Studies on Transition-metal–Peptide Complexes. Part 1. Equilibrium and Thermochemical Study of the Copper(II) Complexes of Glycylglycine, Glycyl-DL-α-alanine, DL-α-Alanylglycine, and DL-α-Alanyl-DL-α-alanine

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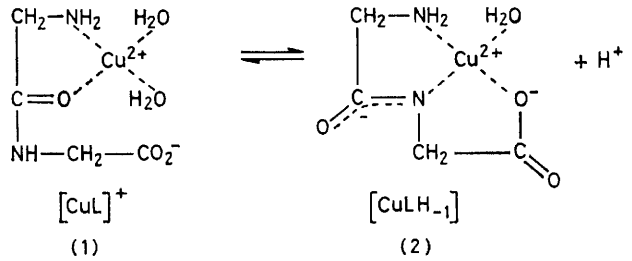
pH Titrimetry and calorimetry have been used to determine the stoicheiometries, stability constants, and enthalpies and entropies of formation of the complexes formed in the systems of copper(II) with glycylglycine, glycyl-DL-α-alanine, DL-α-alanylglycine, and DL-α-alanyl-DL-α-alanine, at ionic strength I = 0.2 mol dm^{-3} KCl and at 25 °C. There is no possibility of the titrimetric indication of the formation of the complexes $[CuL_2]$ and $[CuL_2H_{-2}]^{2-}$ (L = dipeptide anion $H_2N–CHR–CO–NH–CHR'–CO_2^-$) in these equilibrium systems, even when their maximum concentration is 10—15%. The systematic changes within the series have been interpreted by simultaneous consideration of the electron-donating and steric-hindrance effects of the methyl groups. From the values of the formation constants and enthalpy changes, it is concluded that equatorial–axial co-ordination of the second peptide ligand occurs in the complex $[CuL_2H_{-1}]^-$, while in the binuclear complex $[Cu_2L_2H_{-3}]^-$ an $[OH]^-$ ligand bridges the two $[CuLH_{-1}]$ units equatorially.

During the past 20 years intensive investigations have been carried out on the copper(II) complexes of biologically important ligands.[1] Great attention has been paid to elucidating and interpreting the thermodynamic and structural characteristics of the di- and oligo-peptide complexes.[2–7] It is generally accepted that with the simple aliphatic dipeptides Cu^{II} forms complexes of stoicheiometry $[CuL]^+$, $[CuLH_{-1}]$, $[CuLH_{-2}]^-$, $[CuL_2H_{-1}]^-$, and $[Cu_2L_2H_{-3}]^-$. Most recently, however, Brookes and Pettit [7] also assumed formation of the complex $[CuL_2]$ in the copper(II)–glycyl-L-α-alanine system.†

Views regarding the role of the donor groups in the complexes formed are uniform only for the species $[CuL]^+$, $[CuLH_{-1}]$, and $[CuLH_{-2}]^-$. It is considered that in the complex $[CuL]^+$ the NH_2 and the peptide C=O group are co-ordinated to the copper(II) ion. This complex is characterized by a pK value of *ca.* 4. Dissociation of the proton occurs on the nitrogen atom of the peptide bond. In the case of the copper(II)–glycylglycine complex the process is accompanied by the following structural rearrangement. The species $[CuLH_{-2}]^-$ is generally



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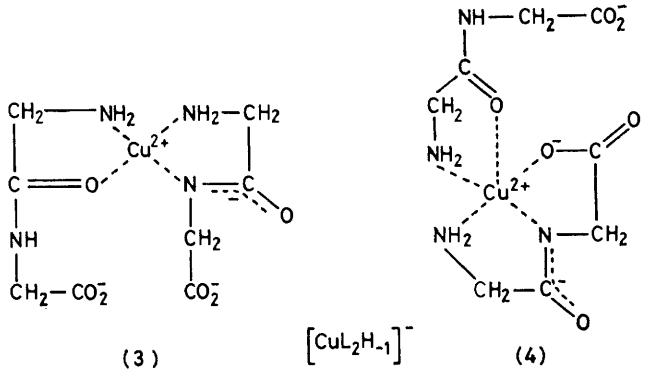
regarded as a mixed hydroxo-complex in which the water molecule in the equatorial plane is replaced by an $[OH]^-$ ligand.

† In the formulae of the complexes L^- is the anionic form of the dipeptide, *i.e.* in general $H_2N–CHR–CO–NH–CHR'–CO_2^-$. The complexes are represented by their *stoicheiometric composition*, independently of the arrangement of the donor groups. The absence of those protons which are acidic *only* in the copper(II) complexes and/or the presence of an $[OH]^-$ ligand is uniformly denoted by a negative subscript for H, as they are undistinguishable on the basis of equilibrium analysis alone. The water molecules remaining in the first co-ordination sphere of the Cu^{II} are omitted as the relevant formation constants do not take account of the water concentration.

Opinions differ as to the structures of the complexes $[CuL_2H_{-1}]^-$ and $[Cu_2L_2H_{-3}]^-$. In the case of $[CuL_2H_{-1}]^-$, only equatorial co-ordination of the donor groups was first considered. It was assumed that the C=O group of the second peptide ligand expels the CO_2^- group of the



(3) (4)

first ligand from the co-ordination sphere. More recently, Kaneda and Martell [6] presumed equatorial–axial co-ordination of the second ligand. These two structural conceptions are illustrated above.

There are also different views as to the arrangement of the donor groups in the complex $[Cu_2L_2H_{-3}]^-$. Kaneda and Martell [6] assumed equatorial–axial co-ordination *via* a bridging $[OH]^-$ ligand and a nitrogen atom from one of the peptides, whereas Brookes and Pettit [7] suggested equatorial coupling *via* only the $[OH]^-$ ligand, as follows.

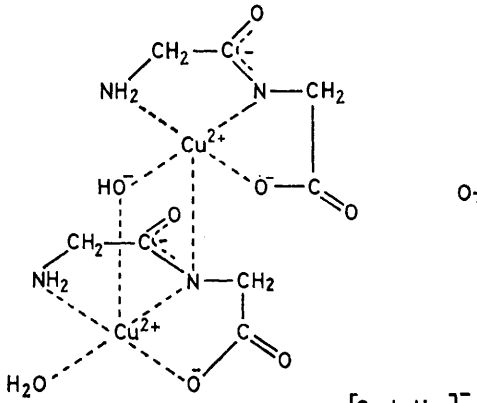
For many copper(II)–dipeptide parent complexes and their mixed complexes with 2,2'-bipyridyl (among others), Sigel [5] made a detailed examination of the effect of the alkyl chain on the equilibrium conditions. One of his

[1] 'Stability Constants of Metal–Ion Complexes,' eds. L. G. Sillen and A. E. Martell, *Special Publ.*, The Chemical Society, London, 1964, No. 17; 1971, No. 25.
[2] A. P. Brunetti, E. J. Burke, M. C. Lim, and G. H. Nancollas, *J. Solution Chem.*, 1972, **1**, 153.
[3] H. A. Skinner and E. W. Tipping, *Rev. Chim. minérale*, 1972, **9**, 51.
[4] T. P. A. Kruck and B. Sarkar, *Inorg. Chem.*, 1975, **14**, 2383.
[5] H. Sigel, *Inorg. Chem.*, 1975, **14**, 1535.
[6] A. Kaneda and A. E. Martell, *J. Co-ordination Chem.*, 1975, **4**, 137.
[7] G. Brookes and L. D. Pettit, *J.C.S. Dalton*, 1975, 2106.

most important findings was that if one of the hydrogens of the CH_2 group adjacent to the terminal NH_2 is replaced by an alkyl group the stability of the complex $[CuL]^+$ decreases while its acidic strength increases. In contrast, the only effect of an alkyl group substituted on the CH_2 adjacent to the CO_2^- group is to increase the electron density on the NH_2 group.

Some of the bonding conceptions outlined above are based primarily on thermodynamic results relating to the copper(II)–dipeptide complexes. In spite of the fact that a number of workers have made calorimetric studies, the heats of formation available are not comprehensive. Skinner and Tipping [3] carried out a complete calorimetric analysis of the copper(II)–glycylglycine system, but only the heats of formation of the complexes $[CuL]^+$ and $[CuLH_{-1}]$ are known for other simple dipeptides.[2]

Accordingly, the aim of this work was to determine the stoicheiometries and thermodynamics of the complexes formed in the equilibrium systems containing Cu^{II} and the four simplest dipeptides obtainable from glycine and alanine, *i.e.* glycylglycine, glycyl-DL-α-alanine, DL-α-alanylglycine, and DL-α-alanyl-DL-α-alanine.* It was hoped that the results would contribute towards the solution of the debated questions outlined above.



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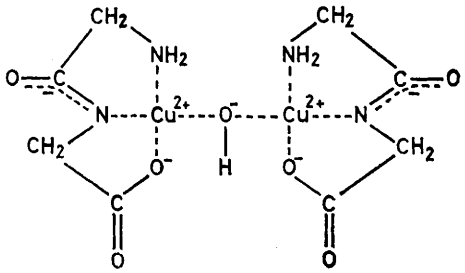
$[Cu_2L_2H_{-3}]^-$



(6)

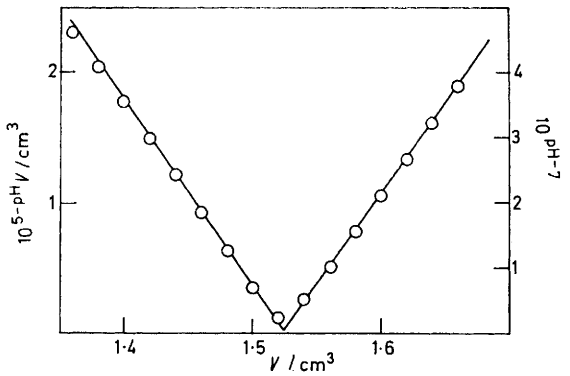
EXPERIMENTAL

The dipeptides (Reanal) used were purified by repeated recrystallization from water–alcohol. Their purities and the concentrations of the stock solutions were checked by application of the Gran function.[8,9]

The concentration of the $CuCl_2$ stock solution was determined by the following pH titration method. Glycine (*ca.* 20 mol equiv.) was added to a known amount of the stock solution, which was then titrated with KOH solution. In this system, in the range $\bar{n} > 1.5$, practically only process (i) takes place on the action of alkali. In the

$$[CuL]^+ + HL^{\pm} \longrightarrow [CuL_2] + H^+ \qquad (i)$$

presence of a large excess of ligand, $[HL^{\pm}]$ is constant and thus (i) can be regarded formally as a weak acid–strong base reaction, *i.e.* the relevant Gran function is linear. Following formation of the complex $[CuL_2]$, the glycine remaining in excess is neutralized. Because of the large excess of glycine, in the initial stage of this process the system can be regarded as a solution of a strong base, where the role of the ionic product of water, however, is taken over by the 'ionic product' of glycine ($[H^+][L^-]$). The Gran function characteristic for the section of the titration with a strong base beyond the equivalence point can therefore be used at the beginning of the titration of the excess of glycine. The Figure shows the straight lines resulting from transformation of the data of a titration curve (obtained as described) into Gran functions. It can be seen from the Figure that this method permits a very accurate determination of the amount of alkali necessary for formation of the complex $[CuL_2]$. The method also has the advantage that it is possible to determine the concentrations of all of the stock solutions used in the investigation by the same procedure and referred to the same substance (potassium hydrogenphthalate).



Gran functions constructed from pH-titration data for solutions (25 cm³) containing 0.2 mol dm⁻³ glycine and 0.01 mol dm⁻³ $CuCl_2$. [KOH] = 0.238 mol dm⁻³

pH Titrations were made with a Radiometer PHM 52 pH-meter, using G 202 C glass and K 401 calomel electrodes, on samples with an initial volume of 25 cm³ at an ionic strength I = 0.2 mol dm⁻³ KCl at 25 °C and in the range pH 3.5—11. The electrode system was calibrated by the method of Irving *et al.*[10] The metal-ion and ligand concentrations of the individual samples are listed in Table 1. For each system at least 150 experimental points were utilized to

* Henceforward the anionic form of the ligands are denoted by GG^- (glycylglycinate), GA^- (glycyl-DL-α-alaninate), AG^- (DL-α-alanylglycinate), and AA^- (DL-α-alanyl-DL-α-alaninate).

[8] G. Gran, *Acta Chem. Scand.*, 1950, **4**, 599.

[9] F. J. C. Rossotti and H. S. Rossotti, *J. Chem. Educ.*, 1965, **42**, 375.

[10] H. Irving, M. G. Miles, and L. D. Pettit, *Analyt. Chim. Acta*, 1967, **38**, 475.

calculate the stability constants. A previously modified variant [11,12] of the SCOGS program [13,14] was used to evaluate the experimental results.

The calorimetric measurements were carried out by stepwise titration in an LKB 8700-1 calorimeter. Values of

TABLE 1

Compositions (c/mol dm^{-3}) of solutions of copper(II)–dipeptide systems examined by pH titrimetry

Peptide	Copper					
0.010	0.000	0.001	0.002	0.003	0.005	0.010
0.005	0.000	0.001	0.002	0.003	0.005	
0.002	0.000	0.001	0.002			

the protonation heats were obtained by calorimetric titration of solutions with an initial volume of 90 cm^3, containing 0.004 mol cm^{-3} HCl and 0.005 mol dm^{-3} dipeptide. In the determination of the enthalpy changes of the complex-formation processes the ligand concentration was 0.005 mol dm^{-3} and the metal ion : ligand ratio was 1 : 1 or 1 : 2. For each system at least 25 experimental points were utilized in determining the heats of formation.

The experimental data were converted into heat quantities by the method reported earlier.[15] The resulting heat change is given by means of the changes in the number of moles and in the heats of formation (Δm_j and ΔH_j) of the individual complexes as in (1), where Δm_w is the change in

$$\Delta q = \Sigma \Delta m_j \Delta H_j + \Delta m_w \Delta H_w \qquad (1)$$

the number of moles of water, and ΔH_w is the heat of the reaction $H^+ + OH^- \longrightarrow H_2O$. The Δm_j values were calculated from the concentration distribution of the complexes *via* equation (2), where V is the volume, A_j is the association in question, and the indices i and f refer to the

$$\Delta m_j = [A_j]_f V_f - [A_j]_i V_i \qquad (2)$$

initial and final states, respectively. The program already referred to [11] was supplemented with a block (operating on the basis of the least-squares principle) generally applicable to the evaluation of calorimetric-titration results.

RESULTS AND DISCUSSION

From studies relating to the copper(II) complexes of amino-acids it is known that at pH > 6, with an excess of ligand, the complex $[CuL_2]$ predominates. It is surprising that in the copper(II)–dipeptide systems formation of the complex $[CuL_2]$ has been assumed only recently. Formation of the complex $[CuL_2H_{-2}]^{2-}$, containing both ligands in deprotonated form, would also be conceivable for dipeptides.

However, when formation of the complexes $[CuL_2]$ and $[CuL_2H_{-2}]^{2-}$ was assumed, evaluation of the experimental data for the copper(II)–glycylglycine system did not lead to acceptable results. In this case the calculation problem is 'ill conditioned', and the values of the constants are uncertain. Accordingly, the calculation problem was varied by assuming different formation constants for the complexes $[CuL_2]$ or $[CuL_2H_{-2}]^{2-}$. These values were fixed, and the formation constants for the complexes $[CuL]^+$, $[CuLH_{-1}]$, $[CuL_2H_{-1}]^-$, and $[Cu_2L_2H_{-3}]^-$ were then calculated. The results of such calculations for various assumed values of the formation constant of the complex $[CuL_2]$ are given in Table 2. From these tabulated data the value of $\Delta\bar{v}$, which expresses the accuracy of the approximation to the titration curves, lies within the limits of experimental error even if the formation of $[CuL_2]$ is not assumed. The value of $\Delta\bar{v}$ decreased further up to log $\beta_{CuL_2} = 11.0$, and increased only in the interval log $\beta_{CuL_2} > 11.0$. This means that in this equilibrium system the complex $[CuL_2]$ cannot be detected by pH titration even at its maximum concentration of 15%. When chemical considerations are also taken into account, it is unlikely that log β_{CuL_2} is *ca.* 11; a value of log β_{CuL_2} of *ca.* 10—10.5 and a corresponding formation of 2—5% of the complex appear realistic.

Similar calculations with the assumption of formation of the complex $[CuL_2H_{-2}]^{2-}$ showed that *ca.* 10—15% is the amount which is likewise undetectable in this equilibrium system.

TABLE 2

Results of the evaluation of the experimental data obtained for the copper(II)–glycylglycine system assuming various formation constants for the complex $[CuL_2]$

log β_{CuL_2}	log β_{CuL}	log $\beta_{CuLH_{-1}}$	log $\beta_{CuLH_{-2}}$	log $\beta_{CuL_2H_{-1}}$	log $\beta_{Cu_2L_2H_{-3}}$	$10^2[CuL_2]/c_{Cu}$	$\Delta\bar{v}$/cm^3
$-\infty$	5.580	1.326	−8.044	4.449	−4.517	0	0.005 8
9.5	5.575	1.325	−8.045	4.450	−4.519	0.5	0.005 7
10.0	5.566	1.323	−8.047	4.451	−4.522	1.5	0.005 6
10.5	5.536	1.317	−8.051	4.455	−4.532	5.0	0.005 2
11.0	5.426	1.299	−8.065	4.468	−4.563	15	0.004 8
11.5	4.610	1.249	−8.106	4.499	−4.649	40	0.009 5

This relatively high value of the undetectable concentration of the complex $[CuL_2]$ can be explained in that the formations of the complexes $[CuL_2]$ and $[CuLH_{-1}]$ in the presence of an excess of ligand are both accompanied by the release of two protons. Consequently, they behave nearly identically as regards the pH effect of their formation, and thus to a certain extent they can replace one another. Evaluation of samples with a metal-ion : ligand concentration ratio of 1 : 1 is not disturbed by the assumption of even a comparatively high value of log β_{CuL_2}, since the complex $[CuL_2]$ can be formed only in very low concentration.

Taking into account the above uncertainty in the compositions of the complexes formed, a larger error must be ascribed to the values of the individual stability constants

[11] I. Nagypál, *Acta Chim. Acad. Sci. Hung.*, 1974, **82**, 29.
[12] A. Gergely, I. Nagypál, and E. Farkas, *Acta Chim. Acad. Sci. Hung.*, 1974, **82**, 43.
[13] D. D. Perrin and I. G. Sayce, *Talanta*, 1967, **14**, 833.
[14] I. G. Sayce, *Talanta*, 1968, **15**, 1397.
[15] A. Gergely and I. Sóvágó, *J. Inorg. Nuclear Chem.*, 1973, **35**, 4355.

than would arise from statistical analysis. Accordingly, the estimated errors of the individual constants are: log $\beta_{CuL} \sim \log \beta_{Cu_2L_2H_{-3}} \pm 0.06$; log $\beta_{CuLH_{-1}} \sim \log \beta_{CuL_{-2}} \sim \log \beta_{Cu_2LH_{-1}} \sim 0.03$ unit. For the same reasons, the error in the ΔH values obtained from the results of the calorimetric measurements is *ca.* ± 2 kJ mol^{-1} for $[CuL]^+$ and $[Cu_2L_2H_{-3}]^-$ and ± 1 kJ mol^{-1} for $[CuLH_{-1}]$, $[CuLH_{-2}]^-$, and $[CuL_2H_{-1}]^-$ complexes. Accordingly, the estimated errors in the ΔS values are ± 3 J K^{-1} mol^{-1} for $[CuLH_{-1}]$, $[CuLH_{-2}]^-$ and $[CuL_2H_{-1}]^-$, and ± 6 J K^{-1} mol^{-1} for $[CuL]^+$ and $[Cu_2L_2H_{-3}]^-$ complexes.

TABLE 3

Formation constants and enthalpy and entropy changes of complexes formed in the copper(II)–glycylglycine–proton system

Composition	log β	$-\Delta G$ kJ mol^{-1}	$-\Delta H$ kJ mol^{-1}	ΔS J K^{-1} mol^{-1}
$HL^{\pm}$	8.13 ±0.01	46.4	44.3 ±0.5	7 ± 2
H_2L^+	11.30 ±0.02	64.5	45.6 ±0.8	63 ± 3
$[CuL]^+$	5.56 ±0.06	31.7	29 ±2	8 ± 6
$[CuLH_{-1}]$	1.33 ±0.03	7.6	−3 ±1	35 ± 3
$[CuLH_{-2}]^-$	−8.04 ±0.03	−45.8	−46 ±1	1 ± 3
$[CuL_2H_{-1}]^-$	4.46 ±0.03	25.4	28 ±1	−10 ± 3
$[Cu_2L_2H_{-3}]^-$	−4.51 ±0.06	−25.7	−38 ±2	41 ± 6

TABLE 4

Formation constants and enthalpy and entropy changes of complexes formed in the copper(II)–glycyl-DL-α-alanine–proton system

Composition	log β	$-\Delta G$ kJ mol^{-1}	$-\Delta H$ kJ mol^{-1}	ΔS J K^{-1} mol^{-1}
$HL^{\pm}$	8.20 ±0.01	46.8	45.4 ±0.5	5 ± 2
H_2L^+	11.37 ±0.02	64.9	47.1 ±0.8	60 ± 3
$[CuL]^+$	5.76 ±0.06	33.0	27 ±2	20 ± 6
$[CuLH_{-1}]$	1.55 ±0.03	8.8	−3 ±1	40 ± 3
$[CuLH_{-2}]^-$	−7.94 ±0.03	−45.3	−47 ±1	8 ± 3
$[CuL_2H_{-1}]^-$	4.63 ±0.03	26.4	24 ±1	8 ± 3
$[Cu_2L_2H_{-3}]^-$	−4.18 ±0.06	−23.8	−37 ±2	43 ± 6

TABLE 5

Formation constants and enthalpy and entropy changes of complexes formed in the copper(II)–DL-α-alanylglycine–proton system

Composition	log β	$-\Delta G$ kJ mol^{-1}	$-\Delta H$ kJ mol^{-1}	ΔS J K^{-1} mol^{-1}
$HL^{\pm}$	8.19 ±0.01	46.7	45.5 ±0.5	4 ± 2
H_2L^+	11.34 ±0.02	64.7	47.2 ±0.8	58 ± 3
$[CuL]^+$	5.25 ±0.06	30.0	25 ±2	15 ± 6
$[CuLH_{-1}]$	1.35 ±0.03	7.7	−3 ±1	35 ± 3
$[CuLH_{-2}]^-$	−8.16 ±0.03	−46.6	−47 ±1	0 ± 3
$[CuL_2H_{-1}]^-$	3.95 ±0.03	22.5	21 ±1	4 ± 3
$[Cu_2L_2H_{-3}]^-$	−4.66 ±0.06	−26.6	−38 ±2	40 ± 6

The log β, ΔG, ΔH, and ΔS data obtained by the methods discussed in the Experimental section are listed in Tables 3—6. The following important conclusions may be drawn.

TABLE 6

Formation constants and enthalpy and entropy changes of complexes formed in the copper(II)–DL-α-alanyl-DL-α-alanine–proton system

Composition	log β	$-\Delta G$ kJ mol^{-1}	$-\Delta H$ kJ mol^{-1}	ΔS J K^{-1} mol^{-1}
$HL^{\pm}$	8.26 ±0.01	47.1	46.2 ±0.5	3 ± 2
H_2L^+	11.34 ±0.02	64.7	47.9 ±0.8	57 ± 3
$[CuL]^+$	5.33 ±0.06	30.4	28 ±2	7 ± 6
$[CuLH_{-1}]$	1.43 ±0.03	8.2	−5 ±1	44 ± 3
$[CuLH_{-2}]^-$	−8.01 ±0.03	−45.7	−49 ±1	11 ± 3
$[CuL_2H_{-1}]^-$	4.13 ±0.03	23.6	22 ±1	6 ± 3
$[Cu_2L_2H_{-3}]^-$	−4.39 ±0.06	−25.1	−41 ±2	53 ± 6

(*a*) As regards the proton complexes of type $HL^{\pm}$ the formation constant is highest for AA^-, the data relating to AG^- and GA^- are similar, and the stability of GG^- is lowest. The stability increase referred to GG^- reflects the electron-donating effect of the Me group. The almost identical values for GA^- and AG^- indicate that the effect of the Me group on log β_{HL} is not influenced by whether this group is situated on one or other side of the peptide bond. It is surprising, and difficult to interpret when the electron-donating property of the Me group is considered, that Brunetti *et al.*[2] observed a change in the opposite direction from this in the case of AG^-, GA^-, and AA^-. However, our results relating to the heats of formation of the proton complexes $HL^{\pm}$ agree well with their reported data with regard to both absolute and relative values.

(*b*) Comparison of the stability constants of the complexes $[CuL]^+$ reveals that the following relations hold between them:

$$\beta_{Cu(AG)} < \beta_{Cu(GG)} < \beta_{Cu(GA)} < \beta_{Cu(AA)}$$

This can be interpreted by simultaneous consideration of the effects of the Me group in donating electrons and causing steric hindrance. The Me group between the NH_2 group and the peptide bond causes steric hindrance and thus the stability decreases in spite of the fact that Me increases the electron density of the donor groups. On the other hand, the Me adjacent to the CO_2 group acts only as an electron donor since this molecular unit does not form a chelate ring in the complex $[CuL]^+$. The above relations of the stability constants are also exhibited in the data of Brunetti *et al.*[2] and Sigel.[5]

(*c*) The heats of formation of the complexes $[CuL]^+$ nearly coincide with those of $[CuL]^+$ where HL is an

aliphatic amino-acid, which indicates, in agreement with earlier findings,[16] that these complexes contain only one Cu–N bond [*cf.* structure (1)].

Comparison of the formation constants and enthalpy changes of the various deprotonated complexes is made difficult by the fact that their values arise from the resultants of a number of part processes. For comparison, therefore, the equilibrium constants of some of the more important part processes are given in Tables 7—10. Table 7 contains the equilibrium constants of the processes $[CuLH_{-1}] + H^+ \rightleftharpoons [CuL]^+$. From the data of this Table, if the complexes $[CuL]^+$ are treated as weak acids, the pK values in the case of GG^- and GA^- are almost the same and *ca.* 0.3 log unit larger than the corresponding values for AG^- and AA^-, which similarly agree. The deprotonation and accompanying structural rearrangement are therefore promoted by the Me group attached to the carbon atom adjacent to the NH_2.

TABLE 7

Equilibrium constants and thermodynamic data for the processes $[CuLH_{-1}] + H^+ \rightleftharpoons [CuL]^+$ in the copper(II)–dipeptide systems

Ligand	log K	$-\Delta G$ / kJ mol^{-1}	$-\Delta H$ / kJ mol^{-1}	ΔS / J K^{-1} mol^{-1}
GG^-	4.23 ± 0.06	24.1	32 ± 2	−26 ± 6
GA^-	4.22 ± 0.06	24.1	30 ± 2	−21 ± 6
AG^-	3.91 ± 0.06	22.3	28 ± 2	−20 ± 6
AA^-	3.90 ± 0.06	22.3	33 ± 2	−37 ± 6

Table 8 presents the thermodynamic parameters of the processes $[CuLH_{-1}] + L^- \rightleftharpoons [CuL_2H_{-1}]^-$. Although the tabulated log K values are substantially larger than those typical of the behaviour of unidentate ligands, they are much smaller than the equilibrium constants of the processes $[CuL]^+ + L^- \rightleftharpoons [CuL_2]$ involving the amino-acid complexes. At the same time, the ΔH values roughly agree with the data obtained for the processes $[CuL]^+ + L^- \rightleftharpoons [CuL_2]$ for aliphatic amino-acids. It may be concluded from this latter experimental result that an equatorial Cu–NH_2 bond is produced in the above process. However, the chelate ring probably closes not in the equatorial plane, but axially in accordance with structure (4), *via* the C=O group of the ' second ' ligand. The axial co-ordination means the release of a comparatively loosely bound water molecule, and this process can therefore not be associated with a significant translational entropy increase. However, the co-ordination in itself means a stiffening of the ligand, and thus an entropy decrease. Accordingly, structure (4) is in agreement with the ΔH and ΔS data. This structural arrangement is also supported by results on the mixed complexes copper(II)–dipeptide–amino-acid.[17] The following relation exists between the data relating to the four dipeptides: log $K_{(GG)} \sim$ log $K_{(GA)} >$ log $K_{(AG)} \sim$ log $K_{(AA)}$. This can be similarly interpreted in terms of steric hindrance by the Me group.

TABLE 8

Equilibrium constants and thermodynamic data for the processes $[CuLH_{-1}] + L^- \rightleftharpoons [CuL_2H_{-1}]^-$ in the copper(II)–dipeptide systems

Ligand	log K	$-\Delta G$ / kJ mol^{-1}	$-\Delta H$ / kJ mol^{-1}	ΔS / J K^{-1} mol^{-1}
GG^-	3.13 ± 0.03	17.8	31 ± 1	−45 ± 3
GA^-	3.08 ± 0.03	17.6	27 ± 1	−32 ± 3
AG^-	2.60 ± 0.03	14.8	24 ± 1	−31 ± 3
AA^-	2.70 ± 0.03	15.4	27 ± 1	−38 ± 3

Tables 9 and 10 give the thermodynamic parameters of the processes $[OH]^- + [CuLH_{-1}] \rightleftharpoons [CuLH_{-1}(OH)]^-$ and $[CuLH_{-1}(OH)]^- + [CuLH_{-1}] \rightleftharpoons [(CuLH_{-1})_2(OH)]^-$. If the formations of $[CuLH_{-2}]^-$ and $[Cu_2L_2H_{-3}]^-$ are interpreted in accordance with the given processes, there is no appreciable difference in the thermodynamic data for the complexes formed with the various dipeptides.

TABLE 9

Equilibrium constants and thermodynamic data for the processes $[OH]^- + [CuLH_{-1}] \rightleftharpoons [CuLH_{-1}(OH)]^-$ in the copper(II)–dipeptide systems *

Ligand	log K	$-\Delta G$ / kJ mol^{-1}	$-\Delta H$ / kJ mol^{-1}	ΔS / J K^{-1} mol^{-1}
GG^-	4.45 ± 0.05	25.4	13 ± 2	−40 ± 4
GA^-	4.33 ± 0.05	24.7	12 ± 2	−42 ± 4
AG^-	4.31 ± 0.05	24.6	13 ± 2	−39 ± 4
AA^-	4.38 ± 0.05	25.0	13 ± 2	−41 ± 4

* For the derivation of the data, values of pK_W = 13.82 and ΔH_W = −56.73 kJ mol^{-1}, determined in separate experiments, were used.

TABLE 10

Equilibrium constants and thermodynamic data for the processes $[CuLH_{-1}(OH)]^- + [CuLH_{-1}] \rightleftharpoons [(CuLH_{-1})_2(OH)]^-$ in the copper(II)–dipeptide systems

Ligand	log K	$-\Delta G$ / kJ mol^{-1}	$-\Delta H$ / kJ mol^{-1}	ΔS / J K^{-1} mol^{-1}
GG^-	2.20 ± 0.06	12.5	11 ± 2	5 ± 6
GA^-	2.21 ± 0.06	12.6	14 ± 2	−5 ± 6
AG^-	2.15 ± 0.06	12.3	11 ± 2	4 ± 6
AA^-	2.18 ± 0.06	12.5	13 ± 2	−2 ± 6

Within the series examined, the co-ordination ability of the fourth co-ordination site with regard to the OH^- ion is practically independent of the positions of the Me groups of the already bound peptide ligands. Furthermore, the ΔH values for the above two processes are almost the same, and thus the significant difference in the equilibrium constants arises from the difference in the entropy changes. This experimental finding indicates that essentially identical chemical bonds are formed in the two processes, *i.e.* structure (6) appears to be the more realistic for the complex $[Cu_2L_2H_{-3}]^-$.

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