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Anatomy of a Redox-Active Ligand

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1.1 Introduction

Over the past decades, redox-active ligands have transitioned from chemical curiosities to staples in current coordination systems. Their versatile nature allows them to encompass molecular strategies ranging from the design of single-molecule magnets to enlarging chemical reactivity through productive electronic communication between the ligand scaffold and a metal center.

Learning more about this subject takes us on a tour of its origins, which are profoundly rooted in biological systems [1] although cooperativity between metal and ligand was first observed in the laboratory in 1966 by Harry Gray on metal–dithiolate synthetic complexes with no biological or biochemical motivation [2]. No connection is at first made between these findings and the biochemical or biological fields, and it almost seems as if the two evolved in complete independence for some time before being conceptually reunited for a few decades.

Ligand participation has always been well known to coordination chemists, but the specific case of redox-active ligands implies a strong orbital overlap and proximity in energy levels between ligand and metal, resulting in complexes with molecular orbitals located on both metal center and ligand. This goes beyond the established electronic action of ligands in the Green formalism (also known as the Covalent Bond Classification Method), in which molecular orbitals can be metal- or ligand-based but imply less orbital mixing [3]. The electronic participation of the ligands then becomes so strong that the matter is sometimes the subject of controversy regarding the relative implications of metal and ligand [4].

Redox-Active Ligands: Concepts and Catalysis, First Edition. Edited by Marine Desage-El Murr.

1.2 Biological Inspiration: From the Enzyme to the Flask, a Continued Journey

1.2.1 Radicals in Biological Systems

Since a seminal report by Ehrenberg and Reichard on an amino-acid-based radical [5], later identified as a tyrosine radical [6], the implication of radicals in biological functions has become a topic of renewed interest. The most prevalent biologically relevant radicals are based on glycine, cysteine, tyrosine, and tryptophan residues [7] and all play pivotal roles in enzymatic catalytic functions, as reviewed by Stubbe and van der Donk [8]. These functions encompass a broad range of enzymes from ribonucleotide reductases (class-I RNRs), in which a diiron(III)–tyrosyl-radical cofactor is involved in the catalytic conversion of nucleotides into deoxynucleotides [9] to prostaglandin H synthase (PGHS), which also relies on an iron-tyrosyl radical system to effect the conversion of arachidonic acid (AA) into prostaglandin endoperoxide G_2 (PGG_2), a key step in the biosynthesis of the prostaglandin family. This ubiquity extends to numerous enzymes, cytochrome c peroxidase, DNA photolyase, galactose oxidase (GAO), and amine oxidases being just a few of them.

The specific role of radicals in these enzymes is to perform chemical transformations in a controlled fashion, a notion that is often not readily associated with radical reactivity. In this case, the metalloenzymes harness the reactivity of radicals to avoid possible shortcomings, such as uncontrolled side reactions. Extensive tuning of the redox properties by the environment within the protein is responsible for the very different kinds of chemical reactivities that can be accomplished by these radicals. Indeed, it is well known that the pK_a and reduction potential of a specific amino acid residue can vary dramatically depending on its surroundings through electronic and H-bonding effects. The protein-based radical is generated by the action of a neighboring metallocofactor and then proceeds to catalyze a chemical transformation, and can do so through multiple turnover sequences before regenerating the initial (non-radical) form of the protein residue.

1.2.2 Redox Cofactors: Electrons and Protons in Metalloenzymatic Systems

The field of research dealing with redox-active ligands has roots in the natural redox cofactors found in (metallo)enzymes and involved in electron transfer [10, 11]. Three major families are involved in electron and proton transfer in natural systems: quinones, nicotinamides, and flavins. These redox cofactors are mostly derived from amino acids through post-translational modifications and thus offer a wider structural landscape than the original amino acids. A few of the more elaborate structures are presented in Figure 1.1, especially in the quinone family [12]. Interestingly, active research in this area has unraveled new cofactors such as a nickel-pincer nucleotide (NPN) coenzyme [13], which provides fruitful inspiration for chemists to design catalytic systems [14, 15].

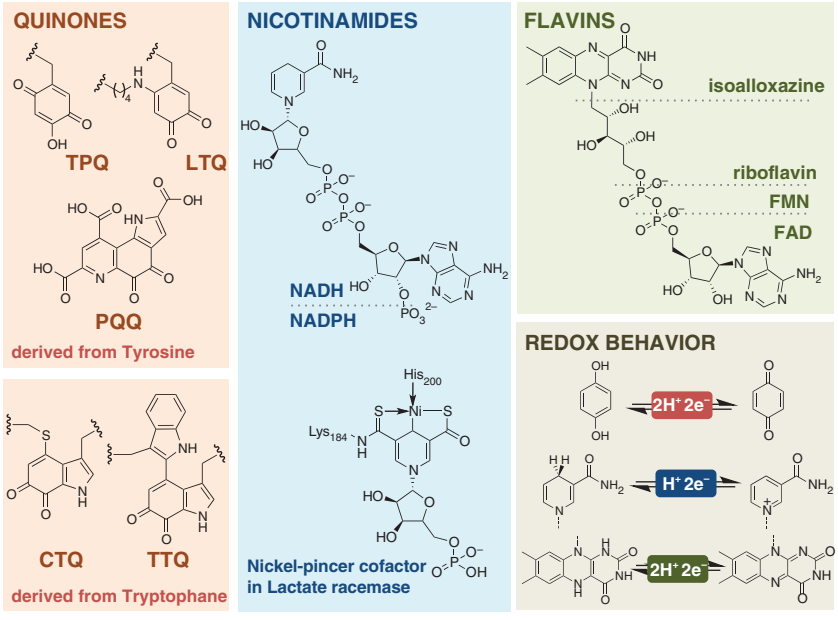
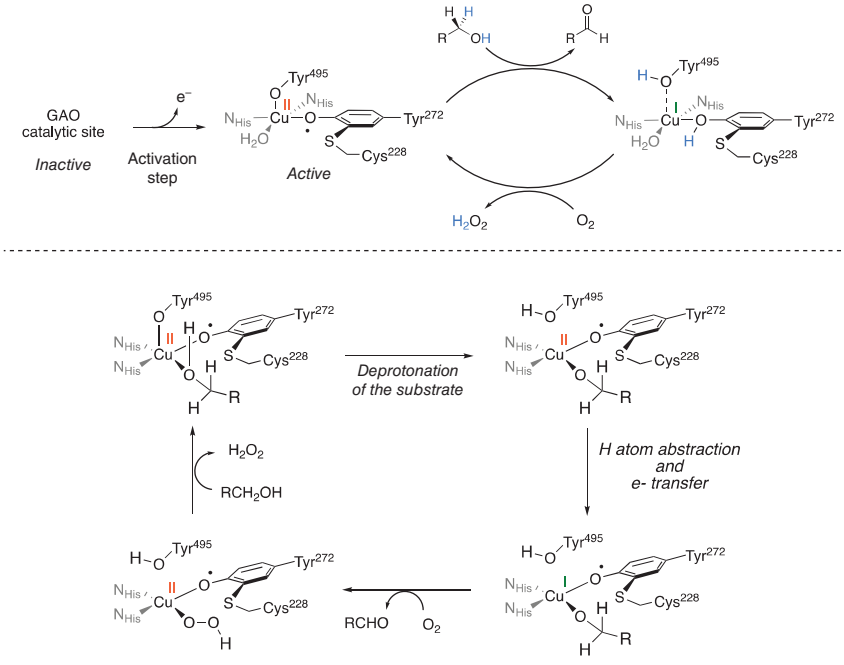


Figure 1.1 Three main families of redox cofactors and their redox behavior.
Source: Desage-El Murr [10]/with permission of John Wiley & Sons.

Among the most studied biocatalytic systems with built-in redox-active ligands is the GAO enzyme, which performs the two-electron oxidation of alcohols into aldehydes using molecular O_2 as an external oxidant. Established crystal structures have proved the catalytic site of this enzyme to feature a copper (II) ion embedded in a ligand framework consisting of two histidine imidazoles and two tyrosine phenolate residues (Scheme 1.1) [16]. Initial activation of the catalyst by single-electron oxidation generates the active form of the complex, which can then oxidize the primary alcohol. Overall, this is a two-electron process in which one of the electrons is accepted by the tyrosyl radical and the second electron by the copper center, which is consequently reduced to Cu(I). In this example, the Tyr_{272} moiety acts as an electronic storage unit, accepting one electron and allowing the active site to perform a two-electron redox process with the copper participating formally only by one electron (Δ d.o.$_{Cu} = 1$).

The distinctive mechanism and electronic structure of this enzyme have attracted much attention from chemists and opened the way to the design of several GAO mimic systems [17, 18]. Unsurprisingly, alcohol oxidation under aerobic conditions has thus been one of the first reactivities to be reported with redox-active complexes of 3Dmetals [19]. The GAO's unique catalytic system is both a starting point and a proof of concept for strategies aiming to explore new oxidative reactivities of metal centers bound to redox-active ligands [20]. These redox-active ligands are able to stabilize one electron through their radical ligand form and have been successfully applied to the oxidation of simple or activated alcohols. Selected representative structures (Figure 1.2) include salen derivatives and iminosemiquinones.



Scheme 1.1 The galactose oxidase reactivity (top) and detailed catalytic cycle (bottom).

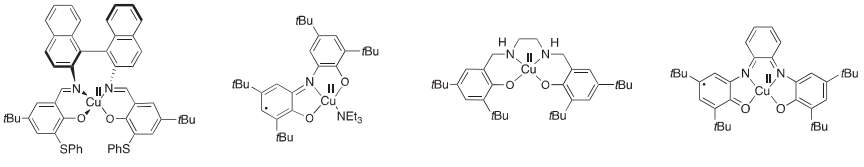


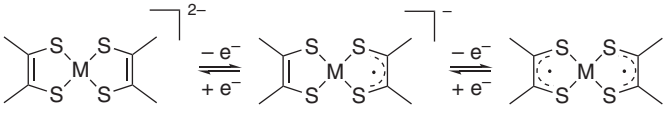
Figure 1.2 Selected copper complexes for alcohol oxidation inspired by GAO.

Examples of this redox-active behavior are, of course, not confined to copper and extend to most naturally abundant 3D metals. The uncertainty in the oxidation state of metal centers in biological systems is a prevalent topic, and P450 compound I (P450-I) was found to have an Fe(IV) oxidation state and an oxidized radical ligand, while the formal oxidation state would be Fe(V) [21].

1.3 Chemical History: Puzzle-Solving for Coordination Chemists

1.3.1 The Curious Case of Metal Complexes with Dithiolene Ligands

The chemistry of coordination complexes of 3D metals with dithiolene ligands led to the discovery of fully synthetic systems exhibiting ligand non-innocence. The intriguing electronic structure of these complexes was studied by three groups [22–25], and these seminal contributions established the possibility of storing



Scheme 1.2 Redox activity in metal (M) dithiolene complexes.

electrons on the ligands. This behavior implies that the metal's spectroscopic redox state is different from its formal theoretical redox state, which has strong implications for the chemical and electronic reactivity of the complexes [26]. This field, its founding contribution, and its consequences have been reviewed by Eisenberg and Gray, who have provided an in-depth account of the pivotal role of this early family of redox-active ligands [27] (Scheme 1.2).

An early definition of what an innocent ligand is was provided by Jorgensen, who stated that "*ligands are innocent when they allow oxidation states of the central atoms to be defined*." [28] This definition suggests that, for specific ligands, electronic transfer can be favored at the ligand rather than at the metal. This rather unusual behavior in coordination chemistry is observed in cases where ligands and metals have inverted energy levels compared to the more classic situation where the metal has the lowest energy orbitals and is hence the favored site for redox transfers.

These observations on model metal–dithiolene complexes pervade the periodic table, and many metals can be engaged in redox activity with dithiolene ligands [27]. Conversely, the dithiolene motif can be a subpart of a more complex ligand architecture, such as in pterin–dithiolene, observed in the biological realm and involved in several molybdoenzymes [29], and still finds cutting-edge applications such as CO_2 electroreduction [30, 31].

1.3.2 What are the Basic/Minimal Features?

The initial observations on dithiolene spurred a strong interest within the coordination chemistry community, and several other families of ligands were established to be able to exert similar behavior [32, 33]. The concept of non-innocence in a ligand can come across as elusive, and while some ligands clearly do not belong to this category, others (bipyridines, for example) can act as innocent or non-innocent ligands depending on the electronic mapping of the metal complex and more crucially the chemical context and process being catalyzed.

Although the terminology introduced in the 1966 seminal work by Jørgensen is more a definition of what a non-innocent ligand is not, the original assertion clearly shows that non-innocent ligands are molecular scaffolds able to delocalize part of the electronic density of the complexes in which they participate, becoming – in addition to the metal center – a place where redox processes can also take place. The reason for this is the higher energy HOMO levels of these ligands compared to typical ligands, and non-innocent ligands will therefore participate in electronic transfers through an inverted bonding process. This specificity can broaden the scope of redox events that a metal can perform by overcoming the limitations imparted by its original electronic structure [34].

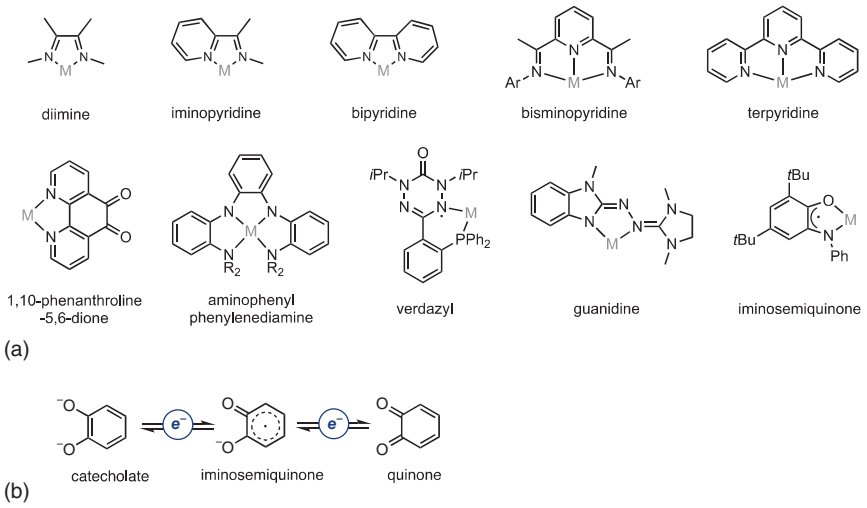


Figure 1.3 (a) Selection of representative redox-active ligands and (b) redox behavior of redox-active catecholate ligands.

Typical non-innocent ligands contain conjugated multiple bonds, aromatic or heteroaromatic moieties, extended π-conjugation, and a low-lying π* system (Figure 1.3). Classical 1,4-dihetero-1,3-diene chelates (such as α-diimines, dithiolenes, and o-quinones) are archetypical structures of non-innocent ligands [34], but many other families of ligands have been shown to behave as possible non-innocent ligands, including small-molecule derived ligands such as NO, CO, and O_2 [35, 36]. As a consequence, virtually any combination of these features can lead to a family of redox-active ligands. While diamines, catechols, porphyrins, mono- [37] and bisiminopyridines [38], and ligands stabilizing aminyl radicals [39] are among the most famous ones, original subfamilies arise such as hybrid ligands combining N and O coordination sites on extended p-conjugated systems (e.g. 1,10-phenanthroline-5,6-dione) [40, 41], verdazyls [42], tetrazines [43], or indigo derivatives [44]. The subtle and complex nature of the interactions operating between ligands and metals in redox-active systems has fostered extensive discussions aimed at defining the specific attributes of such ligands. A series of highlights [45], reviews [46, 47], and dedicated special issues [48–52], offer in-depth insights into this rich and creative branch at the crossroads of coordination chemistry and catalysis.

1.3.3 Classification According to Modes of Action

To understand the concept of redox-active ligands, one must bear in mind the classical roles of a ligand, which include providing solubility within the catalytic system, protecting the metal from aggregation eventually leading to ill-defined reactive species or nanoparticles, and from possible side reactivities. Through their actions, redox-active ligands will be able to promote an additional electronic

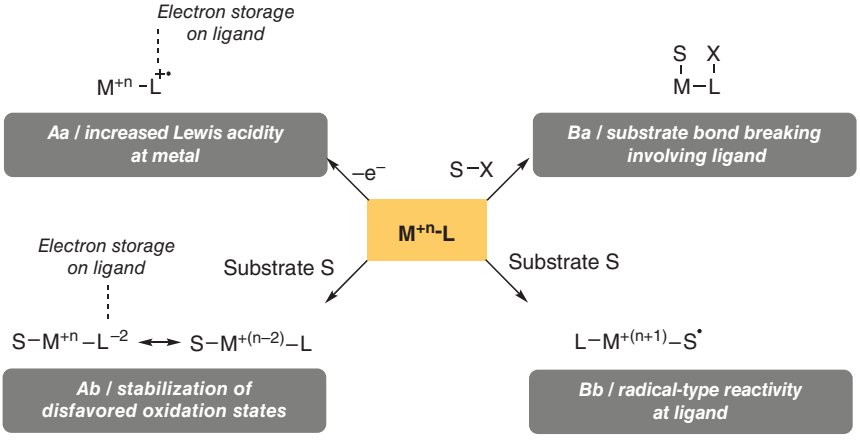


Figure 1.4 Classification of redox-active ligand behavior by de Bruin and Lyaskovskyy.

dialogue between the metal and ligand and foster radical reactivities and open-shell intermediates, thus redefining the well-known elementary steps that form the basis of coordination and organometallic mechanisms.

Aiming at rationalizing the role of redox-active ligands, Lyaskovskyy and de Bruin proposed in a landmark contribution a classification [53] according to two types of reactivities, each divided into two subcategories (Figure 1.4). The two types of reactivities are based on the distinction between either (A) purely electronic participation of the ligands or (B) their involvement in bond-breaking or bond-making events. In category A, subdivision arises from the distinction between storing electron density on the ligands to (Aa) tune the Lewis acidity of the metal center or (Ab) stabilize disfavored metallic oxidation states, while category B is divided according to reactivity examples where (Ba) the ligand becomes involved in bond formation/breaking or (Bb) the substrate becomes a redox-active ligand upon binding and achieves a radical state to perform bond formation.

As can be seen from this classification, the detailed mechanisms by which redox non-innocence can manifest itself are diverse and, most importantly, imply transient species with different degrees of electronic (de)localization. Redox non-innocence is by essence a dynamic and context-dependent notion, and the fact that redox activity *could* happen due to structural particularities does not mean that it *will* happen. This observation raises the central question of observability, detailed rationalization, and spectroscopic means by which this phenomenon can be studied.

1.4 Combining Spectroscopy and Theory: How to Spot a Redox-Active Ligand?

As stated above, the presence of a redox-active ligand in a system is a necessary but insufficient condition and does not imply that the latter will necessarily display redox events on the ligand. Indeed, this behavior is very much dependent on the

reaction conditions and the subtle energetic considerations arising from the nature of both metal and ligand. While the prediction of redox-active ligand-based behavior is elusive, spectroscopic and analytical tools provide the opportunity to observe and quantify these events [54]. Worthy of note is the fact that the concept of redox-active ligand is often invoked in cases where textbook ligand classifications such as the Green formalism produce an oxidation state of the metal that differs from the measured spectroscopic state [55].

The redox state of a redox-active ligand can be determined by X-ray crystallography, but this method only works for discrete, stable, and isolable species and is not optimal for *in situ* reactivities. Several spectroscopies aimed at closely monitoring the presence of unpaired electrons and the electronic structure of the complexes can be extremely useful in the context of the study of redox-active ligands. These include electronic paramagnetic resonance (EPR) and UV-vis, and must be coupled with theoretical calculations to get the full electronic picture of the system.

Specifically, EPR can offer very detailed insights into the presence of unpaired electrons, and the relative metal- and ligand-based contributions can be determined based on the value of *g*-factors. This kind of information is paramount to the understanding and rationalization of reactivity [56]. UV-visible absorption spectroscopy also provides information on the oxidation state, with intense IVCT bands being indicative of metal-to-ligand or ligand-to-metal charge transfers (MLCT and LMCT, respectively).

Theoretical calculations are indispensable to elucidate the nature of the orbitals involved in electron transfer [57]. While classical density functional theory (DFT) approaches can be sufficient, in some cases, full treatment with multireference methods such as CASSCF calculations is useful [58].

1.5 Non-innocent, Cooperative, Electro-Active, or Redox-Active?

1.5.1 Defining Terms

The concept of ligands storing electrons in a reversible fashion, under specific circumstances and settings, has led to a semantic problem in deciding on the most appropriate description to use. The term "non-innocence" actually refers to the seminal paper [28] by Jørgensen, who provided a definition of what an "innocent" ligand should be, i.e. a ligand that does not impair ambiguity in determining the oxidation state of the metal center, or, in the author's own terms, "*Ligands are innocent when they allow oxidation states of the central atoms to be defined*." Interestingly, the term "non-innocence" actually became more prevalent than the original "innocent" one and now defines the field. However, this concept is somewhat vague and open to interpretation, and the competing "redox-active" terminology is getting traction.

The key point to distinguish between non-innocent and redox-active is the fact that the former points toward ligand participation in the "redox burden" of the complex, for example, by having open-shell radical ligands, while the latter captures the

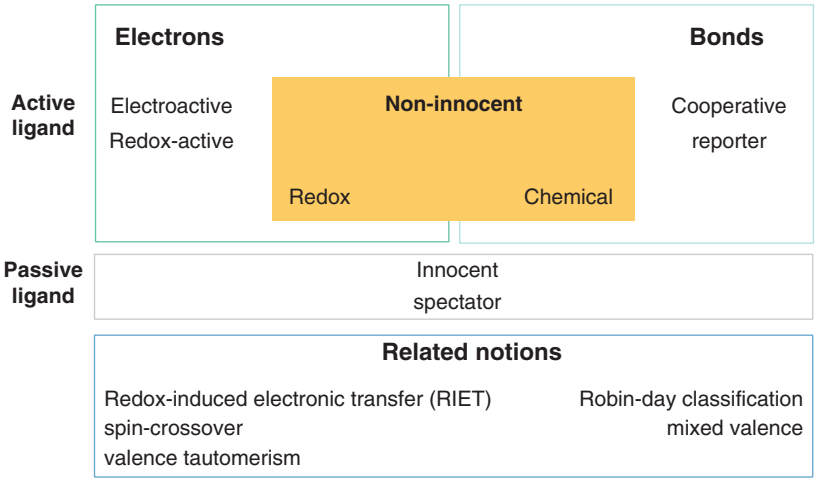


Figure 1.5 Glossary of terms used to describe the field of ligands storing electrons.

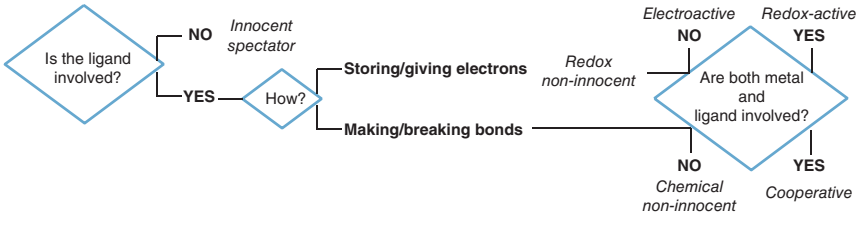


Figure 1.6 Flowchart for classification of the role of the ligand.

idea that redox events in electron transfer can occur at the ligand in addition to or instead of occurring at the metal center [48], as is well demonstrated in the example of amidophenolate/iminosemiquinone/iminobenzoquinone ligands [59].

Several terms have been coined to describe the ability of a ligand to participate in either electron transfer or bond-forming events, and the variety of terms, often used interchangeably, can lead to confusion. Figure 1.5 summarizes some of the most commonly used, distinguishing between electron transfer and bond formation. Subdivisions are made according to whether the ligand is active or passive. Ligands that are not active are called spectator or innocent ligands, which refers to the vast majority of cases, while active ligands can be further classified depending on whether they are involved in storing/giving electrons or making/breaking bonds. Figure 1.6 proposes a flowchart to help discriminate between these notions, bearing in mind that some, if not all, are often used interchangeably in many literature reports.

1.5.2 Related Notions

In addition to these terms, several related notions dealing with electron transfer or spin states are often useful to consider and relate to well-established behaviors and fields in coordination chemistry, often bridging diverse communities. These include

spin-crossover (SCO), which is a key concept in the field of molecular magnets, and the design of information storage molecular devices [60]. Such compounds are usually coordination complexes that display electronic bistability and can switch between low-spin and high-spin states, and redox-active ligands can play a role in their molecular design [61].

Another related notion is valence tautomerism (VT), which refers to a reversible intramolecular electron transfer between the metal center and redox-active ligands in metal complexes under stimuli such as light, temperature, or pressure [62]. This is a bridging notion, as reversible VT can lead to hysteresis and bistability for SCO compounds or fast interconversion for catalysis with metal complexes with redox-active ligands [63].

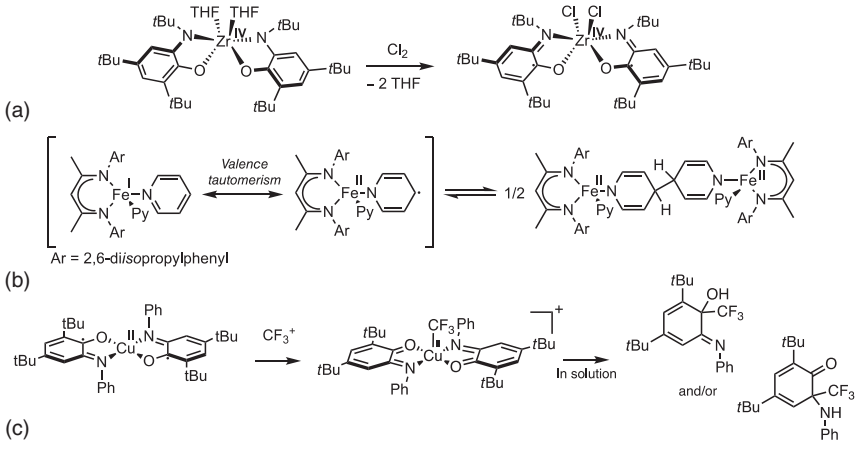
Redox-induced electronic transfer (RIET) covers the intriguing area of an initial redox event followed by electronic reorganization ultimately leading to the opposite redox event as the net outcome (oxidation leading to reduction, or reduction leading to oxidation) [64]. This peculiar effect has been documented, for example, in the context of cobalt [65] and copper [66] complexes with guanidine redox-active ligands.

1.6 Unusual Ligands and Unusual Reactivities with a Redox-Active Ligand

The synthetic applications of redox-active ligands have been discussed in reviews [47, 53, 59, 67, 68], and some are presented in this book. A full account is not the purpose of this section, which instead focuses on the most common modes of activation. The array of possible reactivities enabled by complexes with redox-active ligands is too broad to be summarized but essentially falls into two categories: catalytic or stoichiometric. The first category is contingent on a successfully established catalytic cycle with strong electronic implications from the ligand, much more than a mere Lewis acid or base effect. This comes with challenges and can prove difficult as the ligand storing electron density is by definition activated toward reactivity and becomes a reactive platform, which leads to the second category. The following sections offer a glimpse of these transformations, starting with chemical reactivity occurring at the ligand, then radical reactivity, and lastly two-electron reactivity.

1.6.1 Reactivity at Ligand

A report has shown that an oxidative addition taking place at the Zr(IV) center of a redox-active complex with two reduced amidophenolate ligands results in a preserved Zr(IV) center with two ligands in their oxidized iminosemiquinone redox state (Scheme 1.3a) [69]. Although not leading to chemical reactivity at the ligand, this is an edifying example showing that the depth of interaction between the metal and ligand is a clear determining factor of these systems, and results in complexes where the molecular orbitals are extended and delocalized over the whole structure. In many other cases, the ligand becomes a reacting site where bonds can be irreversibly formed.



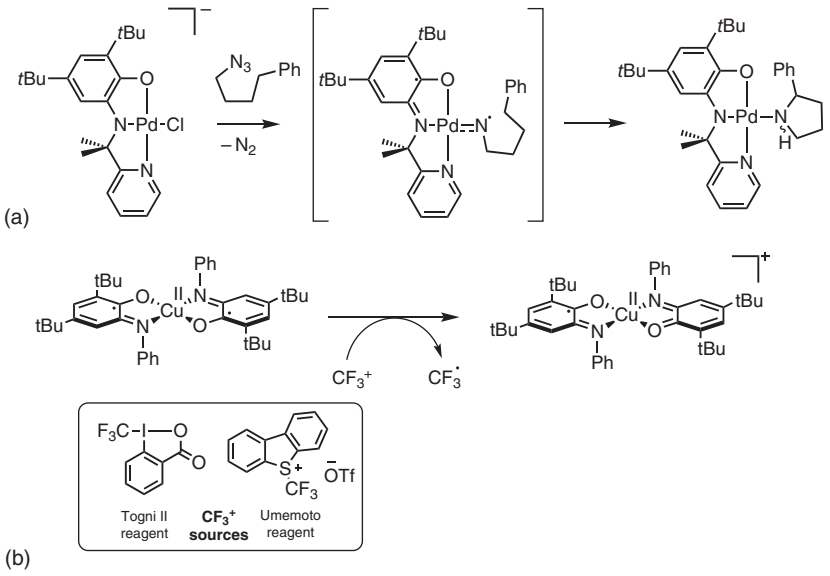
Scheme 1.3 (a) Oxidative addition implying only ligand-based redox events, (b) reversible dimerization of activated pyridine ligands in an iron complex, and (c) CF_3 group transfer on iminobenzoquinone ligand in the copper complex.

The field of redox-active ligands is rife with unwanted side reactions, including chemical reactivity at the ligand or at the metal. These reactivities depend on the metal as much as on the ligand structure, as within a single family of redox-active ligands, some complexes can undergo ligand-based C—C coupling reactions while others seem inert under the same reaction conditions. Reactivity at the ligand can come in many forms, such as the reversible dimerization implying C—C bond formation at an activated pyridine ligand in iron complexes with β-diketiminate ligands [70] (Scheme 1.3b) or the nonreversible introduction of a CF_3 group on iminobenzoquinone ligands in a copper complex, resulting in the overall *umpolung* of an electrophilic source into a nucleophilic CF_3 transfer on electrophilic positions (Scheme 1.3c) [71, 72].

1.6.2 Open-Shell Reactivity: Radical Formation

Since redox-active ligands are often involved in single-electron transfer, their reactivity can be channeled toward the selective production of radical species. Specifically, ligand-to-substrate single-electron transfer has been reported as a new mode of activation in ligand-centered reactivity and catalysis [73]. This type of activation is related to catalysis with photoredox manifolds in the sense that open-shell species – either metallic or organic – are involved in the catalytic cycle and overall reaction mechanism, but differs from photoredox catalysis as the trigger for the electron transfer is purely of redox origin and does not result from photoactivation.

Scheme 1.4 illustrates this open-shell reactivity with two different metals: Pd and Cu, and redox-active ligands of the semiquinone type. In the first transformation (Pd, a), a nitrene radical is generated *via* an inner-sphere process, while in the second transformation, a trifluoromethyl CF_3 radical is released through an outer-sphere process. Both reactions have in common, however, the fact that the

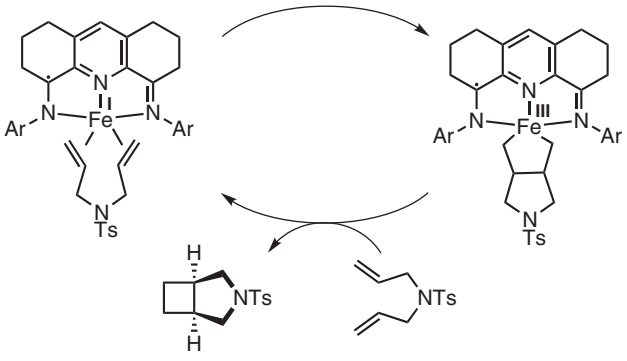


Scheme 1.4 Single electron reactivity with Pd and Cu complexes bearing iminosemiquinone ligands.

switch in radical density occurs from the ligand to the substrate, shuttling either from amidophenolate to iminosemiquinone (Pd) or from iminosemiquinone to iminobenzoquinone (Cu).

1.6.3 Two-Electron Chemistry: C—C Bond Formation

In addition to their promotion of single-electron transfers and radical chemistry, redox-active ligands can also facilitate two-electron steps, thus enabling first-row transition metals to achieve noble metal-like reactivity [74]. Classical two-electron reactivities such as C—C bond formation often involve two-electron steps such as oxidative addition and reductive elimination and are mainly carried out by complexes of noble metals in relatively high ligand field bearing ligands such as N-heterocyclic carbenes or phosphines. Redox-active ligands, on the contrary, provide a relatively weak ligand field and can enable C—C bond formation through distinct mechanistic pathways [75]. This can be illustrated by an example of intramolecular [2 + 2] cycloaddition catalyzed by an iron complex with a modified bis(imino)pyridine ligand, a tetrahydroacridyl-derived bis(imino)pyridine ligand (Scheme 1.5) [76]. In-depth mechanistic studies evidenced the intermediacy of an $S = 1$ iron intermediate best described as intermediate-spin iron(III) ($S_{Fe} = 3/2$) antiferromagnetically coupled to a chelate radical anion ($S_{ligand} = 1/2$).



Ar = 2,6-di*iso*propylphenyl

Scheme 1.5 Distinct electronic pathway implying ligand-based redox activity for the iron-catalyzed [2 + 2] cycloaddition.

1.7 Perspectives and Concluding Remarks

As highlighted throughout this chapter, the concept of redox-active ligand can be static or dynamic, reversible or irreversible, and possibly lead to catalysis. This dynamic and context-dependent notion unlocks new modes of action and offers exciting perspectives in coordination chemistry and organometallic reactivity or catalysis. The field has greatly progressed over the last decades, and while much insight has been gained into these systems, taking them from laboratory curiosities to task-performing systems, the field has probably not yet reached its full maturity. A reason for this is the lack of predictive tools to design fit-for-purpose systems and trace the choice of metal and redox-active ligand to a specific synthetic target. The steep development of machine-learning approaches could hold potential responses to this limitation. Future directions in the field also include the development of chirality in redox-active ligands to enable enantioselective processes, combinations of redox-active ligands, and bimetallic complexes [77, 78]. There is no doubt that the future lies wide open and full of opportunities.

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