A Computational Investigation into the Mechanism of the Histone Acetyltransferase, Gcn5

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Post-translational modifications (PTMs) can have a profound effect on protein structure and function. One such PTM is the acetylation of a histone (a protein involved in DNA binding). In this reaction, an enzyme catalyzes the transfer of the acetyl group from acetyl CoA to a free lysine on the histone. This transfer neutralizes the positively charged lysine, which allows the DNA to be exposed for transcription. In our study, we focus on the acetyltransferase, Gcn5. Details regarding the reaction mechanism used by Gcn5 remain obscured. However, current mechanistic hypotheses suggest that the reaction occurs through a tetrahedral oxyanion intermediate, which is stabilized by a hydrogen bond to a nearby residue, i.e. an oxyanion hole. We utilize molecular dynamics (MD) simulations and quantum mechanics/molecular mechanics (QM/MM) calculations in order to further probe possible mechanistic schemes of this reaction.