Chemical Modelling- interaction of Phenyl acetic acid hydrazide and Leucine through Divalent Manganese ion

Dr.Ch.ChinnaSatyanrayana, Lecturer, Department of Chemistry,
S.K.B.R.College, Amalapuram, E.G.Dt.,A.P. India

Abstract: Chemical modelling studies on the ternary systems of Mn(II) with Phenyl acetic acid hydrazide and Leucine were carried out potentiometrically in 30% aquo-dimethylformamide medium using Calvin-Wilson titration technique and the data was analyzed using Miniquad-75 program.   Phenyl acetic acid hydrazide was found to act as a bidentate ligand bonding through carbonyl oxygen and terminal nitrogen. In the presence of Leucine this resulted in the formation of a variety of mixed ligand species of the type MLX, $MLXH_{-2}$, ML_2X, ML_2XH_{-1}, ML_2XH_{-2} MLX_2H_{-1} and MLX_2H_{-2}, where, M= Mn(II) L= Phenyl acetic acid hydrazide and XH= Leucine. These ternary species were found to be more stable than the corresponding binary complexes.

Introduction:

Many reactions of biological importance involve the intermediate formation of mixed-ligand species, in which a metal ion is simultaneously bound to two or more ligands. The specificity and selectivity of the vital enzymatic reactions have been attributed to the formation of such a type of ternary species. In order to understand the effect of complexation on these biologically important reactions, one must know the actual form of the species formed in the biological fluids. Therefore, the speciation studies, which throw light on the actual form of a particular substance in solution, have been received much attention in recent years. Acid hydrazides belong to a group of nitrogenous organic compounds that find extensive applications in chemical analysis, industry, agriculture and chemotherapy. As a result of their antimicrobial, antifungal and antibacterial properties [1-3], acid hydrazides are of great biological importance. The formation of metal complexes plays an important role in the enhancement of their biological activity [4-8]. Dihydrazide coated tablets are used to obtain an intentional late-burst release of the drug [9]. In view of the important factors connected to the formation of mixed ligand complexes in solution, the authors have taken up a study on the interaction of Phenyl acetic acid hydrazide and Leucine with divalent transition metal ions. These systems can serve as useful models for a better understanding of naturally occurring phenomenon.

Experimental:

REAGENTS: All inorganic chemicals (BDH) were of analytical reagent grade and were used without further purification. Phenyl acetic acid

hydrazide (Fluka) was prepared freshly in dimethylformamide (DMF) just before the titrations as it is not soluble in water.

APPARATUS: The pH-metric titrations were carried out with a Control Dynamics pH meter model APX 175 E/C in conjunction with a 0-14 pH range glass electrode and a calomel electrode.

A tip less double walled Pyrex glass vessel of 100 ml capacity fitted with a perspex lid, through which the electrodes, gas inlet and outlet tubes and burette tip were admitted, was used for carrying out the potentiometric titrations. The temperature of the solution was maintained by passing water from a thermostat through the annular space between the walls of the titration cell. The experimental solution was earthed by means of a platinum wire sealed in a glass tube. In order to prevent the introduction of an earth loop, the pH meter, thermostat and magnetic stirrer were earthed to the same terminal. Purified nitrogen gas was passed through the experimental solution both before and during titration to expel carbon dioxide.

Data Acquisition and Analysis:

Requisite volumes of hydrochloric acid (to give an overall concentration of 2.0×10^{-2} mole.dm^{-3}), sodium chloride (ionic strength was maintained at 0.1 mole.dm^{-3}) and water in the presence and absence of metal ions and ligands in a total volume of 50 cm^3 was titrated with ~0.2 mole.dm^{-3} sodium hydroxide. A number of titrations were performed with different concentration ratios of metal ion, hydrazide and amino acid. In all the titrations freshly prepared solutions of hydrazide and amino acid were employed. The data from different experiments with different metal to ligand ratios were refined separately using Miniquad-75 program [10], to yield species relevant to that particular composition. This method has been found to be superior[11] compared to the analysis of the entire data from all the titrations at a time, as the main part of the error in the stability constants derives from the variability from one titration to another. Therefore, the authors processed the data from the different compositions separately using Miniquad-75 program.

Results and Discussion:

Knowledge on the distribution of various protonated species of the ligands and the binary species is an essential prerequisite in order to understand the various interactions that exist in a solution containing a metal ion and several ligands. Therefore, as a prelude to the determination of formation constants of mixed ligand complexes, the author has taken up a study on the protonation equilibria and binary metal-ligand systems of both Phenyl acetic acid hydrazide (PAAH) and Leucine under the present experimental conditions.

The best-fit model of the Phenyl acetic acid hydrazide, obtained using Miniquad-75 program, contained only one protonation constant (β_{011}) corresponding to the protonation at the terminal nitrogen atom. In high alkaline conditions aroyl hydrazines are known to lose a proton [12] (fig.1) from the enolic form. In the case of PAAH (L), this type of dissociation leading to the formation of LH_{-1} species may be well above the pH region of study and therefore the corresponding formation constant, β_{01-1}, was not converged. However, in the presence of a metal ion this ligand may lose this enolic proton forming deprotonated species.
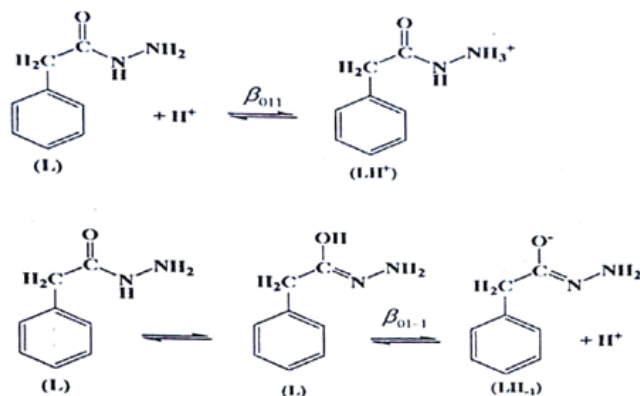

Figure 1: Proton-ligand equilibria of PAAH

The best-fit models for Mn(II)-PAAH binary systems (table 1) indicate the formation of such deprotonated species. The species, $MnLH_{-1}$, $MnLH_{-2}$ and MnL_2H_{-2} may contain metal ion bonded to ligand in enolic form. The probable structures of MnL and $MnLH_{-1}$ species are shown in Fig.2.

Table 1: Proton-ligand and binaryManganese (II)-ligand systems of phenyl acetic acid hydrazide and Leucine in 30% aquo-dmf medium at 30.0 $\pm$0.1 ^{0}C and I= 0.1 mol dm^{-3}

Ligand	Species mlh	log β_{mlh} (SD)
PAAH	011	2.90 (4)
	110	3.59 (2)
	12 0	6.21 (3)
	11-1	-3.92 (4)
	11-2	-11.72 (2)
	12-2	-9.08 (3)
Leucine	011	9.764(4)
	012	12.494(2)
	110	3.152 (4)
	120	5.69 (5)

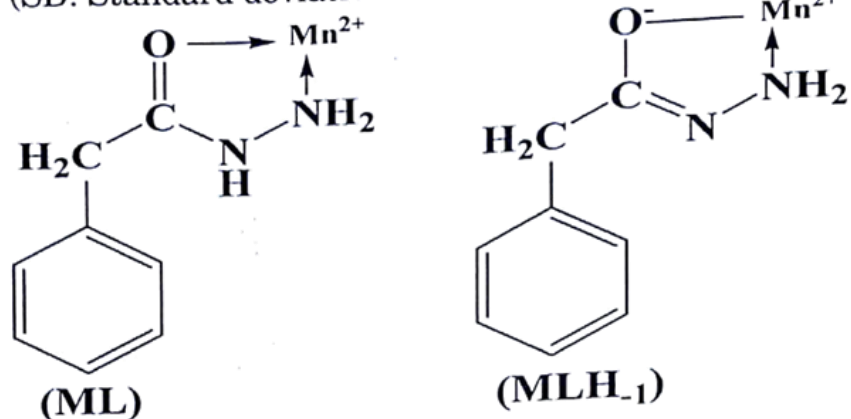(SD: Standard deviation in the least significant digit)

Fig.2 Metal complexes, MnL and MnLH.₁ of hydrazides

The amino acid Leucine (XH) is found to act as a monodentate ligand bonding through carboxylate oxygen in the formation of MnXH species and as a bidentate in MnX and MnX₂ type of species bonding through both carboxylate oxygen and amino nitrogen. The corresponding formation constants are shown in Table 1.
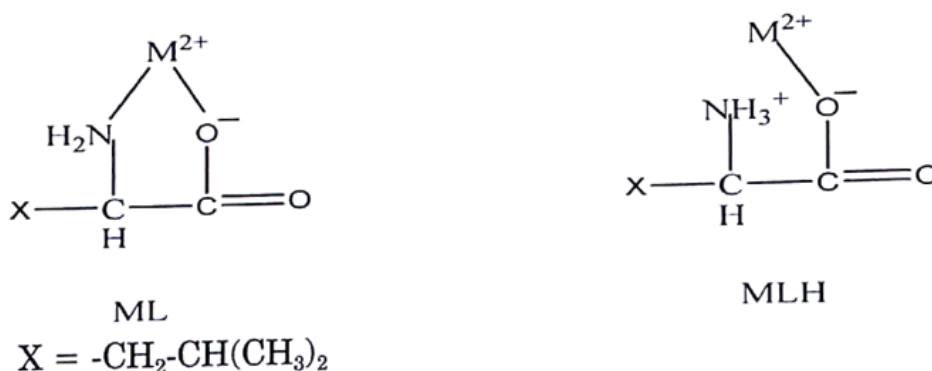

$X = -CH_2-CH(CH_3)_2$

Fig.3: Metal - leucine complexes, MnL and MnLH.₁

METAL ION-PAAH- LEUCINE SYSTEMS: The best-fit models obtained for 1:1:1, 1:2:1 and 1:1:2 (Mn^{2+}: PAAH: Leucine) concentration ratios, after refinement using Miniquad-75 program along with statistical parameters are included in Table 2. The pH metric titration curves (figs. 4 for 1:1:1, 1:2:1 and 1:1:2 compositions respectively) for Mn(II)-PAAH-Leucine system, exhibit one buffer region below 3.5 pH and another above 8.0 pH. The simulated titration curve assuming only the formation of binary species deviated from the experimental one only above 8.0 pH. Therefore, the second buffer region must correspond to the formation of ternary species. The data was subjected to analysis by Miniquad-75 program choosing various chemical models. The best-fit models thus obtained for all the compositions are included in table 2. The inclusion of species MnLX,

$MnLX_2$, MnL_2X, MnL_2XH_{-1}, MnL_2XH_{-2}, $MnLX_2H_{-1}$ and $MnLX_2H_{-2}$ gave a better agreement between the experimental and simulated data. The species distribution diagrams (figs. 4 for 1:1:1, 1:2:1 and 1:1:2 compositions respectively) show a crowding of these species above 8.0 pH.
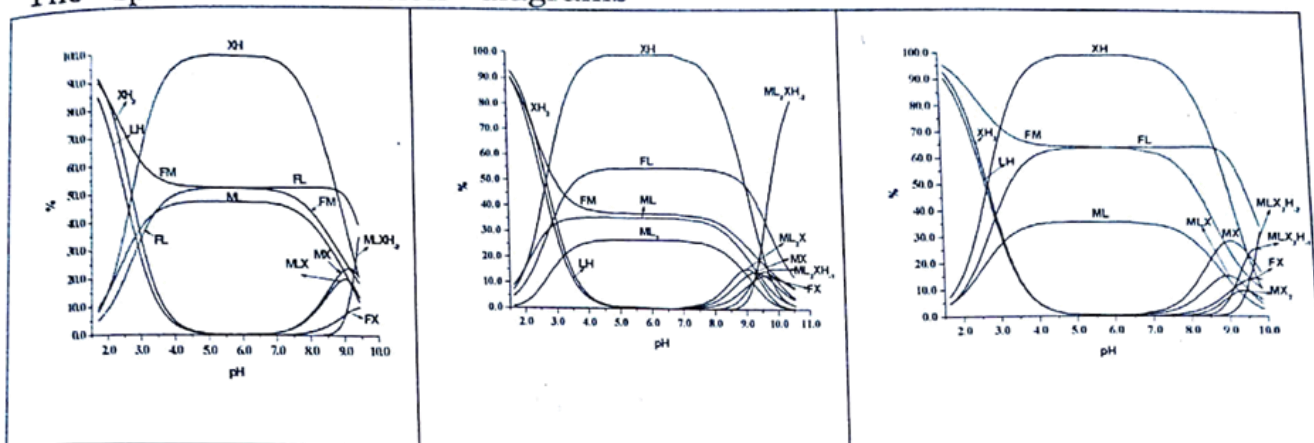
| 1:1:1 | 1:2:1 | 1:1:2 Figure |

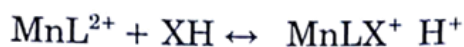4: Species distribution diagrams for Mn(II)-PAAH-leucine systems

Table: 2: Best-Fit Models For Managanese(Ii)-Paah-Leucine Systems In 30% Aquo-Dmf Solution

Metal ion	Composition (M:L:X)	Species mlxh	$\log \beta_{mlxh}$	
Mn^{2+}	1:1:1	0101	2.904	U/NP = 2.582X 10^{-7}
		0011	9.764	χ^2= 8.11
		0012	12.494	R =0.00265
		1100	2.317	Skewness= 0.32
		1010	3.152	Kurtosis=4.34
		1110	5.476 (11)	NP=79
		111-2	-13.003 (3)	
	1:2:1	1200	4.532	U/NP = 5.072X 10^{-10}
		1210	8.021(7)	χ^2= 13.50
		121-1	-1.321(24)	R =0.002119
		121-2	-8.597 (26)	Skewness= 0.09
				Kurtosis=3.33
				NP=61
	1:1:2	1020	5.690	U/NP = 8.152X 10^{-8}
		112-1	-0.743 (7)	χ^2= 6.79
		112-2	-10.526 (5)	R =0.00189
				Skewness= 0.35
				Kurtosis=2.79
				NP=61

*Figures in the parentheses are the standard deviations in the least significant digit.

The formation of MnLX species may be considered to be due to the following equilibria,

$$MnLXH^{2+} \quad \leftrightarrow \quad MnLX^+ + H^+$$

$$MnL^{2+} + XH \leftrightarrow \quad MnLX^+ \; H^+$$

$$MnX^+ + MnL^{2+} \quad \leftrightarrow MnLX^+ + Mn^{2+} \text{ and } MnL^{2+} + X^- \quad \leftrightarrow MnLX^+$$

Although the solution equilibria studies cannot give the structure of the complexes, depending on the nature of the ligands and pH region of their existence probable structure as shown in Fig.5 may be assigned to MnLX species.
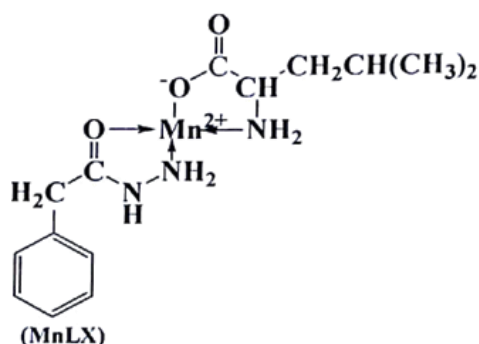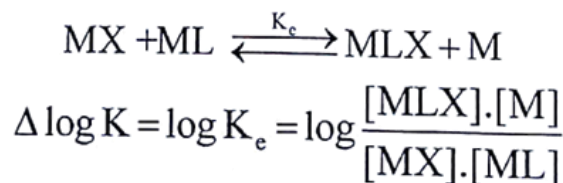

(MnLX)

Fig.5 Probable structure of MnLX species

The relative stability of a mixed ligand complex in comparison with its parent binary complexes is best quantified[13,14] by considering $\Delta \log K$ obtained using the equation,

$$\Delta \log K = \log \beta_{ML_lX_x} - \left(\log \beta_{ML_l} + \log \beta_{MX_x} \right)$$

The difference, $\Delta \log K$, is also equal to the logarithm of the equilibrium constant of the equilibrium,

$$MX + ML \xrightleftharpoons{K_e} MLX + M$$

$$\Delta \log K = \log K_e = \log \frac{[MLX].[M]}{[MX].[ML]}$$

In this formulation, the stabilities of reactions between ligand "X" and aqua metal ion and ligand,"X" and ML are compared.

$$M^{2+} + X \rightleftharpoons MX$$

$$ML + X \rightleftharpoons MLX$$
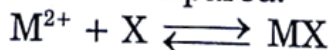
Since more coordination positions are available on the aquo metal ion in comparison with 'ML' the first reaction is statistically more probable in comparison with the second one, leading to – *ve* values of $\Delta \log K$. This is normally observed in simple binary systems where $\log K_1$, is always greater

than $\log K_2$. On the contrary in the case of mixed -ligand complexes for certain combination of ligands log K is found to be $+ve$ or greater than the statistically expected value indicating the tendency towards mixed ligand complex formation. The $\Delta \log K$ values obtained for some ternary species are shown in tables 3.

The $\Delta \log K$ values are greater than the statistically expected value[15, 16] (for octahedral configuration it is -0.4, planar: -0.6, distorted octahedral: -0.9 to -0.3) suggesting a greater stability of ternary species compared to binary. The extra stability may be attributed to intramolecular interactions between ligands.

Table 3: $\Delta \log K$ Values for some ternary species

Species	$\Delta \log K$
MnLX	$= \log\beta_{1110} - (\log\beta_{1100} + \log\beta_{1010}) = 0.007$
MnL$_2$X	$= \log\beta_{1210} - (\log\beta_{1200} + \log\beta_{1010}) = 0.337$
MnL$_2$X$_{-1}$	$= \log\beta_{121-1} - (\log\beta_{120-1} + \log\beta_{1010}) = -0.769$
MnL$_2$X$_{-2}$	$= \log\beta_{121-2} - (\log\beta_{120-2} + \log\beta_{1010}) = -0.341$

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