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Dimethylanilinic *N*-Oxides and Their Oxygen Surrogacy Role in the Formation of a Putative High-Valent Copper−Oxygen Species

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Supporting Information

ABSTRACT: The reaction of *p*-cyano-*N*,*N*-dimethylaniline *N*-oxide, an O-atom donor, with different copper(I) complexes (at room temperature and in acetone) indicates the formation via O-atom transfer of a high-valent copper oxyl species, $Cu^{II}-O^{\bullet}$, a putative key intermediate in the catalytic cycle of copper-containing monooxygenases. The formation of *p*-cyano-*N*-hydroxymethyl-*N*-methylaniline and *p*-cyano-*N*-methylaniline as the main products of the reaction highlight the capability of this species to hydroxylate strong C−H bonds (bond dissociation energy ∼ 90 kcal/mol). A plausible mechanism for the reactivity of this catalytic system is proposed.

High-valent copper−oxygen intermediates, such as a copper oxyl ($Cu^{II}-O^{\bullet}$), have been considered to be a potentially powerful oxidant in the catalytic mechanism of copper-containing monooxygenases.[1] Reaction barriers for substrate hydroxylation [through H-atom abstraction (HAA)] have been predicted, and they are significantly lower for $Cu^{II}-O^{\bullet}$ than other intermediates like $Cu^{II}-O_2^{\bullet-}$ (copper superoxo) or $Cu^{II}-OOH$ (copper hydroperoxo) species. Recent works from Marletta et al.[2] and Walton and co-workers[3] evaluate the role of a hydrogen-bonding network in the second coordination sphere of lytic polysaccharide monooxygenase (LPMO) enzymes, which supports, in different ways, the formation of $Cu^{II}-O^{\bullet}$ species as relevant intermediates in the substrate hydroxylation mechanism.

A triplet state copper(II) oxyl, with this description being the best fitting for the species at this oxidation state level based on theoretical−computational analyses,[4] has also recently become a relevant intermediate for the catalytic mechanism of particulate methane monooxygenase (pMMO), based on studies that support the mononuclear nature of the copper active site of this enzyme.[5] Both pMMO and LPMOs need a very reactive copper−oxygen species, able to activate the strong C−H bond of their substrates [bond dissociation energy (BDE) = 101.1 and 103.8 kcal/mol for C1 and C4, respectively, in the polysaccharide substrate[1f,6] and 104 kcal/mol for methane], and a $Cu^{II}-O^{\bullet}$ intermediate is a good candidate (Figure 1).

Nevertheless, despite its proposition, the copper oxyl species has not been observed experimentally in solution, neither in synthetic models nor in enzymes. $Cu^{II}-O^{\bullet}$ species have been observed just in the gas phase, where they have been shown to be able to attack the strong C−H bonds in methane.[8] In

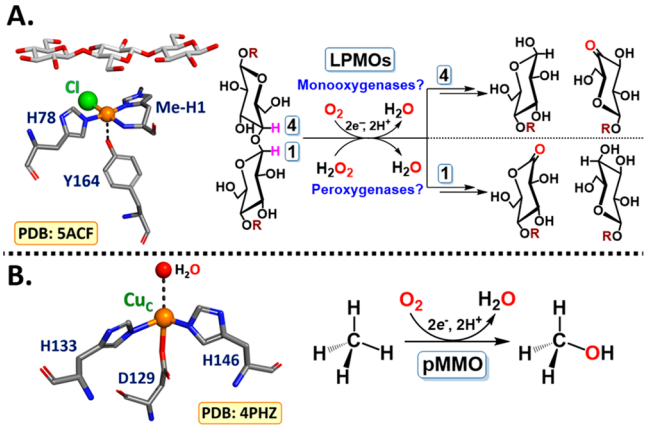

Figure 1. (A) LPMO active site. The general reaction considers the two possible cosubstrates of the enzyme, O_2 and H_2O_2.[7] (B) pMMO Cu_C site and general reaction. The Cu_C site was recently considered as the site where O_2 binding/activation and methane oxidation occur.[5b]

synthetic model systems, there have been several hints that point toward the existence of $Cu^{II}-O^{\bullet}$ species.[8,9] However, the closest reported species to copper oxyl in biomimetic systems is what might be referred to as its conjugate acid, $Cu^{III}-OH$, which has been studied and characterized by Tolman and co-workers,[10] and it has been shown to be able to attack substrates with enthalpies ranging from 76 kcal/mol (e.g., 9,10-dihydroanthracene) to 99 kcal/mol (e.g., cyclohexane).

Because of the complicated mechanism required to generate high-valent metal oxo intermediates starting with O_2, which involves multiple steps including proton and electron transfer, alternative sources of oxygen have been used to bypass the full pathway.[11] These oxygen surrogate compounds include, among others, iodosobenzene, cumene hydroperoxide, and *N*,*N*-dimethylaniline *N*-oxides (DMAOs), and the pathway that could be utilized would be an *O-atom shunt* (Figure 2), related to the "peroxide-shunt" well-known in cytochrome P-450 monooxygenase (bio)chemistry. Indeed, some amino *N*-oxide compounds have shown reactivity with $Cu^{I/II}$ salts in olefin epoxidation reactions,[12] iminium ion formation,[13] and substrate hydroxylation,[14] and $Cu^{II}-O^{\bullet}$ species have been proposed as the reactive species in each of these reactions.

We have been inspired to examine new oxygen surrogate chemistry with Cu ion, in part because of a report by Roberts

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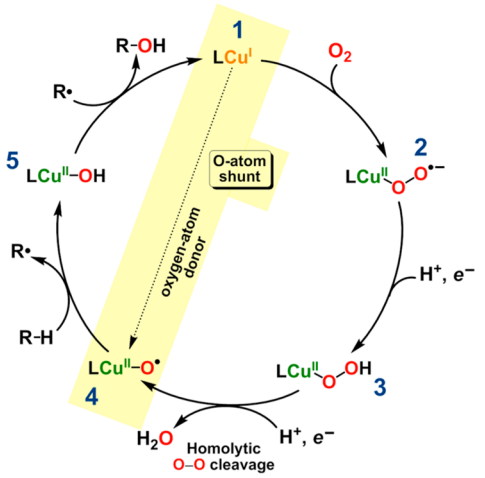

Figure 2. Representation of one of the proposed mechanisms for copper-containing monooxygenases, having a copper oxyl as the reactive species responsible for the substrate hydroxylation. The *O-atom shunt* from species **1**–**4** (Cu^{II}–O$^•$) is highlighted in yellow.

and Jones,[11e] where tertiary anilinic *N*-oxides were used to directly generate a P450-mediated oxidant capable of HAA N-dealkylation of the *N*,*N*-dimethylaniline (DMA) derived from oxygen donation. Thus, in the present work, the reactivity of a series of copper(I) complexes and DMAOs as oxygen surrogates (Figure 3) was tested at room temperature in

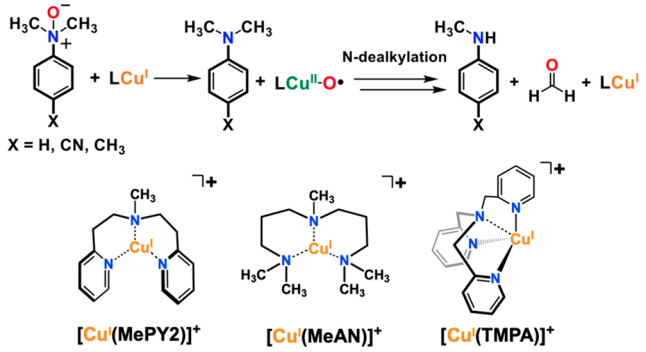

Figure 3. (Top) General reaction scheme proposed for the N-dealkylation reactions carried out by a putative (L)Cu^{II}–O$^•$ species, generated by O-atom transfer from dimethylanilinic *N*-oxides to a series of copper(I) complexes (bottom).

acetone-d_6, using varying [Cu^{I}(L)]$^+$/DMAO ratios (1:1, 1:2, 1:5, and 1:10; [Cu] = 1.5 mM and [*N*-oxide] = 1.5, 3, 7.5, and 15 mM, respectively). The reactions were monitored by ^{1}H NMR spectroscopy under anaerobic conditions, and it was possible to observe, along with the consumption of DMAOs, the formation of DMAs as substrates, followed by the hydroxylation of DMAs (~C–H BDEs are 90 kcal/mol[15]) and the subsequent N-dealkylation step, thereby obtaining the *N*-methylaniline compound plus aldehyde. These results, along with trapping experiments using excess substituted phenols, point toward the formation of a copper(II) oxyl intermediate.

Independent reactions of [Cu^{I}(MePY2)][B(C$_6$F$_5$)$_4$] with three different *N*-oxides, viz., DMAO, *p*-methyl-*N*,*N*-dimethylaniline *N*-oxide (MDMAO), and *p*-cyano-*N*,*N*-dimethylaniline *N*-oxide (CDMAO), were tested in N-dealkylation reactions, where the ratio of copper(I) complex/*N*-oxide equaled 1:10 ([Cu] = 1.5 mM; [*N*-oxide] = 15 mM). ^{1}H-NMR spectra were taken over time until *N*-oxide was fully consumed. The results, shown in Figure S2, lead to two noteworthy conclusions: (1) the copper(I) complex reaction with *N*-oxides is catalytic with respect to the metal compound; (2) the measurable difference in the reaction rate observed among the different *N*-oxides (Figure S2) is in line with literature precedents that have proposed that O-atom transfer to the metal-ion complex was the rate-limiting step of the reaction.[11d,e] The O-atom transfer is easier for DMAs which are electron-poor based on the time course observed; CDMAO is the *N*-oxide most efficient in transferring its O atom.[16]

The reaction of [Cu^{I}(MePY2)][B(C$_6$F$_5$)$_4$] (Figure 3) with CDMAO was thus studied in greatest detail, as shown in Figure 4. Here, the time course for oxygenation/oxidation of *p*-

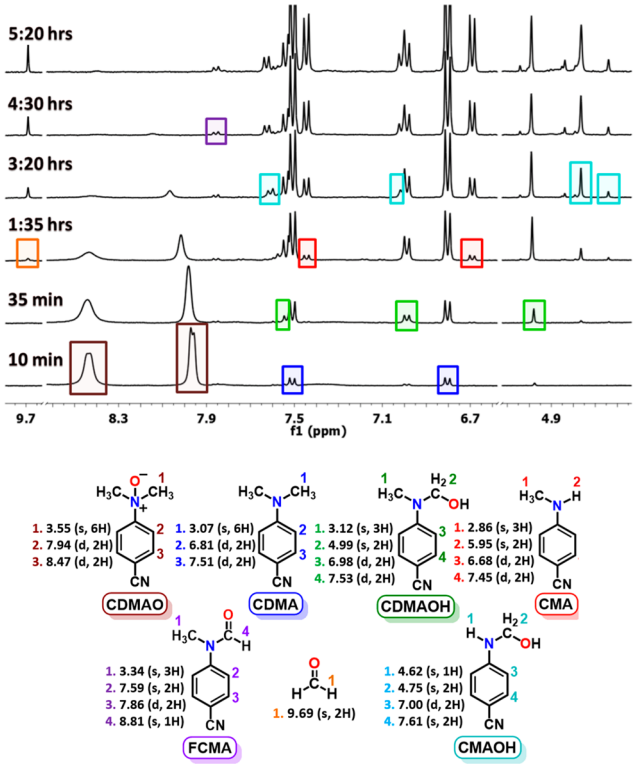

Figure 4. (Top) ^{1}H NMR spectrum (aromatic region mainly) during the reaction of [Cu^{I}(MePY2)][B(C$_6$F$_5$)$_4$] with CDMAO at 298 K in acetone-d_6 ([Cu] = 1.5 mM; [*N*-oxide] = 15 mM). (Bottom) ^{1}H NMR assignment for each identified species.

cyano-*N*,*N*-dimethylaniline (CDMA) is followed in the aromatic region of the ^{1}H NMR spectra. Consumption of CDMAO (highlighted in brown) is observed over time, along with the formation of CDMA (in blue). From this point, the products derived from the oxidation of CDMA are observed (Figures S3 and S5), allowing us to obtain mechanistic information about the oxidative reaction pathways. The first product (highlighted in green) was characterized by ^{1}H NMR and ^{1}H–^{1}H COSY NMR spectroscopies and electrospray ionization mass spectrometry (Figures S10 and S11) as *p*-cyano-*N*-hydroxymethyl-*N*-methylaniline (CDMAOH), a carbinolamine species produced by a hydroxylation reaction, a key species in the catalytic mechanism. After that and as a result of the decomposition of CDMAOH, *p*-cyano-*N*-methylaniline (CMA; in red) and formaldehyde (in a complementary manner; in orange) are formed. The presence of CH$_2$=O

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was also determined via spectrophotometric detection using the Nash test (Figure S13).[17] To a small extent, further oxidation of CMA occurs, leading to the formation *p*-cyano-*N*-hydroxymethylaniline (CMAOH; in cyan) and oxidation of CDMAOH in the formation of *N*-formyl-*p*-cyano-*N*-methylaniline (FCMA; in purple); these latter products were detected by ^{1}H NMR and ^{1}H−^{1}H COSY NMR spectroscopies. The formation of *p*-cyanoaniline (CA; as a possible downstream most highly oxidized product) was not observed in these $[Cu^I(L)]^+$/CDMAO systems, unlike for the chemistry of *p*-cyanoanilinic *N*-oxide with heme iron compound I like or other metal oxo systems.[11b,18] The same reaction was carried out with other Cu(I) complexes (see Table S1).

Control experiments were performed[19] in order to rule out the involvement of certain side reactions. The reactivity of a copper(I) precursor, $[Cu^I(CH_3CN)_4]^+$, with CDMAO surprisingly showed reactivity similar to the system with MePY2. Yields of oxidized products were higher; however, the reactions were quite slow (Table S1). It is difficult to establish a correlation among the $[Cu^I(L)]^+$/CDMAO systems based on the reaction rates, yields, and measured Cu^{II}/Cu^I reduction potentials for the copper complexes. However, it seems that copper systems with higher redox potentials lead to higher reaction yields, i.e., a much greater consumption of the *N*-oxide CDMAO, leading to greater amounts of oxidized CDMA (Table S1). In fact, it is well established that the tridentate chelates MePY2 and MeAN possess $[Cu(L)]^{2+/+}$ reduction potentials which are much more positive than those found for $[Cu(TMPA)]^{2+/+}$ or with TMPA derivatives.[1e] Also, in the present study, we found that $[Cu^I(MePY2)]^+$ was by far the most efficient catalyst; also the overall material balance was excellent (Table S1). It is relevant to mention recent reports where LPMO-inspired copper complex model systems, also bearing tridentate ligands with one central alkylamino (as in MePY2) and two N-heterocyclic donor groups (e.g., imidazolylpyridyl[20a] or benzimidazolyl[20b]), were shown to possess promising reactivity toward strong C−H bonds.

Considering the products formed during the CDMA oxidation reaction, and the sequence in which they are generated during the catalytic cycle (Figures 4 and S4 and S6), a catalytic mechanism is proposed (Figure 5), where the transfer of the O atom is the rate-determining step, and a LCu^{II}−$O^\bullet$ species is the active oxidant that is able to react with

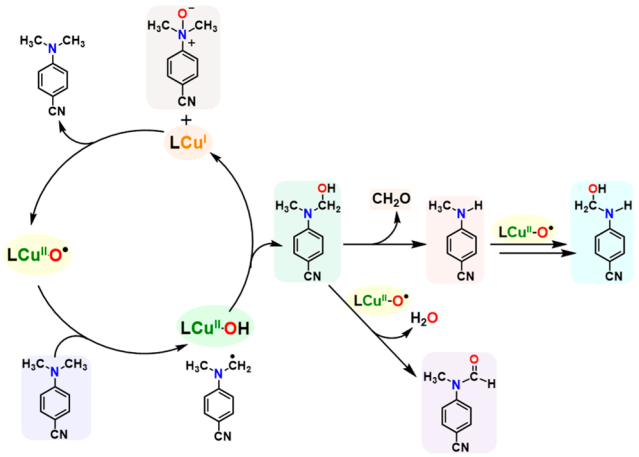

Figure 5. Proposed catalytic mechanism for the reaction between $[Cu^I(MePY2)][B(C_6F_5)_4]$ and CDMAO (ratio 1:10).

the strong C−H bond of the methyl group in DMAs (~90 kcal/mol). A rebound step, formally a hydroxyl-radical transfer from LCu^{II}−OH complex species produced by the initial HAA of the substrate by the copper(II) oxyl, completes the cycle. Further experiments to probe the possibility of an initial electron-transfer oxidation mechanism for N-dealkylation[21] are being pursued but are beyond the scope of this report.

Trapping experiments were performed in order to show that oxidation of CDMA is generated directly by a copper−oxygen oxidant, ruling out in this way that oxidation products of CDMA might arise upon direct transformation within an initial CDMAO−Cu^I(L) adduct, likely forming upon the initial interaction of CDMAO with the cuprous complex.[22] For the system with 2,4-di-*tert*-butylphenol (DTB-ArOH), 2 equiv of 2,4-di-*tert*-butylphenoxy radical (DTB-ArO$^\bullet$) are formed for each 1 equiv of CDMAO that is consumed; CDMA oxidation is inhibited in favor of the much "easier" DTB-ArOH substrate, drastically so when large excesses of DTB-ArOH are employed (Table S2). These radicals, which are generated from the reaction of DTB-ArOH with the putative LCu^{II}−$O^\bullet$ species and then with the LCu^{II}−OH compound produced (Figures 5 and 6), lead to the well-known radical-coupling step, forming 1

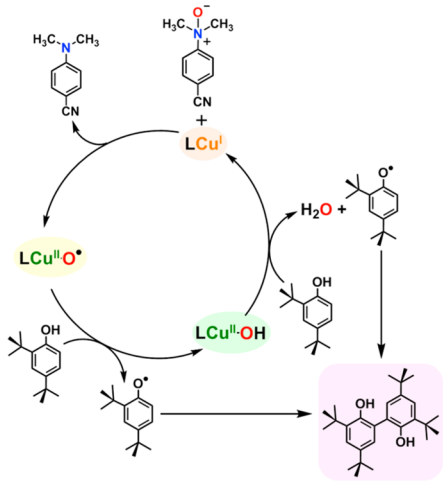

Figure 6. Proposed catalytic mechanism for the trapping experiment with DTB-ArOH for the $[Cu^I(L)]^+$/CDMAO system.

equiv of 3,3′,5,5′-tetra-*tert*-butylbiphenyl-2,2′-diol (Figures 6 and S14). This mechanism is in agreement with other reported trapping experiment reactions well-known for metal oxo species, where the same phenol is used.[23] Note that DTB-ArOH is not oxidized by aniline *N*-oxides in the absence of $[Cu^I(MePY2)]^+$ (see also the Supporting Information).

Trapping experiments with 2,4,6-tri-*tert*-butylphenol (TTB-ArOH) also show inhibition in the oxidation of CDMA.[19] However, the most relevant observation is that the phenolic products for the systems $[Cu^I(MeAN)]^+$/CDMAO/DTB-ArOH[19] and $[Cu^I(MePY2)]^+$/CDMAO/TTB-ArOH[19] are different from what can be obtained when O_2 was used as the oxidant, in the systems $[Cu^I(MeAN)]^+/O_2$/DTB-ArOH[24] and $[Cu^I(MePY2)]^+/O_2$/TTB-ArOH.[19] This reinforces the supposition that a different copper−oxygen intermediate (we propose it to be LCu^{II}−$O^\bullet$) is generated in the pathway that uses the O-atom donor instead of O_2.

In conclusion, we suggest the formation of a highly reactive copper(II) oxyl species upon O-atom transfer from the O-atom donor to the reduced LCu^I complex. The cupryl species forms

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slowly and performs strong C−H oxidation reactions, which could potentially shed light on the involvement of such high-valent reactive species in the catalytic cycle of copper monooxygenases. Further research involving the effects of the coordination environment and geometry of the LCu^{I} systems on the oxidation rates and product yields is ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.inorgchem.9b02066.

Synthetic and analytical details (methodologies, ^{1}H NMR, and UV−vis spectra) (PDF)

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Notes

The authors declare no competing financial interest.

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