

pH-dependent conformational changes in proteins: What is the meaning of a pK_a ?

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The acid-base behavior of amino acids is an important subject of study due to their prominent role in enzyme catalysis, substrate binding and protein structure. If a protein can exist in two conformations, it is possible for a residue to have two different “microscopic” pK_a values because of changes in its interactions with the protein environment. In this work we explore these issues using Nitrophorin 4 as a case study. In this protein, Asp30 plays a key role in triggering a pH-dependent conformational change. Using constant pH molecular dynamics we found two distinct microscopic Asp30 pK_a s: 8.5 in the low-pH structure and 4.3 in the high-pH structure. Using a simple model, we estimated the apparent pK_a to be 6.5, in excellent agreement with experimental data. This value must be interpreted as the pH at which the population transition between the two conformations takes place. The strong coupling that exists between the solvent pH, protonation state and protein conformation makes it impossible to interpret experimental pK_a data by looking at an individual conformation, instead of ensembles.