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Methyl Transfer from a Cobalt Complex to Ni(tmc)$^{+}$ Yielding Ni(tmc)Me^{+}: A Model for Methylcobalamin Alkylation of CO Dehydrogenase[†,1]

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Carbon monoxide dehydrogenase (CODH) is a nickel-containing enzyme found in certain methanogenic, sulfate-reducing, and acetogenic bacteria including *Clostridium thermoaceticum* which catalyzes, at different sites, both the oxidation of CO to CO_2 and the synthesis of acetyl-coenzyme A via the Wood pathway.[2] The latter process is a multistep synthesis which requires coupling of a Me group from a corrinoid protein (C/Fe-SP), CO, and the thiolate, coenzyme A (CoA).[3] The redox active site for acetyl-CoA production as deduced from EXAFS and EPR spectroscopies consists of 1 Ni, 3−4 Fe, and more than 4 S atoms.[4] The Ni resides in a planar S_4 or N_2S_2 donor environment.[4a,b] While the active site structure remains unclear, model studies utilizing mononuclear Ni species have reproduced many of the proposed steps in the catalytic cycle.[5] Elegant work of Holm and co-workers produced *tbp* $Ni(NS_3)Me^{+}$ [1] and demonstrated CO insertion to yield a stable Ni-acyl and subsequent thioester formation upon reaction with thiols.[5a,b] Ragsdale has recently established that at the site of acetyl-CoA synthesis in CO dehydrogenase, CO binds to Fe rather than Ni.[6] He proposes a bimetallic migratory insertion in which Fe−CO and Ni−Me form M−C(O)Me (M = Fe or Ni). Spectroelectrochemical and EPR studies support that Me and CO bind to the same state of the enzyme, which is one electron reduced from the resting state.[7] Consequently, several groups have proposed that a Ni(I) center is the acceptor of the nonenzymatic transfer of the Me group from methylcob(III)alamin to CODH.[2a,5a] However, precedents for alkyl transfer from MeCo to Ni(I) do not exist in the organometallic literature.[8] Herein we describe a successful strategy that provides the first example of Me transfer from MeCo to Ni(I) yielding a stable Ni(II)Me species.[9]

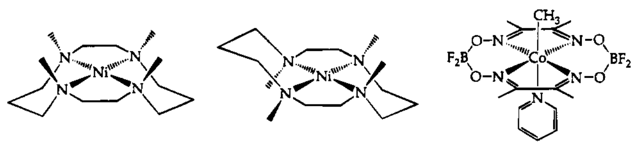
R,S,R,S-Ni(tmc)$^{2+}$ *R,R,S,S*-Ni(tmc)$^{2+}$ $MeCo(dmgBF_2)_2py$

Figure 1.

Addition of $MeCo(dmgBF_2)_2py$[10](MeCo) to 2 equiv of Ni(tmc)OTf,[1,11] Figure 1, in dmso results in an immediate color change from light green to kelly green. Products of the reaction (which proceeds in 80% yield based on $Co(I)^{-}$) are given in eq 1. $Co(I)^{-}$ production was confirmed and quantified by comparison to the electronic and ^{1}H NMR spectra of an authentic sample prepared by Na/Hg reduction of $Co(dmgBF_2)_2$.[12] The ^{1}H NMR spectrum of the reaction mixture displayed resonances consistent with formation of paramagnetic Ni(tmc)Me^{+}.[13] Most characteristic is the broad singlet at δ −332 for the $NiCH_3$ protons.[14,15] This resonance is present in samples of both the *R, S, R, S* and *R, R, S, S* isomers of Ni(tmc)Me^{+} independently synthesized according to Barefield's procedure.[13,14] While the $NiCH_3$ chemical shift is insensitive to the identity of the isomer, the macrocycle ligand protons allow us to distinguish between the two species in solution.[14] In the spectrum of the lower symmetry *R,R,S,S*-Ni(tmc)Me^{+}, there are 13 tmc resonances, while the *R,S,R,S* displays only seven. At present, due to the presence of several different paramagnetic species in solution, we are unable to conclusively determine whether one or both Ni(tmc)Me^{+} isomers are generated in reaction with $MeCo(dmgBF_2)_2py$.[16] The 1:2 MeCo:Ni(tmc)$^{+}$ stoichiometry was deduced by ^{1}H NMR and electronic spectroscopies of the reaction mixture: if the reaction is carried out with a 1:1 stoichiometry, some MeCo remains unreacted and 50% Co(I) is produced, while at a 1:2 ratio, all the MeCo is consumed with 80% $Co(I)^{-}$ detected.

$$MeCo(dmgBF_2)_2py + 2\,Ni(tmc)^{+} \rightarrow Co(dmgBF_2)_2py^{-} + Ni(tmc)Me^{+} + Ni(tmc)^{2+} \quad (1)$$

Production of Ni(tmc)Me^{+} has also been established by its characteristic reactivity patterns with the electrophiles H_2O and

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† Dedicated to Jack Halpern on the occasion of his 70th birthday.

(1) Abbreviations: tmc, 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane; $dmgBF_2$, (difluoroboryl)dimethylglyoximato; py, pyridine; C/Fe-SP, corrinoid iron−sulfur protein; NS_3, $N(CH_2CH_2SR)_3$ (R = Pr^{i}, Bu^{t}); OTf, triflate.

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(8) Espenson and Bakac have studied the reaction of Ni(II) (Ni(cyclam)$^{2+}$) with alkyl radicals yielding transient Ni(III) complexes, Ni(cyclam)R^{2+}, in which the radicals were generated by photolysis of organocobalt complexes: Kelley, D. G.; Marchaj, A.; Bakac, A.; Espenson, J. H. *J. Am. Chem. Soc.* **1991**, *113*, 7583.

(9) Significantly, Espenson has reduced $RCo(dmgBF_2)_2py$ with Ni(tmc)$^{+}$ in aqueous media. Under these conditions, hydrolysis of $RCo(dmgBF_2)_2py^{-}$ is the dominant decomposition pathway, with no evidence supporting Co−Me homolysis. In the present study, the anhydrous conditions preclude hydrolysis and apparently allow homolysis to proceed. Shi, S.; Bakac, A.; Espenson, J. H. *Inorg. Chem.* **1989**, *30*, 3410.

(10) Since Ni(tmc)$^{+}$ reacts rapidly with protons to yield Ni(tmc)$^{2+}$ and H_2, the fluoroborate derivative $MeCo(dmgBF_2)_2py$ rather than the cobaloxime was used in all studies. (a) Schrauzer, G. N.; Windgassen, R. J. *J. Am. Chem. Soc.* **1966**, *88*, 3738. (b) Bakac, A.; Espenson, J. H. *J. Am. Chem. Soc.* **1984**, *106*, 5197.

(11) Ni(tmc)$^{2+}$ exists as two independent isomers which do not interconvert under mild conditions. However, addition of one electron yields the d^9, Ni(I) species in which the *R,S,R,S* and *R,R,S,S* isomers are in equilibrium. Ni(tmc)$^{+}$ may be prepared independently by Na/Hg reduction, and the *R,R,S,S* isomer has been structurally characterized in our labs (Riordan, C. G.; Ram, M. S.; Hubin, T.; Haggerty, B.; Rheingold, A. L. Manuscript in preparation).

(12) $Co(dmgBF_2)_2^{-}$ ^{1}H NMR (dmso-d_6): δ 1.76, 12 H. UV−visible λ_{max} (ϵ, M^{-1} cm^{-1}) (dmso): 439 (sh), 528 (sh), and 645 (1.0×10^{4}) nm.

(13) D'Aniello, M. J.; Barefield, E. K. *J. Am. Chem. Soc.* **1976**, *98*, 1610.

(14) ^{1}H NMR (dmso-d_6): (*R,S,R,S*)-[Ni(tmc)Me][BPh_4] δ 123.10, 101.28, 75.07, 51.83, 32.57, 7.19, 6.93, 6.80, −3.47, −7.47, −332; *R,R,S,S*-[Ni(tmc)Me][OTf] δ 163.3, 139.4, 99.43, 74.96, 50.13, 34.83, 31.37, 17.10, −3.17, −5.40, −7.40, −11.6, −14.2, −332. UV−visible (independent of isomer) λ_{max} (ϵ, M^{-1} s^{-1}) (dmso); 352 (1.7×10^{3}) nm. This is the first report of *R,R,S,S*-Ni(tmc)Me^{+}. Synthetic details and complete spectroscopic characterization will be reported elsewhere.

(15) Lin, S.-K.; Juan, B. *Helv. Chim. Acta* **1991**, *74*, 1725.

(16) Since *R,S,R,S*- and *R,R,S,S*-Ni(tmc)$^{+}$ are in equilibrium in solution and each reacts with alkyl halides at similar rates (Ram, M. S.; Bakac, A.; Espenson, J. H. *Inorg. Chem.* **1986**, *25*, 3267), we suggest that both isomers of Ni(tmc)Me^{+} are formed in the reaction.

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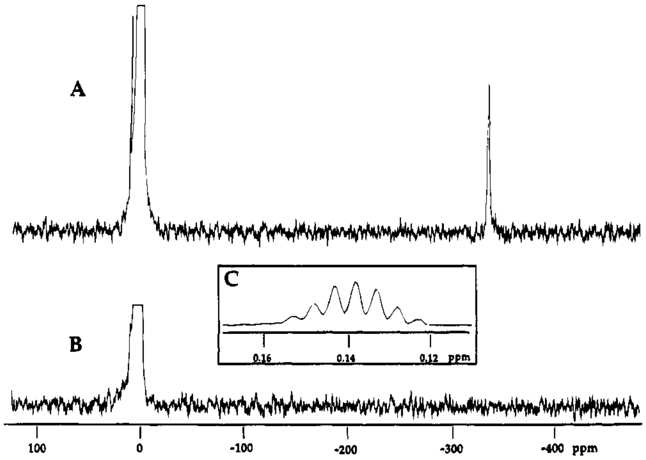

Figure 2. (A) ^{2}H NMR spectrum (dmso) of reaction mixture showing production of Ni(tmc)CD$_3^+$ (δ −332). (B) ^{2}H NMR spectrum after *in situ* hydrolysis of Ni(tmc)CD$_3^+$ with H$_2$O. (C) ^{1}H NMR spectrum (dmso-d_6) of methane produced upon hydrolysis confirming the expected 7-line pattern ($^2J_{HD}$ = 1.9 Hz) for the CD$_3$H isotopomer.

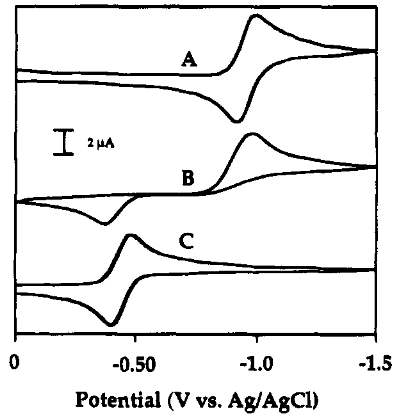

Figure 3. Cyclic voltammetry of (A) Ni(tmc)$^{2+}$ (Ni(II/I) couple), (B) MeCo(dmgBF$_2$)$_2$py (MeCo(III/II) reduction and Co(II/I) couple), and (C) Co(dmgBF$_2$)$_2$py (Co(II/I) couple) in dmso. Experimental parameters are indicated in ref 19.

HgCl$_2$. Ni(tmc)CD$_3^+$ is generated cleanly by reaction of CD$_3$-Co(dmgBF$_2$)$_2$py with excess Ni(tmc)$^+$, Figure 2A. Addition of H$_2$O results in quantitative hydrolysis of the Ni−CD$_3$ bond with formation of Ni(tmc)OH$^+$ and CD$_3$H as the only methane isotopomer, Figure 2B, C. Alternatively, the MeNi bond may be cleaved effectively with HgCl$_2$. Addition of solid HgCl$_2$ to dmso solutions containing Ni(tmc)Me$^+$ results in an immediate color change from deep green to red with concomitant precipitation of an off-white solid. The ^{1}H NMR spectrum of the homogeneous portion displays a singlet (δ 0.76, $^2J_{^{199}\mathrm{Hg}-^1\mathrm{H}}$ = 222 Hz) for MeHgCl. Quantitation reveals *ca.* 50% yield of MeHgCl based on MeCo.

A mechanism which uses MeCo(dmgBF$_2$)$_2$py as a "MeI equivalent" analogously to the methylation of Ni(tmc)$^+$ studied by Espenson and Bakac[17] is consistent with the products and stoichiometry of the reaction.[18] The initial step is rapid one electron transfer from Ni(tmc)$^+$ to MeCo, generating Ni(tmc)$^{2+}$ and MeCo$^-$, eq 2.

$$\mathrm{MeCo(dmgBF_2)_2py + Ni(tmc)^+ \rightleftharpoons MeCo(dmgBF_2)_2py^- + Ni(tmc)^{2+}} \quad (2)$$

$$\mathrm{MeCo(dmgBF_2)_2py^- \rightleftharpoons Co(dmgBF_2)_2py^- + Me^\bullet} \quad (3)$$

$$\mathrm{Ni(tmc)^+ + Me^\bullet \rightleftharpoons Ni(tmc)Me^+} \quad (4)$$

Cyclic voltammetry experiments performed in dmso have confirmed the favorable energetics of this process, Figure 3.[19] The electrochemically reversible Ni(tmc)$^{2+/+}$ couple is centered at −960 mV (vs Ag/AgCl). The chemically irreversible MeCo reduction occurs at −990 mV (sweep rate, 20 mV/s). The second step involves MeCo$^-$ bond homolysis, yielding Co(I)$^-$ and Me$^\bullet$, eq 3.[9,20] The rate constant for homolysis of a similar MeCo$^-$ species, methylcob(II)alamin, measured electrochemically is 4400 s^{-1} at 25 °C.[20] Lastly, Me$^\bullet$ is captured by the second equivalent of Ni(tmc)$^+$, eq 4. This coligation rate has been measured in aqueous media[17] using the radical clock probe 1-hexenyl$^\bullet$ (generated by reduction of 6-bromo-1-hexene). At 25 °C, the rate of R$^\bullet$ capture by Ni(tmc)$^+$ is 6 × 10^7 M^{-1} s^{-1}.

It is important to evaluate our proposed mechanism in the context of the parameters of CODH catalysis. Reduction of methylcob(III)alamin on the C/Fe-SP occurs at slightly less than −1.0 V, while the redox potential for the methyl binding site of CODH is poised at approximately −450 mV. Consequently, CODH is incapable of reductively activating methylcob(III)-alamin. Ragsdale confirmed the lack of reaction by reducing methylated C/Fe-SP to −560 mV and determined that less than 5% of methyl groups were lost.[21] Furthermore, the stereochemistry of methyl transfer from Me-H$_4$folate to acetyl-CoA employing CHDT-H$_4$folate proceeds with overall retention of configuration, consistent with inversion during the Co to CODH step.[22] Our radical mechanism is most consistent with racemization. While the present model system clearly demonstrates, for the first time, such a Me transfer process, the mechanism of transfer appears different from that occurring in the biological system. This is most likely a result of the differences in relative redox potentials between the C/Fe-SP-CODH system and our model. To more closely model the process *and* mechanism of Me transfer, the relative redox potentials of the MeCo and Ni(I) complexes should be altered to more accurately reflect these relative differences. To accomplish this change, one need only to substitute the axial pyridine ligand in MeCo(dmgBF$_2$)$_2$py with PBu$_3$. Such a change shifts the MeCo couple approximately 500 mV more negative.[10a] This places the relative couples at a separation similar to that in C/Fe-SP-CODH. We are currently pursuing Me transfer under these conditions.

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Supplementary Material Available: Electronic spectra of the reaction mixture and independently synthesized Ni(tmc)Me$^+$ and Co(dmgBF$_2$)$_2$py$^-$ (1 page). 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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[17] The electrochemistry of the systems are similar as well. Both electron transfer processes are endergonic but accessible because of the chemical irreversibility of MeI and MeCo reduction, respectively. Bakac, A.; Espenson, J. H. *J. Am. Chem. Soc.* **1986**, *108*, 713.

[18] At present it is not possible to differentiate this electron transfer-initiated mechanism with direct Me transfer followed by electron transfer:

$$\mathrm{MeCo(dmgBF_2)_2py + Ni(tmc)^+ \rightleftharpoons Co(dmgBF_2)_2py + Ni(tmc)Me^+}$$

$$\mathrm{Ni(tmc)^+ + Co(dmgBF_2)_2py \rightleftharpoons Co(dmgBF_2)_2py^- + Ni(tmc)^{2+}}$$

Experiments employing (5-hexenyl)Co(dmgBF$_2$)$_2$py are in progress to distinguish between these two possibilities.

[19] All experiments were recorded in a cell consisting of a glassy carbon working electrode (1 mm), Pt wire as the counter electrode, and Ag/AgCl as the reference electrode. dmso solutions contained 0.1 M electrolyte (Bu$_4$N$^+$PF$_6^-$) and 10 mM sample. Potentials were referenced to internal Fc/Fc$^+$ (+410 mV vs Ag/AgCl).

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