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Copper/TEMPO Redox Redux: Analysis of PCET Oxidation of TEMPOH by Copper(II) and the Reaction of TEMPO with Copper(I)

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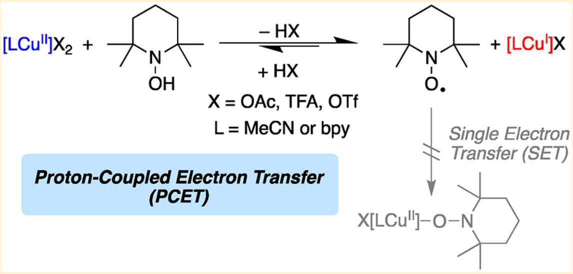
Supporting Information

ABSTRACT: Copper salts and organic aminoxyls, such as TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl), are versatile catalysts for aerobic alcohol oxidation. Previous reports in the literature contain conflicting proposals concerning the redox interactions that take place between copper(I) and copper(II) salts with the aminoxyl and hydroxylamine species, TEMPO and TEMPOH, respectively. Here, we reinvestigate these reactions in an effort to resolve the conflicting claims in the literature. Under anaerobic conditions, $Cu^{II}X_2$ salts [X = acetate (OAc), trifluoroacetate (TFA), and triflate (OTf)] are shown to promote the rapid proton-coupled oxidation of TEMPOH to TEMPO: $Cu^{II}X_2$ + TEMPOH → $Cu^{I}X$ + TEMPO + HX. In the reaction with acetate, however, slow reoxidation of $Cu^{I}OAc$ occurs. This process requires both TEMPO and HOAc and coincides with the reduction of TEMPO to 2,2,6,6-tetramethylpiperidine. Analogous reactivity is not observed with trifluoroacetate and triflate species. Overall, the facility of the proton-coupled oxidation of TEMPOH by Cu^{II} salts suggests that this process could contribute to catalyst regeneration under aerobic oxidation conditions.

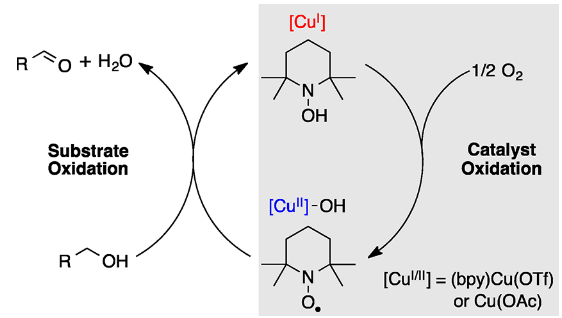


■ INTRODUCTION

Combinations of a copper salt and organic aminoxyl, such as TEMPO (2,2,6,6-tetramethylpiperidine *N*-oxyl), represent some of the most effective catalyst systems for the aerobic oxidation of alcohols.[1−11] The most widely used catalysts feature 2,2′-bipyridine (bpy) as the ancillary ligand. The alcohol oxidation reactions often proceed at room temperature with ambient air as the oxidant, undergo the chemoselective oxidation of primary alcohols in the presence of secondary alcohols,[7,8] tolerate diverse functional groups including sulfides and amines,[7−11] and have been applied to process scale applications in the pharmaceutical industry.[12−14] Mechanistic studies have shown that Cu^{II} and aminoxyl engage in a cooperative mechanism in which the two one-electron oxidants promote the efficient two-electron oxidation of the substrate.[15−22] Following alcohol oxidation, the reduced catalyst system is regenerated by O_2, completing the overall catalytic cycle depicted in Scheme 1.

Many details of the catalyst oxidation half-reaction are not well understood. Reactions between O_2 and nitrogen-ligated copper complexes have been the subject of extensive fundamental study.[23−27] Reactive Cu/O_2 species, including superoxo, peroxo, and oxo species, are often invoked in hydrogen-atom transfer (HAT) reactions, and HAT from weak O−H bonds, such as those in TEMPOH and phenols, has been demonstrated in several fundamental studies of reactive Cu/O_2 species.[28−31] These precedents prompted us to propose that analogous reactivity could be involved in the catalyst reoxidation half-reaction of Cu/aminoxyl-catalyzed aerobic alcohol oxidations.[8] In a complementary effort, we demonstrated electrochemical alcohol oxidation with a (bpy)Cu/TEMPO catalyst system,[21] and the data from this study implicated a mechanism in which Cu^{II} mediates the oxidation of TEMPOH to TEMPO under anaerobic conditions. In both the aerobic and anaerobic mechanisms, oxidation of the hydroxylamine to an *N*-oxyl radical is proposed to proceed with the reduction of Cu^{II} to Cu^{I} (Figure 1A).

Scheme 1. Simplified Mechanism for Cu/TEMPO-Catalyzed Alcohol Oxidation



Sheldon and co-workers have separately reported that TEMPO reacts with $Cu^{I}OAc$ in acetonitrile to generate a Cu^{II}-TEMPO complex (i.e., with a $TEMPO^{-}$ ligand), as evident from the appearance of a 670 nm band in the UV−visible spectrum of the reaction mixture (Figure 1B).[15] The oxidation of Cu^{I} by TEMPO has been invoked as a mechanism

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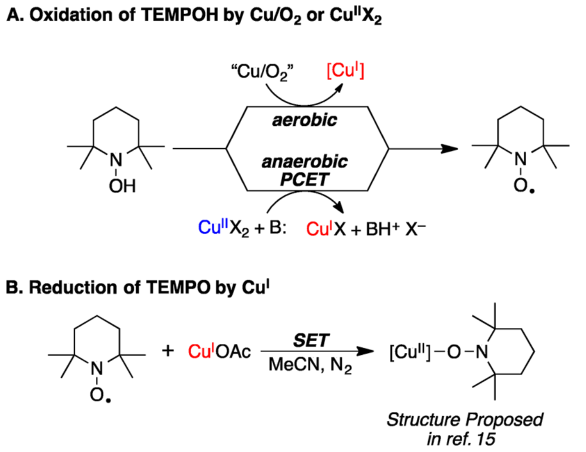

Figure 1. Previously proposed reactions between Cu and TEMPO(H), including (A) the oxidation of TEMPOH by Cu/O_2 or $Cu^{II}X_2$ and (B) the reduction of TEMPO by Cu^I.

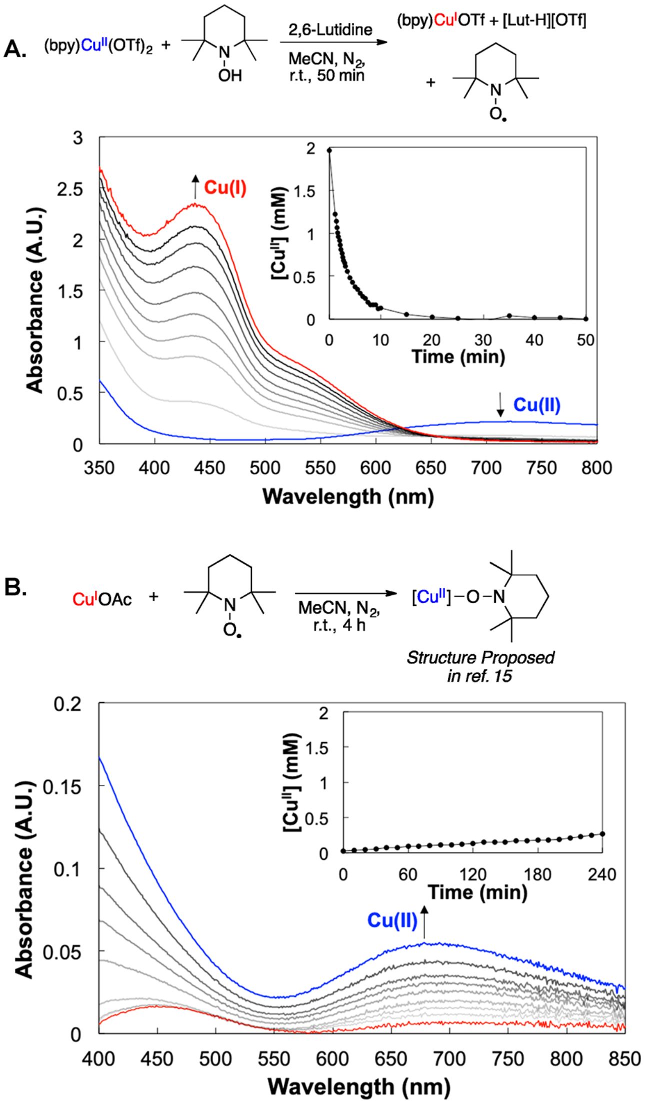

Figure 2. UV−visible analysis of reactions between copper(I/II) salts and TEMPO(H) species. (A) Oxidation of TEMPOH by $(bpy)Cu^{II}(OTf)_2$ under anaerobic conditions, replicating conditions reported by Badalyan et al.[21] Conditions: 2 mM TEMPOH, 2 mM $Cu^{II}OTf_2$, 2 mM 2,2′-bipyridine, 100 mM 2,6-lutidine, MeCN, 273 K, and 50 min. (B) Oxidation of Cu^IOAc by TEMPO, replicating conditions reported by Dijksman et al.[15] Conditions: 2 mM TEMPO, 2 mM Cu^IOAc, MeCN, 273 K, 4 h. The Cu^{II} concentration was obtained by constructing a UV−visible calibration curve of $Cu^{II}OAc_2$ in MeCN at 670 nm.

for catalyst reoxidation in several studies of catalytic aerobic alcohol oxidation.[6,15,32] Although several well-defined Cu^{II}-aminoxyl complexes have been reported in the literature, all of these precedents formally correspond to Cu^{II} complexes bearing an aminoxyl rather than an aminoxide (e.g., $TEMPO^-$) ligand.[33−35] Nonetheless, the reaction in Figure 1B provides an alternative mechanism for Cu^I oxidation in the catalytic reactions.

The reactions presented in Figure 1A,B are not directly the microscopic reverse of each other, but they nevertheless appear to be contradictory. Here, we report a study of reactions between copper(I/II) salts and TEMPO(H) in an effort to resolve this apparent contradiction. We show that a series of $Cu^{II}X_2$ salts (X = OAc, TFA, OTf) mediate the efficient proton-coupled oxidation of TEMPOH to afford Cu^IX, TEMPO, and HX. We also observe the oxidation of Cu^I in the presence of TEMPO; however, this reactivity is observed with Cu^IOAc but not with Cu^ITFA or Cu^IOTf sources. In addition, this reaction requires the presence of AcOH, it exhibits slow rates, and it occurs with cleavage of the N−O bond in TEMPO, generating 2,2,6,6-tetramethylpiperidine as a byproduct. Electrochemical and spectroscopic studies of different Cu salts and TEMPO/TEMPOH under similar reaction conditions provide a foundation for understanding these results, all of which suggest that the simple one-electron oxidation of Cu^I by TEMPO is not a favorable reaction and does not contribute to catalytic alcohol oxidation reactions.

■ RESULTS AND DISCUSSION

Reproduction of Previous Results That Appear To Be Contradictory. We began our study by revisiting the reactions between copper(I/II) salts and TEMPO(H) species that were reported previously by us[21] and by Sheldon and co-workers[15] (Figure 2). The reaction conditions and reagents are somewhat different in the two studies; however, the original conditions were retained in order to enable direct assessment of the results. The first experiment probed the stoichiometric reaction of $(bpy)Cu^{II}(OTf)_2$ with TEMPOH and 2,6-lutidine in MeCN under N_2 by UV−visible spectroscopy (Figure 2A). The addition of TEMPOH led to the rapid reduction of Cu^{II} to Cu^I, as evident from the disappearance of the Cu^{II} absorption band at 720 nm and the appearance of a strong absorption feature at 440 nm, attributed to bpy-ligated Cu^IOTf. The second experiment probed the reaction of TEMPO with Cu^IOAc in MeCN (Figure 2B; no bpy ligand was included in this reaction in order to match the originally reported conditions[15]). A new absorption feature at 670 nm emerged slowly over the course of 4 h, consistent with the formation of Cu^{II} under these reaction conditions. The λ_{max} observed in this spectrum matches that of $Cu^{II}OAc_2$ in MeCN, suggesting that the Cu^{II} product may not correspond to the original proposed $[Cu^{II}{-}ONR_2]$ adduct (further discussion below).[36] These observations validate the previously reported observations.

Assessment of Reactions between Copper(I/II) Salts and TEMPO(H) Species under Uniform Conditions. The different reagents in the two reactions, including the presence/

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absence of bpy as a neutral ligand, the presence/absence of base, and the use of OAc/OTf as an anionic ligand, could influence the reaction outcome. We therefore tested the reaction of TEMPOH with three different $Cu^{II}X_2$ sources (X = OAc, TFA, and OTf) in the absence of bpy and base (Figure 3). The reactions proceed rapidly in all cases and lead to a reduction of Cu^{II}, as evident by the disappearance of the absorption band between 670 and 760 nm. No further reaction is apparent following the oxidation of TEMPOH by $Cu^{II}TFA_2$ and $Cu^{II}OTf_2$; however, the reduction of $Cu^{II}OAc_2$ to $Cu^{I}OAc$ by TEMPOH is followed by a slow reappearance of Cu^{II}, as evident by the reappearance of the broad absorption feature at 670 nm. The latter result notwithstanding, these data show that TEMPOH undergoes rapid oxidation by $Cu^{II}X_2$ salts, even in the absence of the 2,2′-bipyridine and 2,6-lutidine additives present in Figure 3A.

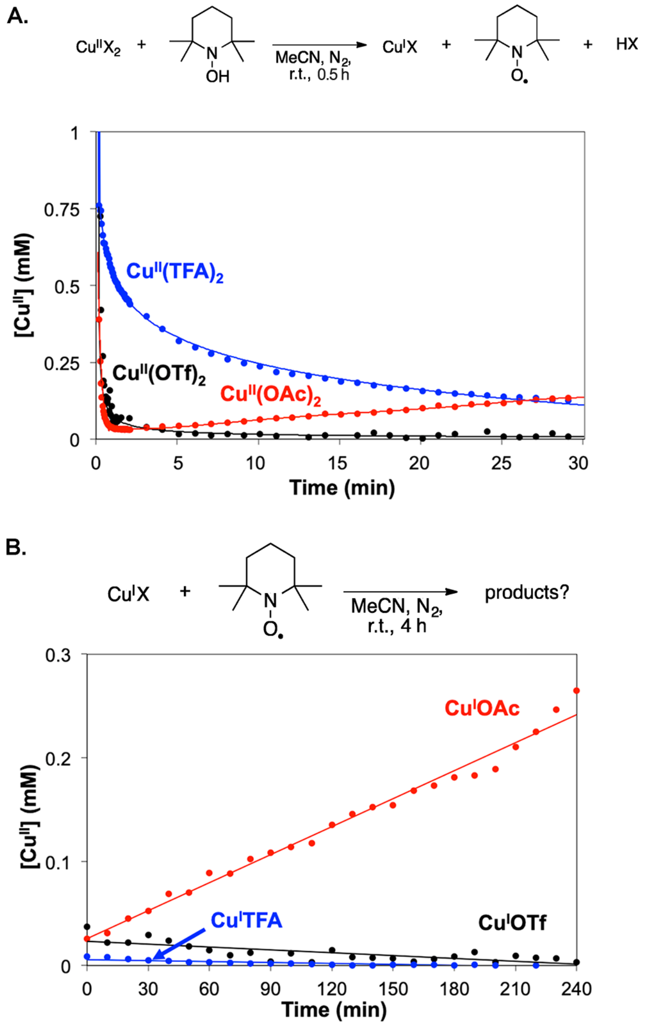

Figure 3. Analysis of reactions between copper(I/II) salts and TEMPO(H) species with different anions (X = OAc, TFA, OTf). (A) Reduction of $Cu^{II}X_2$ species observed upon addition of TEMPOH. Single-wavelength data obtained at 670 nm (OAc, red), 715 (TFA, blue), and 760 (OTf, black). Conditions: 2 mM TEMPOH, 2 mM $Cu^{II}X_2$, MeCN, 273 K, 0.5 h. For second-order fits to the kinetic data and estimated rate constants, see Figure S5 in the Supporting Information. (B) Optical changes observed at 670, 715, and 760 nm upon addition of TEMPO to solutions of $Cu^{I}OAc$, $Cu^{I}TFA$, and $Cu^{I}OTf$, respectively, in MeCN. Oxidation to Cu^{II} is observed only with $Cu^{I}OAc$. Conditions: 2 mM TEMPO, 2 mM $Cu^{I}X$, MeCN, 273 K, 4 h. Cu^{II} concentrations in panels A and B were obtained by constructing UV−visible calibration curves of the corresponding $Cu^{II}X_2$ salts in MeCN at their respective λ_{max}. Lines reflect smooth fits of the data simply to guide the eye.

The slow regeneration of Cu^{II} in the reaction of TEMPOH with $Cu^{II}OAc_2$ in Figure 3A resembles the appearance of Cu^{II} in the reaction of $Cu^{I}OAc$ and TEMPO in Figure 2B. This similarity prompted us to investigate reactions of different $Cu^{I}X$ salts (X = OAc, TFA, OTf) with TEMPO (Figure 3B). TEMPO was added to a solution of the $Cu^{I}X$ species in MeCN, and the reaction was monitored by UV−visible spectroscopy at the λ_{max} wavelength corresponding to the d−d transition of the Cu^{II} species (670−760 nm). Only in the case of $Cu^{I}OAc$ was formation of Cu^{II} observed from the reaction (Figure 3B; cf. red trace for OAc versus the blue and black traces for TFA and OTf).

Several experiments were carried out to further probe the (re)generation of Cu^{II} observed from reactions conducted in the presence of acetate. The reduction of $Cu^{II}OAc_2$ by TEMPOH was monitored over a longer time period (Figure 4, black trace) under the original experimental conditions, and a 91% yield of Cu^{II} was obtained after 8 h. Recognizing that adventitious O_2 could contribute to the background oxidation of Cu^{I}, efforts were made to ensure the rigorous exclusion of oxygen from the reaction mixture (see sections VI−VIII in the Supporting Information for details). Even under these conditions, the slow formation of Cu^{II} was observed over 8 h but in much smaller amounts (Figure 4, red trace). An analogous experiment was conducted starting from $Cu^{I}OAc$ and TEMPO and 1 equiv of HOAc, mimicking the product mixture expected from the reaction of $Cu^{II}OAc_2$ and TEMPOH. The resulting time course (Figure 4, blue trace) is very similar and corresponds to a 15% yield of $Cu^{II}OAc_2$. Repetition of the latter experiment, but in the absence of HOAc, resulted in a negligible formation of Cu^{II} (Figure 4, green trace).

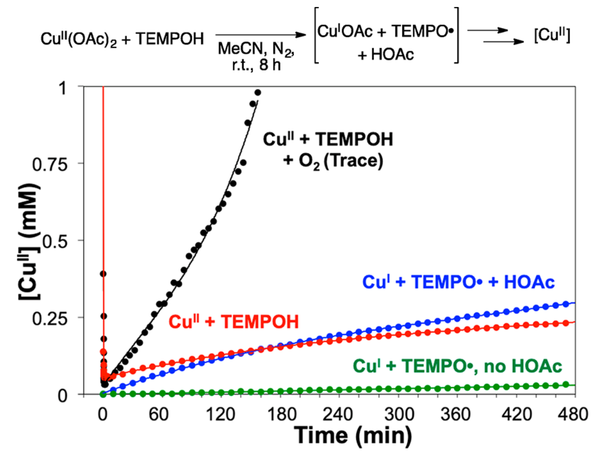

Figure 4. Single wavelength (λ = 670 nm) UV−visible time courses monitoring $[Cu^{II}]$ from reactions between copper(I/II) acetate and TEMPO(•/H). Conditions: 2 mM $Cu^{II}OAc_2$ or $Cu^{I}OAc$, 2 mM TEMPO or TEMPOH, ±2 mM HOAc, 4 mL of MeCN, N_2 or 15 mTorr static vacuum, 273 K, 8 h. Cu^{II} concentrations were obtained by constructing a UV−visible calibration curve of $Cu^{II}OAc_2$ in MeCN at 670 nm. Lines reflect smooth fits of the data simply to guide the eye.

Efforts were undertaken to identify the oxidant that accounts for the slow oxidation of $Cu^{I}OAc$. A small amount of 2,2,6,6-

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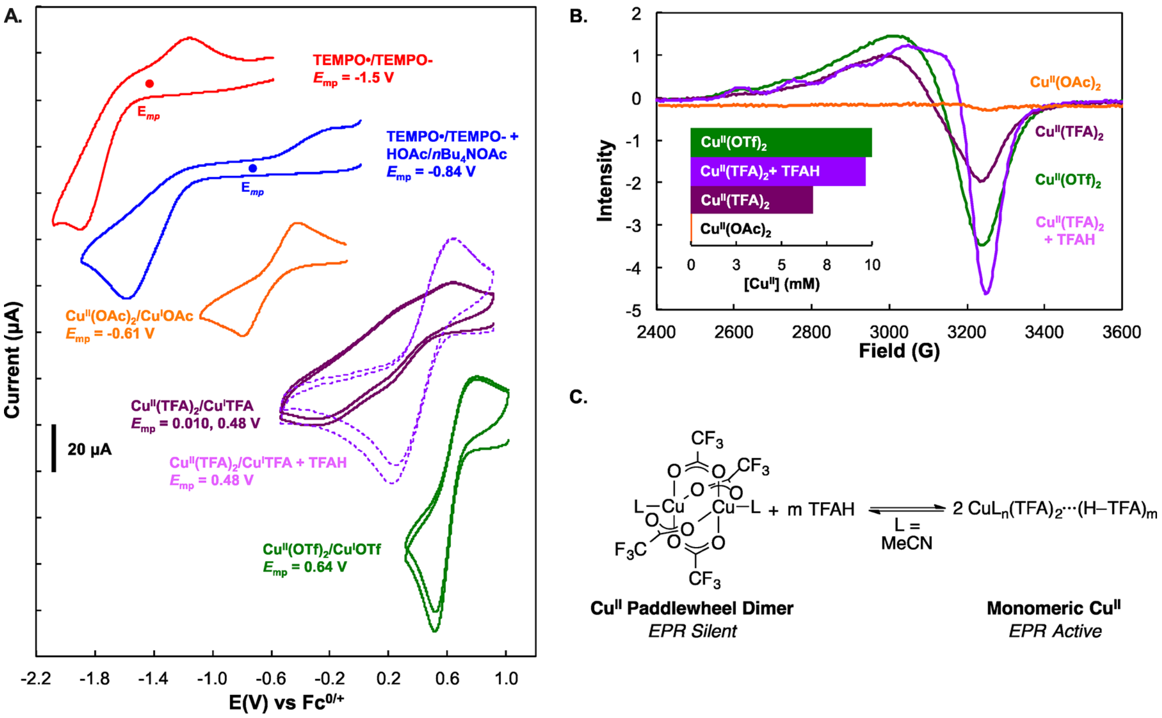

Figure 5. (A) Cyclic voltammograms of TEMPO in the presence and absence of HOAc/*n*Bu$_4$NOAc buffer and of Cu^{II}X$_2$ salts. CV conditions (TEMPO): 2 mM TEMPO, ±20 mM HOAc, ±20 mM *n*Bu$_4$NOAc, 0.1 M Bu$_4$NPF$_6$, MeCN, 200 mV/s scan rate. CV conditions (Cu^{II}X$_2$): 2 mM CuX$_2$, ±10 mM TFAH, 0.1 M Bu$_4$NPF$_6$, MeCN, 100 mV/s scan rate, glassy carbon working electrode, Pt wire counter electrode. (B) EPR spectra of Cu^{II} salts. 10 mM Cu^{II}X$_2$, ±50 mM TFAH, MeCN, 150 K. (C) Proposed equilibrium between the EPR-silent [Cu^{II}TFA$_2$]$_2$ paddlewheel dimer and EPR-active monomeric Cu^{II}TFA$_2$, promoted by TFAH.

tetramethylpiperidine (TMPH, 6%) was identified by GC–MS from the anaerobic reactions between Cu^{II}OAc$_2$/TEMPOH and Cu^{I}OAc/TEMPO/HOAc. Recognizing that the conversion of TEMPO to TMPH/H$_2$O is a 3e$^-$/3H$^+$ redox process (see further discussion below), this reaction accounts for the oxidation equivalents needed for the formation of the observed 15% yield of Cu^{II}OAc$_2$ observed in Figure 4 (blue trace).

Analysis of Cu^{II}X$_2$ Species in Solution. The influence of the anion (OAc, TFA, or OTf) and the role of HOAc on the (slow) regeneration of Cu^{II} (cf. Figures 3 and 4) prompted us to obtain cyclic voltammograms (CVs) of the different Cu salts and TEMPO under conditions relevant to the reactions (Figure 5A). The TEMPO/TEMPO$^-$ and TEMPO/TEMPOH redox couples are electrochemically irreversible, consistent with previous reports in the literature;[37−39] however, approximate midpoint potentials (E_{mp}) of −1.5 and −0.84 V vs Fc$^+$/Fc were estimated from CVs obtained in the absence[40] and presence of a buffered mixture of HOAc/Bu$_4$NOAc (Figure 5A, red and blue traces). The different Cu^{II}X$_2$ salts exhibit quasi-reversible CV features, with values that differ by >1 V, depending on the identity of the anionic ligand: E_{mp}(Cu$^{II/I}$) = −0.61 V (OAc) and 0.64 V (OTf) vs Fc$^+$/Fc. The CV of Cu^{II}TFA$_2$ exhibits two ill-defined quasi-reversible redox features at 0.010 and 0.48 V. The addition of 5 equiv of trifluoroacetic acid (TFAH) to this solution, however, leads to the appearance of a single quasi-reversible wave at 0.48 V.

The three Cu^{II}X$_2$ salts were also analyzed by electron paramagnetic resonance (EPR) spectroscopy. (See Figure 5B for spectra of frozen MeCN solutions.) Cu^{II}OAc$_2$ exhibits negligible EPR activity, consistent with it being present in solution as the EPR-silent [Cu(OAc)$_2$]$_2$ paddlewheel dimer.[41,42] Cu^{II}OTf$_2$ exhibits an axial EPR signal consistent with a monomer Cu^{II} species solvated by MeCN.[43] Cu^{II}TFA$_2$ exhibits an EPR signal with only 67% of the signal intensity of Cu^{II}OTf$_2$; however, the intensity increases to 96% when 5 equiv of TFAH is present.

The above CV and EPR data suggest that two different Cu^{II}TFA$_2$-derived species are present in solution, consistent with an equilibrium mixture of the EPR-silent [Cu(TFA)$_2$]$_2$ dimer and the EPR-active monomer (Figure 5C). This observation is consistent with the presence of a single electroactive species present in the CV obtained from this mixture (Figure 5B). Consistent with this interpretation, X-ray crystal structures of both monomeric Cu^{II}TFA$_2$(H$_2$O)$_4$ and paddlewheel dimeric [Cu^{II}TFA$_2$]$_2$·2MeCN have previously been obtained by the recrystallization of Cu^{II}TFA$_2$ from H$_2$O and MeCN, respectively.[44] We postulate that TFAH favors monomeric Cu^{II} via hydrogen bonding to the Cu-bound trifluoroacetate ligands.

Mechanistic Analysis and Discussion. Cu^{II}X$_2$ sources with all three anionic ligands, X = OAc, TFA, OTf, promote the rapid oxidation of TEMPOH to TEMPO, as shown in Figure 3A. The data presented also show, however, that Cu^{I}OAc undergoes oxidation to Cu^{II}OAc$_2$ in the presence of TEMPO (Figure 4), resembling the observations reported previously.[15] The reaction is complicated by the facile oxidation of Cu^{I} by O$_2$, even in trace quantities, (Figure 4), but the oxidation of Cu^{I}OAc by TEMPO via cleavage of the N–O bond to form TMPH can also account for the slow generation of Cu^{II} under these conditions.

The effect of bpy on the Cu$^{II/I}$ redox potential was analyzed in a previous mechanistic study of Cu/TEMPO-catalyzed

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alcohol oxidation,[18] but the contribution of the anionic ligand in the $Cu^{II/I}$ redox potential in bpy-free catalyst systems has not been characterized.[5,15,45] The strong influence of the anionic ligands on the $Cu^{II/I}$ redox potentials exceeds what might be expected on the basis of the anion basicity alone. This deviation is attributed to the ability of acetate (and, to a lesser extent, trifluoroacetate) to stabilize Cu^{II} via the formation of the carboxylate-bridged dicopper paddlewheel complex. In the case of acetate, the $Cu^{II/I}$ redox potential approaches that of the TEMPO/TEMPOH redox potential (Figure 5A). The two different $Cu^{II/I}$ redox potentials observed with TFA, which are assigned to dimeric and monomeric structures and which differ by nearly 400 mV, highlight the stabilizing effect of dimer formation.

The anionic ligand effects on the $Cu^{II/I}$ redox potentials rationalize why $Cu^{I}OAc$ is the only $Cu^{I}X$ species that undergoes oxidation by TEMPO under anaerobic conditions (cf. Figures 3 and 4). Single-electron transfer from Cu^{I} to TEMPO is thermodynamically unfavorable, and the lack of reactivity observed in the absence of HOAc is consistent with this conclusion (cf. Figure 4, green trace). The proton-coupled reduction of TEMPO to TEMPOH by $Cu^{I}OAc$ (cf. Figure 6A) is also unfavorable, but this reaction is only slightly uphill and should be thermally accessible: estimated ΔE_{mp} (TEMPO/TEMPOH − $Cu^{II/I}$) ≈ 200−300 mV or 4.5−7 kcal/mol. The TEMPOH generated in this manner can undergo disproportionation to TMPH and oxoammonium ($TEMPO^+$) (Figure 6B), as observed previously.[15,46−50] The involvement of this process is supported by the detection of 6% TMPH and 15% $Cu^{II}OAc_2$ following the oxidation of $Cu^{I}OAc$ in the presence of TEMPO and HOAc (cf. Figure 4 and associated text). The $TEMPO^+$ generated from this step can then oxidize another equivalent of $Cu^{I}OAc$ (Figure 6C).[51] The net reaction arising from these steps, shown in Figure 6A−C, shows that 3 equiv of $Cu^{I}OAc$ is oxidized for each equiv of TEMPO converted to TMPH.

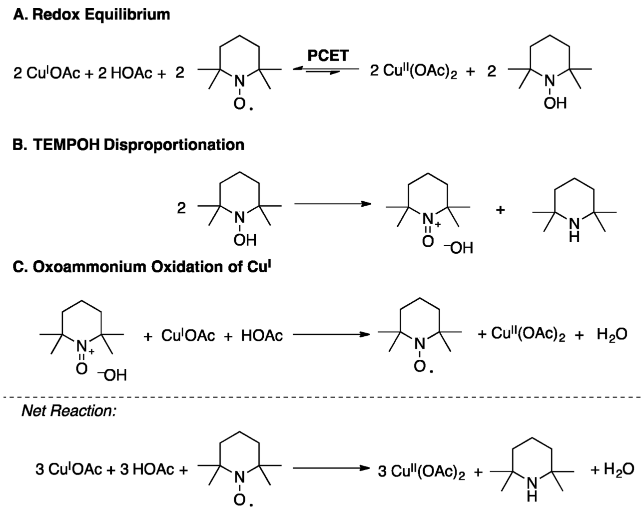

Figure 6. Elementary steps proposed to explain the oxidation of $Cu^{I}OAc$ by TEMPO in the presence of HOAc. (A) Redox equilibrium between $Cu^{I}OAc$/HOAc/TEMPO and $Cu^{II}OAc_2$/TEMPOH. (B) TEMPOH disproportionation to TMPH and $TEMPO^+$. (C) $TEMPO^+$-mediated oxidation of $Cu^{I}OAc$.

■ CONCLUSIONS

The results described here demonstrate that a series of different $Cu^{II}X_2$ sources (X = OAc, TFA, and OTf) mediate the efficient proton-coupled oxidation of TEMPOH to afford the aminoxyl radical. The reported oxidation of $Cu^{I}OAc$ by TEMPO has been reproduced; however, this reactivity is attributed to the presence of trace O_2 in the reaction mixture or a slower oxidation process that involves the cleavage of the N−O bond of TEMPO. $Cu^{II}X_2$-mediated PCET oxidation of TEMPOH provides the basis for the regeneration of the TEMPO cocatalyst during anaerobic (electrochemical) alcohol oxidation, and the facility of this process suggests that it could also contribute under aerobic oxidation conditions, without requiring the involvement of reactive Cu/O_2 species.[52] The identity of the anionic (X) ligand has a significant influence on the $Cu^{II/I}$ redox potential, but the rapid oxidation of TEMPOH is observed in all cases, even with the low-potential $Cu^{II}OAc_2$ species. These results are rationalized by the involvement of proton transfer in the oxidation process, whereby the beneficial effect of more basic anionic ligands offsets the lower $Cu^{II/I}$ redox potentials.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.inorgchem.9b01326.

Experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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