Computational studies addressed to the catalytic mechanism of the alpha sub-unit of Tryptophan Synthase
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Abstract.

Tryptophan Synthase (TSase) is a bi-functional enzyme that catalyzes the last two steps in the synthesis of tryptophan (trp), in different actives site. The active site of the α-subunit catalyzes the formation of indole and gliceraldehyde-3-phosphate (G3P) from indole 3- glycerolphosphate (IGP). Indole is then transported through a 25Å physical tunnel to the active site of the β-subunit where it is added to a molecule of acrylate, derived from serine, to produce trp, in a PLP dependent reaction [1].

In this work, we studied the reaction that takes place in the α-active site of TSase using computational means and QM/MM hybrid methodologies [2]. The results show that the reaction occurs in a stepwise general acid-base mechanism. The first step requires the participation of a water molecule that protonates C3 of the indole ring and receives a proton from αGlu49. In the second step, αGlu49 abstracts a proton from the glycerolyl hydroxyl of IGP through a water molecule, triggering the C–C
bond cleavage to give indole and G3P. The rate-limiting step of this reaction is the first one that requires an activation free energy of 17.74 kcal/mol. This result agrees extremely well with the available experimental data that predicts reaction rate of 3.0-3.7 s⁻¹, which corresponds to a free energy barrier of 17.37-17.50 kcal/mol.

The results obtained in this work provide important details about TSase that can now be used for the development of new transition state analogues inhibitors targeting TSase – an important drug target used in the treatment and prophylaxis of tuberculosis that is caused by the *Mycobacterium tuberculosis* pathogen.

References
