Reactive Intermediates

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

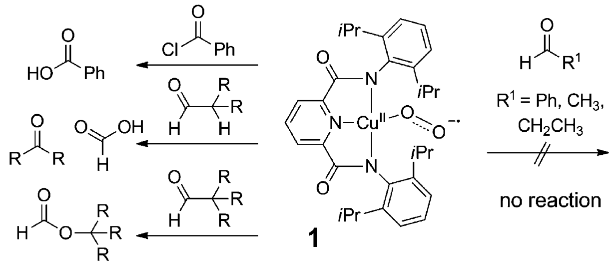
*Paolo Pirovano, Adriana M. Magherusan, Ciara McGlynn, Andrew Ure, Amy Lynes, and Aidan R. McDonald**

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.[1a,4] 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.[5] In ring-cleaving dioxygenases, the Fe–superoxide moiety is believed to undergo radical C–O bond formation with metal-bound catecholate.[6] In contrast, in the α-ketoglutarate (α-KG) dependent oxygenases, an Fe^{III}–superoxide intermediate is postulated to react with the α-keto carbon atom of α-KG by nucleophilic attack.[7] Likewise, in the pterin-dependent hydroxylases, a nucleophilic Fe^{III}–superoxide is proposed to attack an electrophilic carbon atom of pterin.[8] An Fe^{III}–superoxide intermediate in a Rieske dioxygenase mutant was recently trapped and spectroscopically characterized,[9] however, rather than display electrophilic HAA or nucleophilic reactivity, this species decayed through electron transfer. Overall, strong experimental support for the role of enzymatic metal–superoxide intermediates that act 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 an assessment of the reactivity of the metal-bound superoxide ligand.[1c,10] 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.[11] 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,[12] in the other as a presumed nucleophile.[13] Valentine and Sawyer also extensively investigated the chemistry of superoxide and metals.[14] In general, metal–superoxide model complexes display electrophilic reactivity. To the best of our knowledge, no direct evidence for a metal-bound superoxide that reacts 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 toward electrophilic carbonyl groups.

Of the metal–superoxide complexes we tested, only Tolman's [*N*,*N*′-bis(2,6-diisoproylphenyl)-2,6-pyridinedicar-



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

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[*] P. Pirovano, A. M. Magherusan, C. McGlynn, A. Ure, A. Lynes, Dr. A. R. McDonald
School of Chemistry and CRANN/AMBER Nanoscience Institute, Trinity College Dublin
College Green, Dublin 2 (Ireland)
E-mail: aidan.mcdonald@tcd.ie
Homepage: http://www.tcd.ie/Chemistry/staff/people/mcdonald/

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boxamido]-superoxo-copper(II) complex[10h] (**1**, Scheme 1) was suitably reactive. Indeed, Tolman and co-workers surmised that **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 toward acyl chloride substrates, electrophiles that commonly react with metal–peroxide complexes.[10a,15] Complex **1** was reacted with benzoyl chloride (PhC(O)Cl, 10 equiv) at −80 °C in THF/DMF (3:1). An immediate reaction occurred, resulting in the disappearance of the characteristic electronic absorption feature ($\lambda_{max} = 627$ nm) assigned to **1** within 40 s (Figure 1). ^{1}H NMR and GCMS analysis of the 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 $\lambda_{max} = 627$ nm feature of **1** against time and fitting the resulting curve (Figure S1 in the Supporting Information). 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 PhC(O)Cl ($4.49\,\text{M}^{-1}\,\text{s}^{-1}$) was relatively high compared to k_2 values determined for the reaction between aldehyde electrophiles and nucleophilic peroxide complexes (Table 1).[15e,16] This observation is not unexpected as the acyl chloride is anticipated to be more electrophilic than an aldehyde. Complex **1** is thus a capable nucleophile that reacts rapidly with an electrophilic acyl chloride substrate at low temperatures.

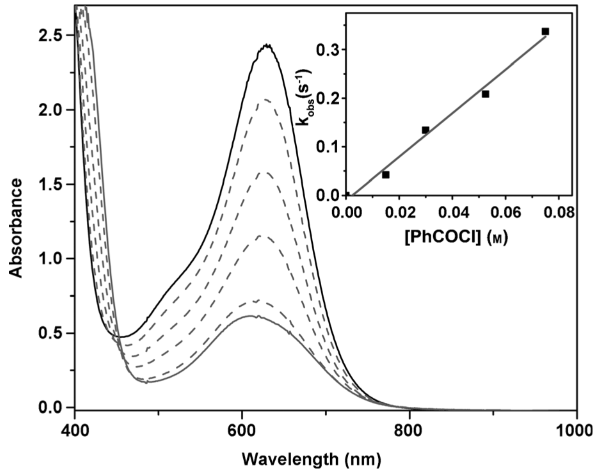


Figure 1. UV/Vis spectral changes observed in the reaction between **1** (1.5 mM, solid black trace) and PhC(O)Cl (15 mM) in THF/DMF (3:1) at −80 °C to give [Cu^{II}X(L)] (gray trace). Inset: Plot of the pseudo-first order rate constant (k_{obs}) versus [PhC(O)Cl].

In the reaction between **1** and acyl chlorides, we determined k_2 values for a series of *para*-substituted benzoyl chloride substrates (p-R-PhC(O)Cl, R = tBu, H, F, Cl, NO$_2$). We hypothesized that a Hammett plot of the log($^{R}k_2/^{H}k_2$) versus the *para*-substituent (σ_p) would be linear and result in a positive ρ value, providing proof of a nucleophilic attack by **1** on p-R-PhC(O)Cl. Indeed, Nam and co-workers utilized this approach to demonstrate the strong nucleophilic character that certain metal–peroxide complexes possess.[16c–f] However, the Hammett plot gave 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 group.

For a better understanding of the nucleophilic reactivity of **1**, we investigated its reactivity in aldehyde deformylation reactions. Previous reports demonstrated that metal-bound peroxide ligands are proficient deformylating reagents.[15e,16] These studies provided an understanding of the nucleophilic properties of a variety of metal–peroxide complexes. Complex **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. When **1** was prepared with K^{18}O$_2$ and reacted with PPA, the resulting acetophenone displayed near-quantitative ^{18}O incorporation. Complex **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 $0.062\,\text{M}^{-1}\,\text{s}^{-1}$ and $1.43\,\text{M}^{-1}\,\text{s}^{-1}$ 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 $\Delta H^{\neq}$ values (PPA = 40 kJ mol^{-1}; CCA = 35 kJ mol^{-1}) were comparable to those determined for the reaction between

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

	k_2 [M^{-1} s^{-1}] (T [°C])	$\Delta H^{\neq}$ [kJ mol^{-1}] (T [°C])	$\Delta S^{\neq}$ [J K^{-1} mol^{-1}] (T [°C])
1[b]	0.062 (−80)	40 (−90 to −60)	−63 (−90 to −60)
[Fe^{III}(η_2-OO)(TMC)]$^{+}$[c,d]	0.041 (15)	13 (0 to +20)	−24 (0 to +20)
[Fe^{III}(η_1-OOH)(TMC)]$^{2+}$[e]	0.13 (−40)		
[Co^{III}(η_2-OO)(14-TMC)]$^{+}$[f]	0.058 (0)	55 (−10 to +20)	−90 (−10 to +20)
[Co^{III}(η_2-OO)(13-TMC)]$^{+}$[f]	0.015 (25)	62 (+5 to +35)	−77 (+5 to +35)
[Ni^{III}(η_2-OO)(TMC)]$^{+}$[g]	0.04 (25)		

[a] PPA = 2-phenylpropionaldehyde. [b] This work. [c] TMC = tetramethylcyclam. [d] Ref. [15e]. [e] Ref. [16g]. [f] Ref. [16c]. [g] Ref. [16d].

PPA/CCA and Fe^{III}–peroxide and Co^{III}–peroxide complexes (Tables 1 and S1). The entropy of activation values ($\Delta S^{\neq}$, 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.

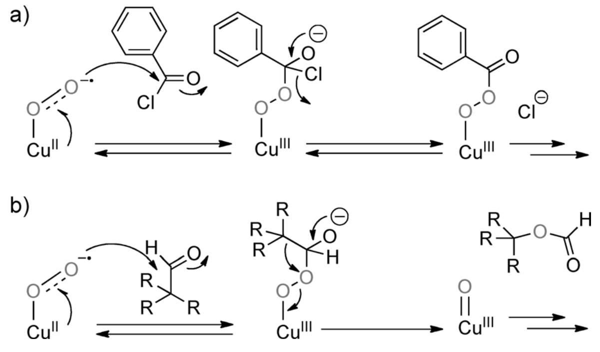
Interestingly, a comparison of the k_2 values determined for the reaction between metal–peroxide complexes and PPA/CCA with those established for **1** suggests that **1** is a very reactive oxidant (Tables 1 and S1). For PPA, at −80 °C **1** displayed a k_2 value (0.062 M^{-1}s^{-1}) comparable to those determined for Fe^{III}–peroxide, Ni^{III}–peroxide, 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}(η_1-OO$^-$)(TMCS=2-mercaptoethyl)-4,8,11-trimethyl-1,4,8,11-tetraazacyclotetradecane), which contains a peroxide dianion ligand that reacted with PPA at −90 °C at such high rates that accurate kinetic analysis was not possible.[17] We assume the two anionic nitrogen donors of the dicarboxamide ligand in **1** render the superoxide ligand very basic/nucleophilic. Complex **1** is thus highly reactive compared to its metal–peroxide counterparts.

Previous studies demonstrated that *para*-substituted benzaldehydes (p-R-PhC(O)H) can provide mechanistic insights into nucleophilic deformylation reactivity.[16c–f] For Mn^{III}–peroxide, Fe^{III}–peroxide, and Co^{III}–peroxide complexes, a plot of log($^{R}k_2/^{H}k_2$) 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** toward p-R-PhC(O)H (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-PhC(O)H at −80 °C in THF/DMF (3:1).[18] p-R-PhC(O)H's would be considered more electrophilic than PPA or CCA, therefore these observations were unexpected. Metal–peroxide complexes that were previously found to be reactive toward PPA or CCA showed higher reaction rates toward p-R-PhC(O)H's.[16c–f]

By comparing the aldehyde substrates that were reactive toward **1** (PPA/CCA) and those that were poorly reactive (p-R-PhC(O)H's), we postulated that the α-H or α-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).[19] 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-C substitution. No reaction was observed upon addition of 100 equivalents of acetaldehyde (EtA, primary α-C) or propanal (PrA, secondary α-C) to **1** at −80 °C in THF/DMF (3:1). As discussed above, PPA/CCA (tertiary α-C) were reactive toward **1**. Finally, **1** reacted with 100 equivalents of trimethylacetaldehyde (TMA, quaternary α-C) 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 toward **1**. All of the electron-poor aldehyde substrates (p-R-PhC(O)H, EtA, PrA) showed poor reactivity. In contrast, electron-poor p-R-PhC(O)Cl substrates were very reactive toward **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 carbonyl-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.[20] We determined that the superoxide ligand in **1** does not dissociate in order to perform the oxidation of aldehyde substrates (Figure S16).[21] Importantly, we assumed electron transfer from the Cu^{II} center to the superoxide ligand upon attack on the electrophilic carbonyl group, giving 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 that the nucleophilic attack was not rate-determining in the decay of **1**. For the acyl chloride reaction (Scheme 2a), we believe the superoxide ligand simply displaces the chloride, giving a Cu^{III}–peracetate complex, rather than undergoing a Criegee-type rearrangement, because chloride is a good leaving group. The peracetate complex likely decays through O−O bond scission to give 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 a nucleophilic attack, but rather the readiness of the chloride to act as a leaving group.



Scheme 2. Mechanisms for the initial steps in the reaction between **1** and a) PhC(O)Cl and b) PPA/CCA/TMA.

In contrast, in the reaction between **1** and aldehyde substrates, we believe Criegee rearrangement must occur in order to give the ketone products (Schemes 2b and S1). The Criegee rearrangement, in which 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**. Our observations mirror trends observed in Baeyer–Villiger oxidation reactions where the migration of substituents during rearrangement is usually determined according to the trend: tertiary alkyl > cyclohexyl > secondary alkyl > primary alkyl.[22] The migrating group is formally an anion, however, a transient cation forms during the rate-determining migration step. We propose that electron-rich α-C aldehyde substrates will readily undergo Criegee rearrangement because the transient cation is stabilized. In contrast, electron-poor α-C substrates will not undergo Criegee rearrangement, because the transient cation will not be stabilized. In conclusion, aldehyde substrates with electron-rich α-C atoms are susceptible to deformylation by **1** because Criegee rearrangement is facile.

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 giving carboxylic acids. Complex **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, resulting in a metal–peroxide species followed by an oxo-iron(IV) oxidant. Present work in our group is directed toward understanding the postulated Cu^{III}–peroxide species (Scheme 2) and their decay products.

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