Designing Ligands for Oxidizing Complexes

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Higher oxidation state complexes of transition metals become progressively rarer the further to the right the element is found in the periodic table. For early transition metals the d^0 states are the principal ones found in nature. For the middle transition metals (first row: Cr, Mn, Fe), the d^0 states are found in small numbers of mostly synthetic, reactive oxidants. For later transition metals (first row: Co, Ni, Cu), the d^0 states are unknown in stable compounds. Nearly all middle and later transition metal compounds have comparatively low formal oxidation states. For example, the *Chemical Abstracts Formula Index* lists more than 102 000 copper compounds, alloys noninclusive, that were identified from 1965 to 1990. Copper possesses 11 valence electrons, but +IV is the highest state observed in a coordination complex, and it is found only in $[CuF_6]^{2-}$.[1] For iron, more than 115 000 compounds were characterized in the same period, but d^0 Fe(VIII) is known only in FeO_4,[2,3] and one can estimate that fewer than 0.2% of iron compounds have oxidation states greater than +III. Nevertheless, high oxidation state middle transition metal compounds are important in chemistry and biology as oxidants. The first goal of our program was to learn how to make high oxidation state and strongly oxidizing middle and later transition metal compounds that are stable. This has provided direction for our research in ligand design, a direction that incorporates our second goal: learning how to make better homogeneous oxidants. I will begin by pointing out an important distinction between the two roles transition metal ions play in oxidation reactions.

In metal-based oxidizing agents, the metal can have one of two principal roles.[4] (i) When a *metalloredox-active oxidant* oxidizes a substrate, the event is accompanied by a formal oxidation state reduction at the metal center. We originally defined the term *prima facie metallo-oxidant* for this class, but now prefer *metalloredox-active oxidant*.[4] (ii) When a *metallotemplate oxidant* oxidizes a substrate, the metal does not undergo a formal oxidation state change. Instead, the metal activates the primary oxidant and/or substrate and/or arranges the primary oxidant and substrate in a favorable geometry for oxidation to proceed. Permanganate[5,6] and chromium(VI) compounds[5,7] are classic examples of metalloredox-active oxidants in chemistry. As examples in biology, metalloredox-active oxidants are found at the active site of cytochrome P-450 enzymes, where the weight of evidence indicates that iron(IV) oxoporphyrin radical cations oxidize many different substrates,[8] and in methane monooxygenase, where a high-valent oxo-bridged diiron species oxidizes methane to methanol.[9–12] The enantioselective oxidations of prochiral allylic alcohols by TBHP catalyzed by titanium tartrate complexes provide examples of metallo-template oxidations.[13] Recognizing these two classes of metallo-oxidants is important because the further development of each class appears to present different challenges.

Major achievements such as the Sharpless systems[13] have been made in metallotemplate oxidations with comparatively mild processes where weak C–H bonds and other easily oxidized bonds in ligands are clearly tolerable. The sensitivity of ligands to oxidative decay has not confined metallotemplate oxidation chemistry perhaps because the metal center is not directly part of the oxidizing entity. The real oxidant is further removed from ancillary ligands than in metalloredox-active oxidants.

Some of the frontier challenges in metalloredox-active oxidant chemistry are demanding oxidations such as the selective oxidation of unactivated C–H bonds. These problems require that ligand systems be especially inert to oxidation. It is difficult for chemists to follow nature's approach to solving the ligand sensitivity problem for finding effective metallo-oxidants for demanding oxidations. Nature efficiently catalyzes intrinsically slow substrate oxidations by using numerous selectivity-directing features that are extrinsic to the reaction itself. Reaction sites and transition states are crafted not only to accelerate desired reactions but also to exclude undesired processes such as attack at the ligand system and the protein. Our work is focused on developing ligands that might lead to improved metalloredox-active oxidants for demanding oxidations.

In the early 1980s, ligand design looked to be well worth exploring as a tool for expanding high oxidation state middle and later transition metal chemistry and

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as a step toward better metalloredox-active oxidants. In seminal work, Dale Margerum and his group had shown that the deprotonated amide ligands of small polypeptides could be used to stabilize Cu(III) and Ni(III) thermodynamically.[14] Furthermore, Margerum showed that the secret of this conveyed stability was the strong amido-*N* σ-donor capacity which correlates well with the pK_a of the parent amide.[15] The polypeptides decomposed in the oxidized complexes, but the decomposition could be blocked when the ligand C—H groups were replaced with C—CH_3.[16] Chang and Ebina introduced polyfluorination of porphyrins to give oxidation catalysts that were much longer lived than the hydrogen-substituted analogues,[17] thereby laying the foundation for wide investigations into protected-porphyrin-based oxidizing systems.[18] We had set out to look for ligands that are resistant to oxidation and also strongly donating.[19-21] We expected that incorporating these properties in ligands would allow us to develop high-valent complexes with normal shelf lives. We also expected to be able to manipulate reactivity by changing metal ions and by modifying ligand donor properties. The search has led to a still expanding group of concepts that are useful for guiding ligand development in this area,[22] and it has provided us with unexpected opportunities to contribute to knowledge.

The Ligand Design Approach

Design-oriented coordination chemists generally view a chelating ligand as a collection of adjustable components: the donor atoms and their basicities; the donor functional groups and their spatial orientation and electronic and steric properties; the chelate rings and their sizes, structures, strains, and relationships to each other; the ring substituents and their electronic and steric effects; the acyclic or macrocyclic nature of the chelate; the cavity size of a macrocycle; etc. Ligand design can be viewed as the process by which the components are varied either for curiosity's sake or to control the properties of a targeted system. The process has a distinguished history in, for example, macrocyclic ligand chemistry,[23,24] crown ether and related chemistry,[25] and porphyrin chemistry.[26] Here, only one part of the design process for our ligands is highlighted: the protection of ligands from oxidative degradation.

Generally, the frontier orbitals of an oxidizing transition metal complex are primarily metallic in character. Usually, one can design so-called "innocent" [27] ligand complements to ensure that this is the case. In such a complex, the oxidizing metal ion is easily reduced if the closest source of reducing equivalents, the ligand system, can be oxidized in any way. Therefore, three primary questions about ligand oxidative degradations are evident: (1) What reactions are possible for any specific ligand complement? (2) Are individual reactions general to a range of ligand systems and metal ions? (3) Can specific reactions be blocked by ligand modifications? An important secondary question concerns whether a ligand oxidative degradation is intramolecular or intermolecular. Iterative design has been employed to probe these questions. One starts with a polydentate ligand thought to be suitable. A metal is coordinated in a low valent state, and the complex is chemically or electrochemically oxidized by one or more electrons in an inert medium. If the oxidized complex so produced is unstable, the degradation process is studied. Complete mass balance is sought to assist in understanding the fate of the ligand and the metal. When the sensitive ligand group has been identified, it is replaced with a substitute thought to be less sensitive and the process is repeated. If the high-valent complex produced by oxidation is stable, it is fully characterized, then oxidized again to induce ligand decay. The process stops when oxidation/ligand degradation cannot be observed using chemical or electrochemical techniques in carefully dried, oxidation resistant media. Oxidation processes have been observed at more positive potentials than 2 V (SCE) in liquid SO_2 solvent for the systems studied.[28]

The Ligand Protection Rules

The three primary questions posed above can be answered as follows: (1) It has been possible to trace each found oxidative degradation to a specific ligand group. (2) Individual electron-releasing ligand reactions appear to point to general principles of ligand protection. (3) As a general rule, specific electron-releasing ligand reactions can be blocked by appropriate ligand modifications. To stimulate the process of unifying the chemistry of oxidative ligand degradations with general concepts, we expand here on previously suggested ligand protection rules.[22] The rationalizations of the ligand degradations that lead to rules I, II, and III are mechanistic and cannot be proven to be correct, only to be wrong.

Rule I. *For chelate rings, a hydrogen atom should not be placed on an atom that is β to an oxidizing metal center, if the α-atom can support an increase in the bond order with the β-atom.* Degradations resulting from this feature are well-established in the literature. There are two types. In the first, the redox process is stoichiometrically localized on the ligand, e.g., amine to imine. Such processes are often viewed as useful syntheses of new ligands, and many are considered

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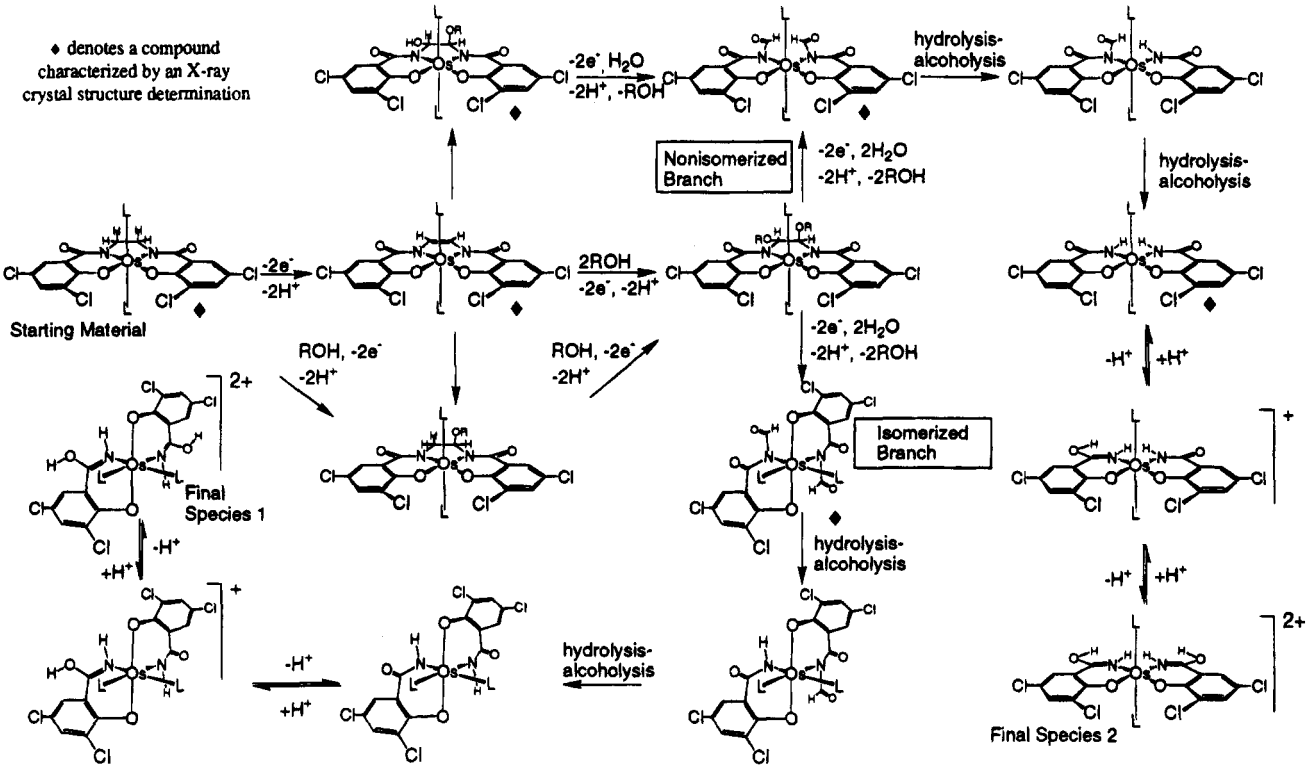
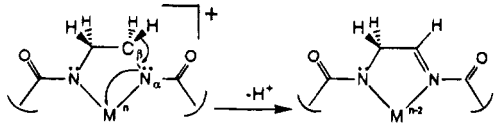


Figure 1. Characterized intermediates in degradation of a diamido-*N*-diphenoxido acyclic chelate.

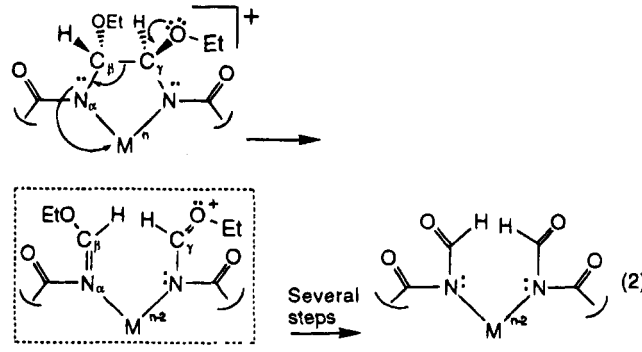
to be radical in nature.[29] The examples we discovered (Figure 1) are of a second type, where the redox process occurs at both the metal and the ligand. These ligand degradations appear to be best formulated as two-electron processes, and eq 1 shows what happens to the sensitive portion of one of the ligands.[19,30]



(1)

Here it is useful to introduce a concept to emphasize the possible presence of communication channels comprised of overlapping orbitals between the metal ion and remote ligand sites that establish favorable conditions for oxidative ligand degradations. The reaction of eq 1 can be conceptualized as a remote reductive elimination, in this case a 1,3-reductive elimination (1,3-RE), with the β-carbon atom in the 1-position and the metal atom in the 3-position. Removal of the proton results in a formal two-electron reduction of the metal. The microscopic reverse is an example of a remote oxidative addition, in this case a 1,3-oxidative addition (1,3-OA). The concept can be generalized. Two-electron remote oxidative addition reactions are possible whenever a remote ligand site is able to formally withdraw two electrons from the metal ion by bonding to a two-electron acceptor. The conditions for a remote oxidative addition reaction appear to be most favorable when the remote site is conjugated with the metal. One-electron remote OA/RE reactions can be defined in a parallel fashion. Remote OA/RE reactions appear to be widely distributed in transition metal chemistry and include higher order processes (1,5 etc.). The example in eq 1 points to the facile nature of the 1,3-RE when the departing two-electron acceptor is a proton. The degradation can be blocked by aromatizing the C—C bond[19] or substituting alkyl for H.[16]

Rule II. *A heteroatom should not be attached to a five-membered chelate ring on an atom that is γ to an oxidizing metal center, if the heteroatom has an available lone pair to stabilize forming cationic character on the γ-atom as the endocyclic β—γ bond is oxidatively cleaved by the metal.* This rule may point to a more facile degradation than does rule I.[19,30,31] The example shown in eq 2 is a remote 1,3-RE where the two-electron acceptor in the reverse 1,3-OA is a carbocation.



(2)

Rule III. *A heteroatom should not be employed as an α-donor atom in a five-membered chelate ring, if it has an available lone pair to stabilize forming cationic character on the β-atom as the endocyclic β—γ bond is*

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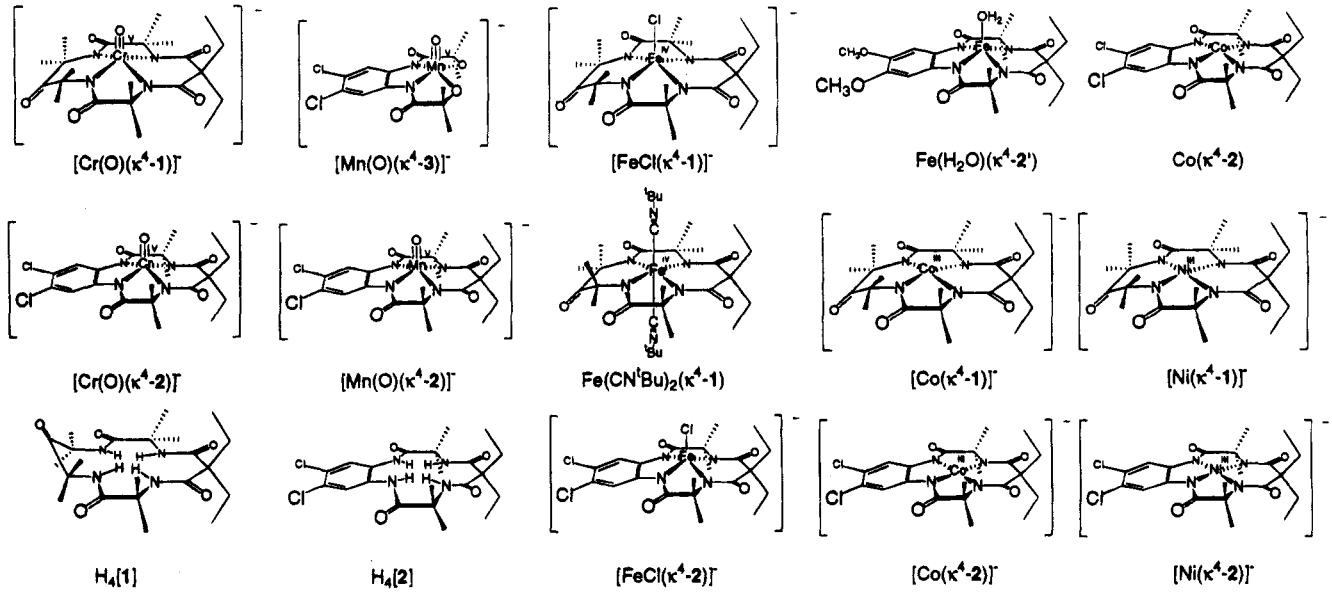
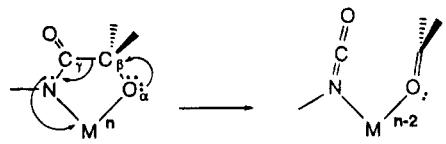


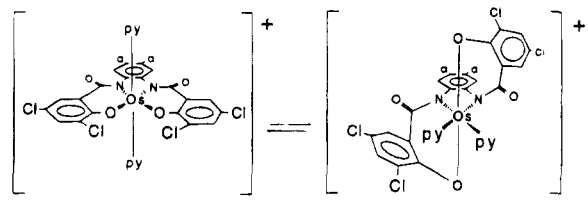
Figure 2. Structurally characterized complexes of macrocyclic tetraamido-*N* ligands.

oxidatively cleaved by the metal. This rule derives from a process proposed to account for a slowly degrading oxidation catalyst (eq 3).[32] We surmise that the O_α heteroatom stabilizes forming cationic character at the β-carbon in the transition state of the proposed degradation. The process can be viewed as a 1,3-RE with a coordinated acetone zwitterion functioning as the two-electron acceptor in the reverse 1,3-OA. Photochemical decomposition of a planar Co(III) complex containing the five-membered ring produces acetone.[33] The ligand sensitivity appears to be effectively checked when the alkoxide donor is replaced by an amido-*N* donor. The amido-*N* lone pair is orthogonal to the C—C σ^*-orbital in the planar form of the chelate ring and can only be marginally available to stabilize cationic character at the β-carbon when the ring distorts. The lone pair availability has been restricted as much as possible by placing the five-membered ring in a macrocycle.[34]



(3)

Rule IV. *If the goal is to produce a strong electron-transfer oxidant, amido-N donors should be avoided as internal donors in acyclic chelate ligands.* When all electron-releasing, bond-breaking processes have been identified and blocked in amido-*N*-containing chelates, intramolecular isomerization processes can occur to produce nonplanar amido-*N* ligands to stabilize oxidizing metal centers (eq 4). The isomerizations can also compete with ligand degradation reactions.[19,30,31] Nonplanar amido-*N* ligands are much stronger donors than their planar counterparts, and this difference provides the driving force for the discovered isomerizations.[35] Our systems provided the first distinctly nonplanar amides in inorganic chemistry.[36] The studies were extended to give nonplanar amides in three separate classes: (I) the class just described where nonplanar amides are formed reversibly because of electronic demands at the metal[35,36] probably via an intramolecular twist mechanism,[37] (II) amides that are nonplanar because of ring constraints like those in organic chemistry,[19,38] and (III) amides that are nonplanar as a result of steric effects.[39] Although formation of class I nonplanar amides provides a fascinating vignette on ligand adaptability when the metal has need of additional electron density, the isomerizations complicate the study when the purpose is simply to obtain stable, strongly oxidizing complexes. The isomerizations can be blocked by enclosing amido-*N* donors in macrocycles.[34]



(4)

The combination of these four rules brings us through a number of ligand generations to the macrocyclic tetraamides of Figure 2,[40] H_4[**1**][22] and H_4[**2**].[34] These ligands are leading to the planned contribution to high oxidation state middle and later transition metal chemistry. Their oxidation resistance also permits the isolation of strongly oxidizing complexes.[34] The ligand H_4[**1**] with its all-aliphatic ring systems is an "innocent" [27] ligand. A detailed discussion of ligand

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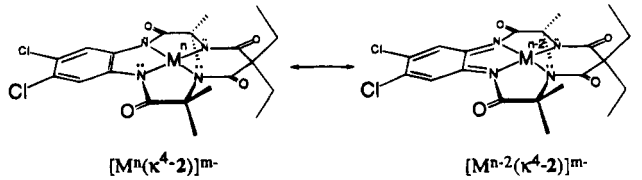

Figure 3. Resonance contributors in a π-delocalized noninnocent ligand complex.

innocence/noninnocence is outside the scope of this Account, but from a coordination chemist's point of view, H_4[**1**] is considered to be innocent because the nitrogen donors are electronegative and because there is only one reasonable closed-shell form in which the ligand can be conceptually removed from the metal, i.e., $[\mathbf{1}]^{4-}$. Thus, the formal oxidation state in high valent complexes is considered to be unambiguous. By comparison, H_4[**2**] is considered to be a "noninnocent" [27] ligand because an oxidation site can be localized on the metal or on the phenylenediamido-*N* unit or delocalized over both. The ligand system can be removed in two reasonable closed-shell forms, i.e., $[\mathbf{2}]^{4-}$ and $[\mathbf{2}]^{2-}$ (Figure 3). The innocence of $[\mathbf{1}]^{4-}$ and noninnocence of $[\mathbf{2}]^{4-}$ in complexes have been probed by a number of techniques such as Mössbauer spectroscopy and X-ray crystallography (see below). In many ways, H_4[**2**] is more interesting than H_4[**1**] because the metal and the noninnocent component of the ligand can be viewed as an adjustable delocalized site for redox processes. I will now interrupt the ligand design theme to highlight a rather obvious problem with decaying oxidation catalysts that is apparent from the longest ligand oxidation/hydrolysis decay sequence uncovered employing the strategy discussed above.

A Paradox with Decaying Oxidation Catalysts

The sequence of Figure 1 is shown not for detailed analysis, which is not possible within the space constraints of an Account, but instead to alert the reader to a general concern with metal-catalyzed oxidation processes where the metal catalyst degrades. The sequence was found when the osmium(IV) starting material was tested as a potential electrocatalyst for alcohol oxidations. A catalytic system was obtained, but the first flow of current does not emanate from catalytic alcohol oxidation. Instead, it results from a systematic degradation of the ethylene group of the starting complex's five-membered chelate ring. One can assert not only that the characterized species of Figure 1 are present in the degradation sequence but also that their one-electron-oxidized products are present, showing that at least 30 discrete species are involved from the starting material to the final observable complexes.[30,31] An isomerization to produce nonplanar amido-*N* ligands (see rule IV) occurs in the middle of the sequence leading to two parallel diastereomeric branches for further degradation. Other intermediates were formed in the degradation sequence in concentrations that were too low to allow for isolation and complete characterization. The two final observed species, labeled as such in the sequence, are the principal materials present while the alcohol is undergoing electrocatalytic oxidation. However, the system undergoes further degradation to intractable species that are not catalytically active.

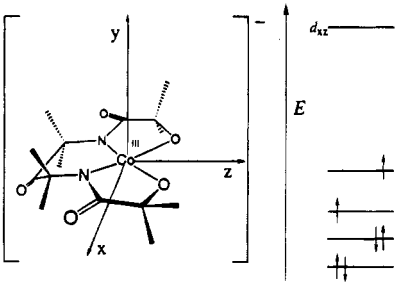

Figure 4. C_{2v} symmetry of an intermediate spin ($S = 1$), planar, four-coordinate cobalt(III) complex showing estimated ordering of frontier molecular orbitals.

The detection and characterization of this very complex degrading oxidation catalyst system highlights an obvious paradox. If the catalyst system decays to inactive materials, any single degradation intermediate or any combination of intermediates could be the actual catalyst or catalysts. If the slowest step in a decay sequence comes first, the rate of loss of catalytic activity will coincide with the rate of loss of the starting material, although the ligands of the catalytically active species could be substantially different from those of the starting material. Characterization of another intermediate in a decay sequence preceding the catalytically active complex simply takes one to a new starting material with an uncertain relationship to the actual catalyst. For example, in the electrocatalytic alcohol oxidation just described, we do not know that any residual portion of the starting chelate is coordinated to the true catalyst.

Developing High Oxidation State Middle and Later Transition Metal Chemistry

The tetraanions $[\mathbf{1}]^{4-}$ and $[\mathbf{2}]^{4-}$ bond to the first-row metals, Cr through Cu. Metal insertion procedures typically give yields of >90% after isolation. These ligands and earlier generation acyclic diamido-*N*-dialkoxido analogues[41] present a very strong planar, four-coordinate, σ-field to each metal ion. The interaction occurs primarily with just one metal d-orbital, which thus becomes distinctly σ-antibonding. This orbital is never found to be occupied for d-electron counts less than nine. The spin state usually observed is obtained by distributing the metal d-electrons according to Hund's rule among the remaining four d-orbitals. The isolation at high energy of the one metal d-orbital that becomes strongly σ-antibonding is represented in Figure 4 for a structurally characterized, intermediate spin ($S = 1$), planar, four-coordinate cobalt(III) complex.[42,43]

Derivative high-valent complexes of the tetraamide macrocycles are stable under ambient conditions in appropriate solvents and in the solid state. Each of the representative compounds shown in Figure 2 has been structurally characterized. Most are remarkably resistant to hydrolysis. Anion $[Mn(O)(\kappa^4\text{-}\mathbf{3})]^-$, with an early generation acyclic ligand, was the first

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isolated manganese–monooxo complex.[4] It is subject to hydrolysis on standing in water, but $[Mn(O)(\kappa^4\text{-}\mathbf{2})]^-$ is not, allowing for O-atom exchange of the oxo ligand with water.[44] This illustrates an important design principle. Hydrolysis of $[Mn(O)(\kappa^4\text{-}\mathbf{3})]^-$ probably proceeds via initial protonation of the alkoxide donors. A similar process is not possible in $[Mn(O)(\kappa^4\text{-}\mathbf{2})]^-$ as there is no basic site for protonation to initiate the decomplexation process. The anions, $[Mn(O)(\kappa^4\text{-}\mathbf{3})]^-$ and $[Mn(O)(\kappa^4\text{-}\mathbf{2})]^-$, are not strong O-atom transfer agents, presumably because of the high donor capacity and negative charge of the chelates. The Cr(V) analogues, $[Cr(O)(\kappa^4\text{-}\mathbf{1})]^-$ and $[Cr(O)(\kappa^4\text{-}\mathbf{2})]^-$, are also not reactive O-atom transfer agents toward olefins.[45] However, these very stable chromium compounds cleave DNA.[46] We have found that it is not necessary to change the ligand systems significantly to get oxidizing species in the presence of organic substrates and peroxides as hinted at below.

The complex $[Fe^{IV}Cl(\kappa^4\text{-}\mathbf{1})]^-$ is the first example of high-spin ($S = 2$) iron(IV) in a homogeneous coordination complex.[47,48] The dianion $[Fe^{III}Cl(\kappa^4\text{-}\mathbf{1})]^{2-}$ contains iron(III) in the rare intermediate spin state ($S = {}^3/_2$).[47] The isocyanide complex $Fe^{IV}(CN^tBu)_2(\kappa^4\text{-}\mathbf{1})$ is a six-coordinate, intermediate-spin ($S = 1$) iron(IV) complex of a potentially strong π-acid where the π-acidity is not expressed.[49] The compound's stability indicates that the $Fe^{IV}(\kappa^4\text{-}\mathbf{1})$ unit is indiscriminate in terms of the axial ligands it will accept. Compounds $[Fe^{IV}Cl(\kappa^4\text{-}\mathbf{2})]^-$ [50] and $Fe^{IV}(H_2O)(\kappa^4\text{-}\mathbf{2}')$,[51] containing noninnocent macrocyclic tetraamides, are better considered as species intermediate between Fe(IV) and Fe(III). Comparisons of their structural and Mössbauer properties with those of their Fe(III) partners and of the innocent macrocyclic tetramide complexes, $[Fe^{IV}Cl(\kappa^4\text{-}\mathbf{1})]^-$, $[Fe^{III}Cl(\kappa^4\text{-}\mathbf{1})]^{2-}$, and $Fe^{IV}(CN^tBu)_2(\kappa^4\text{-}\mathbf{1})$, indicate that the potential π-noninnocent character of the phenylenediamido-*N* units is expressed in the two species to different degrees.

The chemistry of planar, four-coordinate cobalt(III) has been considerably developed.[32,34,38,43,52,53] In some cases it has been shown that planar Co(III) complexes can catalyze O-atom transfers,[32] including enantioselective ones,[54] implicating the intermediacy of a Co(V)–oxo complex that retains a significant portion of the starting chelate (a Co(V)–oxo complex would be isoelectronic with an Fe(IV)–oxo complex). Compounds $[Co^{III}(\kappa^4\text{-}\mathbf{1})]^-$,[38] $[Co^{III}(\kappa^4\text{-}\mathbf{2})]^-$, and related species[34] contain intermediate-spin ($S = 1$) centers. The one-electron-oxidized complex, $Co(\kappa^4\text{-}\mathbf{2})$, is a hydrocarbon-soluble, solution-stable oxidant with a reduction potential of 1.27 V vs NHE.[34] This compound and related species are more accurately formulated as Co(III) complexes with one-electron-oxidized phenylenediamido-*N* units than as Co(IV) complexes. The compound $[Ni^{III}(\kappa^4\text{-}\mathbf{1})]^-$ is a planar, four-coordinate nickel(III) species with an innocent ligand complement.[55] It is the first structurally characterized example of this geometry for Ni(III) and has $g_\perp > g_\parallel$ in the EPR spectrum. Physical evidence indicates that the analogue $[Ni(\kappa^4\text{-}\mathbf{2})]^-$ is best formulated as a nickel(III) complex.[56]

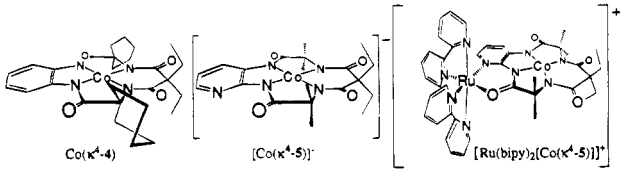

Figure 5. Recently produced complexes for oxidation studies.

Developments in Oxidation Chemistry

As noted in the introduction, one aim of our work is to develop ligands that might lead to improved metalloredox-active oxidants. As we have learned how to make progressively more robust ligands, we have begun exploring their use in oxidation processes. Much of our current work is focused on these studies. Three ongoing developments are presented here. The first is based on the known properties of the oxidized cobalt complex, $Co(\kappa^4\text{-}\mathbf{2})$ (Figure 2), and related complexes with different substitution patterns on the aromatic ring.[34] We have enhanced the hydrocarbon solubility by increasing the size of the aliphatic substituents as in $Co(\kappa^4\text{-}\mathbf{4})$ (Figure 5) to produce strong oxidants that are very soluble in alkanes, and we are exploring uses of these unusual reagents.[57]

The second focus is based on a desire to gain broad control over the redox properties of tetraamido-*N* macrocyclic complexes without having to change the basic nature of the oxidation-resistant ligand system. This problem is being attacked by developing switching ligands. Switching ligands are ligands which coordinate to a primary metal site, say a potential O-atom transfer site, and have one or more secondary sites, called switching sites, for the reversible acquisition of charge. The idea is to change the reactivity at the primary site by coordination of a variety of ions or by electron transfer events at crafted switching sites. Switching ligands offer the promise of metalloxidants with chameleon-like electronic properties. For example, switching ligand complexes might be capable of reacting with mild oxo-forming reagents to produce a relatively unreactive oxo complex that would become a reactive O-atom transfer agent after a switching event. In the structurally characterized cobalt(III) complex $[Co(\kappa^4\text{-}\mathbf{5})]^-$ there is a bidentate switching site consisting of the pyridine and adjacent amide-O donors. Whereas the cobalt(II) derivative of $[Co(\kappa^4\text{-}\mathbf{5})]^-$ is able to reduce O_2 by an outer sphere

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process, coordination of the dication $[Ru(bipy)_2]^{2+}$ produces $[Ru(bipy)_2[Co(\kappa^4\text{-}\mathbf{4})]]^+$, which clearly binds O_2. Electrochemical studies reveal that the bound O_2 molecule can undergo a multielectron reduction under appropriate conditions.[58]

The third focus is on catalytic oxidation processes. One example is the C—H bond activation chemistry discovered when we attempted to produce $[Fe(O)(\kappa^4\text{-}\mathbf{2})]^-$, the iron(V)—oxo analogue of $[Cr^V(O)(\kappa^4\text{-}\mathbf{2})]^-$ and $[Mn^V(O)(\kappa^4\text{-}\mathbf{2})]^-$. This system is the subject of much work and of a manuscript currently in preparation.[50]

Concluding Remarks

In accord with the purpose of *Accounts* articles, I have focused here on the systems developed in our laboratories. Original systems for stabilizing high oxidation state and strongly oxidizing middle and later transition metal complexes have been developed in other laboratories. I would like to call the readers' attention to the recent work in high-valent iron chemistry of Que et al. in producing dioxo-bridged nonheme species[11] and Vogel et al.[59] in metallocorrole chemistry for examples of exciting recent developments.

I believe that high oxidation state middle and later transition metal chemistry remains largely undeveloped. I hope that young inorganic chemists starting on new careers with a taste for synthesis, spectroscopy, and reaction chemistry and prepared to deal with the implications of working with paramagnetic systems will adopt this field as their own. Clearly one impediment has been the instability of most ligands when coordinated in oxidizing complexes. It is encouraging that it appears to be possible to categorize individual oxidative ligand degradations at the conceptual level. This should stimulate new research since, even if the concepts suggested here prove to be less than optimal, they at least provide a starting point for finding the correct concepts to guide researchers in designing superior oxidation resistant ligands. Much more can and should be done to perfect ligands for oxidizing homogeneous complexes. Protecting ligand systems from oxidative degradation is only one of the apparent themes. Better systems with multifunctional reaction sites are needed to move closer in biomimetic chemistry to what nature actually does to effect demanding oxidations. So often in chemistry, a challenging redox process requires a diversity of electronic properties of a metal ion catalyst that cannot be achieved with a static set of ligands. For example, the reduced form of a redox reagent might need to be electron-rich to react with a primary oxidant such as oxygen to produce an oxo complex, but then the oxo complex might need to be electron-poor to attack a resistant substrate. In general, nature does not choose to attain diverse electronic properties at an enzyme active site by developing a static ancillary ligand system. Rather, nature handles these challenges by using systems in which sequential reactions are arranged in time and space to achieve, among other things, the necessary electronic diversity.[8-12] As ligand oxidative sensitivity is becoming better understood, it is becoming more appropriate to generate synthetically ambitious multifunctional oxidants to execute targeted reactions by using a number of reactions to selectively amount the desired activation barriers.

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