Enzyme Models

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The Conversion of Nickel-Bound CO into an Acetyl Thioester: Organometallic Chemistry Relevant to the Acetyl Coenzyme A Synthase Active Site**

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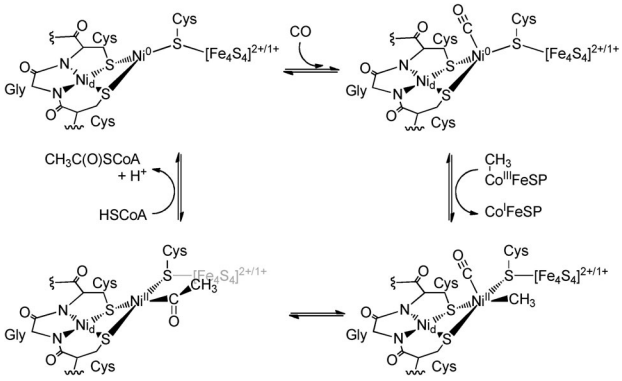
The carbon monoxide dehydrogenase/acetyl coenzyme A synthase (CODH/ACS) is a bifunctional enzyme which couples the reduction of CO_2 to CO [Eq. (1)] to the conversion of CO and coenzyme A (HSCoA) to give acetyl coenzyme A ($CH_3C(O)SCoA$), which is a central metabolite [Eq (2); CH_3-$Co^{III}FeSP$ = methylated corrinoid iron sulfur protein].[1–3]

$$CO_2 + 2\,H^+ + 2\,e^- \overset{\text{CODH}}{\rightleftharpoons} CO + H_2O \qquad (1)$$

$$CH_3\text{-}Co^{III}FeSP + CO + HSCoA \overset{\text{ACS}}{\rightleftharpoons} CH_3C(O)SCoA + Co^{I}FeSP + H^+ \qquad (2)$$

After CO is produced within the CODH subunit of the enzyme, it is guided through a channel to the active site of the ACS subunit (A cluster), which consists of a dinuclear Ni core linked via a cysteinate bridge to an 4Fe-4S cluster (Scheme 1, upper left).[3,4] At this site, an acetyl thioester, namely acetyl coenzyme A $CH_3C(O)SR$ (R = CoA), is generated from the constituents of CO, a thiol (HSR), and a methyl moiety, which is provided by a corrinoid iron–sulfur protein (ultimately a methylcobal(III)amine).[1–5] Although protein single-crystal X-ray diffraction investigations have significantly enhanced the understanding of the active site structure in recent years,[4,6,7] the mechanism by which the conversion of Equation (2) is realized at the bimetallic core has been a matter of intense debate for over a decade, especially with respect to the binding sequence of the three substrates.[1,4,8–10] In the meantime, a consensus has been reached that HSCoA is the last substrate to bind.[10,11] It is also widely accepted that the resting state contains both Ni centers in the oxidation state +II, and that Ni_d mainly serves the stabilization of the structure. Reduction of Ni_p, either to Ni^I or even to Ni^0, produces the active state that is capable of creating the acetyl moiety from CO and a methyl species.[12] For this process, two scenarios are conceivable: 1) a H_3C–Ni^{II} unit is formed first, followed by CO insertion into the Ni–C bond, or 2) CO gets coordinated at the reduced Ni center in the initial step, and subsequently the cobalamin transfers CH_3^+ onto the resulting Ni–CO species. A proposed mechanism favoring the second option is depicted in Scheme 1.[4]



Scheme 1. The ACS catalytic cycle as proposed by Fontecilla-Camps et al.[4]

However, there are also other suggestions based on route 1,[12,13] and today one of the prevailing views assumes a "random binding"[10,14] of either methyl or CO, in which case 1 and 2 would proceed simultaneously.

Bioinorganic model compounds can reveal important insights concerning the functioning of enzyme active sites: they provide information as to which kind of reaction pathways are plausible from the point of view of molecular chemistry considering the existence or elusiveness of precedent cases from that area. The CODH/ACS has been a stimulus for a variety of studies on structural[2,9,15,16] and functional[2,5,16,17] low-molecular-weight analogues in the past. Aiming at functional mimics, synthetic efforts have focused on mononuclear as well as dinuclear Ni complexes that simulate potential elementary steps of the ACS subunit.[18] In this context, methyl groups have been successfully transferred from cobalt to Ni^I, and there is also evidence for the oxidative addition of carbon electrophiles to Ni^0.[16b] Various examples from organonickel chemistry confirm the assumption that CO is able to insert into Ni–C bonds,[17] and addition of CO to dinuclear thiolate-coordinated nickel compounds containing a methylnickel(II) moiety has led to thioester formation.[5,19]

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A recent breakthrough has been the successive reaction of a $Ni^{II}Ni^{0}$ precursor, first with methylcobaloxime and then with a thiolate to give a $Ni^{II}Ni^{II}$ complex that subsequently reacts with CO to give an $CH_3C(O)SCoA$ analogue.[5a] While these results have contributed evidence that the initial formation of a H_3C–Ni unit followed by CO insertion is principally feasible, to date there is no precedence from the field of organonickel chemistry supporting route 2, although corresponding investigations have been encouraged[5a] and are certainly motivated by biochemical results.[14,20]

Herein we provide, to the best of our knowledge, a unique example of a Ni–CO complex that is converted first into a Ni–$C(O)CH_3$ compound by a formal transfer of CH_3^+ and then into a thioester through treatment with a thiol.

Recently, we reported that treatment of a reduced β-diketiminato-ligated nickel dinitrogen complex[21a] with CO leads to a complex of the type $K_2[\{L^{tBu}Ni(CO)\}_2]$ (**I**, $L^{tBu} = [HC\{C(tBu)NC_6H_3(iPr)_2\}_2]^-$) containing two nickel(0) centers coordinating one CO ligand each.[21b] Compound **I** is thermally stable but highly sensitive towards air, and it is also accessible by reduction of the nickel(I) compound $[L^{tBu}Ni(CO)]$ with KC_8.[21b] Considering its low coordination number and oxidation state, the Ni–CO unit in **I** seemed ideal for a modeling study concerning the reaction sequence 2, which, as outlined above, was considered as one mechanistic option for the construction of the acetyl moiety within the active site of the CODH/ACS. Methyl iodide was chosen as the methylating reagent simulating the cobalamin cofactor for the CH_3^+ transfer. Correspondingly, compound **I** was treated with MeI, and work-up led to a diamagnetic product. A ^{1}H NMR investigation of a C_6D_6 solution indicated the presence of an acetyl unit ($\delta(C(O)CH_3) = 0.45$ ppm), thus suggesting a nickel(II)–acetyl complex $[L^{tBu}NiC(O)CH_3]$ (**1**) as the product (Scheme 2). The ^{13}C NMR spectrum of **1** contained a low-field $C(O)CH_3$ resonance at 243.8 ppm, which is characteristic for η^2-acetyl ligands.[22] It is comparable to that found for the nickel(II)–acetyl complex $[(dppp)Ni\{\eta^2\text{-}C(O)CH_3\}]^+$ (co-existing with $[(dppp)Ni(CO)(CH_3)]^+$ as part of an equilibrium in solution; $\delta(C(O)CH_3) = 242.9$ ppm)[23] and also to the resonance of a nickel(II)–acyl complex $[(dtbpe)Ni\{\eta^2\text{-}C(O)CH_2tBu\}]^+$ ($\delta(C(O)CH_2tBu) = 248.3$ ppm).[24]

Crystallization from various solvents led to single crystals suitable for X-ray diffraction, which, however, were very sensitive to the X-ray irradiation and always decomposed during the data collection, so that the latter could never be completed. Combination of three data sets belonging to the early stages (first 60 frames) of the measurements allowed for a solution revealing the molecular structure of **1**.[25] Complex **1** shows static disorder for the acetyl ligand (the two different conformations are shown in the Supporting Information), and only the major conformer is depicted in Figure 1. Although the disorder limits a discussion concerning the binding parameters of the nickel–acetyl moiety, it becomes obvious that, as expected on basis of the NMR analysis, the acetyl ligand is bound to the $L^{tBu}Ni^{II}$ unit in a side-on fashion, which has been rarely observed for nickel complexes.[24]

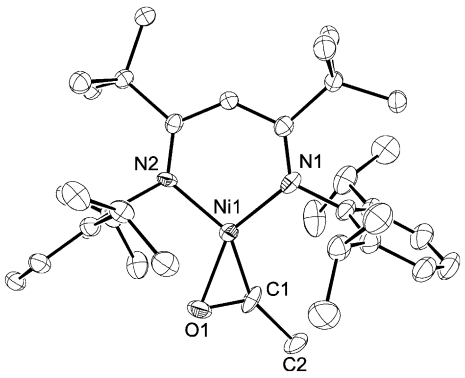
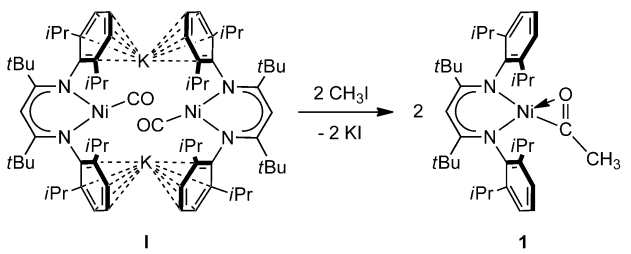


Figure 1. Molecular structure of **1**. Ellipsoids are set at 50% probability; hydrogen atoms are omitted for clarity. Because of disorder in the position of the acetyl ligand, the bond lengths and angles of the atoms C1, C2, and O1 are not discussed. Selected bond lengths [Å] and angles [°]: N1–Ni1 1.881(4), N2–Ni1 1.908(4); N1-Ni1-N2 99.61(15).



I 1

Scheme 2. Synthesis of **1**.

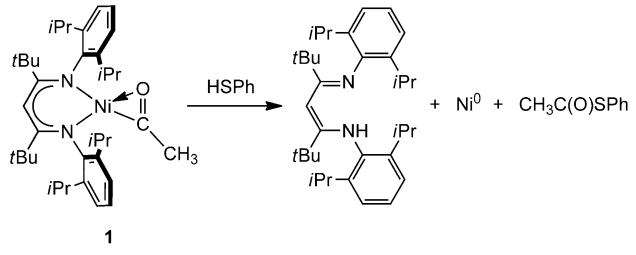
To elucidate the binding situation, DFT calculations (Gaussian 09, B3LYP/6-31G*)[28] were carried out: Setting out with the structure shown in Figure 1, geometry optimization was performed, which indeed converged with a structure containing the acetyl entity in a side-on mode, thus supporting the result of the crystal structure investigation. An natural bond order (NBO) analysis showed that the bonding can be rationalized by an interaction of a negatively charged ligand L^{tBu}, a Ni^{II} ion, and a negatively charged acetyl ligand $(C(O)CH_3)^-$. Although the NBO analysis assigns a bond between Ni and the acetyl C atom, the corresponding bond orbital comprises only 31% of a Ni atomic orbital and 69% of a C atomic orbital, justifying a treatment of this bond as being highly polarized and allocating the bond electrons to the carbon atom of the acetyl group as described. Remarkably, the stabilizing energy caused by donor–acceptor interactions between empty valence orbitals of the Ni atom and both the free electron pairs of the acetyl oxygen atom and π electrons of the CO bond sums to 320 kJ mol^{-1}. This is comparable to the stabilizing energy obtained by interactions of the lone pair at each N atom with empty Ni valence orbitals (190 and 350 kJ mol^{-1} for the two different N atoms) in the same molecule. The small Ni-C-O angle might therefore be due to the stabilization of the molecule by interaction of oxygen valence electrons with empty Ni orbitals. Furthermore, the structure of the hypothetical molecule $[L^{tBu}Ni(CO)(CH_3)]$ (**2**) was optimized and its energy compared with that of **1** to establish whether **2** could in principle be an intermediate on

the way to **1** by analogy to what has been suggested by Fontecilla-Camps et al. (Scheme 1).[4] Its free energy at room temperature turned out to be only 39.7 kJ mol^{-1} higher than that of **1**, that is, **2** may well be an intermediate of the conversion depicted in Scheme 2. However, to definitely confirm this or to rule it out, respectively, the entire energy profile would have to be calculated, which is difficult starting from **I** and CH_3I.

It was of interest to assign the absorption of the Ni-η^2-acetyl moiety in the IR spectrum. A band at 1584 cm^{-1} was observed in a region where acetyl moieties with a side-on binding mode commonly absorb.[22,24] To confirm its assignment to ν(CO), the ^{13}C isotopologue of **1** was synthesized by employing ^{13}CO for the synthesis of the precursor **I**. Indeed, its IR spectrum differed from that of the ^{12}C isotopologue only in the band for the ν(CO) stretching mode, which was shifted to 1545 cm^{-1}. This observed isotope shift ($\Delta\nu(^{12}CO-^{13}CO) = 39$ cm^{-1}) is in agreement with that predicted by theory ($\nu(^{12}CO) = 1628$ cm^{-1}, $\nu(^{13}CO) = 1590$ cm^{-1}, $\Delta\nu(^{12}CO-^{13}CO) = 38$ cm^{-1}).[28]

Unlike other β-diketiminato Ni–X complexes,[21] compound **1** is quite stable to water, as proved by ^1H NMR spectroscopy (even after 3 days in contact with water, the major part of the sample still remained undecomposed). Having created an acetyl group from CO and CH_3^+ in a way that may be of relevance to the ACS reactivity, the question naturally arose as to whether the next step, C–S bond formation, could also be simulated within the same system, in analogy to a precedence setting out with thiols.[17a,b] Therefore, an NMR tube experiment was performed in which a solution of 10 mg of **1** in 0.6 mL [D_8]THF was treated with 1.5 equivalents of thiophenol serving as a HSCoA analogue. During the course of the reaction, a dark brown suspension was formed. The NMR tube containing the reaction mixture was thus centrifuged before recording spectra to separate the solution from a dark brown solid. The ^1H NMR spectrum obtained indicated complete conversion of the nickel–acetyl complex **1** to give phenyl thioacetate $PhSC(O)CH_3$ (assigned through comparison with authentic samples) and the protonated β-diketiminato ligand HL^{tBu} (Scheme 3). Apart from that, only signals from unreacted thiol were observed.

The conversion of **1** and HSPh in THF was also investigated by liquid IR spectroscopy: The IR spectrum of the reaction mixture featured a strong absorption band at 1713 cm^{-1} caused by the stretching vibration of the carbonyl group in $PhSC(O)CH_3$.[29] The yield based on the conversion of [$L^{tBu}Ni\{\eta^2$-$C(O)CH_3\}$], **1**, and HSPh into the thioester was determined by ^1H NMR spectroscopy using DMF as the internal standard. The reaction turned out to be quite fast: Within a few minutes, the set of signals for **1** disappeared completely, and the yield of the thioester amounted to 40%, while the yield of the protonated ligand was almost quantitative. Based on this observation, we conclude that the precipitate formed concomitantly beside elemental nickel may also contain insoluble nickel(II) thiolates.[17b,30] Interestingly, the reaction of **1** with thiolates KSR (R = Et, Ph) in CD_2Cl_2 and [D_8]THF, respectively, proved to be extremely slow (after 4 weeks, the reaction mixture contained only traces of thioester). This observation argues against a mechanism involving a direct nucleophilic attack of the thiol HSPh at the bound acetyl ligand, and at the same time necessitates thoughts on the role of the proton. We can exclude that the first step of the reaction consists of a ligand protonation and that the thioester formation then takes place at nickel species, which do not contain L^{tBu}: The reaction of **1** with equimolar amounts of the acid 2,6-lutidinium triflate to give HL^{tBu} proceeds slowly, and after completion addition of HSPh does not lead to *S*-phenylthioester formation.[31] Hence, a more likely scenario is a prebinding of the thiol followed by a concerted proton shift, umpolung, and reductive elimination.[13]



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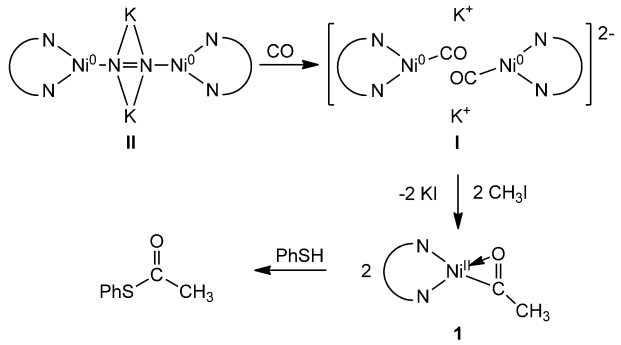
Scheme 3. Reaction of **1** with thiophenol.

Scheme 4 assembles the essence of the findings made up to this point. Setting out from a nickel(0) carbonyl compound (**I**) generated from a nickel(0) precursor (**II**) and CO, we have been able to prepare a nickel acetyl complex (**1**), which in turn reacts with thiophenol, resulting in HL^{tBu} and thioester formation. Thus, this reaction sequence combines mimics of the ACS substrates to give an analogue of its product, and this raises the question in how far the ligand L^{tBu} resembles the $N_2Ni_dS_2$ metalloligand at Ni_p beyond the obvious bidenticity. Apparently, the electronic situations resulting from the $N_2Ni_dS_2/S_{Cys}$ versus L^{tBu} ligation are quite similar: Treating the enzyme in the fully oxidized resting state with CO leads to a reduced Ni^I–CO state that shows a ν(CO) absorption at 1995 cm^{-1} in the IR spectrum,[2,9,32] while the Ni^I pendant of **I**, [$L^{tBu}Ni(CO)$], absorbs at 2020 cm^{-1}.[21b] The fact that the ACS reactivity reported herein involves a Ni^0 center might indicate



Scheme 4. A reaction sequence that mimics the acetyl coenzyme A synthase function. Reactions include carbonylation of a nickel(0) precursor (**II**), methylation of the resulting carbonyl complex (**I**) to give an acetyl compound (**1**), and thioester formation after reaction with a thiol.

that the enzymatic system also intermediately receives a further electron from its environment to develop its function as suggested by Fontecilla-Camps et al.[4] and Hall et al.,[13] although there is still no precedence for Ni^0 in a biological system.

In summary, the results show that an ACS mechanism in which the Ni_p site in the A cluster takes up a CO molecule prior to the transfer of the methyl group is plausible on the grounds of molecular organometallic chemistry. Insofar they provide support for a random binding of the ACS substrates, if not for an exclusive binding of CO in the initial step. Our model contains a Ni^0 center, that is, nickel in an oxidation state conceivable for an intermediate reduced form of the ACS, and thus may hint to a $Ni^{II}Ni^0$ core there. Future studies will address the relevance of the oxidation state for this kind of reactivity.

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Keywords: acetyl coenzyme A synthase · β-diketiminates · coordination chemistry · enzyme models · nickel

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[25] Crystallographic data for **1**: $C_{37}H_{56}N_2NiO$, $0.3\times0.3\times0.3\ mm^3$, $M_r = 603.55$, monoclinic, $P2_1/n$, $a = 9.442(2)$, $b = 23.723(5)$, $c = 15.210(3)$ Å, $\beta = 98.75(3)°$, $V = 3367.3(12)$ Å^3, $Z = 4$, $T = 100(2)$ K, $F_{000} = 1312$, $\mu = 0.606\ mm^{-1}$, $\Theta = 3.32 - 27.80$, collected reflections 25 837, unique reflections 7773 ($R_{int} = 0.1426$), GoF = 1.050, $R_1 = 0.1110$, $wR_2 = 0.2496$, largest difference peak and hole 1.121/−1.827 e Å^{-3}. The structures were solved by direct methods (SHELXS-97)[26] and refined versus F^2 (SHELXL-97)[27] with anisotropic temperature factors for all non-hydrogen atoms. All hydrogen atoms were added geometrically and refined by using a riding model. CCDC 831011 (**1**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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[31] The system **1**/2,6-lutidinium triflate/KSPh leads of course to thioester formation, as HSPh is produced in the first step; the addition of water instead of 2,6-lutidinium triflate as a proton source does not trigger the reaction. See the Supporting Information for full details.

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