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Thermodynamic Selectivity of Mixed-Ligand Cu(II) Complexes of Dipeptides and Phenoxy Acid Herbicides: Structure-Stability-Activity Correlations

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Non-covalent peptide-herbicide intramolecular interactions have been examined in solution in ternary complexes of the type $CuAL^+$ or Cu(HA)L, where A^- = anion of dipeptide like Gly-Phe, HA^- = anion of Gly-Tyr and L^- = anion of phenoxy acid herbicide like phenoxyacetic acid (PAA); 2-chloro phenoxyacetic acid (2-CPA); 2,4-dichlorophenoxyacetic acid (2,4-D); 2,5-dichlorophenoxyacetic acid (2,5-D); 2,4,5-trichlorophenoxyacetic acid (2,4,5-T); 4-chloro-2-methylphenoxyacetic acid (MCPA); 2-(2,4-dichloro-phenoxy)propionic acid (2,4-DP); 4-(4-chloro-2-methylphenoxy)butyric acid (MCPB) or 4-(2,4-dichlorophenoxy) butyric acid (2,4-DB). The protonation constants of ligands and stability constants of binary and ternary complexes have been determined by potentiometric pH-titration at 25 ºC and $\mu = 0.1$ M (KNO_3) together with the thermodynamic data. From these parameters and the UV-Visible and ESR spectra of the complexes, it has been established that, besides Cu(II)-ligand coordination characteristics of simple dipeptides and phenoxy acid ligands, there are interactions between the *d*-electron orbitals of Cu(II) and the 6π-electron systems of aromatic rings and between hydrophobic parts of the molecules. A linear correlation between pK_a/or stability constants of binary/ternary complexes of chlorophenoxyacetic acids and Hammett σ-values indicates that they share a common mode of action.

Key Words: Phenoxy acids, Herbicides, Dipeptides, Stacking, Calorimetry.

INTRODUCTION

Biological systems show a high specificity and selectivity in interaction between macromolecules or a macromolecule and a foreign molecule before they are able to proceed with their function[1,2]. Several new and revised concepts and approaches have been made on host-guest relationships and preorganized systems[3,4]. The role of metal complexes in specific molecular recognition has been shown when the interactions involve nucleic acids and proteins[5,6]. Because of the important relationship between function and the shape of biomolecules, non-covalent interactions are crucial to the biological activity[6,7].

The biological evidences presented seem consistent with the hypothesis that plant growth regulators, such as, indole-3-acetic acid (IAA); 2,4-dichlorophenoxyacetic acid (2,4-D), *etc.*, act as chelating agents either by forming true chelate compounds or complexes of some sort. If they, in fact, act as growth regulators by virtue of complex forming properties[8-10], they might act by removing metal ions which would otherwise restrict growth or they might act as enzyme inhibitors.

Accordingly, in order to explore the role of protein and biological metal ions binding with phenoxy herbicides in views of chelation hypothesis, we have carried out a detail investigation on ternary metal complexation equilibria involving Cu(II) (as a model metal ion) dipeptides (as model proteins) of glycine with phenylalanine or tyrosine; glycyl-L-phenyl alanine (Gly-Phe) and glycyl-L-tyrosine (Gly-Tyr) and a series of phenoxy herbicides, such as, PAA (inactive); 2-chloro phenoxyacetic acid (2-CPA); 2-(2,4-dichlorophenoxy)propionic acid (2,4-DP); 2-(2,5-dichlorophenoxy) propionic acid (2,5-DP); 2,4,5-trichloro-phenoxyacetic acid (2,4,5-T); 4-chloro-2-methylphenoxy acetic acid (MCPA); 2-(2,4-dichlorophenoxy) propionic acid (2,4-DP); 4-(4-chloro-2-methylphenoxy)butyric acid (MCPB) or 4-(2,4-dichloro phenoxy)butyric acid (2,4-DB) (all active).

The stoichiometries, thermodynamic data for the complexes formed in the equilibrium systems together with the results of UV-Visible and ESR spectroscopic studies have been interpreted to explore the mode of bonding of these ligands and the possibility of the above mentioned micro-processes.

EXPERIMENTAL

The dipeptides were obtained from Sigma chemical Co. and were used without further purification. Phenoxy acids were obtained from Fluka AG Buchs Switzerland, copper nitrate and other chemicals were BDH reagent of AR grade. Weighed amounts of ligands and copper nitrate were dissolved in 60 % aq. dioxane (v/v) medium. A carbonate free doubly distilled water was employed in preparing solutions and were used after standardization.

The protonation constants of ligands and stability constants of their copper(II) complexes have been determined through potentiometric pH-titration technique for 25 mL samples having metal ion:ligand ratio 1:1 and 1:2 for binary and 1:1:1 ratio for ternary systems. In each case, the ionic strength was adjusted to 0.1 M (KNO_3) at 25.0 ± 0.1ºC in thermostated potentiometric vessel. Changes in pH were followed using a radiometer pH M 64 instrument fitted with a glass-calomel electrodes assembly. Enthalpy changes were measured using LKB 8700-1 calorimeter under similar conditions with a continuous titration technique[11].

Spectroscopic measurements were performed using Cary 1411 spectrophotometer over the spectral range 350-800 nm. Circular dichroism (CD) spectra were measured on a Jasco-J-20 automatic recording spectropolarimeter. The ESR spectral measurements were made on Jeol JES-ME-3X spectrometer at 9.12 GHz and at liquid-nitrogen temperature.

The protonation constants, concentration stability constants for binary and ternary metal complexes and species distribution as a function of pH have been calculated using standard computer programs[12,13].

RESULTS AND DISCUSSION

Dipeptide deprotonation and Cu(II)-dipeptide complexes

Typical titration curves for proton-ligand systems were used for calculation of the pK_a-values for the proton-ligand systems (primary ligands) which are summarized in Table-1. A neutral dipeptide (H_2A) can form the protonated species (H_3A^+, H_2A, HA^- and A^{2-}), the last proton to ionize being the phenolic proton of tyrosine group. It is noteworthy that the pK ($-N^+H_3$) groups are usually high, which can presumably be explained by

TABLE-1
STABILITY CONSTANTS AND THERMODYNAMIC PARAMETERS**
OF BINARY METAL COMPLEXES OF Cu(II) WITH DIPEPTIDES
(Temp. = 25 ºC, μ = 0.1 M KNO_3)

Equilibrium	log β*	$-\Delta G^o$ (kJ mol^{-1})	$-\Delta H^o$ (kJ mol^{-1})	ΔS^o (JK^{-1} mol^{-1})
Gly-Phe system				
pK (–COOH) = 3.15, pK ($-N^+H_3$) = 8.22				
$Cu^{2+} + A^- \rightleftharpoons [CuA]^+$	5.46	31.15	26.6	15.27
$[CuA]^+ \rightleftharpoons [CuAH_{-1}] + H^+$	1.70	9.70	-4.2	46.64
$[CuAH_{-1}] + A^- \rightleftharpoons [CuA_2H_{-1}]^-$	4.68	26.70	14.5	40.94
Gly-Tyr system				
pH (–COOH)= 3.18, pK ($-N^+H_3$) = 8.26, pK (–OH) = 10.12				
$Cu^{2+} + HA^- \rightleftharpoons [Cu(HA)]^+$	5.32	30.36	26.3	13.62
$[Cu(HA)]^+ \rightleftharpoons [Cu(HA)H_{-1}] + H^+$	1.40	7.99	-4.6	42.25
$[Cu(HA)H_{-1}] + HA^- \rightleftharpoons [Cu(HA)_2H_{-1}]^-$	4.30	24.54	14.4	34.03

*For Gly-Phe: $\log\beta = \log K^{Cu}_{CuA} + \log K^{CuA}_{CuA_2}$, and

For Gly-Tyr: $\log\beta = \log K^{Cu}_{Cu(HA)} + \log K^{Cu(HA)}_{Cu(HA)_2}$

**Uncertainty in ΔH^o ± 0.1 kJ mol^{-1} and in ΔS^o ± 0.3 JK^{-1} mol^{-1}

electrostatic and/or hydrophobic interactions between the tyrosyl and glycyl residues. In the case of carboxylic group deprotonation, the process was observed to be almost entirely entropic. Infact, it consists of a charge separation and of a resulting large scale re-organization of the solvent around the reacting parameters.

The pH-metrically and calorimetrically determined stability constants and thermodynamic data (ΔG^o, ΔH^o and ΔS^o) for Cu(II) - dipeptide binary complexes of the four dipeptides are reported in Table-1. Compared with the Phe-containing dipeptides (HA), those containing Tyr (H_2A) have an additional dissociable proton on the phenolic hydroxy group, however, this begins to dissociate only at high pH. For ease of comparison of Gly-Tyr, we have used the overall thermodynamic quantities and data on the dissociation of phenolic hydroxy group (Table-1) to calculate quantities characteristic of the formation of the metal complexes of the ligands HA^-, protonated on the phenolic hydroxy group (Table-1).

A good agreement of the data reveals that the bonding modes of the species $[CuA]^+$ and $[Cu(HA)]^+$, $[Cu(AH_{-1})]$ and $[Cu(HA)H_{-1}]$, and $[CuA_2H_{-1}]^-$ and $[Cu(HA)_2H_{-1}]^-$ formed at pH < 8 are similar and in accordance with what was observed for the simple aliphatic dipeptides[14]. In presence of Cu(II), the amide proton undergoes dissociation to form species $[Cu(HA)H_{-1}]$ similar to the simple [CuA]. At pH > 8, however, the deprotonation of the phenolic hydroxy group causes differences in the complex-forming properties of the ligands, as manifested in the stability constants and spectral properties.

Phenoxy acids deprotonation and Cu(II)-phenoxy acid complexes

The protonation constants of phenoxy acids (Table-2) have little difference in their magnitudes. A slight difference may be expected either due to increase in chain length of the side chain or number and position of substituent groups in the ring in this class of compounds. A decrease in the pK_a values has been observed with the increase in the number of chloro substitution in the ring which has been interpreted due to the electron withdrawing nature of these groups. Also, the increase in the magnitudes of pK_a values on increasing side chain length is observed, showing the weak dissociation ability of long side chain phenoxy herbicides. It was concluded from thermodynamic data that the dissociation processes of phenoxy acids are enthalpically and entropically favoured.

Analysis of species distribution curves resulted the concentrations of CuL^+ and CuL_2 to be 40 and 55 %, respectively, in the higher pH range. The indistinguishable magnitudes of stability constants of binary complexes clearly indicate a some what similar electronic environment at oxygen atoms involved in coordination, irrespective of nature of the ligand considered. The halogen substitution and their positions in the phenyl ring have

little but an important role in lowering protonation and stability constants of complexes. The complexation processes are followed by considerable decrease in free energy (ΔGº) and are highly enthalpically as well as entropically favoured (Table-2).

TABLE-2
STABILITY CONSTANTS AND THERMODYNAMIC PARAMETERS* OF BINARY METAL COMPLEXES OF Cu(II) WITH PHENOXY ACIDS
(Temp. = 25 ºC, μ = 0.1 M KNO_3)

Phenoxy acid	pK_a	$\log K^{Cu}_{CuL}$	$\log K^{CuL}_{CuL_2}$	log β	$-\Delta G^o$ (kJ mol^{-1})	$-\Delta H^o$ (kJ mol^{-1})	ΔS^o (JK mol^{-1})
PAA	4.46	3.24	2.93	6.17	35.21	14.5	69.50
2-CPA	4.43	3.28	2.97	6.25	35.66	14.2	72.01
2,4-D	4.27	3.22	2.87	6.09	34.75	13.7	70.64
2, 5-D	4.33	3.26	2.94	6.20	35.38	14.0	71.74
2,4,5-T	4.15	3.20	2.72	5.92	33.78	13.5	68.65
MCPA	4.30	3.16	2.82	5.98	33.95	15.2	62.92
2,4-DP	4.36	3.08	2.80	5.88	33.55	15.0	62.25
MCPB	4.38	2.92	2.60	5.52	31.50	14.90	55.70
2,4-DB	4.34	2.94	2.63	5.57	31.78	14.8	56.98

*Uncertainty in $\Delta H^o \pm 0.1$ kJ mol^{-1} and in $\Delta S^o \pm 0.2$ JK^{-1} mol^{-1}

Cu(II)-dipeptide-phenoxy acid systems

The superimposable nature of 1:1:1, MAL titration curve with 1:1 MA titration curve in the lower pH region and then lowering of the former from the later curve indicated the formation of ternary complex with a dipeptide. Thus, the sequence of complexation in a ternary system may be expressed by the following equations for Gly-Phe system:

$$Cu^{2+} + A^- \rightleftharpoons CuA^+;\ K^{Cu}_{CuA} = \frac{[CuA^{2+}]}{[Cu^{2+}][A^-]} \quad (1)$$

$$CuA^+ + L^- \rightleftharpoons CuAL;\ K^{CuA}_{CuAL} = \frac{[CuAL]}{[CuA^+][L^-]} \quad (2)$$

$$Cu^{2+} + A^- + L^- \rightleftharpoons CuAL;\ \beta^{Cu}_{CuAL} = \frac{[CuAL]}{[Cu^{2+}][A^-][L^-]} \quad (3)$$

In the higher pH range, the dissociation of amide proton from the ternary species occurs according to the following equilibrium:

$$CuAL \rightleftharpoons [CuAH_{-1}L]^- + H^+;\ K^{CuAL}_{CuAH_{-1}L} = \frac{[Cu(AH_{-1})L^-][H^+]}{[CuAL]} \quad (4)$$

Similar equations may be written by replacing A^- by HA^- for Gly-Try system as this dipeptide have additional phenolic proton.

The visible and ESR spectral results have indicated maximum absorption at about 580 nm ($\varepsilon = 90$) and the appearance of a charge-transfer band at 380 nm (Fig. 1). The significant decrease in intensity of the ESR signal in the pH range 8.5-10.5 is consistent with the formation a ternary complex of the type CuAL or Cu (HA)L, in which phenoxy oxygen is bonded to copper(II) ion. This also suggests that there is no involvement of phenolate group in metal ion coordination. EPR spectra recorded in this pH range did not show any detectable signal. The corresponding CD spectra showed some interesting features, at about 380 nm the CT band was overcome by new band at about 330 nm, with the opposite sign of its $\Delta\varepsilon$ value. This may be attributed to the formation of N_{amido}-Cu bond.

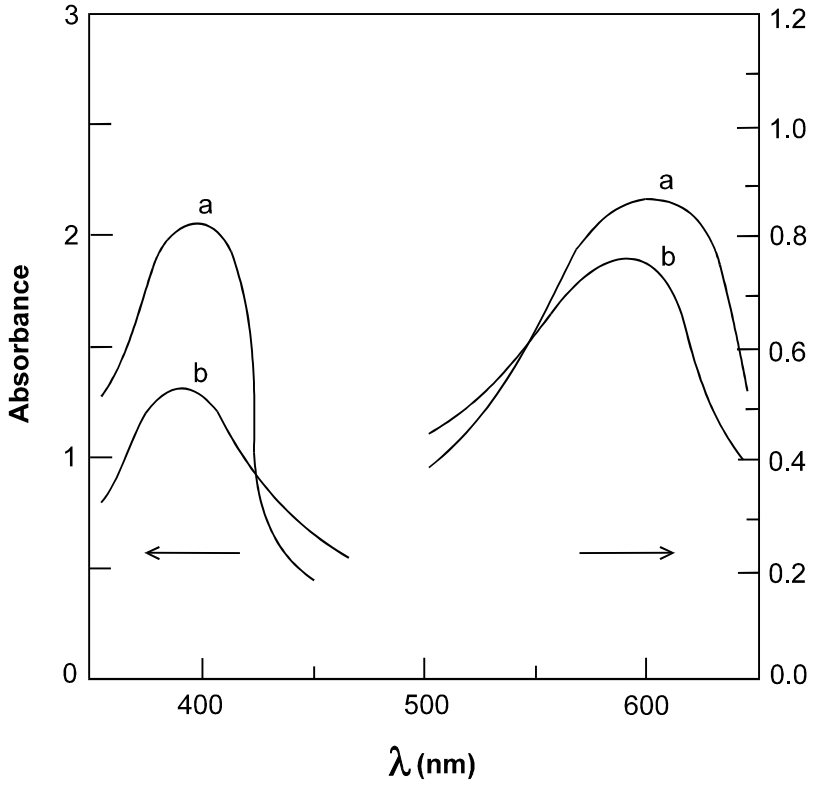

Fig. 1. Visible spectra of 1:1:1 ternary systems at pH 8.0 (a) Cu (II)-Gly-Tyr-MCPB system; (b) Cu (II)-Gly-Phe-MCPB system

The values of stability constants of ternary complexes together with the thermodynamic quantities have been reported in Table-3. It is evident that the magnitudes of stability constants of ternary complexes are less

than those for CuL^+ or CuL_2 complexes (Table-2). For the systems having MCPB and 2,4-DB the values of stability constants of ternary complexes are more than those for other phenoxy acids.

The general trend of these constants may be expressed as follows:

$$\log K^{Cu}_{CuL} > \log K^{CuA}_{CuAL} > \log K^{CuL}_{CuL_2} \quad (L = MCPB \text{ or } 2,4\text{-DB}); \text{ and}$$

$$\log K^{Cu}_{CuL} > \log K^{CuL}_{CuL_2} > \log K^{CuA}_{CuAL}$$

(L = PAA; 2-CPA; 2,4-D; 2,5-D; 2,4,5-T; MCPA or 2,4-DP)

where A = dipeptide, conventionally used for A^- or HA^-.

The negative values of ΔG° and ΔH° (exothermic coordination) indicates that the binary as well as ternary complexation processes are enthalpically favoured. The low negative values of ΔS° which are close to zero indicate that ternary complexation processes do occur and they are also entropically favoured.

From the analysis of representative species distribution curves of 1:1:1 Cu(II)-Gly-Phe-MCPB system (Fig. 2), it is obvious that the concentration of ternary complex, CuAL exceeds the concentration of the corresponding CuA^+ species at high pH. The maximum concentration of ternary complexes have been found to be in the range 55-70 %. Comparing these concentrations with the concentrations of CuL^+ in each system, it was found that the concentration curve of CuL^+ for MCPB system were lying below 20 % while those for other phenoxy acids slightly above 20 %. This indicates the high stability of ternary complexes with MCPB or 2,4-DB than those of the corresponding species with other phenoxy acids. A linear relation-exists between the values of stability constants of ternary and 1:1 binary complexes (Tables 2 and 3) which shows that the affinity of association of L^- with MA^+ in ternary systems follows, in general, the same pattern as it does with free aqueous metal ions, $M(H_2O)_n^{2+}$.

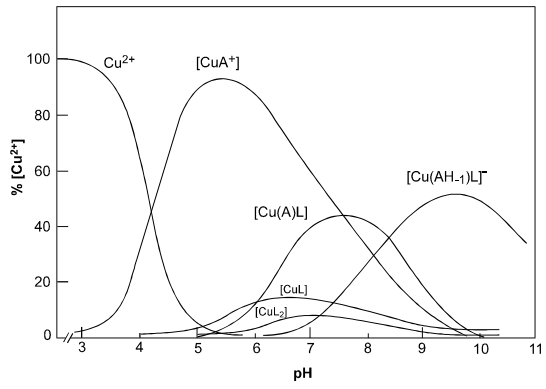

Fig. 2. Concentration distribution curves of complexes formed in 1:1:1 Cu(II)-Gly-Phe-MCPB system as a function of pH

The values of $\Delta \log K_{Cu}$, defined by equation[7]

$$\Delta \log K_{Cu} = \log K^{CuA}_{CuAL} - \log K^{Cu}_{CuL} \quad (5)$$

are always negative (Table-3). It should be pointed out here that these values represent overall effect of direct or indirect ligand-ligand interactions. Long chain phenoxy acids, MCPB and 2,4-DB, have higher $\Delta \log K_{Cu}$ values than those for others phenoxy acids.

TABLE-3
STABILITY CONSTANTS AND THERMODYNAMIC PARAMETERS* OF TERNARY COMPLEXES OF Cu(II) WITH DIPEPTIDES INVOLVING PHENOXY ACIDS (Temp. = 25 ºC, μ = 0.1 M KNO_3)

Dipeptide	Phenoxy aicd	$\log\beta^{Cu}_{CuAL}$	$\log K^{CuA}_{CuAL}$	$\Delta \log K_{Cu}$	log X	$-\Delta G°$ (kJ mol^{-1})	$-\Delta H°$ (kJ mol^{-1})	$-\Delta S°$ (JK mol^{-1})
Gly-Phe	PAA	8.29	2.83	-0.41	0.27	16.15	20.2	13.59
	2-CPA	8.32	2.86	-0.42	0.25	16.32	20.4	13.69
	2,4-D	8.31	2.85	-0.37	0.39	16.26	20.3	13.56
	2,5-D	8.33	2.87	-0.39	0.32	16.38	20.4	13.49
	2,4,5-T	8.26	2.80	-0.40	0.46	16.26	20.0	12.55
	MCPA	8.22	2.76	-0.40	0.32	15.75	19.2	11.58
	2,4-DP	8.16	2.70	-0.38	0.30	15.41	19.4	13.39
	MCPB	8.33	2.87	-0.05	1.00	16.38	20.3	13.15
	2,4-DB	8.33	2.87	-0.07	0.95	16.38	20.5	13.83
Gly-Tyr	PAA	8.10	2.78	-0.46	0.41	15.86	19.8	13.22
	2-CPA	8.12	2.82	-0.48	0.37	15.98	19.8	12.32
	2,4-D	8.13	2.81	-0.41	0.55	16.03	20.0	13.32
	2,5-D	8.15	2.83	-0.43	0.48	16.15	20.2	13.59
	2,4,5-T	8.08	2.76	-0.44	0.62	15.75	19.6	12.92
	MCPA	8.08	2.76	-0.40	0.56	15.75	19.2	11.58
	2,4-DP	7.92	2.60	-0.48	0.34	15.75	19.6	12.92
	MCPB	8.17	2.85	-0.07	1.20	16.26	20.6	14.56
	2,4-DB	8.22	2.90	-0.04	1.25	16.55	20.4	12.92

*Uncertainty in $\Delta H° \pm 0.1$ kJ mol^{-1} and in $\Delta S° \pm 0.2$ JK^{-1} mol^{-1}

The characterization of stability of ternary complexes from log X values has also been made. But, it suffers from disadvantage that the stability constants of ternary complexes have been compared to the stability of binary 1:2 parent complexes, which are not on the way of formation of these complexes[7]. The sequence of log X values, in general, has been found to be the same as in the case of $\Delta \log K_{Cu}$ values with a few exceptions.

Intramolecular aromatic ring stacking

The Δ log K_{Cu} and log X values measure the stability of ternary complexes with respect to binary ones. An increase in Δ log K_{Cu} and log X values (Table-3) for MCPB and 2,4-DB supports enhancement of stability due to intramolecular aromatic ring stacking.

The characterization of such interactions has further been made from calculations of $\Delta\Delta$ log K_{Cu} and Δ log X (Table-4) using equations.

$$\Delta\Delta \log K_{Cu} = \Delta \log K^{Cu}_{CuAL} - \Delta \log K^{Cu}_{CuAL'} \quad (6)$$

and, $\Delta\log X = \log X_{CuAL} - \log X_{CuAL'}$

where L = MCPB or 2,4-DB and L′ = PAA; 2-CPA; 2, 4-D; 2, 5-D; 2, 4, 5-T; MCPA or 2,4-DP.

TABLE-4
PREDICTION OF INTRAMOLECULAR AROMATIC RING STACKING BASED ON COMPARISON OF Δ log K AND log X VALUES
Gly-Phe (A) SYSTEM

System	$\Delta\Delta$ log K	Δ log X
Cu(A) (MCPB/PAA)	+0.36	+0.73
Cu(A) (MCPB/2-CPA)	+0.37	+0.75
Cu(A) (MCPB/2,4-D)	+0.32	+0.61
Cu(A) (MCPB/2, 5-D)	+0.34	+0.68
Cu(A) (MCPB/2,4,5-T)	+0.35	+0.54
Cu(A) (MCPB/MCPA)	+0.35	+0.68
Cu(A) (MCPB/2,4-DP)	+0.33	+0.70
Cu(A) (2,4-DB/PAA)	+0.39	+0.68
Cu(A) (2,4-DB/2-CPA)	+0.35	+0.70
Cu(A) (2,4-DB/2,4-D)	+0.30	+0.56
Cu(A) (2,4-DB/2,5-D)	+0.32	+0.63
Cu(A) (2,4-DB/2,4,5-T)	+0.33	+0.49
Cu(A) (2,4-DB/MCPA)	+0.33	+0.65
Cu(A) (2,4-DB/2,4-DP)	+0.31	+0.63

These values are always positive which indicate that longer the side chain in phenoxy acid higher would be the effect of intramolecular aromatic ring stacking. However, this effect is more pronounced in ternary complexes of MCPB and 2,4-DB due to longest side chain in comparison to other phenoxy acids, irrespective of the dipeptide involved. A tentative structure of stacked ternary complex, Cu(II)-Phe-Gly-MCPB, has been shown in Fig. 3. These results find further support from the solution equilibrium studies on ternary complexes of aromatic amino acids[7,15].

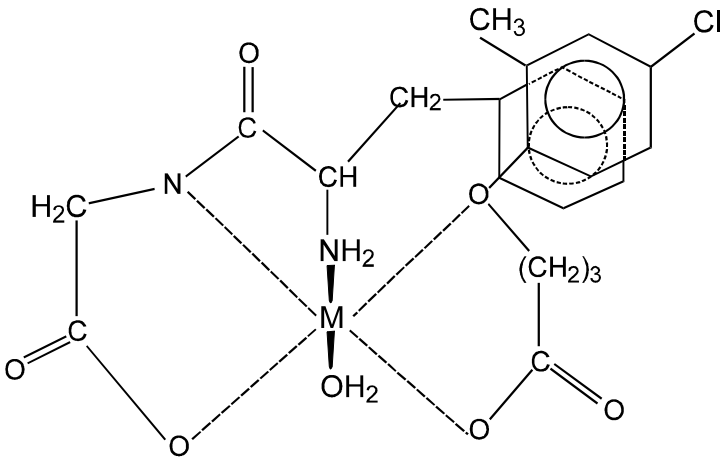

Fig. 3. Tentative structure of stacked ternary Cu(II)-Phe-Gly-MCPB complex

Structure-stability-activity correlations

It is possible to correlate the stability constant data with Hammett substituent constants[16] (σ) in order to predict the quantitative informations about the effect of substituents on the reactivity of phenoxy herbicides. It has been assumed that the reaction constant of a series of substituted 2-CPA is independent of 2-chloro or 2-methyl group. Accordingly, the steric influence of 2-chloro or 2-methyl substituent group to the reactivity of side chain is constant when 4-, 5- or multiple 4, 5-chloro groups are introduced in the ring of 2-CPA or MCPA. The σ (or Σσ) values have been used as though the 2-chloro or 2-methyl group was absent and 2-CPA or MCPA, itself, has been given a σ-value of zero. Thus, the values of σ for 2,4-D and 2,5-D have been used as 0.23 and 0.37, respectively[16]. The value Σσ for 2,4,5-T has been obtained taking additivity concept into consideration. Correlation methods have been used to show the applicability of Hammett equation to pK_a values of phenoxy acids (Table-2) with negative value of reaction constant (ρ = -0.43). The negative value of ρ indicates that the dissociation of phenoxy acids are not facilitated by chloro groups. The regression line of linear correlation obtained is as follows (eqn. 7);

$$pK_a = 4.36 - 0.43\ \sigma;\ r = 0.87 \quad (7)$$

The regression analysis of the linear correlations of 1:1 and 1:2 binary complexes of phenoxy acids with σ-values has given high values of correlation coefficients, r, being equal to 0.78 and 0.85, respectively.

A reverse trend has been observed for correlation of these stability parameters with pK_a-values. However, the effect of substituents on the stability of ternary complexes has been examined by performing regression

analysis as stated above. The correlation of stability constants of ternary complexes of Cu(II) with a dipeptide and Hammett σ-values are evaluated in the form of regression lines.

For Cu(II) -(A) - MCPB system

$$\log K_{CuAL}^{CuA} = 3.03 - 0.03\sigma; \quad r = 0.67(Gly - Phe) \tag{8}$$

For Cu(II)-A - 2,4-DB system

$$\log K_{CuAL}^{CuA} = 2.75 - 0.06\sigma; \quad r = 0.72(Gly - Tyr) \tag{9}$$

Thus, the Hammett equation is equally applicable to the substituted 2-CPA or MCPA with the same degree of accuracy as it may be in the case of substituted PAA.

On the basis of above results, a metal ion-protein-herbicide interaction as a new model mechanism of action of plant growth regulators has been proposed. According to this mechanism, the plant growth regulating activity may be due to the extraction of metal ions from enzymes by these phenoxy acid ligands and formation of mixed ligand complexes with other biomolecules or with a metallo-protein itself. The formation of such species produce some specific structures which cause physiological response by creating disturbance in all the enzymatic equilibria from their normal action resulting growth regulation. Further, the linear correlations of stability constant data of binary and ternary complexes of biologically active substances (2-CPA, 2,4-D; 2,5-D; 2,4,5-T, *etc*.) with Hammett substituent constants (σ) suggest that they share a common mode of action.

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