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Mechanism of Copper/Azodicarboxylate-Catalyzed Aerobic Alcohol Oxidation: Evidence for Uncooperative Catalysis

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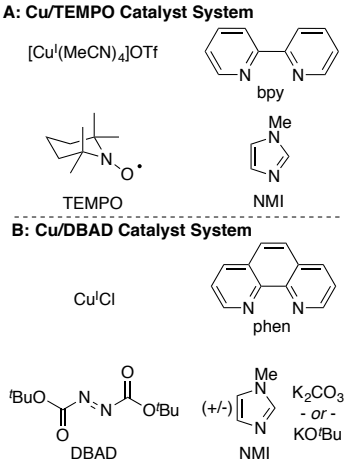
Abstract

Cooperative catalysis between Cu^{II} and redox-active organic cocatalysts is a key feature of important chemical and enzymatic aerobic oxidation reactions, such as alcohol oxidation mediated by Cu/TEMPO and galactose oxidase. Nearly twenty years ago, Markó and coworkers reported that azodicarboxylates, such as di-*tert*-butyl azodicarboxylate (DBAD), are effective redox-active cocatalysts in Cu-catalyzed aerobic alcohol oxidation reactions, but the nature of the cooperativity between Cu and azodicarboxylates is not well understood. Here, we report a mechanistic study of Cu/DBAD-catalyzed aerobic alcohol oxidation. In situ infrared spectroscopic studies reveal a burst of product formation prior to steady-state catalysis, and gas-uptake measurements show that no O_2 is consumed during the burst. Kinetic studies reveal that the anaerobic burst and steady-state turnover have different rate laws. The steady-state rate does not depend on [O_2] or [DBAD]. These results, together with other EPR and in situ IR spectroscopic and kinetic isotope effect studies, reveal that the steady-state mechanism consists of two interdependent catalytic cycles that operate in sequence: a fast Cu^{II}/DBAD pathway, in which DBAD serves as the oxidant, and a slow Cu^{II}-only pathway, in which Cu^{II} is the oxidant. This study provides significant insight into the redox cooperativity, or lack thereof, between Cu and redox-active organic cocatalysts in aerobic oxidation reactions.

Introduction

Homogeneous catalysts for aerobic alcohol oxidation have been the focus of extensive investigation.[1] Noble-metal catalysts, such as those based on Ru[2] and Pd,[3] are comparatively well characterized and often proceed via β-hydride elimination from a metal–alkoxide intermediate. This pathway is facilitated by the closed-shell nature of the transition metal and the propensity of second-row metals to undergo two-electron redox steps. Meanwhile, a number of recent studies have demonstrated the synthetic utility of copper-based catalysts for aerobic alcohol oxidation.[1b,e-f,4,5] A particularly effective class of catalysts features a bpy-ligated Cu species in combination with TEMPO (TEMPO = 2,2,6,6-tetramethylpiperidine-*N*-oxyl) or a different nitroxyl radical cocatalyst (Chart 1A).[4] Mechanistic studies of these catalyst systems[6] highlight the role of redox cooperativity between the Cu^{II} center and the organic cocatalyst, both of which undergo one-electron redox processes to achieve the net two-electron oxidation of alcohols. This mechanistic feature is reminiscent of galactose oxidase, which features a mononuclear Cu center with a coordinated redox-active phenoxyl radical (Figure 1),[7] and a number of related biomimetic catalyst systems.[8]

Chart 1. Cu/TEMPO and Cu/DBAD Aerobic Alcohol Oxidation Catalyst Systems



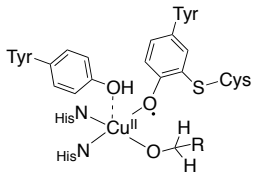


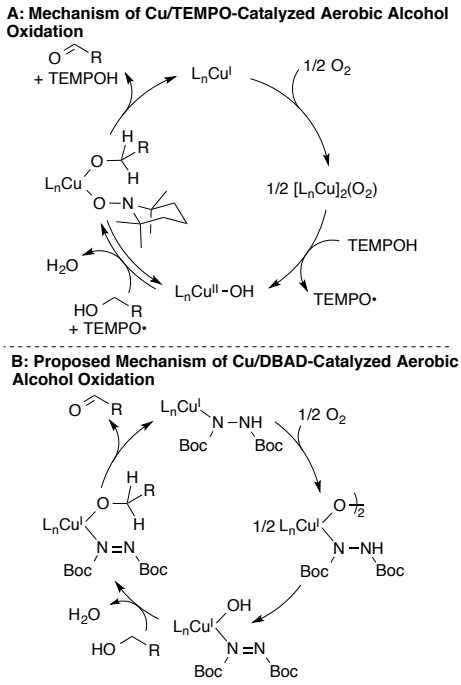
Figure 1. Active site structure of galactose oxidase.

In 1996, Markó and coworkers reported a Cu-based catalyst system for aerobic alcohol oxidation that has a number of features in common with the Cu/nitroxyl catalyst systems, but uses an azodicarboxylate, such as di-*tert*-butyl azodicarboxylate (DBAD), as a cocatalyst rather than a nitroxyl (Chart 1B).[5a] Subsequent studies showed that this catalyst system exhibits broad synthetic scope, including utility with both activated and aliphatic 1° and 2° alcohols, as well as alcohols containing nitrogen- and sulfur-containing functional groups. The optimal catalytic Cu/DBAD reaction conditions are somewhat less favorable than the corresponding conditions for Cu/nitroxyl reactions. For example, they are typically performed at higher reaction temperatures, use a relatively expensive solvent (fluorobenzene), and employ pure O_2 rather than air as the source of oxidant.[9] Recent efforts have begun to address these issues, however,[5g] and the overall effectiveness of the reactions surpasses the majority of other homogeneous metal catalyst systems for aerobic alcohol oxidation. Moreover, the use of DBAD as a cocatalyst raises a number of fundamental questions concerning the redox cooperativity between the Cu and DBAD.

The mechanism of Cu/DBAD-catalyzed alcohol oxidation proposed by Markó,[5] a simplified version of which is shown in Scheme 1, exhibits a number of similarities to the mechanism elucidated for Cu/nitroxyl-catalyzed alcohol oxidation.[6b-f] For example, in both cases, the C–H bond cleavage is proposed to proceed through hydride transfer from a Cu–alkoxide to the coordinated organic cocatalyst via a six-membered-ring transition state. For the Cu/DBAD

catalyst system, the reduced Cu^{I}/$DBADH_2$ complex is proposed to undergo aerobic oxidation to a Cu^{I}(OH)/DBAD complex, which can undergo ligand exchange with an alcohol to begin another round of turnover. An important distinction between these mechanisms is the involvement of one- versus two-electron redox reactivity of the organic cocatalysts, TEMPO and DBAD, respectively.

Scheme 1. Simplified Mechanisms for Aerobic Alcohol Oxidation with Cu/TEMPO (A) and Cu/DBAD (B) Catalyst Systems.

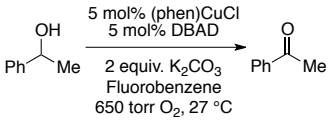


Many aspects of the Cu/DBAD-catalyzed reaction mechanism have not yet been elucidated, including the identity of the catalyst resting state and the turnover-limiting step of the reaction. Herein, we report kinetic and in situ spectroscopic studies of Cu/DBAD-catalyzed alcohol oxidation, which reveal that the mechanism is more complex that previously recognized. The reaction proceeds via the alternating involvement of two interdependent catalytic cycles, one in which DBAD mediates two-electron alcohol oxidation and the second of which involves alcohol

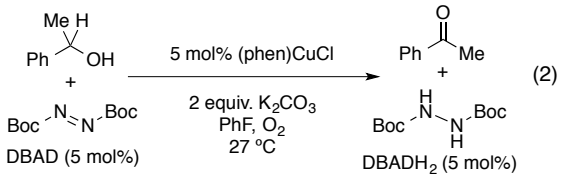
oxidation by Cu^{II} without the involvement of DBAD. The results reveal a distinct lack of redox cooperativity between Cu and DBAD, and they contrast the cooperativity evident in the Cu/TEMPO catalyst system and Cu/organic-cofactors in enzymatic aerobic oxidation reactions. The implications of these results for development of new synthetic aerobic oxidation catalysts are discussed.

Results

Cu/DBAD-Catalyzed Oxidation of 1-Phenylethanol: Observation and Analysis of a Kinetic Burst. Kinetic studies of the oxidation of 1-phenylethanol were initiated by using conditions similar to those reported by Markó and coworkers (eq 1).[10] Product formation and cocatalyst speciation (i.e., DBAD/$DBADH_2$) were monitored in situ by IR spectroscopy, and changes in oxygen pressure were measured within a sealed and temperature-controlled flask by using gas-uptake methods.[3c,d] The in situ IR data reveal a burst of product formation within the first two minutes of the reaction, quantitatively correlating with the conversion of DBAD into $DBADH_2$ (Figure 2A). Control reactions indicate that negligible reactivity occurs in the absence of Cu.[11] The gas-uptake data show that O_2 is not consumed during the burst; O_2 consumption only begins when all of the DBAD is reduced (Figure 2B). If $DBADH_2$ is used as the cocatalyst precursor, a kinetic burst is not observed, and oxygen consumption begins immediately upon exposure of the reaction mixture to substrate (Figure S2). Collectively, these data show that DBAD acts as the stoichiometric oxidant during the burst (eq 2).



(1)



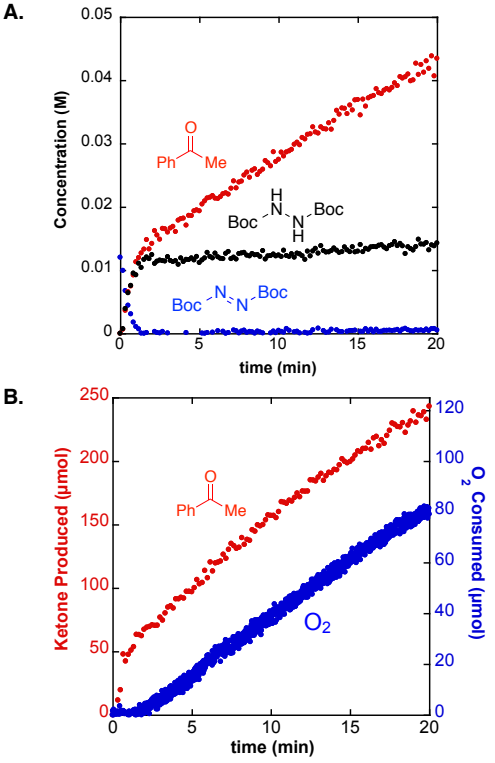


Figure 2. (A) Representative early time-course data for (phen)CuCl/DBAD-catalyzed aerobic oxidation of 1-phenylethanol (eq 1). (B) Comparison of in situ IR and gas-uptake time course showing the induction period for O_2 consumption during the kinetic burst of product formation in the presence of DBAD. Reaction conditions: 0.25 M 1-phenylethanol in 5 mL fluorobenzene, [(phen)CuCl] = 12.5 mM, [DBAD] = 12.5 mM, 2 equiv. K_2CO_3, 650 torr O_2, 27 °C.

The kinetic dependence of the burst rate on each reaction component was determined by analyzing initial rates of DBAD consumption in situ by IR spectroscopy under a nitrogen atmosphere. The rate exhibits a nearly linear dependence on [(phen)CuCl]. The data are influenced by the poor solubility of (phen)CuCl at ≥ 12 mM (solid (phen)CuCl is visible in the reaction mixture), which causes the rate to plateau at high [(phen)CuCl]. A saturation dependence on [DBAD] and first-order dependence on [alcohol] is also observed (Figure 3).[12]

These data show that the burst arises from anaerobic oxidation of alcohol with DBAD as the oxidant, and the dependence of the rate on (phen)CuCl (and negligible rate in the absence of Cu) indicates that (phen)CuCl activates DBAD in the alcohol oxidation reaction.[5b]

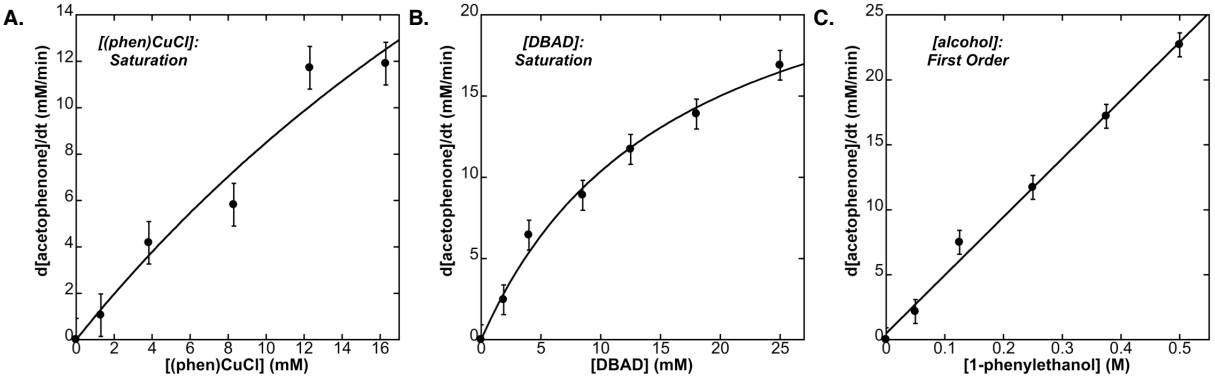


Figure 3. Kinetic data from the anaerobic kinetic regime of 1-phenylethanol oxidation by (phen)CuCl/DBAD catalyst system assessing the kinetic dependence on (A) [(phen)CuCl] (B) [DBAD] and (C) [alcohol]. Rates were obtained by monitoring DBAD consumption using in situ IR spectroscopy. Error bars correspond to ±σ for three trials under the standard reaction conditions. Standard reaction conditions: 0.25 M 1-phenylethanol in 5 mL fluorobenzene, [(phen)CuCl] = 12.5 mM, [DBAD] = 12.5 mM, 2 equiv. K_2CO_3, 1 atm N_2, 27 °C. Standard conditions were employed, except for the concentration of the component being varied. Reaction time course data is included in the Supporting Information (Figures S8, S10 and S12).

Cu/DBAD-Catalyzed Oxidation of 1-Phenylethanol: Analysis of Steady-State Catalytic Turnover. Analysis of product formation and O_2 consumption during steady-state catalytic turnover revealed a 2:1 product-to-O_2 stoichiometry (Figure 2B, Figure S3). In situ IR spectroscopic data reveal that $DBADH_2$ is the only form of the cocatalyst present during steady-state turnover (i.e., no DBAD was detected). Rates of product formation during the aerobic phase were monitored in situ by IR using $DBADH_2$ as the cocatalyst precursor to avoid complications associated with the kinetic burst observed with DBAD as the cocatalyst precursor.[13] The initial-rate data reveal that the steady-state catalytic rate exhibits a saturation dependence on [(phen)CuCl], a zero-order dependence on [$DBADH_2$] and pO_2, and a first-order dependence on

[alcohol] (Figures 4 and S15).[14] The curvature in Figure 4A again is undoubtedly influenced by the poor solubility of (phen)CuCl at ≥ 12 mM.[12]

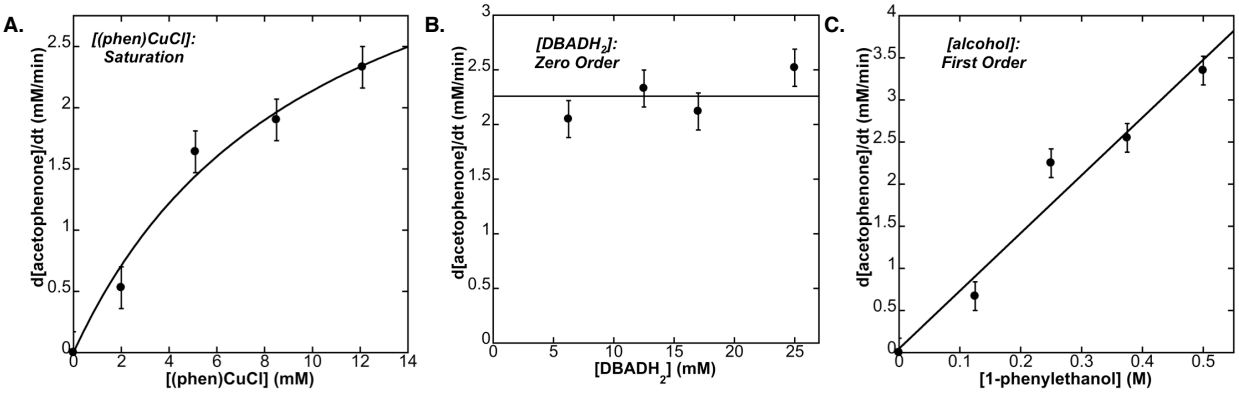


Figure 4. Kinetic data from the aerobic kinetic regime of 1-phenylethanol oxidation by (phen)CuCl/$DBADH_2$ catalyst system assessing the kinetic dependence on (A) [(phen)CuCl] (B) [$DBADH_2$] (C) [alcohol]. Rates were obtained by monitoring product formation by in situ IR spectroscopy. Error bars correspond to ±σ for four trials under the standard reaction conditions. Standard reaction conditions: 0.25 M 1-phenylethanol in 5 mL fluorobenzene, [(phen)CuCl] = 12.5 mM, [$DBADH_2$] = 12.5 mM, 2 equiv. K_2CO_3, 1 atm O_2, 27 °C. Standard conditions were employed, except for the concentration of the component being varied. Reaction time course data is included in the Supporting Information (Figures S9, S11 and S13).

(Phen)CuCl has been reported to mediate stoichiometric and catalytic oxidation of alcohols in the absence of DBAD.[5d,15] In order to assess the relationship between this process and the (phen)CuCl/DBAD conditions, aerobic oxidation of 1-phenylethanol was monitored by in situ IR spectroscopy in the absence of DBAD. Figure 5 compares the results obtained in the presence and absence of $DBADH_2$ ($DBADH_2$ was used as the cocatalyst to avoid the burst phase, as noted above). The catalytic rate with $DBADH_2$ was two-fold faster than the rate in the absence of the cocatalyst (Figure 5A). Furthermore, EPR spectra of the catalytic reaction mixtures with and without $DBADH_2$ revealed the presence of Cu^{II} signals with superhyperfine coupling derived from the phenanthroline ligand (Figure 5B). Simulation of the EPR spectra indicate that two different (phen)Cu^{II} species are present, and the simulations are consistent with two nitrogen ligands coordinated to the copper centers (see Figure S23 and Supporting Information for

details).[16] Double integration of the signal and calibration relative to an external standard showed that >80% of the copper in both reactions is present as EPR-active Cu^{II} species. Moreover, the nearly identical spectra observed in the presence and absence of $DBADH_2$ suggest that $DBAD(H_2)$ is not coordinated to the Cu center. This result aligns with the in situ IR data, which show that all of the cocatalyst is present as free $DBADH_2$.

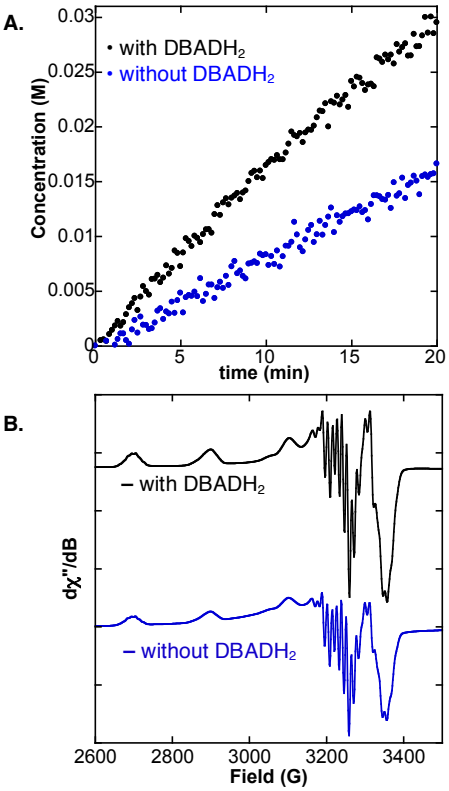


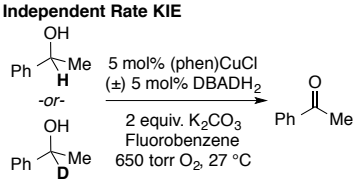
Figure 5. (A) Comparison of reaction time courses with and without $DBADH_2$. Reaction conditions: 0.25 M 1-phenylethanol in 5 mL fluorobenzene, [(phen)CuCl] = 12.5 mM, [$DBADH_2$] = 12.5 mM, 2 equiv. K_2CO_3, 650 torr O_2, 27 °C. (B) EPR spectra of catalytic reaction mixtures: during aerobic turnover with and without added DBAD. Reaction conditions: 1.0 M 1-phenylethanol in 2 mL fluorobenzene, [(phen)CuCl] = 10 mM, [DBAD] = 10 mM, 2 equiv. K_2CO_3, 1 atm O_2, 27 °C. EPR spectra were collected at 115 K, with a microwave frequency of 9.30 MHz.

Kinetic Isotope Effect (KIE) Studies. Kinetic isotope effects were measured in two different ways, via comparison of the independent rates of oxidation of 1-phenylethanol and 1-phenylethanol-1-d_1 and via intramolecular competition with PhCHDOH as the substrate, and the KIEs were obtained for both Cu/DBAD and Cu-only reaction conditions. The independent rate

measurements for aerobic oxidation of 1-phenylethanol and 1-phenylethanol-1-d_1 revealed that reactions with the Cu/DBAD and Cu-only catalyst systems exhibited similar KIEs: k_H/k_D = 2.1 ± 0.3 (Cu/DBAD) and 2.0 ± 0.2 (Cu-only) (Scheme 2A). These two catalyst systems exhibited different intramolecular competition KIEs, however: k_H/k_D = 3.9 ± 0.1 (Cu/DBADH$_2$) and 2.5 ± 0.1 (Cu-only) (Scheme 2B). An intramolecular competition KIE was also measured for anaerobic Cu/DBAD-mediated alcohol oxidation, reflecting the reactivity during the burst phase. In this case an even larger KIE was observed: k_H/k_D = 5.4 ± 0.2 (Scheme 2B). Two mechanistically significant outcomes from these studies include (1) the similarity between the independent-rate KIE for Cu/DBADH$_2$ conditions, the independent-rate KIE for Cu-only conditions, and the intramolecular-competition KIE for the Cu-only conditions (KIEs = 2.1–2.5), and (2) that the intramolecular-competition KIE for Cu/DBAD catalytic conditions (3.9) is halfway between the KIEs observed for the anaerobic Cu/DBAD and Cu-only conditions (5.4 and 2.5, respectively). The implications of these observations are elaborated below.

Scheme 2. KIE Experiments for Cu/DBAD Alcohol Oxidation Reactions.

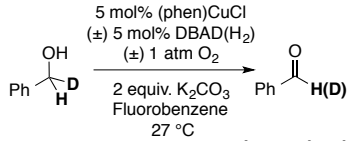
A: Independent Rate KIE



KIE ***with*** DBADH$_2$ = **2.1** ± 0.3

KIE ***without*** DBADH$_2$ = **2.0** ± 0.2

B: Intramolecular Competition KIE



(phen)CuCl	DBAD(H$_2$)	O$_2$	Intramolecular Competition KIE[a]
+	+	-	5.4 ± 0.2
+	+	+	3.9 ± 0.1
+	-	+	2.5 ± 0.1

[a]KIE values determined using ^{1}H NMR spectroscopy. Errors are the standard deviation of three independent reactions. Reaction conditions: 0.25 M substrate in 5 mL fluorobenzene, [(phen)CuCl] = 12.5 mM, [DBAD(H$_2$)] = 12.5 mM, 2 equiv. K_2CO_3, 1 atm O_2 or N_2, 27 °C. (The anaerobic experiment used DBAD, and the aerobic experiment used DBADH$_2$.)

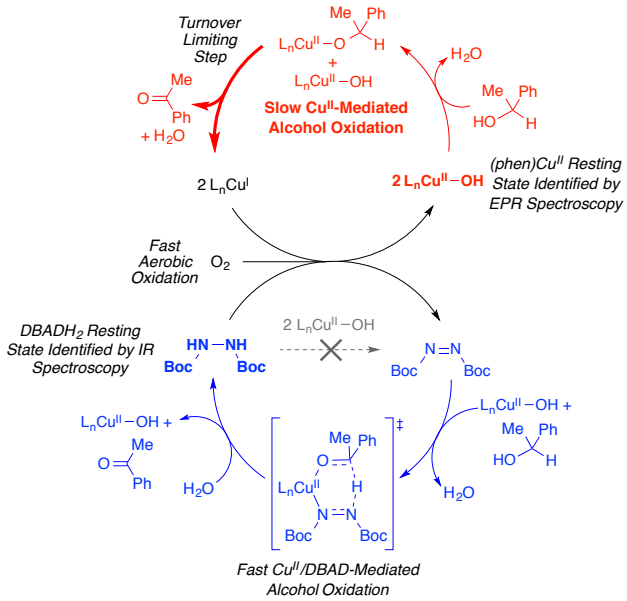
Discussion

Proposed Mechanism and Its Relationship to Experimental Results. The original mechanism proposed for Cu/DBAD-catalyzed aerobic alcohol oxidation (cf. Scheme 1B) is chemically plausible and accounts for the overall stoichiometry of alcohol oxidation and cocatalyst regeneration by O_2,[5] but several features are not consistent with the experimental data presented above. Briefly, (1) this mechanism does not provide a clear basis for the kinetic burst at the start of the reaction, together with a lack of pO_2-dependence on the rate of the burst or steady-state turnover, (2) it does not rationalize the different kinetic isotope effects obtained with different substrate probes and/or under different conditions, (3) it does not predict that Cu^{II} and $DBADH_2$ should be predominant catalyst resting state or that these cocatalysts do not form a resting-state complex under catalytic conditions, and (4) it does not explain the two-fold difference in rate between (phen)Cu-catalyzed alcohol oxidation in the presence and absence of DBAD (cf. Figure 5).

A revised mechanism consistent with each of these observations is shown in Scheme 3 and features two interdependent catalytic cycles: (1) a fast Cu^{II}/DBAD pathway (bottom, blue cycle) in which DBAD serves as a two-electron oxidant, and (2) a slow Cu^{II}-only pathway (top, red cycle) in which two equivalents of Cu^{II} serve as the oxidant. The Cu^{I} species formed in the latter pathway activate O_2 and contribute to four-electron oxidation of the cocatalyst system: 2 Cu^{I} → 2 Cu^{II} and $DBADH_2$ → DBAD. The overall turnover-limiting step of the catalytic bicycle is (phen)Cu^{II}-mediated oxidation the alcohol (top left step in Scheme 3), as revealed by the steady-state rate law (rate ∝ [(phen)Cu^{II}]·[alcohol], cf. Figure 4) and the presence of (phen)Cu^{II} and $DBADH_2$ as the cocatalyst resting states. The kinetic burst exhibits a kinetic dependence on [(phen)CuCl], [DBAD] and [alcohol], and it arises from the use of DBAD as the source of

cocatalyst. The combination of (phen)CuCl and DBAD promotes very rapid O_2-independent alcohol oxidation by a pathway that resembles the blue pathway at the bottom of Scheme 3.[5b,11]

Scheme 3. Proposed Mechanism for Cu/DBAD-Catalyzed Aerobic Alcohol Oxidation.



This revised mechanism also rationalizes all of the other experimental data. It correctly predicts a zero-order pO_2-dependence on the reaction because neither alcohol oxidation by (phen)Cu^{II} during steady-state turnover nor Cu/DBAD-mediated alcohol oxidation in the burst involves O_2. The KIE value observed during steady-state Cu/DBAD catalytic turnover (KIE = 3.9) is the average of the KIEs observed for stoichiometric Cu/DBAD-mediated alcohol oxidation in the burst (KIE = 5.4) and for steady-state turnover with the Cu-only catalyst system (KIE = 2.5). This result is rationalized by the required sequence of the two cycles in Scheme 3: the fast Cu/DBAD cycle can take place only after Cu^{I} is formed in the Cu-only cycle because Cu^{I}/O_2 is needed to mediate the oxidation of $DBADH_2$ to DBAD. The two-fold difference in rate between the Cu/DBAD vs. Cu-only catalyst systems has a similar rationale. Involvement of the fast DBAD-mediated pathway means that the Cu/DBAD catalyst system oxidizes two

equivalents of alcohol for each turnover of (phen)CuCl.[17] The common turnover-limiting C–H cleavage process in the Cu-only and Cu/DBAD-catalyzed reactions explains the very similar KIE values observed with these two catalyst systems, which are also similar to the intramolecular-competition KIE for the Cu-only conditions (Scheme 2).

Analysis of Cu/DBAD Redox Cooperativity and Comparison to Cu/TEMPO Alcohol Oxidation and Enzymes. As noted in the Introduction, the Cu/DBAD catalyst system closely resembles the Cu/TEMPO system with respect to the catalyst components (Chart 1). The results herein suggest that the catalytic mechanisms exhibit both similarities and differences. Cu/DBAD-mediated alcohol oxidation is believed to involve a transition state that closely resembles the transition state for alcohol oxidation by Cu/TEMPO (Figure 6).[6b,c,f] The similar KIEs observed for stoichiometric Cu/DBAD-mediated oxidation of PhCHDOH (KIE = 5.4) and the same reaction with Cu/TEMPO (KIE = 5.4–6.1) may support this relationship.[4b,6a]

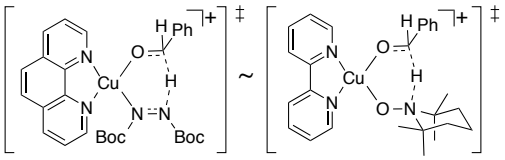


Figure 6. Comparison of the proposed transition-state structure for Cu/DBAD-mediated alcohol oxidation and the transition-state structure for Cu/TEMPO-mediated alcohol oxidation.

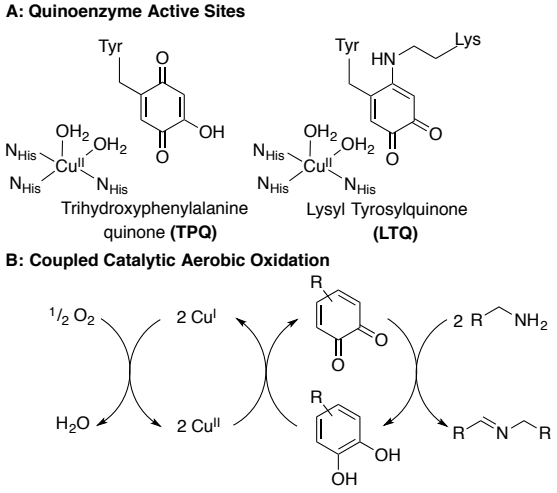
The differences appear to arise from poor cooperativity between the Cu and DBAD cocatalysts. In the Cu/TEMPO reactions, Cu^{II} and TEMPO are directly involved in the substrate oxidation step and generate Cu^{I} and TEMPOH as byproducts of the reaction. These reduced cocatalysts then undergo aerobic oxidation to complete the cycle. In the Cu/DBAD reactions, the Cu^{II} species serves as a Lewis acidic template for the alkoxide and DBAD, and substrate oxidation involves two-electron reduction of the DBAD cocatalyst to the hydrazine oxidation

level. Cu^{II} is not reduced in this step. This reactivity is consistent with the ability of non-redox-active Lewis acids, such as Zn^{II} and Mg^{II}, to promote stoichiometric azodicarboxylate-mediated alcohol oxidation.[18] Markó and coworkers similarly exploited this reactivity in (phen)CuCl-catalyzed oxidation of alcohols with stoichiometric DBAD.[5b] In order to achieve catalytic turnover, $DBADH_2$ must be oxidized back to DBAD, but Cu^{II} is not an effective oxidant for this reaction under these conditions. Therefore, Cu^{II} and $DBADH_2$ accumulate as the catalyst resting states.[19] A more-reactive oxidant is accessible from the reaction of Cu^{I} and O_2.[20] Whereas Cu^{I} is a natural byproduct of the alcohol oxidation step in Cu/TEMPO-catalyzed alcohol oxidation, Cu^{I} forms via a comparatively slow Cu-only alcohol oxidation pathway in the Cu/DBAD-catalyzed reaction.[5d,15,21]

The above analysis shows that the Cu and DBAD cocatalysts exhibit poor redox cooperativity relative to other aerobic oxidation reactions involving transition-metal/organic cocatalyst systems. Different forms of cooperativity have been observed in such reactions. In alcohol oxidation reactions catalyzed by Cu/TEMPO and the enzyme galactose oxidase, Cu^{II} and the oxyl radical serve as coupled one-electron oxidants that participate jointly in oxidation of the alcohol and are subsequently regenerated together by reaction with O_2 (cf. Scheme 1A and Figure 1). An alternative form of cooperativity is evident in copper amine oxidases, which feature an active-site Cu center together with a quinone cofactor, derived from post-translational modification of a tyrosine residue (Scheme 4A). The quinone species mediate amine oxidation without the involvement of Cu, but Cu plays an important role in aerobic oxidation of the hydroquinone to quinone, following substrate oxidation (Scheme 4B).[22] Similar concepts have been implemented in bioinspired amine oxidation reactions involving quinone catalysts,[23] including examples in which Cu-based cocatalysts are used to facilitate aerobic oxidation of the

hydroquinone species.[24,25] This form of cooperative catalysis is featured in a wide range of aerobic oxidation reactions in chemistry and biology.[26,27]

Scheme 4. (A) Copper Amine Oxidase Active Sites and (B) Coupled Catalytic Aerobic Oxidation Cycle.



The differences between the Cu/TEMPO and Cu/DBAD catalyst system arises, in part, from the one-electron vs. two-electron redox chemistry of TEMPO and DBAD, respectively. Nevertheless, role of quinones in copper amine oxidase examples in Scheme 4 illustrates that the breakdown in cooperativity in Cu/DBAD-catalyzed alcohol oxidation is not a necessary consequence of using a two-electron cocatalyst. Instead, the breakdown is linked to the inability of Cu^{II} to oxidize $DBADH_2$ in a manner similar to the hydroquinone in Scheme 4B. Regeneration of DBAD is possible only after Cu^{II} mediates the slower DBAD-free alcohol oxidation. These insights have important implications for the development of cooperative catalyst systems for aerobic oxidation. For example, it raises the possibility that modified catalyst systems could be identified in which a more effective redox couple than $(phen)Cu^{II}/(phen)Cu^{I}$ could enable oxidation of $DBADH_2$ to exploit the faster rates associated with the DBAD-based alcohol oxidation cycle. Another option would be the identification of a

less-oxidizing azo compound that could promote rapid alcohol oxidation while being compatible with oxidation by Cu^{II}. Future progress toward these goals could provide the basis for the development aerobic oxidation reactions that expand beyond alcohol oxidation.

Conclusions

The mechanistic study of Cu/DBAD-catalyzed alcohol oxidation described above highlights both similarities and differences relative to Cu/TEMPO- and Cu/quinone-catalyzed aerobic oxidation reactions and related enzymatic oxidation reactions. An unusual catalytic bicycle was identified that arises from a breakdown in the redox cooperativity between the Cu and DBAD cocatalysts. Cu/DBAD neither functions in a directly coupled process like Cu/TEMPO and galactose oxidase nor in a coupled multi-cycle mechanism similar to copper amine oxidases and synthetic mimics. The former difference reflects the one-electron vs. two-electron redox activity of TEMPO and DBAD, respectively, and the latter difference reflects the inability of Cu^{II} to promote the oxidation of $DBADH_2$ to DBAD. The concepts elucidated from this study provide an important foundation for future studies directed toward the development of new catalyst systems for selective aerobic oxidation of organic molecules.

ASSOCIATED CONTENT

Supporting Information. Experimental details for data acquisition and additional kinetic data are available free of charge via the Internet at http://pubs.acs.org.

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9. Exceptions to these generalizations have been demonstrated. For example, Markó has shown that bubbling air may be used to substitute for pure O_2 (see ref. 5a), and Tsunoda and coworkers recently developed modified conditions, including the replacement of phen with 4,7-diphenyl-1,10-phenanthroline, that permit Cu/DBAD-catalyzed aerobic alcohol oxidation to proceed at room temperature in toluene (see ref. 5g).

10. Fluorobenzene was shown to be a superior solvent relative to toluene, see ref. 5c.

11. The anaerobic Cu/DBAD-mediated burst of product formation is significantly faster than catalytic turnover, regardless of the initial oxidation state of the Cu source (i.e., CuCl vs. $CuCl_2$). See Supporting Information Figure S4.

12. The poor solubility of CuCl in fluorobenzene prevented the preparation of stock solutions, which led to scatter in kinetic plots. Reaction solutions become homogeneous upon addition of substrate below 12 mM (phen)CuCl. See Supporting Information for details.

13. Steady-state catalytic turnover proceeds at a similar rate regardless of the choice of cocatalyst precursor. DBAD or $DBADH_2$ (see Figure S1).

14. Our intent in probing the [$DBADH_2$] dependence under aerobic conditions was to assess the role of DBAD under conditions relevant to the optimized catalytic conditions [Cu:DBAD(H_2)

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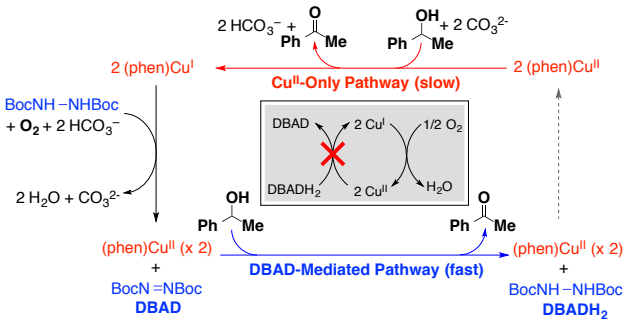
TOC Graphic


2 HCO3− +
Ph
Me
O
OH
+ 2 CO32-
Ph
Me
2 (phen)CuI
CuII-Only Pathway (slow)
2 (phen)CuII
BocNH−NHBoc
+ O2 + 2 HCO3−
2 H2O + CO32-
DBAD
2 CuI
1/2 O2
DBADH2
2 CuII
H2O
OH
Ph
Me
O
Ph
Me
(phen)CuII (x 2)
+
BocN=NBoc
DBAD
DBAD-Mediated Pathway (fast)
(phen)CuII (x 2)
+
BocNH−NHBoc
DBADH2