Nickel-Promoted Reductive C–S Bond Cleavage: A Model for the First Step in the Reaction Promoted by Methyl Coenzyme M Reductase

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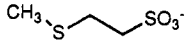
Received May 8, 1992

Sulfur-ligated Ni complexes are of interest as active-site models of the Ni-containing enzymes[1] hydrogenase (H_2-ase),[2] methyl coenzyme M reductase (Me-CoM reductase),[3] and CO-dehydrogenase (CODH).[4] Me-CoM reductase catalyzes the last step in the reaction sequence which converts CO_2 to CH_4 in methanogenic bacteria. This step involves the cleavage of the methyl thioether C–S bond of the substrate methyl coenzyme M (Me-S-CoM). Ni(I) is believed to be the active species responsible



Me-S-CoM

for promoting this reaction.[5] However, it has been difficult to probe the mechanism by which this occurs, since Me-CoM reductase rapidly loses activity upon breakage of whole cells during purification. Only one Ni complex, Ni^{II}(dioxo[16]aneN_5), has been shown to induce stoichiometric methane formation from Me-S-CoM;[6] however, the mechanism proposed to explain this reaction is difficult to understand, and involves a Ni(II/III), as opposed to a Ni(I/II), redox couple. Other nickel complexes have been shown to desulfurize thioethers in the presence of reducing agents (e.g., $LiAlH_4$); however, the reactive Ni species have not been characterized.[7] As part of a systematic study aimed at determining the influence of the local Ni coordination environment on reactivity, we have synthesized a series of structurally related sulfur-ligated Ni(II) complexes,[8] including

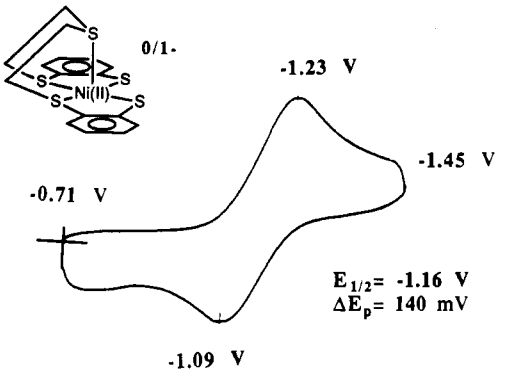


Figure 1. Cyclic voltammogram (100 mV/s) for the quasi-reversible reduction of $Ni^{II}L_{S5}$ (**1**) in DMF solution at 25 °C. Peak potentials vs SCE are indicated.

$Ni^{II}L_{S5}$ (**1**).[8,9] Since redox changes (Ni(III) → Ni(II) and/or Ni(II) → Ni(I)) appear to play an important role in the mechanisms of the enzymes mentioned above, we have also examined the redox chemistry of these molecules. Herein, we report a Ni-promoted reductive C–S bond cleavage reaction that represents a plausible chemical model for the first step in the reaction promoted by Ni in Me-CoM reductase.

Experimental Section

Unless noted otherwise, all reactions were carried out under a pure dinitrogen atmosphere using standard Schlenk or glovebox techniques. Solvents were dried over sodium benzophenone (THF) or BaO (DMF), freshly distilled under nitrogen, and freeze–thaw-degassed three times before use. Naphthalene (Aldrich) was sublimed at ambient temperature. Tetrabutylammonium tetrafluoroborate (Bu_4NBF_4) was recrystallized from ethyl acetate/pentane (v/v, 10/1, ×3) before use. NiL_{S5} (**1**)[8,9] and $[Ni^{III}(bdt)_2]^-$ (**6**)[10] were prepared as described elsewhere.

Physical Measurements. NMR spectra were recorded on either a Bruker AF-300 or a Bruker AC-200 spectrometer. UV/vis/near-IR spectra were recorded using a Hewlett-Packard HP Model 8450 spectrometer interfaced to an IBM PC. Electrochemical measurements were made at ambient temperature using standard Princeton Applied Research instrumentation (PAR-273 potentiostat/galvanostat), with a glassy carbon working electrode, a platinum wire counter electrode, a SCE reference electrode, and Bu_4NBF_4 supporting electrolyte. EPR spectra were recorded in DMF at 10 K, using a Bruker ESP300 X-band spectrometer with an NMR gaussmeter, a frequency counter, and an Oxford Instruments ER910A cryogenic system.

Sodium Naphthalenide (NaNap). Naphthalene (0.038 g, 0.30 mmol) and Na (0.007g, 0.30 mmol) were combined in 1 mL of THF-d_8, and the mixture was stirred for ~2 h to afford an intensely green/brown solution. Freshly prepared sodium naphthalenide solutions were used for all reactions.

NiL_{S5} + 2NaNap Monitored by ^{1}H NMR. Two equivalents of sodium naphthalenide (78 μL of a 0.30 M solution) in THF-d_8 was added to a THF-d_8 solution (0.5 mL) of NiL_{S5} (0.005 g, 0.012 mmol). The reaction was monitored by ^{1}H NMR. ^{1}H NMR: δ 6.9 (dd, J_1 = 6 Hz, J_2 = 2.5 Hz, $[Ni^{II}(bdt)_2]^{2-}$ (**2**)), 6.4 ppm (dd, J_1 = 6 Hz, J_2 = 2.5 Hz, **2**); δ 5.3 ppm (s, ethylene); δ 2.32 ppm (s, ethylene sulfide); δ 1.29 (m, $-CH_2-$, low molecular weight (lmw) polyethylene), 0.89 (m, CH_3, lmw polyethylene) ppm.

Results and Discussion

$Ni^{II}L_{S5}$ (**1**)[11] displays a quasi-reversible reduction wave at $E_{1/2}$ = −1.16 V (vs SCE, ΔE_p = 140 mV, scan rate = 100 mV/s) in DMF solution (Figure 1). Both the anodic current and ΔE_p are

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(10) bdt = benzene-1,2-dithiolate: (a) Cha, M.; Sletten, J.; Critchlow, S. C., Kovacs, J. A. Submitted for publication in *Inorg. Chem.* (b) Baker-Hawkes, M. J.; Billig., E.; Gray, H. B. *J. Am. Chem. Soc.* **1966**, *88*, 4870. $Ni^{II}(bdt)_2^{2-}$ (**2**) was prepared by reducing **6** with NaNap in THF.

(11) The synthesis and structure of $Ni^{II}L_{S5}$ (**1**) have been described previously; see refs 8 and 9.

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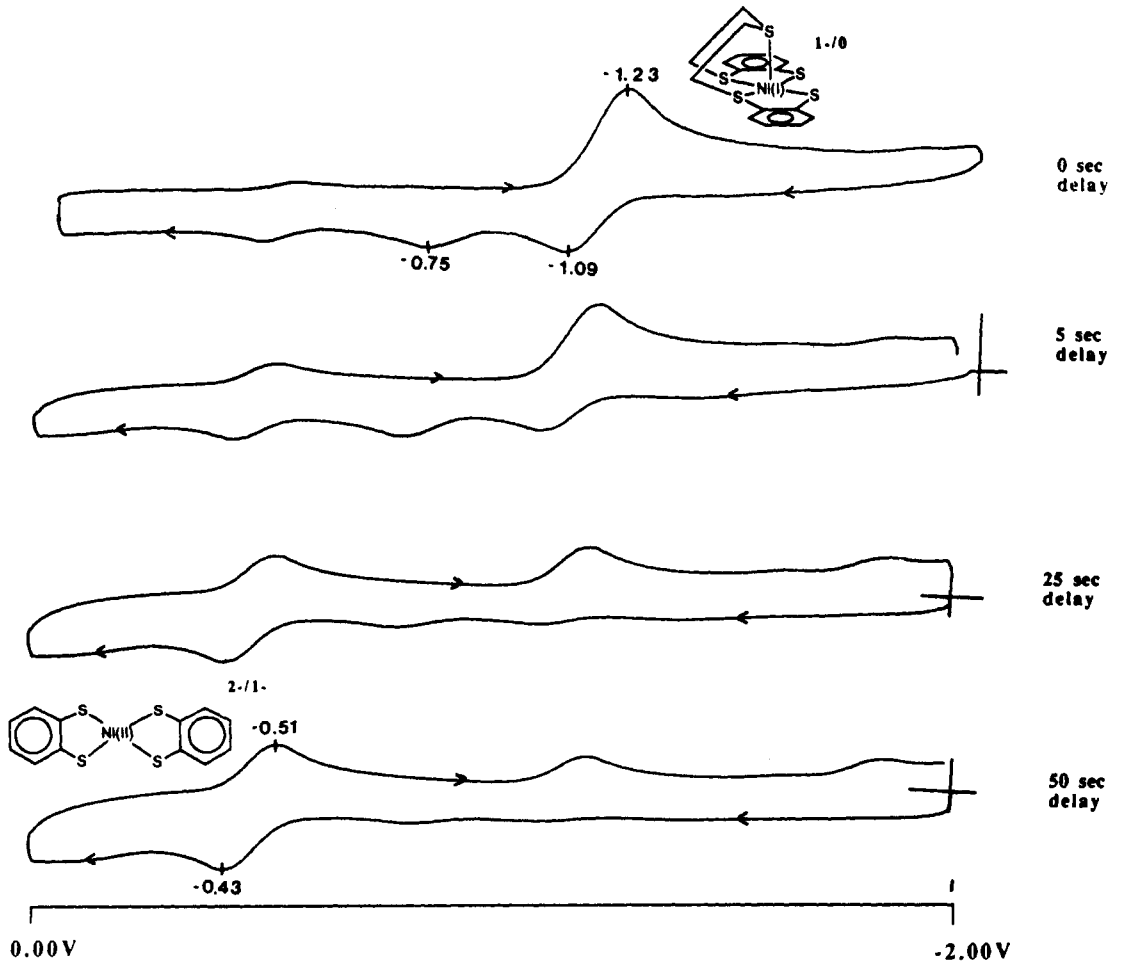

Figure 2. Reaction of electrochemically generated $Ni^{I}L_{S5}$ (**3**) monitored by cyclic voltammetry (100 mV/s) in DMF at 25 °C for redox-active products and intermediates. Peak potentials vs SCE are indicated. Reaction time = delay time (indicated) + (|–2000 mV (starting potential) – E_p(product or intermediate)|)/100 mV/s.

dependent on the scan rate. Solutions containing only free ligand Na_2L_{S5} do not display any waves in this potential range. The reduced species is highly reactive and completely disappears before reoxidation can occur if slower scan rates (i.e., <10 mV/s) are used. Cyclic voltammograms (Figure 2) which were initiated at a potential sufficiently negative (–2 V) to generate this reactive species and then swept over a wider potential range (–2.0 V → 0.0 V) in the oxidizing direction revealed two new electrochemically active species (E_p = –0.75 V and $E_{1/2}$ = –0.47 V) that appeared over time. The concentration of one of these species ($E_{1/2}$ = –0.47 V) increased in proportion to the length of time (delay time) poised at the –2 V starting potential. The concentration of the initial reduced species decreased[12] as the delay time was increased and almost disappeared after 59 s.[13] The species observed at –0.75 V appears to be an intermediate, since it grew in before the final product ($E_{1/2}$ = –0.47 V) and then disappeared as the final product grew in.[14] The intermediate and final products formed in the electrochemical experiment shown in Figure 2 were not observed if the experiment was started at a potential that is more anodic than –1.09 V, implying that they are derived from the reduced species generated at –1.16 V. The half-wave potential of the final product ($E_{1/2}$ = –0.47 V) is identical to that of the square planar Ni(II) monomer $[Ni^{II}(bdt)_2]^{2-}$ (**2**)[10] (Figure 3). The final product **2** was identified by ^1H NMR and by converting it to its more stable oxidized form,[15] $[Ni^{III}(bdt)_2]^-$ (**6**), which has an intense characteristic near-IR band[10] at 880 nm. Thus, electrochemical reduction converts $Ni^{II}L_{S5}$ (**1**) to $[Ni^{II}(bdt)_2]^{2-}$ (**2**)—a reaction (Figure 4)

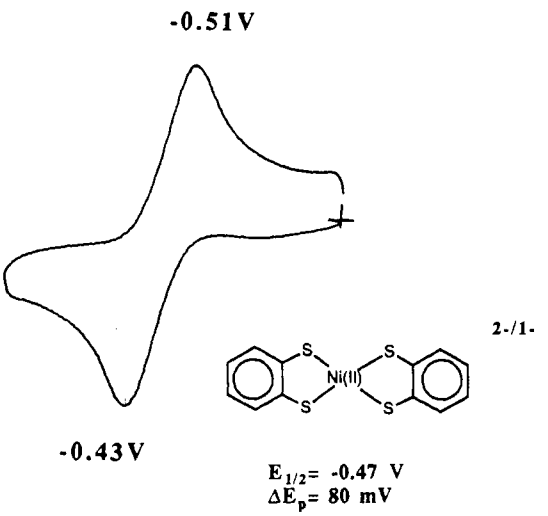

Figure 3. Cyclic voltammogram (100 mV/s) of $[Ni^{II}(bdt)_2]^{2-}$ (**2**) in DMF solution at 25 °C. Peak potentials vs SCE are indicated.

(12) All of the scans displayed cathodic current (E_p = –1.23 V) in the reverse scans (0.0 V → –2 V), which results from the reduction of $Ni^{II}L_{S5}$ (**1**). This is because the interface region is constantly replenished with the oxidized starting compound **1** via diffusion from the bulk solution.

(13) 59 s = delay time (50 s) + 9 s ([2000 mV (starting potential) – 1100 mV (Ni(I) reoxidation potential)]/100 mV/s).

(14) The background current increases as the reaction progresses. This is probably because one of the products adsorbs onto the electrode surface.

(15) $[Ni^{III}(bdt)_2]^-$ (**6**) was generated by introducing air into a reduced sample of **1** + 2NaNap (t = 20 min) and identified by UV/vis/near-IR spectroscopy.

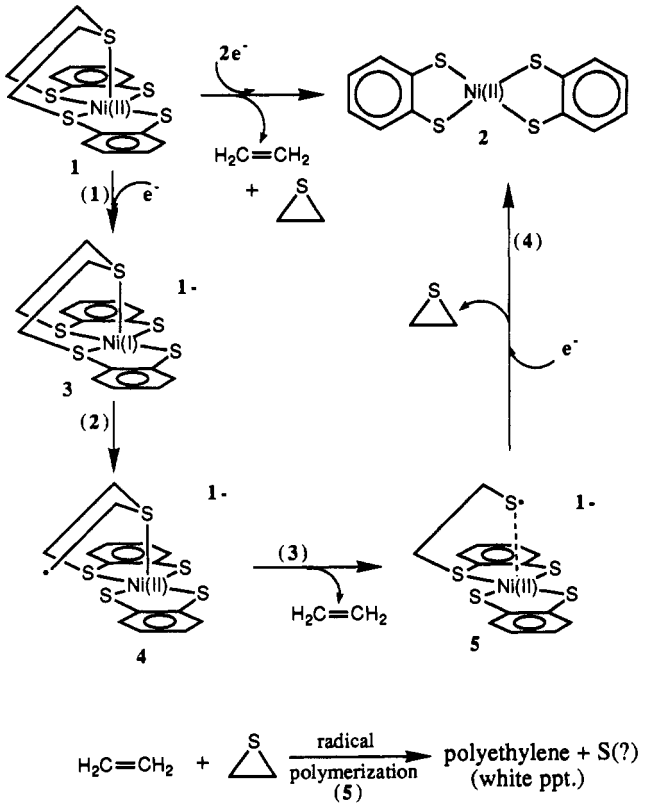

Figure 4. Proposed mechanism for the reductively induced conversion of $Ni^{II}L_{S5}$ (**1**) to $[Ni^{II}(bdt)_2]^{2-}$ (**2**).

which involves the cleavage of two Ni-bound thioether C–S bonds and which results in the removal of the diethyl sulfide "backbone" from the L_{S5} ligand. It was recently reported that a similar dealkylation reaction takes place upon addition of ^{n}BuLi to $Ni^{II}L_{S5}$.[16] The mechanism of this reaction and the nature of the reactive species responsible for this reaction have not been addressed, however.

Chemical reduction of $Ni^{II}L_{S5}$ (**1**), using sodium naphthalenide (NaNap), was monitored by ^{1}H NMR in THF-d_8 and found to require 2 equiv of NaNap. The C–S bond cleavage reaction requires that Ni be present; free Na_2L_{S5} does not react with NaNap. Addition of 1 equiv of NaNap to a solution containing **1** afforded a small amount of ethylene and a complex paramagnetic NMR spectrum which was difficult to interpret. With 2 equiv, the spectrum (t = 20 min) showed resonances corresponding to the products $[Ni^{II}(bdt)_2]^{2-}$ (**2**; 66% calculated by integration relative to naphthalene), ethylene (20% calculated by integration with respect to **2**), ethylene sulfide (5% calculated by integration with respect to **2**), and low molecular weight polyethylene.[17] Over the course of 1 h, the signal for ethylene sulfide disappeared, the polyethylene signals grew in, and a white precipitate appeared. Attempts to isolate the white precipitate by increasing the scale of the experiment (×10) gave only gelatinous solutions from which no solid products could be isolated. Preliminary EPR studies showed that a rhombic signal (Figure S1, supplementary material) with g = 2.056, 2.036, 2.001 grows in and then disappears within 5 min. This is followed by the appearance of an isotropic signal with g = 2.002. Prior to both of these, a fleeting signal (g = 2.199, 2.094, 2.028) is observed, which could be assigned to a Ni(I) species. However, further studies are required in order to establish this.[18] The EPR and CV results suggest that $Ni^{I}L_{S5}$ is the initial species formed in the reduction of $Ni^{II}L_{S5}$ and that at least two other odd-electron intermediates are involved in the mechanism of the observed dealkylation.

A mechanism proposed to explain the observed Ni-promoted reductive C–S bond cleavage reaction is shown in Figure 4. The mechanism involves the initial one-electron reduction of a Ni(II) ion (step 1). This affords a highly reactive 19-electron Ni(I) species, **3**, which rapidly transfers its $(d_{x^2-y^2})^*$ electron to the σ^* orbital of a $C–S_{eq}$ bond. This causes the C–S bond to rupture (step 2), which results in the formation of intermediate **4**. Homolytic cleavage of the $C–S_{ap}$ bond that is adjacent to the carbon radical formed in step 2 is then driven by the formation of ethylene (step 3). This produces a S radical, **5**, which is stabilized by interacting with the Ni ion. Intermediate **5** could also be described as a Ni(III)–thiolate species. Addition of a second electron then promotes the cleavage of the second $C–S_{eq}$ bond, which results in the formation of **2** along with ethylene sulfide (step 4). The fact that polyethylene is observed when this reaction is monitored by ^{1}H NMR implies that a radical chain side reaction[19] takes place which consumes the ethylene sulfide and most of the ethylene (reaction 5). The white precipitate that forms probably consists of polyethylene and sulfur.

The details regarding the mechanism by which Ni promotes C–S bond cleavage in Me-CoM reductase are not known. Possible roles for Ni in this enzyme include substrate binding, electron transfer, or methyl group transfer.[3b,20] Several mechanisms have been proposed,[3b,21-23] which are based on the chemistry of Co(I)-containing vitamin B_{12}, where Ni(I) acts as a nucleophile, and which involve the formation a Ni–Me intermediate. For example, it was recently proposed[23] that nickel(I) octaethylisobacteriochlorin-promoted[25] C–X (X = halogen) bond cleavage models the cleavage reaction promoted by Me-CoM reductase[24] and occurs via a nucleophilic attack involving a three-electron nucleophile that was described later as being the "fastest transition-metal nucleophile on record".[23] However, our results suggest that C–S bond cleavage occurs via a single electron-transfer mechanism (Figure S2, supplementary material), which would result in the formation of a Ni–SR bond. This contrasts with the nucleophilic attack mechanism, which would afford a Ni–alkyl bond. Ni(I) tetraazamacrocycles have been shown to promote C–X bond cleavage by a similar radical mechanism;[26] however, they are unreactive toward thioethers. The Ni-promoted cleavage of the C–S bonds in complex **1** does appear to involve a Ni(I) intermediate, which is observable on the CV time scale. This lends support to the proposal that Ni(I) is the reactive species in Me-CoM reductase.

It is possible that Ni(I) also promotes C–S bond cleavage in CODH.[1a,4] CODH catalyzes reversible C–C and C–S bond formation in the biosynthesis of acetyl-CoA (CoA-S-C(O)Me)

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from a thiol (CoA-SH), a Me group, and CO.[27] The active catalyst has been proposed to contain Ni in the +1 oxidation state[28] (possibly spin-coupled to an Fe_4S_4 cluster).[29] The site to which the Me group binds in CODH has been proposed to be a cysteinyl sulfur[30] and/or a Ni ion, and it has been suggested[28b] that a metal ion mediates in CH_3 transfer from Me-S-Cys. Our results suggest that, in CODH, Ni(I) could be responsible both for the release of a Me group from Me-S-Cys and for promoting the release of CO from (CoA)S-C(O)Me by reductively cleaving a C–S bond.

The main conclusion of this paper is that Ni(I) prefers one electron (single electron-transfer) as opposed to two-electron (nucleophilic) chemistry when it is cleaving C–S bonds. This is the first example of a well-characterized synthetic Ni complex that is capable of reductively cleaving C–S bonds. We are currently probing the kinetics of the observed C–S bond cleavage by monitoring the reaction using EPR and UV/visible spectroscopy.

Acknowledgment. Financial support from the National Institutes of Health (Grant GM45881) is gratefully acknowledged. We thank Paul Lindahl for recording and interpreting our EPR spectra.

Supplementary Material Available: X-Band EPR spectrum of NiL_{S5} (**1**) + 2.5 equiv of sodium naphthalenide in DMF at 10 K and a schematic drawing of the proposed electron-transfer mechanism of reductive C–S bond cleavage by methyl coenzyme M reductase (2 pages). Ordering information is given on any current masthead page.

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