Research Paper Engineering

Study of the Physio-chemical Properties of Metal Complex of diamino-N-(aminoiminomethyl)-6-chloropyrazine carboxamide monohydrochloride as Therapeutic agent

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ABSTRACT

It has been shown that the biological activity of many drugs can be enhanced upon complexing with metal ions. The biologically active compounds become more effective and bacterio-static upon chelation with metal ions. In the context of present research work, drugs are used as ligand or chelating agents that contain atoms or groups like N, O, P etc that can attach with metals or metal ions by coordinate linkages to form complexes. The biological activity of drug has been shown to be enhanced on complexing with metal ions, hence promoting their use in Pharmacology. The present work deals with the synthesis of metal complexes derived from diuretic drugs and their physio-chemical analysis to find out ligand- metal ratio of these complexes in solution. For the structure elucidation of the complex "Monovariation method" has been used to ascertain the ligand-metal ratio in the complex. The stability constant of the formed complex was calculated by molar conductance measurement using Modified Job's method. The analysis has been carried out using conductometry and pHmetry.

Keywords: Diuretic drugs, transition metals, complexes, ligand, conductometry.

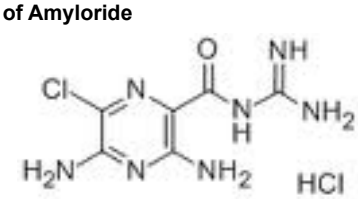
Introduction:-

Diuretics, according to modern pharmacology, are described as medicines or substances that help to reduce the amount of water in body and promote formation of urine by kidney. They are used to treat the buildup of excess fluid in body i.e. edema. But their application to the management of hypertension has outstripped their use in edema. They are among the most widely used prescribed drugs for the treatment of high blood pressure.

Although a large number of therapeutic agents are known, the literature survey reveals that very little work has been done on the metal complexes of diuretic drugs. In this paper I have attempted to prepare transition metal complexes of the diuretic drug Amyloride and to study their compositions.

Amyloride is a direct acting potassium sparing diuretic, used in the management of hypertension and congestive heart failure. It promotes the loss of sodium and water from the body but without depleting potassium. Amyloride is 3,5-diamino-N-(aminoiminomethyl)-6-chloropyrazine carboxamide monohydrochloride dihydrate. Its molecular formula is C6H8ClN7O. HCl.2H2O. The molecular weight of monohydrochloride is 266.09

Structure of Amyloride



Materials and method

1) Conductometric titrations for detection of Metal-Ligand ratio (Monovariant method):-

To confirm metal-ligand ratio, conductometric titrations were carried out at room temperature using analytical grade metal salts. Titrations were carried out with "systronics conductivity-meter" using dip type conductivity cell having cell constant 1 at room temperature.

Solution of drug having strength 0.01m was prepared using methanol: water mixture (3:2) of 100ml. Similarly, 0.02M of metal salt was prepared and these stock solutions were suitably diluted as and when required.

5ml of drug solution (0.01M) was diluted to 50ml in a beaker and kept at thermostatic bath at 25◦C (ligand solution). This was titrated conductometrically against 0.02M metal salt solution taken in a burette. Conductance was recorded after every addition of 0.5ml of metal salt solution with constant stirring at constant temperature.

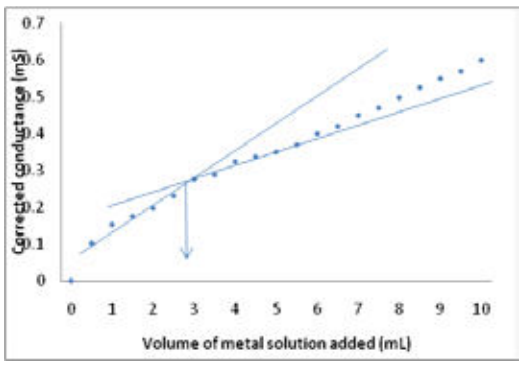
Volume corrections were applied as—
Conductance= {(V+v)/V}*(Observed Conductance)
where V=initial volume of ligand solution
v=volume of metal solution added
Titration results are recorded in table 1.

Table 1. Conductometric titration between Amyloride drug solution and PbCl2.4H2O

S.No.	Volume of metal salt added (ml)	Observed Conductance (mS)	Corrected Conductance (mS)
1.	0	0	0
2.	0.5	0.10	0.102
3.	1.0	0.15	0.153
4.	1.5	0.17	0.175
5.	2.0	0.19	0.197
6.	2.5	0.22	0.231
7.	3.0	0.24	0.276
8.	3.5	0.27	0.288
9.	4.0	0.30	0.324
10.	4.5	0.31	0.337
11.	5.0	0.32	0.350
12.	5.5	0.34	0.370
13.	6.0	0.36	0.400
14.	6.5	0.38	0.420
15.	7.0	0.40	0.450
16.	7.5	0.41	0.470
17.	8.0	0.43	0.498
18.	8.5	0.45	0.526
19.	9.0	0.47	0.550
20.	9.5	0.48	0.570
.21.	10.0	0.50	0.600

Results were plotted in the form of a graph between corrected conductance and volume of metal salt. From the equivalence point in the graph, ratio between metal and ligand was noted to be 1:1. Results are recorded in graph 1.

Graph 1: Conductometric titration between Amyloride drug and PbCl2.4H2O.



2) Modified Job's Method of continuous variation for determining composition and stability constant of complex Equimolar solutions of ligand and metal solutions were prepared and three series C1, C2, C3 of solutions were made. In set C1 metal salt solution was filled with volume 0.0ml to 12.0ml and total volume was made to 12.0ml in each.

Similarly, in C2 ligand solution was filled and set C3 was prepared by mixing metal salt solution from 0.0ml to 12.0ml and ligand solution from 12.0ml to 0.0ml.

Conductance was recorded for each solution. Δ Conductance was calculated as "C1+C2-C3"Graphs were plotted between corrected conductance and mole metal-ligand ratio. The composition and stability constants were determined from the equivalence point in the graph.The study was carried out using Amyloride drug as ligand and Pb (II) as metal salt. The results are recorded in table 2a and 2b.

Conductance of Amyloride drug and PbCl2.2H2O (Modified Job's Method)

Table 2a: Concentration of metal= 0.01M Concentration of ligand=0.01M

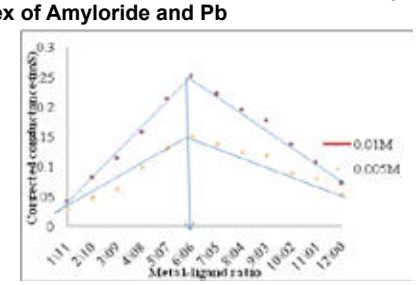
S.No	Ratio	M:S	S:L	M:L	Δconductance	Corrected. Conductance
		(C1)	(C2)	(C3)	(C1+C2-C3) (mS)	(mS)
1	0:12	0.082	0.102	0.120	0.06	0
2	1:11	0.120	0.105	0.135	0.09	0.030
3	2:10	0.131	0.109	0.130	0.11	0.050
4	3:9	0.150	0.110	0.136	0.124	0.064
5	4:8	0.180	0.130	0.150	0.16	0.100
6	5:7	0.201	0.150	0.159	0.192	0.132
7	6:6	0.209	0.180	0.177	0.212	0.152
8	7:5	0.211	0.187	0.199	0.199	0.139
9	8:4	0.213	0.191	0.220	0.184	0.124
10	9:3	0.215	0.195	0.230	0.180	0.120
11	10:2	0.218	0.200	0.268	0.150	0.090
12	11:1	0.220	0.206	0.286	0.140	0.080
13	12:0	0.230	0.208	0.313	0.115	0.055

Table 2b: Concentration of metal= 0.005M

Concentration of ligand=0.005M

S.No	Ratio	M:S	S:L	M:L	Δconductance	Corrected Conductance
		(C1)	(C2)	(C3)	(C1+C2-C3) (mS)	(mS)
1	0:12	0.04	0.089	0.091	0.038	0
2	1:11	0.054	0.090	0.093	0.051	0.013
3	2:10	0.078	0.087	0.095	0.070	0.032
4	3:9	0.097	0.087	0.096	0.088	0.050
5	4:8	0.107	0.086	0.097	0.096	0.058
6	5:7	0.132	0.086	0.098	0.120	0.082
7	6:6	0.151	0.086	0.099	0.138	0.100
8	7:5	0.159	0.084	0.122	0.121	0.083
9	8:4	0.164	0.083	0.137	0.110	0.072
10	9:3	0.168	0.081	0.153	0.096	0.058
11	10:2	0.171	0.080	0.165	0.086	0.048
12	11:1	0.175	0.075	0.185	0.065	0.027
13	12:0	0.178	0.068	0.190	0.056	0.018

Graph: 2 Conductometric estimation of composition of complex of Amyloride and Pb



(3) Synthesis of complex of Amyloride with Pb(II)

For the synthesis of complex, 0.005M solutions of Amyloride drug and Lead chloride (PbCl2) were prepared. On mixing both the solutions the pH was adjusted to 8.2 using freshly prepared NaOH solution. This solution was refluxed for 4 hours and kept undisturbed for 7 days. Brown coloured product was obtained. The product was washed, filtered, dried and weighed.

% yield -8%

Result and discussion

Turner and Anderson have modified Job's method for the determination of stability constants. If the initial concentration of metallic ions and ligands are "a" and "b" respectively then stability constant "K" is given by the equation—

$$K=\frac{x}{(a-x)(b-x)}$$

where "x" is the concentration of the complex.

If two solutions on the two curves have the same conductance then a1, a2 and b1, b2 represent the concentration of the metal and the ligand respectively for 1:1 complex. Thus, following equation can be derived from equation (1)—

$$\frac{a_2-a_1}{a_1-x}=\frac{b_1-b_2}{b_2-x}$$

From graph 2, = (0.01*2)/12= 0.00166
b1= (0.01*10)/12=0.00833
a2= (0.005*3)/12=0.00125
b2= (0.005*9)/12=0.00375.

From equation 2, value of x comes out to be—
x= 0.00145
Thus, from equation 1 —
K= 1.003599 x 103
Or log K= 3.00156

Free energy change ΔG= -2.303 RT log K
Or ΔG= -4.134 Kcal/mol

Through this analysis, it has been observed that the formation of complex of Amyloride with bivalent metal cations like Pb(II) takes place in the ratio 1:1. The modified Job's method of continuous variation was used to calculate the stability constant of the complex and the free energy change. The value of free energy change is negative showing the feasibility of complex formation. The results are recorded in table 3.

After determining the metal-ligand ratio, the stability constant and free energy changes, the complex was synthesized. These findings might be useful in the optimization of Amyloride as lead for future development of diuretic drugs for hypertension.

Table 3: Physio-chemical characteristics of ligand Amyloride and its Pb-complex

S.No	Compound/complex	Molecular formula	Colour	% Elemental Analysis				
				C	H	N	Cl	Pb
1.	Amyloride	C6H8ClN7O.HCl	Pale yellow	(27.05)	(3.006)	(36.82)	(13.34)	-
2.	Amyloride-Pb	C6H8ClN7O.HCl-Pb	Light brown	(22.42)	(2.49)	(30.52)	(11.05)	(17.11)

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