# From Force Fields to QM/MM and back: Modelling chemical change in coenzyme $B_{12}$ dependent enzymes

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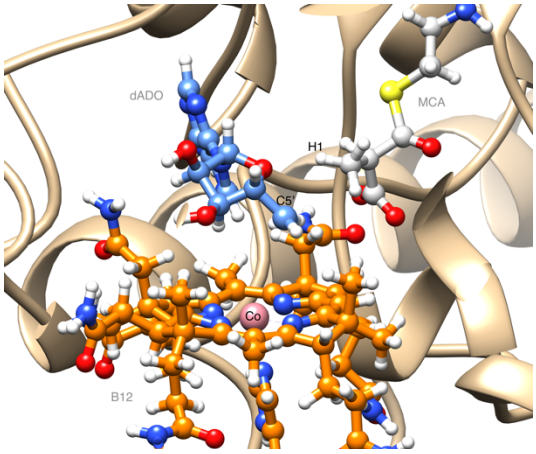
Coenzyme $B_{12}$ (5'-deoxyadenosylcob(III)alamin, dAdoCbl) is one of the most prominent organometallic cofactors due to the presence of a carbon-cobalt (Co-C) bond, which is the key to enzymatic reactions utilizing coenzyme $B_{12}$ as a cofactor: The homolytic cleavage of the Co-C bond, which leads 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. Model system design, the treatment of dispersion and solvent effects as well as basis set size can lead to large variance in the computed Bond Dissociation Enthalpy (BDE) for the homolytic cleavage of the Co-C bond.[1,2,3] Concomitantly, the accurate description of the H-atom transfer reaction is known to be very sensitive to the level of theory applied.[3–7] Nevertheless, there are model chemistries that enable an accurate and balanced 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.[3] This information can be used to produce even more cost-effective empirical Hamiltonians such as the Empirical Valence Bond (EVB) method, which reduces the computational cost to a MM type description of the system and a single diagonalization of a N*x*N (N = 2 or 3) matrix. This allows us to investigate the free energy profile related to the enzymatic transformations within the enzyme with MD simulations on larger time-scales, while retaining the QM/MM accuracy.

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