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Kinetics and Mechanism of the Chloride-Assisted Oxidative Dealkylation of Alkylcobalamins by Iron(III) Ions

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The stoichiometry and kinetics of the reactions between alkylcobalamins and Fe^{3+} ions in acid solutions have been examined. Iron(III) demethylates CH_3–B_{12} very slowly in perchlorate solution. In the presence of chloride, however, the demethylation readily occurs with a 1.8:1.0 stoichiometry (Fe^{3+}:CH_3–B_{12}). This reaction produces H_2O–B_{12}^+, CH_3Cl, and Fe^{2+}. The dealkylation is first order in R–B_{12} and first order in Fe^{3+} at low $[Fe^{3+}]_{tot}$ but approaches zero order as its concentration is increased. This hyperbolic dependence upon $[Fe^{3+}]_{tot}$ is interpreted in terms of a fast association between R–B_{12} and Fe(III), followed by a rate-limiting dealkylation step. Kinetic study on the Cl^- effect suggests that the active Fe^{3+} species are $FeCl_n^{3-n}$. The comparable dealkylation rates for protonated base-off CH_3–B_{12}, methylaquo(3,5,6-trimethylbenzimidazolyl)cobamide, and protonated base-off C_2H_5–B_{12} suggest that the rate-limiting step is a one-electron transfer from R–B_{12} to $FeCl_n^{3-n}$ to generate a transient R–B_{12}^+ intermediate, which undergoes further reactions to yield the products observed.

Introduction

The mechanisms for the reactions between methylcobalamin and electrophiles have attracted a great deal of attention.[1] These reactions are generally characterized as direct displacements of the cobalt atom by attack at the α-carbon. However, our recent studies on the reactions between CH_3–B_{12} and Pt(II)/Pt(IV) couples,[2] $AuCl_4^-$,[3] or $IrCl_6^{2-}$[4] indicate that an electron-transfer process may be involved in these reactions. An interesting kinetic characteristic of these reactions is that chloride ions in solution greatly enhance the demethylation rates.[2–4]

Anion-assisted electron-transfer reactions are well studied in inorganic systems.[5] We have chosen iron(III) ions for the investigation of electron-transfer reactions of alkylcobalamins and their Cl^- effect because the ligand exchange and redox reactions of Fe^{3+} are well understood.[6] In this report, we present kinetic and mechanistic data of the chloride-assisted dealkylation of methylcobalamin, methylaquo(3,5,6-trimethylbenzimidazolyl)cobamide, and ethylcobalamin by Fe^{3+} in acid solution.

Experimental Section

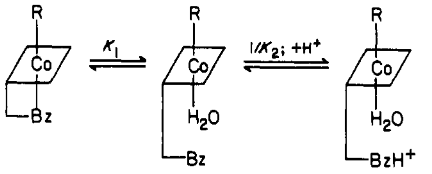
Materials. Methyl- and ethylcobalamin were prepared according to published procedures.[7] Methylaquo(3,5,6-trimethylbenzimidazolyl)cobamide was prepared from its cyano aquo derivative[8] and CH_3I. Nonyellow $Fe(ClO_4)_3$ and other chemicals were reagent grade and were used as received.

Stoichiometry and Reaction Products. Consumption ratio of Fe^{3+}:CH_3–B_{12} was determined by spectrophotometric titration at 520 nm at pH 1 (α band of H_2O–B_{12}^+) with a Cary Model 15 spectrophotometer. A slight excess of CH_3–B_{12} over Fe^{3+} was used in the stoichiometric study. The corrinoid product was identified spectrophotometrically. Methyl-transfer products were examined by a pulse Fourier transform ^{13}C NMR (90% enriched in $^{13}CH_3$–B_{12}) 300-MHz Nicolet spectrometer (4 °C) or a Becker gas chromatograph, Model 417, with a column (8 ft × 2 mm) of 5% FFAP on Chromosorb W-AW-DMCS (80–100 mesh) at 45 °C. It should be noted that only stoichiometric amounts of Fe^{3+} (1.0 M Cl^-, pH 2) were used in the NMR experiments in order to minimize the broadening of NMR signals. The oxidation state of the iron product was examined by a standard iodometric titration. The iron product was separated from the B_{12} product by phenol extraction before the titration.

Kinetic Measurements. Reaction rates were measured by absorbance increase at 520 or 350 nm (α and γ band for H_2O–B_{12}^+) with a Cary Model 14 or 15 spectrophotometer. All reactions were carried out at 23 ± 0.3 °C under a dim light. Ionic strength was maintained at 1.0 M with NaCl and/or $NaClO_4$. The pH was controlled in the range 0–3 with HCl or $HClO_4$. A large excess of Fe^{3+} over alkylcobalamin was used in all rate measurements, so that $[Fe^{3+}]_{tot}$ remained essentially constant. A typical [R–B_{12}] was 1.2×10^{-4} M. At high levels of Cl^- (≥0.25 M), plots of ln $(A_\infty - A_t)$ vs. time gave straight lines for ca. 80% of the reactions. Reproducibility was better than 10%. At $[Cl^-] \leq 0.10$ M, the reactions became progressively slower, with plots of ln $(A_\infty - A_t)$ vs. time being linear for only 50% of the reactions. Thus, we are facing a dilemma: on the one hand, the data could be accurately measured at $[Cl^-] \geq 0.25$ M, but the assumptions that are necessary for a quantitative analysis could not be justifiably made. On the other hand, the data obtained at $[Cl^-] \leq 0.10$ M, which could be quantitatively analyzed, were less accurate. In this report, kinetic data at $[Cl^-] \leq 0.10$ M were estimated from the Ln $(A_\infty - A_t)$ vs. time plots of the initial 50% of the reactions.

Results

The thermodynamic parameters of the alkylcobalamins "base-on" and "base-off" conversion (eq 1) have been estimated



(1)

as follows: $pK_2 = 5.0$ (1.0 M KCl, 25 °C),[9] $pK_1 = 2.0$ and 1.3 (1.0 M NaCl, 23 °C) for CH_3–B_{12} and C_2H_5–B_{12},[10] respectively. Equilibrium is more favorable to the base-off form in perchlorate medium as compared to the chloride medium. Methylaquo(3,5,6-trimethylbenzimidazolyl)cobamide appears only in the base-off form.

Stoichiometry and Reaction Products. The demethylation of CH_3–B_{12} by Fe^{3+} in 1.0 M perchlorate solution proceeded inconveniently slowly, with only a small amount (<5%) of CH_3–B_{12} demethylated in 24 h at room temperature. In the presence of Cl^-, however, demethylation readily occurred, yielding H_2O–B_{12}^+ as the sole corrinoid product. Repetitive

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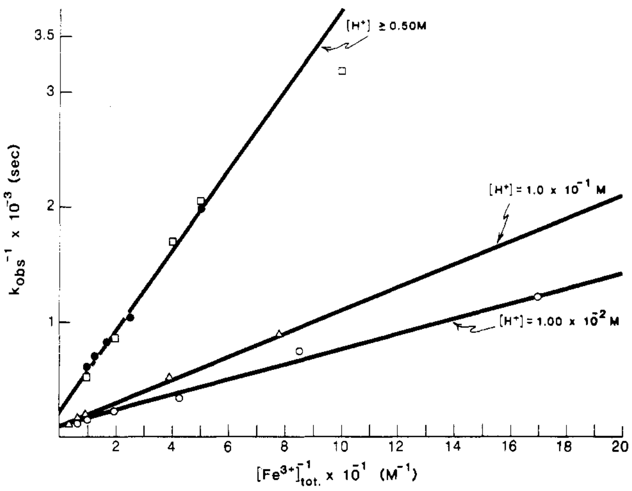

Figure 1. Plots of k_{obsd}^{-1} vs. $[Fe^{3+}]_{tot}^{-1}$ for the reactions of CH_3–B_{12} with Fe^{3+} at various pH values ($[CH_3$–$B_{12}] = 1.2 \times 10^{-4}$ M; $\mu = 1.0$ M (HCl + NaCl); temp = 23 °C): ●, $[H^+] = 1.0$ M; □, $[H^+] = 0.50$ M.

spectral scans of the reaction of CH_3–B_{12} with Fe^{3+} at 1.0 M Cl^- (pH 2) showed isosbestic points at 490 and 370 nm. Spectrophotometric titration showed that the reaction occurs with a 1.8 (±0.10):1.0 stoichiometry (Fe^{3+}:CH_3–B_{12}). The identical result in the electronic spectral change was obtained under a nitrogen atmosphere. However, the failure to observe B_{12r} or B_{12s} intermediate does not rule out its occurrence during the course of reaction (vide infra).

Carbon-13 NMR studies with $^{13}CH_3$–B_{12} showed that the major ^{13}C resonance (~70%) of the methyl-transfer products appears at 28.9 ppm (downfield shift with respect to external TSP), indicating the predominant demethylation product is CH_3Cl. In addition to CH_3Cl, demethylation by stoichiometric amounts of Fe^{3+} in the presence of oxygen (1.0 M NaCl, pH 2) generates minor amounts of methane (2.54 ppm), formaldehyde (77.6 ppm), and unidentified species (33.3 ppm). The production of CH_3Cl was confirmed by GC.

A standard iodometric titration of the reaction solution after the removal of H_2O–B_{12}^+ by phenol extraction demonstrated that Fe^{2+} is the iron product. Therefore, the major reaction of CH_3–B_{12} with Fe^{3+} in the presence of Cl^- can be described by eq 2.

$$CH_3\text{–}B_{12} + 2Fe^{3+} + Cl^- + H_2O \rightarrow H_2O\text{–}B_{12}^+ + CH_3Cl + 2Fe^{2+} \quad (2)$$

Although CN^- also serves as a bridging ligand in some inorganic systems, $Fe(CN)_6^{3-}$ demethylates CH_3–B_{12} extremely slowly even in 1.0 M Cl^- solution (pH 2, 23 °C). The sluggish demethylation of CH_3–B_{12} by $Fe(H_2O)_6^{3+}$ or $Fe(CN)_6^{3-}$ suggests that the Fe^{3+} demethylation requires Cl^- in the inner coordination sphere.

Kinetic Measurements. The dealkylation of CH_3–B_{12} by Fe^{3+} in 1.0 M Cl^- solution is first order in CH_3–B_{12}, in accord with eq 3. The reaction is first order in Fe^{3+} at relatively low

$$-d[CH_3\text{–}B_{12}]/dt = k_{obsd}[CH_3\text{–}B_{12}] \quad (3)$$

levels of Fe^{3+} but approaches zero order as the Fe^{3+} concentration is increased. Plots of k_{obsd}^{-1} vs. $[Fe^{3+}]^{-1}$ for the demethylation of CH_3–B_{12} in the pH range 0–2 are shown in Figure 1. An interpretation for this hyperbolic dependence is that CH_3–B_{12} associates with Fe^{3+} ion prior to the rate-limiting demethylation step (eq 4 and 5).

$$CH_3\text{–}B_{12} + Fe^{III} \xrightleftharpoons{K} CH_3\text{–}B_{12}, Fe^{III} \quad (4)$$

$$CH_3\text{–}B_{12}, Fe^{III} \xrightarrow{k} H_2O\text{–}B_{12}^+, \text{etc.} \quad (5)$$

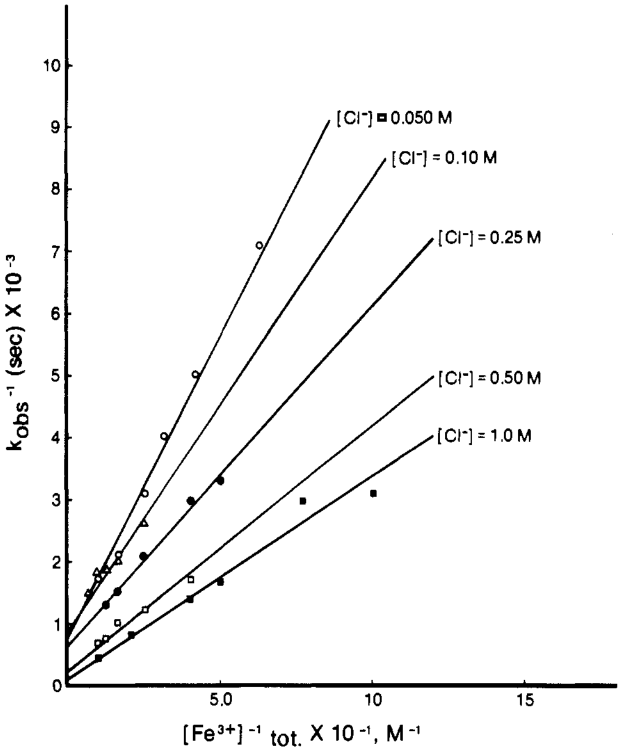

Figure 2. Plots of k_{obsd}^{-1} vs. $[Fe^{3+}]_{tot}^{-1}$ for the reactions of CH_3–B_{12} with Fe^{3+} at various Cl^- concentrations ($[CH_3$–$B_{12}] = 1.2 \times 10^{-4}$ M; $[H^+] = 0.50$ M; $\mu = 1.0$ M (maintained with $NaClO_4$); temp = 23 °C).

Figure 1 also shows that the demethylation rate increases as the H^+ concentration decreases at $0.01 \text{ M} \leq [H^+] \leq 1.0$ M. This $[H^+]$ dependence is obviously due to the protonation of 5,6-dimethylbenzimidazole moiety and its resulted base-on ⇌ base-off conversion (eq 1). The inhibition by H^+ thus indicates the base-on form is more reactive than the base-off form to the demethylation by Fe(III) ion. The intercepts in Figure 1 are nearly identical, indicating the rates for the limiting step are nearly the same for both the base-on and base-off CH_3–B_{12}. Therefore, the difference in reactivities between base-on and base-off forms lies in the difference between the association constants, K. It is not possible, however, to have a meaningful quantitative analysis for the $[H^+]$ dependence with the data in hand because of the complexity of the $[Cl^-]$ effects as described in the following section. At $[H^+] \geq 0.50$ M, the demethylation rates are no longer dependent on the H^+ concentration, indicating that kinetic data obtained at $[H^+] \geq 0.50$ M can be reasonably assigned to the base-off form. Therefore, all the kinetic measurements described below were performed at $[H^+] \geq 0.5$ M in order to simplify the kinetic analysis. It should also be noted that the demethylation rates measured at pH 3 (not shown) are slower than those at pH 2. We fail to identify the exact cause, although an apparent reason is that $Fe(H_2O)_6^{3+}$ is an acid with $pK_a = 3.0$.[11]

Kinetic data for the demethylation of CH_3–B_{12} by Fe^{3+} at various Cl^- concentrations are plotted as k_{obsd}^{-1} vs. $[Fe^{3+}]^{-1}$ in Figure 2. A table listing these kinetic data is available in the supplementary material. Comparison of the demethylation by Fe^{3+} in Cl^- medium with that in ClO_4^- medium, or by $Fe(CN)_6^{3-}$ in both Cl^- and ClO_4^- media, indicates that the active Fe^{3+} species is $Fe(H_2O)_{6-n}Cl_n^{3-n}$ (eq 6 and 7) (this is

$$Fe^{3+} + Cl^- \xrightleftharpoons{K'} FeCl^{2+} \quad (6)$$

$$FeCl^{2+} + Cl^- \xrightleftharpoons{K''} FeCl_2^+ \quad (7)$$

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Table I. Kinetic Parameters for the Demethylation of Base-Off CH_3-B_{12} by Fe^{3+} Ions[a]

$[Cl^-]$, M	10^3a, s^{-1}	10^2b, s^{-1} M^{-1}	$[Cl^-]$, M	10^3a, s^{-1}	10^2b, s^{-1} M^{-1}
0.050	1.7	0.95	0.50	3.3	2.7
0.10	1.3	1.3	1.0	5.0	3.0
0.25	1.4	1.7			

[a] $[H^+] = 0.50$ M; $\mu = 1.0$ M; temp = 23 °C.

defined as primary Cl^- effect so as to distinguish from the secondary Cl^- effect to be addressed later). We have neglected $FeCl_3$ or higher complexes. When eq 6 and 7 are incorporated into eq 4 and 5, eq 8–11 are obtained.

$$CH_3\text{-}B_{12} + FeCl^{2+} \overset{K_3}{\rightleftharpoons} CH_3\text{-}B_{12}, FeCl^{2+} \quad (8)$$

$$CH_3\text{-}B_{12}, FeCl^{2+} \xrightarrow{k_3} H_2O\text{-}B_{12}^+, \text{etc.} \quad (9)$$

$$CH_3\text{-}B_{12} + FeCl_2^+ \overset{K_4}{\rightleftharpoons} CH_3\text{-}B_{12}, FeCl_2^+ \quad (10)$$

$$CH_3\text{-}B_{12}, FeCl_2^+ \xrightarrow{k_4} H_2O\text{-}B_{12}^+, \text{etc.} \quad (11)$$

Rabinowitch and Stockmayer have measured the values of K' and K'' as 4.2 and 1.3 M^{-1} at $\mu = 1.0$ M (26.7 °C) respectively.[12] This K' value has been confirmed by Connick et al.[13a] However, a very precise value of $K' = 2.9 \pm 0.09$ M^{-1} at 1.0 M ClO_4^- and 25 °C was obtained by King et al.[13b] Hence, the value of 2.9 M^{-1} was used throughout this report. The above equations lead to the following rate law at each individual Cl^- concentration:

$$k_{obsd} = [k_3K_3K'[Cl^-] + k_4K_4K'K''[Cl^-]^2[Fe^{3+}]_{tot}] / [1 + K'[Cl^-] + K'K''[Cl^-]^2 + K_3K'[Cl^-][Fe^{3+}]_{tot} + K_4K'K''[Cl^-]^2[Fe^{3+}]_{tot}] \quad (12)$$

Plots of k_{obsd}^{-1} vs. $[Fe^{3+}]_{tot}^{-1}$ at each Cl^- concentration yield

$$\text{intercept} = \frac{1}{a} = \frac{K_3K' + K_4K'K''[Cl^-]}{k_3K_3K' + k_4K_4K'K''[Cl^-]} \quad (13)$$

$$\text{slope} = \frac{1}{b} = \frac{1 + K'[Cl^-] + K'K''[Cl^-]^2}{k_3K_3K'[Cl^-] + k_4K_4K'K''[Cl^-]^2} \quad (14)$$

Values of a (in s^{-1}) and b (in s^{-1} M^{-1}) in a $[Cl^-]$ range 0.050–1.0 M are listed in Table I.

In the studies of oxidative demethylation of CH_3-B_{12} by $IrCl_6^{2-}$ or $AuCl_4^-$,[3,4] it was found that the chloride ions in solution significantly enhance the demethylation rates. The $[Cl^-]$ is also expected to have a significant secondary effect on the demethylation by Fe^{3+}; i.e., the magnitudes of K_3, K_4, k_3, and k_4 are all expected to increase as Cl^- concentration is increased. If it is assumed that $FeCl_2^+$ and higher complexes can be neglected at $[Cl^-] \leq 0.25$ M, then eq 13 and 14 can be simplified to eq 15 and 16. Thus, we estimate $k_3 = (1.4$

$$a = k_3 \quad (15)$$

$$b = \frac{k_3K_3K'[Cl^-]}{1 + K'[Cl^-]} \quad (16)$$

$\pm\ 0.3) \times 10^{-3}$ s^{-1} and $K_3 = 35 \pm 10$ M^{-1} (23 °C, $\mu = 1.0$ M). The secondary $[Cl^-]$ effect is not significant at this level of Cl^-. However, at $[Cl^-] \geq 0.50$ M, the $[Cl^-]$ effect on the magnitudes of k_3 and K_3 cannot be ignored, as manifested by the observation that the a values increase significantly at $[Cl^-] \geq 0.50$ M. This secondary effect, together with the complication arising from the fact that $FeCl_2^+$ species can no longer be neglected, make a quantitative analysis of the kinetic data obtained at $[Cl^-] \geq 0.50$ M extremely difficult.

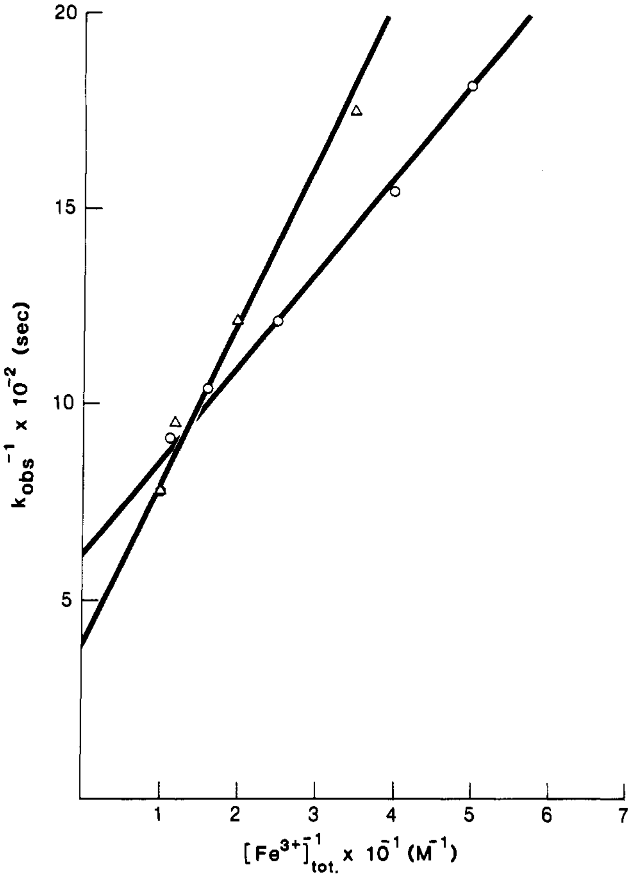

Figure 3. Plots of k_{obsd}^{-1} vs. $[Fe^{3+}]_{tot}^{-1}$ for the reactions of Fe^{3+} with ethylcobalamin and methylaquo(3,5,6-trimethylbenzimidazolyl)cobamide ($[R\text{-}B_{12}] = 1.2 \times 10^{-4}$ M; $[H^+] = 0.50$ M; $\mu = 1.0$ M (HCl + NaCl); temp = 23 °C): ○, C_2H_5-B_{12}; △, methylaquo(3,5,6-trimethylbenzimidazolyl)cobamide.

Kinetic data for the dealkylation of ethylcobalamin and methylaquo(3,5,6-trimethylbenzimidazolyl)cobamide by Fe^{3+} (1.0 M Cl^-) are shown in Figure 3. These reactions were carried out at $[H^+] = 0.50$ M, so that only the base-off species need to be considered. Note that the 5,6-dimethylbenzimidazole moiety is less tightly coordinated to cobalt in C_2H_5-B_{12} than that in CH_3-B_{12}. Kinetic analysis yields $a = 2 \times 10^{-3}$ s^{-1} and $b = 4 \times 10^{-2}$ s^{-1} M^{-1} for C_2H_5-B_{12} and $a = 3 \times 10^{-3}$ s^{-1} and $b = 6 \times 10^{-2}$ s^{-1} M^{-1} for methylaqua(3,5,6-trimethylbenzimidazolyl)cobamide (23 °C, 1.0 M Cl^-).

Discussion

The extremely slow demethylation of CH_3-B_{12} by $Fe(H_2O)_6^{3+}$ (i.e., reaction performed in perchlorate solution) or $Fe(CN)_6^{3-}$, in contrast to the reactions with $FeCl_n^{3-n}$, indicates that the chloride ligands are required to mediate the reaction between the Fe(III) center and CH_3-B_{12}. A noteworthy point in the kinetic study is the hyperbolic dependence of demethylation rate upon the iron(III) concentration. As suggested for the oxidative demethylation by $AuCl_4^-$,[3] this nonlinear dependence is taken as an indication that a preassociation of the reactants (K_3 or K_4) occurs prior to the rate-limiting dealkylation step (k_3 or k_4). However, as we have pointed out,[14] the preassociation, as well as the chemical characterization of this precomplex, must remain tentative until more direct methods than kinetics are used.

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Two mechanisms could account for the cleavage of the Co–C bond by $FeCl_n^{3-n}$. The first is a direct electrophilic attack at the α-carbon of alkylcobalamins to generate a $(CH_3)Fe^{III}$ or $-Fe^{I}$ intermediate, which then undergoes further reactions to yield the products observed. This mechanism is similar to that of the reactions of organopentaaquachromium(III) ions with I_2, Br_2,[15] or Hg^{2+} [16] and the reactions between alkylcobaloximes with Hg^{2+}.[17,18] The reactions between methylcobalamin and Hg^{2+} [19] or $PdCl_4^{2-}$ [20] were also interpreted in terms of this mechanism. However, the comparable dealkylation rates by $FeCl_n^{3-n}$ for base-off CH_3–B_{12} and C_2H_5–B_{12} are not consistent with this mechanism. The alternative mechanism, which appears to be more consistent with the kinetic data shown in Figure 3, involves a one-electron transfer from R–B_{12} to $FeCl_n^{3-n}$, as depicted in Scheme I.

Scheme I

$$R\text{–}B_{12} + FeCl_n^{3-n} \overset{k_{et}}{\rightleftharpoons} R\text{–}B_{12}^{+} + Fe^{2+} + nCl^-$$

$$R\text{–}B_{12}^{+} + FeCl_n^{3-n} \xrightarrow{H_2O} H_2O\text{–}B_{12}^{+} + Fe^{2+} + RCl + (n-1)Cl^-$$

The chemical and electrochemical one-electron oxidations of organocobaloximes or other B_{12} model compounds have been thoroughly investigated by Halpern et al.[21] In a recent paper,[22] Tamblyn et al. described an important oxidative demethylation of dimethylcobalt(III) macrocycles in which the homolytic scission of one of the Co–C bonds of the cation radicals was shown. These studies demonstrate that alkylcobalt compounds are effective one-electron donors. We have prviously shown that methylcobalamin can undergo one-electron oxidation with oxidants such as $IrCl_6^{2-}$ [4] or $AuCl_4^-$,[3] thus providing a precedence for the electron transfer between CH_3–B_{12} and $FeCl_n^{3-n}$.

Two modes could explain the fate of the CH_3–B_{12}^+ cation radical resulting from the electron-transfer reaction. The first one is delineated in Scheme II, which involves a nucleophilic attack at the α-carbon by Cl^-. This mode is similar to the nucleophilic displacement reactions of the cation radicals derived from alkylcobaloximes.[23]

Scheme II

$$CH_3\text{–}B_{12}^{+} \xrightarrow{Cl^-} CH_3Cl + B_{12r}$$

$$B_{12r} + FeCl_n^{3-n} \xrightarrow{H_2O} H_2O\text{–}B_{12}^{+} + Fe^{2+} + nCl^-$$

The second mode is described in Scheme III. In a previous paper,[4] we have presented evidence that the transient CH_3–B_{12}^+, generated by the reaction with $IrCl_6^{2-}$, undergoes a homolytic scission with a second molecule of $IrCl_6^{2-}$ to yield CH_3Cl and $IrCl_5(H_2O)^{2-}$.[24] Scheme III is similar to this mechanism. This suggestion seems to be feasible in light of the recent report on the formation of alkyl chloride from the reduction of chloroiron(III) by an alkyl radical.[25] Scheme III is also supported by the ^{13}C NMR study that methane and formaldehyde were formed when $^{13}CH_3$–B_{12} was demethylated by $FeCl_n^{3-n}$ in the presence of oxygen. However, it is important to note that our present data do not allow us to clearly distinguish these two modes.

Scheme III

$$CH_3\text{–}B_{12}^{+} \xrightarrow{H_2O} H_2O\text{–}B_{12}^{+} + CH_3\cdot$$

$$CH_3\cdot + FeCl_n^{3-n} \rightarrow CH_3Cl + Fe^{2+} + (n-1)Cl^-$$

In conclusion, the present report demonstrates the electron transfer from CH_3–B_{12} to the Fe(III) center, culminating in the cleavage of a Co–C bond. This electron transfer, however, requires chloride ligand in the inner coordination sphere of the Fe(III) ion.

Acknowledgment. I thank Dr. Harry P. C. Hogenkamp for kindly supplying all of the corrinoids used in this study. This research was carried out in his laboratory.

Registry No. Cl^-, 16887-00-6; Fe^{3+}, 20074-52-6; methylcobalamine, 13422-55-4; methylaquo(3,5,6-trimethylbenzimidazolyl)cobamide, 61829-19-4; ethylcobalamine, 13422-56-5.

Supplementary Material Available: Table listing kinetic data for the demethylation of CH_3–B_{12} by Fe^{3+} (1 page). Ordering information is given on any current masthead page.

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