Nickel-Mediated Formation of Thioesters from Bound Methyl, Thiols, and Carbon Monoxide: A Possible Reaction Pathway of Acetyl-Coenzyme A Synthase Activity in Nickel-Containing Carbon Monoxide Dehydrogenases

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Abstract: Current mechanistic proposals for the acetyl synthase activity of nickel-containing carbon monoxide dehydrogenases (CH_3−THF + CoA·SH → CoA·SCOCH$_3$ + THF; THF = tetrahydrofolate, CoA·SH = coenzyme A) implicate a Ni catalytic center and the steps [Ni−CH_3] → [Ni−$COCH_3$] → CoA·SCOCH$_3$. The second step presumably involves attack by the sulfur nucleophile of coenzyme A at the acyl carbon atom in the overall reaction [Ni^{II}−$COCH_3$] + RS(H) → RSCOCH$_3$ + Ni^{II} (+ H^+) + 2e$^-$. We have previously demonstrated these steps in Ni(II) complexes with physiological-type ligation. In this work, it is shown that the reaction of acyl and thiolate ligands coordinated to Ni(II) affords thioesters in high yield. The complex [Ni(bpy)(CH_3)$_2$], established to be planar by an X-ray structure determination, reacts with 1 equiv of arenethiol to afford diamagnetic planar [Ni(bpy)(CH_3)(SR)] (**8**) with R = *p*-$C_6H_4CH_3$, 2,6-$C_6H_3(CH_3)_2$ (**8b**), mesityl (**8c**), 2,4,6-C_6H_2iPr$_3$, and 2,6-$C_6H_3Cl_2$ (**8e**) (bpy = 2,2′-bipyridyl). An analogous reaction gives [Ni(bpy)(C_2H_5)(S-mesityl)] (**12**) from [Ni(bpy)(C_2H_5)$_2$]. Planar structures of **8c,e** were confirmed by X-ray analysis. Complexes **12** and **8** with different R substituents undergo thiolate ligand exchange in THF with $K_{eq} \approx 1$. Reaction of **8e** with 1 equiv of carbon monoxide yields the acyl complex [Ni(bpy)($COCH_3$)(S-2,6-$C_6H_3Cl_2$)] (**9a**), whose planar coordination unit was confirmed by X-ray methods. Treatment of the complexes **8** in THF with more than 3 equiv of carbon monoxide yields [Ni(bpy)(CO)$_2$] and the thioesters RSCOCH$_3$ in 96−100% yield *in situ*. A solution initially containing **8b** and **12** gave under the same conditions four thioesters in equal amounts, consistent with four complexes in the equilibrated solution prior to reaction with carbon monoxide. Reaction of **9a** in THF with carbon monoxide produced 2,6-dichlorophenyl thioacetate quantitatively, indicating that Ni(II)−acyl−thiolate complexes are intermediates in thioester formation. The overall reaction is [Ni(bpy)(R′)(SR)] + 3CO → RSCOR′ + [Ni(bpy)(CO)$_2$] (R′ = CH_3, C_2H_5); the two electrons in the generalized reaction are captured by the metal as Ni(0). A related and necessarily intramolecular reaction of [Ni(bpy)($SCH_2CH_2CH_2$)] was confirmed and shown to produce γ-thiobutyrolactone in quantitative yield *in situ*. Evidence supporting an analogous intramolecular path for reaction systems based on **8** is summarized. This investigation provides the first examples of Ni-mediated acyclic thioester synthesis and demonstrates a possible means of enzymatic thioester formation should coenzyme A$^-$ and an acetyl group coordinate to the Ni(II) catalytic center.

Introduction

The nickel-containing enzymes carbon monoxide dehydrogenases (CODHs) are complex multi-subunit entities containing iron−sulfur clusters and nickel catalytic sites. They are central to the Wood−Ljungdahl pathway for the anaerobic fixation of carbon dioxide and the synthesis of acetate.[1-3] All CODH enzymes catalyze the CO/CO_2 interconversion reaction 1. Additionally, certain of these enzymes catalyze the acetyl coenzyme A synthase reaction 2

$$CO + H_2O \rightleftharpoons CO_2 + 2H^+ + 2e^- \quad (1)$$

$$CH_3\text{−THF} + \text{CoA·SH} + CO \rightarrow \text{CoA·SCOCH}_3 + \text{THF} \quad (2)$$

(THF = tetrahydrofolate, CoA·SH = coenzyme A) resulting in the formation of the thioester acetyl coenzyme A (acetyl-CoA), the hydrolysis of which yields acetate. This reaction is the sum of the final steps in autotrophic CO or CO_2 fixation by means of acetyl-CoA synthesis.

The metal centers in these enzymes are largely undefined. For the CODH from *Clostridium thermoaceticum*, the most thoroughly investigated enzyme, current evidence favors three metal centers[4] containing a total of two nickel atoms, 11−15 iron atoms, and *ca.* 14 sulfide atoms.[5] Center A is a NiFeS entity that in the presence of CO is reduced and develops an $S = {}^1/_2$ EPR spectrum. The odd spin is delocalized over Ni, Fe, and bound CO sites, leading to the proposal of a covalently linked assembly minimally formulated as Ni−X−Fe_4S_4; bridge atom/group X is unidentified. Center B is a $[Fe_4S_4]^{2+/1+}$ cluster that functions in electron transfer. Center C contains Fe and presumably Ni and appears to be the catalytic site of reaction 1. There is clear evidence that reactions 1 and 2 proceed at different centers. Treatment of the enzyme with 1,10-phenanthroline does not affect CO oxidation activity but abolishes synthase activity, apparently by removing Ni from center A.[6]

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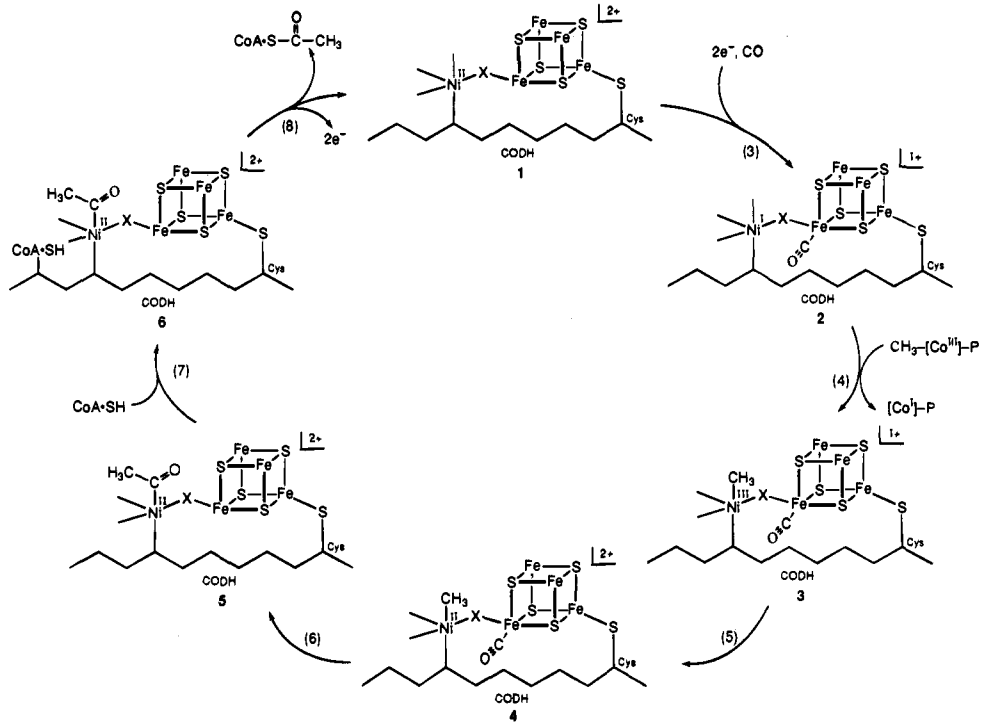

Figure 1. Schematic representation of a possible pathway for the formation of acetyl coenzyme A based on the bridged assembly Ni–X–Fe_4S_4 as a minimal representation of center A in CODH. The initial binding of CO to Fe is based on resonance Raman results.[9] Certain aspects of the scheme are unresolved, including the order of CO binding (reaction 3) and methyl transfer (reaction 4) and the formation of an acyl group on Ni directly (reactions 4–6) or its formation on Fe (by methyl migration to bound CO) and subsequent transfer to Ni (not shown). Oxidation states are indicated; note that the close juxtaposition of Ni and Fe_4S_4 offers an effective means of rapid reduction of the presumably unstable [Ni^{III}–CH_3]. The scheme is an elaboration of the results and considerations of Qiu *et al.*[9a]

Thus, center A is the synthase catalytic site. This conclusion has been otherwise supported by kinetics studies which have demonstrated that the CO-bound form of center A is kinetically competent as an intermediate in the synthesis of acetyl-CoA.[4,7]

Recently, CO bound at reduced center A has been directly detected by FTIR[8] (ν_{CO} 1993 cm^{-1}) and resonance Raman[9] spectroscopies. With use of metal and carbon isotopes, Qiu *et al.*[9] have demonstrated that CO binds at an Fe site (ν_{FeC} 360 cm^{-1}) in the probable $[Fe_4S_4]^{1+}$ cluster portion of center A. This is the kinetically competent intermediate noted above. In Figure 1, we have elaborated the working hypothesis of Qiu *et al.*[9] into a minimal reaction scheme of acetyl-CoA synthase activity whose constant feature is a Ni site coupled through an unknown bridge X to a Fe_4S_4 cluster. Combined Mössbauer[10] and ENDOR[11] results for the CO-bound intermediate suggest the composition $NiFe_{\geq 3}S_{\geq 4}CO$ with sulfur present at sulfide.[12] On the basis of EXAFS analyses,[16] the Ni atom is in a predominantly sulfur coordination environment where the ligands are expected to be mainly from protein side chains. In this scheme, the resting state (**1**) contains Ni(II) and $[Fe_4S_4]^{2+}$. Reaction 3 results in reduction of both Ni(II) and the cluster and CO binding to the latter (**2**), consistent with the resonance Raman results.[9] Oxidative addition of methyl cation from the corrinoid Fe–S protein[2,17] to Ni(I) in reaction 4 leads to a [Ni^{III}–CH_3]/$[Fe_4S_4]^{1+}$ species (**3**), which would be expected to internally equilibrate in reaction 5 to [Ni^{II}–CH_3]/$[Fe_4S_4]^{2+}$ (**4**). Cluster oxidation labilizes CO, which inserts into the Ni–C bond, resulting in a [Ni^{II}–$COCH_3$]/$[Fe_4S_4]^{2+}$ intermediate (**5**) generated in overall reaction 6. Because the environment of CO-bound center A is altered when a tryptophan residue involved in the binding of coenzyme A to the protein is chemically modified,[2,18] it is probable that CoA•SH binding to CODH in reaction 7 places the former in the vicinity of the Ni site (**6**). Attack of CoA•SH on the acyl carbon atom of **6** affords acetyl-CoA in reaction 8 (R = CoA).

$$[Ni^{II}\text{–}COCH_3] + RSH \rightarrow RSCOCH_3 + Ni^{II} + H^+ + 2e^- \quad (8)$$

We are endeavoring to place certain structural and reactivity aspects of CODH chemistry on a rational basis by the synthesis

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(12) One apparent possibility is a cubane-type $NiFe_3S_4$ cluster, examples of which have been synthesized[13] and detected in proteins.[14] We have presented strong evidence that such a cluster does not exist in *Rhodospirillum rubrum* CODH,[15] which, however, does not possess acetyl-CoA synthase activity.

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and property elucidation of Ni−Fe−S clusters[13,15] and demonstration of certain Ni-mediated transformations pertinent to recent proposals of the pathway of acetyl-CoA synthase reactivity.[2,9,19] In this context, the transformations in reaction sequence 9 at a mononuclear, five-coordinate, structurally

$$[Ni^{II}-Cl] \rightarrow [Ni^{II}-CH_3] \rightarrow [Ni^{II}-COCH_3] \rightarrow Ni^0 + RSCOCH_3 \quad (9)$$

defined Ni(II) site with physiologically acceptable ligation have been proven.[19] Carbonylation of the $[Ni^{II}-CH_3]$ species and high-yield conversion of the resultant acyl complex to thioesters upon reaction with thiols or tholates provide a basis for similar proposed events in the enzyme reaction sequence. In this investigation, we demonstrate another possible pathway of Ni-mediated thioester formation using different mononuclear Ni-(II) species that also support traversal of the second and third steps of sequence 9.

Experimental Section

Preparation of Compounds. All operations were carried out under a pure dinitrogen atmosphere. The solids obtained by the procedures that follow were substantially pure and useful for subsequent reactions. Analytical samples as microcrystalline solids were obtained by volume reduction of the filtered THF reaction solutions and by allowing the solutions to stand at room temperature. In the following compounds, bpy = 2,2′-bipyridyl.

(a) Nickel(II) Complexes. [Ni(bpy)Me(S-*p*-C_6H_4Me)]. A solution of 0.160 g (1.28 mmol) of *p*-toluenethiol in 7 mL of THF was added dropwise to a dark green stirred solution of 0.310 g (1.27 mmol) of $[Ni(bpy)Me_2]$[20] in 30 mL of THF, causing a color change to deep purple. The volume was reduced to 20 mL, and 15 mL of ether was added, producing a black precipitate. The reaction mixture was allowed to stand for 10 min and then filtered, affording 0.312 g (69%) of dark purple product. ^{1}H NMR (THF-d_8): δ 9.28 (d, 1), 8.68 (d, 1), 8.16 (m, 2), 8.06 (t, 1), 8.00 (t, 1), 7.52 (t, 1), 7.48 (t, 1) (bpy), 7.40 (*o*-H), 6.71 (*m*-H), 2.14 (*p*-Me), −0.06 (Ni-Me). Anal. Calcd for $C_{18}H_{18}N_2NiS$: C, 61.23; H, 5.14; N, 7.93; Ni, 16.61; S, 9.08. Found: C, 61.18; H, 5.06; N, 7.99; Ni, 16.55; S, 9.11.

[Ni(bpy)Me(S-2,6-$C_6H_3Me_2$)]. A solution of 0.091 g (0.655 mmol) of 2,6-dimethylbenzenethiol in 5 mL of THF was added dropwise to a stirred solution of 0.153 g (0.625 mmol) of $[Ni(bpy)Me_2]$ in 20 mL of THF, causing a color change to dark purple. The reaction mixture was allowed to stand for 5 min and was reduced in volume to *ca.* 7 mL, 8 mL of hexanes was added slowly with stirring. The solution was allowed to stand for 30 min, during which time a dark solid separated. This material was collected by filtration and washed with hexanes to afford the product as 99.5 mg (41%) of a dark purple solid. ^{1}H NMR (THF-d_8): δ 7.50−9.47 (bpy), 6.86 (*m*-H), 6.79 (*p*-H), 2.51 (*o*-Me), −0.43 (Ni-Me). Anal. Calcd for $C_{19}H_{20}N_2NiS$: C, 62.16; H, 5.49; N, 7.63; Ni, 15.99; S, 8.73. Found: C, 62.02; H, 5.43; N, 7.69; Ni, 16.04; S, 8.67.

[Ni(bpy)Me(S-2,4,6-$C_6H_2Me_3$)]. The procedure for [Ni(bpy)Me(S-*p*-C_6H_4Me)], but with use of 0.325 g (1.33 mmol) of mesitylenethiol[21] and 0.202 g (1.33 mmol) of $[Ni(bpy)Me_2]$, gave 0.167 g (32%) of product as a black solid. ^{1}H NMR (THF-d_8): δ 9.47 (d, 1), 8.69 (d, 1), 8.16 (t, 2), 8.04 (t, 2), 7.55 (t, 1), 7.50 (t, 1) (bpy), 6.71 (*m*-H), 2.45 (*o*-Me), 2.11 (*p*-Me), −0.42 (Ni-Me). Anal. Calcd for $C_{20}H_{22}N_2NiS$: C, 63.06; H, 5.82; N, 7.35; Ni, 15.40; S, 8.40. Found: C, 62.92; H, 5.86; N, 7.28; Ni, 15.46; S, 8.52.

[Ni(bpy)Me(S-2,4,6-$C_6H_2iPr_3$)]. A solution of 0.259 g (1.09 mmol) of 2,4,6-triisopropylbenzenethiol[22] in 5 mL of THF was added dropwise to a stirred solution of 0.254 g (1.04 mmol) of $[Ni(bpy)Me_2]$ in 60 mL of THF. The color of the solution changed from dark green to deep blue-purple. The reaction mixture was stirred for 5 min, and the volume was reduced to 20 mL. Hexane (20 mL) was added, resulting in the separation of a dark solid. This material was collected and washed with hexane and ether to afford 0.191 g (39%) of product as a dark purple microcrystalline solid. ^{1}H NMR (THF-d_8): δ 9.50 (d, 1), 8.69 (d, 1), 8.15 (t, 2), 8.05 (t, 2), 7.57 (t, 1), 7.49 (t, 1) (bpy), 6.83 (*m*-H), 4.47 (*o*-CH), 2.76 (*p*-CH), 1.17 (m, Me), -0.34 (Ni-Me). Anal. Calcd for $C_{26}H_{34}N_2NiS$: C, 67.11; H, 7.36; N, 6.02; Ni, 12.61. Found: C, 67.03; H, 7.42; N, 5.96; Ni, 12.64.

[Ni(bpy)Me(S-2,6-$C_6H_3Cl_2$)]. The procedure for [Ni(bpy)Me(S-*p*-C_6H_4Me)], but with use of 0.196 g (1.09 mmol) of 2,6-dichlorobenzenethiol and 0.266 g (1.09 mmol) of $[Ni(bpy)Me_2]$, gave 0.200 g (45%) of product as a black solid. ^{1}H NMR (THF-d_8): δ 9.31 (d, 1), 8.59 (d, 1), 8.20 (d, 2), 8.06 (m, 2), 7.51 (m, 2) (bpy), 7.15 (*m*-H), 6.80 (*p*-H), −0.28 (Me). Anal. Calcd for $C_{17}H_{14}Cl_2N_2NiS$: C, 50.09; H, 3.46; Cl, 17.37; N, 6.86; Ni, 14.38; S, 7.86. Found: C, 49.88; H, 3.55; Cl, 17.48; N, 6.78; Ni, 14.31; S, 7.94.

[Ni(bpy)(COMe)(S-2,6-$C_6H_3Cl_2$)]. Carbon monoxide (16.2 mL, 0.66 mmol) was injected into the head space of a 100-mL flask containing a stirred solution of 0.270 g (0.66 mmol) of [Ni(bpy)(Me)-(S-2,6-$C_6H_3Cl_2$)] in 10 mL of THF at −5 °C. Upon addition of CO, the solution changed from red-purple to brick red. The reaction mixture was stirred for 45 min; 7 mL of pentane was added, producing a red precipitate. The solid was collected by filtration and washed thoroughly with pentane to afford 0.170 g (59%) of pure product as a purple-red solid. ^{1}H NMR (THF-d_8): δ 7.50−8.23 (m, 8) (bpy), 7.15 (*m*-H), 6.72 (*p*-H), 2.39 (COMe). IR (KBr): ν_{CO} 1632 cm^{-1}. Anal. Calcd for $C_{18}H_{14}Cl_2N_2NiOS$: C, 49.59; H, 3.24; N, 6.43. Found: C, 49.38; H, 3.30; N, 6.57.

[Ni(bpy)Et(S-2,4,6-$C_6H_2Me_3$)]. A solution of 57.8 mg (0.38 mmol) of mesitylenethiol in 5 mL of THF was added dropwise to a stirred solution of 97 mg (0.36 mmol) of $[Ni(bpy)Et_2]$[20,23] in 15 mL of THF. The color of the solution changed from dark green to dark blue after *ca.* 50 s. The reaction mixture was stirred for 3 min and was reduced in volume to 10 mL. Hexane (8 mL) was added, and the mixture was allowed to stand for 30 min. The product was collected by filtration as 72 mg (51%) of black solid and was identified by its ^{1}H NMR spectrum (THF-d_8): δ 9.57 (d, 1), 8.78 (d, 1), 8.14 (m, 2), 8.07 (t, 1), 8.01 (t, 1), 7.57 (t, 1), 7.51 (t, 1) (bpy), 6.72 (*m*-H), 2.51 (*o*-Me), 2.12 (*p*-Me), 0.48 (Et).

(b) Thioesters. The compounds RCOSMe with R = *p*-C_6H_4Me,[24] 2,6-$Me_2C_6H_3$,[24] mesityl,[24] and 2,6-$Cl_2C_6H_3$ and RCOSEt with R = mesityl were prepared by a published method.[25] Compounds were identified by ^{1}H NMR and mass spectra.

Reactions of [Ni(bpy)Me(SR)] with CO. These reactions were monitored by ^{1}H NMR and GC−MS; all operations were carried out under anaerobic conditions. In a typical NMR experiment, *ca.* 10 μmol of Ni(II) complex was weighed in an NMR tube; 0.5 mL of THF-d_8 and 1 μL of a 10 μM solution of Si_2OMe_6 in THF-d_8 were added. The spectrum was recorded after 10 min. Carbon monoxide (3 or more equiv) was injected by syringe into the evacuated head space of the tube, the contents were gently mixed, and a spectrum was recorded within 20−60 min after injection. For a given system, these spectra and that recorded after 24 h were invariant. The percent yield of thioester RSCOMe was determined by comparing the integrated intensities of the methyl signals of each compound with that of the siloxane internal standard. An appropriate relaxation delay was employed in order to ensure accurate comparison between the Ni−methyl and organic methyl signals. In a typical GC−MS experiment, *ca.* 5 mg of [Ni(bpy)Me(SR)] was weighed into a small ampule and 3 mL of THF was added to dissolve the complex. The head space of

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Table 1. Crystallographic Data[a] for [Ni(bpy)Me_2] (**7**), [Ni(bpy)Me(S-2,4,6-$C_6H_2Me_3$)] (**8c**), [Ni(bpy)Me(S-2,6-$Cl_2C_6H_3$)] (**8e**), and [Ni(bpy)(COMe)(S-2,6-$Cl_2C_6H_3$)] (**9a**)

	7	**8c**	**8e**	**9a**
formula	$C_{12}H_{14}NiN_2$	$C_{20}H_{22}NiN_2S$	$C_{17}H_{14}Cl_2N_2NiS$	$C_{18}H_{14}Cl_2N_2NiOS$
fw	244.96	381.16	407.98	435.99
cryst syst	monoclinic	monoclinic	monoclinic	monoclinic
space group	$P2_1/c$	$P2_1/c$	$P2_1/n$	$P2_1/c$
Z	4	4	4	4
a, Å	17.530(7)	8.843(2)	7.898(2)	12.304(8)
b, Å	9.342(2)	14.103(3)	20.170(5)	9.139(5)
c, Å	7.316(2)	14.366(3)	10.592(3)	15.791(9)
β, deg	114.21(2)	90.62(2)	99.61(2)	98.14(5)
V, Å^3	1092.6	1791.7	1663.7	1757.8
ϱ_{calcd}, g/cm^3	1.49	1.41	1.63	1.65
T, K	298	233	233	233
μ, mm^{-1}	1.74	1.20	1.61	1.53
R^b (R_w),[c] %	3.36 (3.90)	5.07 (4.75)	4.77 (4.69)	6.76 (6.85)

[a] All data collected with graphite-monochromatized Mo Kα radiation. [b] $R = \sum||F_o| - |F_c||/\sum|F_o|$. [c] $R_w = [\sum w(|F_o|^2 - |F_c|^2)/\sum w|F_o|^2]^{1/2}$.

the ampule was evacuated, CO (3 or more equiv) was introduced by syringe, and the ampule was shaken. A 1-μL sample was removed for injection into a Hewlett Packard 5890 gas chromatograph interfaced with a JEOL AX-505H mass spectrometer. Thioesters were separated by GC, identified by chemical ionization using ammonia as the reagent gas, and quantified by selected ion recording. A similar procedure was employed for analysis of the reaction products of a mixture of [Ni(bpy)Me(S-2,6-$Me_2C_6H_3$)] and [Ni(bpy)Et(S-2,4,6-$Me_3C_6H_2$)] with CO. Solutions of varying concentrations were prepared by dilution of an equimolar stock solution of the two complexes in THF with neat THF. Carbon monoxide (3 or more equiv) was injected into the head space of each sample. The thioester products were separated and quantified by GC–MS.

X-Ray Structural Determinations. Diffraction-quality crystals of the compounds in Table 1 were obtained by recrystallizations from toluene/ether (**7**), THF (**8c**), THF–pentane (**8e**), and THF–hexane (**9a**). Data were collected on a Nicolet P3F automated diffractometer using graphite-monochromatized Mo Kα radiation. Lattice parameters and orientation matrices were determined by least-squares fits of 25 machine-centered reflections with $15° \le 2\theta \le 25°$. Three reflections were monitored periodically during the data collections; no significant decay was observed. Data were processed with the program XTAPE of the SHELXTL PLUS structure determination package. Empirical absorption corrections were applied with the program XEMP. All compounds crystallized in the monoclinic system. Space groups were confined by successful solutions and refinements of the structures. Structures were solved by direct methods. Remaining non-hydrogen atoms were located from difference Fourier refinement with a few intervening cycles of least-squares refinements. With several exceptions, all atoms were described anisotropically. Owing to data limitations, the phenyl ring of **8e** and the phenyl and pyridyl rings of **9a** were refined as rigid groups with individual temperature factors for the carbon atoms. In final least-squares refinements, hydrogen atoms were placed 0.96 Å from bonded carbon atoms and were assigned the isotropic temperature factor 0.08 Å^2. In these cycles, each parameter shifted by <3% of its esd and highest residual peaks in the final Fourier difference maps did not exceed 0.8 e/Å. Final R-factors are listed in Table 1.[26]

Other Physical Measurements. ^{1}H NMR spectra were recorded on a Bruker AM-500 spectrometer. Infrared spectra were obtained with a Nicolet IR/42 spectrophotometer. FAB-MS spectrometry was performed on a JEOL JMS-AX505H instrument.

Results and Discussion

Choice of Reaction System. Reaction sequence 9 is the first case in which Ni-based transformations relevant to proposals for acetyl coenzyme A synthase activity were proven with molecules having physiological-type ligands.[19] The sequence utilized trigonal bipyramidal complexes of the type [Ni(N($CH_2CH_2SR)_3$L]$^{1+}$ (R = *i*Pr, *t*Bu). Reaction of the L = acyl species with 1 equiv of NaSEt or with 1.2 equiv of several thiols in THF resulted in quantitative thioester formation immediately (thiolate) or over a 12-h period (thiol). The two electrons implicated in the thioester synthesis reaction 8 were consumed in the formation of elemental nickel, and the proton was captured by the liberated ligand. With thiolate as the reactant, the unprotonated ligand and Ni(0) were formed. These reactions appear to proceed by direct nucleophilic attack of RSH/RS$^-$ at the coordinated acyl carbon atom. Any prior coordination of the nucleophile is improbable given the tripodal nature and steric bulk of the ligand; the latter defines a pseudo-cavity for coordination of one ligand trans to the nitrogen atom. Thus the system is not suitable for the investigation of a second pathway of thioester formation in which the sulfur nucleophile and acyl group are simultaneously bound to a Ni center prior to reaction. Such an arrangement could result in intramolecular thioester formation.

In an extensive study of the reactivity of [Ni(bpy)R_2] (R = Me, Et), first prepared by Wilke and Herrmann[20] in 1966, reaction sequence 10 has been demonstrated by Yamamoto and co-workers.[27-32] Here, 1 equiv of alkane is liberated by reaction with a proton donor, followed by insertion of CO in the remaining Ni–C bond to afford an acyl complex. Intra- and/or intermolecular attack of bound nucleophile Y of the acyl group affords the product ester, amide, or anhydride and reduction to Ni(0), which is captured in well-defined compounds such as [Ni(PR'_3)$_2$($CO)_2$] or [Ni(bpy)($CO)_2$].[33] The relationship to reaction 8 and the last step of reaction 9 is evident. Indeed, in an early mechanistic consideration of CODH synthase activity, Walsh and Orme–Johnson[34] noted the possible relevance of one instance of Ni-mediated ester formation[27] to their proposed pathway.

$$[NiL_2R_2] + YH \xrightarrow[RH]{} [NiL_2R(Y)] \xrightarrow{CO} [NiL_2(COR)Y] \longrightarrow RC(O)Y + [NiL_2(CO)_2] \quad (10)$$

L_2 = bpy, ($R'_3P)_2$; YH = ArOH, R'_2NH, $R'CO_2H$
L_2 = dppe, YH = ArSH[32]

We have investigated reaction system 10 as a means of thioester synthesis mediated at a Ni(II) center. Our systems are comprised of reactants with L_2 = bpy, R = Me/Et, and YH = RSH. As such, they lack a bridged Fe–S cluster as in Figure 1; consequently, electrons generated in thioester formation are not passed to an external acceptor but are retained at the Ni center. The systems are intended to convey the feasibility of thioester formation when an acyl group and a thiolate

(26) See paragraph at the end of this article concerning supplementary material.

(27) Kohara, T.; Komiya, S.; Yamamoto, T.; Yamamoto, A. *Chem. Lett.* **1979**, 1513.
(28) Komiya, S.; Yamamoto, A.; Yamamoto, T. *Chem. Lett.* **1981**, 193.
(29) Yamamoto, T.; Kohara, T.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1720.
(30) Yamamoto, T.; Kohara, T.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2010.
(31) Komiya, S.; Akai, Y.; Tanaka, K.; Yamamoto, T.; Yamamoto, A. *Organometallics* **1985**, *4*, 1130.
(32) Kim, Y.-J.; Osakada, K.; Sugita, K.; Yamamoto, T.; Yamamoto, A. *Organometallics* **1988**, *7*, 2182. (dppe = bis(1,2-diphenylphosphino)-ethane.)
(33) Nyholm, R. S.; Short, L. N. *J. Chem. Soc.* **1953**, 2670.
(34) Walsh, C. T.; Orme-Johnson, W. H. *Biochemistry* **1987**, *26*, 4901.

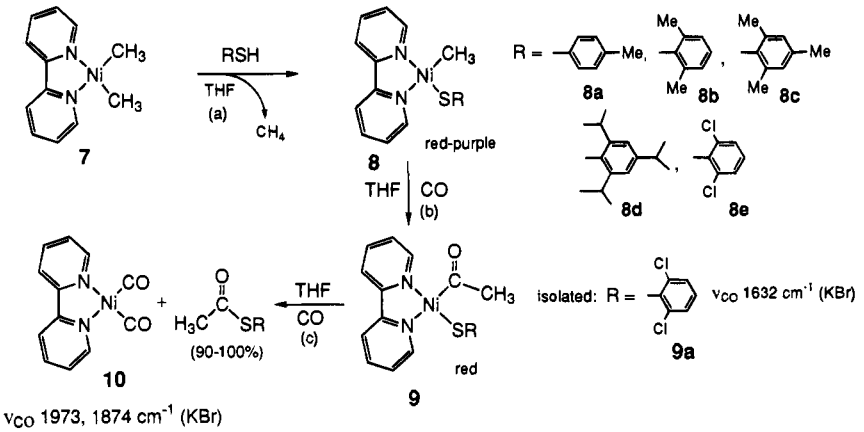


Figure 2. Nickel-mediated formation of thioesters based on the *minimal* reaction sequence **7** → **8** → **9** → $RSCOCH_3$ + **10** in THF solution; the compound numbering scheme is indicated. Complexes **7**–**9** are planar. A presumed 5-coordinate intermediate in the reaction **8** + CO → **9** is omitted. The formation of thioester from **9** is likely induced by CO interaction with the complex, a step also not shown.

Chart 1

[Ni(bpy)Me_2]	**7**
[Ni(bpy)Me(SR)]	**8**
[Ni(bpy)Me(S-*p*-C_6H_4Me)]	**8a**
[Ni(bpy)Me(S-2,6-$C_6H_3Me_2$)]	**8b**
[Ni(bpy)Me(S-2,4,6-$C_6H_2Me_3$)]	**8c**
[Ni(bpy)Me(S-2,4,6-$C_6H_2iPr_3$)]	**8d**
[Ni(bpy)Me(S-2,6-$C_6H_3Cl_2$)]	**8e**
[Ni(bpy)(COMe)(SR)]	**9**
[Ni(bpy)(COMe)(S-2,6-$C_6H_3Cl_2$)]	**9a**
[Ni(bpy)$(CO)_2$]	**10**
[Ni(bpy)Et_2]	**11**
[Ni(bpy)Et(S-2,4,6-$C_6H_2Me_3$)]	**12**
[Ni(bpy)(SCH$_2$CH$_2$CH$_2$)]	**13**

nucleophile are bound at a common Ni(II) atom. The following compounds **7**–**13** (Chart 1) are of primary interest in this investigation; of these, **8** and **9** are general structural types and **8a**–**e** and **9a** are specific examples. The complexes **8** offer the potential advantages of coordinative unsaturation allowing CO binding in a five-coordinate intermediate (possibly of trigonal bipyramidal stereochemistry[35]) and strong σ-bonding ligands which should increase the electron density at the Ni atom, thereby enhancing such binding. Reaction systems are summarized in Figure 2.

Structures and Reactions. (a) [Ni(bpy)Me(SR)] Complexes. Complex **7** reacts smoothly with a stoichiometric amount of arenethiol to afford the complexes **8**, which are precursors of thioesters. Complex **12** was prepared from **11** in an analogous manner. The structure of **7**, shown in Figure 3, is planar with an imposed mirror plane normal to the molecular plane. Selected bond distances and angles are reported in Table 2. The molecule displays a characteristic bpy bite angle less than 90° and other unexceptional metric features. In particular, the Ni–C bond length of 1.923(4) Å is in the range of such distances (1.904(7)–1.949(4) Å) in the other two [Ni(bpy)R_2] alkyl complexes that have been structurally defined.[36]

Five examples of complex **8** were prepared with arenethiolate ligands[37] and isolated in 39–69% yield as dark purple or black solids. The structures of **8c** and **8e** are given in Figure 4 and Figure 5 (upper), respectively; metric data are collected in Table 2. Both molecules are planar with nearly identical bond distances and angles in the coordination sphere. The Ni–S bond distances (Table 2) are within the usual range of 2.14–2.21 Å for terminal thiolate ligation in planar Ni(II) complexes.[38,39] The Ni–C distances are identical to that in **7** and in [Ni(bpy)(OCH$_2$-

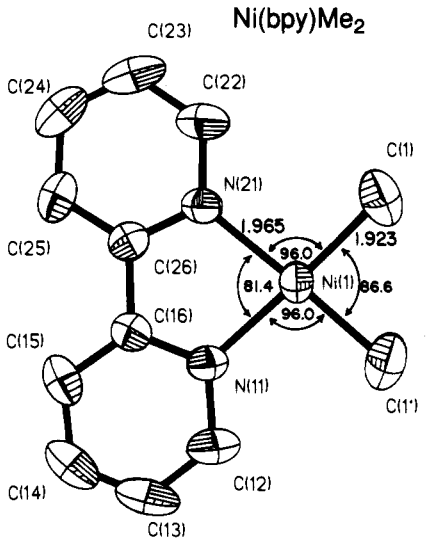


Figure 3. Structure of [Ni(bpy)Me_2] showing the atom labeling scheme, 50% probability ellipsoids, and selected bond distances and angles; there is an imposed mirror plane perpendicular to the molecular plane.

Table 2. Selected Bond Distances (Å) and Angles (deg) for [Ni(bpy)Me_2] (**7**), [Ni(bpy)Me(S-2,4,6-$C_6H_2Me_3$)] (**8c**), [Ni(bpy)Me(S-2,6-$C_6H_3Cl_2$)] (**8e**), and [Ni(bpy)(COMe)(S-2,6-$C_6H_3Cl_2$)] (**9a**)

distance/angle	**7**	**8c**	**8e**	**9a**
Ni–N(11)	1.965(3)	1.973(3)	1.980(8)	1.98(1)
Ni–N(21)		1.936(3)	1.93(1)	1.95(1)
Ni–C(1)	1.923(4)	1.921(4)	1.92(1)	1.81(2)
Ni–S(1)		2.171(1)	2.149(4)	2.180(6)
C(1)–O(1)				1.24(3)
N(11)–Ni–N(21)	81.4(1)	82.1(1)	82.0(4)	82.5(5)
N(21)–Ni–C(1)	96.0(1)	93.9(1)	95.5(5)	94.2(8)
N(11)–Ni–S(1)		92.4(1)	92.2(3)	93.8(4)
C(1)–Ni–X	86.6(2)[a]	93.8(1)[b]	90.0(4)[b]	89.6(7)[b]
Ni–S(1)–C(31)		115.1(1)	116.6(4)	113.7(4)

[a] X = C(1'). [b] X = S(1).

(35) Macgregor, S. A.; Lu, Z.; Eisenstein, O.; Crabtree, R. H. *Inorg. Chem.* **1994**, *33*, 3616.

(36) (a) 2,2'-Bipyridylyl-5-nickela-3,3,7,7-tetramethyl-*trans*-tricyclo-[4.1.0.0^{2,4}]heptane: Binger, P.; Doyle, M. J.; McMeeking, M.; Krüger, C.; Tsay, Y.-H. *J. Organomet. Chem.* **1977**, *135*, 405. (b) 2,2'-Bipyridylyl-1-nickelacyclopentane: Binger, P.; Doyle, M. J.; Krüger, C.; Tsay, Y.-H. *Z. Naturforsch.* **1979**, *34b*, 1289.

(37) In limited attempts, we were not able to obtain a pure sample of a complex [Ni(bpy)Me(SR)] with R = alkyl.

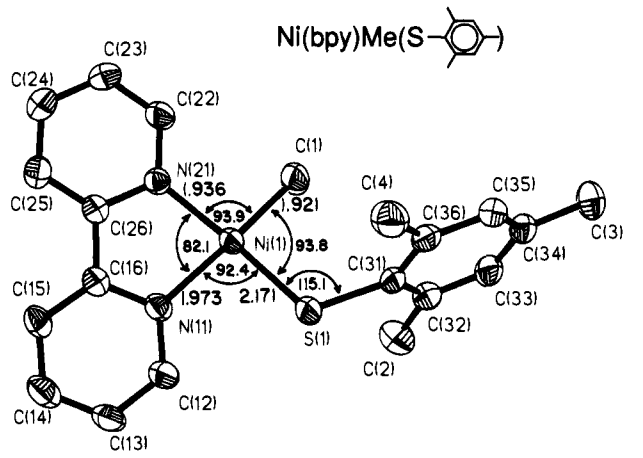


Figure 4. Structure of [Ni(bpy)Me(S-2,4,6-$C_6H_2Me_3$)] showing the atom labeling scheme, 50% probability ellipsoids, and selected bond distances and angles.

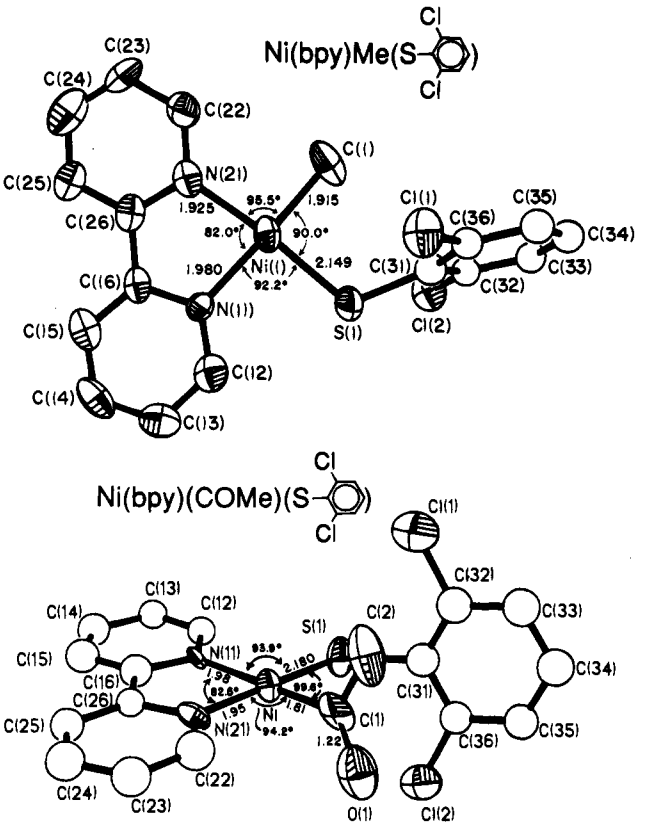


Figure 5. Structures of [Ni(bpy)Me(S-2,6-$C_6H_3Cl_2$)] (upper) and [Ni(bpy)(COMe)(S-2,6-$C_6H_3Cl_2$)] (lower) showing the atom labeling scheme, 50% probability ellipsoids, and selected bond distances and angles. Open circles represent atoms that were isotropically refined.

CH_2CH_2)] (1.921(8) Å),[40] one of only three [Ni(bpy)RY]-type complexes whose structures had been determined[41] prior to this work. The trans influence of methyl exceeds that of thiolate inasmuch as the Ni–N distances trans to the former are longer than those trans to the latter by *ca.* 0.04–0.06 Å. The ^{1}H NMR spectrum of **8c** in THF, presented in Figure 6, is typical of the set; assignment of bpy protons was made by standard 2-D methods. For **8a–e** in THF, the characteristic Ni–Me signal is located upfield at δ −0.06 to −0.43; this signal occurs at δ −0.03 in **7**.

In THF solution, complexes **8** and **12** undergo the thiolate exchange reaction 11. For example, 2 mM **8e** and **12** equilibrate

$$[Ni(bpy)Me(SR)] + [Ni(bpy)Et(SR')] \rightleftarrows [Ni(bpy)Me(SR')] + [Ni(bpy)Et(SR)] \quad (11)$$

rapidly to form a mixture of four components at equal concentrations that are most easily recognized by their Ni–R resonances: δ 0.48 (**12**), −0.28 (**8e**), −0.42 (**8c**), and −0.71 ([Ni(bpy)Et(S-2,6-$C_6H_3Cl_2$)]). In this low-polarity medium, ligand exchange is expected to occur through an associative pathway involving a five-coordinate $Ni_2(\mu\text{-SR})(\mu\text{-SR}')$ intermediate. Given that [Ni(terpy)(S-2,4,6-C_6H_2iPr$_3$)$_2$] is mononuclear while [Ni(terpy)(SPh)$_2$]$_2$ is binuclear with thiolate bridges,[42] the reaction between **12** and **8d**, containing the sterically encumbered ligand, was examined. However, ligand exchange was again observed with $K_{eq} \approx 1$.

(b) Thioester Formation. Treatment of THF solutions of **8a–c,e** with more than 3 equiv of carbon monoxide resulted in an immediate color change from dark blue or purple to red and the formation of a brick-red precipitate. The IR spectrum of the latter showed ν_{CO} = 1872 and 1973 cm^{-1} (KBr), identifying the product as the dicarbonyl complex **10**.[33] Examination of the product solution by MS and ^{1}H NMR demonstrated the presence of thioester. The NMR spectrum of the product solution from the **8c**/CO reaction system given in Figure 6 (lower) clearly shows the signals of mesityl thioacetate and a residual amount of sparingly soluble **10**. These observations are consistent with the occurrence of the Ni-mediated thioester synthesis reaction 12. In some experiments with large excesses of carbon monoxide, small amounts of free bpy, presumably formed by reaction of CO with **10**, were observed by NMR.

$$[Ni(bpy)Me(SR)] + 3CO \rightarrow RSCOMe + [Ni(bpy)(CO)_2] \quad (12)$$

The presumed Ni–acyl intermediate (as in sequence 9) was sought as follows. A solution of **8e** in THF was exposed to 1.0 equiv of carbon monoxide. The above color change and precipitation occurred. Addition of pentane to the reaction solution caused separation of a dark solid which when recrystallized from THF–hexane afforded red crystals. The methyl chemical shift (δ_{COMe} 2.39) and IR feature (ν_{CO} 1632 cm^{-1}) of the product are consistent with formation of an acyl species. This was confirmed by an X-ray structure analysis, showing the product to be the desired acyl complex **9a**; its structure is presented in Figure 5 (lower), allowing a direct comparison with predecessor complex **8e** (upper). The molecule has a planar NiN_2SC coordination unit; the acyl group and the phenyl ring of the thiolate substituent are oriented at dihedral angles of 85.2° and 96.9° relative to the coordination plane and 27.5° with respect to each other. Dimensions of the Ni–COMe group are

(38) (a) Watson, A. D.; Pulla Rao, Ch.; Dorfman, J. R.; Holm, R. H. *Inorg. Chem.* **1985**, *24*, 2820. (b) Krebs, B.; Henkel, G. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 769. (c) Sellmann, D.; Prechtel, W.; Knoch, F.; Moll, M. *Z. Naturforsch.* **1992**, *47b*, 1411. (d) Yamamura, T.; Tadokoro, M.; Tanaka, K.; Kuroda, R. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1984. (e) Farmer, P. J.; Reibenspies, J. H.; Lindahl, P. A.; Darensbourg, M. Y. *J. Am. Chem. Soc.* **1993**, *115*, 4665.

(39) Sellmann, D.; Schillinger, H.; Knoch, F.; Moll, M. *Inorg. Chim. Acta* **1992**, *198-200*, 351.

(40) Matsunaga, P. T.; Hillhouse, G. T. *J. Am. Chem. Soc.* **1993**, *115*, 2075.

(41) (a) 2,2′-Bipyridylyl-1-nickela-5-methyl-2,4-dioxalan-3-one: Kaiser, J.; Sieler, J.; Braun, U.; Golič, L.; Dinjus, E.; Walther, D. *J. Organomet. Chem.* **1982**, *224*, 81. (b) 2,2-Bipyridylyl(iminoborato)nickel(II): Hoberg, H.; Götz, V.; Krüger, C. *J. Organomet. Chem.* **1979**, *169*, 219.

(42) Baidya, N.; Olmstead, M.; Mascharak, P. K. *Inorg. Chem.* **1991**, *30*, 929. (terpy = 2,2′:6′,2″-terpyridine.)

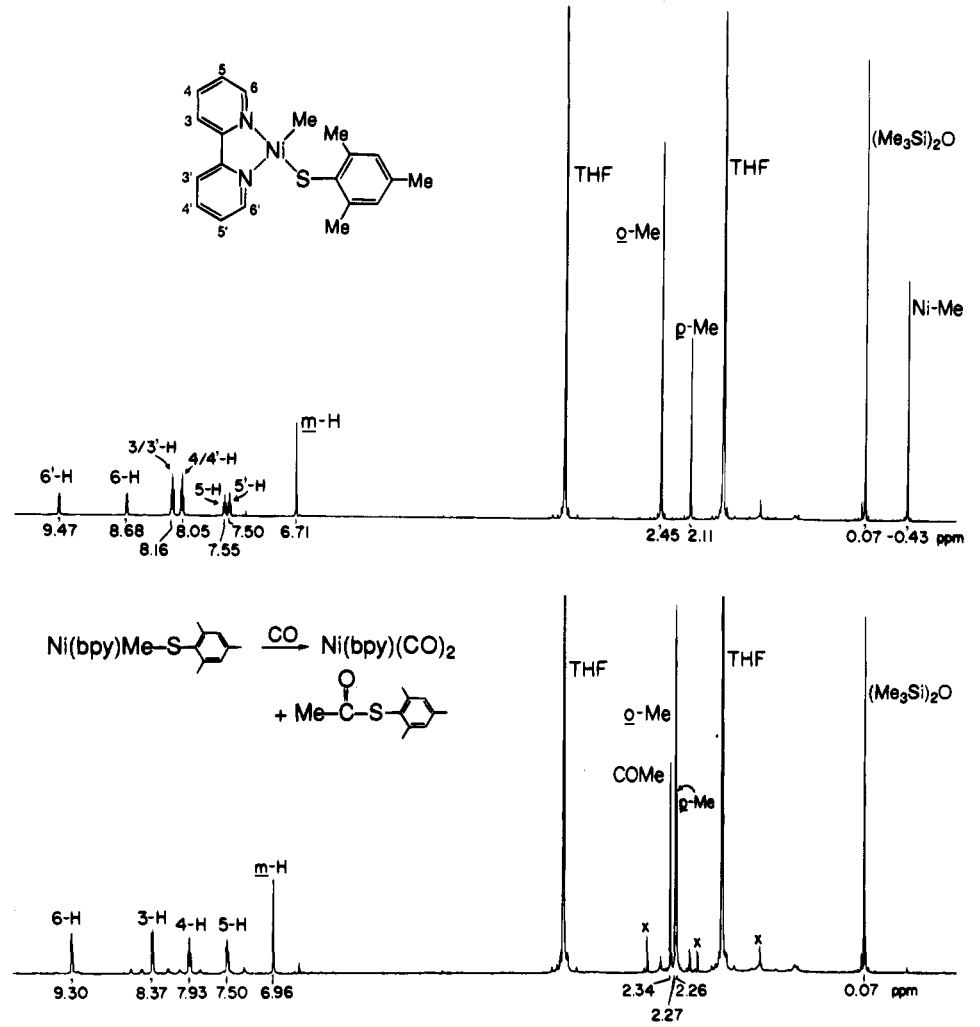
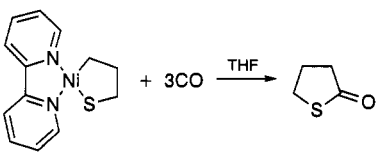


Figure 6. ^{1}H NMR spectra in THF-d_8 of [Ni(bpy)Me(S-2,4,6-$C_6H_2Me_3$)] (upper) and the products of the reaction of this complex with CO (lower). Signal assignments are indicated; the siloxane was used as an internal intensity reference.

similar to those of other planar Ni(II) acyls.[43] The S(1)···C(1) separation of 2.82 Å places the thiolate sulfur atom at a favorable position for intramolecular nucleophilic attack. Indeed, of complexes **8a**–**e**, only **8e** permitted the isolation of an acyl derivative **9**, apparently because the 2,6-dichloro substituents reduce the thiolate nucleophilicity to the point where isolation of the acyl intermediate becomes feasible. We note that **8e**, **9a**, $[Ni(N(CH_2CH_2SR)_3)L]^{1+}$ (R = *i*Pr, *t*Bu; L = Me, COMe),[19] and $[Ni(o\text{-}C_6H_4(S)SMe)_2Me]^{1-}$ [39] are the only examples of methyl or acyl Ni complexes which are not stabilized by (nonphysiological) coligands such as ternary phosphine, cyclopentadienyl, or carbon monoxide and are among the few such complexes in the Ni(II) state.

Three types of experiments leading to thioester formation were performed. Complexes **8a**–**e** were individually reacted with excess carbon monoxide; the thioester products were quantitated by integration *in situ* of ^{1}H NMR signals vs that of an internal standard. The results, summarized in Table 3, demonstrate that reaction 12 is quantitative. In a second type of experiment, equimolar THF solutions of complexes **8b** and **12** (whose thiolate ligands differ only by *p*-H vs *p*-Me) were exposed to more than 3 equiv of carbon monoxide, and the organic products were detected and quantitated by a GC–MS procedure. The four thioesters RSCOMe and RSCOEt (R = 2,6-$C_6H_3Cl_2$, mesityl) were found to occur in exactly equimolar amounts, a result invariant over the concentration range 17–66 mM in each initial complex. The formation of these products is another manifestation of the ligand exchange reaction 11 with $K_{eq} \approx 1$. In a third experiment, acyl complex **9a** when treated with more than 2 equiv of CO was found to afford 2,6-dichlorophenyl thioacetate in quantitative yield (Table 3). This result constitutes proof for the intermediacy of a discrete Ni^{II}–acyl intermediate in overall reaction 12.

The foregoing results do not demonstrate whether thioester formation occurs by an intra- or intermolecular reaction of intermediate **9**. Crossover experiments based on a reaction system such as [Ni(bpy)(CH_3)(SR)]/[Ni(bpy)(CD_3)(SR′)]/CO, in which ligand R′S$^-$ is a deuterium-labeled version of RS$^-$, would be ambiguous because of the occurrence of thiolate ligand exchange. A necessarily intramolecular pathway applies to reaction 13, recently described by Matsunaga and Hillhouse,[44]



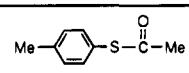
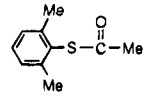
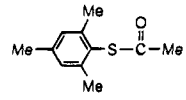
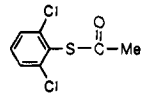
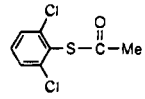
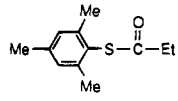
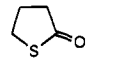
(13)

13

which utilizes cyclic alkanethiolate complex **13**.[45] A 27%

(43) (a) Huttner, G.; Orama, O.; Bejenke, V. *Chem. Ber.* **1976**, *109*, 2533. (b) Carmona, E.; Gonzàlez, F.; Poveda, M. L.; Atwood, J. L.; Rogers, R. D. *J. Chem. Soc., Dalton Trans.* **1980**, 2108.

Table 3. Yields of Ni-Mediated Thioester Formation Reactions[a]

Ni(II) complex[b]	thioester	yield,[c] %
[Ni(bpy)Me(S-*p*-C_6H_4Me)]		100
[Ni(bpy)Me(S-2,6-$C_6H_3Me_2$)]		100
[Ni(bpy)Me(S-2,4,6-$C_6H_2Me_3$)]		96
[Ni(bpy)Me(S-2,6-$C_6H_3Cl_2$)]		100
[Ni(bpy)(COMe)(S-2,6-$C_6H_3Cl_2$)]		100
[Ni(bpy)Et(S-2,4,6-$C_6H_2Me_3$)]		99
[Ni(bpy)($SCH_2CH_2CH_2$)]		100 (96)[d]

[a] THF solutions, 25 °C; for details, *cf.* the Experimental Section. [b] 5–12 mM. [c] Mean of two reactions. [d] Benzene solution, three determinations.

isolated yield of γ-thiobutyrolactone was reported for a reaction performed in benzene with 1 atm of carbon monoxide. We have examined this reaction in THF and benzene solutions under the experimental conditions used for other systems and find by NMR signal integration average yields *in situ* of 100% and 96%, respectively (Table 3).

The quantitative yields in reaction 13 require a solely intramolecular pathway to thiolactone formation. Several observations support this pathway in reaction systems based on the complexes **8**: the cis arrangement of thiolate and acyl groups in intermediate **9** (positioned at an S···C=O distance of 2.82 Å in **9a**), essentially quantitative yields of thioesters in all systems, implying a facile pathway to product formation. While a $Ni_2(\mu\text{-}SR)_2$ five-coordinate bridged intermediate with cis thiolate and acyl groups is readily conceived as the most probable initial intermediate on an intermolecular pathway, its formation appears superfluous to product formation compared to the more efficient intramolecular reaction of mononuclear intermediate **9**. We are unable to identify any cause of enhanced reactivity of acyl or thiolate ligands in such an intermediate; in any event, thioester formation by such a species devolves to an intramolecular process. On the basis of observations related to reaction scheme 10,[27-32] it is likely that thioester formation from **9** is induced (or at least assisted) by interaction of carbon monoxide with the complex in one of at least two events required to generate the product dicarbonyl complex **10**. If CO binding to **9** is a discrete event, a five-coordinate intermediate is less probable than **9**. Because it does not include all steps, the scheme in Figure 2 is a *minimal* representation of thioester formation via an intramolecular pathway. Any subsequent resolution of the reaction pathway by kinetics will require rapid methods; reactions between **8** and carbon monoxide under the conditions used here are instantaneous.

Summary. This work provides the first examples, in the form of overall reaction 12, of (acyclic[44]) thioester formation mediated at a nickel center. Structures of precursor Ni(II)–methyl–thiolate complexes **8** and intermediate Ni(II)–acyl–thiolate complexes **9** formed from **8** and CO have been established in the crystalline state; given the strong field nature of these diamagnetic complexes, mononuclear structures in solution are entirely probable. With reference to the scheme in Figure 1, should CoA·SH (in the thiol or deprotonated form) attack the [Ni^{II}–$COCH_3$] group of **6**, the previous reaction system[19] shown to execute sequence 9 is at this stage of development of the problem a reasonable analogue. The present investigation demonstrates a second pathway: reaction of *bound* thiolate and acyl groups to form a thioester. While we strongly favor an intramolecular pathway, an intermolecular process with a binuclear intermediate still demonstrates the reactivity of these coordinated ligands. Further examination of enzymatic ester formation would be aided, *inter alia*, by an improved knowledge of the locus and mode of substrate binding and by further structural definition of the catalytic site. We are currently investigating the formation of bridged assemblies containing Ni(II) covalently linked to an Fe–S cluster.

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Supplementary Material Available: X-ray crystallographic data for the compounds in Table 1, including crystal and data collection parameters, atom coordinates, thermal parameters, bond angles and distances, and calculated hydrogen atom coordinates (26 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(44) (a) Matsunaga, P. T.; Hillhouse, G. L. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1748. For related work, *cf.*: (b) Matsunaga, P. T.; Mavropoulos, J. C.; Hillhouse, G. L. *Polyhedron* **1995**, *14*, 175.

(45) While the sulfur atom and the acyl group in the five-membered $NiSCH_2CH_2C{=}O$ ring of the intermediate in this pathway are favorably positioned for reaction, the lone pairs on the sulfur atom are not directed at the acyl carbon atom. A similar feature is found in acyl complex **9a** (Figure 4), but in this case, it is unclear whether the conformation observed in the crystalline state is the same as in solution. Given the facile occurrence of reaction 13, lone pair orientation in the ground state is evidently not a factor in the intramolecular thioester formation.