Communication

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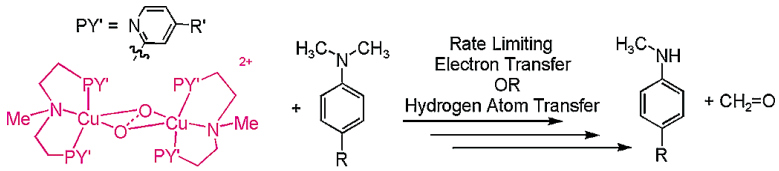

Mechanism Switches Depending on the Identity of Both R and R'!

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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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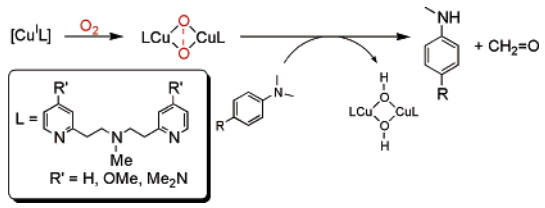
Hydroxylation reactions performed by Cu(I)-dioxygen adducts are biologically important; yet the diverse nature of active site structures and substrate types leaves many mechanistic questions unresolved.[1−3] For example, tyrosinase *o*-phenol hydoxylations (proceeding from a Cu^{II}_2-μ-η^2-η^2-peroxo species) appear to occur via an electrophilic mechanism.[1,4] However, recent model studies by Tolman and Itoh suggest that Cu^{II}_2-peroxo/Cu^{III}_2-bis-μ-oxo complexes are capable of oxidizing substrates through rate-limiting hydrogen atom transfer (HAT) pathways.[2a,5,6] Studies on dopamine-β-hydroxylase (DβH) and for peptide oxidative *N*-dealkyation by peptidylglycine α-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.[3]

To better understand how Cu^{II}-peroxo species oxidize substrates, we recently reported on the preparation of a series of Cu^{I} complexes, $[Cu^{I}(MePY2)^{R'}]^+$, where Cu is contained within bis[2-(2-(4-R′-pyridyl)ethyl]methylamine tridentate ligands ($MePY2^{R'}$, R′ = H, MeO, Me_2N; Scheme 1).[7] These complexes readily react with dioxygen, forming the corresponding Cu_2^{II}-O_2 adducts $[(Cu_2^{II}(MePY2)^{R'})_2(O_2)]^{2+}$ ($\mathbf{1}^{R'}$, R′ = H, MeO, Me_2N), where the Cu_2^{II}-peroxo complex is in equilibrium with the corresponding Cu_2^{III}-bis-μ-oxo adduct.[7−9] Also, $\mathbf{1}^{R'}$ 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 use of R−DMAs has yielded rich new insight into the nature of oxidations induced by Cu(I)-dioxygen adducts. In fact, oxidations by $\mathbf{1}^{R'}$ can occur through both a rate-limiting ET or a HAT pathway, as has been suggested for high valent Fe-oxo porphyrinates.[10,11]

Dichloromethane solutions of dioxygen adducts $\mathbf{1}^{R'}$ 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 $^{18}O_2$ reactions[14] suggests a "rebound" type mechanism analogous to P450 chemistry. This indicates an overall C−H 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 $\mathbf{1}^{R'}$ (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 $\mathbf{1}^{H}$ run in a 1:1 mixture of R−DMA:H−DMA demonstrate a strong R-group dependence on the relative rates (k_{rel}). As R is made more electron-donating, k_{rel} increases (Table 1). A linear free-energy correlation gives a large negative ρ value ($\rho = -2.1$, $r^2 = 0.99$).[14]

Scheme 1



Scheme 2

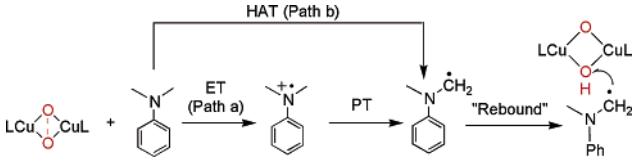


Table 1. k_{rel}: R−DMA Competition Studies (CH_2Cl_2, −80 °C)[16]

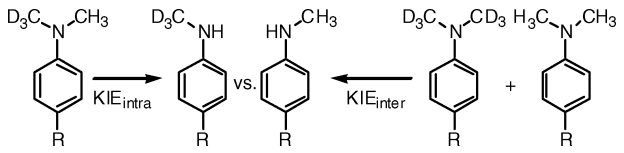
	$\mathbf{1}^{H}$	$\mathbf{1}^{Me2N}$	$\mathbf{1}^{MeO}$	σ^+
MeO−DMA	11.4 (3)	2.3 (2)	12.4 (2)	−0.65
Me−DMA	2.5 (1)	1.2 (1)	2.2 (1)	−0.26
H−DMA	1.0	1.0	1.0	0.00
CN−DMA	0.02 (1)	0.53 (3)	0.48 (1)	0.67
ρ (r^2)	−2.1 (0.99)	−0.47 (0.98)	−0.99 (0.92)	

Table 2. KIE_{intra} versus KIE_{inter} for the *N*-Dealkylation of R−DMA in CH_2Cl_2 at − 80 °C[17]

	$\mathbf{1}^{H}$ [a]	$\mathbf{1}^{Me2N}$ [a]	$\mathbf{1}^{MeO}$ [a]	$E_{1/2}$ [b]
MeO−DMA	4.7 (8)/ 1.7 (6)	7.3 (4)/ 2.7 (2)	7.5 (2)/ 2.3 (4)	0.53
Me−DMA	4.6 (6)/ 2.3 (3)	5.8 (8)/ 3.8 (2)	5.0 (7)/ 3.0 (2)	0.72
H−DMA	4.1 (6)/ 2.4 (6)	12.0 (9)/ 11.4 (15)	6.1 (7)/ 2.7 (6)	0.92
CN−DMA	2.6 (8)/ 2.1 (8)	14.9 (7)/ 15.0 (4)	13.9 (11)/ 13.1 (19)	1.21

[a] KIE_{intra}/KIE_{inter}. [b] CH_2Cl_2 at room temperature (V vs SCE).[10b]

Scheme 3



Such a situation is suggestive of a rate-limiting ET process,[15] followed by a PT from the DMA radical cation to the Cu-oxo core.

This rate-limiting ET mechanism is also supported by the intra- and intermolecular deuterium kinetic isotope effect profiles (KIE_{intra} and KIE_{inter}, see Table 2 and Scheme 3).[10a,b,13] In the case of the intramolecular *N*-dealkylation reactions, the KIE_{inter} profile for $\mathbf{1}^{H}$ shows a sharp increase as σ^+ (and $E_{1/2}$) for R−DMAs become more

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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_{intra}. In the case of the intermolecular reaction, there is a negligible difference in the isotope effect (KIE_{inter}) as σ^+ becomes more negative (Table 2), indicating that the ET event is mostly irreversible. If there was a reversible preequilibrium ET followed by a rate-limiting PT (peET/PT), one would expect to observe a KIE_{inter} profile that increases as σ^+ becomes more positive.[10g] The flat KIE_{inter} profile indicates that the PT step has little influence on the overall oxidation of R−DMA by $\mathbf{1^H}$. In other words, the product is determined by the (mostly irreversible) ET in the intermolecular reaction, and not the PT step.

A rate-limiting ET is also supported by comparison of the absolute values obtained for KIE_{intra} versus KIE_{inter} (see Scheme 3). This is a powerful mechanistic probe for distinguishing between an ET or a HAT process.[10e] For a HAT mechanism, the KIE_{intra} should be nearly identical to the KIE_{inter}.[10e] This is because the rate of HAT versus deuterium atom transfer will be proportional to the C−H versus C−D bond dissociation enthalpies (BDEs). The difference in BDEs should be approximately the same in the intra- versus the intermolecular reaction. In the case of the ET process, the expectation is that $KIE_{inter} < KIE_{intra}$.[10e] This is because in the intermolecular reaction the product will be determined by the ET event, while in the intramolecular reaction the PT event can potentially determine the product. For $\mathbf{1^H}$, the values obtained for KIE_{inter} are all less than those obtained for KIE_{intra}, which fully supports a rate-limiting ET pathway for the oxidative *N*-dealkylation of R−DMA (Table 2, Scheme 2a). Also, both KIE_{intra} and KIE_{inter} values are relatively small in magnitude, in line with a rate-limiting ET mechanism.[17]

The situation is different in the case of $\mathbf{1^{Me2N}}$. Competition reactions do not show a strong R-group dependence, with k_{rel} 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 ($\rho = -0.49$, $r^2 = 0.98$).[15] The KIE profiles are largely inconclusive (Table 2), showing no distinct pattern for either HAT or ET.[13] In the case of both KIE_{inter} and KIE_{intra}, what is observed is 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.[10g]

A comparison of the magnitudes of the KIE_{inter} versus KIE_{intra} using the criterion mentioned above sheds further light on our results. For R = MeO and Me, the data suggest that $\mathbf{1^{Me2N}}$ oxidizes R−DMA through a rate-limiting ET mechanism ($KIE_{inter} < KIE_{intra}$), while for the less reducing R−DMAs (H and CN), oxidation appears to occur through a rate-limiting HAT ($KIE_{inter} \approx KIE_{intra}$). 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 $\mathbf{1^H}$, we established rate-limiting ET (vide supra). However, $\mathbf{1^{Me2N}}$ is a weaker one-electron oxidant,[18] and the μ-oxo groups in its Cu_2O_2 moiety should be more basic (as it possesses the stronger donor ligand $MePY2^{Me2N}$).[7] Thus, one would expect slower electron transfer and faster proton transfer in reactions of R−DMAs with $\mathbf{1^{Me2N}}$ relative to $\mathbf{1^H}$; 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 $\mathbf{1^{Me2N}}$. 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 Cu_2O_2 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 $\mathbf{1^{Me2N}}$ from ET to HAT. By similar criteria, a changeover in mechanism is also suggested for $\mathbf{1^{MeO}}$ (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 $\mathbf{1^{R'}}$. The reaction pathways are controlled by changes in the ease of substrate one-electron oxidation and also the reduction potentials of $\mathbf{1^{R'}}$ (which are determined by ligand electronics).[7,8] Coupled to all of this will be changes in the pK_a's of the bis-μ-oxo-ligands in $\mathbf{1^{R'}}$, with stronger donor ligands (R′ = Me_2N and MeO) expected to produce better oxo bases (as H^+ acceptors). Further investigations are needed to sort out these details.

Acknowledgment. This work was supported by the NIH (K.D.K., GM28962; J.S., GM 067447).

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.

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(9) The R′ group identity influences the peroxo/bis-μ-oxo equilibrium (more bis-μ-oxo isomer is present with more electron-donating R′)[8] and rates of THF and MeOH oxidation (>1500× increase in THF oxidation rate for R′ = Me_2N vs R′ = H).[7]
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(12) Yields for R−MA are $\mathbf{1^H}$, ∼60%; $\mathbf{1^{MeO}}$, ∼80%; and $\mathbf{1^{Me2N}}$, ∼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 $Cu_2(O_2)$ core, and that the low isotope incorporation is due to exchange of the carbonyl oxygen with residual water in the solvent.[13]
(15) Johnson, C. D. *The Hammett Equation*; Cambridge University Press: Cambridge, U.K., 1973.
(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 (k_H/k_D could reach a maximum of 23.1).
(18) Shearer, J.; Karlin, K. D., unpublished results. For example, $\mathbf{1^H}$ will oxidize certain ferrocene derivatives that $\mathbf{1^{Me2N}}$ will not.

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