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Binuclear Complexes Containing a Methylnickel Moiety: Relevance to Organonickel Intermediates in Acetyl Coenzyme A Synthase Catalysis

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Organonickel species have been implicated as catalytic intermediates in several enzyme reactions,[1] specifically transformations that shuttle one carbon species within the anaerobic world. Archaea and anaerobic bacteria grow autotrophically using carbon dioxide or sulfate as their terminal electron acceptors.[2] Examples of proposed bioorganometallic enzyme intermediates include the methylnickel species in methyl coenzyme reductase (MCR) and acetyl coenzyme A synthase (ACS), and Ni-CO adducts in carbon monoxide dehydrogenase (COdH) and ACS. Until very recently, the evidence supporting the involvement of such novel biological species has been indirect, that is, direct spectroscopic or structural authentication of such species is lacking. However, several recent reports provide the first direct evidence for a methylnickel(III) state in MCR[3] and a Ni(CO_2) adduct in COdH.[4]

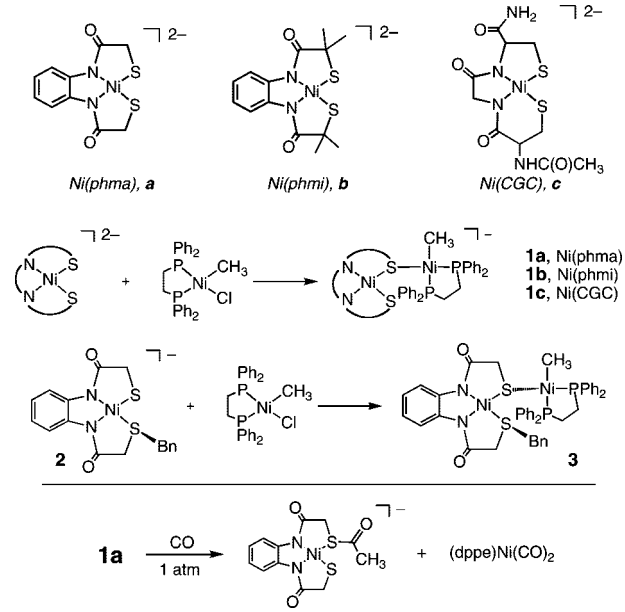
The ACS enzyme, found in archaea and sulfate-reducing bacteria, possesses an unprecedented active site cluster of [Fe_4S_4]Ni_2 composition.[5,6] The two Ni sites are structurally distinct with consensus building toward Ni_p (proximal to the Fe_4S_4 cluster) as the locus for methyl binding.[7,8] Since the first protein structure report in 2002, a number of laboratories including ours[9,10] have modeled aspects of the binuclear NiNi site.[11] Herein, we report initial efforts to prepare binuclear complexes containing a methylnickel moiety and explore their dynamic properties and reactivity to provide further understanding of organonickel catalysis in biology.[12]

A series of binickel complexes containing a methylnickel moiety were prepared via condensation of monomer precursors. This condensation strategy has been applied extensively using Ni(N_2S_2) complexes leading to their apt moniker "metalloligands." In the present context the Ni(N_2S_2) species serve as monodentate donors that mimic key aspects of the Ni_d site with K_2[Ni(CGC)][10] replicating the exact coordination motif. Addition of any one of three (diamidodithiolato)nickel complexes to (dppe)Ni(CH_3)Cl[13] proceeds to the thiolato-bridged binuclear complexes, **1**, Scheme 1. The red-to-orange complexes have been characterized by electronic absorption, ^{1}H, ^{31}P NMR and high resolution mass spectroscopies, and in one case by X-ray diffraction.

The structure of the anion, **1a** is depicted in Figure 1 (left). A single thiolato bridge supports the binuclear core with slightly different Ni−S distances, 2.192(1) and 2.230(1) Å. The Ni−C distance is typical for a square planar site, 1.966(2) Å. The orientation of the two square planes defined by the respective metal coordination spheres places the methyl group in proximity of the other Ni. The Ni−Ni distance, 2.952(1) Å, is most similar to the distance found in the structure of the reduced A cluster from *C. hydrogenoformans*, 3.0 Å an unmethylated enzyme state containing two square planar Ni sites.[6]

The three complexes differing in the identity of the Ni(N_2S_2) ligand present disparate solution behavior as diagnosed by ^{31}P NMR spectroscopy (Supporting Information). At room temperature the ^{31}P NMR spectra of **1b** and **1c** display sets of sharp resonances.[14] In contrast, the room temperature ^{31}P NMR spectrum of **1a** contains two

Scheme 1



very broad signals, barely discernible above the baseline. At 265 K, a set of resonances emerges which sharpen upon further cooling ultimately resolving to two broad singlets, $\delta = 58, 41$. Upon warming to room temperature, the ^{31}P NMR spectrum is again void of signals, indicating a reversible process. Warming solutions of **1b** above ambient temperatures results in significant line broadening with coalescence reached at ca. 336 K. The variable temperature data reflect a fluxional process in which the methyl and thiolate donors exchange positions. Quantitative analysis of the temperature-dependent (243−278 K) ^{31}P NMR spectral data of **1a** using line shape analyses yields $\Delta G^{\ddagger}_{280K} =$ 12(2) kcal/mol, $\Delta H^{\ddagger} = 17(2)$ kcal/mol and $\Delta S^{\ddagger} = 18(3)$ cal/mol-K. At 310 K, k(**1a**) is 250 times larger than k(**1b**) indicating reduced lability for the more electron-rich thiolates in the latter. The modest free energy and particularly the large positive activation entropy required suggests that the dynamic process proceeds via a dissociative

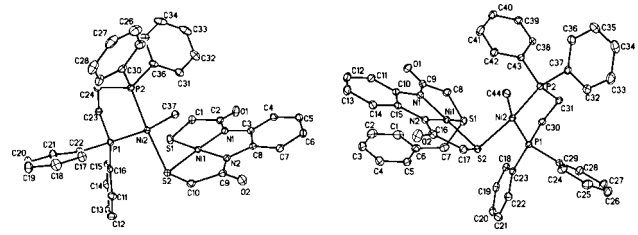


Figure 1. Structural diagrams of the anion, **1a** (left) and **3** (right); hydrogen atoms omitted for clarity. Ni−CH_3 distances are 1.966(2) and 1.963(2) Å, respectively.

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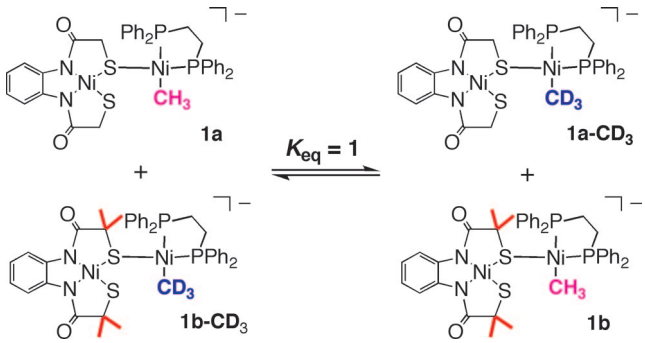
Scheme 2



exchange involving thiolate dissociation, $[Ni(dppe)Me]^+$ isomerization and religation.[15] Indeed, thiolate exchange is facile as demonstrated by two experiments. First, the crossover experiment depicted in Scheme 2 proceeds within the time of mixing equimolar solutions of **1a** and **1b-CD$_3$** generating an equilibrium mixture of all four species with $K_{eq} = 1$. Alternatively, addition of $K_2[Ni(phmi)]$ to **1a** rapidly generates an equilibrium mixture of **1a** and **1b**.

To examine complexes in which intramolecular exchange is not possible, selective alkylation of one thiolate donor was performed. The target organonickel derivative, **3**, was prepared via sequential benzylation followed by condensation, Scheme 1. The structure of **3** is contained in Figure 1 (right). The Bn and $Ni(dppe)CH_3$ fragments are found on opposite faces of the Ni(phma) unit, that is, only the anti isomer is present in the solid state (and solution). The Ni−C distance is 1.963(2) Å and the Ni—Ni separation is 3.184(1) Å, the latter parameter reflecting greater steric congestion than in **1a**. The ^{31}P NMR spectrum of **3** at room temperature contains two signals consistent with no/slow exchange on the NMR time scale. The stability of **3** establishes that a single thiolate bridge is sufficient for complex formation.

The ability of these small molecules to promote stoichiometric thioester formation was assessed. Exposure of a DMSO solution of **1a-CD$_3$** (or **1a**) to 1 atm of CO results in a rapid color change from orange to green resulting in the formation of $[Ni(phma\text{-}C(O)CD_3)]^-$ (86%) and $(dppe)Ni(CO)_2$, Scheme 1. The former species contains a single thioester while maintaining the nickel ligation as deduced by ES-MS analysis. Monitoring the fate of the CD_3 group by ^{2}H NMR spectroscopy reveals complete loss of the Ni−CD_3 ($\delta = 0.48$) with concomitant growth of a resonance at $\delta = 2.13$. In samples of **1a** exposed to ^{13}CO, this resonance (in the ^{1}H NMR spectrum) is a doublet, $^2J_{CH} = 7$ Hz consistent with acyl assignment. The products are proposed to result from CO insertion generating a binuclear Ni−C(O)Me followed by reductive elimination. Similar thioester formation from monomeric nickel alkyl/thiolate complexes has been described;[16] the present results extend these studies for the first time to a binuclear complex.

In sum, a series of NiNi binuclear complexes have been synthesized in an effort to model the methylnickel intermediate proposed at the A-cluster of ACS. Through facile condensation reactions employing suitable precursors several different $[Ni(N_2S_2)]$ fragments were installed in creating the binuclear complexes. The structural differences among these metalloligands have imparted disparate properties on the binuclear complexes evident by their solution state dynamic behavior. Significantly, the kinetic lability of the thiolate bridges serves to highlight a potential role for reversible Ni−S bond rupture in opening coordination sites at Ni_p that could be requisite for elementary steps in catalysis, that is, CO and/or CoA binding, a point supported by computational studies.[8] While carbonylation results in thioester formation at the bridging thiolate, a transformation not observed in the enzymatic reaction, the mechanism of the model reaction remains to be deduced. The enzyme does not acetylate the bridging Cys residues as these thiolates are expected to be poorer nucleophiles. Given thiolate lability it is conceivable that an incipient $[(dppe)Ni(C(O)Me)]^+$ fragment is subject to external attack by $[Ni(phma)]^{2-}$, that is, intermolecular thioester formation. Contemporaneous efforts have sought to prepare methylnickel complexes via the biologically relevant transmethylation from organocobalt reagents.[17] The diversity of these molecules may lead to differing reactivity that will allow for comprehensive model studies of proposed intermediates along a catalytic pathway that is still not fully understood.

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Supporting Information Available: Experimental details, characterization data, and crystallographic information (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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