Identifying crucial amino acids in FeS cluster proteins with pK_a analysis

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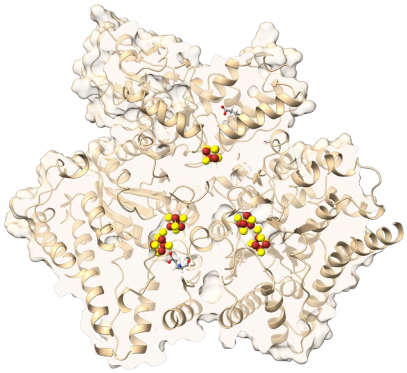

The pK_a values of amino acids and, as a result, their protonation states are subject to conformational changes in the protein, e.g. upon ligand binding. In the double cubane cluster protein (DCCP) and its reductase (DCCP:R), ATP-binding introduces conformational changes that are proposed to tune the redox potential of its FeS clusters [1],[2]. Changes in protonation states of critical amino acids link the conformational changes to the redox potential. A thorough conformational and pK_a analysis, prior to relatively expensive dynamic calculations, allows for first insights into its mechanisms upon ATP-binding and -hydrolysis.
The pK_a values are obtained with the Karlsberg^{2+} package [3],[4]. Karlsberg^{2+} solves the Poisson-Boltzmann equation for pH-adapted conformations to calculate the pK_a values of titratable amino acids. These estimated pK_a values are compared for different structures before and after ATP-binding to identify crucial amino acids.
Preliminary findings with this workflow indicate protonation of Glu157$_{DCCP:R}$ in proximity of the [4Fe4S] cluster upon ATP-binding. In direct proximity to the unusual [8Fe9S] double cubane, deprotonation of Glu140$_{DCCP}$ causes the formation of a salt bridge to Lys146$_{DCCP}$, potentially playing a role in the substrate reduction at this cluster.
With these findings, future quantum chemical calculations can be better targeted to the identified amino acids, enabling the quantification of their impact on the redox potential of FeS clusters and the corresponding catalytic mechanism.

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