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A selective discussion on oxo-bridged diiron (III,III) centers in chemistry related to bio-functional activity

Dr. Suranjana Chatterjee
Department of Chemistry, Ananda Mohan College, Kolkata 700009, India

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Corresponding Author: **Dr. Suranjana Chatterjee**

Abstract
Diiron (III, III) oxo- bridged core is playing significant role in various biologically active compounds. Several synthetic diiron compounds are prepared which are the structural and functional models of these bio active centers. Extensive study over these compounds helps us to gain an idea about the mechanistic pathways adopted in the bio active centers. *In vivo* studies are highly expensive and critical. Analysis of these complexes outside the bio-environment is comparatively simple but give us an idea about the mechanistic overview of the metal centers which guide us for further proceedings.

Keywords: Iron, Oxo Bridge, Hemerythrin, Methylmonoxygenase, Model Complex

Introduction

Binuclear oxo-bridged iron species have received much attention in bio-inorganic chemistry due to the wide occurrence of such unit(s) present in different organisms and their performance of a range of biological activities such as the storage and transport of dioxygen (in hemerythrin, Hr),[1, 24] hydroxylation of alkanes (in methylmonoxygenase, MMOH), [2, 25] phosphate ester hydrolysis (in purpleacidphosphatase PAP) [3, 26] and DNA synthesis (in ribonucleotidereductase, RNR). [4] A series of model systems have also been developed in parallel to contribute better understanding of the mechanism of action of the bio-molecules and eventually to mimic their activities. Complexes capable of acting as functional model for the diiron non-heme proteins must have either a free coordination site or a ligand (unsaturated metal center), which can be replaced easily by an incoming substrate molecule**.** These complexes have undoubtedly sharpened our insights into the structural and physical properties of polyiron oxo centers in biology. While such synthetic achievements can be admired for their intrinsic beauty, they are limited in their ability to elucidate chemical details underlying their reactivity and the fine tuning of the electronic factors that affect the dynamics of their substitution or electron-transfer reactions. Ligand substitution or exchange reactions are of interest, for they help to define the parameters that control substrate molecule access to oxo-bridged iron centers in proteins and uncovering the redox principles used by Nature to tune the iron centers to perform diverse functions.

The situation appears somewhat surprising when one looks at the rich literature on the substitution and redox kinetics of mononuclear iron(III) species. The lack of information on reactivity is most probably due to the great stability of the μ-oxo diferric unit that translates to inertness under a variety of conditions and in fact, one likely reason for large number of the synthetic complexes is that the Fe–O–Fe unit is difficult to avoid in ferric chemistry. [5, 27] A second reason may be the gross instability of the mixed-valent and diferrous units which translates to a lack of selectivity. Proper interpretation of kinetic data of mononuclear analogous thus demands a detail knowledge of the solution properties of oxo-bridge iron complexes.

Model complexes

Complexes with N-donor ligands and N, O-donor ligands were known long ago. [6] Usually short Fe–O(oxo) distances are characteristic of the diferric Fe–O–Fe units. The Fe–O distance range from 173 pm to 182 pm, with the average being 177 pm. The Fe–O–Fe angle is quite flexible, ranging from 139°–180° and the extent of antiferromagnetic spin coupling between the two Fe^{III} ions increases with increase in the bridge angle. The electronic transitions of these complexes have been assigned from analyses of absorption and CD spectra, polarised single crystal spectra and Raman excitation profiles. The band in the UV-vis region is assigned to oxo–Fe^{III} LMCT transitions. For the μ-oxo-diiron(III) complexes, the symmetric stretch of the Fe–O–Fe unit occurs between 380 to 540 cm^{-1} and asymmetric stretch occurs between 725 and 885 cm^{-1}. Because of the point

group symmetries, the former has the higher intensity in Raman spectra, while the later is more readily observed in IR spectra. Excitation profiles of the scattering intensity for the symmetric Fe–O–Fe stretching bond in Raman spectra have assisted in assignment of electronic transitions in these complexes.

The first oxo-bridged diiron (III) complex was prepared by Pfieffer *et al.* in 1933. [7] They were able to synthesise and characterise the Schiff–base derivative [(Fe^{III}salen)$_2$O] (salen = N,N′-ethylenebis(salicyldeneiminato)) without the aid of any spectroscopic or structural instrumentation. Shortly afterwards the phenanthroline dimers were prepared but formulated as having a dihydroxo bridge. Anomalously low magnetic moments were first observed for diiron(III) complexes in early thirties and were ascribed to binuclear species with oxo or dihydroxo bridging. In the sixties, Lewis and co-workers [8-10] put forward a general model for antiferromagnetic exchange between two high-spin (S = 5/2) iron(III) centers. Cyclic voltammetry of [Fe(salen)$_2$]O and [Fe(TPP)]$_2$O (TPP = Tetraphenylporphinato dianion) show chemically reversible one electron reductions of $E_{1/2} \sim -1$ V *versus* SCE. Subsequent reduction steps are irreversible. The tribridged complex $[Fe_2O(OAc)_2(MTACN)_2]^{2+}$ shows a quasi-reversible one electron wave at $E_{1/2} \sim -0.37$ V *versus* SCE. For these three complexes controlled potential coulometry results in production of metastable mixed-valent species, which have resisted all attempts in isolation at that time. Although since several new complexes within this category have appeared continually, a renaissance in this area began in 1983 with the synthesis of two μ-oxobis(μ-carboxylato)diiron(III) 'hemerythrin site models' independently in the laboratories of Lippard [11] and Wieghardt. [12] The compound synthesised by Lippard *et al.* mimicked the geometric, magnetic and electronic spectral properties of the diiron(III) center in the metHr and metmyoHr. Antiferromagnetic behaviour was apparent from the calculated J value of –122 cm^{-1}, reported for metaquoHr. Also, the Fe–N and Fe–O (acetate) bond lengths are those typical of high spin iron(III) while the Fe–O(oxo) distances also agree well with literature values for antiferromagnetically coupled oxo-bridged high spin diiron(III) compounds. Crystal structure of another compound namely μ-oxo-bis-fac-[triaqua-1,10-phenanthrolineiron(III)]tetrakis(nitrate)monohydrate was reported in 1984 [13] which had a geometry typical of high spin iron(III) with the two Fe–O(oxo) distances 176.5 and 178.4 pm and the Fe–O–Fe angle 162.0°. In the same year, Loehr and coworkers found the crystal and molecular structure of the (μ-oxo)bis[aquabis(phenanthroline)iron(III)] complex. [14] This complex is a good model for the vibrational spectroscopic properties of the binuclear iron proteins Hr and RNR. Lippard *et al.* reported the assembly and characterisation of accurate model for the diiron center in Hr with tri-1-pyrazolylborate ligands and one oxo and two carboxylato bridge in 1984. [15] The geometry of the $[Fe_2O(O_2CR)_2]$ (R = H, CH_3, C_6H_5) core of these compounds is nearly congruent with that found in the azidomet forms of the marine invertible oxygen transport proteins, Hr and myoHr. Qualitatively the UV-vis spectra of these complexes bear a striking resemblance to that of azidometHr. Quantitatively, however the prominent peaks between 400 and 500 nm are six times less intense that those observed in the spectrum of the protein sample. Cyclic voltammetric studies of the complex revealed an irreversible reduction accompanied by formation of a mononuclear form, which itself undergoes a reversible one-electron oxidation. The instability of the μ-oxo diiron(II) unit in the model compound parallels that of reduced deoxy form of the protein. Magnetic susceptibilities of these model compounds over the range 2.9<T<300K revealed the diiron center to be antiferromagnetically coupled with a spin exchange coupling constant J = –121 cm^{-1}, a value close to that (–134 cm^{-1}) of metHr. Holm *et al.* [10] explained the observed increase in J value with increasing the bridge angle of Fe–O–Fe unit in complexes of the type [Fe(salen)]^{2}O in terms of a MO model of antiferromagnetic coupling with an important π-super exchange pathway.

Pseudohalide containing (μ-oxo)bis(μ-carboxylato)diiron(III) compounds (Hr model) [16] have been synthesised & characterised with molecular formula $[Fe_2O(\mu\text{-XDK})(bipy)_2(L)_2]$ (where L = NCS,NCS, NCSe, N_3 and XDK – doubly deprotonated form of m-xylenediamine bis-(Kemp's triacidimide)). The spectroscopic properties are fully consistent with their respective solid-state structures. Although many more examples of μ-oxo bridged diiron(III) complexes modeling non-heme iron proteins are there. Model complexes of other oxo-bridged diiron proteins and some points on mixed-valent diiron species and diferrous species.

Que and coworkers [17] synthesised and characterised a series of (μ-oxo)diiron(III) complexes that reproduced the protein-tetraoxoanion stoichiometry found in purple acid phosphatases. These investigations used the correlation between Raman symmetric Fe–O–Fe vibration mode and the energy of the long wavelength visible absorption band as a method to use. Toftland and coworkers [18] also reported some (μ-oxo)diiron(III) complexes with tris(2-pyridylmethyl)amine ligand, namely $[tpa(OH)FeOFe(H_2O)tpa](ClO_4)_3$ and $[tpa(Cl)FeOFe(Cl)tpa](ClO_4)_2$ which showed a bit lower value of J. There is also a report of low-spin oxo-bridged diiron complex of bis(difluoro(dimethylglyoximato)borate).

Although there are good model complexes for the completely reduced Fe_2^{II} and oxidised Fe_2^{III} and species containing active dimetallic centers, no mixed-valent $Fe^{II}Fe^{III}$ complexes with a hydroxo or oxo bridge mimicking semimetHr was reported till Weighardt and coworkers synthesise and characterised spectrophotometrically [L $Fe^{III}(\mu\text{-OH})(\mu\ piv)_2Fe_2^{II}L](ClO_4)_2$ where L is 1,4,7-trimethyl-1,4,7-triazacyclononane and piv is pivalic acid anion in 1995. On the other hand $Fe^{II}Fe^{III}$ complexes with a bridging phenoxy group were well known at that time. In 1997, Styring *et al.* [19] were able to characterise the mixed-valence Fe^{III}–O–Fe^{II} form spectroscopically which was obtained by controlled potential electrolysis of an acetonitrile solution of the dinuclear species [(trispicMeen)Cl Fe^{III}–O–Fe^{III}Cl(trispicMeen)]Cl(OH)$(H_2O)_7$ (trispicMeen = N,N,N′-tri(2-pyridylmethyl)-N′-methylethane-1,2-diamine). Tolman and Que [20] used bulky terphenyl carboxylates and related benzyl substituted benzoates to assemble a variety of new diiron(II) complexes analogous to nonheme diiron protein sites. They have also reported the generation of diiron(II,III) complexes from one electron oxidation of the diiron (II,II) species. These mixed-valent complexes are of interest due to fundamental reasons and because of their relevance to numerous such mixed-valent sites found in proteins, studies of which have focused on understanding how their structural

features relate to their functionally important magnetic and redox behaviour. In most diiron(II,III) complexes the high spin ions couple antiferromagnetically to yield an S = 1/2 ground state. Que *et al.* [21] also reported the formation of $Fe^{III}Fe^{IV}$ species from a diiron(II) precursor *via* a peroxo intermediate. Depending on their earlier success in generating Fe(III)Fe(IV) species from the reaction of diiron(III) precursors with H_2O_2, [22, 28] they report the first example of a synthetic diiron(II) complex that reacts with dioxygen to generate in sequence an Fe(III)Fe(III) peroxo species and an Fe(III)Fe(IV) complex.

Fish and coworkers [23] prepared pertinent biomimetic model of MMO, $[Fe_2O(OAc)(tmima)_2]^{3+}$ (tmima = tris((1-methylimidazol-2-yl)methyl)amine) (**1**) and $[Fe_2O(H_2O)_2(tmima)_2](ClO_4)_4$ (**2**). This group of workers also provided mechanistic aspects of the C-H bond functionalization reactions of several hydrocarbons with **2** as catalyst using anhydrous TBHP in presence of oxygen gas (O_2) and acetonitrile (CH_3CN) as solvent. **1** can catalytically functionalizes a wide variety of alkanes with hydrogen peroxide or tert.butylhydroperoxide (TBHP) in presence of O_2 gas.

Beside handful examples of structural models of different forms of Hr, functional model of this protein is also present. In order to construct functional models for Hr series of diferrous benzoate bridged compounds $[Fe_2^{II}(Htppdo)(PhCOO)(ClO_4)_3$, $[Fe_2^{II}(Htppdo)((p-Cl)PhCOO(ClO_4)_3$, $[Fe_2^{II}(Htppdo)((p-Cl)PhCOO)](BF_4)_3$ and $[Fe_2^{II}(Htppdo)((p-Cl)PhCOO)](ClO_4)_3$ were synthesised where Htppdo=N,N,N′,N′-tetrakis(6-pivalamido-2-pyridylmethyl)-1,3-diaminopropan-2-ol. With this novel dinucleating polypyridine ligand the complexes prepared have hydrophobic pockets constructed by *tert*-butyl groups attached to the pyridine rings which keep the dioxygen binding site covered; thus, mimicking the hydrophobic peripheral structure of diiron active site of Hr. These complexes in acetone demonstrate reversible dioxygen binding at –50°C yielding diiron-peroxo complexes. The peroxo anion binds with the diiron core in a μ-1,2 bridging mode. These findings suggest that thermodynamic stability and reversible oxygen binding depend on the hydrophobic environment over the diiron core rather than the redox potential at the iron atoms.

Reactivity and mechanistic studies on the redox reactions of (μ-oxo) diiron(III) complexes started with the aim of understanding natural process involving metalloproteins. However, reactivity studies appear to be occasional and mechanistic studies are rare outside a protein environment. The situation appears somewhat surprising when one looks at the rich literature on the substitution and redox kinetics of mononuclear iron(III) species. The lack of information on reactivity is most probably due to the great stability at the μ-oxo diferric unit that translates to inertness under a variety of conditions and in fact one likely reason for large number of the synthetic complexes is that the Fe-O-Fe unit is difficult to avoid in ferric chemistry. A second reason may be the gross instability of the mixed-valent and diferrous units, which translates to lack of selectivity. Proper interpretation of kinetic data of mononuclear analogous thus demands a detailed knowledge of the solution properties of oxo-bridged iron complexes.

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