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Potentiometric study of vitamin D₃ complexes with cobalt (II), nickel (II) and copper (II) in water–ethanol medium

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Abstract

Vitamin D₃ complexes with cobalt (II), nickel (II) and copper (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 mol L⁻¹ 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 except for CuL₂. The calculated overall stability constants β , for CoL, NiL and CuL are, respectively, in logarithms, 7.6, 7.8 and 9.3, in harmony with the Irving–Williams order of stability. Under the experimental conditions, the only protonated species MLH detected was with copper. © 1998 Elsevier Science Inc. All rights reserved.

1. Introduction

As many metallic cations are involved in human metabolism, we have undertaken a study of metallic complexes obtained with vitamin D₃ (vitD) and its hydroxylated derivatives: 25-hydroxy vitD, 1 α ,25-dihydroxyvitD or 24R,25-dihydroxyvitD.

VitD, shown in Fig. 1, is able to complex calcium (II), cadmium (II) [1] or cobalt (II) [2]. With cobalt, the complexes with the metabolites of vitD were identified spectrophotometrically and we reported the approximate stability constant in aqueous solution. Thus with 25-hydroxycholecalciferol and with 1 α ,25-dihydroxycholecalciferol the stability constants with cobalt (II) are $\log \beta = 4.7$ and $\log \beta = 6.1$, respectively [2]. In another previous study we demonstrated that the complex [CoCl₂(1,25-(OH)₂vitD)₄] differed from vitD and cobalt(II) chloride in its physiological properties [3]; for instance, the cerebral gamma glutamyl transpeptidase activity in intact rats is increased by 27% with cobalt(II), 39% with 1 α ,25-dihydroxy-cholecalciferol and 70% with the complex [CoCl₂(1,25-(OH)₂vitD)₄] during summer. It is well known that vitD and its derivatives are sensitive to dioxygen and light. So, if the stability of its me-

tallic complexes are high, we might expect the stability of vitD to be enhanced. We may remark here that the study of metal complexes of vitD and its metabolites may help in the increase of activity of γ -glutamyltranspeptidase. The deficiency of this enzyme has been identified in certain mentally retarded patients [4].

In this paper, we present the results of complexation of vitD with cobalt (II), nickel (II) and copper (II) in water–ethanol medium at 298 K and at a constant ionic strength (0.1 mol L⁻¹). 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 and instrumentation

All chemicals were of analytical grade and were used without further purification. All solutions were made with a mixture of bidistilled, deionized and carbon dioxide free water (30%,v/v) and ethanol (70%) from

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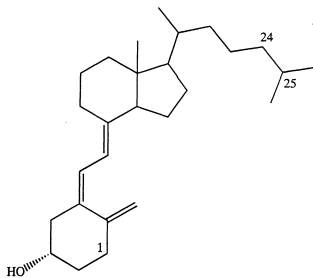


Fig. 1. Structure of vitamin D₃ (cholecalciferol).

Merck (Brazil). VitD (cholecalciferol) was purchased from Sigma-Aldrich, France. Its solutions were freshly prepared prior to their use.

The solutions of the metals were obtained from nitrate salts (Carlo-Erba, Brazil) and their concentrations were determined by complexometric titration [5]. The carbonate free KOH solution (0.1 mol L⁻¹) was standardised against potassium hydrogenophthalate and the supporting electrolyte was KNO₃ (Baker and Adamson, USA).

The ligand solution was transferred to the reaction vessel and was titrated with the KOH solution, first in the absence of metal ion and then in its presence.

2.2. Method

The potentiometric titrations were carried out under inert atmosphere using 0.1 mol L⁻¹ KOH water–ethanol solutions with continuous nitrogen flow. The temperature was set with the help of a water jacket at 25.0 ± 0.1°C (Microquímica MQBTC 99-20) and the ionic strength was maintained at 100 mmol L⁻¹, using potassium nitrate solutions. The titrant (standard KOH–CO₂ free) was added to the solution of vitamin D₃ (0.1 mmol) in the presence of either 0.05 mmol or 0.1 mmol of the metal ions.

The pK_w, was determined to be 14.71 at 25 ± 0.1°C (298 K) in the present medium and the p[H] (–log₁₀ [H⁺]) values were measured using a Micronal pHmeter, B-375 model (SP, Brazil), fitted with a glass electrode and a calomel reference electrode calibrated with standard adjusted ionic strength HCl and KOH water–ethanol solutions. All other experimental details have been described in our previous publications [6,7].

VitD was kept under inert atmosphere in a Schlenke glass and was always transferred to the reaction vessel using another Schlenke glass stopped with Suba-Seal (Sigma, USA) and weighed, dissolved in ethanol p.a. and then transferred with the help of a syringe to the titration vessel, previously prepared with all other reactants and under inert atmosphere.

The titration of the hydroxyl group was carried out after stabilisation of the first p[H] value of the system with constant increments of 0.10 or 0.02 mL. All titrations were made in the presence of HNO₃ (Merck, Brazil) in 30% v/v H₂O and ethanol (70%) solutions. To ensure that all titrations would start from p[H] values

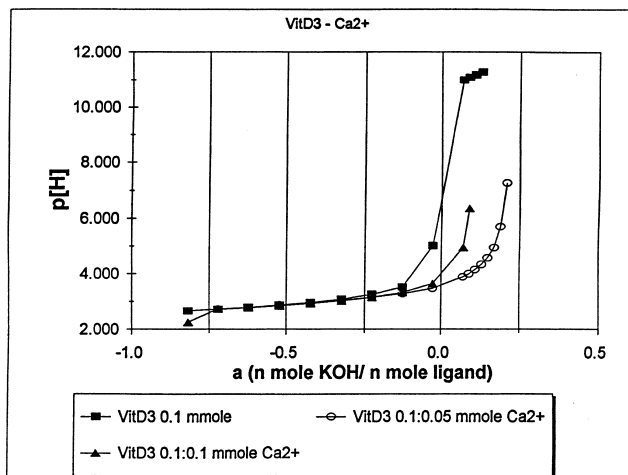


Fig. 2. Potentiometric (p[H]) profile of 0.1 mmol of vitD and 0.1 and 0.05 mmol of calcium (II).

under 3.0, the concentration of the acid, determined by Gran's plot, was about 0.1 mol L⁻¹. The titration of this strong acid is represented by points plotted in the negative range of the x-axis in Figs. 2–5.

2.3. Data treatment

All equilibrium constants were calculated using the “Best 7” microcomputer program [8,9]. The basic algorithm of this program is stated in Eq. (1):

$$T_i = \sum_{j=1}^{NS} e_j \beta_j \prod_{K=1}^i [C_k]^{e_{ij}}, \quad (1)$$

where T_i is a statement of the mass balance of the i th component of the j th species summed over all present species NS . Each species concentration consists in a product of the overall stability constant and individual concentration $[C_k]$ raised to the power of the

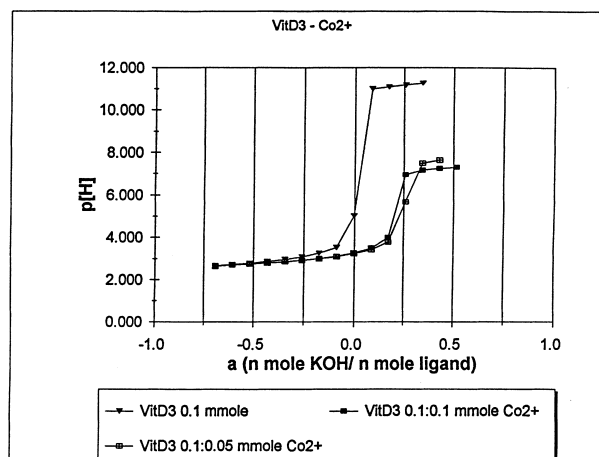


Fig. 3. Potentiometric (p[H]) profile of 0.1 mmol of vitD and 0.1 and 0.05 mmol of cobalt (II).

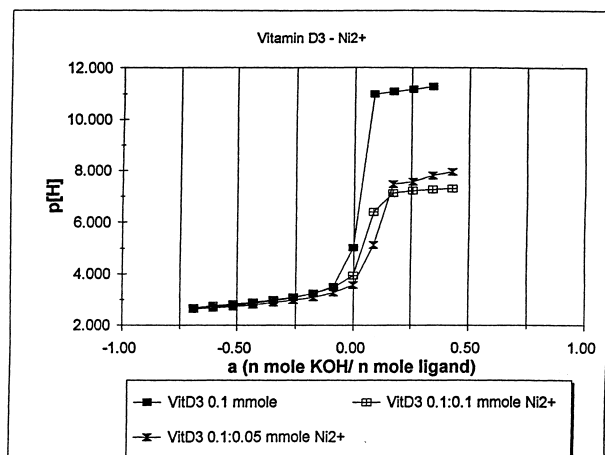


Fig. 4. Potentiometric (p[H]) profile of 0.1 mmol of vitD and 0.1 and 0.05 mmol of nickel (II).

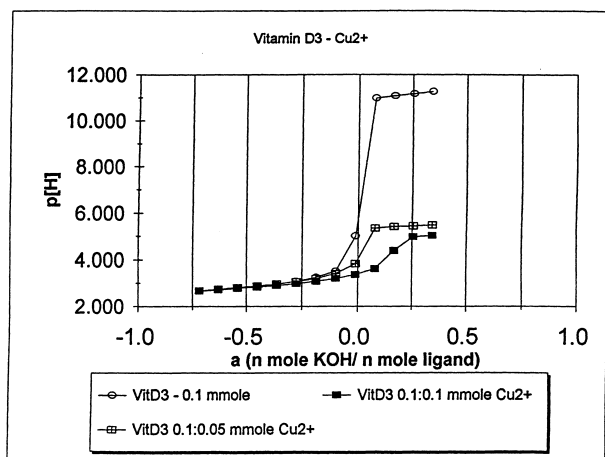


Fig. 5. Potentiometric (p[H]) profile of 0.1 mmol of vitD and 0.1 and 0.05 mmol of copper (II).

stoichiometric coefficient e_{ij} . The set of simultaneous equations obtained is solved for each component $[C_k]$. The value of $[C_k]$ is particular when its represents the calculated concentration of H^+ , which is then compared with the measured hydrogen ion concentration. The standard deviation σ_{fit} in p[H] units [8,9] is obtained according to Eq. (2):

$$\sigma_{fit} = \sqrt{\frac{U}{N}}, \quad (2)$$

where $N = \sum w$ and

$$U = \sum w(pH_{obs} - pH_{calcd})^2, \quad (3)$$

$$w = \frac{1}{(pH_{i+1} - pH_{i-1})^2}. \quad (4)$$

The use of the algorithm for computing equilibrium constants in “Best” program involves the following sequence: (i) start with a set of known or estimated overall

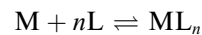
stability constants (β) and compute $[H^+]$ at all equilibrium points; (ii) compute the weighted sum of the squares of the deviations in p[H] as in Eq. (3); (iii) adjust the unknown stability constants and repeat the calculations until no further minimisation of U can be obtained, thus providing the final calculated β values.

The 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 literature [10] and were fully employed in all calculations.

The species distribution curves were drawn with the microcomputer program SPE [8,9]. In general, three titrations were made: one with the ligand alone and two others with ligand and metals in various metal to ligand ratios. They were chosen in order 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 OH deprotonated vitD. All reported results are the average of three potentiometric titration experiments.

3. Results and discussion

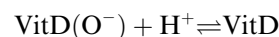
The average overall formation constants β_n were obtained as follows:



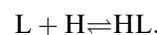
with

$$\beta_n = \frac{[ML_n]}{[M][L]^n}.$$

In this solvent, the protonation constant for the hydroxyl group in vitD is $\log K = 12.4$ [11]:



or



Figs. 2–5 depict the potentiometric p[H] profiles for each titration of vitD with Ca^{2+} , Co^{2+} , Ni^{2+} and Cu^{2+} , respectively. They show that in all cases, whatever the metal to ligand ratio and whatever the cation, these systems undergo rapid hydrolysis, 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.

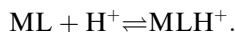
Table 1

Logarithmic values for the formations constants of the complexes of vitD with Co^{2+} , Ni^{2+} and Cu^{2+} ions at 298 K (β = overall stability constants; K = stepwise stability constants)

	Cobalt (II)	Nickel (II)	Copper (II)
$\log K_1 = \log \beta_1$	7.6 ± 0.1	7.8 ± 0.3	9.3 ± 0.3
$\log K_H$	n.d.	n.d.	5.5 ± 0.3
$\log K_2$	6.5 ± 0.1	6.0 ± 0.3	
$(\log \beta_2)$	(14.1)	(13.8)	n.d.

n.d.: not detected.

Table 1 summarises the logarithms of the stability constants for the observed species. It was not possible to calculate the stability constants for the complexes involving calcium because of their very low formation which prevented any reasonable evaluation using the program. The K_H stability constant is relative to the protonation equilibrium of the ML species:



The absence of ML_2 species with Cu(II) is partially due to the formation of insoluble compounds at about p[H] values of 5.0. The ML_2 complexes with cobalt and nickel have relatively high values, and this can be explained by a possible interaction between the hydrophobic moiety of both vitD molecules in the ML_2 complex as previously described in the literature [1].

Figs. 6–8 present the distribution diagrams for the formation constants obtained from saturated solutions of vitD and Co^{2+} , Ni^{2+} and Cu^{2+} , respectively, with the metal ion concentration set at 100%. These diagrams show the maximum formation of the protonated complex species MLH between vitD and the cupric ion for a p[H] value of 2.2. The other present species are ML at p[H] = 7.8 for Co^{2+} and at 8.0 and 8.6, respectively, for Ni^{2+} and Cu^{2+} . Finally, the maximum formations of ML_2 complexes occur at p[H] = 11.2 for Co^{2+} and p[H] = 11.3 for Ni^{2+} . This complex is absent in the case of cupric ion as has been already pointed out.

The K_1 constants follow the Irving–Williams' order of stability [12,13]: there is a slight increase when passing from cobalt (II) to nickel (II) followed by a steep rise in stability for the cupric ion. In a previous publication, we have explained that this order depends on the second ionisation potentials of the elements [13].

Although the maximum formation of the complex species occur for p[H] values higher than 7.4, there are a large quantity of complex compounds that are stable around physiological values of p[H]. This may open new horizons concerning the physiological aspects and medical applications of these complexes.

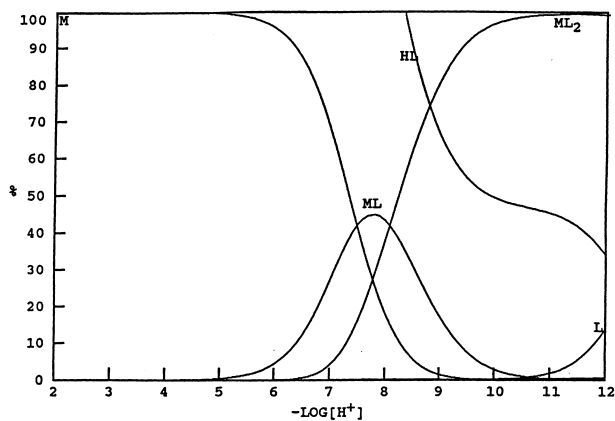


Fig. 6. Species distributions of saturated solutions of vitD and Co^{2+} (M) for p[H] values from 2.0 to 12.0 The metal concentration is set at 100%.

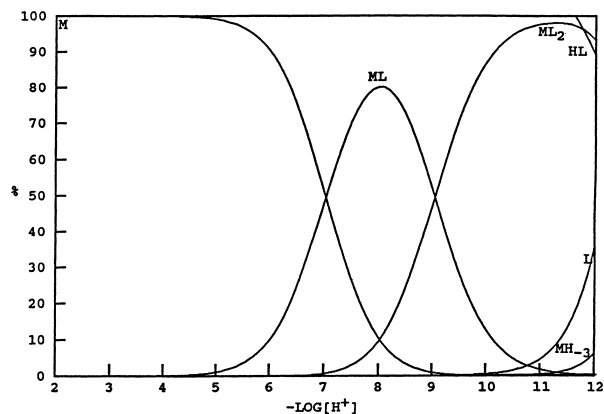


Fig. 7. Species distributions of saturated solutions of vitD and Ni^{2+} (M) for p[H] values from 2.0 to 12.0. The metal concentration is set at 100%. H_{-x} indicates $[OH^-]_x$.

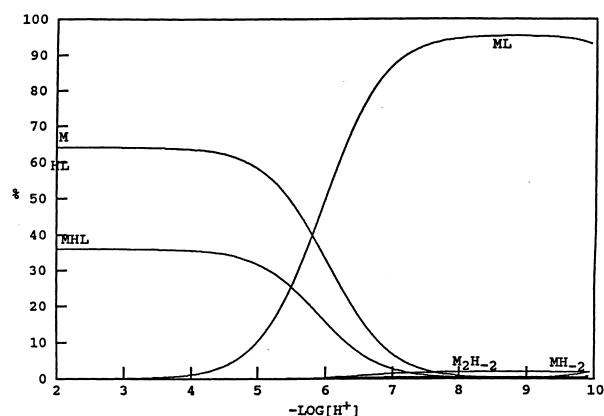


Fig. 8. Species distributions of saturated solutions of vitD and Cu^{2+} (M) for p[H] values from 2.0 to 10.0. The metal concentration is set at 100%. H_{-x} indicates $[OH^-]_x$.

Acknowledgements

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