Computational modeling of methyl transfer reactions catalyzed by cobalamin-dependent methionine synthase enzyme

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The cobalamin-dependent methionine synthase enzyme (MetH) catalyzes the transfer of the methyl group from methyltetrahydrofolate (CH_3-H_4folate) to homocysteine (Hcy) thus forming methionine (Met). The key step in the catalytic cycle involves displacement of the methyl group from the methylcobalamin cofactor (MeCbl) to Hcy in which the cobalamin cofactor serves as an intermediate cycling between hexa-coordinated methyl-cob(III)alamin and tetra-coordinated cob(I)alamin complexes. It is generally believed that the enzyme operates via an S_N2-type nucleophilic displacement. However, a related mechanism, referred to as *reductive cleavage* has been also suggested [1]. According to this mechanism, the cofactor is initially reduced by transfer of an electron from the deprotonated Hcy, forming a π–corrin based radical, followed by Co-C bond cleavage.

The transfer of the methyl group from the MeCbl cofactor to the Hcy substrate results in the formation of the cob(I)alamin intermediate which exhibits a complex electronic structure, between Co(I) and Co(II)-radical corrin states. It was found that the correlated ground state wave function consists of a closed-shell Co(I) (d^8) configuration and a diradical contribution, which can be described as a Co(II) (d^7)-radical corrin $(\pi^*)^1$ configuration. Moreover, the contribution of the two configurations depends on the Co-N(His_{759}) distance [2].

Once every ~2000 turnovers, the MetH-bound cobalamin cofactor (Co^{1+}Cbx) is converted to the inactive cob(II)alamin (Co^{2+}Cbx) form, from which Co^{1+}Cbx has to be recovered in order to ensure efficient catalysis. The Co^{+2}/Co^{+1} is a thermodynamically challenging reaction because the midpoint reduction potentials of the physiological reducing agents are considerably more positive than that of the Co^{2+}Cbx cofactor. Based on spectroscopic and X-ray structure studies the generation of tetra-coordinated Co^{1+}Cbx has been invoked to be the key molecular determinant of the enzyme-mediated redox tuning of Co^{+2}/Co^{+1} process. However an alternative catalytic strategy for driving Co^{+2}/Co^{+1} reduction can be envisioned if one takes into account the formation of a biologically relevant Co^{+1}--H bond [3].

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