

The effect of tensile stress on the conformational free energy landscape of disulfide bonds.

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Rok wydania

2014

Czasopismo

PLoS One

Numer woluminu

9

Strony

e108812/1-e108812/7

DOI

10.1371/journal.pone.0108812

Kolekcja

Naukowa

Język

Angielski

Typ publikacji

Artykuł

Streszczenie

Disulfide bridges are no longer considered to merely stabilize protein structure, but are increasingly recognized to play a functional role in many regulatory biomolecular processes. Recent studies have uncovered that the redox activity of native disulfides depends on their C–C–S–S dihedrals, and . Moreover, the interplay of chemical reactivity and mechanical stress of disulfide switches has been recently elucidated using force–clamp spectroscopy and computer simulation. The and angles have been found to change from conformations that are open to nucleophilic attack to sterically hindered, so–called closed states upon exerting tensile stress. In view of the growing evidence of the importance of C–C–S–S dihedrals in tuning the reactivity of disulfides, here we present a systematic study of the conformational diversity of disulfides as a function of tensile stress. With the help of force–clamp metadynamics simulations, we show that tensile stress brings about a large stabilization of the closed conformers, thereby giving rise to drastic changes in the conformational free energy landscape of disulfides. Statistical analysis shows that native TDi, DO and interchain Ig protein disulfides prefer open conformations, whereas the intrachain disulfide bridges in Ig proteins favor closed conformations. Correlating mechanical stress with the distance between the two –carbons of the disulfide moiety reveals that the strain of intrachain Ig protein disulfides corresponds to a mechanical activation of about 100 pN. Such mechanical activation leads to a severalfold increase of the rate of the elementary redox reaction step. All these findings constitute a step forward towards achieving a full understanding of functional disulfides.

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Adres publiczny

<http://dx.doi.org/10.1371/journal.pone.0108812>

Plik został wygenerowany dnia 2026-10-07 09:44:50

Adres w repozytorium <https://old.chem.uni.wroc.pl/pl/repozytorium/8THGXkb>.