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To cite this version:
A.L.R Mercê, B Szpoganicz, M A Khan, X Do Than, G Bouet. Potentiometric study of vitamin D3 complexes with manganese(II), iron(II), iron(III) and zinc(II) in water-ethanol medium. Journal of Inorganic Biochemistry, 1999, 73 (3), pp.167-172. 10.1016/s0162-0134(99)00014-8 . hal-03199232

HAL Id: hal-03199232
https://univ-angers.hal.science/hal-03199232
Submitted on 16 Apr 2021

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Potentiometric study of vitamin D₃ complexes with manganese(II), iron(II), iron(III) and zinc(II) in water–ethanol medium

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Received 20 October 1998; received in revised form 14 January 1999; accepted 15 January 1999

Abstract
Vitamin D₃ (LH) complexes with manganese(II), iron(II), iron(III) and zinc(II) were identified in water–ethanol medium (30/70). Their stability constants were determined at 298 K and at a constant ionic strength of 0.100 M using potentiometric methods. The computerisation of the experimental data showed the presence of ML (M = metal, L = deprotonated vitamin D₃) and ML₂ species in all cases; in addition, the ML₃ iron(III) complex was detected. The calculated overall stability constants \( \beta \) for Mn²⁺L, Fe²⁺L, Fe³⁺L and Zn²⁺L are, respectively, in logarithms, 12.4, 16.5, 28.5 and 16.5. Under the experimental conditions, the only protonated species MLH detected was with iron(III).

Keywords: Potentiometry; Vitamin D₃ metallic complexes; Water–ethanol

1. Introduction

Many metallic cations are involved in human metabolism as well as in oligotherapy. For instance, transition metal ions such as manganese(II), iron(II), cobalt(II) or zinc(II) give higher enzymatic activity levels compared to magnesium(II) for some native and mutant enzymes with Mg²⁺ as natural cofactor [1]. Zinc(II), cadmium(II), cobalt(II) and magnesium(II) could readily bind to apoalkaline phosphatase of Escherichia coli at various sites, leading to different effects upon the activity of the enzyme [2].

In a previous article [3], we determined the stability constants of vitamin D₃ (vitD) or cholecalciferol complexes involving cobalt(II), nickel(II) and copper(II) in water–ethanol medium.

In the present paper, we describe the results of the complexation of vitD with manganese(II), iron(II), iron(III) and zinc(II) in water–ethanol medium at 298 K and at a constant ionic strength (0.100 M). Usually, both potentiometric and spectrophotometric techniques could be used for computerised determinations. In the case of vitD, its instability in aqueous solution and to light exposure did not allow us to perform spectrophotometric measurements. The complexes were identified potentiometrically and their respective formation constants were calculated.

2. Experimental

2.1. Reagents

All chemicals were of analytical grade and were used without further purification. All solutions were made with a mixture of bidistilled, deionised and carbon dioxide-free water (30%, vol./vol.) and ethanol (70%) from Merck (Brazil). VitD (cholecalciferol) was purchased from Sigma-Aldrich (France). Solutions were freshly prepared prior to their use.

The solutions of zinc(II) were obtained from nitrate (Carlo-erba, Brazil) salt and quantified by complexometric titration [4]. Those of manganese(II) chloride were made by appropriate dilutions of Titrisol™ (Merck). Anhydrous FeCl₃ (Merck) and Fe(CIO₄)₂·2H₂O (GFS Chemicals, USA) were manipulated under inert atmosphere and were weighted in the solid state. The carbonate-free KOH solutions (0.100 M) were standardised against potassium hydrogeno-
The titration of the overall formation constants of the systems. All titrations were carried out in the presence of HNO$_3$ (Merck) in 30% H$_2$O–70% ethanol (vol./vol.) solutions of about 0.8 M, determined by Gran’s plot. This ensured that the titrations would start from p[H] values under 3.0. The titration of this strong additional acid is represented by points plotted in the negative range of the x axis in Fig. 1.

2.3. Data treatment

All equilibrium constants were calculated using the microcomputer program Best 7. All mathematical details have been previously described [3,5–8].

Mole and millimole units were used to express the quantities of reagents, and the hydrolysis constants in the present solvent for all the metal ions studied were obtained from the literature [9] and were fully employed in all calculations. The species distribution curves were drawn with the microcomputer program SPE [5–8]. In general, three titrations were made: one with the ligand alone and two others with ligand and metals in various metal-to-ligand ratios. These ratios were chosen in such a way as to favour the formation of 1:1 and 1:2 complex species (ML and ML$_2$ respectively) where M is the metal ion and L the deprotonated vitD. The solution of vitD and Fe$^{3+}$ in a 1:3 ratio at 1 × 10$^{-3}$ M could not be made because of the low solubility of this system at low p[H] values. All reported results are the average of three potentiometric titration experiments.

3. Results and discussion

The average overall apparent formation constants $\beta_n$ were obtained as follows from the stepwise equilibrium:

$$ M + L \rightleftharpoons ML \quad \text{with:} \quad \beta_1 = \frac{[ML]}{[M][L]} \quad (1) $$

$$ ML + H \rightleftharpoons MLH \quad \text{with:} \quad \beta_2 = \frac{[MLH]}{[ML][H]} \quad (2) $$

$$ ML + L \rightleftharpoons ML_2 \quad \text{with:} \quad \beta_3 = \frac{[ML_2]}{[M][L]} \quad (3) $$

$$ ML_2 + L \rightleftharpoons ML_3 \quad \text{with:} \quad \beta_4 = \frac{[ML_3]}{[M][L]^2} \quad (4) $$

where M is the metal ion and L the deprotonated vitD, VitD(O$^-$). In this solvent, the value of the protonation constant for the hydroxyl group in vitD is log $K$ = 12.4 [10]:

$$ \text{VitD(O$^-$) + H}^+ \rightleftharpoons \text{VitD} \quad (5) $$

or

$$ L + H \rightleftharpoons HL $$

Fig. 1 depicts the potentiometric p[H] profiles for each titration of vitD (13 points) with Mn$^{2+}$ (12 and 15 points),...
Fe\(^{2+}\) (11 and 14 points), Fe\(^{3+}\) (50 and 57 points) and Zn\(^{2+}\) (23 and 29 points) respectively. They show that in all cases, irrespective of metal-to-ligand ratio and cation, these systems undergo rapid hydrolysis and solvolysis, preventing, in some cases, the determination of the formation constants of the complex species. Higher ratios of ligand-to-metal titrations did not prevent this immediate hydrolysis and solvolysis.

Fig. 1 shows that there is a strong depletion in the values of p[H] when the ligand is in the presence of metal ions. The titration curves for Mn\(^{2+}\) complexes show an inflexion point at α = 3.0 (3.0 base equivalent) and at 0.85, 3.4 and 1.4 respectively for Fe(II), Fe(III) and Zn(II).

Table 1 summarises the logarithms of the stability constants for all the complex species detected by potentiometric titrations calculated on the basis of the equilibria (1) to (5), taking care to avoid the formation of hydroxo and/or solvo complexes. The formation constants of 1:1, 1:2 and 1:3 metal-to-ligand ratio complexes were evaluated from the p[H] profiles for solutions containing 1:1 and 1:2 molar stoichiometry of cation to ligand. The species under investigation were those

| Table 1 |
| Logarithmic values * for the formation constants of the complexes of vitD with Mn\(^{2+}\), Fe\(^{2+}\), Fe\(^{3+}\) and Zn\(^{2+}\) ions at 298 K (β = overall stability constant; K = stepwise stability constant) |

<table>
<thead>
<tr>
<th></th>
<th>Manganese(II)</th>
<th>Iron(II)</th>
<th>Iron(III)</th>
<th>Zinc(II)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log K(_1) = log β(_1)</td>
<td>6.6 ± 0.1</td>
<td>8.5 ± 0.1</td>
<td>15.5 ± 0.1</td>
<td>8.8 ± 0.3</td>
</tr>
<tr>
<td>Log K(_2)</td>
<td>n.d.</td>
<td>n.d.</td>
<td>3.0 ± 0.1</td>
<td>n.d.</td>
</tr>
<tr>
<td>Log K(_3)</td>
<td>5.8 ± 0.1</td>
<td>8.0 ± 0.1</td>
<td>13.0 ± 0.1</td>
<td>7.7 ± 0.3</td>
</tr>
<tr>
<td>Log K(_4)</td>
<td>(12.4)</td>
<td>(16.5)</td>
<td>(28.5)</td>
<td>(16.5)</td>
</tr>
<tr>
<td>Log K(_5)</td>
<td>n.d.</td>
<td>n.d.</td>
<td>6.2 ± 0.1</td>
<td>n.d.</td>
</tr>
<tr>
<td>Log β(_1)</td>
<td>(34.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*n.d. = not detected.
expected according to common principles of coordination chemistry.

ML₃ species were only detected in the presence of the strong Lewis acid Fe³⁺, which is able to deprotonate and hold a third molecule of vitD. Although there was formation of insoluble products at pH values of about 6.0, there was not enough concentration of ML₃ species to be detected by potentiometric titration.

Figs. 2-5 depict the distribution diagrams for the formation constants obtained from saturated solutions with vitD and Mn²⁺, Fe²⁺, Fe³⁺ and Zn²⁺ respectively, with the metal ion concentration set at 100% and calculated from pH = 2 to 12. These diagrams show the maximum formation of the complex species ML between vitD and the metallic ion for a pH value of 9.0 (Mn²⁺), 7.0 (Fe²⁺), 3.0 (Fe³⁺) and 7.0 (Zn²⁺). The maximum formation of ML₂ complexes occurred at pH = 12.0 for Mn²⁺, 10.0 for Fe²⁺, 6.0 for Fe³⁺ and 11.3 for Zn²⁺. Finally, the maximum formation of the complex ML₃ with Fe³⁺ is located at pH = 10.

The metal ions Fe²⁺ and Fe³⁺ show some complex species throughout the range of pH under study, despite the formation of metal hydroxide precipitates at pH values below

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**Fig. 2.** Species distributions of solutions of vitD (L) (2.5 × 10⁻³ M) and Mn²⁺ (M) (2.50 × 10⁻³ M) for pH values from 2.0 to 12.0. The metal concentration is set at 100%. H⁻ indicates [OH⁻].

**Fig. 3.** Species distributions of saturated solutions of vitD (2.5 × 10⁻³ M) and Fe²⁺ (2.50 × 10⁻³ M) for pH values from 2.0 to 12.0.
or near neutral values. The metal ions Mn$^{2+}$ and Zn$^{2+}$ form stable complexes above pH values of 7.0 and 5.0, respectively.

Fe$^{3+}$ ions led to the highest stability constants in this series (Table 1). This indicates that there is no steric hindrance in this species for which the maximum formation is centred around pH = 10.2.

Fig. 6 shows the relation between the first stability constant $K_1$ relative to equilibrium (1) and the atomic number of the metal used in this study and in our previous paper [3]. It may be remarked here that the tendency of the curve shows that copper(II) leads to the highest stability of the complex. This follows the well-known Irving-Williams series [11] with the exception of the complex with Fe$^{3+}$. The progression of this series in alcoholic medium has been recently verified for the metal ions under consideration [12] and has been explained on the basis of the second ionisation potential of the ions. It has been shown to be valid equally in the case of dog, bovine and human serum albumin complexing copper(II) and zinc(II) [13,14]. Though our experiments were performed under inert atmosphere to prevent ferrous ions from oxidation, the high value of $K_1$ in the case of Fe$^{2+}$ could be explained on the basis of an equilibrium between Fe(II) and Fe(III) ions.
Acknowledgements

The authors thank the sponsor Universidade Federal do Paraná, UFPR, Brazil.

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