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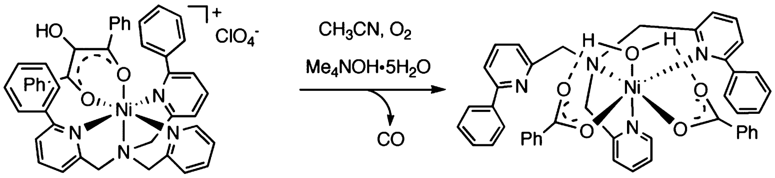

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Aliphatic Carbon−Carbon Bond Cleavage Reactivity of a Mononuclear Ni(II) *cis-β*-Keto−Enolate Complex in the Presence of Base and O_2: A Model Reaction for Acireductone Dioxygenase (ARD)

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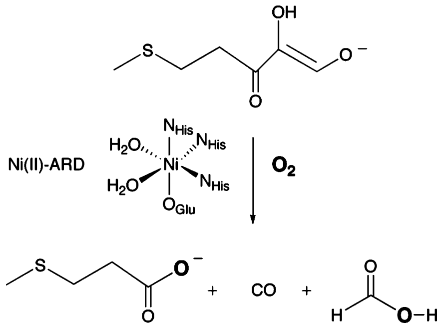
This report describes the synthesis, characterization, and aliphatic carbon−carbon bond cleavage reactivity of a Ni(II) *cis-β*-keto−enolate complex, $[(6\text{-}Ph_2TPA)Ni(PhC(O)C(OH)C(O)Ph)]ClO_4$ (**1**, 6-Ph_2TPA = *N*,*N*-bis((6-phenyl-2-pyridyl)methyl)-*N*-((2-pyridyl)methyl)amine). In the presence of 1 equiv of base and O_2, **1** undergoes reaction to produce $[(6\text{-}Ph_2TPA)Ni(O_2CPh)_2(H_2O)]$ (**2**) and CO.

Metal-containing dioxygenases catalyze the incorporation of both oxygen atoms of O_2 into one or more substrates. Examples include Rieske and catechol dioxygenases, which catalyze oxidative hydroxylation and ring-opening reactions of aromatic substrates, respectively, and typically have a nonheme iron center.[1] Recently, examples of dioxygenases that catalyze oxidative aliphatic carbon−carbon bond cleavage have been reported. These include the acetylacetone dioxygenase Dke1 from *Acinetobacter johnsonii*[2] and quercetin 2,3-dioxygenase.[3,4] The latter enzyme contains either a nonheme iron[3] or copper[4] ion within the active site, depending on the source from which the enzyme is obtained. Notably, quercetin dioxygenase is a rare example of a CO-forming enzyme. The only other prokaryotic metalloenzyme that catalyzes the dioxygenolytic release of CO is the 1,2-dihydroxy-3-oxo-(*S*)-methylthiopentene 1,3-dioxygenase (acireductone dioxygenase, ARD).[5] This enzyme catalyzes the O_2-dependent oxidation of the acireductone substrate to yield formic acid, carbon monoxide, and 2-methylthiopropionate (Scheme 1). Isotope labeling studies using $^{18}O_2$ have shown that the oxygen atoms are incorporated as shown in Scheme 1. This reaction is a shunt out of the methionine salvage pathway in *K. pneumoniae*.[5] ARD is the only known example to date of a Ni(II)-containing dioxygenase.[6] EXAFS experiments suggest that in the resting state the Ni(II) center in ARD is ligated by three histidine donors, one carboxylate, and two water ligands.[7] In the presence of substrate, EXAFS data obtained under anaerobic conditions suggest bidentate coordination of the acireductone substrate with release of one histidine ligand and one water molecule.[7]

To begin to investigate possible coordination motifs of an ARD-type substrate on a mononuclear Ni(II) center, we have initiated studies of the coordination chemistry of the monoanion of 2-hydroxy-1,3-diphenylpropan-1,3-dione (Figure 1 (bottom)).[8] While not an exact replica of the ARD substrate, use of this bulky analogue has enabled the isolation and characterization of a novel mononuclear Ni(II) *cis-β*-keto−enolate complex with relevance to the proposed substrate-bound species in ARD. Notably, in the presence of 1 equiv of base, this complex is reactive with O_2 to produce reaction products, including CO, consistent with an ARD-type reaction.

Scheme 1



Under a nitrogen atmosphere, admixture of equimolar amounts of 6-Ph_2TPA,[9] $Ni(ClO_4)_2 \cdot 6H_2O$,[10] $Me_4NOH \cdot 5H_2O$, and 2-hydroxy-1,3-diphenylpropan-1,3-dione in CH_3CN resulted in the formation of a deep orange solution. Following removal of the CH_3CN under reduced pressure, the remaining orange solid was redissolved in CH_2Cl_2 and filtered through a Celite/glass wool plug. The product of this reaction, $[(6\text{-}Ph_2TPA)Ni(PhC(O)C(OH)C(O)Ph)]ClO_4$ (**1**, Scheme 2), was isolated in two ways. Pentane diffusion into the CH_2Cl_2 filtrate at room temperature produced a few small orange−brown crystals suitable for X-ray crystallography. However, a higher yield of the product (92%) was obtained via hexane addition to the CH_2Cl_2 filtrate, which resulted in the deposition of an analytically pure orange powder.

X-ray crystallographic studies of **1** revealed the presence of a distorted octahedral mononuclear Ni(II) cation having bidentate coordination of the monoanion of 2-hydroxy-1,3-diphenylpropan-1,3-dione (Figure 2). Consistent with a delocalized enolate formulation for the bound chelate anion in this complex are similar bond distances for the Ni(II)-coordinated C−O donors (C(37)−O(1) 1.276(3) Å and C(39)−O(2) 1.278(3) Å) and similar C−C bond distances within the chelate ring. As expected, the C(38)−O(3)H distance in **1** (1.407(3) Å) is ~0.13 Å longer than the other C−O bond distances noted above. The hydroxyl proton of **1**, which was located and refined independently, is involved in a hydrogen bonding interaction with the perchlorate anion.

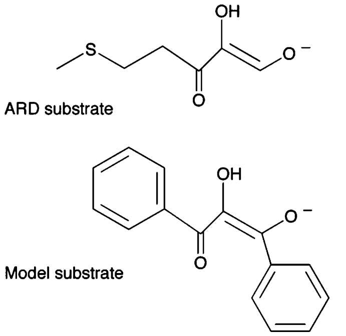


Figure 1. Comparison of ARD and model substrate.

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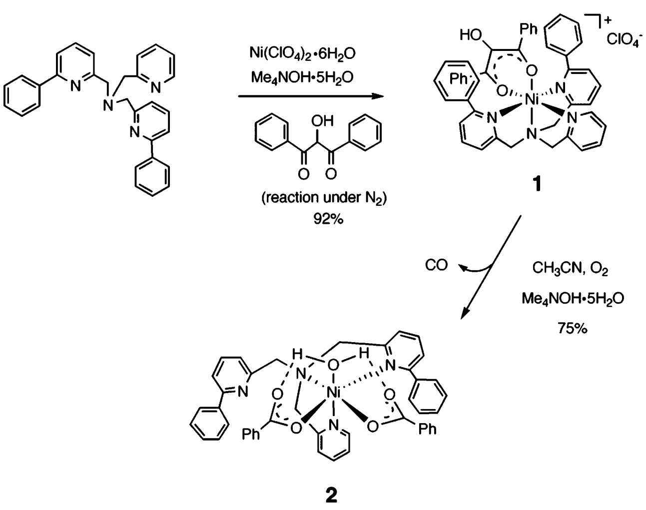
Scheme 2



Complex **1** has also been characterized by ^{1}H NMR and electronic absorption and infrared spectroscopy. In the ^{1}H NMR (Figure S1(c)), **1** exhibits resonances for the β-protons of the pyridyl rings in the range of 30−60 ppm. This is similar to other mononuclear Ni(II) complexes of the 6-Ph_2TPA ligand.[11] The electronic absorption spectrum of **1** has a distinctive feature at 394 nm ($\epsilon = 2400$ $M^{-1}cm^{-1}$; Figure S2). The infrared spectrum of **1** contains a broad, intense ν_{O-H} stretch at 3430 cm^{-1}.

In the proposed catalytic cycle of ARD, a Ni(II)-coordinated doubly deprotonated enediolate substrate is suggested to undergo reaction with O_2.[7b] In an attempt to obtain the same protonation level in the synthetic system, isolated **1** was treated with 1 equiv of $Me_4NOH{\cdot}5H_2O$ under a nitrogen atmosphere. This resulted in a shift of the electronic absorption feature to 420 nm ($\epsilon = 2500$ $M^{-1}cm^{-1}$) (Figure S2), suggesting the formation of a new complex in solution. Efforts to isolate this complex are currently in progress. Addition of excess O_2 to the solution resulted in rapid bleaching of the orange color at ambient temperature and formation of a single new Ni(II) complex, [(6-Ph_2TPA)Ni($O_2CPh)_2(H_2O)$] (**2**, Scheme 2). Complex **2** was characterized by X-ray crystallography, ^{1}H NMR (Figure S1(d)), UV−vis, FAB-MS, FTIR, and elemental analysis.

An ORTEP drawing of **2** is shown in Figure 3. The mononuclear Ni(II) center in **2** has two monodentate coordinated benzoate anions, one water ligand, and κ^3-coordination of the 6-Ph_2TPA ligand. The water ligand donates hydrogen bonds to both of the Ni(II)-bound carboxylate ligands.

Treatment of **1** with $Me_4NOH{\cdot}5H_2O$ (1 equiv) and $^{18}O_2$ (99%, ICON Services) in CH_3CN yielded **2-^{18}O** having a single ^{18}O atom incorporated into each carboxylate ligand in the majority of the sample. As shown in Figures S3 and S4, FAB-MS analysis of **2-^{18}O** revealed a molecular ion peak at $m/z = 623$, a value consistent with the formulation [(6-Ph_2TPA)Ni($^{16}O^{18}OCPh$)]$^+$. Production of CO in the reaction leading to the formation of **2** was detected using the palladium chloride method, in which elemental palladium is deposited upon reaction with CO in the presence of water.[12]

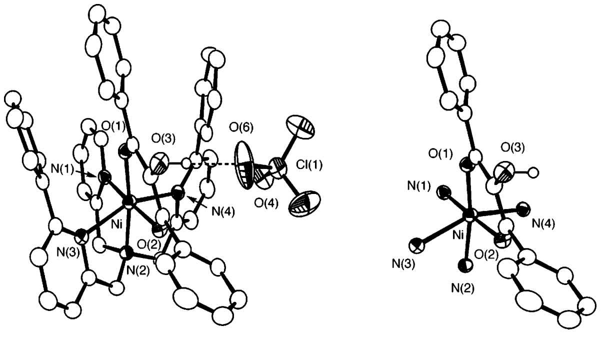


Figure 2. (Left) ORTEP drawing of **1**. (Right) ORTEP drawing of the Ni(II) coordination environment in the cationic portion of **1**. Ellipsoids are depicted at the 50% probability level. All hydrogen atoms except the hydroxyl proton have been omitted for clarity.

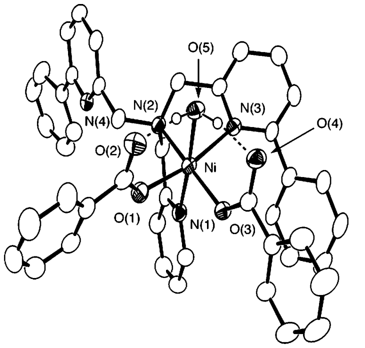


Figure 3. ORTEP drawing of [(6-Ph_2TPA)Ni($O_2CPh)_2(H_2O)$] (**2**). Ellipsoids are depicted at the 50% probability level. All hydrogen atoms except the water protons have been omitted for clarity.

Overall, this work provides the first functional model system of relevance to the active site chemistry of acireductone dioxygenase (ARD). Our ongoing efforts are focused on elucidating mechanistic details of this novel oxidation reaction.

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Supporting Information Available: X-ray crystallographic (CIF) files for **1** and **2**; ^{1}H NMR spectra of **1**, **2**, and other Ni(II) complexes of the 6-Ph_2TPA ligand; UV−vis spectra of **1** and this complex in the presence of 1 equiv of $Me_4NOH{\cdot}5H_2O$; FAB-MS spectrum of **2-^{18}O**. This material is available free of charge via the Internet at http://pubs.acs.org.

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