Ethers and Epoxides; Thiols and Sulfides

Klein, D. (2012). Ethers and Epoxides; Thiols and Sulfides. *En Organic Chemistry* (pp. 623-631). USA: Wiley.

DO YOU REMEMBER?

Before you go on, be sure you understand the following topics.
If necessary, review the suggested sections to prepare for this chapter.

- Reading Energy Diagrams (Section 6.6)
- S_N2 Reactions (Sections 7.4, 7.7)
- Halohydrin Formation (Section 9.8)
- Mechanisms and Curved Arrows (Sections 6.8-6.11)
- Oxymercuration-Demercuration (Section 9.5)

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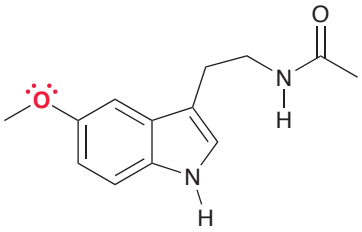
14.1 Introduction to Ethers

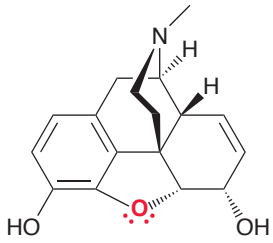
Ethers are compounds that exhibit an oxygen atom bonded to two R groups, where each R group can be an alkyl, aryl, or vinyl group.

An ether

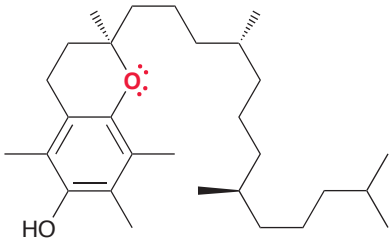
The ether moiety is a common structural feature of many natural compounds, for example:



Melatonin
A hormone that is believed to regulate the sleep cycle

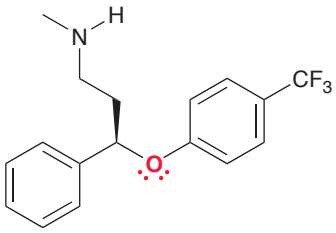


Morphine
An opiate analgesic used to treat severe pain

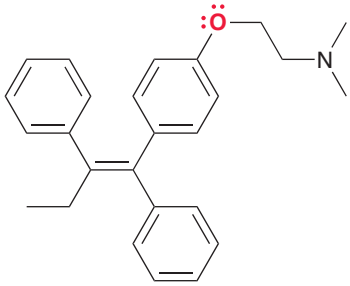


Vitamin E
An antioxidant

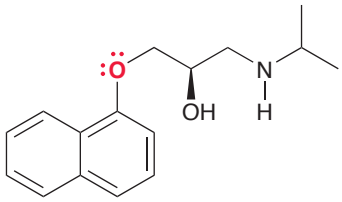
Many pharmaceuticals also exhibit an ether moiety, for example:



(*R*)-Fluoxetine
A powerful antidepressant sold under the trade name Prozac®



Tamoxifen
Inhibits the growth of some breast tumors

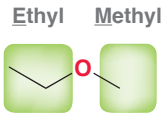


Propanolol
Used in the treatment of high blood pressure

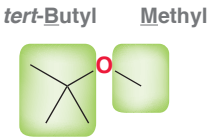
14.2 Nomenclature of Ethers

IUPAC rules allow two different methods for naming ethers.

1. A common name is constructed by identifying each R group, arranging them in alphabetical order, and then adding the word "ether", for example:

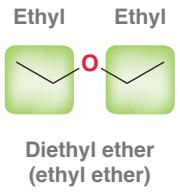


Ethyl methyl ether

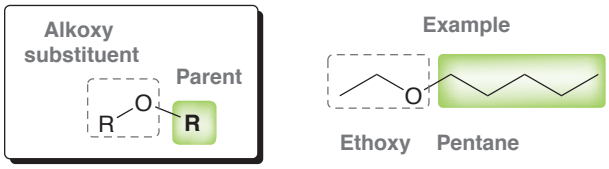


***tert*-Butyl methyl ether**

In these examples, the oxygen atom is connected to two different alkyl groups. Such compounds are called **unsymmetrical ethers**. When the two alkyl groups are identical, the compound is called a **symmetrical ether** and is named as a *di*alkyl ether.



2. A systematic name is constructed by choosing the larger group to be the parent alkane and naming the smaller group as an **alkoxy** substituent.



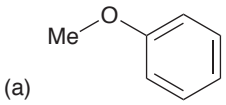
Systematic names must be used for complex ethers that exhibit multiple substituents and/or chirality centers. Let's see some examples.

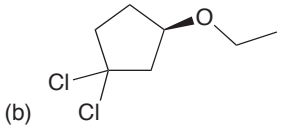
SKILLBUILDER

14.1 NAMING AN ETHER

LEARN the skill

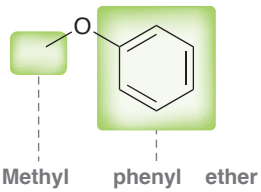
Name the following compounds:



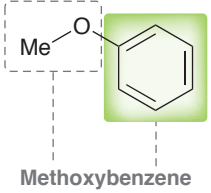


SOLUTION

(a) To assign a common name, identify each group on either side of the oxygen atom, arrange them in alphabetical order, and then add the word "ether."

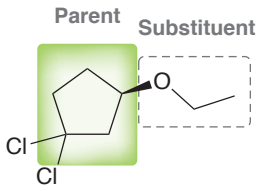


To assign a systematic name, choose the more complex (larger) group as the parent, and name the smaller group as an alkoxy substituent.

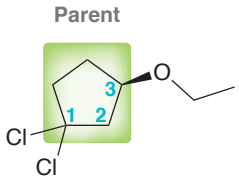


This compound therefore can be called methyl phenyl ether or methoxybenzene. Both names are accepted by IUPAC rules.

(b) The second compound is more complex. It has a chirality center and several substituents. Therefore, it will not have a common name. To assign a systematic name, begin by choosing the more complex group as the parent.



The cyclopentane ring becomes the parent, and the ethoxy group is listed as one of the three substituents on the cyclopentane ring. Locants are then assigned so as to give the lowest possible numbers to all three substituents (1,1,3 rather than 1,3,3):

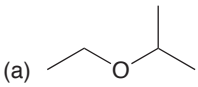


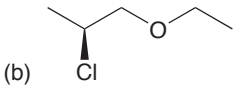
The configuration of the chirality center is identified at the beginning of the name:

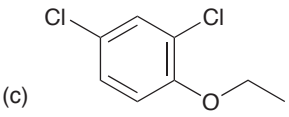
(*R*)-1,1-Dichloro-3-ethoxycyclopentane

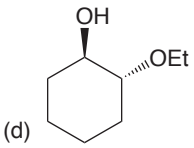
PRACTICE the skill

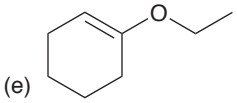
14.1 Provide an IUPAC name for each of the following compounds.











APPLY the skill

14.2 Draw the structure of each of the following compounds.

(a) (*R*)-2-Ethoxy-1,1-dimethylcyclobutane

(b) Cyclopropyl isopropyl ether

14.3 There are six ethers with molecular formula $C_5H_{12}O$ that are constitutional isomers.

(a) Draw all six constitutional isomers.

(b) Provide a systematic name for each of the six compounds.

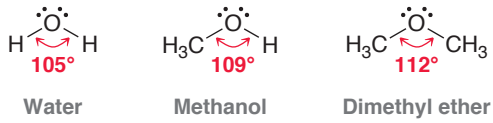
(c) Provide a common name for each of the six compounds.

(d) Only one of these compounds has a chirality center. Identify that compound.

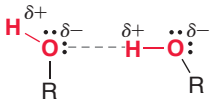
need more **PRACTICE?** **Try Problems 14.30, 14.32**

14.3 Structure and Properties of Ethers

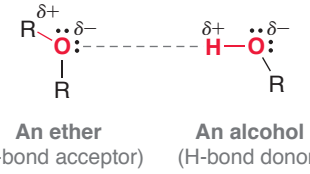
The geometry of an oxygen atom is similar for water, alcohols, and ethers. In all three cases, the oxygen atom is sp^3 hybridized, and the orbitals are arranged in a nearly tetrahedral shape. The exact bond angle depends on the groups attached to the oxygen atom, with ethers having the largest bond angles.



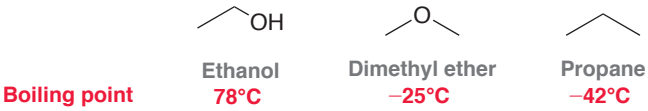
In the previous chapter, we saw that alcohols have relatively high boiling points due to the effects of intermolecular hydrogen bonding.



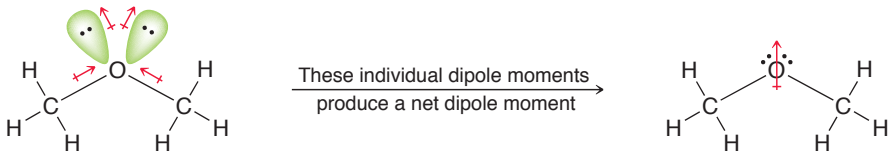
An ether can act as a hydrogen bond acceptor and can interact with the proton of an alcohol.



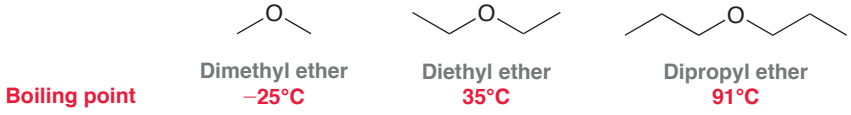
However, ethers cannot function as hydrogen bond donors, and therefore, ethers cannot form hydrogen bonds with each other. As a result, the boiling points of ethers are significantly lower than their isomeric alcohols.



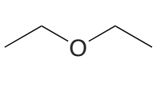
In fact, the boiling point of dimethyl ether is almost as low as the boiling point of propane. Both dimethyl ether and propane lack the ability to form hydrogen bonds. The slightly higher boiling point of dimethyl ether can be explained by considering the net dipole moment.



Ethers therefore exhibit dipole-dipole interactions, which slightly elevate the boiling point relative to propane. Ethers with larger alkyl groups have higher boiling points due to London dispersion forces between the alkyl groups on different molecules. This trend is significant.

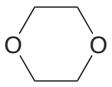


Ethers are often used as solvents for organic reactions, because they are fairly unreactive, they dissolve a wide variety of organic compounds, and their low boiling points allow them to be readily evaporated after a reaction is complete. Below are three common solvents.



Diethyl ether

Tetrahydrofuran

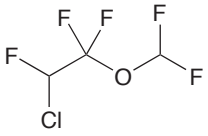


1,4-Dioxane

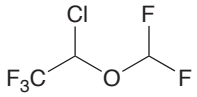
MEDICALLYSPEAKING

Ethers as Inhalation Anesthetics

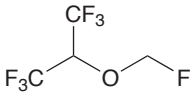
Diethyl ether was once used as an inhalation anesthetic, but the side-effects were unpleasant, and the recovery was often accompanied by nausea and vomiting. Diethyl ether was eventually replaced by halogenated ethers, such as the ones shown below.



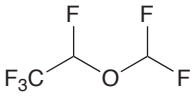
Enflurane



Isoflurane



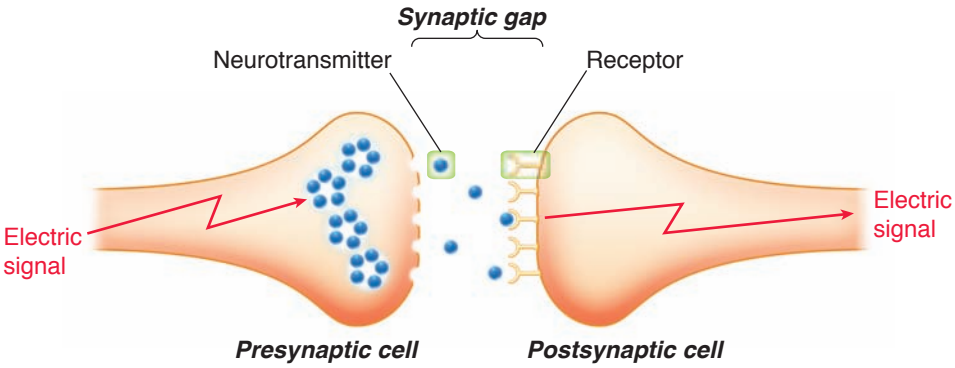
Sevoflurane



Desflurane

Enflurane was introduced in the mid-1970s and was eventually replaced by isoflurane. The use of isoflurane is now also declining as the newer generation ethers (sevoflurane and desflurane) are being more heavily used.

Inhalation anesthetics are introduced into the body via the lungs and distributed by the circulatory system. They specifically target the nerve endings in the brain. Nerve endings, which are separated by a synaptic gap, transmit signals across the gap by means of small organic compounds called neurotransmitters (shown as blue balls in the following figure).



A change in ionic conductance (electrical signal) causes the presynaptic cell to release neurotransmitters, which travel across the synaptic gap until they reach the receptors at the postsynaptic cell. When the neurotransmitters bind to the receptors, a change in conductance is triggered once again. In this way, a signal either can be relayed across the synaptic gap or can be stopped, depending on whether the neurotransmitters are allowed to do their job. Several factors are involved that either can inhibit or increase the function of the neurotransmitters. By controlling whether signals are sent or stopped at each synaptic gap, the nervous system is able to control the various systems in the body (similar to the way a computer uses zeros and ones to perform all of its functions).

Inhalation anesthetics disrupt the normal synaptic transmission process. Many mechanisms of action for anesthetics have been suggested, including the following:

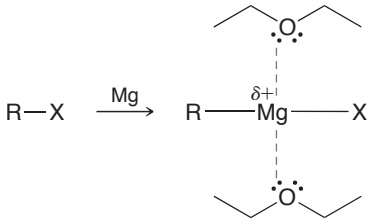
1. Interfering with the release of neurotransmitters from the presynaptic nerve cell
2. Interfering with the binding of the neurotransmitters at the postsynaptic receptors
3. Affecting the ionic conductance (the electrical signal that causes neurotransmission)
4. Affecting reuptake of neurotransmitters into the presynaptic cell

The main mechanism of action is likely to be a combination of many of these factors.

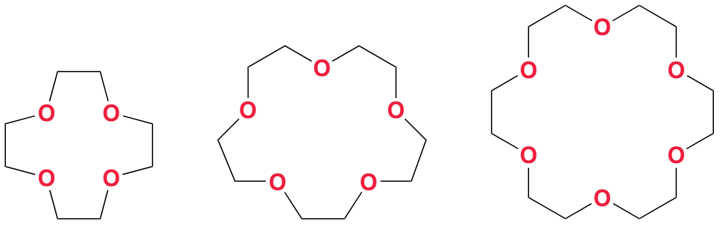
14.4 Crown Ethers

BY THE WAY
Although, like ethers, alcohols (ROH) also have an oxygen atom with lone pairs, they cannot be used to stabilize Grignard reagents, because alcohols possess acidic protons. As we saw in Section 13.6, Grignard reagents cannot be prepared in the presence of acidic protons.

Ethers can interact with metals that have either a full positive charge or a partial positive charge. For example, Grignard reagents are formed in the presence of an ether, such as diethyl ether. The lone pairs on the oxygen atom serve to stabilize the charge on the magnesium atom. The interaction is weak, but it is necessary in order to form a Grignard reagent.

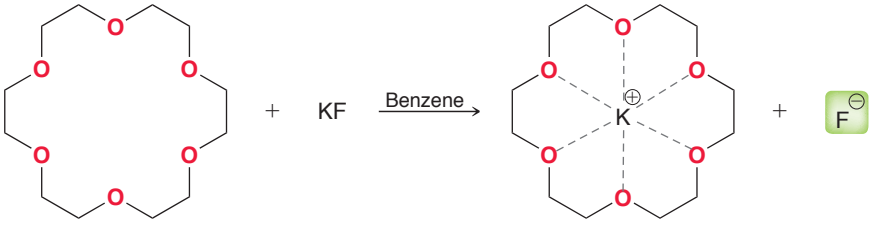


Charles J. Pedersen, working for Du Pont, discovered that the interaction between ethers and metal ions is significantly stronger for compounds with multiple ether moieties. Such compounds are called **polyethers**. Pedersen prepared and investigated the properties of many cyclic polyethers, such as the following examples. Pedersen called them **crown ethers** because their molecular models resemble crowns.



These compounds contain multiple oxygen atoms and are therefore capable of binding more tightly to metal ions. Systematic nomenclature for these compounds can be complex, so Pedersen developed a simple method for naming them. He used the formula X-crown-Y, where X indicates the total number of atoms in the ring and Y represents the number of oxygen atoms. For example, 18-crown-6 is an 18-membered ring in which 6 of the 18 atoms are oxygen atoms.

The unique properties of these compounds derive from the size of their internal cavities. For example, the internal cavity of 18-crown-6 comfortably hosts a potassium cation (K^+). In the electrostatic potential map in Figure 14.1a, it is clear that the oxygen atoms all face toward the inside of the cavity, where they can bind to the metal cation. The space-filling model in Figure 14.1b shows how a potassium cation fits perfectly into the internal cavity. Once inside the cavity, the entire complex has an outer surface that resembles a hydrocarbon, rendering the complex soluble in organic solvents. In this way, 18-crown-6 is capable of solvating potassium ions in organic solvents. Normally, the metal cation by itself would not be soluble in a nonpolar solvent. The ability of crown ethers to solvate metal cations has enormous implications, in both the field of synthetic organic chemistry and the field of medicinal chemistry. As an example, consider what happens when KF and 18-crown-6 are mixed together in benzene (a common organic solvent).



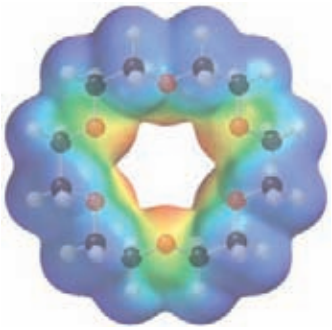
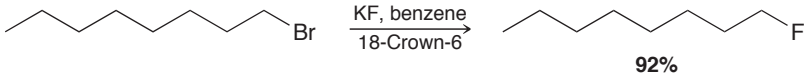


FIGURE 14.1a
An electrostatic potential map of 18-crown-6 shows the oxygen atoms facing the inside of the internal cavity.

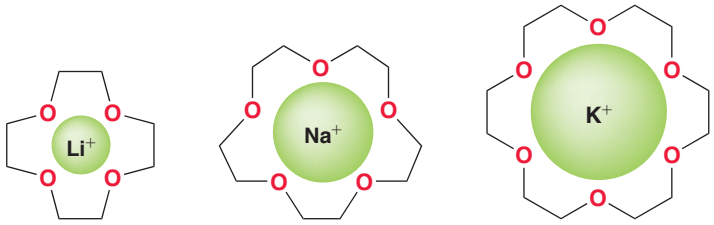
FIGURE 14.1b
A space-filling model of 18-crown-6 shows that a potassium cation can fit nicely inside the internal cavity.

Without the crown ether, KF would simply not dissolve in benzene. The presence of 18-crown-6 generates a complex that dissolves in benzene. The result is a solution containing fluoride ions, which enables us to perform substitution reactions with F^- as a nucleophile. Generally, it is too difficult to use F^- as a nucleophile, because it will usually interact too strongly with the polar solvents in which it dissolves. The strong interaction between fluoride ions and polar solvents makes it difficult for F^- to become "free" to serve as a nucleophile. However, the use of 18-crown-6 allows the creation of free fluoride ions in a nonpolar solvent, making substitution reactions possible. For example:



Another example is the ability of 18-crown-6 to dissolve potassium permanganate ($KMnO_4$) in benzene. Such a solution is very useful for performing a wide variety of oxidation reactions.

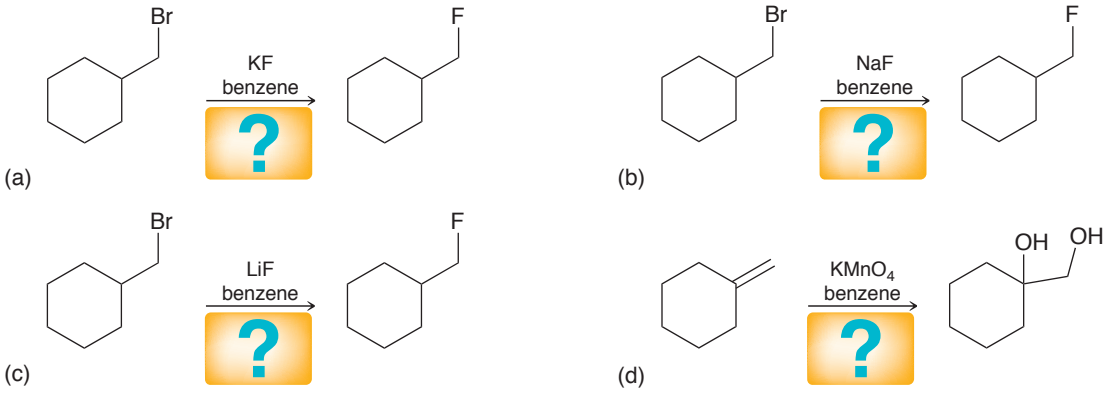
Other metal cations can be solvated by other crown ethers. For example, a lithium ion is solvated by 12-crown-4, and a sodium ion is solvated by 15-crown-5.



The discovery of these compounds led to a whole new field of chemistry, called *host-guest chemistry*. For his contribution, Pedersen shared the 1987 Nobel Prize in Chemistry together with Donald Cram and Jean-Marie Lehn, who were also pioneers in the field of host-guest chemistry.

CONCEPTUAL CHECKPOINT

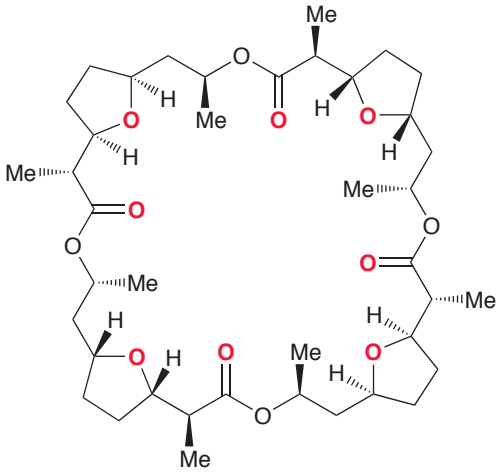
14.4 Identify the missing reagent needed to achieve the following transformations:



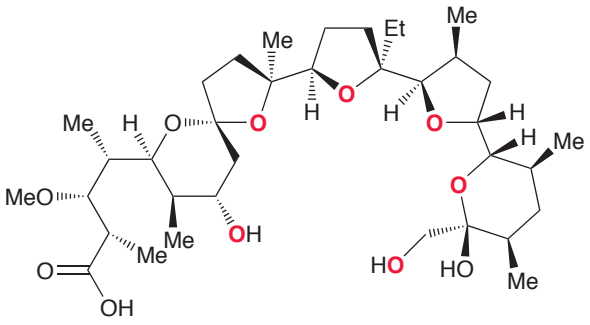
MEDICALLYSPEAKING

Polyether Antibiotics

Some antibiotics function very much like crown ethers. For example, consider the structures of nonactin and monensin.

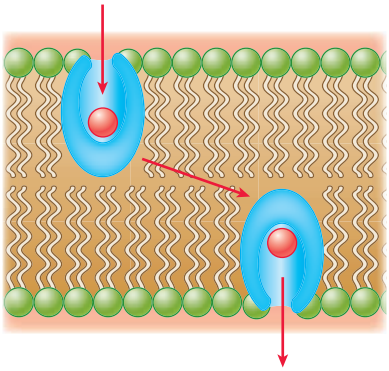


Nonactin



Monensin

These compounds are polyethers and therefore are capable of serving as hosts for metal cations, much like crown ethers. These polyethers are called *ionophores* because the internal cavity is capable of binding a metal ion. The outside surface of the ionophore is hydrocarbon-like (or *lipophilic*), allowing it to pass through cell membranes readily.

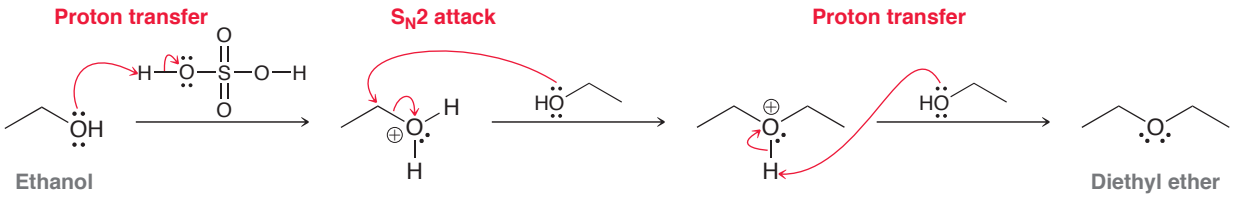


In order to function properly, cells must maintain a gradient between the concentration of sodium and potassium ions inside and outside the cell. That gradient is established because ions are not free to pass through the cell membrane, except through special ion channels where K^+ ions are pumped into the cell and Na^+ ions are pumped out of the cell. Ionophores effectively render the cell membrane permeable to these ions. The ionophores serve as hosts to the ions, carrying them across the cell membrane and destroying the necessary concentration gradient. In this way, ionophores interrupt cell function, thereby killing bacteria. Many new ionophores are currently under investigation as new potential antibiotics.

14.5 Preparation of Ethers

Industrial Preparation of Diethyl Ether

Diethyl ether is prepared industrially via the acid-catalyzed dehydration of ethanol. The mechanism of this process is believed to involve an S_N2 process.



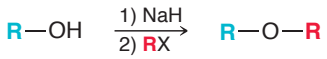
A molecule of ethanol is protonated and then attacked by another molecule of ethanol in an S_N2 process. As a final step, deprotonation generates the product. Notice that a proton is used

in the first step of the mechanism, and then another proton is liberated in the last step of the mechanism. The acid is therefore a catalyst (not consumed by the reaction) that enables the S_N2 process to proceed.

This process has many limitations. For example, it only works well for primary alcohols (since it proceeds via an S_N2 pathway), and it produces symmetrical ethers. As a result, this process for preparing ethers is too limited to be of any practical value for organic synthesis.

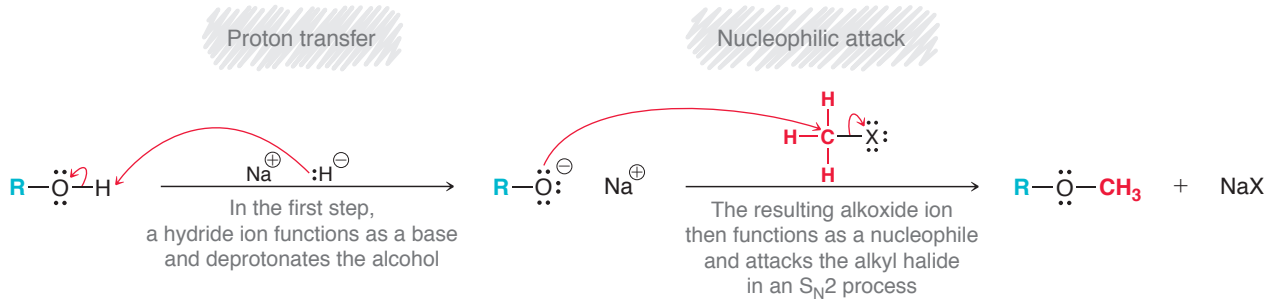
Williamson Ether Synthesis

Ethers can be readily prepared via a two-step process called a **Williamson ether synthesis**.



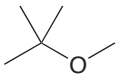
We learned both of these steps in the previous chapter. In the first step, the alcohol is deprotonated to form an alkoxide ion. In the second step, the alkoxide ion functions as a nucleophile in an S_N2 reaction (Mechanism 14.1).

MECHANISM 14.1 THE WILLIAMSON ETHER SYNTHESIS



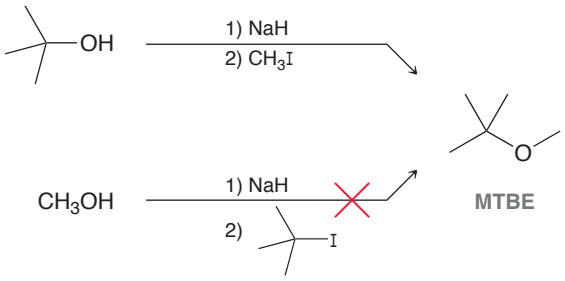
BY THE WAY

The *tert*-butyl group is alphabetized by the letter "b" rather than "t," and therefore, the *tert*-butyl group precedes the methyl group in the name. This compound is commonly called MTBE, which is an acronym of the incorrect name.



***tert*-Butyl methyl ether (MTBE)**

This process is named after Alexander Williamson, a British scientist who first demonstrated this method in 1850 as a way of preparing diethyl ether. Since the second step is an S_N2 process, steric effects must be considered. Specifically, the process works best when methyl or primary alkyl halides are used. Secondary alkyl halides are less efficient because elimination is favored over substitution and tertiary alkyl halides cannot be used. This limitation must be taken into account when choosing which C—O bond to form. For example, consider the structure of *tert*-butyl methyl ether. MTBE was used heavily as a gasoline additive until concerns emerged that it might contribute to groundwater contamination. As a result, its use has declined in recent years. There are two possible routes to consider in the preparation of MTBE, but only one is efficient.



The first route is efficient because it employs a methyl halide, which is a suitable substrate for an S_N2 process. The second route does not work because it employs a tertiary alkyl halide, which will undergo elimination rather than substitution.