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F430 Model Chemistry. An Investigation of Nickel Complexes as Catalysts for the Reduction of Alkyl Halides and Methyl Coenzyme-M by Sodium Borohydride

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The ability of nickel(II) macrocycle and coordination complexes **1−8** to mediate the reductive dehalogenation of cyclohexyl bromide and the CH_3−S bond cleavage of methyl CoM by sodium borohydride in diglyme/alcohol, DMF/alcohol, or acetonitrile/alcohol was investigated. Methyl CoM, or $CH_3SCH_2CH_2SO_3^-$, is the cofactor that carries the methyl group in the final step of methanogenesis in methanogenic bacteria. Because of the potential for production of the heterogeneous catalyst nickel boride during these reactions, the activities of several nickel salts that afford nickel boride when reduced with borohydride were examined for purposes of comparison. Complexes **1−8** homogeneously catalyze the dehalogenation of cyclohexyl bromide by sodium borohydride. The facility of the reaction varies markedly with the structure of the ligands and the solvent composition. Nickel boride is a moderately active heterogeneous catalyst for the dehalogenation of cyclohexyl bromide and produces small yields of methane from methyl CoM and borohydride. When excess nickel boride is generated *in situ*, the yield of methane increases to 54%. The other isolated products, ethanesulfonate and a product derived from the CH_3−S part of methyl CoM, show that nickel boride preferentially cleaves the CH_2−S bond of methyl CoM, which is the opposite of the enzymatic selectivity. Freshly prepared Raney nickel, a second heterogeneous nickel compound, quantitatively cleaves methyl CoM to methane and ethanesulfonate. None of the complexes **1−8** produced significant amounts of methane from methyl CoM and sodium borohydride in the mixed solvents or in aqueous solution.

Factor F430 is the nickel−hydrocorphinoid prosthetic group of the enzyme methyl coenzyme M reductase (MCR).[1−5] The enzyme catalyzes the reductive cleavage of the thioether cofactor methyl coenzyme-M (CH_3−S−CoM) by the thiol cofactor H−S−HTP[6] to afford methane and the heterodisulfide CoM−S−S−HTP in the final step in methanogenesis.[7,8] The enzyme may also be involved in the reductive dehalogenation of halogenated hydrocarbons by methanogenic bacteria.[9−11] The nickel atom of F430 undergoes oxidation state changes during catalysis by the enzyme. Active MCR exhibits two distinct Ni^I EPR signals, which are designated MCR-red1 (axial) and MCR-red2 (rhombic).[12−14] Addition of the substrate CH_3−S−CoM converts MCR-red2 to MCR-red1 whereas addition of H−S−CoM leads to an increase in the MCR-red2 signal.[14] Other distinct EPR signals are observed in the presence of inhibitory, halogenated substrate analogues of both CH_3−S−CoM and H−S−HTP.[15] Thus, substrates appear to bind either directly to Ni^I−F430 or close enough to change the environment of the Ni(I) atom.

The involvement of Ni(I) in MCR led to great interest in the chemistry of the Ni^I forms of F430 and Ni isobacteriochlorins,[16−22] the only tetrapyrrolic compounds that afford isolable Ni(I) complexes when reduced.[23−25] Ni^I−F430M and $Ni^I(OEiBC)^-$ react rapidly and catalytically with alkyl halides, alkyl *p*-toluenesulfonates, and alkylsulfonium ions in nonaqueous solvents to afford alkanes and alkenes via the intermediacy of alkyl−nickel species. In contrast, the complexes do not appear to cleave the C−S bond of methyl CoM or other methyl thioethers. Reaction of $Ni^I(OEiBC)^-$ with ammonium methyl CoM afforded only 0.002 equiv of methane, but significant

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amounts of H_2 were produced by the concurrent reaction of Ni(I) with the acidic ammonium ion.[21] No methane was detected when tetraphenylphosphonium methyl CoM was used. Ni^{I}−F430M was reported to be unreactive toward methyl CoM.[17] The report addressed neither the identity of the counterion nor the possible formation of H_2.

Few reports exist of attempts to cleave the C−S bond of methyl CoM with other nickel-containing compounds. Ni^{I}−tetraazamacrocyclic complexes generated by pulse radiolysis in aqueous solution produced methane from methyl CoM in yields varying from trace levels at pH 7.4 to over 10% at pH 9.4.[26] The Ni^{I} complex [Ni(tmc)](OTf) showed no evidence of reaction, aside from precipitation, with tetrabutylammonium methyl CoM in organic solvents.[27] The nickel complex of the ligand 1,4,7,10,13-pentaazacyclohexadecane-14,15-dione was reported to cleave methyl CoM to methane and H−S−CoM in a slow, stoichiometric process.[28] However, we recently showed that the complex is unreactive toward methyl CoM and that the observed cleavage is caused by a yet unidentified impurity.[29]

The formation of small amounts of methane from methyl CoM and Ni^{I}(OEiBC)$^{-}$ when the ammonium salt was used and the complete absence of methane when the tetraphenylphosponium salt was used might implicate transient nickel hydride species in the cleavage of methyl CoM. The hydride complexes HNi(OEiBC)$^{n-}$ ($n = 0$ or 1) were shown to be intermediates in the formation of H_2 from Ni^{I}(OEiBC)$^{-}$ and proton donors[21] and in the formation of *cis*- and *trans*-2-butene by isomerization of the 1-butene that is produced during the reaction of Ni^{I}(OEiBC)$^{-}$ and 1-bromobutane.[22] To date, the lability of these complexes has precluded even their generation as the predominant Ni(OEiBC)-containing species in solution. Nickel hydride species may also be involved in the chemistry of F430. Addition of such mild proton donors as alcohols and thiols to Ni^{I}−F430M eliminated the induction period normally observed during reaction with sulfonium ions.[17,19]

Recently, two nickel macrocycles were reported to catalyze the reduction of alkyl or aryl halides by sodium borohydride in ether/alcohol or acetonitrile/alcohol mixed solvents. In both cases, nickel hydride complexes were suggested as intermediates. Ni(tmtaa), **1**, exhibited a rhombic EPR signal typical of a Ni(I) species in the presence of a 100-fold excess of $NaBH_4$.[30,31] The signal rapidly decreased upon addition of bromocyclohexane, which implied the species is involved in catalysis. The greater anisotropy of the signal compared to that of authentic [Ni^{I}(tmtaa)Na(thf)$_3$], which is produced by sodium amalgam reduction,[32] was attributed to coordination of either H^- or BH_4^- to Ni(I). Deuterium incorporation experiments suggested that nickel hydride species may be involved in the reductive dehalogenation of aromatic halides catalyzed by **2**.[33] Furthermore, **2** is an electrocatalyst for the reduction of H^+ to H_2.[34] No reported case of transition metal catalyzed H_2 production has not involved metal hydrides.[34]

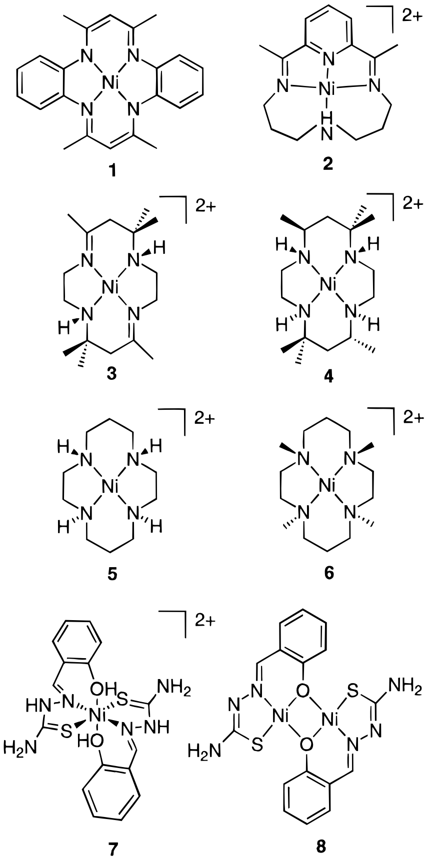

Figure 1. Nickel complexes investigated in this study.

The possible involvement of nickel hydride species in the cleavage of methyl CoM led us to examine the ability of **1** and **2** in the presence of $NaBH_4$ to cleave methyl CoM and dehalogenate alkyl halides. We also investigated other representative nickel macrocycles and nickel coordination complexes for which evidence of hydride or borohydride intermediates existed, Figure 1. The isomeric complexes **4** and **4′**, which can be produced by borohydride reduction of **3** and **3′**, form borohydride complexes whose reactivity have not been investigated.[35] Complexes **7** and **8**, which differ in ligand to nickel stoichiometry and ligand protonation, were reported to catalyze H/D exchange between D_2 and ethanol OH protons and silane alcoholysis, respectively.[36,37]

A potential complication in this study is the formation of nickel-containing solids that are active heterogeneous catalysts. Simple nickel salts are reduced by $NaBH_4$ in aqueous solution to afford nickel boride, a solid whose composition is typically represented as Ni_2B but that also contains absorbed or interstitial hydrogen.[38] If recent work on the borohydride reduction of cobalt and iron salts can be extrapolated to nickel, the solid can consist of several different metal boride phases, ultrafine metal particles, and $M(BO_2)_2$ depending upon the solvent and the reaction conditions.[39,40] Nickel boride catalyzes rapid hydrolysis of $NaBH_4$, dehalogenation of halogenated hydrocarbons, hydrogenation of olefins and functional groups, and

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desulfurization of many sulfur-containing functional groups.[38,41−46] Nickel boride was reported to approach Raney nickel in activity, but to have somewhat different selectivity. A real possibility exists that nickel boride could form during $NaBH_4$ reductions catalyzed by **1**−**8**, given both the potential lability of some of these Ni(II) complexes and the tendency of Ni(I) complexes to dissociate and disproportionate in solution.[47] Thus, for purposes of comparison, we also included the heterogeneous catalysts nickel boride and Raney nickel in the current study.

The results reported in this paper show that nickel complexes **1**−**8** are homogeneous catalysts of widely varying activity for the reduction of alkyl halides by $NaBH_4$. Nonetheless, all are uniformly inactive as catalysts for cleavage of the C−S bonds of methyl CoM. Nickel boride and Raney nickel are both effective stoichiometric reagents for the cleavage of methyl CoM. However, unlike enzymatic cleavage by MCR, the CH_2−S bond appears to be cleaved in preference to the CH_3−S bond.

Experimental Section

Materials. Compounds used in this study were HPLC, reagent, or the best available commercial grade. Alkyl halides were examined for purity by GC and were repurified by appropriate means if impurities were detected. Anhydrous alcohols and 2-methoxyethyl ether (diglyme) were purchased in Sure/Seal bottles and used as received. Other solvents used were freshly purified and thoroughly degassed by a minimum of three freeze−pump−thaw cycles. Acetonitrile was refluxed over CaH_2 and then distilled. THF was distilled from sodium benzophenone ketyl. DMF was dried over silica gel for 1 week and then distilled under reduced pressure.

The nickel complexes 6,8,15,17-tetramethyl-5,14-dihydrodibenzo-[*b*,*i*] [1,4,8,11]tetraazacyclotetradecine nickel, **1**;[48] [2,12-dimethyl-3,7,11,17-tetraazabicyclo[11.3.1]heptadeca-1(17),2,11,13,15-pentaene]nickel(II) perchlorate, **2**$(ClO_4)_2$;[49] [*meso*-5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradeca-4,11-diene]nickel(II) perchlorate, **3**$(ClO_4)_2$;[49] *trans-III*-[*C-meso*-5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane]nickel(II) perchlorate and borohydride, **4**$(ClO_4)_2$[49] and **4**$(BH_4)_2$ (corresponds to isomer IIa in the literature report);[35] *trans-III*-[1,4,8,11-tetraazacyclotetradecane]nickel(II) perchlorate, **5**$(ClO_4)_2$;[50] *trans-III*-[1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane]nickel(II) perchlorate, **6**$(ClO_4)_2$;[51] bis(salicylaldehyde thiosemicarbazone)nickel(II) chloride, **7**Cl_2;[36] and bis[(salicylaldehyde thiosemicarbazonato)nickel-(II)], **8**[37] were prepared by literature methods. *Caution!* Perchlorate salts of metal complexes can be explosive and must be handled with care. It is very important that such compounds not be heated or subjected to mechanical shock as solids.

Tetramethylammonium borohydride was prepared by methathesis of sodium borohydride and tetramethylammonium hydroxide.[52] Ammonium methyl CoM was prepared by reaction of methyl iodide and 2-mercaptoethanesulfonic acid sodium salt (coenzyme M) in concentrated ammonia solution.[53] Coenzyme M should be handled under an N_2 atmosphere to prevent its partial oxidation to coenzyme M disulfide, an authentic sample of which was prepared by I_2 oxidation of a basic aqueous solution of coenzyme M.[54] Methyl CoM and coenzyme M disulfide are not readily separable. Raney nickel was prepared from aluminum−nickel alloy (Aldrich #22,165-1) by the procedure for Raney W-2.[55] The catalyst was stored under absolute ethanol in a refrigerator and used within a week of preparation.

General Procedures for Reactions Catalyzed by Nickel Compounds. Dehalogenation of Alkyl Halides. Solid nickel compound (6.0×10^{-5} mol) and $NaBH_4$ (6.0 mmol) were placed in a 50 mL Schlenk flask that was equipped with a stir bar. The contents of the flask were placed under N_2, the stirrer was started, and 5.0 mL of a degassed mixture of solvent (diglyme, DMF, or acetonitrile), alcohol, and alkyl halide was added by syringe. The volume ratio of these components were 9.6:1:1.4 in digylme, 8.9:1:1 in DMF, and 10:1:1 in acetonitrile. *n*-Hexane was added as an internal standard in diglyme and DMF. Evolution of hydrogen was vigorous initially, but generally was not observable after an hour. The solution was sampled at appropriate intervals for product analysis by GC.

Cleavage of Methyl Coenzyme M. Solid $NaBH_4$ (200 mg, 5.29 mmol), ammonium methyl CoM (60 mg, 0.35 mmol), and nickel compound (0.12 mmol, about 50 mg for most compounds) were placed in a 100 mL Schlenk flask that was equipped with a stir bar. The contents of the flask were placed under N_2, the stirrer was started, and 5.0 mL of the solvent or solvent mixture of choice was added by syringe. The headspace gases were sampled at appropriate intervals.

Cleavage of Methyl Coenzyme M by Raney Nickel. Freshly prepared Raney nickel was washed 10 times with degassed H_2O to remove the ethanol under which it had been stored. The washed nickel was placed in a 1000 mL Schlenk flask, and 20 mL of H_2O and a stir bar were added. The mixture was degassed with three freeze−pump−thaw cycles. The thawed mixture was not exposed to dynamic vacuum to prevent loss of absorbed H_2 from the Raney nickel. Solid ammonium methyl CoM was added while the solution was frozen. The headspace of the flask was evacuated, the water was permitted to thaw, and stirring was initiated. After 7 h, the headspace gases were analyzed by GC. The contents of the flask were filtered to remove Raney nickel, and the water in the filtrate was removed under vacuum at room temperature. The residue was dissolved in D_2O and characterized by ^1H NMR. An analogous experiment was conducted in D_2O. The procedure differed only in that the initial 10-fold washing of Raney nickel was performed with D_2O and the filtered reaction solution was concentrated, but not taken to dryness, before it was characterized by NMR.

Methane production was also quantified using a Toepler pump. Freshly prepared Raney nickel (4.0 g) was washed and placed in a 100 mL three-neck flask. Then 20 mL of degassed, distilled water and a stir bar were added. Ammonium methyl CoM (0.455 g) was placed in an L-shaped tube that had a male standard taper joint and the tube was inserted in a side neck of the flask. An adapter that consisted of a Teflon vacuum valve with a male standard taper joint on one arm and an o-ring joint on the other was placed in the center neck of the flask. The remaining neck was fitted with a stopper. The contents of the flask were degassed by three freeze−pump−thaw cycles on a Schlenk line. The evacuated flask assembly was connected to the Toepler pump section of the high vacuum line, and the catalyst suspension was frozen. The flask was evacuated, the adapter valve was closed, and the L-shaped side arm was flipped to dump the ammonium methyl CoM onto the frozen catalyst suspension. The contents were allowed to thaw and stirring was initiated. After 7 h, gas evolution had ceased. The water in the flask was frozen in a dry ice acetone slush bath and the gas in the flask was collected with the Toepler pump and circulated through a heated CuO catalyst bed to remove H_2, which had desorbed from the Raney nickel under vacuum. Water vapor from both the reaction solution and the catalytic oxidation of H_2 was removed by circulation through a dry-ice acetone cooled trap. Periodically, the gas was collected in the calibrated volume of the Toepler pump and its pressure was measured. Gas circulation through the catalyst bed continued until the measured pressure was constant. The number of moles of gas in the sample was calculated using the ideal gas law. A portion of the collected gas was expanded into a sample bulb. The bulb was removed from the vacuum line and its contents were analyzed by GC to confirm its composition. No H_2, N_2, or O_2 was detected. However, the methane was found to contain

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a few percent of CO_2. If the CO_2 is assumed to result from partial oxidation of methane, its presence in the Toepler pump sample will not affect yield calculations.

Cleavage of Methyl Coenzyme M by Nickel Boride. Ammonium methyl CoM (59 mg, 0.34 mmol), $NiCl_2·6H_2O$ (1.05 g, 4.4 mmol), and $NaBH_4$ (0.36 g, 9.5 mmol) and a stir bar were placed in a 1000 mL Schlenk flask. The flask was evacuated and cooled in an ice bath. Then 25 mL of degassed distilled water was added by syringe and stirring was started. After 10 h, the headspace gases were analyzed by GC. The contents of the flask were filtered to remove nickel boride and the water in the filtrate was removed under vacuum at room temperature. The residue was dissolved in D_2O and characterized by ^1H NMR. An analogous experiment was conducted in D_2O. The filtered reaction solution was concentrated, but not taken to dryness, before it was characterized by NMR.

The methane produced in this reaction could not be quantified using a Toepler pump because the amount present in the gas mixture produced was too small to permit an accurate determination of its quantity. Large quantities of H_2 evolve as a consequence the production of nickel boride and in the subsequent nickel boride catalysed hydrolysis of $NaBH_4$, even when the relative ratios of $NaBH_4$ to $NiCl_2·6H_2O$ to substrate is reduced to 21:7:1. Although smaller ratios than this evolve less H_2 per mole of substrate, they also result in reduced yields of methane.

Product Analysis. Product yields were typically determined in simultaneous duplicate experiments. Alkane products were analyzed by gas chromatography or by GC/MS. A Hewlett-Packard 5890A GC and 3396A integrator were used. Compounds were identified by comparison of their retention times to those of authentic pure compounds or mixtures of known composition. The quantities of compounds present were determined by external calibration methods. Reproducibility of determinations was typically better than 10%, both within duplicate experiments and between independent repetitions. The gas sample valve system and procedures used for sampling and analyzing headspace gases were described previously.[21] Cyclohexane, cyclohexene, and cyclohexyl bromide were separated on a 6-ft 10% OV-17 column. Low molecular weight hydrocarbons (C_1-C_4) and fixed gases were separated on a 6-ft Poropak Q column. A flame ionization detector was used in most cases. A thermal conductivity detector was used for H_2, CO, and CO_2. Argon was used as the carrier gas in H_2 analyses. All columns were thoroughly conditioned prior to use and regenerated after each run by holding the oven temperature at 200 °C until the solvent or other strongly retained peaks came off the column.

Results

Reductive Dehalogenation of Cyclohexyl Bromide. The nickel complex catalyzed borohydride reductions of alkyl halides in solvent/alcohol mixtures are complicated reaction systems. The components and products may not be mutually miscible or soluble over a broad range of compositions. Many of the individual components are mutually reactive. Because of the multiple competing reactions, we did not examine the kinetics in detail. We limited our investigation to a qualitative assessment of product yields at several representative reaction times. The reaction systems investigated were generally confined to a composition of $NaBH_4$ to substrate to nickel complex of 100:50−70:1 and volume ratios of solvent to alcohol to substrate of about 10:1:1. We also examined the significance of several possible competing reactions.

Alkyl halides can be reduced directly by $NaBH_4$ in uncatalyzed reactions. In contrast to previous reports,[31] we found that the rate of the uncatalyzed reduction of cyclohexyl iodide is nearly competitive with the catalyzed rates. The rates of both catalyzed and noncatalyzed reductions of cyclohexyl chloride are rather slow. Thus, we restricted our investigation to cyclohexyl bromide.

The alcohol cosolvent is an active participant in both the catalyzed reduction of alkyl halides and in competing reactions. Alcohols react directly with $NaBH_4$ to produce H_2, alkyl borates, and alkoxy borohydrides. The latter may also serve as a reducing agent in these reductions.[31] In the absence of nickel compounds, the reaction between methanol and $NaBH_4$ in diglyme is complete in 30 min when both are present in concentrations comparable to those employed in the catalytic reductions. The uncatalyzed reaction between ethanol and $NaBH_4$ in diglyme requires 6 h to reach completion. $NaBH_4$ appears to be stable to isopropyl alcohol and *tert*-butyl alcohol in diglyme solution. In the presence of nickel complexes, the rate of alcoholysis of $NaBH_4$ can be greatly accelerated. Analysis of the solution by GC during catalyzed reductions establishes that the alcohol cosolvent is consumed and alkyl borates are concurrently produced. If the alcohol is totally consumed before the substrate is exhausted, the reduction stops. The reaction does not resume if more $NaBH_4$ is added.

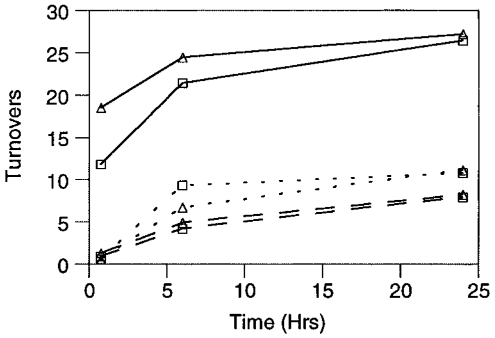

Figure 2. Dehalogenation of cyclohexyl bromide by $NaBH_4$ catalyzed by $NiCl_2$ (□) and $Ni(acac)_2$ (△) in diglyme/ethanol (—), DMF/ethanol (– –), or CH_3CN/ethanol (···).

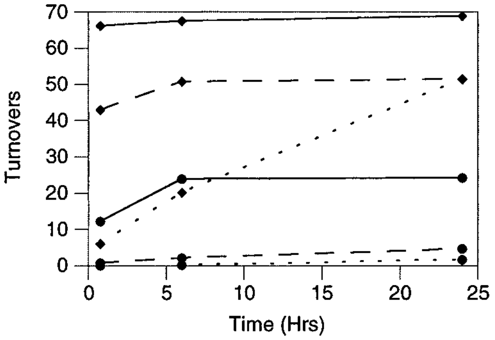

Figure 3. Dehalogenation of cyclohexyl bromide by $NaBH_4$ catalyzed by **1** (●) and **2** (◆) in diglyme/ethanol (—), DMF/ethanol (– –), or CH_3CN/ethanol (···).

H_2 is always present in the reaction system because it is generated from $NaBH_4$. Its role in the reaction was examined in experiments that were conducted under an atmosphere of H_2 in the absence of $NaBH_4$. No detectable amounts of cyclohexane were produced from cyclohexyl bromide by any of the nickel compounds investigated. Moreover, addition of H_2 did not noticably increase the product yield in any of the catalyzed borohydride reductions.

Cyclohexene was not detected in solution during the vast majority of the reductions. Two exceptions were observed at longer reaction times for reductions catalyzed by **1** in DMF/EtOH and in THF/MeOH, solvents in which the conversion of cyclohexyl bromide to either cyclohexane or cyclohexene is quite poor. None of the nickel compounds **1**−**8** catalyze the reduction of cyclohexene by either $NaBH_4$ or H_2.

The number of turnovers catalyzed by compounds **1**−**5**, **7**, **8**, $NiCl_2·6H_2O$, and $Ni(acac)_2$ in three different mixed solvent systems as a function of time are shown in Figures 2−5. $NiCl_2·6H_2O$ and $Ni(acac)_2$ represent salts or weak complexes that afford nickel boride when reacted with $NaBH_4$. An important point illustrated by Figure 2 is that the reduction of cyclohexyl bromide by $NaBH_4$ is in fact catalytic in nickel boride.

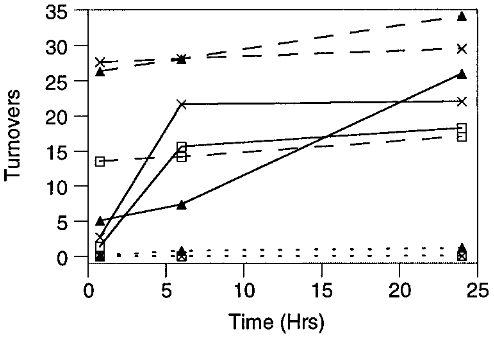

Figure 4. Dehalogenation of cyclohexyl bromide by $NaBH_4$ catalyzed by **3** (□), **4** (×), and **5** (▲) in diglyme/ethanol (—), DMF/ethanol (– –), or CH_3CN/ethanol (···).

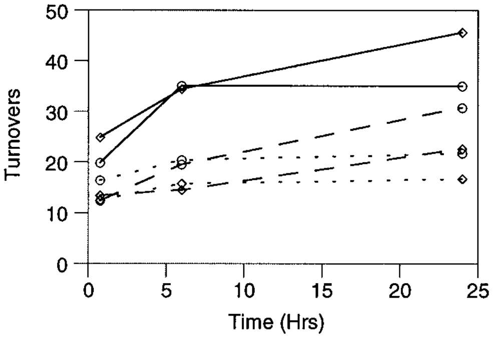

Figure 5. Dehalogenation of cyclohexyl bromide by $NaBH_4$ catalyzed by **7** (○) and **8** (◇) in diglyme/ethanol (—), DMF/ethanol (– –), or CH_3CN/ethanol (···).

Reductions catalyzed by **1** were investigated over a wider range of conditions than other compounds. **1** is most effective in diglyme/alcohol mixed solvent, but does not affect complete reduction of cyclohexyl bromide in any of the systems examined. Total conversion and rates are greatest when methanol is the alcohol cosolvent and decreases for ethanol, 2-propanol, and *tert*-butyl alcohol. The reaction does not appear to be adversely affected when it is run under air, but conversion is greatly decreased when wet alcohol (95% ethanol) is used. No reduction occurs in diglyme alone. **1** is a substantially less effective catalyst in DME, DMF, or THF/alcohol mixed solvents.

No visible changes were observed in the intensely colored solutions of **1** ($\epsilon_M \approx 2.7 \times 10^4$) when $NaBH_4$ was added. Solutions were filtered at the conclusion of the reaction to determine whether particulates had formed. In most cases, **1** was recovered nearly quantitatively from the filtrate. Some particulates were recovered after 48 h in 4:2 diglyme/methanol, but this was well after reduction of cyclohexyl bromide had ceased. The UV−vis spectrum of **1** is not affected by the addition of several equivalents of borohydride. The spectrum of **1** is different in DMF solution, consistent with the contention that DMF coordinates to nickel in **1**.[31]

Compound **2** is by far the most effective catalyst in this study. Reduction of cyclohexyl bromide is nearly complete in less than 45 min in diglyme/ethanol. The reaction solution appears homogeneous during catalysis. Nickel-containing particles are produced in diglyme or DMF mixed solvents if substrate is omitted, but only after many hours. The imine double bonds of **2** are also reduced during the reaction.[33] It is not certain whether **2**, its saturated analog, or both complexes are responsible for catalysis.

Solutions of the perchlorate salts of **3**−**5** change color during catalysis from the yellow characteristic of square planar, low-spin Ni(II) macrocycles to pink-violet. Some pale green precipitate forms in diglyme/ethanol solutions. A substantial amount of a greenish-white precipitate forms in acetonitrile/ethanol solution. Borohydride complexes of the *C-meso* (*7R,14S*) and *C-racemic* (*7R(S),14R(S)*) isomers of **4** were described.[35] Similar colors and catalytic activities are noted when these compounds are used in place of **4**$(ClO_4)_2$. One difference is that **4**$(BH_4)_2$ can affect slightly less than four turnovers of the reduction of cyclohexyl bromide in the absence of added $NaBH_4$. Figure 4 shows that the catalytic effectiveness of **3**−**5** is inversely related to the formation of precipitate. Activity is highest in DMF/ethanol where no precipitate is observed. The compounds have little activity in acetonitrile/ethanol where substantial amounts of precipitate are formed. The tetramethylcyclam complex **6** is roughly 10 times less active in DMF/ethanol than the unsubstituted cyclam **5**. Consequently, the reactions of **6** in other solvents were not investigated.

Table 1. Absorption Spectral Data for High-Spin Ni(II) Cyclam Complexes

complex	λ_{max}, nm (ϵ, M^{-1} cm^{-1})			ref
cis-Ni(cyclam)(en)$^{2+}$ [a]	880 (10.8)	535 (8.4)	343 (13.6)	57
cis-Ni(cyclam)$(H_2O)_2{}^{2+}$ [a]	900 (9.5)	550 (5.5)	345 (11)	57
5 + $NaBH_4$ [b]	893	523	343	
trans-[Ni(cyclam)$(H_2O)_2$]Cl_2·$4H_2O$ [c]	667 (2.4)	507 (3.1)	333 (3.7)	58
trans-[Ni(cyclam)Cl_2] [d]	672 (3.3)	520 (7.2)	345 (15.6)	58

[a] Aqueous solution. [b] Acetonitrile solution. [c] Single crystal. [d] Chloroform solution.

We attempted to isolate and identify the species that were present during the reactions of **5** and **6** in order to determine whether they were borohydride complexes. Addition of from 1 to 6 equiv of $NaBH_4$ to yellow solutions of **5**$(ClO_4)_2$ in either diglyme, DMF, or acetonitrile affords pink-violet solutions and green precipitates (except in DMF) within an hour.[56] The analogous reaction for **6**$(ClO_4)_2$ requires roughly 6 h. The pink-violet solutions of **5** are sensitive to air and to such protic solvents water or alcohol. No IR bands attributable to coordinated borohydride were observed in the DMF solution. The UV−vis spectrum of the acetonitrile solution, Table 1, resembled closely those of high-spin Ni(II) *cis*-cyclam complexes,[57] which can be distinguished from those of high-spin Ni(II) *trans*-cyclam complexes[58] by the presence of an intense near-infrared band near 900 nm.[59] The green precipitate is air stable, but releases gas when reacted with water, alcohols, $CHCl_3$, or CH_2Cl_2. The band for perchlorate anion is absent from the IR spectrum of the solid, which resembles that of *C-meso* **4**$(BH_4)_2$,[35] Table 2. The latter compound was suggested to contain two trans borohydride ions interacting with the nickel by single Ni−H−B bridges. When $(CH_3)_4NBH_4$ is substituted for $NaBH_4$, solutions of **5**$(ClO_4)_2$ turn pink-violet but no precipitate forms. Concentration of an acetonitrile solution affords a pink-violet solid whose IR spectrum resembles that of *C-racemic* **4**$(BH_4)_2$, Table 2. The latter compound was suggested to contain a cis coordinated macrocycle, a bidentate coordinated borohydride ion, and a noncoordinated borohydride counterion.

7 and **8** exhibit similarities in reactivity in the various mixed solvents, Figure 5. The two compounds differ in ligand to metal ratio and the protonation state of the ligand. Conversion of **7** to **8** was demonstrated in basic solution.[37] In addition, the dimeric **8** is in equilibrium with a solvated monomeric form in coordinating solvents. The differences in reactivity observed

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(56) *Caution!* Reference 35 reports that reaction of **4**(ClO_4) and $NaBH_4$ can lead to precipitation of mixed borohydride−perchlorate salts that explosively decompose when heated.
(57) Billo, E. J. *Inorg. Chem.* **1981**, *20*, 4019−4021.
(58) Mochizuki, K.; Kondo, T. *Inorg. Chem.* **1995**, *34*, 6241−6243.
(59) Vitiello, J. D.; Billo, E. J. *Inorg. Chem.* **1980**, *9*, 3477−3481.

Table 2. IR Data in the B−H Stretching Region[a]

C-meso-**4**$(BH_4)_2$[b]		2073 m	2118 s	2190 m	2290 sh	2320 m	2370
C-racemic-**4**$(BH_4)_2$[b]	1990 s	2080 m	2170 sh	2240 s	2300 s	2380 s	2430 s
5 + $NaBH_4$[c]			2137 s	2226 s	2291 s	2333 s	2387 sh
5 + $(CH_3)_4NBH_4$[d]	1990 m	2067 m	2144 m	2231 s	2298 s	2327 s	2394 m

[a] KBr pellet. [b] Reference 35. [c] Precipitate from reaction in CH_3CN. [d] Solid from concentration of CH_3CN solution.

here may reflect differences in the kinetics of equilibration starting from the two different complexes. Consistent with this, the catalytic activity of nickel salts plus the free salicylaldehyde thiosemicarbazone ligand was comparable to that of preformed complexes.

Reductive Cleavage of the C−S Bond of Methyl Coenzyme M. (a) Nickel Complexes. The ammonium salt of methyl CoM has poor solubility in acetonitrile, diglyme, and THF. It has slightly better solubility in DMF. We used methanol in the mixed solvent systems to enhance the solubility of the substrate. Detectable, but exceedingly small amounts of methane are produced by reaction of the substrate, 5 equiv or more of $NaBH_4$, and between 10 and 67 mol % of one of the compounds **1**−**8**. The number of turnovers range from 7×10^{-4} for **1** to 8×10^{-3} for **4**. These correspond to yields of 0.01 to 0.1% based on the amount of methyl CoM present. The nickel salts $NiCl_2 \cdot 6H_2O$ and $Ni(acac)_2$ are somewhat more effective catalysts, showing 0.05 turnovers or roughly 1% conversion of substrate.

Our concern that the limited solubility of ammonium methyl CoM could be a contributing factor to the low yields of methane led us to carry out analogous experiments in aqueous mixed solvent systems and in water. The pH of the aqueous portion was varied from 7 to 13 because the hydrolysis of $NaBH_4$ is appreciably slower in basic solution. Despite the good solubility of ammonium methyl CoM in water, the yields of methane remained exceedingly small in all solvents. An H_2 atmosphere had no effect on the reaction.

(b) Nickel Boride. The above observations establish that relatively larger amounts of methane are formed in systems that become heterogeneous. The yield of methane is small, but less than an equivalent of nickel boride is formed in situ. The yield of methane increases as the ratio of nickel to methyl CoM is increased. Once the ratio is about 7, the yield of methane levels off at 54%. At least 2 mol of $NaBH_4$ are required per mole of nickel salt. Lower ratios lead to greatly decreased yields of methane.

Minor amounts of two other products were detected in the headspace gases above the aqueous nickel boride reaction. One is ethane, which could result from recombination on the nickel surface of methyl radicals produced by cleavage of the CH_3−S bond of methyl CoM. Alternatively, ethane could result from cleavage of both the S−CH_2 and CH_2−SO_3^- bonds of methyl CoM. Reduction of the sodium salt of coenzyme M thiol affords ethane and the second, unidentified compound in amounts comparable to that produced from methyl coenzyme M. Thus, the two products derive from the coenzyme M portion of the substrate.

The compounds remaining in solution after the reduction of methyl CoM by nickel boride were examined. The solution was filtered, evaporated to dryness, and redissolved in D_2O. The ^1H NMR spectrum showed the presence of ethanesulfonate, 2.76 (q, 2H) and 1.11 (t, 3H), and a comparable amount of an unidentified compound whose spectrum consisted of two singlets near 3.16 (s) and 2.18 (br) ppm that integrated in a 2:1 ratio, respectively. No methyl CoM remained. In independent experiments the width of the upfield singlet ranged from reasonably sharp to quite broad, the shifts of the two singlets changed somewhat, and the relative amounts of ethanesulfonate and the unidentified compound was variable. When D_2O was used as the solvent, the reaction was run at 0 °C, and the filtrate was concentrated rather than evaporated, no new peaks appeared in the NMR spectrum. Thus, it is unlikely that any water soluble, volatile compounds were present but lost on evaporation. Changes in the ^1H NMR spectrum of ethanesulfonate established that near quantitative incorporation of one deuterium atom into the methyl group had occured. Previous work showed that the hydrogen incorporated in the product during desulfurization by nickel boride in methanol/THF solution originates from $NaBH_4$ and to a lesser extent from the protic solvent.[46] The above results suggests that the hydrogen or hydride absorbed on nickel boride can be completely exchanged with D_2O.

A definitive structure was not established for the unidentified compound. The 2:1 intensity ratio of the peaks, the absence of spin−spin coupling between peaks, and the structural fragments available from methyl CoM would seem to point to a species like the dimethyl(methylthio)sulfonium ion, $(CH_3)_2SSCH_3^+$. The chemical shifts reported for salts of this cation are 3.27 (6H) and 2.92 (3H) ppm for the $CF_3SO_3^-$ salt in CD_2Cl_2[60] and 3.10 (6H) and 2.80 (3H) ppm for the PF_6^- salt in CD_3CN.[61] Thiosulfonium ions are highly reactive ions that readily dissociate and act as a source of RS^+ in the presence of neutral or anionic nucleophiles. In the presence of methyl disulfide the upfield singlet is exchange broadened and can shift upfield more than 0.3 ppm through exchange averaging with the CH_3S groups in the disulfide.[62] We examined the spectrum of an authentic sample of $(CH_3)_2SSCH_3^+BF_4^-$ in D_2O. The cation was not stable in this solvent. The spectrum observed immediately after preparation of the solution had peaks at 3.23 and 2.19 ppm, which correspond to those of the unidentified compound. However, peaks corresponding to $(CH_3)_3S^+$ (2.63), CH_3SSCH_3 (2.45), and $(CH_3)_2S$ (1.89 ppm) were also present and constituted the majority of the integrated intensity in the spectrum. The relative amounts of the compounds in the sample changed with time. The unidentified compound may not be $(CH_3)_2SSCH_3^+$, but it can be derived from it. Another important observation is that the unidentified compound was not observed when the sodium salt of coenzyme M thiol was reduced by nickel boride. Taken together, these establish that the unidentified compound is derived from the CH_3−S portion of methyl coenzyme M. Thus, nickel boride preferentially cleaves the CH_2−S bond of methyl CoM rather than the CH_3−S bond.

(c) Raney Nickel. A 15-fold excess of freshly prepared Raney nickel in water cleaves ammonium methyl CoM to methane quantitatively as determined by GC analysis. The methane yield was confirmed by Toepler pump experiments. Although H_2 desorption from the Raney nickel complicated the measurement, the methane yield was found to be 100 ± 6%.

The products that remained in solution were identified by ^1H NMR. The spectrum showed only the presence of ethanesulfonic acid and on occasion a trace (∼2%) of the unidentified compound that was observed in the nickel boride reactions. No

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(60) Ravenscroft, M.; Roberts, R. M. G.; Tillett, J. G. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1569−1572.

(61) Goodrich, R. A.; Treichel, P. M. *J. Am. Chem. Soc.* **1966**, *88*, 3509−3511.

(62) Smallcombe, S. H.; Caserio, M. C. *J. Am. Chem. Soc.* **1971**, *93*, 5826−5833.

deuterium was incorporated in the ethanesulfonic acid when the reaction was conducted in D_2O. Thus, the hydrogen source in Raney nickel is unexchangable.

Smaller excesses of Raney nickel led to large decreases in the yield of methane. Less than 10% of the possible methane was recovered when a 4-fold excess of Raney nickel was used. Samples of Raney nickel that had been stored after preparation (i.e. commericially prepared active catalyst) were less active and gave smaller yields of methane. These samples also led to formation of ethane, which constituted about 4% of the total headspace gases.

Our results differ from those described in footnote 23 of ref 28. This report stated that Raney nickel desulfurizes methyl CoM to afford a mixture of nickel sulfide, methane, ethane, methanol, ethanol, and an uncharacterized oil.

Discussion

Figures 2−5 clearly illustrate that turnover rates for the catalyzed borohydride reductions of cyclohexyl bromide are substantially affected by the solvent and the structure of the catalyst precursor. The differences between the rate profiles for $NiCl_2 \cdot 6H_2O$ and $Ni(acac)_2$, which form nickel boride in the presence of $NaBH_4$, and compounds **1**−**8** is evidence against a significant role for nickel boride in the reactions catalyzed by **1**−**8**. Consistent with this, no insoluble particulates were collected by filtration of the reaction medium. Additionally, **1**−**8** fail to hydrogenate cyclohexene in the presence of $NaBH_4$, which generates H_2 (and possibly diborane) under the reaction conditions. Cyclohexene is hydrogenated by nickel boride in the presence of H_2.[41] Finally, the greatly reduced activity of **1**−**8** in the cleavage of methyl CoM relative to salts that are reducible to nickel boride implies that little if any nickel boride is formed from these complexes. Thus, homogeneous catalyst species appear to be responsible for the activities depicted in Figures 3−5.

Many mechanisms could operate in the homogeneous nickel complex catalyzed dehalogenation of halocarbons by borohydride. Borohydride might simply serve to reduce the starting Ni(II) complex to a Ni(I) complex. Ni(I) complexes react with the halocarbons by electron transfer or atom abstraction[63−65] to afford an alkyl or aryl radical or by nucleophilic displacement of the halide[20−22] to afford an alkyl− or aryl−nickel complex. Alternatively, borohydride might react with the nickel complex to afford nickel−hydride or nickel−borohydride complexes. A hydride complex could also form by protonation of a Ni(I) complex by solvent. Both types of complexes could potentially serve as a hydride transfer agent in a nucleophilic displacement of the halide.

No clear or consistent mechanistic picture emerged from previous investigations of **1** and **2**. The dehalogenation of cyclohexyl bromide catalyzed by **1** was suggested to proceed through both electron transfer and nucleophilic substitution of halide by a hydride derived from either a nickel−hydride or −borohydride complex.[31] Tertiary 1-bromoadamantane was reduced by **1** and $NaBH_4$ much more slowly than the secondary cyclohexyl bromide, which is inconsistent with exclusive operation of an electron transfer mechanism that leads to radicals. **1** catalyzed the reduction of cyclohexyl bromide by $NaBD_4$ in diglyme/ethanol to afford a 62:38 mixture of C_6H_{12}/$C_6H_{11}D$. The complementary reaction employing $NaBH_4$ in diglyme/ethanol-d_6 afforded a 84:16 mixture. The authors imply that cyclohexyl radical produced by electron transfer from **1**$^-$ only abstracts hydrogen from the solvent. Thus, the deuterium incorporation results were seen as evidence of two simultaneous pathways. Analogous deuterium incorporation experiments were reported in the investigation of dehalogenation of aromatic halides catalyzed by **2**.[33] No deuterium was incorporated in naphthalene produced by reduction of 1-bromonaphthalene by $NaBH_4$ in D_2O/acetonitrile, whereas 84% monodeuterionaphthalene was obtained with $NaBD_4$ in D_2O/acetonitrile. Deuterium incorporation fell to 28% when $NaBD_4$ was used in C_2H_5OH/acetonitrile and 0% when $NaBH_4$ was used in C_2H_5OD/acetonitrile. Thus, hydrogen was incorporated into the product from both borohydride and from the C−H bonds of ethanol. In contrast to the conclusion reached for **1**, a mechanism involving electron transfer from Ni(I) was favored. In addition to hydrogen abstraction from solvent, the aryl radicals formed abstract a hydrogen atom directly from borohydride or indirectly through an intermediate nickel hydride species. Abstraction from borohydride has precedent[66,67] and can result in a radical chain process that propogates by electron transfer from the resulting $BH_3^{\bullet-}$ to aryl halide. Other evidence supported the electron transfer mechanism. Addition of cumene retarded the rate of debromonation of 1-bromonaphthalene and resulted in formation of bicumyl. Hydrazine could be used to replace borohydride as the reductant.

Because of the complexity of the reaction systems, we did not attempt to determine which mechanism(s) operates. However, some of our observations may be relevant to the question. The absence of the dehydrohalogenation product cyclohexene would appear to be inconsistent with a mechanism involving nucleophilic attack of Ni(I) on cyclohexylbromide.[21,22] Several observations suggest the involvement of borohydride complexes. The changes in the UV−vis spectrum of **5** from that typical of a square-planar, low-spin Ni(II) cyclam complex to that of a high-spin Ni(II) *cis*-cyclam complex during catalysis and the IR spectra of solids obtained from reaction of **5** with borohydride salts are consistent with the formation of borohydride complexes. The ability of **4**$(BH_4)_2$ to effect nearly four turnovers in the absence of added $NaBH_4$ demonstrates that borohydride complexes are catalytically competent. However, these observation do not require that a borohydride complex be the catalytically active species rather than a species formed in a mechanistically insignificant side equilibrium or a precursor to the active species. In addition, our failure to observe direct evidence for formation of a hydride or borohydride complex in the reactions of **1**, **2**, **7**, or **8** does not rule out a role for such complexes.[68]

Regardless of the mechanism(s) operating in the dehalogenations catalyzed by **1**−**8**, it is clear that all of these complexes are inactive as catalysts for cleavage of the C−S bonds of methyl CoM by borohydride. Two conclusions are evident when these results are combined with those for $Ni^I(OEiBC)^-$ [20−22] and Ni^I−F430[17,19] and our recent refutation[29] of the report[28] that the nickel complex of 1,4,7,10,13-pentaazacyclohexadecane-14,15-dione cleaves methyl CoM. First, no creditable report exists in the literature of a mononuclear nickel complex that can cleave methyl CoM to methane in high yield. Second, the facility of a complex in reducing halocarbons or other electrophiles does not imply facility in cleaving methyl CoM.

At present, nickel boride and Raney nickel are the only compounds, aside from the enzyme methyl CoM reductase, that have been demonstated to cleave methyl CoM. Both require a substantial excess of nickel relative to methyl CoM to achieve a significant yield. Both are high surface area heterogeneous

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(63) Bakac, A.; Espenson, J. H. *J. Am. Chem. Soc.* **1986**, *108*, 713−719.

(64) Bakac, A.; Espenson, J. H. *J. Am. Chem. Soc.* **1986**, *108*, 719−723.

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(66) Barltrop, J. A.; Bradbury, D. *J. Am. Chem. Soc.* **1973**, *95*, 5085−5086.

(67) Groves, J. T.; Ma, K. W. *J. Am. Chem. Soc.* **1974**, *96*, 6527−6529.

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solids that contain a substantial amount of absorbed hydrogen. Furthermore, the two solids cleave both the CH_3-S and CH_2-S bonds of methyl CoM to afford methane, ethanesulfonate, and presumably nickel sulfide. Nickel boride appears to preferentially cleave the CH_2-S bond, as evidenced by the side product that is derived from the CH_3-S fragment.

Biological Significance. Several issues must be resolved to understand how the enzyme methyl coenzyme-M reductase functions. These include but are not limited to the following questions. (1) What is the role of the Ni(I) atom in Ni^I-F430? (2) Can Ni^I-F430 react directly with methyl CoM or is a prior activation of F430 or of the substrate required? (3) How does the enzyme specifically direct the C−S bond cleavage to the CH_3-S bond of methyl CoM? (4) What is the role of the thiol cofactor HS−HTP? (5) How and when is the S−S bond of the heterodisulfide product CoM−S−S−HTP formed?

An objective of this study was to examine whether complexes that might react through nickel hydride intermediates can cleave methyl CoM. Although complexes **1**−**8** had significant but varying activity in catalyzing the reduction of cyclohexyl bromide by borohydride, none were active toward methyl CoM. Because of the uncertainty about the mechanism(s) operating in the halocarbon reductions, we cannot assert that mononuclear nickel hydride complexes are unreactive toward methyl CoM. However, if the reactive intermediates for complexes **1**−**8** in the halocarbon reductions are Ni(I) complexes rather than nickel hydride complexes, our results would increase the weight of evidence that Ni(I) complexes do not react directly with methyl CoM.

An alternative explanation was advanced to rationalize the small yields of methane obtained by reaction of Ni(I) complexes with methyl CoM.[26] Methyl free radicals are trapped efficiently by methyl CoM. Subsequent reactions of the radical adduct do not ultimately afford methane. Trapping of radicals by methyl CoM was sugested to be fast compared to either capture by the nickel complexes (colligation) used in the study, which were sterically hindered about the nickel, or hydrogen abstraction from the solvent (water). Thus, the low yield of methane would not imply a failure of Ni(I) complexes to react with methyl CoM but rather would be a consequence of diversion of intermediates into nonproductive pathways. The diversion would not occur in the enzyme because excess methyl CoM would not be present. We do not believe that this explanation applies to the current study. The majority of complexes **1**−**8** are not sterically hindered about the nickel, so radical capture by nickel will be fast. In particular, the rate constant for colligation of methyl radicals by **5** is about 1×10^9 M^{-1} s^{-1}, which is near the diffusion control limit.[69] Furthermore, if present, methyl radicals should rapidly abstract hydrogen from either the alcohol cosolvent or borohydride, which are present in greater concentration than methyl CoM.

Given the question about the activity of nickel hydrides, it is noteworthy that Raney nickel and nickel boride, two nickel solids that contain absorbed hydrogen and perhaps surface hydrides, are capable of cleaving methyl CoM to afford methane in substantial yield. These heterogeneous solids have a mechanistic advantage over mononuclear hydrides, though, in that adjacent nickel atoms can stabilize the sulfur-containing byproduct and concurrently the sulfur-containing byproduct serves to stabilize the less-than-optimally coordinated nickel atoms in these high surface area solids. The reaction mechanisms of these solids are not directly relevant to the enzyme, which has an mononuclear nickel site. However, the observed preference of nickel boride for cleavage of the CH_2-S bond of methyl CoM illustrates that the enzyme specifically cleaves the less reactive C−S bond. This specificity may be achieved by a tight binding of cofactors such that only the CH_3-S bond is presented to the active site. Methyl coenzyme-M reductase does not readily tolerate modifications of the structure of the cofactors.[70] The methyl CoM analogue 3-(methylthio)propanesulfonate, which differs by addition of one methylene group, is inactive as are alkyl CoM analogues with alkyl groups larger than ethyl.[71] Similarly, changes in the carbon chain length in HS−HTP from heptanoyl to hexanoyl or octanoyl lead to complete loss of activity.[8]

One proposal for the mechanism of the enzyme is that the thiyl radical of cofactor HS−HTP, which is postulated to result from one-electron reduction of F430 by $HTP-S^-$, couples with methyl CoM to afford the sulfuranyl radical, $HTP-S-S^{\bullet}(CH_3)(CoM)$.[72,73] The sulfuranyl radical transfers a methyl radical to Ni^I-F430 to afford $CH_3-Ni^{II}-F430$ and the heterodisulfide CoM−S−S−HTP. This should be a more favorable reaction than transfer of methyl radical or cation from methyl CoM to Ni^I-F430. Subsequent cleavage of $CH_3-Ni^{II}-F430$ by H^+ affords methane. The proposal suggests a means of activating the reaction, a role for HS−HTP, and a way to specifically form the S−S bond of the heterodisulfide. It does not explain by itself the specificity for CH_3-S rather than CH_2-S bond cleavage of methyl CoM. In light of the proposal, it is curious that the unidentified byproduct from methyl CoM that survives the nickel boride reaction can be derived from a dialkyl(alkylthio)sulfonium compound. The later is related to a sulfuranyl radical by a one electron oxidation.

Summary

The principal findings and conclusions of this study are as follows.

(1) Complexes **1**−**8** are homogeneous catalysts for the dehalogenation of cyclohexyl bromide by sodium borohydride.

(2) The effectiveness of the catalysis varies widely with the structure of the complex and the composition of the solvent.

(3) The mechanism(s) of the dehalogenation by the complexes has not been established. Some complexes are converted to borohydride complexes during the reaction. The absence of cyclohexene during the dehalogenation reactions argues against nucleophilic attack of Ni(I) species on cyclohexyl bromide.

(4) None of the complexes cleave methyl CoM to methane in the presence of sodium borohydride. Thus, the facility of a nickel complex in reducing halocarbons or other electrophiles does not imply facility in cleaving methyl CoM.

(5) The solids nickel boride and Raney nickel cleave the thioether C−S bonds in methyl CoM when present in excess. Excess Raney nickel cleaves both C−S bonds to afford ethanesulfonate and methane quantitatively. Excess nickel boride preferentially cleaves the CH_2-S bond of methyl CoM. The yield of methane in the latter reaction is substantially less than quantitative.

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