

N₂S₂Ni Metallothiolates as a Class of Ligands that Support Organometallic and Bioorganometallic Reactivity**

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That Cys-X-Cys tripeptide linkages can serve as tetradentate N₂S₂ ligands, utilizing carboxamido nitrogen and cysteinyl sulfur atoms as donors in metalloenzyme active sites, has recently been verified in several protein crystal structures.^[1–5] It was further discovered that the nickel-bound Cys-Gly-Cys NiN₂S₂ moiety of acetyl coA synthase binds through bidentate bridging thiolate groups to a second nickel center which mediates the organometallic reactions required of the biocatalyst (the assembly of CH₃⁺, CO, and SR[−] into the acetyl coA thioester CH₃C(=O)SR).^[1,2] The (Cys-Gly-Cys)Ni unit joins a host of synthetic NiN₂S₂ complexes that are known to form multimetal clusters through μ-SR interactions. Nature's control of binuclearity in the construction of an organometallic catalyst presents the intriguing possibility that the NiN₂S₂ complexes might be suitable for development as a novel class of ligands for organometallic chemistry and catalysis. To this end we have characterized a series of NiN₂S₂ complexes, four of which are shown in Figure 1, according to their electron-donating ability and stereochemical fea-

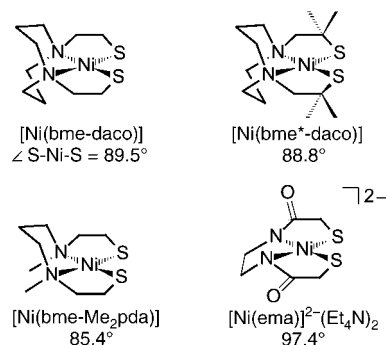


Figure 1. NiN₂S₂ complexes used as S-donor ligands; bme-daco = 1,5-(1,5-diazacyclooctane)di(ethylthiolate), bme*-daco = di(2-methyl-2-propylthiolate), bme-Me₂pda = N,N'-dimethyl-2,9-diazanonanedithiolate, ema^{4−} = 2,7-dioxo-3,6-diazaoctanedithiolate.

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tures.^[6–9] These characteristics are contrasted to the classical ligands of organometallic chemistry, diphosphines and diimines. The results are presented herein along with an organometallic reaction principle that models steps in acetyl coA synthase as well as CO/olefin copolymerization catalysis.

According to Equation (1), NiN₂S₂ derivatives of tungsten tetracarbonyl were prepared from the labile-ligand complex, *cis*-[(piperidine)₂W(CO)₄].^[10] Vibrational mode assignments and ν(CO) stretching frequencies are listed in Table 1.

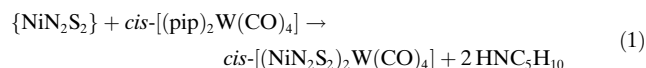


Table 1: IR data for [(NiN₂S₂)W(CO)₄] and [(L₂)W(CO)₄] complexes.^[a]

NiN ₂ S ₂ or L ₂	(A ₁)	(B ₁)	(A ₂)	(B ₂)
(bme-daco)Ni	1995	1871	1853	1819
(bme*-daco)Ni	1996	1871	1857	1816
(bme-Me ₂ pda)Ni	1993	1876	1843	1826
[Ni(ema)] ²⁻	1986	1853	1837	1791
dmpm ^[b]	2007	1885	1885	1863
bipy ^[c] or <i>o</i> -phen ^[d]	2006	1887	1870	1830
pip ^[e]	2000	1863	1852	1809

[a] ν(CO) cm⁻¹, DMF solution spectra; assignments under C_{2v} symmetry. [b] dmpm = dimethyl phosphinomethane. [c] bipy = bipyridine. [d] *o*-phen = *o*-phenanthroline. [e] pip = piperidine.

Of note is the similarity of the ν(CO) values for the W(CO)₄ derivatives containing neutral NiN₂S₂ units; the corresponding ν(CO) values for species with the dianionic complex, [Ni(ema)W(CO)₄]²⁻ are shifted negatively from these by 8 to 35 cm⁻¹, dependent on the vibrational mode compared. Thus as might be expected and as indicated by the CO stretching frequencies, this dianionic ligand transfers more electron density to the W(CO)₄ unit than the neutral NiN₂S₂ ligands.

Also listed in Table 1 are the ν(CO) values for *cis*-[(pip)₂W(CO)₄] and representative classical bidentate P- and N-donor ligands in [(L₂)W(CO)₄] complexes. From this data we conclude that the electron-donating ability of neutral NiN₂S₂ S-donor ligands towards the {W(CO)₄} fragment is greater than that of diphosphines, and closer in donor ability to the *o*-phen and bipy ligands. The dianionic NiN₂S₂ ligand derived from the ema tetraanion is a significantly better donor. The electron-donating ability of these ligands to the W(CO)₄ moiety is: [Ni(ema)]²⁻ > {NiN₂S₂}⁰ > phen > (pip)₂ > bipy > dmpm. The molecular structures of three [(NiN₂S₂)W(CO)₄] complexes are presented as ball and stick drawings in Figure 2; for comparison, the structure of [(*o*-phenanthroline)W(CO)₄] is also shown.^[11] The orientation chosen for these depictions stresses the most prominent structural feature of the nickel dithiolates: the dihedral angle or hinge at the Ni(μ-S)₂W linkage that generates distinct asymmetry to the molecule. Thus, the C_{2v} symmetry used to assign the ν(CO) IR spectra holds only for the atom donor sets in the first coordination sphere; the overall symmetry from the molecular structure is C_s. The dihedral angles defined by the intersection of best planes of NiN₂S₂ and

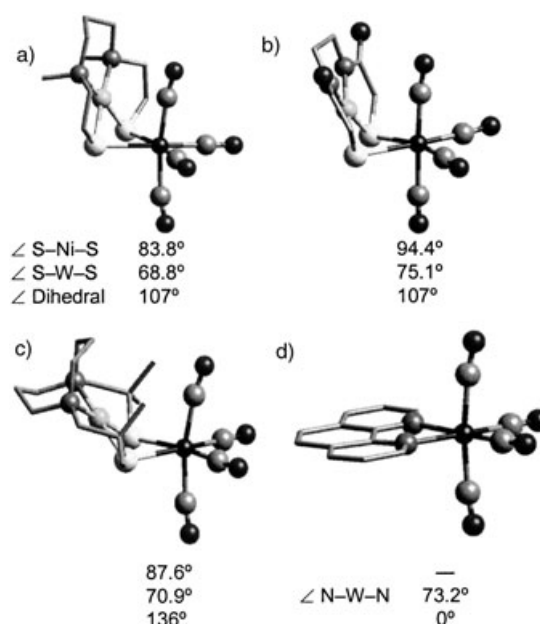


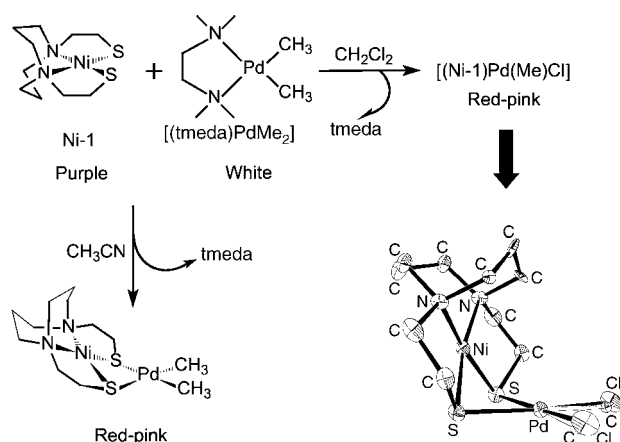
Figure 2. Ball-and-stick molecular structures of a) [Ni(bme-Me₂pda)W(CO)₄], b) [Ni(ema)W(CO)₄]²⁻, c) [Ni(bme*-daco)W(CO)₄], and d) [(*o*-phenanthroline)W(CO)₄]. The dihedral angle is for the intersection of the best planes of NiN₂S₂ and WS₂C₂.

WS₂C₂ are identical, 107°, for the relatively flat [Ni(ema)]²⁻ and the Ni(bme-Me₂pda) metallothiolate ligands, however, the steric bulk of the geminal dimethyl groups on the carbon α to the thiolate sulfur in the [(bme*-daco)Ni] complex opens the hinge to 136°. The Ni...W separations of [Ni(ema)W(CO)₄] (2.928 Å), [Ni(bme-Me₂pda)W(CO)₄] (3.033 Å), and [Ni(bme*-daco)W(CO)₄] (3.389 Å), reflect the different hinge angles of the complexes. There is some deviation from linearity of the CO groups closest to the NiN₂S₂ plane, however the observed angles do not correlate with steric bulk of the ligands. Note that the analogous CO groups in the phenanthroline derivative of {W(CO)₄} also bend away from the position of the substituent ligand, despite the fact that there is no possibility of a steric or lone-pair assist to this deformation.

Listed in Figure 2 are the S-W-S angles, the “bite angles” of the NiN₂S₂ bidentate ligands. The largest, 75.1° is for the rigid ema ligand; the more flexible, neutral ligands have bite angles of around 70°. In addition, the S-Ni-S angles of the tungsten-bound ligand, show only minor decreases from those S-Ni-S angles in the free ligand (Figure 1 and Figure 2). As the S-W bonds are longer than the S-Ni bonds, the S-W-S bite angles are from 15–22° smaller than the corresponding S-Ni-S angles of the free NiN₂S₂ ligands.

As the electron-donor abilities and the relatively flat form of the NiN₂S₂ ligands mimic diimine ligands we sought a model reaction for the purpose of contrasting organometallic reactivity supported by diimine and NiN₂S₂ ligands. A logical choice is the classical CO insertion process of interest in CO/olefin copolymerization catalysis. This reaction also serves as a biomimic of the CO insertion process of acetyl coA synthase. While the exogenous (that is, as related to the NiN₂S₂ moiety) nickel center is the active metal in both

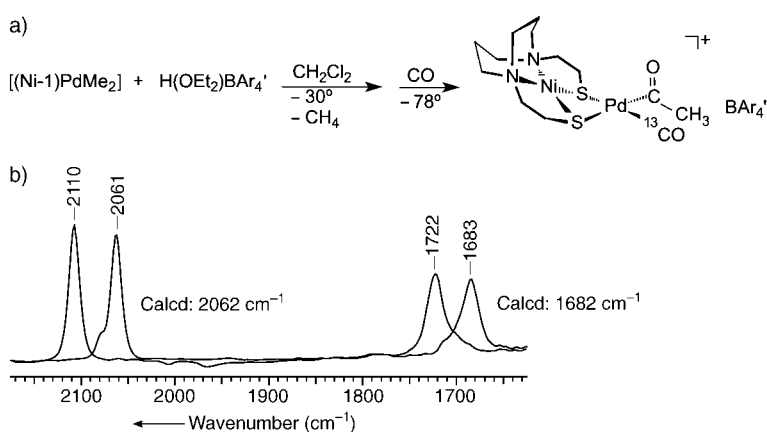
processes, the palladium analogue offers greater stability and the chance for isolating intermediates. The tmeda ligand-displacement route developed by Boersma, Van Koten, et al. for the preparation of diphosphine and diimine derivatives of $\{NiMe_2\}$ and $\{PdMe_2\}$ units, was used for the preparation of $[Ni(bme-daco)PdMe_2]$ Scheme 1.^[12] In CH_3CN , the red-pink product obtained is $[Ni(bme-daco)PdMe_2]$ as evidenced by mass spectral analysis. Unfortunately, high-quality crystals were not forthcoming. Crystals suitable for X-ray diffraction studies were acquired from the reaction performed in CH_2Cl_2 . These crystals analyzed as the chloro-methyl derivative $[Ni(bme-daco)Pd(Me)Cl]$ whose molecular structure is shown as a thermal ellipsoid plot in Scheme 1. In it, the NiN_2S_2 unit from $[(bme-daco)Ni]$ (Ni-1), binds to palladium through bridging sulfur interactions forming a square-planar $\{S_2Pd(Me)Cl\}$ unit in which the methyl



Scheme 1. Displacement of tmeda from $[(tmeda)PdMe_2]$ by $[Ni(bme-daco)]$ in CH_2Cl_2 and MeCN. The crystal structure of the product obtained in CH_2Cl_2 is also shown; tmeda = *N,N,N',N'*-tetramethyl-1,2-ethanediamine.

and chlorine atoms are disordered; they were modeled with 50% occupancy of each site. The dihedral angle between the two square planes is 101.3° , and the $Ni\cdots Pd$ separation is 2.802 Å.

In accordance with the method of Brookhart et al., for the generation of an open site on an analogous $[(o\text{-phenanthroline})PdMe_2]$ ^[13] complex Scheme 2 depicts the reactivity of $[(Ni-1)PdMe_2]$ with acid ($HBAR'_4$; $Ar' = 3,5\text{-}(CF_3)_2C_6H_3$) in CH_2Cl_2 at $-30^\circ C$. On cooling this solution to $-78^\circ C$, purging with CO produced a compound with $\nu(CO)$ infrared bands at 2110 and 1722 cm^{-1} , assigned to a terminal and an acetyl CO group, respectively, consistent with the structure proposed in Scheme 2. With ^{13}C -labeled CO (95% enriched), shifts in both the terminal and the acetyl CO positions match the calculated predictions of $\nu(^{13}CO)$ bands, supporting the assignment (Scheme 2 b). For the analogous $[(o\text{-phen})Pd(CO)\{C(=O)Me\}]^+$, the $\nu(CO)$ bands are at 2127 (terminal CO) and 1745 cm^{-1} , (acetyl $C=O$),^[13] which reflects the poorer electron-donating ability of *o*-phen compared with Ni-1 towards the Pd^{2+} center, as also seen with the $\{W(CO)_4\}$ probe moiety.



Scheme 2. a) Reaction of $[(Ni-1)PdMe_2]$ with acid and CO. b) IR spectra of the reaction product and of the ^{13}C -labeled product which agrees well with the calculated isotope-shift bands.

Isotopic labeling was also used to explore the exchange reaction of bound with free ^{13}CO in $[(Ni-1)Pd(CO)\{C(=O)Me\}]^+$ in CH_2Cl_2 . Under a ^{13}CO atmosphere over the course of 30 min at $-78^\circ C$, the IR spectrum of the solution showed approximately 75% enrichment of the terminal CO position while the acetyl ^{12}CO band remained the major species. Nevertheless, there was some build-up of a shoulder on the lower energy side of the 1722 cm^{-1} band which indicated minor incorporation of ^{13}CO into the acetyl position.

The facile nature of the terminal CO exchange with free ^{13}CO at $-78^\circ C$ deserves comment. As the processes which might create an open site, chelate ring-opening or CO dissociation, are expected to have activation barriers that could not be overcome at such low temperatures, we assume that CO exchange proceeds by an associative process. A similar five-coordinate intermediate would also account for the deinsertion process that is required for the apparent incorporation of some of the ^{13}C label into the acetyl site. On the other hand, the strength of the $Pd-S$ bond in the NiS_2Pd chelate system is unknown and the breaking of one NiS_2-Ni bond in the theoretical model of acetyl coA synthase was computed as a probably route for creating the open site required for CO uptake and catalysis.^[14] Further discussion at this time would just be speculation.

In 1995, Holm and Tucci demonstrated an essential feature of acetyl coA synthase, the coupling of a thiolate and a nickel-bound acetyl group using the $[(bipy)NiMe_2]$ complex which readily reacts with a RSH source forming $[(bipy)NiMe(SR)]$ with subsequent thioester formation upon introduction of CO gas.^[15] NaSMe was added to $[(Ni-1)Pd(CO)\{C(=O)Me\}]^+$ in CH_2Cl_2 at $-30^\circ C$. On warming the dark red solution to $22^\circ C$, over the course of 1 h, the IR spectrum showed diminished bands for the carbonyl groups of the NiPd complex and growth of a band at 1686 cm^{-1} , consistent with that of a pure sample of $MeSC(=O)Me$. Whether the formation of the thioester occurred by nucleophilic attack of the $^-[SR]$ or reductive elimination of the acetyl requires further study.

These results suggest the NiN₂S₂ complexes which model a soft bidentate binding site for redox-active exogenous nickel centers in nature should also be considered as a new class of synthetic ligands for organometallic chemistry. An intriguing aspect of the ligands to be developed is the extensive stereochemical potentiality, best illustrated by the overlay of the [(Ni-1)Pd(Me)Cl] with the [(phen)Pd(CO){C(=O)Me}]⁺ complex, Figure 3.^[13] One face of the square planar d⁸Pd

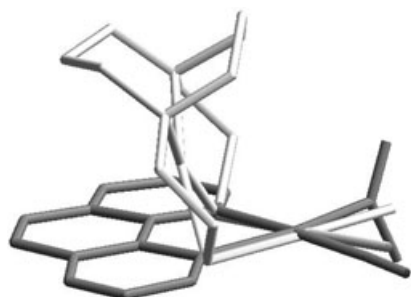


Figure 3. Cerius model overlay of [(Ni-1)Pd(Me)Cl] (white) with the [(phen)Pd(CO){C(=O)Me}]⁺ (gray) ion.

active metal center is flanked by the square plane of the NiN₂S₂ ligands in [(Ni-1)Pd(Me)Cl], while the other is open. Substrates approaching the open site are expected to experience strong orientational preferences due to this feature and hence lead to regioselectivity. Chirality can also be introduced into the ligands at several places.

In conclusion, the $\nu(\text{CO})$ frequencies probed by the {W(CO)₄} and Pd-acetyl moieties indicate that NiN₂S₂ ligands are much better electron donors than conventional diphosphines and diimines, yet with the capability of stabilizing low-oxidation-state metals, such as W⁰ and Pd^{II}. The NiN₂S₂ complex serves as a ligand to a Pd-alkyl metal center that undergoes CO addition and insertion reactions similar to those of Brookhart's catalyst. Moreover, the reactivity of the [NiN₂S₂Pd-alkyl] complex with CO and an ⁻[SR] source to produce a thioester is the first example of a heterobimetallic complex that is able to mimic the final step mediated by the acetyl coA synthase enzyme active site.

Experimental Section

See Supporting Information for all additional syntheses. CCDC-253549–253552 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

[Ni(bme*-daco)W(CO)₄]: The yellow [W(CO)₄(pip)₂] (0.12 g, 0.26 mmol) was dissolved in CH₂Cl₂ (20 mL) and heated to 40 °C for 10 min under an N₂ atmosphere. To this was added dropwise a lilac-purple solution of [Ni(bme*-daco)] (0.09 g, 0.26 mmol) dissolved in CH₂Cl₂ (10 mL). The resulting red-brown solution was heated for an additional 10 min at 40 °C, and then stirred at 22 °C ultimately producing a brown precipitate. The solvent and piperidine were removed under vacuum and the brown solid washed with benzene (25 mL × 2) and diethyl ether (25 mL × 2). The solid was extracted with CH₂Cl₂ and orange-red crystals were obtained from vapor diffusion of hexane into this solution, yield 0.11 g (65%) elemental

analysis (%) calcd for C₁₈H₂₈N₂Ni₁O₄S₂W₁: C 33.6, H 4.39, N 4.36; found: C 32.1, H 4.49, N 4.49. UV/Vis in DMF solution: $\lambda_{\text{max}}(\epsilon) = 306$ (5002), 372 (1382), 420 (1480), 504 nm (495).

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