with hydrolysis of the phosphodiester linkages.[16] The efficiency of religation after cleavage by these differing metal ions in the presence of $Ru(DIP)_2Macro^{n+}$ [18] is given in Table I along with cleavage efficiencies for the different added metals. As may be seen in the table, *the greatest extent of religation is apparent with the nonredox active metal ions: Zn(II), Cd(II), and Pb(II).* The efficiency of religation[19] of cleaved DNA is 40% for these metals and may be compared to the 50% yield that one would expect if hydrolysis gave the equally probable 3′- and 5′-phosphate products.[5,20,21] Despite high levels of cleavage, only a small but significant level of religation is found both with cobalt and copper; these cleavage reactions must be operating at least in part through redox chemistry.[22,23]

So as to determine whether $Ru(DIP)_2Macro^{n+}$ acts essentially to deliver locally high concentration of metal ion to the DNA helix for nucleophilic attack, we examined DNA cleavage by the same metal ions also in the presence of phenanthroline. The same trend with coordinated phenanthroline complexes[24] as was seen for $Ru(DIP)_2Macro^{n+}$ is apparent, though with lower efficiency. Relative levels of cleavage[25] for the phenanthroline complexes were 1.0, 0.49, 0.20, and 0.25 upon coordination with Cu(II), Co(II), Zn(II), and Cd(II), respectively, a series which resembles that seen upon activation of $Ru(DIP)_2Macro^{n+}$. Moreover a low level of religation has been detected with the phenanthroline complexes of the nonredox active metal ions, zinc and cadmium.

These results illustrate how DNA strand scission may be accomplished nonoxidatively. In our model, a DNA binding moiety may be coupled to a metal cation so as to deliver its coordinated nucleophile to the phosphate backbone for hydrolysis of the anionic diester. The reactions described here are not efficient, especially in comparison to oxidative chemistry, and the parameters to optimize efficiency, e.g., coordination number, geometry, and ligand set, need still to be determined. Yet this work may be usefully applied to elucidate the mechanisms of natural endonucleases and in the development of artificial restriction enzymes.

Acknowledgment. We are grateful to the National Institutes of Health (GM33309) and National Science Foundation (CHE85-17354, Alan T. Waterman Award) for their financial support. We thank also Prof. A. Sargeson for helpful discussions.

(16) DNA samples were cleaved by $Ru(DIP)_2Macro^{n+}$ with added metals to the same extent (to provide a constant form II substrate concentration) and allowed to react with T4 DNA ligase, which requires 5′-phosphate and 3′-hydroxyl termini for ligation.[17] After reaction with 5–7 units of T4 DNA ligase for 6 h at 4 °C, samples in the presence or absence of ligase were treated with proteinase K containing 0.4% SDS and 3 mM EDTA and then ethanol precipitated at −20 °C. All samples were then resuspended in buffer containing 50% glycerol and bromphenol blue and electrophoresed on 1% agarose gels containing 2 μM ethidium in the gel and gel buffer. After electrophoresis at 50 V for 2 h, the gels were illuminated from below with ultraviolet light and photographed. DNA-bound ethidium in the gel unwinds and therefore resolves relaxed closed, religated DNA from the nicked circular form. The mobilities of each DNA form were determined by comparison to religated controls (DNA nicked initially by a restriction enzyme and then religated). Levels of religation were quantitated by densitometry.

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(18) DNA with bound $Ru(DIP)_2Macro^{n+}$ and added metal inhibits ligase to a varied extent. Bound ruthenium may be removed to the greatest extent by DNA treatment with DMSO or tren. DNA nicked by a restriction enzyme, incubated with $Ru(DIP)_2Macro^{n+}$ and metal, and followed by wash with 0.3 M NaCl, EDTA, and then several ethanol precipitations, inhibits the conversion to the relaxed closed form by as much as 50% after treatment with ligase.

(19) It should be noted that because the assay measures ligation by the conversion of form II DNA to the completely closed circle, if a mixture of hydrolytic and redox cleavage products occur on the same circle, religation of the hydrolytic species would not be detected; the assay therefore indicates religation only if cleavage is solely through a hydrolytic path.

(20) In the absence of a stereochemical bias imposed by the cleaving moiety, nucleophilic attack on the phosphodiester could yield both the 5′-phosphate, 3′-hydroxyl and 3′-phosphate, 5′-hydroxyl termini, despite even small differences in acidity (see, for example, ref 8). We have on occasion observed with the nonredox active metal ions religation efficiencies as high as 89%. Such a stereochemical bias for cleavage to the S′-phosphate may be rationalized based upon binding and reaction from the major groove.

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(22) Redox active metals would appear not to be advantageous for metal activation of naturally occurring DNA binding enzymes.

(23) HPLC analysis showed high levels of free bases released for the cobalt-promoted reaction, consistent with oxidative cleavage of the sugar moiety in the presence of cobalt.

(24) A stoichiometry of 2.5:1 phenanthroline per metal ion was employed in these reactions to maintain some level of unsaturation in coordination in these labile complexes. A mixture of mono-, bis-, and tris-substituted phenanthroline complexes is most likely to be present.

(25) For these reactions metals were added at a concentration of 33 μM. Cleavage was conducted with 33 μM DNA-phosphate, incubated for 7 h at 50 °C, pH 9.0. After this incubation, percent form II DNA produced was 81, 39, 16, and 20 for Cu(II), Co(II), Zn(II), and Cd(II), respectively.

A New Method for the Activation of Metal-Bound Methyl Groups. Oxidative Disproportionation to Coordinated Ethylene and Methane

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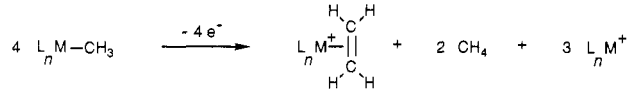
An efficient catalytic conversion of methane to a less volatile fuel would be of considerable practical importance.[2] Recently, several homogeneous transition-metal complexes have been found to oxidatively insert into the methane carbon–hydrogen bond.[3] However, this addition is reversible, and only a limited number of reactions of the coordinated methyl group have been found to date.[3b] In this communication, we describe a new transformation of coordinated methyl groups, illustrated schematically in eq 1. This oxidative disproportionation converts half of the methyl groups to coordinated ethylene, which is readily displaced from metals.[2i]



(1)

Methyl complex $(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(CH_3)$ (**1**),[4] ferricinium cation $[(\eta^5\text{-}C_5H_5)_2Fe]^+PF_6^-$ (1.0 equiv), an internal standard, and CD_3CN were combined at −78 °C and then warmed (eq 2). Gas evolution occurred when the CD_3CN melted (ca. −46 °C). The reaction was monitored by ^1H and ^{31}P NMR, which showed (−15 °C) the formation of methylidene complex $[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(=CH_2)]^+PF_6^-$ (**2**, 47%),[5] deuterioacetonitrile complex $[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(NCCD_3)]^+PF_6^-$ (**3**-d_3, 51%),[5] and methane (δ 0.18). We have previously reported that

(1) (a) University of Trondheim. (b) University of Utah. (c) Correspond with this author at Utah State University, Logan, UT 84322.

(2) See, inter alia: (a) Gesser, H. D.; Hunter, N. R.; Prakash, C. B. *Chem. Rev.* **1985**, *85*, 235. (b) Lin, C.-H.; Ito, T.; Wang, J.-X.; Lunsford, J. H. *J. Am. Chem. Soc.* **1987**, *109*, 4808. (c) Olah, G. A.; Gupta, B.; Farina, M.; Felberg, J. D.; Ip, W. M.; Husain, A.; Karpeles, R.; Lammertsma, K.; Melhotra, A. K.; Trivedi, N. J. *Ibid.* **1985**, *107*, 7097. (d) Otsuka, K.; Komatsu, T. *J. Chem. Soc., Chem. Commun.* **1987**, 388. (e) Labinger, J. A.; Ott, K. C.; Mehta, S.; Rockstad, H. K.; Zoumalan, S. *Ibid.* **1987**, 543. (f) Sofranko, J. A.; Leonard, J. J.; Jones, C. A. *J. Catal.* **1987**, *103*, 302. (g) Labinger, J. A.; Ott, K. C. *J. Phys. Chem.* **1987**, *91*, 2682. (h) Kimble, J. B.; Kolts, J. H. *CHEMTECH* **1987**, *17*, 501. (i) A related thermal methyl ligand transformation, involving a change in metal oxidation state, appeared during the review stage of this study: Ke, M.; Rettig, S. J.; James, B. R.; Dolphin, D. *J. Chem. Soc., Chem. Commun.* **1987**, 110.

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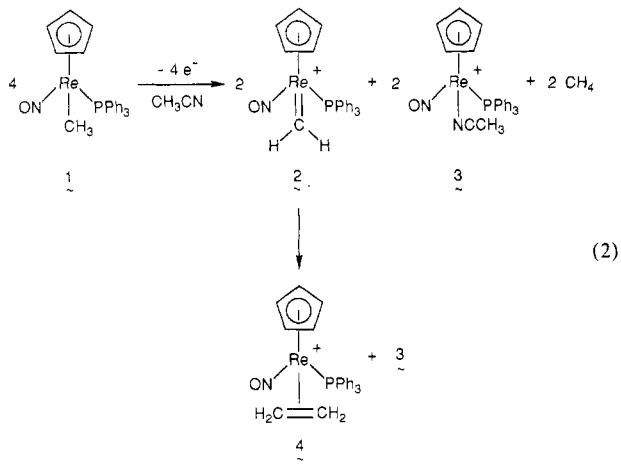

(2)

2 disproportionates in acetonitrile to ethylene complex $[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(H_2C{=}CH_2)]^+PF_6^-$ (**4**) and **3**.[5] Accordingly, after 2.5 h at room temperature, **4** and **3**-d_3 were present in a 1.0:3.1 ratio and essentially quantitative spectroscopic yields.

An analogous reaction was conducted on a preparative scale in CH_3CN. Ethylene complex **4** and acetonitrile complex **3** were isolated in 22% (88% of theory) and 69% (92% of theory) yields, respectively.[6] The methane yield was 49.2–50.9% (two runs, ≥99% of theory) by Toeppler line analysis. Mass spectrometry indicated no significant amounts (<2%) of other gases. The CH_4/CH_3D ratio was ≥99:1 in both CH_3CN and CD_3CN. Reaction of $(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(CD_3)$ (**1**-d_3; ca. 90:10 d_3/d_2)[5] in either CH_3CN or CD_3CN as described for **1** above gave a 82:18 CD_4/CD_3H ratio.

The mechanism of the preceding transformation was probed by electrochemical techniques. The derivative cyclic voltammetry (DCV)[7] response for the oxidation of **1** in $CH_3CN/Bu_4N^+PF_6^-$ (0.1 M) at a voltage sweep rate (ν) of 100 V/s (Figure 1a) indicated a quasi-reversible charge transfer to produce a relatively long-lived cation radical, $\mathbf{1}^{\bullet+}$. At a lower ν (0.4 V/s) the derivative peak ratio $((I_p')_b/(I_p')_f)$ was considerably less than unity (Figure 1b), indicating the presence of a chemical followup reaction of moderate rate. Reaction-order analysis[8] clearly showed second-order behavior at substrate concentrations ranging from 0.5 to 6.0 mM. The rate of disappearance of $\mathbf{1}^{\bullet+}$ was measured at temperatures ranging from −24 to 20 °C, and application of the rate law $-d[\mathbf{1}^{\bullet+}]/dt = 2k[\mathbf{1}^{\bullet+}]^2$ gave k (0 °C) = 1130 M^{-1} s^{-1}, $\Delta H^{\ddagger}$ = 0.1 kcal/mol, and $\Delta S^{\ddagger}$ = −46 eu.[9] Such near-zero apparent activation enthalpies, and highly negative activation entropies, are commonly associated with exothermic (but endergonic) preequilibrium dimerizations followed by a subsequent rate-determining step.[10] Accordingly, the rate of disappearance of $\mathbf{1}^{\bullet+}$-d_3, derived from **1**-d_3, gave k_H/k_D (0 °C) = 3.0, indicating that carbon–hydrogen bond cleavage occurs in or prior to the rate-determining step.

Constant current coulometry with linear sweep voltammetry monitoring of the disappearance of **1**[11] indicated the consumption of 1.1 Faraday/mol of **1**, establishing an overall one-electron process. The initial decomposition products of $\mathbf{1}^{\bullet+}$ were monitored as reported in a related study.[12] The electrode rest potential was adjusted to 0.40 V (vs Ag/Ag^+), where generation of $\mathbf{1}^{\bullet+}$ occurred continuously. A DCV scan initiated under these conditions is shown in Figure 2. Four reduction peaks labeled a (−0.04 V), b (−1.49 V), c (−1.94 V), and d (−2.18 V) on the negative-going sweep, and one peak on the return sweep for the oxidation of **1** (0.02 V), were observed. Peak a is due to the reduction of residual $\mathbf{1}^{\bullet+}$, and the remaining peaks were assigned to the reduction of **2** (b), **4** (c), and **3** (d) by comparison to reduction peaks for authentic samples. The combined intensities of the nearly equal peaks (b and d) suggest that equal quantities of **2** and **3** are initially formed, analogously to the chemical oxidation described above, and that **4** results from subsequent dimerization of **2**.

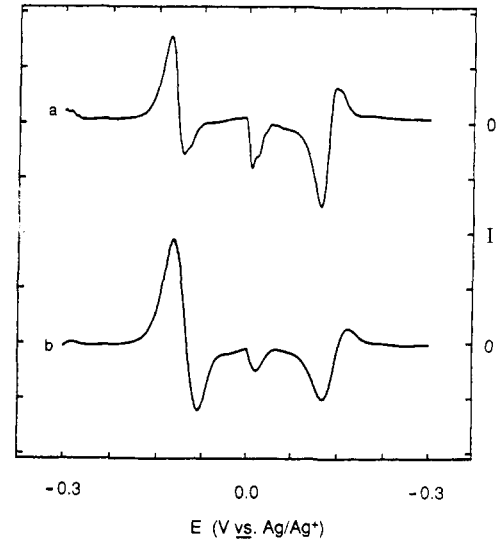

Figure 1. Derivative cyclic voltammograms of $(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(CH_3)$ (**1**, 2 mM) in $CH_3CN/Bu_4N^+PF_6^-$ (0.1 M) at a Pt microelectrode (d = 400 μm) at 20 °C and (a) 100 V/s, (b) 0.40 V/s.

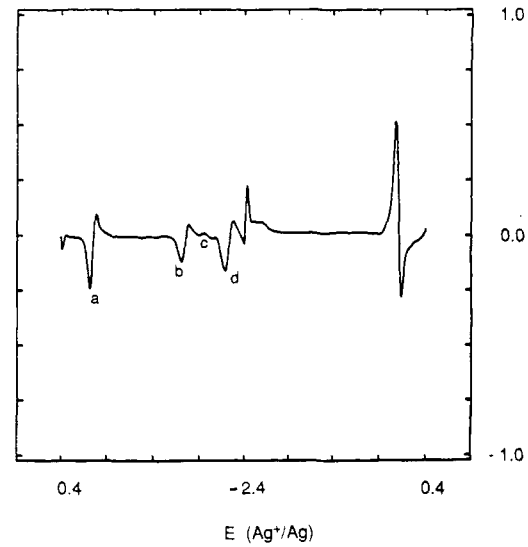

Figure 2. Derivative cyclic voltammogram as in Figure 1a but initiated during controlled potential steady-state electrolysis of **1**. Peaks a, b, c, and d correspond to the reduction of $\mathbf{1}^{\bullet+}$, **2**, **4**, and **3**.

Finally, the rate of disappearance of optically active (S)-$\mathbf{1}^{\bullet+}$, generated from (+)-(*S*)-**1**,[13] was found to be 1.6 times faster than that of racemic $\mathbf{1}^{\bullet+}$. This indicates that $\mathbf{1}^{\bullet+}$ retains configuration in solution and that the $(S)/(S)$ reaction is distinctly preferred over the $(S)/(R)$ reaction. Exclusive $(S)/(S)$ reaction ("enantiomer self recognition") would give a rate acceleration of 2.0.[5] This suggests a high degree of interaction between the two rhenium centers along the dimerization/C–H bond-breaking reaction coordinate.

(6) The ethylene ligand in **4** is displaced by $C_6H_5CH_2CN$ (170 °C, 37 h, ≥90% conversion). This gives nitrile complex $[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(NCCH_2C_6H_5)]^+PF_6^-$, which shows spectral properties similar to acetonitrile complex **3**[5] and has been independently synthesized, isolated, and completely characterized: Fernández, J. M., unpublished data.

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(8) Parker, V. D. *Acta Chem. Scand.* **1983**, *B37*, 163.

(9) Double potential step chronoamperometry data exclude any significant amount of direct reaction of $\mathbf{1}^{\bullet+}$ and **1** under our conditions (Supplementary Material).

(10) For a recent discussion, see: Parker, V. D.; Tilset, M. *J. Am. Chem. Soc.* **1986**, *108*, 6371.

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The above data indicate that simple electron transfer from **1** initiates a cascade of reactions that afford as initial detectable species complexes **2** and **3**. Since the coupling of methylidene ligands to coordinated ethylene is a very general reaction,[14] we anticipate that the formation of a displaceable ethylene ligand may be possible from a variety of other methyl complexes. The nature of the dimeric intermediate formed from $\mathbf{1}^{\bullet+}$ is not presently known. However, the dimethyl diosmium complex *cis*-$Os_2(CO)_8(CH_3)_2$ has been previously shown by Norton to eliminate CH_4 at 120 °C and form the bridging methylidene complex $Os_2(CO)_8(\mu\text{-}CH_2)$.[15] In conclusion, we speculate that this simple but previously unrecognized methyl ligand activation might aid the development of an efficient method for homogeneous methane functionalization. This study also demonstrates the enhanced capability possible by the complementary use of chemical and electrochemical electron-transfer methods that cannot be achieved with either alone.

Acknowledgment. We thank the Norwegian Research Council for Science and Humanities, Statoil (VISTA program administered by the Norwegian Academy of Science and Letters), the U.S. Department of Energy, and NATO for support of this research.

Supplementary Material Available: Additional data and a figure for double potential step chronoamperometry experiments (2 pages).[9] Ordering information is given on any current masthead page.

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A Convergent General Synthetic Protocol for Construction of Spirocyclic Ketal Ionophores: An Application to the Total Synthesis of (-)-A-23187 (Calcimycin)

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The ionophore antibiotics encompass a class of biologically important molecules whose members are structurally quite diverse and often stereochemically complex.[1] A-23187 (calcimycin), cezomycin, and X-14885A (**1a-c**),[2-4] isolated from cultures of various strains of *Streptomyces*, are representatives of a growing class of these ionophores known to selectively transport divalent cations, particularly calcium ions (Scheme I).[5] The important biological activity and unusual structural features of this group, including a 1,7-dioxaspiro[5,5]undecane ring system on which seven stereogenic centers are arrayed and α-keto pyrrole and benzoxazole residues, have stimulated a number of synthetic studies.[6,7]

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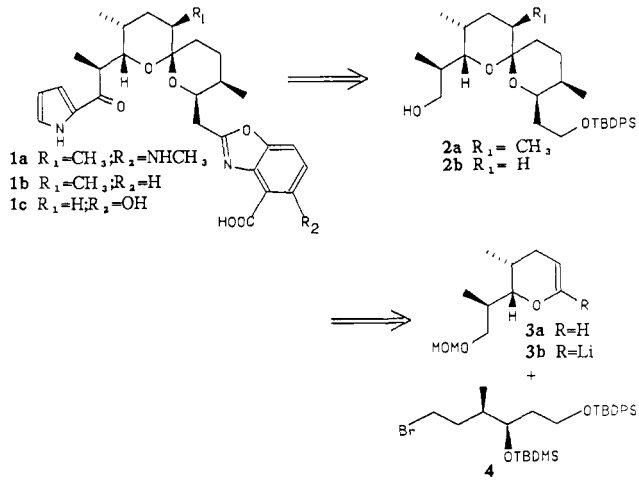
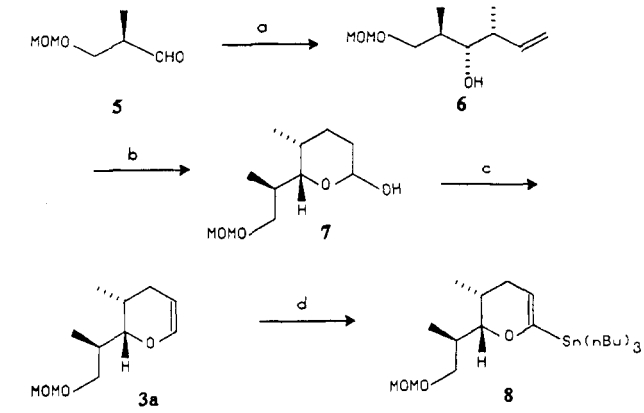
Scheme I

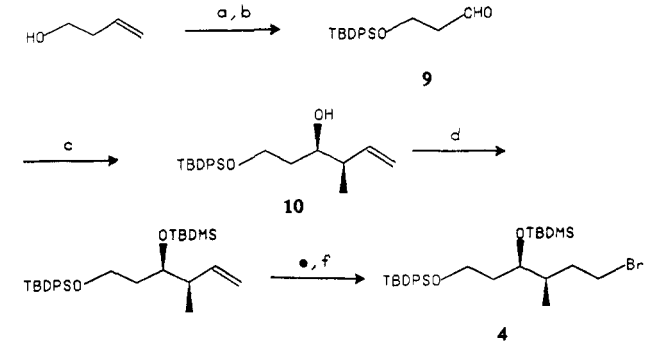


Scheme II[a]



[a] Reagents: (a) crotyltributylstannane (1.4 equiv), $MgBr_2$-Et_2O (2 equiv), CH_2Cl_2, -23 °C, 3 h; (b) BH_3-THF (1 equiv), THF, room temperature, 12 h, then successive addition of CH_3OH (1 equiv), 0 °C → room temperature, 2 h, $LiCH(SPh)OCH_3$ (3 equiv) in THF, -40 °C → -10 °C, 2 h, $HgCl_2$ (3 equiv), -10 °C → room temperature, 3 h, and H_2O_2 (12 equiv), pH 7, room temperature, 3 h; (c) MsCl (1.5 equiv), Et_3N (3 equiv), CH_2Cl_2, 14 h; (d) KO-*t*-Bu (3 equiv), *n*-BuLi (3 equiv), THF, -78 °C, 1 h then Bu_3SnCl (3.2 equiv), -78 °C → room temperature, 45 min.

Scheme III[a]



[a] Reagents: (a) TBDPSCl (1.1 equiv), imidazole (2 equiv), DMF, room temperature, 6 h; (b) O_3, CH_2Cl_2-CH_3OH (7:3), -78 °C; DMS, -78 °C to room temperature, 6 h; (c) (*Z*)-crotyldiisopinocampheylborane (1 equiv), THF, -78 °C, 5 h; H_2O_2, NaOH; (d) TBDMSOTf (1.3 equiv), Et_3N (3 equiv), CH_2Cl_2, room temperature, 1 h; (e) B-H_3-THF (1.5 equiv); H_2O_2, NaOH; (f) Ph_3P (2 equiv), CBr_4 (2 equiv), Et_2O, room temperature, 6 h.

Our interest in exploiting methodology for the generation and coupling of cyclic vinyl ether anions, developed in our labora-

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