Axial ligation to low spin iron(II) macrocycles: inorganic and biomimetic applications

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Abstract - The chemistry of FeN₄ complexes analogous to hemes are presented emphasizing the fundamental dissociative mechanism for axial ligation. Implications of kinetic and equilibrium data to our understanding of metal ligand bonding are discussed. Applications of this class of complexes to inorganic photochemistry, biomimetic chemistry, and novel linear chain supermolecules are presented.

A variety of planar macrocyclic tetradentate nitrogen donor ligands (N₄) in conjunction with two monodentate axial ligands generally give relatively inert low spin complexes trans-FeNₓXY. These complexes are distinctly colored, are readily soluble in organic solvents and undergo clean axial ligand substitution reactions. Along with hemes, they comprise a distinct class of inorganic complexes which bridge the gap between classical Werner complexes and generally more inert organometallic or π-acid complexes. Extensive work on FeNₓXY systems in recent years provides a considerable body of systematic quantitative data with which to understand the inorganic chemistry of the heme group as well as considerable insight into fundamental concepts of metal ligand bonding.

Some of the ligand systems which have been investigated are summarized below. The resulting FeNₓXY complexes are electrically neutral (Fe₆F₆P₆,Fe₆P₆,Fe₆(dioxime)₆), unpositively (Fe(TOHpm)₆) or dipositively (FeTIM,FeTAAB, Fe14ane, Fe15ane) charged.

Axial Ligands: P(OBu)₃ tributylphosphine
BeNC benzylisocyanide
TMIC tosylmethylisocyanide
DIB 1,4 diisocyanobenzene
MeIm methylimidazole
py pyridine
CO carbon monoxide

N₄ = TPP tetraphenylporphyrin
p protoporphyrin IX dimethyl ester or related porphyrins
Pc phthalocyanine
(DMGH)₂ bis-dimethylglyoximate
(BQDM)₂ bis benzoquinonedioximate
(NPQH)₂ bis naphthoquinone dioximate
DOHpn diacetylmethylenediacetylmethoximonoximato
TIM 2,3,9,10 tetramethyl 1,4,8,11 tetraazacyclotetradeca
14ane 1,4,8,11 tetraazacyclotetradecane
TAAB tetrabenzo [b,f,j,n][1,5,9,13]tetraazacyclhexadecine

Spectral features. The visible spectra of iron porphyrins and phthalocyanines are dominated by intense π-π transitions which are only slightly perturbed by the axial ligands (~40nm). The saturated low spin Fe[14ane]²⁺ derivatives give weaker d-d bands. The other systems all display intense MLCT bands. These bands shift much more dramatically with changes in the axial ligands. As shown in table 1 the MLCT band shifts to higher energy as π-acceptor ligands are introduced which lower dxz,yz. The position of the MLCT band is also critically dependent on the N₄ ligand and can be moved at will through the visible region with changes in the π-conjugation of N₄ as demonstrated for Fe(DMGH)₂ and Fe(NPQH)₂ derivatives. This feature is especially useful in photochemical studies and photochromic applications. Correlations of ligand lability with the MLCT band
are observed pointing to an important role of $\pi$-bonding. The effects of the $N_4$ ligand on the axial $\pi$-bonding properties of iron are apparent in $\nu_{\text{CO}}$ for the carbonyl derivatives which range from 1970 cm$^{-1}$ in hemes and Fe(DMGH)$_2$(MeIm)(CO) up to 2028 cm$^{-1}$ in neutral Fe(NDQH)$_2$(MeIm)(CO) and even higher for $+$2 charged complexes. The $\nu_{\text{CO}}$ does not generally correlate with the lability of CO except for systematic variations:

- with $\pi$-conjugation: Fe(NDQH)$_2$ > Fe(NDPH)$_2$ > Fe(DMGH)$_2$
- with charge: Fe TIM$^{3+}$ > FeDOHpn$^+$ > Fe(DMGH)$_2$

**AXIAL LIGATION REACTIONS**

An overwhelming body of evidence (which we won't present here) exists for a simple dissociative mechanism for axial ligand substitution in all Fe$N_4XY$ systems. Since ligand binding and release are mechanically simple, both the kinetics (lability) and thermodynamics (stability) can be understood in terms of the same basic concepts. The nature of the $N_4$ ligands generally limits reactivity to the axial sites, minimizes structural distortion of the pentacoordinate species, and prevents isomerization. For hemes, pentacoordinate complexes (the reactive intermediate in ligand substitution reactions of the six coordinate species) can be detected spectroscopically through synthetic tricks $^8,21,22$ or via flash photolysis$^8-7$ and in some cases may be isolated and structurally characterized$^{23,24}$. Few, if any reactive intermediates, are this well characterized in all of inorganic chemistry.

Equilibrium constants for ligation to iron (e.g., 1-4) are related to corresponding on ($k^+$) and off ($k^-$) rate constants. These fundamental parameters are now known for a vast array of ligands providing a comprehensive data base with which to understand the mutual effects of ligands on the substitutional reactivity of coordination complexes.

\[
\begin{align*}
  \text{FeN}_4X_2 & \xrightleftharpoons[k^-x]{k^+x} \text{FeN}_4X \xrightleftharpoons[k^-y]{k^+y} \text{FeN}_4XY \\
  \text{FeN}_4 + X & \rightarrow \text{FeN}_4X \quad K = k^+x/k^-x \\
  \text{FeN}_4X + X & \rightarrow \text{FeN}_4X_2 \quad K^x = k^+x/k^-x \\
  \text{FeN}_4X_2 + Y & \rightarrow \text{FeN}_4XY + X \\
  K_{x,y} &= (k^x_y/k^+x)(k^x_x/k^-y)
\end{align*}
\]

**Off rates.** Table 2 shows the range of labilities found as a function of $N_4$, and the leaving ligand, $L$. The values of $AG^*$ shown correspond to rate constants from $10^2$ to $10^{-4}$ s$^{-1}$. In addition, the lability of ligands in these systems are dramatically dependent on the trans ligand. For example MeIm lability spans six orders of magnitude in
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Fe(DMGH)(MeIm)T \rightarrow \text{T} = \text{MeIm}, \quad \text{py} > \text{PPh}_3 > P(\text{OBu})_3 > \text{BzNC} : \text{CO}. \quad \text{The delabilizing effect of } \pi- \text{acceptors is explained in terms of a loss of synergistic } \pi- \text{bonding as the good donor (MeIm) is removed. The trans effect series has been explored in some depth for hemes, FePc, Fe(DMGH)$_2$, Fe(BQDH)$_2$, and Fe(NPQH)$_2$. The trans effect differs as a function of both the nature of the leaving ligand and the K$_a$ macrocycle. What emerges is a strong case for a delocalized bonding picture in which every ligand in a complex has an effect on the bonding of every other ligand. Rate constants, $k_-$ or the corresponding $\Delta H^*$, provide a good measure of metal ligand bond strengths since the on-rate constants $k_+$ are nearly diffusion controlled. The use of this data to better understand the deceptively simple notion of a metal ligand bond strength has been presented elsewhere.}

On-rates. Addition rates to pentacoordinate hemes are quite rapid $^{4-8} \, (k=10^7-10^8 \, \text{mol}^{-1} \, \text{s}^{-1})$. While directly determined on-rates for other FeN$_4$ systems are not currently known, competitive methods show that these pentacoordinate species are similarly weakly discriminating$^9$, $^{11}$, $^{13}$ and are likely to have similar rate constants. Addition of a ligand to a vacant coordination site is one of the most fundamental processes imaginable yet only a handful of rate constants for such reactions are currently known. $^{25-27}$

One expects that this reaction would be complicated for iron (II) hemes since the spin state of the 5 and 6 coordinate species are different. Theoretical work for thermal reactions requiring electronically forbidden surface crossings is not highly developed. $^{24}$ Rates for spin equilibrating iron complexes involving only expansion but not breakage of metal ligand bonds seem to depend primarily on Franck-Condon factors$^{24}$ and are typically much faster than Fe-X bond making in hemes. Known on-rates to hemes and related complexes do not reveal any important spin effects other than those associated with Franck-Condon factors. For example triplet oxygen adds to either quintet hemes or doublet cobalt porphyrins$^{25}$ with comparable rates. Imidazoles, isocyanides, and O$_2$ add to hemes with similar rates but CO adds about 10x slower. The somewhat greater rates for CO or imidazole addition to flat (triplet) hemes compared to high spin pentacoordinate hemes is likely due to barriers associated with movement of the iron in the heme plane. The slower rates for CO addition to T-state pentacoordinate hemes$^{31}$ is a clear example of how the on-rate barrier may be increased by strain associated with movement of the iron into the heme plane. Steric effects which block access to the vacant site have been shown to have profound effects on addition rates. $^{9}$, $^{12}$, $^{2}$ This feature found in capped hemes and hemoproteins has been clearly documented for a variety of bulky and diatomic ligands in cyclophane hemes. $^6$

PHOTOCHEMISTRY

FeN$_4$XY systems provide a rich supply of relatively substitution inert complexes for the investigation of photochemical axial ligand substitution reactions. The photodissociation of CO from hemes is well known. All FeN$_4$ systems investigated to date show a high quantum yield for CO photolysis and lower values for isocyanides, phosphines, and imidazoles. $^{34,35,35}$ The greater thermal inertness of the non-heme systems is a distinct advantage.

Extensive investigations of Fe(DMGH)$_2$ and Fe(NPQH)$_2$ complexes have been carried out involving a variety of axial ligands. Data for the photosubstitution reactions

$$\text{hv} \rightarrow \text{FeN}_4 \text{LT} \rightarrow \text{FeN}_4 \text{TE} + \text{L} \quad (5)$$

are fully consistent with a D mechanism in which the ligand L is lost from a photoactive state generating a pentacoordinate intermediate FeN$_2$T. The reactivity of the pentacoordinate intermediate is quantitatively probed through competitive trapping studies and the concentration dependence of $\phi$. Its reactivity is essentially identical to that of the corresponding intermediate formed in dissociative thermal substitution reactions. Since both thermal and photochemical substitution reactions of FeN$_4$XY systems proceed via the same dissociative mechanism, they provide an ideal system to investigate the effect of electronic structure on metal ligand bond strength. The temperature dependence of the off-rate constant, $k_{-L}$, affords $\Delta H^*_{-L}$, a good measure of the ground state Fe-L bond strength.

The corresponding excited state bond activation enthalpy, $\Delta H^*_{-L'}$, is not as easily obtained. The quantum yields for ligand photodissociation are found to be temperature dependent from which an apparent activation energy may be obtained. While $\Delta E_{\text{app}}$ may include factors associated with the temperature dependence of competing photophysical processes, the major contribution to $\Delta E_{\text{app}}$ is likely the metal ligand bond strength in the excited state. The $\Delta E_{\text{app}}$ for Fe(DMGH)$_2$(MeIm)X for X = CO, P(\text{OBu})$_3$, BzNC and PPh$_3$ are -1, 4.3, 4.6, and 8.1 kcal/mole and these correlate with the observed quantum yields. A
common low-lying thermally equilibrated ligand field state probably of picosecond lifetime involving population of $d_{z^2}$ is likely responsible for the gross similarities in the photochemistry of hemes and other FeN₆ systems described here. The ligand field state is apparently populated with high efficiency, from $\pi^*$ states in the case of hemes and phthalocyanines or from MLCT states for other FeN₆ complexes. This state should have axial ligand bonding comparable to high spin hemes or corresponding cobalt(II) analogues, both of which contain one electron in $d_{z^2}$.

Structural data for these analogues indicates axial ligand bond lengths 0.2 to 0.3Å longer than low spin Fe(II). The enthalpy for piperidine binding to (pip)CoTPP is $-1.7$ kcal/mole and the off-rate constant $k_{pip}$ may be estimated as a $10^8$ s$^{-1}$ for CoTPP(pip).

**BIOMIMETIC STUDIES**

The availability of a variety of FeN₆ systems showing chemistry qualitatively similar to hemes but quantitatively quite different provides numerous possibilities for biomimetic studies. An iron phthalocyanine reconstituted myoglobin displays properties which clearly illustrate the delicate balance of chemical interactions which determine a metalloprotein's reactivity. In native hemoglobin and myoglobin the unusual pentacoordinate geometry of the heme is often said to be conferred on the heme by the protein. The vacant sixth coordination site is of course critical to the reversible oxygen binding function of these proteins. The artificial protein, FePcMb, adopts a six coordinate geometry with iron coordinated to both proximal and distal histidines. The relative binding strengths of imidazole to FePc and hemes as indicated by the rate constant $k^0 = 10^3$ s$^{-1}$ vs 1500 s$^{-1}$ is clearly a determining factor. The precise structure of the metalloprotein is a compromise between conformational factors and metal ligand bonding. In this example, a change in the nature of the N ligand can alter the iron imidazole bonding by ~8kcal/mole and dramatically alter the structure. A six coordinate metalloprotein must break an iron histidine bond prior to ligand addition thus retarding ligation of small molecules in both the kinetic and thermodynamic sense. Myoglobin reconstituted with the macrocyclic derivative FeTAA$^{23}$ seems to give similar results. Here we see the importance of the unusual lability of hemes. The ready availability of hemes and their well-developed synthetic chemistry is largely responsible for the tremendous attention and success of heme biomimetic studies. Contrast work on cobaloximes vs vitamin B with that on iron dioximes vs hemes. Yet it is clear that a vast number of unexplored possibilities exist for biomimetic studies of non-heme FeN₆ systems. The lacunar supermolecules of FeN₆ tetraimines developed by Busch are the most prominent examples. The remarkable properties of the glycopeptide antibiotic bleomycin has received considerable attention. This molecule is structurally closely related to the macrocyclic iron derivatives described here suggesting that bleomycin like activity might be found in suitably modified FeN₆ systems.

**LINEAR CHAIN SUPERMOLECULES**

The kinetic and photochemical control of reactivity possible in more inert FeN₆ systems has led us to explore the synthesis of specifically sequenced chains of FeN₆ units connected via linearly bidentate ligands. Ligands such as pyrazine (pz), 4,4’bipyridine, (bipy), and 1,4-dicyanobenzene (DIB) may be used to synthesize chains in a systematic fashion much like the synthesis of small segments of biopolymers. The axial ligand bonds serve as both blocking and activating groups.

**Fig. 1.** Linear chain of Fe(NPQH)$_2$, FeTIM$^{+2}$, and Fe(DMGH)$_2$, where linking ligands X or Y may be bipy, pz, or DIB.

Only sufficiently inert systems (certainly not hemes) are suitable for creating viable chains. The kinetic characteristics of a variety of FeN₆ (and some RuN₆) systems are now available. This data is especially useful in planning the synthesis of viable linked systems.
TABLE 3  SUMMARY OF LINKED COMPLEXES

<table>
<thead>
<tr>
<th>L</th>
<th>N₄</th>
<th>N₄'</th>
<th>L'</th>
<th>λ_{max}(nm)ᵃ</th>
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<tr>
<td>Homobinuclear: LFeN₄₋DIB-FeN₄L</td>
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<tr>
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<td>DMGH</td>
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<tr>
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<td></td>
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<tr>
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<td>Py</td>
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<td>546,430,380</td>
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</table>

ᵃ. TIM complexes as PF₆⁻ salt in CH₃CN, all others in CHCl₃.

Homo- and heterobinuclear compounds as well as some trinuclear compounds prepared to date are listed in Table 3.

Simple homobinuclear complexes are obtained in almost quantitative yield by reaction of a labile FeN₄L₂, L = py, MeIm, or CH₃CN with 1/2 equivalent of 1,4-diisocyanobenzene (DIB). The strong trans delabilizing effect of isocyanides renders the resulting complex substitution inert preventing polymerization. Heterobinuclear complexes are obtained by reaction of a labile FeN₄L complex with a pure FeN₄(DIB) complex. Reactions proceed cleanly and may be readily followed by visible spectroscopy. For example the reaction

\[
\text{Fe(NPQH)₂(MeIm)}₂ + \text{Fe(DMGH)₂(MeIm)(DIB)} \rightarrow \text{(MeIm)Fe(NPQH)₂-DIB-Fe(DMGH)₂(MeIm)} + \text{MeIm}
\]

is characterized by a decrease of 702 nm due to Fe(NPQH)₂(MeIm)₂ and an increase at 548 nm characteristic of the naphthoquinone species coordinated to DIB. The free NC sites in a sample can be spectrophotometrically titrated via equation 6. Products are purified by column chromatography giving isolated materials showing single spot purity by TLC and characteristic nmr spectra, and visible spectra essentially the superposition of those of the corresponding mononuclear chromophores. These linked chromophores have potential for systematic studies of long range electron or energy transfer, as well as for biomimetic studies involving multiple recognition sites arrayed in a linear chain.

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