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Structure-based differences between the metal ion selectivity of two siderophores desferrioxamine B (DFB) and desferricoprogen (DFC): Why DFC is much better Pb(II) sequestering agent than DFB?

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ABSTRACT

Complexation of desferrioxamine B (DFB) and desferricoprogen (DFC) with Cd(II) and Pb(II) toxic ions as well as complexation of DFC with Ca(II) and Mg(II) essential metals have been investigated and the results have been compared to those with other metal ions. The two siderophores have moderate Cd(II)-binding ability, but both, and especially DFC, bind Pb(II) in high stability complexes. Surprisingly, significant differences exist between Pb(II)-complexation of DFB and DFC. Namely, a maximum of two hydroxamate groups of a DFB coordinate to a Pb(II) ion, the third one binds to another metal ion with high preference and the formation of a trinuclear species, $[Pb_3(DFBH)_2]^{2+}$, is predominant even at 1:1 metal to ligand ratio in this system. On the contrary, DFC forms mononuclear complex, [ML], with much higher stability and the formation of the trinuclear complex is negligible compared to DFB. The $6s^2$ electron-pair of Pb(II), which remains always inert during complexation with hydroxamic acids and also with DFB, seems to become active in the DFC complexes (due to the effect of the double bonds in β-position to each hydroxamate), what, at least in some extent, allows the coordination of all the three hydroxamates of DFC to the same Pb(II) ion. This way of interaction (unique with a hydroxamate-based compound) results in significant stability increase, and, as a consequence, DFC is much better Pb(II)-chelating agent than DFB. Although DFC forms unexpectedly high stability complexes with Mg(II) compared to Ca(II), but even Mg(II), compared to many other metals, is not an efficient DFC-binding metal. Therefore, any sequestration of this biologically very important metal is not likely from a living organism by DFC.
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1. Introduction

Due to the relatively moderate basicity of a hydroxamate (logarithmic value of the corresponding protonation constant, is ca. 9 [1]) compared to a catecholate (logarithmic overall constant ($\log\beta_2$) for the two catecholate oxygens is ca. 23–25 [2]), metal ions are able to compete at much lower pH (e.g., under physiological conditions) with hydroxamic than with catecholic protons. This might be an important reason why hydroxamate-based microbial siderophores are frequently chosen metal chelators for many purposes. It is also known that the numerous biological effects of hydroxamic acids (for example, their capability for inhibition of various metalloenzymes or for sequestration of different metal ions) are strongly connected to their metal complexation [3,4]. Because of the long-term usage of the desferrioxamine B (DFB) (its formula is shown in Scheme 1), first of all for the treatment of thalassemic patients, this compound might be the most famous representative of the hydroxamate-based siderophore family [5,6].

DFB also ameliorates tissue damages arising from inflammatory reactions [7,8], reduces heme-mediated low density lipoprotein (LDL) oxidation and endothelial injury [9], inhibits oxidized LDL-induced damage of macrophages [10] and improves endothelial function in patients with coronary artery disease [11]. Due to its intravenous application [12] and the side effects [13], application of DFB to prevent atherosclerosis by complexing harmful catalytic iron in blood vessels is limited. A poor uptake of this siderophore in the gastrointestinal tract [14] can be assigned mainly to the positively charged terminal ammonium group. This assumption is supported by the fact that the fungal trihydroxamate-type desferricoprogen (DFC) (Scheme 1), which is uncharged under physiological conditions [15], was orally active, accumulated in the liver and was secreted via its iron-complex into the feces and urine in a rat model [16]. Similarly to DFB, DFC was found to increase the resistance of LDL to heme-catalyzed oxidation and attenuate the cytotoxicity of the oxidation products of LDL to human vascular endothelium. Moreover, DFC was found also to

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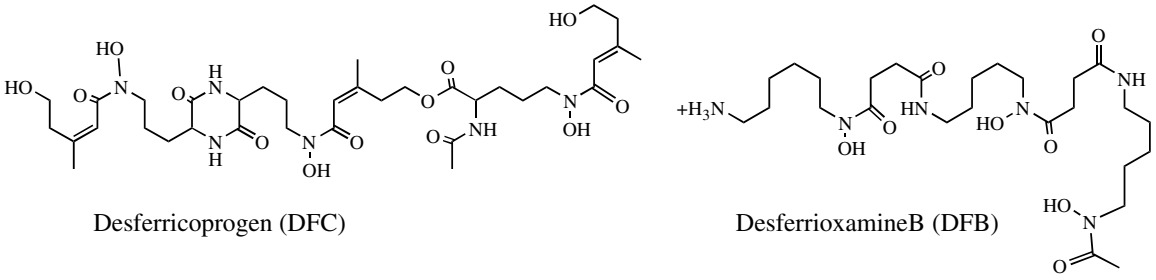

Scheme 1.

hinder the heme-mediated oxidation of human atherosclerotic soft plaque lipids. Based on the results, the consumption of traditional mould-ripened foods and the development of functional foods with increased trihydroxamate contents are believed to represent powerful tools in the prevention of cardiovascular disorders [16]. However, the development and introduction of desferricoprogen-enriched functional food in anti-atherosclerotic diets need information about the interaction of this siderophore with various metal ions, including essential alkaline earth metals, namely Mg(II), which is protective against various diseases, e.g., hypertension [17], and Ca(II), which has an adverse effect on vascular calcification, a risk factor e.g. in patients with chronic kidney disease [18,19].

Metal complexation of DFB and its structural models has been extensively studied for years in our laboratory [20–25] and DFC has also been involved in a recent project [15]. Fe(III), Ga(III), Al(III), In(III), Cu(II), Ni(II), Zn(II) and Fe(II) complexes of the two siderophores and also the Ca(II)–DFB and Mg(II)–DFB systems [20] have been studied. According to the results, both the DFB and DFC are effective metal chelators. In addition to Fe(III), they form high stability complexes with Ga(III), Al(III), In(III), Cu(II), Ni(II) and Zn(II), but the stability of the Mg(II)–DFB and especially the Ca(II)–DFB complexes is quite low. Furthermore, these siderophores oxidize Fe(II) under anaerobic conditions and the well-known Fe(III) complexes are exclusively formed [22,23,15]. Beside the numerous similarities, differences also exist between the metal binding ability of DFC and DFB. Namely: (i) the double bond situating in β-position to each hydroxamic function causes a slight increase in the stability of the mono-chelated complexes of DFC; (ii) metal ions with relatively large ionic radius (like Cu(II), Ni(II), Zn(II), In(III)) form slightly more stable bis- and tris-chelated complexes with DFC, containing a bit longer chains, but the trend is the opposite with smaller metal ions (like Fe(III), Al(III), Ga(III)) and here the complexes of DFB are a bit more stable; (iii) the coordination of the two adjacent hydroxamates to the same Cu(II) is favoured only with DFC, but not with DFB. As a consequence, formation of the trinuclear complex, $[Cu_3L_2]$, is favoured with DFC, but it is not formed with DFB [15].

As a continuation of the previous work, the interaction between DFC and Ca^{2+} as well as Mg^{2+} has been investigated in the present work. Moreover, to evaluate the possibility of the sequestration of two toxic metals by these natural compounds, Cd(II)- and Pb(II)-binding ability of DFB and DFC (for which only a few data have been previously published in the literature [26,27]) was also within the scope of this work.

2. Experimental

2.1. Chemicals

Details of purification of desferricoprogen from *Penicillium chrysogenum* and *Neurospora crassa* cultures are involved in our previous paper [15]. DFB was produced by CIBA Geigy. *N*-Me-Acrylhydroxamic acid (*N*-Me-Acrha) and *N*-Me-Acetohydroxamic acid (*N*-Me-Aha) were synthesized according to the procedures in Refs. [28,29], respectively.

The purity of the ligands and the concentrations of the ligand stock solutions were determined by Gran's method [30]. The metal ion stock solutions were prepared by dissolving $Pb(NO_3)_2$ in dilute HNO_3 (0.001 M), $Cd(NO_3)_2$ and $CaCl_2$ in distilled water, MgO in the necessary, known amount of HCl. All of the metal containing salts were Reanal products. The concentration of the Cd(II) stock solution was determined gravimetrically via precipitation of quinolin-8-olates, while the concentration of Ca(II), Mg(II) and Pb(II) stock solutions by complexometric titrations, using EDTA (Aldrich) as titrant.

2.2. pH-potentiometric studies

The pH-potentiometric measurements were carried out at an ionic strength of 0.2 M, which was set with KNO_3 in the cases of Pb(II)- and Cd(II)-containing systems (because of the low water solubility of $PbCl_2$ and the relatively high stability of chloro complexes of Cd(II)) and with KCl, if Ca(II) or Mg(II) metal ions were used. The temperature was always 25.0 ± 0.1 °C. Carbonate-free KOH solution (0.2 M) was used as titrant. HNO_3 and HCl stock solutions were prepared from cc. HNO_3 and cc. HCl. The concentrations of the KOH and acid stock solutions were determined by pH-potentiometric titrations using the Gran's method [30].

A Radiometer pHM 93 instrument with Metrohm double junction combined electrode (type 0219.100) was used for pH-metric measurements with a Metrohm 715 Dosimat automatic burette. The electrode system was calibrated according to Irving et al. [31], and the pH-metric readings could, therefore, be converted into hydrogen concentration. The water ionization constant (pK_W) determined in the present work in the presence of KNO_3 is 13.78 ± 0.01, while in the presence of KCl is 13.76 ± 0.01.

All the pH-potentiometric titrations were performed over the pH range of 2–10 in the case of Cd(II)-containing samples, while 2–11 or up to precipitation in all the other cases. The initial volume of the samples was 10.00 cm^3. The ligand concentrations were varied within the range 0.01–0.001 M and the metal ion concentrations were varied according to the ratios. The metal–siderophore ratios were 1:1, 1:1.5 and 1:2 in the case of Mg(II), 1:0.6, 1:1, and to achieve well measurable extent of complexation, also high metal excesses, 5:1 and 10:1, were used with Ca(II). The ratios were 1:1, 1:1.5 and 1.5:1 with Pb(II) and Cd(II). During the measurements with the model monohydroxamic acids, *N*-Me-Acrha and *N*-Me-Aha, the metal–ligand ratio was varied within the range 1:1–1:6. The samples were completely deoxygenated by bubbling purified argon for approx. twenty minutes before the measurements. The equilibrium calculations were performed by the PSEQUAD computer program [32]. Since the measurable hydrolysis of the Pb(II) ion starts at pH ca. 6, the hydrolytic species, with their

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