The Motor behind the Thiol/Disulfide Redox Potential is the Release of Conformational Strain

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Insight in disulfide/thiol redox potentials is of pivotal importance, for example, to understand the specificity and mechanism of thiol-disulfide switches in cellular redox pathways. In the thioredoxin (Trx) superfamily, it is well documented that the disulfide reduction potential is related to the pK_a of the nucleophilic cysteine [1]. However, also non-pH dependent factors as intra-molecular strain and conformational space due to the protein chain can influence the disulfide/thiol redox potential [2]. Protein disulfides can adopt a wide variety of conformations, each having different energies. Limited experimental data suggests that disulfides adopting a high energy have an enhanced likelihood for reduction, but the exact nature of this relation is not clear [2]. Using a computational approach, we give insight into the conformational dependence of the redox behaviour of the disulfide bond, which relates structure to reactivity. The relative energy of different conformations of the diethyl disulfide model system correlates with the disulfide/thiol redox potential $E°$. Insight in the calculated redox potentials is obtained *via* quantitative molecular orbital theory [3] and *via* the decomposition of $E°$ into a vertical electron affinity and a subsequent reorganization term. We have identified the determinants of the disulfide conformational energies and characterized the barrier to rotation around the disulfide bond. Our findings on the diethyl disulfide model system can be transferred to examples from the Protein Data Base (PDB).

In conclusion, the pK_a dependence of the disulfide/thiol redox potential is well documented, but hitherto, its conformational dependence was not. Our computational studies [4] clearly show that the disulfide redox potential is linked to the disulfide conformation, both in model systems and in examples from the PDB. Strained disulfide conformations with a high conformational energy ΔE_{rel} have a strong tendency to be reduced. We show that this is not caused by a higher electron affinity of the strained disulfide conformation. Instead, the motor behind its facile reduction is the release of intra-molecular strain as the thiol is formed.

References

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