Ethers

Ethers are organic compounds with two alkyl groups attached to an oxygen.
- Water has no alkyl groups attached and alcohols have one alkyl group attached.

The two alkyl groups can be the same group (symmetrical) or different (unsymmetrical).

![Symmetrical Ethers](image1)

- Symmetrical
- Unsymmetrical
The lack of labile hydrogens cause ethers
to have vastly different properties than alcohols

1) Boiling Point

RO-H bond allows alcohol to form hydrogen bonding
(each hydrogen bond is ~4-5 Kcal/mol)

With the lack of these hydrogen bonds, ethers have much lower boiling points
2) pKa

With no labile hydrogens, ethers have no acidic hydrogens to abstract

Due to the lack of acidic hydrogens, ethers are used in many organic reactions where alcohols would be impossible to use

\[
\text{MgBr} \quad \text{ether} \quad \text{Grignard reaction}
\]

\[
\text{OH} \quad \text{LAH reduction}
\]
3) Complexation

The lone pair of electrons on oxygen can be used to form Lewis acid type complexes with various π acceptors

Grignard	boron complexes
crown ethers
Nomenclature

There are different ways to name ethers

-common names

Use alkyl alkyl ether system

\[ \text{ethyl methyl ether} \]
\[ \text{diethyl ether} \]

-IUPAC names

Alkoxy alkane system
Find longest continuous chain with the alkoxy substituent
Name using same rules for alkanes learned previously

\[ \text{methoxy ethane} \]
\[ \text{1-ethoxy butane} \]
Synthesis

We have already seen the most common methods to synthesize ethers

$$\text{OH} \xrightarrow{\text{NaH}} \text{ONa} \xrightarrow{\text{CH}_3\text{I}} \text{O}$$

Williamson Ether Synthesis

$$\text{Hg(OAc)}_2 \xrightarrow{\text{ROH}} \text{HgOAc} \xrightarrow{\text{NaBH}_4} \text{OR}$$

addition to alkenes
Reaction of Ethers

Ethers are relatively unreactive
-main reason that they are common solvents for organic reactions

One of the few reactions that they can undergo is alkyl cleavage with HI or HBr

Very similar to alcohol reactions observed in chapter 11

HI > HBr >> HCl
Autoxidation

Serious issue with ether solvents

Over time the ether can be oxidized to a peroxide

\[
\begin{array}{c}
\text{ether} \quad \xrightarrow{\text{air}} \quad \text{peroxide}
\end{array}
\]

These peroxides are potentially explosive

Therefore ether solvents should not be kept in open containers for long periods and especially DO NOT distill these solvents that have been kept after long periods of time
Cyclic Ethers

There are many types of cyclic ethers depending upon the ring size.

We have already seen three membered ring ethers called EPOXIDES.

The naming of epoxides can either be from the starting alkene used to synthesize the OXIDE.

\[
\text{propene} \xrightarrow{RCO_2H} \text{propene oxide}
\]

Or the EPOXY nomenclature is used to designate the substituent.

\[
\text{1,2-epoxy pentane}
\]
Selectivity in Epoxide Formation

When synthesizing an epoxide from an alkene with peracid, the peracid is acting as a source of an electron deficient oxygen, therefore the most electron rich double bond will react preferentially.
Epoxides can also be synthesized from haloxydrins.

The haloxydrin can react through an intramolecular Williamson ether synthesis.
Reaction of Epoxides

Unlike straight chain ethers, epoxides react readily with good nucleophiles
Reason is release of ring strain in 3-membered ring
(even with poor alkoxide leaving group)

\[
CH_3O^- + \text{Epoxide} \rightarrow O\text{-alkyl ether}
\]

Same reaction would never occur with straight chain ether
Most GOOD nucleophile will react through a basic mechanism.
Epoxides will also open under acidic conditions

Can use weaker nucleophiles in this manner since we have a better leaving group

Common examples of nucleophiles include water or alcohols
Differences in Regiochemistry

The base catalyzed opening of epoxides goes through a common $S_{N}2$ mechanism, therefore the nucleophile attacks the least hindered carbon of the epoxide

$$\text{CH}_3\text{MgBr} \rightarrow \text{O} \rightarrow \text{CH}_3\text{CH}_2\text{OH}$$

In the acid catalyzed opening of epoxides, the reaction first protonates the oxygen. This protonated oxygen can equilibrate to an open form that places more partial positive charge on more substituted carbon, therefore the more substituted carbon is the preferred reaction site for the nucleophile

$$\text{O} \rightarrow \text{H}^+ \rightarrow \text{CH}_3\text{OH} \rightarrow \text{H}_2\text{O}$$
4-Membered Ring Ethers

Called Oxetanes

\[
\begin{array}{c}
\text{oxetane} \\
\end{array}
\]

Least common cyclic ether

5-Membered Ring Ethers

The saturated version is called tetrahydrofuran (THF)
-hydrogenated form of conjugated aromatic called furan

\[
\begin{array}{c}
furan \\
\end{array}
\]

\[
\begin{array}{c}
tetrahydrofuran (THF) \\
\end{array}
\]
6-Membered Ring Ethers

Conjugated version is called pyran
-saturated version is tetrahydropyran (THP)
Also called OXANE

![Pyran](image1) ![Tetrahydropyran](image2)

pyran  tetrahydropyran

Derivation of two oxygen containing saturated ring
Called DIOXANE

![Dioxane](image3)

1,4-dioxane
1,4-Dioxane is related to Dioxin
(Dibenzodioxin)

Unfortunately the media often incorrectly refers to a toxic substance that is chlorinated as dioxin

2,3,7,8-tetrachlorodibenzodioxin (TCDD)

TCDD is a toxic substance
Silyl Ethers

Analogous to dialkyl ethers, if an oxygen atom is attached to one carbon and one silicon atom it is called a silyl ether.

\[
\begin{align*}
&\text{H}_3\text{C} - \text{O} - \text{Si} - \text{CH}_3 \\
&\text{H}_3\text{C} \quad \text{CH}_3
\end{align*}
\]

Silyl ethers find wide use as an alcohol protecting group.
As seen previously, many reactions are not possible with OH groups present.

For example, cannot perform Grignard reactions due to labile hydrogen.

\[
\text{CH}_3\text{MgBr} \quad \xrightarrow{} \quad \text{OH} \quad \rightarrow \quad \text{O} \quad \text{O}^{-}
\]

Grignard reagents cannot react at carbonyl with alcohol present in molecule.

If alcohol in one part of the molecule prevents reaction, a common approach is to attach a protecting group.

Need a protecting group that can be easily attached and removed before and after desired reaction.
TIPS (Tri-Isopropyl-Silyl) Protecting Groups

Alcohols can be converted into silyl ethers using silyl chlorides under basic conditions.

TIPS is one common group, but there are many silyl ether variants used - usually the steric demands of various reactions will dictate which silyl ether is best.
Labile hydrogen is no longer present with TIPS protecting group

Thus the desired Grignard reaction can now be accomplished

After desired reaction is completed, the protecting group can be removed

Common to use fluoride source (tetrabutylammonium fluoride for example) to break silyl ether bond to regenerate alcohol
Thioethers
(sulfides)

Replacing the oxygen atom of ethers with a sulfur atom generates a thioether
(also called sulfide)

Common name is to name two alkyl parts and then have sulfide as root name

\[ \text{S} \quad \text{Ethyl methyl sulfide} \]

IUPAC naming uses the same alkoxy alkane naming for ethers,
but “alkylthio” replaces “alkoxy”

\[ \text{S} \quad \text{Methylthioethane} \]
Thiols are acidic

Due to larger polarizability of sulfur relative to oxygen, thiols are more acidic

\[
\text{SH} \quad \text{NaOH} \quad \text{S}\quad
\]

\[\text{pK}_a \approx 10\]

The thiolates can be used to generate sulfides in a $S_N2$ reaction

\[
\text{S}\quad \quad \text{CH}_3\text{I} \quad \text{S}
\]

As seen previously, the more polarizable sulfur anion gives a high yield of $S_N2$ reaction

Due to nucleophilicity, sulfides can react further to generate sulfonium ions

\[
\text{S} \quad \quad \text{CH}_3\text{I} \quad \text{S}^+\]
These sulfonium salts are used as methylating agents biologically.

Common methylating agent in living cells is S-Adenosyl methionine (SAM)

S-Adenosylmethionine (SAM) → S-Adenosylhomocysteine (SAH)
Sulfides can also be Oxidized

Being a third row atom, sulfur can be oxidized to states with more than 8 electrons in the outer shell.

\[
\text{H}_2\text{O}_2 \xrightarrow{\text{CH}_3\text{CO}_2\text{H}} \text{SO} \xrightarrow{\text{H}_2\text{O}_2 \text{CH}_3\text{CO}_2\text{H}} \text{SO}_2
\]

sulfide \hspace{2cm} sulfoxide \hspace{2cm} sulfone

Cannot do this chemistry with ethers, relatively unreactive towards oxidation (except autoxidation to form peroxides)
The IR spectrum does not have many diagnostic peaks for an ether.
Mass Spectrometry

Common fragmentation of ethers is an $\alpha$-cleavage

$\text{[alkyl-O-alkyl]}^+ \rightarrow \text{[alkyl-O-alkyl]}^+ \leftrightarrow \text{[alkyl-oxonium ion]}$

Or loss of alkyl group adjacent to oxygen

$\text{[alkyl-O-alkyl]}^+ \rightarrow \text{[alkyl-O-alkyl]}^+ \rightarrow \text{[alkyl-O-alkyl]}^+ \leftrightarrow \text{[alkyl-oxonium ion]}$

Both fragmentations result in a resonance stabilized oxonium ion
NMR Spectroscopy

Remember position of shifts in $^1$H and $^{13}$C NMR for ether compounds