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Metal-binding Ability of Desferrioxamine B

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Abstract. The metal complex formation properties of the naturally-occurring hydroxamate-type siderophore Desferrioxamine B is surveyed with special emphasis on its solution speciation. The most likely binding-modes of the complexes formed with this ambidentate ligand are also evaluated. A brief survey of the implications of metal chelation in the therapeutic role of DFB in the treatment of metal overloads is also given.

Key words: Desferrioxamine B, Metal complexes, Solution speciation, Metal overload.

1. Introduction

Desferrioxamine B (DFB) is a naturally-occurring hydroxamate-type siderophore (low molecular mass iron chelator). The linear trihydroxamic acid is composed of alternating 1,5-diaminopentane and succinic acid residues. Its major role in Nature is the solubilization and transport of iron. The biological rationale for the production of DFB (and other siderophores) by microorganisms is the irreplaceable role of iron in both oxidation states in the reduction processes of cells, combined with the extreme insolubility of iron(III) hydroxide under physiological conditions: at pH $\sim$7 the equilibrium concentration for Fe^{3+} is around 10^{-18} mol dm^{-3}. Microorganisms need Fe(III) at least at a μmolar level. Only powerful chelating agents can mobilize iron from the environment and facilitate the transport of iron into the microbial cells.

Due to its high affinity towards hard metal ions, DFB is used as a metal-sequestering agent to treat certain metal overload diseases. It is currently used in the treatment of either acute or chronic iron poisoning. Given in infusion, it is the currently favoured drug for the iron chelation therapy of patients receiving regular blood transfusions for the treatment of β-thalassemia [1]. DFB has also been used to treat Al(III) overload [2] and has been investigated for use with ^{67}Ga as a contrast agent for radiography [3].

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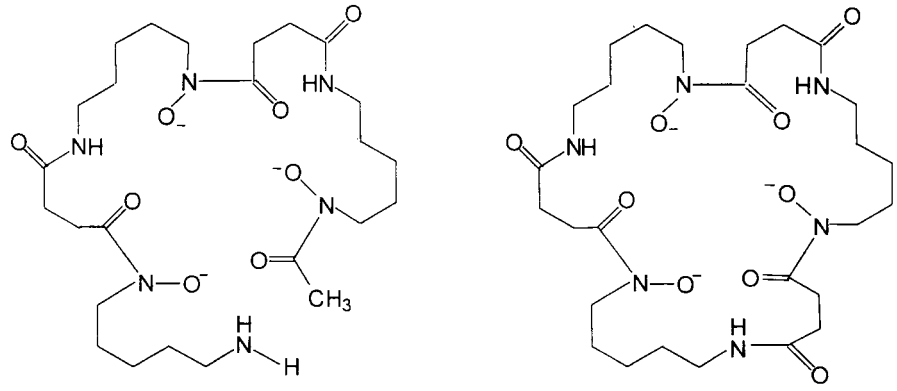


Figure 1. The structure of Desferrioxamine B and Desferrioxamine E.

In this paper, the metal-binding ability of DFB is reviewed with special emphasis on the solution speciation of this polydentate ligand. A brief survey of the implications of metal chelation in the therapeutic role of DFB in the treatment of metal overloads is also given.

2. Ligand Properties

2.1. Acid-base chemistry of DFB

DFB is a linear molecule containing three hydroxamate functions, with a primary amino group at one end (see Figure 1). The molecule therefore has four protonation constants; these are listed in Table I. The first constant relates to the terminal amino group, and the other three to the hydroxamate groups. Although these latter three values relate to the same type of functional group, their ratios are not equal, and they differ a little from the value expected on the basis of statistical considerations ($\log(K_{H_2A}/K_{H_3A}) = \log(K_{H_3A}/K_{H_4A}) = 3$) [4], indicating that the hydroxamate groups are not entirely isolated within the molecule. These groups are separated from each other by 9 atoms in the chain, and hence no through-chain interactions can occur between them. However, the chain is rather flexible and thus through-space interactions between the three hydroxamate groups are very likely. It is clear from the protonation constants listed in Table I that the ligand DFB exists mostly in the fully protonated form H_4DFB in the physiological pH range.

Table I. Stepwise protonation constants (log K_{HL})[a] of Desferroxamine.

	Ref. 5[b]	Ref 6[c]	Ref 7[d]	Ref. 7[e]	Ref. 8[f]	Ref. 9[g]	Average[h]
K_{HL}	>11	10.79	10.89	10.87	10.84	10.85	10.85 (4)
K_{H_2L}	9.70	9.55	9.55	9.57	9.46	9.45	9.52 (6)
K_{H_3L}	9.03	8.96	8.98	8.97	9.00	8.96	8.97 (2)
K_{H_4L}	8.39	8.32	8.32	8.35	8.3	8.33	8.32 (2)

[a] $K_{H_nL} = [H_nL]/[H][H_{n-1}L]$.
[b] t = 20 °C, I = 0.1 $NaClO_4$.
[c] t = 25 °C, I = 0.1 KCl.
[d] t = 25 °C, I = 0.1 KNO_3.
[e] t = 25 °C, I = 0.1 $NaClO_4$.
[f] t = 25 °C, I = 0.2 KCl.
[g] t = 25 °C, I = 0.2 KCl.
[h] t = 25 °C, I = 0.1–0.2.

2.2. General aspects of metal ion coordination

As concerns the metal-binding ability of DFB the basic binding mode of the ligand is the simultaneous coordination of the six oxygen donors through the formation of 3 × (O^-, =O) chelates in octahedral or distorted octahedral geometry. In these complexes, the ligand wraps around the metal ion to form high stability complexes of 1 : 1 stoichiometry, which have the formula MLH (the terminal non-coordinating amino group being protonated).

A good linear relationship exists [6] between the stability constants of the complexes MLH (log β_{MLH}) and the monohydroxo complex formation constants (log $K_{M(OH)}$) of the metal ions (see Figure 2). Similar relationships have been found for other ligands containing negatively charged O donors, such as phenolate or carboxylate [6]. The slopes of such correlations are dependent on the basicity of the RO^- donors of the chelating ligands. This linear relationship indicates the same binding mode in all of these metal complexes of DFB, as their stabilities are determined only by the affinity of the metal ion for the negatively charged oxygen donors, characterized quantitatively by log $K_{M(OH)}$.

Although the three 5-membered chelate rings are separated by 9 atoms within the ligand molecule, the simultaneous coordination of the three chelate rings, and hence, the formation of a special chelating system may be expected to afford an extra stabilization (extra-chelate effect) for the metal complexes as compared with the stability constants of the metal–tris(acetohydroxamato) complexes. However, the connecting chains between the hydroxamate donors are rather long and thus the chelating sites function almost independently. Indeed, the connecting chains may provide such an unfavorable entropy effect for metal complexation that no chelate effect is observed at all. In order to illustrate this, stability data on the corresponding Fe(III), Al(III), Ni(II) and Zn(II) complexes are listed in Table II. It is interesting to note that this extra-chelate effect clearly occurs in the stability con-

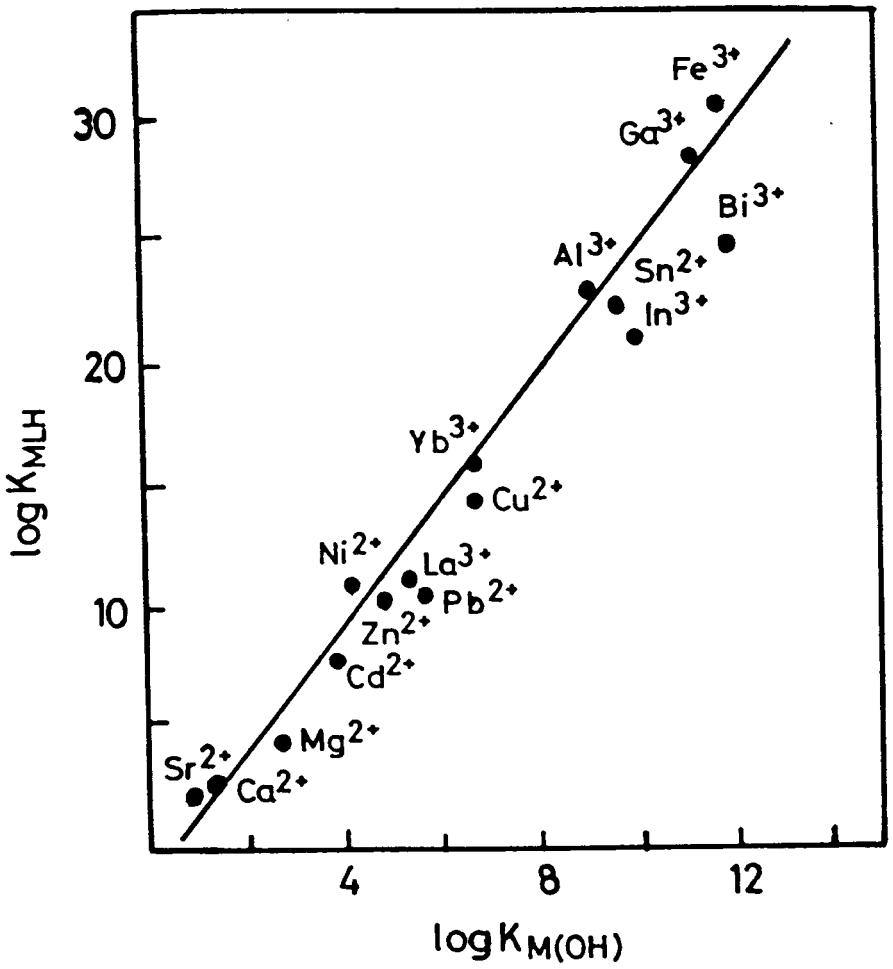


Figure 2. Correlation of log K_{MLH} values for DFB against log $K_{\mathrm{M(OH)}}$ values for various metal ions. Data are taken from Refs. [5–7].

stants of the trivalent Fe(III) and Al(III) complexes, but not in those of the divalent transition metal ions. For the divalent transition metal ions, stability constants of the complexes ML_3 of acetohydroxamic acid are available in the literature only for Ni(II) and Zn(II) [11]. Due to the lack of sufficient data, no detailed explanation can be given for this experimental finding. It seems certain that differences in the ionic size of the metal ions are not the only factor responsible for the controversial effects observed. Although there is little or no stability enhancement for polyhydroxamates relative to monohydroxamates, the much stronger metal-binding ability of the latter is clearly demonstrated by the pM (= $-\log [M^{n+}]$) values, which are much lower for DFB than for the monofunctional acetohydroxamate under identical experimental conditions (c_M = 1 μmol dm^{-3}, c_{ligand} = 50 μmol dm^{-3}, pH = 7.4) (see Table II).

Table II. Extra chelate effect and macrocyclic effect of the metal complexes of DFB and DFE.

	Fe(III)	Al(III)	Ni(II)	Zn(II)
$M + 3L^- \leftrightarrow ML_3$[a]	28.3[b]	21.5[c]	11.7[d]	1176[d].
pM	16.5[e]	12.1[f]	6.1	6.1
M + HDFB ↔ MDFBH	30.6[b]	24.1[g]	10.9[b]	11.1[b]
Extra-chelate effect	+2.3	+2.6	−0.8	−0.5
pM	27.6	21.2	6.7	7.2
M + DFE ↔ MDFE	32.5[b]	–	12.2[b]	12.1[b]
Macrocyclic effect	+1.9	–	+1.3	+1.0
Extra-chelate + macrocyclic effects	+4.2	–	+0.5	+0.5
pM	28.4	–	8.2	8.0
Ionic radius, Å	0.64	0.54	0.69	0.74

[a] L^- = acetohydroxamate ($CH_3(CO)NO^-$), log K_{HL} for the ligand is 9.37 [5]
[b] Ref [10].
[c] Ref [6].
[d] Ref [11].
[e] Acetohydroxamate cannot prevent precipitation of $Fe(OH)_3$, accordingly, calculated from the solubility product $K_{s0} = [Fe][OH]^3 = 38.7$ [12].
[f] Acetohydroxamate is able to keep Al(III) in solution, amorphous $Al(OH)_3$ allows pAl = 10.7 [13].
[g] Ref [6].

At the same time, when the stability constants of the metal complexes of the cyclic derivative of DFB (desferrioxamine E = DFE, see Figure 1) are compared with those of the open-chain DFB, a significant stability increase, due to the cyclic arrangement of the hydroxamate donors (macrocyclic effect), can be observed for all metal ions. This is in accordance with expectations, as the endocyclic arrangement of these hydroxamate functions may represent some degree of preorganization, and hence a lowering of the unfavorable entropy effect [14].

3. Metal Complexation Equilibria

The overall stability constants ($\beta_{pqr}=[M_pL_qH_r]/[M]^p[L]^q[H]^r$) of the complexes of DFB with divalent and trivalent metal ions are listed in Tables III and IV, respectively. Besides the log β values, for the sake of comparison equilibrium constants for specified complex formation steps are also included in the tables. The processes are always defined in the first column of the tables.

Table III. Cumulative stability constants (log β) for the complexes of DFB with divalent metal ions

	Mg(II)[a]	Ca(II)[a]	Sr(II)[b]	Fe(II)[b]	Co(II)[b]	Ni(II)[a]	Cu(II)[a]	Zn(II)[a]	Pb(II)[c]	Sn(II)[c]
MLH_3	–	–	–	31.5	33.9	33.20	36.99	33.40	35.35	43.47
MLH_2	23.85	22.41	–	25.9	27.1	27.66	33.10	28.17	29.70	40.76
MLH	14.66	13.25	13.2	–	21.33	19.71	23.98	20.40	20.89	32.01
ML	3.8	3.03	–	–	–	8.89	13.73	10.36	–	–
M_2LH	–	–	–	–	–	–	32.09	–	27.18	43.05
MLH + H	9.19	9.16	–	–	6.75	7.95	9.12	7.77	8.81	8.75
MLH_2 + H	–	–	–	5.6	5.8	5.54	3.89	5.23	5.65	2.71
MLH ↔ ML + H	10.8	10.22	–	–	–	10.82	10.25	10.04	–	–
MLH + M	–	–	–	–	–	–	8.11	–	6.29	10.04
Ionic radius, Å	0.72	1.00	1.18	0.78	0.75	0.69	0.73	0.74	1.19	0.93

[a] Ref. [8], t = 25 °C, I = 0.2 KCl.
[b] Ref. [13], t = 20 °C, I = 0.1.
[c] Ref. [7], t = 25 °C, I = 0.1 KNO_3.

Table IV. Cumulative stability constants (log β) for the complexes of DFB with trivalent metal ions

	Al(III)[a]	Ga(III)[a]	In(III)[a]	Fe(III)[a]	Bi(III)[b]	La(III)[c]	Yb(III)[c]
MLH_3	–	–	–	–	–	34.3	36.1
MLH_2	36.11	–	34.54	42.33	38.3	28.3	31.7
MLH	34.93	38.96	31.39	41.39	34.4	21.9	27.0
ML	24.50	28.17	21.39	30.99	–	–	–
M_2LH	–	–	–	33.7[d]	–	–	–
MLH + H	1.18	–	3.15	0.94	3.9	6.4	4.7
MLH_2 + H	–	–	–	–	–	6.0	4.4
MLH $\leftrightarrow$ ML + H	10.43	10.31	10.00	10.40	–	–	–
MLH + M	–	–	–	2.7	–	–	–
Ionic radius, Å	0.54	0.62	0.80	0.64	1.03	1.03	0.87

[a] Ref. [6], t = 25 °C, I = 0.1 KNO_3.
[b] Ref. [7], t = 25 °C, I = 0.1 KNO_3.
[c] Ref. [13], t = 20 °C, I = 0.1.
[d] Ref. [14], t = 25 °C, I = 1.0 NaCl.

3.1. COMPLEXES OF DIVALENT METAL IONS

As may be seen in Table III, the MLH complexes of most of the divalent metal ions take up two protons in a stepwise way (see rows 6 and 7 in Table III), each of them being accompanied by the break of a hydroxamate chelate formed between DFB and the metal ion. The lower these constants, the lower the tendency of the MLH or MLH_2 complexes to protonation. The data in Table III show that MLH tends to protonate with log $K_{MLH} \sim 9.0 \pm 0.2$, with the exceptions of Co(II), Ni(II) and Zn(II). These metal ions take up a proton in a pH-range more than one unit lower, which otherwise means that they more readily expel the last hydroxamic proton from DFB. The most likely explanation for this is that these metal ions fit much better into the trihydroxamate MLH complex (see the considerable differences in their ionic radii in the last row of Table III: the transition metal ions are significantly smaller than the other metal ions). While Cu(II) has a similar ionic radius to those of Co(II), Ni(II) and Zn(II), its reduced ability to liberate the final proton is related to its preferred coordination geometry [7, 8]. It forms tetragonal bipyramidal complexes with weak axial coordination sites.

A logical consequence of this size effect would be the availability of the final hydroxamate function to bind an additional metal ion. Accordingly, those metal ions which less readily tend to form a third chelate in the MLH complex (e.g. Cu(II), Pb(II) and Sn(II)) are better able to form a dinuclear complex (see the speciation curves for the Cu(II)–DFB system in Figure 3). In this complex (see Structure I in Figure 4) one metal ion is probably bis-chelated, while the other is

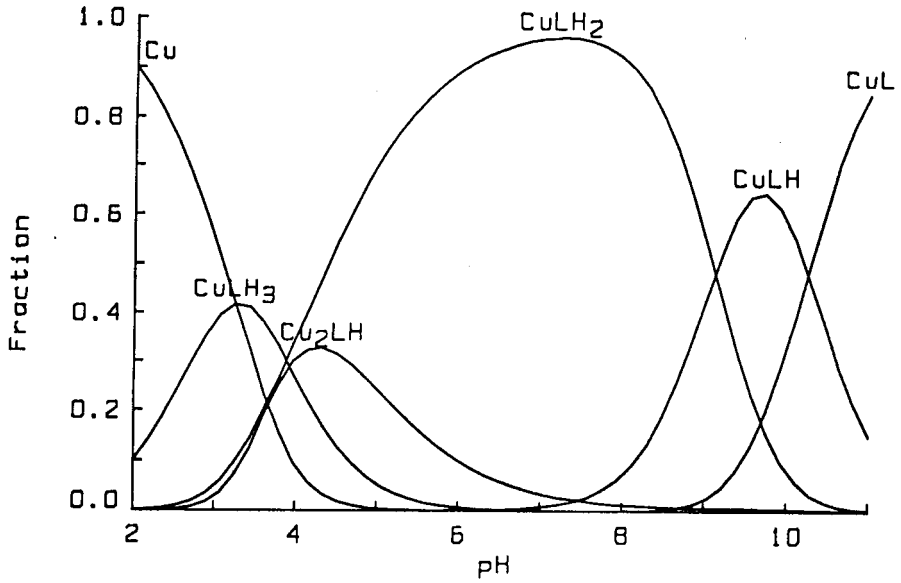


Figure 3. Speciation curves of the complexes formed in the Cu(II)-DFB system.

only mono-chelated. The other possible binding mode (Structure II in Figure 4), with the symmetrical coordination of the two metal ions, seems less likely [16].

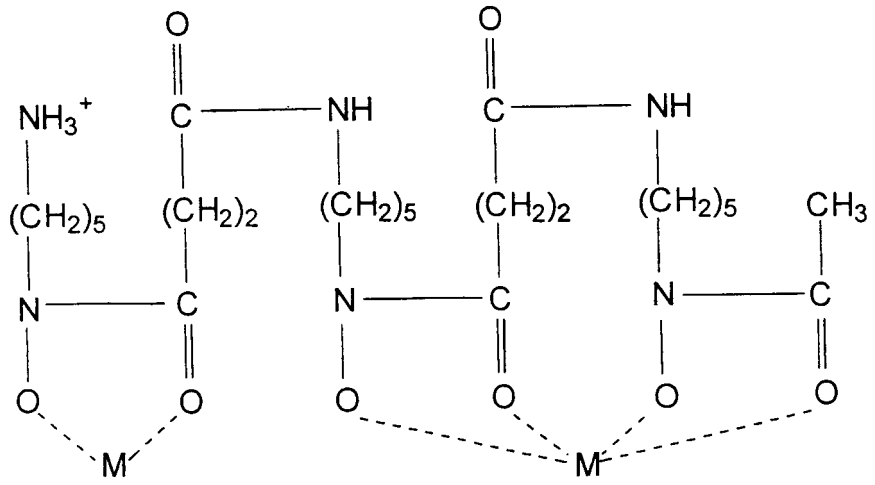
No trihydroxamato complexes could be detected with the much weaker ligand binder alkaline earth metal ions. As an illustration, species distribution curves for the Ca(II)-DFB and Mg(II)-DFB systems are depicted in Figures 5 and 6. A comparison of the stability constants of MDFBH with those of the corresponding monohydroxamate and dihydroxamate complexes indicates that only a mono-chelated complex is formed with Ca(II), while (at least partly) the formation of a bis-chelated species can also be assumed for Mg(II) [17]. The smaller Mg(II) seems to be better accommodated into the structure of the DFB molecule.

Transition metal ions form mono-chelated MLH_3 complexes with $\log K_{MLH_3} \sim 5.5 \pm 0.3$, with the exception of Cu(II), which forms a significantly stronger bis-hydroxamato complex, in accordance with its position in the Irving–Williams series [18]. Accordingly, $CuLH_2$ protonates at more acidic pH range than the corresponding complex of other transition metal ions.

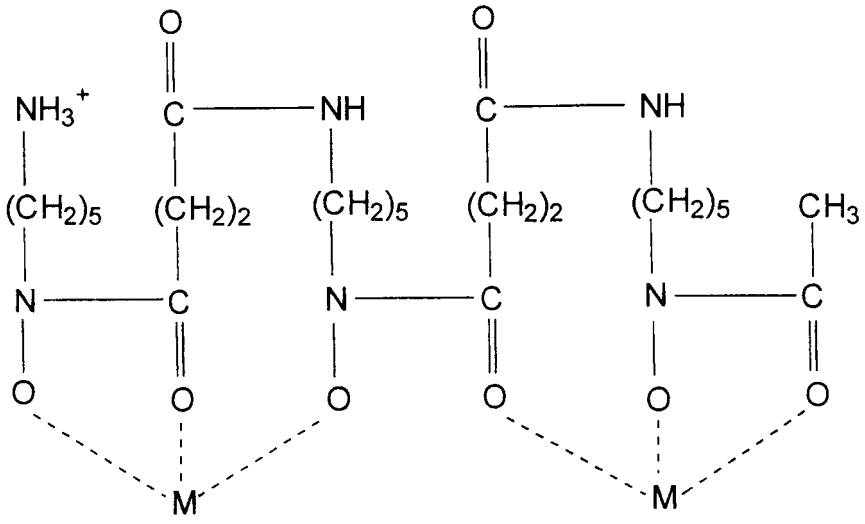
3.2. Complexes with trivalent metal ions

Trivalent metal ions (which are harder in nature) form much stronger complexes with the purely oxygen donor DFB than do the divalent metal ions, indicating the significantly more ionic character of the bonds (see Table IV).

As an illustration, speciation curves for the Fe(III)–DFB system are depicted in Figure 7. It can be seen from Table IV and Figure 7 that the tris-hydroxamato MLH complexes predominate in a wide pH range. The first proton is taken up



Structure I



Structure II

Figure 4. Tentative structures of the M_2LH complex of DFB.

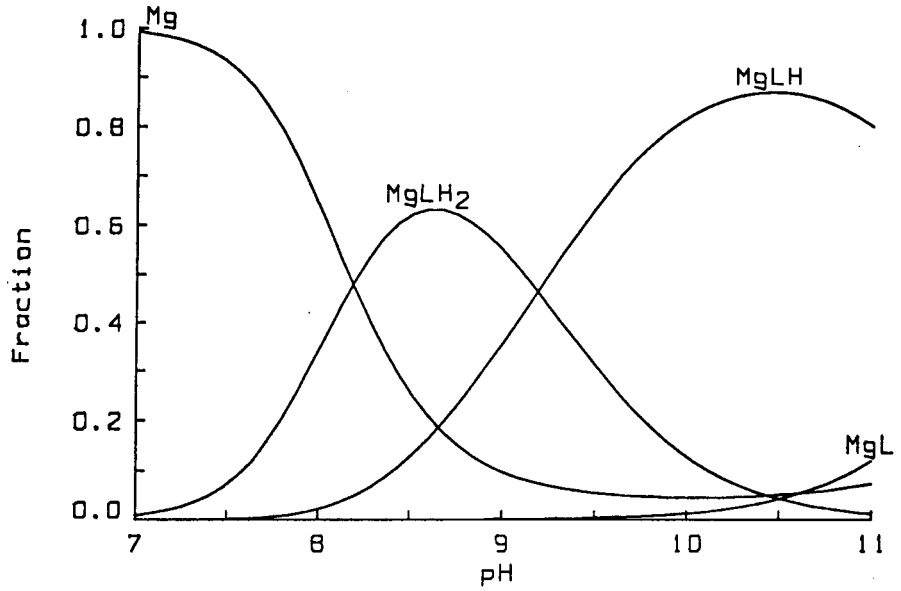


Figure 5. Speciation curves of the complexes formed in the Mg(II)–DFB system, c_M = 0.005 mol dm^{-3}, c_{ligand} = 0.005 mol dm^{-3}.

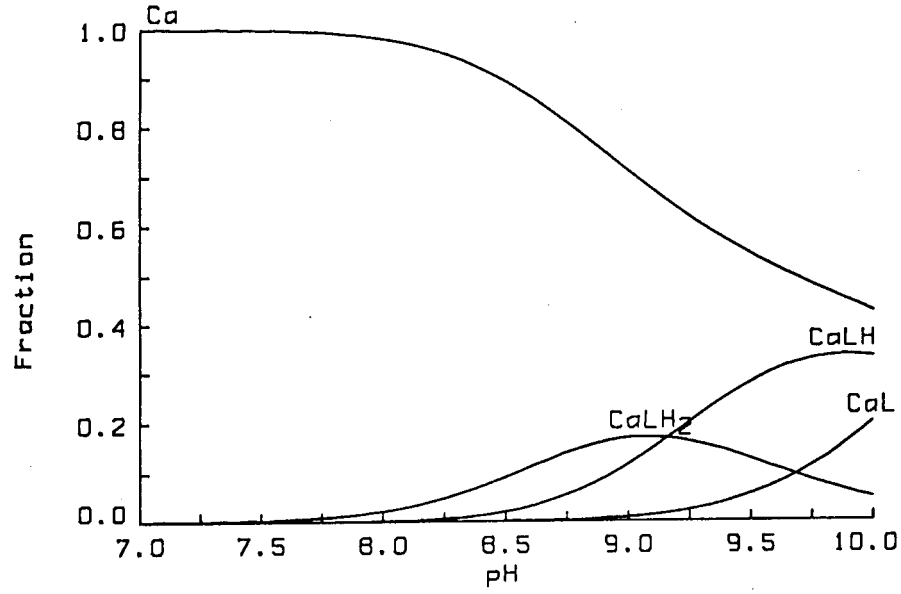


Figure 6. Speciation curves of the complexes formed in the Ca(II)–DFB system, c_M = 0.001 mol dm^{-3}, c_{ligand} = 0.005 mol dm^{-3}.

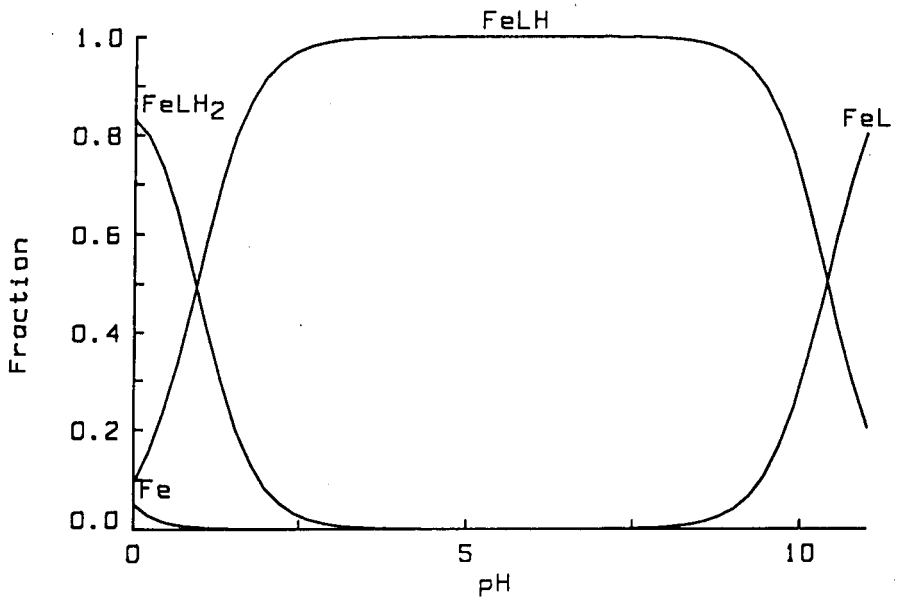


Figure 7. Speciation curves of the complexes formed in the Fe(III)–DFB system, c_M = 0.001 mol dm^{-3}, c_{ligand} = 0.005 mol dm^{-3}.

by the hexacoordinated MLH complex to form the bis-chelated species MLH_2 in the fairly acidic pH range. Due to the high affinity of DFB for most of these trivalent metal ions, the monohydroxamato MLH_3 complexes would form in the very acidic pH range, and thus their stability constants could not be determined by the conventional pH-metric techniques. La(III) and Yb(III) form significantly weaker complexes with DFB than those of the other trivalent metal ions. This can be explained by their much larger size; they do not fit well into the MLH structure.

In the basic range, most of the MLH complexes undergo deprotonation. The proton is liberated mostly from the non-coordinated terminal ammonium group of the ligand. For the divalent transition metal ions and alkaline earth ions (which form less stable MLH complexes), the parallel process of ionization of a coordinated water molecule, resulting in mixed hydroxo MLH(OH) complexes, can also be assumed. With highly hydrolysable metal ions such as Pb(II), Sn(II) and Bi(III), precipitation occurs in the basic pH range [7].

Since DFB is a hexadentate ligand with three unsymmetrical bidentate functional units, 16 geometrical and optical isomers are theoretically possible for the metal complexes [19]. Ion-exchange separations on the kinetically inert Cr(III) complexes and ^{13}C NMR studies on the Ga(III) and Al(III) complexes demonstrated that there are only two significant isomers in solution, and in principle these are interconverted simply by flipping of the N-terminal hydroxamate [20].

For a better understanding of siderophore-mediated iron transport, great efforts have been made to clarify the kinetics of the dissociation reaction represented by

the equilibrium $FeDFBH^+ + 3H^+ \leftrightarrow Fe^{3+} + H_4DFB^+$ [21–23]. This reaction has been found to proceed in four kinetically distinguishable stages. The four successive reactions proved to be very fast (proceeding in the ms range), fast (in tenth of a sec), slow (in sec) and very slow (in min) under the conditions applied [20]. Five intermediate species between the fully coordinated complex and the completely dissociated product were detected by means of spectral and/or kinetic techniques. A mechanism was proposed whereby the intermediates corresponded to the stepwise unwrapping of DFB from Fe(III), starting with the N—O oxygen atom at the protonated amine end of the ligand. It was suggested that the detailed mechanism established for monohydroxamato–iron(III) dissociation was applicable to the dissociation of each hydroxamate group of DFB, including the important role of coordinated H_2O *cis* to the dissociating hydroxamate group, the acid dependence, and the role of the hydroxamate group in the transition state of the dissociating complex.

3.3. Complexes with metal oxocations and oxoanions

Because of their high polarizing power, transition metal ions in a high oxidation state readily form oxocations in the acidic pH range, and oxoanions in the basic pH range. These metal ions contain oxo groups in the coordination sphere besides water molecules. On reaction with complexing agents, either the water molecules or both the water molecules and the oxo groups can be displaced, resulting in either normal oxo complexes or non-oxo complexes. The vanadium and molybdenum ions afford examples of both types of complexation. The stoichometries and stability constants of the complexes formed in the DFB systems of vanadium(IV), vanadium(V) and molybdenum(VI) are listed in Table V.

When aqueous solutions of oxovanadium(IV) and DFB are mixed, a deep-red colour develops in the pH range 1–4. The complexes formed have molar absorptivities of a few thousand, i.e. about a hundred times higher than the usual value for VO(IV) complexes [24, 25]. This spectral behavior is an unambiguous indication of the formation of a hexacoordinated tris-hydroxamato non-oxo vanadium(IV) complex as in the following reaction:

$$VO^{2+} + H_4DFB^+ \leftrightarrow VDFBH^{2+} + H_2O + H^+ \quad (1)$$

As the pH is increased up to neutral, the colour of the solution starts to fade from pH $\sim$ 3, and by pH $\sim$ 7 the solution has the light-blue colour characteristic of normal VO(IV) complexes. EPR spectroscopy likewise indicates the formation of a non-oxo vanadium(IV) complex in the acidic pH range. The anisotropic spectrum in frozen solution at pH $\sim$ 2 points to the parameters g_1 = 1.946, A_1 = 101 10^{-4} cm and g_2 = 1.949, A_2 = 122 10^{-4} cm^{-1}, which may be interpreted as arising from the splitting of the perpendicular vanadium(IV) resonances in a complex with a predominantly d_{z^2} ground state. The d_{z^2} ground state is distinctive of hexacoordinated non-oxo complexes of vanadium(IV) with a geometry distorted

Table V. Cumulative stability constants (log β) for vanadium(IV), vanadium(V) and molybdenum(VI) complexes of DFB

Reaction	log β
Vanadium(IV)[a]	
$VO^{2+} + DFB^{3-} + 3H^{+} \leftrightarrow VDFBH^{2+} + H_2O$	40.13
$VO^{2+} + DFB^{3-} + 2H^{+} \leftrightarrow VODFBH_2^{+}$	37.09
$VO^{2+} + DFB^{3-} + H^{+} \leftrightarrow VODFBH$	29.66
Vanadium(V)[a]	
$VO_2^{+} + DFB^{3-} + 5H^{+} \leftrightarrow VDFBH^{3+} + 2H_2O$	45.0
$VO_2^{+} + DFB^{3-} + 3H^{+} \leftrightarrow VODFBH^{+} + H_2O$	42.46
$VO_2^{+} + DFB^{3-} + 2H^{+} \leftrightarrow VO_2DFBH_2$	37.54
$VO_2^{+} + DFB^{3-} + H^{+} \leftrightarrow VO_2DFBH$	28.74
Molybdenum(VI)[b]	
$MoO_4^{2-} + DFB^{3-} + 6H^{+} \leftrightarrow MoO_2DFBH_2 + 2H_2O$	53.14

[a] Ref. [9], t = 25 °C, I = 0.6 M NaCl.
[b] Ref. [8], t = 25 °C, I = 0.2 M KCl.

toward trigonal prismatic as a consequence of the steric requirements, in order to accommodate three chelate rings around the metal ion [9]. Similar structures are found in V(IV)–tris-catecholates, for example. A speciation diagram and the proposed binding modes of the complexes formed are shown in Figures 8 and 9, respectively.

The kinetics of the formation and hydrolysis of the normal mono- and bis chelated oxovanadium(IV) complexes of DFB: $VODFBH_2^{+}$ and $VODFBH_3^{2+}$ showed that the unwrapping of the bis chelated species appears to be ca. 50 times faster with VO(IV) than with Fe(III). This is qualitatively in accordance with the different charge of the central metal ion. It was found also that formation of the mono-chelated complex proceeds via two parallel pathways involving the hydrolyzed and the non-hydrolyzed VO(IV)-aqua species. The monohydroxo species $VO(OH)^{+}$ was found to react with DFB ca. 10^3 times faster than the $VO(IV)^{2+}$ form [25].

Similar oxo group displacement reactions also occur in the dioxovanadium(V)–DFB system in the acidic pH range 0–3 [9, 27].

$$VO_2^{+} + H_4DFB^{+} \leftrightarrow VODFBH^{+} + H_2O + H^{+}$$

$$VODFBH^{+} + 2H^{+} \leftrightarrow VDFBH^{3+} + H_2O$$

The ^{51}V NMR resonance at -447 ppm can be ascribed to the VO^{3+} complex involving bis- or tris-chelated hydroxamate binding modes, while a further downfield

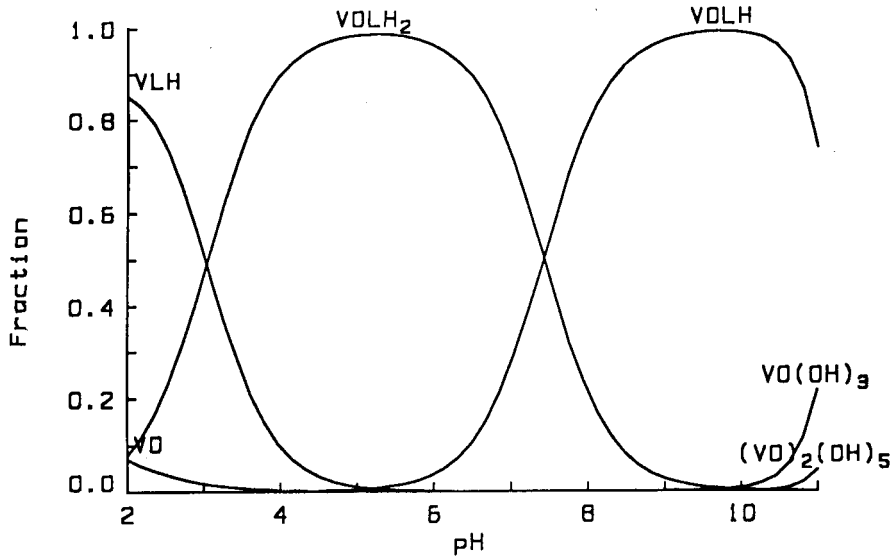


Figure 8. Speciation curves of the complexes formed in the V(IV)–DFB system, c_M = 0.001 mol dm^{-3}, c_{ligand} = 0.005 mol dm^{-3}.

shift of the NMR signal to −199 ppm indicated the formation of a hexacoordinated vanadium(V) complex containing a non-oxo vanadium(V) central ion [9]. Above pH > 5, normal mono- and bis-hydroxamate-chelated VO_2(V) complexes are formed, while at pH > 9, oxoanions of vanadium(V), such as HVO_4^{2-} also occur (see Figure 9), although the formation of other vanadium(V) polyanions is suppressed, due to the exceptionally strong binding ability of the tris-hydroxamate ligand.

It is very interesting, however, that with MoO_4^{2-} partial or full oxo-group displacement does not occur [8]. pH-Metric titration measurements suggested that a single species was formed in the MoO_4^{2-}–DFB system. This species was formed quantitatively at pH ∼ 2 and decomposed above pH ∼ 5 (see Figure 10). The complex formation may be characterized by the simple equilibrium

$$MoO_4^{2-} + H_4DFB^+ + 2H^+ \leftrightarrow MoO_2DFBH_2^+ + 2H_2O. \quad (2)$$

Spectrophotometric measurements clearly indicated that this bis-chelated DFB complex can prevent the formation of polyoxomolybdates [8].

These results reveal that the affinity of the hard donor atoms for highly charged metal ions allows the tris-hydroxamate DFB to displace the oxo groups of the oxocations VO^{2+} and VO_2^+, but not those of MoO_2^{2+}, via complexation reactions. Although the coordination of a single hydroxamate function is not extremely strong, the exceptionally high vanadium(IV)- and vanadium(V)-binding ability of DFB is due to the favorable arrangement of the three bidentate chelating sites within the molecule, which results in a symmetric environment around the sequestered ion. In comparison, molybdenum(V) is less effective in non-oxo complex

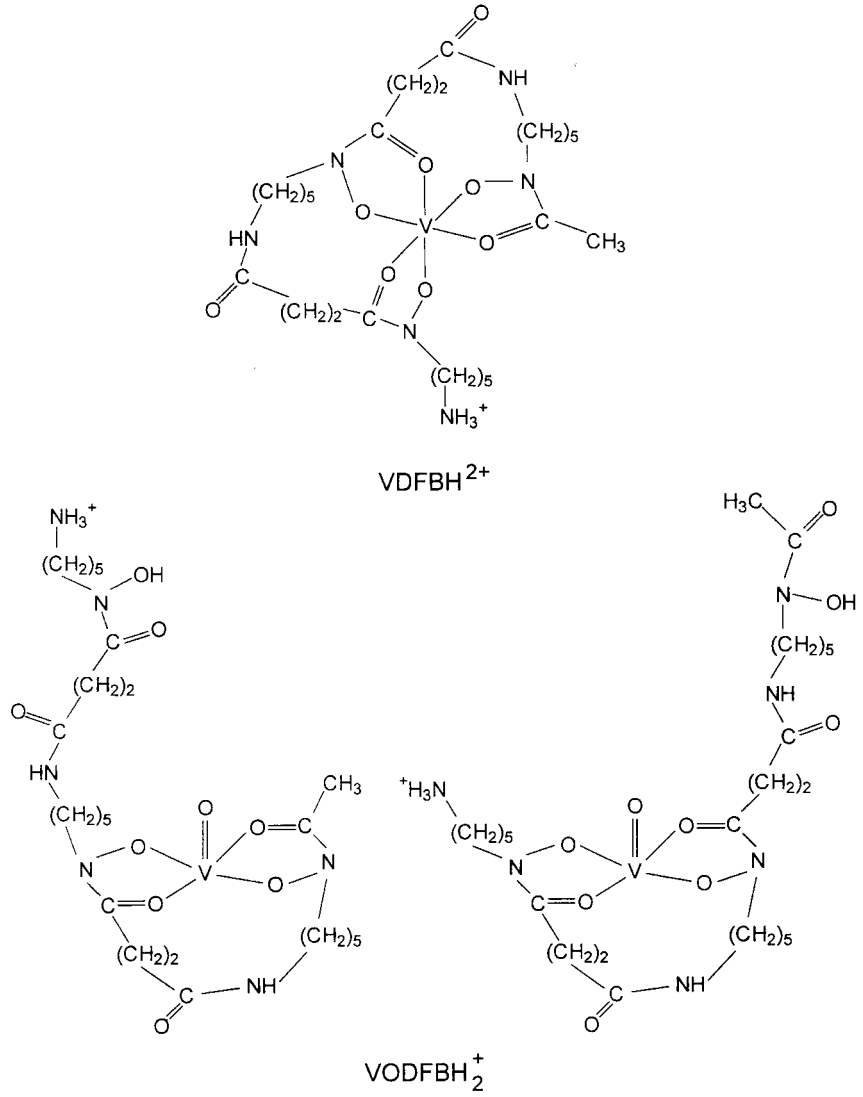


Figure 9. Proposed structures of the vanadium(IV)–DFB complexes.

formation. It forms a bis-chelated MoO_2(VI) complex in the wide pH range 2–6. This difference is most probably due to the higher charge of the central metal ion [8].

4. Medicinal Applications of DFB

The capability of DFB to form high stability complexes with hard metal ions suggested its potential use in the removal of these metal ions from organism in cases of their detrimental accumulation. It forms simple, stable 1 : 1 complexes of relatively

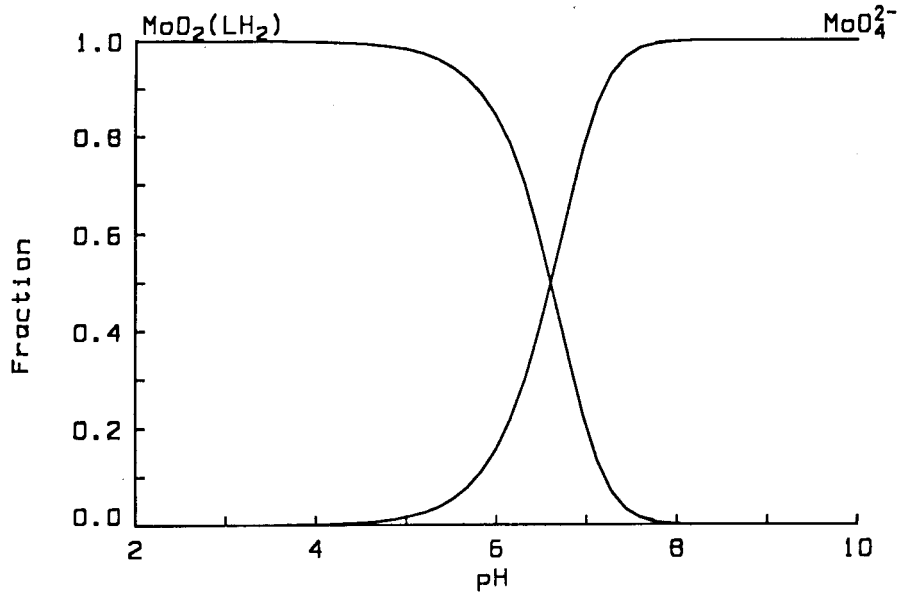


Figure 10. Speciation curves of the complexes formed in the Mo(VI)–DFB system, c_M = 0.001 mol dm^{-3}, c_{ligand} = 0.005 mol dm^{-3}.

low molecular mass with the metal ions, which can easily be removed by excretion. Two practical applications based on chelation-therapy are briefly surveyed here: the removal of Fe(III) and Al(III) in the treatment of metal overload.

The desirable properties of organic chelators [28] for the treatment of iron overload include a high affinity and selectivity for the target metal ion, and a corresponding low affinity for other metal ions, oral effectiveness, access of the chelator to the metal ion pools, a long half-life of the free chelator and, in order to minimize toxicity, a limited lipophilicity of the metal-free chelator, rapid elimination of the metal-ligand complex from the body, and no re-absorption or re-distribution of the metal from the complex. The chelator should be inexpensive, should lack acute toxic effects and should have a good long-term tolerability. DFB meets only some of these requirements.

4.1. IRON OVERLOAD

Normal iron stores in human subjects comprise up to 2 g, present in roughly equal amounts in the reticuloendothelial system, the hepatic cells and the skeletal muscle. The main causes of iron overload can be either the absorption of excessive amounts of iron from the diet (as in the case of haemochromatosis or chronic liver disease) or its accumulation due to repeated blood transfusion (as in the case of thalassaemia). In these diseases, body iron stores can be increased to 15–20 g or more [28]. Accumulations of 200–400 mg Fe/kg may be lethal. Before the regular use of DFB in

transfusional iron overload the life expectancy of patients e.g. with thalassaemia, was no more than 20 years. The intramuscular or subcutaneous administration of DFB results in a significantly prolonged life expectancy, although patients still die from the abnormalities associated with the iron overload. The major limitation to the use of DFB is its lack of effectiveness when administered orally, and particularly in developing countries, its high cost. The need for an inexpensive orally active iron chelator is urgent. There has been very intensive research in this field and strong competition between pharmaceutical firms in order to produce new marketable drugs. Ciba-Geigy plans to introduce a new drug, probably a relative of HBED (N,N'-bis(2-hydroxybenzyl)ethylenediamino-N,N'-diacetate) [29].

4.2. ALUMINIUM OVERLOAD

DFB is now used extensively for the treatment of renal patients for aluminium-related conditions, such as dialysis encephalophathy, osteomalacia and microcytic anaemia. The first (and successful) attempt to remove aluminium from patients with dialysis encephalopathy by using the chelating agent DFB was made in 1979 [30]. The drug operates by raising serum aluminium levels, whilst at the same time appearing to reduce aluminium toxicity. The increased aluminium concentration during DFB treatment is clearly accompanied by changes in Al(III) speciation (the stable $AlDFBH^+$ complex is formed) as relatively large amounts of the element (up to $\sim$95%) may be rapidly removed by dialysis [31]. The most serious side-effects of DFB therapy originate from the ability of DFB to complex Fe(III) and interfere with its metabolism.

There has been a single report in the literature of the use of DFB in the treatment of Alzheimer's disease [32], which showed that sustained intramuscular administration of DFB (which sequestered Al(III)) slowed down the clinical progression of the dementia associated with Alzheimer's disease.

5. Conclusions

The results summarized in this paper reveal how the natures of the metal ions (charge, size, valence-shell electron structure) influence their interactions with the natural iron transport siderophore desferrioxamine B. Because of the biological importance involved a considerable proportion of the publications deal with the structural and kinetic parameters that determine the iron-binding and release properties of DFB and its analogues (see e.g. Ref. [33]). In the knowledge of the relationship between the structural and functional parameters concerted steps can be taken towards the design of supramolecular arrangements, as discussed in a recent paper [34].

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