

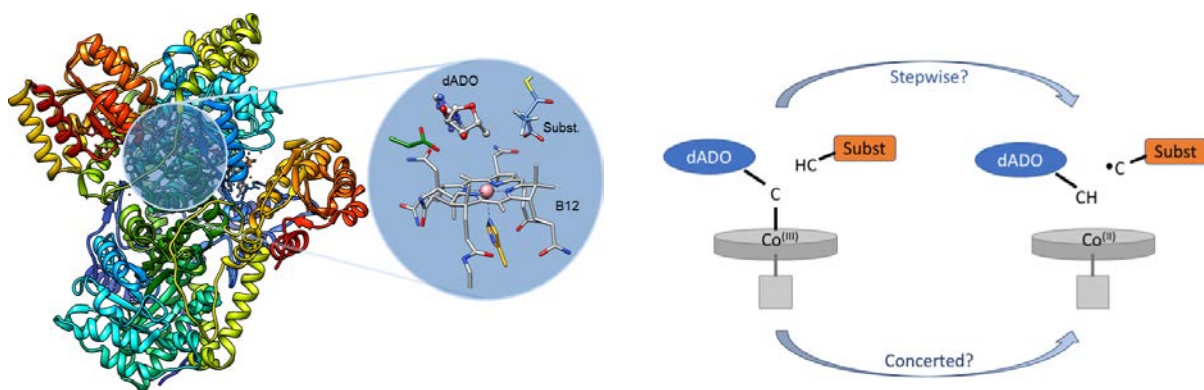
# Modelling the reactions catalyzed by coenzyme B<sub>12</sub> dependent enzymes: Accuracy and cost-quality balance

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Coenzyme B<sub>12</sub> (5'-deoxyadenosylcob(III)alamin, dAdoCbl) is one of the most prominent organometallic cofactors due to the presence of a carbon-cobalt (Co-C) bond, which is the key to enzymatic reactions utilizing coenzyme B<sub>12</sub> as a cofactor: The homolytic cleavage of the Co-C bond, which leads to the formation of a 5'-dAdo radical, is highly encouraged in the enzymatic environment compared to the nonenzymatic reaction. In a (subsequent or concerted) second step, the 5'-dAdo radical is involved in an H-atom transfer reaction, generating a substrate radical and 5'-dAdo. However, the accurate theoretical description of both elementary reactions is challenging. More recently, the Co-C cleavage was investigated with dispersion-corrected DFT and LPNO-CCSD calculations utilizing the full coenzyme.[1] This and another study[2] have elucidated the importance of the model system design and, especially, the inclusion of dispersion and solvent corrections. Concomitantly, the accurate description of the H-atom transfer reaction is known to be very sensitive to the level of theory applied.[3–5] Our goal is to find a model chemistry that ensures an accurate description of both reactions, Co-C cleavage and H-atom transfer. We discuss the differences between typical model systems, the effects of dispersion and solution corrections and finally present a suitable ONIOM(QM/MM) setup that simultaneously reduces the computational costs and retains the accuracy of non-approximate calculations on the full coenzyme system, for both types of reactions. All these efforts help us to tackle the decades-long controversy about the actual mechanism among the different classes of coenzyme B<sub>12</sub> dependent enzymes.



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