

Thermodynamics of Complex Formation : Stabilities of Complexes of Copper(II) with Dipeptides in Aqueous Media

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The metal-ligand stability constants of the copper chelates of a few dipeptides have been determined at 20°, 30°, 40° and 50° ± 0.02°C and $\mu = 0.1 M$ (NaClO₄) in aqueous medium. The thermodynamic parameters for the proton-ligand and metal-ligand stability constants have been obtained by the temperature coefficient method. The chelates are both enthalpy and entropy stabilized. The thermodynamic functions ΔG and ΔH of dipeptide complexes of copper(II) have been analysed in terms of electrostatic(e) and nonelectrostatic(non) parts. From the relative magnitudes of ΔG_{el} and ΔG_{non} values, it is concluded that the nonelectrostatic forces are stronger than the electrostatic forces in the mono complexes. A significant decrease in the electrovalent character of the metal-ligand bond occurs on coordination of second molecule of dipeptide.

Since the metal ions and many ligands carry a charge, the thermodynamic functions associated with their complex formation involve electrostatic factors arising from the charges on these ions in addition to the factors of chemical nature characteristic of the reactants free from the electrostatic interactions. The separation of these functions into electrostatic and nonelectrostatic parts, which play an important role in knowing the net reaction tendency, was first attempted by Gurney¹ for proton ionization reactions and this method was later extended to complex formation reactions²⁻⁵. However, the later works²⁻⁵ were confined to the general discussions on the application of the Gurney's method. Anderegg⁶, and Degisher and Nancollas⁷, especially gave the interpretation of nonelectrostatic enthalpy changes. Gergely *et al.*⁸ carried out thermochemical studies on the complex formation between copper(II)-dipeptides and explained the results on the basis of conventional thermodynamic functions. However, in the present study an effort is made to discuss the nature of metal-ligand bond in copper(II)-dipeptide complexes by evaluating electrostatic and nonelectrostatic parts of the thermodynamic functions ΔG and ΔH .

Materials and Methods

The dipeptides such as DL- α -alanyl-DL-methionine, DL-alanyl-DL-norvaline, glycylsarcosine, glycyl-L-asparagine and glycyl-DL-valine were obtained from Sigma Chemical Co., USA and were used as such. Copper nitrate solution ($1.0 \times 10^{-2} M$) was prepared from AR (BDH) reagent. All the solutions were prepared in doubly distilled water ($pH = 6.8$; sp. cond.

$= 1.6 \times 10^{-6}$ mhos). Initial ionic strength of all the solutions was maintained at 0.1 M by adding sodium perchlorate solution. Experiments were conducted at 20°, 30°, 40° and 50° ± 0.02°C. Initially the pH meter was standardized at 25°C using appropriate buffer solution^{9,10} of pH 4.01 and 9.13 equilibrated for 30 min before measurement. The details regarding other chemicals and measurement of pH have been described in earlier papers¹¹⁻¹³.

Irving and Rossotti's method¹⁴ was used to calculate the \bar{n} and pL values from the pH titration curves. The log K values were computed¹⁵ by adopting (i) half \bar{n} method, (ii) successive approximation method and (iii) least squares method. The averages of the three were considered for log K values and then used to calculate the thermodynamic parameters as usual. The correlation coefficient for the linear plots of log K versus $1/T$ was recorded and the values of ΔH were considered to be reliable only when the correlation coefficient was close to 0.999. The error estimates in ΔH (± 0.84 kJ mol⁻¹) and ΔS (± 2.5 JK⁻¹ mol⁻¹), were made from the standard data of King¹⁶.

Results and Discussion

The negative ΔH and positive ΔS (Tables 1 and 2) for the formation of 1:1 and 1:2 copper(II) chelates of dipeptides indicate that both enthalpy and entropy factors favour the complex formation. The exothermic ΔH values could result from the covalent interaction of metal ion and oxygen of carbonyl group of peptides. The copper(II) dipeptide chelates have higher ΔH in relation to ΔG than the copper glycinate¹⁷ ($\Delta G = -48.95$ kJ mol⁻¹, $\Delta H = -27.25$ kJ mol⁻¹, and $\Delta S = 69.39$ JK⁻¹ mol⁻¹). It is well known that with simple aliphatic dipeptides copper(II) forms complexes of stoichiometry $[CuL]^+$, $[CuL H_{-1}]$ etc. In the

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Table 1—Electrostatic and Cratic Components of Thermodynamic Parameters of Mono Complex Formation Reaction of Copper(II) with Dipeptides in Aqueous Media at 30°C

 Dipeptides: (1) α - α -alanyl- α -methionine; (2) α -alanyl- α -norvaline; (3) glycosarcosine; (4) glycy-l-l-asparagine; (5) glycy-l-dl-valine

Dipeptide	ΔG_1	ΔH_1	ΔS_1	C	a	ΔG_{el}	ΔG_{non}	ΔH_{el}	ΔH_{non}	ΔS_{el}	T* (°C)
1	-37.54	-29.01	28.04	-373.75	10.94	-13.42	-34.19	5.14	-34.19	61.48	253
2	-37.83	-30.47	20.98	-330.81	12.67	-11.91	-36.07	4.56	-35.07	54.42	293
3	-37.08	-29.26	25.75	-359.77	11.39	-12.96	-34.28	4.97	-34.23	59.18	263
4	-37.41	-30.26	23.66	-347.67	12.08	-12.49	-35.07	4.81	-35.07	57.09	279
5	-33.61	-27.21	20.86	-330.05	11.53	-11.87	-31.85	4.56	-31.81	54.29	267

 ΔG and ΔH in kJ mol^{-1} ; and ΔS in $\text{JK}^{-1} \text{mol}^{-1}$

 Standard deviation: $\Delta G = \pm 0.08 \text{ kJ mol}^{-1}$; $\Delta H = \pm 0.84 \text{ kJ mol}^{-1}$; $\Delta S = \pm 2.5 \text{ JK}^{-1} \text{mol}^{-1}$.

Table 2—Electrostatic and Cratic Components of Thermodynamic Parameters of Bis-complex Formation Reaction of Copper(II) with Dipeptides in Aqueous Media at 30°C

Dipeptide*	ΔG_2	ΔH_2	ΔS_2	C	a	ΔG_{el}	ΔG_{non}	ΔH_{el}	ΔH_{non}	ΔS_{el}	T* (°C)
1	-29.76	-22.82	22.95	-342.75	9.62	-12.33	-27.55	4.72	-27.54	56.39	220
2	-32.64	-27.34	17.59	-310.22	12.31	-11.16	-31.60	4.26	-31.89	51.04	285
3	-29.76	-25.25	14.79	-293.20	11.95	-10.53	-29.34	4.01	-29.30	48.24	277
4	-29.68	-25.71	13.29	-284.06	12.48	-10.19	-29.59	3.93	-29.64	46.73	289
5	-25.62	-20.94	15.38	-296.76	10.10	-10.66	-25.08	4.09	-25.04	48.82	233

*See Table 1.

 ΔG and ΔH in kJ mol^{-1} ; and ΔS in $\text{JK}^{-1} \text{mol}^{-1}$.

 Standard deviation: $\Delta G = \pm 0.08 \text{ kJ mol}^{-1}$; $\Delta H = \pm 0.84 \text{ kJ mol}^{-1}$; $\Delta S = \pm 2.5 \text{ JK}^{-1} \text{mol}^{-1}$.

complex $[\text{CuL}]^+$, the $-\text{NH}_2$ and the peptide $\text{C}=\text{O}$ groups are coordinated to the copper ion. Dissociation of the proton occurs on the nitrogen of the peptide bond. The bond between the metal ion and the peptide oxygen atom will be essentially electrostatic in character, leading to ΔH values similar to those of copper glycinate. The relative difference in ΔH and ΔS between copper(II)-amino acid and copper(II)-dipeptide chelates is due to the difference in the nature of coordination to the metal ion. In dipeptides, the carboxyl groups are not bound to the copper ion, while in amino acid chelates the oxygen of the carboxylate group is involved in binding.

Gergely *et al.*⁸ have shown that in the structural rearrangement of $[\text{CuL}]^+$ into $[\text{CuLH}_{-1}]$, the reaction involves a large positive ΔS and a small negative ΔH . The 1:1 chelates reported by us may also be of the type $[\text{CuLH}_{-1}]$ and the ΔS noted may be the overall reaction made up of the following two equilibria (Eqs 1 and 2).



In order to have a meaningful discussion of the thermodynamic quantities and to get an insight into the extent of ionic and covalent nature of the complexes, ΔG and ΔH have been separated into electrostatic and nonelectrostatic components. The

electrostatic components of ΔG and ΔH were calculated from Eqs (3) and (4)

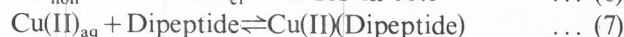
$$\Delta G_{el} = -\nu(\Delta S + R\Delta n \ln 55.5) \quad \dots (3)$$

$$\Delta H_{el} = (T - \nu)(\Delta S + R\Delta n \ln 55.5) \quad \dots (4)$$

where Δn represents the change in the number of solute particles in an ion association reaction and ν is the temperature characteristic of the solvent (219 K for water). The non-electrostatic parts of enthalpy and free energy were calculated from Eqs (5) and (6) respectively and values are presented in Tables 1 and 2.

$$\Delta H_{non} = \Delta H - \Delta H_{el} \quad \dots (5)$$

$$\Delta G_{non} = \Delta G - \Delta G_{el} - \Delta n RT \ln 55.5 \quad \dots (6)$$



For the equilibrium involving mono complex formation and which has been represented by Eq. (7), ΔG_{non} values are more negative than ΔG_{el} values (Table 1) indicating that nonelectrostatic forces are stronger than electrostatic forces in 1:1 chelates. The difference in the electrostatic and nonelectrostatic components remains almost constant in all the complexes of copper(II) with the dipeptides, indicating thereby that metal chelation reaction occurs by a similar mechanism. The enthalpy data also support the above consideration.

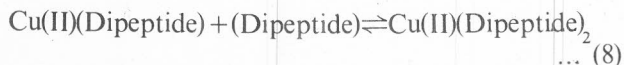
Thermodynamic data computed for the equilibrium involving bis-complex formation and represented by Eq. (8).

Table 3—Electrostatic and Cratic Components of Thermodynamic Parameters of Equilibrium (3) of Copper(II) with Dipeptides in Aqueous Media at 30°C

Dipeptide*	ΔG_r	ΔH_r	ΔS_r	$\Delta G_{r,e}$	$\Delta G_{r,c}$	$\Delta H_{r,e}$	$\Delta H_{r,c}$	$\Delta G_{r,t}$	$\Delta S_{r,t}$
1	-7.73	-6.17	5.05	2.68	-2.68	-1.05	-5.18	-2.51	-12.21
2	-5.14	-2.84	3.38	3.05	-2.97	-1.17	-1.67	-0.08	-13.84
3	-7.34	-4.01	10.99	1.38	-3.51	-0.54	-3.51	-2.13	-6.27
4	-7.69	-4.56	10.41	1.50	-3.97	-0.59	-3.97	-2.42	-6.86
5	-7.94	-6.27	5.52	2.59	-5.31	-1.00	-5.27	-2.72	-11.79

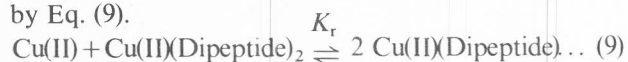
*See Table 1.

ΔG and ΔH in kJ mol^{-1} ; and ΔS in $\text{JK}^{-1} \text{mol}^{-1}$.



show that differences in electrostatic and nonelectrostatic components are relatively lower indicating considerable decrease in the ionic character of the binary complexes of dipeptides.

It is observed from the Tables 1 and 2 that ΔG_1 is more negative than ΔG_2 for all the copper chelates of dipeptides; indicating that mono complex formation is an energetically favoured path. As suggested by Ting Poi and Nancollas⁹ these observations can best be interpreted by considering the equilibrium represented by Eq. (9).



The thermodynamic quantities for equilibrium (9) were obtained using Eqs (10-12) and the values so obtained are given in Table 3

$$\Delta G_r = \Delta G_1 - \Delta G_2 \quad \dots (10)$$

$$\Delta H_r = \Delta H_1 - \Delta H_2 \quad \dots (11)$$

$$\Delta S_r = \Delta S_1 - \Delta S_2 \quad \dots (12)$$

The ΔG_r values could further be divided into statistical, electrostatic and cratic parts⁹ as

$$\Delta G_r = \Delta G_{\text{stat}} + \Delta G_{r,e} + \Delta G_{r,c} \quad \dots (13)$$

where first term on RHS of Eq. (13) represents free energy contributions attributable to purely statistical causes and K_{stat} is the value of K_r , if reaction (9) proceeds statistically. $\Delta G_{r,e}$ and $\Delta G_{r,c}$ are the electrostatic and covalent components of free energy change ΔG_r , respectively. K_{stat} can be assessed from the considerations of the different reaction paths. For bidentate ligand involved in complex formation with copper(II) ion, $K_{\text{stat}} = 8$ and hence $\Delta G_{\text{stat}} = RT \ln K_{\text{stat}} = 5.14 \text{ kJ mol}^{-1}$ and $\Delta S_{\text{stat}} = R \ln K_{\text{stat}} = 17.14 \text{ JK}^{-1} \text{ mol}^{-1}$. The electrostatic and covalent components may be calculated using Eq. (14) to (17).

$$\Delta G_{r,e} = -\nu(\Delta S_r - R \ln K_{\text{stat}}) \quad \dots (14)$$

$$\Delta H_{r,e} = (T - \nu)(\Delta S_r - R \ln K_{\text{stat}}) \quad \dots (15)$$

$$\Delta G_{r,c} = \Delta G_r - \Delta G_{r,e} - \Delta G_{\text{stat}} \quad \dots (16)$$

$$\Delta H_{r,c} = \Delta H_r - (T - \nu)(\Delta S_r - R \ln K_{\text{stat}}) \quad \dots (17)$$

The statistically corrected values for ΔG_r and ΔS_r were obtained from Eqs (18) and (19) respectively.

$$\Delta G_{r,t} = \Delta G_r - \Delta G_{\text{stat}} \quad \dots (18)$$

$$\Delta S_{r,t} = \Delta S_r - \Delta S_{\text{stat}} \quad \dots (19)$$

Following conclusions can be drawn from the computed values set out in Table 3.

(i) The positive $\Delta G_{r,e}$ in the bis-complexes arise as a result of destabilization induced by repulsion between two ligands in bis-complex and probably because of large size of these ions.

(ii) The negative $\Delta G_{r,c}$ and $\Delta H_{r,c}$ values indicate that nonelectrostatic forces in the bis complex are weaker than those in the corresponding mono complexes.

(iii) Since ΔH_2 is less negative than ΔH_1 (Tables 1 and 2), the formation of bis-complexes is not favoured.

(iv) Negative values of $\Delta S_{r,t}$ suggest that entropy factor is not so favourable in comparison to the statistical factor for the mono complex formation.

(v) The negative $\Delta G_{r,t}$ values are obvious because even the nonelectrostatic forces favour the mono complex formation.

(vi) Recently Murakami and Takashi¹⁸ have introduced three more parameters to examine the thermodynamics of chelation. The quantities a , c and T^* were calculated according to the procedure given by these authors. These parameters have been estimated for Cu-EDTA chelates and the magnitude of a -values in all the dipeptides is higher than that in the EDTA chelates. The much larger values, may be due to the structural rearrangement of complexes of $[\text{CuL}]^+$ into $[\text{CuLH}_{-1}]$. As pointed out by these authors T^* values are higher than 100°C.

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