Estimating Free Energy Differences using Molecular Dynamics Simulations: Amino Acid Side Chain pKa Values in Cytochrome bc1

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Estimating free energy changes and the associated equilibrium constants for chemical reactions is central to understanding the extent of a reaction and, indeed, is necessary to know whether or not a reaction will even occur. Since the cytochrome bc1 complex (cyt bc1) is a key component involved in energy use by most organisms, understanding free energy changes associated with the reactions it catalyzes is fundamental to understanding its function.

Cyt bc1 catalyzes electron transfer (ET) coupled to the generation of a proton gradient that drives ATP synthesis. ET inhibitors of bacterial cyt bc1 that replace the natural ubiquinone/ubiquinol ligands are antibiotics and inhibitors of fungal cyt bc1 are fungicides. It is hypothesized that protein-ligand interactions, as well as ET chemistry, are mediated by amino acid side chain protonation equilibria. This contribution describes the use of constant pH molecular dynamics and free energy perturbation simulations to predict the protonation equilibria of ionizable amino acid side chains near ligand binding sites in cyt bc1, as well as their implications for the proposed protein-ligand interactions. We focus on the His161 side chain proposed to function in proton-coupled electron transfer.