

15.12: THIOETHERS (SULFIDES) AND SILYL ETHERS

Thiols and sulfides are the "sulfur equivalent" of alcohols and ethers. You can replace the oxygen atom of an alcohol with a sulfur atom to make a thiol; similarly, you can replace the oxygen atom in an ether with S to make the corresponding alkyl sulfide. This is because thiols contain the C-S-H functional group, while sulfides contain the C-S-C group.

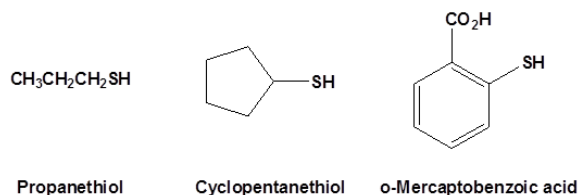
OXIDATION STATES OF SULFUR COMPOUNDS

Oxygen assumes only two oxidation states in its organic compounds (−1 in peroxides and −2 in other compounds). Sulfur, on the other hand, is found in oxidation states ranging from −2 to +6, as shown in the following table (some simple inorganic compounds are displayed in orange).

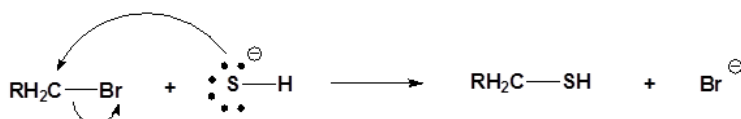
Sulfur Oxidation States in Organic Compounds					
−2	−1	0	+2	+4	+6
H_2S $\text{R}-\text{S}-\text{H}$ thiols $\text{R}-\text{S}-\text{R}$ sulfides $\text{R}-\text{S}^+-\text{R}$ sulfonium ions	$\text{R}-\text{S}-\text{S}-\text{R}$ disulfides	S elemental $\text{R}-\text{S}(=\text{O})-\text{R}$ sulfoxides $\text{R}-\text{S}(=\text{O})_2-\text{R}$ sulfonic acids	$\text{R}-\text{S}(=\text{O})_2-\text{R}$ sulfones $\text{R}-\text{S}(=\text{O})_2-\text{OH}$ sulfonic acids	SO_2 $\text{R}-\text{S}(=\text{O})_2-\text{OH}$ sulfonic acids $\text{R}-\text{O}-\text{S}(=\text{O})_2-\text{O}-\text{R}$ sulfite esters	SO_3 $\text{R}-\text{O}-\text{S}(=\text{O})_2-\text{O}-\text{R}$ sulfate esters

THIOLS

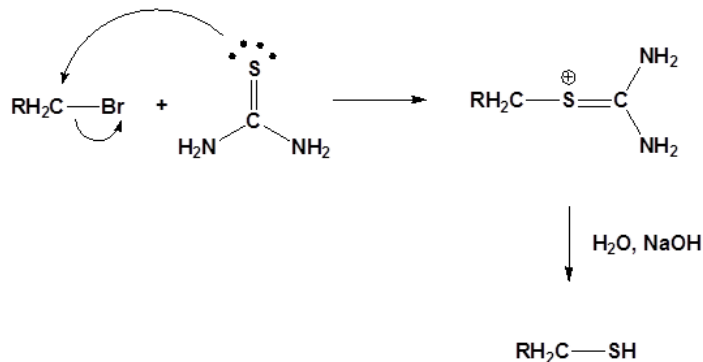
Thiols are often called "mercaptans," a reference to the Latin term mercurium captans (capturing mercury), since the -SH group forms strong bonds with mercury and its ions. Thiols are analogous to alcohols. They are named in a similar fashion as alcohols except the suffix -thiol is used in place of -ol. By itself the -SH group is called a mercapto group.



Thiols are usually prepared by using the hydrosulfide anion (−SH) as a nucleophile in an $\text{S}_\text{N}2$ reaction with alkyl halides.

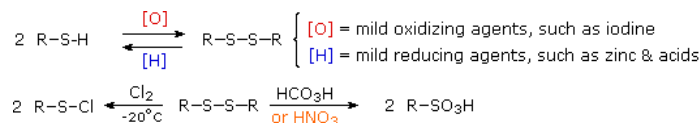


One problem with this reaction is that the thiol product can undergo a second $\text{S}_\text{N}2$ reaction with an additional alkyl halide to produce a sulfide side product. This problem can be solved by using thiourea, $(\text{NH}_2)_2\text{C}=\text{S}$, as the nucleophile. The reaction first produces an alkyl isothioureia salt and an intermediate. This salt is then hydrolyzed by a reaction with aqueous base.



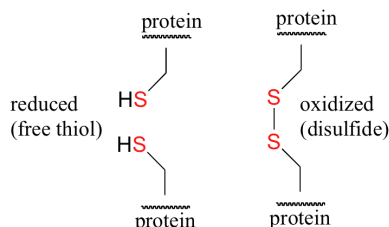
DISULFIDES

Oxidation of thiols and other sulfur compounds changes the oxidation state of sulfur rather than carbon. We see some representative sulfur oxidations in the following examples. In the first case, mild oxidation converts thiols to disulfides. An equivalent oxidation of alcohols to peroxides is not normally observed. The reasons for this different behavior are not hard to identify. The S-S single bond is nearly twice as strong as the O-O bond in peroxides, and the O-H bond is more than 25 kcal/mole stronger than an S-H bond. Thus, thermodynamics favors disulfide formation over peroxide.

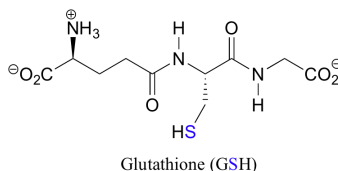


DISULFIDE BRIDGES IN PROTEINS

Disulfide (sulfur-sulfur) linkages between two cysteine residues are an integral component of the three-dimensional structure of many proteins. The interconversion between thiols and disulfide groups is a redox reaction: the thiol is the reduced state, and the disulfide is the oxidized state.

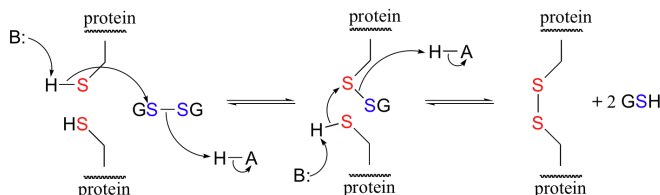


Notice that in the oxidized (disulfide) state, each sulfur atom has lost a bond to hydrogen and gained a bond to a sulfur - this is why the disulfide state is considered to be oxidized relative to the thiol state. The redox agent that mediates the formation and degradation of disulfide bridges in most proteins is glutathione, a versatile coenzyme that we have met before in a different context (section 14.2A). Recall that the important functional group in glutathione is the thiol, highlighted in blue in the figure below. In its reduced (free 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'.

A new disulfide in a protein forms via a 'disulfide exchange' reaction with GSSH, a process that can be described as a combination of two S_N2-like attacks. The end result is that a new cysteine-cysteine disulfide forms at the expense of the disulfide in GSSG.

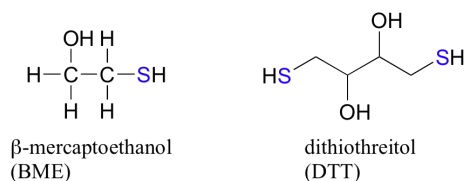


In its reduced (thiol) state, glutathione can reduce disulfides bridges in proteins through the reverse of the above reaction.

Disulfide bridges exist for the most part only in proteins that are located outside the cell. Inside the cell, cysteines are kept in their reduced (free thiol) state by a high intracellular concentration of GSH, which in turn is kept in a reduced state (ie. GSH rather than GSSG) by a flavin-dependent enzyme called glutathione reductase.

Disulfide bridges in proteins can also be directly reduced by another flavin-dependent enzyme called 'thioredoxin'. In both cases, NADPH is the ultimate electron donor, reducing FAD back to FADH₂ in each catalytic cycle.

In the biochemistry lab, proteins are often maintained in their reduced (free thiol) state by incubation in buffer containing an excess concentration of b-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, forms an intramolecular disulfide in its oxidized form.

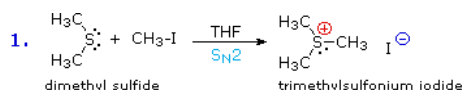


SULFIDES

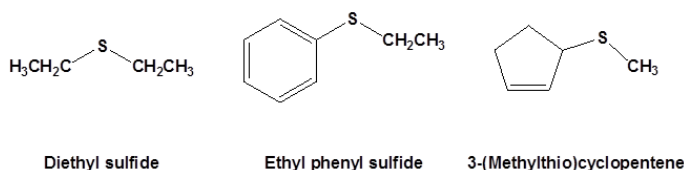
Sulfur analogs of ethers are called **sulfides**. Sulfides are less common than thiols as naturally occurring compounds. However, sulfides—especially disulfides (C-S-S-C)—have important biological functions, mainly in reducing agents (antioxidants). The chemical behavior of sulfides contrasts with that of ethers in some important ways. Since hydrogen sulfide (H₂S) is a much stronger acid than water (by more than ten million fold), we expect, and find, thiols to be stronger acids than equivalent alcohols and phenols. Thiolate conjugate bases are easily formed, and have proven to be excellent nucleophiles in S_N2 reactions of alkyl halides and tosylates.



Although the basicity of ethers is roughly a hundred times greater than that of equivalent sulfides, the nucleophilicity of sulfur is much greater than that of oxygen, leading to a number of interesting and useful electrophilic substitutions of sulfur that are not normally observed for oxygen. Sulfides, for example, react with alkyl halides to give ternary sulfonium salts (equation # 1) in the same manner that 3°-amines are alkylated to **quaternary ammonium salts**. Although equivalent oxonium salts of ethers are known, they are only prepared under extreme conditions, and are exceptionally reactive.

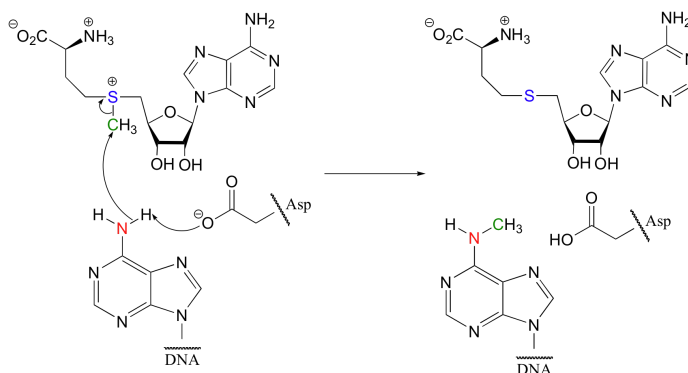


sulfides are named using the same rules as ethers except *sulfide* is used in the place of *ether*. For more complex substance alkylthio is used instead of alkoxy.



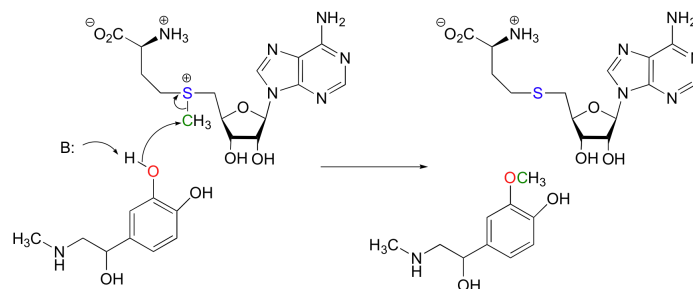
SAM METHYLTRANSFERASES

The most common example of sulfonium ions in a living organism is the reaction of S-Adenosylmethionine. Some of the most important examples of S_N2 reactions in biochemistry are those catalyzed by S-adenosyl methionine (SAM) – dependent methyltransferase enzymes. We have already seen, in chapter 6 and again in chapter 8, how a methyl group is transferred in an S_N2 reaction from SAM to the amine group on the nucleotide base adenosine:



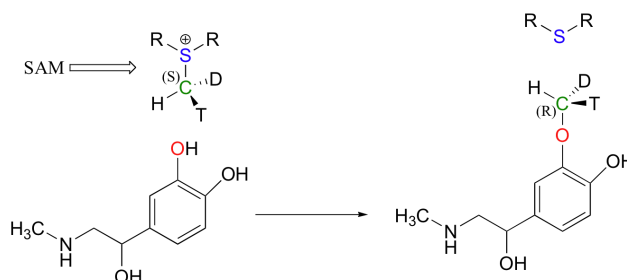
(*Nucleic Acids Res.* 2000, 28, 3950).

Another SAM-dependent methylation reaction is catalyzed by an enzyme called catechol-O-methyltransferase. The substrate here is epinephrine, also known as adrenaline.



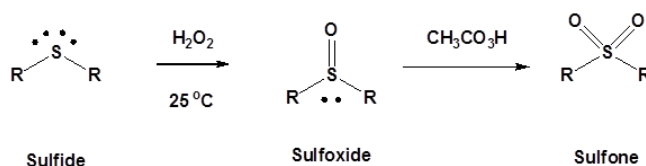
Notice that in this example, the attacking nucleophile is an alcohol rather than an amine (that's why the enzyme is called an O-methyltransferase). In both cases, though, a basic amino acid side chain is positioned in the active site in just the right place to deprotonate the nucleophilic group as it attacks, increasing its nucleophilicity. The electrophile in both reactions is a methyl carbon, so there is little steric hindrance to slow down the nucleophilic attack. The methyl carbon is electrophilic because it is bonded to a positively-charged sulfur, which is a powerful electron withdrawing group. The positive charge on the sulfur also makes it an excellent leaving group, as the resulting product will be a neutral and very stable sulfide. All in all, in both reactions we have a reasonably good nucleophile, an electron-poor, unhindered electrophile, and an excellent leaving group.

Because the electrophilic carbon in these reactions is a methyl carbon, a stepwise S_N1 -like mechanism is extremely unlikely: a methyl carbocation is very high in energy and thus is not a reasonable intermediate to propose. We can confidently predict that this reaction is S_N2 . Does this S_N2 reaction occur, as expected, with inversion of stereochemistry? Of course, the electrophilic methyl carbon in these reactions is achiral, so inversion is not apparent. To demonstrate inversion, the following experiment has been carried out with catechol-O-methyltransferase:



Here, the methyl group of SAM was made to be chiral by incorporating hydrogen isotopes tritium (^3H , T) and deuterium (^2H , D). The researchers determined that the reaction occurred with inversion of configuration, as expected for an S_N2 displacement (*J. Biol. Chem.* **1980**, 255, 9124).

Sulfides can be easily oxidized. Reacting a sulfide with hydrogen peroxide, H_2O_2 , at room temperature produces a sulfoxide (R_2SO). The oxidation can be continued by reaction with a peroxyacid to produce the sulfone (R_2SO_2).



A common example of a sulfoxide is the solvent dimethyl sulfoxide (DMSO). DMSO is a polar aprotic solvent.

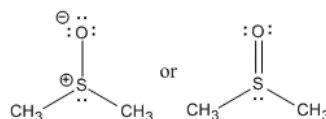


Figure AB16.3. DMSO is a very polar, aprotic solvent.

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