

Methylation by Methyl Vitamin B₁₂

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Summary Methyl vitamin B₁₂ is shown to be capable of transferring methyl groups to Hg^{II}, Tl^{III}, Pt^{II}, and Au^I; two different reaction paths are involved, one of which, with Hg^{II} or Tl^{III}, is an acid-base reaction while the other is probably an oxidation-reduction reaction for it requires both Pt^{II} and Pt^{IV}, or Au^I and Au^{III}.

METHYL VITAMIN B₁₂ (MeB₁₂) has been shown to methylate Hg^{II} ions in a simple acid-base reaction¹ which may be one of the ways in which methylmercury is produced in living systems. Here we show that several other metals can be methylated producing methylating agents which could react much more rapidly than MeB₁₂ or methylmercury in further methyl transfer within biological systems.

For a comparison with Hg^{II} we have studied the metal ions of Pd, Pt, Ag, Au, Cd, Tl, and Pb. Methyl transfer was studied spectrophotometrically by adding controlled amounts of the metal ions to solutions of MeB₁₂ in a spectrophotometer cell. All reactions were carried out at 25°C in solutions buffered between pH 0 and 5 and in the presence of various anions. In all cases the product of the reaction was vitamin B_{12a} and the rate of the reaction could be followed and rate constants determined. The fate of the methyl group was determined by g.l.c. analysis.

In the case of thallium it was found that Tl^{III} salts but not Tl^I salts displaced the methyl group from the methyl vitamin. The reaction is first order in both Tl^{III} and MeB₁₂ and occurs over a wide range of pH and in a variety of buffer media. In chloride solutions the sole product is methyl chloride. The reaction resembles that of Hg^{II}.¹

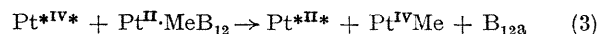
K₂PtCl₄ and K₂Pt(CN)₄ (0.01M) have no effect on MeB₁₂ (2.5 × 10⁻⁵M) under any of the conditions used. Over a wide pH range and in various salt media K₂PtCl₆ (4 × 10⁻⁴M) slowly demethylates MeB₁₂ but this reaction has been shown to be due to the partial reduction to Pt^{II} [equation (1)] by the following observations. Very fast and complete demethylation of MeB₁₂ occurs if K₂PtCl₄, 1.0 × 10⁻⁴M, and K₂PtCl₆, 2.5 × 10⁻⁵M, are both added. The reaction is stoichiometric in the Pt^{IV} salt. At pH 1.0 in chloride media the product is 100% methyl chloride as shown by g.l.c. but at pH 5.0, and at low chloride concentrations (< 10⁻³M) in acetate buffer, only 10%, at most, of the released methyl was seen as methyl chloride. The addition of acid or of sodium chloride (1.0M) caused the release of all the methyl as methyl chloride.



Equation (1) omits the essential role of PtCl₄²⁻, but the reaction rate [equation (2)] is dependent on all the components. Methyl transfer probably occurs in a reaction

$$\text{Reaction rate} = k \cdot [\text{MeB}_{12}] [\text{Pt}^{\text{II}}] [\text{Pt}^{\text{IV}}] \quad (2)$$

involving the Pt^{II} complex as an acceptor. Effectively the



methyl transfer is a two electron redox switch.

MeB₁₂ (2.5 × 10⁻⁵M) does not react with carefully deoxygenated solutions of NaAuCl₂ (1.0 × 10⁻²M) under

various conditions. There is no initial reaction with NaAuCl_4 ($3 \times 10^{-5}\text{M}$) although after some time the reaction starts but is not completed. Addition of $5 \times 10^{-5}\text{M}$ NaAuCl_2 and NaAuCl_4 causes an immediate very rapid reaction which goes to completion. The stoichiometry and rate expression of the reaction are similar to those for the reaction using platinum salts. The product of the reaction is methyl chloride. A redox mechanism is clearly implied and we shall report elsewhere on the release of methyl groups from MeB_{12} through the action of oxidising agents such as Fe^{III} and $\text{Fe}(\text{CN})_6^{3-}$ in the presence of methyl acceptors such as chloride.

Thus there are at least two very different mechanisms by which methyl transfer can occur; both can lead to rapid release of methyl groups from MeB_{12} . The first consists of acid attack by an acid such as Hg^{II} or Tl^{III} (Cd^{II} , Pb^{II} , and

In^{III} are ineffective); the other is a two-electron redox switch during which a methyl group is transferred. The latter type of reaction needs both valence states of platinum or gold. In each case the first step of the reaction is the production of the methylated metal and, as is well known, these compounds can be extremely hazardous. In the second step of reaction the methyl group can be rapidly transferred further to a good nucleophile such as chloride or bromide. The reaction could undoubtedly be used to methylate biological molecules. Methylmercury is not readily decomposed to mercury ions and methyl groups but the other methylated metals react rapidly.

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