

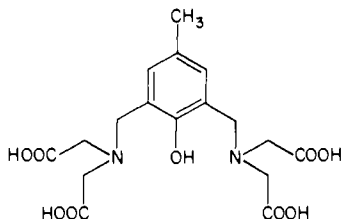
Structures of Binuclear and Tetranuclear Iron(III) Complexes as Models for Ferritin Core Formation

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Oxo-bridged iron units have been found to serve as the metal sites of a variety of proteins. Hemerythrin and ribonucleotide reductase have been shown to have binuclear iron centers bridged by an oxo group, while the purple acid phosphatases are proposed to have a similar site because of the presence of strong antiferromagnetic coupling.¹ Ferritin, the mammalian iron storage protein, consists of a polynuclear iron-oxo core surrounded by a protein shell.^{2,3} In an effort to model such sites, we have prepared iron(III) complexes of the binucleating ligand *N,N'*-(2-hydroxy-5-methyl-1,3-xylylene)bis(*N*-(carboxymethyl)glycine)⁴ (L). A binuclear complex is isolated from acid solution, while



a tetranuclear complex is formed in basic solutions. The structure of the tetranuclear complex is unique and distinct from the other two examples of a polynuclear iron-oxo complex with greater than three iron centers.⁵ A comparison of the structures of these complexes of the same binucleating ligand may provide insight into the nucleation process involved in the formation of the ferritin core.

Addition of 2 equiv of base followed by 1 equiv of iron(III) to an aqueous solution of L results in the formation of a purple complex (λ_{\max} 545 nm, ϵ_M 1100) with a spectrum quite similar to that observed for the iron(III) complex of *N*-(*o*-hydroxybenzyl)-*N*-(carboxymethyl)glycine.⁶ This complex is most likely the mononuclear iron(III) complex of L. Addition of a second aliquot of base and iron(III) to the purple solution yields a red solution (λ_{\max} 460 nm, ϵ_M 635) from which crystals of a complex having the stoichiometry $\text{Fe}_2\text{L}(\text{OH})(\text{H}_2\text{O})_2$ are obtained. Further addition of an equivalent of base per iron(III) affords an orange solution (λ_{\max} 350 nm, ϵ_M 5900; 550 nm (sh), ϵ_M 190), from which a complex with the formulation $\text{Q}_4[\text{Fe}_4\text{L}_2(\text{O})_2(\text{OH})_2]$ is obtained.

Paramagnetic NMR spectra of the complexes indicate the presence of antiferromagnetic interactions in the binuclear and tetranuclear complexes, resulting in the progressive decrease in the isotropic shifts observed for the mononuclear, binuclear, and tetranuclear complexes. The isotropic shifts observed for high-spin ferric complexes are proportional to the Fermi contact interaction constant and the susceptibility of the complex.⁷ The former would be expected to be similar for similar complexes;⁸ thus the decrease

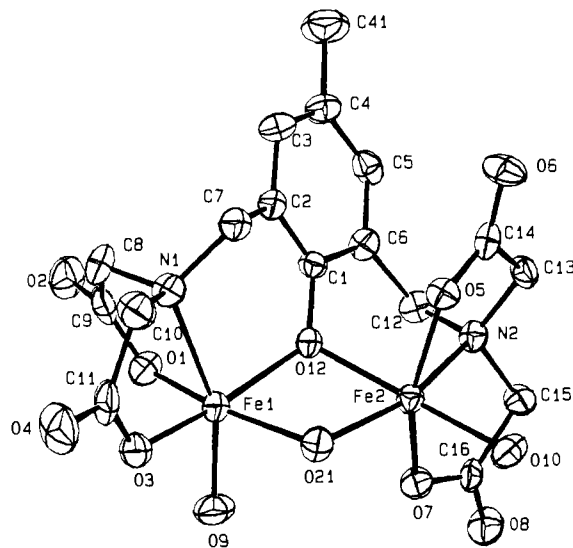


Figure 1. Structure of $[\text{Fe}_2\text{L}(\text{OH})(\text{H}_2\text{O})_2]$ showing 50% probability ellipsoids and atom labeling scheme. Hydrogen atoms omitted for clarity. The iron-phenolate bonds Fe1-O12 and Fe2-O12 are 2.002 (3) and 2.019 (4) Å, respectively. The iron-hydroxy bonds Fe1-O21 and Fe2-O21 are 1.979 (4) and 1.940 (3) Å, respectively. The iron-carboxylate distances are all 1.97 ± 0.01 Å. The iron-iron separation is 3.14 Å.

observed would reflect primarily changes in the susceptibility of the complexes.^{7,9} The resonance of the para methyl group on the binucleating ligand occurs at 58 ppm for the binuclear complex in D_2O , compared to 90 ppm in the mononuclear iron complex of this ligand. This corresponds to a ca. 35% decrease in isotropic shift and is indicative of a weak antiferromagnetic interaction ($-J < 15 \text{ cm}^{-1}$). On the other hand, the methyl resonance of the tetranuclear complex appears at 8.6 ppm, corresponding to a >90% decrease in isotropic shift and strong antiferromagnetic coupling ($J \sim -100 \text{ cm}^{-1}$). The solid-state magnetic moments of the binuclear and the tetranuclear complexes, 5.1 and $1.7 \mu_B$, respectively, are consistent with these observations.

The binuclear complex can be recrystallized from water to afford small parallelepipeds in the space group $C2/c$ suitable for X-ray analysis.¹⁰ An ORTEP plot of the binuclear complex is shown in Figure 1. The iron centers are coordinated in distorted octahedra and bridged by the phenolate and hydroxide oxygen atoms, which are somewhat asymmetrically disposed between the irons. These bridging units would be expected to mediate a weak antiferromagnetic interaction between the iron centers. Indeed, $\text{Fe}_2(\text{sal}_3\text{trien})(\text{OH})\text{Cl}_2$, a binuclear iron(III) complex of similar structure with metal centers bridged by phenolate and hydroxide, exhibits a J of -8 cm^{-1} .¹¹ For $\text{Fe}_2\text{L}(\text{OH})(\text{H}_2\text{O})_2$, two water ligands complete the coordination shells and provide exchangeable sites for binding other ligands. The binding of peroxide to the binuclear complex has been observed, yielding an unstable and reactive complex, and will be the subject of a future report.

Crystals of the tetranuclear complex in the space group $P2_1/n^{12}$ were obtained by slow vapor diffusion of acetone into a methanolic

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(10) $[\text{Fe}_2\text{L}(\text{OH})(\text{H}_2\text{O})_2]$ cell constants are $a = 21.074$ (6) Å, $b = 10.260$ (3) Å, $c = 23.931$ (9) Å, $\beta = 102.25$ (3)°, $Z = 8$, $V = 5056.3$ Å³. With the use of 2502 of 3971 reflections, for which $I(\text{obsd}) > 1\sigma(I)$, collected at 298 K with Mo K α ($\lambda = 0.71073$ Å) radiation out to $2\theta = 48^\circ$ on an Enraf-Nonius CAD4 X-ray diffractometer, the structure was solved by Patterson and Fourier methods and refined anisotropically to $R_1 = 0.054$, $R_2 = 0.058$.

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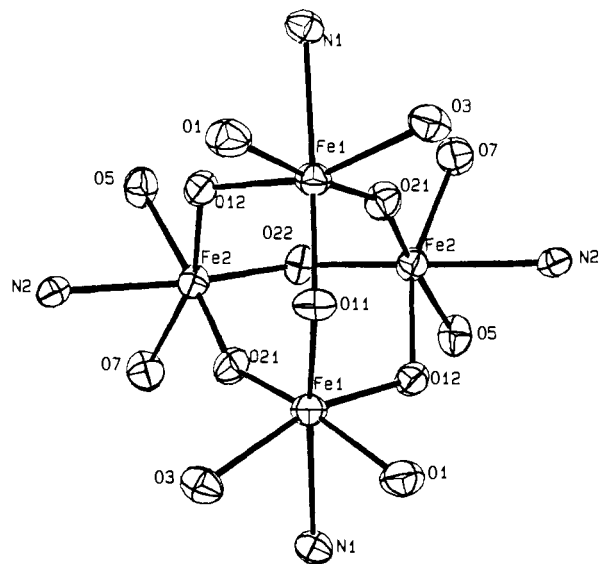


Figure 2. Structure of the Fe_4O_6 core of $[\text{Fe}_4\text{L}_2\text{O}_2(\text{OH})_2]^{4+}$ showing 50% probability ellipsoids and atom labeling scheme. The tetrahedral iron core is cumulatively bridged on each edge by two phenolates (Fe1-O12, 2.074 (3) Å; Fe2-O12, 2.084 (3) Å), two hydroxides (Fe1-O11 and Fe2-O22, both 1.989 (2) Å), and two oxo ligands (Fe1-O21, 1.792 (3) Å; Fe2-O21, 1.790 (3) Å). The iron-iron separations across the phenolate, the hydroxo, and the oxo bridges are 3.631 (1), 3.442 (1), and 3.469 (1) Å, respectively, with Fe-O-Fe angles of 121.65 (13)°, 119.24 (24)°, and 151.23 (19)°, respectively. The iron-carboxylates range from 2.095 (3) Å for Fe2-O5 to 2.127 (3) Å for Fe1-O3.

solution of the binuclear complex with an excess of pyrrolidine. An ORTEP plot of the Fe_4O_6 core is shown in Figure 2. Two binuclear pieces have fused into a distorted tetrahedron of irons bridged by six oxygens in a structure similar to that of $(\text{tacn})_4\text{Mn}_4\text{O}_4$.¹³ In the process of fusion, two water ligands are displaced. The four iron atoms are coordinated in distorted octahedra and cumulatively bridged by two phenolates, two hydroxides, and two oxo ligands. The oxo bridges undoubtedly provide the pathway for the strong antiferromagnetic coupling observed for this cluster.

Comparison of the iron-ligand bond lengths for the two structures reveals substantial weakening of the bonds to the binucleating ligand in the tetranuclear complex. The iron-phenolate bond lengths have increased by about 0.07 Å and the iron-carboxylate bond lengths by at least 0.12 Å. Correspondingly, short Fe-oxo bonds (1.79 Å) in the tetranuclear complex replace the Fe-OH₂ bonds (2.01 Å) in the binuclear complex. Although phenolates are unlikely to be involved in the coordination of iron in ferritin,¹⁴ these observations may be relevant to the formation of the iron core of ferritin. Various studies have suggested the importance of binuclear complex formation in initiating core nucleation in ferritin.^{2,15,16} The protein shell, probably via its carboxylates, plays an important role in this process.^{2,16-18} The conversion of the binuclear complex to the tetranuclear form that we observe suggests the next stage in the process, where the core-protein shell interactions weaken and the continuation of core growth occurs on the core itself without the aid of the protein shell.

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Supplementary Material Available: Tables of atomic positional and thermal parameters for $[\text{Fe}_2\text{L}(\text{OH})(\text{H}_2\text{O})_2] \cdot 3.8\text{H}_2\text{O}$ and $(\text{C}_4\text{H}_{10}\text{N})_4[\text{Fe}_4\text{L}_2(\text{O})_2(\text{OH})_2] \cdot 2\text{CH}_3\text{OH} \cdot \text{C}_3\text{H}_6\text{O} \cdot \text{H}_2\text{O}$ (11 pages). Ordering information is given on any current masthead page.

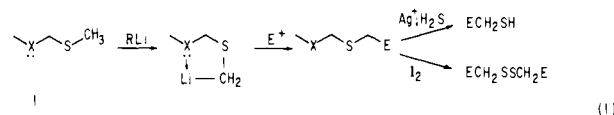
(2-Tetrahydrofuranyl)- and (2-Tetrahydropyranyl)(thiomethyl)lithium: Methanethiol Carbanion Equivalents

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Alkanethiols are of considerable importance as starting materials for preparation of a vast array of sulfur-containing structures. It is therefore surprising that synthetic approaches to these key compounds are quite limited.¹ We sought a fundamentally new approach to alkanethiol synthesis based on a methanethiol carbanion (HSCH_2^-) synthon which would permit carbon functionalization with the wide range of reagents employed in carbanion chemistry.^{2,4} A reagent **1** containing carbon geminally substituted with a thiomethyl group and an oxygen or nitrogen substituent seemed suitable for our purposes since the latter group could assist deprotonation of the thiomethyl group by metal coordination⁷ and could subsequently facilitate hydrolytic release of thiol along with water-soluble carbonyl byproducts (eq 1).⁸ We further envisioned that cleavage of the protected thiols



under oxidative conditions could lead directly to disulfides.⁸ Thus the initial reagent could also serve as a $^-\text{CH}_2\text{SSCH}_2^-$ synthon. Of the several reagents examined, 2-(methylthio)tetrahydrofuran (**2**) and 2-(methylthio)tetrahydropyran (**3**) seemed ideal. We describe herein the generation and electrophilic substitution of (2-tetrahydrofuranyl)(thiomethyl)lithium (**4**) and (2-tetra-

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