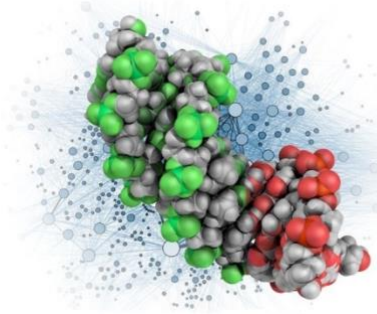

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Development of computational tools to enhance the study of catalytic mechanisms

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Graphical Abstract

molUP

Abstract

Computational methods have been widely used to characterize the catalytic mechanisms of several chemical systems namely enzymes. However, enzymes are studied using big chemical systems containing several thousands of atoms generating huge amounts of data that are hard to manipulate and analyze efficiently. Therefore, we developed molUP that is a user-friendly plugin for VMD to handle QM and ONIOM calculations performed using Gaussian software. MolUP allows loading output files from Gaussian calculations and performs analysis concerning the structure of the chemical system as well as their energies and vibrational frequencies. Furthermore, molUP provides a graphical interface to manipulate the length of atomic bonds and the amplitude of angles and dihedral angles. Users can also easily choose which atoms belong to each ONIOM layer and the atoms that are free to move during a geometry optimization. At the end, molUP is capable of saving the new structure as a new Gaussian input file, ready to run a new calculation. Since molUP is a VMD extension, users can also benefit from the many features and resources available on VMD.

In order to demonstrate the potential of MolUP, we will also present the results that have been carried out in our research group regarding

	the catalytic mechanism of Serine HydroxyMethylTransferase (SHMT), using a QM/MM approach. SHMT is a pyridoxal-5'-phosphate (PLP)-dependent enzyme [1-3] that catalyzes the α-*elimination of* L-*serine, where a methyl group is transferred from the substrate to a second cofactor, tetrahydrofolate (THF). The reaction occurs in six sequential steps from which the first one is the rate-limiting step with an activation barrier of 18.3 kcal/mol that closely fits the experimental* k_{cat} *of 0.98±0.06* s^{-1} [4] ($\Delta G^{\ddagger} \approx 18.2$ kcal/mol). This first step involves the nucleophilic attack of nitrogen from THF to the β-carbon of the substrate, promoting the α-*elimination of the* CH_2OH *group of the substrate. The subsequent steps involve an intramolecular cyclization within the THF cofactor where the elimination product of the first step is incorporated, generating the 5,10-methyl-THF. At the end, the quinonoid intermediate (substrate + PLP) is protonated, producing glycine.*

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