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Solution Studies of Cd(II) and Gd(III) Involving Malonic Acid and Some Catecholamines

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Abstract: ***The solution equilibria of mixed ligand complexes of Cd(II) and Gd(III) with primary ligand A[A = malonic acid] and secondary ligand B [B = Tyrosine, Dopa (3,4 dihyroxyphenylalanine), Dopm(Dopamine)] having (1:1:1) mol ratio in aqueous solution is investigated potentiometrically at different temperatures (20ºC±1, 30ºC±1 and 40ºC±1) and at three ionic strengths (μ=0.05M, 0.10M and 0.15M). Equilibrium analysis shows that the ternary complexes are formed in stepwise manner. Stability constants of the complexes have been determined through the method suggested by Chaberek and Martell as modified by Dey et al. and refined by SCOGS (stability constant of generalized species) computer program. Speciations of various species formed in different equilibria are obtained. The thermodynamic parameters, such as free energy change ΔG°, enthalpy change ΔH° and entropy change ΔS° are obtained by Van't Hoff equation. The value of ΔG° and ΔH° are negative whereas ΔS° is positive. The relative stability of ternary complexes as compared to binary species is expressed in term of ΔlogK. Values of ΔlogK are positive in most of the systems which suggest that the formation of ternary complexes is favorable. However in few cases ΔlogK is found to be negative. The stability of Gd(III) complexes are found to be greater than that of Cd(II) complexes.***

Keywords: malonic acid, catecholamines, ternary complexes, speciation, SCOGS.

1. Introduction

Malonic acid has received considerable attention owing to the fact that it can be metabolized to acetyl coenzyme-A and is involved in fatty acid synthesis, aromatic synthesis and mevalonate synthesis [1],[2]. It is important intermediate in synthesis of vitamins B1, B6, barbiturates, non-steroidal anti-inflammatory agents, other numerous pharmaceuticals, and agrochemicals flavor and fragrance compounds [3].

Catecholamines play an important role in health and disease. The change of catecholamine level have been correlated with stress, heart disease, change in blood pressure, thyroid hormone level and various type of mental illness[4]-[6]. The metabolites are often the primary assay target because of their higher concentration and greater stability. Catecholamines are well known for their use in neurotransmitter process and in the treatment of Parkinson disease [7]-[9]. A prominent feature of Parkinson's disease is the loss of dopamine in the striatum and many therapeutic investigations for the disease are aimed at restoring dopamine signaling [10]. Tyrosine is a precursor to neurotransmitters and increases plasma neurotransmitter levels.[11] Several studies have found tyrosine to be useful during conditions of stress, which helps to meet the reductions in stress hormone levels [12]. The neurotransmitters dopamine and dopa mediate the generation and growth of gold nano particles (Au-Nps). The plasmon absorption of the Au-Nps allows the quantitative colorimetric detection of the neurotransmitters [13]. Dopamine has pharmacologically appropriate effects in the management of low cardiac output associated with compromised renal function, such as severe congestive heart failure [14],[15]. The biological importance of tyrosine, dopa and dopm prompted us to investigate the complex forming tendency of these ligands in solution.

The present paper deals with the solution study of mixed ligand complex formation of M [M= Cd(II) and Gd(III)] with primary ligand A [A= Malonic acid ((Mal)] and secondary ligand B [B = tyrosine(Tyr), 3,4 dihyroxyphenylalanine (Dopa) and dopamine (Dopm)] under specified experimental conditions.

Experimental: All the systems were investigated under equimolar concentration ratio. For each set of titration moles of alkali required per mole of ligand / metal. 'a' was determined and curves were obtained by plotting pH vs 'a'.

Solution: All the reagents used were of highest purity Merck/Aldrich products. Solutions were prepared in doubly distilled CO_2-free water having pH ≈ 6.8. Solutions of metal and ligand (each 0.01M) were prepared by dissolving accurately weighed amounts in double distilled water.

Instrument: An Elico digital pH-meter model LI-127 with ATC probe and combined electrode type (CL-51B-Glass Body; range 0-14 pH unit; 0-100°C Automatic/Manual) with accuracy ±0.01 was employed for pH-measurement.

Experimental conditions: Various sets of titration mixtures were prepared and titrated against standard sodium hydroxide solution (0.10M) at three different ionic strengths (μ = 0.05M, 0.10M and 0.15M) maintained by adding different concentration of $NaNO_3$ solution to each titration mixture at temperatures 20°C±1 , 30ºC±1 and 40ºC±1.Temperature was maintained by Siskin Julabo, thermostat model V-12B.

1) Acid titration: HNO_3 (2.0×10^{-3}M).
2) Ligand 'A' titration: HNO_3 (2.0×10^{-3}M) + Ligand 'A' (1.0×10^{-3}M).
3) Ligand 'B' titration: HNO_3 (2.0×10^{-3}M) + Ligand 'B' (1.0×10^{-3}M).
4) Metal (M)-Ligand 'A' (1:1) titration: HNO_3 (2.0×10^{-3}M) + Ligand 'A' (1.0×10^{-3}M) + Metal nitrate (1.0×10^{-3}M).

5) Metal (M)-Ligand 'B' (1:1) titration: $HNO_3(2.0\times10^{-3}M)$ + Ligand 'B'($1.0\times10^{-3}M$) + Metal nitrate ($1.0\times10^{-3}M$).
6) Metal (M) - Ligand 'A' –Ligand 'B' (1:1:1) titration: HNO_3 ($2.0\times10^{-3}M$) + Ligand 'A' ($1.0\times10^{-3}M$) + Ligand 'B' ($1.0\times10^{-3}M$) + Metal nitrate ($1.0\times10^{-3}M$).

Where, Ligand 'A' = Malonic acid (Mal) and **Ligand 'B'** = Tyrosine, Dopa, Dopm and **M** = Cd(II) and Gd(III)

2. Results and Discussion

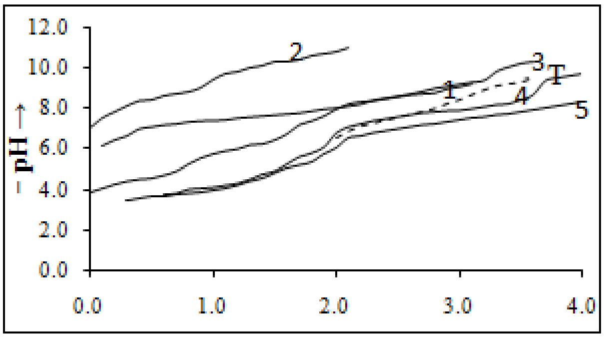

Figure 1: pH vs. 'a' curves for Gd(III) -Mal-Tyr (1:1:1) system

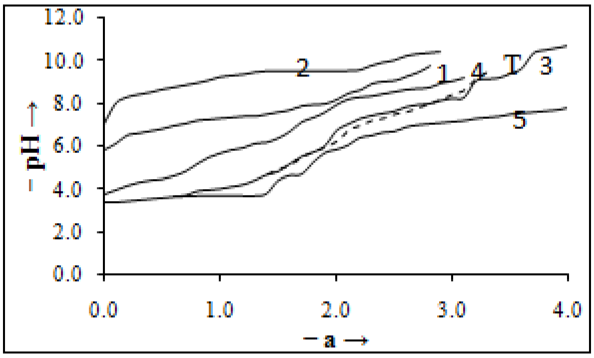

Figure 1: pH vs. 'a' curves for Gd(III) -Mal-Dopa (1:1:1) system

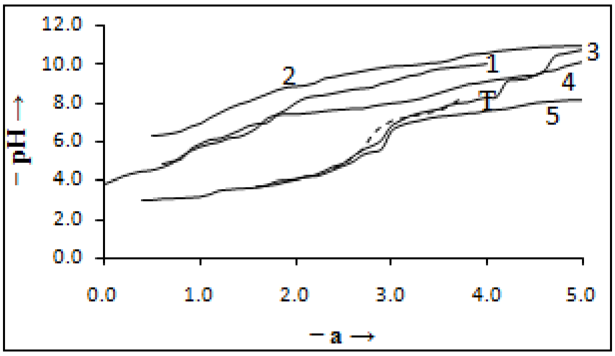

Figure 1: pH vs. 'a' curves for Gd(III) -Mal-Dopm (1:1:1) system

In figs.1–3. Temperature = 30±1ºC, μ = 0.10M maintained by NaNO3, Curve: 1 Ligand A (Mal) Titration Curve. Curve : 2 Ligand B (Tyr/Dopa/Dopm) Titration Curve Curve : 3 Metal-Ligand A (1:1) Titration Curve. Curve : 4 Metal-Ligand B (1:1) Titration Curve. Curve : 5 Mixed-Ligand (1:1:1) Titration Curve. Curve 'T' Theoretical Composite Curve

The experimental data are used to obtain titration curves (pH vs. 'a') where, a = moles of alkali added per mole of ligand/metal, and titration curves are given in figs. 1-3. The ligand titration curve 1 shows that the deprotonation of ligands A occurs in two distinct steps and curve 2 indicates that the liberation of proton up to pH≈8.0 showing the strong basic nature of ligand B. Further, the deviation of metal–ligand curves (curves 3 and 4) from ligand curves suggests the formation of binary complexes. Curve 5 depicts the metal-ligand A - ligand B (1:1:1) titration of Cd(II)/Gd(III) – Mal- Tyr/Dopa/Dopm ternary systems. Curve 5 in all the figs. is seen to be superimposed on 1:1 (MA) titration curve up to pH ≈ 5.0 followed by an inflection at 'a' 2.0. It is then shifted toward right hand side from ligand titration curves (curve1 and 2), metal-ligand titration curves (curve 3 and 4) and theoretical composite curve (T). The theoretical composite curve is obtained by plotting the theoretical addition of the values of 'a' corresponding to ligand titration curve of ligand A to the metal – ligand (1:1) titration curve of other ligand B. Another inflection at 'a'= 3.0, indicates that the formation of mixed ligand complex occurs in stepwise manner i.e. by coordination of ligand B to MA complex which leads to the formation of ternary species. Various equilibria and the corresponding equilibrium constants for the investigated ternary metal-ligand systems are represented as follow:

<u>M -Malonic acid - Tyrosine</u>

Step-I : Interaction of metal and primary ligand A

$$M+H_2A \underset{\log K^{H}_{MAH}}{\overset{0\leq a\leq 1}{\rightleftharpoons}} MAH + H^{+} \quad \text{----} \quad (1)$$

$$M+HA \underset{\log K^{M}_{MAH}}{\overset{0\leq a\leq 1}{\rightleftharpoons}} MAH \quad \text{----} \quad (2)$$

$$MAH \underset{\log K^{H}_{MA}}{\overset{1\leq a\leq 2}{\rightleftharpoons}} MA + H^{+} \quad \text{----} \quad (3)$$

$$M+A \underset{\log K^{M}_{MA}}{\overset{0\leq a\leq 2}{\rightleftharpoons}} MA \quad \text{----} \; (4)$$

Step-II: Interaction of metal and primary ligand complex species with secondary ligand B

$$MAH + HB \underset{\log K^{M}_{MABH2}}{\overset{1\leq a\leq 2}{\rightleftharpoons}} MABH_2 \quad \text{----} \quad (5)$$

$$MABH_2 \underset{\log K^{H}_{MABH}}{\overset{2\leq a\leq 3}{\rightleftharpoons}} MABH + H^{+} \quad \text{-----}(6)$$

$$MA+ HB \underset{\log K^{M}_{MABH}}{\overset{2\leq a\leq 3}{\rightleftharpoons}} MABH \quad \text{------} \; (7)$$

$$MABH \underset{\log K^{H}_{MAB}}{\overset{3\leq a\leq 4}{\rightleftharpoons}} MAB + H^{+} \quad \text{-----------} \; (8)$$

$$MA + B \underset{\log K^{H}_{MAB}}{\overset{2\leq a\leq 4}{\rightleftharpoons}} MAB \quad \text{----------} \; (9)$$

<u>M -Malonic acid - Dopa</u>

Step-I: Same as represented in equations 1-4

Step-II

$$MA + H_2B \underset{\log K^{M}_{MA}}{\overset{2\leq a\leq 3}{\rightleftharpoons}} MABH_2 \quad \text{--------} \; (10)$$

<u>M -Malonic acid – Dopm</u>

Step-I: Same as represented in equations 1-4

Step-II

$$\mathrm{MAH + H_2B} \xrightleftharpoons[\log K^{M}_{MABH3}]{1 \leq a \leq 2} \mathrm{MABH_3} \quad ---- \quad (11)$$

$$\mathrm{MABH_3} \xrightleftharpoons[\log K^{H}_{MABH2}]{2 \leq a \leq 3} \mathrm{MABH_2 + H^+} \quad ----- \quad (12)$$

$$\mathrm{MA + H_2B} \xleftarrow[\log K^{M}_{MABH2}]{2 \leq a \leq 3} \mathrm{MABH_2} \quad ------ \quad (13)$$

$$\mathrm{MABH_2} \xrightleftharpoons[\log K^{H}_{MABH}]{3 \leq a \leq 4} \mathrm{MABH + H^+} \quad ------- \quad (14)$$

$$\mathrm{MA + HB} \xrightleftharpoons[\log K^{M}_{MABH}]{2 \leq a \leq 4} \mathrm{MABH} \quad ---------- \quad (15)$$

$$\mathrm{MABH} \xrightleftharpoons[\log K^{H}_{MAB}]{4 \leq a \leq 5} \mathrm{MAB + H^+} \quad --------- \quad (16)$$

$$\mathrm{MA + B} \xrightleftharpoons[\log K^{M}_{MAB}]{2 \leq a \leq 5} \mathrm{MAB} \quad ---------- \quad (17)$$

(Charges have been omitted for the sake of simplicity).

Various approaches for the calculation of stability constant involving stepwise equilibria are reported in literature [16]-[19]. In the present work the treatment based on the algebraic method of Chaberek and Martell [20],[21] as modified by Dey et al. [22] has been used for the calculation of various constants in proton-ligand and metal-ligand in binary and ternary systems. The stability constants obtained at various ionic strengths were extrapolated to zero ionic strength in order to obtain thermodynamic stability constants. These values are given in tables (1-3).

The values of the thermodynamic stability constants $\log K^{\mu\rightarrow 0}$ were used to determine the standard free energy change (ΔG°) for the complexation reaction from Van't Hoff isotherm:

$$\Delta G° = -2.303RT \log K^{\mu\rightarrow 0} \text{ ----- } (18)$$

The Gibb's Helmholtz equation ($\Delta G° = \Delta H° - T\Delta S°$) and Van't Hoff equation can be put in the following form:

$$\log K^{\mu\rightarrow 0} = \frac{-\Delta H°}{2.303\,R}\,\frac{1}{T} + \frac{\Delta S°}{2.303\,R} \text{ --- } (19)$$

The standard enthalpy change (ΔH°) and entropy change (ΔS°) have been determined by linear least square fit method by plotting a graph between $\frac{1}{T}$ vs $\log K^{\mu\rightarrow 0}$ using equation (19).

$$\text{Slope} = \frac{-\Delta H°}{2.303\,R} \text{ and Intercept} = \frac{\Delta S°}{2.303\,R}$$

The values of ΔG°, ΔH° and ΔS° are presented in table (3). The negative values of ΔG° in each case indicate that the complexation is spontaneous. The negative enthalpy changes (ΔH°) for the complexation suggest that all the complexation reaction are exothermic, favorable at lower temperature and the metal ligand binding process is enthalpy driven and metal-ligand bond are fairly strong. The positive values of ΔS° indicate that the formations of these complexes are entropically favoured.

According to Sigel [23], the relative stability of ternary complex MAB as compared to that of the binary complex MA can be quantitatively expressed in different ways. The most suitable comparison is in term of ΔlogK. This parameter can be calculated from the reaction of secondary ligand B either with MA or with free metal ion. According to the following equation and values of ΔlogK for ternary complexes are given in table (4).

$$\Delta \log K_{MAB} = \log K^{MA}_{MAB} - \log K^{M}_{MB} \text{ ----}(20)$$

The reaction represents the following overall equilibrium:

$$\Delta \log K_{MAB} = \log \beta_{MAB} - (\log \beta_{MA} + \log \beta_{MB}) \text{ ----}(21)$$

The magnitudes of ΔlogK are strongly influenced by statistical differences in the formation of complex as well as differences in bonding. In most of the systems values of ΔlogK are found to be positive which indicate that the ternary complexes are more stable than the binary complexes. This is perhaps due to the complete satisfaction of primary valancy (oxidation number) and the secondary valancy (coordination number) of metal cations, thereby leading to more stable complexes. The higher stability of ternary complexes of Gd(III) can be attributed to greater coordination number of Gd(III) as compared to Cd(II). The negative value in some ternary systems of Cd(II) can be attributed to the availablity of less number of coordination sites on binary complexes of Cd(II) thereby decreasing the flexibility of secondary ligand B to coordinate with MA species. Further MA complex of Gd(III) bears mono-negative charge whereas that of Cd(II) bears di-negative charge. Hence the secondary ligand B has to face greater repulsion in the latter case, which in turn leads to negative value of ΔlogK

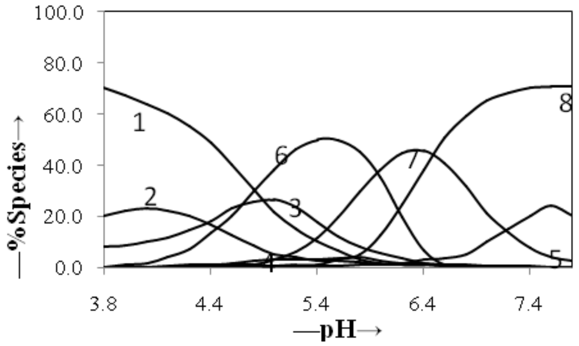

Figure 4: Speciation Curves for Gd(III)-Mal-Tyr(1:1:1) System

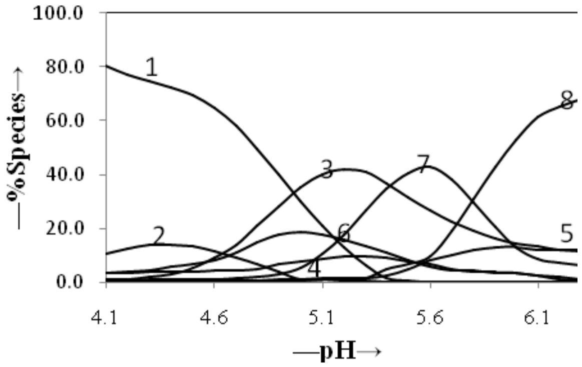

Figure 5: Speciation Curves for Cd(II)-Mal-Tyr(1:1:1) System, in figs. 4-5, Curve 1: [M]; 2 [MAH]; 3[MA]; 4 [MBH]; 5 [MB]; 6 [$MABH_2$]; 7 [MABH]; 8 [MAB]

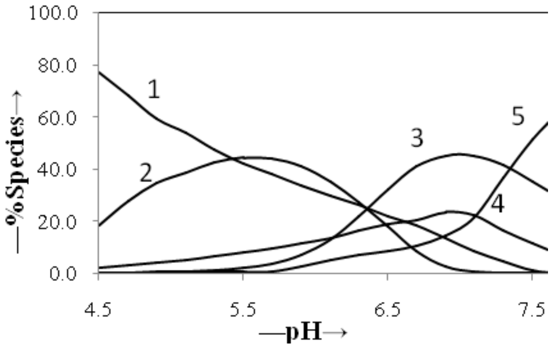

Figure 6: Speciation Curves for Gd(III)-Mal-Dopa(1:1:1) System

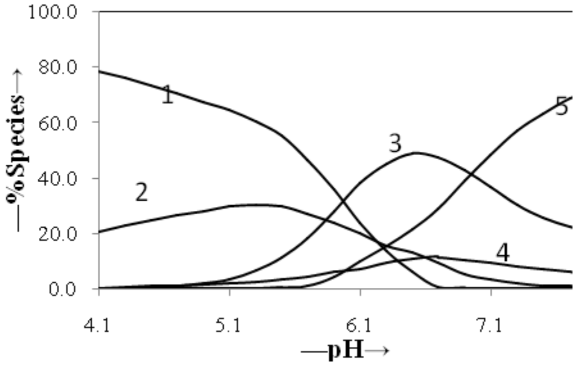

Figure 7: Speciation Curves for Cd(II)-Mal -Dopa(1:1:1) System. In Figs. 6-7 Curve 1: [M]; 2 [MAH]; 3[MA]; 4 [MBH_2]; 5 [$MABH_2$]

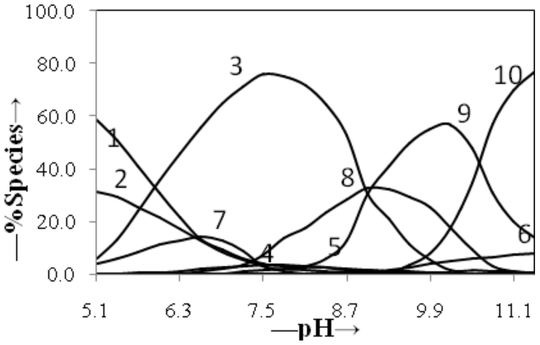

Figure 8: Speciation Curves for Gd(III)-Mal-Dopm(1:1:1) System

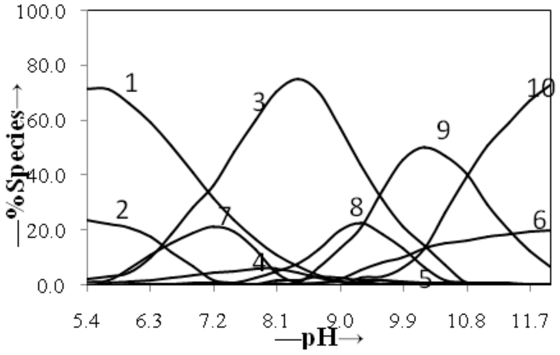

Figure 9: Speciation Curves for Cd(II)-Mal-Dopm(1:1:1) System. In figs. 8-9, Curve 1: [M]; 2 [MAH]; 3[MA]; 4 [MBH_2]; 5 [MBH]; 6 [MB]; 7 [$MABH_3$]; 8 [$MABH_2$]; 9 [MABH]; 10 [MAB]

In figs. 4–9. Temperature = 30±1ºC, μ = 0.10M maintained by NaNO3

Speciation curves are obtained for various systems by using SCOGS computer program [24]-[26]. Speciation curves for Cd(II)/Gd(III)-Mal-tyr are shown in figs. (4-5), these curves follow the same trend. It can be seen that the formation of MAH species occurs up to pH≈4.0 and then concentration of MAH and free metal decreases continuously. Thereafter MA species is formed by deprotonation of MAH complex. Simultaneously formation of protonated ternary species $MABH_2$ also comes in to existence. However the concentration of these two species is less than 25% in both the systems. Deprotonation of $MABH_2$ species leads to the formation of MABH in pH range ≈ 5.0 to 6.5 and 2 ≤a≤ 3.Thereafter the MAB species is formed by the coordination of ligand B to MA complex. At a≈2 formation of MAB species is commences and attains a maximum value of ≈70% at a≈4. MAB ternary complex is the predominant species in both the systems. Formation of MAB occurs through two alternative equilibria (Ref. eq. 8 and 9). The equation 8 represents the formation of MAB by deprotonation of MABH species, whereas equation 9 shows the formation of MAB by coordination of ligand B (deprotonated form) to MA species.

Figures 6 and 7 correspond to the Cd(II)/Gd(III)-Mal-Dopa systems. These curves show that the two ligands coordinate in two distinct steps with metal ion above pH≈5.0. Mixed ligand complexes come in to existence above pH≈6.5 and concentration of binary and ternary complexes (MBH_2 and $MABH_2$) increases up to pH≈7.0. After that concentration of binary species decreases and ternary species increases. The percentage of $MABH_2$ species is maximum ≈70%. The equation 10 represents the formation of $MABH_2$ by coordination of H_2B species to MA complex.

All the systems involving Dopa are confined below pH≈8.0 to avoid errors due formation of polymeric species at higher pH therefore dissociation of protonated species was not considered.

Figures 8 and 9 show the percent distribution curves of Cd(II)/Gd(III)-Mal-Dopm system. These curves show that the formation of non-protonated species [MA] as a major species up to pH≈6.5 which shows that all the proton in ternary complex species is attached to Dopm site. After pH≈6.5 concentration of free metal M, MAH and MA species is decreased and $MABH_3$ is increased.

Speciation curves also show that in such systems above pH≈7.5 $MABH_2$ is formed by dissociation of $MABH_3$ as well as by association of MA and H_2B species (Ref. eq. 12 and 13). MABH and MAB also seem to be formed in both the ways, i.e. by combination of ligand 'B' with MA and dissociation of higher protonated ternary complexes (Ref. Eq. 14-17).

3. Conclusion

The protonation constants of the ligands choosen are found to show the following trend:
Dopm > Dopa > Tyrosine > Malonic acid

The stability of binary complexes also follows the same trend. In ternary systems malonic acid acts as primary ligand in all the systems. In the ternary systems involving tyrosine, Dopa and Dopm as secondary ligand, it is seen that the most stable ternary complexes are formed with Dopm. This is in agreement with the fact that Dopm is most basic amongst the selected ligands. The stability constants of metal complexes are found to be in accordance with basicity of the ligands. Hence the metal complexes of Dopm are higher than Dopa and tyrosine, Dopm binds to the metal ion in pyrocatechol mode. The binding of metal to the ligand may be assumed to be via the amino group and by bridging any one of the phenolato oxygen. It forms eight membered chelate ring with high size are considered to be sterically unfavorable. Alternatively, metal can bind to Dopm with two phenolato oxygen and form five membered ring this type of binding is favorable [27].

Comparing the stability of metal-ligand species (binary and ternary) of Dopa and Dopm it is seen that more stable complexes are formed in Dopm than Dopa. This is due to less steric hindrance and small size of Dopm as compared to Dopa leads to more stable complex in the former system. Dopa coordinates with metal ion in glycine like mode in lower pH range. This is in confirmation with the earlier reports which state that Dopa behaves as ambidentate ligand changing its coordination mode depending on pH [28]-[32]. It is established that at higher pH Dopa coordinates in pyrocatechol mode consequently leading to polymeric species [33]. In present investigation the formation of MAB species is established in lower pH range.

Tyrosine bears structural similarity to Dopa, hence the stability constant values with these ligands are nearly same. This indicates that both the ligands coordinate with the metal in glycine like mode. However, the slightly lower values of equilibrium constants obtained in case of tyrosine as compared to Dopa can be attributed due to their basicity difference.

The Gd(III) complexes are more stable than Cd(II) complexes. This can be explained on the basis of high charge and higher coordination number of Gd(III) ion. The metal-ligand stability constants logK decrease with an increase in temperature and ionic strengths. The negative value of both free energy (ΔG°) and enthalpy (ΔH°) and positive value of entropy (ΔS°) confirms the favorable condition for complex formation.

Table 1: Thermodynamic protonation constants of ligands ($\log\beta^{\mu\rightarrow 0}$)

Parameters	Malonic acid								
	20°C			30°C			40°C		
$\log\beta_1^{HA}$ $\log\beta_2^{H2A}$	6.73 9.89			6.50 9.80			6.30 9.60		
	Tyr			Dopa			Dopm		
	20°C	30°C	40°C	20°C	30°C	40°C	20°C	30°C	40°C
$\log\beta_1^{HB}$	10.10	10.00	9.92	10.52	10.35	10.26	12.76	12.24	11.86
$\log\beta_2^{H2B}$	18.20	18.12	18.00	20.10	20.02	19.96	20.32	20.10	20.01
$\log\beta_3^{H3B}$	-	-	-	28.84	28.84	28.60	29.28	29.10	29.10

$$\log\beta_1^{HA} = pK_2^H$$
$$\log\beta_2^{H2A} = pK_1^H + pK_2^H$$

$$\log\beta_1^{HB} = pK_3^H$$
$$\log\beta_2^{H2B} = pK_2^H + pK_3^H$$
$$\log\beta_3^{H3B} = pK_1^H + pK_2^H + pK_3^H$$

Table 2: Thermodynamic formation constants of binary complexes

Parameters	Cd(II)-Mal			Gd(III)-Mal		
	20°C	30°C	40°C	20°C	30°C	40°C
$\log K_{MAH}^{M}$	4.38	4.31	4.27	4.95	4.85	4.65
$\log K_{MAH}^{H}$	-5.55	-5.48	-5.40	-4.32	-4.25	-4.20
$\log K_{MA}^{H}$	-6.32	-6.20	-6.10	-5.48	-5.37	-5.32
$\log\beta_{MAH}$	10.95	10.90	10.85	12.05	12.00	11.96
$\log\beta_{MA}$	5.62	5.53	5.45	6.85	6.77	6.65
	Cd(II)-Tyr			Gd(III)-Tyr		
$\log K_{MBH}^{M}$	4.58	4.42	4.34	4.70	4.52	4.46
$\log K_{MBH}^{H}$	-6.64	-6.5	-6.42	-5.85	-5.79	-5.71
$\log K_{MB}^{H}$	-7.84	-7.8	-7.74	-7.98	-7.83	-7.75
$\log\beta_{MBH}$	14.25	14.2	14.1	14.4	14.35	14.15
$\log\beta_{MB}$	6.24	6.12	6.02	6.77	6.88	6.57
	Cd(II)-Dopa			Gd(III)-Dopa		
$\log K_{MBH2}^{M}$	4.80	4.72	4.65	4.90	4.85	4.75
$\log K_{MBH2}^{H}$	-6.28	-6.19	-6.12	-6.98	-6.91	-6.56
$\log\beta_{MBH2}$	24.96	24.90	24.84	24.96	24.85	24.78
	Cd(II)-Dopm			Gd(III)-Dopm		

log $K^{M}_{MBH_2}$	4.25	4.20	4.15	5.60	5.25	4.98
log K^{M}_{MBH}	6.20	6.17	5.65	6.96	6.80	6.68
log $K^{H}_{MBH_2}$	-7.54	-7.18	-7.10	-7.97	-7.84	-7.72
log K^{H}_{MBH}	-8.47	-8.20	-7.84	-8.45	-8.40	-8.32
log K^{H}_{MB}	-8.26	-8.00	-7.80	-9.06	-8.60	-8.45
log β_{MBH2}	23.89	23.65	23.45	25.00	24.50	24.05
log β_{MBH}	19.02	18.95	18.32	19.10	18.80	18.61
logβ_{MB}	12.45	11.95	11.03	17.88	17.81	17.75

Table 3: Thermodynamic formation constants and thermodynamic parameters of ternary systems

Cd(II)-Mal- Dopa								
Parameter	20ºC		30ºC		40ºC		-ΔH^{o} kJmol^{-1}	ΔS^{o} Jk^{-1}mol^{-1}
	log $K_{\mu\to0}$	-ΔG^{o} kJmol^{-1}	log $K_{\mu\to0}$	-ΔG^{o} kJmol^{-1}	log $K_{\mu\to0}$	-ΔG^{o} kJmol^{-1}		
log$K^{M}_{MABH_2}$	18.20	102.10	18.10	105.00	17.85	103.55	22.36	271.88
Gd(III)-Mal- Dopa								
log$K^{H}_{MABH_2}$	18.70	203.31	18.59	107.85	18.22	105.70	31.31	251.97

Cd(II)-Mal-Tyr

Parameter	20ºC		30ºC		40ºC		-ΔH^{o} kJmol^{-1}	ΔS^{o} Jk^{-1}mol^{-1}
	log $K_{\mu\to0}$	-ΔG^{o} kJmol^{-1}	log $K_{\mu\to0}$	-ΔG^{o} kJmol^{-1}	log $K_{\mu\to0}$	-ΔG^{o} kJmol^{-1}		
logK^{M}_{MAB}	12.70	71.24	12.25	71.06	11.80	68.45	55.38	53.61
log$K^{M}_{MABH_2}$	14.25	79.94	13.45	78.03	12.90	74.84	77.95	4.75
log$K^{MAH}_{MABH_2}$	10.85	60.86	10.60	61.49	10.20	59.17	41.02	67.97
log$K^{MBH}_{MABH_2}$	9.50	53.29	9.35	54.24	9.15	53.08	21.68	107.22
log$K^{H}_{MABH_2}$	-5.67	-	-5.45	-	-4.87	-	-	-
logK^{M}_{MAHB}	17.80	99.86	17.20	99.78	16.56	96.07	76.58	78.88
logK^{M}_{MABH}	14.50	81.45	13.75	79.97	13.32	77.27	71.52	31.78
logK^{MAH}_{MABH}	11.95	67.04	11.85	68.74	11.75	63.23	70.43	186.68
logK^{MBH}_{MABH}	10.70	60.02	10.45	66.62	10.00	54.82	78.64	53.61
logK^{MA}_{MABH}	8.65	48.52	8.50	49.31	8.35	48.44	18.46	102.43
logK^{MB}_{MABH}	4.35	24.40	4.25	22.33	4.15	17.11	12.30	41.17
logK^{H}_{MABH}	-7.10	-	-6.78	-	-6.54	-	-	-
logK^{MA}_{MAB}	8.95	50.21	8.85	51.34	8.60	49.89	22.56	94.77
logK^{MB}_{MAB}	5.70	31.77	5.55	32.19	5.30	30.14	25.30	22.92
logK^{H}_{MAB}	-8.66	-	-8.52	-	-8.46	-	-	-

Gd(III)-Mal-Tyr

Parameter	20ºC		30ºC		40ºC		-ΔH^{o} kJmol^{-1}	ΔS^{o} Jk^{-1}mol^{-1}
	log $K_{\mu\to0}$	-ΔG^{o} kJmol^{-1}	log $K_{\mu\to0}$	-ΔG^{o} kJmol^{-1}	log $K_{\mu\to0}$	-ΔG^{o} kJmol^{-1}		
logK^{M}_{MAB}	15.46	86.73	14.84	115.70	14.78	85.75	38.02	86.09
log$K^{M}_{MABH_2}$	17.10	95.93	48.14	98.16	74.36	94.91	48.14	164.28
log$K^{MAH}_{MABH_2}$	18.85	105.75	17.65	102.39	16.39	95.08	61.54	150.30
log$K^{MBH}_{MABH_2}$	16.15	90.60	15.10	87.60	14.24	82.69	60.17	102.44
log$K^{H}_{MABH_2}$	-6.75	-	-6.54	-	-5.84	-	-	-
logK^{M}_{MAHB}	21.50	120.61	20.58	119.39	99.92	115.56	95.86	83.86
logK^{M}_{MABH}	19.35	108.55	18.55	107.69	17.94	104.08	85.47	77.16
logK^{MAH}_{MABH}	20.05	112.48	19.10	110.63	17.83	103.44	50.87	208.89

$logK^{MBH}_{MABH}$	18.00	100.98	17.36	100.71	16.32	94.68	86.16	49.78
$logK^{MA}_{MABH}$	16.95	95.09	16.25	94.27	15.44	87.57	69.06	87.11
$logK^{MB}_{MABH}$	10.55	59.18	9.94	57.66	9.67	56.10	32.82	89.03
$logK^{H}_{MABH}$	-8.15	-	-7.89	-	-7.78	-	-	-
$logK^{MA}_{MAB}$	8.95	50.21	8.54	49.54	8.30	48.15	38.84	37.71
$logK^{MB}_{MAB}$	5.48	30.74	5.37	31.15	5.34	30.40	14.90	53.99
$logK^{H}_{MAB}$	-8.38	-	-8.20	-	-7.84	-	-	-

Cd(II)-Mal-Dopm

Parameter	20ºC		30ºC		40ºC		$-\Delta H^o$ kJmol^{-1}	ΔS^o Jk^{-1}mol^{-1}
	$\log K_{\mu\to0}$	$-\Delta G^o$ kJmol^{-1}	$\log K_{\mu\to0}$	$-\Delta G^o$ kJmol^{-1}	$\log K_{\mu\to0}$	$-\Delta G^o$ kJmol^{-1}		
$logK^{M}_{MAB}$	16.13	90.49	15.48	89.90	15.34	88.99	45.43	190.51
$logK^{M}_{MABH_3}$	13.99	78.48	13.67	79.30	13.42	77.85	34.60	149.16
$logK^{MAH}_{MABH_3}$	9.15	51.33	8.98	50.35	8.40	48.73	44.86	20.87
$logK^{MBH_2}_{MABH_3}$	9.95	55.76	9.56	55.46	9.32	54.07	37.20	62.42
$logK^{H}_{MABH_3}$	-4.32	-	-4.40	-	-4.28	-	-	-
$logK^{M}_{MABH_2}$	15.48	86.84	15.42	89.46	14.28	82.84	81.24	22.97
$logK^{M}_{MAHBH}$	16.63	93.29	16.61	96.36	16.39	95.08	16.13	264.04
$logK^{MBH_2}_{MABH_2}$	11.92	66.87	11.64	67.53	11.46	66.48	31.73	121.77
$logK^{MAH}_{MABH_2}$	9.98	55.43	9.68	56.16	9.42	54.65	28.72	91.14
$logK^{MA}_{MABH_2}$	10.64	59.69	10.43	60.51	10.31	59.81	19.69	135.94
$logK^{H}_{MABH_2}$	-5.24	-	-6.82	-	-5.08	-	-	-
$logK^{M}_{MAHB}$	17.32	99.52	17.30	100.36	17.21	99.84	20.24	271.50
$logK^{M}_{MABH}$	12.12	67.99	12.08	70.08	11.96	69.38	10.39	196.83
$logK^{MAH}_{MABH}$	11.63	65.25	11.48	66.60	11.40	66.13	13.67	175.58
$logK^{MBH}_{MABH}$	14.64	82.13	14.57	84.52	14.51	84.18	7.93	253.12
$logK^{MA}_{MABH}$	9.91	55.59	9.88	56.44	9.68	56.15	15.31	138.05
$logK^{MB}_{MABH}$	8.46	49.14	8.30	49.89	8.21	49.54	12.85	123.30
$logK^{H}_{MABH}$	-6.24	-	-6.16	-	-6.04	-	-	-
$logK^{MA}_{MAB}$	8.76	14.14	8.66	50.24	8.56	49.39	16.41	111.82
$logK^{MB}_{MAB}$	7.79	43.70	7.72	44.78	7.45	43.22	22.29	73.71
$logK^{H}_{MAB}$	-8.66	-	-8.26	-	-8.10	-	-	-

Gd(III)-Mal-Dopm

Parameter	20ºC		30ºC		40ºC		$-\Delta H^o$ kJmol^{-1}	ΔS^o Jk^{-1}mol^{-1}
	$\log K_{\mu\to0}$	$-\Delta G^o$ kJmol^{-1}	$\log K_{\mu\to0}$	$-\Delta G^o$ kJmol^{-1}	$\log K_{\mu\to0}$	$-\Delta G^o$ kJmol^{-1}		
$logK^{M}_{MAB}$	21.05	118.03	20.95	121.54	20.90	121.02	8.88	372.41
$logK^{M}_{MABH_3}$	18.58	104.23	18.07	104.83	17.97	104.25	34.73	235.12
$logK^{MAH}_{MABH_3}$	14.94	83.87	14.90	86.44	14.75	85.57	12.44	243.93
$logK^{MBH_2}_{MABH_3}$	15.50	56.95	15.45	89.63	15.35	89.05	9.57	264.23
$logK^{H}_{MABH_3}$	-4.98	-	-4.90	-	-4.81	-	-	-
$logK^{M}_{MABH_2}$	20.40	114.44	20.13	116.78	19.90	114.45	30.49	286.05
$logK^{M}_{MAHBH}$	20.30	113.88	19.30	110.98	19.25	111.68	58.12	185.72
$logK^{MBH_2}_{MABH_2}$	16.25	91.16	16.05	93.11	15.95	92.53	17.77	249.87
$logK^{MAH}_{MABH_2}$	14.20	79.66	14.06	8.57	14.00	81.22	11.76	231.29
$logK^{MA}_{MABH_2}$	15.72	88.19	15.55	90.25	15.51	59.81	12.03	259.25

$\log K^{H}_{MABH_2}$	-5.34	-	-5.12	-	-4.92	-	-	-
$\log K^{M}_{MAHB}$	18.73	105.19	18.62	108.02	18.54	89.98	20.24	186.30
$\log K^{M}_{MABH}$	14.40	80.78	14.10	81.80	14.02	107.56	21.88	199.89
$\log K^{MAH}_{MABH}$	13.35	74.89	13.18	76.46	13.02	81.33	20.24	186.30
$\log K^{MBH}_{MABH}$	24.28	140.86	24.20	140.39	24.10	139.81	11.21	426.59
$\log K^{MA}_{MABH}$	19.45	109.11	19.12	110.93	18.95	108.78	43.35	224.21
$\log K^{MB}_{MABH}$	14.12	79.32	13.98	81.10	13.93	80.75	11.76	229.76
$\log K^{H}_{MABH}$	-7.89	-	-7.87	-	-7.76	-	-	-
$\log K^{MA}_{MAB}$	14.10	79.10	13.95	80.93	13.90	80.65	11.62	229.75
$\log K^{MB}_{MAB}$	10.70	60.02	10.59	61.43	10.41	60.39	18.32	142.45
$\log K^{H}_{MAB}$	-8.96	-	-8.58	-	-8.39	-	-	-

Table 4: Value of Δlog K for ternary complexes

Parameters	20°C		30°C		40°C	
	$\log\beta^{\mu\to0}$	Δlog K	$\log\beta^{\mu\to0}$	Δlog K	$\log\beta^{\mu\to0}$	Δlog K
	Cd(II)-Mal-Tyr					
$\log\beta_{MABH2}$	30.90	5.70	30.20	5.10	29.69	4.74
$\log\beta_{MABH}$	24.20	4.33	24.10	4.37	23.84	7.29
$\log\beta_{MAB}$	12.70	0.84	12.25	0.60	11.80	0.33
	Gd(III)-Mal-Tyr					
$\log\beta_{MABH2}$	33.60	7.15	32.54	6.19	31.84	5.71
$\log\beta_{MABH}$	29.20	7.95	28.14	7.02	26.16	6.46
$\log\beta_{MAB}$	15.46	1.73	14.84	1.30	14.78	0.18
	Cd(II)-Mal-Dopa					
$\log\beta_{MABH2}$	35.43	-0.34	35.20	-0.40	35.04	-0.44
	Gd(III)-Mal-Dopa					
$\log\beta_{MABH2}$	37.24	0.23	37.10	0.25	37.00	0.24
	Cd(II)-Mal-Dopm					
$\log\beta_{MABH3}$	41.84	7.24	41.63	6.84	40.30	6.00
$\log\beta_{MABH2}$	35.65	5.68	35.50	5.65	35.26	6.08
$\log\beta_{MABH}$	24.76	0.12	24.50	0.10	24.24	0.47
$\log\beta_{MAB}$	16.13	-1.94	15.48	-2.00	14.34	-2.14
	Gd(III)-Mal-Dopm					
$\log\beta_{MABH3}$	45.92	8.87	45.35	8.85	45.17	9.14
$\log\beta_{MABH2}$	40.40	9.25	39.39	8.59	39.27	8.68
$\log\beta_{MABH}$	31.77	5.82	31.32	5.82	31.17	5.91
$\log\beta_{MAB}$	27.05	0.45	26.95	0.38	26.90	0.55

$\log\beta_{MABH3} = \log K^{M}_{MABH_3} + \log\beta_1{}^{HA} + \log\beta_1{}^{H2B}$ $\log\beta_{MABH} = \log K^{M}_{MABH} + \log\beta_1{}^{HB}$
$\log\beta_{MABH2} = \log K^{M}_{MABH_2} + \log\beta_1{}^{HA} + \log\beta_1{}^{HB}$ $\log\beta_{MAB} = \log K^{M}_{MAB}$

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