

P010 A Coupled Equilibrium Shift Mechanism in Calmodulin-Mediated Signal Transduction

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Calmodulin (CaM) is a ubiquitous calcium-binding protein that plays a key role in signal transduction. We show by using experimentally restrained molecular dynamics simulations that the ensemble of conformations representing the calcium-bound state of CaM (Ca-CaM) includes a range of structures closely similar to those present when CaM is bound to a wide variety of ligands. Detailed analysis of the state in which CaM is bound to the myosin light chain kinase (CaM-MLCK) reveals that correlated motions within Ca-CaM direct the structural fluctuations towards complex-like substates. This phenomenon enables initial ligation of MLCK at the C-terminal domain of CaM and induces a population shift among the substates accessible to the N-terminal domain, thus giving rise to the cooperativity associated with binding. On the basis of these results, and by bringing together modern protein energy landscape theory with classical allostery models, we suggest that a coupled equilibrium shift mechanism controls the efficient binding of CaM to a wide range of ligands.