Stabilities of Some Amino Acids-M(II)-Imipramine Ternary Complex

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The antidepressant imipramine has been investigated pH-metrically in the presence of Mn(II), Co(II), Ni(II), or Zn(II) and some amino acids viz. glycine (Gly.), valine (Val.) and histidine (His.). The formation constants of the binary or ternary complexes formed were calculated. The results were compared with respect to the metal ions or the second ligand.

Mixed ligand complexes play an important role in biological process. Mixed chelation commonly occurs in biological fluids and various potential ligands are likely to compete for metal ions in vivo [1]. Also enzymes are known to be activated by metal ions [2].

Imipramine is one of the most widely used drugs for the treatment of depression. It has been studied and determined in a low level using different methods [3,4]. By careful inspection in the literature, it was observed that there is no avilable data concerning the mixed complexes of imipramine and amino acids.

In the present study, the mixed ligand complexes of imipramine hydrochloride as a primary ligand and some amino acids as secondary ligand with metal ions like Mn^{+2}, Co^{+2}, Zn^{+2} were investigated pH-metrically. The binary and ternary systems of some amino acids have been studied by several authors using different electrochemical techniques. Sigel et al have investigated mixed ligand complexes containing amino acids in ternary systems of biochemical importance [5].

The Irving - Rossotti [8] method has been used for the potentiometric determination of the formation constants of the different complexes formed in the binary system, M^{2+}: Imipramine or M^{2+}: amino acid. The method has been extended [9] to calculate the formation constants of the ternary systems (M^{2+}: Imipramine: amino acid).

EXPERIMENTAL

Imipramine as a hydrochloride (Sigma) was dissolved in double - distilled water. The amino acids were dissolved in bidistilled water by direct weighing. The usual sets were prepared for 1:1 binary (ML) and 1:1:1 ternary (MAL) complexes keeping the ionic strength constant at 0.1$NaNO_3$. A solution of 0.2 mol dm^{-3}

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carbonate - free sodium hydroxide was used to titrate the following solutions:

A) Binary Complexes
a) 0.01 mol dm^{-3} HCl
b) a + 0.01 mol dm^{-3} ligand (Imipramine, Gly. His. Val.)
c) b + 0.01 mol dm^{-3} metal ion.

B) Ternary Complexes
a) 0.01 mol dm^{-3} HCl
b) a + 0.01 mol dm^{-3} ligand (His. Val. Gly.)
c) b + 0.01 mol dm^{-3} Imipramine
d) c + 0.01 mol dm^{-3} metal ion
e) b + 0.01 mol dm^{-3} imipramine + 0.01 mol dm^{-3} metal ion

where A is a set of solutions titrated for the binary system and B for the ternary system. All the measurments were carried out using an Orion 601 ionalayzer digital pH- meter and reproducible pH readings were plotted against ml added of 0.2 mol dm^{-3} NaOH. Fig.1 shows the titration curves of imipramine -Mn(II)-glycine system as a representative one.

RESULTS AND DISCUSSION

Protonation Constants

The values of $\bar{n}_A$ were calculated from the data of titration curves of set A (a,b) using the following equations [6]

$$\bar{n}_A = Y + \frac{(V_1 - V_2)(N^0 + E^0)}{(V_0 + V_1)\,T_L^0}$$

where $\bar{n}_A$ is the average number of proton associated per ligand. Y the displaceable hydrogen atoms, E^0 and T_L are the initial concentrations of the mineral acid and

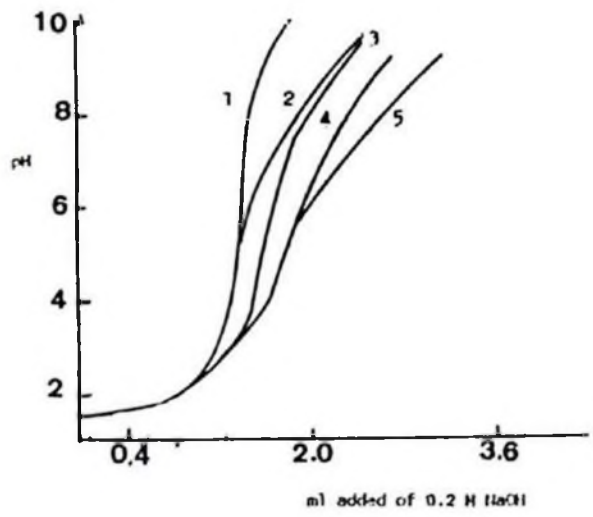
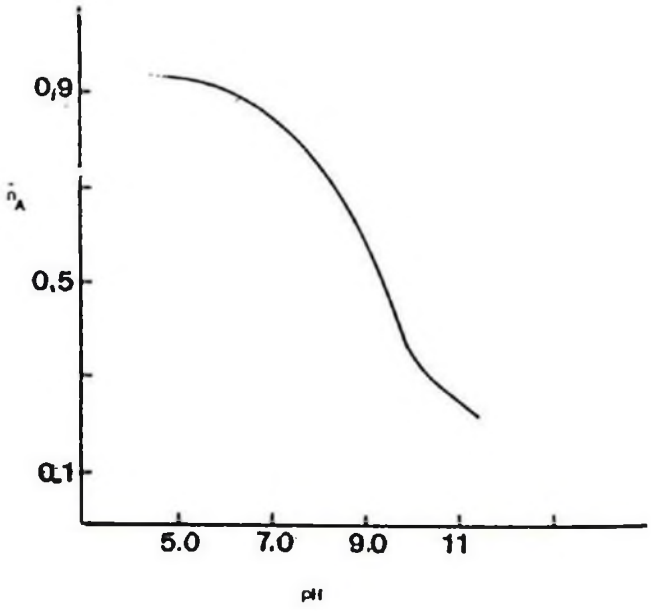


Fig.1 Titration curves
1) 0.01 M HCl. 2) 1 + 0.01 M glycine 3) 1 + 0.01 M imipramine 4) 3 + 0.01 M Mn(II) 5) 2 + 0.01 M imipramine + 0.01 M Mn(II)



lg.2 Proton - imipramine formation curve.

the ligand, respectively, V_1 and V_2 the volumes of alkali of normality N° required for the acid and the ligand titrations respectively at a given pH and V_0 is the initial volume of the solutions (25 ml in each case). n- pH plots are made (Fig.2). Protonation constant of imiprimine was calculated and found to be 9.35.

In the same manner, the protonation constants of the investigated amino acids were determined; the values obtained agree very well with the reported ones [8]. The first dissociation constant for all the amino acids studied were found to be too low (<2.00) and were not used in the present calculations.

Binary Systems

Imipramine has two sites to coordinate metal ions - the heterocyclic nitrogen atom and the nitrogen of the side chain. The shift of the curve 3 from the curve 2 in set A (Fig. not shown) indicates the formation of a complex betwen imipramine and the investigated metal ion. A structure (containing a five membered ring formed by the two nitrogen atoms and the metal ions) has been suggested for the imipramine metal complexes.

The stability constants of the binary complexes formed by imipramine Gly., His. or Val. with Mn, Co, Ni and Zn have been calculated from the titration curves using the half n method. The values with amino acids (see Table 1) agree very well with the reported values [9, 10].

Table 1

Formation constants of binary and ternary complexes formed in the present study
Ionic Strength 0.1 $NaNO_3$ Temp 25° C

Constant	Mn(II)	Co(II)	Ni(II)	Zn(II)
Imipramine				
Log K^{M}_{MA}	4.4	4.55	4.95	5.15
Glycine				
Log K^{M}_{ML}	4.45	4.80	5.20	5.40
Log K^{MA}_{MAL}	5.30	5.50	4.75	5.80
Δ LogK	0.85	0.70	-0.45	0.40
- Δ G	7.201	7.473	6.445	7.881
Valine				
Log K^{M}_{ML}	4.15	4.35	4.75	5.55
Log K^{MA}_{MAL}	4.65	4.80	5.00	4.60
Δ Log K	0.50	0.55	0.25	-0.95
- Δ G	6.318	6.522	6.794	6.250
Histidine				
Log K^{M}_{ML}	4.55	5.10	6.30	6.75
Log K^{MA}_{MAL}	4.05	4.15	4.30	4.25
Δ Log K	0.50	0.95	2.00	2.50
- Δ G	5.503	5.639	5.843	5.775

Δ Log K = log K^{MA}_{MAL} - log K^{M}_{ML} ,
log K^{MA}_{MAL} - Δ G = 2.303 RT

Ternary Systems

From the titration curves obtained (Fig.1), it was noticed that the curves strongly overlapped with the corresponding ones of the binary systems (M^{2+} -Imipramine) at low pH's. But above certain pH (values depending on the nature of amino acid as well as the metal ion), the ternary

titration curves diverage from that of the corresponding binary one. That lead to suggest that the coordination of amino acid with the binary M- imipramine complex can be illustrated as follows

M (imipramine) + amino acid (a.a) $\rightleftharpoons$ M (imip.) (a.a)

The addition of the amino acid to the (M-imip.) binary complex species in the ternary systems resemble the combination of it with $M(H_2O)_6^{+2}$ in binary systems. The shift of the curve 5 from the curve 4 in set B was used for the calculation of $\bar{n}_{mix}$ (average number of the secondary ligand- associated with one M(imip.) ion). Using the following equation [6]

$$\bar{n}_{mix} = \frac{(V_5 - V_4)\,[N^0 + E^0 + T_L^0\,(Y - \bar{n}_A)]}{(V^0 + V_4)\,n_A\,T_M^0}$$

where T_M^0 is the concentration of M(imip.) which equalsto the concentration of M^{2+} used, Y is the dissociable protons of imipramine: values of $\bar{n}_A$ for the secondary ligand at different pH values were obtained from the amino acids. The remaining symbols have the same definitions as described elsewhere [11]. The free ligand exponent (pL_{mix}) was calculated using $\bar{n}_{mix}$ and the following equation:

$$pL_{mix} = \log\left(\frac{\sum_{y=0}^{y=Y} B^{II}_y\,(1/10)^n}{T_L^0 - \bar{n}_{mix}\,T_M^0}\;\frac{V_0 + V}{V_0}\right)$$

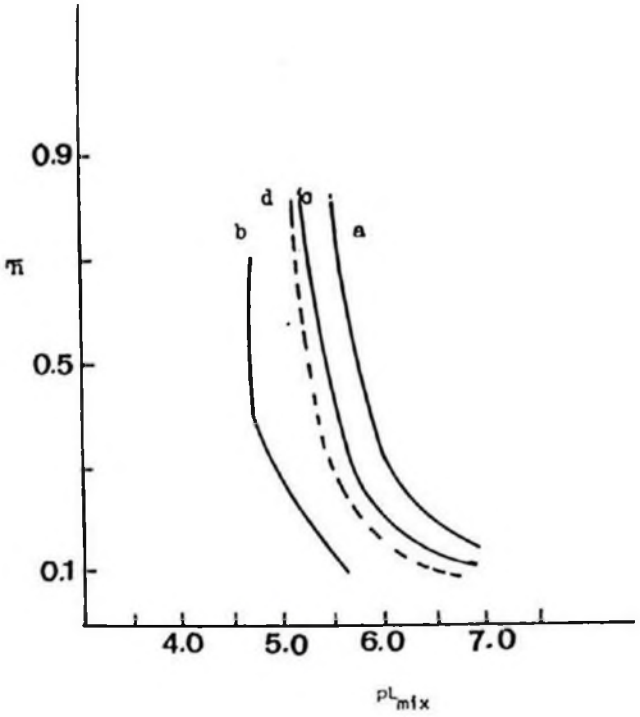


Fig.3 Formation curves for the M(II)-glycine- imipramine system where M(II) is a) Zn(II), b)Ni(II), c)Co(II) d)Mn(II).

Plotting of $\bar{n}_{mix}$ vs. pL_{mix} give the formation curves correponding to the various mixed ligand M^{2+} - Imip. - a.a systems. Fig.3 is given as a representative case showing the formation curves of M^{2+} - imipramine-glycine systems where M^{2+} is Mn, Co, Ni or Zn. The stability constants log K^{MA}_{MAL} have been evaluated by half $\bar{n}$ method and reported in Table 1. Δ log K may be expressed as the equilibrium constant for the reaction

$$MA + ML \rightleftharpoons MAL + M$$

and its value may be regarded as a measure of coordination tendency of L toward MA relative to M [12]. From

Table 1, one can observe that the values of Δlog K are postive for the system M^{2+}-Imip-Gly., and negative for the system M^{2+} -Imip-His. The positive value in the former system may be attributed to the cooperative effect [13] while the negative values in the latter system can be attributed to the steric effect and to the fewer number of sites in the M^{2+}-Imip complex. to coordinate His. than the aquated M^{2+}. Also histamine acts as a bidentate ligand in ternary system coordinating to metal ions through amino and imidazole nitrogens (histamine type of coordination) [14,15] but behaves as a tridentate in binary systems, which coordinate through N,N and carboxylic O^- [16]. The ternary systems containing valine are more stable than the corresponding binary ones which may be attributed to the existence of intramolecular hydropobic interactions [5].

It was found that the stability constant in the binary systems follows the order His. > Gly. > Val. This behaviour may be due to the effective basicity. For the ternary systems, the order is approximately reversed- Gly. > Val. > His., His. acts as a bidentate in the ternary systems as explained above and Gly. forms the more stable complexes due to the exceptional stabilities of glycinato chelate [17].

The stability sequence with respect to metal ions (Table 1) generally follows Irving-William's order i.e. Mn <Co <Ni <Zn

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