



Co(II) and Co(III) hydroxamate systems: A solution equilibrium study

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ABSTRACT

The interaction of Co(II) with monohydroxamates (Aha, Bha and MeAha), dihydroxamates (2,5-DIHA, 2,5-*H,H*-DIHA, 2,4-DIHA, 2,3-DIHA, 2,2-DIHA, 3,4-DIHA and 3,3-DIHA) and trihydroxamates (DFB and DFC) was investigated in aqueous solution. According to the pH-metric results mono-, bis- and tris-complexes are formed with monohydroxamic acids, but if the metal to ligand ratio is less than 1:3, mixed hydroxo complexes also exist at high pH. With dihydroxamates, the stability trend of the mono-chelated complexes (Co(HDIHA)) follows the trend of the basicity of the ligands, but significant effect of the length and structure of the connecting chain on the stability of the bis-chelated complexes was found. Interestingly, the best fit of the pH-potentiometric results was obtained without the tris-chelated species (Co₂(DIHA)₃), unlike the case of 2,5-*H,H*-DIHA, and this was also supported by both the ESI-MS and UV-Vis results. Different protonated and non-protonated complexes (depending on the pH) are formed with the two trihydroxamate-based siderophores. The higher stability of the complexes formed with DFC is originated from the conjugation of the double bonds (situating one in β-position to each hydroxamate function) and the hydroxamate functions in this siderophore. The redox stability of the Co(II)-siderophore complexes was also investigated. Following the oxidation of the central metal ion to Co(III), cyclic voltammetric investigation of the complexes was made. Both the DFB and DFC containing complexes showed irreversible reduction of the Co(III) complexes. Based on the approximate stability constants determined by the cyclic voltammetric results, extremely high stability tris-chelated complexes can be formed in the Co(III)-DFB and especially in the Co(III)-DFC systems.

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1. Introduction

Although cobalt is less frequently involved in metalloenzymes compared to some other first-row transition metals (e.g. manganese, iron, copper and zinc), this metal is essential to all living organisms including humans. Cobalamin-based proteins and some other proteins (e.g. methionine aminopeptidase 2 and nitrile hydratase) bind cobalt(II) directly in their active center [1]. Co⁶⁰ is used in the cancer therapy and food sterilization and also as a radioactive tracer both in biological and industrial applications. Based on its characteristic spectra, cobalt is also used as a spectroscopic probe in metalloenzymes to investigate the structural basis of catalytic properties in zinc enzymes and the co-ordination environment of active zinc sites in other proteins [2]. However, because the above detailed great importance of cobalt is not in direct correlation with the interaction of this metal with hydroxamates, cobalt-hydroxamate complexes have been investigated only quite rarely in the past. Still, a few equilibrium data are known for cobalt(II) – simple monohydroxamate complexes [3–6] and the interaction of the trihydroxamate-based natural siderophore, DFB with Co(II) was also investigated [3,7].

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Quite recently, several groups have shown interest in investigation of various cobalt-hydroxamate complexes. For example, hydroxamic acids are well-known inhibitors of metallohydrolases. To get deeper insight into the mechanism of inhibition, numerous dinuclear complexes (including Co(II) containing ones) as structural and functional models for catalytic centers have been synthesized and characterized and their interaction with different hydroxamic acids in the solid state has been investigated [8–10]. Remarkable results have recently been published by Hambley and his co-workers. They synthesized different kinetically inert Co(III) complexes as carriers to deactivate hydroxamate-based MMP (Matrix Metalloproteinases) inhibitors by chelation through the hydroxamate binding group. In these studies the goal is the development of Co(III)-containing prodrugs for selective delivering of MMP inhibitors to target tumor sites. At the sites, the bioreduction of the complex results in the formation of the much less stable and much more labile corresponding Co(II) species. Activation of the inhibitor molecule is expected by its dissociation from that latter complex [11–14].

Very surprising results were published in the literature about the stability of the Co(III)-DFB complex. The value is five orders of magnitude larger compared to that for the Fe(III)-DFB [7].

As it can be seen above, some interesting results are already available relating the Co(II) and Co(III) hydroxamate complexes,

but great number of questions have remained still open. This initiated our solution equilibrium investigation on selected Co(II)–hydroxamic acid systems.

2. Experimental

2.1. Chemicals

Acetohydroxamic acid (Aha) and benzohydroxamic acid (Bha) were commercially available chemicals (Sigma and Aldrich). *N*-Methyl-acetohydroxamic acid (MeAha) [15], the dihydroxamic acids (3,4-DIHA, 3,3-DIHA, 2,5-DIHA, 2,5-*H,H*-DIHA, 2,4-DIHA, 2,3-DIHA and 2,2-DIHA) [16,17] and desferricoprogen (DFC) [18] were prepared by the reported procedures. Desferrioxamine B (DFB) was produced by CIBA Geigy. The purity of the ligands and the concentrations of the ligand stock solutions were determined by Gran's method [19].

The metal ion stock solution was prepared from $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$, by dissolving the salt in doubly distilled water. The concentration of the solution was determined gravimetrically via precipitation of the quinolin-8-olates.

2.2. Potentiometric studies

All pH-potentiometric measurements were carried out at 25.0 °C and an ionic strength of $2 \times 10^{-1} \text{ mol dm}^{-3}$ (KCl). Carbonate-free KOH solution of known concentration (ca. $2 \times 10^{-1} \text{ mol dm}^{-3}$) was used as titrant. HCl stock solution was prepared from cc. HCl (both the acid and base were Merck products) and their concentrations were determined by pH-metric titrations.

The pH-metric titrations were made with a Radiometer pHM 93 instrument equipped with a Metrohm combined electrode (type 6.0234.100). The titrant was added from a Metrohm 715 Dosimat automatic burette. The electrode system was calibrated according to Irving et al. [20] and the pH-metric readings could be converted into hydrogen concentration. The $\text{p}K_w$ calculated from strong acid – strong base titrations was 13.76 ± 0.01 . The pH-potentiometric titrations were performed throughout the approximate pH range 2.0–11.0 (or below precipitation). The samples were in all cases completely deoxygenated by bubbling purified argon for ca. 15 min before starting and also during the titration. The initial volume of the samples was either 20.0 or 10.0 or 8.0 ml, depending on the amount of the ligand. The ligand concentration varied in the range of 1×10^{-3} – $5 \times 10^{-3} \text{ mol dm}^{-3}$ and the metal to ligand ratio ranged from 1:1 to 1:5. The experimental results were utilized to establish the stoichiometry of the species and to calculate the stability constants. Calculations were performed with the computer program PSEQUAD [21]. Volumes of the titrant were fitted and the accepted fittings were always below $1 \times 10^{-2} \text{ ml}$.

2.3. Spectrophotometric studies

A Perkin Elmer Lambda 25 spectrophotometer was used to record the UV–Vis spectra in the region 350–800 nm. Path length was 1 cm. The spectrophotometric method was utilized to study the geometry of the formed complexes. The measurements were carried out by preparing individual samples which contained ionic strength of $2 \times 10^{-1} \text{ mol dm}^{-3}$ KCl and the metal ion concentration was $5 \times 10^{-3} \text{ mol dm}^{-3}$ in all cases and $8 \times 10^{-3} \text{ mol dm}^{-3}$ in the case of DFC. The metal ion to ligand ratio was 1:1 both at the Co(II)–trihydroxamate and the Co(II)–dihydroxamate systems, 1:1.5 in the case of Co(II)–dihydroxamates, 1:3 at Co(II)–Aha and 1:5 at Co(II)–Aha and Co(II)–MeAha systems. The spectra were registered at different pH values, pH was set by KOH solution. Individ-

ual spectra were calculated for the complexes by deconvolution of the registered spectra.

2.4. ESI-MS measurements

A Bruker Biotof II ESI-TOF instrument equipped with a Cole Palmer 74900 Series pump (sample flow rate of $2 \times 10^{-3} \text{ ml min}^{-1}$) was used to perform ESI-MS measurements. All experiments were carried out both in the positive and negative ion mode.

The Co–Bha, Co–2,5-DIHA, Co–2,5-*H,H*-DIHA, Co–3,4-DIHA, Co–2,2-DIHA, Co–DFB systems were analyzed by ESI-MS. The ligand concentration was $2 \times 10^{-3} \text{ mol dm}^{-3}$ in the case of Bha, $1 \times 10^{-3} \text{ mol dm}^{-3}$ at 2,5-DIHA, 2,5-*H,H*-DIHA, 3,4-DIHA, 2,2-DIHA and $5.5 \times 10^{-4} \text{ mol dm}^{-3}$ at DFB. The metal to ligand ratios were 1:5 (Bha), 1:2 (DIHAs) and 1:1 (DFB). The pH ~ 9.4 was set by KOH solution in all cases, under argon gas bubbling.

2.5. Cyclic voltammetry

Cyclic voltammetric measurements were carried out only on the siderophore complexes. Metrohm 746 VA Trace Analyser was used to the measurements. The calibration of the system was made by aqueous solution of $\text{K}_3[\text{Fe}(\text{CN})_6]$ ($E_{1/2} = 0.458 \text{ V}$ versus NHE in $5 \times 10^{-1} \text{ mol dm}^{-3}$ KCl) [22]. A glassy carbon working electrode was used in each measurement. Before the measurements the working electrode was polished with alumina paste (particle size $5 \times 10^{-2} \mu\text{m}$). The reference electrode was Ag/AgCl/ 3 mol dm^{-3} KCl ($E_{1/2} = 209 \text{ mV}$ versus NHE). The scan rate was 50 mV s^{-1} during the determination of the redox potentials. The metal concentration was $3 \times 10^{-3} \text{ mol dm}^{-3}$ in the case of DFB and the ligand concentration was $9 \times 10^{-3} \text{ mol dm}^{-3}$. At the DFC system the metal concentration was $1.5 \times 10^{-3} \text{ mol dm}^{-3}$ and the ligand concentration was $4.5 \times 10^{-3} \text{ mol dm}^{-3}$. Metal to ligand ratio was 1:3 in both cases. The measurements were made in the presence of $5.0 \times 10^{-3} \text{ mol dm}^{-3}$ KNO_3 electrolyte. The pH of the samples was ~ 9 in all cases and the measurements were made in the voltage range +200 to –600 mV. All measurements were carried out at 25.0 °C, and the volume of the samples were 1.5 ml. The first experiment was performed on the Co(II) containing samples, where any measurable electrochemical process was not found. For this reason, the second experiment was started with the oxidation of the central metal ion of the complexes. This was done by two different ways. (1) The sample was left on air for 24 h. (2) H_2O_2 was used as oxidizing agent as was done in Ref. [7]. In both cases, the characteristic spectra [7] of the Co(III)-complexes could be registered. The cyclic voltammetric measurements were done and the voltammograms registered on these oxidized samples. Since there was possibility only for the determination of the E_{pc} (cathodic peak potential) and there was not for the E_{pa} (anodic peak potential) on these systems, estimated values for the $E^0(\text{M}^{\text{III}}\text{H}_x\text{L}/\text{M}^{\text{II}}\text{H}_x\text{L})$ could be determined.

The formal redox potentials (E^0) could be used to calculate the tentative stability constants for the Co(III)-containing complexes by using the following equation:

$$E^0(\text{M}^{\text{III}}\text{H}_x\text{L}/\text{M}^{\text{II}}\text{H}_x\text{L}) = E^0(\text{M}^{\text{III}}(\text{H}_2\text{O})_6/(\text{M}^{\text{II}}(\text{H}_2\text{O})_6)) + \frac{RT}{nF} \ln(\beta_{\text{II}}/\beta_{\text{III}})$$

where $E^0(\text{M}^{\text{III}}\text{H}_x\text{L}/\text{M}^{\text{II}}\text{H}_x\text{L})$ is the formal potential of the complex, $x = 1$ in the case of DFB and $x = 0$ in the case of DFC, $E^0(\text{M}^{\text{III}}(\text{H}_2\text{O})_6/(\text{M}^{\text{II}}(\text{H}_2\text{O})_6))$ is the redox standard potential of Co(III)(aq)/Co(II)(aq) (1.8 V [23]), $\beta_{\text{II}}/\beta_{\text{III}}$ is the quotient of the overall stability constants of the appropriate complexes.

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