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# Potentiometric investigation of complexation of Benazepril hydrochloride drug with transition metal ions

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**Abstract**

In the present work we investigate the stability constant ofBenazepril hydrochloridedrug withtransition metal ions Co, Ni, Cu, Zn, and Cd using potentiometric titration technique in 20%(v/v) ethanol-water mixture at 27 °C temperature and at an ionic strength of 0.1M $NaClO_4$.{Metal to ligand ratio=1:5& 1:1}The method of Calvin and Bjerrum as adopted by Irving and Rossotti has been employed to determine proton ligand (pKa) and metal-ligand stability constant (logK) values. It is observed that a transition metal ion forms 1:1 and 1:2 complexes.

**Keywords:** Stability Constant,transition metal ions, Benazepril drug, Potentiometric.

## 1. Introduction

Chemistry of drugs attracts many researchers because of its application in medicinal study.The stability of metal complexes with medicinal drugs playsa major role in the biological and chemical activity. Metal complexes are widely used in various fields, such as biological processes pharmaceuticals, separation techniques, analytical processes etc.To understand the complex formation ability of the ligands and the activity of complexes, it is essential to have the knowledge about solution equilibria involved in the reactions. The extent to which the ligand binds to metal ions is normally expressed in terms of stability. Potentiometric titration is accepted as a powerfuland simple electro analytical technique for determination of stability constants. Most of thed-block elements form complexes. There are different kinds of ligand used for complexation. For the present investigation, we selectedBenazepril hydrochloride (BEN).Benazepril hydrochloride, (3-[(1-ethoxy carbonyl- 3 -phenyl-(1*S*)-propyl)-amino]-2,3,4,5 -tetrahydro- 2 –oxo-1-(3*S*)-benazepine-1-acetic acid hydrochloride), is a prodrug type angiotensin-converting enzyme (ACE) inhibitor,which is proved effective in treating congestive heart failure and hypertension. The family of ACE inhibitors inhibits the angiotensin-converting enzyme, which is involved in the conversion of angiotensin I to angiotensin II. The physical properties of medicinal drug Benazepril hydrochloride are shown below:

After a review of literature survey and in continuation of our earlier work with complexation of medicinal drugs[1-20], we have carried out a solution study on the complexationof Benazepril hydrochloride drugwith transition metal ions $Co^{2+}$, $Ni^{2+}$, $Cu^{2+}$, $Zn^{2+}$ and $Cd^{2+}$using pH metrically in 20% (v/v)ethanol-water mixture at constant ionic strength of 0.1M $NaClO_4$.

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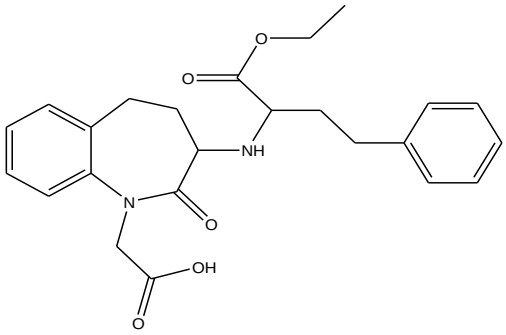
| Sr. No. | Physical property | Value |
|---|---|---|
| 1 | Molecular weight | 460.98.g/mol |
| 2 | Phase | Solid (at STP) |
| 3 | Melting point | 189 °C |
| 4 | Boiling Point | 691.2 °C |
| 5 | Density | 1.269 g/cm$^3$ |
| 6 | Colour | White |
| 7 | Solubility | Soluble in water (>100 mg/mL) |



.HCl

***Figure 1: Benazepril hydrochloride(molecular formula is $C_{24}H_{29}N_2O_5Cl$)***

## 2. Materials and Solution.

The ligand Benazepril hydrochloride is soluble in 20% (v/v) ethanol-water mixture.NaOH, $NaClO_4$,$HClO_4$ and metal salts were of AR grade.The solutions used in the pH metric titration were prepared in double distilled water. The NaOH solution was standardized against oxalic acid solution (0.1M) and standard alkali solution was again used for standardization of $HClO_4$. The metal salt solutions were also standardized using EDTA titration. All the measurements were made at 27 $^0$Cin 20%(V/V) ethanol-water mixture at constant ionic strength of 0.1M $NaClO_4$.The thermostat model SL-131 was used to maintain the temperatureconstant. The pH measurement were made using a digital pH meter model Elico L1-120 in conjunction with a glass and reference calomel electrode (reading accuracy ±0.01 pH units) the instrument was calibrated at pH 4.00 ,7.00 and 9.18 using the standard buffer solutions .

**II. Potentiometric procedure.** For evaluating the protonation constant of the ligand and the formation constant of the complexes in 20 %( v/v) ethanol-water mixture with different metal ions we prepare the following sets of solutions.

(A) $HClO_4$ (A)
(B) $HClO_4$+BEN (A+ L)
(C) $HClO_4$+ BEN + Metal (A+ L+ M)

The above mentioned sets prepared by keeping M: Lratio, the concentration of perchloric acid and sodium perchlorate (0.1M) were kept constant for all sets. The volume of every mixture was made up to 50ml with double distilled water and the reaction solution were potentiometerically titrated against the standard alkali at temperature27 $^0$C.

**Table 1. Proton-ligand and metal-ligand stability constant of Benazepril drugin 20 % (v/v) ethanol-water medium (Metal to ligand ratio=1:5)**

| pKa | logK | $Co^{2+}$ | $Ni^{2+}$ | $Cu^{2+}$ | $Zn^{2+}$ | $Cd^{2+}$ |
|---|---|---|---|---|---|---|
| 3.6486 | $logK_1$ | 2.9307 | 2.7270 | 3.3414 | 2.8581 | 2.9483 |
| | $logK_2$ | 2.8569 | 2.6955 | 2.9836 | 2.7614 | 2.8977 |
| | $log\beta$ | 5.7876 | 5.4225 | 6.3250 | 5.6195 | 5.8460 |

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**Table 2. Proton-ligand and metal-ligand stability constant of Benazepril drugin 20 % (v/v) ethanol-water medium (Metal to ligand ratio=1:1)**

| pKa | logK | $Co^{2+}$ | $Ni^{2+}$ | $Cu^{2+}$ | $Zn^{2+}$ | $Cd^{2+}$ |
|---|---|---|---|---|---|---|
| 3.6486 | $logK_1$ | 3.8413 | 3.8522 | 4.4513 | 3.8440 | 4.0110 |
| | $logK_2$ | - - - | - - - | - - - | - - - | - - - |
| | $log\ \beta$ | 3.8413 | 3.8522 | 4.4513 | 3.8440 | 4.0110 |

## 3. Result and Discussion

Benazepril Hydrochlorideis antihypertensive drug. Its structural form shows one carboxylic group one secondary amine and one nitrogen in heptacyclic ring. Apart from these groups drug also contains two carbonyl groups one is cyclic and another is exocyclic one. Out of these groups -COOH is dominating one. It has been an established fact that carboxylate group is most co-ordinating group. Benazepril hydrochloride under experimental conditions shows only one pKa value (3.6486) corresponding to -COOH group in the acidic range. This indicates deprotonation of functional group other than -COOH does not take place. The proton ligand stability constant (pKa) of Benazepril drug is determined by point wise calculation method as suggested by Irving andRossoti. Metal ligand stability constant (logK) transition metal ions with Benazepril drug (ligand) were calculated by point wise and half integral method of Calvin and Bjerrum as adopted by Irving and Rossotti has been employed.For the present investigation we have studied the stability constant of divalent transition metal ions. Since we got $\bar{n}_A$ between 0.2 to 0.8 and 1.2 to 1.8 indicating 1:1 and 1:2 complex formations.

The order of stability constants for these metal complexes was as follows:

**$Cu^{2+}$> $Cd^{2+}$> $Co^{2+}$> $Zn^{2+}$> $Ni^{2+}${*Metal to ligand ratio=1:5* and**

**$Cu^{2+}$> $Cd^{2+}$> $Ni^{2+}$> $Zn^{2+}$> $Co^{2+}$ {*Metal to ligand ratio=1:1*}**

The above stabilities of metal complexes with ligand are similar to the observations made by several research workers and are in accordance with Irving and Williams order. In the present metal ions, Copper has available d orbital with low energy hence show maximum stability whereas it decreases in zinc complexes due to the lack of vacant d orbital having low energy. This natural order is particularly valid for nitrogen and oxygen donor ligands, irrespective of nature of ligands. Similarly extra stability of Cu (II) complex is attributed to unique electronic configuration of Cu (II) and John-Teller effect. The low value of logK for Ni (II) and Co (II) indicates that their complexes may not be planar.

## 4. Conclusion

In the present investigation, stability constants of transition metal complexes with Benazepril Hydrochloride drug at 1:5 and 1:1 metal-ligand ratio were studied at 27 $^0$C. It is found that stability constant of transition metal complexes when metal-ligand ratio 1:5 is greater than those of transition metal complexes when metal-ligand ratio is 1:1. This indicates that at higher concentration of ligand more stable complexes are formed.

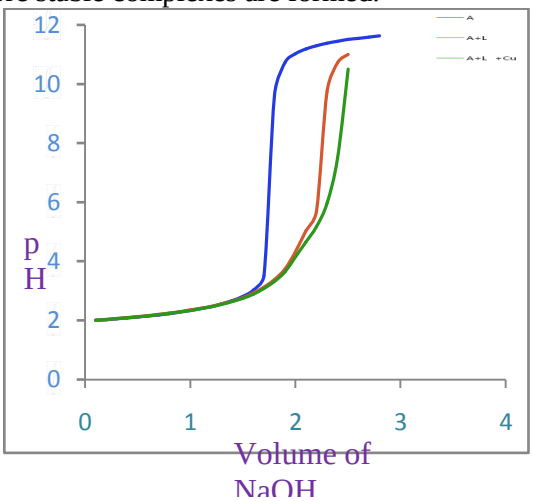


*Figure 2: The pH metric titration curve for Cu (II)-BEN*

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