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Reactive Intermediates

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Nucleophilic Reactivity of a Copper(II)-Superoxide Complex**

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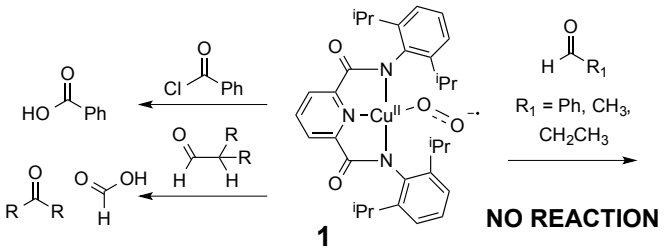
***Abstract**: Metal-bound superoxide intermediates are often implicated as electrophilic oxidants in dioxygen activating metalloenzymes. In the nonheme iron α-ketoglutarate dependent oxygenases and pterin dependent hydroxylases, however, Fe^{III}-superoxide intermediates are postulated to react by nucleophilic attack on electrophilic carbon atoms. By reacting a Cu^{II}-superoxide complex (**1**) with acyl chloride substrates, we have found that a metal-superoxide complex can be a very reactive nucleophile. Furthermore, **1** was found to be an efficient nucleophilic deformylating reagent, capable of Baeyer-Villiger oxidation of a number of aldehyde substrates. The observed nucleophilic chemistry represents a new domain for metal-superoxide reactivity. Our observations provide support for the postulated role of metal-superoxide intermediates in nonheme iron α-ketoglutarate dependent and pterin-dependent enzymes.*

Metal-superoxide species have been implicated as reactive intermediates in the catalytic cycles of a variety of Cu- and Fe-containing metalloenzymes.[1] In the Cu-hydroxylase enzymes, dopamine-β-hydroxylase (DβH) and peptidylglycine α-hydroxylating monooxygenase (PHM), a Cu^{II}-superoxide moiety is postulated to act as an electrophilic hydrogen-atom abstraction (HAA) reagent.[2] X-ray diffraction characterization of a Cu^{II}-superoxide species in PHM provided structural support for this hypothesis.[3] In the nonheme iron enzyme superfamily, Fe^{III}-superoxide intermediates have been ascribed roles as both electrophilic and nucleophilic reactants. For example, in isopenicillin N synthase (IPNS), 2-hydroxyethylphosphonate dioxygenase (HEPD), 2-hydroxypropylphosphonic acid epoxidase (HppE), 1-aminocyclopropane-1-carboxylic acid oxidase (ACCO), an Fe^{III}-superoxide unit is proposed to perform HAA during O_2-activation.[4] In contrast, in the α-ketoglutarate (α-KG) dependent oxygenases, an Fe^{III}-superoxide intermediate is postulated to react with the α-keto-carbon of α-KG by nucleophilic attack.[5] Likewise, in the pterin-dependent hydroxylases a nucleophilic Fe^{III}-superoxide is proposed to attack an electrophilic carbon atom of pterin.[6] An Fe^{III}-superoxide intermediate in a Rieske dioxygenase mutant was recently trapped and spectroscopically characterized,[7] however, rather than display electrophilic HAA or nucleophilic reactivity, this species decayed by electron transfer. Overall, strong experimental support for the role of enzymatic metal-superoxide intermediates acting as electrophilic oxidants exists, whereas little to no support for their postulated roles as nucleophiles has been reported to date.

A number of mononuclear Cu^{II}-superoxide model complexes have been trapped and characterized, allowing for an assessment of the reactivity of the metal-bound superoxide ligand.[1c, 8] These complexes displayed the ability to effect a variety of transformations (HAA, electron transfer, O-atom transfer) that mimic the electrophilic chemistry of copper hydroxylases. Mononuclear Fe^{III}-superoxide complexes remain elusive, while a single example of a dinuclear Fe^{II}-$(OH)_2$-Fe^{III}-superoxide complex exists.[9] This complex was capable of acting as an electrophile in the oxidation of phenols. Evidence for the involvement of Fe^{III}-superoxide intermediates in the activation of dioxygen by Fe^{II} model complexes exists, in one case the postulated Fe^{III}-superoxide species acted as an electrophilic HAA reagent,[10] in the other as a presumed nucleophile.[11] In general, metal-superoxide model complexes display electrophilic reactivity. To the best of our knowledge, no direct evidence for a metal-bound superoxide ligand reacting as a nucleophile has been described to date. As such, no experimental verification of the postulated nucleophilic reactivity of Fe^{III}-superoxide species in the α-KG and pterin-dependent nonheme iron enzymes exists. Herein we describe our investigations into the nucleophilic reactivity of a metal-superoxide model complex towards electrophilic carbonyls.



Scheme 1. Complex **1** and reactions that were investigated.

Of the metal-superoxide complexes that we tested, only Tolman's [N,N'-Bis(2,6-diisoproylphenyl)-2,6-pyridinedicarboxamido]-superoxo-copper(II) complex[8h] (**1**, Scheme 1) was suitably reactive. Indeed, Tolman surmised **1** was likely a good nucleophile, given that it was readily protonated, and displayed poor HAA reactivity. The nucleophilic character of **1** was first tested in its reaction towards acyl chloride substrates,

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electrophiles that commonly react with metal-peroxide complexes.[8a, 12] **1** was reacted with benzoyl chloride (PhCOCl, 10 equiv.) at -80 °C in THF/DMF (3:1). An immediate reaction occurred resulting in the disappearance of the characteristic electronic absorption features (λ_{max} = 627 nm) assigned to **1** within 40 s (Figure 2). ^{1}H NMR and GCMS analysis of the post-reaction products indicated the formation of benzoic acid. A pseudo first-order rate constant (k_{obs}) for the reaction was calculated by plotting the change in absorbance intensity of the λ_{max} = 627 nm feature of **1** against time and fitting the resulting curve (Figure S1, see supporting information file). The second-order rate constant (k_2) was determined by plotting k_{obs}-values determined under a series of substrate concentrations followed by calculating the slope of the resulting linear plot (Figure 1, inset). The k_2-value determined for the reaction between **1** and PhCOCl (4.49 $M^{-1}s^{-1}$) was relatively high compared to k_2-values determined for the reaction between aldehyde electrophiles and nucleophilic peroxide-complexes (Table 1).[12e, 13] This observation is not unexpected as the acyl chloride is anticipated to be more electrophilic than an aldehyde. **1** is thus a capable nucleophile that reacts rapidly with an electrophilic acyl chloride substrate at low temperatures.

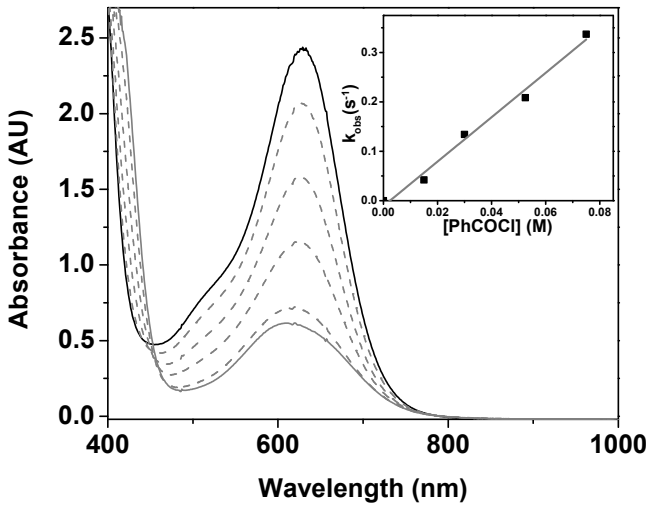


Figure 1. UV-vis spectral changes observed in the reaction between **1** (1.5 mM, solid black trace) and PhCOCl (15 mM) in THF/DMF (3:1) at -80 °C to yield $[Cu^{II}X(L)]^-$ (gray trace). Inset: a plot of the pseudo-first order rate constant (k_{obs}) versus [PhCOCl].

In the reaction between **1** and acyl chlorides we determined k_2-values for a series of *para*-substituted benzoyl chloride substrates (*p*-R-PhCOCl, R = ^{t}Bu, H, F, Cl, NO_2). We hypothesized that a Hammett plot of the $\log({}^Rk_2/{}^Hk_2)$ versus the *para*-substituent Hammett parameter (σ_p) would be linear and yield a positive ρ-value, providing proof of a nucleophilic attack by **1** on *p*-R-PhCOCl. Indeed, Nam has utilized this approach to demonstrate the strong nucleophilic character that certain metal-peroxide complexes possess.[13c-f] However, the Hammett plot yielded a ρ-value close to 0 (Figure S7, all substrates displayed comparable k_2-values). These observations provide a strong indication that the rate-determining step in the reaction between **1** and acyl chlorides is not the nucleophilic attack of the superoxide ligand on the electrophilic carbonyl.

For a better understanding of the nucleophilic reactivity of **1**, we investigated its reactivity in aldehyde deformylation reactions. Previous reports have demonstrated metal-bound peroxide ligands are proficient deformylating reagents.[12e, 13] These studies have provided an understanding of the nucleophilic properties of a variety of metal-peroxide complexes. **1** reacted with 100 equivalents of 2-phenylpropionaldehyde (PPA) at -80 °C in THF/DMF (3:1) (Figure S8). The reaction was complete within 400 s, and GC-MS and ^{1}H NMR analysis of the reaction mixture showed the formation of acetophenone. **1** also reacted with 100 equivalents of cyclohexanecarboxaldehyde (CCA) at -80 °C in THF/DMF (3:1) (Figure S11). The reaction was complete within 20 s, and GC-MS and ^{1}H NMR analysis of the reaction mixture showed the formation of cyclohexanone. The k_2-values determined for the reactions between **1** and PPA and CCA at -80 °C were 0.062 $M^{-1}s^{-1}$ and 1.43 $M^{-1}s^{-1}$ respectively (Figures S9 and S12). Further insight into the reaction between **1** and PPA/CCA was obtained by determining the activation enthalpy and entropy of the reactions. The $\Delta H^{\ddagger}$ values (PPA = 40 $kJmol^{-1}$; CCA = 35 $kJmol^{-1}$) were comparable to those determined for the reaction between PPA/CCA and Fe^{III}- and Co^{III}-peroxide complexes (Tables 1 and S1). The entropy of activation values ($\Delta S^{\ddagger}$, PPA = -63 $JK^{-1}mol^{-1}$; CCA = -80 $JK^{-1}mol^{-1}$) were large and negative, indicative of a bimolecular reaction (See figures S10 and S13). The obtained kinetic and thermodynamic parameters clearly demonstrate that **1** is an effective nucleophilic deformylating reagent that displays reactivity properties similar to those reported for nucleophilic deformylation reactions performed by metal-peroxide complexes.

Table 1. Rate constants and activation enthalpy and entropy values for the deformylation of PPA[a] by metal-dioxygen complexes.

	k_2 (T) $[M^{-1}s^{-1}(°C)]$	$\Delta H^{\ddagger}$ (T) $[kJmol^{-1}(°C)]$	$\Delta S^{\ddagger}$ (T) $[JK^{-1}mol^{-1}(°C)]$
1[b]	0.062 (-80)	40 (-90 to -60)	-63 (-90 to -60)
$[Fe^{III}(\eta_2\text{-OO})(TMC)]^{+}$[c,d]	0.041 (15)	13 (0 to +20)	-24 (0 to +20)
$[Fe^{III}(\eta_1\text{-OOH})(TMC)]^{2+}$[e]	0.13 (-40)		
$[Co^{III}(\eta_2\text{-OO})(14\text{-TMC})]^{+}$[f]	0.058 (0)	55 (-10 to +20)	-90 (-10 to +20)
$[Co^{III}(\eta_2\text{-OO})(13\text{-TMC})]^{+}$[f]	0.015 (25)	62 (+5 to +35)	-77 (+5 to +35)
$[Ni^{III}(\eta_2\text{-OO})(TMC)]^{+}$[g]	0.04 (25)		

[a] PPA = 2-phenylpropionaldehyde. [b] This work. [c] TMC = tetramethylcyclam [d] Ref. [12e]. [e] Ref. [14]. [f] Ref. [13c]. [g] Ref. [13d]

Interestingly, comparison of the k_2-values determined for the reaction between metal-peroxide complexes and PPA/CCA with those established for **1** suggests that **1** is a very reactive oxidant (Tables 1 and S1). For PPA, at -80 °C **1** displayed a k_2-value (0.062 $M^{-1}s^{-1}$) comparable to those determined for Fe^{III}-, Ni^{III}-, and Co^{III}-peroxide complexes at significantly higher temperatures (between -40 and 25 °C, k_2 = 0.015 - 0.13 $M^{-1}s^{-1}$, Table 1). The only model complex that displayed higher deformylation rates than **1** is $[Fe^{III}(\eta_1\text{-}OO^{-})(TMCS)]$, which contains a peroxide dianion ligand that reacted with PPA at -90 °C at such high rates that accurate kinetic analysis was not possible.[15] **1** is thus highly reactive compared to its metal-peroxide compatriots.

Previous studies have demonstrated that *para*-substituted benzaldehydes (*p*-R-PhCHO) can provide mechanistic insights into nucleophilic deformylation reactivity.[13c-f] For Mn^{III}-, Fe^{III}-, Co^{III}-peroxide complexes, a plot of $\log({}^Rk_2/{}^Hk_2)$ versus σ_p was linear with a positive ρ-value. This observation indicated that the peroxide ligand in these complexes was reacting as a nucleophile. With this in mind, we investigated the reactivity of **1** towards *p*-R-PhCHO (R = H, NMe_2, OMe, Me, Cl, NO_2). However, no reaction was observed upon exposure of **1** to up to 100 equivalents of *p*-R-PhCHO at -80 °C in THF/DMF (3:1).[16] *p*-R-PhCHO's would be considered more

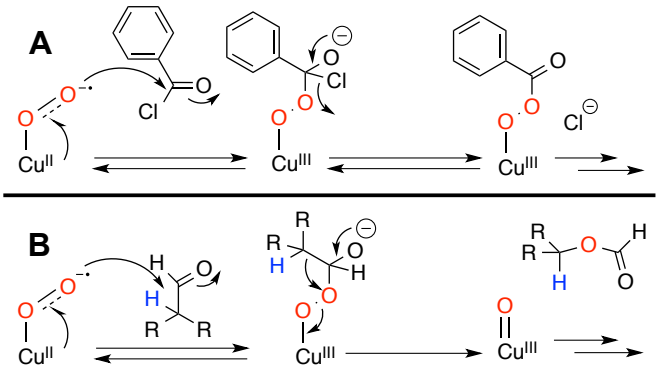
electrophilic than PPA or CCA, therefore these observations were unexpected. Metal-peroxide complexes previously found to be reactive towards PPA or CCA showed higher reaction rates towards *p*-R-PhCHO's.[13c-f]

By comparing the aldehyde substrates that were reactive towards **1** (PPA/CCA) and those that were poorly reactive (*p*-R-PhCHO's), we postulated that the α-H or -C atoms in the aldehyde substrates play a critical role. We investigated the role of the α-H atom by determining the k_{obs}-value for the reaction between **1** and α-deutero-cyclohexanecarboxaldehyde (α-D-CCA).[17] No difference in rate constants for α-H-CCA and α-D-CCA was observed. This would suggest that no acid-base or HAA process involving the α-H atom occurred in the deformylation reaction. We then reacted **1** with aldehyde substrates with varying degrees of α-carbon substitution. No reaction was observed upon addition of 100 equivalents of acetaldehyde (EtA, primary α-carbon) or propanal (PrA, secondary α-carbon) to **1** at -80 °C in THF/DMF (3:1). As discussed above PPA/CCA (tertiary α-carbon) were reactive towards **1**. Finally, **1** reacted with 100 equivalents of trimethylacetaldehyde (TMA, quaternary α-carbon) at -80 °C in THF/DMF (3:1) (k_2 = 0.41 $M^{-1}s^{-1}$, Figures S13 and S14). In summary, the rates of aldehyde deformylation by **1** were controlled by the degree of substitution of the α-C-atom, but not by the availability of an α-H atom in the aldehyde substrate.

The degree of α-C-substitution controls how electron-rich the α-C-atom is. All of the more electron-rich α-C-substrates, PPA, CCA and TMA, were reactive towards **1**. All of the electron-poor aldehyde substrates (*p*-R-PhCHO, EtA, PrA) showed poor reactivity. In contrast, electron poor *p*-R-PhCOCl substrates were very reactive towards **1**. We put these contrasting observations down to one of the following: different reaction mechanisms exist for acyl chloride and aldehyde substrates; *or* the rate-determining step is not influenced by the electrophilicity of the α-C atom; *or* both.

We propose mechanisms for the reactions between **1** and acyl chloride or aldehyde substrates (Schemes 2 and S1) based on mechanisms proposed for metal-peroxide Baeyer-Villiger oxidations.[18] Importantly, we have assumed electron transfer from the Cu^{II} centre to the superoxide ligand upon attack on the electrophilic carbonyl, yielding a Cu^{III}-peroxide intermediate. As in Baeyer-Villiger oxidations, we assumed the initial nucleophilic attack of the superoxide ligand is reversible. We tentatively suggest that the experimental evidence supports this, because the Hammett plot (Figure S7) indicated nucleophilic attack was not rate-determining in the decay of **1**. For the acyl chloride reaction (**A**) we believe the superoxide ligand simply displaces the chloride yielding a Cu^{III}-peracetyl complex, rather than undergoing a Criegee-type rearrangement, because chloride is a good leaving group. The peracetyl complex likely decays via O-O bond scission to yield benzoic acid. Despite the fact that the acyl chloride substrates are likely quite electrophilic, we believe the driving force in their reaction with **1** is not nucleophilic attack, but rather the readiness of the chloride to act as a leaving group.

In contrast, in the reaction between **1** and aldehyde substrates (**B**), we believe Criegee rearrangement must occur in order to yield the ketone products (Schemes 2 and S1). The Criegee rearrangement, where the α-C atom attacks the distal O-atom resulting in O-O bond scission, is presumably irreversible. We believe the Criegee rearrangement step determines the substrate selectivity observed in deformylation reactions performed by **1**. We propose that electron-rich α-C substrates will readily undergo Criegee rearrangement, because they have a nucleophilic α-C atom. We propose that electron-poor α-C substrates will not undergo Criegee rearranegment, because it would be less favoured with electron-poor α-C-atoms. In conclusion, aldehyde substrates with electron-rich α-C-atoms are susceptible to deformylation by **1** because Criegee rearrangement is facile.



Scheme 2. Mechanisms for the initial steps in the reaction between **1** and PhCOCl (**A**) and PPA/CCA (**B**).

In summary, we have demonstrated that the Cu^{II}-superoxide complex, **1**, is a very reactive nucleophilic oxidant. The copper-superoxide complex reacted with acyl chloride substrates yielding carboxylic acids. **1** was also found to be an efficient aldehyde deformylating reagent, capable of Baeyer-Villiger oxidation of electron-rich aldehydes. The observed nucleophilic chemistry represents a new domain for metal-superoxide reactivity. Trapped synthetic and biochemical metal-superoxide intermediates have so far demonstrated electrophilic reactivity. We have demonstrated that a metal-bound superoxide ligand can act as a potent nucleophile, providing experimental support for the postulated role of metal-superoxide intermediates in nonheme iron α-KG and pterin-dependent enzymes. In these enzymes, the superoxide ligand reacts with an electrophilic carbon-atom yielding a metal-peroxide species followed by an oxoiron(IV) oxidant. Present work in our lab is directed towards understanding the postulated Cu^{III}-peroxide species (Scheme 2) and their decay products.

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[16] At higher [*p*-R-PhCHO], a slow decrease in intensity of the λ_{max} = 627 nm feature of **1** over time was observed, indicating **1** was reacting with *p*-R-PhCHO at high [*p*-R-PhCHO]. However, at high [*p*-R-PhCHO] the substrates displayed poor miscibility with the solvent, preventing accurate kinetic analysis.

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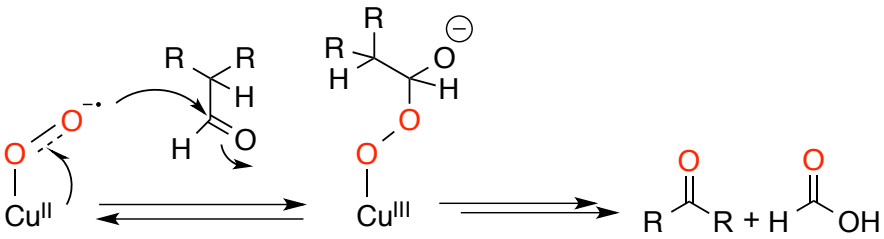
Nucleophilic Reactivity of a Copper(II)-Superoxide Complex



Nucleophilic Superoxide. A metal-superoxide complex has been found to be a highly reactive nucleophile at low temperatures (-80 °C). The copper(II)-superoxide complex reacts readily with certain electrophiles and is capable of the nucleophilic deformylation of electron-rich aldehydes (Baeyer-Villiger oxidation). These observations provide experimental support for the postulated nucleophilic reactivity of metal-superoxide intermediates in the catalytic cycles of certain nonheme iron enzymes.