Stereoselectivity in the Formation of Mononuclear Complexes of Histidine and some Bivalent Metal ions †

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The formation constants of complexes of Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Pb^{2+}, and $[VO]^{2+}$ with D- and L-histidine have been measured at 25.0 °C and I = 0.10 mol dm^{-3} ($K[NO_3]$). The importance of protonated complexes in all the systems studied has been demonstrated and the structures of the various species are discussed. Thermodynamic stereoselectivity has been confirmed in the bis(histidinato)-complexes of Co^{2+}, Ni^{2+}, and Zn^{2+}, and has been also found in the monoprotonated bis(histidine) complexes of Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+}. Stereoselectivity as exhibited in the enthalpy change (ΔH) accompanying formation of bis(histidinato)cobalt(II) has been measured calorimetrically; ΔH for formation of the *meso*-bis complex is more favourable by 2.4 ± 0.2 kJ mol^{-1}.

HISTIDINE (His) shows more distinctive tridentate character than any other component amino acid of proteins, with the possible exception of cysteine (Cys). It therefore forms stable bis complexes with metal ions but has little tendency to form tris complexes. Since His contains an asymmetric centre, three unprotonated bis complexes are possible, [M(L-HisO)$_2$], [M(D-HisO)$_2$], and [M(L-HisO)(D-HisO)].‡ The first two complexes will have identical stabilities, while the last complex, containing ligands with opposite chiralities, is diastereoisomeric to them and could well have a different formation curve and a different stability.[1] Such stereoselectivity is negligible when the amino acid is bidentate or tridentate with the additional donor centre being weakly co-ordinating or ' hard ' [*e.g.* aspartic acid (Asp) or asparagine (Asn) [2,3]]. When the third centre has a ' soft ' character, such as sulphur in penicillamine, stereoselectivity is significant.[4] With His the third donor centre is the imidazole nitrogen atom and stereoselectivity has been detected in the formation of bis complexes with Co^{2+}, Ni^{2+}, and Zn^{2+}.[3,5,6] With Ni^{2+} and Zn^{2+} this stereoselectivity is the result of a more favourable enthalpy of formation of the mixed (*meso*) complex compared to the optically homogeneous species.[3] Complexes of Cu^{2+} with His are particularly interesting. Stereoselectivity is negligible in the formation constants of the bis complexes, [Cu(HisO)$_2$],[6,7] although calorimetric studies have shown a small but significant difference in the enthalpies of formation, the species [Cu(L-HisO)$_2$] being preferred to the *meso*-complex [Cu(L-HisO)(D-HisO)].[3] Such apparently contradictory results can be explained only by assuming a more favourable entropy change on formation of the *meso*-bis complex which exactly compensates for the less favourable enthalpy change for the reaction. As a result, the free-energy change on formation of the bis complexes indicates that there is negligible stereoselectivity. Complexes of Cu^{2+} with His are particularly important since they are included in 98% of the amino-acid complexes in blood plasma. Mixed copper complexes of His with other amino acids have recently been shown to form stereoselectively in the biological pH range, making a detailed study of this region important.[8]

At intermediate pH values the imidazole nitrogen atom is partially protonated (log K 6.09). As a result, equilibria of His with metal ions are complicated by the formation of partially protonated complexes and changes in co-ordination centres. In addition, polynuclear copper complexes have been detected at high pH.[9,10] Equilibria between Cu^{2+} and L-His have been studied in detail by a number of workers,[9-12] but studies with other metals have been less thorough and the formation of protonated complexes has generally been regarded as negligible.[9] As a result protonated species have been ignored in studies on the stereoselectivity of histidine complexes.[3,5,6] The donor centres of His change as the

† No reprints available.
‡ HisO = Histidinato(1−).

[1] A. T. Advani, H. M. N. H. Irving, and L. D. Pettit, *J. Chem. Soc.* (*A*), 1970, 2649.
[2] J. H. Ritsma, G. A. Wiegers, and F. Jellinek, *Rec. Trav. chim.*, 1965, **84**, 1577.
[3] D. S. Barnes and L. D. Pettit, *J. Inorg. Nuclear Chem.*, 1971, **33**, 2177.
[4] J. H. Ritsma and F. Jellinek, *Rec. Trav. chim.*, 1972, **91**, 923.
[5] J. H. Ritsma, J. C. Van de Grampel, and F. Jellinek, *Rec. Trav. chim.*, 1969, **88**, 411.
[6] P. J. Morris and R. B. Martin, *J. Inorg. Nuclear Chem.*, 1970, **32**, 2891.
[7] V. A. Davankov and P. R. Mitchell, *J.C.S. Dalton*, 1973, 1012.
[8] G. Brookes and L. D. Pettit, *J.C.S. Chem. Comm.*, 1975, 385; 1974, 813.
[9] D. D. Perrin and V. S. Sharma, *J. Chem. Soc.* (*A*), 1967, 724.
[10] T. P. Kruck and B. Sarkar, *Canad. J. Chem.*, 1973, **51**, 3549; 3555, 3563.
[11] D. R. Williams, *J. Chem. Soc.* (*A*), 1970, 1550; *J.C.S. Dalton*, 1972, 790.
[12] J. L. Meyer and J. E. Bauman, *J. Amer. Chem. Soc.*, 1970, **92**, 4210.

pH changes, particularly at intermediate pH values. With Cu^{2+} these changes have been studied potentiometrically,[10,11] calorimetrically,[11] and spectroscopically,[13-15] yielding conclusions which are often contradictory. Literature relating to the complexes of His has been reviewed recently by Sundberg and Martin.[16]

We report the results of a detailed potentiometric study of the partially protonated complexes of D-, L-, and DL-histidine with Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Pb^{2+}, and $[VO]^{2+}$ with a particular interest in stereoselective formation of some of the complexed species. Stereoselective formation of the racemic bis complex [Co(L-HisO)(D-HisO)] is well established,[5,6,15] but the system is difficult to study as a result of facile oxidation to Co^{III} by atmospheric oxygen. By working under argon it has now been possible to confirm from calorimetric studies that the stereoselectivity is largely the result of a more favourable enthalpy of formation of the mixed complex.

EXPERIMENTAL

Optically pure histidine (His) was obtained from the Sigma Chemical Co. (SIGMA grade). The racemic mixture was prepared by mixing equal amounts of the D and L isomers to eliminate differences in purity between racemic and optically homogeneous samples.

Complex-formation constants were calculated from potentiometric-titration curves measured at 25 °C and I = 0.10 mol dm^{-3} ($K[NO_3]$). The glass electrode was calibrated in terms of hydrogen-ion concentrations. Calculations were made with the aid of the MINIQUAD computer program,[17] using a range of metal to ligand ratios.

Calorimetric measurements were made at 25 °C in an LKB 8700 reaction and solution calorimeter. Amino-acid solutions (100 cm^3, *ca.* 0.02 mol dm^{-3}) were equilibrated in the reaction vessel and a concentrated solution of Co^{2+} (such that the final Co^{2+} : His ratio was 1 : 2.1) was in the ampoule. Acidities were adjusted so that at the final pH complexes other than $[Co(HisO)_2]$ would be at a minimum and the degree of formation of the bis complex would be greater than 97%. The heat of protonation of His and heat of dilution of the Co^{2+} solution were measured in independent experiments.[3] After correcting for the heat of dilution, the heat change measured approximated to that evolved in the overall reaction (1). The enthalpy change on formation of the bis complex could therefore be calculated from the measured

$$Co^{2+} + HisO^- + His + [OH]^- \longrightarrow [Co(HisO)_2] + H_2O \quad (1)$$

heat of reaction by allowing for: (*i*) the heat of formation of water due to the change in pH (−56.4 kJ mol^{-1}); (*ii*) the heat of protonation of $HisO^-$; and (*iii*) the heat of dilution of the metal ions.

It was impossible to eliminate oxidation of the Co^{II} to Co^{III} using nitrogen as an inert atmosphere. Oxidation was accompanied by a large exothermic heat change, giving a non-linear gradient to the temperature–time curve after the reaction, and by a change in colour from colourless to yellow-brown. Problems of oxidation were eventually overcome by saturating all solutions with argon and filling the calorimeter vessel in a glove-bag which was flushed with argon. It was assumed that the formation of hydrolysed species was very small at the final pH of the calorimetric experiments (seven replicate experiments for each of D-, L-, and DL-histidine) and that any species other than the bis complexes would contribute equally to the D, L, and DL complexes.

RESULTS AND DISCUSSION

Calculated protonation and metal-complex formation constants for D- and L-histidine are shown in Table 1

TABLE 1

Formation constants for the optically active complexes of D- and L-histidine at 25.0 °C and I = 0.10 mol dm^{-3} ($K[NO_3]$) (log β_{xyz} values, standard deviations being in parentheses)

					L-HisO⁻	
	x	y	z	D-hisO⁻		a
H^+	0	1	1	9.115(2)	9.120(1)	9.12 [b]
	0	1	2	15.209(4)	15.221(2)	15.17
	0	1	3	16.93(3)	16.92(2)	16.93
Co^{2+}	1	1	0	6.825(3)	6.823(3)	6.87 [c]
	1	1	1	11.43(3)	11.44(3)	
	1	2	0	12.340(7)	12.347(7)	12.38
	1	2	1	18.29(3)	18.36(2)	
Ni^{2+}	1	1	0	8.628(2)	8.636(2)	8.66 [c]
	1	1	1	12.21(3)	12.28(3)	
	1	2	0	15.466(5)	15.456(6)	15.50
	1	2	1	20.49(4)	20.49(5)	
Cu^{2+}	1	1	0	10.127(1)	10.135(2)	10.13
	1	1	1	14.070(6)	14.13(1)	14.06
	1	2	0	18.122(3)	18.095(6)	18.10
	1	2	1	23.920(3)	23.921(5)	23.64
	1	2	2	27.63(2)	27.48(5)	26.85
	1	1	−1	2.39(2)	2.47(3)	2.13
	1	2	−2	7.75(2)	7.58(7)	8.01
Zn^{2+}	1	1	0	6.486(3)	6.476(3)	6.57 [c]
	1	1	1	11.41(2)	11.42(2)	
	1	2	0	12.068(5)	12.075(5)	12.19
	1	2	1	17.87(2)	17.89(2)	
	1	2	2	23.53(9)	23.56(9)	
Pb^{2+}	1	1	0	5.930(8)	5.946(5)	5.96 [d]
	1	2	0	10.10(9)	10.11(9)	9.0
	1	2	1	17.17(7)	17.13(8)	
	1	2	2	23.35(5)	23.39(4)	
$[VO]^{2+}$	1	1	0	9.059(6)	9.040(8)	
	1	2	0	15.49(2)	15.48(2)	
	1	2	1	21.33(2)	21.42(2)	
	1	2	2	25.9(1)	26.0(1)	
	1	1	−1	3.43(2)	3.48(2)	

[a] Literature values. [b] Ref. 19. [c] Ref. 5. [d] Ref. 9 (37 °C, I = 0.15 mol dm^{-3}).

together with a selection of literature values for comparison. The constants quoted are generally overall formation constants for the complex species $[M_x(HisO)_yH_z]$, *i.e.* as in equation (2) where the neutral

$$\beta_{xyz} = [M_x(HisO)_yH_z]/[M]^x[HisO]^y[H]^z \quad (2)$$

histidine molecule is His. Stepwise formation constants and formation constants for partially hydrolysed species follow the accepted conventions.[18] The close agreement

[13] H. Sigel and D. B. McCormick, *J. Amer. Chem. Soc.*, 1971, **93**, 2041.
[14] G. Rotilio and L. Calabrese, *Arch. Biochem. Biophys.*, 1971, **143**, 218.
[15] C. C. McDonald and W. D. Phillips, *J. Amer. Chem. Soc.*, 1963, **85**, 3736.
[16] R. J. Sundberg and R. B. Martin, *Chem. Rev.*, 1974, **74**, 471.
[17] A. Sabatini, A. Vacca, and P. Gans, *Talanta*, 1974, **21**, 53.
[18] G. Brookes and L. D. Pettit, *J.C.S. Dalton*, 1975, 2106.

between values for the two isomers is to be expected and confirms the purity of the materials used.

Before considering stereoselectivity in the histidine complexes, several points emerge from a comparison of the constants found with those reported by other workers.

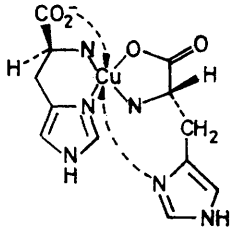
Complexes with Cu^{2+}.—Formation constants for complexes with Cu^{2+} are in close agreement with those from the most thorough of the studies carried out previously.[10,19] Titrations covered the pH range of 3.5—8.5. When only the species $[Cu(HisO)]^+$, $[Cu(HisO)_2]$, $[Cu(His)]^{2+}$, and $[Cu(HisO)(His)]^+$ were considered the best statistical fit gave a value of R of 9.43% where R in equation (3) is summed over the mass-balance equations

$$R = [(T_{obs.} - T_{calc.})^2/T_{obs.}^2]^{\frac{1}{2}} \qquad (3)$$

(T) in total metal, total ligand, and total ionisable hydrogen for all data points. Inclusion of the partially hydrolysed species [Cu(HisO)(OH)] reduced R to 0.58%, and inclusion of the dimer $[Cu_2(HisO)_2(OH)_2]$ reduced R to 0.20%. The inclusion of further possible species had no significant effect on the statistics of the fit, the complexes contributing to the general species distribution by a negligible amount.

Various structures have been assigned to the copper(II)–histidine complexes. From potentiometric and calorimetric evidence Williams has argued that the four donor atoms in the equatorial plane of $[Cu(L\text{-}HisO)_2]$ are the four nitrogen atoms (4N).[11] From visible and i.r. spectroscopy Kruck and Sarkar tentatively support this mode of bonding,[10] while Sigel and McCormick, using n.m.r. spectroscopy and the line-broadening effect of a paramagnetic ion, suggest that a carboxyl oxygen donor partially replaces one of the nitrogen donors in the co-ordination plane.[13] This is supported by Rotilio and Calabrese from e.s.r. studies.[14]

Bonding of four N atoms implies that both $HisO^-$ are bonding in, essentially, a histamine-like way. Measured enthalpy values demonstrate that the first $HisO^-$ co-ordinates to Cu^{2+} more exothermically than does histamine, while the reverse order is found for co-ordination of the second ligand.[11,12] In order to account for this it has been suggested that one or both carboxyl groups are free in the bis complex while in the mono complex the carboxyl group is attached axially. The



(I)

thermodynamic and spectral anomalies are explained if there is a change in the type of co-ordination geometry when the second $HisO^-$ is added to give a bis complex with one $HisO^-$ co-ordinating like histamine and the other like glycine (NNNO bonding), as shown in (I) for the optically active complex $[Cu(L\text{-}HisO)_2]$. If the Cu–N (imidazole) bond contains significant d–π bonding, the '*trans* effect' will tend to favour a carboxyl-oxygen donor in the *trans* position rather than another imidazole

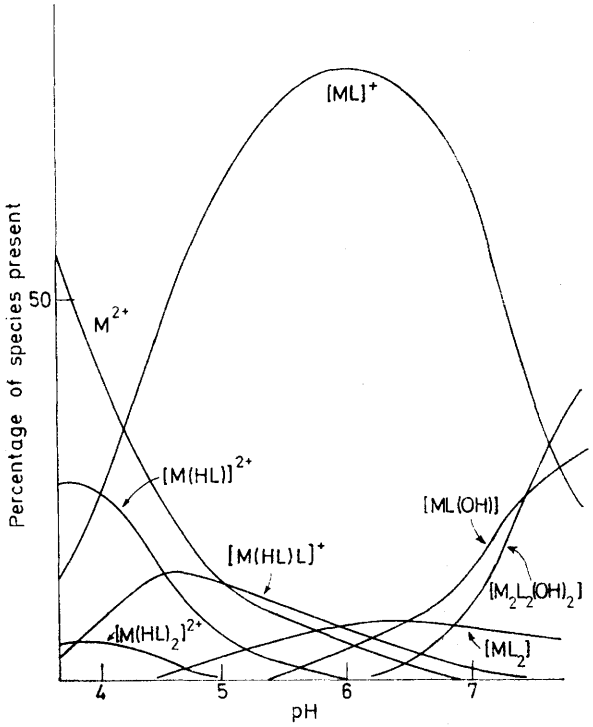


FIGURE 1 Species distribution curves for a 1 : 1 mixture of Cu^{2+} and L- (or D-) histidine (HL)

nitrogen atom. Such a tendency against symmetrical *trans* co-ordination has been suggested in various ternary complexes [20] and there is a large amount of evidence that ternary histidine complexes tend to be markedly more stable than would be expected on statistical grounds.[8,10,19] The high value for $\log(K_{CuL}/K_{CuL_2})$ for histamine complexes (3.07) also shows the preference for mixed co-ordination of the N and O donors (from H_2O) in equilibrium (4).

$$[Cu(histamine)(OH_2)_2] + \text{histamine} \rightleftharpoons [Cu(histamine)_2] + 2H_2O \qquad (4)$$

All possible copper complexes with His molecules were found to be significant, particularly the $[Cu(HisO)(His)]^+$ species which involved 60% of the copper in a 1 : 2 copper–histidine mixture at pH 5.5. The structure of this complex will be discussed with analogous complexes of other transition-metal ions. Partially hydrolysed complexes were important above pH 6 for 1 : 1 ratios and above pH 8 for 1 : 2 ratios. We found no evidence for the presence of simple hydroxo-complexes

[19] H. C. Freeman and R. P. Martin, *J. Biol. Chem.*, 1969, **244**, 4823.

[20] H. Sigel, R. Caraco, and D. Prijs, *Inorg. Chem.*, 1974, **13**, 462.

or of the species $[Cu(HisO)_2(OH)]^-$. However, the species $[Cu(HisO)(OH)]$ and $[Cu_2(HisO)_2(OH)_2]$ were important. A typical species-distribution graph for a 1 : 1 copper–histidine mixture is shown in Figure 1.

Complexes of $[VO]^{2+}$.—These should resemble those of Cu^{2+}, the predominant co-ordination number towards other ligands being four. However, vanadyl ions are more extensively hydrolysed at intermediate pH values than are Cu^{2+} ions.[21] Formation-constant data for vanadyl complexes with amino acids are very limited. Fortunately His forms comparatively stable complexes with the vanadyl ion, hence hydrolysis is restricted and hydrolysed species were found to be only minor components of the mixtures. Titrations were made on 1 : 1 and 1 : 2 vanadium(IV)–histidine mixtures under rigorously oxygen-free conditions. Hydrolysis and diolation constants for the vanadyl ion alone [21] were included as constants in the calculations which yielded the results shown in Table 1. The precision is a little lower than with Cu^{2+}, but the model selected fitted the experimental results well over the range pH 3.5—6.5.

The $[VO(HisO)]^+$ complex is less stable than the copper analogue by 1.1 log units, while the $[VO(HisO)_2]$ complex is less stable by 2.7 log units, and in general the quotient K_{ML}/K_{ML_2} is larger for vanadyl than for other transition-metal ions. This relative instability of the bis(histidinato)oxovanadium(IV) complex is in full agreement with the first ligand co-ordinating in a tridentate fashion while the second can only be bidentate, the sixth co-ordination position being taken up by the vanadyl oxygen. For this reason the monoprotonated bis complex is unusually stable with respect to the unprotonated bis complex. Values for the ionisation constants of the vanadyl complexes compare closely with the corresponding values of copper(II)–histidine complexes. A typical species distribution for a 1 : 2 vanadium(IV)–histidine mixture is shown in Figure 2.

$$[M(HisO)(His)]^+ \longrightarrow [M(HisO)_2] + H^+; \quad pK_{Cu}\ 5.80,\ pK_{VO}\ 5.85 \quad (5)$$

$$[M(His)_2]^{2+} \longrightarrow [M(HisO)(His)]^+ + H^+; \quad pK_{Cu}\ 4.0,\ pK_{VO}\ 4.6 \quad (6)$$

Complexes with Other Bivalent Metal Ions.—In all cases the statistical fit of calculated to measured concentrations was improved significantly by the inclusion of the monoprotonated complexes $[M(His)]^{2+}$ and $[M(HisO)(His)]^+$. Typical improvements in R values were from 0.50 to 0.10%. Incorporation of protonated complexes into the equilbrium caused small or negligible changes in values for $\beta_{M(HisO)}$ but larger changes in $\beta_{M(HisO)_2}$ coupled with a marked improvement in the calculated standard deviations in the constants. The protonated complexes accounted for a maximum of 10% of the total metal ions in the equilibrium mixtures. In previous work their presence was discounted,[9] but it is clearly significant if minor. This is in agreement with independent spectral evidence.[22] Apart from these protonated species, agreement with other published constants is good and there was no evidence for significant formation of hydroxo-complexes below pH 7.5.

Lead was present largely as the mono complex $[Pb(HisO)]^+$, the bis complex becoming important only above pH 7. This would be expected for a tridentate ligand bonding to a purely tetrahedral cation when co-ordination of a second ligand would necessitate the breaking of a metal–ligand bond towards the first ligand. The bidentate nature of histidine in $[Pb(HisO)_2]$ is illustrated by comparing the formation constant of the bis complex (log β 10.10) with that of the bis(glycine) complex (logβ 9.98). Zinc shows a more variable co-ordination number and hence forms a bis complex more readily.

The Structure of Protonated Histidine Complexes.—This has been interpreted in a number of different ways since

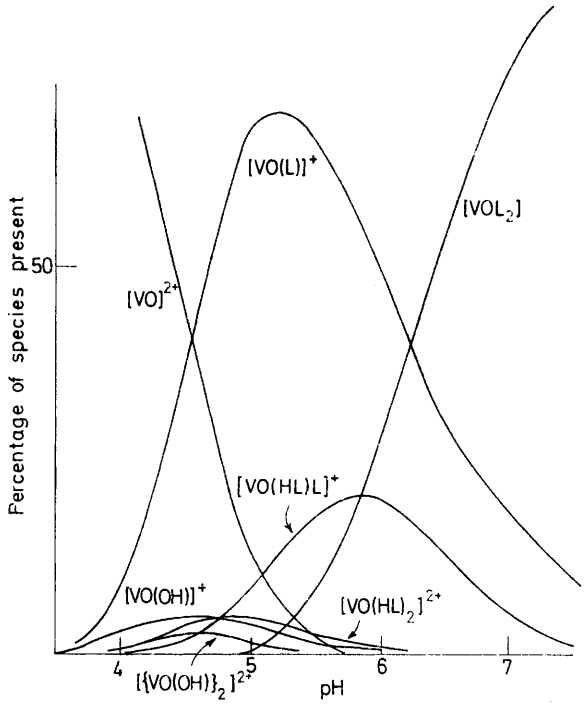


FIGURE 2 Species distribution curves for a 1 : 2 mixture of $[VO]^{2+}$ and L- (or D-) histidine (HL)

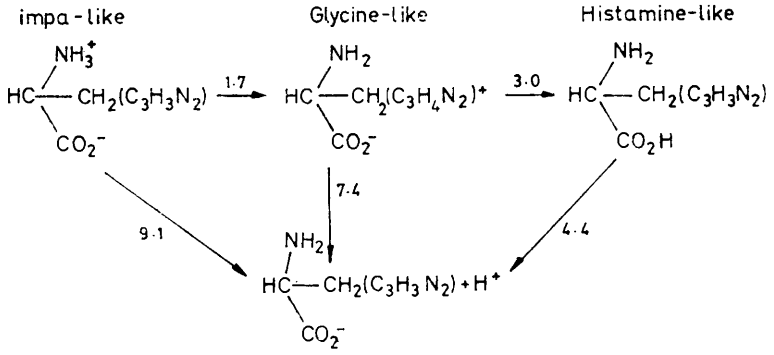
His can co-ordinate in three different ways: like glycine; like histamine; or like imidazolepropionic acid (impa). It is therefore probable that the overall formation constant will contain contributions from the three possible ' micro-constants '.

In a solution of neutral histidine (His) the hydrogen ion is thought to be almost exclusively on the α-NH_2 nitrogen donor, leaving the carboxyl and imidazole groups free for impa-type co-ordination. Hydrogen-ion

[21] M. M. Khan and A. E. Martell, *J. Amer. Chem. Soc.*, 1968, **90**, 5011.

[22] R. H. Carlson and T. L. Brown, *Inorg. Chem.*, 1966, **5**, 268; C. C. McDonald and W. D. Phillips, *J. Amer. Chem. Soc.*, 1963, **85**, 3736.

rearrangements must therefore take place on the histidine if other forms of co-ordination are to be important. The micro-constants (pK values) for these rearrangements have been estimated as follows: [16]



If the bonding in $[M(His)]^{2+}$ is other than impa-like, the stepwise equilibria should be expressed as in (7) and the

$$H^+ + HisO^- \longrightarrow His \xrightarrow[\text{rearrangement}]{\text{proton}} His \xrightarrow{M^{2+}} [M(His)]^{2+} \quad (7)$$

appropriate constant for the proton rearrangement included. It is not sufficient to assume that $\log K_{M(His)} = \log \beta_{111} - \log \beta_{011}$. If the appropriate estimated corrections are included, $\log K_{M(His)}$ (corrected) can be compared with $\log K_{ML}$ values for glycine, histamine, and impa. The best agreement is found with the glycine values supporting glycine-like co-ordination in the protonated complexes.

Further support for glycine-like co-ordination is found by considering the complex $[M(HisO)(His)]^+$ as a ternary complex with the ligands $HisO^-$ and His (A and B). In reaction (8) the equilibrium constant, $\Delta\log K$, may be expressed as in (9). This quantity has been used

$$Cu^{2+} + [Cu(AB)] \longrightarrow [CuA]^+ + [CuB]^+ \quad (8)$$

$$\Delta\log K = \log K_{CuA} - \log K_{Cu(AB)}{}^{CuB} \quad (9)$$

by Griesser and Sigel [23] to distinguish between nitrogen–nitrogen (NN) and nitrogen–oxygen (NO) chelate formation. In the ternary histidine–phenylalanine complex the second ligand must bond like glycine and gives the following comparative values for $\Delta\log K$:

A (NN)	B (NO)	ΔlogK
$HisO^-$	His	0.35
$HisO^-$	phenylalanine	0.37 [8]
2,2′-bipyridyl	glycine	0.35 [23]
(NO)	(NO)	
His	His	0.52
His	phenylalanine	0.55

These values argue strongly against histamine (NN)-like bonding but, since impa-like bonding is also NO type (albeit an imidazole N), they do not distinguish conclusively between glycine-like and impa-like. In crystals of $[Cu(His)_2]^{2+}$ however, the bonding is certainly glycine-like.[24]

Stereoselectivity in Histidine Complexes.—Stereoselectivity in the formation of bis complexes of D- (or L-) and DL-histidine with Co^{2+}, Ni^{2+}, and Zn^{2+} is well established.[3,5,6] With Cu^{2+} there appears to be no evidence for stereoselectivity in the formation constants of the bis complex, although enthalpy values show a preference for the optically active complex, $[Cu(L\text{-}HisO)_2]$, the reverse situation to that found with Ni^{2+} and Zn^{2+}.[3,11] We have now repeated the determination of the formation constants, including protonated complexes in the equilibria. Formation constants calculated from titration data for a racemic mixture of histidine (β_{rac} values) must be corrected to give true formation constants for the species $[M(D\text{-}HisO)(L\text{-}HisO)]$ (β_{+-} values) since the mixture will also contain both $[M(D\text{-}HisO)_2]$ and $[M(L\text{-}HisO)_2]$.[5,6] In the absence of stereoselectivity, the calculated values for $\log \beta_{+-}$ would be **0.30** log units greater than those for $\log \beta_{++}$ or $\log \beta_{--}$ as a result of statistical factors.[1] An additional complication is the possibility of stereoselectivity in the protonated complexes, $[M(HisO)(His)]^+$. This was neglected in previous studies since the existence of such complexes was not considered quantitatively.

Problems associated with the inclusion of corrections and the calculation of relative equilibrium concentrations of the various stereoisomers can be minimised by considering the titration of racemic histidine with a metal ion as a ternary system of M, D-$HisO^-$, and L-$HisO^-$. Table 1 demonstrates that constants calculated for D- and L-histidine are effectively the same. However, small rounding errors were minimised by including the constants for the formation of optically active complexes (Table 1) as fixed constants in the MINIQUAD calculation of constants for the various ternary species. The results are shown in Table 2 together with some comparison values.

The stereoselectivity previously reported for the bis complexes of Co^{2+}, Ni^{2+}, and Zn^{2+} is confirmed and, in addition, significant stereoselectivity was also found in the monoprotonated complexes. The extent of the stereoselectivity in the bis complexes is in good agreement with reported values, and is not changed significantly by the incorporation of protonated species. In particular the absence of stereoselectivity in the $[Cu(HisO)_2]$

[23] R. Griesser and H. Sigel, *Inorg. Chem.*, 1971, **10**, 2229.
[24] B. Evertsson, *Acta Cryst.*, 1969, **B25**, 30.

complexes is confirmed. Our results gave no evidence for stereoselectivity in the Pb^{2+} and $[VO]^{2+}$ complexes, although this may be the result of the somewhat larger errors. However, large differences were not expected since $[VO]^{2+}$ would resemble Cu^{2+}, and Pb^{2+} tends to be tetrahedral rather than octahedral. With Co^{2+} and Ni^{2+} stereoselectivity in the monoprotonated complexes is similar to that with the fully ionised complexes (*i.e.* the *meso*-complex is the more stable). With Zn^{2+} the histidine complexes of Ni^{2+}, Cu^{2+}, and Zn^{2+}.[3] We measured the heats of formation of $[Co(D\text{-HisO})_2]$, $[Co(L\text{-HisO})_2]$, and $[Co(L\text{-HisO})(D\text{-HisO})]$ under rigidly oxygen-free conditions, seven duplicate determinations being made of each value for ΔH. As expected, values for D-$HisO^-$ and L-$HisO^-$ were effectively the same ($-\Delta H = 49.14 \pm 0.10$ and 48.92 ± 0.09 kJ mol^{-1}). The apparent value for the racemic mixture was significantly larger (50.46 ± 0.09 kJ mol^{-1}). This value

TABLE 2

Stereoselectivity in histidine complexes at 25.0 °C and $I = 0.10$ mol dm^{-3} ($K[NO_3]$) assuming complexes of formula $[M_w(D\text{-HisO})_x(L\text{-HisO})_yH_z]$

	w	x	y	z	log β_{wxyz}	log β_{wxyz} − 0.30	log β_{mean}	Δlog β	
Co^{2+}	1	1	1	0	12.94(1)	12.64	12.34	−0.30(1)	−0.23,[a] −0.12 [b]
	1	1	1	1	18.90(3)	18.60	18.33	−0.27(6)	−0.36,[a] −0.26,[b] −0.45 [c]
Ni^{2+}	1	1	1	0	16.24(1)	15.94	15.46	−0.48(1)	
	1	1	1	1	21.24(4)	20.94	20.49	−0.45(7)	
Cu^{2+}	1	1	1	0	18.41(1)	18.11	18.11	0	
	1	1	1	1	24.11(1)	23.81	23.92	0.11(2)	0.10 [d]
	1	1	1	2	28.00(3)	27.70	27.56	−0.14(8)	
Zn^{2+}	1	1	1	0	12.492(6)	12.19	12.07	−0.12(1)	−0.21,[a] −0.13 [b]
	1	1	1	1	18.03(4)	17.73	17.88	0.15(5)	
Pb^{2+}	1	1	1	0	10.1(3)	9.8	10.1	0.3(3)	
	1	1	1	1	17.50(8)	17.2	17.2	0	
	1	1	1	2	23.73(9)	23.4	23.4	0	
$[VO]^{2+}$	1	1	1	0	15.58(3)	15.28	15.48	0.20(5)	
	1	1	1	1	21.32(7)	21.02	21.38	0.36(10)	

log $\beta_{mean} = 0.5$ (log $\beta_{D\text{-HisO}}$ + log $\beta_{L\text{-HisO}}$) from Table 1; Δlog β = log β_{mean} − (log β_{wxyz} − 0.30).

[a] Ref. 5 and 25. [b] Ref. 6. [c] J. R. Blackburn and M. M. Jones, *J. Inorg. Nuclear Chem.*, 1973, **35**, 1605. [d] Calculated from data in ref. 25.

situation may be reversed, but the constants have comparatively large standard deviations so that the difference is probably not significant. The species make only very minor contributions to the equilibrium in this case.

The small difference found between the protonated complexes of Cu^{2+} is interesting. Although small, it appears to be real with the optically active bis complexes being favoured. Support for this small but significant difference is found in some data of Ritsma [25] and in the stereoselectivity recently reported in some protonated ternary complexes containing histidine.[8] The complex $[Cu(HisO)(His)]^+$ has a maximum concentration between pH 5 and 6 and is significant to above pH 7. Stereoselectivity in the formation of the complex may, therefore, be of biological importance.

On statistical grounds the contributions of the bis complexes (assuming no stereoselectivity) would be 25% for $[M(D\text{-HisO})_2]$ or $[M(L\text{-HisO})_2]$ and 50% for [M(D-HisO)(L-HisO)]. Percentages calculated from the results reported in Table 2 are:

	$[M(L\text{-HisO})_2]$	[M(L-HisO)(D-HisO)]	Ref. 6
Co^{2+}	17	66	62
Ni^{2}	12	76	72
Cu^{2}	25	50	50
Zn^{2+}	22	56	62

	$[M(L\text{-HisO})(L\text{-His})]^+$	$[M(L\text{-HisO})(D\text{-His})]^+$
Co^{2+}	18	64
Ni^{2+}	13	74
Cu^{2+}	28	44
Zn^{2+}	30?	40?

Stereoselectivity in Enthalpy Changes accompanying Complex Formation.—This has been detected with

was corrected for the presence of the calculated concentrations of the optically active complexes to give a corrected value of 51.42 kJ mol^{-1}. Calculated thermodynamic quantities for the bis(histidine) complexes of Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+} are in Table 3.

TABLE 3

Thermodynamic values (kJ mol^{-1}) for the bis complexes $[M(D\text{- or }L\text{-HisO})_2]$ at 25.0 °C and $I = 0.10$ mol dm^{-3} ($K[NO_3]$)

	$\frac{1}{2}(\Delta H_{DD} + H_{LL})$	ΔH_{DL} (corrected)
Co^{2+}	−49.03	−50.42
Ni^{2+}	−69.08 *	−71.63
Cu^{2+}	−83.63 *	−81.58
Zn^{2+}	−47.77 *	−50.25

For the reaction $0.5\,[M(L\text{-HisO})_2] + 0.5[M(D\text{-HisO})_2] \longrightarrow M(L\text{-HisO})(D\text{-HisO})]$

	ΔG	ΔH	$T\Delta S$	$T\Delta S - RT\ln 2$
Co^{2+}	−3.42	−1.39	2.03	+0.3
Ni^{2+}	−4.45	−2.55 *	1.90	+0.2
Cu^{2+}	−1.72	+2.05 *	3.77	+2.0
Zn^{2+}	−2.40	−2.48 *	−0.08	−1.8

* Ref 6.

Entropy changes for the equilibrium reaction given in Table 3 were corrected for statistical factors by incorporating the term $R\ln 2$. When this was included, stereoselectivity in the complexes of Co^{2+} and Ni^{2+} was shown to be entirely an enthalpy difference (standard deviation in $T\Delta S$ *ca.* 0.2 kJ mol^{-1}) reflecting differences in the bond energies in the active and racemic complexes. With Zn^{2+} the entropy change appears to favour the optically active bis complex (after correcting for statistical

[25] J. H. Ritsma, Thesis, Groningen, 1973.

factors) and opposes the enthalpy change which favours the *meso*-complex. The absence of an entropy contribution to the stereoselectivity of complexes of Co^{2+} and Ni^{2+} is reasonable since co-ordination of both water and histidine would be octahedral. Stereoselective entropy effects in the ligand-exchange reactions $[M(OH_2)_6]^{2+} + 2\ HisO^- \longrightarrow [M(HisO)_2] + 6H_2O$ are not likely to be great. With Cu^{2+} and Zn^{2+}, on the other hand, significant changes in co-ordination pattern on ligand exchange are likely. In crystals of $[Zn(HisO)_2]$ the geometry is a very distorted octahedron, approaching a tetrahedron,[26] and all the evidence suggests that in $[Cu(HisO)_2]$ the co-ordination along the z axis is weak and the bond is long. Significant stereoselectivity in the entropy changes on complex formation is therefore likely. The apparent absence of stereoselectivity in the formation of the $[Cu(HisO)_2]$ complexes is therefore the result of a co-incidental cancelling of enthalpy and entropy terms of the stereoselectivity, as suggested earlier. It is interesting to note that the co-ordination scheme suggested in (I) would lead to stereoselectivity reflected in enthalpy changes in favour of the optically active bis complex as is found experimentally.

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[26] M. M. Harding and S. J. Cole, *Acta Cryst.*, 1963, **16**, 643.