Dioxygen Activation

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Solid-State Chemistry at an Isolated Copper(I) Center with O_2**

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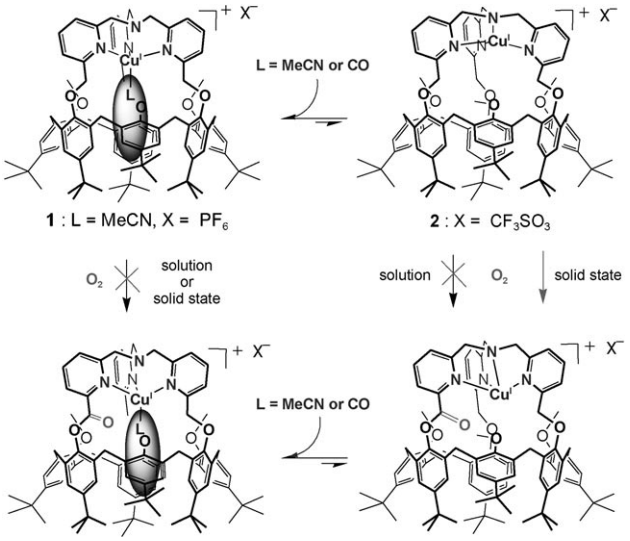
The controlled oxygenation of organic compounds at room temperature by O_2 remains a challenge of the most importance.[1] In that context, metalloenzymes are fascinating natural factories that perform regio- and stereoselective oxygenation of organic substrates.[2,3] Among these, copper monooxygenases such as PHM (peptidylglycine α-hydroxylating monooxygenase),[4] DβH (dopamine β-hydroxylase),[5] and TβH (tyramine β-hydroxylase)[6] catalyze a two-electron oxidation process corresponding to the insertion of an oxygen atom into a C–H bond with O_2 and two electrons provided by ascorbate, thus releasing water. Quercetinase, in contrast, catalyzes a four-electron oxidation process with the oxygenation–decarbonylation of quercetine.[7] For these enzymes, it has been demonstrated that the reactive chamber contains a single copper center. In the case of monooxygenases, however, a second copper center is present approximately 10 Å away, which allows sequential transfer of electrons from ascorbate to the catalytic site. In analogy to the well-known cytochrome P450 chemistry, it has been long proposed[8] that two electrons are required to activate O_2 at a copper center, leading to the hypothesis that $Cu^{II}OOH$ (or more recently suggested CuO) was the reactive species in copper monooxygenases.[9,10] Relatively recently, however, a series of studies, either biochemical,[11,5] chemical,[12] or theoretical,[13] have suggested that $Cu^{II}OO^{\bullet}$, corresponding to an only one-electron-reduced O_2 species, might well be the reactive species responsible for the C–H bond breaking process in these enzymes. More recently, while exploring the properties of a copper center isolated in the tris(aminoethyl)amine (tren) cap[14] of our calix[6]arene-based model compounds,[15] we discovered that the Cu^{I} complex reacts with O_2 to produce a species that leads to the oxygenation of the ligand, in which the insertion of one and two oxygen atoms was detected.[14c] In view of the geometrical constraints of the system, this study has provided evidence that a mononuclear Cu^{I} center can activate O_2 for breaking a C–H bond. Herein, we report a study related to a system of the same family of calixarene-based ligands, but with a tris(2-pyridylmethyl)amine (tmpa) cap[16,17] in place of the tren unit.

Two different cuprous complexes based on the calix[6]tmpa ligand[16] (Scheme 1) have been synthesized and isolated. Complex **1** was isolated from a THF/CH_2Cl_2 mixture containing equimolar amounts of calix[6]tmpa and $[Cu(MeCN)_4]PF_6$. Complex **2** was obtained from the reaction of CuOTf (Tf = trifluoromethanesulfonyl) with the ligand in toluene. Both complexes were characterized by ^{1}H NMR spectroscopy (Figure 1). The spectra displayed signatures depicting C_{3v} symmetry for the calixarene cone and tmpa cap. Complex **1** showed an extra resonance at $\delta = -1.02$ ppm, which attested to the presence of a guest ligand ($MeCN_{in}$) derived from the synthetic procedure. Such a high-field-shifted resonance indicates inclusion of the ligand into the aromatic core provided by the calixarene macrocycle. Its binding to the metal center, in the absence of free acetonitrile ($MeCN_{out}$), emphasizes the very high affinity of this guest for the cuprous host. Adding a few extra molar equivalents of MeCN to the $CDCl_3$ solution of the complex did not change the NMR profile; however, saturation transfer experiments showed that $MeCN_{out}$ and $MeCN_{in}$ were in exchange.



Scheme 1. Guest ligand binding in solution and solid-state O_2 reaction at the Cu^{I} center embedded in the calix[6]tmpa ligand.

Complex **2** displayed a slightly different profile with broader peaks, which are attributable to a more flexible

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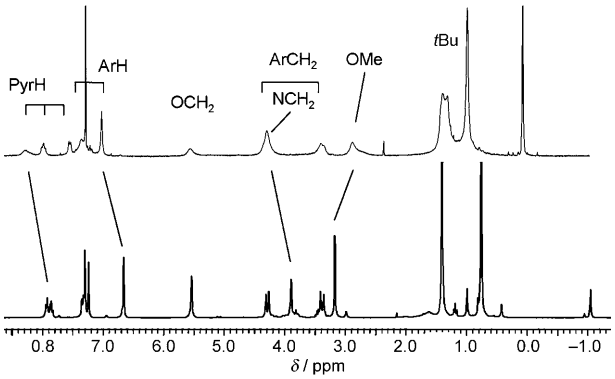


Figure 1. ^{1}H NMR spectra ($CDCl_3$, 250 MHz, 300 K) of complexes **1** (bottom) and **2** (top).

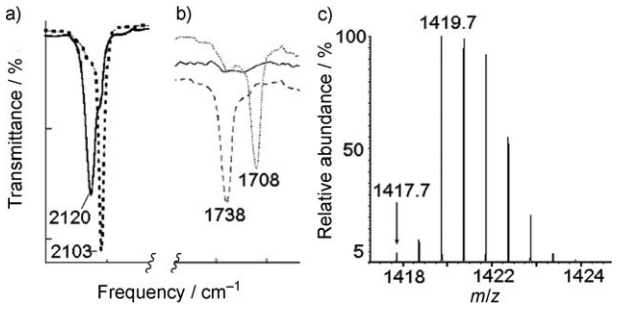
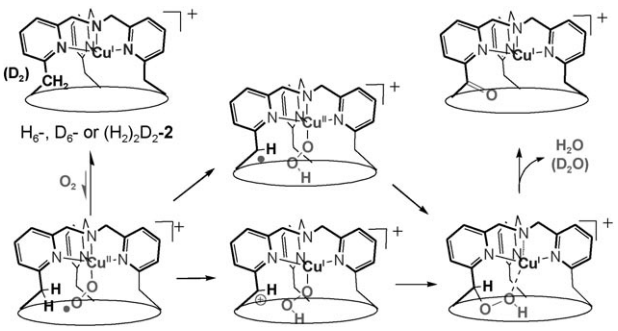


Figure 2. a,b) Infrared spectra of **2** before and after exposure to air: a) ν_{CO} band of the CO adduct of cuprous complex **2** before (dashed line) and after (solid line) exposure to O_2 in the solid state (the samples were dissolved in CH_2Cl_2 into which CO was bubbled); b) vibration frequency shift in the C=O region of **2**: before oxidation (solid line), after oxidation under $^{16}O_2$ (dashed line), after oxidation under $^{18}O_2$ (dotted line). c) ESI-MS spectrum of $[D_2(H_2)_2]$-**2** exposed as a solid to atmospheric dioxygen for 9 days.

conformation owing to the lack of guest ligand. The chemical shifts of the protons belonging to the tmpa cap were also more downfield, which indicates a slightly more Lewis acidic metal center. Addition of MeCN to complex **2** led to the appearance of the $MeCN_{in}$ peak together with a change of the calixarene signature, which became identical to that of complex **1**. More interestingly, when CO was bubbled into a solution of complex **2** in $CDCl_3$ free of MeCN, a change of the NMR signature and an IR stretch at 2103 cm^{-1} were observed, attesting to the coordination of CO to the cuprous center. The presence of one molar equivalent of MeCN completely inhibited CO binding. The value of the stretching vibration (12 cm^{-1} higher than that reported for the non-calixarene based tmpa cuprous analogue) indicates a moderately electron-rich center, similar to those in $[Cu(calix[6]trisimidazole)(CO)]^+$ complexes (2092–2102 cm^{-1}), but significantly less than that in $[Cu(calix[6]tren)(CO)]^+$ (2075 cm^{-1}).

Neither complex **1** nor complex **2** showed any reactivity toward dioxygen in $CDCl_3$, CD_2Cl_2, or CD_3CN for more than a week, as checked by proton NMR spectroscopy. In the solid state, however, they behaved very differently. Solid complex **1** was stable in air for months. In contrast, we discovered that complex **2**, although remaining colorless and EPR silent, had undergone structural changes after 8 h of exposure to air. Indeed, bubbling CO into a solution of the air-exposed (in the solid state) complex **2** in CH_2Cl_2 led to the appearance of a new ν_{CO} absorption band shifted 17 cm^{-1} to higher energy relative to that exhibited by the complex kept in the glove box (Figure 2). ^{1}H NMR analyses of the solid sample dissolved in $CDCl_3$ revealed a change of the initial C_{3v} signature into a more complicated one with a number of additional resonances. Addition of a few molar equivalents of CH_3CN to the NMR tube led to the appearance of two high-field-shifted resonances: one at $\delta = -1.02$ ppm that corresponds to the intact complex with $MeCN_{in}$ bound to the cuprous ion, the other at $\delta = -0.97$ ppm attesting to the formation of a new cuprous species that remained capable of binding MeCN inside the calixarene cavity. Integration of the peaks showed a conversion of approximately 40%. Finally, ESI-MS analyses showed two new sets of peaks, one at m/z 1417.7 and the other at 1457.8 corresponding to $[M+Cu+14]$ and $[M+Cu+MeCN+14]$, respectively (confirmed by MS–MS). The ratio of these +14 products relative to the intact material confirmed the approximate 40% conversion. When solid complex **2** was submitted to an atmosphere of $^{18}O_2$, increments of 2 mass units were observed by ESI-MS for both products ($[M+Cu+16]$ and $[M+Cu+MeCN+16]$), relative to the complex treated in air or with $^{16}O_2$. The isotope pattern was, in each case, consistent with the insertion of one O atom and the removal of two H atoms, and no appreciable trace of $[M+Cu+O]$ compound. IR spectroscopic analyses of the oxygenated products revealed a new stretching band at 1738 cm^{-1} that was shifted to 1708 cm^{-1} for the complex treated with $^{18}O_2$ (calculated value: $\tilde{\nu}(^{18}OC) = 1692$ cm^{-1}). Altogether, these data indicate the formation of a new C=O bond by a sequence of oxygenation/dehydrogenation (+O−2H) of a CH_2 moiety belonging to the calix[6]tmpa ligand.

Considering that the value of the CO stretch fits very well with the formation of an ester function, we suspected the site of attack by dioxygen to be one of the methylene linkages that seal the calixarene core to the tmpa cap. To confirm this proposal through isotope labeling, the hexadeuterated ligand $[D_6]$calix[6]tmpa was synthesized, for which all three CH_2 groups were replaced by CD_2 (Scheme 2). The corresponding cuprous triflate complex indeed led, after reaction in air in the solid state, to oxygenated products with mass increments of +16−4 (instead of +16−2 for the protiated complex), which



Scheme 2. Possible pathways for the oxygenation of complex **2** in the solid state.

demonstrates that the oxygen atom insertion into the ligand is associated with the removal of two deuterium atoms.

Very interesting results stemmed from competitive oxygenation of both ligands. Indeed, a special sample of complex **2** was synthesized with an approximately 1:1 mixture of protiated and hexadeuterated ligands and then left in air as a finely ground colorless solid. Samples were analyzed by ESI-MS to evaluate the kinetic isotope effect (KIE) possibly associated with the oxygenation process. The kinetic data did not show an exponential increase of the oxygenated product as expected for a pseudo-first-order process. Rather, it exhibited a parabolic dependence over time, thus providing evidence of diffusion-controlled processes for both compounds (Fick's law). However, the hexadeuterated compound $[D_6]$-**2** reacted much more slowly than the protiated one (KIE extrapolated at the origin = 6.4(1.0)). Assuming that the oxygenation process follows a mixed kinetic law leading to a masked KIE, we synthesized a ligand combining two CH_2 arms with one CD_2 arm to obtain the intramolecular KIE. The Cu^I complex $[D_2(H_2)_2]$-**2** based on this ligand was then treated with O_2 in the solid state at room temperature. The ESI-MS pattern of the corresponding oxygenated complex is shown in Figure 2. From these data, an estimated intramolecular KIE of 21 was obtained.[18] Such a high value denotes a nonclassical KIE and possible hydrogen tunneling.[19] Accordingly, measurements at 277 and 313 K also led to high KIE values, 29 and 15, respectively. An Arrhenius plot indicated a difference of the apparent activation energies $\Delta E_a = 14\ kJ\,mol^{-1}$ exceeding the zero point energy difference of the C–H and C–D bonds (ca. 5 $kJ\,mol^{-1}$) and a ratio of the preexponential factors $A_H/A_D = 0.06$, which is lower than the normal value of 0.6.[20]

Considering that 1) the reaction occurs in the solid state, 2) the presence of $MeCN_{in}$ completely inhibits the oxidative process, 3) when a mixture of ligand and complex **2** was subjected to O_2 in the solid state, the ESI-MS analyses revealed that only the Cu complex had incorporated an O atom, with no trace of oxygenated free ligand, 4) no Cu^{II} is accumulated upon reaction of **2** with O_2, and 5) a single oxygenated product is detected at a temperature up to 40 °C,[21] we deduce that the oxidation is a metal-centered process and does not involve radical diffusion chemistry. We thus propose the transient formation of a mononuclear $[CuO_2]^+$ adduct (presumed to be a Cu^{II} superoxide complex)[22] as a first intermediate in the course of the oxidative process, although we have not been able to detect any intermediate. In solution, the equilibrium leading to its formation remains largely displaced in favor of the starting material, which is in agreement with literature data related to classical tmpa-based copper chemistry.[23] In the solid state, which facilitates the contact of Cu^I with O_2, it reacts with the close CH_2 group of the ligand leading, ultimately, to a four-electron process with the formation of a C=O moiety and no detectable alcohol. The fact that, quite remarkably and in contrast to the calix[6]tren case,[14c] Cu remains cuprous in the final product and that a single oxygenated product[21] is formed upon reaction of **2** with O_2 can be explained by the electron-withdrawing effect of the newly formed C=O moiety that decreases the electron density at the Cu^I center, hence disfavoring further O_2 activation.

A possible mechanism (Scheme 2) relies on the intramolecular two-electron oxidation of the proximal C–H bond by the mononuclear $[CuO_2]^+$ center (either through a radical pathway or through direct hydride abstraction),[13b] followed by the fast intramolecular evolution of the resulting alkylhydroperoxide[24] toward the formation of the keto product with release of H_2O.[25] Kinetics have indicated that C–H bond cleavage is a relatively fast process, hence suggesting that the $[CuO_2]^+$ intermediate is quite reactive.

In conclusion, this study describes a unique case of oxygenation in the solid state of an organic moiety (a CH_2 group) by O_2 mediated by a single Cu^I center. The reaction is chemo- and regioselective, giving a keto product. This selectivity attests to a metal-centered four-electron oxidation reaction, a process that has been scarcely reported with other model complexes.[26] The reaction displays a nonclassical intrinsic KIE value of 21 at room temperature, which is by far the highest value ever recorded for a monocopper reactive center.[19] Interestingly, in the natural systems DβH and PHM, unusually high KIE values have also been reported (10.9 at 35 °C and 10.6 at 37 °C, respectively, values that might actually be underestimated),[5] thereby suggesting tunneling as well.[27] It is also important to note that in the herein reported reaction, Cu^I activates O_2 but remains in the same oxidation state in the final product, which is, to our knowledge, the first case of its kind. It shows that if the oxidation were to be not directed toward the ligand itself but toward an exogenous substrate, it could act catalytically. Finally, this case study unambiguously shows that O_2 interaction at an isolated Cu^I ion can give rise to a species reactive enough to break a C–H bond, at least in substrates activated by a heteroatom or a π system in the α position. Most importantly, it also shows that a single Cu^I center in interaction with O_2 can mediate an even-electron transfer process without the assistance of a redox cofactor, which is a key point for the development of a catalytic process devoted to the oxidation of organic substrates. We are actively working on the design of new experiments and new complexes to identify the detailed mechanism and direct the oxidizing power of the system toward guest substrates.

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