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Communication

Spectroscopic evidence for cobalt(II) complexes with 25-hydroxycholecalciferol and 1 α ,25-dihydroxycholecalciferol in aqueous solution

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We report here the first spectrophotometric determination of metallic complexes obtained with 25-hydroxycholecalciferol (25-OHD₃) and 1 α ,25-dihydroxycholecalciferol [1,25-(OH)₂D₃] (Figure 1) and cobaltous chloride in aqueous NaCl solutions.

As far as we know, this system has not been studied hitherto. It is well known that vitamin D₃ (cholecalciferol) and vitamin B₁₂ are the two main vitamin factors in growth regulation⁽¹⁾. On the other hand, it has been

demonstrated that cholecalciferol is biologically inactive and that the mono- and dihydroxylated derivatives of this compound are the active metabolites⁽²⁾.

During the last few years, only two papers have reported complexes of ergocalciferol (vitamin D₂) and cholecalciferol. The first⁽³⁾ dealt with the synthesis of tricarbonyliron complexes with calciferol or ergocalciferol. The second⁽⁴⁾ described complexes of cholecalciferol and calcium(II) and cadmium(II) in EtOH/H₂O (70% v/v) solutions. In the latter, Qitao *et al.*, using a potentiometric-pH titration method at constant ionic strength (0.1 M), concluded that both the metals gave 1:1 and 1:2 complexes. The authors also calculated the stepwise stability constants (37° C) as log K₁ = 3.37 and log K₂ = 3.96 for the calcium(II) complex and for cadmium(II) compounds, 6.46 and 7.18, respectively.

The initial vitamin solution was obtained by dissolving a known weight of 25-OHD₃ or 1,25-(OH)₂D₃ (e.g. 500 mg) in anhydrous EtOH (25 cm³). This parent solution was kept under a nitrogen atmosphere at -20° C. CoCl₂·6H₂O (Prolabo, p.a.) was dissolved in aqueous (9 g l⁻¹) NaCl (Merck, p.a.). The vitamin and the metallic solutions were then diluted in order to obtain the same molarity. The aqueous solutions of 25-OHD₃ and 1,25-(OH)₂D₃ are not very stable, consequently the mixtures were prepared just before recording the experimental spectra.

The continuous variations method was then applied at 25° C, according to Job's pioneering work⁽⁵⁾, using corrected absorbance A_{corr} in order to keep only the spectrum of the complex at a fixed wavelength^(6,7): $A_{corr} = A_{exp} - (C_M \cdot \epsilon_M + C_V \cdot \epsilon_V)$, where A_{exp} is the experimental absorbance, C_M the molarity of cobalt(II) solution and ϵ_M its molar extinction coefficient, C_V the molarity of hydroxylated cholecalciferol solution and ϵ_V the corresponding molar extinction coefficient.

It is well known that cobaltous aqueous solutions undergo very weak visible absorption⁽⁸⁾, so it is not possible to perform the continuous variations method when using the absorption peaks of cobalt(II) aqueous solutions. We therefore used only the spectra of 25-OHD₃ and 1,25-(OH)₂D₃ at two different wavelengths and with two different solutions. The final concentrations of solutions were 10⁻⁵ and 2.10⁻⁵ mol l⁻¹, obtained by dissolving an aliquot of the parent alcoholic solution.

The spectrum of both 25-OHD₃ and 1,25-(OH)₂D₃ solutions exhibits only one absorption band at 250 nm.

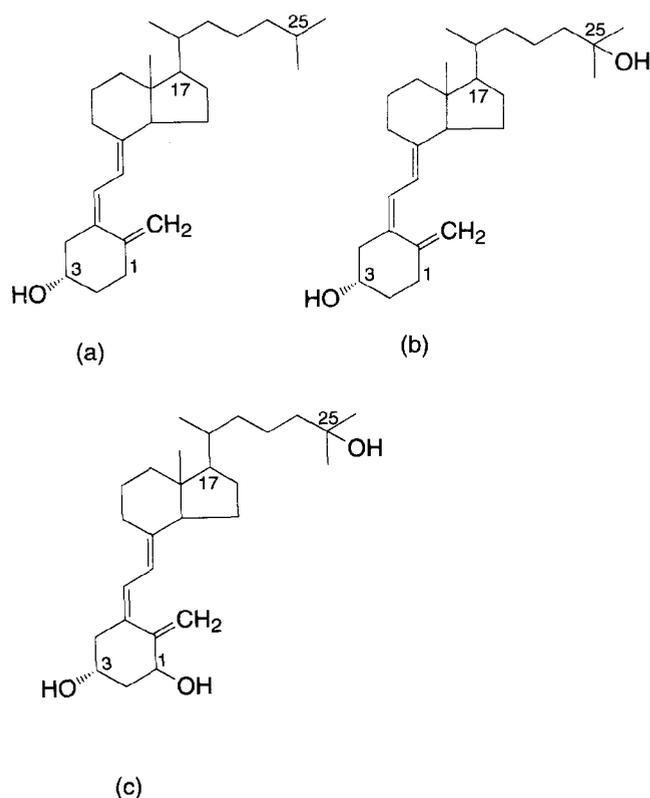


Figure 1. Chemical structures of cholecalciferol and its hydroxylated derivatives: a = cholecalciferol (vitamin D₃), b = 25-hydroxycholecalciferol (25-OHD₃) and c = 1 α ,25-dihydroxycholecalciferol [1,25-(OH)₂D₃].

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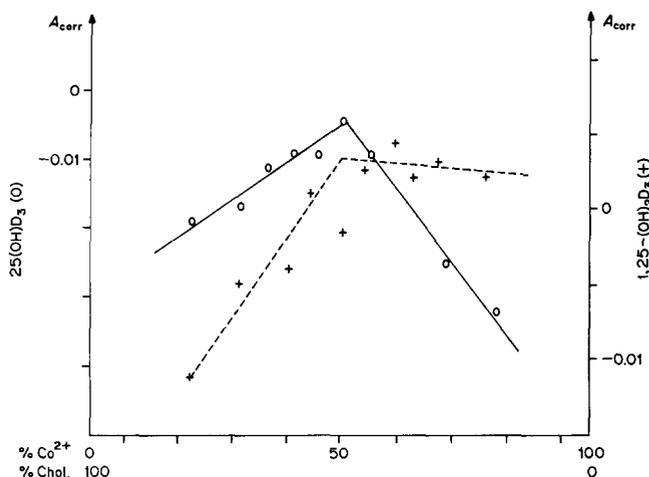


Figure 2. Application of continuous variations.

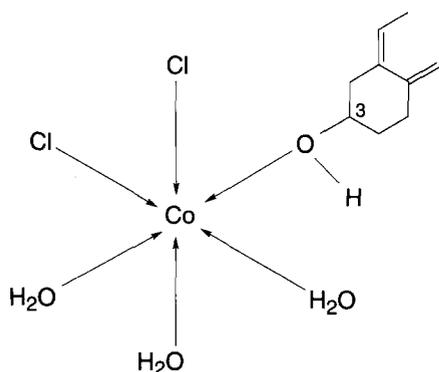


Figure 3. Proposed structures for the identified complexes.

Hence the wavelengths studied were 255 and 260 nm. The application of Job's method (corrected absorbance) is given in Figure 2. Thus, one complex is obtained: 1 molecule of 25-OHD₃ or 1,25-(OH)₂D₃ with 1 CoCl₂ (1:1 type).

In this complex, the cobalt(II) cation is surrounded by six ligands: one 25-OHD₃ or 1,25-(OH)₂D₃, two chloride ions and three molecules of H₂O leading to a six-coordination. Notably, the spectra of these species do not exhibit any absorption in the vicinity of 660 nm and do not imply tetrahedral cobalt(II)⁽⁹⁾.

Because of steric hindrance, the C(3) hydroxyl oxygen atom is the only coordinating atom. As an aqueous NaCl solution is neutral, this hydroxyl cannot be ionised (as an acid) and the electronic doublet can readily give a coordination bond. On the other hand, the C(17) side chain (Figure 1) is a hydrophobic pole in cholecalciferol but 25-OHD₃, as well as 1,25-(OH)₂D₃, have an extra OH in C(25) and so are less hydrophobic than cholecalciferol. This explains why we do not observe the formation of 1:2 type complexes in this series. In fact, a hydrophobic bond, as described by Qitao in cholecalciferol⁽³⁾ could not occur with the hydroxylated compounds. The hydrophilic moieties of both 25-OHD₃ and 1,25-(OH)₂D₃ allow us to obtain 1:1 complexes which have not been previously reported.

We have also calculated the estimated values of the overall stability constants β , assuming that at a given wavelength, e.g. 260 or 255 nm, only cholecalciferol absorbs and the absorption spectra allows us to calculate the molarity of the "free" hydroxycholecalciferol. The calculated values are $\log \beta = 4.7 \pm 0.2$ for 25-OHD₃ and 6.1 ± 0.2 for 1,25-(OH)₂D₃. The uncertainty of the values is given with a confidence interval of 90%.

Further studies on these systems are now in progress in order to elaborate the physiological and therapeutic aspects of these complexes.

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