studied previously. In most cases the formation constants are close to comparable values reported in the literature but a few deserve special comment. With Phe and Trp the ratio $K_{110} : K_{120}$ is unusually small compared to values with other amino-acids. This has been noticed by other workers [26] and is of importance when considering possible stereoselectivity in the ternary complexes. Although the copper(II)–glutamic and –aspartic acid systems have been widely studied differing conclusions have been drawn. Some workers have not considered protonated complexes [27] while others disagree on their importance,[13,28] neglecting the protonated species $[Cu(HL)_2]$ and $[Cu(HL)L]$. The results reported here show that both of these complexes contribute between 3 and 5% in the range pH 3—4.5 in a 1 : 1 metal : ligand mixture. Omission of these species from calorimetric studies could therefore cause significant errors. A comparison of the values for $\log\beta_{110}$ in Table 1 suggests that glutamic acid bonds glycine-like whereas aspartic acid must be terdentate, in agreement with the findings of other workers.[13,29]

[26] J. L. Meyer and J. E. Bauman, *J. Chem. and Eng. Data*, 1970, **15**, 404.

[27] M. K. Singh and M. N. Srivastava, *J. Inorg. Nuclear Chem.*, 1973, **35**, 2433.

[28] J. H. Ritsma, G. A. Wiegers, and F. Jellinek, *Rec. Trav. chim.*, 1965, **84**, 1577.

[29] M. R. Harrison and F. J. C. Rossotti, *Chem. Comm.*, 1970, 175.

There is a wide variation in the literature values for log β_{110} and log β_{120} for the copper(II)–2,2′-bipyridyl and –oxalic acid systems. Computation of the results in the present study was confusing since two minima were found for each system, corresponding to the two varying pairs of values reported in the literature. Statistical fits for both pairs of constants were equally acceptable, *e.g.* for the copper(II)–2,2′-bipyridyl systems the values were:

	Model 1	Model 2
log β_{110}	6.69(2)	8.10(2)
log β_{120}	12.05(2)	13.44(2)
χ^2	18.0	27.7
R factor	0.002 5	0.002 1

By repeating the titrations using different metal : ligand ratios, model 2 was eventually selected. The ratio $K_{110} : K_{120}$ for model 2 is larger than may be expected. However, it is compatible with a change in co-ordination which is thought to take place as a result of steric factors when a second molecule of bipy is co-ordinated.[30]

Only two ternary species were formed in significant concentrations, the [MAB] species (1110) and the protonated complex $[MABH]^+$ (1111 species). This 1111 species did not appear to be present in all cases, and when present it was always of minor importance. For example, with Phe it reached a maximum concentration of *ca.* 6% at pH 4.5. Values calculated for the ternary complexes of Cu^{II} with D- and L-His and some L-amino-acids which are normally regarded as bidentate ligands are reported in Table 2. Values calculated for $\Delta\log K$ and $\log X$ are also included.

In all cases in Table 2 the values for $\log X$ are significantly greater than 0.6, suggesting that the ternary complexes are very stable relative to their binary analogues. However, the values for $\Delta\log K$ are generally *ca.* −0.6, the only exceptions being L-Phe (−0.34) and, particularly, L-Trp (+0.34), with the D-isomers showing smaller deviations from −0.6 (−0.53 and −0.12 respectively); Pro shows a significant opposite deviation (−0.82). In fact, the high values of $\log X$ are a reflection of the ratio of the stepwise formation constants for the binary Cu^{II}–His system, the value for log K_{110} − log $K_{120}{}^{110}$ (2.14) being much greater than expected statistically. This is, presumably, a result of the tridentate character of the $[HisO]^-$ ion. Values for $\Delta\log K$ indicate that only in the cases of Phe and Trp are the stabilities of the ternary complexes significantly greater than expected. The result for [Cu(D-HisO)(L-TrpO)] is particularly striking since it means that $[L\text{-TrpO}]^-$ bonds to $[Cu(D\text{-HisO})]^+$ in preference to Cu^{2+} (aq).

Stereoselectivity, as characterized by differences in stability between the complexes [Cu(D-HisO)(L-A)] and [Cu(L-HisO)(L-A)], was found to take two forms. With Phe and Trp, the *meso* ternary complex was significantly more stable than that containing ligands of the same chirality, *i.e.* log β_{1110}(D-HisO) − log β_{1110}(L-HisO) = $\Delta\log\beta_{1110}$ was positive. With Val and Leu the value for $\Delta\log\beta_{1110}$ was small and negative, although probably significant, while with Ser, Thr, Met, and Pro it was apparently zero, calculated values for the ternary species with D- and L-His being the same within three standard deviations. This confirms the findings of Freeman and Martin [14] for the Cu–His–Thr system. Titration curves for the ternary mixtures containing D- and L-His were reproducible to within 0.006 pH units over the range pH 4—8 when no stereoselectivity was detected. With Val, titration curves for the two isomers of His differed by up to 0.04 pH units ($\Delta\log\beta_{1110}$ 0.06) and with Phe and Trp the differences were up to 0.15 and 0.3 pH units respectively.

The common characteristic of the three amino-acids involved with this positive stereoselectivity is that all contain aromatic substituent groups, the stereoselectivity being of the same sign as that reported in the parent bis complexes of His with a number of metals.[22] Steric factors may play a significant role, but an alternative explanation which involves some sort of aromatic ring–copper(II) interactions is also possible as normally short interatomic distances between Cu^{II} and neighbouring phenyl rings have been detected in a number of complexes.[31] Such interaction is also supported by the relatively large values for the second stepwise formation constants of $[Cu(PheO)_2]$ and $[Cu(TrpO)_2]$.[26] If this interaction is present the ligands can be regarded as potentially tridentate making stereoselectivity more likely.

The formation constants for ternary complexes of $[Cu(D\text{- or }L\text{-HisO})]^+$ with a number of potentially tridentate L-amino-acids are given in Table 3. The amino-acids studied were L-2,4-diaminobutyric acid (dba), L-ornithine (Orn), L-lysine (Lys), L-arginine (Arg), L-glutamic acid (Glu), and L-aspartic acid (Asp). Two ternary species were generally present, the 1111 and 1110 species. With Glu and Asp the diprotonated 1112 complexes were also formed at low pH although in low concentrations only. As with the previous systems studied, titration curves were reproducible to 0.005 pH units and the solutions of D- and L-His had identical titration curves. The curves for the ternary system (Cu–D/L–His–L–Asp) differed by >0.07 pH units at 50% ternary complex formation and with the ω-amino-acids the curve differed by >0.1 pH units.

Values for $\Delta\log K_{1110}$ did not differ dramatically from the statistically expected value of −0.6 showing that there is no marked stabilization of the ternary complexes. Values for $\log X$ are again greater than expected statistically. The values for log $K_{1111}{}^{1100}$ for the ω-amino-acids follow the same trend as the stabilities of the parent mono complexes and the log K_{HL} values of the parent acids. This suggests that the mode of bonding is glycine-like in all the complexes. The monoprotonated

[30] C. K. Jørgensen, *Acta Chem. Scand.*, 1955, **9**, 1362; F. P. Dwyer, M. A. Goodwin, and E. C. Gyarfas, *Austral. J. Chem.*, 1963, **16**, 544.

[31] W. A. Franks and D. Van der Helm, *Acta Cryst.*, 1970, **B27**, 1299; D. Van der Helm and C. E. Tatsch, *ibid.*, 1972, **B28**, 2307.

1111 complexes are well defined in each case. The bonding site of this extra proton cannot be stated unambiguously since protonated forms of both His and the other amino-acids exist in appreciable concentrations over much of the titration curves. Stabilization of the ternary 1111 complexes of both aspartic and glutamic acid is apparent from both $\Delta\log K_{1111}$ and $\log X_{1111}$ values. The stability of such protonated ternary complexes may be explained by hydrogen bonding between the two ligands of the ternary species.

There is significant stereoselectivity in most of the ternary systems. With the ω-amino-acids (with the exception of dba) the monoprotonated ternary complexes containing ligands of the same chirality {*e.g.* [Cu(L-HisO)(L-OrnO)H]$^+$} are more stable than the *meso* isomers {*e.g.* [Cu(D-HisO)(L-OrnO)H]$^+$}. Stereoselectivity in the neutral ternary complexes was, however, insignificant. Stereoselectivity was also insignificant in the ternary complexes of Glu, but with Asp the opposite stereoselectivity to that with ω-amino-acids was found. The fully ionized *meso* complex [Cu(D-HisO)(L-AspO)] was more stable than that with both ligands of the same optical hand by 0.08 log units. In the monoprotonated complexes stereoselectivity was smaller, tending to favour ligands of the same chirality.

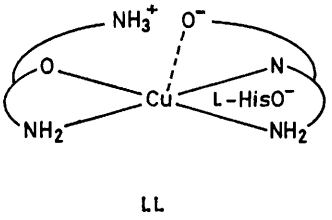
These results for the ω-amino-acids may be explained by an electrostatic interaction (hydrogen bonding) between the protonated ω-NH_3^+ side chain of the amino-acid and the CO_2^- group of the [HisO]$^-$ ion which can take up an apical position as shown. If the structures of the complexes in solution are similar to that found in the ternary complex [Cu(L-HisO)(L-ThrO)],[15] *i.e.* with the α-amino-groups *cis*, then the ω-NH_3^+ and the histidine CO_2^- groups are indeed on the same side of the copper(II) ion for ligands of the same chiralty. Insufficient flexibility in the shorter side chain of L-dba may account for the absence of stereoselectivity in its ternary complex with [Cu(HisO)]$^+$. Stereoselectivity in the deprotonated ternary complex with L-Asp, this time favouring the species having ligands of opposite chirality, is to be expected if the interactions shown above are significant. In this ternary complex the two negatively charged CO_2^- groups will be on the same side of the complex in [Cu(L-HisO)(L-AspO)] and so will tend to destabilize the species compared to the isomer [Cu(D-HisO)(L-AspO)] in which the CO_2^- groups are on opposite sides. Similar stabilization of complexes containing two ligands of the same optical hand has been found in [Cu(L-HisO)H]$^{2+}$,[22] and in protonated ternary complexes of [Cu(L-HisO)]$^+$ with some substituted histidine molecules.[23]

The concentration of these monoprotonated ternary complexes reaches a maximum at *ca.* pH 6, the mixed complex containing over half the bound copper. Such stereoselective complex formation could, therefore, have important biological implications and provide a possible mechanism for biological stereoselectivity.

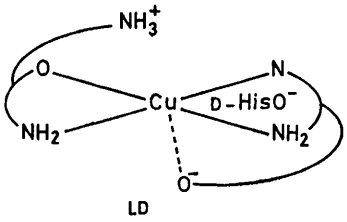
TABLE 3

Complex-formation constants for the ternary complexes of D/L-histidinatocopper(II) with some potentially tridentate amino-acids at 25.0 °C and I = 0.10 mol dm^{-3} (K[NO_3]). Standard deviations are given in parentheses

	L-dba	L-Orn	L-Lys	L-Arg	L-Glu	L-Asp
D-His						
$\log\beta_{1112}$					26.68(2)	26.40(9)
$\log\beta_{1111}$	26.745(6)	27.373(7)	27.78(1)	29.126(4)	22.697(6)	22.79(1)
$\log\beta_{1110}$		17.24(2)	17.12(2)		17.864(2)	18.266(4)
$\log X_{1111}$	2.21	2.18	2.04	2.02	2.12	2.33
$\Delta\log K_{1111}$	−0.50	−0.55	−0.61	−0.61		
$\Delta\log K_{1110}$					−0.79	−0.92
L-His						
$\log\beta_{1112}$						26.58(5)
$\log\beta_{1111}$		27.493(9)	27.883(1)	29.250(6)		22.85(1)
$\log\beta_{1110}$	As above	17.25(2)	17.12(2)		As above	18.183(4)
$\log X_{1111}$		2.42	2.23	2.27		2.03
$\Delta\log K_{1111}$		−0.43	−0.51	−0.48		
$\Delta\log K_{1110}$						−1.00
$\Delta\log\beta_{1111}$	0	−0.12	−0.10	−0.12	0	−0.06
$\Delta\log\beta_{1110}$		0	0		0	0.08



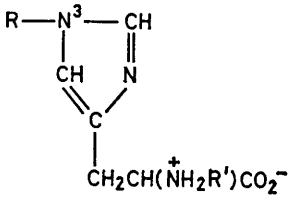
LL



LD

The results for stereoselectivity in the ternary complexes of [Cu(D/L-HisO)]$^+$ with L-amino-acids were checked by measuring the formation constants of ternary complexes of N^3-benzyl-L-histidine (bzh) and $N^\alpha N^3$-dibenzyl-L-histidine (dbzh) with Cu^{II} and D- and L-

amino-acids. Measured constants are given in Table 4. The L-isomers of the substituted histidines were used exclusively but stereoselectivity was studied by using



bzh R=$PhCH_2$, R'=H
dbzh R=R'=$PhCH_2$

both the D- and L-isomers of the other amino-acids. Protonated complexes were formed in some cases (111 species) but the maximum concentrations were <5% of the total metal bound. Values for log$X$ for dbzh were always lower than for bzh. This is a reflection of the smaller ratio of $K_{110}:K_{120}$ for the copper(II) complexes of dbzh. Values for both $\Delta\log K$ and log$X$ for the ternary systems with Phe and Trp indicate extremely stable ternary complexes. In particular Trp has a greater affinity for [Cu(dbzhO)]$^+$ and [Cu(bzhO)]$^+$ than for Cu^{2+}(aq) itself. The behaviour of these complexes, therefore, parallels very closely that of the His analogues.

As with His itself there is a large measure of stereoselectivity in the ternary complexes with Trp and Phe, favouring amino-acids of opposite chirality and being greatest for the Trp systems. The decreasing order of stereoselectivity with both Trp and Phe is bzh > His > dbzh. It is interesting to note that the stereoselectivity observed with bzh and Val is of opposite sign to that with Trp and Phe, again paralleling the Cu^{II}–His–Val system. Stereoselectivity appears to be insignificant in the Cu^{II}-Glu-bzh system but is appreciable in Cu^{II}-Glu-dbzh, favouring the ternary complex with amino-acids of opposite chirality. Again this parallels the results for the ternary complexes of Cu^{II}-Glu-His.

Ternary complexes of [Cu(D/L-HisO)]$^+$ with a number of dipeptides were also studied with the aim of determining the mode of bonding of simple dipeptides in ternary complexes as well as searching for stereoselectivity. Ternary complexes with diaminoethane (en) and 2,2'-bipyridyl (ligands with two nitrogen donors) and with oxalic acid (two oxygen donors) were also studied. The reason for including these ligands was to determine whether the complex [Cu(HisO)]$^+$ had discriminating properties towards the type of donor atoms presented by the second ligand in the ternary complex, using the arguments advanced by Sigel.[1] The results are given in Table 5 together with those for bzh with bipy for comparison.

With the dipeptides the precision of the calculated formation constants for the ternary complexes was lower than for amino-acids. The equilibria were very complicated in the region of the pH scale in which deprotonation of the peptide amide nitrogen atom in the presence of Cu^{II} normally takes place. No stereoselectivity was detected in the ternary systems with dipeptides, values with D- and L-His being identical to within two standard deviations. Stereoselectivity was not anticipated with the other ligands in Table 5 since they are not optically active.

In the binary complexes of Cu^{II} with dipeptides in the pH 5—9 region the major species is the 11—1 species in which the proton on the peptide nitrogen atom is ionized allowing formation of an amide–copper bond.[24]

TABLE 4

Complex-formation constants for the ternary complexes of L-bzh and L-dbzh with Cu^{II} and some L-amino-acids at 25.0 °C and I = 0.10 mol dm^{-3} (K[NO_3]). Standard deviations are given in parentheses

	L-bzh			L-dbzh		
	logβ_{1110}	log$X$	$\Delta\log K$	logβ_{1110}	log$X$	$\Delta\log K$
D-Trp	18.672(4)	3.19	0.45	17.289(6)	2.25	0.31
L-Trp	18.178(9)	2.20	−0.03	16.859(7)	1.39	−0.11
$\Delta\log\beta$	0.49			0.43		
D-Phe	18.003(1)	2.64	−0.09	16.624(5)	1.65	0.26
L-Phe	17.716(1)	2.00	−0.40	16.475(7)	1.35	−0.41
$\Delta\log\beta$	0.29			0.15		
D-Val	17.630(3)	1.75	−0.61	16.42(1)	1.17	−0.58
L-Val	17.689(6)	1.87	−0.55	16.42(1)	1.17	−0.58
$\Delta\log\beta$	−0.06			0		
D-Glu	18.019(6)	2.22	−0.72	16.759(3)	1.53	−0.74
L-Glu	18.018(6)	2.21	−0.71	16.640(4)	1.29	−0.86
$\Delta\log\beta$	0			0.12		

TABLE 5

Complex-formation constants for the ternary complexes of D/L-histidinatocopper(II) and some L-dipeptides, together with some related model complexes at 25.0 °C and I = 0.10 mol dm^{-3} (K[NO_3]). Standard deviations are given in parentheses

	Gly-L-Phe	Gly-L-Val	L-Val-L-Val
D (or L)-His			
logβ_{1110}	15.56(5)	15.10(9)	15.02(6)
log$\beta_{111\text{-}1}$	6.59(9)		
$\Delta\log K_{1110}$	−0.45	−0.78	−0.29
L-His			
	bipy	$H_2C_2O_4$	en
logβ_{1111}	21.62(1)	19.8(1)	
logβ_{1110}	16.291(7)	16.22(1)	19.24(1)
logX_{1110}	−0.32	3.86	0.91
$\Delta\log K_{1110}$	−1.92	−0.56	−1.38
L-bzh			
logβ_{1111}	21.79(5)		
logβ_{1110}	17.10(3)		
logX_{1110}	2.17		
$\Delta\log K_{1110}$	−1.19		

Ionization of this proton in ternary complexes of His is clearly of minor importance at pH <8 with Gly-L-Phe and could not be detected at pH <9 with L-Val-L-Val or Gly-L-Val. This is not surprising. Before ionization of the amide proton the dipeptides behave as comparatively weak bidentate ligands. Since $[HisO]^-$ bonds to Cu^{II} as a tridentate ligand, the driving force for ionization of the amide proton in the ternary complex with dipeptides must be drastically reduced.

The values of $\Delta\log K_{1110}$ for the Cu^{II}–$H_2C_2O_4$–L-His system indicate a stability for the ternary complex close to that expected statistically, but $\Delta\log K_{1110}$ for the ternary systems with en and particularly with bipy show that these ternary complexes are less stable than expected. The $[Cu(HisO)]^+$ complex does, therefore, have a preference for oxygen rather than nitrogen as donor group in the second ligand. The tendency is not as great as that shown by $[Cu(bipy)]^{2+}$ (the system studied by Sigel [1]), but it is clearly present and suggests that the $[HisO]^-$ ligand is bonding with two nitrogen donors in the equatorial plane. Values for $\Delta\log K_{1111}$, however, are much closer to −0.6 and suggest that the monoprotonated ligands bond through one nitrogen- and one oxygen-donor atoms. Values for $\Delta\log K_{1110}$ for the ternary complexes with dipeptides also suggest that the dipeptides are co-ordinating through one N and one O donor atom. It is not possible by this method, however, to tell whether the co-ordinated nitrogen is an imidazole or an amine nitrogen atom.

[7/760 *Received, 5th May,* 1977]