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Research Article

POTENTIOMETRIC AND SPECTROPHOTOMETRIC STUDIES ON THE COMPLEXES OF ZINC (II) WITH CAPTOPRIL

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ABSTRACT

The interaction of zinc (II) ions with captopril (cap) (1-[(2S)-3-mercapto-2-methyl propionyl]-L-proline) was investigated by potentiometric and optical means. The dissociation constants of captopril and the stability constants of the binary zinc were calculated. Stability constants of the binary complexes at 25°C and in 0.1 M ($NaNO_3$) ionic strength in aqueous solution have been determined potentiometrically. The complex formation were characterized. The results indicate that the overall ratio of the complex Zn: cap is 1 : 2. UV-Vis spectroscopy gave additional support to the results.

INTRODUCTION

Captopril is considered to be antihpertensive drugs and assisted in the relief of chronic heart failure. It may have an effect on reduction of left atrial size and on insulin receptor in hypertension [1-3]. Captopril inhibits tumor growth [4] and protects agaist heart attack[5]. In vitro a combination of captopril with aspirin significantly inhibites the platelet aggregation [6]. Zinc is considered to be one of the most important elements to a healthy immune system and is also needed for the growth and repair of tissues throughout our bodies. Zinc oxide topically (applied to the skin) is used to treat diaper rash, minor burns, severely chapped skin, or other minor skin irritations [7]. Complexes of Zn(II) metal ions with some anti-inflammatory pharmaceuticals have been synthesized and characterized [8]. Zn^{II} complexes of omeprazole i.e., 5-methoxy-2[(4methoxy-3,5dimethyl-2-pyridinyl) methylsulfinyl]–1H–benzimidazole as ant- ulcerative drugs were characterized [9]. In the central nervous system, Zn is not uniformly distributed throughout the brain. It is found at higher concentrations in certain regions such as the hippocampus and cortex and in lesser amounts in cerebellum [10]. Zinc deficiency induces neuronal cell death and could also be a condition that increases the sensitivity of neurons to the deleterious action of toxicant metals [11] and zinc can exert antioxidant actions [12].

A combination of captopril and dopamine may prevent dopamine induced myocardial injury [13]. Captopril bind to zinc [14] in AC- enzyme and increase urinary zinc loss and may deplete zinc stores. The bioavailability of captopril [15] may be reduced in presence of an anti acid. A combination of spectrophtometric and potentiometric metheds were previously used [16-18]. This work aimed to investigate the equilibria of captopril and its binary complexes with zinc (II) in aqueous solution, the composition and stability of the complexes are to be determined. And also to study the effect of pH on the reaction progress. In the current study spectrophotometric and potentiometric methods were used to study the complex equilibria and to get better information about the equilibria in solution and dissociation constants of captopril and the stability constant of its complexes.

MATERIALS AND METHODS

Apparatus

Absorption spectra were recorded on a OPTIMA SP-3000 PLUS Spectrophotometer equipped with 1cm matched quartz cells. The pH measurements were carried out using a Jenway

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3305 pH meter with a combined glass electrode. The glass electrode was calibrated before each titration with two Merck standard buffer solutions, first with the pH 7.0 followed by a pH 4.0. The pH measurements were done in aqueous solutions. All measurements were carried out at a temperature of ~25ºC.

Chemicals and solutions

Captopril was manufactured by Dar Al Dawa, Na`ur-Jordan and was used as received. Aceten tablets (50 mg) the only available commercial dosage forms were purchased from the local market. Standard solution of captopril (2×10^{-2} mol L^{-1}) was prepared in bistilled water and diluted as necessary. All chemicals and reagents were of analytical grade. Metal salt: $ZnSO_4.7H_2O$ of Analar products were obtained from Merck (Germany) were used for preparation of solutions of the corresponding metal ions. Stock solutions of zinc (II) were prepared in bidistilled water. The working solutions were prepared by dilution. The metal concentration was determined by conventional methods [19]. Nitric acid, sodium nitrate, sodium hydroxide and potassium hydrogen phthalate were supplied by Aldrich Co.). Standard NaOH hydroxide was also prepared. The acidity of solutions investigated was adjusted by the addition of either HNO_3 or NaOH solution. The ionic strength was maintained constant at I = 0.1 M ($NaNO_3$).

Potentiometric study

In the binary systems studied, the following solutions were titrated potentiometrically with 0.2 mol L^{-1} standard carbonate - free sodium hydroxide solutions standardized against standard potassium hydrogen phthalate:

1. solution 1 x 10^{-3} mol L^{-1} nitric acid.
2. solution (a) + 1 x 10^{-3} mol L^{-1} captopril.
3. Solution (b) + 1 x 10^{-3} mol L^{-1} Zn^{2+}.

The total volume was completed to 50 ml by adding deionized water and the titrations were carried out at 25 ºC.

RESULTS AND DISCUSSION

Proton–Ligand dissociation constants

The titration curves obtained for cap are shown in Figure

The values of $\bar{n}_H$ (the ligand proton association) as determined according to Irving and Rossotti [20] were compiled from the titration data at pH difference equal 0.1.

$$(cap\text{-}H_2) \rightleftharpoons (cap\text{-}H)^- + H^+ \quad (pH\ 6.0 - 7.6) \qquad \text{..... 1a}$$

$$K_{(cap\text{-}H_2)}^{H} = [(cap\text{-}H)^-][H^+] / [(cap\text{-}H_2)] \qquad \text{..... 1b}$$

$$(cap\text{-}H)^- \rightleftharpoons (cap)^{2-} + H^+ \quad (pH\ 9 - 10.5) \qquad \text{..... 2a}$$

$$K_{(cap\text{-}H^-)}^{H} = [(cap)^{2-}][H^+] / [(cap\text{-}H)^-] \qquad \text{..... 2b}$$

Calculation of proton ligand dissociation constants were carried out by plotting $\bar{n}_H$ against pH values, the values of log K_1H and log K_2H (the first carboxylic and second mercapto proton dissociation constants of the studied captopril) are the pH values corresponding to $\bar{n}_H$ = 0.5 and 1.5, respectively. The pK_1 and pK_2 values obtained by treatment of several sets of potentiometric data were found to be 6.65 and 8.45, respectively.

Dissociation of carboxyl proton begins at pH ~ 6.0, over pH 7.8 the anion $(cap\text{-}H)^-$ is prevalent. Dissociation of the second mercapto proton originates from pH 9 and the monoanionic species of $(cap\text{-}H)^-$ undergoes ionization by rising the pH as seen in the following equilibria:

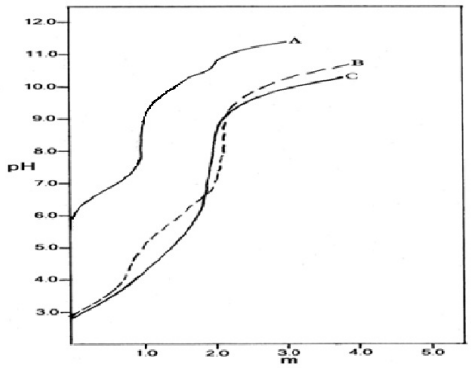
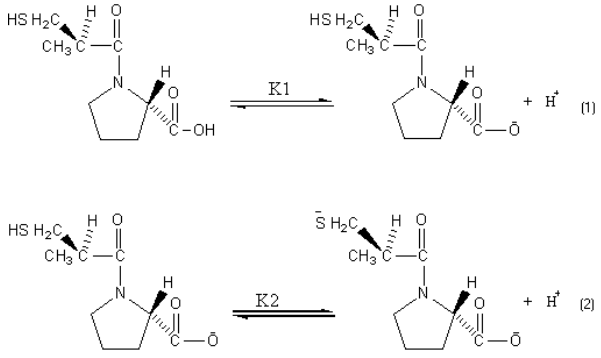


Fig 1 Potentiometric titration curves of Binary systems of Zn^{2+} with cap [m = moles of alkali per mole of metal ion], in H_2O at 25 °C. A) deprotonated cap, B) 1:2 Zn^{2+} - cap and C) 1:1 Zn^{2+} - cap.

Thus, the acid–base equilibria to be considered in the pH range 6 - 10.5 can be shown in the following scheme:



Scheme 1 The dissociation constants of captopril.

Binary metal – ligand systems

Most pharmaceuticals contain electron donor groups likely to bind metal ions occurring naturally [21]. Potentiometric

equilibrium titration curves of zinc(II) – cap is taken as being representative example (Figure 1). In the titration curve, the inflection is significantly lower with respect to that of the free captopril, indicating the formation of complex by release of protons. Potentiometric information based on assumption of formation of complex (1:2) with the formation of two six member rings via mercapto and oxopropyl groups. The titration curves of zinc(II) – cap solutions (Figure 1(C)) differs well the curve separated at pH 6.70. Captopril (Figure 1(A)), demonstrating replacement of two SH protons due to complexation. This shows that captopril binds to zinc through a thiol group [22] and gives 2:1 ligand – metal complex. A ligand–proton formation curve was obtained by plotting the degree of formation ($\bar{n}_H$) the ligand–proton association against pH, using the relationship derived by Irving and Rossotti [20].

$$\bar{n}_H = Y + \frac{(V^{I} - V^{II})}{(V^{\circ} + V^{I})} \frac{(N^{\circ} + E^{\circ})}{T_{C_L^{\circ}}} \quad ------(3)$$

The formation curves of the complexation equilibria obtained by plotting the degree of complex formation ($\bar{n}$) versus the (-log) of the ligand (pL).

$$\bar{n} = \frac{(V^{III} - V^{II})(N^{\circ} + E^{\circ}) + T_{C_L^{\circ}}(Y - \bar{n}_H)}{(V^{\circ} + V^{I})\bar{n}_H T_{C_M^{\circ}}} \quad ------(4)$$

$$pL = \log \frac{\sum_{n=0}^{n=i} \beta_n^H [H^+]^n}{T_{C_L^{\circ}} - \bar{n} T_{C_M^{\circ}}} . \frac{V^{\circ} + V^{III}}{V^{\circ}} \quad ---(5)$$

Where β_n^H is the reciprocal acid dissociation constant of the ligand (proton-ligand stability constant).

The stability constants for the equilibria for complexes 1: 1 (eq. 6) and 1:2 (eq. 7) metal–ligand complexes were calculated from potentiometric titration curves with 1:2. Table1 showed the captopril complexes stability constants. Captopril behaviour may be based on the bidentate nature.

The corresponding equilibria may be represented as follows:

$$Zn^{2+} + (cap\text{-}H)^- \rightleftharpoons Zn(cap) + H^+, \quad K_{Zn(cap)} \quad \ldots\ldots (6)$$

$$Zn(cap) + (cap\text{-}H)^- \rightleftharpoons Zn(cap)_2^{--} + H^+, \quad K_{Zn(cap)_2} \quad \ldots\ldots. (7)$$

Figure 1 display that the reaction of zinc and captopril begging when the carboxylic proton has been dissociated. The use of large single charged anions such as nitrate minimize the electrostatic interaction that exist between anions and metal ions.

Table 1 Stability constants of complexes containing 1:1 Zn: cap ratio of metal Ions with [Temp. 25 c°, I=0.1M (KNO_3); pK_1 and pK_2 for (cap) are 6.65 and 8.45 respectively].

Metal ion	M log K ML	M log K ML_2	M log β ML_2
Znl (II)	6.8	5.95	12.84

The released two protons in complex of Zinc - captopril complex based on the assumption of moles that is required for deprotonation of two mercapto group of two ligand molecules. The potentiometric titration graph of 1:1 show a distinct inflection at m= 1 in addition to other inflection at m =2, (m=number of moles of alkali added for mole of metal ion) corresponding to the stepwise formation of ML and ML_2 complex species. The results obtained for the formation of the binary complexes investigated are shown in (Table 1).

Electronic absorption spectra

The absorption spectra of captopril in bidistilled water was studied in UV region (200-330 nm) at different values of pH. The spectra obtained indicate that the position of absorption band with maximum wavelength λ at 210 nm at pH 7.7 and in 0.1 M ionic strength ($NaNO_3$).

The complex formation of Zn^{2+} with captopril was examined at different pH values in $1.0x10^{-4}$M equimolar solutions. The λ_{max} of the binary system reflect the formation of a complex with λ_{max} = 314 nm at pH 7.7. In media of pH >7.7 the band is shifted to longer wavelengths, a beahviour which refers to probable formation of another type of complex species which may be bonded to the S atom at λ= 363 nm. The absorbance of the band increases with rise of pH attaining a maximum value (pH 8.0), then reduces. The absorption spectra of the eqimolar system were recorded in the pH range 6.0-10.6 using a blank containing the same concentration of cap.

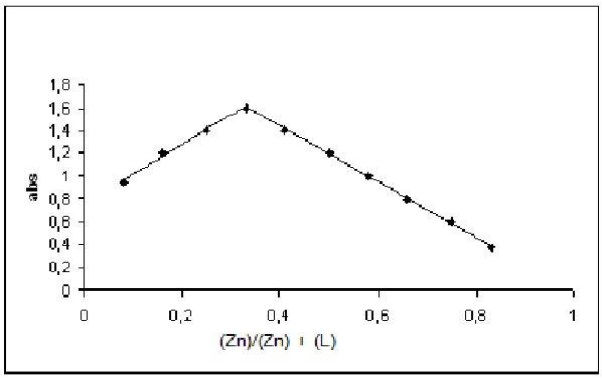


Fig 2 Job's plots of Zn + cap complex (λ_{max} =363 nm)

On comparison of the electronic absorption spectra of the free ligand cap with that of the chelated Zn(II), it makes the band spectra of the ligand shifted to longer wavelength and this is evidence for the formation of the coordination compound.

Stoichiometry of the complexes

The stoichiometric ratio of Zn^{2+}- cap complexes was determined by using the usual two spectrophotometric methods of namely Job's continuous variation method [23] (Figure 2) and The molar ratio method [24]. The two methods confirmed the formation of 1:2 (M:L) complex.

CONCLUSIONS

Inorganic compounds/drugs account for only small proportions of all those in modern. Analytical data and stoichiometry analysis suggest ligand to metal ratio of 2:1 for all the complex. The results of our formation constant studies indicated that coordination of Zn^{2+} by captopril is strong and regarding optimum formation of the complex as a function of pH indicated that the range for optimum chelation was pH 5 – 9 in the pH range of human body.

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