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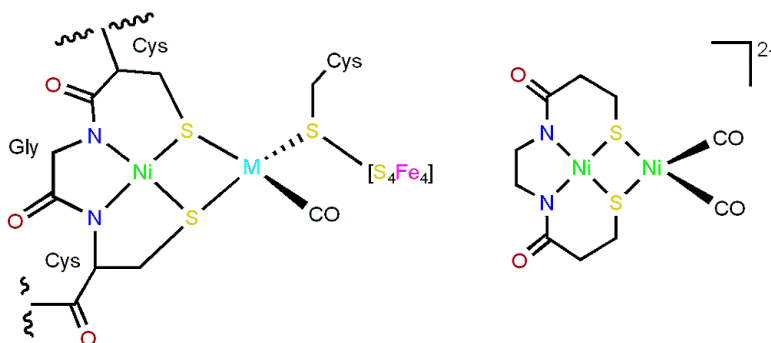
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Structural Analogues of the Bimetallic Reaction Center in Acetyl CoA Synthase: A Ni–Ni Model with Bound CO

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The enzymatic processing of industrially important small molecules, e.g., dihydrogen, carbon monoxide, and dinitrogen, presents inspiration for organometallic catalysis based on evolutionarily optimized reaction centers. In the case of CO, carbon monoxide dehydrogenase/acetyl CoA synthase bifunctional enzymes (CODH/ACS), as found in *Moorella thermoacetica* (f. *Clostridium thermoaceticum*), are important in the global carbon cycle.[1,2]

The crystallographic characterization of the ACS enzyme, as described separately by Doukov et al. and Darnault et al.,[3,4] revealed an unprecedented hexametallic three-component active site. The three components are (i) an Fe_4S_4 cluster attached via a μ-SR group to an extra-cluster metal center, a motif also seen in the Fe-only hydrogenases;[5] (ii) a four-coordinate, proximal metal site, featuring Cu, Ni, or Zn, which in turn is bound to the third component; (iii) a square planar distal Ni ligated to the protein backbone via two amides (deprotonated) and two thiolates (Figure 1).[2] Initial crystallographic characterization found copper in the proximal position,[3] but more recent work proposes that the active form of the enzyme in fact contains nickel in this site, which oscillates between square planar (oxidized) and tetrahedral (reduced) geometries.[4] Both Cu(I) and Ni(0) would have similar coordination preferences (as would Ni(I)[6]), and both metals are plausible binding sites for CO.

As a first step in understanding the catalytic mechanism implied by the ACS structure, we have synthesized structural analogues of the active site. Our approach, adopted also by Riordan et al.,[7] is to set aside the $[Fe_4S_4(SR)_4]^{2-}$, which is unlikely to bind substrate, and to focus on the two monometallic subunits, i.e., the metal center that is bridged to square planar Ni via a pair of thiolato bridges. Dithiolato-bridged bimetallic structures have often been achieved using nickel diamino dithiolates as building blocks,[8–11] and we adopted this approach.

The 1:1 reaction of $[Cu(NCMe)_4]BF_4$ and the nickel hexamethylated diamino dithiolate (abbreviated **NiS₂N₂**)[12] yielded the red-brown derivative $[Cu_2\{\mathbf{NiS_2N_2}\}_2]^{2+}$, which was crystallographically shown to adopt the dimeric "stair-case" structure. This dication proved to be a versatile precursor to heterobimetallic derivatives via ligand-induced scission of the Cu_2Ni_2 core. Thus, treatment of $[Cu_2\{\mathbf{NiS_2N_2}\}_2]^{2+}$ with PR_3 (R = ^iPr, NMe_2) afforded the bimetallic derivative $[\{(R_3P)(MeCN)Cu\}\{\mathbf{NiS_2N_2}\}]^+$ (Scheme 1), as shown by NMR and ESI-MS measurements. Excess phosphine effected no further reaction. Survey studies assayed using ESI-MS shows that excess methylimidazole (MeIm) cleaves $[Cu_2\{\mathbf{NiS_2N_2}\}_2]^{2+}$ to form $[\{(MeIm)(MeCN)Cu\}\{\mathbf{NiS_2N_2}\}]^+$, which does not react with CO. Addition of 1 equiv of MeNC to $[Cu_2\{\mathbf{NiS_2N_2}\}]^{2+}$ produced $[\{(MeNC)(MeCN)Cu\}\{\mathbf{NiS_2N_2}\}]^+$, but excess MeNC resulted in the extraction of Cu^+, yielding $[Cu(CNMe)_4]^+$. Crystallographic characterization of $[\{(^iPr_3P)(MeCN)Cu\}\{\mathbf{NiS_2N_2}\}]^+$ revealed, as in the ACS active site, a tetrahedral metal center bound to both thiolates of the planar **NiS₂N₂** metallo ligand. The fourth coordination site on the copper center is occupied by a labile MeCN ligand.
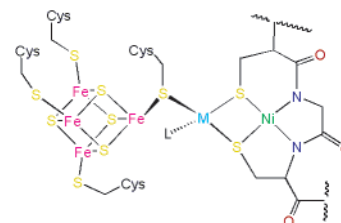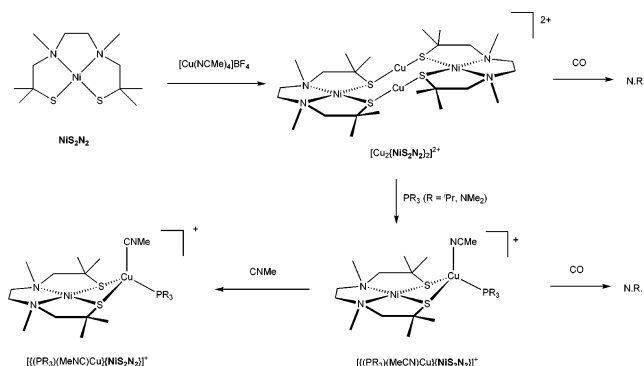

Figure 1. Drawing of the active site of ACS (M = Cu, Ni, Zn).

Scheme 1. Preparation of Cu–Ni Models Using Nickel Diamino Dithiolate

Although $[\{(^iPr_3P)(MeCN)Cu\}\{\mathbf{NiS_2N_2}\}]^+$ shows no affinity for CO, it does form a stable adduct with MeNC (ν_{CN} = 2194 cm^{-1}), an electron-rich analogue of CO. The binding of MeNC demonstrates the lability of the MeCN ligand and the Lewis acidity of the Cu(I) site.

Following these studies on **NiS₂N₂**, we pursued models in which the ligand superstructure was more clearly biomimetic. The planar Ni center in ACS is bound by a diamido–dithiolato donor set provided by a cys-gly-cys sequence.[3,4] This coordination environment, while otherwise unprecedented in nature, has been previously investigated in synthetic systems[7,13,14] and is reminiscent of the nitrile hydratase binding site.[15–17] The diamido dithiolate derived from 3-mercaptopropionic acid and ethylenediamine[18] had not been previously used as a ligand, although it can be readily prepared on a large scale and it features an *unsaturated* backbone as in ACS. The salt $(Et_4N)_2[\mathbf{NiS_2N'_2}]$ adopts the expected square planar structure. Capitalizing on the aforementioned methodology, reaction of $(Et_4N)_2[\mathbf{NiS_2N'_2}]$ and $[Cu(NCMe)_4]PF_6$ in the presence of P^iPr_3 afforded $(Et_4N)[\{(^iPr_3P)Cu\}\{\mathbf{NiS_2N'_2}\}]$ (Scheme 2). Crystallographic studies confirm that copper is trigonal planar ($\sum$ angles = 359.3°). The Cu–S and Ni–S distances are 2.287 and 2.202 Å, respectively, vs 2.204 and 2.186 Å seen in the Cu form of ACS.[3] The Cu···Ni distance is 2.672 Å in the model and 2.792 Å in the enzyme.[3] The absence of the MeCN ligand (the solvent for crystal growth) may reflect the enhanced donor power of $[\mathbf{NiS_2N'_2}]^{2-}$ vs $[\mathbf{NiS_2N_2}]$, which stabilizes three-coordinate 16e Cu(I). Again, this bimetallic complex shows no affinity for CO, despite the coordi-
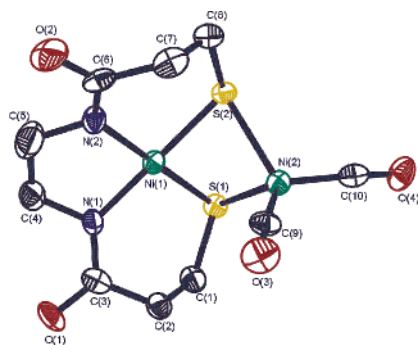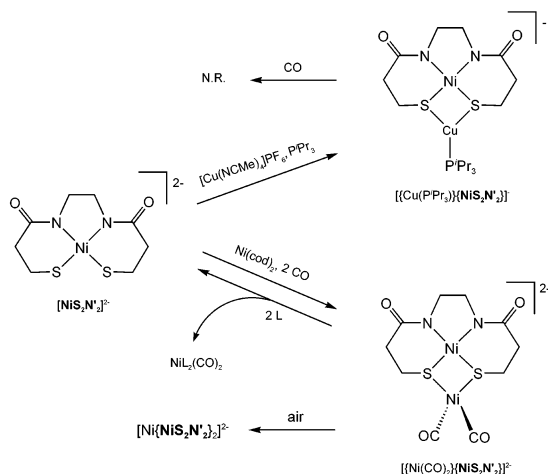
Figure 2. Molecular structure of the anion in $(Et_4N)_2[\{(CO)_2Ni\}\{NiS_2N'_2\}]$ (50% thermal ellipsoids). Distances (Å) and angles (°): Ni(1)−Ni(2) 2.805, S(1)−Ni(1)−S(2) 83.2, Ni(1)−S(av) 2.195, Ni(2)−S(av) 2.347, Ni(2)−C(av) 1.754.

Scheme 2. Preparation of Cu−Ni and Ni−Ni Models Using Nickel Diamido Dithiolate

native unsaturation at Cu. We could not find literature examples of Cu(I)−phosphine−CO complexes. The cyclic voltammogram of $(Et_4N)[\{(^iPr_3P)Cu\}\{NiS_2N'_2\}]$ features a low potential oxidation at +180 mV (irreversible, vs Ag|AgCl), attributed to the Ni(II)/Ni(III) couple. This couple is shifted by 480 mV vs the $[NiS_2N'_2]^{2-/-}$ couple at −300 mV (irreversible, vs Ag|AgCl). Krüger and Holm observed comparably low oxidation potentials in related nickel diamido dithiolates.[14]

Further work on these models was motivated by the nonreactivity of our Cu−Ni species toward CO and Darnault et al.'s evidence that the proximal metal center in the active form of ACS is Ni.[4] We found that treatment of $(Et_4N)_2[NiS_2N'_2]$ with nickel(0) bis-(cyclooctadiene), $Ni(cod)_2$, at −40 °C followed by mild carbonylation (1 atm, 20 min, −5 °C) afforded the red-brown salt $(Et_4N)_2[\{(CO)_2Ni\}\{NiS_2N'_2\}]$ (Scheme 2). The IR spectrum of this bimetallic species displays a pair of ν_{CO} bands at 1948 and 1866 cm^{-1} (MeCN solution). ^1H and ^{13}C NMR spectroscopy indicates a symmetric Ni(0)−Ni(II) structure, consistent with the crystallographic characterization (Figure 2). The overall structure of $[\{(CO)_2Ni\}\{NiS_2N'_2\}]^{2-}$ resembles that proposed by Darnault et

al. for the reduced bimetallic subunit of the active ACS enzyme. Detailed comparison between our model and the Darnault structure is complicated by the uncertainty in the oxidation state of the enzyme crystals as well as variable site occupancy.

The synthesis of $[\{(CO)_2Ni\}\{NiS_2N'_2\}]^{2-}$ can plausibly be proposed to proceed via the intermediacy of $[\{(cod)Ni\}\{NiS_2N'_2\}]^{2-}$, but we have not yet isolated this species. Whereas $[\{(CO)_2Ni\}-\{NiS_2N'_2\}]^{2-}$ is quite stable in solution and in the solid state under inert atmosphere, it is labile with respect to donor ligands and to air, like the biological system. Addition of PPh₃ removed the Ni(0) center, affording $Ni(CO)_2(PPh_3)_2$,[19] and exposure to air rapidly degraded the complex to give $[Ni\{NiS_2N'_2\}_2]^{2-}$ (ESI-MS).

In summary, we report a series of d^8-d^{10} bimetallic systems bearing a stoichiometric and structural resemblance to the bimetallic site of ACS as described by Doukov et al. and by Darnault et al.[3,4] The preparation of such species supports the mechanism for ACS activity proposed by Darnault et al.[4] The nonreactivity of our Ni−Cu derivatives toward CO contrasts with the stability of the NiCO derivative. Although further work is indicated, especially on the CO-localized reactivity, our findings provide first-generation models for a biological role for nickel carbonyls.[4]

Supporting Information Available: Synthesis and characterization of $[Cu_2\{NiS_2N_2\}_2](BF_4)_2$, $[\{(^iPr_3P)(NCMe)Cu\}\{NiS_2N_2\}]PF_6$, $(Et_4N)_2-[NiS_2N'_2]$, $(Et_4N)[\{(^iPr_3P)Cu\}\{NiS_2N'_2\}]$, and $(Et_4N)_2[\{(CO)_2Ni\}-\{NiS_2N'_2\}]$ (PDF, CIF, JPEG). This material is available free of charge via the Internet at http://pubs.acs.org.

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