Experimental and Simulated Thioredoxin 1 Dynamics Evidence the Exchange Path of a Tightly Bound Water Molecule Essential for Biological Activity

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Thioredoxins are small ubiquitous proteins that present disulfide reductase activity. We showed that the activity is intrinsically linked to the protein dynamics, which is involved in the exchange of tightly bound water important for activity. The activity site lies in a loop (Cys30-Gly31-Pro32-Cys33) where the disulfide reduction involves the initial nucleophilic attack of the Cys30 thiolate on the substrate disulfide. The structures of the oxidized and reduced forms were determined by X-ray crystallography and NMR. The complete path of all the discrete structural states involved in the catalysis is unknown, because they are hidden as minor structural states (excited states). We performed MD simulations of the TrxI, starting from the NMR structure to study the relationship of the active site with the whole protein structure and with the environment. We showed in 3 different temperatures and force fields (100 ns) order parameters similar to the measured by NMR, showing a good convergence with the experimental data. Additionally, we could probe the tightly bound water molecule, which interacts with residues Asp24 and Cys30, with long lifetime (>5 ns) in agreement with the literature.

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