

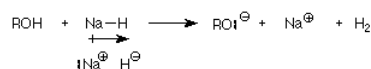
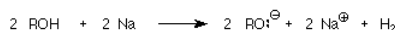
## 1.14: Ethers, Epoxides, Thiols

### Alcohol Acidity - Making Alkoxide Ions

The acidity of alcohols is very comparable to that of water. That is, both water and most alcohols have  $pK_a$ 's in the range of 15-16. As acids go, this makes them quite weak. Another way to say that the acidities of water and of alcohols are about the same is to say that the equilibrium constant for the following reaction is about 1.



Of course, saying that water and alcohols have about the same acidity also means that hydroxide ion and alkoxide ions have about the same base strength. One practical consequence of this is that we can't completely convert an alcohol (ROH) to its conjugate base, the alkoxide ( $RO^-$ ), by using hydroxide ion ( $HO^-$ ) as the base because hydroxide ion isn't any stronger than a typical alkoxide ion. Instead there are two other reactions which work and which are commonly used



In the first of these, it is hard to see what is serving as the base which removes the  $H^+$  from the alcohol. In a formal sense, two sodium atoms provide an electron each to make the new sigma bond in  $H_2$ , so perhaps it makes sense to call those electrons the strong base.

In the second reaction, the identity of the strong base is easier to see. In sodium hydride (NaH), the NaH bond is very strongly polarized, much more than the B-H bond in sodium borohydride, so that we can realistically regard it as an ionic compound ( $Na^+ :H^-$ ) so that the  $:H^-$  serves as the base. Since the hydrogen molecule ( $H_2$ ) is such a weak acid that we never think of it as an acid, its conjugate base  $:H^-$  is a very strong base.

### Making Ethers

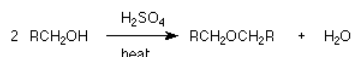
Now that we know about the acidity of alcohols and how to make alkoxide ions, their conjugate bases, we can ask "What are these alkoxide ions good for?" Since they are strong bases, we would also expect them to be good nucleophiles, and they are. We've seen their basic properties used in carrying out the [Claisen condensation](#) and occasional uses in other reactions with carboxylic acid derivatives, but their most direct use as synthetic reagents comes in their reactions with primary alkyl halides.



It is important to understand that this reaction only succeeds if the alkyl halide is primary. We'll take up the reasons for this later. Keep in mind that the most useful way to make an alkyl halide is from an alcohol, so that we could extend our reaction sequence by adding steps at the beginning to show how the alkoxide and the alkyl halide are made from alcohols:

The product of this reaction sequence is an ether,  $ROCH_2R'$ , so we have a synthetic method for making an ether from two alcohols, with the important restriction that one of the alcohols is primary.

There is also an acid catalyzed reaction which makes a symmetrical ether, one in which the two alkyl groups attached to the oxygen are identical. In this reaction a primary alcohol is heated with an acid catalyst (usually sulfuric acid). A molecule of water is lost and the ether is formed from two molecules of the alcohol.



Again, it is important to realize that this reaction can only be used on primary alcohols and that the ether produced this way is symmetrical.

### Ethers as Solvents

Ethers are generally unreactive compounds. The C-O bond is polar, but breaking it is difficult. We will look at the reasons for this later.

The lack of reactivity of the ether functional group is one reason for the common use of ethers as solvents. A solvent has to dissolve the reactants to be useful, and it also must not react with the reactants present. In many cases, ethers meet these requirements well. They are fairly non-polar, since only the ether functional group contributes any polarity, so they dissolve most organic compounds easily. The unshared electron pairs on oxygen make them weak bases which allows them to dissolve some fairly polar reagents like Grignard reagents and lithium aluminum hydride. The lack of any acidic hydrogens, even those which are fairly weakly acidic like the OH hydrogens of alcohols, means that ethers are compatible with materials like Grignard reagents and lithium aluminum hydride which react with and are destroyed by alcohols. You will have seen ethers as solvents in many reactions. Two ethers which are commonly used as reaction solvents are:



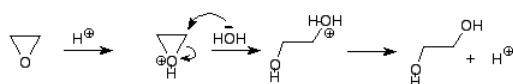
In lab, you also have used diethyl ether as a solvent for extractions. This takes advantage of ether's ability to dissolve most non-ionic organic compounds, its immiscibility (doesn't mix) with water, and the fact that ionic compounds are generally insoluble in diethyl ether. Since THF is miscible with water, it is not useful as an extraction solvent

## Epoxides - Ring Strain

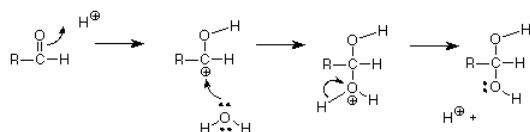
There is one type of ether which is quite reactive. The key structural feature of these ethers is that the oxygen atom is contained in a three-membered ring. Such ethers are called **epoxides**. The internal angles of such a ring will be near  $60^\circ$ , and this pushes the bonding electrons much closer together than the  $109.5^\circ$  we would expect from the a VSEPR estimate or from  $\text{sp}^3$  hybridization. Thus epoxides have high energies compared to "ordinary" ethers. One result is that epoxides are, in contrast to "ordinary" ethers, rather reactive compounds. Such rings are regarded as "strained" because the deviation of their bond angles from normal values leads to extra reactivity.

We'll look at two examples:

**Acid-Catalyzed Hydrolysis:** The name of this reaction recalls the acid-catalyzed hydration of ketones and aldehydes -- the first reaction we studied this semester. In fact, if we look at the mechanism of the acid catalyzed hydrolysis of the simplest epoxide:

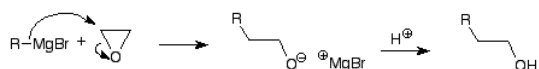


and compare it to the acid catalyzed hydration of an aldehyde:



we see that the steps in the two mechanisms are identical. In each case, the acidic  $\text{H}^+$  adds to the oxygen atom. This pulls electron density away from the attached carbon atom, making it susceptible to attack by the weakly nucleophilic oxygen of water. A carbon-oxygen bond is broken, and the reaction is completed by regeneration of the  $\text{H}^+$  catalyst. (We'll be in a position to look at the [stereochemistry](#) of this reaction in about three weeks).

The resemblance between these two mechanisms suggests that the reactions of epoxides are similar to those of carbonyl groups. More precisely, epoxide reactivity is intermediate between the reactivity of ethers (pretty unreactive) and carbonyl groups (reactive with selected reagents). Another example of this lies in the addition of Grignard reagents to epoxides. Again, we'll look at the simplest case (ethylene oxide), where there are no alkyl groups on the carbons of the epoxide.



Here again, we have a direct analogy with the [reaction of an aldehyde or ketone with a Grignard reagent](#). As a synthetic reaction, this is best used with ethylene oxide, since complications are prevalent with more complex epoxide. The synthetic outcome of this reaction is to make a new primary alcohol which is two carbons longer than the Grignard reagent.

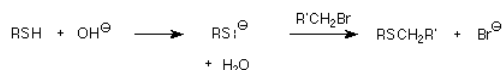
We'll defer discussion of the synthesis of epoxides until we look at the [addition reactions of alkenes](#).

## Thiols and Crosslinks

Our last topic for today is thiols -- the group of compounds in which the oxygen of an alcohol has been replaced by a sulfur. As one might expect given the close relationship between oxygen and sulfur in the periodic table, there are some similarities between alcohols and thiols. We will not examine the synthesis of thiols; rather, we'll look at some of their properties.

Perhaps the most obvious property of thiols, at least those which are small enough to be volatile, is their extremely disagreeable odor. This is understandable if we regard them as derived from hydrogen sulfide (rotten egg odor) in the same way that alcohols can be regarded as derived from water. Butanethiol ( $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{SH}$ ) is actually added to natural gas before it is distributed by pipeline so that the odor will signal the presence of a leak before it leads to dangerous concentrations of the gas. Chemists who work with thiols are careful to use them in the hood!

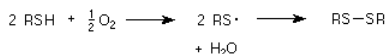
The SH group in a thiol is more acidic than the OH group in an alcohol. That means that the  $\text{RS}^-$  (thiolate ion) can be conveniently made by reacting a thiol (RSH) with hydroxide ion ( $\text{OH}^-$ ). The thiolate ion is a good nucleophile, so it can react readily with a primary alkyl bromide to produce a thioether:



The SH group has important roles to play in biochemistry. We've seen how the sulfur serves as a leaving group in the Claisen-like reaction which makes the carbon-carbon bonds in fatty acid biosynthesis. This is quite general, since thioesters (the name for an ester containing a sulfur in the leaving group position) are very common in biochemical processes.

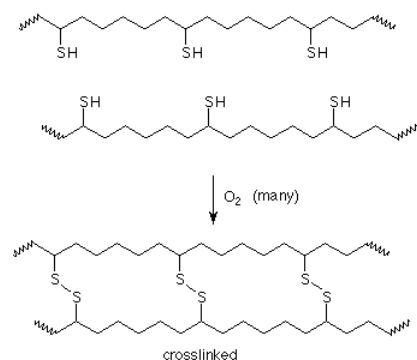
The thiol group is also important in the structure of proteins. Keep in mind that proteins are polyamides -- long chains of amino acids linked together by amide linkages. These chains can coil around and adopt a variety of shapes, some fairly straight and regular and others snarled like a tangled fishing line. For many purposes such as those in which proteins serve as enzymes (biochemical catalysts), it is essential that the protein have only one shape. Thiols contribute to maintaining that shape

The chemistry of this depends on the fact that the S-H bond can be oxidized by very mild oxidizing agents such as oxygen ( $\text{O}_2$ ). This reaction produces a sulfur atom which has an unpaired electron. Two such sulfur atoms can join to produce a sulfur-sulfur bond. The reaction is outlined as follows:



The new functional group is called a disulfide and the bond between the two sulfurs is called a disulfide bond.

If two polymer chains which include SH groups are positioned so those groups are close together, the oxidation reaction makes a link between the two chains, much like rungs link the side rails of a ladder. The new links are called crosslinks and the new structure is much more rigid than was the case with the flexible polymers prior to crosslinking.



The original process for the vulcanization of natural rubber (which involved heating the gummy natural material with sulfur) probably produced such crosslinks, although the details of the chemistry are different. In proteins the amino acid which provides the SH groups is cysteine ( $\text{HSCH}_2\text{CHNH}_3^+\text{COO}^-$ ). The protein keratin, found in hair, skin and feathers, is rich in cysteine. Crosslinks through disulfide bonds formed by the mild oxidation of cysteine are important in maintaining the shape of these systems.

Home permanents work by controlling crosslinking. The first step is to apply a mild reducing agent which converts the disulfide bonds to two SH groups. The hair is "clamped" into the desired shape, then a mild oxidizing agent is added to form disulfide bonds between SH groups which have been moved close together in the new shape. These bonds "lock" neighboring keratin protein chains into the new shape, rendering it "permanent," at least until it grows out.

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