Serine HydroxyMethylTransferase: Inhibit it or Improve it?

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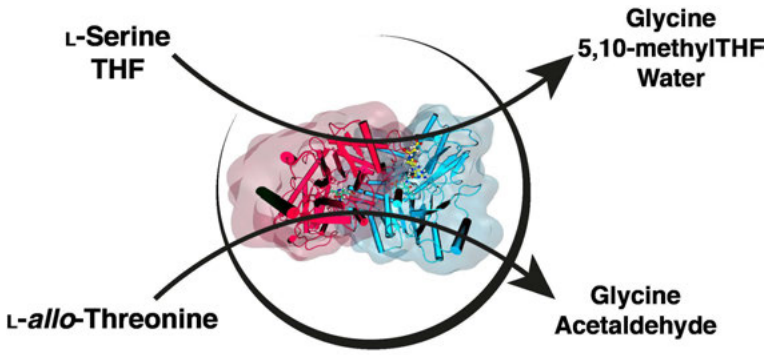
Computational methods provide a unique way to unravel the catalytic mechanism of enzymatic reactions at an atomistic level that cannot be obtained by experimental means. In this work, the catalytic mechanism of Serine HydroxyMethylTransferase (SHMT) was studied using computational means. SHMT requires pyridoxal-5'-phosphate (PLP) [3] and tetrahydrofolate (THF) as a cofactor to catalyze the conversion of L-Serine to Glycine. This enzyme has been classified as an important drug target against malaria [1] and an important industrial catalyst that can be used to produced enantiomeric pure compounds.

The calculations were carried out using QM/MM methodologies using the ONIOM scheme B3LYP/6-31G(d):FF99SB for the geometry optimizations and B3LYP/6-311++G (3df,2pd):FF99SB for the single-point energy calculations.

Our calculations revealed that the α-elimination of L-serine and consequent conversion of THF into 5,10-methyl-THF occurs in six sequential steps. The first step involves the nucleophilic attack of a nitrogen atom of the THF to the β-carbon of the substrate (bounded to the PLP cofactor) leading to the α-elimination of the substrate. This is the rate-limiting step of the full reaction that has an activation energy of 18.8 kcal/mol, which closely agrees with the experimental kinetic results (k_{cat} = 5.44 s^{-1}; ~18.2 kcal/mol) [2].

SHMT is also able to catalyze the production of aldehydes in a THF-independent mechanism, e.g., L-allo-threonine is converted to acetaldehyde and glycine. Experimental results showed an increase in the activity of the enzyme when an active site glutamate is mutated by a glutamine. The mechanism behind this alternative reaction is also being investigated as well as, further modifications that can enhance the efficiency of SHMT to produce these pure enantiomeric compounds. These results will propose new and improved ways to enhance the production of regio- and stereoselective compounds which is one of the Achilles' heels of the chemical industries.



Acknowledgments: This research was funded by the project IF/01310/2013. The author also acknowledges FCT for the Ph.D. grant (SFRH/BD/115396/2016).

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