Thr-101 and HOH-404 in proton exchange of glutathiohydroxyacetone by Glyoxalase I

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Abstract: The catalytic reaction mechanism of Glyoxalase I (GlxI) was well described in the litreture [1,2]. It was demonestarted that two glutamate residuses in the enzymes active site (Glu-99 and Glu-172) are the main groupos of the active sit that direcly participate in the catalytic mechanism. Investigating the crystal structure of human GlxI [3], we found that none of the neighboring residues has direct interaction with the active site. However, we saw that OG1 of Thr-101 makes a bridge with two consecutive hydrogen bonds via a crystal water (HOH-404) to Glu-99. Then, to study the effect of this residue and the crytal water we constructed two different models of active site either with of without these two groups. We applied there two model to study the streospecific proton exchange of glutathiohydroxyacetone by GlxI.

All QM-cluster calculations of were performed using the density functional B3LYP. The structures of reactants, transition states, intermediates, and products were optimized using the 6-31+G(d) basis set for the H, C, N, O and S atoms and the LANL2DZ pseudo potential for the Zn ion. Accurate energies were calculated with single-point calculations on the optimized structures using the larger 6-311++G(2d,2p) basis set for all atoms. To consider the surroundings, solvation effects were evaluated at the B3LYP/6-31+G(d)/LANL2DZ level of theory by performing single-point calculations using the CPCM solvation model. Frequencies of the stationary states on the potential energy surface were calculated to obtain zero-point energies. The frequency calculations were performed at the same level of theory as the geometry optimizations. The final energy of each stationary point discussed in this work was obtained by including the corresponding zero-point energy and the electrostatic part of the solvation energy as a correction to the electronic energy calculated from the higher level single point calculations.

We found that the two models gave similar reaction path but their corresponding energy profiles are a little different and the barrier from the bigger model involving Thr-101 and HOH-404 is lower than that of the smaller model. In conclusion, the crystal water and the threonine residue do not change the reaction path but lower the energy barrier.

Keywords: Stereospecificity; Glyoxalase I; Metalloenzyme; Proton Exchange; Mechanism.

References

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