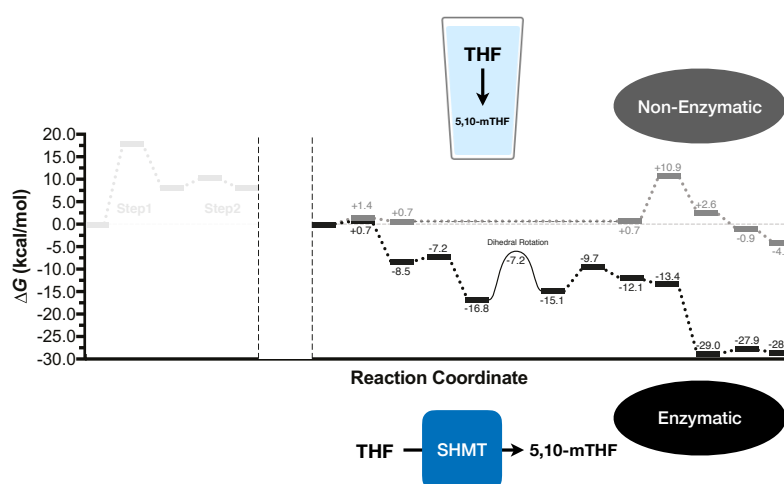


Is the 5,10-methylenetetrahydrofolate cofactor synthesized through a non-enzymatic or enzymatic mechanism?

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Graphical Abstract



Abstract.

The 5,10-methylenetetrahydrofolate (5,10-mTHF) is a cofactor essential for the synthesis of purines and thymidine, which are crucial for the cell viability.[1] The α -elimination of L-serine, catalyzed by the serine hydroxymethyltransferase (SHMT), is the primary source of 5,10-mTHF in the cell. However, the catalytic mechanism behind the synthesis of 5,10-mTHF was unknown, and two divergent theories were proposed for the mechanism. Some authors suggested that the final steps of the 5,10-mTHF synthesis occur in the cytoplasm whereas other authors showed some evidence that the reaction must occur inside the SHMT. [2] In this study, we addressed the entire catalytic mechanism of the PLP-dependent enzyme SHMT using a QM/MM approach and the mechanism of 5,10-mTHF synthesis in aqueous solution. The calculations were prepared and analyzed using molUP [3] for VMD and run on Gaussian09 and ORCA. This work [4] resulted in the entire e detailed catalytic mechanism of SHMT.

The results showed that both hypotheses for the synthesis of 5,10-mTHF shared the two first steps where the -OH group is transferred from the serine to the THF. These reactions occur inside the SHMT and have a ΔG^\ddagger of 18.0 and 2.0 kcal/mol. Then, the reaction can proceed inside the enzyme through 5 sequential steps or in the cytoplasm where only 3 steps are needed. The calculations showed that the mechanism is kinetic and thermodynamically favorable by 0.8 and 24.3 kcal/mol, respectively, when it takes place inside the SHMT. Although the reaction is not impossible in solution, it is very improbable that the THF intermediate might be released to the cytoplasm to overcome a set of reactions that are less favorable when compared to the ones that would occur in the SHMT.

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