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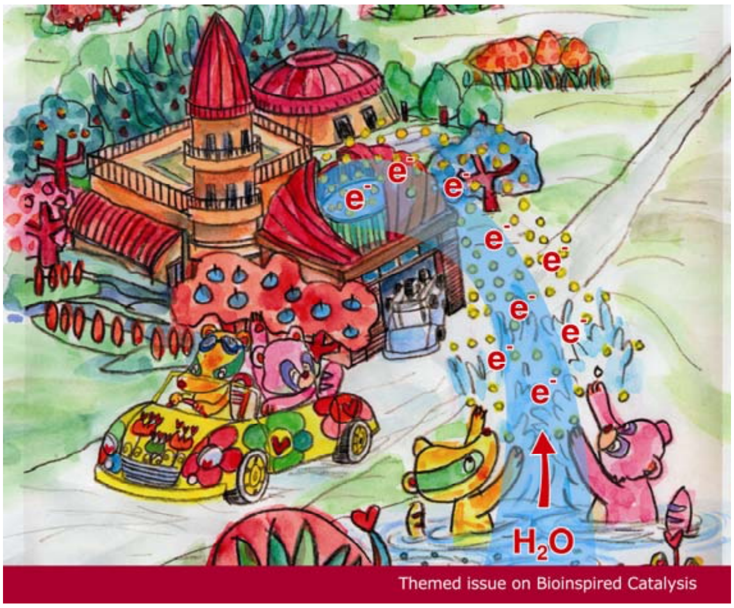

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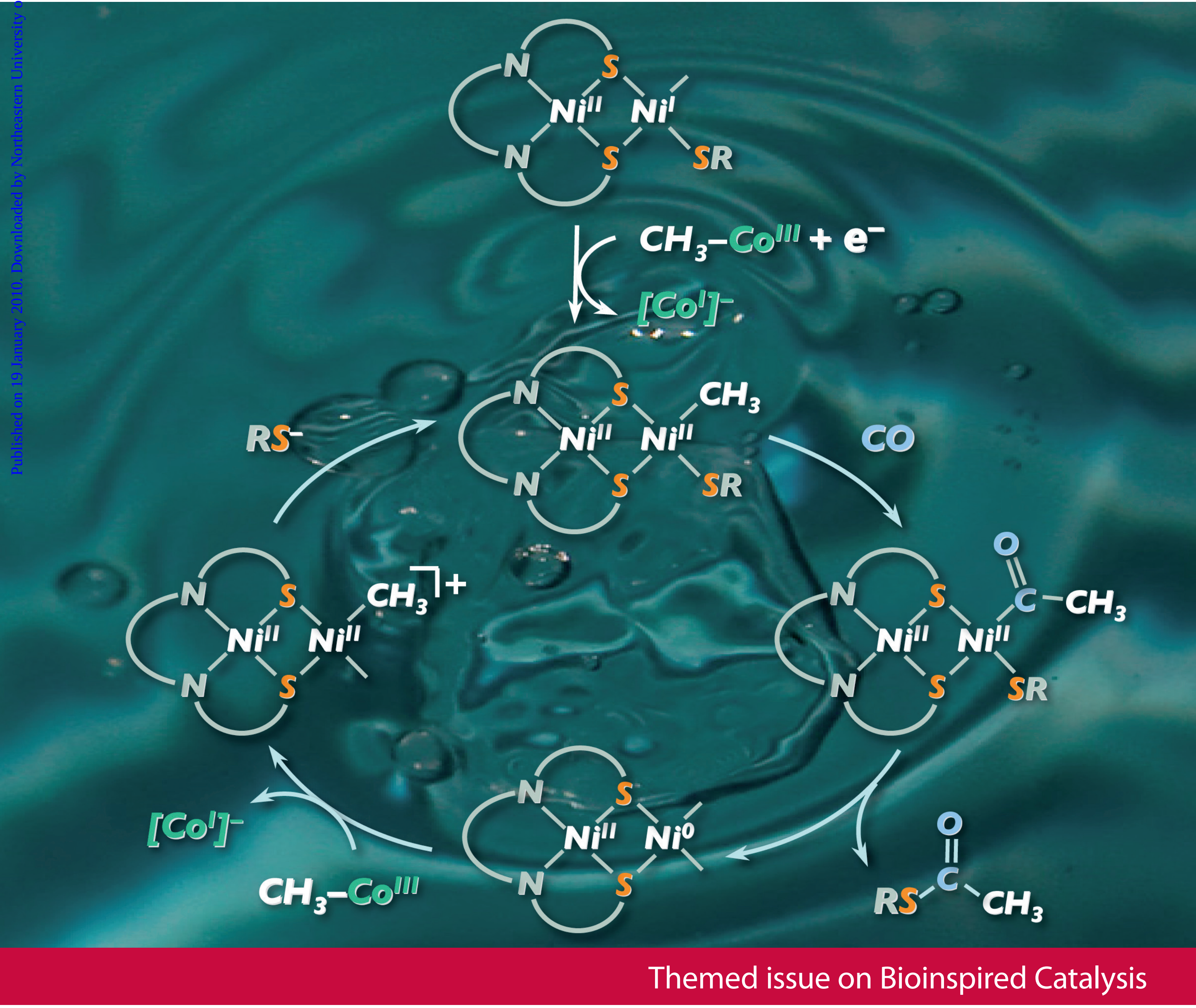

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HOT ARTICLE
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A dinuclear nickel complex modeling of the Ni$_d$(II)-Ni$_p$(I) state of the active site of acetyl CoA synthase†

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The dinuclear Ni(II)-Ni(I) complex Ni^{II}(dadt^{Et})Ni^{I}(SDmp)(PPh$_3$) was synthesized as a Ni(II)$_d$–Ni(I)$_p$ model of the A-cluster in acetyl CoA synthase. This complex was reacted with Co(dmgBF$_2$)$_2$(Me)(Py) and KSDmp successively to afford Ni(dadt^{Et})Ni(Me)(SDmp), which further reacts with CO to afford the acetylthioester CH$_3$C(O)SDmp *via* reductive elimination.

Acetyl-CoA-synthase/CO-dehydrogenase (ACS/CODH) is a novel bifunctional metalloenzyme, carrying out the important function of fixing CO and CO$_2$ in the global carbon cycle.[1] The enzyme produces acetyl-CoA, which is an acetylthioester, from CO, CoA, and a methyl moiety derived from a corrinoid-iron-sulfur protein. The active site of ACS, denoted as the A-cluster, is composed of a redox-active [Fe$_4$S$_4$] cluster and a dinuclear Ni$_d$–Ni$_p$ unit. As shown in Fig. 1, the two nickel atoms designated as Ni$_d$ and Ni$_p$ occupy *distal* and *proximal* positions to the [Fe$_4$S$_4$] cluster, respectively.[2,3]

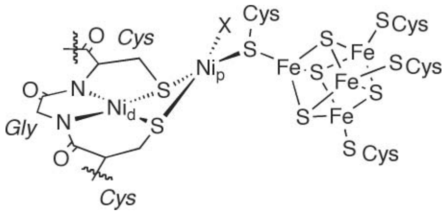
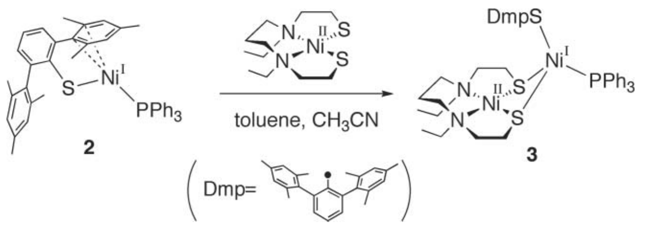


Fig. 1 Schematic view of the ACS active site (A-cluster).

The oxidized form of the A-cluster (A$_{ox}$) has been formulated as {Ni$_d$^{II}-Ni$_p$^{II}-[Fe$_4$S$_4$]$^{2+}$}. However, this state is inactive and requires reduction to promote the methyl group transfer from methylcobalamin. One possible mechanism is based on an active state generated by a two-electron reduction of A$_{ox}$, and the electron configuration of this reduced form has been proposed by Lindahl *et al.* as either {Ni$_d$^{II}-Ni$_p$^{0}-[Fe$_4$S$_4$]$^{2+}$} or {Ni$_d$^{II}-Ni$_p$^{I}-[Fe$_4$S$_4$]$^{1+}$}.[4] On the other hand, Ragsdale has proposed an alternative mechanism that utilizes a one-electron-reduced active state, {Ni$_d$^{II}-Ni$_p$^{I}-[Fe$_4$S$_4$]$^{2+}$}.[1c,5] Recently, we reported the synthesis and some reactions of the dinuclear Ni^{II}(dadt^{Et})-Ni^{0} and Ni^{II}(dadt^{Et})-Ni^{II} complexes (dadt^{Et} = *N*,*N*′-diethyl-3,7- diazanonane-1,9-dithiolate), which serve as structural and functional models of the Ni$_d$^{II}-Ni$_p$^{0} and Ni$_d$^{II}-Ni$_p$^{II} centers of ACS.[6] For instance, we have reported that Ni^{II}(dadt^{Et})Ni^{0}(cod) (cod = cyclooctadiene) reacts with methylcobaloxime Co(dmgBF$_2$)$_2$(Me)(Py)[7] (dmgBF$_2$ = difluoroboryl-dimethylglyoximate) and KSDmp (Dmp = 2,6-dimesitylphenyl) successively to afford Ni^{II}(dadt^{Et})Ni^{II}(Me)(SDmp) (**1**), which further reacts with CO to generate the acetyl CoA analog, CH$_3$C(O)SDmp, *via* reductive elimination.[6a]

In order to expand the scope of our study of A-cluster models, we have examined a system at the Ni^{II}-Ni^{I} reduction level, and this paper describes the synthesis of Ni^{II}(dadt^{Et})Ni^{I}(SDmp)(PPh$_3$) and its reaction with methylcobaloxime. While a variety of A-cluster model complexes have been reported,[6,8] dinuclear Ni(II)–Ni(I) models remain very scarce. Schröder *et al.* detected formation of [Ni^{II}(dadt^{Et})Ni^{I}(dppe)]$^{+}$ by EPR upon electrochemical reduction of [Ni^{II}(dadt^{Et})Ni^{II}(dppe)]$^{2+}$,[8a] while Mascharak *et al.* have prepared Ni^{II}–Ni^{I} complexes *in situ*, *e. g.*, [Et$_4$N][Ni(PhPepS)Ni(dppe)] (PhPepS = *N*,*N*′-Phenylenebis(*o*-mercaptobenzamide)), by chemical reduction of the corresponding Ni^{II}-Ni^{II} complexes.[8e,8h] However, the structures and reactions of these dinuclear Ni^{II}-Ni^{I} complexes have not been reported.

Our isolation of a Ni^{I} thiolate complex, Ni^{I}(PPh$_3$)(SDmp) (**2**),[9] opened a route to synthesize a Ni$_d$^{II}-Ni$_p$^{I} model of the A-cluster using **2** as the Ni(I) building block. The reaction of **2** with Ni(dadt^{Et}) generated Ni^{II}(dadt^{Et})Ni^{I}(SDmp)(PPh$_3$) (**3**) in 72% yield (Scheme 1), and the molecular structure was determined by X-ray analysis.‡ As shown in Fig. 2, the Ni$_p$^{I} site (Ni(2)) of **3** assumes a distorted tetrahedral geometry, where the S(3)–Ni(2)–P bond angle is large, 134.62(4)°. This may be partly due to the steric bulk of SDmp. Another salient feature of the dinuclear structure is a smaller folding angle of the Ni$_2$S$_2$ quadrangle (98.89°), relative to those of the related Ni(II)-Ni(II) complexes, Ni(dadt^{Et})NiL$_2$ (103.5–119.4°).[6,8a,8f]



Scheme 1 Synthesis of Ni^{II}(dadt^{Et})Ni^{I}(SDmp)(PPh$_3$) (**3**).

The magnetic moment of **3** was measured over a 12–300 K range. The observed value of 2.21–2.47 μ_B is consistent with the expected spin state S = 0 at Ni$_d$^{II} (Ni(1)) and S = 1/2 at Ni$_p$^{I} (Ni(2)). The X-band EPR spectrum in toluene displays a broad isotropic signal at 297 K (g_{iso} = 2.20) and a rhombic spectrum at 77 K

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† Electronic supplementary information (ESI) available: Experimental details, spectroscopic and X-ray data and cif file for **3**. CCDC reference number 737907. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b924915j

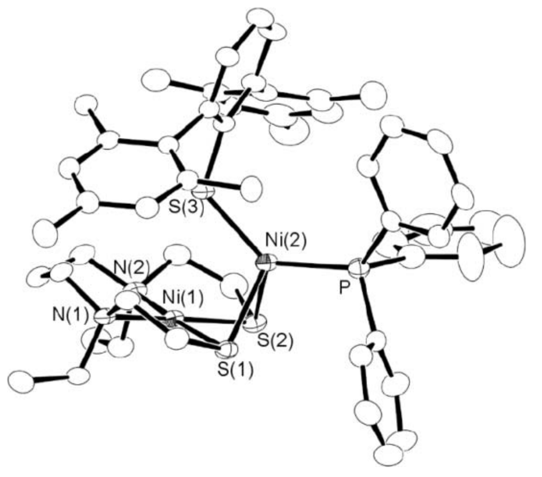


Fig. 2 ORTEP drawing of $Ni(dadt^{Et})Ni(SDmp)(PPh_3)$ (**3**). Thermal ellipsoids are shown at 40% probability. Selected bond distances (Å) and angles (deg); Ni(1)–S(1) 2.1925(12), Ni(1)–S(2) 2.1848(12), Ni(2)–S(1) 2.3529(12), Ni(2)–S(2) 2.3995(13), Ni(2)–S(3) 2.2273(12), Ni(2)–P 2.2309(12), S(1)–Ni(1)–S(2) 82.96(4), S(1)–Ni(2)–S(2) 75.18(4), S(1)–Ni(2)–S(3) 110.51(4), S(1)–Ni(2)–P 108.07(4), S(2)–Ni(2)–S(3) 111.66(4), S(2)–Ni(2)–P 100.45(4), S(3)–Ni(2)–P 134.62(4).

($g_1 \approx 2.62$, $g_2 \approx 2.12$, $g_3 \approx 2.00$), as shown in Fig. 3. No hyperfine splitting from the ^{31}P nucleus was observed in the EPR spectrum. While the *g* values of **3** compare well with those of the tetrahedral Ni^I complex $[PhTt^{tBu}]Ni(CO)$ ($g = 2.64$, 2.02, and 1.95; $PhTt^{tBu}$ = phenyltris((*tert*-butylthio)methyl)borate),[10] they are dissimilar to those of a Ni^{II}-Ni^I complex, the formula of which was reported to be $[Ni^{II}(dadt^{Et})Ni^I(dppe)]^+$ ($g = 2.158$, 2.050, 2.040).[8a] The "semireduced" A-cluster in the $\{Ni_d^{II}\text{-}Ni_p^{I}\text{-}[Fe_4S_4]^{2+}\}$ state was formed *via* one-electron reduction of A_{ox}, which exhibits an EPR spectrum with $g_{\parallel} = 2.10$, $g_{\infty} = 2.03$.[4e] On the other hand, the EPR spectrum of the A_{red}-CO state of ACS, $\{Ni_d^{II}\text{-}Ni_p^{I}(CO)\text{-}[Fe_4S_4]^{2+}\}$, generated by reduction of A_{ox} under a CO atmosphere,[11] shows signals of $g = 2.08$, 2.07, 2.03. The spectral disparity between **3** and these reduced states of ACS indicates that the coordination geometries of the ACS Ni_p^I sites may be somewhat different from that of **3**.[10,12]

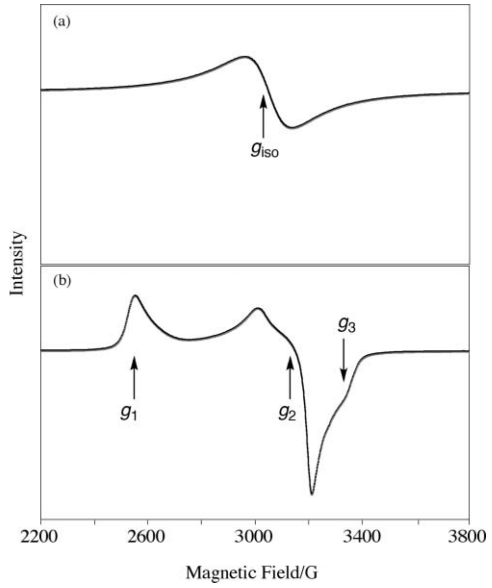
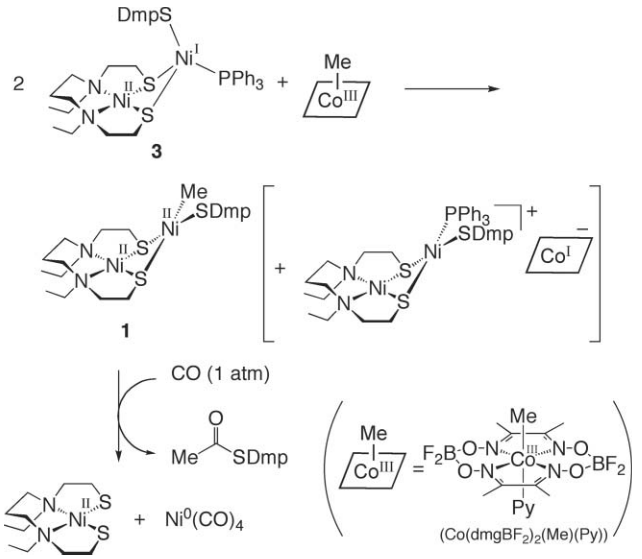


Fig. 3 X-Band EPR spectrum of $Ni(dadt^{Et})Ni(SDmp)(PPh_3)$ (**3**); (a) at 297 K in toluene; (b) at 77 K in frozen toluene.

The cyclic voltammogram of **3** in THF shows irreversible oxidation and reduction waves at $E_{pa} = -0.73$ V ($Ni_d^{II}\text{-}Ni_p^{I} \rightarrow Ni_d^{II}\text{-}Ni_p^{II}$) and $E_{pc} = -1.68$ V ($Ni_d^{II}\text{-}Ni_p^{I} \rightarrow Ni_d^{II}\text{-}Ni_p^{0}$) (*vs* SCE, see ESI†),[13] which are negatively shifted from the corresponding reduction potentials of $[Ni^{II}(dadt^{Et})Ni^{II}(dppe)](PF_6)_2$, $E_{1/2} = -0.47$ V for the Ni^{II}-Ni^{II}/Ni^{II}-Ni^I redox couple and $E_{pc} = -1.22$ V for the reduction of Ni^{II}-Ni^I to Ni^{II}-Ni^0 (*vs* SCE), respectively,[8a] probably because the thiolate $DmpS^-$ is a stronger electron donor than the phosphine chelate dppe.[8i]

The reaction of the dinuclear Ni^{II}-Ni^I model complex **3** and methylcobaloxime was investigated to examine the significance of the Ni_d^{II}-Ni_p^I state in the function of ACS. When complex **3** was mixed with $Co^{III}(dmgBF_2)_2(Me)(Py)$ in a 1 : 1 ratio and charged with CO gas, the acetylthioester $CH_3C(O)SDmp$ was obtained in 43% yield, based on the methylcobaloxime, with concomitant formation of $Ni^0(CO)_4$ and $Ni^{II}(dadt^{Et})$. The yield of the acetylthioester was improved to 90% when two equiv of **3** were allowed to react, whereas further significant improvement was not found from a three equiv addition. Furthermore, a similar 2 : 1 reaction without addition of CO resulted in the formation of $Ni^{II}(dadt^{Et})Ni^{II}(Me)(SDmp)$ (**1**) in 34% yield.[14] These results show that the reaction of **3** and $Co^{III}(dmgBF_2)_2(Me)(Py)$ proceeds in a 2 : 1 ratio. Formally one equiv of **3** accepts the methyl group from the methylcobaloxime to form **1** and cobaloxime in the Co^{II} state, while the second equiv of **3** provides one electron to the Co^{II} site of the cobaloxime, affording a dinuclear Ni^{II}-Ni^{II} cation and an unidentified $[Co^I(dmgBF_2)_2(Py)]^-$ anion. A similar 2 : 1 reaction of mononuclear Ni(I) complex and methylcobaloxime was previously reported by Riordan and co-workers, and the reaction mechanism was investigated by kinetic study.[7,15]

As we have reported earlier, **1** reacts with CO to afford the thioester and a Ni^{II}-Ni^0 species or $[Ni^0(CO)_4 + Ni^{II}(dadt^{Et})]$ *via* reductive elimination. Thus, according to our model study, the methyl group transfer from methylcobaloxime occurs either to the dinuclear $Ni^{II}(dadt^{Et})$-Ni^0 or $Ni^{II}(dadt^{Et})$-Ni^I complex, indicating that methylcobalamin could also react with the ACS active site to produce acetyl-CoA regardless of the oxidation state of Ni_p. For $\{Ni_d^{II}\text{-}Ni_p^{I}\text{-}[Fe_4S_4]^{1+}\}$,[4e] methylcobalamin could react with the Ni_p(I) site to form a Ni_p^{II}-Me species and cobalamin in the formal Co^{II} state, which then could accept one electron from the reduced $[Fe_4S_4]^{1+}$ cluster to be converted into the Co^I state. In our model reaction shown in Scheme 2, the electron that reduces the cobaloxime from Co^{II} to Co^I is supplied by the second equiv of **3**. It is noteworthy that the reaction of the methylcobaloxime with the dinuclear Ni^{II}-Ni^I complex **3** is considerably faster than that with the corresponding Ni^{II}-Ni^0 complex $Ni^{II}(dadt^{Et})Ni^0(cod)$. Although the kinetic studies have not been established, the reaction of **3** with $Co^{III}(dmgBF_2)_2(Me)(Py)$ has completed within 1 h at –40 °C while that of $Ni^{II}(dadt^{Et})Ni^0(cod)$ and $Co^{III}(dmgBF_2)_2(Me)(Py)$ requires 37 h at –30 °C. This result might suggest the significance of the $\{Ni_d^{II}\text{-}Ni_p^{I}\text{-}[Fe_4S_4]^{1+}\}$ state in the catalytic cycle of ACS. However, in our model systems, acetylthioester formation from the reaction of **1** with CO is accompanied by the formation of a Ni^{II}-Ni^0 species. Further modelling studies using dinuclear nickel complexes carrying a



Scheme 2 The reaction of **3** with Co(dmgBF$_2$)$_2$(Me)(Py) and CO.

[Fe$_4$S$_4$] cluster are needed for a better understanding of the function of ACS.

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Notes and references

‡ **Crystal data of 3**. The crystal contains **3** and a toluene molecule in the asymmetric unit. The single crystal was mounted on a loop using oil (CryoLoop, Immersion Oil type B: Code 1248, Hampton Laboratories, Inc.). Diffraction data was collected at −100 °C under a cold nitrogen stream on a Rigaku AFC8 equipped with a Saturn 70 CCD area detector, equipped with a graphite monochromatized Mo-Kα source (λ = 0.71070 Å). Data were collected on 1200 oscillation images with an oscillation range of 0.3°. The frame data were integrated and corrected for absorption using a Rigaku/MSC CrystalClear program package. The structure was solved by a direct method (SIR-97), and was refined by full-matrix least squares on F^2 using SHELXL-97 in a Rigaku/MSC Crystal Structure program package. Anisotropic refinement was applied to all non-hydrogen atoms except for the disordered atoms, and all hydrogen atoms were placed at the calculated positions. Crystal data: $C_{60}H_{72}N_2PS_3Ni_2$; orthorhombic; $P2_12_12_1$ (#19); a = 13.5400(17), b = 14.7402(19), c = 27.322(4) Å; V = 5452.9(12) Å^3; Z = 4; T = 173 K; λ = 0.71073 Å; F(000) = 2260; μ = 0.874 cm^{-1}; ρ_c = 1.298 g cm^{-3}; 44205 reflections (2θ < 55.0°), 12301 unique (R_{int} = 0.040); R_1 = 0.0477 ($I > 2\sigma(I)$), wR_2 = 0.1672 (all data), GOF = 1.104, Flack parameter = −0.043(13).

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