Molecular Dynamics Simulation: The Free Energy Profile for Dissociation of Ligand from CA I Active Site

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Carbonic anhydraseas (CAs) family have been known to catalyze the hydration of carbon dioxide at an extremely high rate. CA I plays fundamental roles in cell to keep the adequate balance between carbon dioxide and bicarbonate. Zinc ion of CA I active site binds three histidine residues (His 94, 96, 119) and the fourth position binds with water molecule (acidic pH) or hydroxyl ion at the higher pH. Thus, it becomes a potential area to inhibit its active site with promoting drugs to control the pH level in cells. The structure of CA I active site contains Zn^{2+} ion. Therefore, the forcefield parameter of Zn metal binds three histidine residues was calculated with potential energy surface (PES). We performed MD simulation and potential mean force (PMF) to obtain the free energy profile as function of distance between mass of ligand and that of CA I active site. The WHAM method was used to obtain the accurate free energy differences from biased molecular simulation. Our result predicted that the free energy reaches a minimum reaction coordinate at $\xi = 8.5$ Å.