CHAPTER 1

Photochemistry of iron complexes

Although iron is the most abundant of the bio-essential metals, and its coordination chemistry is of central importance to bio-inorganic and bioinspired chemistry, its photochemistry has been overshadowed by ruthenium polypyridyl complexes since the 1970s. The photochemistry of iron complexes is nevertheless rich and presents a multitude of opportunities in a wide range of fields. In this chapter, we review the state of the art and especially recent progress in the photochemistry of iron complexes, focusing on aspects of relevance to environmental, biological and photocatalytic chemistry.

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Chapter 1

1.1 Introduction

Photochemistry is an small but essential branch of chemistry, recognized for example, as the basis for the “molecular-machines” honored by the 2016 Nobel prize for chemistry, and is central to most life on this planet. At its most basic level, photochemistry is the conversion of electromagnetic radiation to chemical energy and enables induction of chemical transformations with spatial and temporal control. The chemical transformations and changes in reactivity form the basis of “photodynamic therapy” treatments in medicine and in photo(redox)catalysis, and hence exploring new photochemical processes in both organic and inorganic molecular systems opens opportunities in medicine, materials and chemical reactivity.

The range of organic and inorganic systems of interest to photochemistry is much more limited than for thermal reactivity. This is primarily due to the need for a compound to have an electronically excited state that is sufficiently long lived to engage in energy or electron transfer, or to react with other compounds. From an inorganic perspective, this demand has limited attention to transition metal complexes such as those of chromium, ruthenium and iridium. In the case of iron complexes the lowest excited states are metal centered (e.g., e_g \leftrightarrow t_{2g}) and are displaced with respect to the ground state facilitating rapid radiationless deactivation, and hence quenching photochemical reactivity. Given that there are many new iron complexes reported each year, the challenge is to identify and understand potential approaches to achieving photoreactivity with iron complexes. In this chapter, we will discuss the known photochemistry of iron complexes and categorize the various reaction classes to build a picture of the state of the art.

The reported iron complexes are mostly coordinated with organic ligands in an octahedral or, less often, tetrahedral coordination environment. The photo-processes observed in iron complexes correlate with formal oxidation states, spin states, as well as the ligand environment. Hence, we will begin our discussion by introducing electronic structures and the electronic configurations of iron complexes in their various oxidation states.

The earliest, and perhaps the best-documented, photochemical reactions are the photo-assisted Fenton and photo-induced decarboxylation reactions, both of which are of relevance to environmental and materials science (see section 1.3.1 and section 1.3.2). The photochemically induced release of small molecules, a field of growing importance, is dominated by:

- Release of N_2, for example, from porphyrin-ligated Fe^{III} azide complexes used to generate high valent iron complexes.
- H_2 evolution, for example, through reductive elimination from Fe-hydride complexes, which holds potential in energy storage.
- CO-release, mainly from Fe-CO complexes, which is of importance in CO-related cytoprotection, anti-inflammation, and vasodilatory therapeutic treatments.

Iron is an essential element and its complexes are well recognized as candidates in photometalldrugs in cancer treatment, specifically DNA cleavage and photocytotoxicity as shown by the series of iron complexes discussed in section 1.3.4. Last but not least, photocatalytic reactions using iron complexes are seeing increasing attention, with both heme and non-heme iron complex as photo-catalysts in the oxidation of organic substrates, which is discussed in the penultimate section of this chapter. The contributions made in this thesis are reviewed briefly in the last section.
1.2 Electronic structures and spin states

Iron is the most abundant metal on earth and the known oxidation states of iron range from $\text{Fe}^0$ to $\text{Fe}^{VI}$, all of which have been observed experimentally. Its cations have dominated the field of transition metal oxidation chemistry, due to its great importance in both bioinorganic and synthetic chemistry. The chemistry if iron is enriched by the number of accessible spin states, include high-, intermediate-, and low-spin iron complexes, in each of its stable oxidation states. In bioinorganic and biomimetic chemistry, the majority of iron complexes are in an octahedral or pseudo-octahedral environment. Scheme 1 illustrates the energetic splitting pattern of $d$ orbitals and the electron configurations of the oxidation states of $\text{Fe}^{II}$ to $\text{Fe}^{IV}$ in octahedral environments. The states shown are observed in both heme and non-heme iron complexes and photochemistry involving these complexes has been reported. $\text{Fe}^0$, $\text{Fe}^V$ and $\text{Fe}^IV$ are not included due to the lack of reports on photo activity of their complexes.

Scheme 1. Possible oxidation and spin states of iron complexes in an octahedral geometry (left) and the splitting patterns for $d$ orbitals of oxo-iron(IV) complex in pseudo-octahedral geometry with consideration of the ligand environments (right). Both non-heme and heme ligands are included (structures shown are the representative for each type). All these states are accessible in both non-heme and heme iron complexes.

The energies of all five $d$ orbitals ($d_{xy}$, $d_{xz}$, $d_{yz}$, $d_{x^2-y^2}$, $d_{z^2}$) are degenerate in gas phase $\text{Fe}^{n+}$ ions. However, in ligand field, the relative energies of the $d$ orbitals are determined by the ligand environment. In an ideal octahedral complex, the $5d$ orbitals are split into two degenerate sets, two of higher energy, $d_{z^2}$ and $d_{x^2-y^2}$ ($e_g$ orbitals) and three of lower energy $d_{xy}$, $d_{xz}$, $d_{yz}$ ($t_{2g}$ orbitals). Low-spin Fe$^n$ complexes are the only diamagnetic members of this series of possible oxidation and spin states with the rest being paramagnetic. Amongst the paramagnetic states, there is a special case: the antiferromagnetically coupled arrangement of the $\text{Fe}^{III}$ dimer, in which
there are five alpha d electrons on one Fe$^{3+}$ ion and five beta d electrons on the other. In a pseudo-octahedral complex, the degeneracy is lifted further. For example, in oxo-iron(IV) complexes the five d orbitals are different in energy, and the ligands can change the energy ordering of the orbitals also; the $d_{x^2-y^2}$ orbitals are higher in energy than the $d_{z^2}$ in a heme ligand environment (e.g., compound I of P450) and vice versa in most of the non-heme ligand environments (e.g., N4Py, TMC) (Scheme 1).

The photochemistry of iron complexes was studied extensively prior to the 1970s, but has been overshadowed by the photophysics and chemistry of ruthenium(II) polypridyl complexes with hundreds of variants. The outstanding physical and chemical properties of these Ru$^{ll}$ still play important roles in photochemistry, photophysics, photocatalysis, electrochemistry, photoelectrochemistry, chemi- and electrochemi-luminescence, and electron and energy transfer. Iron and ruthenium are in the same Group (VIII) and are similar in octahedral environments, the metal center and ligand bonding are similar. The most important difference between Fe$^{ii}$ and Ru$^{ll}$ complexes is that almost all the octahedral Ru$^{ll}$ complex are low-spin with a full filled $t_{2g}$ level. Hence, there are only several possible orbital dispositions possible (Scheme 2), (a) the filled metal $t_{2g}$ orbital lies below the filled $\pi$ orbitals of the ligand ($\pi_1$) and $e_g$ orbitals lies above the empty $\pi^*$ orbitals of the ligand ($\pi^*_1$); (b) the fully occupied metal $t_{2g}$ orbitals and empty $e_g$ orbitals lie between the occupied $\pi_L$ orbitals and the empty $\pi^*_L$; (c) the fully occupied $t_{2g}$ orbitals lie between the filled $\pi_L$ orbitals and the empty $\pi^*_L$; in each of the cases, the lowest energy transitions are the intraligand-, metal centered- (Laporte forbidden), and metal to ligand charge transfer transitions, respectively. Scheme 2d shows these four transition types in an octahedral Ru$^{ll}$ complex with polypryidyl ligands. However, for iron complexes the energy difference between $t_{2g}$ and $e_g$ orbitals are much less than for ruthenium complexes. This results in excitation populating the $e_g$ orbitals, which means the lowest excitation for iron complex is populated under irradiation and relax to the ground state much more rapidly than ruthenium complexes.

Scheme 2. (a-c) possible orbital dispositions of d orbitals for octahedral complexes, (d) Electronic transitions in octahedral Ru$^{ll}$ complexes with polypryidyl ligands.
1.3 Photochemistry of iron complexes

Although the excited state transitions in iron complexes under irradiation are not as readily studied as in ruthenium and osmium complexes, they nevertheless exhibit a rich photochemistry and show promise in applications in both catalytic oxidation, biochemistry, environmental chemistry, as well as in material science.

In this chapter, we review the reported photochemistry of iron complexes, including

1. Photo assisted Fenton Reactions.
2. Photo induced ligand degradation-decarboxylation.
3. Photo induced release of small molecules.
5. Photochemistry of iron complexes in catalytic oxidations.

1.3.1 Photo assisted Fenton Reactions

The photo assisted Fenton reaction is one of earliest reported photochemistry on iron complex.²–⁴ The Fenton reaction (H₂O₂/Fe²⁺)⁵,⁶ or Fenton like (H₂O₂/Fe³⁺), are well known reactions, which is mainly used to generate reactive radicals (HO⁺ and HOO⁻) with H₂O as by product and is used widely in the treatment of waste water.⁶–⁹ The production of hydroxyl radicals (HO⁺) is strongly accelerated under irradiation with UV light compared to thermal reactions due to the rapid regeneration of Fe²⁺ through photo reduction of Fe(OH)²⁺. It should be noted the reactions 1-(1, 2, 3) are not the only reactions involved, the exact mechanism of this reaction is still under debate due to the fact that the photoysis of H₂O₂ itself as well as the indistinguishability of Fe⁴⁺ and {Fe³⁺(HO⁺)}⁵.

\[
\begin{align*}
\text{Fe}^{2+} + \text{H}_2\text{O}_2 &\rightarrow \text{Fe}^{3+} + \text{HO}^- + \text{OH}^- \quad (1-1) \\
\text{Fe}^{3+} + \text{H}_2\text{O}_2 &\rightarrow \text{Fe}^{2+} + \text{HOO}^- + \text{H}^+ \quad (1-2) \\
\text{Fe(OH)}^{2+} &\text{hv} \rightarrow \text{Fe}^{2+} + \text{HO}^- \quad (1-3)
\end{align*}
\]

1.3.2 Photo induced ligand degradation - decarboxylation

The photo activity of Fe³⁺ carboxylato complexes, is generally more pronounced than the solvated Fe³⁺ ion, due to ligand to metal charge transfer (LMCT) excitations, which induce the reduction of the transient iron center and oxidative degradation of the organic ligand.¹⁰–¹³ Figure 1 shows one of the most famous examples of such photochemistry, ferrioxalato complexes. The photo-induced reduction of ferrioxalate was first reported by Parker in 1953,¹⁴ followed by the reporting of similar photo activity in complexes of Ligands bearing a carboxylato group (Figure 2).¹¹,¹²,¹⁵ Among these carboxylato ligands, the ferrioxalato complex is widely used as an actinometer in quantum yield measurements.¹⁶ The mechanism of this photoreduction accompanied by degradation of the carboxylato ligand was studies by pump/probe transient absorption spectroscopy and quantum chemical simulations by several groups.¹⁷–²¹ There are two mechanistic aspects still under discussion; especially the steps that follow photoexcitation. Pozdnyakov et al. proposed intramolecular charge transfer from oxalate ligand to Fe⁸⁺ center results in reduction to Fe⁸⁺, which is in contrast to the earlier proposed by Rentzepis and co-workers that the Fe³⁺–O bond cleaves before electron transfer. With the development of ultrafast high resolution transient spectroscopy, in 2017, the Gilbert group¹⁷ reexamined this reaction, they propose a mechanism (Figure 1) in which photo absorption and electron transfer (within 0.1
ps) result in formation of an intermediate ferrioxalate radical anion, which then dissociates rapidly to form thermally excited CO$_2$ and CO$_2^*$. The CO$_2$ relaxes and then leaves the Fe$^{III}$ center and the CO$_2^*$ radical anion remains coordination for ~10 ns.

![Diagram showing proposed pathways for photoinduced ligand degradation of Ferrioxalate.](image)

**Figure 1.** Proposed pathways for photoinduced ligand degradation of Ferrioxalate. For simplification, two oxalates ligands are omitted.$^{15,17}$

The photochemistry of Fe$^{III}$-carboxylate complexes in aqueous solutions is highly dependent on the ligand coordination mode,$^{21}$ as in oxalate (L1), succinate (L5), citrate (L8), and glutarate (L10), these di-carboxylato ligands coordinate strongly with Fe$^{III}$ centers and shows intense LMCT bands, and mostly follow the mechanism in **Figure 1**. In contrast, complexes of, 2-propanoate (L2), 2-oxoacetate (L3), gluconate (L9) which are mono-carboxylate ligands, the photo reaction is dependent on the ligand concentration. Since the carboxylato-complexed Fe$^{III}$ complex is in equilibrium with Fe$^{III}$(OH) species and at low concentration of ligands the photolysis of Fe$^{III}$(OH) dominates, and produces $^\cdot$OH primarily (equation 1-(1-3)).

![Diagram showing structures of the carboxylate ligands.](image)

**Figure 2.** Structures of the carboxylate ligands.

In addition to solely carboxylate ligand environment polypyridine amine based tripodal amine chelated Fe$^{III}$ complexes, $[^{(L_{11})Fe^{III}X}]$, with a carboxylate moiety show ligand degradation under UV irradiation by decarboxylation, proceeding concomitantly with reduction of Fe$^{III}$ to Fe$^{II}$ and formation of CO$_2$ (Figure 3).$^{23}$

In biochemistry, Siderophores are a wide range of compounds produced by bacteria to capture iron. They bear an $\alpha$-hydroxy carboxylic acid functionality and coordinate readily to Fe$^{III}$ ions allowing the passive uptake of iron. Recently, Butler and co-workers$^{24,25}$ reported
photodecarboxylation of Fe(III)-siderophore complexes containing an α-hydroxy acid group. Ligand to metal charge transfer excitation under UV irradiation results in decarboxylation and oxidation of the petrobactin ligand to form a new ligand (loss of the central carboxylic acid group with a 3-ketoglutarate group or an enol group remaining on the original citrate backbone, Figure 3).

**Figure 3.** Examples of ligand decarboxylation of Fe III complex under irradiation. 23,24,26

The photo-induced decarboxylation of Fe III complex bearing carboxylato groups (L1-L10) is of substantial importance in the treatment of environmental pollutants as these small carboxylate ligands are abundant on earth and frequently invoked in bio-geochemical cycles. 22,27–29 Attention has been directed to the ligand system (L11) 23 due to its potential application for catalytic oxidations and possibilities structural variation rather than the photochemical properties of its iron complexes. As mentioned above, the photochemistry of siderophore-like Fe III complexes (L12, L13) holds profound implication for transportation of iron in vivo for phytoplanktonic communities. 25

The application of photo decarboxylation of Fe III complexes in materials was first reported by Melman and co-workers, 30 in which they described gel-sol transitions induced by irradiation of hydrogel with UV or visible light. This hydrogels consists of alginate cross-linked by iron(III) cations in the presence of sacrificial small hydroxy carboxylates compounds. This was further developed by Ostrowski and co-workers, 31 in which no sacrificial components were required. They used photoresponsive coordination hydrogels consisting of Fe(III) ions and the polysaccharides poly[guluronan-co-mannuronan] (alginate, L14) or poly[galacturonan] (pectate, L15), (Figure 4), and the photo-induced Fe III-decarboxylation mechanism is proposed. They also revealed that the photo reactivity was largely influenced by the configuration of the chiral center, which provides additional control over the stability and photo responsiveness of metal-coordinated materials, and is of importance for broader application to biological and tissue engineering. 32,33
1.3.3 Photo-induced releasing of small molecules

1.3.3.1 Photo-induced N-N cleavage – N₂ releasing

The photo-induced release of N₂ from a porphyrin-ligated (L16-17) Fe³⁺ azide complex (thin film), under irradiation of UV-visible (406.7-514.5 nm) light in frozen dichloromethane (30 K) was reported by Wagner and Nakamoto in 1989. Heterolytic cleavage of the N-N bond was accompanied by oxidation of the iron center to form an iron nitrido complex (L)FeV≡N with concomitant evolution of N₂ (Figure 5). The formation of the (L)FeV≡N complex was confirmed by resonance Raman spectroscopy with the ν(Fe-N) band at 876 cm⁻¹ and 873 cm⁻¹ for (L16, L18)FeV≡N and (L17)FeV≡N, respectively. Due to the substantial electron deficiency of (L)FeV≡N, the photochemistry could only be studied in a cryogenic inert matrix or thin film. However, similar to the non-innocence of the porphyrin ligand in oxo-iron(IV) enzymes (P450 compound I), the d⁴-configured iron(V) center, the closed shell dianionic ligand, the d⁵-configured iron(IV) center and the ligand radical monoanion are resonance structures by virtue of magnetic coupling. Hence, the possibility of similar photolysis in redox-innocent non-heme ligand environment is an important question.

Figure 5. Examples of photo-induced oxidation of porphyrin-ligated Fe³⁺ azide complex with a release of N₂.
This photo-induced cleavage of N-N bond was reported by Wieghardt and co-workers\(^\text{36}\) in a non-heme ligand environment (L19, Figure 6), in which the Fe\(^{\text{III}}\) center was located in a pseudo-octahedral ligand environment with azide ligands at its two axial positions while its four equatorial sites were occupied by a the redox-innocent macrocyclic ligand. High valent Fe\(^{\text{V}}\) intermediates were observed at 4 and 77 K by EPR and Mössbauer spectroscopy and in contrast to heme systems, a five-coordinate ferrous species has also been observed in the same reaction which originated from Fe-N homolytic cleavage and coordination of “solvent” acetonitrile. Although the detailed photo excitation mechanism is not established, femtosecond mid-infrared spectroscopy provides insight into the overall dynamics of the photo-induced release of N\(_2\) and formation of Fe\(^{\text{V}}\) process.\(^\text{37–40}\) 266 nm excitation of the Fe\(^{\text{III}}\) azide precursor results in mainly the non-adiabatic cooling (internal conversion, vibrational energy relaxation), and the “productive” channel of N-N cleavage and buildup of the iron(V) product are due to in the “localized” excitation of low frequency N\(_3\) modes, and population of excited states leading to N-N cleavage. Furthermore, due to the relatively high barrier for rebound of Fe\(^{\text{V}}\) with N\(_2\) back to Fe\(^{\text{III}}\) again, the formed dinitrogen collides with its surroundings and diffuses out of the reaction cage readily.\(^\text{37}\)

![Figure 6](image)

**Figure 6.** Examples of photo-induced oxidation (or reduction) of non-heme Fe\(^{\text{III}}\) azide complexes with a release of N\(_2\).\(^\text{36–38,41}\)

The photolysis pathways are highly dependent on reaction conditions and ligand environment. Vöhringer and co-workers\(^\text{38}\) found, in contrast to the studies in cryogenic inert matrices,\(^\text{42}\) that irradiation of the Fe\(^{\text{III}}\) azide precursor (L20) with one nitrogen atom replaced by an acetate group coordinated to the Fe ion in an axial position, trans to the N\(_3\) group, in acetonitrile at room temperature almost exclusively forms the solvent-stabilized ferrous complex by Fe-N cleavage at 266 nm.\(^\text{38}\) L21 was pre-oxidized from ferric to ferryl states by electrochemistry, photo-irradiation of L21 at 650 nm at 77 K results in similar N-N cleavage and evolution of N\(_2\), with formation of the higher oxidation state (L21)Fe\(^{\text{V}}\)=N which is the only identified Fe\(^{\text{V}}\) complex to date.\(^\text{41}\)
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This section is limited to discussion, only a few illustrative examples of the photolysis of Fe-N₃ complexes are discussed. There are an increasing number of ligands developed, incorporating, for example, pyridine moiety into the amine-based ligand backbone by Costas and co-workers, showing similar photo reactivity to the complexes discussed above. It should be noted that, up to now, photo-induced N-N cleavage is still the most common way to convert Fe⁵⁻-azido precursor to Fe⁵⁺ or Fe⁶⁺ complex, with only a few reports of the thermal reactions yielding these species.

1.3.3.2 Photo-induced replacement of labile ligand – CO releasing

Carbon monoxide (CO) is a key molecule in biochemistry; in vivo, it is a natural metabolite and produced mainly by heme oxygenase-1. Certain levels of CO have a positive effect on the body including cytoprotection, anti-inflammation, vasodilatation and are used in therapeutic treatments. However, due to the highly affinity to iron of hemoglobin, excess CO can shut down oxygen transportation. Hence, the controlled release of CO from carbon monoxide releasing molecules (CORMs) is a promising strategy in delivering CO to target tissues in therapies.

Photo-induced CO-release, with precise spatial and temporal control during the treatment is essential and has considerable interest in recent decades. Metal-CO complexes have seen the most attention due to labile coordination of CO metal centres, which under irradiation M-CO bond cleavage and releasing of CO. There are several recent reviews published on this topic and here the field will be mentioned only briefly. Iron, in particular, generates great interests in CORMs studies, and we only focus on the reported Fe-CO photoCORMs here.

Figure 7. Examples of photo-induced carbon monoxide releasing molecules (photoCORMs).

The first Fe-CO photoCORMs for biological application were reported by Motterlini and co-workers in 2002. However, an iron pentacarbonyl [Fe⁰(CO)₅] complex, which shows photo-induced release of CO of [Fe⁰(CO)₅] and related complexes was reported before 1970s. Typically [Fe⁰(CO)₅] was exposed to a cold light source, the releasing CO was detected by measuring the conversion of deoxymyoglobin to carbonmonoxymyoglobin. The CO release proceeds in a step-wise manner, accompanied with a change in the complex’s symmetry. For example, at low temperature (< 20 K), one CO is released to form C₂ᵥ symmetric Fe(CO)₄, prolonged irradiation results in the second release of CO to form Fe(CO)₃, the formed Fe(CO)₃ and Fe(CO)₄ can recombine with CO or the matrix molecules, (e.g., CH₄, Xe) depending on the
irradiation conditions.\textsuperscript{57-61} The detailed mechanism of photolysis was studied using picosecond and nanosecond time-resolved infrared spectroscopy by George and co-workers.\textsuperscript{57} More functional ligands were incorporated into the Fe-CO complex, to control the steric and electronic properties of iron centre through subtle changes introduced by the ligand structure. Lynam and co-workers\textsuperscript{62} developed a series of tricarbonyl complexes containing 2-pyrene ligands (L22\textsubscript{CO}-2), tuning of the substitution on the backbone significantly affects the CO releasing properties.\textsuperscript{62} Late in 2010 Westerhausen and co-workers reported a biogenic dicarbonyl bis(amoethathiolato) iron (II) (L22\textsubscript{CO}-3) complex (Figure 7a), which shows more advantageous properties towards the potentials therapeutic applications. It’s solubility in water, and the CO release triggered by irradiation with visible light (\(\lambda > 400\) nm), has very minor adverse effect in physiological test.\textsuperscript{63} Drawing Inspiration from hydrogenases,\textsuperscript{64} which produce hydrogen, biomimetic models (L22\textsubscript{CO}-4, L22\textsubscript{CO}-5)\textsuperscript{65-69} with an diiron centre with thiolate ligands environment, releases CO under irradiation to generate a solvent coordinated complex (Figure 7b). The CO-releasing rate is sensitive to the thiolates structures, with two monothiolates (“open” form) being more photo reactive than a dithiolate (“closed” form).\textsuperscript{70} The dimercaptopropanoate-bridged diiron hexacarbonyl complex reported by Fan and co-workers\textsuperscript{68} shows rapid CO-release with six CO ligands disassociated within 30 minutes hour and formation of the final product as a water soluble iron thiolate salt.\textsuperscript{68} Epithelial cell tests did not show obvious cytotoxicity. As a common feature of these Fe\textsuperscript{0} and Fe\textsuperscript{1} complexes is that they always undergo full decomposition under irradiation. Kodanko and co-workers\textsuperscript{71} found the non-heme [(N4Py)Fe\textsuperscript{II}(CO)] complex (L22\textsubscript{CO}-6, Figure 7c), which shows similar photo-induced CO release but with extraordinary thermal stability in aqueous solution and the more functionalized polyprindine ligand environment opens possibilities for ligand modification. Furthermore, this complex was modified with a peptide, which promises advantages for photoCORM transportation to a target tissue and further for the therapeutic treatment.\textsuperscript{71}

\textbf{1.3.3.3 Photo-induced reductive elimination Fe-hydride – H\(_2\) evolution}

In contrast to CO-release via a labile ligand coordination, H\(_2\) is generally produced by photo-induced reductive elimination from a Fe-hydride complex which was reviewed by Perutz and Procacci recently.\textsuperscript{72} There are two main classes: monohydride and dihydride complexes. The biomimetic hydrogenase complex (L23\textsubscript{H\(_2\)}-1), a representative example for the Fe-mono-hydrides, was reported by Rauchfuss and co-workers,\textsuperscript{73} which give four turnovers for H\(_2\) evolution under irradiation in the presence of triflic acid (Figure 8a).\textsuperscript{73} The Fe dihydride complexes, are mainly based on Fe-carbonyl (Figure 8b) and Fe-phosphine structures (Figure 8c). Sweany\textsuperscript{74} noted that the H\(_2\)Fe(CO)\textsubscript{p} photolysis results in a characteristic CO stretching band appears for the totally symmetric mode of Fe(CO)\textsubscript{p} by matrix-isolation combined FTIR spectroscopy,. The recombination of Fe(CO)\textsubscript{p} with the released H\(_2\) was inferred from the reappearance of IR bands for H\(_2\)Fe(CO)\textsubscript{p}. In contrast to Fe-carbonyl complexes, Fe-phosphine dihydrides are more photo reactive and have been extensively studied towards the activation of strong C-H bonds under irradiation. Notably the first step under irradiation is still the photo reductive elimination of molecular H\(_2\) (Figure 8c), which leaves a vacant site on the iron centre for small molecule oxidative addition and hence C-H or C-S activation of substrates.\textsuperscript{75-77}
Figure 8. Examples of photo-induced H₂ evolution by Fe-containing complexes.

In addition to the above mentioned complexes, the so called “Janus intermediate”, which has the active site of 4[Fe-S] core with two bridging Fe hydrides (E₄(4H)) was studied by Hoffman and co-workers by in situ EPR and ENDOR spectroscopy. This complex shows photo-induced reductive elimination of H₂ at 20 K, and reverts to (E₄(4H)) by oxidation of H₂ at 175 K.

1.3.4 Potential anticancer metallodrugs – photocytotoxicity of iron complexes

Rosenberg⁷⁸ first reported cisplatin as an anticancer chemotherapy stimulating the development of several platinum-based metal complexes as metallodrugs. However, drug resistance and severe side effects stimulates the search for new non-platinum alternatives.⁷⁹ The successful application of Bleomycin,⁸⁰ an iron-containing natural antibiotic for cancer treatment draws attention to iron complexes and a series of bio-mimic model complexes with a variety of ligand environments have been reported. Pre-clinical testing towards cytotoxicity were carried out in many cases.⁸¹ As candidates for chemotherapy, metallodrugs should have as little negative affect on healthy cells.

Photoactivated or photodynamic treatment (PDT), in which the anticancer drugs is only active under irradiation and non-cytotoxic in the dark, appears to be a promising approach due to its highly spatially selective for the target tumor.⁸²,⁸³ There are a few papers reviews covering the cytotoxicity of iron complexes towards anticancer treatments.⁸¹,⁸⁴–⁸⁶ Here we focus only on the photocytotoxicity of reported iron complexes in recent years.

In order to increase the photo-induced DNA cleavage activity and further the photocytotoxicity (Table 1 lists some cell lines examined in photocytotoxicity studies), there are several aspects that need to be considered: (a) binding properties with DNA, a strong interaction with targets or related proteins for transportation, (b) transport into cells, which is closely related to the lipophilicity of the complex structures, (c) strong absorptivity in the PDT window, (d) proper oxidation states of the metal center considering the reducing environment in the cell, which is capable of generating reactive oxygen species under irradiation for DNA cleavage. The first three
properties can be achieved by ligand modification, while the last plays a central role for in reactive oxygen species generation. Hence, we categorized reported iron complexes by oxidation state of the iron center here.

Table 1. Abbreviations of cell types mentioned in this section.

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<thead>
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<th>Abbreviation</th>
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<th>Abbreviation</th>
<th>Cell type</th>
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<tr>
<td>HeLa</td>
<td>Human cervical carcinoma</td>
<td>MCF-7</td>
<td>Human breast cancer</td>
</tr>
<tr>
<td>HaCaT</td>
<td>Human keratinocytes,</td>
<td>MRC-5</td>
<td>Human fibroblast</td>
</tr>
<tr>
<td>Hep G2</td>
<td>Human hepatocellular carcinoma</td>
<td>A549</td>
<td>Human non-small cell lung carcinoma</td>
</tr>
<tr>
<td>HPL1D</td>
<td>Nontransformed human epithelial lung cells</td>
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1.3.4.1 Photocytotoxicity of Fe\textsuperscript{II} complex

The earlier reports were about several Fe\textsuperscript{II} complexes (Figure 9). Roelfes and co-workers\textsuperscript{87} reported the DNA cleavage activity of a polypyridyl amine-based pentadentate Fe\textsuperscript{II} complex (L24), which is a functional biomimic of Fe-Bleomycin. Its activity was enhanced by irradiation. A series of ligands modified with the covalently attached chromophores were synthesized and these iron complexes show similar photo-activity, in which the photoactivity was enhanced by attachment of the 9-aminoacridine moiety (L25) and reseeded by 1,8-naphthalimide moieties (L26-28). The cleavage of DNA was attributed to the generation of reactive oxygen species (ROS), HO\textsuperscript{•}, O\textsuperscript{2•}, \textsuperscript{1}O\textsubscript{2}, under irradiation (355, 400.8, 473 nm).\textsuperscript{87} In contrast to covalent attachment, the influence of chromophores in photo-enhancing the DNA cleavage activity of L24 was studied with presence of A 9-aminoacridine moiety and A 1,8-naphthalimide. A significant synergistic effect (except few cases) was not observed. ROS are generally accepted as THE actual species responsible for DNA cleavage. However, surprisingly, addition of ROS scavengers (Na\textsubscript{2}S, DMSO and superoxide dismutase), significantly increased DNA cleavage activity. This unexpected result revealed the complexity of the ROS mechanism. That ROS could be the reactive species for DNA cleavage, but the positive effect of scavengers implied the importance of maintaining steady state concentration of ROS for DNA cleavage.\textsuperscript{88} The photocytotoxicity of these complexes towards living cells were also studied and compared with the natural antibiotics Bleomycin, complexes L24 and L25 both show comparable efficiency to nuclear DNA cleavage with Bleomycin. However, via apoptosis and different to the cell cycle arrest induced mitotic catastrophe by Bleomycin.\textsuperscript{89} Lately, Chakravarty and co-workers\textsuperscript{90} reported another Fe\textsuperscript{II} complex (L29), bearing two planar phenanthroline groups which provide for the strong binding to DNA, which show significant photocytotoxicity to HaCaT and MCF-7 cells under visible light irradiation (400 - 700 nm) and only very minor dark toxicity. Very recently, Tabrizi\textsuperscript{91} reported an Fe\textsuperscript{II} pincer complex (L30), which incorporates a NCN pincer and boron dipyromethene group, which also showed photocytotoxicity to HeLa and MCR-5 cells under irradiation (500 nm) with minor dark toxicity. Due to its specific localization in mitochondria in HeLa, it is a potential candidate for mitochondria-targeted theranostic agents.\textsuperscript{91} Notably, Chakravarty and co-workers reported a dipyridoquinoxaline (dpq) Fe\textsuperscript{II} complex capable of cleaving DNA under irradiation at 365 nm, but is photo-inactive under visible light. In contrast, its Fe\textsuperscript{III} complex is photoactive on DNA cleavage in visible light, which shifted their attention to the studies of photocytotoxicity of Fe\textsuperscript{III} with a variety of ligands.\textsuperscript{92,93}
1.3.4.2 Photocytotoxicity of Fe$^{III}$ complex

Chakravarty and co-workers reported a new group of ternary Fe$^{III}$ complexes between 2009 – 2012 with several ligands (L31-L36) (Figure 10). The tetradeinate phenolate-based ligand was designed to bind to Fe$^{III}$ to generate strong LMCT absorption bands in the visible region, the tert-butyl group was attached to increase the lipophilicity and the phenanthroline-based group was attached to increase the DNA binding strength. As a result, all complexes (L31-L36) show strong binding propensity to calf thymus DNA and some proteins (the extent dependent on the substituents on the dipyridophenazine ring), in which the complex of L31 shows remarkable high photocytotoxicity to HeLa and HaCaT cells under visible irradiation and low dark toxicity. The mechanism is similar to that of previously reported Fe$^{II}$ complexes; cell death is through apoptosis, extension of dipyridophenazine with an extra benzene ring (L36) results in even higher photocytotoxicity to HeLa cells. Biotin (vitamin H or B7) is a biomarker overexpressed by some tumor cells and can be used to increase the cytotoxic selectivity. The binding ability to streptavidin to biotin is unaffected by the addition of the iron complex, however, the selective enhancement of photocytotoxicity toward to HepG2 cells over HeLa and HEK293 cells was observed for biotin-attached complexes (L33 and L35). Iron complexes of schiff base phenolate ligands (L37-L45) show photocytotoxicity with irradiation with red light. L37 – L40 complexes are all avid binders to calf thymus DNA and shows strong pUC19 DNA cleavage activity under irradiation. In contrast to non-sugar appendant (L37), the sugar (carbohydrate moiety, the biomarker in some tumor cells) appendant complexes L38 and L39 show significant photocytotoxicity towards HeLa and HaCat cells and no dark cytotoxicity.

Progress in activity against other cellular organelles (endoplasmic reticulum), other than DNA, was made with tridentate Schiff base pyridoxal ligands derived of vitamin B6 such as in L41-43. Complexes of L44 and L45 show less photocytotoxicity compared to those of complexes of pyridoxal vitamin B6 ligands (L42 and L43). It is likely to be due to the greater uptake into the endoplasmic reticulum in the case of vitamin modified complexes than non-vitamin based complexes. Another notable example related to vitamin B6 corporation was reported by Hussain and co-workers. The vitamin B6 modified complex of L40 is photocytotoxic while non-vitamin B6 modified analogue is not.

Another group of iron complexes were reported by Chakravarty and co-workers in 2011 broaden the PDT window to the near IR region. It is important in PDT treatment that light in this region is used as it has the greatest penetration in human tissue. In addition to a dipicolyamine ligand, they introduced a series of catecholate ligands which gave rise to intense
LMCT bands in near IR region 620 – 850 nm (L46 – L49) (Figure 10). The tridentate dipicolylamine group functions as a planar aromatic group with a strong propensity for interaction with DNA. The bidentate dianionic catechol (cat) ligands enhance lipophilicity and the permeability of the cell membrane to the complexes. The order of photocytotoxicity was L48 > L47 > L49 ≈ L46. L48 shows the highest photocytotoxicity due to the tert-butyl group, which increases lipophilicity. In contrast to L49, which contains the dopamine group that increases aqueous solubility but decreases lipophilicity. As in previous studies, the cytotoxicity is due to the apoptosis. By binding to DNA and, under irradiation, DNA cleavage due to formation of reactive oxygen species. Later salicylates were also used as a ligand for FeIII complexes (L51), and also showed photocytotoxicity to HeLa and MCF-7 cells under visible light irradiation with the help of the photoactive anthracenyl group, in contrast to the photo-inactive phenyl complex (L50).

Figure 10. Examples of FeIII complex showing photocytotoxicity.
1.3.4.3 Photocytotoxicity of Fe$^{II}$-oxo dimer complex

As a photo-metallodrug, an iron complex should have as low as possible dark toxicity to healthy cells. In contrast to the Fe$^{II}$ and Fe$^{III}$ oxidation states, complexes in the oxidation states Fe$^{0}$ and Fe$^{1}$ are generally unstable at ambient or physiological conditions. Complexes in the oxidation states Fe$^{IV}$ or higher although also invoked as reactive intermediates in oxidation reactions, are not considered for PDT treatments. Diiron(III) complexes, however, are possible candidates.

The first report of photo-induced DNA cleavage by oxo-bridged diiron(III) complexes was by Chakravarty IN 2008,\textsuperscript{103,104} in which the almost linear Fe-O-Fe centers were coordinated by L-histidine and phenanthroline based ligands (L53- L54) (Figure 11). These complexes display double-strand DNA cleavage under visible light irradiation. The dipyrido quinoxaline (dpq) group (L54) was proposed to bind the DNA through groove binding. What was interesting is that the complexes were flipped when binding with DNA, the two dpq planar groups rotate via the Fe-O-Fe center to a trans configuration in order to reduce the steric effect for binding. In addition, in contrast to the dpa group the phenanthroline (L53) diiron complex showed only single-strand DNA cleavage activity under visible light irradiation. Phenanthroline ligands in complexes L53 and L54 are not only the DNA binder but also the photosensitizer. In contrast, the complex L52. Lacks the photosensitizer group making it photo-inactive towards the DNA cleavage.\textsuperscript{103} Later another group of diiron complexes were reported, which do not have the L-histidine group but another dpq (L56 and L58) or phenanthroline (L55 and L57) ligands attached,\textsuperscript{105} which as predicted\textsuperscript{103} bind more strong to DNA than complexes L52-L54. The near linear oxo-bridged diiron complexes, L55 and L56 are better than the acetate bridged complexes L57 and L58, which is due to the rotation via Fe-O-Fe bond was hindered in acetate bridged diiron complexes (L57 and L58). Photo-induced DNA cleavage activity is wavelength dependent for these complexes: complex L58 shows particular red light activity and the other two are shorter-visible light active, complex L55 is photo-inactive. All the DNA cleavage mechanism of all photo-active complexes mention above (L53, L54, L57, L58) are partially attributed to the Fe-carboxylate group present, as we discussed in section 1.3.2, under irradiation decarboxylation produce reactive radical species, which is responsible for the oxidative DNA cleavage.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{diagram11.png}
\caption{Examples of diiron(III) complex showing photocytotoxicity.}
\end{figure}

The photocytotoxicity of these complexes, under specific conditions (excess H$_2$O$_2$), are established to be more toxic to cancer cells than healthy cells and this difference is amplified by visible light irradiation.\textsuperscript{106} Another photocytotoxic diiron(III) complex (L60) was reported, which does not bear the Fe$^{III}$-carboxylate group but curcumin, this complex shows enhanced stability
and photocytotoxicity towards HeLa and MCF-7 cells under irradiation. Curcumin is proposed to be the photo-active group since the analogous complex L57 is photo-inactive.\textsuperscript{107}

From this section we can conclude that iron (bio-essential metal and low heavy-metal toxicity in vivo cells) complexes have considerable potential to be the photo-metallo-drugs, although photocytotoxicity studies as the anticancer medication are still in early stages. The significant effect on photocytotoxicity due to ligand modification is highly attractive for the inorganic chemists since the abundance of small molecules, which are already well-documented in clinical studies for anticancer treatment or reagent transportation, could be readily incorporated into ligand structures. This increases the possibilities for iron complex as the photometallo-drugs in PDT. However, the mechanisms are still unclear with the lack of the information on the photocytotoxicity of the iron complexes themselves limits understanding of the cytotoxic mechanisms, hence, the close examination of the photoreactivity iron complex will be the essential topic for the further development of this field.

1.3.5 Photochemistry of iron complex in catalytic oxidation reaction

Beyond doubt catalysis has changed the world, the most famous and perhaps most important are the Haber-Bosch (Nitrogen fixing process) and Fisher-Tropsch (converting synthesis gas into hydrocarbons) processes. In both cases heterogeneous iron-based catalysts are applied.\textsuperscript{108} Recently, the developments in organic synthesis for ligand design have opened many opportunities in controlling the reactivity of iron-based homogenous catalyst. Metal/ligand cooperation opens opportunities for the replacement of noble metals by iron in homogenous catalysis. Furthermore, modern spectroscopy provides extensive information about the catalyst structure and mechanism, which has enabled biomimetic approaches to ligand design and achieve new and better reactivity for the iron complexes.

High-valent iron-oxo species are frequently invoked as the reactive species in the substrates the oxidation of organic substrates in both biocatalytic enzymes and catalytic reactions. There are several ways to access high oxidation states, such as: sacrificial oxidants (e.g., H$_2$O$_2$, PhIO, m-CPBA etc.),\textsuperscript{109} electrochemical oxidation,\textsuperscript{110} and photo excitation.\textsuperscript{111} Photochemistry benefits in being non-invasive and atom economic and is drawing more attention in recent years. In this section, we focus on the application of photochemistry in catalytic oxidations by iron complexes. As the photo-induced generation of higher oxidation states or reactive oxygen species can be achieved by two different ways: the direct excitation and the indirect excitation with the use of a photosensitizer.

1.3.5.1 Photoinduced catalytic reaction——the use of a photosensitizer

The use of a photosensitizer to introduce extra energy to a reaction is recently affording considerably attention. In regard to iron catalysis, the most widely used photosensitizer are Ru$^{II}$ complexes (e.g., [Ru(bpy)$_3$]$^{2+}$) due to the outstanding photophysical and photochemical properties. The excited state of [Ru(bpy)$_3$]$^{2+}$ generated under visible light irradiation can engage in electron transfer to form [Ru(bpy)$_3$]$^{3+}$, which is a strong oxidant (1.26 V vs SCE, Figure 12) and can oxidize most iron complexes to their higher oxidation states. This approach is a so-called “multi-catalyst strategy” (Figure 12).
1. The application of photosensitized heme-based catalytic systems

Gray and coworkers\textsuperscript{112} reported the photoinduced generation of high-valent metalloenzyme intermediates in a heme system using the photosensitizer [Ru(bpy)\textsubscript{3}]\textsuperscript{2+} as electron donor (\textbf{Figure 13}) in 1995. The reaction was studied by nanosecond transient absorption method with [Ru(bpy)\textsubscript{3}]\textsuperscript{2+} promoted to its excited state [Ru(bpy)\textsubscript{3}]\textsuperscript{2+*}, followed by the electron transfer to [Ru(NH\textsubscript{3})\textsubscript{6}]\textsuperscript{3+} (electron acceptor, EA) to form the strong oxidant [Ru(bpy)\textsubscript{3}]\textsuperscript{3+}. It can directly oxidize ferric microperoxidase-8 (MP8) [[(P)Fe\textsuperscript{III}]=OH\textsubscript{2} \textsuperscript{59}] to its cation radical ferric form [{(P)Fe\textsuperscript{III}}]Fe\textsuperscript{IV}=O \textsuperscript{51}]. This cation radical species is in equilibrium with its ferryl MP8 [((P)Fe\textsuperscript{IV}=O)] (Compound \textbf{II}). Under acidic conditions (pH < 6) the equilibrium shifts to the left and ferryl MP8 is not observed. At alkaline pH, deprotonation shifts the equilibrium to right and the radical ferric species is not observed. This studies show that the porphyrin ligand centered oxidation is the rate limiting step are not the metal center.\textsuperscript{112} Later, the same concept was applied to the heme Horseradish Peroxidase (HRP).\textsuperscript{113} In this reaction, [Co(NH\textsubscript{3})\textsubscript{5}Cl\textsuperscript{2+} was used as the electron acceptor. The HRP ferryl species (Compound \textbf{II}) is formed via a ferric \pi-cation porphyrin radical species [{(P)Fe\textsuperscript{III}}]Fe\textsuperscript{IV}=O \textsuperscript{51}] intermediates at alkaline pH. Notably, ferryl porphyrin radical species [{(P)Fe\textsuperscript{IV}=O}] (Compound \textbf{I}) by oxidation of Compound \textbf{II} was also observed.\textsuperscript{113}
As discussed above, the rate determining step is the porphyrin-based ligand oxidation and hence this approach is unsuitable for the thiolate-ligated heme cytochromes P450 since the heme is buried deep inside the enzyme. Cheruzel and co-workers\textsuperscript{114} reported a new strategy, in which the photosensitizer [(IA-phen)Ru(bpy)\textsubscript{2}]\textsuperscript{2+} (IA-phen = 5-iodoacetamino-1,10-phenanthroline) was covalently bound to cytochrome P450 BM3 (Ru\textsuperscript{II}\textsubscript{K97C}−Fe\textsuperscript{III}\textsubscript{P450}) (Figure 14). Under irradiation three species with well-defined transient absorption spectra were observed, first *Ru\textsuperscript{II}\textsubscript{K97C}−Fe\textsuperscript{III}\textsubscript{P450}, second Ru\textsuperscript{III}\textsubscript{K97C}−Fe\textsuperscript{III}\textsubscript{P450} and returning back to the initial Ru\textsuperscript{II}\textsubscript{K97C}−Fe\textsuperscript{III}\textsubscript{P450}. Kinetic studies reveal three transient species assigned as Ru\textsuperscript{II}\textsubscript{K97C}−(P\textsuperscript{•}+)Fe\textsuperscript{III}\textsubscript{P450A}(OH\textsubscript{2}), Ru\textsuperscript{II}\textsubscript{K97C}−[(P\textsuperscript{•}+)Fe\textsuperscript{III}\textsubscript{P450B}(OH\textsubscript{2})] and Ru\textsuperscript{II}\textsubscript{K97C}−[(P\textsuperscript{•}+)Fe\textsuperscript{IV}\textsubscript{P450B}(OH)] (Compound II). The conversion of Ru\textsuperscript{II}\textsubscript{K97C}−[(P\textsuperscript{•}+)Fe\textsuperscript{III}\textsubscript{P450B}(OH\textsubscript{2})] to ferryl Ru\textsuperscript{II}\textsubscript{K97C}−[(P)Fe\textsuperscript{IV}\textsubscript{P450B}(OH\textsubscript{2})] (OH\textsubscript{2}) was rationalized by solvent or polypeptide confirmational changes, similar with MP8 and HRP. The conversion from ferric radical cation Ru\textsuperscript{II}−[(P\textsuperscript{•}+)Fe\textsuperscript{III}\textsubscript{P450A}(OH\textsubscript{2})] to ferryl Ru\textsuperscript{II}\textsubscript{K97C}−[(P)Fe\textsuperscript{IV}\textsubscript{P450B}(OH)] is pH dependent, both of which are present transiently and a fast recovery to the initial complex Ru\textsuperscript{II}\textsubscript{K97C}−Fe\textsuperscript{III}\textsubscript{P450} is observed.\textsuperscript{114} Similarly, Farmer and co-workers\textsuperscript{115} reported another example in which the photosensitizer [Ru(bpy)\textsubscript{3}]\textsuperscript{2+} was attached covalently to a heme enzyme via a −(CH\textsubscript{2})\textsubscript{7}− linker (L62). In contrast to Ru\textsuperscript{II}\textsubscript{K97C}−Fe\textsuperscript{III}\textsubscript{P450} I, the distance between photosensitizer and heme unit was large enough to prevent recovery from the ferric porphyrin radical species Ru\textsuperscript{II}−(P\textsuperscript{•}+)Fe\textsuperscript{III} to the initial Ru\textsuperscript{II}−Fe\textsuperscript{III} state. The fate of this ferric radical either oxidizing the iron center to form the ferryl form (Compound II) or oxidize a surrounding amino acid residue, which is in contrast to HRP in L60 (Figure 13). The oxidation of the protein surroundings also suggested that the protein environment significant influenced the reaction.\textsuperscript{115} This linking strategy was already reported by Oishi and co-workers as earlier as 1999, who demonstrated that it facilitated intramolecular electron transfer with observation of the ferric–porphyrin cation radical spectroscopically.\textsuperscript{116}
In addition to the photoxidation strategy in Figure 12b, there is also a photoreductive strategy, in which the electron acceptor ([Ru(NH₃)₆]³⁺, [Co(NH₃)₅Cl]²⁺) is replaced by electron donor (e.g., diethylidithiocarbamate = DTC). As an excitation quencher DTC reduces the excited [Ru(bpy)₃]²⁺* to [Ru(bpy)₃]³⁺, which is a strong reductant (-1.26 V vs SCE). As with the modified photooxidative strategy, a polypyridyl Ru(II) moiety was attached covalently to a heme enzyme, however, the fate of the intermediate Ru(I)-Fe(III) species is not as clear as in the photo oxidative strategy. Nevertheless, C-H functionalization studies show higher total turnover numbers under irradiation with visible light than control reactions,¹¹⁷ which further emphasizes that reactivity can be controlled both by the varying the nature of photosensitizer and modification of the heme structure.¹¹⁸ In short, several successful attempts to induce photochemistry at the iron center of heme metalloenzyme have been described and the field can expect further developments.¹¹₉,¹²₀

2. Photosensitized non-heme based catalytic systems

The number of heme and non-heme iron dependent enzymes involved in oxidations make mimicking such systems highly attractive in biomimetic catalyst design. Several high-valent complexes of bioinorganic relevance have been reported generated with oxidants and there are recently several reports of their photochemical generation. Fukuzumi and co-workers¹¹¹ reported the first photochemical generation of a high-valent iron-oxo complex with the pentadentate polypyridyl ligand N₄Py (L63) in 2010 using a photoinduced oxidative pathway (Figure 12b). The photosensitizer [Ru(bpy)₃]²⁺ when excited with visible light is oxidized by the electron acceptor [Co(NH₃)₅Cl]²⁺ to form [Ru(bpy)₃]³⁺, which in turn oxidizes the non-heme Fe²⁺ complex (L63) to the Fe⁴⁺=O complex (with water as the oxygen source) in a step-wise manner (Figure 15).¹¹¹
Figure 15. Examples of the photosensitized catalytic reactions in non-heme systems.

Later in 2014, Dhar and co-worker\textsuperscript{121} reported the first photochemical generation of iron(V)-oxo with tetra-amidoma-crocyclic TAML ligands (L64 and L65). In this case, they started with Fe\textsuperscript{III} complex as in heme system, and \( \text{S}_2\text{O}_8^{2-} \) was used as electron acceptor. The Fe\textsuperscript{III} state was oxidized to Fe\textsuperscript{IV}=O state first, which is different from the previous case as the [Ru(bpy)\textsubscript{3}]\textsuperscript{3+} formed in photoinduced electron transfer is not strong enough to oxidize Fe\textsuperscript{IV} state to Fe\textsuperscript{V} state. The formation of Fe\textsuperscript{V} was attributed to the \( \text{SO}_4^{2-} \) radical oxidation (\textbf{Figure 15})\textsuperscript{121} and this reactive is intermediate responsible for water oxidation. In 2017, the complex L64 was also studied for its photocatalytic hydroxylation and epoxidation reaction by Sen Gupta and co-workers\textsuperscript{122}. Notably, in this photocatalytic reaction there is no \( \text{SO}_4^{2-} \) radical species present due to the use of [Co(NH\textsubscript{3})\textsubscript{5}Cl\textsuperscript{2+}] as electron acceptor instead of \( \text{S}_2\text{O}_8^{2-} \) and formed (L64)Fe\textsuperscript{IV} monomer immediately form a dimer [[(L64)Fe\textsuperscript{IV}]\textsubscript{2}([\mu-O])\textsuperscript{2+}] as an active oxidant.\textsuperscript{122}

As with heme systems, the covalent linking strategy binding photosensitizer to the iron complex was also used in non-heme systems. Banse and co-workers\textsuperscript{123} reported a chromophore-catalyst complex L65 (\textbf{Figure 16}), in which the non-heme iron complex was attached covalently to the photosensitizer ([Ru(bpy)\textsubscript{3}]\textsuperscript{2+}) as in the heme systems (L61 and L62). The complex [Ru\textsuperscript{II}. Fe\textsuperscript{II}(OH\textsubscript{2})\textsubscript{2}]\textsuperscript{2+} was promoted to the excited state [*Ru\textsuperscript{II}.Fe\textsuperscript{II}(OH\textsubscript{2})\textsubscript{2}]\textsuperscript{2+} under irradiation (\( \lambda = 450 \text{ nm} \)), which then formed [Ru\textsuperscript{III}.Fe\textsuperscript{III}(OH\textsubscript{2})\textsubscript{2}]\textsuperscript{2+} by oxidation with [Ru(NH\textsubscript{3})\textsubscript{6}]\textsuperscript{3+}, followed by intramolecular
electron transfer from iron(II) center to ruthenium(III) center to form $[\text{Ru}^{II}\text{Fe}^{II}(\text{OH})]^{2+}$. The high-valent of $[\text{Ru}^{III}\text{Fe}^{III}(O)]^{2+}$ complex was formed by a second cycle (Figure 16).\textsuperscript{123}

**Figure 16.** Examples of the modified photosensitized catalytic reaction in non-heme systems.

In addition to the photosensitized oxidative formation of high-valent iron complexes, a photosensitized reductive pathway to form a high-valent iron complex was reported, it shows catalytic oxidation of PPh$_3$ with several turnovers.\textsuperscript{124} Instead of an electron acceptor Et$_3$N was used as an electron donor, the formed excited state $[\text{Ru(bpy)}_3]^{2+*}$ was quenched to form Ru(I) complex $[\text{Ru(bpy)}_3]^{+}$ which is a strong reductant (-1.26 V vs SCE). It reduces the diiron(III) complex to mononuclear Fe(II) and subsequently reacts with molecular oxygen to form μ-peroxo diiron(III) complex and then even higher oxidation states of form two iron(IV)-oxo moieties, which is responsible for substrate oxidation (Figure 17). Notably, the modified linked complex L67 shows lower photo-efficiency than the a non-covalently connected Ru/iron system, presumably due to deactivation of the ruthenium complexes excited state by deprotonation of the imidazole linker.\textsuperscript{124} In this studies dioxygen activation and formation of μ-peroxo diiron(III) complex were demonstrated, however, the formation of iron(IV)=O species was not confirmed.

**Figure 17.** Examples of photo-induced reductive formation high-valent iron complex.

In summary, in both heme and non-heme systems, the use of photosensitizers dramatically increase the reactivity of the iron complexes/enzyme. Covalent linking of the photosensitizer and iron complex further contributes to efficiency through intramolecular electron transfer. However, in these systems there is still an obvious question remaining: how are the photoactivity of these
iron complex themselves? These latter systems open opportunities for photo-driven oxidation with a single catalyst.

1.3.5.2 Photo-catalytic reactions through direct photo-excitation of iron complexes

1. Direct photo activation of mononuclear heme iron complexes

Direct photoactivation of a heme complex was reported by Newcomb and co-workers in 2005.\textsuperscript{125} In which the photooxidation of Compound II (a neutral iron(IV)-oxo porphyrin compound) to Compound I (a radical iron(IV)-oxo porphyrin compounds) occurs when under UV irradiation ($\lambda$ = 355 nm, \textbf{Figure 18b}), including the complex L68, horseradish peroxidase (HRP) (L69) and horse skeletal Myoglobin. Usually, compound I models are formed by addition of terminal oxidants ($H_2O_2$, PhIO, m-CPBA) to its porphyrin-iron(III) precursor, followed by reaction with substrates to form the relatively stable compound II. Under irradiation, compound II forms compounds I manifested in a change in the UV-vis absorption spectrum which shows that compound I persists for several seconds in the absence of substrates.\textsuperscript{125}

\textbf{Figure 18. Examples of photolysis reaction on heme system.}

Later, the same group reported photochemical generation of even higher oxidation states, i.e. an iron(V)-oxo porphyrin complex (\textbf{Figure 18c}).\textsuperscript{126} The porphyrin(IV)=O complex has a axial substituent (NO\textsubscript{2}, ClO\textsubscript{2}), which under UV irradiation ($\lambda$ = 350 nm) undergoes heterolytic cleavage to form iron(V)-oxo compounds, which react more than 100 times more rapidly with substrates oxidation than the corresponding iron(IV) compound.\textsuperscript{126}

2. The direct photo activation of dinuclear heme iron complexes

The light-driven catalytic oxidation of substrates using a single iron-containing catalyst is an elusive goal. In this regard, photoinduced disproportionation of porphyrin diiron(III) complexes is one of most promising pathways. Richman and co-workers\textsuperscript{127} reported the first example of photoinduced hetero-cleavage of the oxo-bridge of a $\mu$-oxo porphyrin diiron(III) [(FeTPP)$_2$O]$^{6+}$ complex (L70) with formation of 2 equiv. of Fe$^{6+}$TPP as the final product under UV-irradiation (O$\rightarrow$Fe LMCT band) accompanied by the oxidation of the substrate PPh$_3$. The Fe(III)-Fe(III) complex was regenerated by oxidation by molecular oxygen. Formation of high-valent iron(IV)-oxo intermediates (Fe$^{IV}$OTPP) via disproportionation was proposed based on substrate oxidation outcomes as well as the quantum yield measurements.\textsuperscript{127,128} The water soluble complex (L71) showed similar photoinduced disproportionation reactions.\textsuperscript{129}
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Figure 19. Examples of photo-induced disproportionation of diiron(III) porphyrin complexes.

Nocera and co-workers\(^{130}\) reported a strategy for selective oxidation of substrates using µ-oxo porphyrin diiron(III) complexes under photo catalytic conditions. Cofacial bisporphyrine µ-oxo diiron(III) complexes bearing dibenzofuran (DPD, L74) and xanthene (DPX, L75) (Figure 19), in which the two ‘Pacman’ moieties were used as a pillar to build up a molecular spring architecture, confined the attack on the substrates to favor a side-on geometry. The size of the two spacers controls the pocket size for the substrates and prevents recombination to form the µ-oxo diiron(III) states. The photocatalytic oxidation of substrates (dimethyl sulfoxide) was studied and compared with the complex with such a spacer (L72). The DPD-bridged complex L74 shows similar quantum efficiency with non-bridged complex L72, but much higher oxidation efficiency towards substrates oxidation and hence is a superior photo-catalyst.\(^{130,131}\) Later, this spring-loaded complex was further modified in the porphyrin ring with 3 pentafluorophenyl groups (L73), which showed higher turnover numbers towards sulfide,\(^{132}\) olefin,\(^{132}\) and hydrocarbon oxidation\(^{133}\) under visible light irradiation with molecular oxygen as terminal oxidation and without use of a co-reductant. An ethane linked cofacial diiron(III) µ-oxo porphyrin reported by Rath and co-workers\(^{134}\) showed photocatalytic oxidation of P(OR\(_3\)) (R: Me, Et) via a photoinduced disproportionation reaction mechanism. The pillar linked cofacial diiron(III) µ-oxo porphyrin complexes show a common feature in that they have much smaller Fe-O-Fe angles (150-160°) compared to the 170-178° of non-linked complexes and favor attack on substrates in a side-on manner.\(^{134}\)

The first systems with inequivalent ligands (i.e. heme/Nonheme) was the µ-oxo diiron(III) [(L)Fe\(^{III}\)-O-Fe\(^{III}\)(L’), L77] complex reported by Karlin and co-workers in 2004 (Figure 19c),\(^{135}\) which shows photoinduced catalytic oxidation of a series of substrates, PPh\(_3\) to OPPh\(_3\), tetrahydrofuran to γ-butyrolactone, and toluene to benzaldehyde. Transient absorption spectroscopy indicates that the photoinduced disproportionation of the µ-oxo diiron(III) to form an Fe\(^{IV}\)=O/Fe\(^{II}\) pair
occurs, in which the Fe$^\text{V}$=O is the reactive towards substrate oxidation.$^{135}$ Notably, photoinduced disproportionation of diiron(III) is not the only case reported, with an even higher oxidation state, iron(V) generated by photoinduced disproportionation of a bis-corrole-diiron(IV)-µ-oxo dimer together with one equiv. iron(III). The reactivity of the iron(V) intermediates is greater than that of the corresponding iron(IV) complex.$^{136}$

Form the discussion above, we can conclude that the photo-induced disproportionation of µ-oxo diiron(III)/diiron(IV) is a promising strategy in photocatalytic oxidations with iron complexes. The intermediate high-valent iron complexes formed are key reactive species. However, limitations remain; the quantum yield in these heme systems is quite low due to the large driving force for recombination of Fe(IV)=O and Fe(II) units, which shuts down productive oxidation pathways. Compared to heme system, non-heme iron complex have more flexibility in terms of ligand modification and also the thermal reactivity toward to a variety of substrates with non-heme high-valent iron-oxo complexes has been studied extensively. Hence it is worthwhile to study the possibility of driving non-heme iron complex oxidations photochemically.

3. The direct photo activation of non-heme iron complexes

The potential application of non-heme iron complexes under photochemical conditions requires that they are stable under catalytic conditions (e.g., Fe$^\text{II}$, Fe$^\text{III}$ and Fe$^\text{IV}$ in some cases). The Fe$^\text{II}$ and Fe$^\text{V}$ complexes are highly reactive at ambient conditions. Although non-heme iron photochemistry is dominated by photo-induced decarboxylation of iron(III) complexes, discussed in section 1.3.1, 1.3.2, and more recent reports of the photochemistry of iron(II) complexes in relation to the activation of dioxygen (see below), direct activation is not apparent from the literature.

The photo-induced oxidation of non-heme iron(II) complex in the presence of molecular oxygen as the terminal oxidant (L78 and L79 in Figure 20a) was reported first in 2009.$^{137}$ A non-heme iron(II) complex (L78), designed as a functional biomimic of iron bleomycin and studied extensively in its reactivity with oxidants such as H$_2$O$_2$, forms reactive high-valent iron-oxo species.$^{138}$ Irradiation of the iron complex of L78 in aerobic methanol or H$_2$O results in the formation of corresponding solvent-coordinated iron(III) complex. The reactivity is not observed under anaerobic conditions and the highly favorable coordination of acetonitrile to the Fe$^\text{II}$ center precludes such reactivity in acetonitrile. Later, Bartlett and co-workers reported a non-heme iron(II) complex bearing a tetradentate (bpmcn) ligand (L80 in Figure 20b). This complex undergoes similar photo-induced oxidation from the iron(II) to iron(III) states by activation of dioxygen. In this case, there are two labile coordination sites on the iron center compared with the one site available in the L78 based complex and hence O$_2$ coordination is expected to be more facile. Hence photo-induced oxidation also occurs in acetonitrile.$^{139}$
Figure 20. Examples of photo-induced oxidation of non-heme iron(II) complexes with molecular oxygen as terminal oxidants.

1.4 Photochemistry of non-heme iron complexes and an overview of the thesis

In this thesis, we focus mainly on the photo activation non-heme iron complexes, as well as mechanisms of thermal reactions of non-heme iron complex with \( \text{H}_2\text{O}_2 \). Chapter 2, 3 and 4, focus on photochemically induced activation of iron complexes in the Fe(IV) and Fe(III) oxidation states. In chapter 2, the direct activation of non-heme iron(IV)-oxo complexes and the mechanisms involved are explored. In chapter 3 the photo-catalytic oxidation of methanol under aerobic conditions reveals the involvement of a photo-active non-heme \( \mu \)-oxo bridged diiron(III) complex and its mechanism for photo-induced disproportionation. In chapter 4, the photo-induced oxidative degradation of the non-heme iron polypyridyl complexes under basic conditions are explored and the implications the conclusions reached hold in regard to ligand design is discussed. Chapters 5 and 6 focus on the mechanism of thermal generation of high-valent iron(IV)-oxo complexes by reaction of non-heme iron(II) complexes with \( \text{H}_2\text{O}_2 \). In chapter 5, the generation of an iron(IV)-oxo complex via heterolysis of an O-O bond in an Fe(II)-OOH species formed with stoichiometric \( \text{H}_2\text{O}_2 \) is focused on. In chapter 6, a novel reaction pathway for the reaction of iron(III)-hydroperoxo species with \( \text{H}_2\text{O}_2 \), which is kinetically incompetent in the homolytic cleavage of its O-O to form high-valent iron(IV)-oxo species, is shown to react with \( \text{H}_2\text{O}_2 \) directly under catalytic conditions to produce oxygen and water. The reaction pathways described are shown to be detrimental to the efficiency of the complexes in the catalytic oxidation of organic substrates.
1.5 References

Chapter 1


Chapter 1

3542–3545.


