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Research Article

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Determination of Stability Constants of Ibandronate Complexes with Ca(II), Mg(II) and Sr(II)

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ABSTRACT

In this study, a potentiometric titration method by Calvin-Bjerrum and Irwing-Rosotti was used to investigate binary complexes of ibandronate sodium, a nitrogen-containing bisphosphonate, with Ca(II), Mg(II) and Sr(II). Dissociation constants (pKa) of ibandronate sodium were measured and the stability constants of the complexes formed in aqueous solutions at 22 ºC (I = 0.11 M $NaClO_4$) were determined. The stoichiometry of ibandronate sodium/metal complexes was found as 1/1 for each metal ion.

Key words: *Ibandronate Metal Complexes, Bisphosphonates, pKa of Ibandronate, Potentiometric Titration.*

INTRODUCTION

Ibandronate, chemically designated as [1-hydroxy-3-(methylpentylamino) propylidene] bisphosphonic acid monosodium salt monohydrate, is a nitrogen-containing bisphosphonate effective for the treatment of hypercalcemia of malignancy, postmenopausal osteoporosis, Paget's disease of bone and bone metastases (Figure 1). The bisphosphonates comprehend an entire family of compounds characterized by a P-C-P backbone structure. The first publication on the clinical use of the bisphosphonates appeared in 1969. The synthesis and biological evaluation of considerable number of nitrogen containing bisphosphonates emerged in the 1980s (including risedronate, alendronate, ibandronate and zoledronate) [1, 2]. Bisphosphonates bind strongly to hydroxyapatite crystals and their main effect is to inhibit the dissolution of hydroxyapatite crystals and bone resorption. Their binding to calcium cations within hydroxyapatite is an essential physicochemical event that occurs on the bone surface [3]. Moreover the binding affinities of bisphosphonates can effect their distribution, diffusion and release in bones [4]. A thorough literature survey revealed that many coordination studies have been carried out to determine metal chelating abilities of clinically used bisphosphonates [5].

Jing Ke et al. reported determination of pKa values of alendronate sodium in aqueous solution by potentiometric titration [6]. Interaction between calcium and zoledronate and complex formation was determined by isothermal titration calorimetry [7]. Thermodynamic dissociation constants of alendronate and ibandronate was determined by the regression analysis of potentiometric titration data [8]. Demoro et al. investigated in-solution behaviour of systems containing ibandronate and 3d metal ions (Co^{2+}, Mn^{2+} and Ni^{2+}) and antiparasitic activity of the obtained complexes [9]. Studies about synthesizing new bisphosphonate molecules with a variety of substituents at carbon's atom are still in the subject of the research. Galezowska et al. determined the protonation constants and stability constants of newly synthesized aminobisphosphanetes and their calcium complexes by potentiometry and investigated interaction of these complexes with bovine serum albumine by isothermal calorimetric method [10].

Since ibandronate is soluble in water and due to its chemical structure lack of absorbing chromophores, using potentiometric titration method is highly available to investigate the complexation behaviour. Potentiometric

titration is a fast and sensitive method to investigate metal-ligand complexes with reliable results [11-13]. To the best of our knowledge, coordination studies of ibandronate with calcium(II), magnesium(II) and strontium(II) does not exist in literature. Therefore, in this study, the stability constants of the calcium(II), magnesium(II) and strontium(II) complexes of ibandronate were determined potentiometrically by using Calvin-Bjerrum and Irwing-Rossotti methods [14, 15]. Dissociation constants of ibandronate were also calculated and compared with the published results.

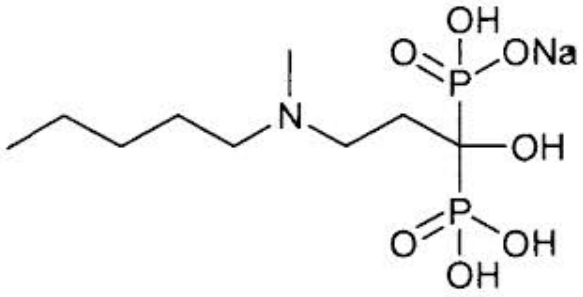

Figure 1. The chemical structure of ibandronate sodium

MATERIALS AND METHODS

Standart Solutions

0.01 M Ibandronate sodium (dissolved in water), 0.1000 M NaOH, 0.0500M $HClO_4$, 0.11 M $NaClO_4$, 0.01 M $Ca(NO_3)_2$, 0.01 M $Mg(NO_3)_2$, 0.01 M $Sr(NO_3)_2$ solutions were prepared.

Titration Solutions:

a) **$HCLO_4$:** 10 mL 0.0500M $HClO_4$ + 5 mL 0.11 M $NaClO_4$ were added and diluted to 50 mL by water.

b) **Ibandronate sodium :** 10 mL 0.0500 M $HClO_4$ + 10 mL 0.0100 M Ibandronate sodium + 5 mL 0.11 M $NaClO_4$ were added and diluted to 50 mL by water (for the determination of the protonation constants of ibandronate).

c) **$HCLO_4$ + Ibandronate sodium + Ca(II) :** 10 mL 0.0500 M $HClO_4$ + 10 mL 0.0100 M Ibandronate sodium + 5 mL 0.11 M $NaClO_4$ + 10 mL 0.0100 M Ca(II) were added and diluted to 50 mL by water (for the determination of the stability constant of ibandronate-Ca(II) complex).

d) **$HCLO_4$ + Ibandronate sodium + Mg(II) :** 10 mL 0.0500M $HClO_4$ + 10 mL 0.0100M Ibandronate sodium + 5 mL 0.11 M $NaClO_4$ + 10 mL 0.0100 M Mg(II) were added and diluted to 50 mL by water (for the determination of the stability constant of ibandronate-Mg(II) complex).

e) **$HCLO_4$ + Ibandronate sodium + Sr(II) :** 10 mL 0.0500M $HClO_4$ + 10 mL 0.0100M Ibandronate sodium + 5 mL 0.11 M $NaClO_4$ + 10 mL 0.0100 M Sr(II) were added and diluted to 50 mL by water (for the determination of the stability constant of ibandronate-Sr(II) complex).

These solutions were titrated with 0.1000 M NaOH for three times at 22 ^oC (Figure 2).

Potentiometric Method: The protonation constants of ibandronate sodium and the stability constants of Ca(II), Mg(II), and Sr(II) complexes of ibandronate sodium were determined potentiometrically using the Calvin-Bjerrum method, and calculations were performed in Microsoft Excel based on the Irving-Rossotti equations.

PH measurements of titrations were carried out using a Radiometer TitraLab 80 automatic titrator equipped with a Radiometer PHC3001-8 combination pH electrode. The electrode was calibrated regularly using standard pH=4 and pH=7 buffer solutions. The titrations were performed in aqueous system at constant ionic strength (0.11 M $NaClO_4$ solution), thermostated at 22 ^oC (±0.1) and a total volume of 50 mL was used for each titration. Titration solutions a, b, c, d and e were prepared and titrated potentiometrically against standard 0.1000 M NaOH solution.

To determine the protonation constants, the solutions of a and b were titrated potentiometrically using 0.1000 M NaOH. Potentiometric titration red and green curves (Figure 2A, 2B, and 2C) of each system were used to calculate the average values $\bar{n}_A$. The equation used for the calculation is:

$$\bar{n}_A = y + [(V_1 - V_2)(N + E^o)] / [(V^o + V1)\, T^o_L]$$

Where V^o is the initial volume (50.0 mL); N is the normality of NaOH (0.1000 M); T^o_L is the ligand concentration (0.0020 M); E^o is the initial concentration of $HClO_4$ (0.0100 M); and y is the total number of dissociable protons on the ligand (y=3); (V_1 - V_2) is the displacement measure of the ligand curve relative to the $HClO_4$ curve where V_1 and V_2 are the NaOH volumes added to reach the same pH reading in both titrations.

The protonation constants were determined from the graph of $\bar{n}_A$ vs pH (Figure 3), the pH values at $\bar{n}_A$ = 0.5, $\bar{n}_A$ = 1.5, designate the $logK_1$ and $logK_2$, respectively (values are shown in Table 1).

To determine the stability constants of the complexes, the solutions of c, d and e were titrated potentiometrically using 0.1000 M NaOH (blue curve in Figure 2A, 2B and 2C). $\bar{n}_L$ values were calculated using the $\bar{n}_A$ values and the equation given below:

$$\bar{n}_L = [(V_3-V_2)(N+E^o+T^o_L(y-\bar{n}_A)] / (V^o+V_2).$$

Where V^o is the initial volume (50.0 mL); N is the normality of NaOH (0.1000 M); T^o_L is the ligand concentration (0.0020 M); E^o is the initial concentration of the $HClO_4$ (0.0100 M); T^o_M is the metal ion concentration (0.0020 M); y is the total number of dissociable protons on the ligand (y=3); (V_3 - V_2) is the displacement measure of the metal curve relative to the ligand curve where V_2 and V_3 are the NaOH volumes added to reach the same pH reading in both titrations. The pL values were calculated using the $\bar{n}_L$ values and the equation given below:

$$pL = \log(1+\beta_1[H^+] + \beta_2[H^+]^2 + / (T^o_L - \bar{n}_L T^o_M)$$

$$\beta_1 = K_1 = 1{,}41.10^{10}$$

$$\beta_2 = K_1.K_2 = 1.41.10^{11} . 7.94.10^5 = 1.12.10^{16}$$

RESULTS AND DISCUSSION

According to the titration curves obtained from the titration data, deviation between $HClO_4$ curve (red curve in Figure 2A, 2B and 2C) and $HClO_4$+Ibandronate sodium curve (green curve in Figure 2A, 2B and 2C) indicates the protonation of ibandronate sodium. The protonation constants were determined from the graph of $\bar{n}_A$ vs pH (Figure 3), the pH values at $\bar{n}_A$ = 0.5, $\bar{n}_A$ = 1.5, designate the $logK_1$ and $logK_2$, respectively:

For $\bar{n}_A$ = 0,5 $logK_1$ = 10.15; $K_1 = 1.41.10^{10}$

For $\bar{n}_A$ = 1,5 $logK_2$ = 5.90; $K_2 = 7.94.10^5$

$logK_1 = pKa_2 = 10.15$

$logK_2 = pKa_1 = 5.90$

The first dissociation constant (pKa_1) for ibandronate sodium was determined as 5.90, and the second one (pKa_2) as 10.15. These values are close to the reported values in a previous study at 5.949 and 10.106, respectively (I = 0.134 mol.L^{-1} KCl, 298.15 K) [8]. Ibandronate sodium has 3 dissociable protons, $logK_3$ constant was determined below 2 that is the result of strong acidity of PO_3H_2 group [16]. This value is out of potentiometric method and was excluded. Under the experimental conditions used in our study, only two deprotanation processes were detected.

Deviation between $HClO_4$+Ibandronate sodium curve (green curve in Figure 2A, 2B and 2C) and $HClO_4$+Ibandronate sodium+metal ion curve (blue curve in Figure 2A, 2B and 2C) indicates the formation of complexation. Figures 4A, 4B and 4C show the formation curves for Ca(II), Mg(II) and Sr(II) complexes of ibandronate sodium, respectively. The stability constants of metal complexes were determined from the $\bar{n}_L$ vs pL curve, where the pL values at $\bar{n}_L$ = 0.5 designate the log K1. The stoichiometry of ibandronate sodium/metal complexes are given as 1/1 for each metal ion and their stability constant values were reported in Table 1.

Table 1. Dissociation constants of ibandranate sodium and stability constants of the Ca(II), Mg(II) and Sr(II) complexes (I = 0.11 mol.L^{-1} $NaClO_4$, 22 °C).

Equilibrium Constants				
Dissociation Constants of Ibandronate		Stability Constants (log$K$) of Metal-Ibandronate sodium Systems		
pK_1	pK_2	Ca – IBA	Mg – IBA	Sr – IBA
5.90	10.15	5.61	5.55	4.90
5.95	10.11	5.57	5.83	4.94
5.94	10.05	5.46	5.67	4.68
The pK_a values are accurate to ±0.06 pK_a units (2α = 0.1) and log$K$ values ±0.19 (2α = 0. 1)				

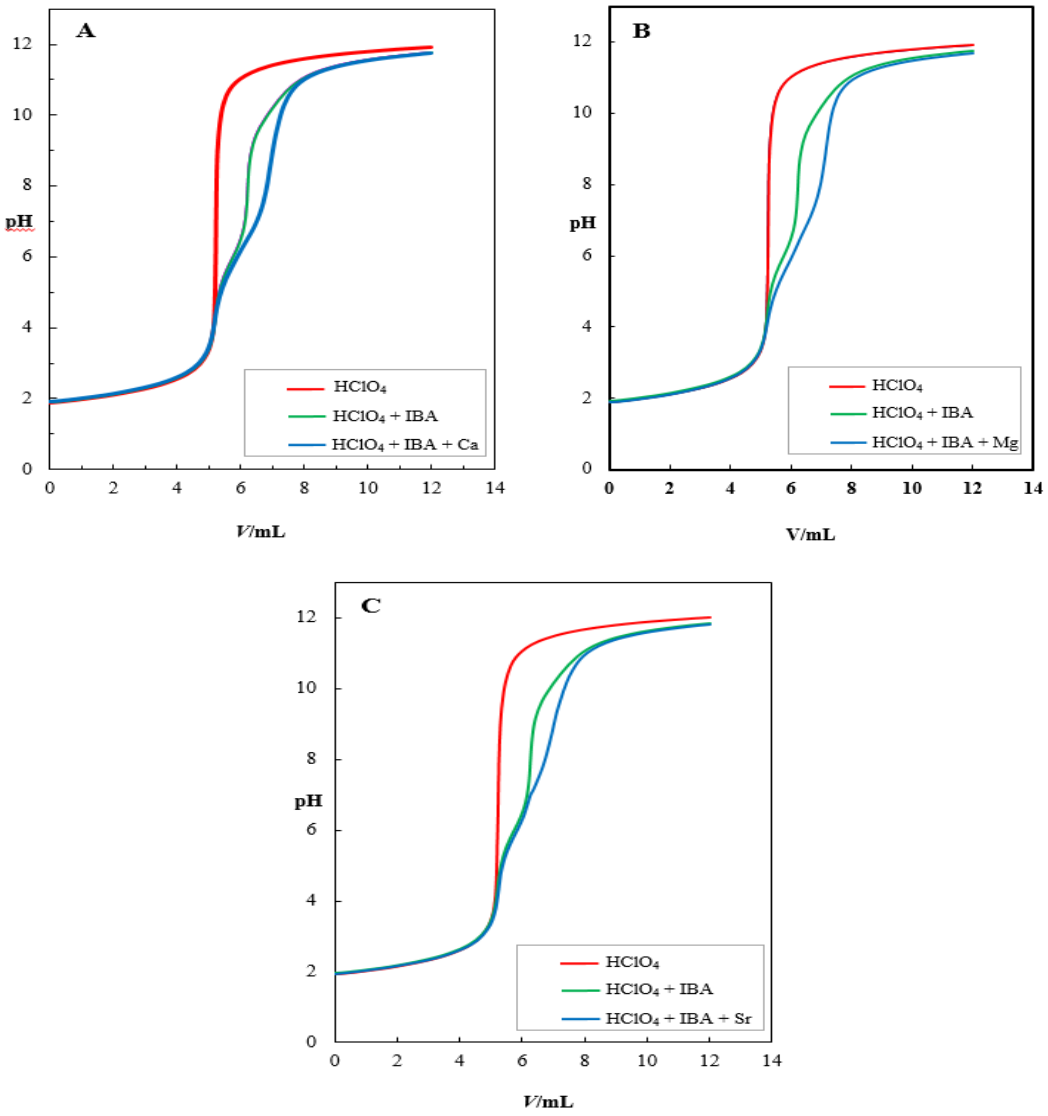

Figure 2. Potentiometric titration curves for the ibandronate sodium-metal ion system

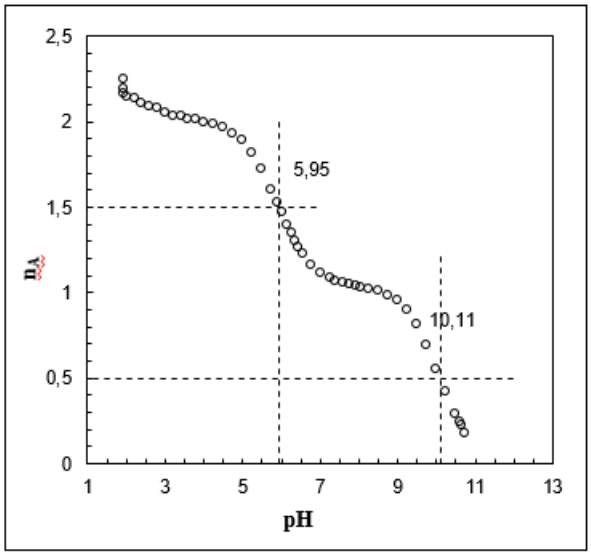

Figure 3. $\overline{n}_A$ vs pH plots of ibandronate sodium. logK$_1$ (protonation) = 10.11 for $\overline{n}_A$ = 0.5, logK$_2$(protonation) =5.95 for $\overline{n}_A$ = 1.5

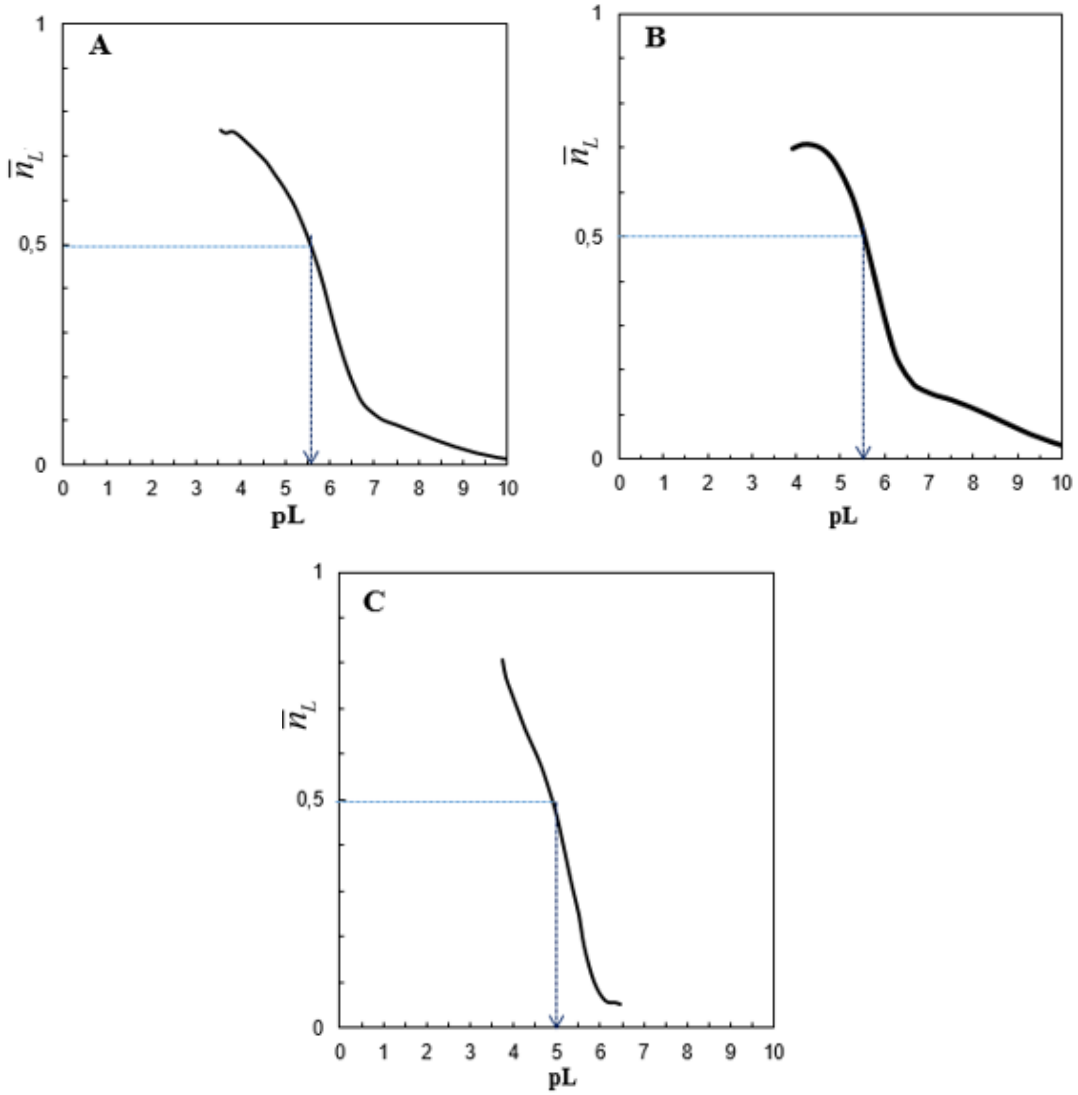

Figure 4. Representative ibandronate sodium-metal ion formation curves. A: Ca(II), B: Mg(II), C: Sr(II)

CONCLUSION

This study describes the complexation behaviour of ibandronate sodium towards Ca(II), Mg(II) and Sr(II). Dissociation constants of ibandronate sodium and stability constants of Ca(II), Mg(II) and Sr(II) complexes were determined in aquous solution by pH-metric titration. The potentiometric results indicated that ibandronte sodium forms stable complexes with the stoichiometri 1/1. After the comparison of the stability constant (log*K*) values that are close to each other, it can concluded that ibandronate has similar tendency to form complexes with these metal ions. To the best of our knowledge, this is the first attempt to caluculate stability constants of ibandronate with Ca(II), Mg(II) and Sr(II) complexes. These findings would be helpful for studies related to understanding pharmaceutical action of bisphosphonates.

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