

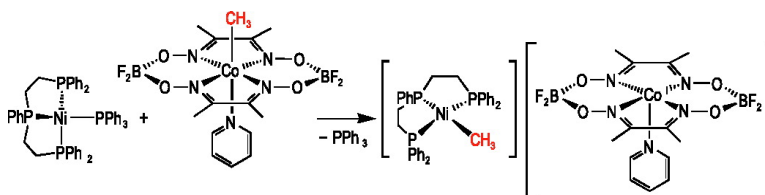
Communication

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Methyl Transfer from Methylcobaloxime to (Triphos)Ni(PPh₃): Relevance to the Mechanism of Acetyl Coenzyme A Synthase

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Acetyl coenzyme A synthase/carbon monoxide dehydrogenase (ACS/CODH) is a bifunctional enzyme found in certain methanogenic, acetogenic, and sulfate-reducing organisms. The reduction of CO₂ to CO and the production of acetyl coenzyme A (acetyl-CoA) allow these organisms to grow autotrophically via the Wood-Ljungdahl pathway.¹ The active site for acetyl CoA synthesis, termed the A cluster, is a metallocluster containing a dinickel site bridged to an Fe₄S₄ cuboidal cluster.² The catalytic assembly of CO, CH₃-cob(III)alamin, and CoA to yield acetyl CoA and cob(I)alamin is proposed to proceed at one of the two nickel ions, the "labile-nickel" site, Ni_p, which resides between the Fe₄S₄ cluster and the diamido, dicysteinato Ni(II)_d site.³

Evidence has been presented in support of an S_N2-type reaction between methylcob(III)alamin and Ni_p with the equilibrium favoring the products.^{3,4} The oxidation state of the nickel nucleophile has yet to be established. Evidence for a Ni_p⁺ state (A_{red}-CO) has been presented.⁵ If this species participates in an S_N2 methylation, a Ni³⁺-Me intermediate would result. However, the products of the transmethylation reaction are diamagnetic, indicating that the proposed Ni³⁺-Me intermediate must be rapidly reduced by one electron, perhaps from the Fe₄S₄ cluster.⁶ Recent kinetic studies suggest that A_{red}-CO is not involved in the catalytic cycle.⁷ An alternative proposal by Lindahl implicates Ni_p⁰ as the nucleophile attacking methylcob(III)alamin generating a Ni²⁺-Me intermediate.³ A transformation accessing the Ni^{2+/0} couple is more favorable from an organometallic perspective.⁸

Previously, the cobalt(III) complex, MeCo(dmgBF₂)₂py (MeCo) was shown to react with 2 equiv of Ni⁺, [Ni(tmc)][OTf], via an electron-transfer mechanism producing the Ni²⁺-Me species, [Ni(tmc)Me][OTf].^{9,10} Here, we demonstrate that the reaction between MeCo and a Ni⁰ source, (triphos)Ni(PPh₃),¹⁰ yields a Ni²⁺-Me complex via a different mechanism. Triphos was selected as an appropriate ancillary ligand because (i) the electronic donor aptitude of bridging thiolates has been likened to phosphines¹¹ and (ii) the flexible chelate supports both tetrahedral and square planar stereochemistries, geometries favored for Ni⁰ and Ni²⁺, respectively. To our knowledge, alkyl transfer from MeCo to Ni⁰ is unprecedented.

Combining equimolar amounts of triphos, Ni(COD)₂, and PPh₃ in THF, followed by stirring for 12 h at ambient temperature and precipitation with pentane, gave a bright orange solid. Recrystallization via slow evaporation of a Et₂O solution provided large orange blocks in modest yield (50%). A diagnostic ³¹P NMR spectrum is obtained in C₆D₆: two signals are observed in a 3:1 ratio corresponding to the PPh₃/Ph₂P and PhP groups of the complex, respectively (δ = 37.5 (m, 3P) and 46.95 (dt, 1P)).

Mixing equimolar amounts of MeCo in CH₃CN and (triphos)-Ni(PPh₃) in THF under an inert atmosphere generates a deep-blue solution, corresponding to formation of the intense Co(I) chromophore, [Co(dmgBF₂)₂py]⁻ ([Co]). The reaction time course can be followed spectrophotometrically, and after ~1 h quantitative

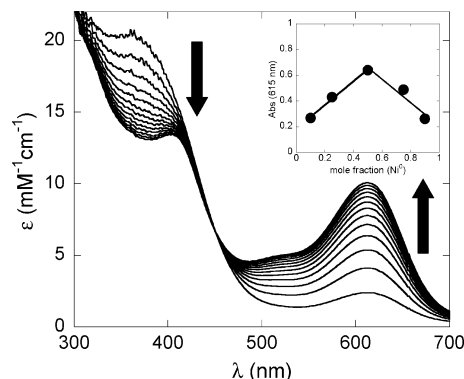
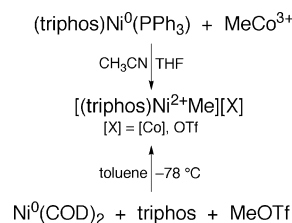


Figure 1. Time course of the formation of [Co] in the reaction of 0.25 mM MeCo and 0.25 mM (triphos)Ni(PPh₃). Spectra were recorded at 4 min intervals at 20 °C (initial scan is at *t* = 4 min). The inset shows the Job plot of the reaction of MeCo and (triphos)Ni(PPh₃). The absorption maxima were reached at 0.5 mole ratio, indicating a 1:1 stoichiometry of reaction.

Scheme 1



formation of [Co] is confirmed (Figure 1). A Job plot analysis establishes a Ni:MeCo stoichiometry of 1:1 (Figure 1, inset).

This reaction can also be followed by ¹H and ³¹P NMR spectroscopies. Mixing solutions of MeCo in CD₃CN and (triphos)-Ni(PPh₃) in C₆D₆ gives immediate formation of deep-blue [Co]. The ³¹P NMR spectrum shows a distinct change in chemical shift of the triphos signals, with them shifting downfield with respect to the signals for (triphos)Ni(PPh₃): δ = 47.8 (d, 2P) and 95.8 (t, 1P) with *J*_{PP} of 23 Hz. These values are consistent with a Ni²⁺ ion bound by triphos in a square-planar environment.¹² The ¹H NMR spectrum shows complete loss of signals attributable to MeCo (δ = 1.2) and growth of two new dmg-containing species. These species are assigned as [Co(dmgBF₂)₂py]⁻ and [Co(dmgBF₂)₂(CD₃CN)]⁻, on the basis of comparison to reported values.^{7b} Indeed, axial ligand exchange at cobalt has been established previously.¹³ More importantly, a new signal arises at δ = 0.34. This resonance integrates to three protons and couples to the phosphorus nuclei of the triphos ligand. The coupling constants are within values observed for phosphine-containing methylnickel(II) complexes (*J*_{HP1} = 4 Hz; *J*_{HP2} = 8 Hz).¹⁴ Taken together, NMR and absorption spectroscopies suggest a clean 1:1 reaction yielding [(triphos)NiMe]-[Co(dmgBF₂)₂py] (Scheme 1).

Addition of a CD₃CN solution of the perdeuteromethyl complex, CD₃Co, to a C₆D₆ solution of (triphos)Ni(PPh₃) gave immediate

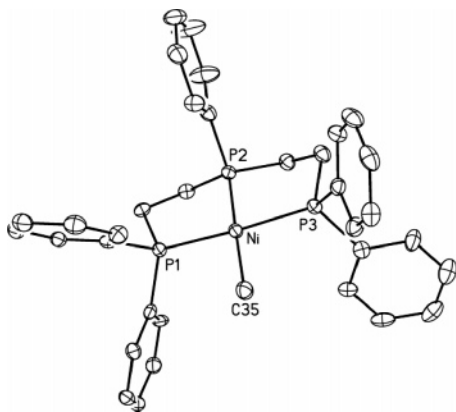


Figure 2. Thermal ellipsoid depiction of the cation of [(triphos)NiMe]OTf. H atoms and OTf[−] removed for clarity. Ellipsoids are shown at 30% probability. Metrical parameters are provided in SI.

formation of [Co]. The ¹H NMR spectrum shows similar spectral features to the reaction with protio MeCo, with the exception of the lack of the Ni–Me signal at $\delta = 0.34$. The deuterium NMR spectrum shows that quantitative transfer of the methyl group is effected, with a single Ni²⁺–CD₃ species produced, $\delta = 0.2$.

Independent synthesis of [(triphos)NiMe]OTf was achieved via oxidative addition of MeOTf to a stoichiometric mixture of triphos and Ni(COD)₂ in toluene at $-78\text{ }^{\circ}\text{C}$.¹⁵ The OTf salt was crystallized by slow diffusion of Et₂O into a saturated toluene solution at room temperature (Figure 2). The spectroscopic data of [(triphos)NiMe]OTf are nearly identical to those of the product of methyl transfer from MeCo to (triphos)Ni(PPh₃). A solution of [(triphos)NiMe]OTf in CD₃CN exhibits ³¹P NMR signals at $\delta = 46.5$ (d, 2P) and 98.0 (t, 1P) (*J*_{PP}: 23 Hz). The Ni–Me signal is observed at $\delta = 0.04$ with an identical coupling pattern. The very similar spectroscopic properties of [(triphos)NiMe]OTf and the transmethylation product, [(triphos)NiMe][Co], corroborate that methyl transfer has been achieved (Scheme 1).

Next, we sought to test the hypothesis that CO ligation to Ni⁰ reduces the nucleophilicity, impeding the transmethylation reaction. In the context of ACS catalysis, this implies an ordered binding of Me⁺ followed by CO. The A_{red}–CO based mechanism necessarily requires initial binding of CO.⁵ Darnault et al. have proposed a mechanism that proceeds through a tetrahedral Ni⁰_P–CO intermediate.^{2b} An alternative mechanism requires that a coordinatively unsaturated Ni⁰_P attacks methylcob(III)alamin prior to CO binding.³ To evaluate these proposals, (triphos)NiCO¹⁶ was reacted with MeCo in CD₃CN/C₆D₆. After 24 h at room temperature, there was no evidence for formation of [(triphos)NiMe]⁺. Approximately 10% of (triphos)NiCO had decomposed, along with concomitant formation of [Co] (see Supporting Information for details). In stark contrast, (triphos)Ni(PPh₃) was methylated quantitatively in ~1 h under similar conditions. These striking differences in reactivity provide chemical precedent in support of the hypothesis that Me binds before CO in ACS catalysis.

We have shown that MeCo can quantitatively methylate a Ni⁰ complex, (triphos)Ni(PPh₃). Electrochemical experiments suggest that this reaction does not take place via electron transfer. The potential of the Ni⁺⁰ couple of (triphos)Ni(PPh₃) (-100 mV vs NHE) is too positive to reduce MeCo (-1.1 V vs NHE). Therefore, we propose that this transformation takes place via an S_N2 mechanism. This small molecule model reaction suggests that the

S_N2 methyl-transfer in ACS/CO₂H can proceed through a Ni⁰ intermediate. Importantly, these studies provide a chemical reactivity-based rationale for the ordered binding of Me, then CO, during ACS catalysis. In vitro experiments and structure-based arguments have proven contentious with regard to the order of binding during catalysis. We are currently investigating the kinetics of this reaction to obtain a more detailed understanding of the mechanism.

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Supporting Information Available: Experimental details, spectral characterization, and full crystallographic data for (triphos)Ni(PPh₃) and [(triphos)NiMe]OTf. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (10) Abbreviations: dm²BF₂ = (difluoroboryl)dimethylglyoximate; tmc = 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane; OTf[−] = trifluoromethanesulfonate; triphos = bis(2-diphenylphosphinoethyl)phenylphosphine.
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