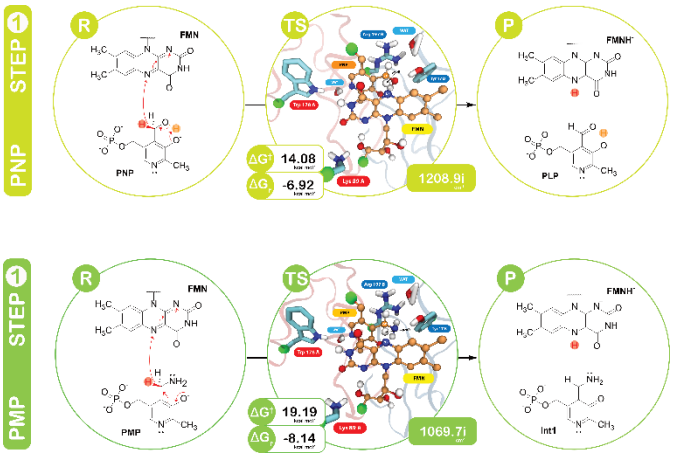
MOL2NET, International Conference Series on Multidisciplinary Sciences

Application of QM/MM Methods in the Study of PNPOx

André Pina[1], *Sérgio F. Sousa*[1], *Nuno M. F. S. A. Cerqueira*[1]

[1] *UCIBIO@REQUIMTE, BioSIM, Departamento de Biomedicina, Faculdade de Medicina, Universidade Do Porto, Alameda Professor Hernâni Monteiro, Porto, 4200-319, Portugal*

Graphical Abstract



Abstract.

Pyridoxal 5'-phosphate (PLP), the active form of the vitamin B_6, is an essential cofactor required by more than 160 families of enzymes. Its role as an electron sink makes it imperative for the catalysis of a myriad of chemical reactions. Contrarily to microorganisms and plants, humans and other mammals are not able to synthesize PLP de novo, resorting to a "salvage pathway" that helps to maintain PLP homeostasis [1]. The correct functioning of this salvage pathway is crucial for the cell, as demonstrated by the correlation between low levels of PLP and the occurrence of severe neurological disorders [2]. It was found that the major culprit is pyridoxine/pyridoxamine 5'-phosphate oxidase (PNPOx), an FMN-dependent homodimeric enzyme responsible for the recycling of pyridoxine 5'-phosphate (PNP) and pyridoxamine 5'-phosphate (PMP) into PLP [3]. Therefore, in order to better understand its role in these disorders, it is of the utmost importance to unveil the catalytic mechanism of PNPOx. To do so we used computational means, namely QM/MM hybrid methodologies [4], to evaluate different mechanistic proposals related to PNPOx reactivity. Models were prepared and evaluated enabling important aspects related to the catalytic modelling of this enzyme to be validated. The results obtained in the present work provide important details about the catalytic mechanism of PNPOx, helping us to understand the importance of some key residues in the active site that can have implications in some PLP-deficiency disorders. More studies are required to fully understand the catalytic mechanism of this important enzyme.

Acknowledgements

We acknowledge FCT for financial support to the PhD grant SFRH/BD/136594/2018, the Starting grants IF/01310/2013 and IF/00052/2014, and to the Project PTDC/QUI-QFI/31689/2017.

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