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**Critical Evaluation of Equilibrium Constants in Solution
Part A: Stability Constants of Metal Complexes**

**CRITICAL SURVEY OF FORMATION
CONSTANTS OF COMPLEXES OF
HISTIDINE, PHENYLALANINE,
TYROSINE, L-DOPA AND
TRYPTOPHAN**

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CRITICAL SURVEY OF THE FORMATION CONSTANTS OF COMPLEXES OF HISTIDINE, PHENYLALANINE, TYROSINE, L-DOPA AND TRYPTOPHAN

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1. INTRODUCTION

This group of amino acids all contain sidechains which are aromatic in character. With the exception of L-DOPA they are all constituents of proteins and are biologically important. L-DOPA is included in the list since, while not found in proteins, it has important physiological properties (72NO).

Chemically histidine has significantly different properties to the other aromatic amino acids because the aromatic imidazole ring contains two nitrogen atoms, one of which protonates in the biologically significant pH range of 6-7. This nitrogen atom can coordinate strongly to transition metal ions and hence has an important influence on the metal complexes which result. This is particularly important when the histidine residue is part of a protein chain. Under these circumstances the imidazole substituent is one of the major points of interaction between proteins and transition metal ions. It is probable that the aromatic substituents in the other amino acids evaluated here also interact with transition metal ions - however, this interaction is rather more subtle and is much less significant thermodynamically.

The simple amino acids (HL) all exist in solution as zwitterions, the amino group being protonated ($-\text{NH}_3^+$) while the carboxyl group is ionized ($-\text{CO}_2^-$). This group protonates in acid solution (pH 2-2.5) to give the complex $[\text{H}_2\text{L}]^+$, and the protonated amino group loses its proton in basic solution (pH 9-10) to give L^- . This proton can be displaced by metal ions to form mono, bis and tris complexes with the ligand behaving as a bidentate chelating agent. Since the extents of proton displacement will be influenced by the stability of the metal complex resulting, titrations of the amino acids in the absence and in the presence of metal ions provides the most accurate and generally used method for measuring metal complex formation constants. This technique, first described in detail by Bjerrum (41B), has been evaluated critically by a number of authors (61RR, 70B). Virtually all studies of formation constants of amino acid complexes have employed this technique, using a glass indicator electrode to follow changes in pH. Various methods have been used to overcome problems resulting from activity effects. The most common method has been to work in a medium of constant ionic strength. Various concentrations have been selected including 0.10 (KCl or $\text{K}[\text{NO}_3]$), 0.15 (NaCl) approximating to biological fluids and 3.0 mol dm^{-3} ($\text{Na}[\text{ClO}_4]$). Results from different ionic backgrounds are not directly inter-comparable. In particular results calculated from titrations in 3 mol dm^{-3} ($\text{Na}[\text{ClO}_4]$) would be expected to be very different from those in more dilute solution. In practice, the difference between KCl, $\text{K}[\text{NO}_3]$ and $\text{Na}[\text{NO}_3]$ as background electrolyte in dilute solution (about 0.1 mol dm^{-3}) is insignificant unless the metal ion has a high affinity for chloride ions (e.g. Pd(II)). Some workers have carried out measurements using a number of different concentrations of ionic medium and extrapolated to infinite dilution to obtain thermodynamic constants. This technique suffers from the fact that the relationship between ionic strength and calculated formation constant is far from linear and depends on the charge of the ions involved. An alternative approach has been to calculate the activity coefficients of the ions by one of the recognised semi-empirical equations (e.g. the Davies equation) and to use this value to correct measured formation constants to thermodynamic constants. This approach is generally

satisfactory in dilute solution ($<0.05 \text{ mol dm}^{-3}$) but is subject to significant errors when the ions are highly charged or when ligands are far from spherical (e.g. many amino-acids and dipeptides).

When a glass electrode is used to measure pH, the calibration technique employed will govern the type of constant calculated. In most early work electrode systems were calibrated with buffer solutions of standard hydrogen ion activity (generally 0.05 mol dm^{-3} potassium hydrogen phthalate of pH 4.00 at 25°C). Calculations have then used concentrations for all reacting species except the hydrogen ions, which were expressed as activities so that mixed constants were calculated. This technique of electrode standardization is not to be recommended but it has been used by many workers in the field and, unfortunately, is still in use by some. Ideally, the electrode should be calibrated in terms of hydrogen ion concentrations to give concentration constants. This can be done by titrating a solution of a strong (i.e. fully dissociated) acid with alkali e.g. $\text{H}[\text{ClO}_4]$ with KOH in the same medium as for the determination of the stability constant, and measuring the E.M.F. across the glass and reference electrodes. Hydrogen ion concentrations can then be calculated for each point of the titration curve assuming complete dissociation of both acid and base, and taking a reliable value for K_w . From these values a suitable value for E^0 for the electrode pair can be calculated and used to correct subsequent potential measurements with that particular electrode pair to give values of hydrogen ion concentration. The value for E^0 must be recalculated at each measurement to cater for changes in asymmetry potential, etc. An alternative technique is to calibrate a standard buffer solution (e.g. potassium hydrogen phthalate) in terms of hydrogen ion concentrations under identical conditions to the titrations to be followed (67IM). This buffer solution can then be assigned an appropriate pH value in terms of concentrations and can be used subsequently to check for changes in electrode characteristics. The linearity of the electrode to pH changes over the pH range to be studied should also be checked once a week, or ideally at each measurement. The Gran-plot procedure may be useful for calibrating electrodes at the beginning or at the end of titrations.

Most measurements on the ligands evaluated here have been carried out at 25°C , but a number have also been determined at 20°C , or over a range of temperatures between 0 - 50°C . A few measurements have been carried out at 37°C .

Potentiometric titrations of mixtures of ligands and metal ions can also give information on the enthalpy change on complex formation, (ΔH), if they are carried out at two or more temperatures, since:

$$\frac{d(\ln K)}{dT} = \frac{\Delta H}{RT^2}$$

This technique has been used by a number of workers and their results will be discussed later. In general, the results lack precision as a result of the interaction of random errors, changes in $\ln K$ being small over the temperature range of 0 - 40°C . If larger temperature ranges are selected experimental problems are considerable, and values for ΔH becomes increasingly temperature dependent. Far more reliable values for ΔH can be found calorimetrically and a number of determinations are evaluated later.

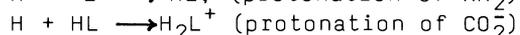
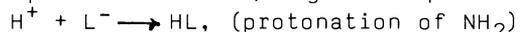
Problems associated with the determination of complex formation constants have been considered in more detail by Anderegg, in his critical evaluation of equilibrium data with nitrilotriacetic acid (80A). Most of his comments apply equally well to the determination of equilibrium data with amino acids.

All the amino acids considered here are asymmetric and exist as two isomers, D and L. As a result, stereoselective effects in the formation of complexes may be significant. Differences in the proton complex formation constants (pK

values) of amino acid are not expected. However, the bis-complexes $M(\underline{L}-L)_2$ and $M(\underline{L}-L)(\underline{D}-L)$ are diastereoisomeric and therefore may differ in properties. Stereoselectivity has been detected in the formation constants of histidine complexes, but it is generally insignificant with the other amino acids (76PS, 79PH).

1.1. Representation of Equilibrium Data.

Proton (or hydrogen ion) complex formation constants are generally expressed as stepwise constants, e.g. the equilibria:

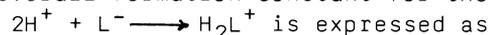


may be expressed as:

$$K_{HL} = \frac{[HL]}{[H][L]}$$

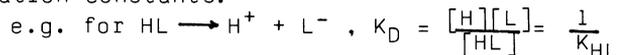
$$K_{H_2L}^{HL} = \frac{[H_2L]}{[HL][L]}$$

The overall formation constant for the reaction:



$$\beta_{H_2L} = K_{HL} \cdot K_{H_2L}^{HL} = \frac{[H_2L]}{[H]^2[L]}$$

It should be noted that acid dissociation constants, K_D , are the reciprocal of formation constants:



Hence $\log K_{HL} = pK_D$,

i.e. pK values for dissociation reactions are identical to log K values for complex formation reactions. Throughout this evaluation formation constants will be used for both proton and metal complex formation.

Formation constants of complexes with metal ions are generally quoted as overall formation constants, β_{xyz} , which refer to formation of the complex $M_xH_yL_z$. Negative subscript values such as β_{1-11} refer to complex formation reactions in which a hydrogen ion which does not normally dissociate is eliminated, e.g.:



This hydrogen ion may originate from either the ligand molecule or a coordinated water molecule.

Constants are normally defined as "mixed" (M) or "concentration" (C). Concentration constants can correctly be called 'thermodynamic' constants provided that the conditions used are clearly specified (i.e. the 'standard state' for the particular determination). Some authors have used the term 'thermodynamic constants' to mean only those applying to infinite dilution, but no such distinction is made in this evaluation. In many cases authors have failed to give precise details of pH standardization method used making quantitative evaluation difficult. In much of the earlier work ionic strengths were often too low to remain effectively constant during a titration, or were not controlled at all. A study of the literature reveals surprisingly few examples of formation constants determined independently under similar conditions of temperature and ionic strength. Hence it is often difficult to select recommended values which have meaningful estimates of accuracy (as distinct from precision). In the following tables estimates of precisions have been included as numbers in brackets when they have been quoted in the literature. They refer to possible error in the last digit.

1.2. Possible Interaction between Copper(II) and Aromatic Rings.

In 1961 it was first reported that the ratio of the stepwise formation constants for the Cu(II)-phenylalanine system differed from that for Cu(II)-aliphatic amino acid complexes, the value for the reaction $\text{CuL} + \text{L} \rightarrow \text{CuL}_2$ with phenylalanine being larger than expected (61IW). It was suggested that the coordinated ligand in the 1:1 complex affected the Cu(II) ion in such a way as to cause it to have a greater affinity than expected for the second phenylalanate ion. Meyer and Bauman (70MB) noted a similar peculiarity in the second stepwise constant for the Cu(II) + tryptophan system. They proposed that π -bonding between the fused aromatic system of the indole group and the copper ion may be taking place in the bis-complex. Similar π -bonding has also been suggested in the Cu(II)-thyroxine complexes (65WF). Work on mixed complexes of Cu(II) with amino acids (72GS, 73GS) showed that the most stable species are formed when one of the ligands is aliphatic and the other aromatic (e.g. phenylalanine or tyrosine).

The formation of bis-Cu(II) complexes of phenylalanine and tryptophan is not stereoselective (66SW, 71WS). However, significant stereoselectivity is found in the formation of mixed complexes of Cu(II) with L-histidine and D/L phenylalanine and tryptophan (77BP), and the $[\text{CuH}_1\text{A}]$ complex where A is glycylphenylalanine is markedly more stable than expected on the basis of the proton complex formation constants of the ligand (75BP).

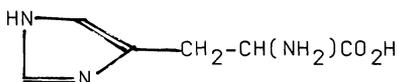
On the basis of these observations it appears that the bonding is glycine-like in the mono complexes but that at least one aromatic ring is associated with the Cu(II) in the bis-complexes. This is probably a result of the smaller charge on the metal ion in the mono-complex after one ligand molecule has coordinated. This will make interaction between electrons in the d-orbitals of the Cu(II) ion and the aromatic system of a second ligand molecule more likely.

Aromatic ring-Cu(II) interaction in the solid state is not evident from the X-ray structure analyses of $[\text{Cu}(\text{phenylalanate})_2]$ (71VL), but it is apparent in some substituted amino acids (72As) and dipeptides (70FV, 77MB), and also in $[\text{Cu}(\text{tyrosinate})_2]$ (72VT).

E.s.r. and optical studies of simple peptides containing phenylalanine, tyrosine or tryptophan residues show a significant decrease in the value for g and a concomitant increase in the energy of d-d transition (77SN). These effects are compatible with Cu(II)-aromatic interactions. Other evidence for an anomalous interaction comes from a comparison of the stepwise formation constants for complexes of Cu(II) with tryptophan and l-methyltryptophan (74W). If glycine-like bonding is assumed, little difference would be expected between the two systems. The values for $\log K_{\text{HL}}$ and $\log K_{\text{ML}}$ are, in fact, almost identical. However, the values for the reaction $\text{ML} + \text{L} \rightarrow \text{ML}_2$ differ by over 3 log units (7.15 and 3.82 respectively) suggesting gross steric hindrance to the co-ordination of a second ligand - in fact more than would be expected. Such hindrance would be likely only if Cu(II)-aromatic ring interaction were significant.

Hence there is much qualitative evidence that, under certain circumstances, amino acids containing aromatic side-chains can behave as tridentate ligands.

2. HISTIDINE - $C_6H_9O_2N_3$.
(2-Amino-3-(4'-imidazolyl)propanoic acid, HL)



The fully protonated histidine cation, $[H_3L]^{2+}$, has three ionizable hydrogen ions, hence histidine can form three different protonated complexes. Over the normal pH range it has three potential donor centres (2 nitrogens and a carboxyl oxygen) although at very high pH values (>13) the pyrrole proton may ionize to give a fourth potential coordination centre. Since it exists as a charged species in both acidic and alkaline solutions ($[H_2L]^+$ and $[L]^-$) both the ligand itself and its complexes tend to be soluble in water over a wide pH range.

2.1. Protonation Constants of Histidine.

The first centre to protonate in the fully ionized histidinate anion, $[L]^-$, is the amino-nitrogen ($\log K \sim 9$) followed by the pyridine-like imidazole nitrogen ($\log K \sim 6$). Since these protonation reactions take place over a very accessible pH range, the constants can be determined comparatively accurately. The last centre to protonate is the carboxyl group ($\log K \sim 2$). This reaction only occurs at low pH: hence the accuracy of its determination is low.

Literature values for the protonation constants are given in Table 2.1. The number of determinations reported is larger than for the other amino acids evaluated here and most were carried out under clearly defined conditions. Hence it is possible to give recommended values, together with standard deviations on these values.

Determinations carried out in solutions of low ionic strength (<0.02 M) will suffer from changes in activity, and have been omitted from this evaluation (52A, 59LR). References 53P, 59MH, 59P, 61V, 65HS, 70MBa, 70MM and 74LB omitted essential experimental information and have also been omitted. The ionic background used in 57LD varies excessively (0.15 - 0.25 M) and the values given in 77BS are identical to those quoted in 72IB, and probably result from the same determination. Constants reported in 69RM are significantly larger than all others and have, as a result, been rejected. Values given in 75PN are only approximate.

A sufficiently large number of 'mixed' (M) constants have been determined at 25 °C for useful comparisons to be made. In general, the agreement is good and changes in ionic strength between 0.1 to 0.2 mol dm^{-3} do not appear to have a significant effect on the values of the constants. Values given in references 55LM, 63CC, 64AR, 68RP, 70CA, 72IB (also 77BS) and 78VZ have therefore been grouped together to provide a recommended mixed constant for the protonation of the histidine anion at 25 °C and with an ionic strength of 0.10 to 0.20 mol dm^{-3} . Mean values calculated from these 7 independent determinations are:

$$\log K_{HL} = 9.17(3), \quad \log K_{H_2L} = 6.07(2), \quad \log K_{H_3L} = 1.8(1)$$

It should be stressed, however, that the use of conditions requiring mixed constants is not to be recommended.

A number of 'concentration' constants have been measured at 25 °C and with an ionic background between 0.10 and 0.16 mol dm^{-3} . References are 64DC, 69FM (D and L histidine), 69MB, 69RG, 73KS, 76BP, 76PS (D and L histidine), 78DO and 79MJ. Values quoted in 79MJ are larger than other comparable values. The remaining values, however, are satisfactorily close in magnitude. References 69FM and 76PS reported values for both chiral forms of histidine and, as expected, did not detect any significant difference. Mean values calculated

from these 10 determinations are:

$$\log K_{HL} = 9.11(2), \quad \log K_{H_2L} = 6.05(3), \quad \log K_{H_3L} = 1.72(9)$$

The only other results which can be compared directly are 67PS and 80NS. These determinations of concentration constants were carried out at 37 °C and with an ionic strength of 0.15 mol dm⁻³, K[NO₃] and Na[ClO₄] respectively. Agreement is fair and, ignoring the different ionic background, mean values are:

$$\log K_{HL} = 8.94(0.04), \quad \log K_{H_2L} = 5.98(0.05), \quad \log K_{H_3L} = 2.3(0.15).$$

Values quoted in reference 71HM have been corrected to infinite dilution although the measurements were carried out in 0.1 mol dm⁻³ (K[NO₃]) solutions. If the correction terms included in the calculations are removed, the recalculated 'mixed' constants are in reasonable agreement with the 'recommended' values given above (e.g. at 25 °C log K_{HL} = 9.20(4), log K_{H₂L} = 6.13(4)). Constants reported in 30BH and 30SA do not give such good agreement. Values quoted in 78VZ have also been corrected by the Davies equation to infinite dilution.

Remaining determinations, particularly those referring to concentration constants in 3.0M Na[ClO₄] (70W and 71JW), may be accepted as 'tentative' constants. Recommended and tentative values for the protonation constants of histidine are given in Table 2.2.

2.2. Enthalpy of Protonation of Histidine.

Enthalpy changes on protonation have been calculated from calorimetric and potentiometric studies. Potentiometric studies (30SA, 64AR, 65AZ, 69RM, 71HM and 78VZ) would be expected to provide enthalpy changes of lower accuracy than those determined calorimetrically, particularly when only two different temperatures are used (30SA) or the values for the formation constants are suspect (69RM). Among the remaining results cited above only 71HM and 78VZ actually calculated the enthalpy changes accompanying protonation.

Calorimetric studies have been reported in the following references 69TS, 70MBa, 70W, 71BP, 71JW and 72W. Calorimetric values for ΔH, as well as those calculated from references 71HM and 78VZ are given in Table 2.3. From these values (69TS, 70MBa, 71BP, 71HM) it is possible to give recommended values for the enthalpy of protonation of histidine at 25 °C and I = 0.10 - 0.15 mol dm⁻³. Recommended values are:

$$\Delta H_{NH_3^+} = -42.9(1.5), \quad \Delta H_{i\text{mH}^+} = -30.0(1.2) \text{ kJ mol}^{-1}$$

2.3. Metal Complex Formation Constants.

Histidine has three potential donor centres: the amine nitrogen, the pyridine-like imidazole nitrogen and the carboxyl group. It is therefore possible to form mono and bis metal complexes but tris complexes are unlikely. Protonated complexes (with either glycine-like or imidazole-propionic acid-like bonding) are to be expected as also are partially hydrolysed species. The particular modes of bonding in the various complexed species, particularly those with Cu(II), have been studied by a variety of techniques including potentiometry, calorimetry, visible and i.r. spectroscopy, n.m.r. and e.s.r. and the references are to be found in 76PS.

Crystal structures of a number of complexes of histidine have been determined by X-ray diffraction methods. While these give information on the coordination centres used in solid complexes, they do not give direct evidence of the structures of complexes in solution. However, they can provide very helpful supporting information. The structures reported are listed in Table 2.11.

In solution, complexes with Cu(II) have been studied in most detail, although equilibria with Cu(II) are also among the most complicated. Complexes with

Co(II), Ni(II) and Zn(II) have also been studied in detail. Data on complexes of other metals are generally limited to only a few studies each, many incomplete, so that only 'tentative' formation constants can be selected.

Stereoselectivity in the formation of bis-complexes (demonstrated by a non-statistical difference in stability between the species $[M(\underline{L}-L)(\underline{D}-L)]$ and $[M(\underline{L}-L)_2]$ (70AI)) has been detected in complexes of Co(II), Ni(II), Cu(II) and Zn(II) (63MD, 69RG, 70MM, 76PS, 76R). With $[CuL_2]$ the differences were found to be small, and present only in the protonated complex $[CuHL_2]^+$. Stereoselectivity appears to be insignificant in complexes of VO(II), Cd(II) and Pb(II). When present, it can arise from stereoselectivity in either enthalpy changes alone (Co(II), Ni(II)) or a combination of both enthalpy and entropy changes (Cu(II), Zn(II)) (76PS).

Where significant stereoselectivity in the formation of bis-complexes has been reported, values for the formation constants of both $[M(\underline{L}-L)_2]$ and $[M(\underline{L}-L)(\underline{D}-L)]$ are given. In some cases published values refer to the apparent formation constants found for the racemic mixture. The values therefore include contributions from $[M(\underline{L}-L)_2]$, $[M(\underline{D}-L)_2]$ and $[M(\underline{L}-L)(\underline{D}-L)]$. Formation constants for the true meso-complex, $[M(\underline{L}-L)(\underline{D}-L)]$, have been calculated from these published values and corrected for statistical factors. They are expressed as $\log \beta_{[M(\underline{L}-L)(\underline{D}-L)]} - 0.30$. The magnitude of the stereoselectivity is the difference between this value and the formation constants for complexes with L-histidine.

Metal complexes are considered in three groups. Complexes with Cu(II) are considered first since many species exist in solution and these equilibria have been studied in detail. Co(II), Ni(II) and Zn(II) form the second group since these have also been carefully studied and their bis-complexes form stereoselectively. The final group includes complexes of other metal ions. In general, data for these ions are more limited and the results can only be regarded as tentative at the best.

2.4. Complexes with Copper(II).

Literature values for the formation constants of complexes with Cu(II) are given in Table 2.4. Many calculations have assumed the presence of only mono and bis complexes in solution. However, other species are clearly significant and a species distribution calculation using 'recommended' formation constants with a metal:ligand ratio of 1:2 is shown in Fig. 2.1. While it is possible to select a pH value at which the only significant species is $[CuL_2]$, no such conditions exist for the $[CuL]^+$ species. Hence calculations of β_{110} (β_{CuL}) which neglect protonated species cannot be regarded as reliable. Of the remaining values the majority refer to concentration constants (C) at 25 °C with an ionic background of 0.1 mol dm⁻³.

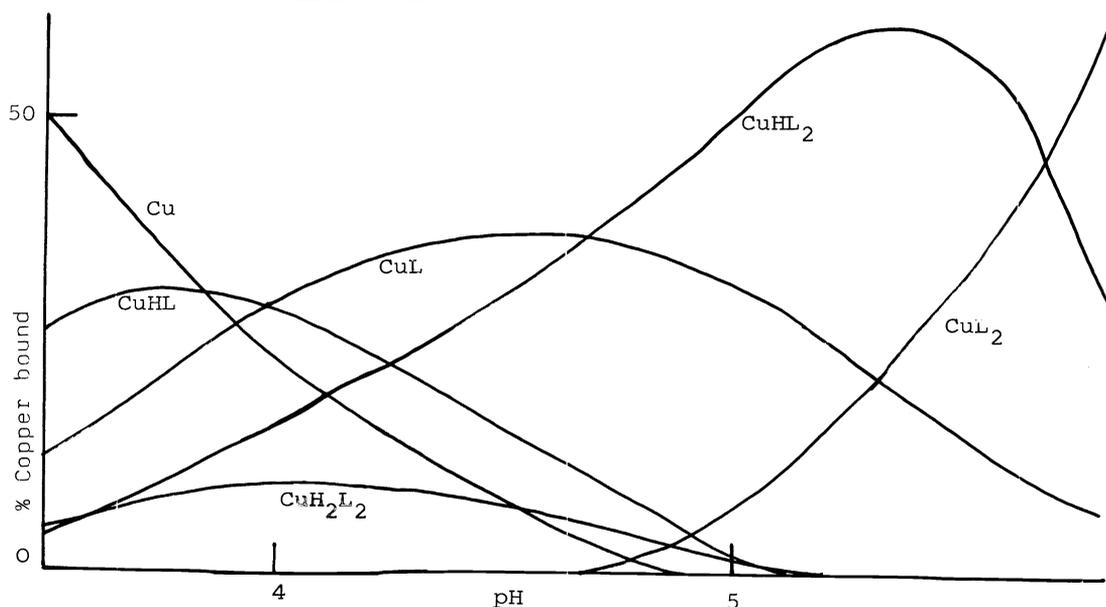
The major species in dilute solution are clearly $[CuHL]^{2+}$ (111), $[CuL]^+$ (101), $[CuHL_2]^+$ (112) and $[CuL_2]$ (102). However, the species $[CuH_2L_2]^{2+}$ (122), $[CuH_{-1}L]$ (1-11) and $[Cu_2H_{-2}L_2]$ (2-22) are also significant, although their formation constants show somewhat lower precision. The significance of these minor species is demonstrated by the fact that the statistics of the fit of calculated to experimental data improved dramatically when they are included in the model, to give calculated data within experimental error of the measured data throughout the pH range of 3.5 - 8.5. The inclusion of further species had no significant effect on the statistics. The partially hydrolysed species, (1-11 and 2-22) are important in 1:1 metal:ligand mixtures but become much less important in 1:2 mixtures. Hence they do not feature in Fig. 2.1. In a number of cases the authors do not provide details of the proton complex formation constants used in calculating the constants for metal complexes (49HB, 50MM, 52K, 66PA, 66TA, 67RP, 68RP, 72KP and 74PS). As a result it is difficult to assess the quality of the constants calculated. Values quoted in

79MJ differ significantly from other comparable values - possibly as a result of differences in the protonation constants.

Two determinations have been reported at 37 °C and with an ionic background of 0.15 mol dm⁻³ K[NO₃] or Na[ClO₄] (67PS and 80NS). The formation constants calculated differ significantly. There is no obvious reason for recommending one determination above the other: hence tentative values at 37 °C and I = 0.15 mol dm⁻³ are not included in Table 2.5. Recommended (R) values for the concentration constants at 25 °C and I = 0.10 mol dm⁻³ are given in table 2.5, together with tentative (T) values at 25 °C and I = 3.0 mol dm⁻³ (Na[ClO₄]).

Stereoselectivity in the formation constants of the bis-complexes is insignificant (70MB, 75R, 76PS) as a result of a coincidental balancing of stereoselectivity in enthalpy and entropy changes. In the monoprotonated bis-complex (112) stereoselectivity is small, but present, favouring the optically active complex [CuH(L-L₂)]⁺ (75R, 76PS).

Figure 2.1. L-Histidine : Cu(II), 2:1



2.5. Complexes of Cobalt(II), Nickel(II) and Zinc(II).

Literature values for the formation constants of complexes with the above metals are given in Table 2.6. In general, the simple mono- and bis-complexes are the only important species present although the presence of protonated complexes in minor concentrations has been found at low pH (76PS).

Recommended (R) values for concentration constants at 25 °C and I = 0.1 mol dm⁻³ are given in Table 2.7, together with tentative (T) values at 25 °C and I = 3.0 mol dm⁻³ Na[ClO₄] and at 37 °C and I = 0.15 mol dm⁻³.

Significant stereoselectivity is found in the formation of bis-complexes of all three metal ions. In all cases the meso-complex is the more stable and it can be calculated that, in solutions of metal ions with a racemic mixture of histidine, the relative concentrations of the bis-complexes are in the region of:

| | $[M(\underline{L}-\underline{L})_2]$ | $[M(\underline{D}-\underline{L})_2]$ | $[M(\underline{L}-\underline{L})(\underline{D}-\underline{L})]$ |
|--------|--------------------------------------|--------------------------------------|---|
| Co(II) | 18% | 18% | 64% |
| Ni(II) | 13% | 13% | 74% |
| Zn(II) | 20% | 20% | 60% |

2.6. Complexes with other Metal Ions.

Values for the formation constants of complexes of other metals with histidine have been reported and literature values are given in Table 2.8. However, in no cases have sufficient reliable determinations been carried out to permit the selection of recommended values. In Table 2.8 values considered reliable have been classed as 'tentative'. Other values are probably reliable but insufficient experimental data are given to allow assessment. Values quoted in 69RM are generally very high in cases in which sufficient determinations have been reported to permit selection of recommended values. Values from 69RM have therefore been rejected. Values in 75PN should also be rejected because they are abnormally low.

2.7. Derivatives of Histidine.

Complexes of a number of N-substituted histidines have also been studied. Literature values of the formation constants (all of which can be regarded as 'tentative') are given in Table 2.9.

Stereoselectivity has been detected in the bis complexes of N^α-substituted histidines with Co(II), Ni(II) and Zn(II), the meso-complexes being more stable than the optically active complexes in all cases (76R). With Cu(II) stereoselectivity was much less significant but was present in the bis-complex of N^α,N^α-dimethylhistidine, the meso-complex again being the more stable. Small stereoselectivity in favour of the optically active protonated bis-complexes was found with N^α-methyl and N^α-benzyl-histidine (75RS).

2.8. Ternary (L-Histidinato)(L-threoninato) Copper(II), CuLT.

This biologically important ternary complex has been studied potentiometrically (69FM, 75BW) and calorimetrically (75BW). No stereoselectivity was detected in the formation of the ternary complex and the overall formation constant ($\log \beta$) was found to be:

75BW: 25 °C and I = 3.0(Na[ClO₄]), $\log \beta_{\text{CuLT}} = 18.60(1)$, $\log \beta_{\text{CuHLT}} = 23.33(3)$

69FM: 25 °C and I = 0.1(K[NO₃]), $\log \beta_{\text{CuLT}} = 17.56$, $\log \beta_{\text{CuHLT}} = 21.90$

The crystal structure of the ternary complex has also been reported (69FG).

2.9. Enthalpy Changes on Complex Formation.

A number of potentiometric studies at different temperatures have been reported, and enthalpy changes calculated (64AR, 65AZ, 69RM, 70CA and 79VZ). In all cases, the results should be treated with caution since the precision of pH measurement is generally low (typically ± 0.02 units) and the technique for the calculation of formation constants is often poor (e.g. reading pL at half \bar{n} values, 70CA). Errors in β values will introduce much larger errors in calculated values of ΔH . This becomes apparent if results in Table 2.10 are examined.

Calorimetric determinations are reported in 67SS, 70JW, 70MB, 70W, 71JW, 71BP, 72W and 76PS. References 70JW and 71JW described the measurement of ΔH values for lanthanide complexes at 25 and 37 °C respectively in 3.0 mol dm⁻³ Na[ClO₄]

Stereoselectivity in enthalpy changes is reported in 71BP and 76PS.

Literature values for measured enthalpy changes, both potentiometric and calorimetric, are reported in Table 2.10. However, only the calorimetric values may be accepted 'tentatively'.

Stereoselectivity in enthalpy changes has been shown to favour the meso-complexes of histidine with Co(II), Ni(II) and Zn(II) (cf. stereoselectivity in formation constants). With Cu(II), the enthalpy change favours the optically active bis complex. Hence the absence of stereoselectivity in the formation constants must be the result of an equal and opposing stereoselectivity in the entropy change.

TABLE 2.1
Protonation Constants of Histidine (HL)
Literature Values

| Ref. | Type of Constant | Medium mol dm ⁻³ | Temp °C | log K _{HL} | log K _{H₂L} | log K _{H₃L} |
|-------|------------------|--|----------------------|-------------------------------|---------------------------------|---------------------------------|
| 30EH | C | → 0 | 23 | 8.95 | 5.98 | 1.78 |
| 30SA | C | → 0 | 0 25 | 9.75 9.12 | 6.83 6.04 | 2.76 1.82 |
| 52A | M? | 0.01 | 20 | 9.20 | 6.08 | 1.82 |
| 53P | M | - | 20 | 9.40 | 6.14 | |
| 55LM | M | 0.15 | 25 | 9.12 | 6.05 | |
| 57LD | M | 0.15 - 0.25 | 25 | 9.20 | 6.17 | |
| 59LR | M | 0.01 | 25 | 9.16 | 6.00 | 1.82 |
| 59MH | ? | - | 25 | 9.2 | | |
| 59P | ? | - | 20 | 9.20 | 6.02 | 1.82 |
| 61JW | M | 0.3(K ₂ SO ₄) | 25 | 9.05(2) | 6.16 | |
| 61V | M | - | 20 | | 6.18 | |
| 63CC | M | 0.2(KNO ₃) | 25 | 9.17 | 6.08 | 1.77 |
| 64AR | M | 0.1(KNO ₃) | 0 25 45 | 9.97 9.18 8.63 | 6.65 6.08 5.66 | |
| 64DC | C | 0.1(KCl) | 25 | 9.08 | 6.08 | 1.92 |
| 65AZ | M | 0.25(KCl) | 0 15 25 40 | 9.81 9.46 9.17 8.86 | 6.62 6.24 6.12 5.88 | 1.98 1.79 1.96 1.85 |
| 65HS | M | 0.025 | 20 | 9.40 | | |
| 67PS | C | 0.15(KNO ₃) | 37 | 8.92 | 5.95 | 2.24 |
| 68RP | M | 0.1(KCl) | 20 | 9.21(10) | | |
| 69FM | C | 0.16(KNO ₃) | 25 ^D L | 9.10(1) 9.12 | 6.03(1) 6.04 | 1.78 1.76 |
| 69MB | C | 0.1(KNO ₃) | 25 | 9.10(1) | 6.02(1) | 1.60(4) |
| 69MM | M | 0.5(KCl) | 25 | 9.20 | 6.10 | |
| 69RG | C | 0.1(KNO ₃) | 25 | 9.10 | 6.04 | 1.65 |
| 69RM | M | 0.2(KNO ₃) | 15 25 40 | 9.67 9.42 9.08 | 6.37 6.22 6.00 | 2.00 2.02 2.06 |
| 70CA | M | 0.12(KCl) | 25 35 45 | 9.16 8.85 8.60 | 6.05 5.67 5.60 | |
| 70MBa | ? | 0.16(KCl) | 25 | 9.21 | 6.17 | 2.02 |
| 70MM | M | 0.1(KCl) | 25 | 9.20 | 6.14 | |
| 70W | C | 3M(NaClO ₄) | 25 | 9.63(1) | 6.97(1) | 2.22(2) |
| 70Z | M | 0.2(KNO ₃ + 0.076CH ₃ CN) | 20 | 9.15 | 6.15 | |
| 71HM | C | → 0 | 25 37 50 | 9.31(4) 9.03(4) 8.73(4) | 6.02(4) 5.80(4) 5.60(4) | |
| 72IB | M | 0.12(NaCl) | 25 | 9.20(2) | 6.08(3) | 1.81(3) |
| 73BJ | M? | 1.0(NaNO ₃) | 25 | 9.20 | 6.08 | 1.82 |
| 73KS | C | 0.15(NaCl) | 25 | 9.11(1) | 6.06(1) | 1.83(2) |
| 75PN | M | 0.1(KCl) | 20 | 9.1(1) | 6.1 | |
| 76BP | C | 0.1(KNO ₃) | 25 | 9.13(1) | 6.05(1) | 1.58(2) |
| 76PS | C | 0.1(KNO ₃) | 25 ^D L | 9.12(1) 9.12(1) | 6.09(1) 6.10(1) | 1.72(2) 1.70(3) |

Table 2.1 Cont.

| | | | | | | |
|-----------|----|---------------------------|------|----------|----------|--------|
| 77BS | M | 0.12(NaCl) | 25 | 9.20(2) | 6.08(3) | 1.81 |
| 78DO | C | 0.1(KNO ₃) | 25 | 9.09(15) | 6.03(15) | 1.8(2) |
| 78VZ | M | 0.2(NaCl) | 15 | 9.46 | 6.25 | |
| | | | 25 | 9.16 | 6.10 | |
| | | | 35 | 8.98 | 5.98 | |
| | | 0.5(NaCl) | 15 | 9.50 | 6.26 | |
| | | | 25 | 9.16 | 6.12 | |
| | | | 35 | 9.00 | 6.00 | |
| 1.0(NaCl) | 15 | 9.52 | 6.27 | | | |
| | 25 | 9.19 | 6.14 | | | |
| | 35 | 9.03 | 6.01 | | | |
| | C | 0 | 25 | 9.28 | 5.97 | |
| 79MJ | C | 0.1(KNO ₃) | 25 | 9.18 | 6.40 | 1.18 |
| 80NS | C | 0.15(NaClO ₄) | 37 | 8.96(3) | 6.00(4) | 2.41 |

TABLE 2.2

Recommended (R) and Tentative (T) Values for the Protonation Constants of Histidine

| Ref. | Type of Constants | Medium mol dm ⁻³ | Temp | log H _L | log K _{H₂L} | log K _{H₃L} |
|--|-------------------|-----------------------------|------|--------------------|---------------------------------|---------------------------------|
| 55LM, 63CC, 64AR, 65AZ, 68RP, 70CA, 72IB. | M(R) | 0.1 - 0.2 | 25 | 9.17 (0.03) | 6.07 (0.02) | 1.8 (0.1) |
| 69FM, 69MB, 69RG, 73KS, 76BP, 76PS. | C(R) | 0.1 - 0.15 | 25 | 9.11 (0.02) | 6.05 (0.03) | 1.72 (0.09) |
| 67PS, 80NS | C(R) | 0.15 | 37 | 8.94 | 5.98 | 2.3 |
| 70W | C(T) | 3.0(NaClO ₄) | 25 | 9.63 | 6.97 | 2.22 |
| 71JW | C(T) | 3.0(NaClO ₄) | 37 | 9.37 | 6.68 | 2.00 |

TABLE 2.3

Single Step Enthalpy changes in the Protonation of Histidine
(kJ mol⁻¹)

| Ref. | Technique | Medium mol dm ⁻³ | Temp °C | -ΔH _{HL} | ΔH _{H₂L} |
|-----------------------|-----------|-----------------------------|---------|-------------------|------------------------------|
| 69TS | Cal | 0.10(KNO ₃) | 25 | 40.6 | 30.5 |
| 70Mba | Cal | 0.16(KCl) | 25 | 43.6 | 29.3 |
| 71BP | Cal | 0.10(KNO ₃) | 25 | 44.1 | 28.7 |
| 71JW | Cal | 3.0(NaClO ₄) | 37 | 35 | 29 |
| 70W, 72W ^a | Cal | 3.0(NaClO ₄) | 25 | 40.4 | 36.6 |
| 71HM | Pot | 0 | 25 | 43.1 | 31.4 |
| 78VZ | Pot | 0 | 25 | 44.8 | 22.6 |

$$^a \Delta H_{H_3L} = -1.0(4)$$

$$\Delta H_{HL} = \Delta H_{NH_3^+}, \quad \Delta H_{H_2L} = \Delta H_{imH^+}.$$

TABLE 2.4
Formation Constants of Complexes of L-Histidine with Copper(II)

| Ref. | Type of Constant | Medium mol dm ⁻¹ | Temp °C | Literature Values | | | | | | |
|-------|------------------|--|---------------------|------------------------------|-------------------------|----------------------|----------------------------------|--|---|--|
| | | | | log β _M | log β _{ML} | log β _{MHL} | log β _{MH₂L} | log β _{MH₂L₂} | log β _{MH₂L₂L₂} | |
| 50MM | M | 0.01 | 25 | 18.33 | | | | | | |
| 57LD | M | 0.15 - 0.25 | 25 | 10.60 | | | | | | |
| 59LR | M | 0.1 | 25 | 10.37 | 14.18 | 3.19 | | | | |
| 59P | ? | ? | 20 | 10.35 | 14.27 | | 24.33 | | | |
| 61JW | M | 0.3(K ₂ SO ₄) | 25 | 10.3-10.5 | | | | | | |
| 63CC | M | 0.2(KNO ₃) | 25 | 10.30 | | | | | | |
| 64DC | M | 0.1(KCl) | 25 | 10.21(5) | 18.32(5) | | | | | |
| 65AZ | M | 0.25(KCl) | 0 15 25 40 | 12.8 11.2 10.7 10.5 | | | | | | |
| 67PS | C | 0.15(KNO ₃) | 37 | 9.79(5) | 17.41(3) | 2.17 | 23.04 | | 6.97 | |
| 69FM | C | 0.16(KNO ₃) | 25 | 10.13(1) | 18.10(1) | 2.13 | 23.65 | 26.85 | 8.02 | |
| 69RM | M | 0.2(KNO ₃) | 15 25 40 | 11.03 10.74 10.43 | 19.94 19.40 18.60 | | | | | |
| 70MBa | ? | 0.16(KNO ₃) | 25 | 10.01(7) | 18.02(7) | 13.58 | 23.71 | | | |
| 70Z | M | 0.2(KNO ₃ + .076MCH ₃ CN) | 20 | | | 13.80 | | 26.20 | | |
| 71HM | C | 0 | 25 | 10.22(2) | 18.20(2) | 14.46(5) | 24.15 | | | |
| 72KP* | M | 0.2(NaClO ₄) | 20 | 10.65 | 18.91 | | | | | |
| 72W | C | 3.0(NaClO ₄) | 25 | 10.09(8) | 19.03(4) | 3.46 | 25.88 | 30.75 | | |
| 73KS | C | 0.15(NaCl) | 25 | 10.20(2) | 18.45(1) | 2.00 | 24.01 | 26.91 | 8.0 | |
| 75R* | C | 0.1(KNO ₃) | 25 | 10.22(3) | 18.11(8) | 14.13(6) | 23.76 | | | |

Table 2.4 Cont.

| | | | | | | | | |
|-------|---|---------------------------|----|-----------|-----------|----------|----------|---------|
| 76BP | C | 0.1(KNO ₃) | 25 | 10.11(1) | 18.08(1) | 14.09(1) | 23.88 | 27.56 |
| 76PS* | C | 0.1(KNO ₃) | 25 | 10.13(1) | 18.10(1) | 14.13(1) | 23.92 | 27.48 |
| 77BS | M | 0.12(NaCl) | 25 | 10.30(10) | 18.07(10) | | | |
| 78SK | C | 0.2(KCl) | 25 | 10.04 | 17.82 | 14.07 | 23.63 | 27.13 |
| 79MJ | | 0.1(KNO ₃) | 25 | 10.37 | 18.07 | 14.42 | 24.17 | 8.0 |
| 80NS | C | 0.15(NaClO ₄) | 37 | 10.27(2) | 18.49(4) | 14.38(4) | 23.96(3) | 27.4(2) |

*Racemic histidine also studied. Stereoselectivity generally insignificant.

TABLE 2.5

Recommended and Tentative Values for the Formation Constants of Complexes of Copper(II) with

L or Racemic Histidine

| Ref. | Type of Constant | Medium mol dm ⁻³ | Temp °C | log β _{ML} | log β _{ML₂} | log β _{MHL} | log β _{MH₋₁L} | log β _{MHL₂} | log β _{M₂H₋₂L₂} |
|--|------------------|-----------------------------|---------|---------------------|---------------------------------|----------------------|-----------------------------------|----------------------------------|---|
| 69FM, 73KS, 75R, 76BP, 76PS, 78SK: | C(R) | 0.1 - 0.2 | 25 | 10.16 (0.03) | 18.11 (0.09) | 14.11 (0.02) | 23.81 (0.07) | 27.2 (0.1) | 7.9 (0.1) |
| 72W | C(T) | 3.0(NaClO ₄) | 25 | 10.09 | 19.03 | 15.62 | 3.5 | 25.88 | 30.75 |

TABLE 2.6

Formation Constants of Complexes of L-Histidine
with Cobalt(II), Nickel(II) and Zinc(II) - Literature Values

$$\log \beta_{\text{meso}} = \log \beta_{[M(\underline{L}-L)(\underline{D}-L)]} - 0.3$$

Cobalt(II)

| Ref. | Type of Constant | Medium mol dm ⁻³ | Temp °C | log β _{ML} | log β _{ML₂} | log β _{meso} |
|-------------------|------------------|-----------------------------|----------|---------------------|---------------------------------|-----------------------|
| 49HB | M? | ? | 25 | 7.30 | 14.63 | |
| 50MM | M? | 0.01 | 25 | | 13.86 | |
| 59LR | M | 0.01 | 25 | 6.92 | 12.44 | |
| 65AZ | M | 0.25(KCl) | 0 | 7.30 | 13.37 | |
| | | | 15 | 7.10 | 12.72 | |
| | | | 25 | 6.77 | 11.90 | |
| | | | 40 | 6.56 | 11.50 | |
| 66PA | ? | ? | 25 | 6.9 | 12.6 | |
| 67PS | C | 0.15(KNO ₃) | 37 | 6.71(2) | 12.06(2) | |
| 69MM | M | 0.5(KCl) | 25 | 6.45 | 11.50 | |
| 69RM | M | 0.2(KNO ₃) | 15 | 7.31 | 13.08 | |
| | | | 25 | 7.20 | 12.84 | |
| | | | 40 | 7.04 | 12.50 | |
| 69RG | C | 0.1(KNO ₃) | 25 | 6.86 | 12.25 | 12.49 |
| 70MM | C | 0.1(KCl) | 25 | 6.92(3) | 12.42(3) | 12.56 |
| 70W | C | 3.0(NaClO ₄) | 25 | 7.44(2) | 13.48(2) | |
| 76PS ^a | C | 0.1(KNO ₃) | 25 | 6.83(1) | 12.35(1) | 12.64 |
| 76R | C | 0.1(KCl) | 25 | 6.90(1) | 12.39(1) | 12.62 |
| 79VZ | M | 0.2(NaCl) | 15 | 6.97(3) | 12.45(4) | |
| | | | 25 | 6.80(2) | 12.24(3) | |
| | | | 35 | 6.70(3) | 12.14(3) | |
| | | 0.5(NaCl) | 15 | 6.89(2) | 12.30(3) | |
| | | | 25 | 6.72(2) | 12.15(4) | |
| | | | 35 | 6.56(3) | 12.01(4) | |
| 1.0(NaCl) | 15 | 6.78(3) | 12.24(3) | | | |
| | 25 | 6.61(3) | 12.05(3) | | | |
| | 35 | 6.51(4) | 11.94(4) | | | |
| " | C | →0 | 25 | 7.32(2) | 13.04(3) | |

^a log β_{MHL} = 11.44(3), log β_{MHL₂} = 18.36(2)

Nickel(II)

| | | | | | | |
|------|---|--------------------------|----|---------|----------|-------|
| 52A | M | 0.01 | 25 | | 15.9 | |
| 57LD | M | 0.15-0.25 | 25 | 8.79 | 15.84 | |
| 59LR | M | 0.01 | 25 | 8.69 | 15.52 | |
| 63CC | M | 0.2(KNO ₃) | 25 | 8.62 | | |
| 65AZ | M | 0.25(KCl) | 0 | 9.28 | 16.99 | |
| | | | 15 | 8.79 | 15.87 | |
| | | | 25 | 8.50 | 15.19 | |
| | | | 40 | 8.30 | 14.70 | |
| 66PA | ? | | 25 | 8.7 | 15.3 | |
| 67PS | C | 0.15(KNO ₃) | 37 | 8.43(2) | 15.14(3) | |
| 69RM | M | 0.2(KNO ₃) | 15 | 9.09 | 16.39 | |
| | | | 25 | 8.92 | 16.05 | |
| | | | 40 | 8.69 | 15.57 | |
| 69RG | C | 0.1(KNO ₃) | 25 | 8.66 | 15.50 | 15.85 |
| 70M | C | 0.1(KCl) | 25 | 8.69 | 15.58 | 15.84 |
| 70W | C | 3.0(NaClO ₄) | 25 | 9.20(1) | 16.65(2) | |

Table 2.6 Cont.

| | | | | | | |
|-------------------|---|--------------------------|----|----------|-----------|-------|
| 72IB | ? | 0.12(NaCl) | 25 | 8.48(1) | 15.24 | |
| 72KP | ? | 0.2(NaClO ₄) | 20 | 8.75 | 14.75 | 15.76 |
| 73BJ | ? | 1.0(NaNO ₃) | 25 | 8.36 | 15.40 | 15.85 |
| 76BP ^b | C | 0.1(KNO ₃) | 25 | 8.67(1) | 15.56(1) | |
| 76PS ^c | C | 0.1(KNO ₃) | 25 | 8.64(1) | 15.46(1) | 15.94 |
| 78DO | C | 0.1(KNO ₃) | 25 | 8.67(15) | 15.52(15) | |
| 79VZ | M | 0.2(NaCl) | 15 | 8.64(1) | 15.52(2) | |
| | | | 25 | 8.45(4) | 15.24(2) | |
| | | | 35 | 8.33(3) | 14.97(3) | |
| | | 0.5(NaCl) | 15 | 8.67(3) | 15.48(4) | |
| | | | 25 | 8.48(2) | 15.19(3) | |
| | | | 35 | 8.34(3) | 15.01(4) | |
| | | 1.0(NaCl) | 15 | 8.79(4) | 15.60(4) | |
| | | | 25 | 8.60(2) | 15.33(3) | |
| | | | 35 | 8.51(3) | 15.14(4) | |
| " | C | →0 | 25 | 8.90(2) | 15.90(3) | |

$$^b \log \beta_{\text{MHL}} = 12.06(6), \quad \log \beta_{\text{MHL}_2} = 20.32(4).$$

$$^c \log \beta_{\text{MHL}} = 12.28(3), \quad \log \beta_{\text{MHL}_2} = 20.49(5).$$

Zinc(II)

| | | | | | | |
|-------------------|---|--------------------------|----|----------|-----------|-------|
| 50MM | ? | 0.01 | 25 | | 12.88 | |
| 52A | M | 0.01 | 20 | | 12.0 | |
| 53P | M | - | 20 | | 12.0 | |
| 55LM | M | 0.15 | 25 | 6.67 | 11.78 | |
| 59LR | M | 0.01 | 25 | 6.63 | 12.30 | |
| 63CC | M | 0.2(KNO ₃) | 25 | 6.57 | | |
| 65AZ | ? | 0.25(KCl) | 0 | 7.00 | 12.96 | |
| | | | 15 | 6.78 | 12.33 | |
| | | | 25 | 6.40 | 11.42 | |
| | | | 40 | 6.52 | 11.59 | |
| 66PA | ? | - | 25 | 6.94(9) | 12.53 | |
| 67PS | C | 0.15(KNO ₃) | 37 | 6.34(1) | 11.69 | |
| 69MB | C | 0.1(KNO ₃) | 25 | 6.49(1) | 11.90(1) | |
| 69RM | M | 0.2(KNO ₃) | 15 | 7.01 | 12.65 | |
| | | | 25 | 6.91 | 12.44 | |
| | | | 40 | 6.78 | 12.15 | |
| 70MM | C | 0.1(KCl) | 25 | 6.56(4) | 12.06(4) | 12.18 |
| 70W | C | 3.0(NaClO ₄) | 25 | 7.07(4) | 12.74(2) | |
| 76BP ^d | C | 0.1(KNO ₃) | 25 | 6.45(1) | 12.01(1) | |
| 76PS ^e | C | 0.1(KNO ₃) | 25 | 6.48(1) | 12.07(1) | 12.19 |
| 76R | C | 0.1(KCl) | 25 | 6.57(1) | 12.07(1) | 12.28 |
| 78DO | C | 0.1(KNO ₃) | 25 | 6.53(16) | 11.92(16) | |

$$^d \log \beta_{\text{MHL}} = 11.30(1), \quad \log \beta_{\text{MHL}_2} = 17.80(2).$$

$$^e \log \beta_{\text{MHL}} = 11.42(2), \quad \log \beta_{\text{MHL}_2} = 17.89(2).$$

TABLE 2.7

Recommended and Tentative Values for the Formation Constants of Complexes of Cobalt(II), Nickel(II) and Zinc(II) with L-Histidine

| | Temp °C | Medium mol dm ⁻³ | Type of Constant | log β _{ML} | log β _{ML₂} | Stereo- selecti- vity with D/L Histidine | Refs. |
|--------|------------|--------------------------------|---------------------|-----------------------|---------------------------------|---|--|
| Co(II) | 25 | 0.1 | <u>C(R)</u> | <u>6.88</u> (0.02) | <u>12.35</u> (0.04) | +0.23 (0.04) | 69RG, 70MM, 76PB, 76R. |
| | 25 | 3.0(NaClO ₄) | C(T) | 7.44 | 1.348 | | 70W |
| | 37 | 0.15 | C(T) | 6.71 | 12.06 | | 67PS |
| Ni(II) | 25 | 0.1 | <u>C(R)</u> | <u>8.67</u> (0.01) | <u>15.50</u> (0.02) | +0.38 (0.06) | 69RG, 70MM, 76BP, 76PS, 78DO. |
| | 25 | 3.0(NaClO ₄) | C(T) | 9.20 | 16.65 | | 70W |
| | 37 | 0.15 | C(T) | 8.43 | 15.14 | | 67PS |
| Zn(II) | 25 | 0.1 | <u>C(R)</u> | <u>6.51</u> (0.04) | <u>12.01</u> (0.04) | +0.15 (0.04) | 69MB, 70MM, 76BP, 76PS, 76R, 78DO. |
| | 25 | 3.0(NaClO ₄) | C(T) | 7.07 | 12.74 | | 70W |
| | 37 | 0.15 | C(T) | 6.34 | 11.69 | | 67PS |

TABLE 2.8

Formation Constants of Complexes of L-Histidine with Metal Ions
Literature Values

(Metal ions are given in alphabetical order, with lanthanide ions at the end)

| Metal Ion | Ref | Type of Constant | Medium mol dm ⁻³ | Temp °C | log β _{ML} | log β _{ML₂} | Recom. or comments |
|--------------|------|--------------------------|---|------------|---------------------|---------------------------------|--|
| Be(II) | 70CA | M | 0.12(KCl) | 25 | 6.28 | 10.98 | |
| | | | | 35 | 5.52 | 10.02 | |
| | | | | 45 | 4.78 | 9.10 | |
| Cd(II) | 53P | ? | ? | 25 | | 11.1 | |
| | 55LM | M | 0.15 | 25 | | 11.10 | |
| | 59LR | M | 0.01 | 25 | 5.65 | 9.79 | |
| | 64AR | M | 0.1(KNO ₃) | 0 | | 11.40 | |
| | | | | 25 | | 10.20 | |
| | 45 | | 9.90 | | | | |
| | 66P | ? | ? | 25 | 5.8(2) | 10.0 | |
| 70MM | M | 0.1(KCl) | 25 | 5.39(4) | 9.66(4) | T | |
| 74WW | C | 3.0(NaClO ₄) | 25 | 6.48(2) | 11.11(3) | T | |
| Cu(I) | 61JW | | 0.3(KSO ₄) | 25 | | 10.4? | |
| | 70Z | M | 0.2(KNO ₃ + 0.076MCH ₃ CN) | 25 | | | log β _{MHL} = 12.80 log β _{MH₂L₂} = 25.20 |
| Fe(II) | 52A | M | 0.01 | 37 | | 9.3 | |
| | 69RM | M | 0.2(KNO ₃) | 15 | 5.39 | 8.74 | |
| | | | | 40 | 5.28 | 8.50 | |
| 70W | C | 3.0(NaClO ₄) | 25 | 5.88 | 10.43 | T | |
| Fe(III) | 58P | | 0.1 | 20 | 4.7(4) | | |

Table 2.8 Cont.

| | | | | | | | | |
|----------------------|-------------------|---|--------------------------|----------|---|--------------|--|---|
| Hg(II) | 66TA | ? | ? | 25 | 20.62(6) | | | |
| | 75LB | M | 0.01(NaNO ₃) | 25 | log $\beta_{MHL}=12.3$, log $\beta_{MH_2L}=19.5$ | | | |
| Mn(II) | 50MM | M | 0.01 | 25 | 7.74 | | | |
| | 52A | M | 0.01 | 20 | < 4 | | | |
| | 52K | ? | 0.1(KCl) | 25 | 3.58 | | | |
| | 67PS | C | 0.15(KNO ₃) | 37 | 3.24(10) | 6.16(9) | | T |
| | 69RM | M | 0.2(KNO ₃) | 15 40 | 3.35 3.32 | 5.78 5.71 | | |
| | 70W | C | 3.0(NaClO ₄) | 25 | 3.91(2) | 6.61(3) | | T |
| Pb(II) | 55LM | M | 0.15 | 25 | 6.84 | | | |
| | 66TA | ? | ? | 25 | 6.36 | | | |
| | 67PS | C | 0.15(KNO ₃) | 37 | 5.96(8) | 9 | | T |
| | 73CT | C | 3.0(NaClO ₄) | 25 | 6.90(1) | 9.8(1) | | T |
| | 76PS ^a | C | 0.1(KNO ₃) | 25 | 5.95(1) | 10.1(1) | | T |
| UO ₂ (II) | 57LD | ? | 0.15 - 0.25 | 25 | 7.71 | | | |
| VO ₂ (II) | 76PS ^b | C | 0.1(KNO ₃) | 25 | 9.04(1) | 15.48(2) | | T |

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| Metal ion | Type of Constant | Medium M | Temp °C | log β_{ML} | log β_{MHL} | log β_{ML_2} | Recom | |
|-----------|------------------|----------|--------------------------|------------------|-------------------|--------------------|---------|---|
| Ce(III) | 67RP | ? | ? | 4.46, 4.30 | | | | |
| | 68RP | M | 0.1(KCl) | 20 | 4.6(2) | | | |
| Dy(III) | 70JW | C | 3.0(NaClO ₄) | 25 | 4.40(6) | 11.2(2) | 9.14(7) | T |
| | 71JW | C | 3.0(NaClO ₄) | 37 | 5.09(10) | 11.6(2) | 9.85(7) | T |
| | 75PN | M | 0.1(KCl) | 20 | 3.2 | | | |
| Er(III) | 70JW | C | 0.1(KCl) | 25 | 4.49(8) | 11.2(1) | 8.99(9) | T |
| | 71JW | C | 0.1(KCl) | 37 | 5.0(1) | 11.40(8) | 9.91(5) | T |
| Gd(III) | 70JW | C | 0.1(KCl) | 25 | 4.4(1) | 11.47(8) | 8.6(1) | T |
| | 71JW | C | 0.1(KCl) | 37 | 4.9(2) | 11.3(2) | 9.16(9) | T |
| | 74PS | ? | 0.1(KCl) | 20 | 4.68 | | | |
| | 75PN | M | 0.1(KCl) | 20 | 3.1 | | | |
| La(III) | 70JW | C | 3.0(NaClO ₄) | 25 | 4.1(1) | 11.8(2) | 5.4(2) | T |
| | 71JW | C | 3.0(NaClO ₄) | 37 | 3.40(5) | 11.07(5) | 6.9(2) | T |
| | 74PS | ? | 0.1(KCl) | 20 | 4.18 | | | |
| | 75PN | M | 0.1(KCl) | 20 | 3.5 | | | |
| Nd(III) | 70JW | C | 3.0(NaClO ₄) | 25 | 4.40(9) | 11.77(7) | 6.6(1) | T |
| | 71JW | C | 3.0(NaClO ₄) | 37 | 3.95(9) | 11.2(1) | 8.12(8) | T |
| | 74PS | ? | 0.1(KCl) | 20 | 4.68 | | 8.44 | |
| Pr(III) | 70JW | C | 3.0(NaClO ₄) | 25 | 4.36(3) | 11.77(7) | 6.2(1) | T |
| | 71JW | C | 3.0(NaClO ₄) | 37 | 3.69(7) | 11.04(6) | 7.78(5) | T |
| | 74PS | ? | 0.1(KCl) | 20 | 4.34 | | 8.43 | |
| Sm(III) | 70JW | C | 3.0(NaClO ₄) | 25 | 4.46(7) | 11.78(5) | 8.71(8) | T |
| | 71JW | C | 3.0(NaClO ₄) | 37 | 4.37(8) | 11.2(2) | 8.8(1) | T |
| | 75PN | M | 0.1(KCl) | 20 | 3.1 | | | |

Table 2.8 Cont.

| | | | | | | | |
|--------------|---|--------------------------|----|--------|---------|----------|---|
| Yb(III) 70JW | C | 3.0(NaClO ₄) | 25 | 4.2(1) | 11.4(2) | 9.83(5) | T |
| 71JW | C | 3.0(NaClO ₄) | 37 | 4.8(2) | 11.6(2) | 10.31(9) | T |
| 75PN | M | 0.1(KCl) | 20 | 3.3 | | | |

$$^a \log \beta_{\text{MHL}_2} = 17.13(8), \quad \log \beta_{\text{MH}_2\text{L}_2} = 23.39(4).$$

$$^b \log \beta_{\text{MHL}_2} = 21.42(2), \quad \log \beta_{\text{MH}_2\text{L}_2} = 26.0(1), \quad \log \beta_{\text{MH}_{-1}\text{L}} = 3.48(2).$$

TABLE 2.9

Formation Constants of Complexes of N-Substituted L-Histidines
at 25 °C and I = 0.10 (KNO₃)
(concentration constants)

Ligands studied:

- I N^α-methylhistidine, C₇H₁₁O₂N₃ (75R, 76R)
- II N^α,N^α-dimethylhistidine, C₈H₁₃O₂N₃ (75R, 76R)
- III N^α-benzylhistidine, C₁₃H₁₅O₂N₃ (75R, 76R)
- IV N³-benzylhistidine, C₁₃H₁₅O₂N₃ (76BP)
- V N³N^α-dibenzylhistidine, C₂₀H₂₁O₂N₃ (76BP)

Proton Complexes:

| Ref. | ligand | log K _{HL} | log K _{H₂L} | log K _{H₃L} |
|------|--------|---------------------|---------------------------------|---------------------------------|
| 75R | I | 9.32 | 5.93 | 1.42 |
| 75R | II | 8.88 | 6.01 | 1.14 |
| 75R | III | 8.32 | 5.94 | 1.30 |
| 76BP | IV | 9.21(1) | 5.52(1) | 1.94(2) |
| 76BP | V | 8.47(1) | 5.51(1) | 2.03(2) |

Complexes with Cu(II):

| Ref. | ligand | log β _{ML} | log β _{ML₂} | log β _{MHL} | log β _{MHL₂} | log β _{MH₂L₂} |
|------|--------|---------------------|---------------------------------|----------------------|----------------------------------|--|
| 75R | I* | 9.62(1) | 16.89(1) | 13.44(1) | 22.27(1) | |
| 75R | II* | 9.05(1) | 13.57(1) | 12.82(1) | 20.87(1) | |
| 75R | III* | 8.87(1) | 15.87(1) | 12.79(1) | 21.20(1) | |
| 76BP | IV | 10.19(1) | 18.52(1) | 13.74(1) | 23.62(1) | 27.05(1) |
| 76BP | V | 8.96(1) | 16.76(1) | 12.46(4) | 21.02(6) | 25.34(6) |

Complexes with Co(II), Ni(II) and Zn(II):

| Metal ion | Ref. | ligand | log β _{ML} | log β _{ML₂} | log β _{MHL} | log β _{MHL₂} |
|-----------|------|--------|---------------------|---------------------------------|----------------------|----------------------------------|
| Co(II) | 76R | I* | 6.82(1) | 12.10(1) | | |
| | 76R | II* | 6.89(1) | 10.30(1) | | |
| | 76R | III* | 6.24(1) | 11.89(1) | | |
| Ni(II) | 76R | I* | 8.55(1) | 15.05(1) | | |
| | 76R | II* | 8.49(1) | 12.14(1) | | |
| | 76R | III* | 7.87(1) | 14.47(1) | | |
| | 76BP | IV | 8.82(1) | 16.11(1) | 11.53(7) | 20.18(9) |
| | 76BP | V | 8.01(1) | 15.14(1) | | 19.32(6) |

Table 2.9 Cont.

| | | | | | |
|--------|------|------|---------|----------|--------------------------------------|
| Zn(II) | 76R | I* | 6.37(1) | 11.34(1) | |
| | 76R | II* | 6.34(1) | 9.04(1) | $\log \frac{K_{11}}{K_{12}} = 10.55$ |
| | 76R | III* | 5.79(1) | 11.06(1) | |
| | 76BP | IV | 6.58(1) | 12.17(1) | |
| | 76BP | V | 5.74(1) | 11.49(1) | 16.92(1) |

* Both racemic and L-ligands studied. For Co(II), Ni(II) and Zn(II) the meso-bis complexes are always more stable than the optically active analogues. For Cu(II) the meso-bis-complex is more stable with ligand(II) while the optically active bis-complex is more stable with ligand(I).

TABLE 2.10

Enthalpy Changes in the Formation of Metal Complexes of L-Histidine
(kJ mol⁻¹)

| Metal | Ref. | Technique | Medium mol dm ⁻³ | T °C | -ΔH _{M_L} | -ΔH _{M_L2} (overall) |
|--------|-------|-----------|-----------------------------------|---------|------------------------------|--|
| Be(II) | 70CA | pot | 0.12(KCl) | 25-45 | 136 | 172 |
| Cd(II) | 64AR | pot | 0.1(KNO ₃) | 0-45 | | 59(4) |
| Co(II) | 65AZ | pot | 0.25(KCl) | 0-40 | 33 | 52 |
| | 67SS | cal | 0.1(KNO ₃) | 22 | | 49.0 |
| | 69RM | pot | 0.2KNO ₃) | 15-40 | | 40 |
| | 70W | cal | 3.0(KClO ₄) | 25 | 23.6(2) | 51.3(3) |
| | 76PS | cal | 0.1(KNO ₂) | 25 | | 49.0(1) |
| | | | | | | |
| | 79VS | cal | → 0 | 15-35 | 21(4) | 25(8) |
| Cu(II) | 65AZ | pot | 0.25(KCl) | 0-40 | | 115 |
| | 67SS | cal | 0.1(KNO ₃) | 22 | | 89.1 |
| | 69RM | pot | 0.2(KNO ₃) | 15-40 | | 92 |
| | 70MBa | cal | 0.16(KNO ₃) | 25 | 48.4 | 89.2 |
| | 71BP | cal | 0.1(KNO ₃) | 25 | | 83.6 |
| | | | | | | |
| | 72W | cal | 3.0(NaClO ₄) | 25 | 43.9(7) | 83.9(8) |
| | | | | | | ΔH _{MHL} = 67(1) |
| | | | | | | ΔH _{MHL} = 108(1) |
| | | | | | | ΔH _{MH₂L} = 130(2) |
| Fe(II) | 69RM | pot | 0.2(KNO ₃) | 15-40 | | 17 |
| | 70W | cal | 3.0(NaClO ₄) | 25 | 18.3(3) | 38.1(5) |
| Mn(II) | 69RM | pot | 0.2(KNO ₃) | 15-40 | | 5 |
| | 70W | cal | 3.0(NaClO ₄) | 25 | 11.3(3) | 21.9(5) |
| Ni(II) | 65AZ | pot | 0.25(KCl) | 0-40 | 48 | 57 |
| | 67SS | cal | 0.1(KNO ₃) | 22 | | 69.4 |
| | 69RM | pot | 0.2(KNO ₃) | 15-40 | | 57 |
| | 70W | cal | 3.0(NaClO ₄) | 25 | 36.1(2) | 79.1(3) |
| | 71BP | cal | 0.1(KNO ₃) | 25 | | 69.1(2) |
| | | | | | | $[\text{Ni}(\underline{\text{L}}-\underline{\text{L}})(\underline{\text{D}}-\underline{\text{L}})]$ = 71.7(2) |

Table 2.10 Cont.

| | | | | | | |
|---|------|-----|--------------------------|-------|---------|---------|
| Zn(II) | 79VZ | cal | → 0 | 15-35 | 25(8) | 46(8) |
| | 65AZ | pot | 0.25(KCl) | 0-40 | 25 | 48 |
| | 69RM | pot | 0.2(KNO ₃) | 15-40 | | 35 |
| | 70W | cal | 3.0(NaClO ₄) | 25 | 23.1(3) | 48.4(4) |
| | 71BP | cal | 0.1(KNO ₃) | 25 | | 47.8(2) |
| $[Zn(\underline{L}-L)(\underline{D}-L)](2)$ | | | | | | |

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(Measured calorimetrically in 3.0(NaClO₄) - overall enthalpy changes - 70JW, 71JW)

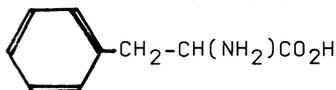
| Ion | T ₀ ^{emp} _C | ΔH _{ML} | -ΔH _{ML2} | -ΔH _{MHL} |
|---------|--|-------------------|----------------------|--------------------|
| La(III) | 25 37 | 11.5(6) 9.1(1) | 19.5(10) 23.4(11) | 11.6(8) 8.1(9) |
| Pr(III) | 25 37 | 10.3(6) 8.5(1) | 21.1(10) 25.4(12) | 12.3(8) 8.8(10) |
| Nd(III) | 25 37 | 7.8(1) 5.5(1) | 20.5(10) 24.6(11) | 10.0(9) 6.4(10) |
| Sm(III) | 25 37 | 2.3(1) 0.2(1) | 15.1(9) 20.1(11) | 10.5(6) 5.0(9) |
| Gd(III) | 25 37 | 7.1(1) 9.0(1) | 8.6(8) 12.9(10) | 4.1(7) 0.8(8) |
| Dy(III) | 25 37 | 9.2(1) 11.1(1) | 8.6(10) 12.3(11) | 4.1(8) 5.5(9) |
| Er(III) | 25 37 | 7.1(1) 8.5(1) | 9.2(8) 13.0(10) | 1.5(6) 5.0(8) |
| Yb(III) | 25 37 | 6.6(1) 7.6(1) | 5.1(7) 9.0(8) | 1.2(6) 4.7(7) |

TABLE 2.11

Crystal Structure Determinations of Metal Complexes of Histidine

| Ref. | Complex |
|------------------------------|---|
| 63HC | [Zn(II)(<u>D</u> -L)(<u>L</u> -L)]5H ₂ O |
| 63KC (refined in 72K) | [Zn(II)(<u>L</u> -L) ₂]2H ₂ O |
| 67CH (neutron study in 76FB) | [Cd(II)(<u>L</u> -L) ₂]2H ₂ O |
| 67FH | [Ni(II)(<u>D</u> <u>L</u> -L) ₂]H ₂ O (as [Ni(<u>L</u> -L) ₂ + Ni(<u>D</u> -L) ₂]2H ₂ O) |
| 68HL | [Co(II)(<u>L</u> -L) ₂]H ₂ O |
| 69E | [Cu(II)(<u>L</u> -HL) ₂] ²⁺ [NO ₃] ₂ ·H ₂ O |
| 70CH | [Co(II)(<u>L</u> -L)(<u>D</u> -L)]2H ₂ O |
| 75T | [Co(III)(<u>D</u> -L)(<u>L</u> -L)] ⁺ Br ⁻ |
| 79T | [Co(III)(<u>L</u> -L) ₂][ClO ₄] ⁻ |
| 78CF | [Cu(II)(<u>L</u> -L)(<u>D</u> -L)]4H ₂ O |
| 78SI | [Ni(II)(<u>L</u> -L) ₂]H ₂ O (isomorphous with the cobalt complex salt of 68 HL) |

3. PHENYLALANINE - $C_9H_{11}O_2N$
(2-Amino-3-phenylpropanoic acid, HL)



The proton complexes of phenylalanine are noticeably weaker (more acidic) than those of glycine as a result of the electron attracting nature of the phenyl ring. For the same reason metal complexes tend to be also less stable than those of glycine.

As a result of the hydrophobic nature of the phenyl group, bis complexes of phenylalanine tend to be markedly less soluble in water than corresponding bis complexes formed from aliphatic amino acids, or from aromatic amino acids containing hydrophylic substituents (e.g. tyrosine).

3.1. Protonation Constants of Phenylalanine.

Literature values for the protonation constants are given in Table 3.1. In many cases authors have used literature values, determined by other workers, for protonation constants when calculating metal complex formation constants (53LD, 56C, 67AM, 74LB). This is an unsatisfactory procedure and introduces doubt into the calculated constants.

Protonation constants calculated from solutions of low ionic strength (50A, 53P) will almost certainly suffer from significant changes in activity during the course of the titrations. Hence values quoted for the constants must be suspect. For reasonably precise values for formation constants, pH measurements should be precise to at least 0.01 pH units. The experimental precision of references 68RP (± 0.03 pH) and 71SS (± 0.1 pH) is therefore too low to be acceptable. Since experimental details, including the technique of electrode calibration, were not included in references 71KS, 72BF and 73BS, the values quoted for the formation constants cannot be evaluated realistically. The value given in 75PN is only an approximation.

As a result of the above considerations, only twelve determinations remain for evaluation. Of these, three refer to mixed constants, electrodes having been calibrated in terms of activities (58P, 66SW, 70MB). Since each determination was at a different ionic strength ($I = 1.0$ Na[ClO₄], 0.37 Na[NO₃] and 0.16 K[NO₃] respectively), intercomparison is impossible.

The remaining nine values reported in the literature all refer to concentration constants. Two determinations, carried out within the same research group, have been corrected to zero ionic strength ('thermodynamic' constants) and have been reported at a range of temperatures between 0 and 40 °C. From the corrected values enthalpy changes (ΔH) were calculated (61IW). Enthalpy changes were also determined calorimetrically (66AG). The quoted formation constants are consistent between the two determinations and may be accepted as tentative constants.

A second pair of determinations have also been carried out by the same research group (71GN and 72GS). The first results covered the temperature range of 20 to 35 °C while the second was at 25 °C. Both refer to an ionic strength of 0.05 mol dm⁻³ (KCl) and they are in good agreement at 25 °C. They may therefore be accepted as tentative constants.

The remaining determinations refer to 25 °C but one refers to an ionic strength of $I = 3.0$ (Na[ClO₄]) (72GW), one to $I = 0.5$ (K[NO₃]) (78L) and the others refer to 0.1 (KNO₃) (77BP, 79MJ, 80JH). From the last three values it is possible to calculate a recommended value for $\log K_{HL}$ at 25 °C and $I = 0.1$ (K[NO₃]). The value for $\log K_{H_2L}$ can only be estimated. The recommended values for the stepwise concentration constants are:

$$\log K_{HL} = 9.15(4)$$

$$\log K_{H_2L} = 2.2$$

The value for $\log K_{DL}$ (measured in D_2O) has been reported as 9.60 (25 °C, $I = 0.1(K[NO_3])$) (80JH). This may be accepted 'tentatively'.

3.2. Enthalpy of Protonation of Phenylalanine.

Enthalpy changes on protonation have been calculated from calorimetric and potentiometric studies. The potentiometric values (66IW, 66AG, 71GN, 71SS, 73BS) would be expected to be of a lower accuracy than the calorimetric values (66AG, 70MB, 72GW) particularly when calculated from imprecise pH values (71SS, 73BS). A direct comparison between the two methods is afforded by 66AG where values for both techniques are reported.

Calorimetric values for ΔH are given in Table 3.2. Values for the protonation of the amino group only (ΔH_{HL}) have been reported since the pH of protonation of the CO_2^- group (pH ~ 2) is less readily accessible. An estimate of the value for ΔH_{2L} in 3 mol dm^{-3} ($Na[ClO_4]$) is reported in 72GW.

3.3. Metal Complex Formation Constants.

Phenylalanine coordinates to metal ions in a glycine-like manner forming mono and bis complexes, although a binuclear $[CuH_2L_2]$ complex has been reported (72WY). Tris-complexes have been reported with Cd(II) (62SC) and Fe(II and III) (72WY). In general, the complexes are a little less stable than the analogous glycinate complexes and they do not appear to have any enhanced stability as a result of metal-phenyl ring interactions. The ratio of the stepwise constants, K_{ML_2}/K_{ML} , is however, slightly larger than with glycine. Only one crystal structure determination has been reported, $[Cu(L-L)_2]$ (71VL). This shows the two phenylalanate ligands to be coordinated in a planar trans arrangements. Powder photographs of complexes of phenylalanine have been described (78DA). There are not sufficient reports of formation constants determined under identical experimental conditions to allow the presentation of 'recommended' constant. However, a number of reported values should be regarded with less confidence than others and these are discussed below. Values which may be accepted 'tentatively' are identified in the tables of literature values. Copper complexes have been studied more than any others. These are, therefore, tabulated separately.

Literature values for the formation constants of complexes with Cu(II) are given in Table 3.3. Values for other metals are Table 3.4.

The early values tend to be very imprecise. The ionic background was low in 50A and 53P and varied excessively in 50A, (0.01 - 0.03 M). Polarography was used in 52LD and 62SC but the reports give insufficient experimental details and the pK values were taken from earlier independent references (e.g. 31C). Similarly, reference 67AM used the protonation constants reported in 52LD (i.e. 31C). Literature values for the protonation constants were also used by 66TA and 74LB. The use of protonation constants determined by other workers using different instrumentation and techniques can introduce considerable errors since systematic errors are often eliminated when both proton and metal complexes are studied under identical conditions. Reference 56C calculated formation constants from conductance measurements. The values found were rather low in comparison to more recent determinations. Reference 62SM used a low ionic strength (0.01 mol dm^{-3}) and the constants calculated were abnormally low, with an unexpected order in the stepwise constants for Ni(II) and Cd(II). The precision of the values was later criticised in reference 71GN. References 68RP and 71SS suffer from low precision (± 0.03 and 0.1 respectively) in pH measurement. This can introduce considerable errors in calculated β values. References 71KS, 72BF, 73BS and 73SK do not contain

sufficient experimental details for an objective evaluation. Values given in 75PN should be rejected (cf. histidine). Simultaneous measurement of pH and pHg was used in 74LB to obtain formation constants of mercury complexes. Unfortunately literature values for the protonation constants were used, and the ionic strength was allowed to vary between 0.10 and 0.12 mol dm⁻³. Reference 70MB is essentially a calorimetric study but the copper complex formation constants reported are somewhat smaller than expected. Values quoted in 79MJ appear to be somewhat lower than the majority of results in Table 3.3.

The remaining determinations (61IW, 66AG, 66SW, 71GN, 72GS, 72WY and 77BP) may be accepted tentatively but they cover a wide range of experimental conditions: 71GN and 72GS, and 61IW and 66AG should be taken as pairs. Both pairs report the determination of enthalpy changes using both potentiometry and calorimetry. Hence they give formation constants over a range of temperatures. What is more, both calculate constants after extrapolation to infinite dilution using the same activity coefficients (66AN). As will be seen from Table 3.3, agreement is reasonably good.

Reference 66SW reports a search for stereoselectivity in the formation of bis-complexes with Cd(II), Cu(II), Ni(II), Pb(II) and Zn(II). The precision is rather low (± 0.05 log units) and no stereoselectivity was detected. The remaining reports (70MB, 72WY, 73CT and 77BP) give precise values at 25 °C in solutions of varying ionic strength. While 70MB and 77BR consider only Cu(II) and 73CT only Pb(II), 72WY includes a calorimetric study of Cu(II), Ni(II) and Co(II).

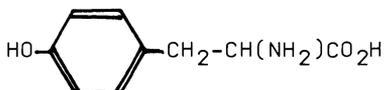
Values which may be accepted tentatively are identified in Tables 3.3 and 3.4.

3.4. Enthalpy Changes on Complex Formation.

A number of potentiometric studies at different temperatures have been reported, and enthalpy changes calculated (61IW, 66AG, 67AG, 71GN, 71SS and 73BS). Three references (66AG, 67AG and 71GN) consider calorimetric determinations also and compare enthalpy values calculated by both methods. The results, particularly in the case of Ni(II), show how poor the agreement can be. A major reason for the low accuracy of enthalpy changes determined potentiometrically is the fact that ΔH values are not necessarily temperature independent. References 66AG and 67AG measured ΔH values at three temperatures calorimetrically and detected a surprising variation with temperature (see Table 3.5). Hence measurement of formation constants at different temperatures can only give a rather crude average value for ΔH at a given temperature. Reference 70MB and 72WY gives enthalpy changes measured calorimetrically only. Literature values for enthalpy changes determined potentiometrically and calorimetrically are given in Table 3.5. Only those determined calorimetrically, however, should be accepted ('tentatively').

4. TYROSINE - C₉H₁₁O₃N

(2-Amino-3-(4-hydroxyphenyl)propanoic acid, H₂L)



Tyrosine is similar to phenylalanine but has, in addition, a para-hydroxyl group on the benzene ring. Since the proton of this group ionizes at about pH 10, the neutral ligand must be regarded as a dibasic acid, H₂L, with three potential coordination centres.

TABLE 3.1
Protonation Constants of Phenylalanine
Literature Values

| | Type of constant | Medium mol dm ⁻³ | Temp °C | log K _{HL} | log K _{H₂L} |
|------|------------------|-----------------------------|---------|---------------------------|---------------------------------|
| 31C | ? | | 25 | 9.13 | 1.83 |
| 49NS | ? | 0.1(NaCl) | 25 | 9.15(5) | 2.16(5) |
| 50A | M | ~0.01 | 20 | 9.31 | 2.04 |
| 50BN | | 0.1(NaCl) | 24 | 9.12(2) | 2.16(2) |
| 53P | ? | 0.005 | 20 | 9.33 | |
| 58P | M | 1.0(NaClO ₄) | 20 | 9.18 | 2.21 |
| 61IW | C | →0 | 0 | 9.95 | 2.28 |
| | | | 10 | 9.66 | 2.21 |
| | | | 20 | 9.38 | 2.20 |
| | | | 30 | 9.15 | 2.23 |
| | | | 40 | 8.89 | 2.20 |
| 66AG | C | →0 | 10 | 9.75 | 2.14 |
| | | | 25 | 9.31 | 2.20 |
| | | | 40 | 8.96 | 2.21 |
| 66SW | M | 0.37(NaNO ₃) | 20 | 9.35 | 2.41 |
| 68RP | M | 0.1(KCl) | 20 | 9.04(10) | |
| 70MB | M | 0.16(KNO ₃) | 25 | 9.02 | |
| 71GN | C | 0.05(KCl) | 20 | 9.20 | 2.09 |
| | | | 25 | 9.08 | 2.09 |
| | | | 30 | 8.97 | 2.09 |
| | | | 35 | 8.85 | 2.09 |
| 71KS | ? | 0.5(KNO ₃) | 25 | 9.06(1) | 2.27(2) |
| 71SS | ? | 0.1(KCl) | 25 | 9.10 | 1.80 |
| | | | 35 | 8.89 | 1.59 |
| | | | 45 | 8.52 | 1.22 |
| 72GS | C | 0.05(KCl) | 25 | 9.11 | 2.20 |
| 72GW | C | 3.0(NaClO ₄) | 25 | 9.61(1) | 2.75(1) |
| 73BS | ? | 0.1(KNO ₃) | 20 | 9.25 | 2.39 |
| | | | 30 | 9.03 | 2.37 |
| | | | 40 | 8.80 | 2.33 |
| | | | 50 | 8.57 | 2.31 |
| | | | 60 | 8.45 | 2.39 |
| 75PN | M | 0.1(KCl) | 20 | 8.4 | |
| 77BP | C | 0.1(KNO ₃) | 25 | 9.19(1) | 2.26(1) |
| 78L | C | 0.5(KNO ₃) | 25 | 9.05(1) | 2.32(1) |
| 79MJ | C | 0.1(KNO ₃) | 25 | 9.15 | 1.81 |
| 80JH | C | 0.1(KNO ₃) | 25 | 9.09 | |
| " | C | 0.1(KNO ₃) | 25 | log K _{DL} =9.60 | |

TABLE 3.2
Enthalpy Changes in the Protonation of Phenylalanine
(determined calorimetrically in kJ mol⁻¹)

| Ref. | Medium mol dm ⁻³ | Temp °C | ΔH _{HL} |
|-------------------|-----------------------------|---------|------------------|
| 66AG | →0 | 10 | -47.7(4) |
| | | 25 | -44.6(4) |
| | | 40 | -44.1(5) |
| 70MB | 0.16(KNO ₃) | 25 | -43.2 |
| 72GW ^a | 3.0(NaClO ₄) | 25 | -50.4(1) |

$$^a \Delta H_{H_2L} = -9.7(5)$$

TABLE 3.3

Formation Constants of Complexes of L-Phenylalanine with
Copper(II) - Literature Values

| Ref. | Type of Constant | Medium mol dm ⁻³ | Temp °C | log β _{ML} | log β _{ML₂} | |
|--------|------------------|-----------------------------|---------|---------------------|---------------------------------|---|
| 50A | M | 0.01 | 20 | | 15.9 | |
| 52LD | ? | 0.06 | 25 | | 14.66 | |
| 56C | ? | 0.027 | 25 | 7.74 | 14.64 | |
| | | → 0 | | 7.87 | 14.77 | |
| 61IW | C | → 0 | 0 | 8.64 | 16.09 | |
| | | | 10 | 8.42 | 15.66 | |
| | | | 20 | 8.31 | 15.39 | T |
| | | | 30 | 8.30 | 15.25 | |
| | | | 40 | 8.06 | 14.84 | |
| 62SM | M | 0.01 | 25 | 7.38 | 14.24 | |
| 66AG | M | 0.02 | 10 | 8.48(3) | 15.91(3) | |
| | | | 25 | 8.25(3) | 15.38(3) | T |
| | | | 40 | 8.13(3) | 15.07(3) | |
| 66SW | M | 0.37(NaNO ₃) | 20 | D 8.00 | 15.08 | |
| | | | L 7.93 | 15.10 | T | |
| | | | LD 8.03 | 15.14 | | |
| 70MB | M | 0.16(KNO ₃) | 25 | 7.51 | 14.25 | |
| 71GN | C | 0.05(KCl) | 20 | 7.90 | 14.82 | |
| | | | 25 | 7.82 | 14.66 | |
| | | | 30 | 7.78 | 14.52 | T |
| | | | 35 | 7.73 | 14.42 | |
| | | → 0 | 25 | 8.18 | 15.18 | |
| 72GS | C | 0.05(KCl) | 25 | 7.78 | 14.77 | T |
| 72WY* | C | 3.0(NaClO ₄) | 25 | 8.25(2) | 15.55(2) | T |
| 77BP | C | 0.1(KNO ₃) | 25 | 7.93(1) | 14.83(1) | T |
| 79MJ** | C | 0.1(KNO ₃) | 25 | 7.62 | 14.22 | |

* log β_{M₂H₋₂L₂} = 4.6(4)
** log β_{MH₋₁L} = 0.51

TABLE 3.4

Formation Constants of Complexes of L-Phenylalanine with Metal Ions (Not
including Cu(II)) - Literature Values

| Metal Ion | Ref. | Type of Constant | Medium mol dm ⁻¹ | Temp °C | log β _{ML} | log β _{ML₂} | Recom or comment |
|-----------|------|------------------|-----------------------------|---------|---------------------|---------------------------------|--|
| Ag(I) | 67AM | C | 0.6 | 25 | 5.30(3) | 7.8(1) | |
| Be(II) | 53P | M | 0.005 | 20 | | 11.9 | |
| Cd(II) | 53P | M | 0.005 | 20 | | 7.2 | |
| | 63SC | ? | 2.0(KNO ₃) | 25 | 4.06 | 6.92 | log β _{ML₃} = 7.77 |
| | 62SM | M | 0.01 | 25 | 3.65 | 7.79 | |
| | 66SQ | M | 0.37(NaNO ₃) | 20 | D 3.87 | 6.72 | |
| | | | | L 3.90 | 6.73 | T | |
| | | | | DL 3.84 | 6.75 | | |
| Ce(III) | 68RP | M | 0.1(KCl) | 20 | 3.5(2) | | |
| Co(II) | 50A | M | 0.01 | 20 | | 7.9 | |
| | 60SM | M | 0.01 | 25 | 4.08 | 8.08 | |
| | 71GN | C | 0.05(KCl) | 20 | 4.05 | 7.52 | |
| | | | | 25 | 4.03 | 7.47 | T |
| | | | | 30 | 4.03 | 7.44 | |
| | | | | 35 | 4.00 | 7.39 | |
| | 72GS | C | 0.05(KCl) | 25 | 4.05 | 7.56 | T |
| | 72WY | C | 3.0(NaClO ₄) | 25 | 4.80(1) | 8.44(4) | T |

Table 3.4 Cont.

| | | | | | | | |
|-------------------------|------|---|--------------------------|----|------|----------|---|
| Fe(II) | 50A | M | 0.01 | 20 | | 6.3 | |
| | 59P | M | 1.0(KCl) | 20 | | 3.36 | |
| | 72WY | C | 3.0(NaClO ₄) | 25 | | 3.74(1) | 7.19(3) log β _{ML₃} |
| Fe(III) | 58P | M | 1.0(NaClO ₄) | 20 | | 8.9 | = 10.7(2) T |
| | 72WY | C | 3.0(NaClO ₄) | 25 | | 10.39(4) | 19.11(10) log β _{ML₃} |
| Mg(II) | 53P | M | 0.005 | 20 | | | 18.7 = 26.0(7) T |
| | 66TA | ? | 0.6(KNO ₃) | 25 | | | 18.6(5) |
| | 74LB | M | 0.1(NaNO ₃) | 25 | 12.4 | 19.6 | T |
| Mn(II) | 71GN | C | 0.05(KCl) | 25 | | 2.4 | 4.7 T |
| | 71SS | ? | 0.1(KCl) | 25 | | 2.94 | |
| | | | | 35 | | 2.89 | |
| | | | | 45 | | 2.84 | |
| | 73BS | ? | 0.1(KNO ₃) | 20 | | 2.39 | |
| | | | | 40 | | 2.33 | |
| | | | | 50 | | 2.31 | |
| | | | | 60 | | 2.39 | |
| Ni(II) | 62SM | M | 0.01 | 25 | | 4.73 | 10.02 |
| | 66SW | M | 0.37(NaNO ₃) | 20 | D | 5.24 | 9.72 |
| | | | | L | | 5.23 | 9.70 |
| | | | | DL | | 5.19 | 9.66 |
| | 67AG | C | 0 | 0 | | 6.61 | 10.52 |
| | | | | 20 | | 5.36 | 10.22 |
| | | | | 40 | | 5.52 | 9.91 |
| | 71GN | C | 0.05(KCl) | 20 | | 5.13 | 9.49 |
| | | | | 25 | | 5.11 | 9.43 |
| | | | | 30 | | 5.08 | 9.40 |
| | | | | 35 | | 5.05 | 9.32 |
| | | | | 25 | | 5.46 | 9.99 |
| | 72GS | C | 0.05(KCl) | 25 | | 5.15 | 9.46 |
| | 72WY | C | 3.0(NaClO ₄) | 25 | | 5.35(3) | 10.48(5) T |
| Pb(II) | 66SW | M | 0.37(NaNO ₃) | 20 | D | 3.99 | 8.88 |
| | | | | L | | 4.02 | 8.86 |
| | | | | DL | | 4.03 | 8.79 |
| | 73CT | C | 3.0(NaClO ₄) | 25 | | 4.63(4) | 8.35(6) T |
| Th(IV) | 71KS | M | 0.5(KNO ₃) | 25 | | 9.30(6) | |
| UO ₂ (II) | 71SS | ? | 0.1(KCl) | 25 | | 6.46 | 12.16 |
| | | | | 35 | | 6.28 | 11.78 |
| | | | | 45 | | 6.01 | 11.33 |
| | 73SK | ? | 0.5 | 25 | | 6.49(3) | |
| Zn(II) | 53P | M | 0.005 | 20 | | | 8.4 |
| | 62SM | M | 0.01 | 25 | | 4.58 | 9.03 |
| | 66SW | M | 0.37(NaNO ₃) | 20 | D | 4.43 | |
| | | | | L | | 4.43 | ~8.5 |
| | | | | LD | | 4.41 | |
| | 71GN | C | 0.05(KCl) | 20 | | 4.31 | 8.40 |
| | | | | 25 | | 4.29 | 8.35 |
| | | | | 30 | | 4.28 | 8.28 |
| | | | | 35 | | 4.24 | 8.24 |
| <u>Lanthanides(III)</u> | | | | | | | |
| Eu | 72BF | ? | 0.1(KCl) | 25 | | 4.35 | 8.25 |
| | 72BF | ? | 0.1(KCl) | 25 | | 4.25 | |
| Gd | 75PN | M | 0.1(KCl) | 20 | | 3.6 | |
| La | 72BF | ? | 0.1(KCl) | 25 | | 3.8 | |
| | 75PN | M | 0.1(KCl) | 20 | | 3.6 | |
| Lu | 72BF | ? | 0.1(KCl) | 25 | | 4.45 | 7.95 |
| Nd | 72BF | ? | 0.1(KCl) | 25 | | 4.2 | |
| Tb | 72BF | ? | 0.1(KCl) | 25 | | 4.3 | 7.8 |

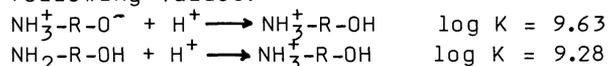
TABLE 3.5

Enthalpy Changes in the Formation of Metal Complexes of L-Phenylalanine
(Stepwise Values in kJ mol⁻¹)

| Metal Ion | Ref. | Technique | Medium mol dm ⁻³ | $t_{\text{Temp}}^{\circ}\text{C}$ | ΔH_1 | ΔH_2 |
|----------------------|--------|-----------|-----------------------------|-----------------------------------|--------------|--------------|
| Co(II) | 71GN | cal | 0.05(KCl) | 27 | 6.3 | 1.3 |
| | 71GN | pot | 0.05(KCl) | - | 4.6 | 9.2 |
| | 72WY | cal | 3.0(NaClO ₄) | 25 | 5.3(8) | 8.1(1.6) |
| Cu(II) | 61IW | pot | → 0 | - | 21.3 | 26.8 |
| | 66AG | cal | → 0 | 10 | 25.1 | 26.7 |
| | | | | 25 | 22.1 | 26.7 |
| | | | | 40 | 20.3 | 23.0 |
| | 66AG | pot | → 0 | - | 24.4 | 28.6 |
| | 70MB | cal | 0.16(KNO ₃) | 25 | 21.9 | 24.1 |
| | 71GN | cal | 0.05(KCl) | 27 | 19.7 | 28.9 |
| | 71GN | pot | 0.05(KCl) | - | 19.2 | 26.8 |
| | 72WY | cal | 3.0(NaClO ₄) | 25 | 19.2(1.8) | 39.2(4.0) |
| | Mn(II) | 71SS | pot | 0.1(KCl) | - | 9.2 |
| 73BS | | pot | 0.1(KNO ₃) | - | 4.6 | |
| Ni(II) | 67AG | cal | → 0 | 10 | 14.2 | 15.0 |
| | | | | 25 | 13.3 | 13.8 |
| | | | | 40 | 10.9 | 12.1 |
| | 67AG | pot | → 0 | - | 5.0 | 31.8 |
| | 71GN | cal | 0.05(KCl) | 27 | 11.3 | 7.9 |
| | | | | | 9.2 | 9.6 |
| | 72WY | cal | 3.0(NaClO ₄) | 25 | 9.8(6) | 14.7(1.2) |
| UO ₂ (II) | 71SS | pot | 0.1(KCl) | - | 40.9 | 34.5 |
| Zn(II) | 71GN | cal | 0.05(KCl) | 27 | 3.8 | 7.1 |
| | 71GN | pot | 0.05(KCl) | - | 7.5 | 11.7 |

4.1. Protonation Constants of Tyrosine.

Tyrosine possesses three protonation constants, corresponding to the coordination of the three protons in $[\text{H}_3\text{L}]^+$. Literature values are given in Table 4.1. Since the protonation constants for the amine nitrogen and the phenolic oxygen are close the two protonation reactions will not be separated clearly but will, to a small extent, take place simultaneously. The measured constants are macro constants which arise from the superimposition of the micro constants characteristic of the two different protonation reactions. These individual micro-constants have been resolved spectrophotometrically (58ME) giving the following values:



Hence the major contribution to the highest constant will be protonation of the phenolic oxygen and the second constant will be mainly protonation of the amine nitrogen. It should be noted, however, that this order is reversed in DOPA (80JH).

When the macro-constants are considered values given in 52A and 53P suffer from a low value for the background ionic strength, and 55ST reports an approximate value for $K_{\text{H}_3\text{L}}$ only. Since the two protonation reactions represented by K_{HL} and $K_{\text{H}_2\text{L}}$ overlap, neglecting K_{HL} will introduce a significant error into the calculated value for $K_{\text{H}_2\text{L}}$. Hence values quoted in 72BF and 76S must be rejected. Allowance for the further protonation of HL was made in 72GS. The value given in 75PN was only an approximation.

From the remaining values it is difficult to select a recommended value for the concentration constants since very few determinations have been reported. However, from references 74GN and 81PS a tentative value for the constants can be given. the values are:

Tentative concentration constants for the stepwise protonation of tyrosine at 25 °C and I = 0.1 - 0.2 (K[NO₃]):

$$\log K_{HL} = 10.10(2), \log K_{H_2L} = 9.03(1), \log K_{H_3L} = 2.1$$

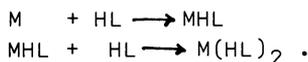
4.2. Enthalpy of Protonation of Tyrosine.

There are two reports of the determination of protonation constants at a range of temperatures (71GN and 76S). The latter values must be rejected since they assumed that the phenolic proton was not labile. Enthalpy changes have also been measured calorimetrically to provide more accurate values than those calculated from the temperature dependence of formation constants (70LB). Values found at 25 °C and I = 0.16 (K[NO₃]) were:

$$\begin{aligned} \Delta H_{HL} &= -24.4 \text{ kJ mol}^{-1} \text{ (largely protonation of } -O^-) \\ \Delta H_{H_2L} &= -42.4 \text{ kJ mol}^{-1} \text{ (largely protonation of } -NH_2) \end{aligned}$$

4.3. Metal Complex Formation Constants.

Tyrosine coordinates to metal ions in a glycine-like manner forming mono and bis complexes. The only report of a tris complex is with Ni(II) (79GKa). The phenolic oxygen does not appear to take part in coordination reactions at pH < 10 with the result that the species [HL]⁻, the tyrosinate ion with the phenol group unionized, is the normal ligand ion. The crystal structure of [Cu(L-tyrosinate)₂] has been reported (72VT) and shown to have an abnormally short Cu-phenyl ring distance. Crystal structures of [Pd(L-tyrosinate)₂·0.5H₂O] (cis) and [Ni(L-tyrosinate)₂·3H₂O] have also been reported (73JH, 78Ha). Neither show any evidence of metal-phenol interactions. Literature values for the metal complex formation constants are listed in Table 4.2. Since all refer to coordination of the tyrosinate ion with the phenolic oxygen protonated, values for log K_{MHL}^{HL} and log K_{M(HL)₂}^{HL} refer, respectively, to the two reactions of the type:



Many of the reported formation constants suffer from similar limitation to the protonation constants (e.g. ionic background too low and variable (53P, 52A, 62SH) or log K_{HL} has been neglected (72BF, 75PN, 76S, 77S)). In addition reference 74LB used literature values for protonation constants and this may have introduced systematic errors, although the results quoted were calculated from the simultaneous measurement of pH and pHg. References 62SM, 72CG and 73BB make no mention of the protonation constants used. Reference 79GKa is a review article which does not give full experimental details, but it can be assumed that these were identical to those normally used by the research group (e.g. 76GK).

Reference 71WS reports a search for stereoselectivity in the complexes of tyrosine with Cd(II), Cu(II), Ni(II), Pb(II) and Zn(II). No stereoselectivity was detected within the limits of accuracy of the measurements (± 0.05 log units).

Evaluation of the values listed in Table 4.2 provides the following tentative constants, which can only be given realistically to one place of decimals.

Tentative concentration constants at 25 °C and I = 0.1

| | $\log K_{MHL}^{HL}$ | $\log K_{M(HL)_2}^{HL}$ | $\log K'$ | $\log K''$ |
|--------|---------------------|-------------------------|-----------|------------|
| Co(II) | 4.0 | 7.3 | 9.4 | 9.8 |
| Cu(II) | 7.8 | 14.6 | 9.4 | 10.1 |
| Hg(II) | 12.3 | 19.5 | 9.4 | 10.1 |
| Ni(II) | 5.0 | 9.2 | 9.4 | 9.8 |
| Zn(II) | 4.2 | 8.2 | 8.9 | 9.4 |

$(K' = [M(HL)_2]/[MHL_2][H], K'' = [MHL_2]/[ML_2][H])$

4.4. Enthalpy Changes on Complex Formation.

Potentiometric studies at different temperatures are reported in references 71GN, 76S and 77S. The formation constants measured in 76S and 77S were calculated using protonation constants which neglected ionization of the phenolic hydrogen. This may have introduced significant errors. In addition, the sign of ΔH is incorrect in 76S(c).

Calorimetric measurement of enthalpy changes has been reported for Cu(II) (70LB), for Cu(II), Co(II), Ni(II) and Zn(II) (71GN) and for Cu(II), Ni(II) and Zn(II) (79GKa). The last reference is a review article which gives few experimental details.

Literature values for enthalpy changes determined potentiometrically and calorimetrically are given in Table 4.3. Only these determined calorimetrically, however, should be considered, and these show a surprisingly large variation. With Cu(II) the following values may be accepted tentatively :

$$\Delta H_{MHL} = -23.1(1.3), \Delta H_{M(HL)_2} = -26(3) \text{ kJ mol}^{-1}$$

TABLE 4.1

Protonation Constants of Tyrosine (H_2L)

| Ref. | Type of Constant | Medium ₃ mol dm ⁻³ | Literature Values | | | |
|------|------------------|---|-------------------|---------------|-----------------|-----------------|
| | | | Temp °C | $\log K_{HL}$ | $\log K_{H_2L}$ | $\log K_{H_3L}$ |
| 35WS | C | 0 | 25 | 10.07 | 9.11 | |
| 52A | M | 0.01 | 20 | 10.43 | 9.19 | 2.20 |
| 53P | M | 0.005 | 20 | 10.43 | 9.23 | |
| 55ST | ? | ? | 25 | | | 2.25 |
| 58ME | M | 0.16(KNO ₃) | 25 | 10.13(1) | 9.11(1) | 2.34 |
| | | 0.4 | 25 | 10.29(1) | 9.12(1) | |
| 70LB | M | 0.16(KNO ₃) | 25 | 10.13 | 9.21 | |
| 71GN | C | 0.05(KCl) | 20 | 10.21 | 9.16 | 2.12 |
| | | | 25 | 10.14 | 9.05 | 2.12 |
| | | | 30 | 10.01 | 8.94 | 2.12 |
| | | | 35 | 9.94 | 8.82 | 1.12 |
| 71WS | M | 0.37(NaNO ₃) | 20 | 10.53(1) | 9.22(1) | 2.54(2) |
| 72BF | M | 0.1(KCl) | 25 | | 8.70(4) | |
| 72GS | C | 0.05(KCl) | 25 | | 9.07 | 2.22 |
| 74GN | C | 0.2(KCl) | 25 | 10.08 | 9.03 | 2.20 |
| 75PN | M | 0.1(KCl) | 20 | | 8.4 | |
| 76S | M | 0.1(KNO ₃) | 25 | | 9.18 | |
| | | | 35 | | 9.20 | |
| | | | 45 | | 9.23 | |
| | | 0.2(KNO ₃) | 35 | | 9.18 | |
| 81PS | C | 0.3(KNO ₃) | 35 | | 9.45 | |
| | | 0.1(KNO ₃) | 25 | 10.14 | 9.03 | 1.88 |

TABLE 4.2
Formation Constants of Complexes of Tyrosine with Metal Ions
Literature Values

| Metal Ion | Ref. | Type of Constant | Medium mol dm ⁻³ | Temp °C | log K _{MHL} ^{HL} | log K _{M(HL)₂} ^{HL} |
|--------------------|-------------------|------------------------|-----------------------------|---------|------------------------------------|--|
| Be(II) | 53P | M | 0.005 | 20 | | 11.1 |
| Ca(II) | 50D | C | 0 | 25 | 0.2 | |
| Cd(II) | 53P | M | 0.005 | 20 | | 6.4 |
| | 71WS | M | 0.37(NaNO ₃) | 20 | D 3.58 L 3.56 DL 3.56 | 6.09 6.08 6.08 |
| Co(II) | 72CG | ? | 0.5(KNO ₃) | 30 | | 8.87 |
| | 52A | M | 0.01 | 20 | | 8.1 |
| Co(II) | 62SM | M | 0.01 | 25 | 4.1 | 8.1 |
| | 71GN | C | 0.05(KCl) | 20 | 3.92 | 7.40 |
| | | | | 25 | 3.93 | 7.38 |
| | | | | 30 | 3.93 | 7.35 |
| | | | | 35 | 3.92 | 7.30 |
| 72GS | C | 0.05(KCl) | 25 | 3.87 | 7.52 | |
| 73BB | ? | 0.1(KNO ₃) | 25 | 4.05(2) | 7.83(4) | |
| 81PS ^a | C | 0.1(KNO ₃) | 25 | 4.03(1) | 7.24(3) | |
| Cu(II) | 52A | M | 0.01 | 20 | | 15.0 |
| | 62SM | M | 0.01 | 25 | 7.0 | 14.5 |
| Cu(II) | 70LB ^b | M | 0.16(KNO ₃) | 25 | 7.92 | 14.86 |
| | 71GN | C | 0.05(KCl) | 20 | 7.79 | 14.67 |
| 25 | | | | 7.75 | 14.57 | |
| 30 | | | | 7.71 | 14.45 | |
| 35 | | | | 7.65 | 14.31 | |
| 71WS | | | | M | 0.37(NaNO ₃) | 20 |
| 72GS | C | 0.05(KCl) | 25 | 7.81 | 14.74 | |
| 73BB | ? | 0.1(KNO ₃) | 25 | 7.90(2) | 15.17(3) | |
| 79GKa ^c | C | 0.2(KCl) | 25 | 7.69 | 14.44 | |
| 81PS ^d | C | 0.1(KNO ₃) | 25 | 7.85(1) | 14.62(3) | |
| Fe(II) | 52A | M | 0.01 | 20 | | 7.1 |
| Hg(II) | 53P | M | 0.005 | 20 | | 17.1 |
| | 74LB | M | 0.1(NaNO ₃) | 25 | 12.3 | 19.5 |
| Mg(II) | 52A | M | 0.01 | 20 | ~2 | |
| Mn(II) | 52A | M | 0.01 | 20 | ~2.4 | |
| | 71GN | C | 0.05(KCl) | 25 | ~1.5 | |
| Ni(II) | 52A | M | 0.01 | 20 | | 10.1 |
| | 62SM | M | 0.01 | 25 | 4.9 | 10.5 |
| 20 | | | | 5.03 | 9.32 | |
| 25 | | | | 5.02 | 9.27 | |
| 30 | | | | 4.99 | 9.22 | |
| Ni(II) | 71GN | C | 0.05(KCl) | 35 | 4.97 | 9.14 |
| | | | | 71WS | M | 0.37(NaNO ₃) |
| 72GS | C | 0.05(KCl) | 25 | 5.15 | 9.57 | |
| 73BB | | 0.1(KNO ₃) | 25 | 5.14(2) | 9.56(2) | |
| 79GKa ^e | C | 0.2(KCl) | 25 | 4.90 | 9.18 | |
| 81PS ^f | C | 0.1(KNO ₃) | 25 | 5.00(1) | 9.27(1) | |
| Pb(II) | 71WS | M | 0.37(NaNO ₃) | 20 | D 4.14 L 4.19 DL 4.9 | 8.55 8.56 8.52 |
| | | | | 20 | | 9.1 |
| Zn(II) | 52A | M | 0.01 | 20 | | 9.1 |

Table 4.2 Cont.

| | | | | | |
|--------------------------------------|---|-------------------------------------|----|---------|--|
| 53P | M | 0.005 | 20 | | 8.0 |
| 52SM | M | 0.01 | 25 | 4.6 | 9.3 |
| 71GN | C | 0.05(KCl) | 20 | 4.15 | 8.28 |
| | | | 25 | 4.16 | 8.27 |
| | | | 30 | 4.19 | 8.25 |
| | | | 35 | 4.20 | 8.21 |
| 71WS | M | 0.37(NaNO ₃) | 20 | 4.18 | 8.24 |
| | | | L | 4.20 | 8.24 |
| | | | DL | 4.20 | 8.29 |
| 79GKa ^g | C | 0.2(KCl) | 25 | 4.12 | 7.95 |
| 81PS ^h | C | 0.1(KNO ₃) | 25 | 4.23(5) | 8.31(3) |
| | | $K' = \frac{[M(HL)_2]}{[MHL_2][H]}$ | | | $K'' = \frac{[MHL_2]}{[ML_2][H]}$ |
| | | log K' | | log K'' | log K _{M(HL)₃} ^{HL} |
| C e d e r i n g | | 9.32 | | 10.06 | |
| | | 9.43 | | 10.11 | |
| | | 9.32 | | 9.11 | 12.05 |
| | | 9.34 | | 9.78 | 12.4 |
| | | 8.89 | | 9.29 | |
| | | 8.94 | | | |

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| Metal Ion | Ref. | Type of Constant | Medium mol dm ⁻³ | Temp °C | log K _{MHL} ^{HL} | log K _{M(HL)₂} ^{HL} |
|-----------|------|------------------------|-----------------------------|---------|------------------------------------|--|
| Y(III) | 75PN | M | 0.1(KCl) | 20 | 2.8 | |
| | 77S | M | 0.1(KNO ₃) | 25 | 4.43 | 8.48 |
| | | | | 35 | 4.92 | 9.35 |
| 45 | 5.41 | 10.22 | | | | |
| La(III) | 72BF | ? | 0.1(KCl) | 25 | 4.2 | |
| | 75PN | M | 0.1(KCl) | 20 | 3.0 | |
| | 77S | M | 0.1(KNO ₃) | 25 | 4.17 | |
| 35 | | | | 4.56 | | |
| 45 | | | | 4.95 | | |
| Pr(III) | 76S | M | 0.1(KNO ₃) | 25 | 4.35 | 8.23 |
| | | | | 35 | 4.68 | 8.80 |
| | | | | 45 | 5.01 | 9.37 |
| Nd(III) | 71BF | ? | 0.1(KCl) | 25 | 4.1 | 7.6 |
| | | | | 76S | M | 0.1(KNO ₃) |
| | 35 | 4.79 | 9.03 | | | |
| 45 | 5.04 | 9.52 | | | | |
| 75PN | M | 0.1(KCl) | | 20 | 3.3 | |
| | | | | 35 | 4.71 | 8.84 |
| | | | | 45 | 4.91 | 9.29 |
| 76S | M | 0.1(KNO ₃) | 25 | 5.10 | 9.72 | |
| Gd(III) | 72BF | ? | 0.1(KCl) | 25 | 4.35 | 8.6 |
| | | | | 75PN | M | 0.1(KCl) |
| | 76S | M | 0.1(KNO ₃) | 25 | 4.63 | 8.80 |
| 35 | 4.92 | 9.35 | | | | |
| 45 | 5.20 | 9.89 | | | | |
| | | | 0.2(KNO ₃) | 35 | 4.84 | 9.22 |
| | | | 0.3(KNO ₃) | 35 | 4.77 | 9.09 |
| Tb(III) | 72BF | ? | 0.1(KCl) | 25 | 4.35 | 8.7 |
| | 75PN | M | 0.1(KCl) | 20 | 3.3 | |
| Dy(III) | 76S | M | 0.1(KNO ₃) | 25 | 4.74 | 9.04 |
| | | | | 35 | 5.04 | 9.61 |
| | | | | 45 | 5.34 | 10.18 |
| | | | 0.2(KNO ₃) | 35 | 4.96 | 9.47 |
| | | | 0.3(KNO ₃) | 35 | 4.88 | 9.33 |
| Er(III) | 72BF | ? | 0.1(KCl) | 25 | 4.4 | 8.5 |
| | 76S | M | 0.1(KNO ₃) | 25 | 4.83 | 9.34 |
| 35 | 5.15 | 9.25 | | | | |

Table 4.2 Cont.

| | | | | | | |
|--------------|---|--|------------------------|----|------|-------|
| | | | | 45 | 5.47 | 10.56 |
| | | | 0.2(KNO ₃) | 35 | 5.07 | 9.82 |
| | | | 0.3(KNO ₃) | 35 | 4.99 | 9.69 |
| 75PN | M | | 0.1(KCl) | 20 | 3.4 | |
| Yb(III) 76S | M | | 0.1(KNO ₃) | 25 | 5.00 | 9.70 |
| | | | | 35 | 5.35 | 10.35 |
| | | | | 45 | 5.70 | 11.00 |
| | | | 0.2(KNO ₃) | 35 | 4.94 | 10.21 |
| | | | 0.3(KNO ₃) | 35 | 4.88 | 10.07 |
| Lu(III) 72BF | ? | | 0.1(KCl) | 25 | 4.55 | 9.1 |

TABLE 4.3

Enthalpy changes in the Formation of Metal Complexes of Mono-protonated L-Tyrosine (Stepwise values in kJ mol⁻¹)

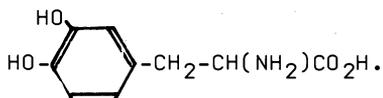
| Metal ion | Ref. | Technique | Medium mol dm ⁻³ | T °C | ΔH _{MHL} | -ΔH _{M(HL)₂} |
|-----------|-------|-----------|--------------------------------|-----------|-------------------|----------------------------------|
| Co(II) | 71GN | cal | 0.05(KCl) | 27 | 2.5 | 7.1 |
| | | pot | 0.05(KCl) | 20-35 | 0.8 | 11.2 |
| Cu(II) | 70LB | cal | 0.16(KNO ₃) | 25 | 22.7 | 23.6 |
| | | 71GN | cal | 0.05(KCl) | 27 | 24.6 |
| | 79GKa | pot | 0.05(KCl) | 20-35 | 16.7 | 25.1 |
| | | cal | 0.2(KCl) | 25 | 22.0 | 30.7 |
| Ni(II) | 71GN | cal | 0.05(KCl) | 27 | 8.3 | 11.7 |
| | | pot | 0.05(KCl) | 20-35 | 7.1 | 13.0 |
| | 79GKa | cal | 0.2(KCl) | 25 | 12.8 | 18.1 |
| Zn(II) | 71GN | cal | 0.05(KCl) | 27 | 5.9 | 10.9 |
| | | pot | 0.05(KCl) | 20-35 | -6.3 | 14.6 |
| | 79GKa | cal | 0.2(KCl) | 25 | 9.2 | 10.8 |

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(Overall Enthalpy of formation of the bis complexes from monoprotonated tyrosine (HL) at I = 0.1 (KNO₃) and T = 25-45 °C (76S, 77S))

| Metal ion (trivalent) | ΔH _{M(HL)₂} ^{HL} |
|--------------------------|---|
| Y | 158 |
| La | 54.3 |
| Ce | 70.7 |
| Pr | 103 |
| Nd | 95.4 |
| Sm | 80.8 |
| Gd | 98.7 |
| Dy | 103 |
| Er | 111 |
| Yb | 118 |

5. **DOPA** - $C_9H_{11}O_4N$
(2-Amino-3-(3,4-dihydroxyphenyl)propanoic acid, H_3L)



DOPA contains two ionizable phenolic protons (cf. tyrosine). Hence the neutral ligand must be regarded as a tribasic acid, H_3L , with four potential co-ordination centres. In general, L-DOPA (the physiologically active form) has been studied but there is no evidence for stereoselectivity.

5.1. Protonation Constants of DOPA.

DOPA possesses four protonation constants corresponding to the coordination of the four protons in $[H_4L]^+$. Two of these will be phenolate (catecholate) protons. The first proton to coordinate (a phenolate proton) has a very high affinity for the L^{3-} ion ($\log K \sim 13$). Hence it can only be removed in solutions of very high pH and the accuracy of the determination of its formation constant is low. The next two protons to coordinate bond to the other phenolate oxygen and the amine nitrogen. These two formation reactions overlap so that macro constants are normally determined. The fourth proton to coordinate is the carboxyl proton ($\log K \sim 2$). Literature values for the protonation constants are given in Table 5.1. Various attempts have been made to resolve the second and third macro constants into their constituent micro constants. From spectroscopic evidence Martin concluded that the amine group has a higher affinity for protons than the second phenolate oxygen ($\log K_{NH_3^+} = 9.17$, $\log K_{OH} = 8.97$) (71M, 75BM). Later work, using the same technique, gave the micro constants $\log K_{NH_3^+} = 9.19$, $\log K_{OH} = 8.99$ (79GK). This interpretation has been criticised with arguments based on linear free energy relationships and kinetic evidence (78J). On this interpretation the phenolate oxygen protonates first ($\log K_{OH} = 9.76$ followed by the amine nitrogen ($\log K_{NH_3^+} = 8.93$). The uncertainty has now been resolved by a proton n.m.r. study in D_2O solution (80JH). This study clearly identifies the second phenolic group of DOPA as being more acidic ($\log K_{OH} = 8.97$) than the amino group ($\log K_{NH_3^+} = 9.20$). In the course of this study, protonation constants in D_2O were measured, and shown to be 0.5 to 0.6 log units higher than in H_2O . Hence the definitive values for the micro-constants ($\log K_{OH} = 8.97$, $\log K_{NH_3^+} = 9.20$) are corrected values, based on the microconstants: $\log K_{OD} = 9.57$, $\log K_{ND} = 9.73$.

When the macro-constants are considered, the earliest reported value (53P) is unsatisfactory since only one dissociation in the pH region of 8-11 is considered. Experimental details are too brief in 77BPa and the value for $\log K_{HL}$ reported in 74GS is unacceptably low. Values reported in 71M, 73BK, 76GK, 78RM and 80JH allow the calculation of recommended protonation constants (concentration constants) at 25 °C and $I = 0.1$ to 0.2 M (K^+ , Na^+ , Cl^- , $[NO_3]^-$). Values found are:

$$\begin{aligned} \log K_{HL} &= 13.4(2), & \log K_{H_2L} &= 9.84(3) \\ \log K_{H_3L} &= 8.77(2), & \log K_{H_4L} &= 2.2(1) \end{aligned}$$

For media of ionic strength 1.0 M ($K[NO_3]$) values given in 68GJ may be accepted tentatively.

The values for $\log K_{D_2L}$ and $\log K_{D_3L}$ given in 80JH (0.1 M ($K[NO_3]$) at 25 °C) may also be accepted tentatively for deuteration reactions.

5.2. Metal Complex Formation Constants.

Since DOPA has four potential coordination sites, many metal complexes can be envisaged. At low and intermediate pH values, amino acid-like bonding is to be expected, with the phenolate oxygens protonated, giving complexes of general formula MH_2L (121) or $M(H_2L)_2$ (142). At high pH values catechol-like

bonding is to be expected, possibly involving the amine nitrogen as well. Complexes of DOPA have been reviewed recently by Gergely and Kiss (79GKa). Literature values for the metal complex formation constants are given in Table 5.2.

Values given in 53P must be rejected since the calculations clearly underestimated the complexity of the system. With Cu(II) in particular, it is clear that the equilibria are very complicated and can only be resolved with any degree of satisfaction using a refined computer based minimization procedure. The graphical methods used in 78RM over-simplify the systems and so give erroneous results. The existence of polynuclear complexes cannot be ruled out. They have been treated quantitatively for Cu(II)(72GJ) and for VO(II) (78J).

When considering the remaining literature values, the use of overall formation constants can be misleading since the magnitudes of most the constants will be strongly dependent on the value for K_{HL} , which cannot be measured accurately. Hence it is best to consider K'_{MH_2L} and $K'_{M(H_2L)_2}$, the constants for the coordination of the metal ion to the diprotonated ligand according to the reactions: $M + LH_2 \rightarrow MH_2L$ (K'_{MH_2L}) and $M + 2H_2L \rightarrow M(H_2L)_2$ ($K'_{M(H_2L)_2}$), when studying amino acid-like coordination. These constants are therefore listed in Table 5.2 also.

5.3. Complexes with Cu(II).

At intermediate pH values, the complexes $[Cu(HL)]^+$ and $[Cu(H_2L)_2]$ are clearly significant species but there is less agreement on other participants in the equilibria. Spectroscopic evidence clearly demonstrates the importance of catecholate - Cu(II) bonding at high pH, but the particular species present are not clearly defined. According to 76GK the dimer, $[Cu_2L_2]^{2-}$, is a major species at pH 7-10 but it is not considered by 77BPa. The experimental details given in 76GK and 79GK together with the satisfactory standard deviations quoted, suggest that the model quoted is the most satisfactory and may be accepted tentatively. The species distribution graph of a 1:2 metal ligand mixture using these figures is given in Fig.5.1. Below pH 6 the equilibrium can be largely satisfied by assuming the species $[Cu(H_2L)]^+$ and $[Cu(H_2L)_2]$ only. Under these circumstances and at 25 °C, I = 0.1 to 0.2 M, the following constants may be accepted tentatively: $\log K'_{MH_2L} = 7.56$, $\log K'_{M(H_2L)_2} = 14.18$. Above pH 6 the system is too complicated, and agreement between different groups too poor, for any formation constants to be recommended tentatively although those given in 76GK appear to be the most reliable.

5.4. Complexes with other Metal Ions.

The situation with Ni(II) is similar to that with Cu(II). Below pH 6 the amino acid-like complexes are the major species and the following constns may be used tentatively

$$\log K'_{MH_2L} = 4.87, \quad \log K'_{M(H_2L)_2} = 8.7 .$$

With Zn(II) the formation of amino acid-like complexes is less clearly defined making it impossible to select any formation constants. In fact, it has been shown that while amino acid-like bonding is preferred in complexes of Ni(II), catechol-like bonding is favoured by Zn(II) (79GK).

With other metal ions there are insufficient data to make any objective assessment.

FIGURE 5.1. DOPA : Cu(II) 2:1

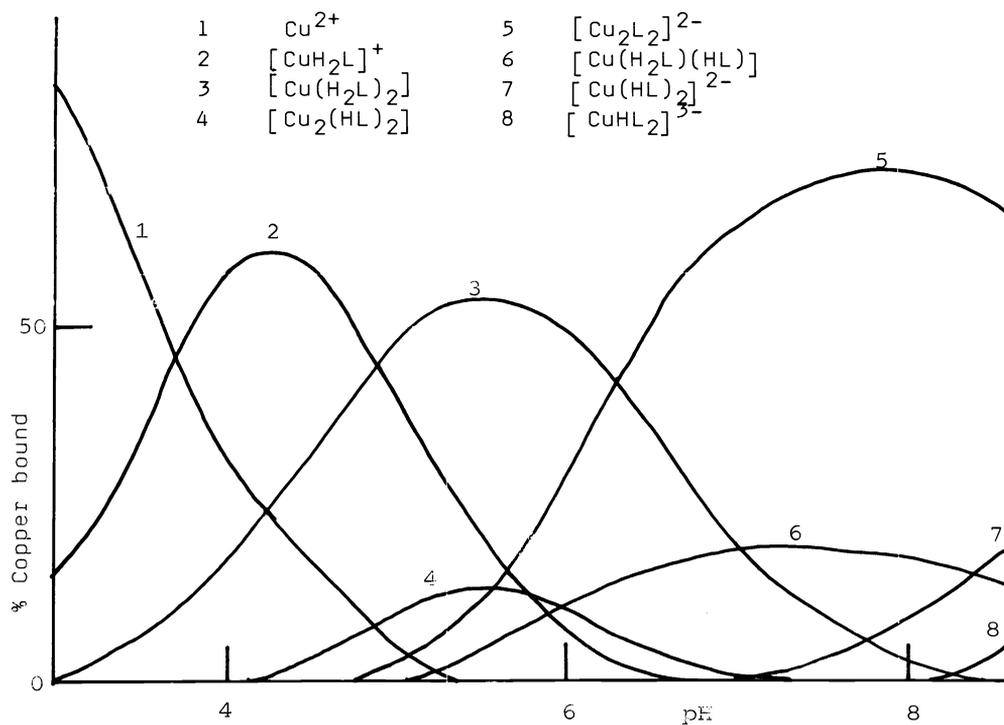


TABLE 5.1
Protonation Constants of DOPA
Literature Values

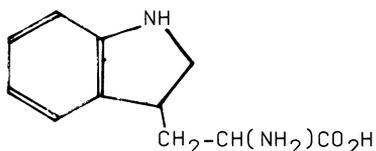
| Ref. | Type of Constant | Medium mol dm ⁻³ | T °C | log K _{HL} | log K _{H₂L} | log K _{H₃L} | log K _{H₄L} |
|-------------------|------------------|-----------------------------|------|---|---------------------------------|--|---------------------------------|
| 53P | M | 0.005 | 20 | | 9.03? | | |
| 68GJ | C | 1.0(KNO ₃) | 25 | 13.4(2) | 9.74(1) | 8.71(2) | 2.31(4) |
| 71M | ? | 0.16(KCl) | 25 | | 9.84 | 8.76 | |
| 73BK | C | 0.1(KNO ₃) | 25 | | 9.89(2) | 8.76(3) | |
| 74GS | C | 0.5(NaNO ₃) | 20 | 11.8(1) | 9.87(5) | 8.81(5) | 2.04(4) |
| 76GK | C | 0.2(KCl) | 25 | 13.4(2) | 9.83(1) | 8.80(1) | 2.22(1) |
| 77BP _a | ? | 0.5(NaClO ₄) | 25 | 12.63 | 9.85 | 8.83 | 2.26 |
| 78RM | C | 0.12(NaCl) | 25 | 13.45(8) | 9.84(5) | 8.74(5) | 2.19(2) |
| 80JH | C | 0.1(KNO ₃) | 25 | | 9.79 | 8.77 | |
| " | C | 0.1(KNO ₃) | 25 | log K _{D₂L} = 10.40 | | log K _{D₃L} = 9.35 | |

TABLE 5.2

Formation Constants of Complexes of DOPA with Metal Ions

| Metal Ion | Ref. | Type of Constant | Medium mol dm ⁻³ | T °C | log β _{ML} | log β _{ML₂} | log K _{MLH₂} | log K _{M(LH₂)₂} | [M _x H _y L _z] _{xyz} | log β |
|-----------|------|------------------|-----------------------------|------|---------------------|---------------------------------|----------------------------------|--|--|----------|
| Be(II) | 53P | ? | 0.005 | 20 | | | | | | 11.6 |
| Cd(II) | 53P | ? | 0.005 | 20 | | | | | | 7.9 |
| | 74GS | C | 0.5(NaNO ₃) | 20 | | | 3.61(4) | | | |
| Co(II) | 73BK | C | 0.1(KNO ₃) | 25 | | | 3.75(3) | | | 7.25(5) |
| Cu(II) | 68GJ | C | 1.0(KNO ₃) | 25 | 12.99 | 24.99 | 7.12(1) | | | 13.41(2) |
| | 74GS | C | 0.5(NaNO ₃) | 20 | | | 7.60(3) | | | 14.51(3) |
| | 76GK | C | 0.2(KCl) | 25 | 25.47 | | 7.52(2) | | | 14.15(3) |
| | | | | | | | | | 132 | 53.81 |
| | | | | | | | | | 222 | 45.33 |
| | | | | | | | | | 202 | 53.35 |
| | | | | | | | | | | 41.90 |
| | | | | | | | | | 132 | 52.40 |
| | | | | | | | | | 122 | 43.75 |
| | | | | | | | | | 112 | 33.60 |
| 77BPa | | ? | 0.5(NaClO ₄) | 25 | 21.70 | | 7.57 | | | 14.20 |
| 78RM | | C | 0.12(NaCl) | 25 | 19.81(?) | | 7.58(9) | | | |
| Mg(II) | 72GJ | C | 1.0(KNO ₃) | 25 | | 4.71 | | | | |
| Ni(II) | 72GJ | C | 1.0(KNO ₃) | 25 | | | 4.96(1) | | | 9.16(1) |
| | 73BK | C | 0.1(KNO ₃) | 25 | | | 4.85(4) | | | 9.13(6) |
| | 74GS | C | 0.5(NaNO ₃) | 20 | | | 4.0(2) | | | 8.73(4) |
| 77BPa | | ? | 0.5(NaClO ₄) | 25 | | | 4.80 | | | 8.74 |
| | | | | | | | | | 163 | 70.32 |
| | | | | | | | | | 143 | 60.70 |
| | | | | | | | | | 133 | 51.40 |
| | | | | | | | | | 123 | 42.00 |
| 79GK | | C | 0.2(KCl) | 25 | 17.1 | | 4.90(2) | | | 8.60(2) |
| Pb(II) | 74GS | C | 0.5(NaNO ₃) | 20 | | | 5.56 | | | 8.7 |
| Zn(II) | 53P | ? | 0.005 | 20 | | | | | | |
| | 72GJ | C | 1.0(KNO ₃) | 25 | 9.94 | 18.06 | | | | |
| | 74GS | C | 0.5(NaNO ₃) | 20 | | | 4.4(1) | | | 7.7 |
| 77BPa | | ? | 0.5(NaClO ₄) | 25 | | | 4.08 | | | |
| | | | | | | | | | 163 | 78.53 |
| | | | | | | | | | 153 | 70.20 |
| | | | | | | | | | 143 | 61.10 |
| | | | | | | | | | 133 | 51.90 |
| | | | | | | | | | 123 | 42.00 |
| | | | | | | | | | 103 | 21.70 |
| 78RM | | C | 0.12(NaCl) | 25 | 12.86 | | | | | |
| 79GK | | C | 0.2(KCl) | 25 | 18.50 | | 3.77(8) | | | |
| | | | | | | | | | 111 | 20.23 |
| | | | | | | | | | 132 | 47.18 |
| | | | | | | | | | 122 | 38.19 |
| | | | | | | | | | 112 | 28.92 |

6. TRYPTOPHAN - $C_{11}H_{12}O_2N_2$
2-Amino-3-(3-indolyl)propanoic acid, HL)



Tryptophan, like phenylalanine, contains an aromatic side chain but, unlike tyrosine, this indolyl group does not contain any readily ionizable protons, and the side chain does not contain any clearly defined donor centres to metal ions.

6.1. Protonation Constants of Tryptophan.

Tryptophan can be regarded as a glycine-like amino acid, HL. The pyrrole-like proton of the indole ring does not ionize under any normal conditions. Literature values for the protonation constants are given in Table 6.1.

Results in 50A and 53P suffer from the low and variable ionic background used, and insufficient experimental details are provided in 73BJ and 73BS. The values in 68RP and 75PN can only be regarded as approximate. The values in 60HD were obtained by a combination of UV spectroscopy and potentiometry. The remaining constants do not include a sufficient number determined under similar conditions to allow the calculation of recommended values. However, a tentative value for the concentration constants at 25 °C and $I = 0.1 - 0.2 \text{ mol dm}^{-3}$ ($K[\text{NO}_3]$) can be presented:

$$\text{i.e. } \log K_{\text{HL}} = 9.34(3), \quad \log K_{\text{H}_2\text{L}} = 2.4.$$

6.2. Enthalpy of Protonation of Tryptophan.

Protonation constants have been measured over a range of temperatures in 60HD, 71IV and 73BS. The only reported calorimetric determinations of the enthalpy of protonation are in 70MB (0.16 mol dm^{-3} ($K[\text{NO}_3]$)) and 70W (3.0 mol dm^{-3} ($\text{Na}[\text{ClO}_4]$)). The results found are given in Table 6.2, and may be accepted tentatively.

6.3. Metal Complex Formation Constants.

Tryptophan coordinates in a glycine-like manner forming mono, bis and tris complexes although the tris complexes are comparatively unimportant except at high ligand:metal ratios. There is some evidence for interaction between Cu(II) ions and the aromatic system of tryptophan, as discussed in the introduction. This evidence is based on thermodynamic measurements since there are no crystal structure determinations for evaluation. Literature values for the formation constants of metal complexes are given in Table 6.3.

Reference 71WS reports a search for stereoselectivity in the complexes of tryptophan with Cd(II), Cu(II), Ni(II), Pb(II) and Zn(II). No stereoselectivity was detected within the precision of the measurements ($\pm 0.04 \text{ log units}$).

Values given in references 50A and 53P suffer from the low and variable concentration of the ionic background used. Values calculated in references 71LC, 72L and 73L were derived from polarographic measurements and do not appear to be based on any protonation constants. They are different from any comparable values and have been rejected. References 68RP, 72IB, 72BJ, 73BS and 75PN give insufficient experimental details for a realistic evaluation and often suffer from a low precision in the original measurements (e.g. $\pm 0.03 \text{ pH units}$ in 68RB). Reference 71IV describes a study of some ternary complexes

but, in the process, calculates the formation constants of some binary complexes. Unfortunately only values for β_{ML} are quoted. If it is assumed that the existence of the bis-complex, $[ML_2]$, was neglected then significant errors would have been introduced into the calculated values for β_{ML} . What is more, the values for the Cu(II) complexes appear to be in error by a factor of up to 100! Values for the formation constants of Hg(II) complexes quoted in 74LB were calculated from the simultaneous measurement of pH and pHg, but suffer from the use of literature values for the protonation constants.

The remaining values (58P, 59P, 70MB, 70W, 71WS, 73CT and 77BP) appear to be acceptable for the varying conditions used, and may be accepted tentatively. However, there are no cases in which a satisfactory comparison may be used to give increased confidence in the values quoted.

6.4. Enthalpy Changes on Complex Formation.

Potentiometric studies at different temperatures have been reported in references 71IV and 73BS. The enthalpy of formation of complexes with Cu(II) (70MB) and with Co(II), Cu(II), Fe(II), Mn(II), Ni(II) and Zn(II) ions (70W) have been measured calorimetrically. Only the calorimetric determinations should be considered (tentatively). Reported values for the enthalpy changes on complex formation are shown in Table 6.4. There is a large difference between the calorimetrically determined values for the enthalpy of formation of $[CuL]^+$ (9.2 kJ mol⁻¹). This may result, partly, from the different ionic backgrounds used but it is much larger than would be expected. Without further measurements it is impossible to recommend one value in preference to the other.

TABLE 6.1

Protonation Constants of Tryptophan (HL)

Literature Values

| Ref. | Type of Constant | Medium mol dm ⁻³ | T °C | log K _{HL} | log K _{H₂L} |
|------|------------------|-----------------------------|------|----------------------------|---------------------------------|
| 50A | M | 0.01 | 20 | 9.55 | 2.20 |
| 53P | M | 0.005 | 20 | 9.57 | |
| 58P | M | 1.0(NaClO ₄) | 20 | 9.43 | |
| 60HD | M | 0.1(KCl) | 2 | 10.00 | 2.46 |
| | | | 25 | 9.40 | 2.46 |
| | | | 44 | 8.90 | 1.46 |
| 68 | M | 0.1(KCl) | 20 | 9.4(1) | |
| 70MB | M | 0.16KNO ₃) | 25 | 9.28 | |
| 70W | C | 3.0(NaClO ₄) | 25 | 9.23(1) | 2.75(2) |
| 71HP | C | 0.15(KNO ₃) | 37 | 9.09 | 2.46 |
| 71IV | C | 0.1(KNO ₃) | 15 | 9.57 | |
| | | | 25 | 9.37 | |
| | | | 37 | 9.01 | |
| | | | 55 | 8.64 | |
| 71WS | M | 0.37(NaNO ₃) | 20 | 9.63(1) | 2.46(3) |
| 72BF | M | 0.1(KCl) | 25 | 9.39(2) | |
| 73BJ | ? | 1.0(NaNO ₃) | 25 | 9.43 | |
| 73BS | ? | 0.1(KNO ₃) | 30 | 9.25 | |
| | | | 40 | 9.04 | |
| | | | 50 | 8.81 | |
| | | | 60 | 8.68 | |
| 75PN | M | 0.1(KNO ₃) | 20 | 8.6(1) | |
| 77BP | C | 0.1(KNO ₃) | 25 | 9.31 | |
| 78L | C | 0.5(KNO ₃) | 25 | 9.47(2) | 2.38(2) |
| 80JH | C | 0.1(KNO ₃) | 25 | 9.33 | |
| | C | 0.1(KNO ₃) | 25 | log K _{DL} = 9.85 | |

TABLE 6.2

Enthalpy Changes in the Protonation of L-Tryptophan (Stepwise Values)
(determined calorimetrically, in kJ mol⁻¹)

| Ref. | Medium mol dm ⁻³ | T °C | ΔH _{HL} | ΔH _{H₂L} |
|------|--------------------------------|------|------------------|------------------------------|
| 70MB | 0.16(KNO ₃) | 25 | -44.6 | |
| 70W | 3.0(NaClO ₄) | 25 | -38.5(5) | -3.3(6) |

TABLE 6.3

Formation Constants of Complexes of Tryptophan with Metal Ions
Literature Values

| Metal Ion | Ref. | Type of Constant | Medium mol dm ⁻³ | T °C | log β _{ML} | log β _{ML₂} | log β _{ML₃} | Recommendation |
|-----------|------|--------------------------|-----------------------------|---------|---------------------|---------------------------------|---------------------------------|----------------|
| Be(II) | 53P | M | 0.005 | 20 | | 11.6 | | |
| Cd(II) | 50A | M | 0.01 | 20 | | 8.1 | | |
| | 53P | M | 0.005 | 20 | | 7.0 | | |
| 71IV | C | 0.1(KNO ₃) | 15 | 3.74 | | | | |
| | | | 25 | 3.66 | | | | |
| | | | 37 | 3.54 | | | | |
| | | | 55 | 3.45 | | | | |
| 71WS | M | 0.37(NaNO ₃) | 20 | D | 4.50 | 8.21 | | |
| | | | LD | 4.51 | 8.19 | | | |
| Co(II) | 50A | M | 0.01 | 20 | | 8.5 | | |
| | 70W | C | 3.0(NaClO ₄) | 25 | 4.58 | 8.90 | 12.25 | T |
| 71IV | C | 0.1(KNO ₃) | 15 | 3.95 | | | | |
| | | | 25 | 3.86 | | | | |
| | | | 37 | 3.79 | | | | |
| | | | 55 | 3.70 | | | | |
| Cu(II) | 50A | M | 0.01 | 20 | | 15.9 | | |
| | 70MB | M | 0.16(KNO ₃) | 25 | 7.80 | 15.10 | | |
| | 70W | C | 3.0(NaClO ₄) | 25 | 8.71 | 16.16 | | |
| | 71HP | C? | 0.15(KNO ₃) | 25 | 8.05 | 15.31 | | |
| | 71IV | C | 0.1(KNO ₃) | 15 | 6.50? | | | |
| 25 | | | | 6.38? | | | | |
| 37 | | | | 6.05? | | | | |
| 55 | | | | 5.74? | | | | |
| 71WS | M | 0.37(NaNO ₃) | 20 | D | 8.27 | 15.47 | | |
| | | | DL | 8.31 | 15.46 | | | |
| 77BP | C | 0.1(KNO ₃) | 25 | 8.02(1) | 15.56(1) | | T | |
| Fe(II) | 50A | M | 0.01 | 20 | | 7.6 | | |
| | 59P | M | 1.0(KCl) | 20 | 3.43 | | | T |
| Fe(II) | 70W | C | 3.0(NaClO ₄) | 25 | 3.92 | 7.39 | ~9.5 | |
| Fe(III) | 58P | M | 1.0(NaClO ₄) | 20 | 9.0 | | | T |
| Hg(II) | 74LB | M | 0.1(NaNO ₃) | 25 | 13.9 | 21.4 | | |
| Mg(II) | 50A | M | 0.01 | 20 | | <4 | | |
| Mn(II) | 50A | M | 0.01 | 20 | | ~5 | | |
| | 70W | C | 3.0(NaClO ₄) | 25 | 2.84 | 5.15 | ~8 | T |
| | 73BS | ? | 0.1(KNO ₃) | 20 | 2.88 | | | |
| 30 | | | | 2.86 | | | | |
| 40 | | | | 2.82 | | | | |
| 50 | | | | 2.79 | | | | |
| 60 | | | | 2.76 | | | | |

Table 6.3 Cont.

| Metal Ion | Ref. | Type of Constant | Medium mol dm ⁻³ | T °C | log β _{ML} | log β _{ML₂} | log β _{ML₃} | Recommendation |
|--------------|------|--------------------------|-----------------------------|--------------|---------------------|---------------------------------|---------------------------------|----------------|
| Ni(II) | 50A | M | 0.01 | 20 | | 10.2 | | |
| | 70W | C | 3.0(NaClO ₄) | 25 | 5.76 | 10.98 | 15.46 | T |
| | 71IV | C | 0.1(KNO ₃) | 15 | 4.88 | | | |
| | | | | 25 | 4.80 | | | |
| | | | | 37 | 4.62 | | | |
| | | | | 55 | 4.43 | | | |
| | 71LC | ? | 0.1(KNO ₃) | 25 | 3.0 | 7.18 | 9.83 | |
| 71WS | M | 0.37(NaNO ₃) | 20 | 5.64 | 10.95 | | | |
| | | | D L LD | 5.68 5.71 | 10.92 10.96 | | T | |
| 73BJ | ? | 1.0(NaNO ₃) | 25 | 5.47 | 10.09 | 13.56 | | |
| Pb(II) | 71WS | M | 0.37(NaNO ₃) | 20 | 5.05 | 9.57 | | |
| | | | | D L LD | 5.11 5.06 | 9.64 9.66 | | |
| | 73CT | C | 3.0(NaClO ₄) | 25 | 4.89(25) | 10.27(10) | | T |
| Zn(II) | 50A | M | 0.01 | 20 | | 9.3 | | |
| | 53P | M | 0.005 | 20 | | 8.2 | | |
| | 70W | C | 3.0(NaClO ₄) | 25 | 5.01 | 9.78 | 13.50 | T |
| | 70WS | M | 0.37(NaNO ₃) | 20 | 5.21 | 9.85 | | |
| D L DL | | | | 5.14 5.19 | 9.86 9.89 | | T | |
| La(III) | 72BF | ? | 0.1(KCl) | 25 | 4.5(1) | 8.6(1) | | |
| | 75PN | M | 0.1(KCl) | 20 | 3.7 | | | |
| Ce(III) | 58RP | M | 0.1(KCl) | 20 | 4.55 | | | |
| Nd(III) | 72BD | ? | 0.1(KCl) | 25 | 4.4(1) | 8.8(1) | | |
| Eu(III) | 72L | ? | 0.2(NaClO ₄) | 25 | 6.80 | | | |
| | 73L | ? | 0.1(NaClO ₄) | 25 | 6.78 | | | |
| Gd(III) | 72BF | ? | 0.1(KCl) | 25 | 5.2(1) | 9.8(1) | | |
| | 75PN | M | 0.1(KCl) | 20 | 4.1 | | | |
| Tb(III) | 72BF | ? | 0.1(KCl) | 25 | 5.2(2) | 9.9(2) | | |
| Lu(III) | 72BF | ? | 0.1(KCl) | 25 | 5.3(3) | 10.0(1) | | |

TABLE 6.4

Enthalpy Changes in the Formation of Metal Complexes of L-Tryptophan
(Stepwise Values in kJ mol⁻¹)

| Metal Ion | Ref. | Technique | Medium mol dm ⁻³ | T °C | -ΔH _{HL} | -ΔH _{H₂L} |
|-----------|------|-----------|-----------------------------|-------|-------------------|-------------------------------|
| Co(II) | 70W | cal | 3.0(NaClO ₄) | 25 | 11.6 | 12.0 |
| | 71IV | pot | 0.1(KNO ₃) | 15-55 | 11 | |
| Cd(II) | 71IV | pot | 0.1(KNO ₃) | 15-55 | 13 | |
| Cu(II) | 70MB | cal | 0.16(KNO ₃) | 25 | 22.9 | 30.2 |
| | 70W | cal | 3.0(NaClO ₄) | 25 | 32.1 | 32.4 |
| | 71IV | pot | 0.1(KNO ₃) | 15-55 | 35 | |
| Fe(II) | 70W | cal | 3.0(NaClO ₄) | 25 | 9.3 | 9.5 |
| Mn(II) | 70W | cal | 3.0(NaClO ₄) | 25 | 11.3 | 10.5 |
| | 73BS | pot | 0.1(KNO ₃) | 20-60 | 5.4 | |
| Ni(II) | 70W | cal | 3.0(NaClO ₄) | 25 | 36.1 | 42.6 |
| | 71IV | pot | 0.1(KNO ₃) | 15-55 | 22 | |
| Zn(II) | 70W | cal | 3.0(NaClO ₄) | 25 | 23.1 | 26.0 |

7. SUMMARY OF RECOMMENDATIONS

A study of the literature data surveyed in sections 2 - 6 demonstrates that the most usual experimental conditions employed for measuring concentration constants are a temperature of 25 °C and an ionic background of 0.1 to 0.16 mol dm⁻³ (K⁺, Na⁺, Cl⁻, [NO₃⁻] [ClO₄⁻]). As a result recommended constants can be given for these conditions only. However, a number of results at 37 °C and/or 3.0 mol dm⁻³ (Na[ClO₄]) may also be accepted tentatively.

Preferred (Recommended (R) or Tentative (T)) formation constants at 25 °C and I = 0.1 - 0.2 mol dm⁻³ are given in Table 7.1.

Recommended values for enthalpy changes are not included since there are insignificant data to summarise usefully. In general, however, protonation of the -NH₂ group has a value of ΔH ~ -43 kJ mol⁻¹, a value which is almost independent of the nature of the amino acid.

TABLE 7.1

Complex Formation Constants (Concentration Constants) at 25 °C and I = 0.1 - 0.2 mol dm⁻³ (K⁺, Na⁺, Cl⁻, [NO₃⁻], [ClO₄⁻])

Proton Complexes

| Ligand | log K _{HL} | log K _{H₂L} | log K _{H₃L} | Recommendation |
|-------------------|---------------------|---------------------------------|---------------------------------|----------------|
| Histidine | 9.11(2) | 6.05(3) | 1.72(9) | R |
| Phenylalanine | 9.15(4) | 2.2 | | R |
| Tyrosine | 10.10(2) | 9.03(1) | 2.1 | R |
| DOPA ^a | 13.4(2) | 9.84(3) | 8.77(2) | R |
| Tryptophan | 9.34(3) | 2.4 | | T |

$$^a \log K_{H_4L} = 2.2(1)$$

Metal Complexes

| ligand | Metal Ion | log β _{ML} | log β _{ML₂} | Recommendation |
|-------------------|---------------------|---------------------|---------------------------------|----------------|
| Histidine(HL) | Co(II) | 6.88(2) | 12.35(4) | R |
| | Cu(II) ^b | 10.16(3) | 18.11(9) | R |
| | Ni(II) | 8.67(1) | 15.50(2) | R |
| | Zn(II) | 6.51(4) | 12.01(4) | R |
| Phenylalanine(HL) | Cu(II) | 7.93 | 14.83 | T |
| Tryptophan(HL) | Cu(II) | 8.02 | 15.56 | T |

| | | log K _{MHL} ^{HL} | log K _{M(HL)₂} ^{HL} | |
|----------------------------|--------|--|--|---|
| Tyrosine(H ₂ L) | Co(II) | 4.0 | 7.3 | T |
| | Cu(II) | 7.8 | 14.6 | T |
| | Ni(II) | 5.0 | 9.2 | T |
| | Zn(II) | 4.2 | 8.2 | T |
| | | log K _{MH₂L} ^{H₂L} | log K _{M(H₂L)₂} ^{H₂L} | |
| DOPA(H ₃ L) | Cu(II) | 7.56 | 14.19 | T |
| | Ni(II) | 4.87 | 8.7 | T |

$$^b \log \beta_{MHL} = 14.11(2), \quad \log \beta_{MH_1L} = 2.0(2),$$

$$\log \beta_{MHL_2} = 23.81(7), \quad \log \beta_{MH_2L_2} = 27.2(1),$$

$$\log \beta_{MH_2L_2} = 7.9(1).$$

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