Mercury Methylation by Methylcobalamin: Kinetics and Mechanisms Revisited

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Mercury (Hg) can be transformed in aquatic environments to the potent neurotoxin mono-methylmercury (CH_3Hg^+) species by anaerobic bacteria and archaea. Recent identification of the two-gene cluster, *hgcAB*, involved in biotic Hg methylation enables us to consider the molecular mechanisms of HgcA, a transmembrane corrinoid (vitamin B_{12}-binding) protein, and its partner ferredoxin, HgcB, in CH_3Hg^+ biosynthesis. HgcA is hypothesized to bind its B^{12} cofactor tail in a configuration in which a strictly conserved Cys residue from HgcA is coordinated to the Co center. The electron-rich Co–S bond could facilitate methyl carbanion ($:CH_3^-$) transfer to Hg^{2+}. Following carbanion transfer, the Co^{3+} in HgcA-B_{12} would need to be reduced to Co^+ before it can accept a methyl group for the next cycle; this reduction could be performed by HgcB.

To better understand the mechanism of Hg methylation by HgcA, we have reexamined the abiotic process of mercury methylation by methylcobalamin with an attempt to produce enzyme mimics. Extensive studies in the 1970s suggest that the methyl group is transferred as a negative ion, i.e., carbanion ($:CH_3^-$) from methylcobalamin to Hg^{2+} [1-2]. Using different types of alkyl substituents coordinated to the axial position of the Co, studies show that the rate of alkyl transfer follows the decreasing order: methyl > ethyl > propyl, signifies the steric influence on accessibility of the carbon attached to Co [1-2]. UV/Vis spectra indicates that the nucleotide tail 5,6-dimethyl-benzimidazole (DMB) of the cobalamin is coordinated to Co during Hg methylation. This tighter binding can increase the e- density on the Co and facilitates electrophilic attack on C leaving group [1-2]. With regard to the Hg species and solution electrolytes, the presence of Hg-binding ligands, such as Cl^-, could significantly reduce the rate of Hg methylation [3-5]. And the methyl transfer reaction is faster in acid than in neutral pH solutions. We discuss the results of these abiotic Hg methylation assays and their significance for understanding the mechanism of the enzymatic system.

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