Coordination chemistry and biology of chelators for the treatment of iron overload disorders

Paul V. Bernhardt*

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Treatment of the medical condition generally referred to as iron overload through the delivery of chelators has recently received a major boost. In 2005 Novartis gained FDA approval for the drug deferasirox, which may be taken orally. Until this time most patients with Fe overload have had to endure long periods of subcutaneous infusions of the orally ineffective drug desferrioxamine (desferal) which has led to major problems with patient compliance. An effective Fe chelator must possess a number of properties for it to be able to complex Fe *in vivo* and be excreted intact. This Perspective will provide an overview of the current state of chelators for Fe overload; both those currently approved and those undergoing preclinical development.

1. Introduction

Iron is an essential and ubiquitous element in all forms of life as it is involved in a multitude of biological processes, yet in excess it is highly toxic. This condition, referred to generally as Fe overload, is not one but many diseases. Space does not permit a comprehensive coverage, and some references to comprehensive reviews on the topic are included.[1–3] Briefly, two of the most common and serious forms of Fe overload result from genetic hemochromatosis (unregulated absorption of Fe from the diet) and transfusional Fe overload.[3] The latter is a side effect of life-sustaining blood transfusions for the treatment of anemias such as β-thalassemia and sickle cell anemia (both conditions associated with abnormal hemoglobin synthesis). Humans are particularly susceptible (more so than other mammals) to Fe overload under conditions of high Fe uptake, since they have no active mechanism for the excretion of excess Fe. Under normal physiological conditions, humans avoid Fe overload by tightly regulated uptake from the diet involving hormones such as hepcidin.[4,5]

There are only a few options available for patients suffering Fe overload including phlebotomy (the periodic withdrawal of blood, the standard treatment for genetic hemachromatosis) or daily chelation therapy, through the administration of drugs that target excess stores of Fe and facilitate is excretion. Other more sophisticated approaches involving gene therapy, or bone marrow and stem cell transplantation offer hope in the future for the prevention of Fe overload but at present these treatments are not viable alternatives to chelation therapy.[6]

Thalassemia, a genetic disorder, in its more severe forms necessitates patients beginning blood transfusions from infancy. If this is not possible, death within the first 4 years of life is almost inevitable.[3] However, these same life-sustaining blood transfusions result in very rapid Fe loading. In the absence of effective chelation therapy to offset associated Fe loading, thalassemia patients die from irreversible damage to the heart and/or liver before 20 years of age. The origin of the toxicity of excess Fe is linked with oxidative stress resulting from so called Fenton chemistry where Fe catalyses the breakdown of hydrogen peroxide to hydroxyl radicals. A simplified version of this reaction, whose mechanism is in no way conclusively established,[7] is shown in eqn (1)

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {}^{\bullet}OH + OH^- \quad (1)$$

The generation of highly reactive hydroxyl radicals within the cell may lead to a number of consequences such as DNA damage[8] and dysregulation of cellular function.[9]

2. Chelation therapy

There are four major issues governing the administration of an Fe chelator: (i) efficacy; (ii) toxicity; (iii) cost and (iv) method of delivery and associated patient compliance with its administration. Obviously a chelator must show a genuine activity to lower Fe levels. To do this the chelator must gain access to tissues where Fe loading has occurred, be able to bind Fe competitively and to

Centre for Metals in Biology, Department of Chemistry, University of Queensland, Brisbane, 4072, Australia. E-mail: P.Bernhardt@uq.edu.au

Paul Bernhardt received his PhD from the University of Newcastle (Australia) in 1991. Following postdoctoral fellowships at the University of Basel and the Australian National University he joined the Chemistry Department at the University of Queensland in 1995. He is currently the Director of the UQ Centre for Metals in Biology.

Paul V. Bernhardt

be excreted as an intact Fe complex. The pM scale was introduced by Raymond and co-workers to provide a way of comparing directly the metal binding affinities of different ligands at physiological pH 7.4 and under typical biological concentrations of metal ions and ligands.[10] The pM value is calculated from the concentration of uncomplexed metal (M, in this case Fe) remaining when a solution containing 1 μM metal ion and 10 μM ligand are at equilibrium at physiological pH 7.4 ($pM = -\log_{10}[M]$).

Fe loading is quantified in humans in various ways including serum ferritin concentrations (the principal Fe storage protein), percentage loading of the Fe transport protein transferrin (normally 20–30% but ~100% for Fe overload sufferers) and liver biopsy. More recently, less invasive MRI methods (the T2* technique)[11] and SQUID magnetic susceptibility protocols[12] have emerged as a way of determining Fe loading in the hearts and livers of patients. These organs are where Fe accumulation results in the most serious medical conditions. Quantifying cardiac Fe loading through T2* MRI appears to be a more reliable method for non-invasive monitoring of the amounts of Fe in the body. Changes in myocardial Fe loading are relatively slow and serve as a good indicator for total body Fe levels,[13] while liver Fe stores are much more kinetically labile and can drop rapidly in response to chelation therapy thus giving a much underestimated indication of total Fe body loading (in particular the heart).

Apart from being non-toxic and active (Phase I and II trials), a new chelator must be able to demonstrate 'non-inferiority' to any currently approved treatment (Phase III trial) in order to gain regulatory approval and to date there are but two that have gained regulatory approval worldwide (desferrioxamine and deferasirox) and one other (deferiprone) has gained limited use in some parts of the world.

The method of administration and the cost of a drug are also very important factors. The incidence of Fe overload from β-thalassemia is at its highest in the developing world. It has been branded an 'orphan disease' in the West due to its rare occurrence.[3] Put another way, an estimated 80–95% of the world's thalassemia patients live in the economically developing areas of the world including South-East Asia, India and the Middle East.[3,14] There has been a continuing controversy surrounding the approval (and non-approval) of certain compounds for the treatment for Fe overload, and economic issues relating to the availability and affordability of drugs in the parts of the world that most need them have fuelled the debate. References to some articles providing an overview of the ongoing discussion are given.[6,15] Without entering into this debate, this review shall focus on the known Fe coordination chemistry of ligands that have shown, or may show, the ability to mobilize Fe from patients suffering Fe overload. The aim is to provide a molecular view of the structure and properties of the chelators and their putative Fe complexes formed *in vivo*.

3. Fe chelators currently in clinical use

(i) Desferrioxamine

The hexadentate chelator desferrioxamine B (DFO) was identified more than 40 years ago as an effective biologically active Fe chelator.[16–19] It was released in the 1960s as the first clinically approved chelator for the treatment of Fe overload. The compound was originally isolated from the fungus *Streptomyces pilosus* where its natural function is indeed as a siderophore (to sequester Fe). Its total synthesis was published[20] some time later. There are other close relatives of DFO that also show similar Fe chelating properties (Fig. 1).

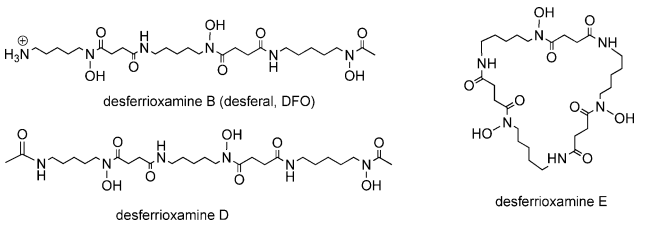


Fig. 1 The desferrioxamine Fe chelators.

DFO forms an Fe^{III} complex of exceptionally high stability (pM 26.6).[21] Crystal structures of this complex have appeared recently[22,23] revealing a distorted octahedral $Fe^{III}O_6$ coordination sphere provided by the three bidentate hydroxamate moieties (Fig. 2). The crystal structures of the ferric complexes of analogues such as desferrioxamine D[24] and desferrioxamine E[25,26] have also been reported. In all cases the ligand binds as a hexadentate O_6 donor where all three hydroxamate groups are deprotonated.

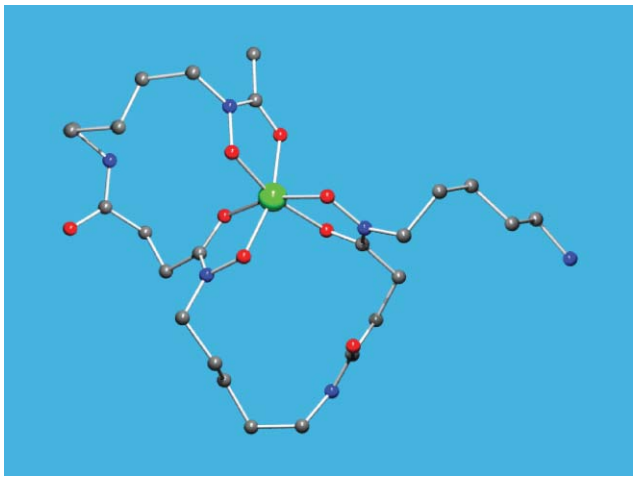


Fig. 2 Crystal structure of ferrioxamine B[22] (H-atoms omitted, Fe - green; O - red; N - blue, C - grey). Coordinates obtained from the Cambridge Structural Database,[27] image created with ORTEP3[28] and rendered with PovRay.[29]

Cyclic voltammetry of $[Fe^{III}(DFO)]^+$ revealed a reversible $Fe^{III/II}$ couple at −475 mV *vs* NHE at pH 7.5,[30] but reversibility is lost at lower pH indicative of protonation of the Fe^{II} complex. The low redox potential indicates that DFO exclusively binds to Fe^{III} *in vivo* and that the ferrous oxidation state is essentially inaccessible to biological reductants.

DFO was patented and developed by Ciba-Geigy in the early 1960s and gained FDA approval in 1968 as a drug for the treatment of Fe overload. Since then, DFO has prolonged the lives of patients afflicted with Fe overload who previously would not have survived past their teen years and has served as the gold standard in Fe chelation therapy. Patent protection of DFO expired only recently and generic versions of the drug have been available since 2003.

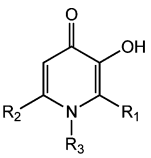
However, DFO has a number of drawbacks. It cannot be given orally but instead it can only be delivered by subcutaneous

infusion. Also, its short plasma life (~20 min) means that infusion must be administered over prolonged and regular periods (16 hours per day, 5–7 days per week). This has resulted in a large proportion of patients (~33%) failing to comply with this regimen.[3] The drug is also very expensive. This is problematic as the incidence of β-thalassemia it at its highest in economically developing regions of the world.

Various polymer-bound analogues of DFO have been reported that maintain the high Fe binding ability of the ligand while improving the method of delivery. A starch-conjugated DFO derivative has been reported[31] that exhibits a much increased plasma life (20–30 h) compared with DFO alone (~20 min). This offers the possibility of a single daily infusion of this conjugate instead of the 12–16 h parenteral delivery of DFO. A different approach, inspired by DFO, has been to produce a hydroxamic acid polymeric hydrogel[32] that may be taken orally and is unable to be absorbed from the stomach where it sequesters Fe before its hyperaccumulation in conditions such as genetic hemochromatosis.

(ii) The 3,4-dihydroxypyridinone (deferiprone) analogues

The problems associated with patient non-compliance and costs associated with DFO therapy have provided the driving force for orally active Fe chelators. The first family of compounds to emerge as potentially orally active drugs for Fe overload chelation therapy were the 3,4-hydroxypyridinone analogues (Fig. 3) and the first reports of the Fe coordination chemistry and biological activity of the lead compound deferiprone (L1) and its analogues appeared about 20 years ago.[33,34]



R_1 = Me	R_2 = H	R_3 = Me	deferiprone (CP20, L1)
R_1 = CONHMe	R_2 = Me	R_3 = Me	CP502
R_1 = $CONMe_2$	R_2 = Me	R_3 = Me	CP509
R_1 = Me	R_2 = H	R_3 = $CH_2CH{=}CH_2$	L1NAll

Fig. 3 The 3,4-dihydroxypyridinone Fe chelators.

All ligands from this family form tris-bidentate-coordinated $Fe^{III}O_6$ complexes. The hydroxyl group in the 3-position deprotonates upon coordination rendering the ensuing Fe^{III} complex charge neutral. A number of tris-chelated Fe^{III} complexes from this family have been structurally characterised (as shown in Fig. 4).[34–38] The Fe coordination chemistry and Fe chelation efficacy of the deferiprone analogues is now very well understood.[39] The ligands are monoprotic acids (pK_a 9–10) and their octanol–water partition coefficients show that they are generally quite hydrophilic ($-1 < \log P < 1$). The complex formation constants for the 1 : 3 Fe^{III} deferiprone complexes are high (pM 20.0) and the tris-coordinated ferric complex of deferiprone is dominant above pH 5.[39,40] Deferiprone when present at millimolar concentrations is even able to compete with serum transport protein transferrin for Fe^{III}.[39] At more clinically relevant (micromolar) concentrations, the 3,4-hydroxypyridinones are not competitive with transferrin for ferric ions. On the other hand, deferiprone has been found to be capable of releasing Fe from the storage protein ferritin, whereas

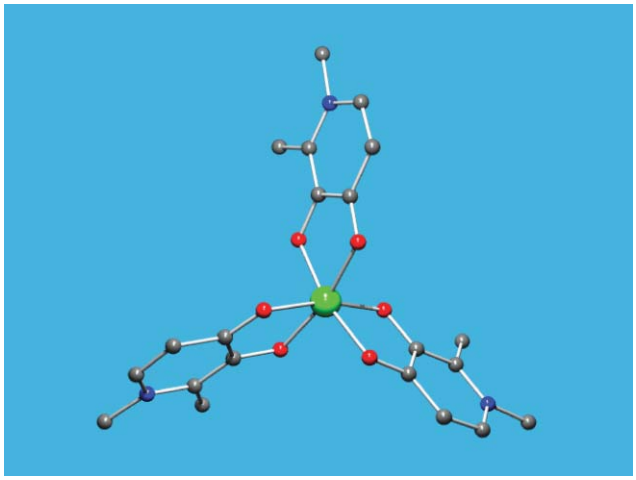


Fig. 4 Crystal structure of the ferric complex of deferiprone[35] (H-atoms omitted, Fe - green; O - red; N - blue, C - grey). Coordinates obtained from the Cambridge Structural Database,[27] image created with ORTEP3[28] and rendered with PovRay.[29]

the larger DFO cannot. This may be attributed to the smaller size of deferiprone and its ability to better penetrate the outer shell of the protein in order to access the ferric oxide/phosphate core of ferritin. A comparative study of the rate at which deferiprone and DFO are able to complex weakly bound Fe within polymeric ferric citrate has been reported.[41] Interestingly, although DFO forms a more stable ferric complex, deferiprone is capable of complexing Fe^{III} at a rate almost 10 times greater under typical physiological concentrations and pH.

Cyclic voltammetry of the ferric complexes of deferiprone, CP502 and CP509 (Fig. 3) revealed reversible $Fe^{III/II}$ redox couples at low potential (from −535 to −620 mV *vs* NHE);[42] too low to be reduced by biological reductants. However, the voltammetry was dependent on the concentrations of complex and ligand. At sub-millimolar concentrations, the apparent redox potentials become pH dependent and undergo large anodic shifts as the pH is successively lowered below pH 9. Partial dissociation of the ferrous complexes is attributed to these observations.

The clinical development of deferiprone and its analogues has been plagued by controversy.[15,43] After promising pre-clinical studies which showed oral activity of deferiprone in animal models,[44–46] mixed reports concerning the toxicity and Fe chelating efficacy of deferiprone in animals[47] and then in humans[48–51] appeared soon afterwards. Development of deferiprone was then stopped by its licensee Ciba-Geigy[52] and heated debate followed[53–55] concerning the purported toxicity of the compound weighed against its possible benefits in being orally active and more acceptable to patients with Fe overload. Later in the 1990s (when under development by the Canadian pharmaceutical company Apotex) controversy again surrounded deferiprone while it was undergoing further human trials.[56]

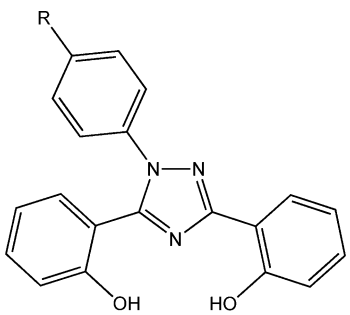
In the absence of a successful Phase III trial (non-inferiority to DFO) deferiprone never gained FDA approval in the USA as a drug for the treatment of Fe overload.[15] However, deferiprone, through its oral activity, was the first compound to address the problem of patient non-compliance with DFO therapy. In 1999 deferiprone finally gained limited approval as an orally administered Fe chelator in Europe (as well in some other parts

of the world) in cases where DFO therapy cannot be given. It is currently available in about 50 countries. Recently deferiprone has found favour in co-administration with DFO[57] and in particular it appears to be effective at reducing severe cardiac Fe loading;[58] the most common cause of fatality of patients with Fe overload.

Deferiprone still has many supporters and new clinical studies continue to appear in parts of the world where the drug is not yet approved.[59] Also a second generation analogue (L1NAll, Fig. 3) has been promoted as a significant improvement to deferiprone.[3] The allyl substituent raises the lipophilicity of the compound and it demonstrates better Fe mobilisation activity than deferiprone. It is metabolised more slowly and apparently is more palatable than the bitter tasting deferiprone.[3]

(iii) Deferasirox and its analogues

The bis-hydroxyphenyl-triazole analogues (Fig. 5) are relative newcomers in the area of clinically useful Fe chelators and there are few papers[60,61] published to date on the Fe coordination chemistry of this compound or its analogues. Much of what is in the public domain appeared in a comprehensive paper by Hegetschweiler and co-workers.[61]



H_2L^x R = COOH (deferasirox)
H_3L^y R = SO_3H
H_3L^z R = H

Fig. 5 The bis-hydroxyphenyl-triazole Fe chelators.

All of the above ligands from this family act as *ONO* tridentate chelates, with deprotonation of both phenolic groups accompanying coordination. The Fe complexes have been isolated and characterised spectroscopically, electrochemically and their formation constants have been determined.[61] Potentiometric titrations of the ligands reveal that the pK_a values of the two phenol groups (in 100% water) lie within the range 8.7 to 11. The pK_a of the carboxylic acid group in deferasirox (H_3L^x) is 3.7 so the ligand is a monoanion at physiological pH 7.4. The Fe^{III} complex formation constants were determined ($\log\beta_1$ = 22.0, $\log\beta_2$ = 36.9) and speciation data indicate that at pH 7.4, the trianionic $[Fe(L^x)_2]^{3-}$ complex is formed exclusively. Electrochemistry of the 1 : 1 Fe^{III} : L complexes at pH 2.9 revealed that reduction to the divalent oxidation state is irreversible and accompanied by rapid dissociation. At pH 12.7, where the bis-ligated complex $[Fe(L^x)_2]^{3-}$ is dominant, a quasi-reversible $Fe^{III/II}$ couple at very low potential (−580 mV *vs* NHE) was seen at a Hg working electrode.[61] The reversibility of this redox couple is diminished at lower pH values, again attributable to partial dissociation of the ferrous complex. A different group reported a similar redox potential (−600 mV *vs* NHE at pH 7.2).[42] In either case it can be concluded that the 1 : 2 Fe : L complexes from this family are effectively redox inactive under physiological conditions. The bis-ligated high spin Fe^{III} complex $[Fe(L^z)_2]^-$ has been characterised crystallographically (Fig. 6).[61]

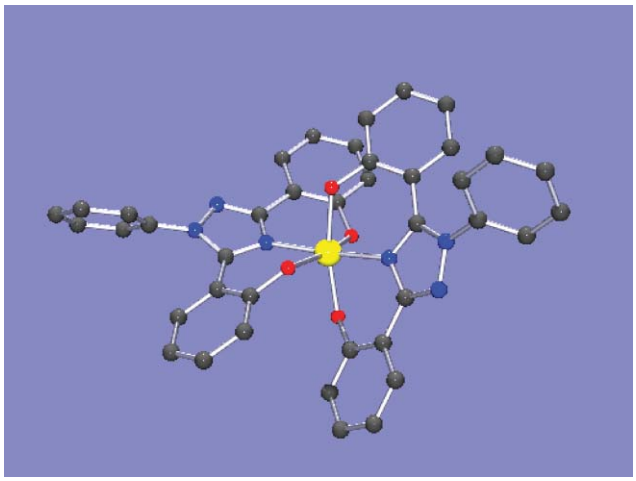


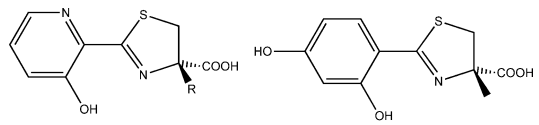
Fig. 6 Crystal structure[61] of the ferric complex of the deferasirox analogue L^z (H-atoms omitted, Fe - yellow; O - red; N - blue, C - grey). Coordinates obtained from the Cambridge Structural Database,[27] image created with ORTEP3[28] and rendered with PovRay.[29]

Deferasirox (trade name Exjade, developed by Novartis) was granted FDA orphan drug status (for fewer than 200 000 potential recipients) and fast-track status (expeditious review of new drugs for life threatening conditions). In 2005 it was approved by the FDA as the first and only drug for use as an orally administered Fe chelator in the USA. It is also available worldwide. Its arrival has been heralded as a great breakthrough in the treatment of Fe overload disorders,[62,63] although recent concerns about its use have been raised in some quarters.[64] Unlike deferiprone which has been given orally in relatively high doses or DFO which must be delivered subcutaneously and continuously over long periods, deferasirox may be administered orally in single daily dose due to its long plasma life (~12 h).

4. New Fe chelators under investigation

(i) The desferrithiocin analogues

The desferrithiocin analogues (Fig. 7) have been known to show a wide spectrum of biological activity for more than 40 years. The first reports with these compounds can be traced to papers from India in the 1960s[65] and 1970s.[66] The Fe complex of the parent compound desferrithiocin was first isolated from *Streptomyces antibioticus* in 1980[67] and the chelator was patented[68] in 1987 and investigated by Ciba-Geigy as a drug for the treatment of malaria.



desferrithiocin R = Me
desmethyldesferrithiocin R = H
deferitrin

Fig. 7 The desferrithiocin analogues.

Desferrithiocin is a diprotic acid with the protonation constants of the phenolic (pK_a 9.9) and carboxylic acid (pK_a 3.3) reported.[69] It is a potentially tridentate *ONO* chelator and the Fe^{III} (and other divalent metal ion) complex formation constants of desferrithiocin and its demethylated analogue (desmethyldesferrithiocin) have been reported (logβ_2 29–30, pM 20.5).[69,70] Despite their relevance to biological activity, publications on the Fe coordination chemistry of the desferrithiocin analogues have been conspicuously rare. The Raymond group reported a comprehensive paper on the Fe complex of desmethyldesferrithiocin (or nordesferriferrithiocin).[70] These chelators, being chiral compounds, lead to a number of possible diastereomers upon complexation with 6-coordinate metal ions.[71] This seemingly has complicated isolation of Fe complexes in isomerically pure forms for crystallographic studies. Indeed very few crystallographically characterised complexes of the desferrithiocin analogues have been published.[70–73] Perhaps the most relevant ones are the Al^{III} complexes of desferrithiocin (Fig. 8) and its demethylated analogue.[70] In any case, the meridional tridentate *ONO* coordination mode of the dianion is clearly established in all known examples. The Fe^{III} complexes exhibit quasi-reversible $Fe^{III/II}$ redox couples in water[70] in the region −160 to −100 mV *vs* NHE, making them accessible to biological reductants.

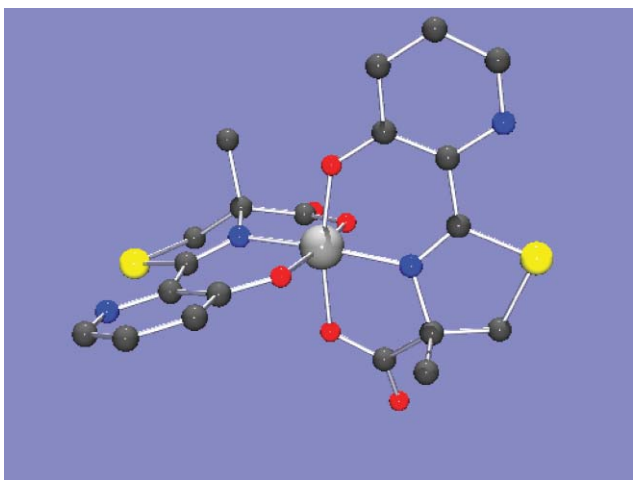


Fig. 8 Crystal structure of the Al^{III} complex of desferrithiocin[70] (H-atoms omitted, Al - light grey; O - red; N - blue, S- yellow, C - dark grey). Coordinates obtained from the Cambridge Structural Database,[27] image created with ORTEP3[28] and rendered with PovRay.[29]

Although desferrithiocin demonstrated high Fe chelating activity and was orally active, it also exhibited unacceptably high toxicity. In particular it was found that the Fe^{III} complex of this ligand was harmful.[74,75] Modifications to the basic structure of the chelator have proven effective in lowering toxicity whilst retaining activity. A significant improvement in this regard was replacement of the pyridyl ring with a phenyl ring (the so called desazadesmethyldesferrithiocin analogues). One of these second generation analogues, deferitrin (Fig. 7), is now undergoing Phase II human trials as an orally active Fe chelator.[76]

(ii) 2-Pyridinecarbaldehyde isonicotinoyl hydrazone (HPCIH) analogues

Our own interest has been in a class of tridentate ligands derived from the parent compound 2-pyridinecarbaldehyde isonicotinoyl hydrazone (HPCIH, Fig. 9). All chelators are monoprotic acids with the hydrazone NH group being the site of deprotonation (pK_a ~10) and consequently they are charge neutral at physiological pH 7.4. The ligands are tridentate *NNO* chelators which coordinate as their monoanion.

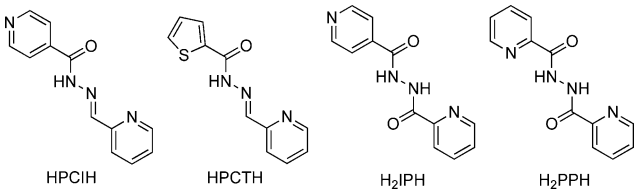


Fig. 9 The HPCIH and H_2IPH analogues.

Unlike most other Fe chelators that have been investigated for potential use in chelation therapy, the HPCIH analogues exclusively target Fe^{II} and not Fe^{III}. This can be attributed to the influence of the 2-pyridyl moiety in stabilising the lower oxidation state in comparison with phenolate or hydroxamate residues found in Fe^{III} chelators such as DFO, deferiprone and deferasirox.

The $Fe^{III/II}$ redox potentials of the Fe complexes HPCIH analogues (> +500 mV *vs* NHE) are outside the range of physiological oxidants. The Fe^{II} complex formation constants with the HPCIH analogues are much lower (pM ~7)[77,78] than found in ferric complexes of DFO, deferiprone and deferasirox. However it is relevant that electrochemical studies coupled with known Fe^{III} complex formation constants of DFO,[30] deferiprone, desferrithiocin[70] and deferasirox[61] indicate that they have an even lower affinity for Fe^{II}. The crystal structure of one of the low spin Fe^{II} complexes of the HPCIH analogues (the 2-bromobenzoic hydrazone) is shown in Fig. 10.

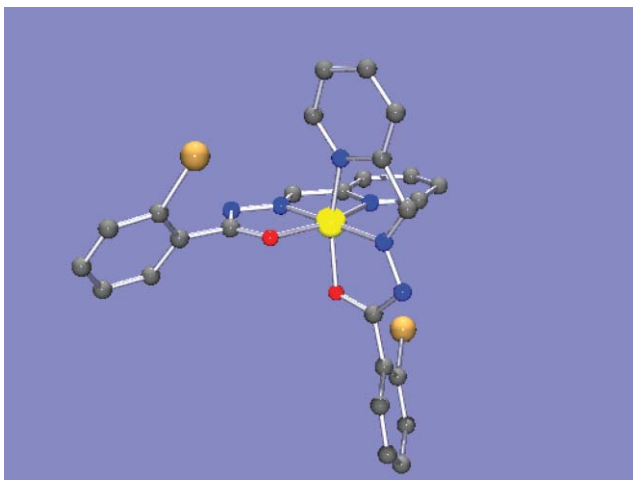


Fig. 10 Crystal structure of the Fe^{II} complex of 2-pyridinecarbaldehyde 2′-bromobenzoyl hydrazone[77] (H-atoms omitted, Fe - yellow; O - red; N - blue, Br- tan, C -grey). Coordinates obtained from the Cambridge Structural Database,[27] image created with ORTEP3[28] and rendered with PovRay.[29]

The HPCIH analogues are very effective at mobilising Fe from Fe-loaded cells and also at preventing further cellular Fe uptake from diferric transferrin.[77,79] They also show low toxicity. Most importantly the lead compound from this group (HPCTH, Fig. 9) has been shown to be orally active in a mouse model.[80]

The fact that the Fe complex formation constants of the HPCIH analogues are modest indicates that a highly stable Fe complex (ferric or ferrous) is not necessary for high Fe chelation efficacy. The so-called labile iron pool or non-transferrin bound iron (NTBI) is a poorly characterised source of intracellular Fe that is believed to be associated with low molecular weight ligands such as citrate and is hence available to chelators. Indeed it is Fe from this NTBI pool that is believed to be the target of current Fe chelators used in the clinic.[81] The levels of NTBI may become elevated in conditions of Fe overload, when serum transferrin becomes saturated (90–100%) with Fe. Under normal physiological conditions transferrin is only 20–30% saturated with Fe. In either case NTBI is believed to be 'in transit' and thus part of a dynamic process of replenishment through cellular Fe uptake or consumption in protein synthesis.[81] The inability of the HPCIH analogues to *directly* compete with transferrin for Fe while (indirectly) being able to prevent cellular Fe uptake from transferrin points to NTBI as the most likely target.

A number of the HPCIH analogues are very effective in mobilising Fe from cells[77,79] yet we have identified functional groups that should be avoided in their design. Most particularly hydrazones with hydrophilic substituents on the non-coordinating aromatic ring such as –OH and $–NH_2$ that impart undesirably high hydrophilicity systematically show poor biological activity. The most active chelators exhibit octanol–water partition coefficients in the range $2 < \log P < 3$.[77] All other physical data (structural, spectroscopic, potentiometric) fail to discriminate between the most and least biologically active Fe chelators.

In the course of our studies of the Fe coordination chemistry of the HPCIH analogues, we identified a most unusual reaction.[82] Complexation of HPCIH with Fe^{III} in aerated neutral aqueous solution leads to the rapid and complete conversion of $[Fe^{III}(PCIH)_2]^+$ (not isolated) to the bis-hydrazine complex $[Fe^{III}(HIPH)(IPH)]$ (Fig. 11). Like their hydrazone parents, the hydrazine H_2IPH (Fig. 9) and its analogues bind as tridentate *NNO* chelators but in this case the central N-donor is one site of deprotonation. The remaining NH group may also be deprotonated upon coordination depending on pH. The crystal structure shown in Fig. 11 finds one ligand doubly deprotonated while the other is singly deprotonated. We have identified both 1 : 1 and 1 : 2 Fe : ligand complexes of these chelators.[83] Most importantly, the H_2IPH analogues have also been found to exhibit excellent Fe mobilisation properties,[83] yet in this case they favour Fe^{III} over Fe^{II}.

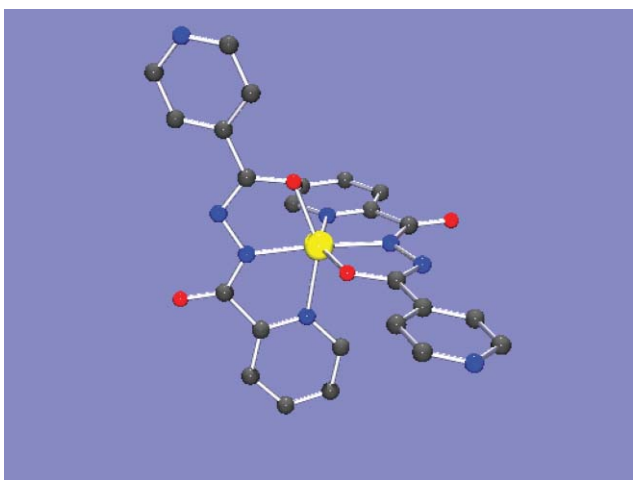


Fig. 11 Crystal structure of the Fe^{III} complex of H_2IPH[82] (H-atoms omitted, Fe - yellow; O - red; N - blue, C - grey). Coordinates obtained from the Cambridge Structural Database,[27] image created with ORTEP3[28] and rendered with PovRay.[29]

The mechanism by which this most unusual hydrazone to hydrazine conversion occurs (a conversion without precedent in the organic chemistry literature) is still a subject of ongoing work but the role of Fe is firmly established as the parent hydrazone (HPCIH) cannot be converted to its corresponding hydrazine (H_2IPH) in the absence of Fe. Partial conversion of the isomeric 2-pyridine carbaldehyde picolinoyl hydrazone to its corresponding hydrazine (H_2PPH) was also found to be catalysed by Fe but in this case a most unusual mixed ligand di-iron triple helicate was found.[84]

5. Future prospects

Chelation therapy has proven to be an effective treatment for Fe overload. β-Thalassemia patients now in their 50s who have undergone DFO chelation therapy since childhood are living proof of the value of this drug. Those afflicted with this disease prior to the emergence of DFO, or who have been unable to cope with the demands or cost of DFO therapy, have typically died in their teens. Compliance with the invasive parenteral administration of DFO remains a major issue and it has been suggested that at least 33% of patients (many of them children) do not comply with its invasive procedure satisfactorily. The very recent emergence of deferasirox as an approved orally active drug is a major breakthrough in the treatment of Fe overload and this compound currently is the benchmark by which all new orally active chelators will be measured in clinical trials. Deferasirox has still only been used for a short time and some patients compliant with DFO therapy have reportedly chosen to remain with this drug until more data become available on deferasirox.[62]

Although structure–activity relationships may be used to tune the biological activity of existing compounds it is still a major challenge to develop an effective Fe chelator that also is non-toxic. It is now apparent that some of the features that were first thought to be critical in the design of an effective Fe chelator such as charge neutrality and high Fe complex formation constants are not prerequisites. There is now a broad spectrum of Fe chelators that have appeared; many of which are charged in both their complexed and uncomplexed state and many of which are unable to compete with targets such as diferric-transferrin for Fe. The complexity of Fe speciation within cells provides different targets (ferric or ferrous Fe) for chelators of various types and it is clear that there are many types of chelators, as yet undiscovered, that may prove effective in the treatment of Fe overload.

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