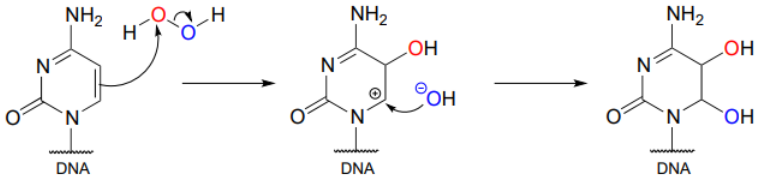
15.9: Hydrogen Peroxide is a Harmful - Reactive Oxygen Species

We get our energy from the oxidation of organic molecules such as fat and carbohydrates, as electrons from these reduced compounds are transferred to molecular oxygen, thereby reducing it to water. Reducing O_2, however, turns out to be a hazardous activity: harmful side products called reactive oxygen species (ROS) are inevitably formed in the process. Recall from the story introducing this chapter that ROS appear to play an important role in the damage that occurs to the brain immediately after a concussion.

Hydrogen peroxide, $HOOH$, is an ROS. Recall peroxides are potent oxidizing agents due to the weakness of the $O-O$ single bond. It is this same weak bond that causes hydrogen peroxide to be dangerous when produced in our bodies, as it can react spontaneously with oxygen or nitrogen nucleophiles and p bonds.

Peroxide formed as a by-product of our metabolism is particularly harmful when it oxidizes DNA bases. In just one of many known examples of oxidative damage, the DNA base cytosine is oxidized to thymine glycol in the presence of hydrogen peroxide. Although mechanistic details for reactions such as these are not yet well understood, one possibility is electrophilic addition:



cytosine thymine glycol

Our bodies have evolved ways to dispose of the harmful reactive oxygen species that are continuously being formed (the only way to stop the production of ROS is to stop breathing oxygen!). Glutathione peroxidase is a remarkable enzyme in that its active site contains selanocysteine, a modified cysteine residue in which the side chain sulfur is replaced by selenium (selenium is very toxic, but we do need a very small amount of it in our diet). Look at a periodic table: selenium is below oxygen and sulfur in the same column. If you think back to the vertical periodic trends in nucleophilicity (section 8.2), you'll recall that just as a thiol is a better nucleophile than an alcohol, a selanol (RSeH) is even more nucleophilic than a thiol. Moreover, the vertical periodic trend in acidity (section 7.3) tells us that a selenol should be more acidic than a thiol - in fact, the pKa of a selenocysteine is about 5.5, meaning that it is mostly in its deprotonated state at physiological pH, making it even more nucleophilic.

Glutathione peroxidase very efficiently catalyzes the reduction of hydrogen peroxide to water and the oxidation of glutathione (GSH) to GSSG, beginning with nucleophilic attack by the enzymatic selanocysteine on a peroxide oxygen. The intermediates in this process are shown below: each step can be thought of as a concerted nucleophilic displacement similar to those that take place in a disulfide exchange reaction.