Distinguishing Rate-Limiting Electron versus H-Atom Transfers in Cu$_2$(O$_2$)-Mediated Oxidative N-Dealkylations: Application of Inter- versus Intramolecular Kinetic Isotope Effects

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Hydroxylation reactions performed by Cu(I)-dioxygen adducts are biologically important; yet the diverse nature of active site structures and substrate types leaves many mechanistic questions unresolved.1–3 For example, tyrosine $\alpha$-phenol hydroxylations (proceeding from a Cu$^{II}$-$\eta^2$-$\eta^2$-peroxo species) appear to occur via an electrophilic mechanism.1,4 However, recent model studies by Tolman and Itoh suggest that Cu$^{II}$-peroxo/Cu$^{III}$-bis-$\mu$-oxo complexes are capable of oxidizing substrates through rate-limiting hydrogen atom transfer (HAT) pathways.2a,5,6 Studies on dopamine-$\beta$-hydroxylase (DjH) and for peptide oxidative N-dealkylation by peptidylglycine $\alpha$-hydroxylating monooxygenase (PHM) previously implicated Cu-hydroperoxo or Cu-superoxo species facilitating observed HAT reactions; however, recent insights suggest that alternative copper-dioxygen derived active species need to be considered.5

To better understand how Cu$^{II}$-peroxo species oxidize substrates, we recently reported on the preparation of a series of Cu complexes, [Cu(I)(MePY2)R]$,^+$, where Cu is contained within bis[2-(2-(4-R$^*$-pyridyl)ethyl)methylamine tridentate ligands (MePY2, R$^*$ = H, MeO, Me,N, Scheme 1).3 These complexes readily react with dioxygen, forming the corresponding Cu$^{II}$-O$_2$ adducts [(Cu$^{II}$- (MePY2)$^8$(O$_2$)]$^+$ (1$^*$, R$^*$ = H, MeO, Me,N), where the Cu$^{II}$-peroxo complex is in equilibrium with the corresponding Cu$^{III}$-bis-$\mu$-oxo adduct.7–9 Also, 1$^*$ readily oxidize substrates such as tetrahydrofuran (THF), alcohols, and N,N-dimethylaniline (DMA).9 para-Substituted DMAs (R$^*$-DMAs) have been used as mechanistic probes, distinguishing between rate-limiting HAT or electron-transfer (ET) pathways, for example in cytochrome P450 (P450) chemistry (Scheme 2).10 Here, we wish to communicate that the transfer (ET) pathways, for example in cytochrome P450 (P450) oxidations induced by Cu(I)-dioxygen adducts. In fact, oxidations -hydroxylase (D$^*$H) and for peptide oxidative N-dealkylation by peptidylglycine $\alpha$-hydroxylating monooxygenase (PHM) previously implicated Cu-hydroperoxo or Cu-superoxo species facilitating observed HAT reactions; however, recent insights suggest that alternative copper-dioxygen derived active species need to be considered.5

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Dichloromethane solutions of dioxygen adducts 1$^*$ under argon (with excess O$_2$ removed) at $-80$ °C readily react with R$^*$-DMA (R$^*$ = MeO, Me, H, CN), affording the corresponding para-substituted N-methylaniline (R$^*$-MA) and formaldehyde in good yields.7,12,13 With N,N-dibenzylaniline as substrate, isolation of the benzaldehyde product from O$_2$ versus 18O$_2$ reactions$^{14}$ suggests a “rebound” type mechanism analogous to P450 chemistry. This indicates an overall C=C bond homolysis proceeding through either an ET followed by a proton transfer (PT), or a HAT pathway (Scheme 2a and b, respectively).

Because the oxidative N-dealkylation yields of R$^*$-MA closely compare for a given 1$^*$ (Table S1),13 we can determine the relative rates of these reactions using competition studies and measured R$^*$-MA yields. Oxidative competition reactions induced by 1$^*$ run in a 1:1 mixture of R$^*$-DMA:DMA at $-80$ °C in CH$_2$Cl$_2$ (Scheme 3).10b,13 Such a situation is suggestive of a rate-limiting ET process, followed by a PT from the DMA radical cation to the Cu-oxo core. This rate-limiting ET mechanism is also supported by the intramolecular deuterium kinetic isotope effect profiles (KIE$_{\text{intra}}$ and KIE$_{\text{inter}}$, see Table 2 and Scheme 3).10b,13 In the case of the intramolecular N-dealkylation reactions, the KIE$_{\text{intra}}$ profile for 1$^*$ shows a sharp increase as $\sigma^+$ (and $E_{\text{L2}}$) for R$^*$-DMAs become more...
negative, eventually reaching an asymptote (Table 2, Figure S4). Better H versus D differentiation occurs because the proton-transfer step becomes slower with DMA radical-cation stabilization by the electron-donating group. This translates into a larger KIE

In the case of the intermolecular reaction, there is a negligible difference in the isotope effect (KIE

values are relatively small in magnitude, in line with a rate-limiting electron-donating group. This translates into a larger KIE

The rate-limiting ET is also supported by comparison of the absolute values obtained for KIE

The situation is different in the case of 1Me2N. Competition reactions do not show a strong R-group dependence, with KIE values increasing only slightly as R is made more electron donating. Table 1. This is reflected in the linear free-energy correlation (13) which yielded a ρ value consistent with either ET or HAT (ρ = −0.49, r2 = 0.98).15 The KIE profiles are largely inconclusive (Table 2), showing no distinct pattern for either ET or HAT. In the case of both KIE

and KIE

is observed to be a general increase in KIE as σ + becomes more positive. Furthermore, the KIEs become large in magnitude, consistent with a rate-limiting C–H bond cleavage. This could occur through a switch in mechanism from rate-limiting ET, to either a HAT or a peET/PT.18 A comparison of the magnitudes of the KIE

versus KIE

using the criterion mentioned above sheds further light on our results. For R = MeO and Me, the data suggest that 1Me2N oxidizes R–DMA through a rate-limiting ET mechanism (KIE

= KIE

< KIE

inter), while for the less reducing R–DMAs (H and CN), oxidation appears to occur through a rate-limiting HAT (KIE

inter ≈ KIE

intra). This is strong evidence in favor of a HAT mechanism. In addition, we favor the HAT over a peET/PT mechanism, as follows: In the case of 1H, we established rate-limiting ET (vide supra). However, 1Me2N is a weaker one-electron oxidant,18 and the μ-oxo groups in its CuO2 moiety should be more basic (as it possesses the stronger donor ligand MePy(2Me2N)5.7 Thus, one would expect slower electron transfer and faster proton transfer in reactions of R–DMAs with 1Me2N relative to 1H, that is, ET would still be rate-limiting. Yet, the KIE values and criteria indicate this is not the case. Thus, peET/PT is unlikely, and we conclude that HAT is operative for H– and CN–DMA in oxidations with 1Me2N. Other precedent comes from (a) that P450 may operate in a similar manner (ET for easily oxidized substrates and HAT for others),11 while (b) studies performed by Tolman and Itoh suggest that CuO2 complexes are capable of performing HAT reactions from alkyl- and benzylamines.5,6

It therefore appears reasonable that as R–DMAs become harder to oxidize, there is a shift in mechanism for oxidative N-dealkylation by copper-dioxygen adduct 1Me2N (data in Table 2) where the less easily oxidized CN–DMA reacts via a rate-limiting HAT pathway and the other substrates (R = H, Me, MeO) are oxidized though an ET pathway.

In conclusion, we have shown that both HAT and ET mechanisms occur for the oxidation of R–DMAs by dioxygen adducts 1H. The reaction pathways are controlled by changes in the ease of substrate one-electron oxidation and also the reduction potentials of 1H (which are determined by ligand electronics).18 Coupled to all of this will be changes in the pKα’s of the bis-μ-oxo-ligands in 1H, with stronger donor ligands (R' = MeN and MeO) expected to produce better oxo bases (as H⁺ acceptors). Further investigations are needed to sort out these details.

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Supporting Information Available: Experimental details, KIE profiles, and linear free-energy plots (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References
(9) The R' group identity influences the peroxyoxo-μ-oxo equilibrium (more bis-μ-oxo isomer is present with more electron-donating R' and rates of THF and MeOH oxidation (+1500× increase in THF oxidation rate for R' = MeN vs R' = H).17
(12) Yields for R = MA are 1H, ~60%; 1MeO, ~80%; and 1Me2N, ~90%.
(13) See Supporting Information.
(14) Yields are low, and 18-O incorporation in benzaldehyde varied from 36% to 68%. We suspect the low yields are due to unfavorable steric interactions between the dibenzyl groups and the Cu(O2) core, and that the low isotope incorporation is due to exchange of the carboxyl oxygen with residual water in the solvent.19
(16) Going from a 10- to 100-fold excess of substrate did not change the relative yields.
(17) All KIE values are within the semiclassical limit for ET and HAT reactions at ~80 °C (kH/D could reach a maximum of 23.1).
(18) Shearer, J.; Karlin, K. D. Unpublished results. For example, 1H oxidizes certain ferrocene derivatives that 1Me2N will not.

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