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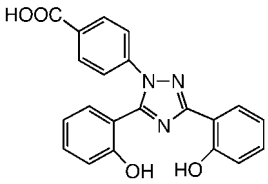
4-[3,5-Bis(2-hydroxyphenyl)-1,2,4-triazol-1-yl]-benzoic Acid: A Novel Efficient and Selective Iron(III) Complexing Agent**

Uwe Heinz, Kaspar Hegetschweiler,* Pierre Acklin, Bernard Faller, René Lattmann, and Hans Peter Schnebli

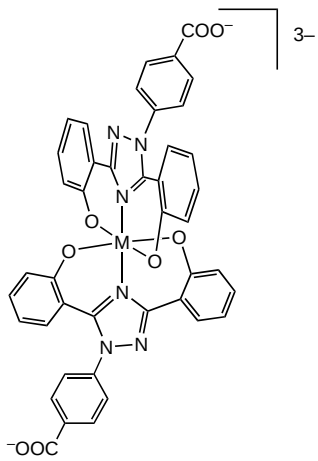
Clinical medicine recognizes several diseases which are due to defects in iron homeostasis.[1] Iron deficiency anaemia is rather common but can be treated easily. By comparison, iron overload is relatively rare but is associated with more severe morbidity. Since man is unable to actively excrete iron, excess iron, once taken up, deposits in tissues in the form of solid FeOOH which then can lead to organ damage and ultimately death. Frequent blood transfusions, as are necessary in the treatment of haematological defects such as β-thalassaemia major (more than 500 000 patients world-wide), are a well recognized cause of iron overload.[2] Therapeutically useful chelators can complex excess tissue Fe^{III}, thus transforming it into a soluble, excretable form. Currently, the siderophore desferrioxamine-B (Desferal) is by far the clinically most widely used chelator. However, this compound has a very short biological half-life and, in addition, cannot be administered orally. Because of this, there has evolved an intensive search for new iron chelators in recent years.[3] Clearly, in addition to low toxicity, appropriate tissue distribution and pharmacokinetics, the metal-binding properties, for example high stability of the Fe^{III} complexes, and high selectivity with respect to other biologically important metals of such compounds will be of central importance.

We herein report on the metal complexing properties of a substituted 3,5-bis(*ortho*-hydroxyphenyl)-1,2,4-triazole in solution. Ryabukhin had already discovered that compounds of this class tend to form complexes with divalent transition metal ions in the form of insoluble polymers.[4] Our studies have shown that the corresponding benzoic acid H_3L[5] exhibits ideal properties for use in the treatment of iron overload. Owing to the good oral bioavailability, tolerance in animal studies, and efficient excretion of iron, this ligand is a possible successor to Desferal.[6]



H_3L

Free H_3L reacts in solution as a weak, triprotic acid, and in the neutral pH range it is present as the carboxylate ion H_2L^-. The nitrogen atoms of the five-membered heterocycle cannot be protonated above pH 2. With Fe^{III} this ligand forms a dark violet 1:1 complex and a deep red 1:2 complex.[7] The peripheral carboxylate group does not participate in the metal-complex formation; [FeL] can therefore be protonated once, and $[FeL_2]^{3-}$ can be protonated twice. In accord with the negative charge $[FeL_2]^{3-}$ is the slightly stronger base. Thus L^{3-} acts as a tridentate meridionally coordinating ligand,[8] where binding of the metal center occurs through the two phenolate groups and one of the nitrogen atoms of the heterocycle. Consequently, the bis complex $[FeL_2]^{3-}$ adopts a *trans*-N_2O_4 coordination. With Al^{III} complex formation is so slow that separate signals for the free ligand, the 1:1 complex, and the 1:2 complex are observable in the ^{1}H NMR spectrum.[9] The individual protonation equilibria, however, exhibit time-averaged signals with pD-dependent shifts. According to these NMR spectroscopic studies, free H_3L is exclusively present below pD 2. In the range $2 < pD < 4$ $[Al(HL)]^+$ is formed, which is subsequently deprotonated to [AlL]. The formation of 1:2 complexes begins above pD 5.5, and at higher pH the 1:1 complex disappears completely. The NMR spectra for the 1:2 complexes show only ten signals for the aromatic protons. Apparently the two ligands are symmetry-equivalent (C_2), which is consistent with the structure proposed for $[ML_2]^{3-}$. In strongly alkaline solutions the complex decomposes to form $[Al(OH)_4]^-$, and in 5 mol dm^{-3} NaOD only the signals of free, deprotonated L^{3-} are observed.



$[ML_2]^{3-}$ (M = Al, Fe)

The various protonation and complex formation equilibria could be elucidated quantitatively by extensive potentiometric and spectrophotometric meas-

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urements. To achieve sufficient solubility over the entire pH range, an H_2O/DMSO mixture with a mole fraction of 0.20 DMSO was generally used.[10] In this medium the pK_a values of H_3L were 4.62(2), 10.13(1), and 12.09(1).[11] When $Fe(NO_3)_3$ and H_3L were combined in concentrations of 5×10^{-4} and 10^{-3} mol dm^{-3}, an acidic solution was obtained in which $[Fe(HL)]^+$ was already formed to an extent of more than 95%. In such a solution the formation constants of the products $[FeL]$, $[Fe(HL)_2]^-$, $[FeL(HL)]^{2-}$, and $[FeL_2]^{3-}$ can be determined by potentiometric titration.[11–13] However, the stability of $[Fe(HL)]^+$ is too high to be measured by using pH-metric methods. This determination was achieved with a series of spectrophotometric measurements.[14] The kinetics of complex formation was also investigated spectrophotometrically.[15] In the acidic range, the kinetics for the formation of $[Fe(HL)]^+$ follow the rate law $d[Fe(HL)^+]/dt = k[Fe^{3+}][H_3L]$, where k is strongly dependent on the pH value: At pH 3.5 the value for k is 7×10^2 s^{-1} mol^{-1} dm^3, at pH 2 it decreases to 30 s^{-1} mol^{-1} dm^3. This result is in good agreement with the concept that the ligand coordinates upon deprotonation. The formation of $[Al(HL)]^+$ proceeds approximately 200 times slower ($k = 3.2$ s^{-1} mol^{-1} dm^3 at pH 3.5).[16] The formation constants of all the Al^{III} complexes were determined potentiometrically.[11] Corresponding studies were also performed for Mg^{II}, Ca^{II}, Cu^{II}, and Zn^{II}. The determination of the formation constants of the Cu^{II} and Zn^{II} complexes proved, however, difficult since the formation of solid phases was observed during the titration.[17] In contrast such precipitation did not occur for Mg^{II} and Ca^{II}.

The results of the equilibria studies are summarized in Table 1. The exceptionally high affinity of L^{3-} for Fe^{III} is demonstrated by the value of 38.6 for $\lg\beta(FeL_2)$. However, the high stability of $[AlL_2]^{3-}$ is a further remarkable feature.

Table 1. Overall formation constants[a] $\lg\beta_{xy}$[b] for the complexes $[ML_xH_y]$ (L = 4-[3,5-bis(2-hydroxyphenyl)-1,2,4-triazol-1-yl]benzoic acid) in H_2O/DMSO.[c]

	Mg^{II}	Ca^{II}	Cu^{II}	Zn^{II}	Al^{III}	Fe^{III}
[ML]	7.6	5.5	18.8	13.3	19.8	23.3
[M(HL)]					24.1	27.5
[ML_2]			23.9	17.5	34.0	38.6
[ML(HL)]					39.4	44.4
[$M(HL)_2$]					44.7	48.7

[a] $\beta_{xy} = [ML_xH_y][M]^{-1}[L]^{-x}[H]^{-y}$. [b] The estimated standard deviations are 0.1 or less. [c] Mole fraction for DMSO: 0.20. For the refinement of the formation constants, the pK_a values of H_3L (4.62, 10.13, 12.09) as well as the total concentration of the reactants were kept constant.

The highly oxophilic Al^{III} is generally believed to have a low affinity for nitrogen donors. The unexpectedly high stability of the Al^{III} complex could be a result of steric factors. The rigid orientation of the donor set having an ideal preorientation, along with the fact that six-membered chelate rings are exclusively formed, obviously favors complex formation with the small Al^{III} cation in particular.[18] In contrast, the affinity for Cu^{II} and Zn^{II} is relatively low, although a preference for nitrogen donors is well established for these metal centers.[19] A rather low affinity for this ligand is also observed with Mg^{II} and Ca^{II}. Particularly, the coordination of a second ligand molecule in dilute solution is not significant. The data thus show that, in view of stability and selectivity, H_3L exhibits ideal conditions for use in the therapy of iron overload. The promising results of the in vivo studies[6] are thus clearly confirmed: In the presence of other biorelevant metals, 4-[3,5-bis(2-hydroxyphenyl)-1,2,4-triazol-1-yl]benzoic acid is a highly selective complexing agent for Fe^{III}. Owing to the high affinity for Al^{III}, the compound could also be of interest for a selective sequestration of aluminum.

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[10] Solubility of H_3L at pH 7.4 in H_2O: 0.4 g dm^{-3}.
[11] All solutions contain the same proportion of DMSO as well as 0.1 mol dm^{-3} KNO_3. The measurements were performed at 25.0 ± 0.1 °C. Because of the constant ionic strength the equilibrium constants are listed as concentration quotients, and the pH value is defined as $-\lg[H_3O^+]$. The calibration of the pH electrode (titration of a 2×10^{-3} mol dm^{-3} HNO_3 solution with KOH) resulted in a value of

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$\lg K_w = -15.56$ for $K_w = [OH^-][H_3O^+]$. The equipment has already been described previously (K. Hegetschweiler, T. Kradolfer, V. Gramlich, R. D. Hancock, *Chem. Eur. J.* **1995**, *1*, 74–88). The computer programs SUPERQUAD (P. Gans, A. Sabatini, A. Vacca, *J. Chem. Soc. Dalton Trans.* **1985**, 1195) and BEST (R. J. Motekaitis, A. E. Martell, *Can. J. Chem.* **1982**, *60*, 2403) were used for evaluation. The complex formation generally took place at such low pH values that hydrolysis of the aqua ions could be neglected.

[12] Spectrophotometric methods were less suited for the evaluation of these subsequent reactions since the spectra of the various protonated complexes differed only slightly. An evaluation with the program SPECFIT[14] in the range $3.4 < pH < 6.4$ yielded the following overall formation constants: $\lg\beta = 23.5(2)$ ($[FeL]$), 38.2(2) ($[FeL_2]^{3-}$), 44.2(2) ($[FeL(HL)]^{2-}$). The formation of $[Fe(HL)_2]^-$, which according to potentiometric measurements (Figure 1) is present to an extent of approximately 10% at pH 5, could not be verified with this method.

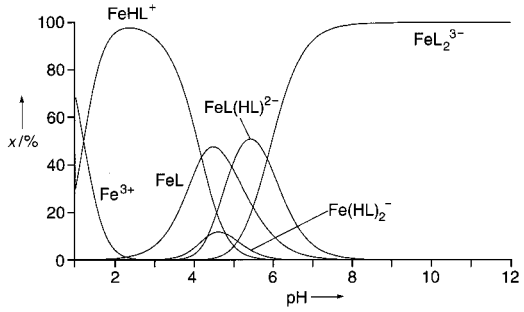

Figure 1. Species distribution (component x [%]) for a complex solution ($[Fe]_t = 5 \times 10^{-4}$ mol dm^{-3}, $[L]_t = 10^{-3}$ mol dm^{-3} in H_2O/DMSO (8/2)). Only the Fe-containing species are shown. The formation constants and the pK_a values from Table 1 were used for the calculations.

[13] A species of the composition Fe:L:H = 1:1:0 can also be interpreted in terms of a binuclear complex [(HL)Fe-(μ-OH)$_2$-Fe(HL)] or [(HL)Fe-(μ-O)-Fe(HL)] (D. M. Kurtz, Jr., *Chem. Rev.* **1990**, *90*, 585–606). The evaluation of the titration curve according to this model, however, led to less satisfactory agreement ($\sigma_{pH} = [\Sigma w(pH_{found} - pH_{calcd})^2/\Sigma w]^{1/2} = 0.0067$ for $[(HL)_2Fe_2(OH)_2]$, $\sigma_{pH} = 0.0023$ for [FeL]).

[14] The determination was performed with solutions of $0.01 < [H^+] < 0.1$ mol dm^{-3}, $[Fe]_t = [L]_t = 1.6 \times 10^{-4}$ mol dm^{-3}, and $\mu = 0.1$ (KNO_3) using a diode array spectrophotometer TIDAS-UVNIR/100-1 from J&M with a HELLMA immersion probe and least squares calculations for evaluation (R. A. Binstead, A. D. Zuberbühler, SPECFIT version 2.10, Spectrum Software Associates, Chapel Hill, NC 27515-4494 (USA); see also H. Gampp, M. Maeder, C. J. Meyer, A. D. Zuberbühler, *Talanta* **1985**, *32*, 257–264).

[15] The measurements were performed at 25 °C on a DX17MV instrument (Applied Photophysics).

[16] The average residence time of a water ligand in $[Al(OH_2)_6]^{3+}$ is approximately 150 times higher than for $[Fe(OH_2)_6]^{3+}$ (D. T. Richens, *The Chemistry of Aqua Ions*, Wiley, Chichester, **1997**).

[17] By analogy with the compounds reported by Ryabukhin,[4] these are probably polymeric complexes. The C,H,N analysis of the Cu complex is in agreement with the formulation $Cu(HL) \cdot 2H_2O$. To prevent the formation of such solid phases, a competition method was used in which the metal cation M^{2+} was applied in the presence of H_3L as either the nitrilotriacetato (NTA) or iminodiacetato (IDA) complex and converted into the 1:2 complex $[ML_2]^{4-}$ by addition of KOH. All the necessary pK_a values and stability constants of H_3NTA and H_2IDA for the H_2O/DMSO system were determined separately.

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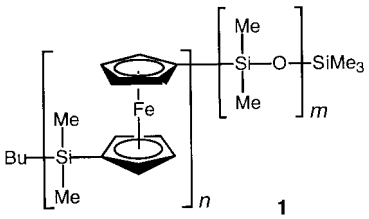
Supramolecular Organometallic Polymer Chemistry: Self-Assembly of a Novel Poly(ferrocene)-*b*-polysiloxane-*b*-poly(ferrocene) Triblock Copolymer in Solution**

Rui Resendes, Jason A. Massey, Hendrik Dorn, K. Nicole Power, Mitchell A. Winnik,* and Ian Manners*

The immiscible segments of a diblock copolymer are known to facilitate self-assembly into a variety of morphologies in the solid state.[1, 2] In solution, the formation of spherical micelles in a block-selective solvent with a core of the insoluble block surrounded by a corona of the soluble block is well known. However, until recently other morphologies have been rare, and even now the number of systems leading to nonspherical morphologies is limited, and our understanding of them remains poor.[3, 4] These phenomena provide an attractive and potentially powerful route to nanostructured materials, as illustrated by recent studies of block copolymer films and solution micelles containing metal or semiconductor nanoparticles in desired domains.[5]

As part of our research on novel poly(ferrocene) block copolymers,[6, 7] we recently reported studies of the self-assembly of the organometallic–inorganic block copolymer poly(ferrocenyldimethylsilane)-*b*-poly(dimethylsiloxane) (PFS-*b*-PDMS, **1**; PFS:PDMS block ratio 1:6, $M_n = 3.51 \times 10^4$, polymer dispersity index (PDI) = 1.10) in the solid state and in solution.[8] Thin films of this material self-assemble to form a



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$n : m = 1.0 : 6.0$

hexagonal array of PFS cylinders within a PDMS matrix, whereas in *n*-hexane, a solvent selective for the PDMS block, cylindrical micelles are formed with a core of PFS surrounded by a sheath of PDMS. As the poly(ferrocene) homopolymer becomes semiconducting on oxidative doping and forms

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