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An Unusual Co(I)–H Interaction: Structural and Mechanistic Ramifications for Methyltransferases

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The cob(II)alamin cob(I)alamin ($\text{Co}^{2+}/\text{Co}^{1+}$) reduction is a common chemical event in a broad family of cytoplasmic methyltransferases and ATP:corrinoid adenosyltransferases, respectively. Despite its broad and general chemical appeal, the $\text{Co}^{2+}/\text{Co}^{1+}$ reduction continues to remain one of the least understood aspects of corrinoid chemistry. This is due in part to the inaccessible redox chemistry of $\text{Co}^{2+}/\text{Co}^{1+}$ couple under cellular conditions i.e., the reduction potential of cob(II)alamin (-500 mV vs SHE) is more negative than that of the common physiological reductants (-280 mV to -440 mV vs SHE) present in the cellular environments. To gain better understanding about the $\text{Co}^{2+}/\text{Co}^{1+}$ reduction, we have utilized the density functional theory and quantum mechanics/molecular mechanics (QM/MM) computational methods. The calculations indicate that cob(I)alamin, a ubiquitous B_{12} intermediate, is not square planar as has been commonly accepted, but a square pyramidal species due to the unusual hydrogen bonding interaction between the Co^{1+} ion and its axial ligands (*Angew. Chem. Int. Ed.* **2011**, *50*, 8702-8705; *Inorg. Chem.* **2012**, *51*, 5533-5538). The Co^{1+} –H interaction exerts an anodic shift of 100 mV vs SHE upon the reduction potential of the $\text{Co}^{2+}/\text{Co}^{1+}$ couple, which explains why this redox process is observed inside transferases. Building upon these new insights, an alternate mechanism for the enzyme-bound $\text{Co}^{2+}/\text{Co}^{1+}$ redox process is suggested that is mediated by the square pyramidal cob(I)alamin rather than its commonly accepted square planar analogue.