COBALAMIN DEPENDENT METHYLATION AND DEMETHYLATION BY VERATROL O-DEMETHYLASE

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The formation and breakage of C-O ether bonds are valuable synthetic transformations contributing to the structural diversification of natural products and pharmaceuticals [1-3]. Moreover, O-methylated phenol derivatives are useful building blocks for the manufacture of antioxidants, flavoring agents, fragrances, dyes, agrochemicals and fine chemicals [4,5]. Despite the large variety of chemical reactions for methylation and demethylation, none reaction is reversible and sustainable. They often lack chemo-, regio- and stereoselectivity and rely on harsh reaction conditions [6]. Thus, the development of milder alternatives such as biocatalytic methylation and demethylation reactions is of high interest [7].

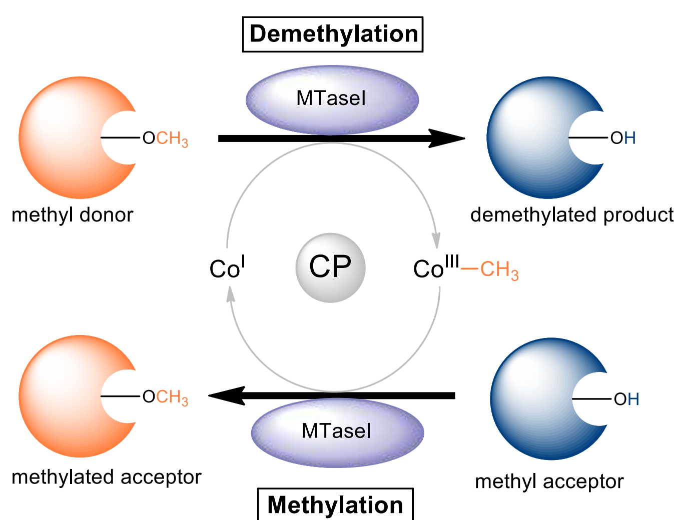

Figure 1: The cobalamin dependent methyltransferase (MTaseI) catalyzes the demethylation of a methyl donor and the methylation of a methyl acceptor alongside with the corrinoid protein (CP) acting as a methyl shuttle.

We present an enzymatic system utilizing cobalamin (vitamin B12) dependent methyl transferases (MTases) derived from the anaerobic bacteria which enable both methylation and demethylation of heteroatoms [8,9]. Naturally, the bacterial system involves four proteins for these reactions whilst our concept requires only two proteins (see Figure 1): the veratrol O-demethylase (MTaseI) from *Acetobacterium dehalogenans* and the corrinoid protein (CP) derived from another origin. The CP incorporates a cobalamin prosthetic group functioning as methyl carrier. Along with the CP the MTaseI catalyzes both, the demethylation of a donor and the methylation of an acceptor substrate in a reversible manner. The activity of the MTaseI relies on the amount of CP and zinc, because it incorporates a zinc binding motif [10]. The approach represents a substrate promiscuous alternative to common chemical and enzymatic methyl transfer methodologies and a valuable extension for the toolbox of available biocatalysts for ether bond formation as well as cleavage.

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