matographed on Florisil. Elution with petroleum ether yielded two fractions. Evaporation of solvent left two yellow oils identified on the basis of spectroscopic properties as **3b** and (MeCpTMS)Fe(CO)$_2$Et. Careful mass spectral analysis of these materials showed no measurable quantities of the possible intermolecular products (Scheme IV), one of which (**2b**) had been previously analyzed by mass spectroscopy. Similar results were obtained when the experiment was repeated with 2.5 mmol of each starting material in 20 mL of THF.

A solution of (Me$_3$SiCp)Fe(CO)$_2$DMPS and **7** (2 mmol) in 20 mL of THF were treated as described in the previous paragraph. A single product was isolated after workup and chromatography, and it was identified as **11** on the basis of spectroscopic data. Mass spectral analysis gave no indication of intermolecular products (Scheme IV). The experiment was repeated by using 1 mmol of each starting material in 100 mL of THF, and a single product identified as **11** was obtained.

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Registry No. **1a**, 31811-63-9; **1b**, 41680-29-9; **1c**, 97279-47-5; **2a**, 80611-30-9; **2d**, 97279-55-5; **2e**, 97279-72-6; **2g**, 97279-74-8; **3a**, 97279-56-6; **3b**, 97279-57-7; **4a**, 97279-58-8; **4b**, 97279-59-9; **5a**, 12570-83-1; **5b**, 97279-48-6; **6a**, 97279-61-3; **6b**, 97279-63-5; **7**, 97279-64-6; **8**, 74102-43-5; **9** (1,2-isomer), 97279-50-0; **9** (1,3-isomer), 97279-54-4; **10**, 97279-66-8; **11**, 97279-67-9; **12**, 97279-77-1; **14a**, 97279-69-1; **14b**, 97279-71-5; **15**, 12080-06-7; TMSCp, 25134-15-0; DMPSCp, 64743-26-6; CpFe(CO)$_2$Na, 12152-20-4; Fe(CO)$_5$, 13463-40-6; (TMSCp)Fe(CO)$_2$Na, 97279-73-7; (DMPSCp)Fe(CO)$_2$Na, 97279-75-9; (MeCp)Fe(CO)$_2$Na, 97279-76-0; (1,2-MeCpTMS)Fe(CO)$_2$Et, 97279-52-2; (1,3-MeCpTMS)Fe(CO)$_2$Et, 97279-51-1; (1,3-(TMS)$_2$Cp)Fe(CO)$_2$Et, 97293-80-6; (TMSCp)Fe(CO)$_2$DMPS, 97279-78-2; (TMSCp)$_2$Fe, 12189-86-5; (MeCp)$_2$Fe, 1291-47-0; ClSiMe$_3$, 75-77-4; EtBr, 74-96-4; ClSiMe$_2$Ph, 768-33-2; chlorodimethylpropylsilane, 17477-29-1; benzyl chloride, 100-44-7; allyl chloride, 107-05-1; 3-chloro-2-methylpropene, 563-47-3; trityl fluoroborate, 341-02-6.

Halide-Assisted Dealkylation of Alkylcobalamins by Iodine. Kinetics and Mechanism

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The reactions of iodine with methylcobalamin and ethylcobalamin in aqueous solution have been examined. Stoichiometry and product analyses show the iodine cleavage of Co–C bond of CH_3-B_{12} proceeds via the reaction CH_3-B_{12} + I_2 + X^- + H_2O → H_2O-B_{12}^+ + CH_3X + $2I^-$. Thus the demethylation of CH_3-B_{12} by I_2 performed in the presence of Cl^- (1.0 M) produces CH_3Cl instead of CH_3I. This stoichiometry, coupled with the kinetic data, strongly supports a mechanism involving an electron transfer from R-B_{12} to I_2 to generate R-B_{12}^+ cation radical. The transient radical undergoes a nucleophilically induced heterolytic cleavage to yield B_{12r} and RX. In methanol solution, the absorption spectrum of a stable charge-transfer complex is observed immediately upon mixing iodine and CH_3-B_{12}. Detailed mechanism for the iodine cleavage of Co–C bonds is discussed.

Introduction

Methylcobalamin (CH_3-B_{12}) is involved in several biological processes, including the methionine synthesis,[1] the formation of methane,[2] the synthesis of acetate from carbon dioxide,[3] and the biomethylation of heavy metals such as mercury[4] and arsenic.[5] In the enzymatic reactions the corrinoid cofactor serves alternately as an acceptor and as a donor for the methyl group. Thus an essential feature in our understanding of the methylcobalamin-dependent biochemical reactions is the formation and cleavage of the cobalt–carbon bond. The Co–C cleavage by an electrophile such as Hg(II), which generally leads to the methylation of the attacking electrophile, has long been considered as a direct displacement of the cobalt atom by attack at the α-carbon.[6] Our recent work on the alkylcobalamin alkylation of Pt(II)/Pt(IV) couples,[7] diaquocobinamide,[8] tetracyanoethylene,[9] and a reinvestigation of Hg(II)[10,11] have, however, raised the question of an alternative route, i.e., the single-electron-transfer (SET) methyl-transfer mechanism. In these studies, the kinetic data were found to be more consistent with the electron-transfer mechanism than with the direct mechanism.[7-10] The kinetic studies however, are not conclusive for the distinguishableness between these two mechanisms. Furthermore, the kinetic and mechanistic data of the methylation of electrophiles are often complicated by the rapid interaction of the electrophile with 5,6-dimethylbenzimidazole base of the alkylcobalamin. Therefore it is important to investigate the alkyl-transfer reactions between alkylcobalamins and

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simple electrophiles which could be free from this complication and provide nonkinetic evidence for the SET mechanism. Iodine appears to be suitable for this purpose.

The charge-transfer and oxidation–reduction properties of iodine, of course, are well understood.[12] Extensive studies on the reactions between halogen and alkylcobaloximes or other B_{12} model compounds have been carried out[13] since the initial discovery that $CH_3Co(CN)_5^{3-}$ reacted with I_2 to form CH_3I,[14] and the observation that halogen cleavage proceeded with inversion of configuration at the α-carbon of saturated alkyl groups of alkylcobaloximes.[15] However, no clear-cut conclusions regarding the reaction mechanisms have been drawn. In contrast to the model compounds, the reactions between alkylcobalamins and halogen have received very little attention except for the brief statements by Bernhauer and Irion[16] and by Hill et al.[17] that the reaction between CH_3-B_{12} and I_2 proceeded slowly in aqueous methanol solution.

In this report, we present kinetic and mechanistic data for the dealkylation of methyl and ethylcobalamin by iodine. Our study provides nonkinetic as well as kinetic results which indicate that the iodine cleavage of alkylcobalamins proceeds by a one-electron-transfer mechanism.

Experimental Section

Materials. All the alkylcorrinoids used in this report were generous gifts from Hogenkamp.[18] Their concentrations in aqueous solutions were determined by the absorption spectra.[19] The aqueous iodine solutions were prepared by dissolving iodine into KI solutions.[20] Typically, 6.42 g of iodine was dissolved in 15 mL of KI solution (12.35 g), which was then diluted to a desired concentration. Methanol solutions of iodine were prepared by direct dissolution of iodine into methanol. The $[I_2]_{tot}$ was determined by a titration with thiosulfate, which was prestandardized by KIO_3. It should be noted that the use of commercial NaI must be avoided. All other chemicals were reagent grade and were used as received except for $NaClO_4$, which was recrystallized from aqueous solution before use.

Stoichiometry and Reaction Products. Consumption ratio of I_2:CH_3-B_{12} was determined by spectrophotometric titration at 350 nm (with CH_3-B_{12} in excess over I_2) and by thiosulfate titration (with I_2 in excess over CH_3-B_{12}). The corrinoid products were identified spectrophotometrically with a Beckman spectrophotometer UV 5260. The alkyl-transfer products from various media were examined with a Shimadzu GC-Mini 2 gas chromatograph with a 6-ft copper column packed with 10% (by weight) apiezon L. liquid phase. The column temperature was set at 45 °C. The reaction mixtures were incubated under a dim light and sealed with serum caps. After an appropriate period of time, 3 μL of the reaction mixture of a 1.0 M perchlorate solution were injected to the GC with a hyperdermic syringe at 90 °C. For the reaction mixture of a 1.0 M NaCl solution, 5 μL of solution and 5 μL of gas from the immediate space above the solution were injected to the GC. Methyl-transfer products were identified by comparison with authentic samples of CH_3I and CH_3Cl. It should be emphasized that in the GC experiments in Cl^- solution, the ratio of $[I^-]$:$[Cl^-]$ was kept at the minimum (1:100). A control experiment with an authentic sample of CH_3I in 1.0 NaCl solution has also been carried out.

Kinetic Measurements. Dealkylation rates for the reactions of iodine with CH_3-B_{12} and C_2H_5-B_{12} in acetate buffer solutions (pH >5) were measured by absorbance decrease at 415 and 430 nm, respectively. Demethylation rates for CH_3-B_{12} at pH ≤3 were monitored at 525 nm (α-band of H_2O-B_{12}^+) with a Cary Model 14 spectrophotometer. These wavelengths provided the most convenient absorbance changes during the course of reactions. It should be noted that 350 nm (γ-band of H_2O-B_{12}^+) could not be used to monitor the reaction because I_3^- has an absorbance maximum at 353 nm. All reactions were carried out at 25 ± 0.3 °C with a circulating water jacket. The reaction components were mixed under a dim light. Iodine solutions were never allowed to come in contact with the hyperdermic syringe needles. Ionic strength was maintained at 1.0 M with $NaClO_4$ or NaCl unless otherwise mentioned. The pH was controlled in the range 2.3–6 with $HClO_4$ or acetate buffer. At least fivefold excess of iodine over alkylcobalamin and at least fivefold excess of KI over iodine were used in all rate measurements so that both $[I_2]$ and $[I^-]$ can be considered as constant. The alkylcobalamin concentrations were in a range (3–10) × 10^{-6} M. For the reactions performed in the presence of chloride ions (0.050–1.0 M), the $[Cl^-]$ was in at least 33-fold excess over $[I^-]$. In acetate buffer solution, plots of ln $(A_\infty - A_t)$ vs. time gave straight lines for 3–4 half-lives. At pH <3, the plots were linear for ca. 3 half-lives. Reproducibility was better than 7%.

Dissociation constants of I_3^- and I_2Cl^-, the 5,6-dimethylbenzimidazole "base-on" ⇌ "base-off" equilibrium constant of CH_3-B_{12} at 1.0 M perchlorate (25 °C), and the charge-transfer complex formation between iodine and CH_3-B_{12} in methanol solution were measured spectrophotometrically with a Beckman UV 5260.

Results

Initial Observations. Methylcobalamin (1.5 × 10^{-5} M) was quantitatively demethylated by iodine in 1.0 M $NaClO_4$ solution ($[I_2]_{tot}$ = 10^{-4} M, with 3.0 × 10^{-4} M I^- present in the mixture, pH 4.7). This reaction produced H_2O-B_{12}^+ as the sole corrinoid product with a half-life of ca. 3 min (25 °C). Isosbestic point appeared at 366 nm. Methylcobalamin was also readily demethylated to H_2O-B_{12}^+ by iodine in 1.0 M NaCl solution under otherwise identical conditions. The half-life for the demethylation in 1.0 M NaCl was ca. 15 min. The demethylation by iodine occurred inconveniently slowly in 1.0 M KI solution. These observations demonstrated that I_2 in aqueous solution, and not I_3^- or I_2Cl^-, is the active dealkylating agent. The exclusion of oxygen from the reaction mixtures did not affect the nature of corrinoid products, and no B_{12r} (cob(II)alamin) or B_{12s} (cob(I)alamin) was accumulated in significant amounts during the reaction courses.

Mixing an aqueous iodine solution with CH_3-B_{12} (or C_2H_5-B_{12}) solution at pH 4.7 did not result in a spectrum indicative of base-off form of alkylcobalamin. Thus, unlike those reactions with Hg(II)[10,11] or $PdCl_4^{2-}$,[21] an aqueous iodine solution could be controlled under conditions which would conveniently dealkylate alkylcobalamin but do not attack the 5,6-dimethylbenzimidazole side chain. This allows an unambiguous kinetic analysis for the iodine dealkylation of CH_3-B_{12} and C_2H_5-B_{12}.

Addition of 10^{-4} M iodine to a 1:1 CH_3OH/H_2O mixture containing 3.5 × 10^{-5} M CH_3-B_{12}, 3.0 × 10^{-4} M KI, and 1.0 M $NaClO_4$ resulted in a rapid base-on to base-off conversion, as manifested by the shift of α-band of CH_3-B_{12} from 520 to 455 nm. This interconversion was completed on mixing. The base-off CH_3-B_{12} was then very slowly

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demethylated to H_2O-B_{12}^+, as shown by the increase of absorbance at 350 nm as a function of time. The dramatic increase of activity of iodine toward the benzimidazole nucleotide base in CH_3OH/H_2O solution is similar to the interaction between CH_3-B_{12} and TCNE,[9] in which both the formation of a charge-transfer complex with the corrin ring and the attachment of a second TCNE molecule to the base are demonstrated. It is also of interest to note that Ce(IV), an oxidizing agent for alkylcobaloximes (13a), is capable of attacking the nucleotide base of CH_3-B_{12} to form the base-off methylcorrinoid.[22]

Stoichiometry and Methyl-Transfer Products. Spectrophotometric titrations at 350 nm of solutions with CH_3-B_{12} in excess over iodine show that the consumption ratio of I_2:CH_3-B_{12} is (0.91 ± 0.070):1.0. The thiosulfate titrations of solutions with iodine in excess over CH_3-B_{12} show the consumption ratio of I_2:CH_3-B_{12} is (1.3 ± 0.10):1.0. The slightly excessive amounts of iodine consumed under this condition are most likely due to the interaction of iodine with corrin ring or nucleotide side chain after a long period of incubation. Pratt has noted that a slight modification on the corrin side chains would not cause a significant change in the electronic spectra.[23]

Demethylation of CH_3-B_{12} (3.0×10^{-3} M) by I_2 in 1.0 M perchlorate solution (in the presence of 1.1×10^{-2} M KI) produces CH_3I. When the demethylation was performed in 1.0 M NaCl (also in the presence of 1.1×10^{-2} M KI), the only demethylation product detected by GC is CH_3Cl. It should be noted that we were able to detect the authentic CH_3I at 0.5 mM level. Thus, the reactions of iodine with CH_3-B_{12} in aqueous solutions can be described by reactions 1 and 2.

$$CH_3\text{-}B_{12} + I_2 + H_2O \rightarrow H_2O\text{-}B_{12}^+ + CH_3I + I^- \quad (1)$$

in the presence of I^- alone

$$CH_3\text{-}B_{12} + I_2 + Cl^- + H_2O \rightarrow H_2O\text{-}B_{12}^+ + CH_3Cl + 2I^- \quad (2)$$

in the presence of both Cl^- and I^- ($[Cl^-] = 91\ [I^-]$)

The reactions of iodine with C_2H_5-B_{12} in the presence of 0.011 M KI and $[Cl^-] \leq 0.10$ M produce only C_2H_5I. In the presence of 1.0 M NaCl and 0.011 M KI, however, about two-thirds of the dealkylation products are C_2H_5I and one third is C_2H_5Cl.

Kinetic Measurements

All the kinetic data are tabulated and are available in the supplementary form.

The dissociation constant for I_3^- (reaction 3) has been estimated as $K' = 1.4 \times 10^{-3}$ M at low ionic strength (25 °C).[24] Awtrey and Connick have measured the molar absorptivities of I_3^-, I_2Cl^-, and I_2 as 26 400, 550, and 1.8 M^{-1} cm^{-1} at 353 nm,[25] respectively. Accordingly, we have estimated the dissociation constants for reactions 3 and 4

$$I_3^- \underset{}{\overset{K'}{\rightleftharpoons}} I_2 + I^- \quad (3)$$

$$I_2Cl^- \underset{}{\overset{K''}{\rightleftharpoons}} I_2 + Cl^- \quad (4)$$

to be $K' = (1.6 \pm 0.15) \times 10^{-3}$ M and $K'' = 0.56 \pm 0.040$ M at 1.0 M ionic strength (25 °C). The proton concentration in the range 10^{-6} to 5.0×10^{-3} M does not have a significant effect on the dissociation constants.

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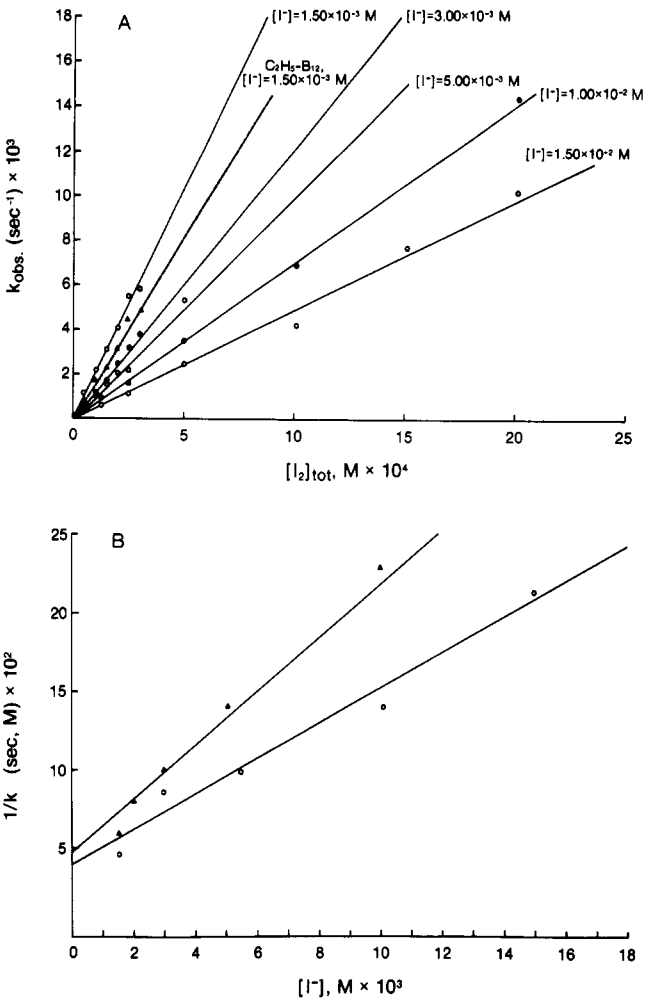


Figure 1. (a) Kinetic data for the dealkylation of alkylcobalamins by iodine at various I^- concentrations (1.0 M $NaClO_4$, pH 5.4): CH_3-B_{12}, ○; C_2H_5-B_{12}, △. (b) Plots of $[I_2]_{tot}/k_{obsd}$ vs. $[I^-]$ for the dealkylation of alkylcobalamins by iodine in 1.0 M $NaClO_4$: CH_3-B_{12}, ○; C_2H_5-B_{12}, △.

The demethylation of CH_3-B_{12} by iodine is first order in both CH_3-B_{12} and iodine in accord with eq 5.

$$\frac{d[H_2O\text{-}B_{12}^+]}{dt} = k_{obsd}[CH_3\text{-}B_{12}] = k[I_2]_{tot}[CH_3\text{-}B_{12}] \quad (5)$$

The values of k are dependent on $[I^-]$. Plots of k_{obsd} vs. $[I_2]_{tot}$ at various $[I^-]$ in 1.0 M perchlorate solutions are shown in Figure 1a. Plots of $1/k$ vs. $[I^-]$ are shown in Figure 1b. The data shown in Figure 1 can be described by the empirical rate law

$$\frac{d[H_2O\text{-}B_{12}^+]}{dt} = \frac{aK'[I_2]_{tot}[CH_3\text{-}B_{12}]}{K' + [I^-]} \quad (6)$$

$$k = \frac{aK'}{K' + [I^-]} \quad (7)$$

The constants a and K' were determined by computer nonlinear least-squares fit: $a = 26 \pm 2.6$ M^{-1} s^{-1} and $K' = (3.4 \pm 0.46) \times 10^{-3}$ M. It is instructive to note at this point that plots of $K'[I_2]_{tot}/k_{obsd}(K' + [I^-])$ vs. $[I^-]^{-1}$ yield a straight line with a zero slop. Here K' value was obtained from spectrophotometric measurements of eq 3. This indicates that the sole effect of $[I^-]$ on the reaction rates is to suppress the dissociation of I_3^-.

The kinetic data for the dealkylation of C_2H_5-B_{12} by iodine in perchlorate media (Figure 1, in Δ) can also be described by eq 6 and 7, with $a = 31 \pm 2.7$ M^{-1} s^{-1} and $K' = (1.6 \pm 0.19) \times 10^{-3}$ M. The values of K' obtained from

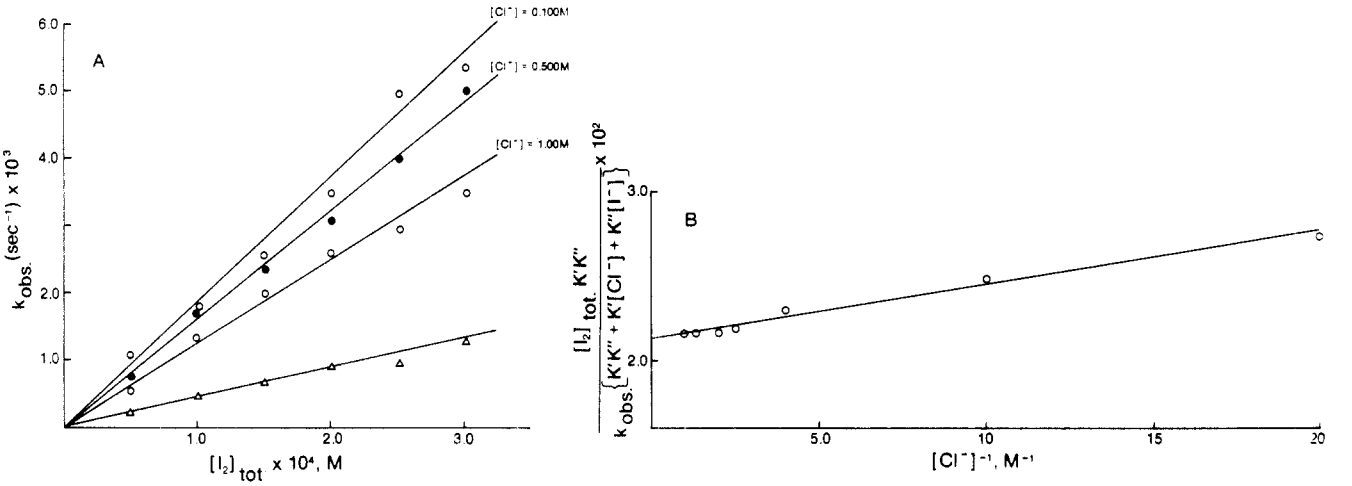


Figure 2. (a) Kinetic data for the dealkylation of alkylcobalamins by iodine at various Cl^- concentration ($[I^-] = 1.50 \times 10^{-3}$ M; μ = 1.0 M (maintained with $NaClO_4$), pH 5.4): CH_3-B_{12}, ○; C_2H_5-B_{12}, △ (only partial data are shown). (b) Plots of $K'K''[I_2]_{tot}/k_{obsd}\{K'K'' + K'[Cl^-] + K''[I^-]\}$ vs. $[Cl^-]^{-1}$ for the demethylation of CH_3-B_{12} by iodine.

the kinetic measurements of CH_3-B_{12} and C_2H_5-B_{12} can be considered as in fair agreement with that obtained from spectrophotometric titration of reaction 3.

In the presence of Cl^-, reaction 4 as well as reaction 3 has to be taken into consideration. Plots of k_{obsd} vs. $[I_2]_{tot}$ for the demethylation of CH_3-B_{12} at various $[Cl^-]$ are shown in Figure 2a. It should be noted that the values of k increase as the $[Cl^-]$ decreases from 1.0 M, reach the maximum at 0.10 M, and then decrease as the $[Cl^-]$ decreases to 0.050 M. This observation demonstrates that there are two $[Cl^-]$ effects operating in opposite directions. One of the $[Cl^-]$ effects obviously is to suppress the dissociation of I_2Cl^- (reaction 4). Under this condition, kinetic data alone are not sufficient to allow the estimation of K' and K''. With the values of K' and K'' obtained from spectrophotometric titrations, we plotted $K'K''[I_2]_{tot}/k_{obsd}\{K'K'' + K'[Cl^-] + K''[I^-]\}$ vs. $[Cl^-]^{-1}$ (Figure 2b). The data shown in Figure 2 can be described by the empirical rate law

$$k_{obsd} = \frac{a'K'K''[Cl^-][I_2]_{tot}}{\{b'[I^-] + [Cl^-]\}\{K'K'' + K'[Cl^-] + K''[I^-]\}} \quad (8)$$

A nonlinear least-squares fit of the data of Figure 2 gives $a' = 47 \pm 1.2$ M^{-1} s^{-1} and $b' = 10 \pm 1.9$ for the iodine demethylation of CH_3-B_{12} in media containing both Cl^- and I^-. It should be emphasized that in solutions containing both iodide and chloride ions, the $[Cl^-]$ was always in large excess over $[I^-]$ ($[Cl^-] \geq 33[I^-]$).

Kinetic data for the dealkylation of C_2H_5-B_{12} by iodine in 1.0 M NaCl solution are plotted in Figure 2a (in Δ). The dealkylation rates are first order in C_2H_5-B_{12} and first-order in $[I_2]_{tot}$ in accord with eq 5. Plots of $[I_2]_{tot}/k_{obsd}$ vs. $[Cl^-]$ are shown in Figure 3. Unlike the demethylation of CH_3-B_{12} in Cl^- media ($[Cl^-] = 0.050$–1.0 M), the second-order rate constants for C_2H_5-B_{12} are not described by eq 8. This is because in the dealkylation of C_2H_5-B_{12}, the $[Cl^-]$ (in the range 0.10–1.0 M) is not able to compete with $[I^-]$ (0.0015 M) for the reaction with the transient intermediate (see Discussion). This is demonstrated by the product analysis which shows the predominant dealkylation product is C_2H_5I. Therefore, the only significant effect inserted by $[Cl^-]$ in the dealkylation of C_2H_5-B_{12} is reaction 4, and the $[Cl^-]$ dependence can be adequately expressed by eq 9 with $K' = 0.0016$ M; a least-squares fit of data

$$k_{obsd} = \frac{a''K'K''[I_2]_{tot}}{K'K'' + K'[Cl^-] + K''[I^-]} \quad (9)$$

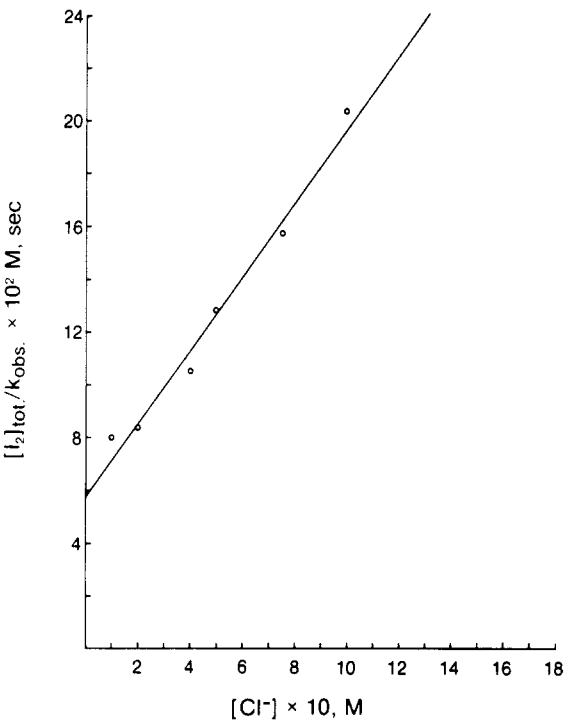
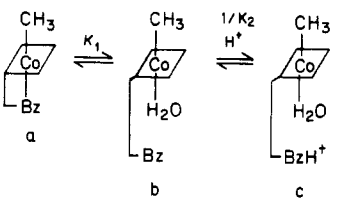


Figure 3. Plots of $[I_2]_{tot}/k_{obsd}$ vs. $[Cl^-]$ for the dealkylation of C_2H_5-B_{12} by iodine at pH 5.4.

shown in Figure 3 gives $a'' = 46 \pm 13$ M^{-1} s^{-1} and $K'' = 0.12 \pm 0.094$ M. With values of K' and K'' obtained from spectrophotometric titrations of eq 3 and 4, plots of $[I_2]_{tot}K'K''/k_{obsd}\{K'K'' + K'[Cl^-] + K''[I^-]\}$ vs. $[Cl^-]^{-1}$ yield a straight line with a zero slope. This indicates that the sole $[Cl^-]$ effect in the dealkylation of C_2H_5-B_{12} is to suppress the dissociation of I_2Cl^- (reaction 4).

The kinetic data for the demethylation of CH_3-B_{12} by iodine as a function of $[H^+]$ are plotted in Figure 4. These data can be interpreted in terms of the protonation of 5,6-dimethylbenzimidazole moiety and its resulting base-on to base-off conversion (eq 10). The pK_2 value has been



(10)

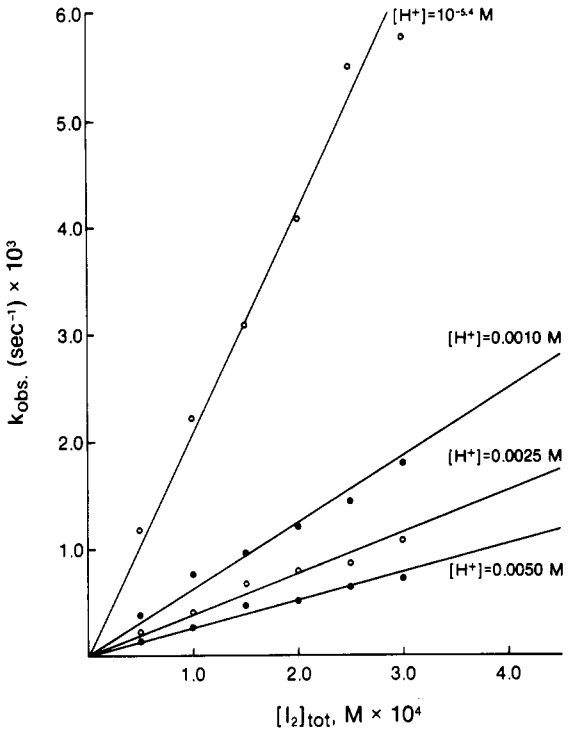


Figure 4. Kinetic data for demethylation of CH_3-B_{12} by iodine as a function of $[H^+]$.

determined by Reenstra and Jencks as 5.0 (25 °C, 1.0 M KCl).[26] On the basis of a previously derived equation,[7c] we have estimated the pK_1 value as 1.6 (25 °C, 1.0 M $NaClO_4$). It should be noted that the common anions (such as Cl^- or ClO_4^-) have a profound effect on the pK_1 values.[22] Incorporating eq 10 into rate law 5, one obtains the rate law

$$k = \frac{k'_a\left(\frac{K'}{K' + [I^-]}\right)K_2 + k'_c\left(\frac{K'}{K' + [I^-]}\right)K_1[H^+]}{K_2 + K_1[H^+]} \quad (11)$$

Here k'_a represents the base-on path, and k'_c represents the protonated base-off path. We have neglected the unprotonated base-off since its concentration is always extremely small. Analyzing Figure 4 according to eq 11 gives $k'_a = 41 \pm 1.8\ M^{-1}\ s^{-1}$ and $k'_c = 2.6 \pm 0.26\ M^{-1}\ s^{-1}$. The base-on route is faster than the base-off route by merely a factor of 16.

Sodium perchlorate has a marginal effect on the dealkylation rates. For example, demethylation of CH_3-B_{12} by I_2 in 1.0 M $NaClO_4$ (0.0015 M KI, pH 5.4, 25 °C) proceeds with $k_{obsd}/[I_2]_{tot} = 20\ M\ s^{-1}$. Reaction performed under otherwise identical conditions but without $NaClO_4$ proceeds with $k_{obsd}/[I_2]_{tot} = 16\ M^{-1}\ s^{-1}$.

Spectroscopic Studies on the Charge-Transfer Complex of CH_3-B_{12} and Iodine. When a solution of CH_3-B_{12} in methanol is mixed with a methanol iodine solution, a new absorption spectrum with a prominent shoulder at 350 nm is immediately observed in the visible–ultraviolet region (Figure 5). In this experiment, an identical concentration of iodine in methanol was used in the reference cell to eliminate the absorption spectrum of iodine, which has an absorption band at 444 nm (822 M^{-1} cm^{-1}). Plots of $(\Delta A)^{-1}$ at 350 nm vs. $[I_2]^{-1}$ are shown in the

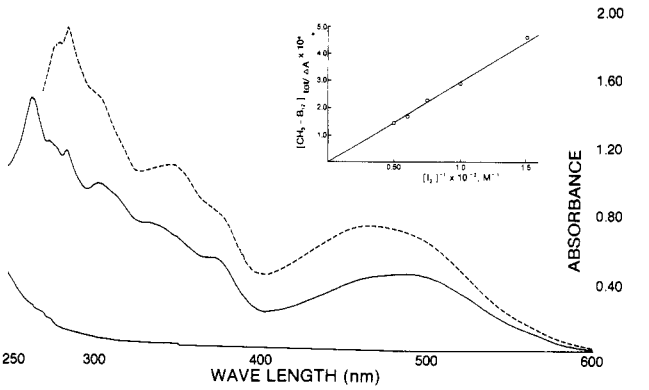


Figure 5. Absorption spectrum of charge-transfer complex of CH_3-B_{12} and iodine in methanol: (—), 6.11×10^{-5} M CH_3-B_{12} alone; (---), 6.11×10^{-5} M CH_3-B_{12} and 1.66×10^{-3} M iodine. Inset: Benesi-Hilderbrand plot of $(\Delta A)^{-1}$ vs. $[I_2]^{-1}$.

inset of Figure 5. It should be noted that in iodine/methanol solution, CH_3-B_{12} appears in the base-off form, as shown by the α-band at 460 nm. Also of importance to note is that there is a slow reaction of CH_3-B_{12} with iodine in methanol, as demonstrated by the spectral change as a function of time. Therefore, the absorbances at 350 nm with various iodine concentrations were recorded as soon as the solutions were mixed together.

Discussion

To account for the iodine cleavage of the Co–C bonds of alkylcobalamins, a mechanism that should be discussed first is the direct displacement of cobalt atom by attack at α-carbon, i.e., electrophilic substitution. In the past, reactions between CH_3-B_{12} and the electrophiles were widely interpreted in terms of this mechanism.[6] The bromine cleavage of Cr–C bond of alkylpentaaquachromium(III) has also been described as a direct mechanism.[27] This mechanism, however, would demand that the demethylation of CH_3-B_{12} by I_2 produces CH_3I under all experimental conditions. This is not what was observed for the demethylation in chloride media. In a control experiment, we have shown that Cl^- does not react with CH_3I to produce CH_3Cl under our experimental conditions. Thus the production of CH_3Cl clearly eliminates the direct mechanism. It could be argued that the demethylation of CH_3-B_{12} proceeds with different mechanisms in Cl^- and ClO_4^- media (i.e., S_E2 mechanism for the reactions in ClO_4^- solution). This possibility is ruled out by the virtually indentical dealkylation rates for C_2H_5-B_{12} and CH_3-B_{12} in perchlorate solution. Therefore, the identification of dealkylation products and the lacking of steric effect of the β-methyl group on the dealkylation rates provide compelling evidence that the direct electrophilic displacement mechanism is not operative in the iodine cleavage of alkylcobalamins.

The formation of CH_3Cl from the iodine demethylation of CH_3-B_{12} can be readily explained in terms of the transient intermediate CH_3-B_{12}^+, generated by one-electron transfer from CH_3-B_{12} to iodine and followed by a nucleophilic attack by the halide ions in solution. This mechanism is totally adopted from the studies of Halpern et al. on the chemical and electrochemical oxidative dealkylation of alkylcobaloximes or other B_{12} model compounds.[28] They have shown the alkylbis(dimethyl-

(26) Reenstra, W. W.; Jencks, W. P. *J. Am. Chem. Soc.* **1979**, *101*, 5780.

(27) (a) Espenson, J. H.; Williams, D. A. *J. Am. Chem. Soc.* **1974**, *96*, 1008. (b) Johnson, M. D. *Acc. Chem. Res.* **1978**, *11*, 57.

glyoximato)cobalt(III) complexes undergo a reversible one-electron oxidation to the corresponding CoR^+ radical cations. These radical cations are stable in aqueous methanol solutions at −78 °C, and they have been characterized as organocobalt(IV) complexes.[28e] At higher temperatures some of the radical cations undergo a nucleophilically induced heterolytic cleavage of the Co–C bonds. Thus, oxidative dealkylation of alkylcobaloximes by $IrCl_6^{2-}$ in the presence of Cl^-, OH^-, or pyridine yields Co(II) and RCl, ROH, or N-alkylated pyridine, respectively. In our studies of the reactions between CH_3-B_{12} and iodine in aqueous solution, the demethylation products were determined by the competition between I^- and Cl^- toward the CH_3-B_{12}^+ intermediate. Thus, in the absence of Cl^-, the CH_3-B_{12}^+ radical reacts with I^- to produce CH_3I and B_{12r} (cob(II)alamin). In the presence of large amounts of Cl^- (e.g., 100-fold excess over I^-), the radical cation reacts with Cl^- to yield CH_3Cl and B_{12r}. The B_{12r} generated by the halide nucleophilic displacement rapidly undergoes further reaction to yield H_2O-B_{12}^+ as the final corrinoid product. The reaction between B_{12r} and iodine has been studied by Espenson et al. and found to be very fast.[29]

A point that must be addressed is that in the proposed electron-transfer mechanism for the iodine cleavage of alkylcobalamins, $I_2^{-}\cdot$ is also produced. Baxendale et al. have reported that the transient $I_2^{-}\cdot$, produced by pulse radiolysis of I^- exhibits an absorption maximum at 380 nm.[30] The equilibrium constant for its formation in aqeuous solution has been estimated to be 1.1×10^5 M^{-1}:

$$I\cdot + I^- \underset{k_{-12}}{\overset{k_{12}}{\rightleftharpoons}} I_2^{-}\cdot \qquad (12)$$

A direct measurement of the reaction of $I\cdot$ with I^- yielded $k_{12} = 1.3 \times 10^{10}$ M^{-1} s^{-1}.[31] Thus, $k_{-12} = 1.2 \times 10^5$ s^{-1} is obtained. The transient $I_2^{-}\cdot$ in aqueous solution decays according to reaction 13.[30]

$$2I_2^{-}\cdot \rightarrow I_2 + 2I^- \qquad (13)$$

The simplest mechanism which would lead to the empirical rate law 6 for the reactions in the absence of Cl^- is that the electron-transfer step is rate limiting and that the halide nucleophilic displacement is much faster than that of the reverse electron-transfer step (i.e., $k'_2[I^-] >> k_{-1}[I_2^{-}\cdot]$). This mechanism is described in Scheme I.

Scheme I

$$CH_3\text{-}B_{12} + I_2 \underset{k'_{-1}}{\overset{k'_1}{\rightleftharpoons}} CH_3\text{-}B_{12}^+ + I_2^{-}\cdot$$

$$CH_3\text{-}B_{12}^+ + X^- \xrightarrow{k'_2} B_{12r} + CH_3X$$

$$B_{12r} + I_2 + H_2O \xrightarrow{\text{rapid}} H_2O\text{-}B_{12}^+ + I_2^{-}\cdot$$

$$2I_2^{-}\cdot \xrightarrow{\text{rapid}} I_2 + 2I^-$$

In Scheme I and the following schemes, an equally plausible reaction for the decay of $I_2^{-}\cdot$ is

$$B_{12r} + I_2^{-}\cdot + H_2O \rightarrow H_2O\text{-}B_{12}^+ + 2I^-$$

If Scheme I is operative, then $a = k'_1$ for the reaction occurs in the absence of Cl^-. However, in the presence of both iodide and chloride, plots of $[I_2]_{tot}K'K''/k_{obsd}[K'K'' + K'[Cl^-] + K''[I^-])$ vs. $[Cl^-]^{-1}$ should yield a slope of zero. This is because we have purposedly performed the reactions with $[Cl^-]$ in large excess over $[I^-]$, so that the demethylation of CH_3-B_{12} is dominated by Cl^- and $k'_{2,Cl}[Cl^-] >> k'_{2,I}[I^-]$ is assured. Thus, $[Cl^-]$ would not appear in the rate expression after eq 3 and 4 are factored in. The slope of Figure 2b is apparently not zero, which argues strongly against Scheme I.

Alternately, one could describe the reactions between alkylcobalamins and iodine with Scheme I but assume that k'_{-1} and k'_2 are comparable. Under this circumstance, it would be necessary to apply a double steady-state approximation for both CH_3-B_{12}^+ and $I_2^{-}\cdot$ intermediates. This would inevitably lead to a very complicated rate expression and does not agree with the empirical rate laws described in eq 6 and 8.

Another mechanism which seemed to be reasonable at first but could be ruled out by the kinetic analysis is described in Scheme II. In Scheme II, the radical paris

Scheme II

$$CH_3\text{-}B_{12} + I_2 \underset{k''_{-1}}{\overset{k''_1}{\rightleftharpoons}} CH_3\text{-}B_{12}^+, I_2^{-}\cdot$$

$$CH_3\text{-}B_{12}^+, I_2^{-}\cdot + X^- \xrightarrow{k''_2} B_{12r}, I_2^{-}\cdot + CH_3X$$

$$B_{12r}, I_2^{-}\cdot + H_2O \xrightarrow{\text{rapid}} H_2O\text{-}B_{12}^+ + 2I^-$$

"CH_3-B_{12}^+,$I_2^{-}\cdot$" and "B_{12r},$I_2^{-}\cdot$" are considered as being confined in a solvent cage. This mechanism would lead to rate law 14. A nonlinear least squares fit of the data

$$\frac{d[H_2O\text{-}B_{12}^+]}{dt} = \frac{k''_1 k''_2[X^-][I_2][CH_3\text{-}B_{12}]}{k''_{-1} + k''_2[X^-]} \qquad (14)$$

shown in Figures 1 and 2 indicates that the values of k''_{-1}/k''_2 are too small to be calculated. This does not agree with the empirical rate laws 6 and 8.

The most plausible mechanism which involves two assumptions is described in Scheme III: (i) The I^- ions can either reduce CH_3-B_{12}^+ to CH_3-B_{12} or nucleophilically attack the α-carbon to produce CH_3I and B_{12r}. (ii) The electron-transfer between CH_3-B_{12}^+ and $I_2^{-}\cdot$ (k_{-1}) is slow as compared to k_2 or k_3.

Scheme III

$$CH_3\text{-}B_{12} + I_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} CH_3\text{-}B_{12}^+ + I_2^{-}\cdot \qquad (15)$$

$$CH_3\text{-}B_{12}^+ + I^- \xrightarrow{k_2} CH_3\text{-}B_{12} + I\cdot \qquad (16)$$

$$CH_3\text{-}B_{12}^+ + X^- \xrightarrow{k_3} B_{12r} + CH_3X \qquad (17)$$

$$B_{12r} + I_2 + H_2O \xrightarrow{\text{rapid}} H_2O\text{-}B_{12}^+ + I_2^{-}\cdot \qquad (18)$$

$$I\cdot + I^- \xrightarrow{\text{rapid}} I_2^{-}\cdot \qquad (19)$$

$$2I_2^{-}\cdot \xrightarrow{\text{rapid}} I_2 + 2I^- \qquad (20)$$

In Scheme III, eq 16 is introduced for the following reason: in the absence of Cl^-, the $[I^-]$ does not participate in the kinetics after the electron-transfer step. Yet the $[Cl^-]$ participates in the kinetics both before and after the electron-transfer step. This apparently indicates that there

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(30) (a) Baxendale, J. H.; Bevan, P. L. T.; Stott, D. A. *Trans. Faraday Soc.* **1968**, *64*, 2389. (b) Elliot, A. J.; Sopchyshyn, F. C. *Int. J. Chem. Kinet.* **1984**, *16*, 1247.

(31) Treinin, A.; Hayon, E. *Int. J. Radiat. Phys. Chem.* **1975**, *1*, 387.

are two reactions between CH_3-B_{12}^+ cation radical and the halide ions. One is the nucleophilic displacement by X^- (reaction 17). The other one is reduction of CH_3-B_{12}^+ by I^- (reaction 16), which is an unproductive reaction. Thus, in the absence of chloride, the $[I^-]$ effects of reactions 16 and 17 cancel out each other. Scheme III leads to rate law 21. Taking into consideration of reactions 3 and 4, one

$$\frac{d[H_2O\text{-}B_{12}^+]}{dt} = \frac{k_1k_3[X^-][I_2][CH_3\text{-}B_{12}]}{k_2[I^-] + k_3[X^-]} \quad (21)$$

gets the rate law

$$\frac{d[H_2O\text{-}B_{12}^+]}{dt} = \frac{k_1k_3K'K''[X^-][I_2]_{tot}[CH_3\text{-}B_{12}]}{\{k_2[I^-] + k_3[X^-]\}\{K'K'' + K'[Cl^-] + K''[I^-]\}} \quad (22)$$

In the mixtures containing no Cl^-, rate law 22 is simplified to eq 23. Under this condition, a of empirical rate

$$\frac{d[H_2O\text{-}B_{12}^+]}{dt} = \frac{k_1k_3K'[I_2]_{tot}[CH_3\text{-}B_{12}]}{(k_2 + k_3)(K' + [I^-])} \quad (23)$$

law 6 equals to $k_1k_3/(k_2 + k_3)$ with values of 26 and 31 for the dealkylation of CH_3-B_{12} and C_2H_5-B_{12}, respectively.

For the demethylation of CH_3-B_{12} performed in the mixtures containing Cl^- in large excess over I^-, a' and b' (empirical rate law 8) equal to k_1 and k_2/k_3, respectively. Thus, Figure 2 yields $k_1 = 47\ M^{-1}\ s^{-1}$ and $k_2/k_3 = 10$ for the demethylation in Cl^- media. Note here k_3 represents path of chloride nucleophilic attack on CH_3-B_{12}^+. The k_1 value obtained from Figure 2 in turn allows us to estimate $k_2/k_3 = 0.81$ for the reaction performed in media containing only I^-. Therefore, the nucleophilic displacement of CH_3-B_{12}^+ by I^- is of a factor of 13 faster than that by Cl^-, totally in accord with the nucleophilicity of the halogen series (in the order of decreasing nucleophilicity[32]):

$$I^- > Br^- > Cl^- > F^-$$

It should be noted that although reaction 16 is essentially the opposite of eq 15 after eq 12 and 13 are factored in, the presence of eq 16 as an independent reaction is necessary because k_{-1} must be assumed to be slow as compared with k_2 and k_3 in order to derive rate law 21. Furthermore, reaction 13 is essentially irreversible in aqueous solution.

While the iodine dealkylation of C_2H_5-B_{12} proceeds with a rate similar to that of CH_3-B_{12} in the absence of Cl^- ions (it should be emphasized that the composite rate constants, i.e. $k' = k_1k_3/(k_2 + k_3)$, were used in the comparison), its dealkylation rate in 1 M Cl^- media is a factor of 3.5 slower than that of CH_3-B_{12} (Figure 2). It produces C_2H_5I as the predominant dealkylation product. This can be explained by the fact that the β-methyl group of C_2H_5-B_{12}^+ imposes a severe steric hindrance to the less powerful nucleophile, i.e., Cl^- vs. I^-. Under this condition, Cl^- is not able to compete with I^- for the transient C_2H_5-B_{12}^+, and the only $[Cl^-]$ effect for the C_2H_5-B_{12} dealkylation is to suppress the dissociation of I_2Cl^- (reaction 4). Thus, a'' in the empirical rate law 9 equals to k'. The least-squares fit of Figure 3 yields $k' = 46\ M^{-1}\ s^{-1}$ and $K'' = 0.12$ M (25 °C). Value of k' agrees well with that obtained from the Cl^--free solution, but the K'' value is off by a factor of 5 from that obtained from spectrophotometric titration of reaction 4. The reaction between B_{12r} and CH_3X (the reverse reaction of reaction 17) has been examined by Blaser and Halpern.[33]

(32) Gould, E. S. "Mechanism and Structure in Organic Chemistry"; Holt, Rinehart and Winston: New York, 1959; p 250.

Under the present experimental conditions, this reaction is too slow to compete with the reaction of iodine (reaction 18).

Although extensive electrochemical studies on vitamin B_{12} derivatives have been carried out,[34] we are aware of no electrochemical studies on the oxidative demethylation of CH_3-B_{12} except for the note by Rubinson et al.[35] They reported that a single irreversible wave was observed with a peak potential of +0.87 V vs. SCE on the initial positive scan. Methanol and H_2O-B_{12}^+ were identified as the oxidative demethylation products. Their study clearly shows that CH_3-B_{12}^+ is extremely unstable in aqueous solution. It is unfortunate that there is no oxidative electrochemical study of CH_3-B_{12} at low temperature available where the CH_3-B_{12}^+ radical might survive. Nevertheless, the electrochemical study by Rubinson et al.,[35] together with the reduction potential of +0.08 V (vs. SCE) for $I_2(aq) + e \rightleftharpoons I_2^{-}\cdot$,[36] indicate that the electron transfer from alkylcobalamin to iodine is likely to be highly endothermic. Then, how can an electron-transfer mechanism by operative?

To resolve this problem, we interpret the electron-transfer reactions within the framework of charge-transfer complex, in which an important driving force is derived from the interaction energy in the ion pair:

$$CH_3\text{-}B_{12} + I_2 \overset{K_{CT}}{\rightleftharpoons} \text{“}CH_3\text{-}B_{12},I_2\text{”} \xrightarrow{k_{et}} \text{“}CH_3\text{-}B_{12}^+,I_2^{-}\cdot\text{”} \quad (24)$$

We consider the electron-transfer step within the charge-transfer complex as “irreversible” because it is followed by a rapid chemical reaction—the nucleophilic displacement by halide ions (reaction 17) or the reduction of CH_3-B_{12}^+ by iodide (reaction 16). The charge-transfer complex mechanism is adopted from the elegant studies of the iodinolysis of alkylmetals such as R_4Sn or R_2Hg.[37] Indeed, absorption spectrum of CT complex of CH_3-B_{12} with iodine in methanol solution is observed immediately upon mixing iodine and CH_3-B_{12} (Figure 5). The Benesi-Hilderbrand's plot shows that the formation constant is too small to be measured spectrophotometrically. The lower limit of the molar absorptivity at 350 nm for the CT complex is estimated to be $2 \times 10^4\ M^{-1}\ cm^{-1}$. The magnitude of the molar absorptivity indicates that the CT complex of CH_3-B_{12} with iodine is mot likely arising from the interaction of corrin π-orbitals and iodine. This is because it is known that the charge-transfer bands of organometallic δ-donors (e.g., $(CH_3)_2Hg$) with electrophiles are broad with rather small formation constants and molar absorptivities.[38] It should be noted, however, that the charge-transfer complex of CH_3-B_{12} with iodine is observed only in methanol solution. It is unfortunate that we were not able to detect the CT complex in aqueous solution because the predominant iodine is in I_3^- or I_2Cl^- form.

The justification of assuming the “irreversibility” of reaction 15 needs to be addressed. Perrin has recently raised questions on the so called “IR case” of an irreversible electron transfer preceding the chemical reaction in many organic reactions now being rethought as proceeding via electron transfer.[39] Although we could not eliminate the

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(37) Fukuzumi, S.; Kochi, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 2141.
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(39) Perrin, C. L. *J. Phys. Chem.* **1984**, *88*, 3611.

possibility of electron-transfer reaction between alkylcobalamin and iodine as occurring by simultaneous electron transfer and nuclear motion without any intermediate, the introduction of reaction 16 can best interpret the kinetic data in our hand. Thus, the kinetic data on the competition between reactions 16 and 17 suggest the existence of the oxidized radical cation intermediate.

The pH-dependent kinetic data (Figure 4) afford us to estimate the iodine demethylation rates for the base-on and base-off forms of CH_3-B_{12}. It is found that the base-on CH_3-B_{12} reacts with iodine with a rate 16 times faster than that of base-off form. It is known that the axial ligand trans to the organo group has a large effect on the rate of heterolytic reactions of the Co–C bonds of organocobalamins or their model compounds.[13,40,41] For example, in the study of base-catalyzed methane formation from methylcobaloximes, it is reported that the methane formation from methyl(pyridine) cobaloxime is at least 4 orders of magnitude slower than that from methylaquocobaloxime.[40] We have also found that IrC_6^{2-} oxidative demethylation for base-on CH_3-B_{12} is 75 times faster than that of base-off form.[22] Therefore, the factor of 16 for the difference between the base-on and base-off forms in the iodine reaction with CH_3-B_{12} represents a compromise between the trans effect on the electron-transfer step (reaction 15) and on the I^- nucleophilic attack (reaction 17). This compromise results in a relatively small difference between the reactivities of base-on and base-off CH_3-B_{12}.

The observation of a rapid base-on to base-off alkylcobalamin conversion by iodine in aqueous methanol media is worth noting. It is known that a number of electrophiles are capable of attacking the 5,6-dimethylbenzimidazole resulting in a base-on to base-off conversion,[9,11,21] which in turn controls the reactivity of methylcobalamin. However, the reaction between CH_3-B_{12} and iodine is the first example of the dramatic change in reactivity with respect to the 5,6-dimethylbenzimidazole in different solvent systems, although the base-on and base-off conversion could simply reflect that the predominant iodine species in CH_3OH/H_2O solution is I_2. It should also be noted that in the presence of I^-, iodine demethylation of the base-off CH_3-B_{12} in CH_3OH/H_2O solution is much slower than that of the base-off CH_3-B_{12} in aqueous solution. At present, we are not able to provide an exact explanation for the slow demethylation in methanol aqueous solution.

In conclusion, this report presents nonkinetic, as well as kinetic evidence, for the electron-transfer mechanism in the iodine cleavage of Co–C bonds of alkylcobalamins. The initial electron transfer is unlikely to involve the Co–C bond orbital, since no steric effect for electron-transfer step of the C_2H_5-B_{12} reaction is found. The mechanism for the reaction between the naturally occurring alkylcobalamin and iodine is reminiscent of the reactions by I_2 and other electrophiles on organometallic compounds of Pb and Sn, which were shown to occur by charge-transfer complexation, electron-transfer mechanism.[42]

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Registry No. CH_3-B_{12}, 13422-55-4; C_2H_5-B_{12}, 13422-56-5; I_2, 7553-56-2.

Supplementary Material Available: Tables of kinetic data for the demethylation of CH_3-B_{12} and kinetic data for the dealkylation of C_2H_5-B_{12} (8 pages). Ordering information is given on any current masthead page.

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