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Short Communication

A Study of Transition Metal Complex of Diuretic Drug and study of its Physico-chemical properties as Potential Therapeutic Agent

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Abstract

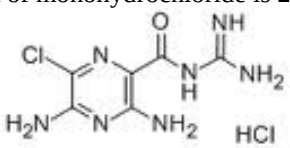
It has been found that biologically active compounds become more effective and bacterio-static upon chelation with metal ions[1]. The biological activity of many drugs has been shown to be enhanced on complexing with metal ions, hence promoting their use in Pharmacology[5]. The pharmaceutical action of such 'drug complexes' are henceforth studied. In the context of present research work, drugs are used as ligands 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. . 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. 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. The complexes of Mn salts are prepared. For the structure elucidation of these complexes "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. 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. These findings might be useful in the optimization of Amyloride as lead for future development of diuretic drugs for hypertension.

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. 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 $C_6H_8ClN_7O.HCl.2H_2O$. The molecular weight of monohydrochloride is 266.09



Material and Methods

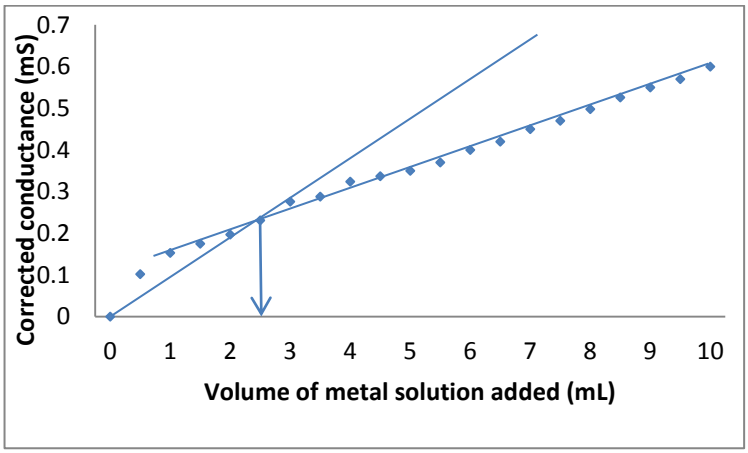
Conductometric titrations for detection of Metal-Ligand ratio (Monovariant method)[4]: Solution of drug having strength 0.01m was prepared using methanol: water mixture (3:2) of 100ml. Similarly, 0.02M of metal salt was prepared and these stock solutions were suitably diluted as and when required.

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. 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[7].

Table 1
Conductometric titration between Amyloride drug solution and $MnCl_2.4H_2O$

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



Graph - 1
Conductometric titration between Amyloride drug and $MnCl_2.4H_2O$

Modified Job's Method of continuous variation[3] 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" [10].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[8]. The study was carried out using Amyloride drug as ligand and Mn (II) as metal salt. The results are recorded in table 2a and 2b. Table 2a and 2bThe results of the tables are plotted in the form of

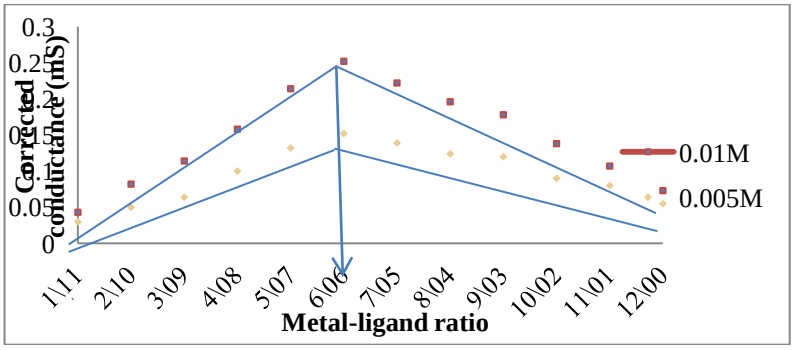
graph 2. The peak in the graph coincides with the ratio of metal and drug in solution[9], which comes out to be 1:1.

Table 2 (a)
Conductance of Amyloride drug and $MnCl_2.2H_2O$ (Modified Job's Method)
Concentration of metal= 0.01M, Concentration of ligand=0.01M

S.No	Ratio	M:S (C1)	S:L (C2)	M:L (C3)	Δconductance (C1+C2-C3) (mS)	Corrected. Conductance (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 2(b)
Concentration of metal= 0.005M, Concentration of ligand=0.005M

S.No	Ratio	M:S (C1)	S:L (C2)	M:L (C3)	Δconductance (C1+C2-C3) (mS)	Corrected Conductance (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
Conduct metric estimation of composition of complex of Amyloidal and Mn

Synthesis of complex of Amyloride with Mn(II): For the synthesis of complex, 0.005M solutions of Amyloride drug and Manganese chloride ($MnCl_2$) 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%**

Results and discussion

Turner and Anderson[2] 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

$$K = \frac{x}{(a-x)(b-x)} \quad \ldots\ldots\ldots\ldots (1)$$

Where "x" is the concentration of the complex.[n]

If two solutions on the two curves have the same conductance then a_1, a_2 and b_1, b_2 represent the concentration of the metal and the ligand respectively for 1:1 complex. Thus, following equation can be derived from equation (1)

$$\frac{a_2 - a_1}{a_1 - x} = \frac{b_1 - b_2}{b_2 - x} \quad \ldots\ldots\ldots (2)$$

From graph 2,

a_1= (0.01*2)/12= 0.00166, b_1= (0.01*10)/12=0.00833

a_2= (0.005*3)/12=0.00125, b_2= (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 10^3 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 Mn(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.

Conclusion

Through this work it has been ascertained that the drug Amyloride forms a complex in solution with bivalent cations like Mn (II) in the ratio of 1:1. The stability constant of the complex and the free energy change values show the feasibility and stability of the formed complex. These findings might be useful in the optimization of Amyloride as lead for future development of diuretic drugs for hypertension.

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