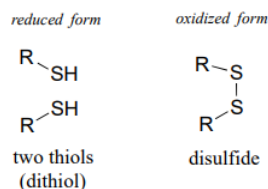


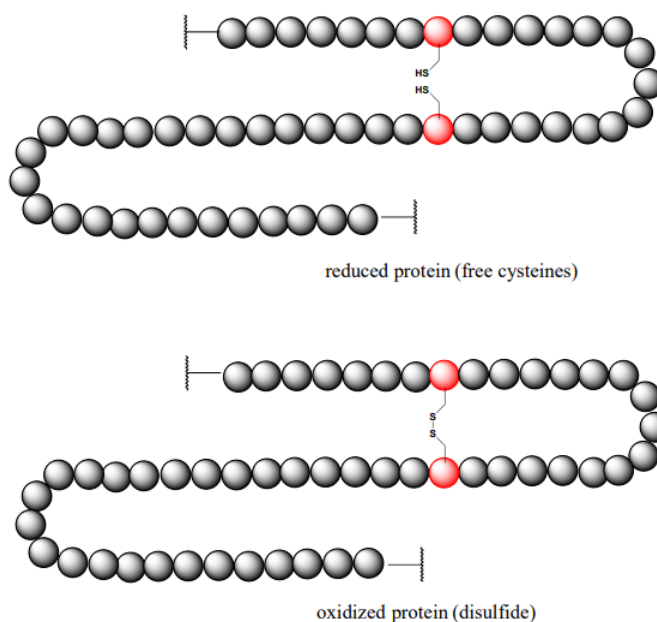
## 15.7: Redox Reactions of Thiols and Disulfides

A **disulfide bond** is a sulfur-sulfur bond, usually formed from two free thiol groups.

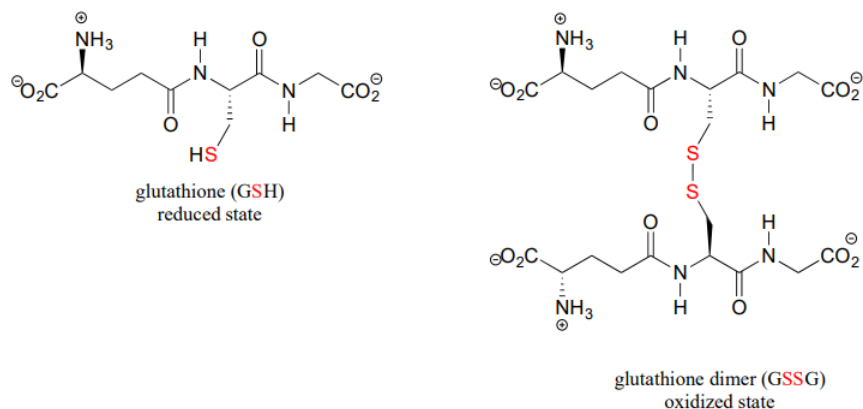


The interconversion between dithiol and disulfide groups is a redox reaction: the free dithiol form is in the reduced state, and the disulfide form is in the oxidized state. Notice that in the oxidized (disulfide) state, each sulfur atom has lost a bond to hydrogen and gained a bond to sulfur.

As you should recall from your Biology courses, disulfide bonds between cysteine residues are an integral component of the three-dimensional structure of many extracellular proteins and signaling peptides.



A thiol-containing coenzyme called glutathione is integrally involved in many thiol-disulfide redox processes (recall that glutathione was a main player in this chapter's introductory story about concussion research). In its reduced (thiol) form, glutathione is abbreviated 'GSH'. In its oxidized form, glutathione exists as a dimer of two molecules linked by a disulfide group, and is abbreviated 'GSSG'.

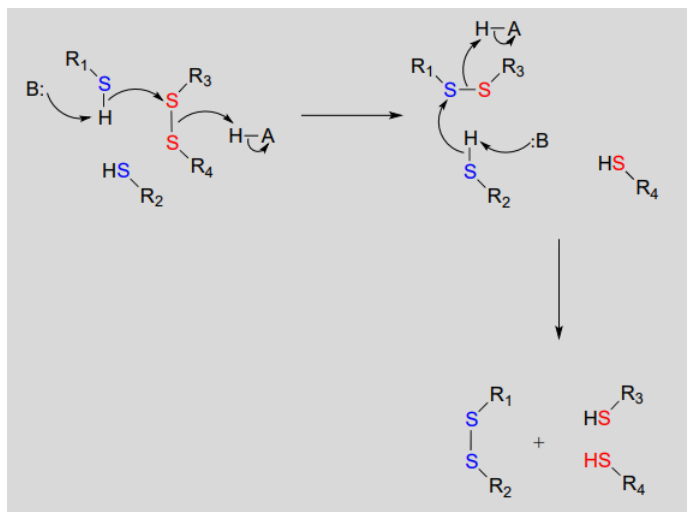


Disulfide bonds and free thiol groups in both proteins and smaller organic molecules like glutathione can 'trade places' through a disulfide exchange reaction. This process is essentially a combination of two direct displacement ( $S_N2$ -like) events, with sulfur atoms acting as nucleophile, electrophile and leaving group.

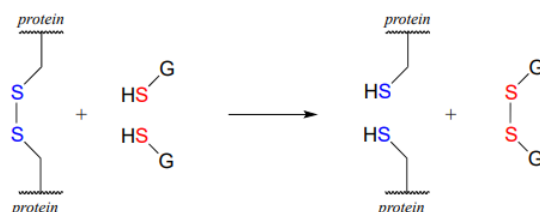
Disulfide exchange reaction



Mechanism:

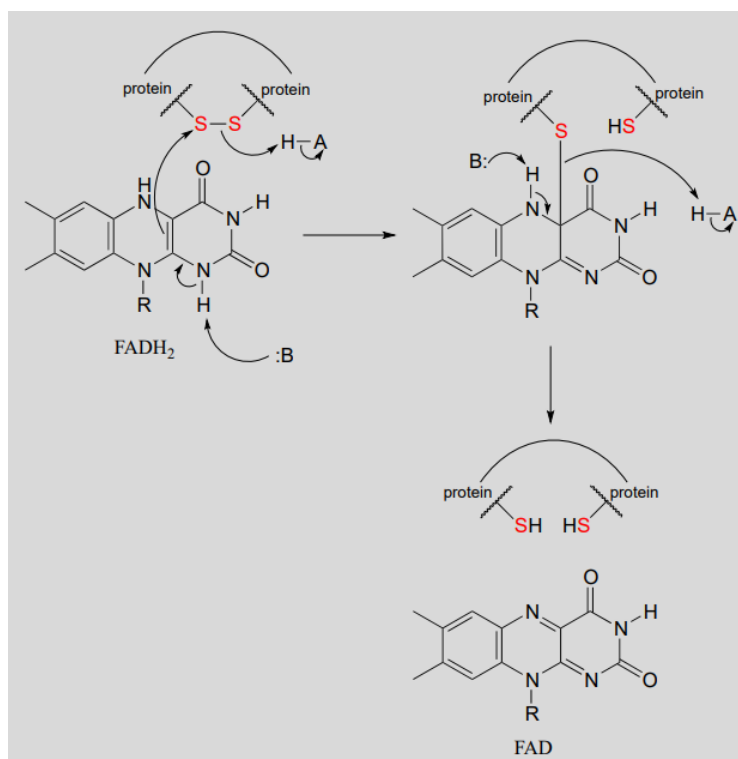


In eukaryotes, the cysteine side chains of intracellular (inside the cell) proteins are almost always in the free thiol (reduced) state due to the high concentration of reduced glutathione (GSH) in the intracellular environment. A disulfide bond in an intracellular protein will be rapidly reduced in a disulfide exchange reaction with excess glutathione.

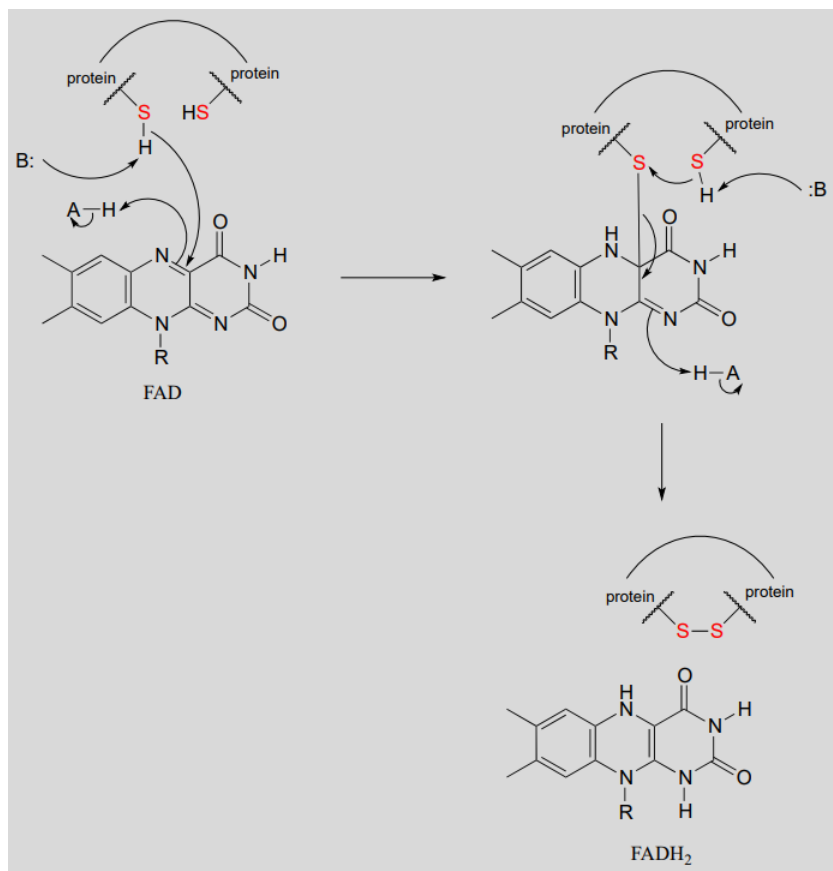


The interconversion of free thiols and disulfides is also mediated by flavin in some enzymes.

Flavin-mediated reduction of a protein disulfide bond

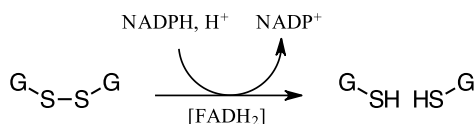


Flavin-mediated oxidation of a protein disulfide bond



As was stated earlier, a high intracellular concentration of reduced glutathione (GSH) serves to maintain proteins in the free thiol (reduced) state. An enzyme called glutathione reductase catalyzes the reduction of GSSG in a flavin-mediated process, with *NADH* acting as the ultimate hydride donor.

Glutathione reductase reaction:



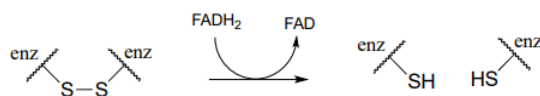
This figure shows oxidized glutathione converted to reduced glutathione by *NADPH*.

The mechanism for this and other similar reactions is not yet completely understood, but evidence points to an initial thiol-disulfide exchange reaction with a pair of cysteines from the enzyme, (phase 1 below) followed by flavin-dependent reduction of the cysteine-cysteine disulfide (phase 2). Finally, (phase 3) *FAD* is reduced back to *FADH*<sub>2</sub> by *NADH*. Frey and Hegeman, *Enzymatic Reaction Mechanisms*, p. 699

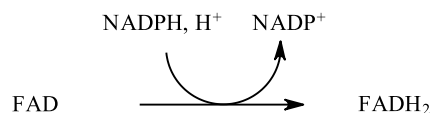
Phase 1: thiol-disulfide exchange (see earlier figure for mechanism):



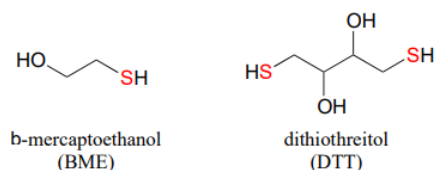
Phase 2: Reduction of protein disulfide by *FADH*<sub>2</sub> (see earlier figure for mechanism)



Phase 3: regeneration of  $\text{FADH}_2$  by  $\text{NADH}$  (see section 15.4B for mechanism)



In the biochemistry lab, proteins are often maintained in their reduced (free thiol) state by incubation in buffer containing an excess concentration of  $\beta$ -mercaptoethanol (BME) or dithiothreitol (DTT). These reducing agents function in a manner similar to that of GSH, except that DTT, because it has two thiol groups, can form an intramolecular disulfide in its oxidized form.



### ? Exercise 15.7.1

Draw structures of the oxidized (disulfide) forms of BME and DTT.

This page titled [15.7: Redox Reactions of Thiols and Disulfides](#) is shared under a [CC BY-NC-SA 4.0](#) license and was authored, remixed, and/or curated by [Tim Soderberg](#) via [source content](#) that was edited to the style and standards of the LibreTexts platform.