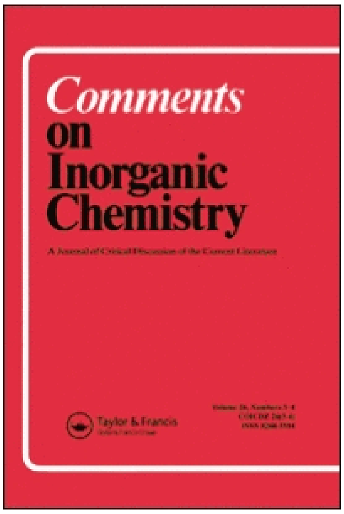

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Polyiron(III) Oxyhydroxide Clusters: The Role of Iron(III) Hydrolysis and Mineralization in Nature

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Polyiron(III) Oxyhydroxide Clusters: The Role of Iron(III) Hydrolysis and Mineralization in Nature

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The compounds which form in aqueous solutions containing iron(III) and chelating ligands are considered and the control of iron(III) hydrolysis as a synthetic strategy for the preparation of iron(III) species of different nuclearities is explained. The relevance of such complexes to naturally occurring iron species is discussed. Hydroxide, oxide, carboxylate and alkoxide bridged iron(III) aggregates are compared to iron(III) clusters in Nature with particular attention paid to the way in which their formation can aid in understanding the biomineralization of iron. The structures of trapped mineralized iron(III) oxyhydroxide clusters are proposed as good models for the iron storage protein ferritin, which itself is best regarded as a cluster species. Synthetic strategies for producing clusters of different shapes and sizes are suggested.

Key Words: *iron(III) chemistry, iron(III) clusters, iron(III) hydrolysis, oxyhydroxide and oxide minerals, biominerals and biomineralization, ferritin, structures of iron(III) complexes and clusters*

1. INTRODUCTION

Iron is the most abundant transition metal on Earth and the fourth most abundant element in the Earth's crustal rocks after oxygen,

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silicon, and aluminum. Virtually every form of life, with the exception of a couple of specialized bacteria, has a requirement for iron.[1] The importance of iron for biological systems stems from a combination of its abundance and its ability to take part in a large number of reactions important in biology, such as electron transfer, oxygen transport and storage, and catalysis.[2] Most of the iron is recycled within an organism being transported within the protein transferrin and stored in the form of an iron(III) oxyhydroxide mineral which is contained within the protein ferritin.[3] The aqueous solution chemistry of iron is dominated by the +2 and +3 oxidation states, which form complexes which easily undergo electron transfer and acid–base reactions. The redox potential of the metal can be modified by varying the interaction with the coordinating ligands. In the early days of life on Earth, the atmosphere was strongly reducing and the +2 oxidation state of iron predominated. As the composition of the atmosphere changed, most dramatically with the release of large quantities of oxygen by photosynthesis, the +3 oxidation state began to predominate in the form of oxide and oxyhydroxide sediments. One consequence of this was that organisms had to develop means of obtaining the iron from insoluble iron(III) species rather than from the soluble iron(II) forms which were available in the sea when the atmosphere was more reducing.[4] Once the iron has been assimilated by an organism it is important that its oxidation state, speciation and reactivity are controlled. Free iron is a toxic species which can catalyze the formation of free radicals and cause damage to cells[5]:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + OH\cdot$$

Ferritin acts as a safe container for the iron, storing it in the form of an unreactive but accessible iron oxyhydroxide.

2. THE HYDROLYSIS OF IRON. MINERALIZATION

The chemistry of iron(III) in aqueous media, as a high spin d^5 ion, is dominated by two features: its hydrolysis and the lack of any ligand field stabilization effects in determining its coordination number and the arrangement of the ligands around the metal. One

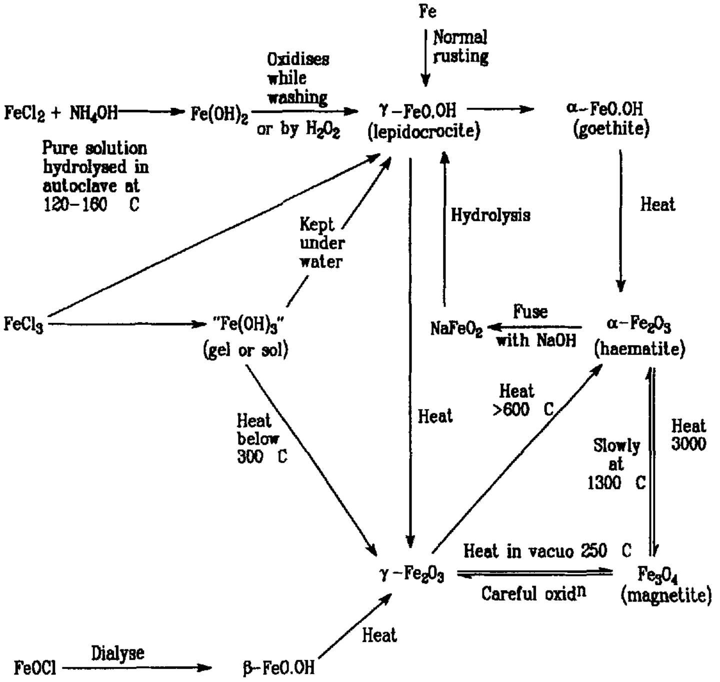


FIGURE 1 The relationship of iron oxyhydroxide and oxide compounds (adapted from Ref. 6).

of the most characteristic features of iron(III) chemistry is its hydrolysis to form iron oxyhydroxide and oxide phases. In fact, the iron can be initially in the +2 or even zero oxidation state, as illustrated in Fig. 1.

For the purposes of this article we confine our attention to iron(III). Iron(III) has an outstanding ability to activate OH bonds as evidenced by its ready hydrolysis. This means that in aqueous solutions of iron(III) water molecules are activated on coordination to the metal center and deprotonate. This is also true for other OH containing ligands as will be seen in Section 4.5. A number of factors can influence the types of species which form in hydrolyzed iron(III) solutions. The overall hydrolysis reaction can be written according to Scheme 1, where intermediate species containing *x* iron centers are formed. The structure of these precursors will

$$(\mathrm{Fe(H_2O)_6})^{3+} \Leftrightarrow \{\mathrm{Fe}_x(\mathrm{O})_y(\mathrm{OH})_z(\mathrm{H_2O})_p\}^{(z+2y-3x)^- \text{ or } (3x-z-2y)^+}$$

$$\Leftrightarrow \text{“Fe(OH)}_3\text{” oxyhydroxide and oxide mineral phases}$$

SCHEME 1

probably influence the phase of the oxyhydroxide mineral formed, which in turn will affect any oxide form which the mineral might age into.

Schneider[7] has detailed some of the structures which can be envisaged once more than 2 iron centers are linked. The local pH gradient is important in determining the sizes of structures which result. Water itself is a rather weak base, but if a stronger base, such as hydrogen carbonate, is present, there will be a high local pH gradient resulting in a small number of large polynuclear complexes. Bases such as imidazoles, which give rise to a low local pH gradient on mixing, form a large number of smaller polynuclear complexes.[8] It is also recognized that the presence of certain anions, such as Cl$^-$, can influence the structural type of the mineral formed: in this case β-Fe.O.OH rather than the α form.[6] Alternatively, as has been demonstrated by Mann and co-workers,[9,10] small amounts of organic species, such as nitrilotriacetic acid, can influence the crystal morphology so that, for example, growth along one of the crystal axes will be favored. These factors are utilized by Nature in both mineralization and biomineralization processes. In most natural systems ligating groups such as carboxylates, amino groups, phenolates, and imidazolates are readily available from, for example, protein side chains. The presence of these groups will modify the hydrolysis of iron(III) in some way, and the reaction scheme below comes into operation, where L^{m-} is a ligand:

$$\{\mathrm{FeL}_n\}^{(mn-3)^-} \Leftrightarrow \{\mathrm{Fe}_x\mathrm{L}_n(\mathrm{O})_y(\mathrm{OH})_z(\mathrm{H_2O})_p\}^{(mn+z+2y-3x)^- \text{ or } (3x-mn-z-2y)^+}$$

$$\Leftrightarrow \text{“Fe(OH)}_3\text{” oxyhydroxide and oxide mineral phases}$$

SCHEME 2

Scheme 2 is our springboard for the rest of this article. Using examples drawn from Nature and from compounds synthesized in the laboratory we can see how control of iron(III) hydrolysis can yield substances tailored for specific purposes. Understanding how this can be achieved will enable us, for example, to maintain iron in soluble easily assimilated monomeric forms; in the form of relatively small clusters; or indeed in mineralized forms in which iron can be stored or fulfill a structural or magnetic role.

3. LOW NUCLEARITY OXYHYDROXIDE SPECIES IN NATURE

Mononuclear and dinuclear iron centers are found in a variety of biological situations. In addition, the oxo-bridged $[\mathrm{LFeOFeL}]^{n+/n-}$ species is important in aqueous environments. Oxyhydroxide bridged oligomeric species are also likely to be common in hydrolyzing environments such as natural waters and possibly also in the gut.

3.1 Mononuclear and Dinuclear Species

Monomeric iron(III) species predominate when there is an excess of ligand present. Perhaps surprisingly at first glance, the amount of base present in aqueous solutions containing iron(III) and excess ligand need not affect the speciation of the iron over a large pH range. It turns out that the speciation is dependent on the ligand properties as explained in Section 4. For example, it is possible to isolate compounds such as $\{\mathrm{Fe(nta)_2}\}^{3-}$ at pH's up to 10 (see Section 4.5). These monomeric iron(III) species are examples of the left-hand extreme of Scheme 2. For iron(III) high spin systems there will be no ligand field stabilization and so there are no restriction on geometry so that iron(III) easily forms 7 coordinate compounds and also compounds with mixed donor sets. This behavior is illustrated in the following sections.

3.1.1 Monomeric Iron(III) Species in Nature

Getting iron(III) into and maintaining iron(III) in a monomeric and water-soluble form is important for iron assimilation by organisms (which are essentially aqueous solutions!). Some lifeforms get iron directly from the Earth's surface, and use specially de-

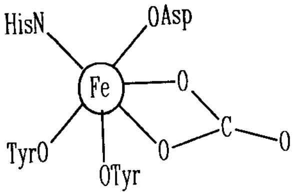


FIGURE 2 The coordination environment of iron(III) in transferrin.

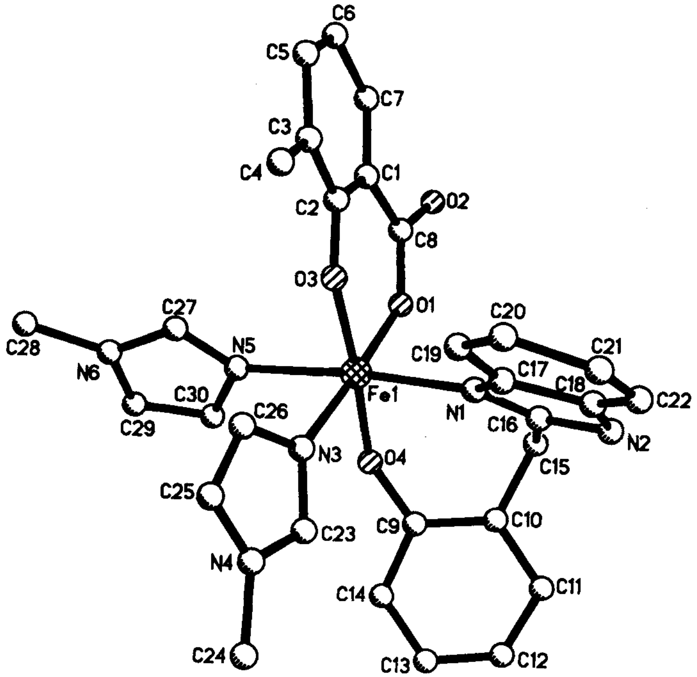


FIGURE 3 A model for the coordination environment of iron(III) in transferrin (Ref. 14).

veloped chelating agents called siderophores[11] to dissolve up the iron. Higher organisms must obtain it through the diet, and it is found that the presence of certain chemicals enhances or inhibits the iron uptake,[12] probably because they hold the iron in a form which can or cannot be transported across the gut. Transferrin, which transports iron around the body, has a monomeric unsymmetrical iron site as indicated in Fig. 2. Several compounds modelling the transferrin sites have been synthesized,[13] the most convincing of which are the ternary iron(III) complexes with bidentate salicylate and phenolate-benzimidazole based ligands. The bis N-methylimidazole adduct of one of these is shown in Fig. 3.[14] Other biologically important monomeric iron(III) sites are found in enzymes such as the catecholases[15] which again display unsymmetrical iron binding.

3.1.2 Naturally Occurring Dimeric Iron(III) Species

In situations where there is more than one iron center present, these are often connected by oxide and hydroxide bridges. The Fe–O–Fe motif is found in a variety of chemical and biochemical situations. The $[Fe^{III}-O-Fe^{III}]^{4+}$ unit is important in the hydrolysis of iron(III) and can be trapped by supplying ligands to block the other five hydrolysis sites on the iron centers. A substantial number of complexes containing this unsupported oxide bridge unit has been reported and crystallographically characterized[16,17] (see Section 4). However, none of these reproduces the spectroscopic properties of the oxo-bridged di-iron centers known to exist in proteins which appear to require support to the oxide bridge in the form of further bridging ligands such as carboxylate or phosphate. In fact, multiply bridged di-iron centers can be produced *in vitro* quite easily by so-called spontaneous self-assembly reactions.[18] The most successful endeavors have been in producing models for the oxygen transport protein haemerythrin. Protein crystallography and extensive magnetic and spectroscopic studies have been performed[19–21] and show that the active site consists of two iron centers linked by an oxide or hydroxide bridge and two carboxylate residues from protein side chains. The deoxy-form consists of two Fe(II) centers while the oxy-form has both irons in the +3 oxidation state.[13] Nearly all the model compounds seek to reproduce the features of the inactive met-form. More recently the protein crystal structure of ribonucleotide reductase (RR) has been determined, revealing that the oxide bridge between the two iron centers is supported by just one carboxylate bridge.[22] Crystallographically characterized models containing two iron(III) centers have been reported as well as iron(II) systems which react irreversibly with dioxygen.[23,24] Two other proteins, purple/pink acid phosphatase (PAP) and methane monoxygenase (MMO), are thought to contain di-iron centers on the basis of spectroscopic and magnetic evidence. Lack of definitive structural data for these has encouraged the exploration of the chemistry and properties of di-iron models bridged by a range of bidentate ligands.[25–27] In all these cases, the di-iron(III) forms are inactive.

It turns out that the aquo dimer with an unsupported oxo bridge can be formed even in the presence of carboxylate functions if they are part of a chelating ligand. It should be recognized that proteins are able to provide specific binding sites with defined geometries through folding of the backbone whereas no such constraints exist in normal aqueous environments. This has led biomimetic chemists seeking to model iron(III) sites in proteins to create special conditions with essentially non-aqueous media and sterically demanding ligands in order to reproduce the features of the biological sites. Since the hydrolysis of iron(III) is such an important natural process, it is of interest to discover how various ligands modify the speciation of the iron. Of course it may be that the $[Fe-O-Fe]^{4+}$ dimer does have a role in biology, for example at the active sites of enzymes such as PAP whose structure is not yet known. In any case, this species will be important in any aqueous environment including natural waters and the gut. These dimeric species also provide the simplest systems for testing out theories of magnetic coupling.[17]

4. AN INVESTIGATION OF THE COMPOUNDS FORMING IN THE EARLY STAGES OF IRON(III) HYDROLYSIS AND MINERALIZATION

The following sections illustrate how factors such as ligand type affect the speciation of iron(III) when the equilibrium in Scheme 2 lies towards the left-hand side. The examples are mostly drawn from work done in this laboratory.

4.1 The Ligands Used

A series of polydentate polycarboxylate ligands—ethylenediaminetetracetic acid (H_4edta = $[CH_2N\{CH_2COOH\}_2]_2$), iminodiacetic acid ($H_2ida = HN(CH_2COOH)_2$), diglycolic acid, ($H_2digly = O(CH_2COOH)_2$, nitrilotriacetic acid ($H_3nta = N(CH_2COOH)_3$), N-2-(acetamido)iminodiacetic acid ($H_2ada = N(CH_2COOH)_2(CH_2CONH_2)$), and N-2-(hydroxyethyl)iminodiacetic acid ($H_3heidi = N(CH_2COOH)_2(CH_2CH_2OH)$)—was used to investigate the effect of ligand functionality on iron speciation in aqueous solution.

4.2 The Iron(III)/edta System

The edta ligand is potentially hexadentate. This means that this system should be the simplest, as the free sites for aquo coordination are usually blocked by the functional groups of the ligand. In fact, the readily adaptable stereochemistry of the high spin iron(III) center allows for a seventh coordination site to be taken by a water molecule in **1** (Fig. 4).[28] However, two other monomeric species have been isolated and crystallized, both six-coordinate, one with hexadentate edta, **2**,[29] the other with one coordinated water and pentadentate edta in which the non-coordinating carboxylate arm is protonated, **3** (Figs. 5 and 6).[30] Although **1** is the easiest species to obtain as single crystals, it has proved impossible to tell which species predominates in aqueous solution. Undoubtedly, pH will be important, but the investigation of this is com-

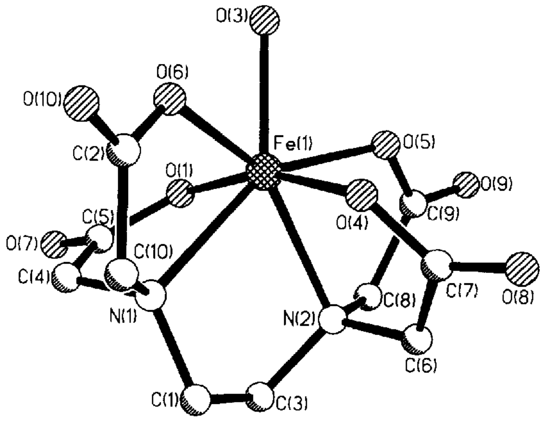


FIGURE 4 The structure of **1**, the $[Fe(edta)(H_2O)]^-$ anion (Ref. 28).

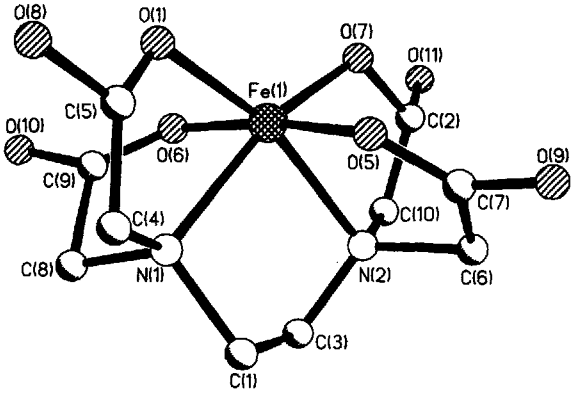


FIGURE 5 The structure of **2**, the $[Fe(edta)]^-$ anion (Ref. 29).

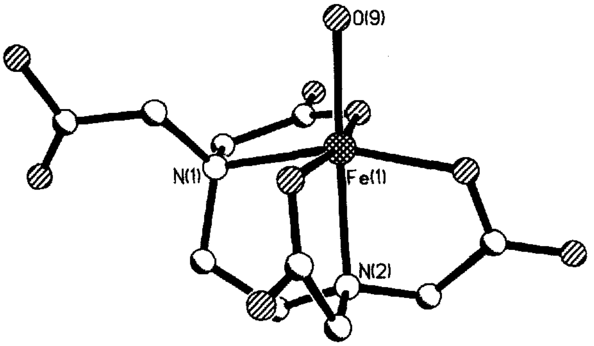


FIGURE 6 The structure of **3**, $[Fe(edtaH)(H_2O)]$ (Ref. 30).

plicated by the formation of dimeric hydrolysis products, as explained below.

4.2.1 The Monomer/Dimer Equilibrium

In the Fe/edta system, the possibilities for olation reactions are limited. With up to six coordination sites blocked at the metal, there are unlikely to be many coordinated water molecules. It would appear to be necessary to have coordinated waters in order to form oxide and hydroxide bridges between metals. It turns out

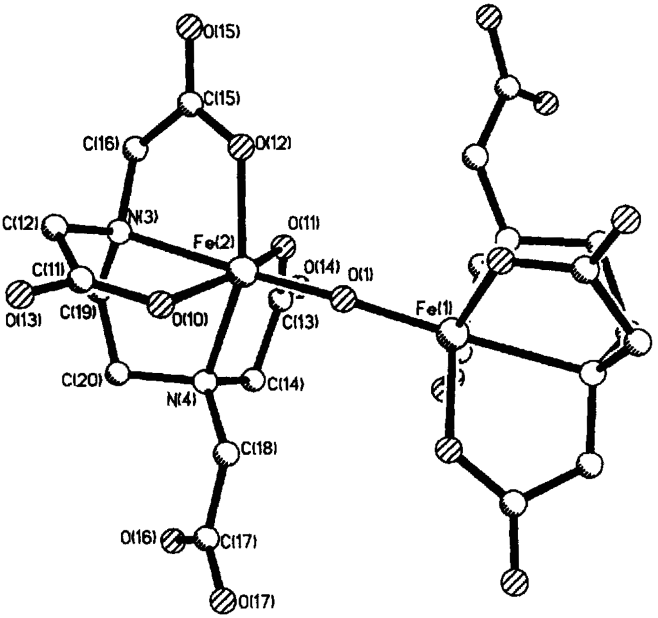


FIGURE 7 The structure of **4**, the $[\{Fe(edta)\}_2O]^{4-}$ anion (Ref. 31).

that an oxide-bridged dimer, **4** (Fig. 7), can be isolated from partially hydrolyzed solutions of Fe and edta.

Three examples of salts of the general formula $M_4[\{Fe(edta)\}_2O]$ ($M = K$, Na or $\frac{1}{2}$ enH_2) have been isolated and crystallographically characterized, and it is found that the Fe–O–Fe angle varies with counter-ion.[31] In all cases so far studied, these are six coordinate species with one of the carboxylate arms of the edta hanging free. However, these carboxylates are deprotonated, as can be seen from the lack of any band corresponding to protonated carboxylate in their IR spectra and on a consideration of charge balance. This poses the question as to the identity of the monomeric precursor. It is also interesting to note that so far the only examples of oxo-bridged iron dimers which are more than six coordinate are those formed between iron(III) and macrocyclic ligands[32] leading to the suggestion that as iron(III) begins to mineralize, more regular coordination geometry is favored.

4.3 The Iron(III)/ida System

Aqueous solutions with iron and ida in a 1:2 ratio provide a comparison with the edta system since ida can be regarded as possessing half of the donor set of edta. To date, only one type of monomeric species, **5** (Fig. 8), and several examples of oxo-bridged dimeric species have been isolated.[31] As in the case of edta, the dimers have different Fe–O–Fe angles, depending on counter-ion. The dimer which crystallizes with four potassium counter-ions and possesses a strictly linear Fe–O–Fe bridge, **6**, is shown in Fig. 9.

The six-coordinate monomeric species, **5**, does not possess a coordinated water molecule, and is similar to the edta monomer, **2**, except that the nitrogens are *cis* but unconnected in the ida system. If the contention that the oxide and hydroxide bridges form from the deprotonation of coordinated waters is correct, then presumably a six or seven coordinate species with one coordinated water analogous to the edta situation (compounds **1** and **3**) must exist. The rather distorted coordination environment of the iron suggests that a water molecule could be accommodated in this way. Presumably the formation of oxo-bridged dimers proceeds via the coordination of a water molecule by an S_N^1 or S_N^2 reaction as indicated in Scheme 3.

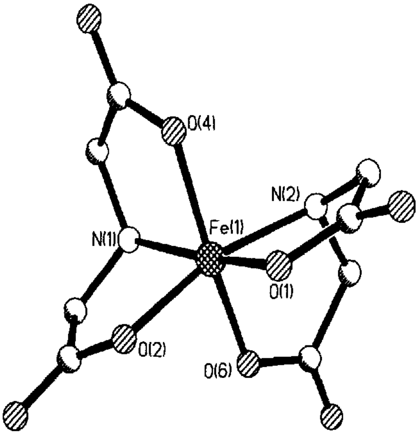


FIGURE 8 The structure of **5**, the $[Fe(ida)_2]^-$ anion (Ref. 31).

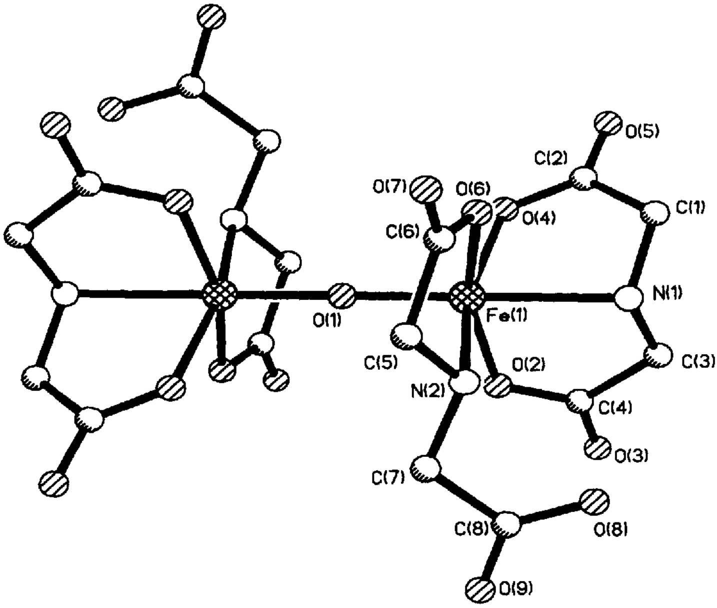
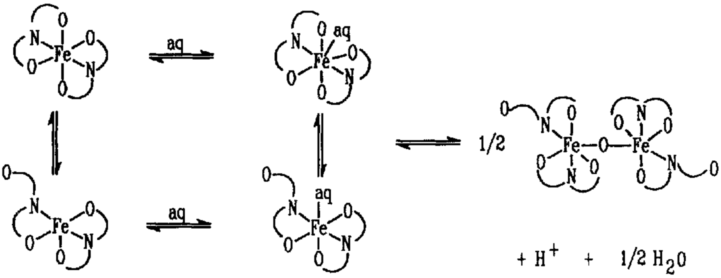


FIGURE 9 The structure of **6**, the $[\{Fe(ida)_2\}_2O]^{4-}$ anion (Ref. 31).



SCHEME 3

4.4 The Iron(III)/digly System

The digly ligand is analogous to ida, with the NH function replaced by an ether linkage. It usually coordinates as a tridentate ligand, and there are examples of both facial and meridonal geometries.

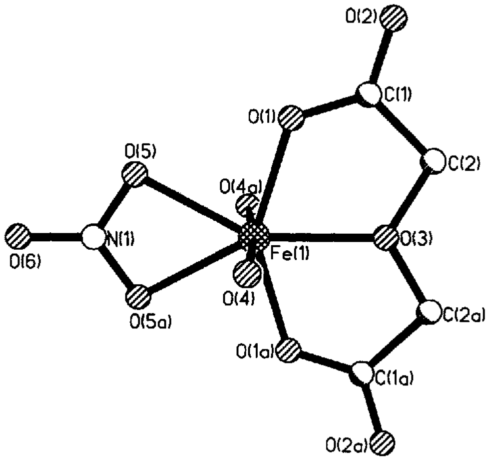


FIGURE 10 The structure of **9**, [Fe(digly)$(H_2O)_2(NO_3)$] (Ref. 37).

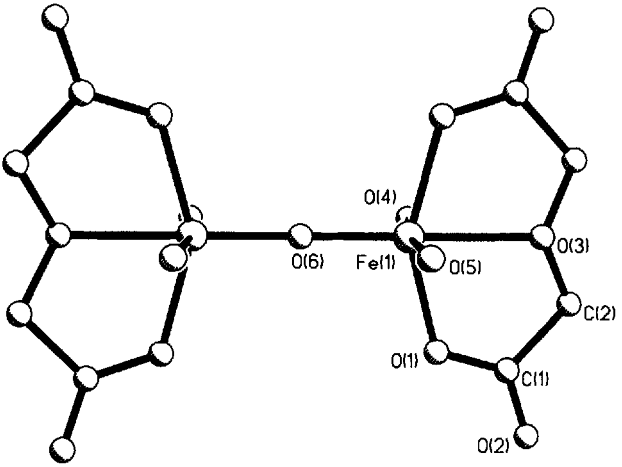


FIGURE 11 The structure of **10**, [{Fe(digly)$(H_2O)_2\}_2O$] (Ref. 38).

In the case of iron(III) it has only been possible to isolate complexes displaying *mer* geometry, which is in direct contrast to the ida complexes, where the ligand always adopts *fac* geometry.[33–35] Also, it has not been possible to crystallize compounds with iron:ligand ratios of anything other than 1:1. In this way, complexes of the general formula [Fe(digly)$(H_2O)_2$X] can be isolated. For X = Cl and Br, **7**, **8**, these are six coordinate species,[36] and for X = NO_3 a seven coordinate species results with a bidentate nitrate, **9** (Fig. 10).[37] Increasing the pH of solutions containing these species results in the formation of the oxo-bridged dimer, **10** (Fig. 11).[38]

The speciation of the iron can be explained in terms of the equilibrium:

$$\{\mathrm{Fe(digly)(H_2O)_2X}\} + \mathrm{OH^-} \Leftrightarrow 1/2[\{\mathrm{Fe(digly)(H_2O)_2}\}_2\mathrm{O}] + \mathrm{X^-} + \mathrm{H^+}$$

The monomeric species predominates when nitrate or halide ligands are available in solution. These can block some of the sites available for the coordination of water and thereby inhibit the deprotonation process. Increasing pH or dilution shifts the equilibrium towards the right-hand side.

4.5 The Iron(III)/nta, Iron(III)/ada and Iron(III)/heidi Systems

The effect which ligand functionality exerts on iron speciation is illustrated by the series of ligands of the type $NR_1R_2R_3$ as indicated in Table I. In aqueous solutions of iron with nta or ada in excess, seven coordinate species result, **11**, **12**. In these, the ligands effectively block all the available coordination sites of the metal, preventing any coordination by water molecules. Both ligands are capable of being tetradentate, and the seven-coordination is the result of complexation by two ligands per iron, one tetradentate and the other tridentate (Figs. 12 and 13). This results in one free

TABLE I

The functional groups of the ligands used

	R_1	R_2	R_3
H_3nta	CH_2COOH	CH_2COOH	CH_2COOH
H_2ada	CH_2COOH	CH_2COOH	CH_2CONH_2
H_3heidi	CH_2COOH	CH_2COOH	CH_2CH_2OH

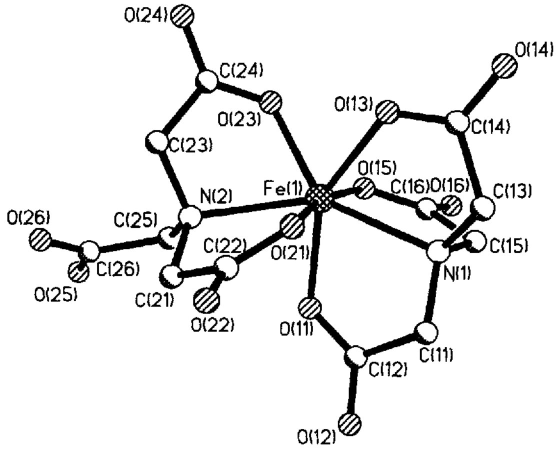


FIGURE 12 The structure of **11**, the $[Fe(nta)_2]^{3-}$ anion (Ref. 39).

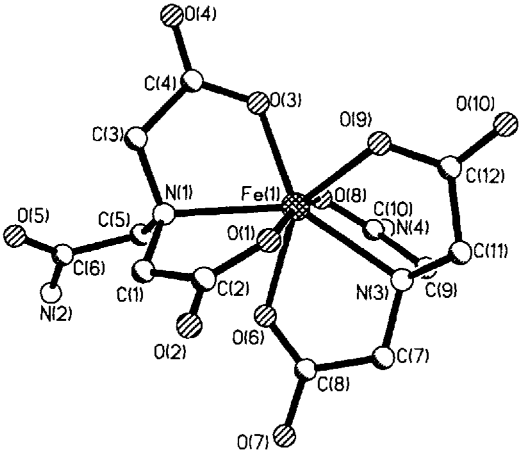


FIGURE 13 The structure of **12**, the $[Fe(ada)_2]^-$ anion (Ref. 31).

(deprotonated) carboxylate arm in the nta case,[39] and one free amide arm in the ada.[31] The coordination by the amide arm has not been observed in complexes with other d-block transition metals. It is possible to raise the pH of solutions containing these species as high as 10 without forming any oxo-bridged complexes.

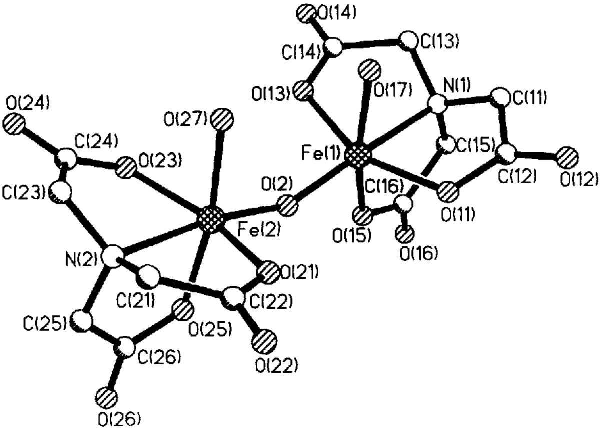


FIGURE 14 The structure of **13**, the $[\{Fe(nta)(H_2O)\}_2O]^{2-}$ anion (Ref. 40).

In fact, there is no evidence for the formation of any discrete oligomeric compounds; the result of raising the pH higher is the formation of $Fe(OH)_3$. If the ratio of iron:ligand is 1:1, then oxo-bridged species become important and the Fe/nta system can easily be hydrolyzed to form the dimer $[\{Fe(nta)(H_2O)\}_2O]^{2-}$, **13** (Fig. 14),[40] even at low pH's (e.g., 4).

Solutions of iron and ada that are 1:1 produce compounds analogous to the Fe/digly system (see Section 4.4). Monomeric species of the general formula $[Fe(ada)(H_2O)X]$, X = Cl, NCS, NO_3, **14**–**16**, can be crystallized from solutions which are relatively concentrated in reactants.[31,37] The structure of **14** with X = Cl is shown in Fig. 15. Similarly, dilution of a solution of $[Fe(ada)(H_2O)X]$ is sufficient to produce the oxo-bridged species $[\{Fe(ada)(H_2O)\}_2O]\cdot 4H_2O$, **17**.

The ligand heidi has obvious similarities to the ligands nta and ada. When excess ligand is present, iron(III) solutions can be stabilized to high pH's as described for the nta system, and it is likely that seven-coordinate species form and block the hydrolysis sites. In solutions where the iron:ligand ratio is 1:1, the dimeric compound, **18** (Fig. 16),[41] becomes important. In this complex, the alcohol function of the heidi ligand has been deprotonated, and forms an alkoxide bridge between the two iron centres. It is un-

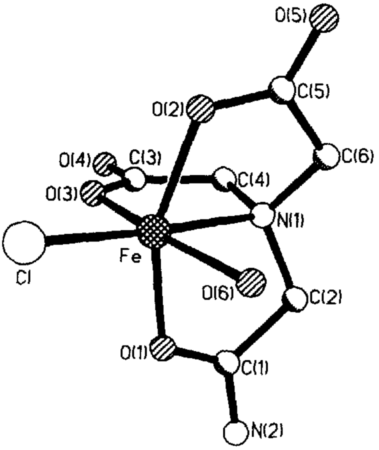


FIGURE 15 The structure of **14**, [Fe(ada)(H_2O)Cl] (Ref. 37).

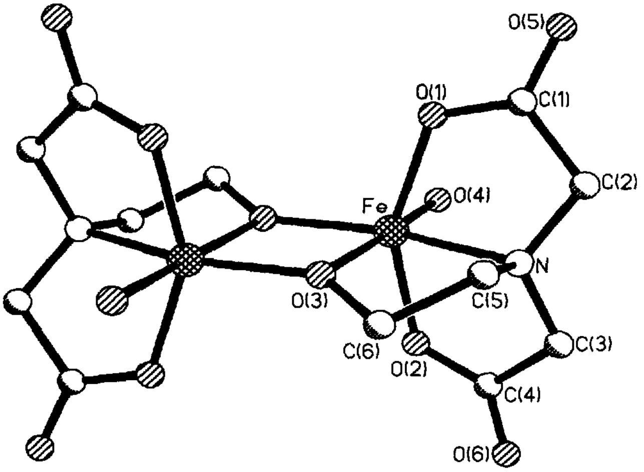


FIGURE 16 The structure of **18**, [Fe(heidi)(H_2O)]$_2$ (Ref 41).

precedented for such an alcohol function to be deprotonated by a d-block metal, and this underlines the ability of iron(III) to deprotonate substrates in much the same way as it deprotonates coordinated water molecules to produce coordinated oxide or hydroxide groups.

5. SMALL IRON(III) OXYHYDROXIDE AGGREGATES

Many polyiron(III) oxo/hydroxo clusters have been prepared with numbers of iron ranging from 3 to 11 plus a heterometallic 17 metal cluster containing 16 iron atoms. However, clusters containing 5, 7 and 9 irons have not yet been isolated. The polyiron clusters characterized to date can in most cases be categorized by the nature of their central core. In general these clusters have been isolated from non-aqueous media although their formation relies on the presence of traces of water in order to provide the oxo and hydroxo bridges. The majority are supported by bidentate bridging carboxylate groups which have been supplied in order to mimic biological situations and also form extra bridges between iron centers. Although no polyiron species with "small" numbers of irons like these have been definitely identified in biological systems, there is some evidence for the existence of a low molecular weight iron pool, containing species such as $Fe_x(OOCR)_y(O)_z$, in organisms such as man.[5] It is possible that the dimeric species are precursors for larger clusters or decomposition products of systems such as the classic basic carboxylate trimer[42]:

$$\{Fe_3(OOCR)_6(O)\}^+ \Leftrightarrow \{Fe_2(OOCR)_2(O)\}^{3+} + Fe^{3+} + 4RCOO^-$$

5.1 Three-Iron Clusters

There are two ways of linking together three iron atoms as shown in Fig. 17 with arcs representing bridging bidentate ligands such as carboxylates and O's oxides or hydroxides. The trimeric triangle type core is well known and has been comprehensively reviewed by Cannon and White.[43] However, the linear type of arrangement

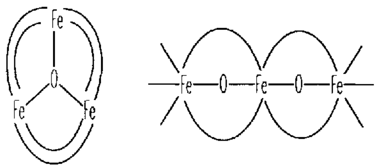


FIGURE 17 The two ways of linking three iron atoms via anion bridges.

of the iron(III) atoms is more unusual and to date only one complex of this type has been isolated.[44]

5.2 Four-Iron Clusters

Several tetranuclear complexes of iron(III) have been isolated to date.[45–51] Three of these complexes have the iron atoms configured as shown in Fig. 18a.[45–47] This type of arrangement is often termed a "butterfly core." The other four tetranuclear complexes have μ_2-O(R) groups with core types similar to that shown in Fig. 18b.[48–51]

5.3 Six-Iron Clusters

Eight hexameric iron(III) complexes have been crystallographically characterized[52–59] and can be grouped into four structural types. Four hexanuclear complexes have a core that is essentially comprised of two Fe_3O triangle units, and this is illustrated in Fig. 19, structure A. These complexes are all derived from further reactions of "basic iron carboxylate" trimers in non-aqueous solvents, which result in two trimer units joining together via carboxylate supported hydroxide bridges.[52–55] Two other types form in alcoholic solutions with iron centers connected by alkoxide rather than hydroxide bridges. There are two examples containing a core which has a central μ_6 oxygen which is octahedrally surrounded by six iron(III) atoms, Fig. 19, structure B.[56,57] In the second type of these alkoxide bridged cores, two layers of iron alkoxide are joined together by μ_4 oxide bridges as shown in Fig. 19, structure

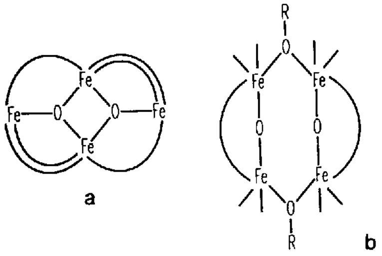


FIGURE 18 The two arrangements observed for tetranuclear iron oxyhydroxide cores.

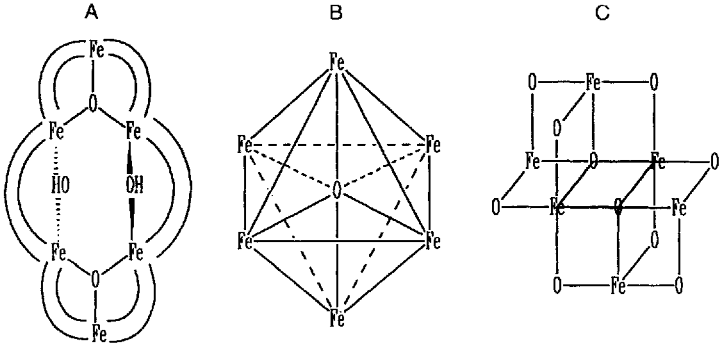


FIGURE 19 The three different iron oxygen core structures of hexameric iron(III) complexes.

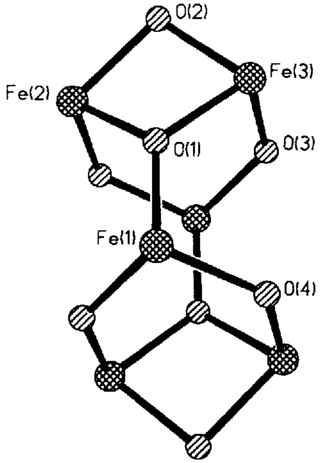


FIGURE 20 The structure of the $[Fe_6(\mu_3\text{-}O)_2(\mu_2\text{-}OH)_6]^{8+}$ core of **19** (Ref. 59).

C.[58] The fourth type $[Fe_6(\mu_3\text{-}O)_2(\mu_2\text{-}OH)_6(ida)_6]^{4+}$, **19**, forms in aqueous solution in the presence of the tridentate polycarboxylate iminodiacetate ligand, ida^{2-} ($H_2ida = HN(CH_2COOH)_2$).[59] The anion of **19** contains an $[Fe_6(\mu_3\text{-}O)_2(\mu_2\text{-}OH)_6]^{8+}$ core (Fig. 20) and is synthesized directly in an aqueous environment, with no intermediate trimer units involved, and none of the hydroxide bridges supported by bridges from any other ligand. The structure can be considered in terms of two Fe_3O triangles, by analogy with the basic iron carboxylate structure type. These triangles are in two parallel planes with the apical iron of one triangle connected to the base irons of the triangle opposite via two inter-trimer μ_2-hydroxo bridges. The two remaining μ_2-hydroxo bridges can be described as intratrimer bridges across the bases of the two triangles. Alternatively, the geometry of the iron core of **19** can be described in terms of two tetranuclear iron butterflies which share the irons at the wing tips.

5.4 A Cluster Containing Eight Irons

To date only one cluster containing eight iron(III) atoms has been synthesized and crystallographically characterized $\{[(C_6H_{15}N_3)_6$-

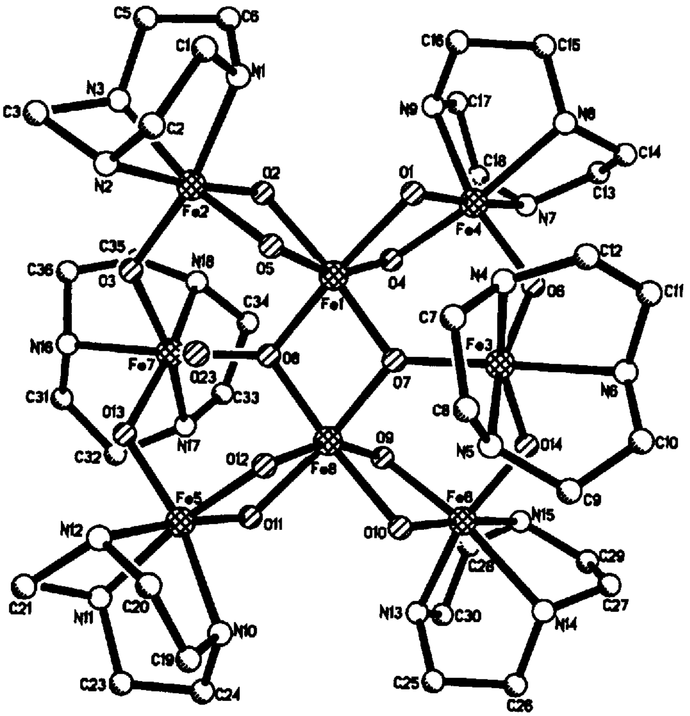


FIGURE 21 The structure of **20**, the $[Fe_8(\mu_3\text{-}O)_2(\mu_2\text{-}O)_6(1,4,7\text{-}TACN)_6]^{8+}$ cation (Ref. 60).

$Fe_8(\mu_3\text{-}O)_2(\mu_2\text{-}OH)_{12}]Br_7(H_2O)\}Br \cdot 8H_2O$, **20**, Fig. 21.[60] This complex was the unexpected hydrolytic product from a system containing iron(III), TACN (1,4,7 triazacyclononane), and base. Again, as for compound **19**, the structure of the central iron oxyhydroxide portion can be visualized in terms of Fe_3O units. Here the central part of the core can be regarded as consisting of two Fe_3O triangles sharing their base irons (Fe1 and Fe8) to give an $Fe_4\text{-}(\mu_3O)_2$ butterfly. The four irons are virtually planar (mean deviation 0.0092 Å) the angle at the hinge of the butterfly being 179.3°. The edges are bridged by $\mu_2\text{-}OHFe(\mu_2OH)_2$. The coordination sites on the outer irons are occupied by facially coordinating TACN ligands. This structure is effectively a portion of a close-packed array of ligand atoms (O and N) with irons occupying octahedral holes.

5.5 A Decanuclear Iron Cluster

A cluster containing ten iron(III) atoms was synthesized by Lippard and Taft in 1990,[61] **21**. Due to the arrangement of the iron atoms in this complex, shown in Fig. 22, it has been nicknamed the "ferric wheel." Each iron is octahedrally coordinated by four μ_2-methoxides and two carboxylates. This structure is probably not particularly relevant to species occurring in aqueous environments.

5.6 An Eleven Iron Cluster

The complex, $[Fe_{11}O_6(OH)_6(O_2CPh)_{15}]$, **22** was synthesized and crystallographically characterized by Lippard *et al.* in 1987. The core of this molecule, shown in Fig. 23, contains eleven iron atoms linked by six μ_3-oxo and six μ_3-hydroxo groups. The iron oxyhydroxide core is enclosed by bidentate bridging carboxylates which effectively control the size and shape of the core. This molecule, although synthesized from non-aqueous media, could prove to be helpful in understanding the nature of the building blocks of the ferritin core[62] and may be representative of the types of structures found in amorphous iron oxides.

5.7 Two Heterometallic Clusters Containing Sixteen Irons

The eleven iron complex discussed in Section 5.6 above was used as a precursor in the synthesis of the mixed metal $[Fe_{16}$-

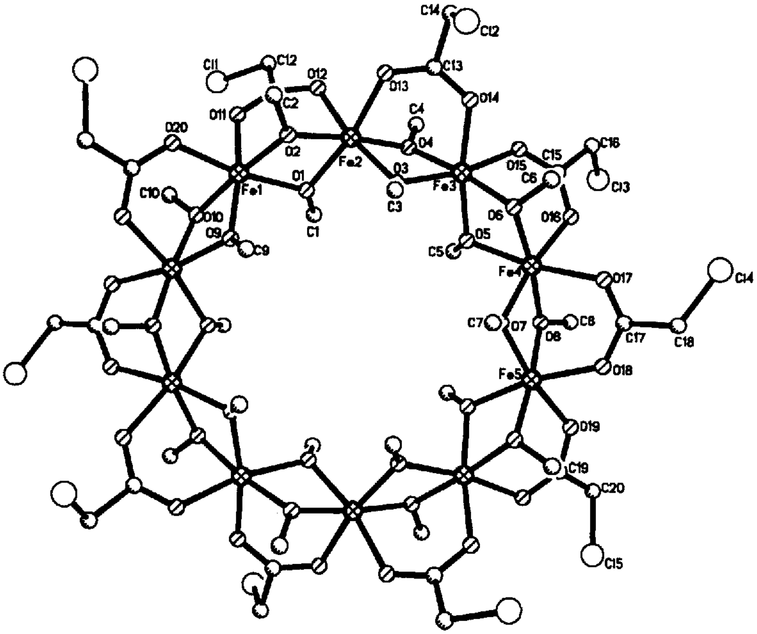


FIGURE 22 Structure of the "ferric wheel," **21**, $[Fe(OMe)_2(O_2CCH_2Cl)]_{10}$ (Ref. 61).

$MO_{10}(OH)_{10}(O_2CPh)_{20}]$ complexes **23**.[63] Two isostructural complexes of this type were synthesized in 1989 by Micklitz and Lippard, with M = Mn, Co and can be considered to be constructed from two $[Fe_{11}O_6(OH)_6(O_2CPh)_{15}]$ molecules with the removal of two $\{Fe_3(OH)(O_2CPh)_5\}^+$ units and the inclusion of a divalent metal ion, Mn or Co in a tetrahedral site. As in the eleven iron cluster, the core contains μ_3-oxo and μ_3-hydroxo groups.

6. THE TRAPPING OF IRON(III) OXYHYDROXIDE MINERALS

As we move further to the right in Scheme 2, more highly ordered iron(III) oxyhydroxide aggregates form until eventually oxyhydroxide mineral phases (ferrihydrite) precipitate from

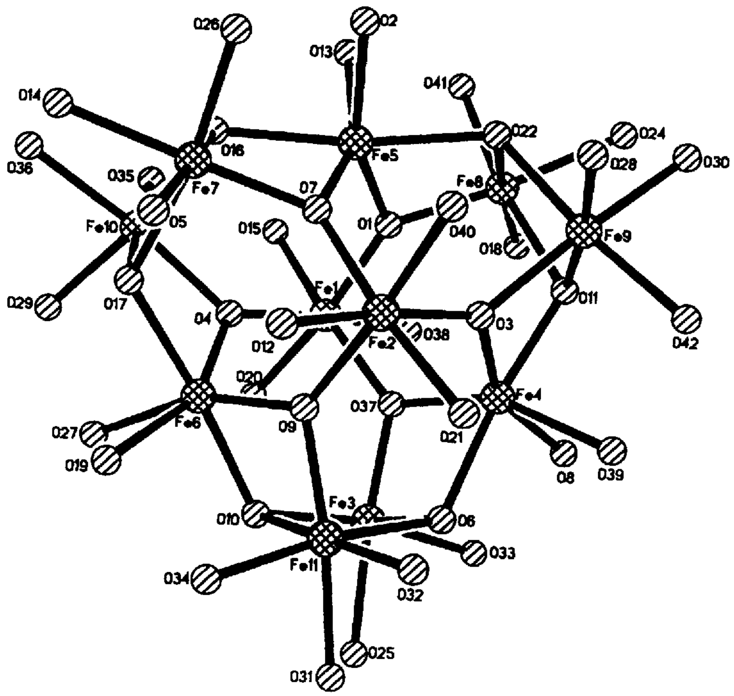


FIGURE 23 The structure of 22, $[Fe_{11}O_6(OH)_6(O_2CPh)_{15}]$. All the carbon atoms of the benzoate groups are omitted for clarity (Ref. 62).

solution. Once ferrihydrite ("$Fe(OH)_3$") has been produced it can be converted into the other mineral phases according to Fig. 1. Until recently the intermediate species $\{Fe_x(O)_y(OH)_z(H_2O)_p\}^{(z+2y-3x)\text{-}or(3x-z-2y)+}$ and $\{Fe_xL_n(O)_y(OH)_z(H_2O)_p\}^{(mn+z+2y-3x)\text{-}or(3x-mn-z-2y)+}$ of Schemes 1 and 2 could only be inferred. We have shown that it is possible to trap mineralized iron species, which form in water, corresponding to $\{Fe_xL_n(O)_y(OH)_z(H_2O)_p\}^{(mn+z+2y-3x)\text{-}or(3x-mn-z-2y)+}$ under carefully controlled conditions. This approach is fundamentally different from that adopted by other groups because it utilizes the natural hydrolysis of iron(III) to provide the cluster species. In this system the water is the most concentrated species present whereas in the non-aqueous syntheses it will be the least concentrated. In one of our typical syntheses the concentration of the iron will be between 0.1 and 0.2M whereas the concentration of the water is 55M.

This synthetic route allows us to investigate the way in which organic substrates can influence the structural type of the mineralized core. This control of inorganic structure by the interaction of organic species is found in Nature in biomineralization processes.

6.1 Biomineralization

Organisms form inorganic minerals by a process called biomineralization. The way organisms control mineral deposition is not yet fully understood, but the key is thought to lie in how organic molecules, such as proteins and polysaccharides, interact with inorganic ions on the surface of the biomineral.[64] The organic molecules not only act as catalysts, reducing the energy needed to initiate nucleation, but also as a template, controlling the kind of structure that the mineral adopts. Therefore any change in the structure and chemistry of the organic molecule will be reflected by corresponding changes in the biomineral's crystal structure. In this way Nature has the ability to dictate structural type and in doing so the functionality of the mineral. Two modes of biomineralization are thought to exist: biologically induced mineralization (BIM) and biologically controlled mineralization or boundary organized biomineralization (BCM or BOB).[65] The iron biomineral ferritin is thought to be an example of biologically controlled mineralization.

Iron biominerals are found fulfilling various functions in a number of organisms: the hard minerals goethite, α-Fe.O.OH, and lepidocrocite, γ-Fe.O.OH, found in the teeth of molluscs such as Limpets and Chitons which scrape algae from rocks; magnetite, Fe_3O_4, is used for navigation in some birds and in magnetotactic bacteria; and ferrihydrite, a mineral type encompassing a range of phases which form as $Fe(OH)_3$ has been suggested as comprising the iron oxyhydroxide core of some ferritins.[66,67] The biomineralization processes which produce minerals such as these can be modelled in the laboratory. This has been achieved by supplying small amounts of anionic or organic species, which can influence structure, to hydrolyzed iron(III) solutions and investigating the phases of the minerals formed.[9,10] Many iron biominerals have had their structures identified by diffraction methods,[68] but the precise structure of the cores of the iron storage proteins ferritin and haemosiderin are notable exceptions. The ability to store iron in an accessible but inert form is vital to the well-being of organisms, and chemists have sought ways to model these systems in order to shed light on the core structure. However, the large nature of the cores, for example containing up to 4000 iron atoms in the case of horse spleen ferritin (HSF), makes structural models difficult. This is because although ferritin is large on a molecular scale, it is small on a mineral scale, and as such it should not be thought of as an infinite structure but rather as a trapped mineral portion or a finite crystallite. Good models for the core of ferritin might be the so-called "Saltman–Spiro" balls. These form in hydrolyzed solutions of iron(III) which contain small amounts of citrate or nitrate.[69,70] The Saltman–Spiro balls are composed of a high molecular weight (RMM = 1.5×10^5) polymer containing about 1200 iron atoms, probably linked by hydroxy and oxy bridges, with citrate ligands attached to the surface. There are thought to be approximately two surface irons bound per citrate.[69] Although this model sounds very attractive, a lack of structural data and reproducibility has made progress difficult. For example, the experimental procedure requires gel filtration of the hydrolyzed species and several fractions are involved. The importance of ferritin has fueled efforts to synthesize and characterize many much smaller oxo-hydroxo bridged iron(III) complexes. However, none of the iron(III) structures described in Section 5 have exhibited the known features of the naturally occurring compounds and are not directly relevant to ferritin as they do not display extended close-packed iron oxyhydroxide cores and/or are produced by non-aqueous routes. For example, the Extended X-ray Absorption Fine Structure (EXAFS) spectra of the iron environments found in the undecairon(III) oxyhydroxide cluster **22** show structural distinctions to those found in the (HSF) ferritin core, although it is suggested that the molecule could be a model for the intermediate species in ferritin formation.[71]

6.2 A Dodecanuclear Cluster Containing Iron(II) and Iron(III)

The recently reported mixed valent dodecanuclear iron cluster synthesized in non-aqueous media, $[Fe^{III}_4Fe^{II}_8(\mu_6\text{-}O)_2(OCH_3)_{18}$-

$(O_2CCH_3)_6(CH_3OH)_{4.67}]$, **24**, contains iron atoms in octahedral holes of a ccp array of oxygen atoms.[72] The structure is of interest because it might model the situation which prevails when mammalian ferritin cores form. There is much evidence to support the view that iron enters the cavity of apoferritin as Fe(II).[5] It is not known whether the iron is first oxidized to iron(III) at special sites along the entry sites to the cavity (the so-called ferroxidase centers) or if it is oxidized once it is within the cavity[2,3] or if both mechanisms are important. Thus, although this compound is not strictly relevant to this article in that it contains Fe(II), it is relevant to our discussion of models for biomineralization.

6.3 A Strategy for Trapping Iron(III) Oxyhydroxide Minerals

In the dimeric iron/heidi species **18** the alcohol function of the ligand forms an alkoxide bridge between two iron centers. Further hydrolysis of the dinuclear heidi alkoxo bridged complex **18** does not result in discrete higher nuclearity species being formed because the way in which the heidi ligand coordinates means that the coordinated waters available for further hydrolysis are on opposite sides of the Fe–Fe vector, making the condensation of two such dimers impossible (Fig. 16). In view of the ability of heidi to form binuclear alkoxo-type bridges, it seemed likely that larger clusters could be isolated from iron/heidi solutions providing the ratio of ligand to iron was reduced so that the function of the ligand was simply to hold two iron centers in place. Using this approach it was possible to isolate compounds in which mineralized oxyhydroxide cores of iron(III) were encapsulated in iron/ligand shells as revealed by a single crystal X-ray diffraction study on one such example **25**.[41]

6.4 Discussion of the Structure of 25 ("Crust")

The formula of **25** is $[Fe_{36}(\mu_3\text{-}O)_{10}(\mu_3\text{-}OH)_{12}(\mu_2\text{-}OH)_{18}(\text{heidi})_{18}\text{-}(H_2O)_{24}](NO_3)_4\cdot 60H_2O$. This structure contains a nineteen and a seventeen iron cluster which crystallize in the same unit cell along with four nitrate anions and sixty waters of crystallization. In view of the obvious difficulties with the nomenclature these are known colloquially in our laboratory as "Crusts," which stands for cluster rust or captured rust, the latter reflecting the way in which an iron

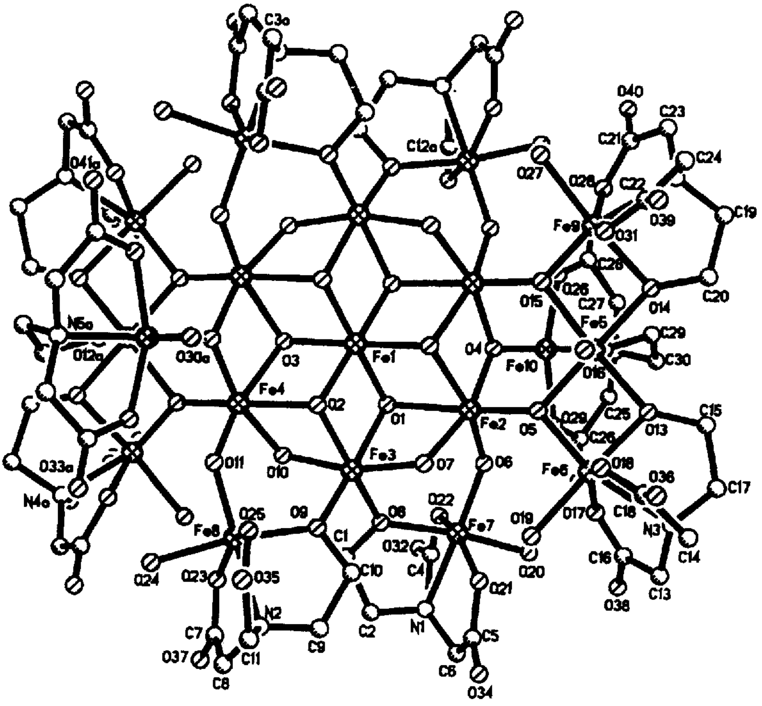


FIGURE 24 The structure of **26**, the $[Fe_{19}(\mu_3\text{-}O)_6(\mu_3\text{-}OH)_6(\mu_2\text{-}OH)_8(heidi)_{10}(H_2O)_{12}]^+$ cation (Ref. 41).

oxyhydroxide mineral has been "caught." These clusters are two examples of a new type of iron-oxo-hydroxo structure and are the largest such structures characterized to date. Their formulae are: $[Fe_{19}(\mu_3\text{-}O)_6(\mu_3\text{-}OH)_6(\mu_2\text{-}OH)_8(heidi)_{10}(H_2O)_{12}]^+$, **26** (Fig. 24) and $[Fe_{17}(\mu_3\text{-}O)_4(\mu_3\text{-}OH)_6(\mu_2\text{-}OH)_{10}(heidi)_8(H_2O)_{12}]^{3+}$, **27** (Fig. 25), and their relationship within the unit cell is shown in Fig. 26. Both structures contain a close-packed core which is enclosed in a shell of iron/heidi units. The central core unit, which is common to both **26** and **27** has the formula $[Fe_7(\mu_3\text{-}OH)_6(\mu_2\text{-}OH)_4\{(\mu_3\text{-}O)Fe\}_2]^{13+}$ and is shown in Fig. 27a. The building blocks for this core are $[Fe_3(OH)_4]^{5+}$ units (cubes with one corner iron missing) shown in Fig. 27b. In the case of **26** this central core unit is surrounded by ten iron/heidi units linked to the core by μ_3-O (e.g., O(5)), μ_2-

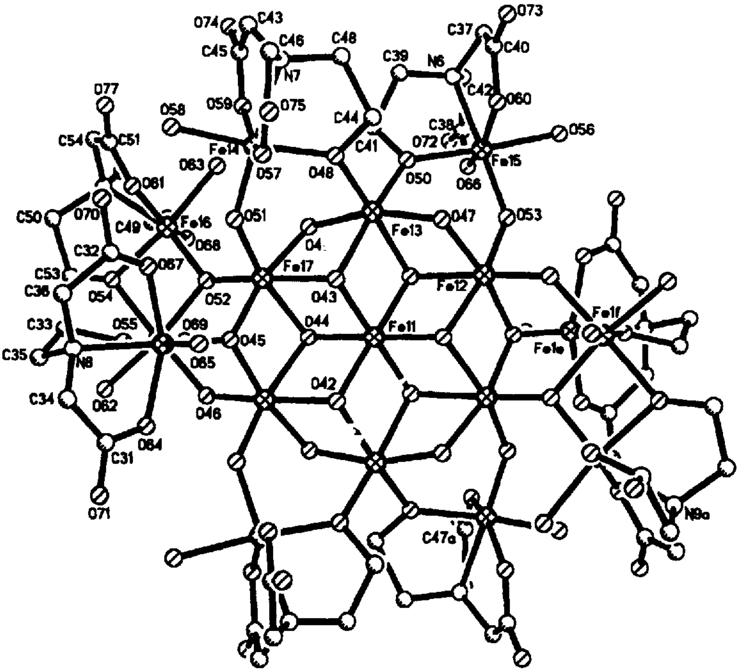


FIGURE 25 The structure of **27**, the $[Fe_{17}(\mu_3\text{-}O)_4(\mu_3\text{-}OH)_6(\mu_2\text{-}OH)_{10}(heidi)_8(H_2O)_{12}]^{3+}$ cation (Ref. 41).

OH (e.g., O(11)) and alkoxo bridges from the heidi (e.g., O(9)), Fig. 24. This gives the outer shell of **26** the formula $\{Fe_{10}(heidi)_{10}(H_2O)_{12}(\mu_3\text{-}O)_4(\mu_2\text{-}OH)_4\}^{12-}$ and an overall charge on **26** of 1+. The vacant sites on the peripheral iron centers are taken up with water molecules so that each iron atom is octahedrally coordinated. Compound **27** is constructed in a similar manner; two symmetry related Fe/heidi units are absent and consequently two μ_2-OH units replace two of the μ_3-O units in **26**. The formula of the cluster shell is $\{Fe_8(heidi)_8(H_2O)_{12}(\mu_3\text{-}O)_2(\mu_2\text{-}OH)_6\}^{10-}$ giving **27** an overall charge of 3+. The assignment of the oxo and hydroxo bridges has been made on the basis of a consideration of the geometry at each oxygen: when the bond angles around the oxygen were tetrahedral the oxygen was assigned as a μ_3-hydroxo whereas when the angle was trigonal it was assigned as a μ_3-oxo.

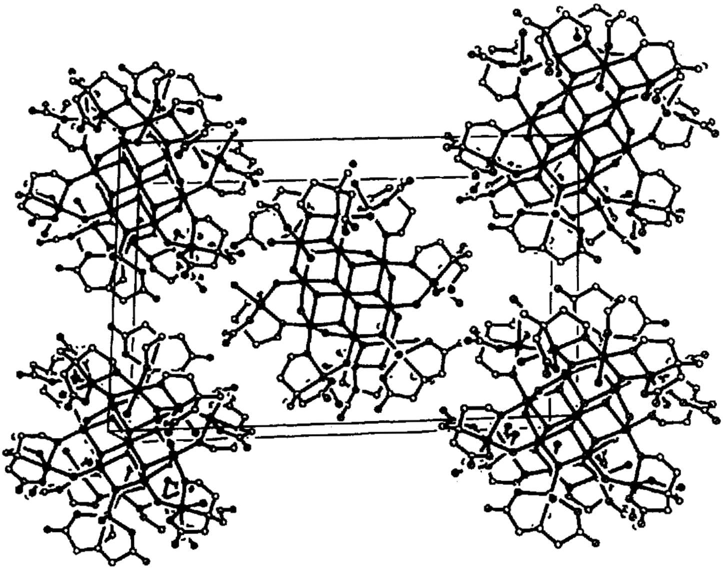


FIGURE 26 The packing of the two clusters in **25**.

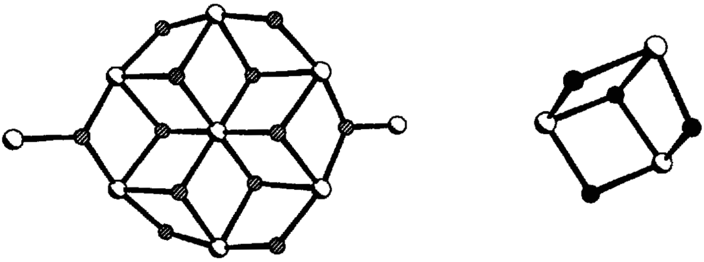


FIGURE 27 (a) The $[Fe_7(\mu_3\text{-OH})_6(\mu_2\text{-OH})_4\{(\mu_3\text{-O})Fe\}_2]^{13+}$ core common to **26** and **27** (b) the $[Fe_3(OH)_4]^{5+}$ building blocks of the core.

These assignments are also supported by the microanalytical data and are in accord with the expected charges on the clusters.

6.5 Relationship of the Structure of **25** to Known Minerals

This structure is unique in the fact that the ligand, heidi, has trapped an iron(III) hydroxo core in a mineral structure in which

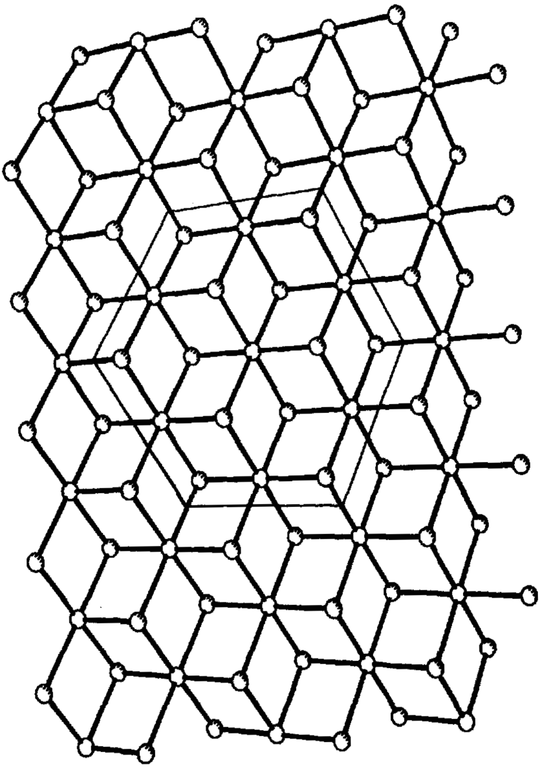


FIGURE 28 The relationship of the central core of the Fe_{19} and Fe_{17} clusters in **25** to the CdI_2 structural type.

it does not naturally occur. If one considers extending the central core of the structure, $[Fe_7(\mu_3\text{-}OH)_6(\mu_2\text{-}OH)_4\{(\mu_3\text{-}O)Fe\}_2]^{13+}$, by replacing the two irons of the two $[\mu_3\text{-}O\ Fe]^+$ units by protons to give $[Fe_7(\mu_3\text{-}OH)_6(\mu_2\text{-}OH)_6]^{9+}$, a structure containing six outer μ_2-OH's results. One could then extend this into a network by binding further $\{FeOH\}^{2+}$ units to produce an infinite two dimensional array of $\{Fe(OH)_2\}^+$. This structure is of the AX_2 type which is typified classically by CdI_2. Cadmium iodide has a hexagonally close-packed (hcp) layer of iodine atoms with cadmium atoms occupying octahedral sites between every other pair of iodine atom layers. Each cadmium is therefore octahedrally coordinated, whereas each iodine only has three nearest neighbors arranged in a trigonal plane all to one side of it. The CdI_2 structure is a layered structure as it consists of repeat units of I–Cd–I . . . I–Cd–I layers with van der Waals attractions between the adjacent iodine layers.[6] The relationship of the central core to the CdI_2 type is shown in Fig. 28 (two superimposed close-packed layers with all octahedral sites filled).[73] However, there are two inaccuracies with this comparison. One is the fact that OH^- ions are being likened to I^- ions. It would therefore be better to compare the structure with a hydroxide mineral crystallizing with an AX_2 structure such as the mineral brucite, $Mg(OH)_2$ or indeed $Fe^{II}(OH)_2$.

Brucite has a layer structure in which each layer consists of two sheets of OH^- ions in a hcp array with a sheet of Mg^{2+} ions between them. Each Mg lies between six OH's, with each OH linked to three magnesiums on one side and surrounded by three OH's of the next layer (see Fig. 29). Due to this arrangement polarization of the OH group occurs. The layers in brucite are

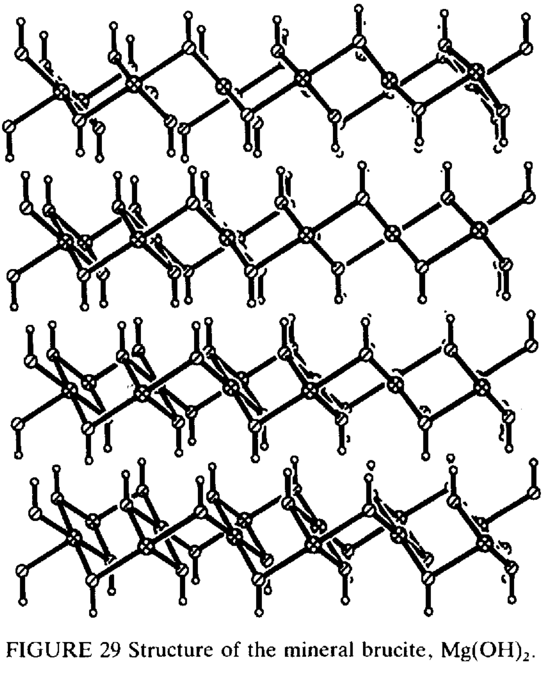


FIGURE 29 Structure of the mineral brucite, $Mg(OH)_2$.

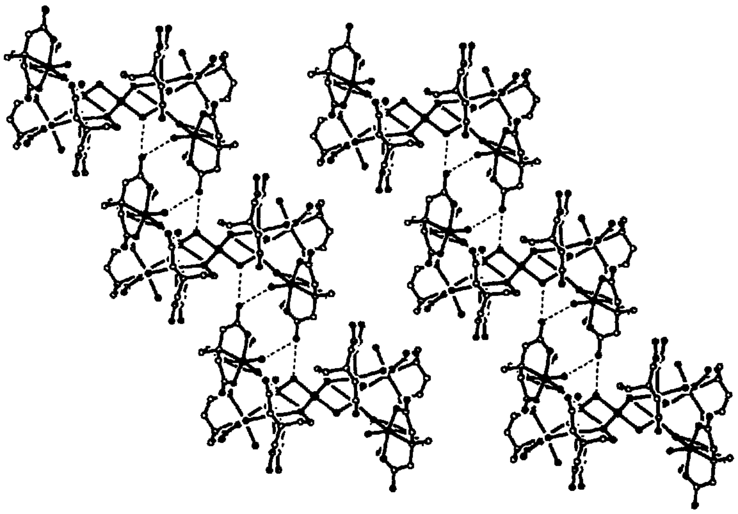


FIGURE 30 Illustration of the packing of the Fe_{19} (**26**) clusters in the lattice of **25** $Fe_{36}C_{108}H_{332}N_{22}O_{226}$.

held together not only by van der Waals forces but also by a "zig-zag" type of hydrogen bond caused by the offset positions of the hydrogens. The protons of the brucite structure are in parallel planes. The distance between adjacent protons in a plane is 3.12 Å while the distance between a proton and its nearest neighbors in the next plane is 1.93 Å and the distance between adjacent proton planes is 0.69 Å.[74] The second inaccuracy is that in **25** the cores consist of OH–Fe–OH sheet structures rather than OH–Fe–OH . . . OH–Fe–OH layered structures. They are prevented from being such by the bulky organic ligand shell surrounds. Figure 30 shows the packing of cluster **26**; however, cluster **27** is packed in a similar way. The cores of **26** and **27** lie at angles of 28.4° to each other (see Fig. 26). In other words the whole lattice consists of two interpenetrating sets of cores at 28.4° to each other.

Iron(III) oxyhydroxides in Nature form different structural types to the one that has been isolated here. In the mineral goethite, α-Fe.O.OH, for example, the irons are in octahedral interstices of the hcp oxygens. However, not all of the oxygens are in the same environment. The hydrogen atoms do not actually lie equi-

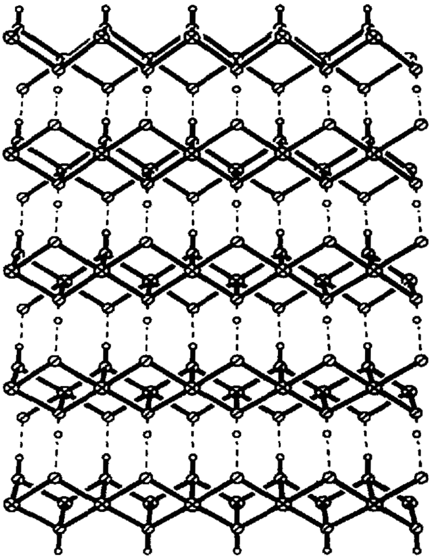


FIGURE 31 The structure of the mineral goethite, α-Fe.O.OH.

distant between the pairs of oxygens but closer to one than the other (see Fig. 31), and are slightly displaced from the straight line joining them. The O . . . HO bond length between the neighboring sheets in goethite is 2.65 Å, and the hydrogen bond length, as expected, is close to 1 Å.[6] The hydrogens are more closely associated with the oxygens on one sheet than the other in goethite, which is therefore said to possess two different types of oxygens: μ_3-O and μ_3-OH. As such, its formula is written as Fe.O.OH.

As noted above, the iron(III) hydroxide mineral trapped in **26** and **27** corresponds to $\{(Fe(OH)_2)^+\}_n$. As an extended lattice this mineral would have to exist with an infinity of positive charges. However, the charge on the trapped mineral is almost entirely compensated by the iron/ligand shell which is thus able to stabilize the structure.

6.6 Relevance of **26** and **27** as Model Compounds for the Ferritin and Haemosiderin Cores

In HSF there is an outer coat of organic ligands from the protein. Iron(III) ions interact with the amino acid residues on the inside

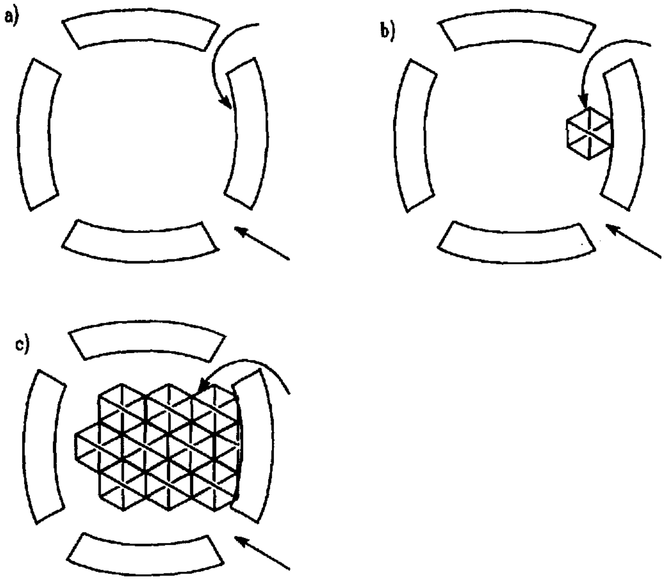


FIGURE 32 Postulated build up of the ferritin core (adapted from Ref. 75). (a) Iron enters the ferritin shell as Fe(II) and is bound at nucleation sites favoring oxidation to iron(III). (b) An iron(III) oxyhydroxide core nucleus forms on the bound iron(III). (c) The result is a trapped finite crystallite containing ca. 4000 iron atoms.

of this coat to form nucleation sites. Further iron(III) ions then attach to these via oxide and hydroxide bridges. More iron(III) ions building on to these in a similar fashion would result in the growth of a single crystallite of an iron(III) oxyhydroxide core (see Fig. 32).[75] It is clear that clusters such as **26** model this situation closely in that they consist of an inorganic mineral core connected to an encapsulating organic shell via iron/ligand "nucleation" sites on the inner surface of this shell.

It is conceivable that the biomineral cores of proteins such as ferritin possess different structural types from those normally encountered for iron(III) minerals, as is the case with the clusters of compound **25**. This could be a direct result of the stereochemical demands imposed by the nucleation sites on the protein shell.

6.7 Outlook

As explained above, clusters such as **26**, **27** and ferritin are examples of trapped minerals. Although attempts can be made to assign the mineral type on the basis of spectroscopic or diffraction methods, the problem always exists that clusters are neither "molecular" nor infinite. In a system such as a crystal lattice we assume the structure is infinite because nearly all of the contents are in identical environments. In clusters this is not the case since there can be several different environments in significant proportions as

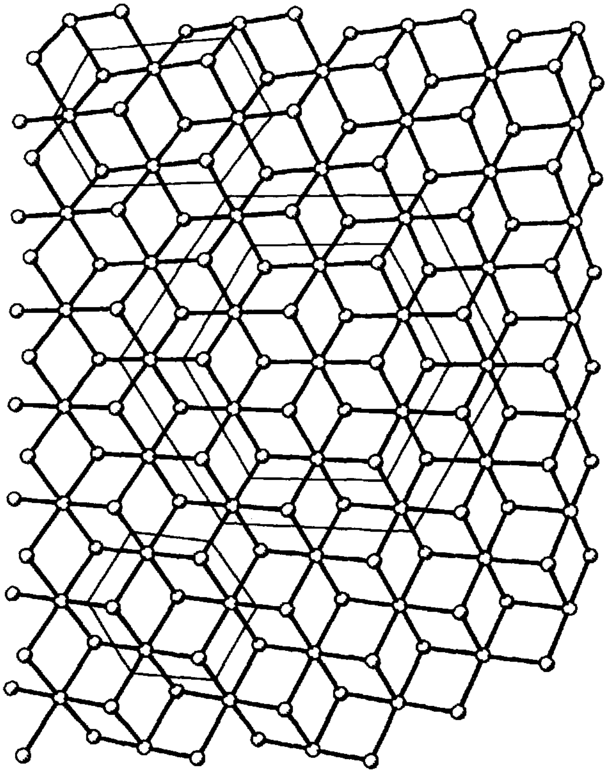


FIGURE 33 Some polyiron hydroxo cores from the $\{(Fe(OH)_2)^+\}_n$ framework. Open circles represent iron centers.

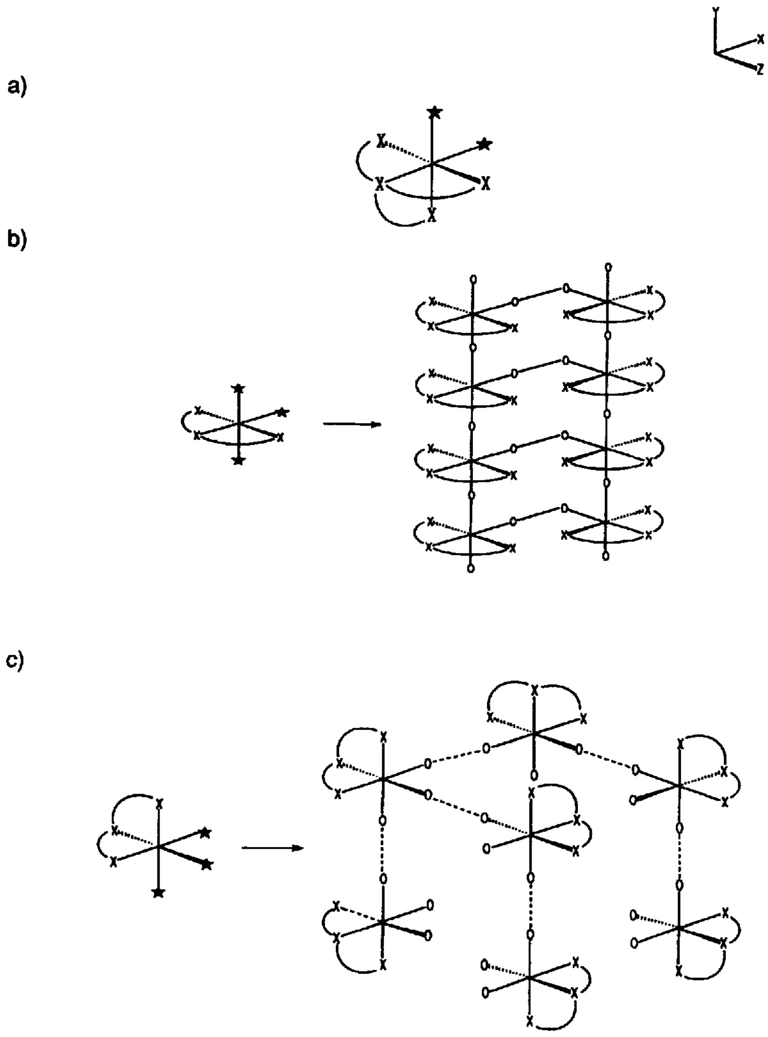


FIGURE 34 The effect of ligand coordination on dimensionality: (a) tetradentate coordination, (b) *mer* coordination and (c) *fac* coordination.

noted above for clusters **26** and **27**. Because of this, clusters are expected to exhibit properties different from those of infinite and molecular systems. An example of this is the superparamagnetic behavior of ferritin cores.[76] In order to explore these effects it will be necessary to synthesize and characterize further examples of trapped minerals. There are two strategies. The first is to modify conditions in order to trap different sizes of cores from the AX_2 structure type as indicated in Fig. 33. Since this is a two dimensional lattice it seems likely that only two dimensional cores will result. The second is to create a situation where a three dimensional core is possible. There are two ways that this might be achieved:

(a) Via the formation of μ_4-O bridges such as exist in the cluster reported by Hagen[58] and in hcp minerals such as goethite and haematite or μ_6-O bridges such as exist in the clusters reported by Hegetschweiler[56,57] and Lippard[72] and ccp minerals such as γ-Fe_2O_3. The relationship of the layer structure of AX_2 hydroxides to those containing μ_4-oxo bridges was explained in Section 6.5, but is unlikely to occur for clusters with cores of the sizes found in **26** and **27** because of steric interference from the ligand, but might be possible for the bigger core sizes.

(b) The use of a tetradentate ligand like heidi blocks four coordination sites of an octahedral iron center. This effectively means that growth can only occur in the *xy* plane as indicated in Fig. 34a. The use of a tridentate ligand offers the possibility of three free coordination sites. If the ligand coordinates *mer* as digly does then again growth can only occur in the *xy* plane. For example we can envisage "ladders" forming (Fig. 34b) if we extend the M—O—M—O bonds of dimers such as compound **10**. If the ligand coordinates *fac* as ida does then three *xyz* coordination sites are free and three dimensional growth is possible (Fig. 34c).

In the ways outlined above it should be possible to explore the effects that charge and denticity in conjunction with mode of coordination of a given ligand can have on iron speciation. Under favorable conditions it will be possible to isolate and characterize even larger examples of trapped oxyhydroxide minerals. Such compounds will shed light on the process of biomineralization and further the understanding of how Nature is able to tailor mineral forms to fulfill specific functions.

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