

EJIBCE 2017

Encontro de Jovens Investigadores de Biologia Computacional Estrutural Departamento de Física, Universidade de Coimbra, 22 de Dezembro

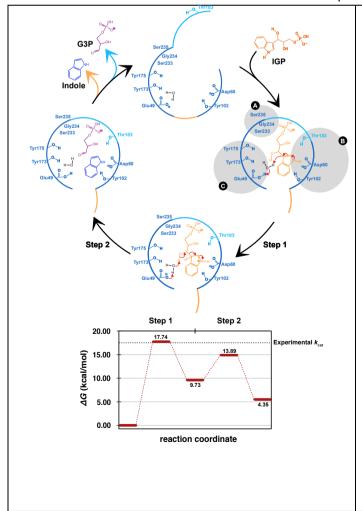


MOL2NET, International Conference Series on Multidisciplinary Sciences <u>http://sciforum.net/conference/mol2net-03</u>

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

Carla S. Silva Teixeira (csteixeira@fc.up.pt)^a, Maria João Ramos (<u>mjramos@fc.up.pt</u>)^a Nuno M. F. Sousa A. Cerqueira (nscerque@fc.up.pt)^a

^a UCIBIO@REQUIMTE, Faculdade de Ciências da Universidade do Porto, Rua do Campo Alegre s/n 4169-007 Porto, Portugal



Abstract.

Tryptophan Synthase (TSase) is a bifunctional 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 gliceraldeyde-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 α Glu49. In the second step, α Glu49 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

[1] N. M. F. S. A. Cerqueira, P. A. Fernandes, M. J. Ramos, J. Chem. Theory Comput., 2011, 7, 1356-1368.

[2] E. F. Oliveira, et al., J. Am. Chem. Soc., 2011, 133, 15496-15505.