Chapter 10
Alcohols and Ethers

The three organic functional groups already studied are either nucleophiles or electrophiles, but not both. Alkyl halides are electrophiles and, in fact, our usual carbon electrophiles so far (Chapters 6 and 7). Alkenes and alkynes are normally nucleophiles, although terminal alkynes can also be electrophilic acids for very strong bases (Chapters 8 and 9).

In contrast, this chapter demonstrates that alcohols compose the most versatile class of organic reagents. Simple alcohols can usefully react as acids, non-acid electrophiles, bases, and non-base nucleophiles. A sure sense of electrophiles and nucleophiles helps to distinguish and anticipate the many reactions of alcohols. In addition, alcohols have already been considered as protic solvents, especially suited for S_N1 and E1 reactions (Sections 6.6 and 7.8).

This chapter also presents a much less reactive organic functional group: ethers. Simple ethers most frequently serve in the laboratory as weakly polar aprotic solvents, and only a strained cyclic version commonly reacts in syntheses.

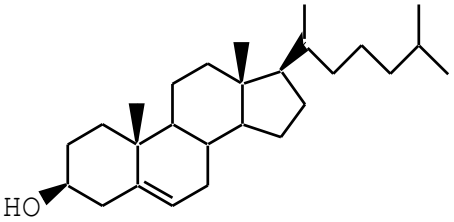
10.1 Notable Alcohols and Ethers

Four of the smallest alcohols are common enough in daily life to have commercial names. Wood alcohol is methanol, a racing car fuel. Grain alcohol is ethanol, the famous intoxicant. Rubbing alcohol is 2-propanol, also named isopropyl alcohol. The antifreeze in car radiators is the double alcohol 1,2-ethanediol, commonly called ethylene glycol. Another well-known alcohol is cholesterol, an essential but sometimes troublesome steroid.

CH_3OH	CH_3CH_2OH	$(CH_3)_2CHOH$
methanol (methyl alcohol) (wood alcohol)	ethanol (ethyl alcohol) (grain alcohol)	2-propanol (isopropyl alcohol) (rubbing alcohol)

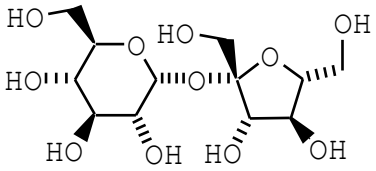
$HOCH_2CH_2OH$

1,2-ethanediol
(ethylene glycol)

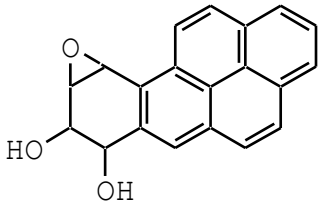


cholesterol

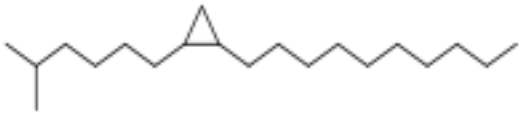
Ethers are also important in biology. Table sugar, that is, sucrose, is a triple ether as well as a multiple alcohol. The main carcinogenic metabolite from cigarette smoke is a cyclic ether (Section 10.8B). This same cyclic ether functional group appears in disparlure, the sex pheromone of the female gypsy moth.



sucrose



smoke carcinogen



disparlure

Puzzle 10.1 ———————————————————————————————————

Locate double bonds alternating with single bonds in a second resonance form of the above smoke carcinogen.

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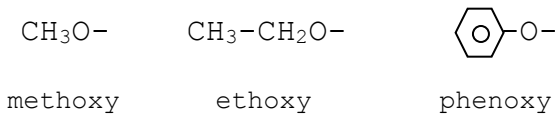
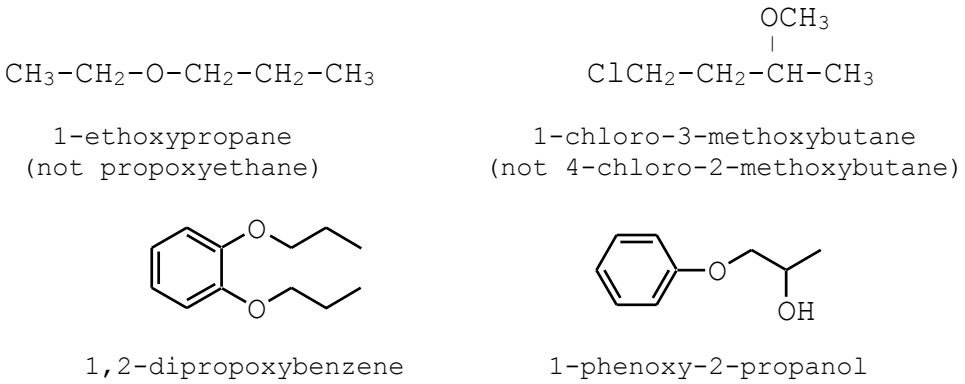
10.2 Nomenclature of Ethers

Section 2.2C presented the IUPAC system for naming alcohols. Here let us name **ethers,** which have two carbon groups on one oxygen. For acyclic ethers the IUPAC system uses the larger or more complex of the two carbon groups as the stem. Then the simpler carbon group plus the oxygen is named as a prefix for the stem. Such combinations of carbon group and oxygen are called **alkoxy** (i.e., alkyl + oxy) **groups** if the carbon group is an alkyl group, and **phenoxy groups**

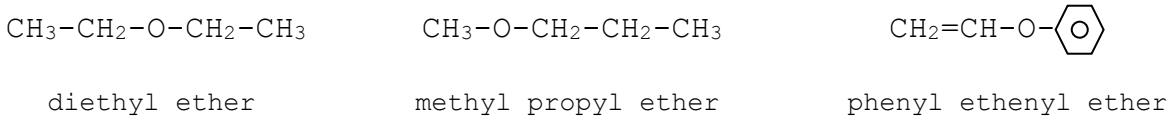
if the carbon group is a phenyl ring. Here are some alkoxy and phenoxy groups:



Accordingly, some IUPAC names for ethers follow:



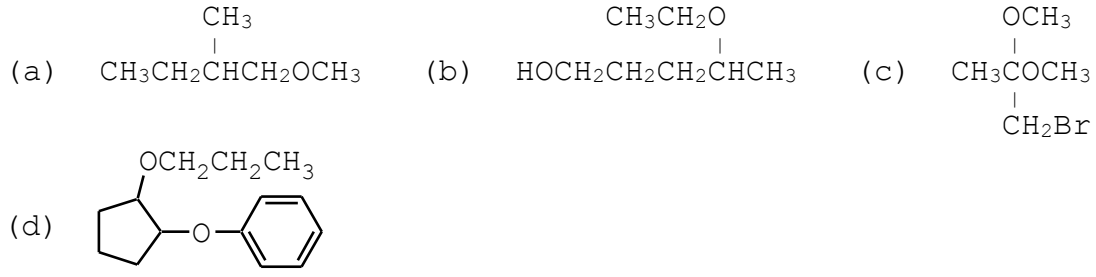
A second, common way of naming simple ethers places *ether* after the names of the two carbon groups. For example:



Like other organic compounds, alcohols and ethers in this book carry IUPAC systematic names except especially cumbersome ones. The common name cholesterol is much more convenient than the IUPAC equivalent, cholest-5-en-3β-ol. IUPAC names for cyclic ethers do not follow these guidelines and will be named only when encountered.

Puzzle 10.2 ———————————————————————————————

Give the IUPAC name for each of these compounds:



Puzzle 10.3 ———————————————————————————————

Draw structures for these compounds:
(a) *cis*-1,3-cyclohexanediol (b) phenoxybenzene (c) (*E*)-1-ethoxypropene
(d) (*R*)-4-chloro-2-methoxy-2-butanol

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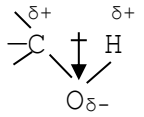
10.3 Physical Properties of Alcohols and Ethers

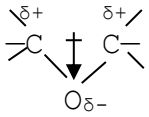
Two important physical properties that we consider for every new class of organic compound are boiling point and solubility. Let us see how the structures of alcohols and ethers affect these properties.

10.3A Boiling Points of Alcohols and Ethers

To predict or rationalize physical properties we must assess intermolecular forces. Both a simple alcohol and a simple ether have electronegative oxygens that form two polar bonds:



an alcohol



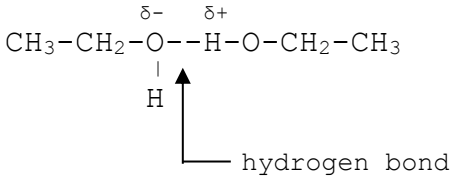
an ether

Because each oxygen is hybridized sp^3 with approximately 109° bond angles, each molecule is polar. So each compound has dipole-dipole forces as well as dispersion forces.

Let us use structural features to explain the relative boiling points of these compounds:

	$CH_3-CH_2-CH_3$	CH_3-O-CH_3	CH_3-CH_2-OH
bp:	-42°C	-25°C	78°C

All three have similar sizes and therefore similar dispersion forces. Yet, nonpolar propane has no dipole-dipole forces and so a lower boiling point than the polar ether and alcohol compounds with dipole-dipole forces. The alcohol has a much higher boiling point than the ether because it has an additional intermolecular force, hydrogen bonding:



Simple ether molecules cannot hydrogen bond among themselves.

Let us analyze another comparison of boiling points:

	CH_3-CH_2-OH	$CH_3-CH_2-CH_2-OH$
bp:	78°C	97°C

Increasing molecular size increases dispersion forces:

as size ↑, dispersion forces ↑ & bp ↑

Table 10.1 further demonstrates the correlation between size and boiling point.

Table 10.1 Boiling Points and Water Solubilities of Simple Alcohols

Name	Structure	Bp/°C	Water solubility at ~25°C/g·100 mL^{-1}
methanol	CH_3OH	65	miscible
ethanol	CH_3CH_2OH	78	miscible
1-propanol	$CH_3CH_2CH_2OH$	97	miscible
1-butanol	$CH_3(CH_2)_3OH$	117	7.4
2-methyl-2-propanol	$(CH_3)_3COH$	82	miscible
1-pentanol	$CH_3(CH_2)_4OH$	138	2.7
1-hexanol	$CH_3(CH_2)_5OH$	158	0.59
1-heptanol	$CH_3(CH_2)_6OH$	176	0.10

Puzzle 10.4

Consider all the $C_4H_{10}O$ constitutional isomers.
(a) Draw and name them. (b) Which has the highest boiling point? Explain.
(c) Which, if any, has stereoisomers?

Puzzle 10.5

The main component of automobile antifreeze is 1,2-ethanediol.
(a) Which has a higher boiling point, 1,2-ethanediol or ethanol? Explain.
(b) Which has a higher boiling point, 1,2-ethanediol or water? Explain.
(c) Based on your answer to part b, which component would evaporate faster from a 50:50 mixture of 1,2-ethanediol and water?

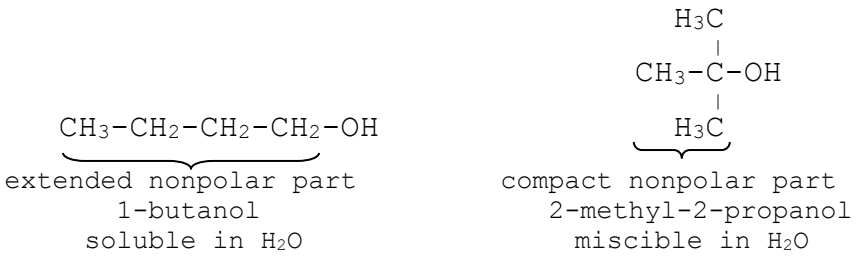
10.3B Solubilities of Alcohols and Ethers

Depending on molecular size and shape, solubility characteristics for alcohols and ethers vary widely. Table 10.1 (Section 10.3A) gives the water solubilities of various simple alcohols. The smaller alcohols of fewer than five carbons are soluble (i.e., > 5 g/100 mL) or even **miscible** in water (i.e., soluble in all proportions). As the number of carbons increases, the solubility in water decreases, so that simple alcohols of more than five carbons are practically insoluble. Why does the solubility decrease this way? As the number of carbons increases, the number of nonpolar carbon-carbon and carbon-hydrogen bonds increases, the overall polarity decreases, and so does the similarity to water. Consequently, water dissolves the larger alcohols less well:

as # of carbons ↑, polarity ↓ & water solubility ↓

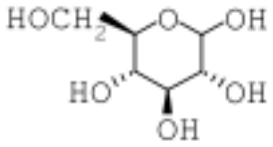
It is interesting that two $C_4H_{10}O$ constitutional isomers, 1-butanol and 2-methyl-2-

propanol, have very different solubilities in water: 7.4 g/100 mL and miscible, respectively. We can explain this difference by the surface areas of the nonpolar parts of the two molecules:



The extended four-carbon chain of 1-butanol has a greater surface area exposed to polar water than does the highly branched, compact four-carbon group of 2-methyl-2-propanol. Therefore, water molecules more easily surround and solvate the latter isomer than the former.

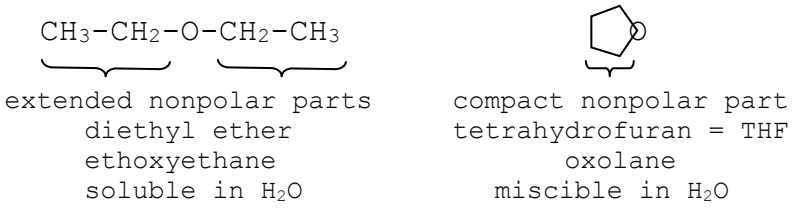
The correlation between the number of carbons and water solubility assumes simple, monofunctional alcohols. With enough polar functional groups even large molecules can be soluble in water. An example is the six-carbon sugar, glucose:



D-glucose

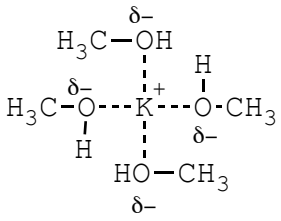
Although having more than five carbons, glucose has six polar functional groups to make it very soluble in water (91 g/100 mL).

Other classes of organic compounds with one polar oxygen functional group, including simple ethers, roughly follow the five-carbon rule of water solubility. For example, diethyl ether (ethoxyethane) is soluble in water (6.0 g/100 mL) and tetrahydrofuran (i.e., THF or oxolane) is miscible:

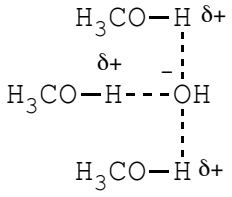


With fewer than five carbons, both ethers are appreciably soluble in water, but tetrahydrofuran is much more so. Again, the more soluble tetrahydrofuran has a more compact nonpolar part, pinned back in a ring to leave the oxygen more accessible for hydrogen bonds with water.

The smallest alcohols, methanol and ethanol, are less polar than water, but still polar enough to dissolve many (not all) ions, both cations and anions. The partial negative charges on their oxygens help solvate cations with ion-dipole forces, while their hydroxy hydrogens solvate anions with hydrogen bonds:



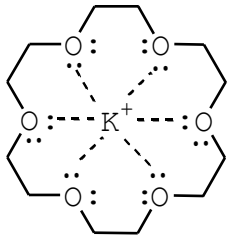
ion-dipole forces with a cation



hydrogen bonds with an anion

Thus potassium hydroxide dissolves in methanol. In addition, by not being too polar, methanol and ethanol can dissolve many kinds of organic compounds. As a result, these two small alcohols, which dissolve many different kinds of reagents, are very common solvents for organic reactions. In contrast, very polar water, which dissolves many ionic and inorganic reagents, does not dissolve the many less polar organic compounds and so is not usually the sole solvent for organic reactions. More often it is used as a co-solvent with a less polar but miscible solvent, such as methanol, ethanol, or tetrahydrofuran.

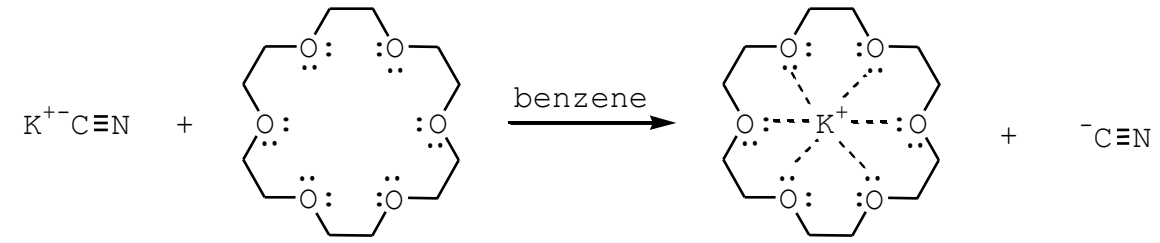
Most ethers, which are generally less polar and aprotic, do not dissolve ions well but are useful solvents for less polar organic reagents. The **crown ethers,** however, solvate certain cations especially well. Crown ethers are macrocyclic (i.e., large-ring) polyethers. For example, 18-crown-6 has 18 ring atoms, six of which are symmetrically disposed ether oxygens:



18-crown-6 solvating K^+

It is called a crown ether for the conformation of its ring puckered out of the plane like a cyclohexane ring and for its "crowning" or surrounding of ions of a certain size. This interior cavity has a diameter of 270 pm barely large enough to fit a potassium ion with a diameter of 266 pm. It is both a good physical and a good chemical fit with six ion-dipole forces between the cation and the lone pairs on the six oxygens. Likewise, the smaller crown ether, 15-crown-5, ideally solvates the smaller sodium ion.

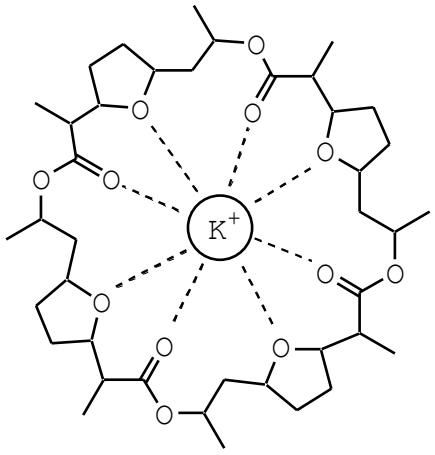
This encircling solvation isolates the cation from its anionic counter ion. Recall that most S_N2 and E2 reactions prefer an aprotic solvent, which dissolves ions without stabilizing reactive anions too much with hydrogen bonds (Sections 6.6 and 7.8). Crown ethers and a nonpolar or slightly polar co-solvent can take the process a step further by fully solvating the cation of a salt while leaving its anion unsolvated and free to react as a stronger S_N2 nucleophile or E2 base. For example, by itself nonpolar benzene is a poor solvent for reactions of potassium cyanide because it does not dissolve ions well. Yet, the addition of 18-crown-6 solubilizes the salt by fully solvating the cation:



insoluble in benzene | 18-crown-6 | soluble in benzene | unsolvated, reactive

The periphery of the 18-crown-6 complex is hydrocarbon and therefore soluble in benzene, but the cyanide ion is unsolvated and therefore very nucleophilic. This crown ether is our first example of a **phase-transfer catalyst**. In general, a phase-transfer catalyst promotes a reaction by assisting in the transfer of an anion into a less polar, aprotic solvent, where it would normally not dissolve. Tetraalkylammonium ions provide a second type of phase-transfer catalyst (Section 15.4).

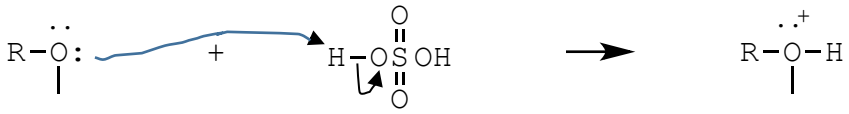
Several natural antibiotics, such as gramicidin, valinomycin, and nonactin, kill bacteria by this principle of solvating cations. For example, inside a bacterial cell nonactin solvates potassium ions on all sides with eight ion-dipole forces:



nonactin solvating K^+

Then with its nonpolar hydrocarbon parts on the outside, the complex transports its ion through the mostly nonpolar cell membrane, which hinders passage of ions (Section 14.8C). Because of depleted potassium ions, which are essential for a healthy cell, the bacterium dies.

Like other organic compounds that contain oxygen, alcohols and ethers are generally soluble in concentrated sulfuric acid. The strong acid protonates the oxygen to make an oxonium ion:



alcohol or ether | sulfuric acid | oxonium ion

Even if the oxonium ion has more than five carbons, its formal positive charge gives it enough polarity to dissolve in the polar solvent sulfuric acid. In fact, a common qualitative analysis test for organic compounds containing an oxygen, nitrogen, or sulfur tries to dissolve the unknown in

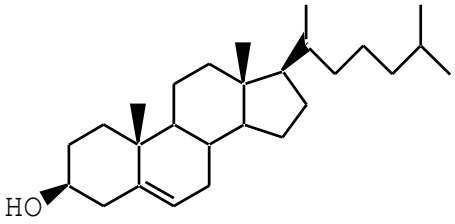
concentrated sulfuric acid.

Puzzle 10.6

Consider 1-pentanol, 2-methyl-1-butanol, and 3-methyl-1-pentanol.
(a) Rank them by solubility in water and explain your ranking.
(b) Rank them by boiling point and explain your ranking.

Puzzle 10.7

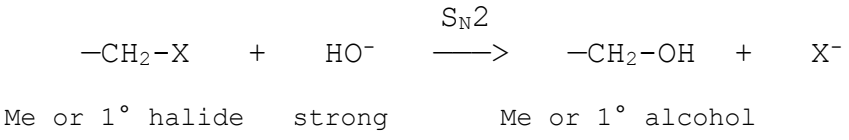
If blood is mostly water, would cholesterol (below) itself be soluble in blood? Explain.



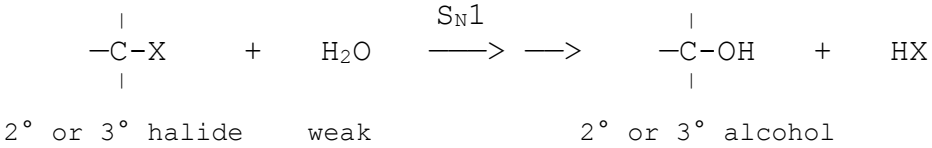
10.4 Syntheses of Alcohols

Because alcohols are such useful, versatile reagents, we should know different ways to make them. Let us review the methods already explored in previous chapters: five ways for making simple alcohols and one for synthesizing 1,2-diols.

In Chapter 6 we saw how nucleophiles can substitute on alkyl halide electrophiles in S_N2 or S_N1 reactions. Because an S_N2 reaction is generally cleaner, more direct, and more useful than the analogous S_N1 reaction (Section 6.8), substitution works best with methyl and primary halides, which favor S_N2 reactions over S_N1 and E2 reactions. Because a normal S_N2 reaction requires a strong nucleophile, the strong hydroxide nucleophile suits the formation of a methyl or primary alcohol:



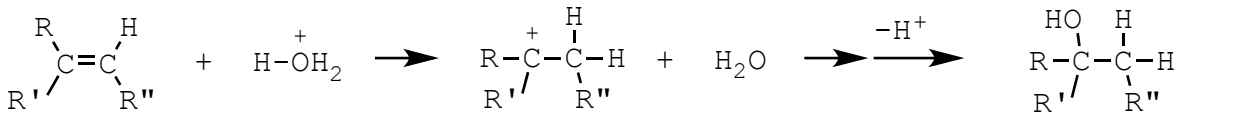
Nucleophilic substitution synthesizes secondary and tertiary alcohols less well. To avoid competing E2 reactions, secondary or tertiary halides should react with a weakly basic nucleophile. So water, the weakly basic analogue of hydroxide ion, is chosen to make a secondary or tertiary alcohol by an S_N1 reaction:



This reaction, however, is always vulnerable to competing E1 eliminations. Also, carbocation rearrangements may lead to unwanted alcohol isomers. As a result, secondary and tertiary alcohols

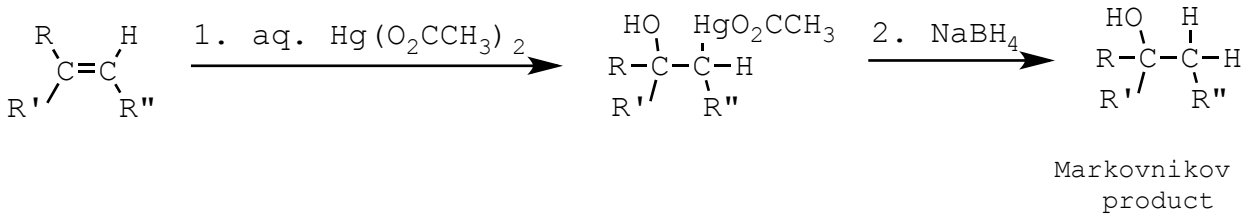
are usually made by other methods, such as hydration of an alkene.

In Chapter 8 we found three addition reactions that hydrate alkenes. Aqueous acid, typically aqueous sulfuric acid, can catalyze the hydration (Section 8.8B):



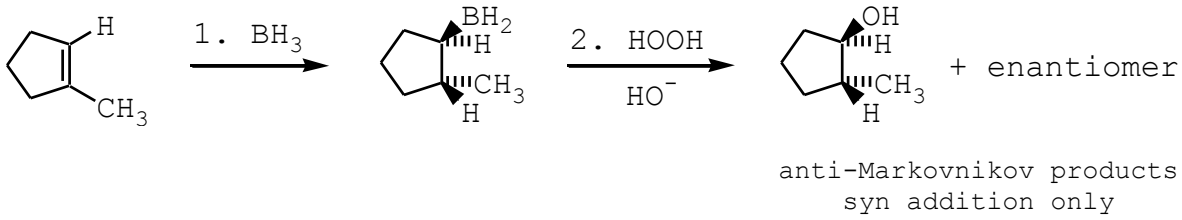
Markovnikov addition prevails by way of the more stable, more substituted of the two possible carbocations. Carbocation rearrangements may occur.

A sequence of two reactions with mercuric acetate and sodium borohydride also hydrates alkenes (Section 8.9):



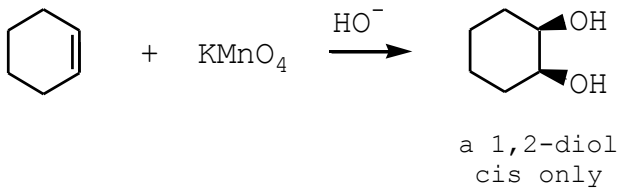
The alkene carbon with more hydrogens adds another hydrogen in a Markovnikov addition. Carbocation rearrangements do not occur because no true carbocation forms.

A different sequence of two reactions provides anti-Markovnikov hydration of an alkene (Section 8.11):



In addition to being regioselective (anti-Markovnikov), this hydration is the only one of the three that is stereoselective, adding syn overall.

To make a 1,2-diol, cold, basic potassium permanganate oxidizes an alkene (Section 8.12A):



The addition is stereoselective and syn.

Other syntheses of alcohols will be examined later: from oxiranes (Sections 10.8B), from aldehydes and ketones (Sections 12.5B and E), from carboxylic acids (Section 13.5B), and from carboxylic acid derivatives (Sections 14.7A-B).

Puzzle 10.8

Show the alcohol constitutional isomers produced from 3-methyl-1-butene and these reagents:
(a) dilute aqueous sulfuric acid (b) mercuric acetate, then sodium borohydride
(c) borane, then basic hydrogen peroxide (d) cold, basic potassium permanganate

Puzzle 10.9

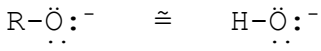
Starting with a simple alkyl halide, outline a synthesis of 1,2-ethanediol, the main component of automobile antifreeze.

10.5 Reactions of Alcohols

As indicated in this chapter's introduction, alcohols compose the most versatile class of organic reagents. Under different circumstances they can react as acids, bases, non-acid electrophiles, and non-base nucleophiles. We will examine each type of reaction in turn.

10.5A Reactions of Alcohols as Acids

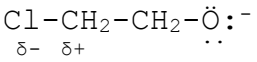
Table 4.1 (Section 4.2) shows that methanol resembles water as a weak acid with a K_a near 10^{-16}. Other simple alcohols have similar K_a values. This similarity to water simply reflects the similarity of their conjugate bases:



relative basicities of alkoxide and hydroxide ions

Both base atoms are anionic oxygens and the remaining atoms are carbons and hydrogens, all of similar electronegativity. Therefore, neither resonance nor inductive effects can affect these simple oxides.

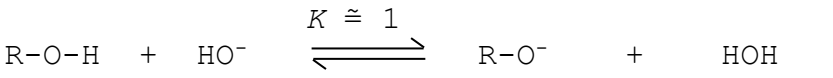
Of course, a more electronegative atom can influence the acidity of an alcohol. For example, the K_a of 2-chloroethanol is 5 x 10^{-15}, indicating an acid 10 times stronger than a simple alcohol. The conjugate base divulges the reason:



Cl stabilizes base electrons inductively

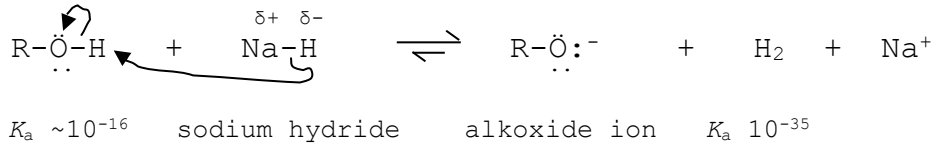
The more electronegative chlorine puts a partial positive charge on its carbon, which attracts and inductively stabilizes oxygen's base electrons. The weaker alkoxide conjugate base means a stronger alcohol acid.

What kind of base can efficiently convert a simple alcohol to its conjugate base alkoxide? As a weak acid, an alcohol needs a strong base to remove a proton. Let us try the strongly basic hydroxide ion:



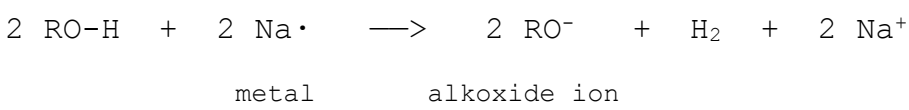
With about equally strong acids on both sides of the equilibrium, the equilibrium constant, *K*, is about one. Although a large excess of hydroxide ion could convert most of the alcohol to its alkoxide ion (by Le Châtelier's Principle), this is not an efficient conversion.

A stronger base than hydroxide ion would react more completely. Examples include amide ion (H_2N^-) and hydride ion (H^-), obtained from a reagent such as sodium hydride (NaH):

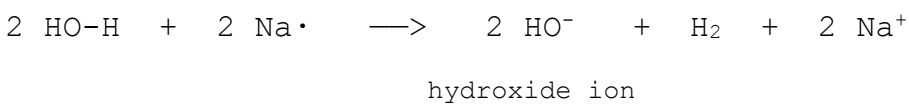


The weaker base (alkoxide ion) and weaker acid (hydrogen) survive this acid-base equilibrium. Note that the hydrogen in sodium hydride takes an electron pair from its bond with the less electronegative sodium to react with the alcohol. Thus, this hydrogen serves as a hydride ion base, not as the usual proton acid.

Another way to make the alkoxide ion adds sodium or potassium metal to the alcohol:



Actually this is not an acid-base reaction, but an oxidation-reduction reaction, where the metal reduces the acidic proton to hydrogen gas. Consequently, metallic sodium with one valence electron must be used instead of a salt such as sodium chloride. This reaction of an alcohol also resembles the analogous reaction of water, which forms hydroxide ion as counterpart to alkoxide ion:



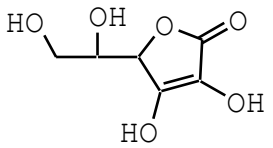
As in so many reactions, an alcohol is the organic analogue of water.

Puzzle 10.10 ———————————————————————————————————

A nitro group (-NO_2) is a substituent in 2-nitro-1-ethanol.
(a) Draw the two main resonance forms for this alcohol.
(b) Is this alcohol more or less acidic than ethanol? Explain.

Puzzle 10.11 ———————————————————————————————————

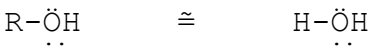
Vitamin C (i.e., ascorbic acid) is needed for healthy cells and tissues:



Which alcohol hydrogen is the most acidic with a surprisingly high K_a of 7 x 10^{-5}? Hint: such an abnormal value probably results from resonance.

10.5B Reactions of Alcohols as Bases

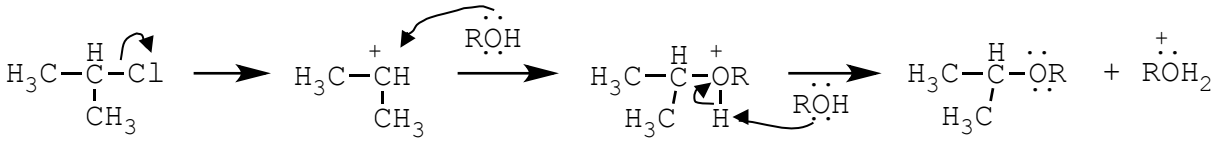
An alcohol also resembles water as a base. This is not surprising because the base atom of each is an uncharged oxygen and neither has resonance or inductive effects:



relative basicities of an alcohol and water

Table 4.1 (Section 4.2) confirms this assessment with similar K_a values of about 10^2 for the conjugate acids of both methanol ($CH_3OH_2^+$) and water (HOH_2^+). These are strong acids because their K_a values are greater than 10^{-7}. Consequently, alcohols and water are weak bases.

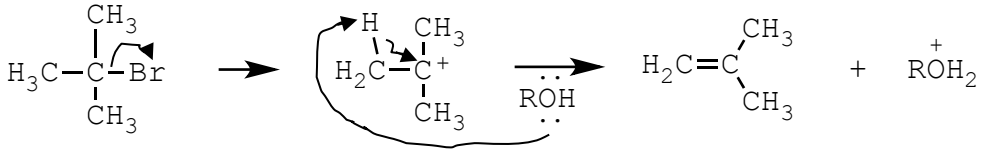
How strong of an acid is needed to protonate an alcohol? As a weak base, an alcohol needs a strong acid. We have already seen such protonation during dissolving in sulfuric acid (Section 10.3B) and two reactions: S_N1 solvolysis and E1 elimination. Among its multiple duties in an S_N1 solvolysis, an alcohol acts as a base, taking a proton from the oxonium ion in the last step (Section 6.5C). For example:



carbocation oxonium ion base ether
strong acid

Like the conjugate acid of methanol (K_a of $CH_3OH_2^+ = 10^2$), this oxonium ion is a strong acid, which becomes uncharged by donating its proton to the alcohol.

In an E1 elimination an alcohol can serve as a base to take a very acidic β proton from the carbocation intermediate (Section 7.2B). For example:



carbocation base alkene
strong acid

A β hydrogen of a carbocation is very acidic because it leaves a uncharged alkene behind. In contrast, a hydrogen on a simple hydrocarbon must leave a very unstable carbanion behind and has a K_a of about 10^{-50} (Table 4.1). Alcohol solvents often serve organic reactions by scavenging very acidic hydrogens.

On the other hand, an alcohol is too weakly basic to abstract a weakly acidic β hydrogen from an electrophile in an E2 reaction (Section 7.3).

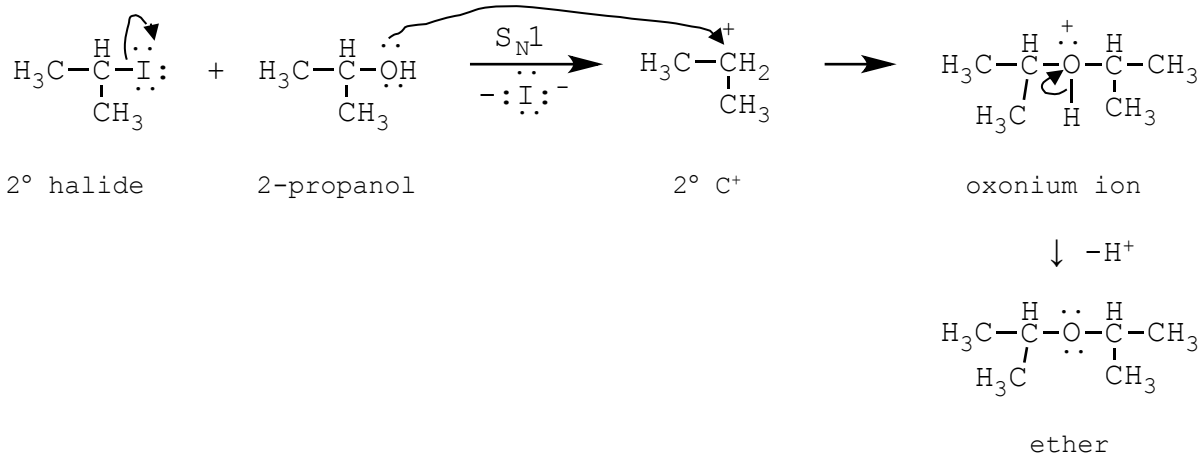
Puzzle 10.12 ———————————————————————————————————

Consider 2-chloro-1-ethanol and ethanol
(a) Which is the stronger base? Explain.
(b) As a base, which would permit a faster E1 reaction? Be careful.

10.5C Reactions of Alcohols as Non-base Nucleophiles

In this and the next two sections we will see reactions of an alcohol reacting as a nucleophile without abstracting a proton. How strong of a nucleophile is an alcohol? We know it as a weak base (Section 10.5B). Yet a weak base that is soft (e.g., Cl^-) can have surprising nucleophilic strength with soft electrophiles (Section 4.8). Alcohols, however, are not only weak bases but also fairly hard nucleophiles because their nucleophilic atom is a rather small oxygen. Consequently, alcohols are weak nucleophiles with both hard and soft electrophiles, and react only with strong electrophiles. Once again, alcohols resemble water in this way.

Accordingly, an alcohol does not pursue an S_N2 reaction with a normal alkyl halide, which is not a strong electrophile. In an S_N1 reaction, however, a very electrophilic carbocation from a secondary or tertiary halide can react with an alcohol. For example:



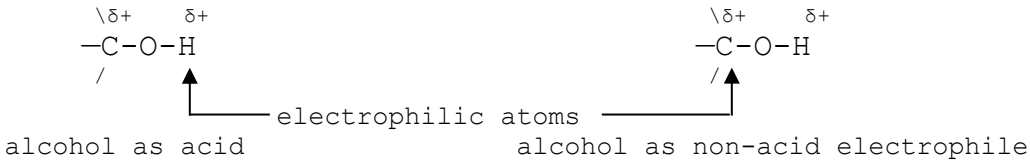
This is a way to make an ether from a secondary or tertiary halide. Yet, E1 reactions generally compete with S_N1 reactions, so this is not an ideal way to make an ether. If an alkoxide ion were used instead of the alcohol, the secondary or tertiary halide would yield an alkene (Section 10.6A).

Puzzle 10.13 ———————————————————————————————————

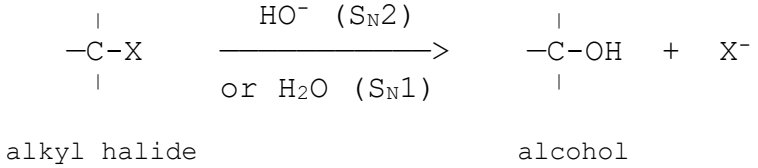
(a) Which reactants could yield di-*tert*-butyl ether?
(b) Which other organic product would form in a competing reaction?

10.5D Reactions Removing the Hydroxy Group from Alcohols

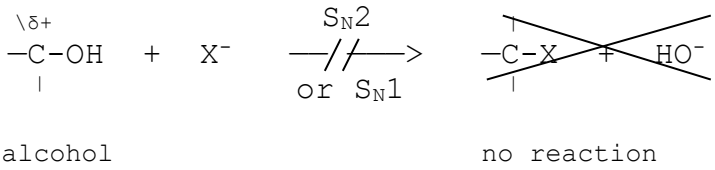
When reacting as an acid, an alcohol's electrophilic atom is its hydroxy hydrogen, which carries a partial positive charge. To react as a non-acid electrophile, an alcohol would use its α carbon, which also carries a partial positive charge:



Our usual carbon electrophile so far is an alkyl halide, which can make an alcohol (Section 10.4):

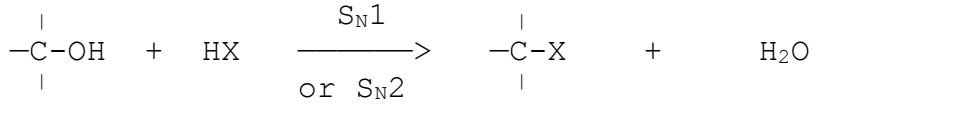


Can we reverse this synthesis to make an alkyl halide from an alcohol? The obvious course is to react the α carbon of the alcohol electrophile with a halide ion nucleophile in either an S_N2 or S_N1 reaction:



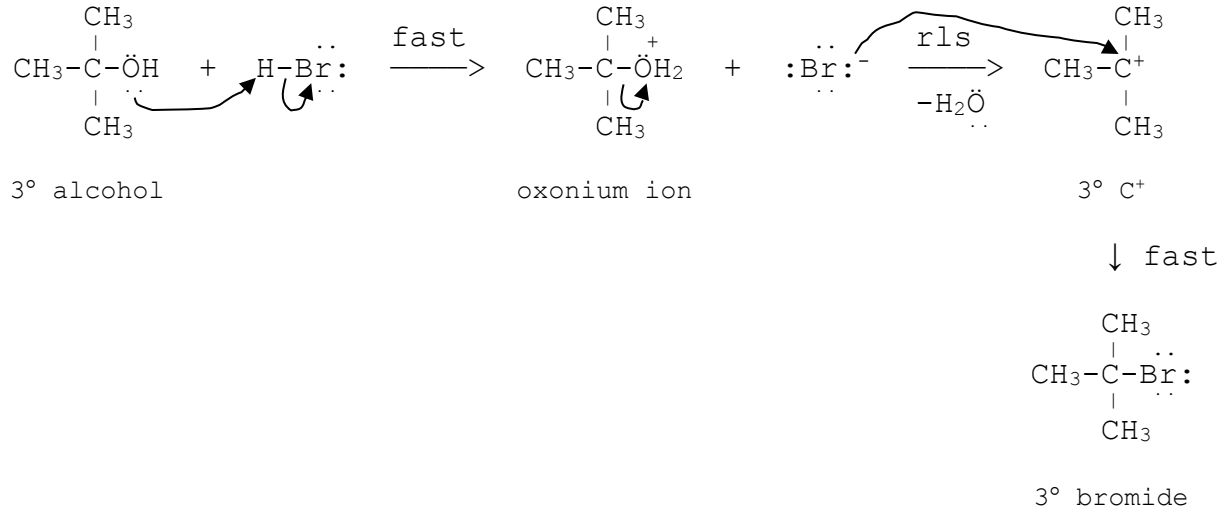
This reaction, however, does not go by S_N2, S_N1, or any other mechanism! Certainly, the halide ion is a strong enough nucleophile for an S_N2 or S_N1 reaction, but the alcohol electrophile is too weak. The alcohol's α carbon has a big enough partial positive charge to attract a nucleophile. The flaw in the alcohol is the hydroxide ion leaving group, which is unstable when leaving with the extra pair of electrons. Its conjugate acid, water, is a weak acid ($K_a \sim 10^{-16} < 10^{-7}$), and so hydroxide is a strong base, too unstable to serve as a leaving group for a normal S_N2 or S_N1 reaction.

How can we remove the hydroxy group of an alcohol? Because hydroxide ion is too strong of a base, does it have a related structure that is a weak base? Indeed, its conjugate acid, water, is a weak base (K_a of $H_3O^+ = 50$) and so a good leaving group. Moreover, it is relatively easy to outfit an alcohol with water as its leaving group. All the hydrogen halides except hydrogen fluoride are acidic enough to protonate an alcohol because their K_a values exceed 10^2, the K_a of ROH_2^+ (see Table 4.1, Section 4.2). Consequently, we have the following useful reactions:



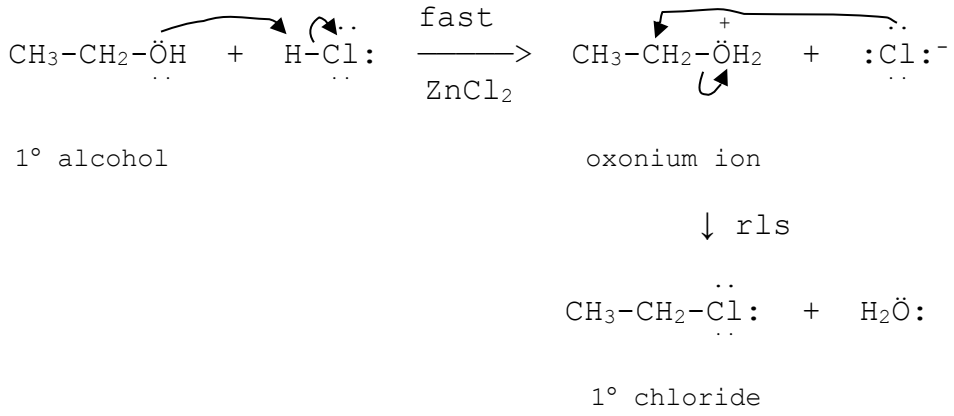
HX is any hydrogen halide except hydrogen fluoride. As the least reactive of the three usable

hydrogen halides, hydrogen chloride often requires a zinc chloride ($ZnCl_2$) catalyst. The alcohol can be any class and the class determines whether the mechanism is S_N1 or S_N2. If the alcohol is tertiary or secondary, an S_N1 mechanism pertains. For example:



The first step is a fast acid-base reaction that turns a poor leaving group into a good one. The rest of the mechanism is normal S_N1. In the rate-limiting second step water leaves behind a tertiary carbocation. In the last step this carbocation adds bromide nucleophile (from hydrogen bromide) to form the desired alkyl halide. Of course, a carbocation rearrangement might occur for this kind of reaction as for any reaction involving a true carbocation. It is reasonable that a secondary or tertiary alcohol prefers S_N1 to S_N2 because of considerable steric hindrance and stabilization of the carbocation by hyperconjugation.

Like a methyl or primary halide, a methyl or primary alcohol prefers S_N2 to S_N1 because of steric openness and the inability to form a methyl or primary carbocation. For example:



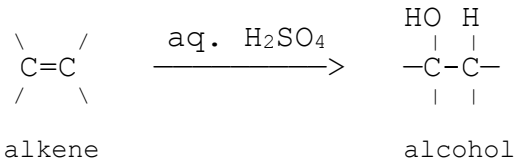
After protonation activates the alcohol with a good leaving group, the chloride ion pursues the sterically open α carbon. Zinc chloride serves as catalyst, often needed by hydrogen chloride. Note that in both S_N1 and S_N2 reactions of alcohols both parts of the hydrogen halide reagent are used: the acidic hydrogen for protonation of the leaving group, and the nucleophilic halide to engage the carbon electrophile.

Because hydrogen chloride sometimes reacts reluctantly with alcohols, other reagents have been developed to form alkyl chlorides from alcohols. Thionyl chloride ($SOCl_2$), phosphorous trichloride (PCl_3), and phosphorous pentachloride (PCl_5) are three different reagents that chlorinate

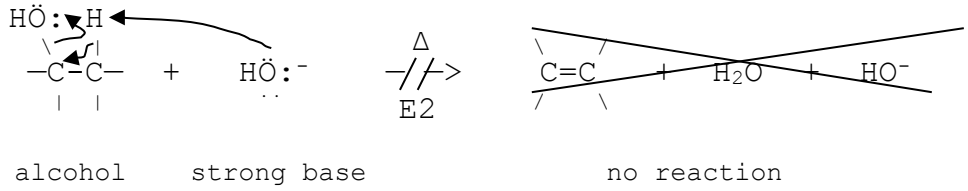
alcohols and also allow less carbocation rearrangement than hydrogen chloride. Like the hydrogen halides they operate on the principle of improving the poor leaving group of alcohols.

Analogous reagents for bromination and iodination of alcohols are phosphorous tribromide (PBr_3) and phosphorous triiodide (PI_3), respectively. They also work by enhancing the leaving group and minimize carbocation rearrangement. The mechanisms of these alternative reactions can vary with conditions and will not be presented here.

So we have succeeded in reversing the synthesis of an alcohol from an alkyl halide. Now let us reverse the hydration of an alkene, which forms an alcohol with aqueous acid (Section 8.8B):

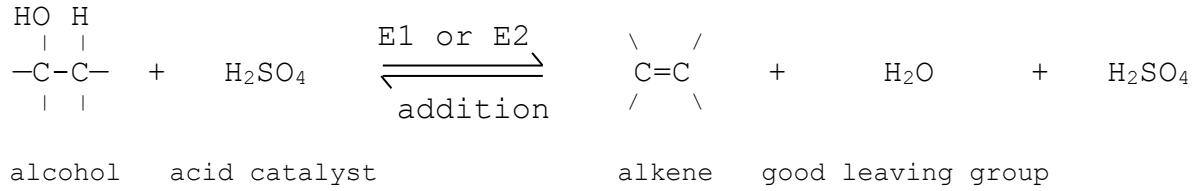


Because an alkyl halide and a strong base yield an alkene by an E2 reaction, let us try the same tactic on an alcohol:



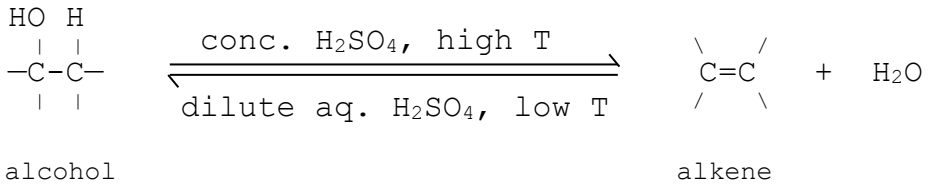
This reaction, however, does not go with hydroxide ion or even stronger bases. Once again, the problem is the hydroxide ion leaving group, poor for normal E2 and E1 reactions, as well as for S_N2 and S_N1 reactions.

We must improve the leaving group by reducing its basicity, and we can do that again by protonating it in strong acid. Yet, this time we do not want a strongly acidic hydrogen halide that also provides a strongly nucleophilic halide ion for substitution. A similar situation arose in Section 8.8B when we wished to hydrate an alkene by protonating the alkene without adding a strong nucleophile to pursue the resulting carbocation. We used sulfuric acid then and so now we use sulfuric acid to dehydrate an alcohol to an alkene:

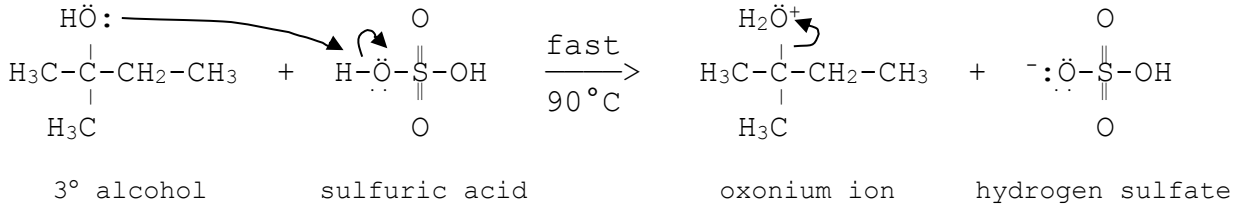


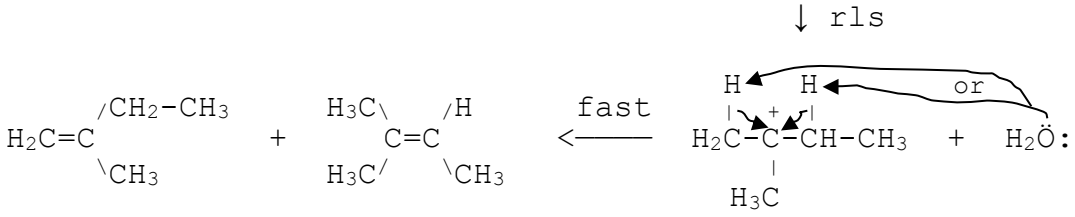
It should not surprise us that sulfuric acid catalyzes this dehydration (i.e., the removal of water) because it catalyzes the reverse, hydration of an alkene to an alcohol. A true catalyst, which is not consumed by reaction, must catalyze the reverse reaction as much as it catalyzes the forward reaction (Section 5.4B).

So this is a reversible equilibrium, which can be shifted toward either the alcohol or the alkene by reaction conditions. Because the dehydration of the alcohol yields water as a byproduct, too much water can shift the equilibrium from the alkene back to the alcohol. Consequently, fairly concentrated sulfuric acid is used for dehydration, whereas dilute aqueous sulfuric acid is used to hydrate an alkene. In addition, a high temperature favors the elimination reaction thermodynamically because of its positive, endothermic $\Delta H°$ and positive $\Delta S°$ (Section 7.1).



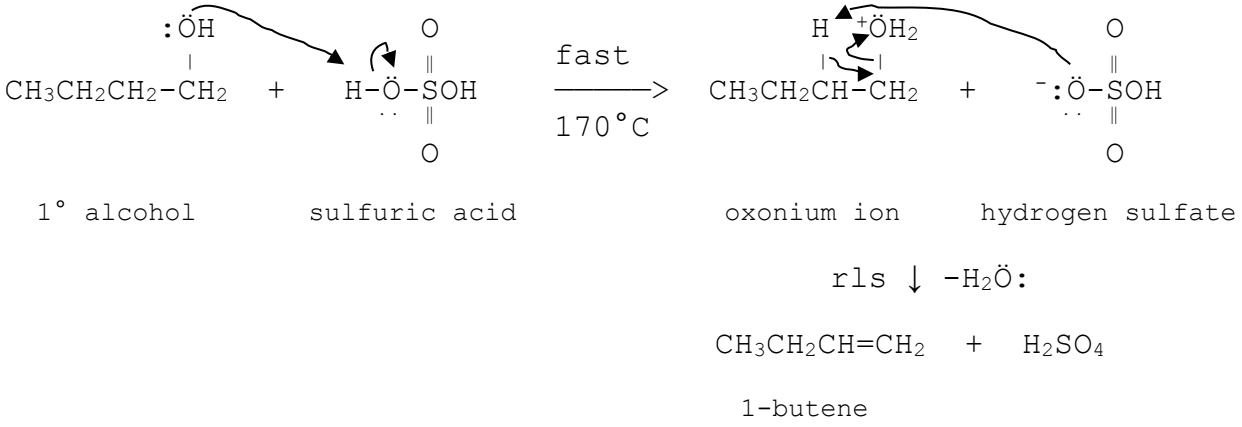
Other than methanol (with too few carbons to form an alkene), any class of alcohol reacts, and the class determines whether an E1 or E2 mechanism occurs. Tertiary and secondary alcohols react by E1. For example:





This mechanism is the exact reverse of the one for acid-catalyzed hydration of an alkene in Section 8.8B. This is natural because the route of least energy must be the same in both directions. An E1 mechanism suits a secondary or tertiary alcohol because a normal E2 reaction needs a strong base (Section 7.3). Yet, a strong base is normally incompatible with a strong acid, such as sulfuric acid, which would immediately neutralize it. Instead, weakly basic hydrogen sulfate ion, the conjugate base of the sulfuric acid, or water can remove a β proton from the carbocation of the E1 reaction. Two different β protons can be taken to yield two different alkene constitutional isomers. As usual, the major isomer has more alkyl substituents on the double bond (Section 7.4). Although this carbocation cannot rearrange, such rearrangement is, of course, possible in other E1 dehydrations of alcohols.

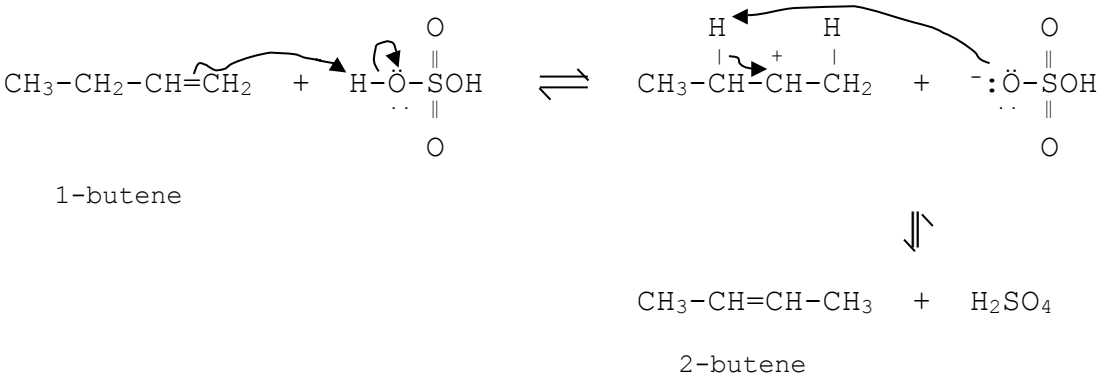
A primary alcohol is dehydrated to an alkene with more difficulty. A higher reaction temperature reflects this difficulty. A sample mechanism illustrates:



Primary alcohols pursue an E2 mechanism because the primary carbocation, needed for E1, is not feasible. On the other hand, E2 normally requires a strong base, which is not normally compatible with the very acidic sulfuric acid. Presumably, the high 170°C temperature is needed for primary alcohols to energize both oxonium ion acid and hydrogen sulfate ion base to react in one E2 step.

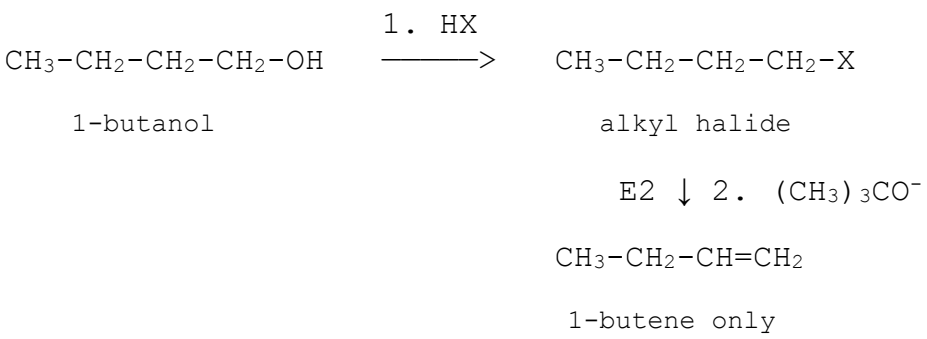
In this section we have used acid to protonate the alcohol's oxygen to facilitate the breaking of the C-O bond in S_N2, S_N1, E2, and E1 reactions. We will use the same method to help cleave C-O bonds in ethers (Sections 10.8A & B), aldehydes (Sections 12.5A & D), ketones (Sections 12.5A & D), and carboxylic acid derivatives (Section 14.5D).

A general problem with dehydrations of alcohols, both E1 and E2, is possible isomerization of the alkene product. For example, the 1-butene isomer product from the above dehydration is not the only alkene produced. In strong acid this alkene isomerizes to 2-butene:



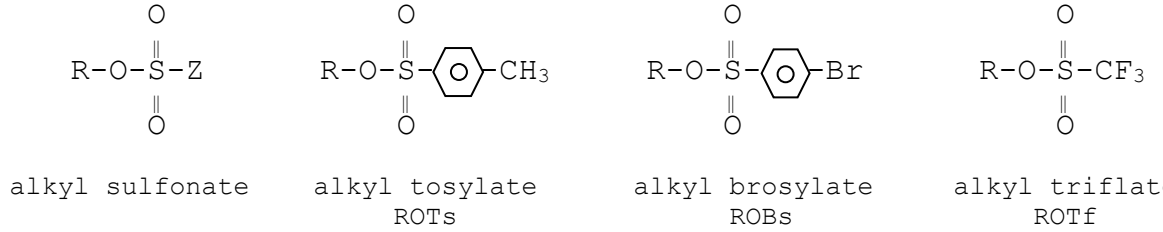
First, the acid protonates the alkene to the carbocation, which then can lose a different β proton to yield a different alkene constitutional isomer. In fact, the stabler 2-butene isomer predominates at equilibrium because it has more alkyl substituents.

To avoid such isomerization when dehydrating an alcohol to an alkene, one may first convert the alcohol to an alkyl halide and then in a second, separate E2 reaction reach the alkene:

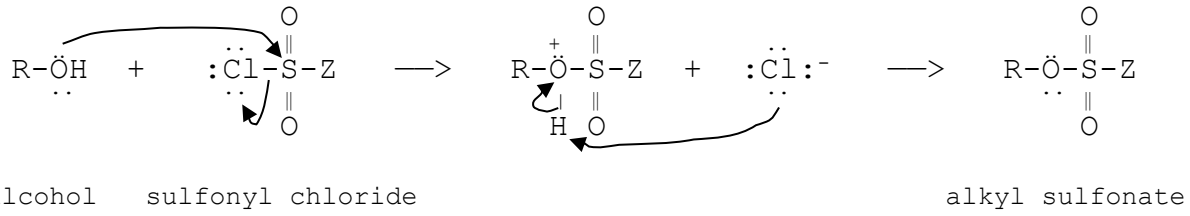


Under basic conditions the alkene product cannot be reprotonated and isomerize. The bulky *tert*-butoxide ion base also minimizes S_N2 substitution on the primary halide. Although this E2 reaction gives only one alkene isomer, an E2 reaction of an alkyl halide with two different β hydrogens yields more than one alkene constitutional isomer (Section 7.4).

Another reaction that converts the alcohol's hydroxy group to a good leaving group forms **alkyl sulfonates,** such as **alkyl tosylates** (ROTs, from *p*-toluenesulfonate), **alkyl brosylates** (ROBs, from *p*-bromobenzenesulfonate), and **alkyl triflates** (ROTf, from trifluoromethylsulfonate):

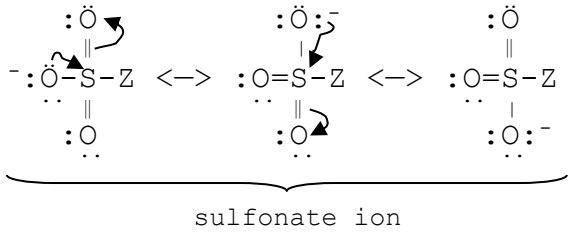


Alkyl sulfonates are generally made from an alcohol and the corresponding sulfonyl chloride:



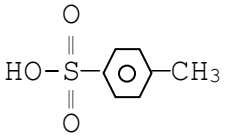
The sulfur is strongly electrophilic because it has many bonds to more electronegative oxygens and chlorine and because it has a good leaving group, chloride ion.

Alkyl sulfonates feature their own good leaving group, sulfonate anion:

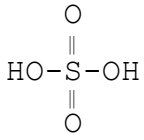


Three equivalent resonance forms (as well as electronegative oxygens) greatly stabilize the sulfonate ion. So, it is a weak base and a good leaving group. This same resonance pattern stabilizes hydrogen sulfate ion, the conjugate base of sulfuric acid (Section 1.5). The large K_a

values for *p*-toluenesulfonic acid and sulfuric acid testify to the great resonance stabilization of the conjugate bases:



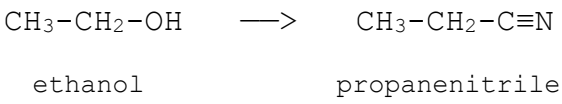
p-toluenesulfonic acid
K_a 4



sulfuric acid
K_a 10^9

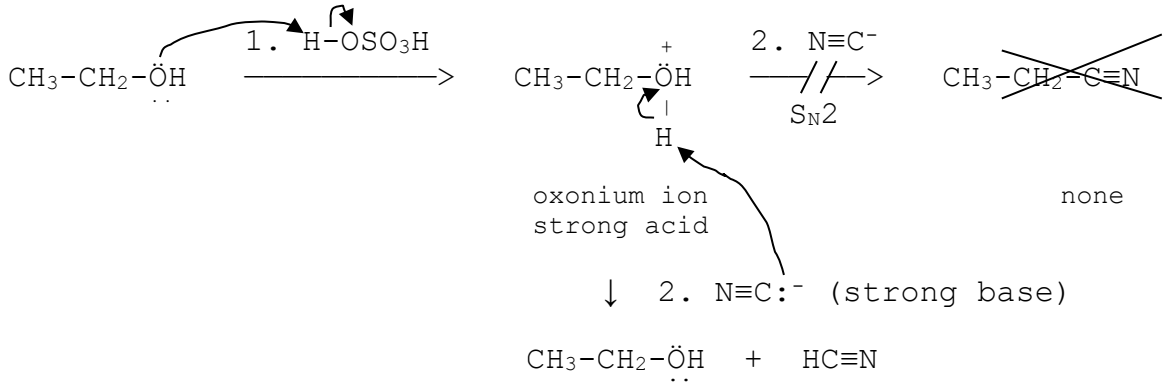
Therefore, after alkyl halides and protonated alcohols, alkyl sulfonates are a third type of carbon electrophile for nucleophilic substitutions and eliminations. In fact, alkyl sulfonates so strongly resemble alkyl halides in reactivity that they are practically interchangeable with alkyl halides. For example, methyl and primary sulfonates prefer S_N2 to S_N1 reactions and require strong nucleophiles, whereas tertiary sulfonates prefer S_N1 reactions and weakly basic nucleophiles.

Let us see how converting an alcohol to an alkyl sulfonate can help synthesize a target molecule. Suppose that we wish to convert ethanol to propanenitrile:



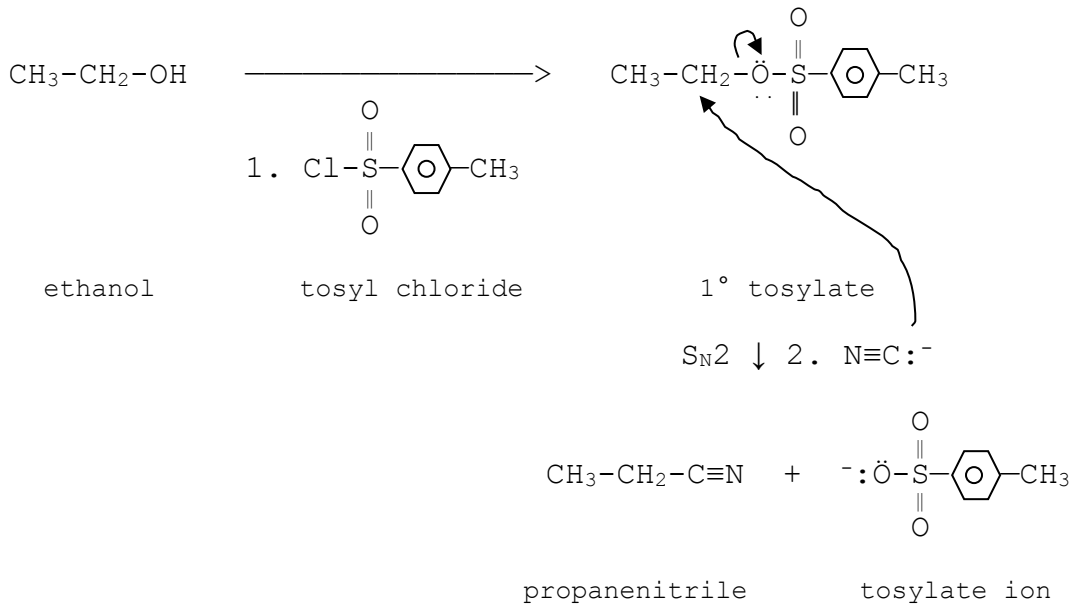
ethanol propanenitrile

A nucleophilic substitution should be able to change functional groups. One might first add a strong acid to activate the alcohol as an electrophile before nucleophilic approach by cyanide ion ($N\equiv C^-$). Yet, in reality this synthesis fails:

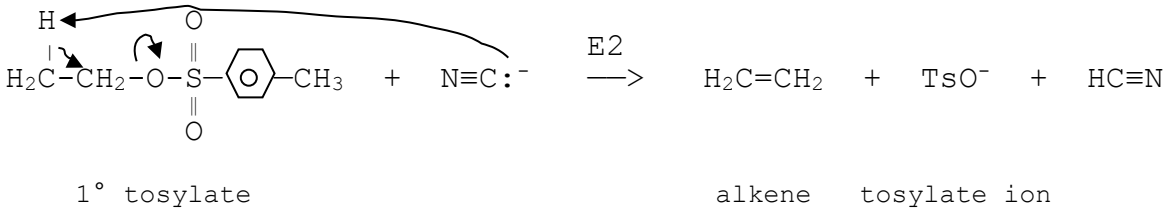


A much faster acid-base reaction supplants the desired S_N2 reaction. Cyanide ion is a strong base because its conjugate acid, hydrogen cyanide, has a K_a of 6 x 10^{-10} (Table 4.1). So, it cannot coexist for long with the strongly acidic oxonium ion. This is a fundamental problem with an alcohol as a carbon electrophile: the necessary activation by protonation creates an oxonium ion, which simply reacts as an acid if the nucleophile is strongly basic.

A less direct process accomplishes the synthesis. The alcohol is converted to an alkyl sulfonate, which properly reacts as an S_N2 electrophile with cyanide ion:

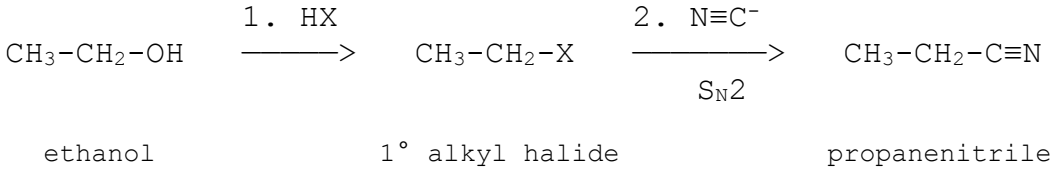


Because the alkyl tosylate is weakly acidic at its β carbon, it can also react, but more slowly, as an E2 acid with cyanide ion:



Because the alkyl tosylate is primary and yields an alkene with no alkyl substituents, however, this E2 reaction competes poorly with the desired S_N2 reaction.

Formation of an alkyl halide can lead to the same goal:



Again, the key to success is the alkyl halide's weak acidity, which permits the S_N2 reaction with minimal E2 interference.

This is the second time that we have converted an alcohol to a different functional group to improve a synthesis. Earlier in this section an alcohol was first converted to an alkyl halide, which then yielded a single alkene isomer by elimination. Of course, now we know that the alcohol could have been converted to an alkyl sulfonate as well. In organic synthesis a less direct reaction sequence is sometimes more efficient than a shorter, more obvious path that gives an undesirable mixture of products.

Puzzle 10.14 ———————————————————————————————————————

(a) Draw the mechanisms for the reactions of 3-methyl-2-pentanol with hydrogen chloride to yield

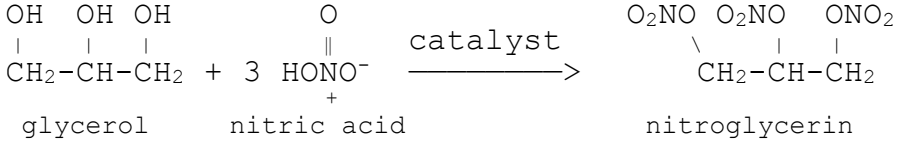
two constitutional isomers.
(b) If thionyl chloride replaced hydrogen chloride in the reaction, which isomer would predominate?

Puzzle 10.15 ———————————————————————————————————

(a) Find the alcohol and the reaction conditions that would mostly make 4-methyl-2-pentene.
(b) Draw the mechanism for this reaction.

Puzzle 10.16 ———————————————————————————————————

Nitroglycerin, the high explosive, can be made in a very hazardous reaction from glycerol (a byproduct of soap manufacture) and nitric acid in the presence of a catalyst.



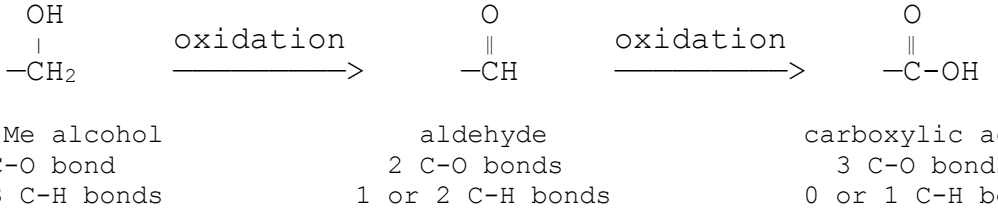
Draw a mechanism for the conversion of one of the alcohol groups to a nitrate group (ignore the catalyst).

———————————————————————————————————

10.5E Oxidation Reactions of Alcohols

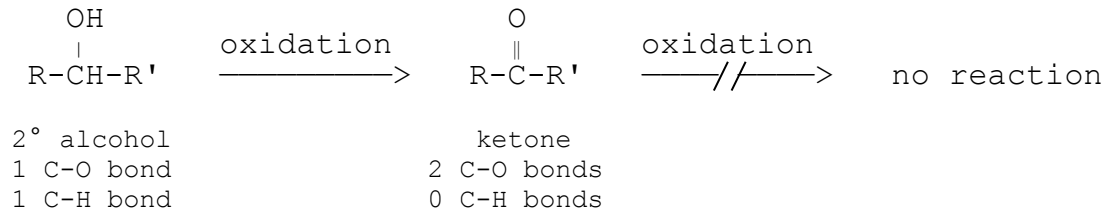
Two more new reactions of alcohols involve their oxidations. Actually, this extends the preceding section because alcohols react as non-base nucleophiles in these oxidations. Yet the importance of these reactions warrants a special section. In Section 8.12 we defined oxidation of an organic compound as a carbon gaining a bond to a more electronegative atom, such as oxygen, or losing a bond to hydrogen. We will oxidize alcohols by simultaneously involving both kinds of bonds.

The alcohol's class decides the normal extent of oxidation. Primary and methyl alcohols can be oxidized in two stages: first to an aldehyde and then to a carboxylic acid.



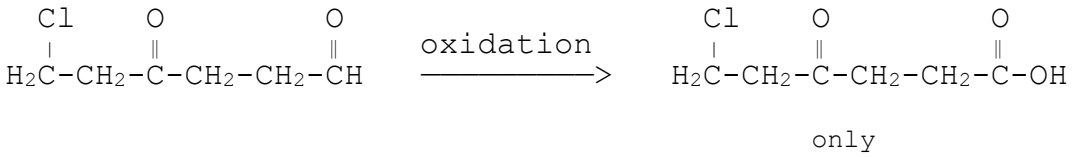
During oxidation, the oxygen-bearing carbon gains bonds to oxygen and loses bonds to hydrogen.

Secondary alcohols are normally oxidized only once to a ketone:



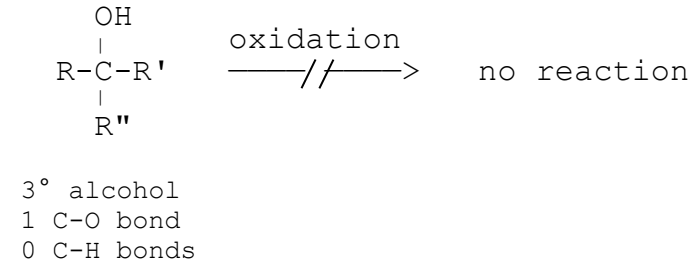
In all of these reactions the carbon attached to the oxygen is oxidized by replacing a bond to

hydrogen with another bond to oxygen. Only a carbon that is bonded to both an oxygen and a hydrogen is cleanly oxidized. Thus, oxidation selects only special carbons:



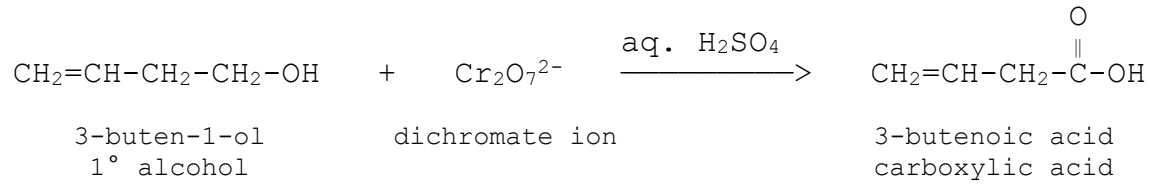
Only the aldehyde carbon has both an oxygen and a hydrogen, and so it is the only one oxidized. The ketone functional group is not normally oxidized because its carbon has no hydrogens. To make room for another bond to oxygen, it is much more difficult to break a carbon-carbon bond than a carbon-hydrogen bond.

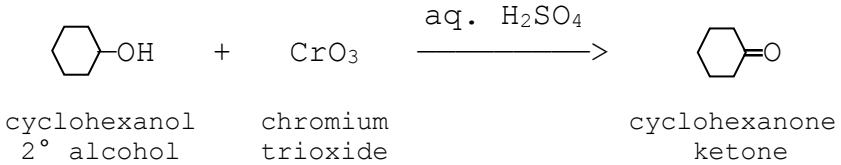
Consequently, a tertiary alcohol is not normally oxidized:



Its carbon bearing an oxygen has no hydrogen to lose during oxidation.

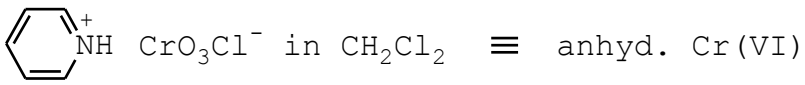
Alcohols are usually oxidized by transition metals in high oxidation states, such as potassium permanganate ($KMnO_4$). The most frequently used oxidants are various forms of chromium(VI), in its highest oxidation state. Chromium trioxide (CrO_3) and dichromate ion ($Cr_2O_7^{2-}$) are two typical forms of chromium(VI) that oxidize methyl, primary, and secondary alcohols. Generally they react in acidic aqueous solution. Two examples follow.





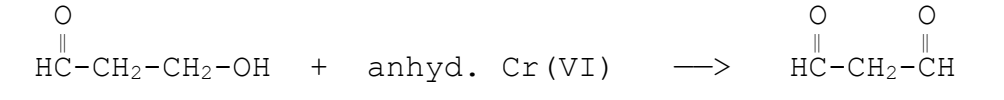
The primary alcohol is oxidized in two steps all the way to its carboxylic acid by way of its aldehyde. Note that the alkene functional gro up remains unreacted. The secondary alcohol is only oxidized by one step to the ketone.

It is possible to stop the oxidation of the primary alcohol at the aldehyde stage by using a milder form of chromium(VI). This milder form can be anhydrous pyridinium chlorochromate, usually used in dichloromethane solvent:

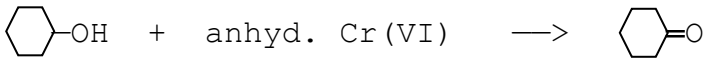


anhydrous pyridinium chlorochromate
mild form of Cr(VI)

Let us abbreviate this reagent in reaction equations as *anhyd. Cr(VI),* which expresses the essentials of the reagent. Anhydrous pyridinium chlorochromate oxidizes primary and secondary alcohols just one step to aldehyde and ketones, respectively. Yet, it does not oxidize aldehydes to carboxylic acids:



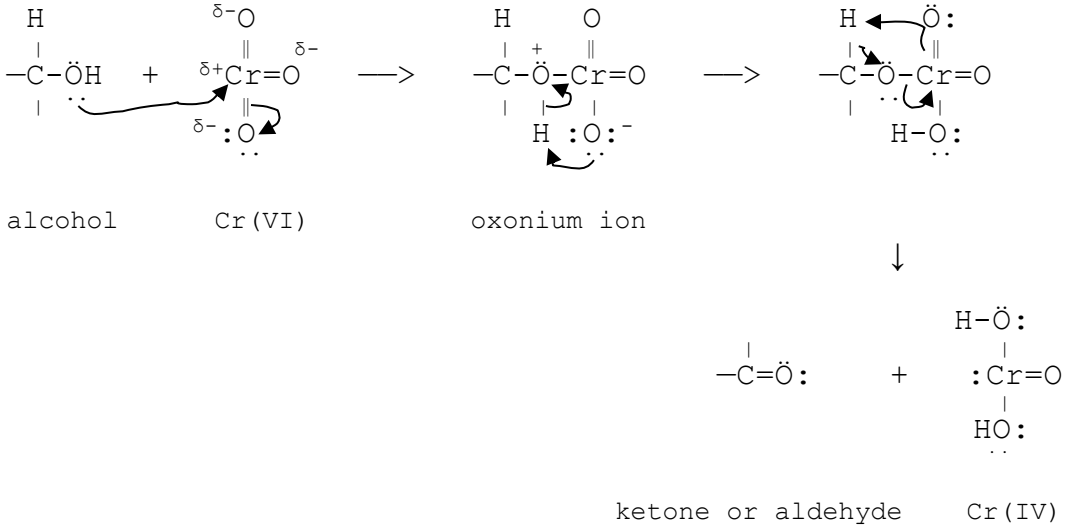
3-hydroxypropanal propanedial
double aldehyde



cyclohexanol cyclohexanone

The first example illustrates the nonreactivity of aldehydes with anhydrous chromium(VI).

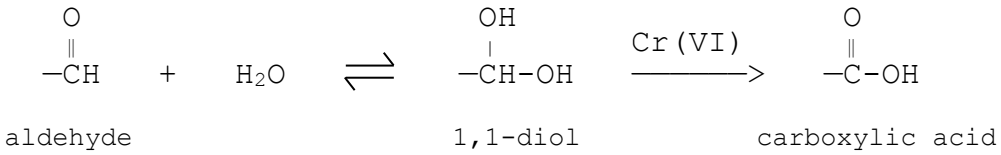
The mechanism of oxidation is complex and somewhat variable, but the essence is reasonable:



In the first step the alcohol reacts as an oxygen nucleophile with the electrophilic chromium of the oxidant. Oxidants generally are electrophiles. So, the oxidizable carbon must have an oxygen to serve as nucleophile. A proton transfer in the second step neutralizes the oxonium ion. Finally, a second proton transfer oxidizes the carbon while reducing the chromium to chromium(IV). Accordingly, the oxidizable carbon must have a hydrogen for this proton transfer. Thus, the mechanism explains the general requirement for a carbon bonded to both an oxygen and a hydrogen.

The mechanism also explains the selectivity of anhydrous chromium(VI). An aldehyde is oxidized by the stronger, aqueous chromium(VI) because water hydrates it to a 1,1-diol (Section

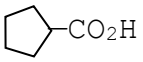
12.5D):



As a nucleophilic alcohol, the 1,1-diol is readily oxidized by chromium(VI). The milder anhydrous chromium(VI) has no water to hydrate an aldehyde into a nucleophilic diol and so cannot oxidize it.

Puzzle 10.17 ———————————————————————————————————

A certain alkene reacts with aqueous sulfuric acid to yield a product that does not react with aqueous chromium trioxide. The same alkene reacts first with borane and then with basic hydrogen peroxide to yield a product that reacts with aqueous chromium trioxide to form the carboxylic acid:



Find the alkene and the organic products of all reactions.

Puzzle 10.18 ———————————————————————————————————

For decades police have used a Breathalyzer to determine the concentration of ethanol in the breath of a suspected drunk driver. A breath sample is mixed with an aqueous solution of excess dichromate ion $Cr_2O_7^{2-}$ in the Breathalyzer. Then the spectrophotometer in the device measures the amount of blue light absorbed by the yellow solution of $Cr_2O_7^{2-}$ that remains after reaction with any ethanol. The greater the concentration of $Cr_2O_7^{2-}$, the more blue light is absorbed. The reduced form of chromium, $Cr_2(SO_4)_3$, absorbs little blue light.
(a) Does ethanol in the breath increase or decrease the amount of blue light absorbed after reaction? Explain.
(b) What does ethanol become during reaction in the Breathalyzer?
(c) Would carbon dioxide in the breath affect the amount of blue light absorbed after mixing? Explain.

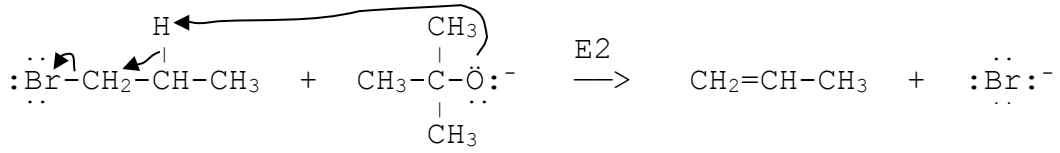
10.6 Reactions of Alkoxide Ions

We do not have to consider the acidity of an alkoxide ion because it is the very basic conjugate base of an alcohol. Also its negative charge nullifies any electrophilicity. That leaves only its basicity and non-basic nucleophilicity to be examined in the next two sections. Thus, alkoxide ions are less versatile reagents than alcohols.

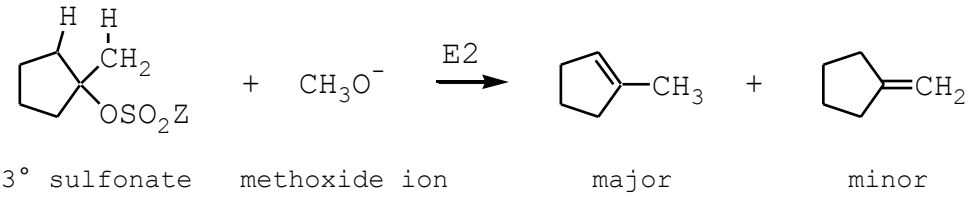
10.6A Reactions of Alkoxide Ions as Bases

Because alcohols resemble water as weak acids with K_a values of about 10^{-16} (Section 10.5A), their conjugate base alkoxide ions resemble hydroxide ions as strong bases. Consequently, unlike alcohols, alkoxide ions suit E2 reactions, which need a strong base (Section 7.3). A bulky

alkoxide, such as *tert*-butoxide ion, can be used with a primary electrophile to sterically hinder S_N2 competition:



With a more sterically hindered secondary or tertiary electrophile, S_N2 reactions compete less well, so a smaller alkoxide suffices for an efficient E2 reaction:



Strong bases, such as alkoxide ion, do not normally react by E1 reactions because they enter E2 reactions before a carbocation forms.

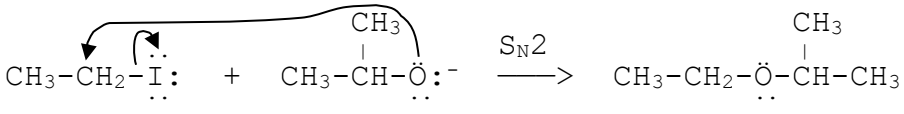
Puzzle 10.19

(a) When the tosylate of 3,3-dimethyl-2-butanol reacts with methoxide ion in an elimination reaction, how many constitutional isomers are produced? Draw the mechanism.
(b) When the same tosylate reacts with methanol in an elimination reaction, more constitutional isomers form. Draw them and the mechanisms leading to them.

10.6B Reactions of Alkoxide Ions as Non-base Nucleophiles

How nucleophilic are alkoxide ions? From the preceding section we know that they are strong bases. Therefore, as long as they are not too bulky (e.g., not the bulky *tert*-butoxide ion), they are strong nucleophiles.

How do they react with a carbon electrophile, such as an alkyl halide or sulfonate? The class of the electrophile determines whether the nucleophilic substitution is S_N2 or S_N1. A methyl or primary electrophile, of course, would react by an S_N2, not an S_N1, reaction. An ordinary S_N2 reaction requires a strong nucleophile, such as an alkoxide ion. For example:

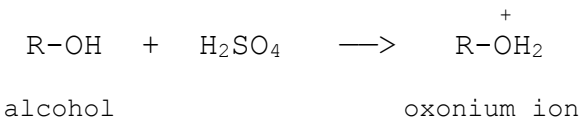


This is the most common and important way to make an ether.

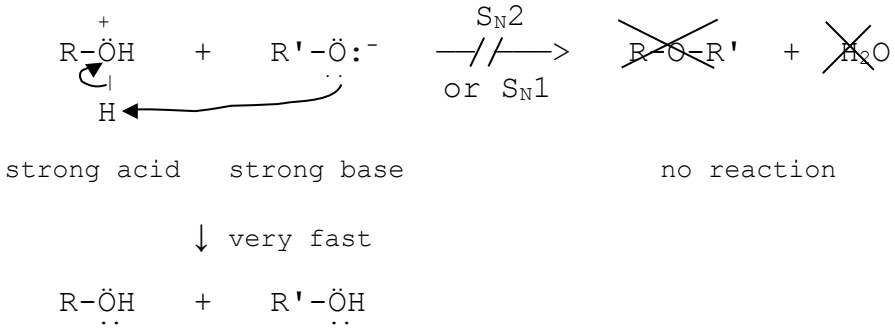
On the other hand, secondary and tertiary electrophiles are more vulnerable than methyl and primary electrophiles to E2 reactions (Section 7.5B). As a result, the strongly basic alkoxide

ion mostly makes alkenes from secondary and tertiary electrophiles, as we saw in the preceding section.

In Section 10.5D we encountered another carbon electrophile, the conjugate acid of an alcohol. This was made by protonating the alcohol with a strong acid, such as sulfuric acid:



Could alkoxide ion react as a non-base nucleophile in an S_N1 or S_N2 reaction with this oxonium ion carbon electrophile? No. Instead the alkoxide ion reacts as a base in a fast acid-base reaction:



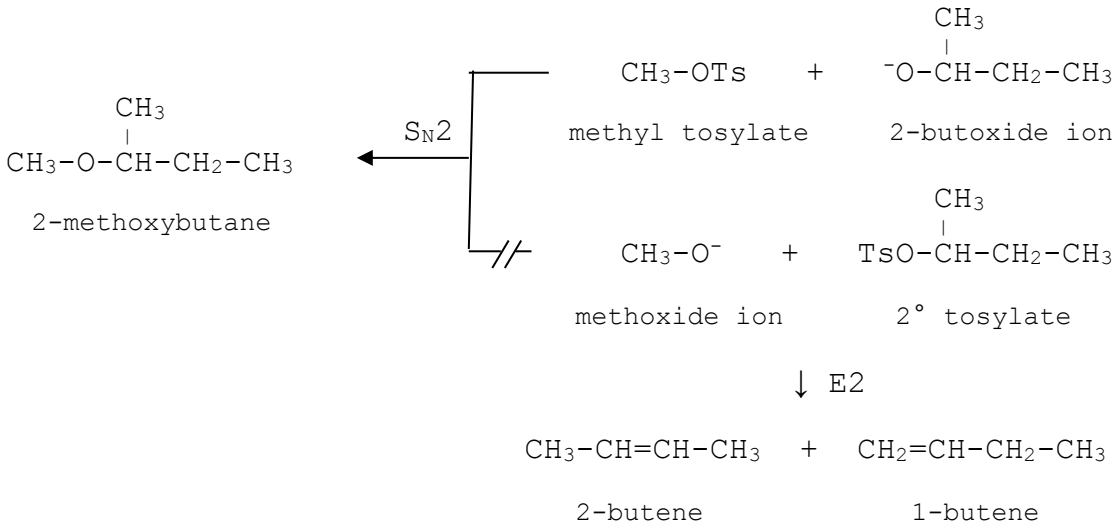
Acid-base reactions are typically very fast, much faster than nucleophilic substitution. Remember that strong acids are incompatible with strong bases and rapidly neutralize them.

Puzzle 10.20 ———————————————————————————————————————

Outline an efficient synthesis of 2-propoxypropane from two alcohols.

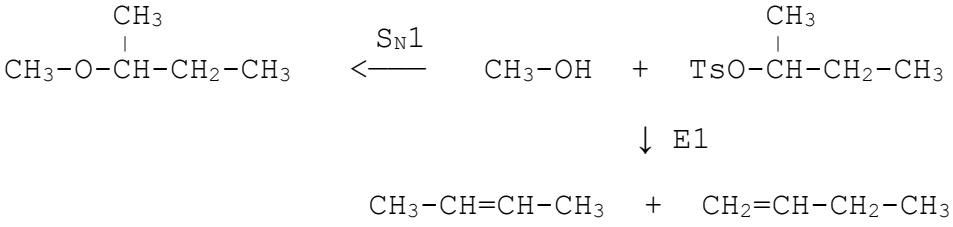
10.7 Syntheses of Ethers

In the preceding section we encountered the standard way to make an ether: an S_N2 reaction between an alkoxide ion nucleophile and a methyl or primary alkyl halide (or sulfonate) electrophile. Accordingly, let us outline a synthesis of the ether, 2-methoxybutane. Two different carbon-oxygen bonds in this ether mean two different syntheses can be considered:



The first, upper synthesis is superior because it uses a methyl electrophile well suited for S_N2 reaction, whereas the second method uses a secondary electrophile more prone to E2 than S_N2 reaction. Always try to design an ether synthesis, like any other S_N2 reaction, with a methyl or primary electrophile.

We also saw in Section 10.5C that an alcohol, instead of an alkoxide ion, can produce an ether by S_N1 reaction with a secondary or tertiary electrophile. So, we might try this synthesis of our target ether:

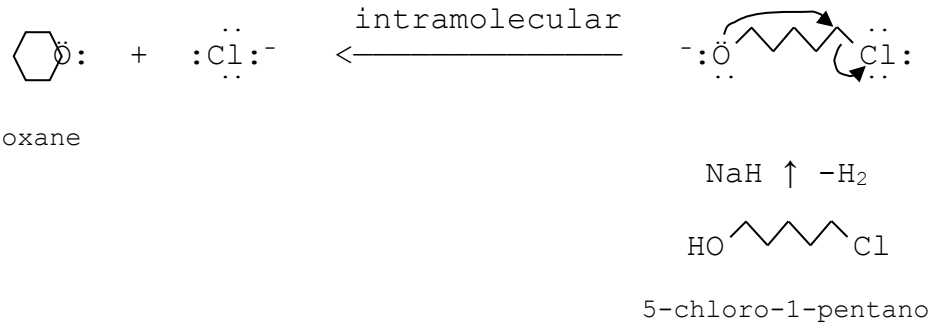


Yet, the inevitable E1 competition makes such an S_N1 synthesis inferior to the previous S_N2 synthesis, as is generally true of S_N1 syntheses (Section 6.8).

Suppose that our target is a cyclic ether, such as oxane (tetrahydropyran):

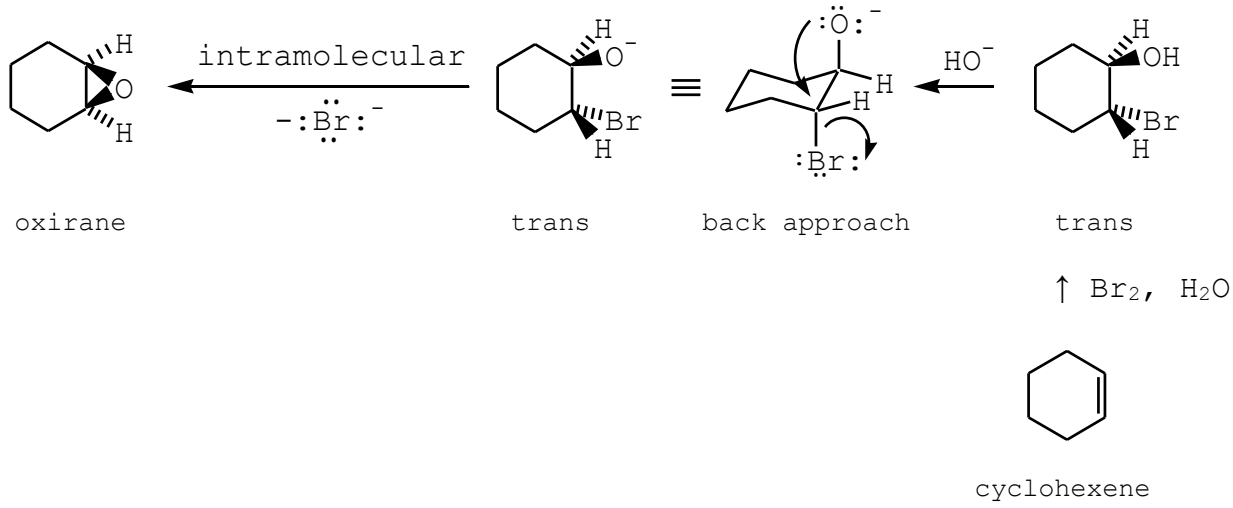
oxane
(tetrahydropyran)

Despite its ring we can assess it for synthesis like any other ether. Because of its symmetry both carbon-oxygen bonds are equivalent, so we do not have to choose between two bond formations. Here is its synthetic outline:

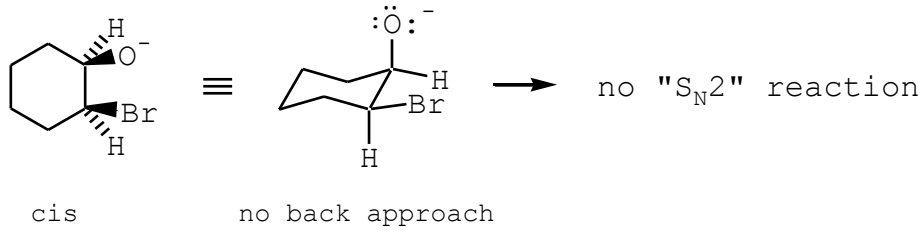


Having the nucleophile and electrophile on the *same* molecule generally leads to ring formation by an *intramolecular* reaction. Here the alkoxide nucleophile and alkyl halide electrophile on the same molecule engage in an intramolecular S_N2-like reaction. This reaction enjoys the usual entropy advantage of intramolecular reactions: a greater probability that nucleophile and electrophile will find each other if they are on the same molecule (Section 5.3D).

An oxirane (i.e., epoxide) can be made likewise. For example:



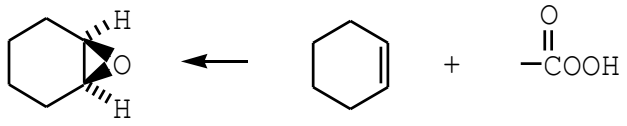
The nucleophilic alkoxide ion and electrophilic halide on adjacent carbons result in a three-membered ring. Having the nucleophile and electrophile on a cyclohexane ring reminds us of the necessary back approach in an S_N2 reaction (Section 6.3B). On a ring the nucleophile and electrophile must be trans, not cis:



Fortunately, halogenation of the cycloalkene in water readily forms the desired trans stereoisomer (Section 8.10C). Note that hydroxide ion is used as the base to make the alkoxide ion although in Section 10.5A it was found to form an ineffective equilibrium. This weaker base works here because the equilibrium is pulled forward by the subsequent intramolecular reaction.

We first met this kind of oxirane synthesis in Section 8.12B, where we also found a more direct synthesis of oxiranes: oxidation of an alkene by a peroxyacid. This method synthesizes the

target oxirane in one step:

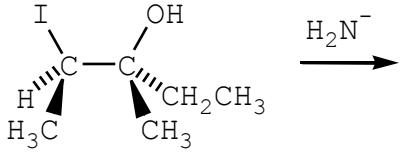


a peroxyacid

Aside from this last special synthesis, the syntheses of ethers depend on the rational joining of a nucleophile and electrophile.

Puzzle 10.21 ———————————————————————————————————

Draw the stereoisomer of the ether product from an intramolecular reaction:

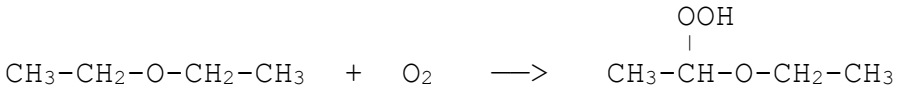


Puzzle 10.22 ———————————————————————————————————

A couple of decades ago methyl *tert*-butyl ether became an important industrial organic chemical. Not only did it replace a toxic lead compound as an octane booster in gasoline, but it also helped gasoline burn more cleanly. Puzzle 8.17 (Section 8.8B) indicated that it can be made from an alkene, an alcohol, and an acid. Beginning with two alcohols, outline a different synthesis of this ether.

10.8 Reactions of Ethers

Ethers are generally much less useful as reagents than alcohols. In fact, they are the least reactive of common organic functional groups. Consequently, they are used more frequently as unreactive, aprotic solvents than as reagents. As solvents, they have the disadvantage of forming **hydroperoxides** with oxygen in the air. For example:



diethyl ether (ethoxyethane)

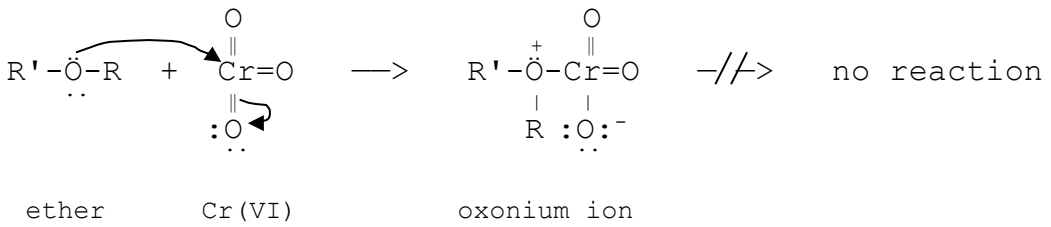
a hydroperoxide

All peroxides feature an oxygen-oxygen bond, which is unusually weak with a bond energy of 214 kJ/mol (Table 1.6, Section 1.8). Hydroperoxides are peroxides with a hydrogen at one end. The weak oxygen-oxygen bond contributes to their reactivity (e.g., peroxyacids of Section 8.12B) and in some cases their notorious explosiveness. Therefore, old ethers should be handled carefully and purified of hydroperoxides.

10.8A Reactions of Simple Ethers

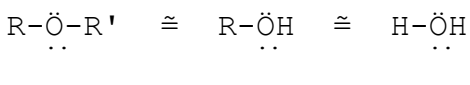
Without a hydrogen on a very electronegative atom, ethers are about as acidic as alkanes. So we need not explore their extremely weak acidity.

As nucleophiles, ethers are less reactive than the weakly nucleophilic alcohols because they have no easy way to disperse the positive charge of the resulting oxonium ion. For example, unlike alcohols, ethers are not oxidized by chromium(VI):



The oxygen of the oxonium ion has no proton to lose to become neutral and stable. Consequently, the oxidation cannot proceed. In contrast, an alcohol can complete the reaction because its analogous oxonium ion can donate a proton to reach a stabler, neutral intermediate before further reaction (Section 10.5E).

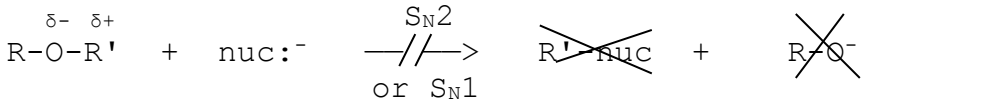
As bases, ethers resemble alcohols and water because of similar structures. An uncharged oxygen is the base atom in each, and no resonance or inductive effect influences the base lone pairs:



relative basicities of ethers, alcohols, and water

Indeed, the K_a values of the conjugate acids of all three types of molecules are about 10^2. Because its conjugate acid is strong, an ether is a weak base. Therefore, only a strong acid can protonate an ether to an oxonium ion.

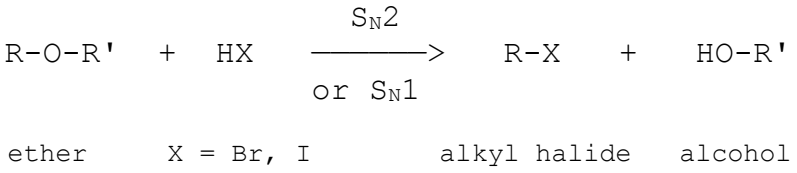
How electrophilic is a simple ether (not an oxirane)? Like an alcohol a simple ether is a poor electrophile because it lacks a good leaving group:



strong base
poor leaving group

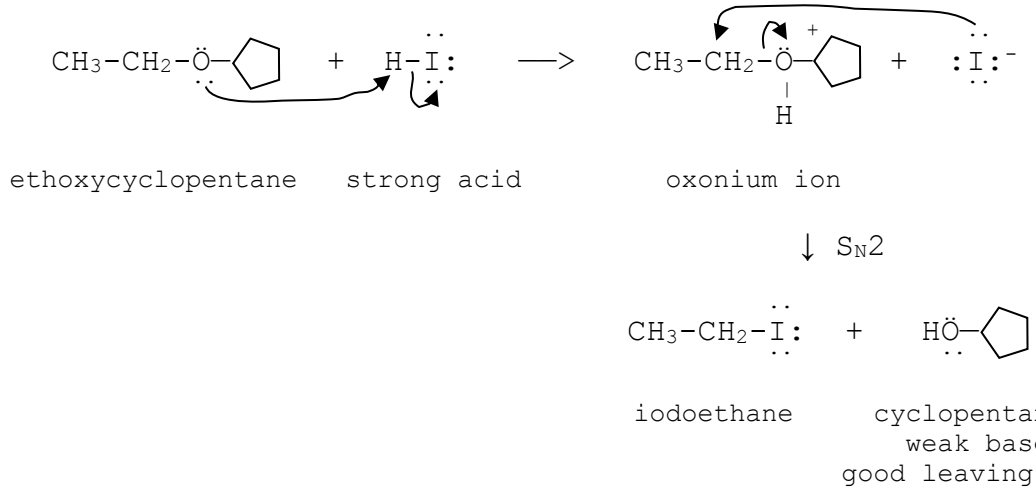
The alkoxide ion leaving group is a strong base and so a poor leaving group for a normal S_N2, S_N1, E2, or E1 reaction. As a result, simple ethers do not react as electrophiles with even the strongest nucleophiles, such as Grignard reagents. In fact, ethers are excellent solvents for Grignard reagents (Section 6.9).

Is there any way to make an ether electrophilic? In Section 10.5D we found the same problem with an alcohol and improved its poor leaving group by protonating it in strong acid, such as a hydrogen halide. The same strategy works with an ether:



The hydrogen halide can be hydrogen iodide or bromide, but generally not hydrogen chloride or fluoride.

As usual, the class of the alkyl group determines whether the mechanism is S_N2 or S_N1. Tertiary groups require S_N1 reactions, but methyl, primary, and secondary alkyl groups undergo S_N2 reactions. For example:



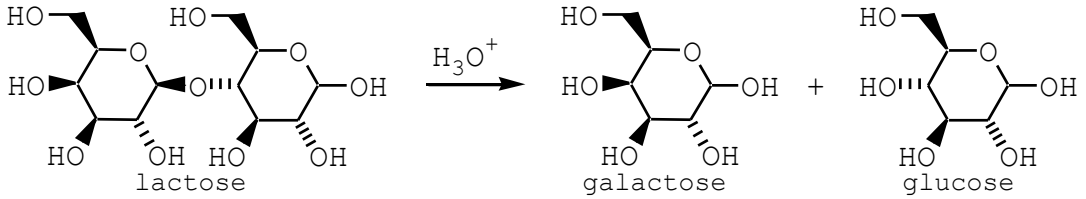
In the first step, protonation of the ether's oxygen provides an oxonium ion with a good leaving group. Then the nucleophilic iodide ion seeks the primary α carbon of the ethyl group, instead of the more sterically hindered, secondary α carbon of the cyclopentyl group. The weakly basic cyclopentanol is the good leaving group. Thus, an ether is cleaved into two smaller molecules: an alkyl halide and an alcohol. This reaction is not common except to degrade a large ether into smaller pieces for easier identification. Despite its rarity it is still the most common laboratory reaction of simple ethers.

Puzzle 10.23 ———————————————————————————————————————

Draw the mechanism for the reaction of a large excess of hydrogen bromide with oxetane:

Puzzle 10.24 ———————————————————————————————————————

Lactose (i.e., milk sugar) is a disaccharide that hydrolyzes in aqueous acid to two monosaccharides: galactose and glucose.



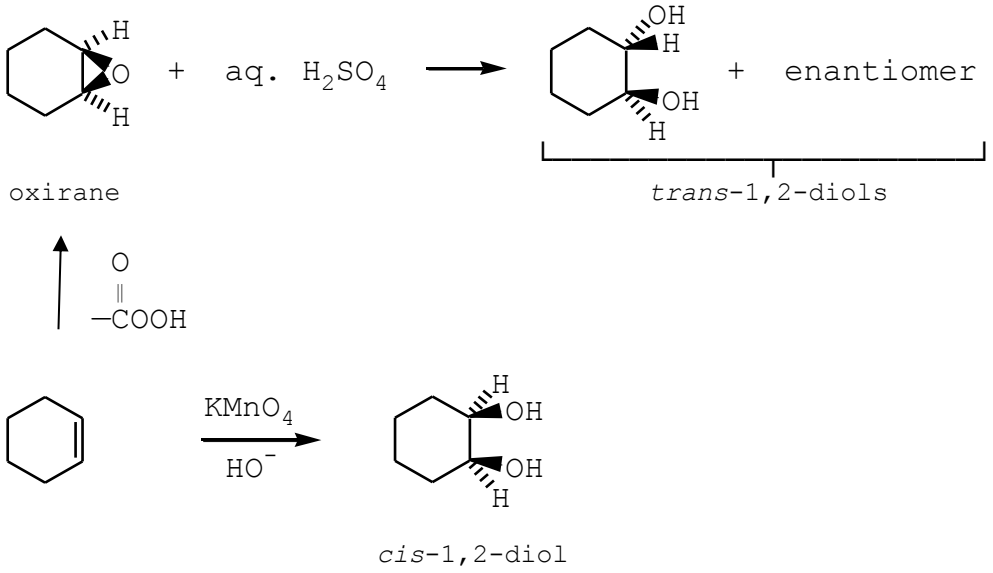
(a) With a mechanism involving a carbocation, show how the ether linking the two monosaccharides in lactose is broken.

(b) During the reaction only one of the two possible carbocations is generated. Why?

10.8B Reactions of Oxiranes

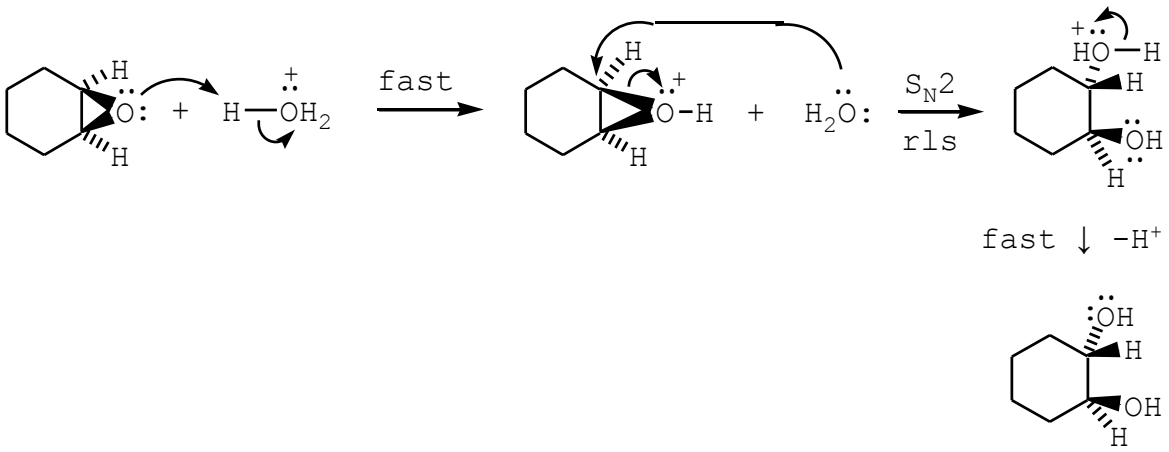
The preceding section indicated that simple ethers are rarely used as synthetic reagents. Yet, another kind of ether, oxiranes (sometimes called epoxides), react in some important syntheses. The difference in reactivity is caused by the oxirane's ring. Table 2.4 (Section 2.7B) indicates that a cyclopropane ring has 115 kJ/mol of ring strain. With a similar amount of ring strain in its three-membered ring, an oxirane reacts much more readily than a simple ether in reactions that open the ring and release the strain.

Aqueous sulfuric acid opens the oxirane ring by acidic catalysis. For example:

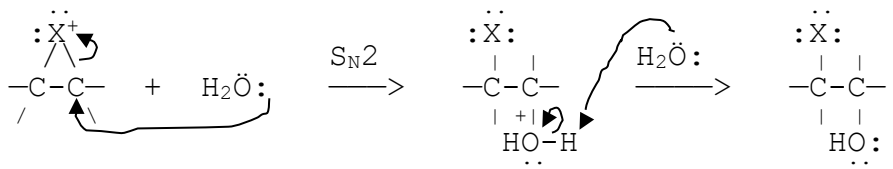


Because the ether is part of a ring, its cleavage does not fragment the molecule like a simple ether (Section 10.8A), but maintains the carbon skeleton. This stereoselective synthesis of *trans*-1,2-diols complements the synthesis of *cis*-1,2-diols by basic potassium permanganate (Section 8.12A). In fact, the synthesis of the trans and cis diastereomers can begin at the same alkene, shown above.

The mechanism includes an unusual S_N2 step:



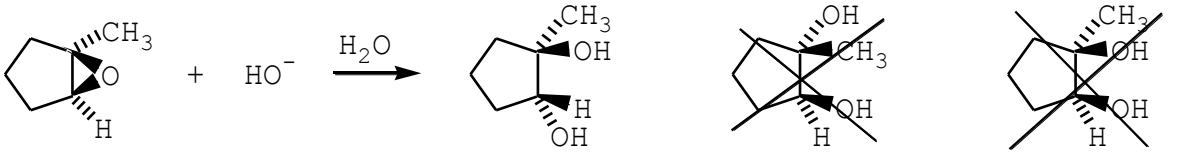
In the first step the strong acid protonates the oxirane like any other ether. The next S_N2 step is unusual because the water nucleophile is weak. Of course, normal S_N2 reactions, using alkyl halides or sulfonates as electrophiles, need strong nucleophiles. Yet, this electrophile, with much ring strain and a positive charge, is much stronger than an alkyl halide or sulfonate. Consequently, the weakly nucleophilic water is strong enough to relieve the ring strain and neutralize the charge. Back approach with inversion of configuration at either electrophilic carbon provides either trans enantiomer. This situation recalls the S_N2 reaction of water with a bridged halonium ion, also featuring a three-membered ring and a positive charge (Section 8.10C):



halonium ion

We have seen how protonation makes a simple ether an acceptable electrophile and makes an oxirane an exceptionally strong electrophile for nucleophilic substitution. Yet, unlike a simple ether an oxirane itself is a feasible electrophile. Although an unprotonated oxirane does not benefit from a positive charge, it still has ring strain ready to be released. Consequently, although a weak nucleophile such as water does not react with oxirane, a strong S_N2 nucleophile does.

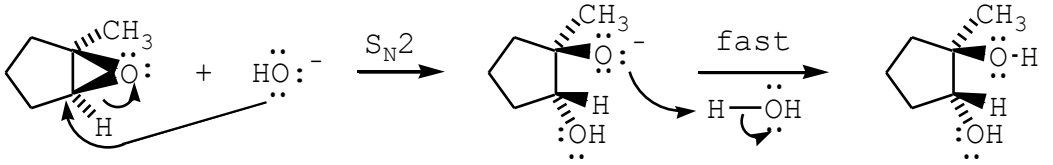
For example, strongly nucleophilic hydroxide ion readily engages an oxirane itself:



trans-1,2-diol only | *trans*-1,2-diol none | *cis*-1,2-diol none

Like aqueous sulfuric acid, aqueous hydroxide ion yields a *trans*-1,2-diol. Yet, this regioselective and stereoselective reaction forms neither the trans diol enantiomer nor the cis diol.

Of course, the mechanism explains both the regioselectivity and the stereoselectivity:

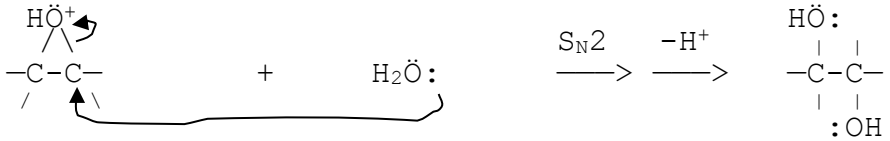


The first step is S_N2 with the regioselective strong nucleophile finding the secondary α carbon instead of the more sterically hindered tertiary α carbon on the other side of the oxirane ring. Hypothetical bonding at the tertiary carbon would yield the wrong trans enantiomer and violate the S_N2 preference for the less hindered α carbon. Back approach and inversion of configuration insure the trans stereoselectivity, whereas front approach and retention would have given the cis stereoisomer.

An unusual feature of this S_N2 reaction is its leaving group, an alkoxide ion. Of course, this is a strong base, which is a poor leaving group in a *normal* nucleophilic substitution. Yet, this is an *unusual* S_N2 reaction, whose relief of ring strain expels the energetic, unstable leaving group. Likewise, in the presence of aqueous acid the ring strain of oxiranes overcomes the normal S_N2 prohibition of weak nucleophiles, as we saw earlier in this section.

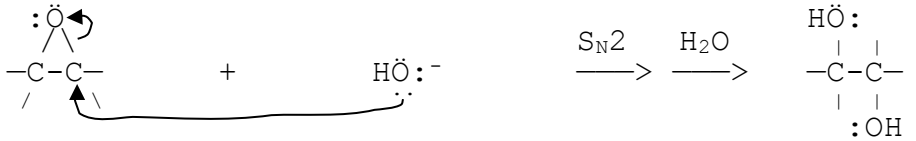
Thus, rules in organic chemistry are extremely useful to explain and predict normal behavior, but exceptional structural features can break these rules. These exceptions make organic chemistry less predictable but also more fascinating and open to creativity.

These two methods of hydrolyzing oxirane rings illustrate the complementarity of successful nucleophiles and electrophiles. In the earlier acid-catalyzed hydrolysis of an oxirane, an *exceptionally strong, cationic* electrophile (the protonated oxirane oxonium ion) could react with the *weak nucleophile,* water.



very strong electrophile weak nucleophile

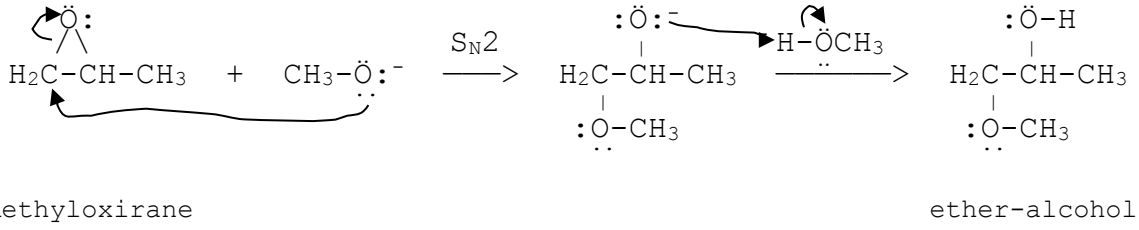
In the later base-catalyzed hydrolysis, a *weaker, uncharged* electrophile (the unprotonated oxirane) requires a *stronger* nucleophile, hydroxide ion.



weaker electrophile stronger nucleophile

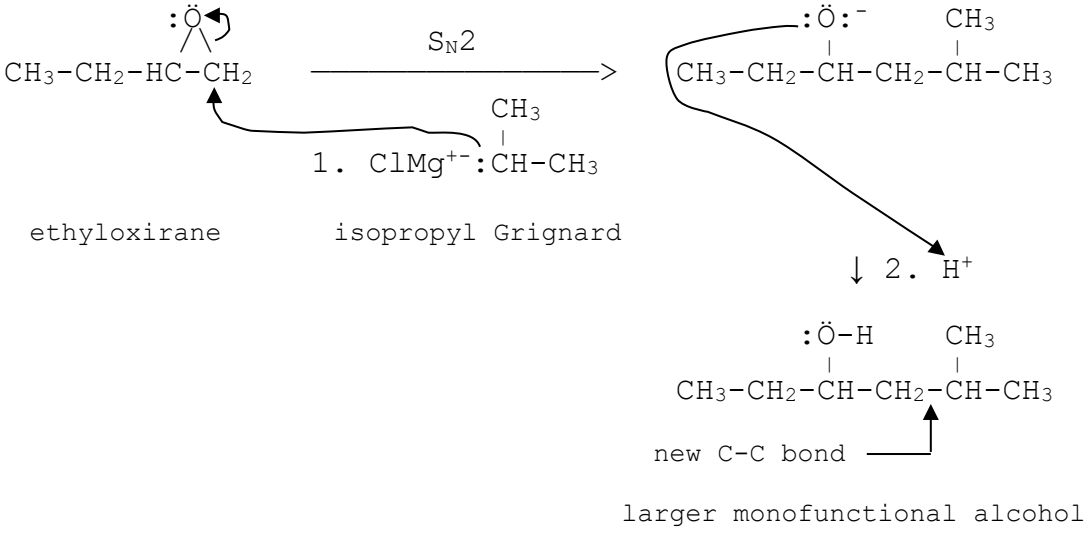
So, the stronger the electrophile the weaker the nucleophile can be, and vice versa.

The synthetic utility of oxiranes lies in their ability to react with many kinds of strong S_N2 nucleophiles, not just hydroxide ions. For example, an alkoxide ion can make an ether-alcohol:



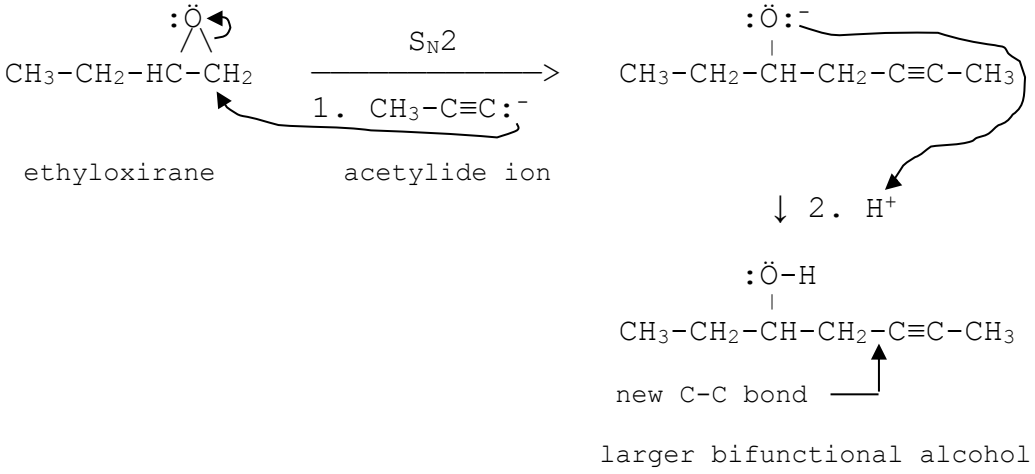
The S_N2 nucleophile naturally substitutes on the more open, primary α carbon of the oxirane, not on the secondary α carbon. Then the protic solvent, methanol, neutralizes the alkoxide leaving group. The product with two functional groups on adjacent carbons is typical of S_N2 reactions with oxiranes.

Yet, there is a strong nucleophile that may leave only one functional group in the product: a Grignard reagent. For example:



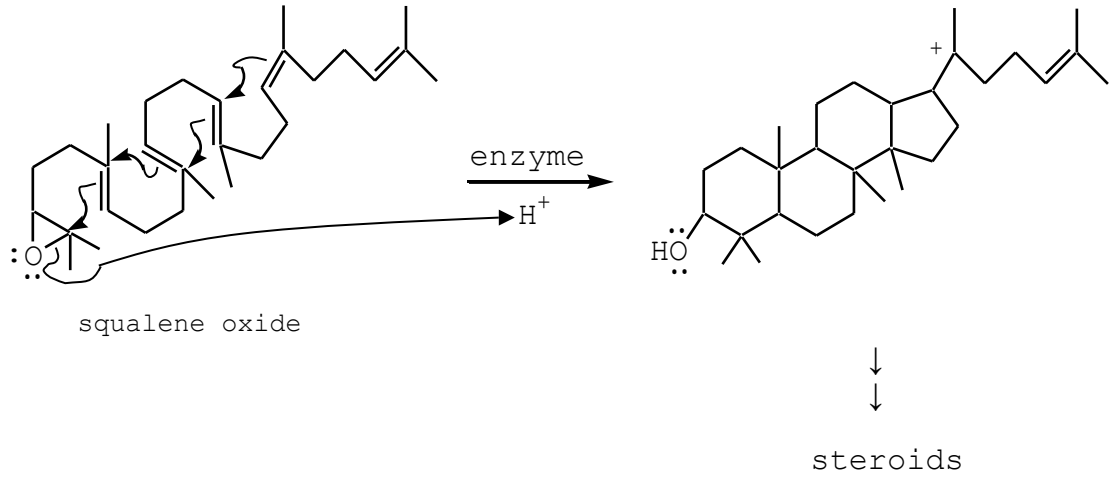
As an S_N2 nucleophile, the Grignard reagent finds the less hindered α carbon of the oxirane. In the second reaction step acid protonates the alkoxide ion. This acid must be added in a separate, second step *after* the Grignard reagent has reacted to avoid protonating and neutralizing the Grignard reagent. The final product is a simple, monofunctional alcohol because the Grignard reagent loses its functionality when forming the carbon-carbon σ bond.

This is our second versatile way of extending a carbon skeleton. The first method used organometallic acetylide ions with methyl or primary halides (or sulfonates) (Section 9.6C). In fact, as a strong nucleophile, an acetylide ion can also react with an oxirane such as the one above:



A larger, bifunctional alcohol results with the nucleophilic group on a carbon adjacent to the alcohol functional group, the typical pattern of product in oxirane reactions. The two functional groups of this alcohol allow more opportunity for further reaction than the monofunctional alcohol from the previous Grignard synthesis (unless the Grignard reagent was phenyl or alkenyl). On the other hand, the Grignard synthesis can add a much greater variety of carbon structures, including branched ones, to the oxirane skeleton, whereas the first two carbons of an acetylide ion cannot be branched. Both reactions, of course, add a carbanion nucleophile to a carbon electrophile, the essence of enlarging a carbon skeleton.

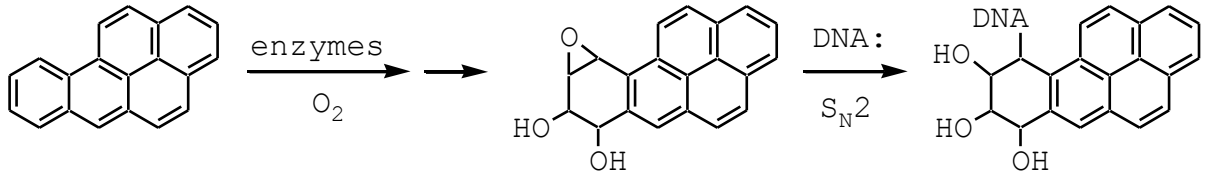
Oxiranes react with various nucleophiles in reactions of practical importance. The biosyntheses of the complex structures of steroids, including cholesterol, progesterone, estrone, testosterone, and cortisone, depend on forming their multiple rings. By providing the electrophilic oxirane for cascading cyclizations, squalene oxide is the precursor for all steroids:



In this amazing sequence of enzyme-catalyzed steps, the oxirane electrophilicity is accentuated by protonation as four properly positioned nucleophilic alkene double bonds simultaneously close the four rings. The sequence of five electron arrows illustrates a perfect head-to-tail pattern. The reactive carbocation intermediate proceeds to steroids by various steps, including carbocation rearrangements.

Smoke from tobacco, barbecues, automobiles, and industry includes another multicyclic compound called benzo[a]pyrene. Once ingested, this nonpolar hydrocarbon cannot be readily excreted through the aqueous channels of the body. Yet, the body has enzyme complexes that

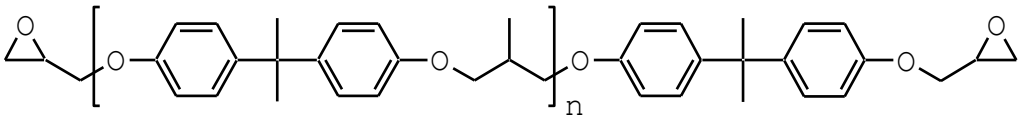
oxidize such foreign hydrocarbons into more polar and water-soluble compounds for easier excretion:



benzo[a]pyrene more polar oxirane DNA adduct

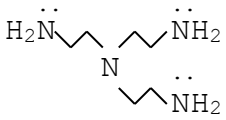
Unfortunately, in this case our enzymes actually harm us because the oxidized product is an oxirane that reacts as an electrophile with the strongly nucleophilic guanine base in DNA. The resulting unnatural DNA adduct does not function properly and is believed to be mutagenic and ultimately carcinogenic.

A final example of the chemistry of oxiranes is epoxy glue. The name comes from the traditional name for oxiranes: epoxides. One tube of the glue contains the electrophile, a polymer with oxirane rings at both ends:



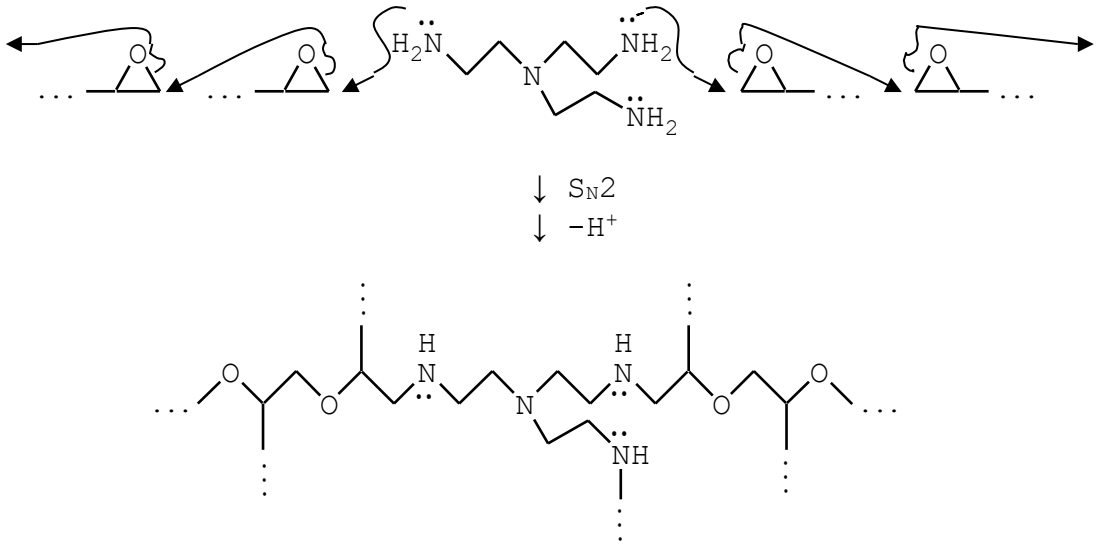
oxirane polymer electrophile

where n is a large integer. The other tube contains a multiple amine nucleophile:



amine triple nucleophile

Mixing the contents induces multiple S_N2 reactions in three dimensions to thoroughly cross-link the polymer and set the glue:

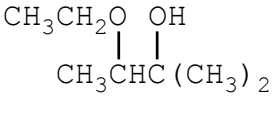


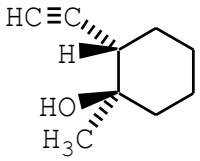
Indeed, the structure of oxiranes makes them potent electrophiles.

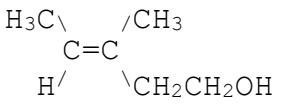
Puzzle 10.25 ———————————————————————————————————————

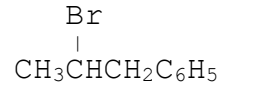
Show how each of these products could be made from an oxirane:

(a) 

(b) 

(c) 

(d) 

(e) 

(f)

Puzzle 10.26 ———————————————————————————————————————

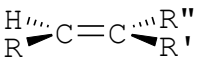
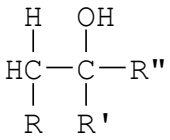
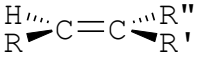
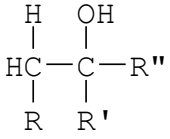
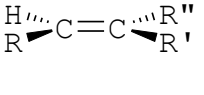
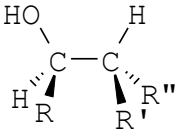
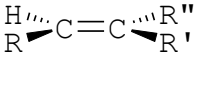
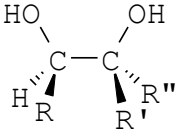
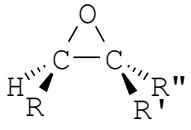
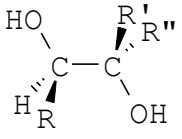
Outline the synthesis of 2,4-dimethyl-2-pentanol from two alcohols of fewer than five carbons.

Chapter Summary

1. Two acceptable methods for naming ethers exist.
2. Because of its hydrogen bonds an alcohol boils at a higher temperature than does an ether of similar size.
3. Water solubility of alcohols and ethers increases with decreasing number of carbons, or with increasing number of oxygens, or with increasing compactness of carbon groups. Simple alcohols and ethers of fewer than five carbons are appreciably soluble in water. Crown ethers activate nucleophilic anions by fully solvating cation counter ions.
4. Simple alcohols can be made efficiently by S_N2 reactions of methyl or primary halides and by three ways of hydrating an alkene, both Markovnikov and anti-Markovnikov additions. Mild oxidation of an alkene can form a 1,2-diol.
5. Like water, alcohols are weak acids, which donate a proton only to a strong base.
6. Like water, alcohols are weak bases, which accept a proton only from a strong acid. They react as weak bases with oxonium ions in S_N1 and E1 reactions.
7. An alcohol itself is a poor carbon electrophile because of a poor leaving group. Yet, protonation by a hydrogen halide allows an alcohol to react as a carbon electrophile in an S_N1 or S_N2 reaction, yielding an alkyl halide. Protonation of its leaving group by concentrated sulfuric acid dehydrates an alcohol in an E1 or E2 reaction, yielding an alkene.
8. Like water an alcohol is a weak nucleophile. As a nucleophile, it can form an alkyl sulfonate, which is a fair non-acidic carbon electrophile like an alkyl halide.
9. Chromium(VI) can oxidize secondary alcohols only to ketones, and primary alcohols to either aldehydes or carboxylic acids. Tertiary alcohols cannot easily be oxidized.
10. Alkoxide ions can react as strong bases in E2 reactions or as strong nucleophiles in S_N2 reactions.
11. Ethers are usually synthesized by an S_N2 reaction between an alkoxide ion and a methyl or primary halide or sulfonate. An alkoxide ion and alkyl halide on the same molecule can make a cyclic ether by an intramolecular reaction.

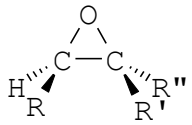
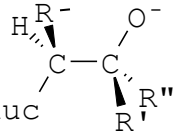
12. Unreactive under most conditions, simple ethers are normally used as solvents, but may be cleaved by hydrogen halides.
13. Having much ring strain, oxiranes are much more reactive electrophiles than simple ethers. Acid- or base-catalyzed hydrolysis opens the ring to a 1,2-diol. Many strong nucleophiles, including organometallic carbanions, react in S_N2 reactions to form many kinds of simple and bifunctional alcohols.

Reaction Summary

Reactants		Product	Section
Syntheses of alcohols			
R-X Me or 1°	HO^- ⟶	R-OH	10.4
R-X 3° or 2°	H_2O ⟶	R-OH	10.4
	aq H_2SO_4		10.4
	1. aq $Hg(O_2CMe)_2$ 2. $NaBH_4$		10.4
	1. BH_3 2. HOOH, HO^-		10.4
	$KMnO_4$, HO^-		10.4
	aq H_2SO_4		10.8B

Reactants		Product	Section

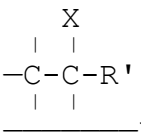
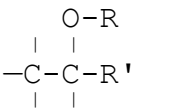
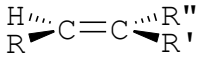
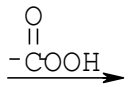
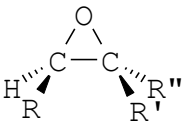
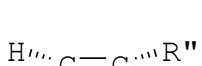
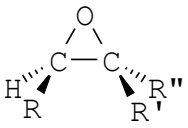
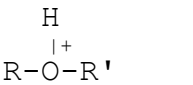
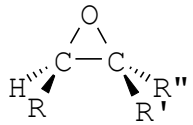
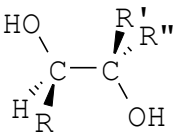
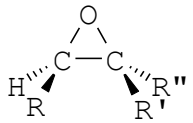
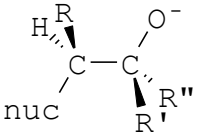
Syntheses of alcohols (continued)

	nuc⁻, strong		10.8B
O ‖ —C—	1. R-M ⟶ 2. H^+ ⟶ M = MgX or Li	OH | —C-R |	12.5B
O ‖ —C—	1. —C≡C^- ⟶ 2. H^+ ⟶	OH | —C-C≡C—	12.5B
O ‖ —C—	N≡C^- ⟶ 2. H^+ ⟶	OH | —C-C≡N	12.5B
O ‖ —C—	1. $LiAlH_4$ ⟶ 2. H^+ ⟶ or $NaBH_4$	OH | —C-H |	12.5E
O ‖ —C—	H_2, Ni ⟶	OH | —C-H |	12.5E
O ‖ —C-OH	1. $LiAlH_4$ ⟶ 2. H^+ ⟶	$—CH_2-OH$	13.5B
O ‖ —C-L | L ≠ N—	1. $LiAlH_4$ ⟶ 2. H^+ ⟶	$—CH_2-OH$	14.7A
O ‖ —C-L | L ≠ N—	1. R-MgX ⟶ 2. H^+ ⟶	OH | —C-R | R	14.7B

Reactions of alcohols

R-OH	H^- ⟶ or Na	$R-O^-$	10.5A
R-OH	strong acid ⟶	$R-OH_2^+$	10.5B

Reactants		Product	Section
Reactions of alcohols (continued)			
R-OH	H X | | —C-C-R' | | ————>	$R\text{-}OH_2^+$, —C=C-R' | |	10.5B
R-OH	X | | —C-C-R' | | ————>	O-R | | —C-C-R' | |	10.5C
R-OH	HX ————> X ≠ F	R-X	10.5D
R-OH	$SOCl_2$ ————>	R-Cl	10.5D
R-OH	PBr_3 ————>	R-Br	10.5D
R-OH	PI_3 ————>	R-I	10.5D
H OH | | —C-C— | |	H_2SO_4, Δ ————>	—C=C— | |	10.5D
R-OH	$Cl\text{-}SO_2$— ————>	O ‖ R-O-S— ‖ O	10.5D
OH | $—CH_2$	anhyd Cr(VI) ————>	O ‖ —CH	10.5
OH | $—CH_2$	aq Cr(VI) or $KMnO_4$ ————>	O ‖ —C-OH	10.5E
OH | R-CH-R'	any Cr(VI) ————>	O ‖ R-C-R'	10.5E
Reactions of alkoxide ions			
$R\text{-}O^-$	H X | | —C-C— | | ————>	R-OH, —C=C— | |	10.6A

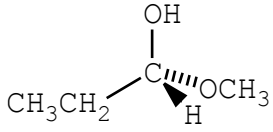
Reactants		Product	Section
Reactions of alkoxide ions (continued)			
$R\text{-}O^-$	$-CH_2\text{-}X$ ⟶	$R\text{-}O\text{-}CH_2-$	10.6B
$R\text{-}O^-$	acid ⟶	$R\text{-}OH$	10.6B
Syntheses of ethers			
$R\text{-}O^-$	$-CH_2\text{-}X$ ⟶	$R\text{-}O\text{-}CH_2-$	10.6B
$R\text{-}OH$	 ⟶		10.5C
	 ⟶		10.7
	1. X_2, H_2O ⟶ 2. HO^- ⟶		10.7
Reactions of ethers			
$R\text{-}O\text{-}R'$	strong acid ⟶		10.8A
$R\text{-}O\text{-}R'$	HX ⟶ X = Br or I	$R\text{-}X$, $HO\text{-}R'$	10.8A
	aq H_2SO_4 ⟶		10.8B
	nuc⁻ strong ⟶		10.8B

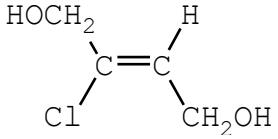
Reactants		Product	Section
Reactions of sulfonates			
$R\text{-}O\text{-}SO_2\text{—}$ Me or 1°	strong nuc^- ⟶	R-nuc	10.5D
$R\text{-}O\text{-}SO_2\text{—}$ 3°	weak nuc^- ⟶	R-nuc	10.5D
H OSO_2— —C-C—	Me_3CO^- ⟶	—C=C—	10.5D

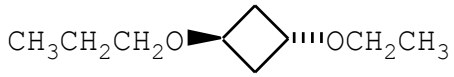
Additional Puzzles

10.27 Give the IUPAC name for each of these compounds:

(a) 

(b) 

(c) 

(d) 

10.28 Correct the mistakes in these names and draw correct structures:
(a) 2-bromo-2-ethoxyethene (b) butoxymethane (c) 1-chloro-4-pentanol
(d) 2-dimethoxypropane (e) 2-bromo-2-propoxy-2-butanol

10.29 Why does water boil at a higher temperature than ethanol (100 vs. 78°C)?

10.30 Estimate the water solubility of triglyme, the common name for the tetraether: $CH_3OCH_2CH_2OCH_2CH_2OCH_2CH_2OCH_3$.

10.31 Show how a deuterated alkyl tosylate could be converted to (*R*)-1-deuterioethanol.

10.32 A single alkene under different reaction conditions can make all of the following alcohols. Find the one alkene and the different reaction conditions.
(a) *trans*-2-methylcyclohexanol (b) 1-methylcyclohexanol
(c) (1*S*,2*R*)-1-methyl-1,2-cyclohexanediol and enantiomer
(d) (1*S*,2*S*)-1-methyl-1,2-cyclohexanediol and enantiomer

10.33 (a) Draw the mechanism for the S_N1 reaction of methanol and 2-bromo-2-methylbutane.
(b) Indicate the three roles of methanol in this reaction.

10.34 (a) Show the reactants and organic products for the reactions in the synthesis of 2-propanol

from 1-propanol.
(b) Show the reactants and organic products for the reactions in the synthesis of 1-propanol from 2-propanol.

10.35 (a) Show the reactants and organic products for the reactions in the synthesis of 2-chloropropane from 1-chloropropane.
(b) Show the reactants and organic products for the reactions in the synthesis of 1-chloropropane from 2-chloropropane.

10.36 Outline two syntheses of propanamine ($CH_3CH_2CH_2NH_2$) from 1-propanol.

10.37 Show the organic products from the reactions of ethanol with these reagents (if no reaction, say so):
(a) aqueous cold H_2SO_4 (b) tosyl chloride (c) H_2N^- (d) HBr
(e) aqueous $Na_2Cr_2O_7$ (f) Na (g) $SOCl_2$ (h) anhydrous pyridinium chlorochromate
(i) NaH (j) Cl^- (k) H_2SO_4, Δ (l) PBr_3 (m) CH_3MgCl (n) $KMnO_4$

10.38 Show the organic products from the reactions of 2-propanol with the reagents of the preceding puzzle.

10.39 Show the organic products from the reactions of 2-methyl-2-propanol with the reagents of the preceding puzzle.

10.40 Consider the possible reactions of ethoxide ion with 2-bromoethanol.
(a) What is the organic product from an S_N2 reaction?
(b) What are the organic products from an acid-base equilibrium?
(c) Is the forward acid-base reaction favored thermodynamically over its reverse reaction? Explain.
(d) Is the substitution or the acid-base reaction faster?

10.41 Show the reagents and organic products for the reactions in the synthesis of a cyclic ether from 1,4-dichloro-4-methylpentane.

10.42 (a) After (*R*)-2-butanol reacts with *p*-toluenesulfonyl chloride (tosyl chloride), the product reacts with potassium hydroxide in 18-crown-6 and diethyl ether in a substitution reaction. Show the stereochemistry of the organic products from both reactions.
(b) After (*R*)-2-butanol reacts with hydrogen iodide, the product reacts with potassium hydroxide in 18-crown-6 and diethyl ether in a substitution reaction. Show the stereochemistry of the organic products from both reactions.
(c) Why do the two reaction sequences produce different products?

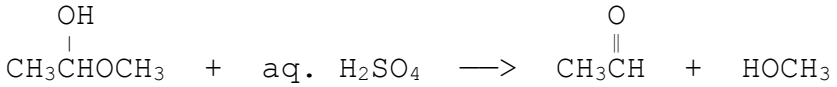
10.43 (*S*)-2-butanol retains its optical activity in aqueous sodium hydroxide, but rapidly loses its activity in aqueous sulfuric acid. Explain.

10.44 Draw the mechanism for the conversion of 2,2-dimethylcyclopentanol with hydrogen bromide to 1-bromo-1,2-dimethylcyclopentane.

10.45 Show the reactants and organic products for the reactions in two different syntheses of pentane from 2-pentanol.

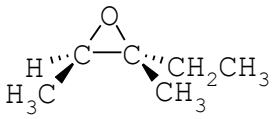
10.46 Show the main organic products from the reaction of hydroxide ion with these compounds (if no reaction, say so):
(a) dimethyl ether (b) oxirane

10.47 Acid can cleave some ethers unusually easily. For example:



Draw the mechanism and explain why the reaction goes easily.

10.48 Show the organic stereoisomers produced by the following reagents with this oxirane:



(a) NaOH, H_2O (b) CH_3NH_2 (c) CH_3OK, CH_3OH (d) $CH_3CH{=}CHLi$, then H_2O
(e) CH_3SLi, H_2O (f) KCN, H_2O (g) $NaC{\equiv}CCH_3$, then CH_3OH

10.49 Show the reagents and organic products for the reactions in the synthesis of 3-methyl-2-butanol from 2-butanol. Ignore stereochemistry. Hint: an oxirane can help.

10.50 Compound **A**, $C_{11}H_{24}O$, reacts with hydrogen iodide to give **B**, $C_{11}H_{23}I$, with little carbocation rearrangement. Treatment of **B** with potassium *tert*-butoxide gives mostly **C** and some **D**, both $C_{11}H_{22}$. **C** and **D** were treated separately with ozone and then with zinc. In each case a 50:50 mixture of $(CH_3)_2CHCH_2CH{=}O$ and $(CH_3)_2CHCH_2CH_2CH{=}O$ was produced. Identify **A**, **B**, **C**, and **D**.

10.51 (a) Draw the mechanism for the reaction of 2-cyclobutyl-2-propanol heated with sulfuric acid to make 3,3-dimethylcyclopentene.
(b) What unusual kind of rearrangement occurs during this reaction, and why does it occur?

10.52 Give reaction conditions for the synthesis of 2-chloro-2-methylbutane from each compound:
(a) 2-bromo-2-methylbutane (b) 2-methyl-2-butanol (c) 3-methyl-2-butanol

10.53 We know that alcohols can be made more electrophilic by protonation. For example:

$$CH_3CH_2OH + HBr \longrightarrow CH_3CH_2OH_2^+ + Br^- \longrightarrow CH_3CH_2Br$$

Consider alternative reactions to the second step above.
(a) Draw the product from the simple addition of bromide ion to the positively charged oxygen of the intermediate oxonium ion without a leaving group leaving. How feasible is this reaction?
(b) Draw the products from bromide ion bonding to the positively charged oxygen with some group leaving. How feasible is this reaction?

10.54 In one qualitative analysis test for certain alcohols, the unknown sample is dissolved in a concentrated aqueous solution of HCl and $ZnCl_2$. The eventual appearance of cloudiness or a separate layer constitutes a positive test for an alcohol.
(a) This test requires the sample to be soluble in the aqueous HCl/$ZnCl_2$ test solution. What kind of alcohol would not work in this test?
(b) In a positive test what product provides the cloudiness or separate layer?

10.55 In a second qualitative analysis test for certain alcohols, the unknown sample is dissolved

in propanone and then treated with aqueous, acidic CrO_3. A positive test shows the original yellow Cr(VI) reduced to a green Cr(III). Which kinds of alcohols would test positive?

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