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REACTIONS OF ALKYLCOBALAMINS WITH PLATINUM COMPLEXES

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CONTENTS

A. INTRODUCTION

Interest in the reactions of methylcobalamin ($CH_3 - B_{12}$) with electrophiles is a direct result of the discovery of methylation of mercuric ions by $CH_3 - B_{12}$ [1–3]. Elucidation of the mechanisms for reactions between $CH_3 - B_{12}$ and electrophiles has been the goal of a number of laboratories for some time [4–7]. Significant progress towards this goal has been achieved with the use of B_{12} model compounds [8,9]. In 1971 Agnes et al. reported an unusual reaction of $CH_3 - B_{12}$ with platinum complexes [10,11], in which the demethylation of $CH_3 - B_{12}$ by these complexes was shown to require the addition of both Pt(II) and Pt(IV) oxidation states. Since then this reaction has been extensively investigated in several laboratories. In 1974 Scovell reported the demethylation of $CH_3 - B_{12}$ by $PdCl_4^{2-}$ [12]. These studies have a significant implication in the understanding of reactions between $CH_3 - B_{12}$ and electrophiles because they revealed features which have not been reflected by the chemical model systems. This is potentially important with respect to the question of why nature selected corrin as the macrocyclic ligand in the $CH_3 - B_{12}$-dependent biological methyl-transfer processes.

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This article reviews the studies of reactions of alkylcobalamins with platinum complexes. The mechanisms for reactions between alkylcobalamins and platinum complexes can be understood readily within the context of electron-transfer reactions in inorganic or organometallic systems [13,14].

B. FUNDAMENTAL PROPERTIES OF ALKYLCOBALAMINS

I first examine the basic properties of alkylcobalamins directly related to the mechanisms for reactions with platinum complexes, placing special emphasis on the properties arising from the corrin ring ligand. An excellent monograph on the inorganic chemistry of vitamin B_{12} derivatives appeared in 1972 [15]. It is known that the corrinoid ring is less π-conjugated than that of porphyrin, with only 12 π-electrons. The C1 and C19 carbons are connected by a single bond. The corrin π-conjugated system is horse-shoe shaped. The corrin is covalently bonded through an amide phosphate ribose side chain to a 5,6-dimethylbenzimidazole group, which coordinates with the cobalt at the α position(bottom). In acid solution, the benzimidazole is protonated and dissociated from the cobalt atom [16]. The alkyl-transfer activity and some properties of alkylcobalamins are very sensitive to the nucleotide side chain base-on and base-off equilibrium.

(i) Ultraviolet–visible spectra and electronic structures

All corrinoid compounds are deeply colored with great variation in color. This makes the different corrinoids easily distinguishable from one other. The very high extinction coefficients permit experiments to be carried out with a tiny amount of material, and therefore absorption spectroscopy plays a very important role in corrinoid chemistry.

The absorption spectroscopic characteristics of vitamin B_{12} derivatives have been reviewed thoroughly by Giannotti [17]. A particularly noteworthy point lies in the UV–visible spectrum of the cobalt-free corrinoid [18]. Comparison of the corrin ring optical spectrum with that of cobalt-containing cobalamins clearly indicates that the optical bands of B_{12} derivatives originate mainly from a π–π^* transition in the corrin ring, although they are not totally free from the influence of the axial ligands or from the cobalt oxidation states. This is important because it indicates that any significant perturbation of the $CH_3 - B_{12}$ electronic spectrum prior to the methyl-transfer step is likely to arise from the interactions on the corrin ring ligand, except for the dissociation of a benzimidazole base from the cobalt.

(ii) Nuclear magnetic resonance spectra

The structure and function of vitamin B_{12} derivatives determined by nuclear magnetic resonance spectroscopy must obviously be based on secure

assignment. Fortunately, the proton, carbon-13 and phosphorus-31 NMR spectra have been carefully examined and securely assigned [19–23]. An interesting discovery which is an extension of the work of Hensens et al., is that the ^1H NMR spectrum of $CH_3 - B_{12}$ in aqueous solution shows concentration-dependent shifts which conform to a monomer–dimer equilibrium [24]. The shift changes on dimerization are characteristic of ring current effects and support a structure in which the corrin rings are adjacent and roughly parallel–planar. The $CH_3 - B_{12}$ dimer is favored by increasing NaCl concentration (but not $NaClO_4$), and disfavored by added miscible organic solvents such as CH_3OH. The energy of dimerization originates at least in part from π–π interactions between corrin rings. This discovery is important in that it indicates that some organic π-compounds or metal complexes may associate with $CH_3 - B_{12}$ facilitating a methyl-transfer reaction. Self-association and association with aromatic compounds are well-known among the metalloporphyrins [25–28]. However, the cobalamin current ring must include the cobalt atom.

(iii) Oxidation–reduction potentials of methylcobalamin

Extensive electrochemical studies on vitamin B_{12} derivatives have been carried out [29]. Lexa et al. have examined the one-electron electrochemical reduction of $CH_3 - B_{12}$ [30]. Of particular importance to the study of reactions between $CH_3 - B_{12}$ and platinum complexes is the electrochemical oxidation of $CH_3 - B_{12}$. Rubinson et al. reported that a single irreversible wave was observed with a peak potential of 0.87 V vs. SCE on the initial positive scan [31]. Methanol and H_2O-B_{12}^+ are the oxidative demethylation products. Their study clearly indicates that the $CH_3 - B_{12}^+$ cation is extremely unstable in aqueous solution. It is unfortunate that there is no study available of the electrochemical oxidation of $CH_3 - B_{12}$ at low temperature where the $CH_3 - B_{12}^+$ cation may survive.

C. METHYLATION OF PLATINUM(II) AND PLATINUM(IV) COUPLES BY METHYLCOBALAMIN

Agnes et al. reported that the demethylation of $CH_3 - B_{12}$ by platinum complexes required the addition of platinum in both Pt(II) and Pt(IV) oxidation states [10,11]. A pathway for this reaction was formulated and called the "redox switch" reaction. Later, in a series of reports, Taylor et al. showed that a mixture of $PtCl_6^{2-}$ and $PtCl_4^{2-}$ reacted with $^{14}CH_3 - B_{12}$ to give a stable $^{14}CH_3Pt$ complex, for which the structure $^{14}CH_3PtCl_3^{2-}$ was suggested [32–35]. The $^{14}CH_3Pt$ product was isolated chromatographically and characterized with respect to its ^1H and ^{35}Cl NMR, X-ray photoelectron and light absorption spectra. On the other hand, we have characterized the CH_3Pt product with respect to its ^{13}C and ^{195}Pt NMR spectra [36–40]. The

^{195}Pt NMR spectrum of a reaction of 1:1:1 $^{13}CH_3 - B_{12}$ (60% ^{13}C): $PtCl_6^{2-}$: $PtCl_4^{2-}$ showed that $PtCl_6^{2-}$ is consumed in the reaction while $PtCl_4^{2-}$ at -1619 ppm ($PtCl_6^{2-}$ reference) remains as a product [37]. In addition a resonance appears at -750 ppm that represents the isotope triplet of a methylplatinum compound. The relative intensities of the peaks agree well with those expected for a C–Pt compound composed of 60% ^{13}C. The ^{13}C–^{195}Pt spin–spin coupling constant obtained from the outer peaks (450 Hz) is in the range reported for other methylplatinum compounds [41]. The ^{195}Pt chemical shift of the methylplatinum product clearly indicates that the methylplatinum species is $CH_3PtCl_5^{2-}$, since it lies between $PtCl_6^{2-}$ and $PtCl_4^{2-}$. Therefore, the ^{195}Pt NMR study leads to the reaction in eqn. (1)

$$CH_3 - B_{12} + Pt(II) + Pt(IV) \xrightarrow{H_2O} H_2O\text{-}B_{12}^+ + CH_3Pt(IV) + Pt(II) \qquad (1)$$

Methylplatinum products were also studied by ^{13}C NMR spectroscopy [37] in the reactions of $^{13}CH_3 - B_{12}$ (90% ^{13}C) with each of $PtCl_4^{2-}/PtCl_6^{2-}$, $PtCl_4^{2-}/Pt(CN)_4Cl_2^{2-}$, $PtCl_4^{2-}/Pt(CN)_5Cl^{2-}$, $Pt(CN)_4^{2-}/PtCl_6^{2-}$, $Pt(CN)_4^{2-}/Pt(CN)_4Cl_2^{2-}$ and $Pt(CN)_4^{2-}/Pt(CN)_5Cl^{2-}$. The methylplatinum produces a pseudo triplet with 1:4:1 relative intensities at 3.3 ppm (465 Hz), 3.4 ppm (463 Hz), 3.3 ppm (462 Hz), -9.6 ppm (378 Hz), -9.4 ppm (380 Hz), -16.3 ppm (311 Hz), respectively (TSP reference). Based on these chemical shifts and spin–spin coupling constants, it was concluded that the methyl group is transferred to the platinum of the Pt(II) reactant.

The kinetics of the demethylation of $CH_3 - B_{12}$ by mixtures of Pt(IV) ($PtCl_6^{2-}$, $Pt(CN)_4Cl_2^{2-}$, $Pt(CN)_5Cl^{2-}$, $Pt(CN)_5I^{2-}$, $Pt(CN)_6^{2-}$) and Pt(II) ($PtCl_4^{2-}$, $Pt(CN)_4^{2-}$) in aqueous solution are consistent with the reversible formation of complexes of $CH_3 - B_{12}$ and Pt(II) to form a binuclear intermediate, followed by a reversible reaction of this complex with Pt(IV) to form a trinuclear intermediate prior to the rate-limiting step (Scheme 1). Spectroscopic evidence (UV–visible region) is presented for both the binuclear and trinuclear intermediates, and the equilibrium constants obtained thereby agree well with those determined from the kinetics [38]. Evidence is presented in support of a Pt(II) bond in the binuclear intermediate at a site on the β-side of the corrin (vide infra). Reaction of this intermediate with Pt(IV) leads to a chloride-bridged $(CH_3 - B_{12}) \cdots Pt^{IV}L_4\text{–}X \cdots Pt^{II}L'_4$ species.

$$CH_3 - B_{12} + Pt^{II}L_4^{2-} \overset{K'}{\rightleftharpoons} CH_3 - B_{12}, Pt^{II}L_4^{2-} \qquad (2)$$

$$CH_3 - B_{12}, Pt^{II}L_4^{2-} + XPt^{IV}L'_4Y^{2-} \overset{K''}{\rightleftharpoons} CH_3 - B_{12}, Pt^{IV}L_4 - X - Pt^{II}L'_4 + Y^- \qquad (3)$$

$$CH_3 - B_{12}, Pt^{IV}L_4 - X - Pt^{II}L'_4 + H_2O \xrightarrow{k} H_2O - B_{12}^+ + CH_3Pt^{IV}L_4X^{2-} + Pt^{II}L'^{2-}_4 \qquad (4)$$

$$CH_3 - B_{12} + PtL_4^{2-} + XPtL'_4Y^{2-} + H_2O \rightarrow H_2O - B_{12}^+ + CH_3PtL_4X^{2-} + PtL'^{2-}_4 + Y^- \qquad (5)$$

Scheme 1

TABLE 1

Kinetic parameters for the demethylation of methylcobalamin by mixtures of platinum(II) and platinum(IV) complexes

$XPtL'_4Y^{2-}$	$PtCl_4^{2-}$		$Pt(CN)_4^{2-}$			
	$k \cdot K''$ ($M^{-1}s^{-1}$)	K' (M^{-1})	$k \cdot K''$ ($M^{-1}s^{-1}$)	k (s^{-1})	K' (M^{-1})	K'' (M^{-1})
Base-on $CH_3 - B_{12}$						
$PtCl_6^{2-}$	1.1×10^2	3.4×10^3	3.5		3.5×10^3	
$Pt(CN)_4Cl_2^{2-}$	1.5×10	5.1×10^3		3.0×10^{-3}	2.0×10^3	8.1×10^3
$Pt(CN)_5Cl^{2-}$	very slow			3.6×10^{-3}	6.5×10^3	1.0×10^3
$Pt(CN)_5I^{2-}$	no reaction				no reaction	
$Pt(CN)_6^{2-}$	no reaction				no reaction	
Base-off $CH_3 - B_{12}$						
$PtCl_6^{2-}$	0.88	3.3×10^2	1.9		2.3×10^2	

$u = 1.0$ M (NaCl); temperature = 23°C.

The values of K' were measurable for all the Pt(II) complexes used. In some systems, i.e. $Pt(CN)_4^{2-}/Pt(CN)_4Cl_2^{2-}$ or $Pt(CN)_4^{2-}/Pt(CN)_5Cl^{2-}$, the rate constant k could be separated from equilibrium constant K''. In other systems, however, only a composite constant $k \cdot K''$ could be obtained. The kinetic parameters are listed in Table 1.

The methylation of $PtL_4^{2-}/XPtL'_4Y^{2-}$ couples by $CH_3 - B_{12}$ is remarkable in that it showed that bonding of platinum complexes to the cobalamin is a prerequisite of the methyl-transfer reaction. It also showed that the platinum products are $CH_3Pt(IV)L_4X^{2-}$ and $Pt(II)L'^{2-}_4$ complexes and that the methyl group is transferred to the platinum of the Pt(II) reactant. These features have not been shown to occur with the B_{12} model compounds. It is thus of special interest to elucidate the mechanism for the Co–C bond cleavage. Three model systems are available.

(a) Direct displacement of the cobalt by attack at the α carbon

Reactions of electrophiles with δ-bonded organotransition-metal complexes involving direct displacement of the metal by attack at the α (saturated) carbon have been reviewed by Johnson [42]. Previously, reactions of mercuric ions with $CH_3 - B_{12}$ were widely discussed in terms of this mechanism [43–45]. This mechanism represents the simplest version for the Co–C bond cleavage by platinum complexes. It has been suggested that direct attack by bound platinum on the Co–C bond in the trinuclear intermediate is unlikely. The kinetic results of the $Pt(CN)_4^{2-}/PtCl_6^{2-}$ system show that the rate constant for the rate-determining step is insensitive to the presence or absence of the axial benzimidazole ligand. Later, I obtained the rate con-

stants for the base-on and base-off $CH_3 - B_{12}$ in the $PtCl_4^{2-}/PtCl_6^{2-}$ system and these indicate that the previous suggestion may be invalid (Table 1).

(b) Homolytic cleavage of the Co–C bond by platinum(III)

The following mechanism is based largely on (i) the knowledge that S_H2 reactions, i.e. $R\cdot$ (or $M\cdot$) + R′–Co(III) → R–R′(or R′–M) + Co(II), can be surprisingly facile [46], and (ii) the knowledge that even classic, two-electron transfers like Pt(II)/Pt(IV) proceed kinetically via two one-electron-transfer steps in an ECE mechanism where C is a geometry or conformation step which triggers the second step [47].

$$CH_3 - B_{12}\text{--}Pt^{IV}L_4\text{–}X\text{--}Pt^{II}L'^{3-}_4 \rightarrow CH_3 - B_{12}\text{--}Pt^{III}L_4\text{–}X\text{--}Pt^{III}L'^{3-}_4$$

$$CH_3 - B_{12}\text{--}Pt^{III}L_4\text{–}X\text{--}Pt^{III}L'^{3-}_4 \rightarrow B_{12r} + CH_3Pt^{IV}L_4X^{2-} + Pt^{III}L'^{-}_4$$

$$B_{12r} + Pt^{III}L'^{-}_4 + H_2O \overset{\text{rapid}}{\rightarrow} H_2O - B_{12}^{+} + Pt^{II}L'^{2-}_4$$

The Pt(III) atom closest to the methyl group undergoes a S_H2 reaction, followed by a rapid one-electron-transfer from B_{12r} to the other Pt(III), all in the solvent cage.

(c) Single-electron-transfer (SET) methyl-transfer mechanism

Methylcobalamin is oxidized by the bound platinum via the following reaction

$$CH_3 - B_{12}\text{--}Pt^{IV}L_4 - X\text{--}Pt^{II}L'^{3-}_4 \rightarrow (CH_3 - B_{12})^{+}(Pt^{III}L_4 - X\text{--}Pt^{II}L'_4)^{4-}$$

Electron transfer may be succeeded by either rapid methyl transfer to platinum within the solvent-caged radical pair, or by dissociation of the radical pair followed by re-encounter with methyl-transfer. Each of these post rate-limiting steps may be considered as homolytic attack of the reduced platinum on the methyl carbon of the $CH_3 - B_{12}^{+}$ cation. This reaction mechanism is reminiscent of the reactions by I_2 and other electrophiles on organometallic compounds of lead and tin, which were shown to occur by charge-transfer complexation, electron-transfer to form a radical pair, and finally transfer of the organic group to the electrophile within the radical pair [14,48].

At present there is no concrete evidence to rule out or support any of the three mechanisms. A noteworthy point, however, lies in the methyl-transfer reaction of methylaquo (3,5,6-trimethylbenzimidazolyl)cobamide with $PtCl_6^{2-}$ and $PtCl_4^{2-}$ [39]. Carbon-13 NMR characterization of the methyl-transfer products showed that 85% are $CH_3PtCl_5^{2-}$, and 15% ethane. Ethane could

have arisen only via radical reaction

$$CH_3\text{–cba} \overset{-e}{\rightleftharpoons} CH_3 - cba^+ \overset{H_2O}{\rightarrow} H_2O - cba^+ + CH_3.$$

This result, together with the dealkylation of alkylcobalamins by $PtCl_6^{2-}$ alone (see below), lead us to favor the single-electron-transfer methyl-transfer mechanism. It should be emphasized that in this mechanism, an important driving force is derived from the interactions within the $CH_3 - B_{12}$ $\cdots$ PtL_4–X $\cdots$ PtL'^{3-}_4 complex. Another important point is that the cleavage of the Co–C bond of the $CH_3 - B_{12}^+$ radical must be much faster than that of the reverse reaction of the electron-transfer step because the electron-transfer from $CH_3 - B_{12}$ to the bound platinum compounds is highly endothermic.

D. INTERACTIONS OF ALKYLCOBALAMINS WITH PLATINUM(II) COMPLEXES

The interaction of $CH_3 - B_{12}$ with platinum(II) complexes such as $PtCl_4^{2-}$, $Pt(CN)_4^{2-}$, $Pt(SCN)_4^{2-}$ and *cis*-$Pt(NH_3)_2(H_2O)_2^{2+}$ in aqueous solution has been examined [40,49,50]. Although these platinum(II) complexes do not demethylate $CH_3 - B_{12}$, they interact with $CH_3 - B_{12}$ on at least three sites. One site, which is occupied by $PtCl_4^{2-}$, $Pt(CN)_4^{2-}$ and $Pt(SCN)_4^{2-}$, is located on the Co–CH_3 side of the corrin macrocycle (β-side), and is involved in the methyl-transfer process in the presence of a Pt(IV) complex [40]. Another site for $Pt(SCN)_4^{2-}$ and *cis*-$Pt(NH_3)_2(H_2O)_2^{2+}$ is the N – 3 of the benzimidazole group, resulting in dissociation of this group from cobalt [49,50]. Similar interactions have been reported for alkylcobalamins with $PdCl_4^{2-}$ [12,51]. An additional site for $Pt(CN)_4^{2-}$ has a binding constant much smaller than that of the first binding site. The ^1H NMR changes indicate perturbations but not dissociation of the benzimidazole group.

Bonding of a platinum(II) complex such as $Pt(CN)_4^{2-}$ or $PtCl_4^{2-}$ to the β-side of the corrin macrocycle results in a significant change in the electronic spectrum of $CH_3 - B_{12}$ [38–40]. The α and γ bands (515 and 340 nm, respectively) of $CH_3 - B_{12}$ are blue-shifted ca. 3 nm, in the presence of the platinum(II) complex and a prominent shoulder appears at 355 nm. It is possible that the binding energy is due, in part, to electrostatic attraction from ion pairing between the dinegatively-charged platinum(II) complex and the positively-charged cobalt macrocycle. However, this is not likely to be the only force of attraction between Pt(II) and $CH_3 - B_{12}$ in the medium of 1 M NaCl, because competition with sodium ions would be expected to interfere with such an interaction. There is another possible type of bonding of Pt(II) to the Co–CH_3 side of the corrin macrocycle. Pt(II) may interact

with the orbitals of the corrin ring π-system to form a complex similar to the well-known syngergic donor–acceptor bond between Pt(II) complexes and olefins or polyenes [52]. The α and γ bands in the electronic spectrum of $CH_3 - B_{12}$ have been atrributed to $\pi \rightarrow \pi^*$ transitions involving orbitals largely on the corrin π-conjugated system [17]. Upon bonding with a Pt(II) complex, the gap between π and π^* orbitals is expected to increase after overlap with the appropriate δ and π orbitals centered on the platinum, and resulting in the blue shift which is observed. The shoulder at 355 nm is similar both to that observed in the interaction of base-off $CH_3 - B_{12}$ with $HgCl_4^{2-}$ (extinction coefficient at 370 nm is 1.2×10^4 M^{-1} cm^{-1}) [53], and to the charge-transfer band between $CH_3 - B_{12}$ corrin π-orbitals and tetracyanoethylene (extinction coefficient at 420 nm is 1.1×10^4 M^{-1} cm^{-1} in CH_3OH–H_2O medium) [54]. Therefore, spectroscopic studies of the interactions between platinum complexes and the $CH_3 - B_{12}$ β-side of the macrocycle lend support to the suggestion that an important driving force for the electron-transfer reactions must be derived from interactions between $CH_3 - B_{12}$ and platinum complexes.

The addition of up to 5 equivalents of $Pt(CN)_4^{2-}$ or $PtCl_4^{2-}$ to aqueous $CH_3 - B_{12}$ (10^{-3} M) does not cause any appreciable change in the ^1H NMR spectrum of $CH_3 - B_{12}$ [40], despite the fact that almost complete comlexation occurs under these conditions as judged from the equilibrium constants of eqn. 2 ($> 10^3$ M^{-1}). The absence of changes in the ^1H NMR spectrum of $CH_3 - B_{12}$ following interaction of platinum complexes with the corrin β-side is not unexpected for the type of bonding described above [52]. An incorrect conclusion concerning the ^1H NMR spectroscopic changes of $CH_3 - B_{12}$ with platinum was drawn in 1979 [36], because it was not known that the ^1H NMR chemical shifts of $CH_3 - B_{12}$ are dependent on the concentrations of $CH_3 - B_{12}$ and NaCl.

E. DEALKYLATION OF ALKYLCOBALAMINS BY $PtCl_6^{2-}$ AND $PdCl_4^{2-}$

During the course of investigation of the methyl-transfer reactions between $CH_3 - B_{12}$ and $Pt(II)L_4^{2-}/XPt(IV)L'_4Y^{2-}$ couples, it was discovered that $PtCl_6^{2-}$ alone could indeed demethylate $CH_3 - B_{12}$. Although the rate of the $PtCl_6^{2-}$ route is negligible compared with that of the $PtCl_4^{2-}/PtCl_6^{2-}$ route, evidence was obtained indicating that it was not initiated by traces of a $PtCl_4^{2-}$ impurity [55], since the demethylation of $CH_3 - B_{12}$ by $PtCl_6^{2-}$ alone is much slower in perchlorate solution than in chloride solution. In contrast, demethylation of $CH_3 - B_{12}$ (4.0×10^{-5} M) by a mixture of 5.0×10^{-3} M $PtCl_6^{2-}$ and 5.0×10^{-5} M $PtCl_4^{2-}$ occurred readily in perchlorate solution with a rate comparable with that in chloride solution.

Demethylation of $CH_3 - B_{12}$ by $PtCl_6^{2-}$ in chloride solution produces

$H_2O - B_{12}^+$, CH_3Cl and $PtCl_4^{2-}$. In bromide solution, however, the demethylation product is CH_3Br. The stoichiometry can be described by

$$CH_3 - B_{12} + PtCl_6^{2-} + X^- + H_2O \rightarrow H_2O - B_{12}^+ + CH_3X + PtCl_4^{2-} + 2Cl^-$$

Kinetic data described by eqn. 6, suggest an association between $CH_3 - B_{12}$ and $PtCl_6^{2-}$ prior to the demethylation step. Thus, the reaction of $CH_3 - B_{12}$ with $PtCl_6^{2-}$ can be delineated with the following mechanism

$$\frac{d[H_2O - B_{12}^+]}{dt} = \frac{k \cdot K[PtCl_6^{2-}][CH_3 - B_{12}]}{1 + K[PtCl_6^{2-}]} \quad (6)$$

$$CH_3 - B_{12} + PtCl_6^{2-} \overset{K}{\rightleftharpoons} CH_3 - B_{12}, PtCl_6^{2-} \quad (7)$$

$$CH_3 - B_{12}, PtCl_6^{2-} + H_2O \overset{k}{\rightarrow} H_2O - B_{12}^+ \text{ etc..} \quad (8)$$

In the studies of demethylation by $PtCl_6^{2-}$, the Pt(IV) concentration exceeds that of $CH_3 - B_{12}$ by a factor of at least 150 in order to avoid take-over by the $PtCl_4^{2-}/PtCl_6^{2-}$ route. Kinetic parameters for the reactions of alkylcorrinoids with $PtCl_6^{2-}$ in chloride media are presented in Table 2.

The product CH_3Br of the reaction of $CH_3 - B_{12}$ with $PtCl_6^{2-}$ in NaBr solution, clearly eliminates direct electrophilic attack at the α carbon by $PtCl_6^{2-}$. Indeed, the product CH_3X can be interpreted readily in terms of the $CH_3 - B_{12}^+$ radical, generated by one-electron-transfer from $CH_3 - B_{12}$ to $PtCl_6^{2-}$. This mechanism is adopted from the work of Halpern et al. on the chemical and electrochemical oxidative dealkylation of alkylcobaloximes and other B_{12} model compounds [56–62]. They have shown that alkylbis(dimethylglyoximato)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 have been characterized

TABLE 2
Kinetic parameters for the reactions of alkylcorrinoids with $PtCl_6^{2-}$

		$k(s^{-1}) \times 10^3$	$K(M^{-1})$
$CH_3 - B_{12}$	Base-on	ca. 4	5.8×10^2
	Protonated base-off	ca. 4	1.5×10
$C_2H_5 - B_{12}$	Base-on	1.2	1.5×10
	Protonated base-off	1.2	3.5
Methylaquo(3,5,6-trimethylbenzimidazolyl)cobamide		3.2	7.1

$u = 1.0$ M(HCl + NaCl); 23°C.

as organocobalt(IV) complexes. 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. Therefore, the product experiments, together with the comparable dealkylation rate constants for $CH_3 - B_{12}$ and $C_2H_5 - B_{12}$ (Table 2) strongly suggest an electron-transfer mechanism for the reactions between alkylcobalamins and $PtCl_6^{2-}$ (eqns. 9–12).

$$CH_3 - B_{12} + PtCl_6^{2-} \overset{K}{\rightleftharpoons} CH_3 - B_{12}, PtCl_6^{2-} \tag{9}$$

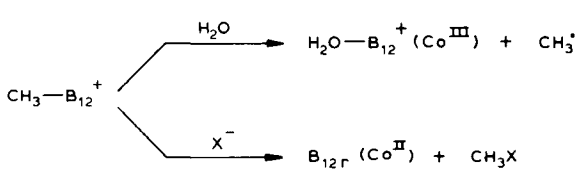
$$CH_3 - B_{12}, PtCl_6^{2-} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} CH_3 - B_{12}^+, PtCl_6^{3-} \tag{10}$$

$$CH_3 - B_{12}^+, PtCl_6^{3-} + X^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} B_{12r}, PtCl_6^{3-} + CH_3X \tag{11}$$

$$B_{12r}, PtCl_6^{3-} + H_2O \overset{k_3}{\rightleftharpoons} H_2O - B_{12}^+ + PtCl_4^{2-} + 2Cl^- \tag{12}$$

where k of eqn. 8 equals $k_1k_2k_3[X^-]/(k_{-1}k_{-2}[CH_3X] + k_{-1}k_3 + k_2k_3[X^-])$. At $[Cl^-] \geqq 0.5$ M, $k_2k_3[Cl^-]$ is much larger than $k_{-1}k_{-2}$ $[CH_3Cl]$ and $k_{-1}k_3$. Thus, k equals k_1.

The mechanism for the demethylation of $CH_3 - B_{12}$ by $PtCl_6^{2-}$, and the methyl-transfer reactions to Pt(II)/Pt(IV) couples can be unified by the concept of single-electron transfer which has been explored by the oxidative dealkylation of alkylcobalamins by $IrCl_6^{2-}$, $Fe(H_2O)_5Cl^{2+}$, I_2, etc. [63–65]. An important driving force for this electron-transfer reaction must be derived from the interactions between $CH_3 - B_{12}$ (perhaps on the corrin ring) and platinum complexes. This suggestion is based on the kinetics and thermodynamics which indicate the electron-transfer step is virtually "irreversible" and highly endothermic. In the methyl-transfer route with Pt(II)/Pt(IV) couples, the Pt(III) radical generated is most likely a five-coordinate species which is capable of accepting a methyl radical to produce the $CH_3Pt(IV)$ product. In the $PtCl_6^{2-}$ route, the Pt(III) radical generated is probably a six-coordinate species which collapses to the $PtCl_4^{2-}$ and CH_3X products. All together, the fate of the $CH_3 - B_{12}^+$ cation radical can be described by eqn. (13).



(13)

The reaction of $CH_3 - B_{12}$ with $PtCl_6^{2-}$ is remarkably similar to that with

$PdCl_4^{2-}$ which produces $H_2O - B_{12}^+$ (and chlorocobalamin), palladium metal and CH_3Cl [12]. Scovell suggested that the demethylation of $CH_3 - B_{12}$ by palladium(II) could be interpreted in terms of direct electrophilic attack at α carbon with a CH_3^- ion transfer from cobalt to palladium. This reaction is complicated by the relatively rapid interaction between palladium(II) and the benzimidazole base, and by the effect of Cl^- ion on the reaction rates. The most unusual aspect of this suggestion concerns the postulate that low-valent d^8 $PdCl_4^{2-}$ is the active electrophile in the formation of the unstable methylpalladium(II) complex from methylcobalamin. On the other hand, it appears that the mechanism for the Co–C bond cleavage can be interpreted within the context of a one-electron transfer (eqns. 14–16).

$$CH_3 - B_{12} + PdCl_4^{2-} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} CH_3 - B_{12}^+, PdCl_4^{3-} \tag{14}$$

$$CH_3 - B_{12}^+, PdCl_4^{3-} + Cl^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} B_{12r}, PdCl_4^{3-} + CH_3Cl \tag{15}$$

$$B_{12r}, PdCl_4^{3-} + H_2O \xrightarrow{k_3} H_2O - B_{12}^+ + Pd^0 + 4Cl^- \tag{16}$$

F. PLATINUM(II) COMPLEX OF METHYLCOBALAMIN AS A POTENTIAL ANTI-TUMOR AGENT

The anti-cancer activities of *cis*-diamminedichloroplatinum(II) (cisplatin) are well established [66–69]. It is known that cisplatin has severe side effects. The cobalamin–platinum complexes are interesting because it has been reported that the administration of pharmacological doses of vitamin B_{12} and leucovorin significantly increased the life-span of leukemic rats treated with cisplatin [70]. These observations suggest that vitamin B_{12} may be used to counteract the side effects of cisplatin chemotherapy. Thus, the cobalamin-(*cis*)diamminediaquaplatinum(II) complexes may represent a new class of platinum-containing anti-tumor agents. (This idea was developed in Professor H.P.C. Hogenkamp's laboratory during 1981–1982.) A platinum(II)-methylcobalamin compound [49,50] was synthesized from $CH_3 - B_{12}$ and *cis*-$Pt(NH_3)_2(H_2O)_2^{2+}$ and its anti-cancer activity tested with leukemic BDF_1 female mice. (The animal test was carried out in Professor R. Borch's laboratory, then in the Department of Chemistry, University of Minnesota.) In the fairly crude experiment with a total of 13 mice, the cobalamin-Pt(II) compound seems to work at least as well as cisplatin. The cobalamin-Pt(II) gave an increased survival time (ILS) of 63%. An equivalent of cisplatin produces an ILS of ca. 50%. Myasishcheva et al. [71] and Soyna et al. [72] also reported that cobalamin-tetrachloropalladate(II) complexes are anti-tumor agents.

G. CONCLUDING REMARKS

Methyl-transfer reactions between methylcobalamin and platinum complexes are significant because they demonstrate that $CH_3 - B_{12}$ is capable of methylating inert metal complexes. The importance of this discovery is enhanced by a subsequent study of the biologically-important methyl-transfer between $CH_3 - B_{12}$ and diaquocobinamide [73]. Extensive mechanistic studies on the reactions of $CH_3 - B_{12}$ with platinum complexes indicate that a classic electrophilic displacement mechanism is not sufficient to explain these reactions. In the past decade, significant advances have been made in understanding oxidative cleavage of macrocyclic Co–C bonds [56–62,74,75]. These advances greatly simplified understanding of the reactions of alkylcobalamins with electrophiles. The main purpose of this review is to show that the twin concepts, charge-transfer complex and electron-transfer reaction [14], can also be applied to understanding the reaction mechanisms of the naturally occurring alkylcorrinoids. The role that the corrin ring ligand plays in this type of electron-transfer reaction is the key to understanding $CH_3 - B_{12}$ methyl-transfer reactions. This may have implications for the mechanisms of environmentally important biomethylation processes with heavy metals such as mercury, lead, tin, selenium and arsenic [76].

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