A comparative structure-based analysis of the pH-dependent reduction potentials of Rieske iron-sulfur proteins
Astrid R. Klingen and G. Matthias Ullmann
University of Bayreuth, Structural Biology/Bioinformatics, Germany

Rieske iron-sulfur proteins carry a [2Fe-2S] cluster coordinated by two histidine and two cysteine residues. Based on their electrochemical properties, Rieske proteins are grouped into two classes: Rieske proteins from hydroquinone-oxidising bc-type cytochrome complexes display high reduction potentials (300-400 mV) that depend on pH in the physiological range. Rieske proteins from bacterial aromatic ring hydroxylating dioxygenase complexes have low reduction potentials (-150 mV) that show no pH-dependence in the physiological range. The difference in pH-dependence between bc-type and dioxygenase Rieske proteins is due to the difference in protonation behavior of the histidine sidechains coordinating the iron-sulphur cluster. Ligand histidine pK-values lie within the physiological range in bc-type Rieske proteins, but above in dioxygenase Rieske proteins. In the presented study, structural differences between a bc-type and a dioxygenase Rieske protein were identified that account for the differences in pH-dependence of their reduction potentials. Based on available high-resolution structures, histidine pK-values and relative reduction potentials were calculated by a combined classical electrostatic/quantum chemical approach. Obtained histidine pK-values of the wildtype structures agree well with experiment. By introducing in silico mutational changes, differences between the two studied proteins were removed. From an analysis of the reduction potentials and pK-values of the mutated structures, differences in electrochemical behavior could be related to structural differences between the two proteins. Presence of hydrogen bonds towards the iron-sulfur cluster together with absence of acidic residues in bc-type Rieske proteins accounts for their higher reduction potentials and lower ligand histidine pK-values.