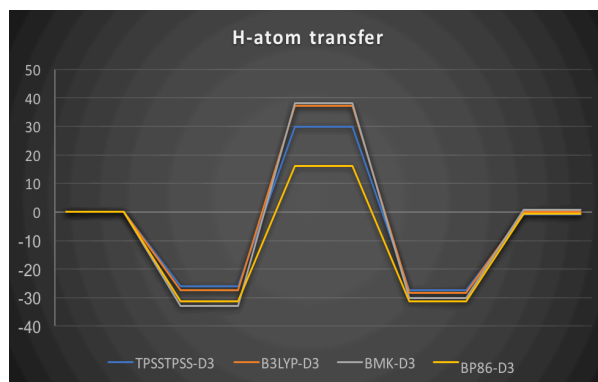
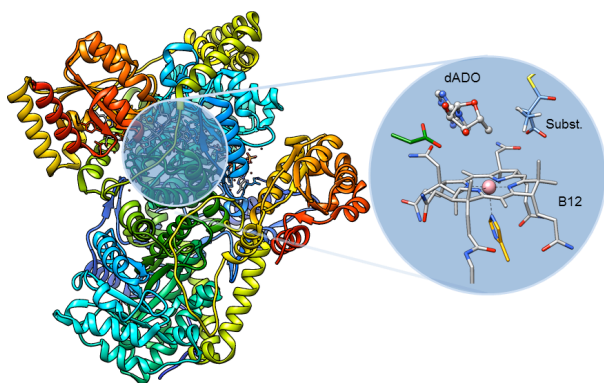


# Modelling the reactions catalysed by coenzyme B<sub>12</sub>-dependent enzymes: Accuracy and cost-quality balance

Christian R. Wick<sup>1,2</sup>, David M. Smith<sup>1,2</sup>

<sup>1</sup> Group for Computational Life Sciences, Division of Physical Chemistry, Ruđer Bošković Institute, Zagreb, Croatia

<sup>2</sup> PULS Group, Friedrich-Alexander-Universität, Erlangen, Germany



Coenzyme B<sub>12</sub> (5'-deoxyadenosylcob(III)alamin, dAdoCbl) is involved in vital enzymatic processes in nature, including humans. It constitutes one of the most prominent organometallic cofactors due to the presence of a carbon-cobalt (Co-C) bond between the central cobalt ion and the 5'-deoxyadenosyl ligand. The general formal mechanism for the initial reaction of coenzyme B<sub>12</sub> dependent enzymes starts with homolytic cleavage of the Co-C bond, which leads to the formation of a 5'-deoxyadenosyl radical and a low-spin cob(II)alamin. In the (subsequent or concerted) second step, the 5'-deoxyadenosyl radical is involved in an H-atom transfer reaction, generating the substrate radical and 5'-deoxyadenosine. Interestingly, the rate of the enzymatically catalysed Co-C homolysis is increased by 12 orders of magnitude compared to the nonenzymatic reaction in solution, which demonstrates the astonishing catalytic power of these enzymes.

The reactions catalysed by coenzyme-B<sub>12</sub>-dependent enzymes have been subject to many theoretical investigations, employing different levels of theory, model systems and methodologies. Recently, the Co-C cleavage was investigated with dispersion-corrected DFT and LPNO-CCSD calculations utilising the full coenzyme.<sup>[1]</sup> This and another study based on a slightly truncated model system<sup>[2]</sup> have elucidated the importance of the model system design and the inclusion of dispersion and solvent corrections for the first time. Concomitantly, the accurate description of the H-atom transfer reaction is known to be very sensitive to the level of theory applied.<sup>[3-5]</sup> Our goal is to find a level of theory 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.

[1] Z. Qu, A. Hansen, S. Grimme, *J. Chem. Theory Comput.* **2015**, *11*, 1037–1045.

[2] K. P. Kepp, *J. Phys. Chem. A* **2014**, *118*, 7104–7117.

[3] D. J. Henry, C. J. Parkinson, P. M. Mayer, L. Radom, *J. Phys. Chem. A* **2001**, *105*, 6750–6756.

[4] M. L. Coote, *J. Phys. Chem. A* **2004**, *108*, 3865–3872.

[5] B. Durbeej, G. M. Sandala, D. Bucher, D. M. Smith, L. Radom, *Chemistry* **2009**, *15*, 8578–85.