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Elaboration of Copper-Oxygen Mediated C–H Activation Chemistry in Consideration of Future Fuel and Feedstock Generation

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Abstract

To contribute solutions for current energy concerns, improvements in the efficiency of C-H bond cleavage chemistry, e.g., selective oxidation of methane to methanol, could minimize losses in natural gas usage or produce feedstocks for fuels. Oxidative C-H activation is also a component of polysaccharide degradation, affording alternative biofuels from abundant biomass. Thus, an understanding of active-site chemistry in copper monooxygenases, those activating strong C-H bonds is briefly reviewed. Then, recent advances in the synthesis-generation and study of various copper-oxygen intermediates are highlighted. Of special interest are cupric-superoxide, Cu-hydroperoxo and Cu-oxy complexes. Such investigations can contribute to an enhanced future application of C-H oxidation or oxygenation processes using air, as concerning societal energy goals.

Introduction

In this article, we highlight certain copper-dioxygen (O_2; molecular oxygen) chemistries, providing information or concepts derived from biochemical or synthetic bioinorganic systems. The emphasis is “oxygen activation” with Cu complexes, especially those containing a single copper ion site, and C-H bond oxidative cleavage in the context of reactions mediated by monooxygenases [1,2], *cf.*, $R–H + O_2 + 2e^- + 2H^+ \rightarrow R–OH + H_2O$, utilizing molecular oxygen as the ‘O’ atom source; the ‘other’ atom derived from O_2 is released in the reduced form of water.

With the decades long soaring of energy demands, one envisions that finding efficient ways to improve methods to utilize current energy resources, or to develop new ones is an important societal goal. One of various targets of interest is to enhance the application of energy sources such as natural gas (i.e., methane; CH_4). The development of new shale gas fracking technology has enabled the very recent steep growth in natural gas output. The efficient control of overflowed shale gas includes liquefaction of methane. Here, a key

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reaction would be the activation of the inert methane C–H bond (BDE = 104 kcal/mol^{-1}). High temperature and pressure (800 °C, 40 atm) are required for the industrial partial oxidation of CH_4 to produce methanol (CH_3OH) [3]. This energy-dense liquid can be a fuel (e.g., in fuel cells or as an additive to blended gasoline) or feedstock. Methanol also provides advantages in its utilization, as there would be minimal loss in transport from a storage site.

Alternative energy resources include biofuels, available from currently plentiful and renewable biomass [4]. Abundant biopolymers such as cellulose, chitin, lignin and starches provide us with potential future sources of primary feedstock in the production of fuels [5]. Hydrolytic chemistry by enzymes or extreme chemical conditions, such as heating with sulfuric acid [6], can lead to useful breakdown products. Recent advances have revealed new classes of enzymes which effect biopolymer breakdown via oxidative chemistry.

In fact, for C–H oxidative cleavage of methane, biopolymers (vide supra), or other substrates, enzymes with copper active sites include lytic polysaccharide monooxygenases (LPMOs), peptidylglycine-α-hydroxylating monooxygenase (PHM), tyrosinases (phenol *o*-hydroxylases) and particulate methane monoxygenase (pMMO), which possess mononuclear (single Cu), non-coupled dicopper or adjacent dicopper active centers. The understanding of the formation, chemical-physical properties and reactivity of diverse biochemical or synthetic copper-oxygen adducts is of great interest. Here, we highlight the structures, functions and nature of copper centers in LPMOs, PHMs, and pMMOs. Highlighting of more recent efforts to generate synthetic analogs, notably those with single Cu active sites, as possibly relevant to monooxygenases will also be provided. If we can learn the manner in which biological systems efficiently activate C-H bond oxidation under ambient conditions, we have the potential to aid efforts to relieve our energy concerns by developing copper catalysts that can oxidatively activate strong C-H bonds.

Lytic Polysaccharide Monooxygenases (LPMOs)

LPMOs have aroused much attention due to their significant roles in potential biomass conversion via oxidative polysaccharide breakdown [5,7,8]. Several families of LPMOs have been categorized; cellulose-active fungal AA9, chitin-degradable bacterial AA10, and chitin-active fungal AA11 [5,7]. Most recently, other LPMOs are shown to be capable of degrading starch [9,10]. There are now many X-ray crystallographic studies showing that all LPMOs possess a mononuclear copper active site where binding to a chelating (bidentate) histidine amino terminus and a second His via εN imidazole ligation (Figure 1a) [7,11,12]. These three N-donors comprise a roughly T-shaped coordination (especially for reduced Cu^I) [13], with the chelating histidine referred to as a ‘His-brace’. In oxidized forms, additional waters coordinate and tyrosine or other aromatic amino-acids reside nearby. Subtle differences in the LPMO active-site structures occur. AA9 enzymes possess an εN-methylated His-brace, a highly unusual biochemical feature (Figure 1a). The type of copper-oxygen intermediate formed during catalysis is unknown, but it must be highly reactive in order to cleave the very strong sugar C–H bond (C1 or C4) (also see below).

Peptidylglycine-α-Hydroxylating Monooxygenase (PHM) and Dopamine-β-Monooxygenase (DβM)

These Cu monooxygenases mediate strong C-H bond activation; for PHM, a glycine-extended prohormone undergoes α-carbon hydroxylation while DβM catalyzes the benzylic hydroxylation of dopamine to give norepinephrine [14,15]. They possess a dicopper active site which is “noncoupled”; the two copper ions are about 11 Å apart (Figure 1b) [16]. One copper ion (Cuh) receives and passes reducing equivalents from ascorbate to Cu_M, where O_2 and substrate binding occurs. An X-ray crystallographic study on a PHM derivative reveals a dioxygen-derived species at the Cu_M site, judged to be a Cu^I/O_2 adduct, formally an end-on superoxide ($O_2^{\bullet-}$) ligand-Cu^{II} complex ($^{\mathbf{E}}\mathbf{S}$; Figure 2) [17]; Dioxygen binding to transition metals involves electron-transfer from metal ion to O_2. Other biochemical and computational studies implicate a Cu^{II}-$O_2^{\bullet-}$ species formed in PHM which effects substrate hydrogen-atom transfer (HAT), eventually leading to product [14,15,18]. With these protein studies and more recent model compound work, fundamental studies on the physical properties and reactivity of mononuclear cupric superoxo species have thus been evoked (vide infra).

Particulate Methane Monooxygenase (pMMO)

pMMO is found in bacterial methanotrophs, and if enough copper is biologically available, this copper-dependent membrane protein is employed to oxidize methane to methanol in order to acquire a carbon source [19,20]. X-ray crystallographic studies exhibit that pMMO possesses three different metal active sites; dicopper, monocopper, and a zinc center [21]. Biochemical studies implicate an asymmetrical dinuclear copper active site [22-24], although Chan et al. [25] hold the view that an as yet unseen pMMO trinuclear Cu center constitutes the active site. The dicopper site displays a short Cu–Cu distance, where the ligands are provided by two His's for one copper and the bidentate N-terminal histidine (‘His-brace’, as in LPMOs) for the other (Figure 1c).

Closer examination of the dicopper centers in X-ray structures (albeit the structures are not of high-resolution) reveals two very tilted Cu-N_{His} bonds (with the Cu-N vector reaching far out of the plane of the imidazole ring), not reasonable for inorganic coordination structures. As LPMO structures also having the His-brace are mononuclear in Cu, we (following others [26]) suggest the pMMO active site may possess only one copper, coordinated by the His-brace and one another His residue. Nevertheless, a dicopper center capable of methane or other alkyl C–H oxidations is worthy of studying, and there are many 2:1 Cu/O_2 derived entities in synthetic chemistry (vide infra).

Synthetic Cu_2/O_2 Complexes and C-H Activation

As copper monooxygenases mediating C-H bond activation have different kinds of active sites (vide supra), it is critical to clarify fundamental aspects for the formation, structural/spectroscopic characteristics, and reactivity of the known Cu^I-O_2 derived species, Figure 2.

Upon oxygenation of a reduced copper ion, an initial product is a mononuclear cupric superoxo (Cu^{II}-$O_2^{\bullet-}$, **^{E}S**) species. Over the years, species **^{E}S** have been difficult to observe because the reactions of **^{E}S** or "side-on" η^2-bound forms (**^{S}S**) with a second mole-equiv of the starting ligand Cu(I) complex are very fast and the binuclear dicopper complexes (μ-1,2-peroxo)Cu^{II}_2 ("trans" **^{T}P**; or a newer "cis" **^{C}P** form [27]), (μ-η^2:η^2-peroxo)Cu^{II}_2 (**^{S}P**) and bis(μ-oxo)Cu^{III}_3 (**O**) (Figure 2) are stable if handled at cryogenic temperatures [28-32]. The dicopper(III) complex **O** seems to be most stable among the three, possibly due to the strong Cu^{III}-oxo bonds, but the nature of the chelating ligand employed controls the chemistry and final structure. However, **O** is well known to attack exogenous substrates, including C–H bonds, in a wide variety of reactions as outlined by Stack, Tolman, Itoh and others [28,33-36].

As described, pMMO is well thought to effect dicopper methane oxygenation chemistry and **O** has been suggested as an intermediate which may form at the active site. Related species which are probably more reactive toward oxidative (oxygenative; overall O-atom insertion) chemistry involving very strong C–H bonds are bis(μ-oxo)$Cu^{II}Cu^{III}$ (**MV**) or (μ-oxo)(μ-hydroxo)$Cu^{II}Cu^{III}$ (**MV-H**) (Figure 2). **MV** is suggested by examination of the literature [23-25,37] or from calculations [38]; Yoshizawa's newer computational analysis [39] suggests further activation, i.e., implementation of enhanced reactivity toward CH_4 as substrate, could come by starting with **O** and injecting a proton and an electron from a nearby tyrosine to give **MV-H**. However, neither **MV** nor **MV-H** species has ever been directly synthesized or identified. These remain as important synthetic targets.

Solomon, Schoonheydt and co-workers have shown that a (*μ*-oxo)Cu^{II}_2 (**Cu_2O**, Figure 2) attacks methane in Cu-loaded zeolites (Cu-ZSM-5) [40], producing CH_3OH at low temperature (∼100 °C) with high selectivity. Some **Cu_2O** synthetic complexes have been reported [41], but they have not yet been shown to undergo interesting C-H bond oxidation chemistry.

An important recent contribution from Stack and coworkers [36] establishes the chemistry of complexes **O** when ligated by a bidentate ligands where at least one donor is a primary amine (-NH_2) (Figure 3). A combination of experimental and computational studies leads to conclusions that might not be expected – the smaller size of the –NH_2 ligand (relative to –NR_2) allows for tight/strong Cu-N bonding and achievement of Cu high-valency in **O**, without loss of oxidative power. Also, the small −NH_2 ligand also allows a substrate closer approach to the O_2-derived copper-oxygen species. This study thus provides possible insight into the presence of the protein terminal His residue as chelating ligand in *p*MMO and/or LPMOs (Figure 1), enzymes with very strong C–H bond containing substrates.

Primary Cu^{I}/O_2 Adducts and Reactivity

As stated above, a Cu^{II}-$O_2^{\bullet-}$ (**^{E}S**) species is the initial adduct produced from the internal electron transfer between a single ligand-Cu^{I} complex and O_2. Then, sequential electron-proton addition from reductants (e.g., ascorbate) and solvent, or H-atom transfer from substrates (see below) to species **^{E}S** may lead to a Cu^{II}-OOH species (**Hp**). Similar reduction-protonation accompanied by O-O bond homolysis should afford a cupric oxyl

(**Cp**) (Cu^{II}-O• ↔ Cu^{III}=O) species (Figure 2); the latter has only been detected in the gas phase [42-44].

Cupric superoxo species are important entities to study, see above [13,17,45]. In fact, previous work has led to X-ray structures (not shown) of one Cu^{II}-$O_2^{\bullet-}$ (**^{E}S**) species with tris(tetramethylguanidino)tren [46], along with two structures [47,48] where the superoxo (or peroxo) [48] moiety is ligated in a "side-on" η^2-binding fashion (**^{S}S**), the latter exhibit limited or no exogenous substrate reactivity due to ligand imposed steric effects. The reactivity toward substrates where C–H oxygenation chemistry is achieved has been a critically lacking aspect of this subfield. However, recent newer ligand designs, e.g., with electron-releasing ligand substituents [49], or application of extreme cryogenic conditions (e.g., down to < 125 °C) [50], have enabled generation of new **^{E}S** complexes which exhibit important reactivity (Figure 4).

Itoh and co-workers [51,52] reported an exciting advance starting in 2009; their −80 °C stabilized **^{E}S** complex with a tridentate alkylamino donor ligand, undergoes intramolecular benzylic C–H oxygenation (Figure 4a). Such reactivity is similar to that of DβM (Figure 1b), thus giving credence to the biochemical [15] and computational studies [18] suggesting that such a Cu^{II}-($O_2^{\bullet-}$) species **^{E}S** (or **^{S}S**) is responsible for the enzyme substrate HAT.

Karlin and co-workers [50] have also carried out detailed mechanistic examinations of **^{E}S** species toward *exogenous* substrates with weak C-H bonds (Figure 4b). The ligand internal H-bonding group affords enough stability to generate the complex at – 125 °C, yet substrate H-atom abstraction occurs.

Another set of −80 °C stabilized **^{E}S** complexes possess 4-dimethylamino [49] or 4-methoxy-pyridyl ligand donors [53]. For the latter, an in-depth mechanistic study was carried out employing phenolic substrates: the **^{E}S** complex effects initial and rate-determining substrate O–H bond HAT, then the phenoxyl radical produced is attacked by a second **^{E}S** complex, all leading to phenol oxygenation and *p*-benzoquinone formation [53].

Kim and co-workers recently employed a new thioether sulfur ligated (N_3S) complex (Figure 4c) [54]. It exhibits enhanced reactivity compared to N_4 ligated **^{E}S** analogs. This work is a breakthrough in synthetic biomimetic research in that the complex mimics the Cu_M center of PHM (Figure 1b) and such studies should lead to a better understanding of the role of the PHM active site methionine ligand.

Mononuclear Cu^{II}-OOH (**Hp**) systems have been also generated and studied, again usually at low temperatures (−80 °C). They may derive from (i) addition of simple copper(II) complex precursors plus H_2O_2 in the presence of base [55,56], perhaps referred to as a shunt pathway (i.e., not derived from dioxygen chemistry), (ii) HAT from e^-/H^+ donors (e.g., phenols) to **^{E}S**, or (iii) addition of 1.5 equiv H_2O_2 to a fully reduced Cu^{I} complex, possibly initially a Fenton chemistry type reaction [55]. In our hands, well-characterized **Hp** complexes may effect oxidative N-dealkylation chemistry (e.g., R_2-NCH_2R' →→ R_2NH + R′C(O)H), that analogous to PHM [57]. However, we found a recent case where the chemistry appears to proceed through Cu–O homolytic cleavage of Cu^{II}– OOH and

subsequent site-specific Fenton chemistry derived from the Cu(I) thus produced reacting with the excess H_2O_2 present [58]. In general, Cu^{II}-OOH (**Hp**) appear experimentally [55,59] and computationally [60] to not be effective oxidants toward C–H HAT.

As mentioned, there is yet no direct evidence or characterization of a Cu^{II}-oxyl (**Cp**) complex, in solution chemistry. However, in one study, Itoh and co-workers [61] provided compelling evidence for the generation of **Cp**, produced from O-O homolysis of a Cu^{II}-OOR complex, leading to a substrate C-H oxygenation. In a DFT computational study, Beckham and co-workers [62] suggest that net C–H hydroxylation in fungal LPMOs may occur by generation of **Cp** (of course starting from Cu^{I}-O_2 chemistry). In relevant studies, Tolman and co-workers [63] have been able to study a high-valent Cu^{III}-OH species (Figure 2) (perhaps a protonated Cu^{II}-oxyl) which effects dihydroanthracene rate-limiting HAT oxidative chemistry.

Aqueous O_2-Reduction, Cu^{I}/O_2 Oxidase or Monooxygenase Chemistries

Aqueous reduction and protonation of molecular oxygen involve sequential electron-proton addition, as shown in Figure 5a; many relevant (de)protonation equilibria, not shown (e.g., $HO_2/O_2^{\bullet-}$; H_2O_2/HO_2^-), are also involved. Note that as O_2 becomes further reduced, the products become stronger oxidants, such as superoxide, hydrogen peroxide ($H_2O_2 + 2e^- + 2H^+ \rightarrow 2H_2O$; E°= +1.35 V (pH = 7) vs. NHE; not shown), and hydroxyl radical (Figure 5a). In (bio)chemical systems, reduced iron or copper complexes ‘reductively activate’ O_2 forming Cu^{I}/O_2 derived species which themselves can continue to be reduced and protonated (Figure 5b) and/or they attack R–H substrates leading R-OH products (Figure 5c,d,e). Ground-state triplet dioxygen is essentially inert to direct reaction with organics (as ground state singlets) [64]. In all cases, the overall reactions are four-electron four-proton processes (Figure 5).

Oxidase enzymes reduce O_2 to water (or H_2O_2 in some cases) where the electrons come from reductants (e.g., cytochrome *c* in cytochrome *c* oxidase (C*c*O)) or from substrates which undergo dehydrogenations (providing protons + electrons; e.g., in ascorbate, diphenols) or multicopper oxidase enzymes such as laccase) [2]. Copper oxidases can be considered or compared to catalysts which mediate cathodic reactions in fuel cells [65], further making an understanding of their chemistry of great relevance in the field of energy. Figure 5b depicts single-Cu site oxidase chemistry, with the point being that here we find O_2-derived copper-oxygen species which must form, i.e., they are critical to the whole process of capturing the energy stored in dioxygen when reduced to water, that being +0.82 V at pH = 7 [2].

However, what is critically lacking is our knowledge of the details depicted in Figure 5b. Future research is required to elucidate fundamental information such as reduction potentials (E° or $E^{\circ\prime}$(pH = 7)), e.g., for Cu^{II}-$O_2^{\bullet-}$ ($^{\mathbf{E}}\mathbf{S}$ or $^{\mathbf{S}}\mathbf{S}$) species, and their reduction to Cu^{II}-peroxo complexes. Alternatively, stepwise or proton-coupled reduction to Cu^{II}-OOH (**Hp**) may be preferred or required; aqueous superoxide anion ($O_2^{\bullet-}$) cannot be reduced without the presence of a proton [64].

Thus, we also need to learn about the basicity of the superoxo complex O-atoms, since a proton is normally required to effect an electron-transfer reduction, but what acid strength (pKa) is needed? The same kind of information, reduction potentials and O-atom basicities, is needed for each subsequent step, Cu^{II}-OOH (**Hp**) + $H^+/e^- \rightarrow Cu^{II}$-O• (**Cp**) + H_2O, and **Cp** + $H^+/e^- \rightarrow Cu^{II}$-OH (Figure 5b). The former step is the critically important reductive cleavage reaction, that important for oxidase (O_2-reduction to water) and for substrate oxygenation (e.g., Figure 5c,d,e). Such chemistries are thus widely applicable to heme, non-heme iron, copper biochemistries and metal-mediated stoichiometric or catalytic substrate oxidation-oxygenation chemistries, thus important for practical and/or industrial situations.

In reality, the amount of basic/fundamental information needed is in fact vastly multiplied from what is discussed and illustrated here; (i) the environment around the metal (the ligand and second sphere) very much influences or even controls factors such as reduction potentials and M-$(H)O_2^{n-}$ basicity, and (ii) all these chemistries need to be evaluated in more complex systems where 2 or 3 proximate copper ions constitute the catalyst center, as occurs in multi-copper oxidases or in C*c*O (with heme-Cu dimetal active site) [1,2]. (iii) Simultaneous multi-electron (i.e., $2e^-$) processes may occur [1], so different with what is represented in Figure 5. Thus, in practice, nature does not utilize mononuclear Cu centers to effect oxidase chemistry; however, an understanding of the Figure 5b chemistry is a critical start.

Figure 5c, d, and e outline pathways in which a monooxygenase may function, as possibly occurs at the PHM Cu_M active site. See earlier works in which such comparisons of pathways have been presented [66,67]. But which entity, ^{E}**S**, ^{S}**S**, **Hp** or **Cp** is the species that initially attacks the substrate to effect HAT from R–H, giving R•? Pathways **c** and **d** involve ^{E}**S** or ^{S}**S** substrate HAT, but they differ in that either 'rebound' of the O-atom to R• occurs at different stages. Klinman and co-workers prefer pathway **c**, but calculations from Chen & Solomon suggest pathway **d** [67]. Other mechanisms have also been suggested [67,68].

If, as strongly suggested, an ^{E}**S** or ^{S}**S** copper-superoxo intermediate effects substrate HAT in PHM, than this dramatically differs from the situation for cytochrome P-450 monooxygenase, the 'classic' system known for C–H oxygenation [69,70]. There, protons and electrons are stepwise added the ferrous-heme O_2-adduct, to form an $iron^{IV}$-porphrin-π-cation-radical (≡ Fe^V), that derived from heterolytic cleavage of an Fe^{III}-OOH intermediate. Closest to that by analogy would be that illustrated by pathway Figure 5e. But there, homolytic O-O reductive cleavage occurs to give a Cu^{II}-oxyl species (**Cp**). If a proton plus protein (or ligand)-derived electron could be further provided, heterolysis could occur, giving a $(X^{\bullet+})Cu^{II}$-oxyl intermediate (≡ Cu^{IV}=O formally) plus H_2O [68].

Figure 5e, itself, represents the situation where Cu^I/O_2 chemistry proceeds to a Cu^{II}–O• (**Cp**) species, the last reactive intermediate possible following reduction-protonation of O_2 at a mononuclear Cu site. As mentioned, based on one recent computational study, it is pathway **5e** and a **Cp** reactive intermediate which is relevant at polysaccharide monooxygenation at the active site of LPMOs [62].

Conclusion and Future Perspectives

The chemistry represented by Figure 5, with all the possible Cu^{I}/O_2 derived reduced and/or protonated intermediates, is for coordination chemists or synthetic bioinorganic chemists, a vast field of research targets for study. The relevance to energy, including savings and increasing efficiency, is clear; the understanding of copper ion complexes as biochemical or synthetic entities able to catalyze oxidation reactions using readily available molecular oxygen is critically important. As described, precedence exists for copper mediated oxidation, i.e., C–H activation and net hydroxylation, of very tough substrates such as methane or polysaccharides. The understanding of such chemistries may also be applicable to the design of copper ion based fuel-cell catalysts. Elucidation of underlying principles and details of reduction, pronation, the timing of these preceding events, Cu-oxy species' (i.e., $^{\mathbf{E}}\mathbf{S}$, $^{\mathbf{S}}\mathbf{S}$, **Hp, Cp**, or even multicopper containing analogs) structure, spectroscopy and electronic-structure (bonding) and determination of reaction mechanisms is an important goal. Determination of reduction potentials for Cu^{I}/O_2 derived reduced species (e.g., $^{\mathbf{E}}\mathbf{S}$, $^{\mathbf{S}}\mathbf{S}$, $^{\mathbf{T}}\mathbf{P}$, $^{\mathbf{S}}\mathbf{P}$, $^{\mathbf{C}}\mathbf{P}$, **O**, **Hp** and **Cp**), and comparison in an absolute or relative sense to those of free O_2-reduced species, is also of fundamental importance.

Some specific conclusions or perspectives are:

1. Energy – copper enzymes

Looking to the chemistry involved at copper enzyme active sites can lead to new insights and thus strategies to save energy via the development of new reagents or catalysts for (i) selective and efficient substrate oxidations-oxygenations, and (ii) fuel cell cathodic O_2-reduction.New chemistries may in the future substitute for the activities of LPMOs, PHM, and pMMO. In addition to protein studies, establishing small molecule model systems and investigating their fundamental properties will be important. Which Cu-O_2 intermediate is effective to carry out what chemistry?

2. Mixed-valent dicopper complexes

Although the dicopper complexes, $^{\mathbf{T}}\mathbf{P}$, $^{\mathbf{S}}\mathbf{P}$ and **O** are well studied, further insights are still needed. However, it is especially important to target the generation and investigations of the chemistry of mixed-valent species like **MV** or **MV-H**. Also, can different sorts $\mathbf{Cu_2O}$ species be discovered that will enable the oxidative attack of strong C-H bonds?

3. Cu-oxyl (Cp) species

This is surely a critical target for study, not only in how it forms (from Cu^{II}-OOH ($^{\mathbf{H}}\mathbf{P}$)) but also as to what is its solution substrate reactivity profile. It is expected to be the most reactive, "hottest", Cu^{I}-O_2 derived species, and a **Cp** species is most likely important in LPMOs, or possibly in pMMO.

4. His-braced monocopper complex

As the His-brace copper ion ligation is critical in LPMOs and pMMO, elucidation of its effect on Cu^{I}/O_2 chemistry is needed. Perhaps the recent study by Stack and co-workers [36] has already provided insight.

5. Cu^{II}-$O_2^{\bullet-}$ Complexes

Very recent breakthroughs in the generation and reactivity of such species indicate that this sub-field can be further explored. The relationship between copper-ligation and ^{E}**S** or ^{S}**S** reactivity requires elucidation. An intriguing point for consideration of monocopper O_2-chemistry is that a new computational study [71] suggests that the reactive species in PHM is a $[Cu^{II}\text{-}O_2^{\bullet-}(H)]^{2+}$ entity, i.e., with a protonated superoxide. $HO_{2\,(aq)}$ is a much stronger HAT reagent than is $O_2^{\bullet-}$ anion [64]. Even with the Lewis acidic Cu(II) ion present and ligated, perhaps $[Cu^{II}\text{-}O_2^{\bullet-}(H)]^{2+}$, as suggested [71], is required to effect HAT chemistry producing R• + Cu^{II}-OOH plus release of that "extra" proton.

6. Thioether-ligated Cu^{II}-$O_2^{\bullet-}$ species

In addition to the recently developed tetradentate sulfur-ligated N_3S-^{E}**S** complex, new reactive overall tridentate N_2S-^{E}**S** are targets for synthetic studies, in relationship to the active site in PHM.

7. Cu^{II}-OOH (Hp) reductive O–O cleavage

Detailed mechanistic investigation of this reaction, i.e., elucidating insights (into pKa of added acids, site of protonation, etc.) is not only critical to the field of Cu^{I}/O_2 chemistry, but also for all fields and aspects of metal-O_2 (bio)chemical reactivity. Such studies can of course also provide insights to the formation and chemistry of the cupryl Cu^{II}-O• (**Cp**) species, see above.

The field of biochemical and synthetic bioinorganic O_2-activation by copper ion is exciting. While numerous insights have been obtained in the last 30 years, many challenges for both fundamental and practical chemistry applications (including to 'energy') remain.

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- Copper-oxygen complexes can effect difficult C–H oxidations in copper monooxygenases.
- The advancement of Cu-oxygen reactivity can contribute to societal energy concerns.
- Differing types of CuO_2 and Cu_2O_2 complexes have been synthesized.
- Copper-superoxo, Cu-hydroperoxo, and cupryl species are key reactive intermediates.
- Copper-monooxygenase substrate likely proceed by varying mechanisms.

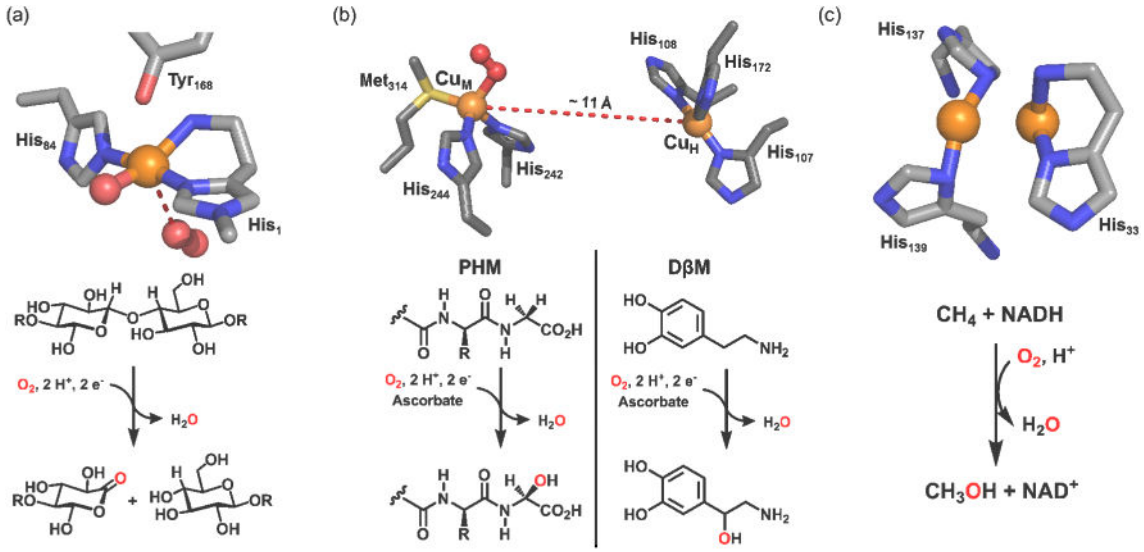

Figure 1.

The X-ray crystal structures of copper active sites and roles of the monooxygenases involved in C-H bond activation; (a) LPMO: AA9 (PDB: 4EIR), (b) PHM (PDB: 1SDW), (c) pMMO (PDB: 1YEW).

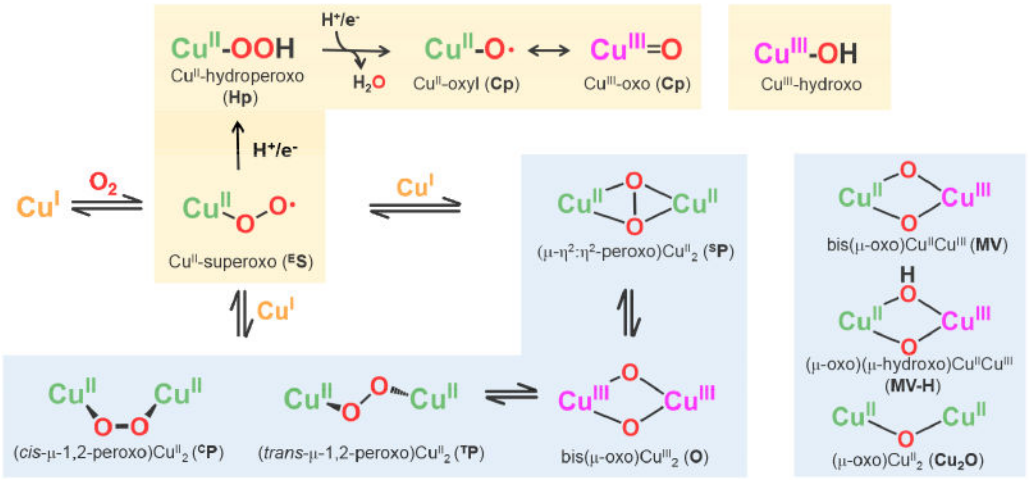

Figure 2.

O_2-derived copper species proposed as reactive intermediates mediating C-H bond activation experimentally or computationally.

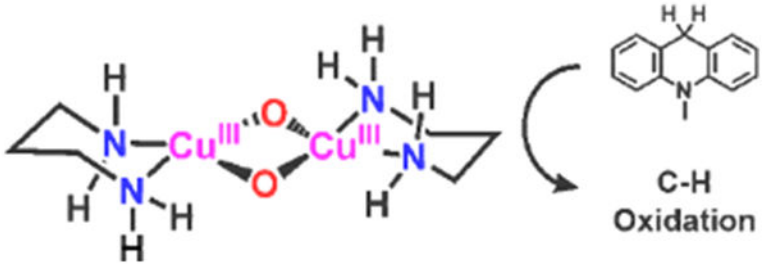

Figure 3.

A high-valent dicopper(III) species **O** ligated by the primary amine, 1,3-propylenediamine, is capable of H-atom abstraction from the C–H bond in 9,10-dihydromethylacridine.

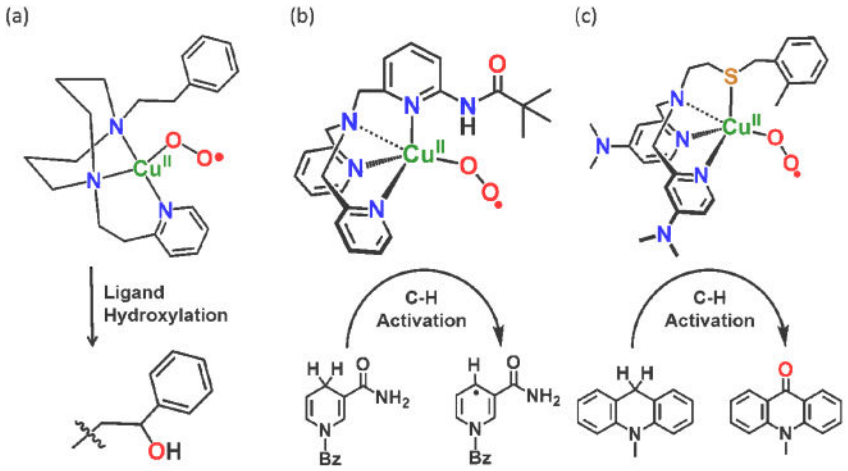

Figure 4.

Spectroscopically characterized $Cu^{II}(O_2^{\bullet -})$ species: (a) Itoh's ^{E}S complex effecting intramolecular benzylic oxygenation (net hydroxylation), (b) Hydrogen-bond stabilized ^{E}S complex effecting exogenous (weak) C-H bond HAT chemistry and (c) Thioether-ligated ^{E}S complex with enhanced reactivity, here, toward 9,10-dihydromethylacridine. Also, see text.

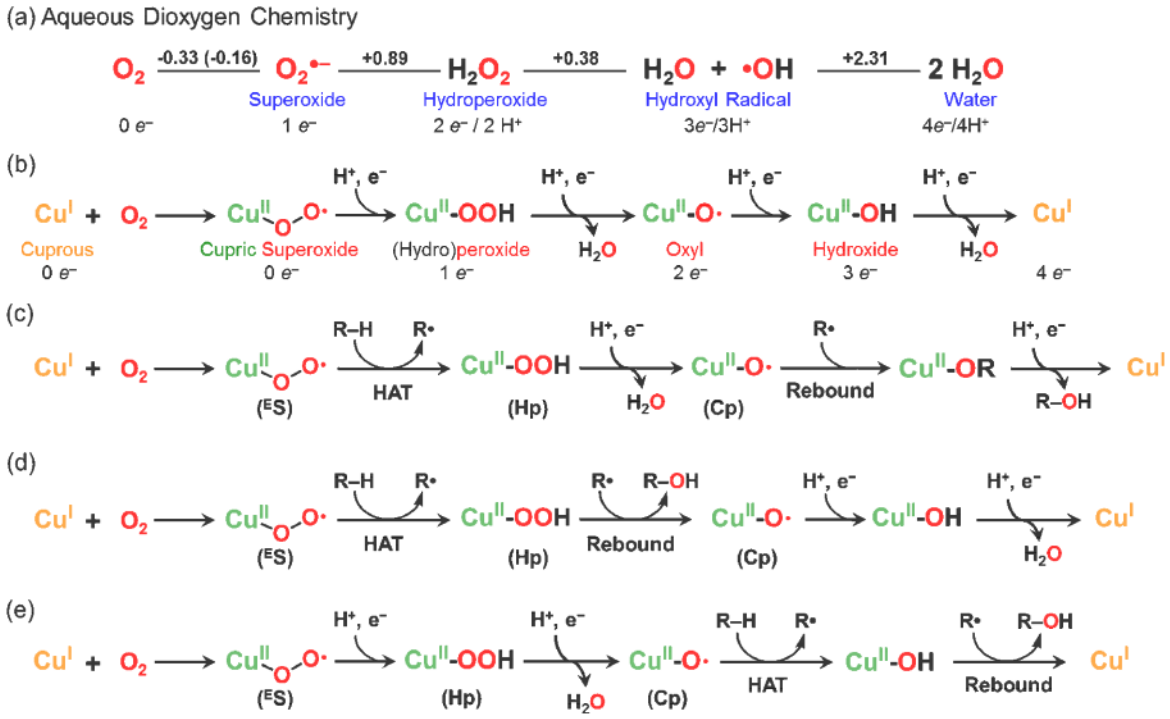

Figure 5.

(a) Aqueous four-electron four-proton O_2-reduction to water; reduction potentials (volts, pH 7). (b) Copper oxidase reactivity and intermediates relevant for single copper site chemistry. (c),(d),(e) Single-copper site stepwise monooxygenase chemistry. As must be the case, overall four-electron reduction chemistry occurs, where two derive from a substrate R–H bond; the other two electrons come from donors such as ascorbic acid. All O_2-derived species, superoxo (**^{E}S**), (hydro)peroxo (**Hp**) or cupryl (**Cp**), must be generated (in some form). The variations in chemistry, (c) vs (d) vs (e), are that for each, initial HAT chemistry with the substrate (R–H → R•) is effected by a different copper-oxygen intermediate, (**^{E}S**), (**Hp**) or (**Cp**). Still, other pathways or mechanisms are possible. Also, see text.