Multi-scale modelling of the mechanical stability of a simple iron-sulfur protein

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The function of iron-sulfur proteins, such as rubredoxin, depends in large part on the stability and reactivity of their ferric-thiolate bonds. Recent atomic force microscopy experiments unexpectedly showed that Fe-S dissociation in rubredoxin single molecules under mechanical stress occurred at relatively low forces. In order to probe the detailed mechanism of forced rubredoxin unfolding, we develop here an approximate molecular dynamics scheme to simulate unfolding trajectories with bond dissociation and employ density functional theory pure quantum chemical (QC) and hybrid quantum chemical molecular mechanical (QC/MM) potentials to describe in detail the mechanism of Fe-S rupture in stretched rubredoxin and in the presence of competing chemical agents such as SCN − and H + . Analysis of hundreds of unfolding trajectories also explains the anisotropic response of stretched rubredoxin when force is applied at different points along the protein primary sequence. We conclude that the stability of ferric-thiolate bonds decreases in the presence of electrophilic and nucleophilic agents. Finally, the combination of quantitative experiments such as single-molecule atomic force microscopy and multi-scale molecular modelling with quantum chemical calculations can accurately describe the stability and reactivity of metalloproteins.