Kinetic Studies of Oxidative Dealkylation of Alkylcobalamins by Hexachloroplatinate(IV)

Yueh-Tai Fanchiang *
Department of Biochemistry, Medical School, University of Minnesota, Minneapolis, MN 55455, U.S.A.

The dealkylation of methylcobalamin (CH_3–B_{12}), methyl 3,5,6-trimethylbenzimidazolylcobamide, and ethylcobalamin (C_2H_5–B_{12}) by $PtCl_6^{2-}$ in acidic solution have been examined. The demethylation of CH_3–B_{12} by $PtCl_6^{2-}$ in perchlorate solution proceeds very slowly. In chloride media, however, the reaction occurs readily, yielding H_2O–B_{12}^+, $PtCl_4^{2-}$, and CH_3Cl. In bromide or pyridine media the methyl-transfer product is CH_3Br or *N*-methylated pyridine. Kinetic studies show that the reactions are first order in alkylcobalamin concentration, with the observed rates displaying a hyperbolic dependence upon [$PtCl_6^{2-}$]. This non-linear dependence is interpreted in terms of a pre-association of the reactants, followed by the dealkylation steps. The rates of dealkylation, after correction for the association constants, are not significantly affected by the ligands *trans* to the alkyl groups. This observation, together with the comparable rates of dealkylation of the base-off forms of CH_3–B_{12} and C_2H_5–B_{12}, is taken as kinetic evidence against direct electrophilic attack at the α carbon, and favouring a one-electron transfer to form a R–B_{12}^+,$PtCl_6^{3-}$ radical pair. The latter collapses to the products observed. The mechanism for the cleavage of Co–C bonds in the oxidized alkylcorrinoid intermediates is discussed.

Ever since the first report of the reaction between methylcobalamin (CH_3–B_{12}) and the $PtCl_6^{2-}$–$PtCl_4^{2-}$ couple,[1] this unusual reaction has been extensively studied by several investigators.[2,3] It is now established that it proceeds as in Scheme 1 (L or L′ = Cl^- or CN^-, X = Cl^-, Y = Cl^- or CN^-).

$$CH_3\text{–}B_{12} + Pt^{II}L_4^{2-} \rightleftharpoons CH_3\text{–}B_{12},Pt^{II}L_4^{2-}$$

$$CH_3\text{–}B_{12},Pt^{II}L_4^{2-} + XPt^{IV}L_4'Y^{2-} \rightleftharpoons CH_3\text{–}B_{12},\ Pt^{IV}L_4\text{–}X\text{–}Pt^{II}L_4'^{3-} + Y^-$$

$$CH_3\text{–}B_{12},Pt^{IV}L_4\text{–}X\text{–}Pt^{II}L_4'^{3-} \xrightarrow{\text{rate limiting}} H_2O\text{–}B_{12}^+ + (CH_3)\text{–}Pt^{IV}L_4X^{2-} + Pt^{II}L_4'^{2-}$$

Scheme 1.

During the course of an investigation [3] of this methyl-transfer process it was found that $PtCl_6^{2-}$ alone could demethylate CH_3–B_{12}. This reaction produces H_2O–B_{12}^+, CH_3Cl, and presumably $PtCl_4^{2-}$. Although the rate of the $PtCl_6^{2-}$ demethylation route is negligibly small compared with the Pt^{IV}–Pt^{II} route, evidence was obtained indicating that it was not initiated by trace amounts of $PtCl_4^{2-}$. This reaction has attracted my attention because $PtCl_6^{2-}$ is known to be very inert to one-electron reduction,[4] and to ligand substitution in the absence of positively charged platinum(II) complexes such as $[Pt(NH_3)_4]^{2+}$.[5]

In this report I present detailed kinetic and mechanistic data on the dealkylation of methylcobalamin, methyl 3,5,6-trimethylbenzimidazolylcobamide, and ethylcobalamin by $PtCl_6^{2-}$ in acidic solution. The comparable dealkylation rates for these alkylcorrinoids support a one-electron-transfer mechanism. The results help refine the understanding of the nature of the rate-limiting step of the methylation of platinum-(II) and -(IV) complexes by CH_3–B_{12}.[3]

Experimental

Materials.—The compounds $Na_2PtCl_6 \cdot 6H_2O$ and K_2PtCl_4 were purchased from D. F. Goldsmith and were recrystallized from aqueous solution (in the dark) before use. Chlorine gas was bubbled through the Na_2PtCl_6 solution before the recrystallization in order to eliminate the Na_2PtCl_4 impurity. [^{13}C]Methyl iodide (90% enriched) was obtained from Stohler. Methyl- and ethyl-cobalamin were prepared according to published procedures.[6] Methyl 3,5,6-trimethylbenzimidazolylcobamide was prepared from its cyanoaquo-derivative [7] and CH_3I. The concentrations of corrinoid solutions were determined from their absorption spectra using the published molar absorptivities.[8] All other chemicals were reagent grade and were used as received.

Stoicheiometry and Reaction Products.—Efforts to measure the stoicheiometry of the reaction between $PtCl_6^{2-}$ and CH_3–B_{12} were made with a Cary 15 spectrophotometer at 260 nm (the absorbance maximum for $PtCl_6^{2-}$) with an excess of $PtCl_6^{2-}$ over CH_3–B_{12}. Corrinoid products were examined spectrophotometrically. Methyl-transfer products were examined by pulse Fourier-transform ^{13}C n.m.r. spectroscopy (25.2 MHz) on a Varian XL-100 MHz instrument or by ^{1}H n.m.r. (270 MHz) on a Bruker 270, and by a Becker model 417 gas chromatograph with a column (8 ft × 2 mm) of 5% 'free fatty acid phase' on Chromasorb W-AW-DMCS (80—100 mesh) at 45 °C. Platinum products were examined spectrophotometrically after the chlorine oxidation of a reaction mixture which had been treated with phenol to remove the corrinoid products.

Kinetic Measurements.—The reaction rates were determined by measuring the absorbance increase at 520 or 350 nm (the absorbance maxima for H_2O–B_{12}^+), as these wavelengths provided the most convenient absorbance changes during the course of the reactions. All reactions were performed at 23 ± 0.3 °C in dim light. The ionic strength was maintained at

* *Present address:* The Department of Chemistry, Kent State University, Kent, Ohio 44242, U.S.A.

1.0 mol dm^{-3} with NaCl or $NaClO_4$. The pH was controlled in a range 0—3 with HCl or $HClO_4$, as appropriate. The $PtCl_6^{2-}$ concentration was in large excess over alkylcorrinoid in all cases; a typical corrinoid concentration was 8×10^{-6} mol dm^{-3}. Except for the reactions performed at $[Cl^-] < 0.50$ mol dm^{-3} or pH > 3, plots of $\log (A_\infty - A_t)$ *vs.* time gave straight lines for more than 75% completion of the reactions, indicating that the reactions are first order in alkylcorrinoid concentration. It should be emphasized that it is important to keep the $[PtCl_6^{2-}]$ in at least 150-fold excess over the alkylcorrinoid. It has previously been shown that the demethylation of CH_3–B_{12} by a relatively low level of $PtCl_6^{2-}$ (*e.g.* stoicheiometric amounts) becomes progressively faster due to the generation of $PtCl_4^{2-}$, the demethylation being dominated by the $PtCl_6^{2-}$–$PtCl_4^{2-}$ route in the early stages. For the same reason, the dealkylation by $PtCl_6^{2-}$ was studied at pH $\leqslant$ 3 and $[Cl^-] \geqslant 0.50$ mol dm^{-3}. At pH > 3 or $[Cl^-] \leqslant 0.10$ mol dm^{-3}, first-order plots could not be obtained regardless of the molar ratios of $PtCl_6^{2-}$ to alkylcobalamin.

Results

The demethylation of 3.4×10^{-5} mol dm^{-3} CH_3–B_{12} by a 150-fold excess of $PtCl_6^{2-}$ in a 1 mol dm^{-3} perchlorate solution (pH 2, 23 °C) is extremely slow. In 1 mol dm^{-3} chloride solution, however, CH_3–B_{12} is quantitatively demethylated to H_2O–B_{12}^+ with a half-life of *ca.* 12 min under otherwise identical conditions. The inability of $PtCl_6^{2-}$ to demethylate CH_3–B_{12} in perchlorate solution is an important observation as regards the contention that demethylation by a high level of $PtCl_6^{2-}$ in chloride solution is due to $PtCl_6^{2-}$ alone, and not to the $PtCl_6^{2-}$–$PtCl_4^{2-}$ couple, *i.e.* the Na_2PtCl_6 samples were contaminated by Na_2PtCl_4. It has previously been demonstrated that a combination of 5.0×10^{-3} mol dm^{-3} $PtCl_6^{2-}$ and 5.0×10^{-5} mol dm^{-3} $PtCl_4^{2-}$ could readily demethylate CH_3–B_{12} (4.0×10^{-5} mol dm^{-3}) in 1.0 mol dm^{-3} perchlorate solution (pH 2), although the rate was somewhat slower than that in chloride solution.[3] This observation, together with the careful purification of Na_2PtCl_6 samples, and the linear plots of $\log (A_\infty - A_t)$ *vs.* time for the initial 75% of the reactions at pH < 3, leads to the conclusion that the compound Na_2PtCl_6 alone is indeed capable of demethylating CH_3–B_{12}. The electronic spectrum in the visible region of a reaction mixture of $PtCl_6^{2-}$ and CH_3–B_{12} in 1.0 mol dm^{-3} Cl^- solution (pH 2) shows isosbestic points at 480 and 370 nm. Identical electronic spectral changes and reaction rates were obtained under a nitrogen atmosphere. A fast spectral scan in the visible region for a reaction mixture at pH *ca.* 7 did not show a spectrum indicative of the base-off form of CH_3–B_{12}.

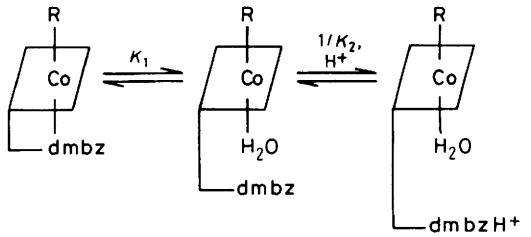
The spectrophotometric titration for the stoicheiometric determination imposed some difficulties, because the $PtCl_6^{2-}$ concentration used had to be very high in order to avoid the Pt^{IV}–Pt^{II} route. Under this condition, the net absorbance change is quite small compared to the total absorbance. This caused a rather large uncertainty. Nevertheless, titration at a ratio of $[PtCl_6^{2-}]$:$[CH_3$–$B_{12}] = 10:1$ indicates that 1 mol of $PtCl_6^{2-}$ is consumed per mol of CH_3–B_{12}.

The demethylation of CH_3–B_{12} by a high level of $PtCl_6^{2-}$ (1.0 mol dm^{-3} Cl^-) yields CH_3Cl as the demethylation product, as determined by ^1H n.m.r. spectroscopy (confirmed with an authentic sample). The production of CH_3Cl is also confirmed by g.c., or by ^{13}C n.m.r. ($^{13}CH_3$–B_{12}, 90% enriched). The ^{13}C resonance appeared at 28.0 p.p.m. [external sodium tetradeuterio-3-(trimethylsilyl)propionate] when the demethylation was complete. In 1.0 mol dm^{-3} Br^- or 0.1 mol dm^{-3} pyridine solution, the ^{13}C resonance appeared at 13.8 or 3.2 p.p.m., indicating that the demethylation product is CH_3Br or *N*-methylated pyridine, respectively.

The platinum product of the demethylation is $PtCl_4^{2-}$, as determined by the detection of increased amounts of $PtCl_6^{2-}$ after the chlorine oxidation of the platinum product solution which had been separated from H_2O–B_{12}^+ by phenol extraction. Overall, the demethylation of CH_3–B_{12} by $PtCl_6^{2-}$ can be described by equation (1).

$$CH_3\text{–}B_{12} + PtCl_6^{2-} + X^- + H_2O \longrightarrow H_2O\text{–}B_{12}^+ + CH_3X + PtCl_4^{2-} + 2Cl^- \quad (1)$$

Kinetic Measurements.—The protonation of 5,6-dimethylbenzimidazole (dmbz) and the resulting 'base-on' to 'base-off' conversion of CH_3–B_{12} or C_2H_5–B_{12} can be expressed as in equation (2). The pK_2 value has been estimated to be 5.0 (1.0



(2)

mol dm^{-3} KCl, 25 °C).[9] The pK_1 values for CH_3–B_{12} and C_2H_5–B_{12} have been estimated to be 2.0 and 1.3 at 23 °C (1.0 mol dm^{-3} NaCl), respectively.[10] It should be noted that the anions in solution have a significant effect on the pK_1 values. For example, the pK_1 values of CH_3–B_{12} in 1.0 mol dm^{-3} NaCl and 1.0 mol dm^{-3} $NaClO_4$ solutions are 2.0 and 1.6 (23 °C), respectively.

Kinetic data for the demethylation of CH_3–B_{12} by $PtCl_6^{2-}$ in 1.0 mol dm^{-3} chloride solution at various pH all show a hyperbolic dependence upon $[PtCl_6^{2-}]$. Plots of $k_{obs.}^{-1}$ *vs.* $[PtCl_6^{2-}]^{-1}$ are shown in Figure 1(*a*). A possible interpretation for the non-linear dependence on $[PtCl_6^{2-}]$ is the formation of a pre-complex between CH_3–B_{12} and $PtCl_6^{2-}$ [reaction (3)]. If it is assumed that the mechanism in equations (4)—(6) operates in which k_1 is a slow, reversible electron-transfer step (see the Discussion section) then the kinetic data shown in Figure 1(*a*) can be expressed by equation (7). A double steady-state approximation for CH_3–B_{12}^+, $PtCl_6^{3-}$, and B_{12r},$PtCl_6^{3-}$ has been applied in the derivation of this equation.

It should be noted that the quality of data obtained at pH 3 is rather poor for the reason stated earlier. It is unfortunate that kinetic data could not be obtained at high pH at which CH_3–B_{12} is predominantly in the base-on form. Taking into consideration equation (2) and letting $k = k_1k_2k_3[Cl^-]/(k_{-1}k_{-2}[CH_3Cl] + k_{-1}k_3 + k_2k_3[Cl^-])$, the general rate

$$CH_3\text{–}B_{12} + PtCl_6^{2-} \overset{K_3}{\rightleftharpoons} CH_3\text{–}B_{12},PtCl_6^{2-} \quad (3)$$

$$CH_3\text{–}B_{12},PtCl_6^{2-} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} CH_3\text{–}B_{12}^+,PtCl_6^{3-} \quad (4)$$

$$CH_3\text{–}B_{12}^+,PtCl_6^{3-} + Cl^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} B_{12r},PtCl_6^{3-} + CH_3Cl \quad (5)$$

$$B_{12r},PtCl_6^{3-} + H_2O \xrightarrow{k_3} H_2O\text{–}B_{12}^+ + PtCl_4^{2-} + 2Cl^- \quad (6)$$

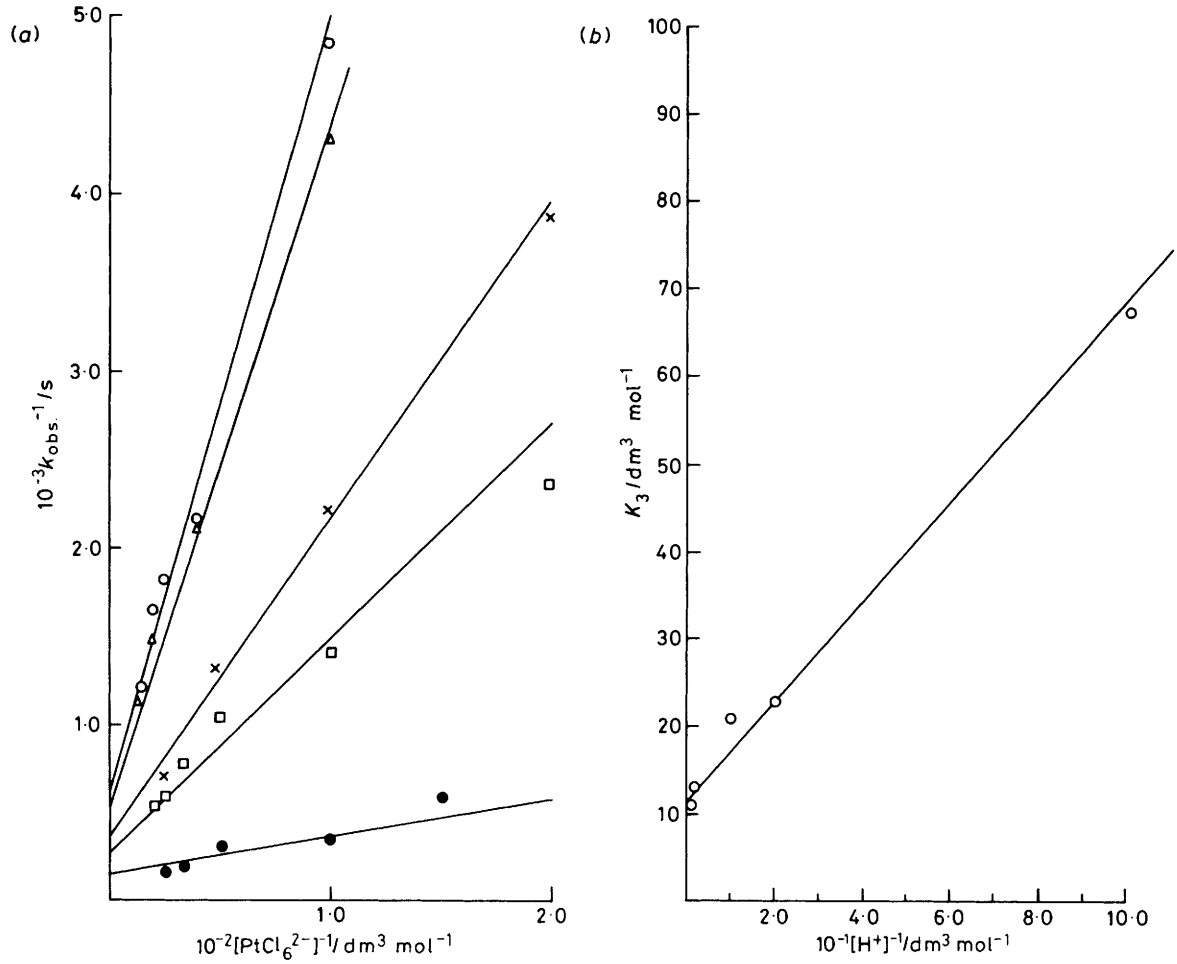


Figure 1. (*a*) Kinetic data for the reactions of methylcobalamin with $PtCl_6^{2-}$. $[CH_3-B_{12}] = (0.8—1.0) \times 10^5$, I = 1.0 mol dm^{-3} (HCl + NaCl); 23 °C. $[H^+]$ = 0.010 (●), 0.050 (□), 0.10 (×), 0.50 (△) and 1.0 mol dm^{-3} (○). (*b*) Plot of K_3 *vs.* $[H^+]^{-1}$. Values of K_3 were obtained from (*a*)

$$k_{obs.} = \frac{k_1k_2k_3[Cl^-]K_3[PtCl_6^{2-}]}{(k_{-1}k_{-2}[CH_3Cl] + K_{-1}k_3 + k_2k_3[Cl^-])(1 + K_3[PtCl_6^{2-}])} \quad (7)$$

$$k_{obs.} = \frac{(k'K_2K_3' + k''K_1K_2K_3'' + k'''K_1K_3'''[H^+])[PtCl_6^{2-}]}{K_2 + K_1K_2 + K_1[H^+] + K_2K_3'[PtCl_6^{2-}] + K_1K_2K_3''[PtCl_6^{2-}] + K_1K_3'''[H^+][PtCl_6^{2-}]} \quad (8)$$

$$k_{obs.} = \frac{(k'K_2K_3' + k'''K_1K_3'''[H^+])[PtCl_6^{2-}]}{K_2 + K_1[H^+] + K_2K_3'[PtCl_6^{2-}] + K_1K_3'''[H^+][PtCl_6^{2-}]} \quad (9)$$

equation incorporating all forms of CH_3-B_{12} will be as in equation (8). Here a prime indicates the kinetic pathway with base-on CH_3-B_{12}, double primes that with unprotonated base-off CH_3-B_{12}, and triple primes that with the protonated base-off form. It should be emphasized that the rate constants k', k'', and k''' are composite constants, *i.e.* $k_1'k_2'k_3'[Cl^-]/(k_{-1}'k_{-2}'[CH_3Cl] + k_{-1}'k_3' + k_2'k_3'[Cl^-])$, *etc.* Taking into account that $K_1 \gg K_2$ and assuming that the unprotonated base-off and protonated base-off forms have similar activities (*i.e.* K_3'' *ca.* K_3''' and k'' *ca.* k'''), equation (8) can be simplified to (9). A plot of $k_{obs.}^{-1}$ *vs.* $[PtCl_6^{2-}]^{-1}$ gives the intercept and slope as in equations (10) and (11). Figure 1(*a*) shows the straight lines in the range pH 0—2. A significant feature is that the intercepts at all pH values fall in a narrow range. An explanation for this observation, which has the support of the kinetic data for methyl 3,5,6-trimethylbenzimidazolylcobamide (see below), is that k' *ca.* k'''. On this basis, it is calculated that $k_1k_2k_3[Cl^-]/(k_{-1}k_{-2}[CH_3Cl] + k_{-1}k_3 + k_2k_3[Cl^-]) = (4 \pm 2) \times 10^{-3}$ s^{-1} at 1.0 mol dm^{-3} Cl^-, and equation (11) can be rewritten as in (12) ($K_2 \ll K_1[H^+]$ in the range pH 0—2).

$$\text{Intercept} = \frac{1}{k} = \frac{K_2K_3' + K_1K_3'''[H^+]}{k'K_2K_3' + k'''K_1K_3'''[H^+]} \quad (10)$$

$$\text{Slope} = \frac{1}{kK_3} = \frac{K_2 + K_1[H^+]}{k'K_2K_3' + k'''K_1K_3'''[H^+]} \quad (11)$$

$$K_3 = (K_2K_3' + K_1K_3'''[H^+])/K_1[H^+] \quad (12)$$

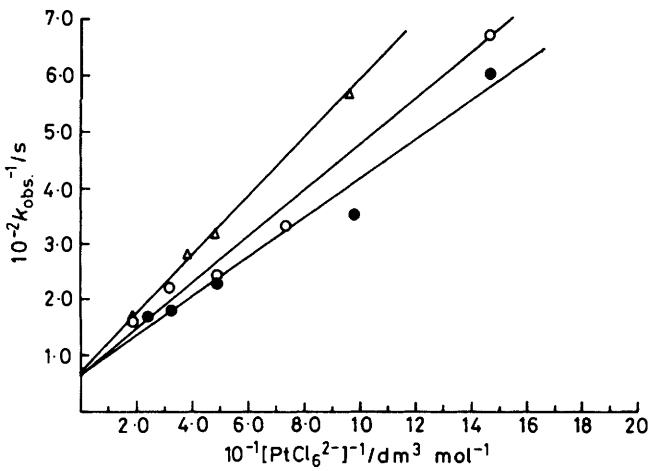


Figure 2. Kinetic data for the reactions of methylcobalamin with $PtCl_6^{2-}$ at various chloride concentrations. $[CH_3\text{-}B_{12}] = 8 \times 10^{-6}$, I = 1.0 mol dm^{-3} (NaCl + $NaClO_4$), pH 2, 23 °C. $[Cl^-]$ = 1.0 (●), 0.75 (○), and 0.50 mol dm^{-3} (△)

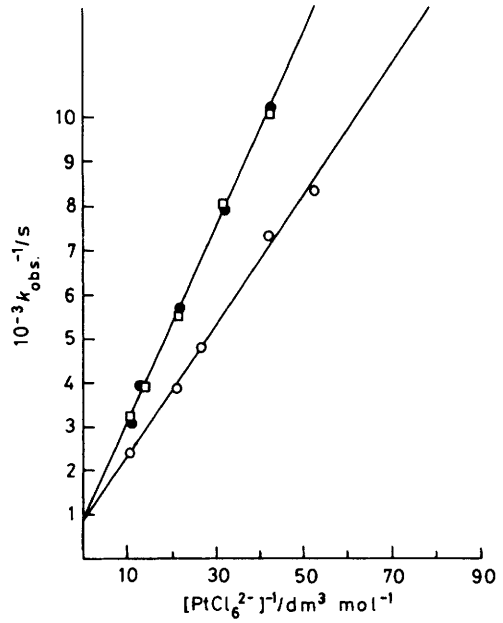


Figure 3. Kinetic data for the reactions of ethylcobalamin with $PtCl_6^{2-}$. $[C_2H_5\text{-}B_{12}] = 1.0 \times 10^{-5}$, I = 1.0 mol dm^{-3} (HCl + NaCl), 23 °C. $[H^+]$ = 0.0010 (○), 0.010 (●), and 0.10 mol dm^{-3} (□)

Plots of K_3 *vs.* $[H^+]^{-1}$ are shown in Figure 1(*b*), thus yielding $K_3''' = (1.5 \pm 0.5) \times 10$ dm^3 mol^{-1} and K_3' *ca.* 5.8×10^2 dm^3 mol^{-1}.

Kinetic data for the demethylation of $CH_3\text{-}B_{12}$ at pH 2 and various Cl^- concentrations (0.50—1.0 mol dm^{-3}) are plotted in Figure 2. Plots of $k_{obs.}^{-1}$ *vs.* $[PtCl_6^{2-}]^{-1}$ show an identical intercept, indicating that $k_2k_3[Cl^-] \gg k_{-1}k_{-2}[CH_3Cl] + k_{-1}k_3$ at $[Cl^-] \geqslant 0.50$ mol dm^{-3}. The $[Cl^-]$ effect on the slopes shown in Figure 2 can be interpreted in terms of two factors: first the effect on the K_1 values, and secondly the effect on the K_3 values. The second effect will be discussed in the following section.

Kinetic data for the reaction of $C_2H_5\text{-}B_{12}$ with $PtCl_6^{2-}$ in 1.0 mol dm^{-3} Cl^- solution (range pH 1—3) are plotted in Figure 3. These data can also be expressed by equation (9). Note that

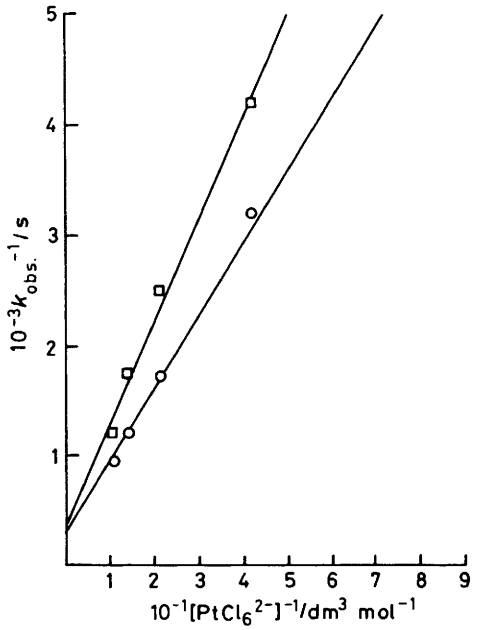


Figure 4. Kinetic data for the reactions of methyl 3,5,6-trimethylbenzimidazolylcobamide with $PtCl_6^{2-}$. [CH_3–cobamide] *ca.* 10^{-5}, $[H^+]$ = 0.010, I = 1.0 mol dm^{-3} (HCl + NaCl + $NaClO_4$), 23 °C. $[Cl^-]$ = 1.0 (○) and 0.50 mol dm^{-3} (□)

Table. Kinetic parameters for reactions of alkylcorrinoids with $PtCl_6^{2-}$ at 1.0 mol dm^{-3} chloride*

Alkylcorrinoid	Form	10^3k/s^{-1}	K_3/dm^3 mol^{-1}
$CH_3\text{-}B_{12}$	Base-on	4 ± 2	5.8×10^2
	Base-off	4 ± 2	1.5×10
$C_2H_5\text{-}B_{12}$	Base-on	1.2	1.5×10
	Base-off	1.2	3.5
Methylated base-off $CH_3\text{-}B_{12}$		3.2	7.1

* I = 1.0 mol dm^{-3} (HCl + NaCl); 23 °C. $k = k_1k_2k_3[Cl^-]/(k_{-1}k_{-2}[CH_3Cl] + k_{-1}k_3 + k_2k_3[Cl^-])$.

the kinetic studies are restricted at pH ⩾ 1 because $C_2H_5\text{-}B_{12}$ is unstable at 1.0 mol dm^{-3} HCl. A compensation is that the reactions are first order in $[C_2H_5\text{-}B_{12}]$ at pH 3. Kinetic measurements on the demethylation of methyl 3,5,6-trimethylbenzimidazolylcobamide, which appears only in the base-off form, in 1.0 mol dm^{-3} chloride solution are shown in Figure 4. The reaction rates, which can be expressed in terms of equation (7), are independent of pH in the range 0—3. The values of k and K_3 obtained for the methylated base-off $CH_3\text{-}B_{12}$ are close to those obtained for the protonated base-off form. The kinetic parameters for the reactions of $PtCl_6^{2-}$ with alkylcorrinoids are listed in the Table.

The effect of $[Cl^-]$ on the demethylation rate of methyl 3,5,6-trimethylbenzimidazolylcobamide is also shown in Figure 4. The cobamide is suitable for the examination of the $[Cl^-]$ effect on the formation constant of the pre-complex because its nucleotide side chain is methylated at N(3) and thus is not capable of co-ordinating to the cobalt atom. It can be seen from Figure 4 that chloride concentrations in the range 0.50—1.0 mol dm^{-3} do not have a significant effect on the k value, suggesting that $k_2k_3[Cl^-] \gg k_{-1}k_{-2}[CH_3Cl] + k_{-1}k_3$. The preassociation constant (K_3) does, however, decrease as $[Cl^-]$ is decreased.

Discussion

Several recent papers have described the oxidative dealkylation of alkylcobalamins by a variety of oxidants such as $IrCl_6^{2-}$,[11] $AuCl_4^-$,[10,12] and $[Fe(H_2O)_5Cl]^{2+}$.[13] Several interesting features are shown by these reactions,[14] including the requirement of chloride ligands in the inner co-ordination spheres, the enhancement of the rates by Cl^- in solution, and, except for $IrCl_6^{2-}$, a hyperbolic dependence of the rates upon the oxidant concentrations. The dealkylation of alkylcobalamins by $PtCl_6^{2-}$ displays all these characteristics. The ion $[Pt(CN)_6]^{2-}$ does not react with CH_3–B_{12}, and while the reaction of $PtCl_6^{2-}$ in perchlorate solution is extremely slow, this ion readily demethylates CH_3–B_{12} in chloride solution. The reaction is first order in $[PtCl_6^{2-}]$ at relatively low concentration, but approaches zero order as $[PtCl_6^{2-}]$ is increased.

This non-linear dependence upon $[PtCl_6^{2-}]$ could be interpreted as due to a change in the rate-limiting step, *e.g.* some sort of activation of the corrinoid occurs prior to the interaction with $PtCl_6^{2-}$. Although this mechanism cannot be ruled out, it has previously been pointed out[14] that this would demand the rates of the rate-limiting steps to be independent of the nature of the oxidants. Thus, the rate constants of the limiting step should be nearly identical for $AuCl_4^-$, $[Fe(H_2O)_5Cl]^{2+}$, and $PtCl_6^{2-}$, which is not the case. On this basis, I suggest an alternative which involves the pre-association of the reactants, followed by dealkylation steps [*i.e.* reactions (3)—(6)]. However, this mechanism as well as the nature of the pre-complex remain tentative until more direct methods than kinetics are used to demonstrate this pre-equilibrium.* Recognizing that the pre-association is proposed on the basis of kinetic observations, it can be concluded from the Table that while the rate-limiting steps are nearly independent of the nature of the ligands *trans* to the alkyl groups, there is a great difference between the association constants for the base-on and base-off forms. This indicates that the electronic effect of the lower base at the α (*trans*) position plays an important role in the pre-association.

Two modes can account for the dealkylation step. One possibility is the direct electrophilic attack at the α carbon of R–B_{12} by the bound $PtCl_6^{2-}$. This mode can be viewed as a Cl^+ transfer from $PtCl_6^{2-}$ concurrent with an R^- transfer from R–B_{12}, and is similar to that proposed for the reduction of *trans*-$[Pt(CN)_4Br(OH)]^{2-}$–$[Pt(CN)_4Br(H_2O)]^-$ by inorganic anions such as $S_2O_3^{2-}$ or SO_3^{2-}.[15] It is not likely to occur based on the following considerations. (1) The dealkylation rates are nearly independent of the ligands *trans* to the alkyl groups. It is well known for organocobaloximes[16,17] or organocobalamins[18] that the rates of heterolytic cleavage of Co–C bonds are very sensitive to the ligands at the *trans* position, in contrast to what was observed in the present study. (2) The dealkylation rates are comparable for CH_3–B_{12} and C_2H_5–B_{12}, strongly indicating that direct electrophilic attack at the α carbon does not occur. (3) The production of CH_3Br or *N*-methylated pyridine in bromide or pyridine solution requires the R–B_{12}^+ intermediate.

The alternative mode is a one-electron transfer from R–B_{12} to $PtCl_6^{2-}$ generating a R–B_{12}^+ and $PtCl_6^{3-}$ radical pair, as shown in equation (4). The chemical and electrochemical one-electron oxidation of organocobalt macrocyclic compounds has recently been well characterized.[17,19] It was found that the oxidized alkylcobaloxime intermediates are very susceptible to nucleophilic displacement.[20] Thus, the oxidized methylcobaloximes would react with Cl^-, OH^-, or pyridine to yield cobalt(II) complexes and CH_3Cl, CH_3OH, or *N*-methylated pyridine. The fate of the CH_3–B_{12}^+,$PtCl_6^{3-}$ radical pair, generated in reaction (4), can be described in a similar manner [reactions (5) and (6)]. Note that, in the present case, B_{12r}-(Co^{II}) is immediately oxidized by $Pt^{III}Cl_6^{3-}$ to yield H_2O–B_{12}^+ and $PtCl_4^{2-}$. The oxidation of B_{12r} by $PtCl_6^{3-}$ results in a net two-electron transfer.

Although extensive electrochemical studies have been carried out on vitamin B_{12} derivatives,[21] there appear to be no electrochemical studies on the oxidative demethylation of CH_3–B_{12}, except for the note by Rubinson *et al.*[22] They reported that a single irreversible wave was observed with a peak potential of +0.87 V *vs.* the saturated calomel electrode on the initial positive scan. Methanol and H_2O–B_{12}^+ were identified as the oxidative demethylation products. Their study clearly demonstrated that CH_3–B_{12}^+ is extremely unstable in aqueous solution. In the chemical oxidative demethylation of CH_3–B_{12} it is the subsequent rapid Co–C bond cleavage that allows the electron transfer to occur. In the present study of $PtCl_6^{2-}$, the transient CH_3–B_{12}^+ is quickly removed by the halide ions [reaction (5)]. This is the main reason for the requirement of the halide ions, and thus the rate constant, k, is composite, $k_1k_2k_3[Cl^-]/(k_{-1}k_{-2}[CH_3Cl] + k_{-1}k_3 + k_2k_3[Cl^-])$. For the extreme case of $k_2k_3[Cl^-] \gg k_{-1}k_2[CH_3Cl] + k_{-1}k_3$, $k = k_1$. Figure 4 also demonstrates the secondary $[Cl^-]$ effect, *i.e.* the magnitude of the association constant (K_3) increases as $[Cl^-]$ is increased.

In summary, this report presents evidence for a one-electron transfer from CH_3–B_{12} to $PtCl_6^{2-}$ to yield a radical pair. In previous studies[3] on the methylation of PtL_4^{2-}–$XPtL_4'Y^{2-}$ couples by CH_3–B_{12} it has been suggested that the rate-limiting step in the methyl-transfer process is a one-electron transfer from CH_3–B_{12} to a $Pt^{IV}\cdots X\cdots Pt^{II}$ intermediate to generate a radical pair which then collapses to yield the observed methyl-transfer products. The present paper demonstrates that the electron transfer from CH_3–B_{12} to the platinum(IV) complex is indeed feasible. It should be pointed out, however, that in the methyl-transfer route for Pt^{IV}–Pt^{II} couples the platinum(III) radical generated is most likely a five-co-ordinated species which is capable of accepting a methyl radical to produce the methylplatinum(IV) product. In the case of the $PtCl_6^{2-}$ route, the platinum(III) radical generated is probably a six-co-ordinated species which collapses to yield the $PtCl_4^{2-}$ product.

* In principle, there should be a spectral change due to the pre-association of reactants, in particular, for an equilibrium constant of 5.8×10^2 dm^3 mol^{-1} (Table). However, this equilibrium constant is an extrapolation from the kinetic study in the range pH 0—2. At pH 7 where CH_3–B_{12} can be considered to be predominantly in the base-on form, appreciable amounts of CH_3–B_{12} would be demethylated by a high level of $PtCl_6^{2-}$ during the mixing time. This difficulty, together with the possibility that the actual spectral change may be small, prevent a meaningful spectral analysis for evidence of the pre-association. Future experiments on this aspect will focus on the inhibition by $CrCl^{2+}$ which is electron-transfer inert and paramagnetic, and ^1H and ^{13}C n.m.r. studies of CH_3–B_{12} in the presence of $CrCl^{2+}$.

Acknowledgements

I am indebted to Drs. J. Pignatello and K. Mann for their stimulating discussions, and to Dr. H. P. C. Hogenkamp for his kind support. This research was carried out during the author's postdoctoral period in his laboratory.

References

1 G. Agnes, S. Bendle, H. A. O. Hill, F. S. Williams, and R. J. P. Williams, *Chem. Commun.*, 1971, 850; G. Agnes, H. A. O. Hill, J. M. Pratt, S. C. Ridsdale, F. S. Kennedy, and R. J. P. Williams, *Biochim. Biophys. Acta*, 1971, **252**, 207.

2 R. T. Taylor and M. L. Hanna, *Bioinorg. Chem.*, 1976, **6**, 281; R. T. Taylor and M. L. Hanna, *J. Environ Sci. Health, Sect. A*, 1976, **11**, 201; R. T. Taylor, J. A. Happe, and R. Wu, *ibid.*, 1978, **13**, 707; R. T. Taylor, J. A. Happe, M. L. Hanna, and R. Wu, *ibid.*, 1979, **14**, 87.
3 Y-T. Fanchiang, W. P. Ridley, and J. M. Wood, *J. Am. Chem. Soc.*, 1979, **101**, 1442; Y-T. Fanchiang, J. J. Pignatello, and J. M. Wood, *Organometallics*, 1983, **2**, 1748, 1752; Y-T. Fanchiang and J. J. Pignatello, *Inorg. Chim. Acta*, 1984, **91**, 147.
4 See R. C. Wright and G. S. Laurence, *J. Chem. Soc., Chem. Commun.*, 1972, 132; G. E. Adams, R. B. Broszkiewicz, and B. D. Michael, *Trans. Faraday Soc.*, 1968, **64**, 1256; J. Halpern and M. Pribanic, *J. Am. Chem. Soc.*, 1968, **90**, 5942.
5 W. R. Mason, *Coord. Chem. Rev.*, 1972, **2**, 241.
6 H. P. C. Hogenkamp, J. E. Rush, and C. A. Swenson, *J. Biol. Chem.*, 1965, **240**, 3641; D. Dolphin, *Methods Enzymol.*, 1971, **18C**, 34.
7 W. Friedrich and K. Bernhauer, *Chem. Ber.*, 1956, **9**, 2030.
8 J. M. Pratt, 'Inorganic Chemistry of Vitamin B_{12},' Academic Press, London, 1972, p. 114.
9 W. W. Reenstra and W. P. Jencks, *J. Am. Chem. Soc.*, 1979, **101**, 5780.
10 Y-T. Fanchiang, *Inorg. Chem.*, 1983, **22**, 1693.
11 Y-T. Fanchiang, *Organometallics*, 1983, **2**, 121.
12 Y-T. Fanchiang, *Inorg. Chem.*, 1982, **21**, 2344.
13 Y-T. Fanchiang, *Inorg. Chem.*, 1984, **23**, 3983.
14 Y-T. Fanchiang, *Int. J. Chem. Kinet.*, 1984, **16**, 277.
15 W. K. Wilmarth, Y-T. Fanchiang, and J. E. Byrd, *Coord. Chem. Rev.*, 1983, **51**, 141.
16 K. L. Brown, *J. Am. Chem. Soc.*, 1979, **101**, 6600.
17 J. Halpern, in 'B_{12},' ed. D. Dolphin, Wiley, New York, 1982, p. 501 and refs. therein.
18 W. W. Reenstra, R. H. Abeles, and W. P. Jencks, *J. Am. Chem. Soc.*, 1982, **104**, 1016.
19 W. H. Tamblyn, R. J. Klinger, W. S. Hwang, and J. K. Kochi, *J. Am. Chem. Soc.*, 1981, **103**, 3161; R. J. Klinger and J. K. Kochi, *ibid.*, 1982, **104**, 4186.
20 P. Abley, E. R. Dockal, and J. Halpern, *J. Am. Chem. Soc.*, 1972, **94**, 659; J. Halpern, M. S. Chan, J. Hanson, T. S. Roche, and J. A. Topich, *ibid.*, 1975, **97**, 1606; J. Halpern, M. S. Chan, T. S. Roche, and G. M. Tom, *Acta Chem. Scand., Ser. A*, 1979, **33**, 141; J. A. Topich and J. Halpern, *Inorg. Chem.*, 1979, **18**, 1339.
21 D. Lexa and J-M. Saveant, *Acc. Chem. Res.*, 1983, **16**, 235.
22 K. A. Rubinson, E. Itabashi, and H. B. Mark, jun., *Inorg. Chem.*, 1982, **21**, 3571.

Received 9*th January* 1984; *Paper* 4/034