Chapter 13. Alcohols, Diols, and Ethers

Overview: Chemistry and reactions of sp³ oxygen groups, particularly oxidation of an alcohol, ether formation, and reactions of oxirane (epoxide) groups.

I. What are alcohols, phenols, and ethers?

<table>
<thead>
<tr>
<th>Alcohols (R-OH)</th>
<th>Primary alcohols (1°-alcohols)</th>
<th>IUPAC names</th>
<th>Common names</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃OH</td>
<td>methanol</td>
<td>methyl alcohol</td>
<td></td>
</tr>
<tr>
<td>CH₃CH₂OH</td>
<td>ethanol</td>
<td>ethyl alcohol</td>
<td></td>
</tr>
<tr>
<td>CH₃CH₂CH₂OH</td>
<td>1-propanol</td>
<td>n-propyl alcohol</td>
<td></td>
</tr>
<tr>
<td>H₃C-C=CH₂OH</td>
<td>2-methyl-1-propanol</td>
<td>isobutyl alcohol</td>
<td></td>
</tr>
<tr>
<td>H₃C=CH₂OH</td>
<td>2,2-dimethyl-1-propanol</td>
<td>neopentyl alcohol</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alcohols (R-OH)</th>
<th>Secondary alcohols (2°-alcohols)</th>
<th>IUPAC names</th>
<th>Common names</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₃C-C-OH</td>
<td>2-propanol</td>
<td>isopropyl alcohol</td>
<td></td>
</tr>
<tr>
<td>H₃C⁻H</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alcohols (R-OH)</th>
<th>Tertiary alcohols (3°-alcohols)</th>
<th>IUPAC names</th>
<th>Common names</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₃C⁻C-OH</td>
<td>2-methyl-2-propanol</td>
<td>tert-butyl alcohol</td>
<td></td>
</tr>
<tr>
<td>H₃C⁻CH₃</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phenols (Ph-OH)</th>
<th>pKa ~10-12</th>
<th>diethyl ether</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃CH₂-O-CH₂CH₃</td>
<td></td>
<td>phenyl vinyl ether</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ethers (R-O-R')</th>
<th>pKa ~19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph-O-CH=CH₂</td>
<td></td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>RO-: alkoxy</th>
<th>CH₃O—</th>
<th>methoxy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃CH₂O</td>
<td></td>
<td>ethoxy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ArO-: aryloxy</th>
<th>PhO—</th>
<th>phenoxy</th>
</tr>
</thead>
</table>

II. Oxidation

Oxidation –

historical use of the term:
(1) oxide (oxyd/oxyde) – the ‘acid’ form of an element; e.g., S + air → oxide of S (acid of sulfur)
(2) oxidation or oxidize – to make such an acid, to make the oxide
(3) oxygen – Lavoisier: substance in the air that makes acids; “the bringer of acids” = “oxygen”
(4) oxidation or oxidize – to increase the % oxygen in a substance (reduction: to reduce the % oxygen)

More modern definition:
oxidation or oxidize – loss of electrons (coupled with reduction as gain of electrons)

Note: The loss of electrons (oxidation) by one atom or compound must be matched by the gain of electrons (reduction) by another.
III. Oxidation state (or number) counting (see: pp 513-4 of the textbook)

Therefore,

"the contribution of an H to the oxidation number of the C is -1"
"the contribution of a C to the oxidation number of the H is +1"

Other examples of oxidation numbers:

1. 

2. 

An atom with a formal charge: incorporate its charge # to its oxidation number. Namely, if an atom has a +1 charge, add +1 to its oxidation number.

Example:

For N \[ 3 \times (-1) + 1 = -3 + 1 \]
For O \[ -1 + 1 = 0 \]

Overall:

Hydrocarbon oxidation-reduction spectrum:

Increasing %O; decreasing %H \(\implies\) "oxidation"
Decreasing %O; increasing %H \(\implies\) "reduction"

Note: used in biochem.: oxidase = dehydrogenase enzyme
IV. Oxidation of alcohols

1°-alcohol

\[
\begin{align*}
\text{RCH}_2\text{OH} & \xrightarrow{[\text{ox}]} \text{RCO}_2\text{H} - 2\text{H}^+ \\
\end{align*}
\]

aldehyde

carboxylic acid

2°-alcohol

\[
\begin{align*}
\text{R'CH(OH)R'} & \xrightarrow{[\text{ox}]} \text{RCO}_2\text{H} - 2\text{H}^+ \\
\end{align*}
\]
ketone

3°-alcohol

not easily oxidized

Oxidation methods:
There are hundreds that differ in experimental conditions, but these follow basically the process shown below.

Historically, most common reagents involve high-valency metals.

1. Cr (VI)-based reagents - all Cr(VI) reagents have toxicity problems

Balancing the oxidation-reduction reaction

\[
\begin{align*}
3 \times \left[ R - \text{CH}_2\text{OH} \right] & \rightarrow \left[ R - \text{C}^\text{O}_2\text{H} + 2\text{H}^+ + 2\text{e}^- \right] \quad ("\text{two-electron} \text{ oxidation")}
\\
2 \times \left[ \text{Cr}^{+6} + 3\text{e}^- \right] & \rightarrow \left[ \text{Cr}^{3+} \right]
\\
\end{align*}
\]

Overall,

\[
\begin{align*}
3 \text{ R - CH}_2\text{OH} + 2 \text{Cr}^{+6} & \rightarrow 3 \text{ R-C}^\text{O}_2\text{H} + 6\text{H}^+ + 2 \text{Cr}^{3+}
\\
"\text{stoichiometry}" 
\end{align*}
\]
1a Chromic acid \[ \text{CrO}_3 + \text{H}_2\text{O} \rightarrow \text{H}_2\text{CrO}_4 \] (\textit{hydrous} conditions)

- Jones’ reagent: \text{CrO}_3/\text{H}_2\text{SO}_4/\text{H}_2\text{O}
  - historically, one of the most commonly used chromium +6-based reagents for the oxidation of alcohols
- Chromate: \text{Na}_2\text{CrO}_4 (sodium chromate)/\text{H}_2\text{SO}_4/\text{H}_2\text{O}
- Dichromate: \text{Na}_2\text{Cr}_2\text{O}_7 (sodium dichromate)/\text{H}_2\text{SO}_4/\text{H}_2\text{O}

1b. \textit{Anhydrous} \text{Cr}^{+6}
- \text{CrO}_3·\text{pyridine}
- pyridinium chlorochromate (PCC): one of the most widely used oxidants!
- pyridinium dichromate (PDC) \[(\text{pyH}^+)_2\text{Cr}_2\text{O}_7^{-2}\]

Oxidation reactions of alcohols using these reagents are carried out in \textit{anhydrous} organic solvents such as dichloromethane and, thus, the oxidation of a primary alcohol stops at the stage of an aldehyde.

**Mechanism for the oxidation with PCC:**

- \text{Cr}^{+4} becomes \text{Cr}^{+3} through redox-disproportionation.
The oxidation of primary alcohols with Jones’ reagent:

\[
\begin{align*}
\text{1°-alcohol} & \quad \text{CrO}_3, \text{H}_2\text{SO}_4, \text{H}_2\text{O} \\
& \quad \text{acetone (solvent)} \\
& \quad \text{aldehyde} \\
& \quad \text{faster step} \\
& \quad \text{carboxylic acid}
\end{align*}
\]

Often, an ester R-C(=O)-OR is a by-product.

Mechanism:
2. Non chromium-based Oxidation Reactions: “greener” methods

i) Swern oxidation:
- usually using dichloromethane (CH$_2$Cl$_2$) as the solvent
- anhydrous (i.e., no water present!), non-acidic conditions
- 1°-alcohol: stops at an aldehyde; 2°-alcohol: gives a ketone

\[
\begin{align*}
R\text{-}C\text{-}O\text{-}H & \quad \xrightarrow{1.} \quad \text{H}_3C\text{-}S\text{-}O\text{-}\text{dimethyl sulfoxide} \\
& \quad \xrightarrow{2.} \quad \text{N} (\text{CH}_2\text{CH}_3)_3 \\
H\text{-}C\text{-}O\text{-}H & \quad \xrightarrow{\text{oxalyl chloride}} \\
R\text{-}C\text{-}O\text{-}H
\end{align*}
\]

Mechanism:

This is the species in the solution after step 1.

\[
\begin{align*}
\text{H}_3C\text{-}S\text{-}O\text{-}\text{dimethyl sulfoxide} & \quad \xrightarrow{\text{H}_3C\text{-}S\text{-}O\text{Cl}} \\
& \quad \xrightarrow{\text{N} (\text{CH}_2\text{CH}_3)_3} \\
\text{Oxidation step!} & \quad \text{"intramolecular process"} \\
& \quad \xrightarrow{\text{H}_3C\text{-}S\text{-}O\text{Cl}} \\
\text{Note:} & \quad 1. \quad \text{H}_3C\text{-}S\text{-}O\text{Cl} \\
& \quad 2. \quad \text{N} (\text{CH}_2\text{CH}_3)_3 \\
\end{align*}
\]
IV. Non chromium-based Oxidation Reactions: “greener” methods (continued)

ii) Sodium hypochlorite (NaOCl): Bleach

Usually under acidic conditions (e.g., in acetic acid); HOCl (hypochlorous acid) is the actual oxidant. As HOCl is not stable, it has to be generated in situ in the reaction medium.

![Reaction mechanism diagram]

V. Reactions of alcohols: Direct conversion of alcohols to alkyl halides

With SOCl₂ (thionyl chloride) or PBr₃ (phosphorus tribromide)

Mechanism for an alcohol to the chloride with SOCl₂/pyridine

![Mechanism diagram]

*Alternatively, \( \text{SOCl}_2 \) that can be formed from SOCl₂ and pyridine may be the reagent that puts S(=O)Cl onto the OH group.

*Similar reactions and mechanisms for the formation of bromides from alcohols with PBr₃.
VI. Ethers (R – O – R’)

1. Synthesis

a. Williamson synthesis

\[ \text{R}^-\text{O}^\ominus + \text{R}'^\oplus \xrightarrow{\text{base}} \text{R}^-\text{O}^-\text{R}' + \text{X}^\ominus \]

**S_N2 reaction**

R’ - X: alkyl halides (usually bromide and iodide, sometimes chloride) or tosylates

R’: usually primary; methyl, allyl (CH=CH-CH-), benzyl (PhCH-).  

\[ \text{R}^-\text{O}^-\text{I} \xrightarrow{\text{NaH} (1 \text{ mol equiv})} \text{R}^-\text{O}^-\text{CH}_2\text{CH}_3 + \text{H}_2 \xrightarrow{\text{(gas)}} + \text{Na}^+ \text{I}^- \]

**Mechanism:**

Sodium alkoxides can also be prepared by the treatment of alcohols with Na.

\[ \text{R}^\ominus \text{O}^-\text{H} + \text{Na} \rightarrow \text{R}^-\text{O}^-\text{Na}^+ + \frac{1}{2} \text{H}_2 \]

**MO interpretation:**

- **σ** bonding orbital
- **σ** anti-bonding orbital

**2°-alkyl halides and tosylates** are occasionally used in the Williamson synthesis, but elimination (E2) competes or dominates, and yields of the ether products are often quite low.  

**3°-alkyl halides:** exclusive elimination (E2).

\[ \text{Na}^+ \text{O}^-\text{H} \xrightarrow{\text{E2}} \text{CH}_3\text{C}^\ominus \text{H}_2\text{C}^\ominus \text{CH}_3 + \text{H}_2 \]

**Not formed!**

Then, how do you make this t-butyl n-propyl ether?

**Phenyl ethers:** More acidic than alcohol OHs. A milder base such as NaOH can be used to generate phenoxides (PhO\ominus).

\[ \text{PhO}^\ominus \xrightarrow{1. \text{NaOH}} \xrightarrow{2. \text{PhNO}_2} \]

80%
VI 2. Cleavage of ethers
In general, difficult to cleave ether C-O bonds (for exceptions, see VII). Can be cleaved by heating with HI (more common) or HBr. Need a strong Brønsted or Lewis acid and a strong nucleophile.

Usually, methyl ether C-O and benzyl ether C-O are those that can be cleaved. Modern methods for cleaving ethers include the use of BBr and AlCl₃ + HSCH₂CH₃.

\[
\text{Cyclic ethers: by an intramolecular } S_n^2 \text{ reaction of an alkoxide}
\]

\[
\begin{align*}
\text{Cl} & \quad \text{NaOH} \\
\text{H} & \quad \text{H}_2\text{O} \\
\text{Na} & \quad \text{S}_n^2 \\
\text{95%} & \quad \text{NaCl}
\end{align*}
\]

• 5- and 6-membered cyclic ether formation: fast
• In general, intramolecular reactions are faster than the corresponding intermolecular (bi-molecular) reactions.
• An intermolecular $S_n^2$ reaction of an alkoxide or hydroxide ion with an alkyl chloride is slow.

Geometrical and stereochemical effects on cyclic ether formation:
Which of the two diastereomeric hydroxy-bromide could form its cyclic ether derivative?

- The alkoxide from A can't undergo an $S_n^2$ reaction with the C-Br.
- $S_n^2$ reaction possible!
VIII. Epoxides (or Oxiranes): Special kind of cyclic ethers (3-membered ethers)

Epoxides (or oxiranes):

\[
\begin{align*}
\text{The ring is strained:} \\
\text{more polarized C-O bonds} & \implies \text{unstable and reactive!}
\end{align*}
\]

nthers:

\[
\begin{align*}
\text{H}_3C & \quad \text{CH}_3 \\
\text{112°} & \quad \text{stable}
\end{align*}
\]

a. Formation:

1. Epoxidation of alkenes with peroxyacid (e.g., \textit{m}-chloroperoxybenzoic acid; see Ch. 8)
2. From halohydrin with a base

\[
\begin{align*}
\text{C-O and C-Cl} & \quad \text{bonds are not} \\
& \quad \text{oriented for an S}_2\text{N process to take place.}
\end{align*}
\]

b. Ring-opening reactions of epoxides: \textit{Epoxides are highly strained and easily undergo ring-opening reactions under both acidic and basic conditions.}

**Acidic conditions:** ring-opening reactions proceed rapidly at low temperatures (usually at room temp or below); elongated C-O bonds of the protonated, highly strained epoxides believed to be the origin of high reactivity.

**Acyclic epoxides**

\[
\begin{align*}
\text{H}_3C & \quad \text{H} & \quad \text{Br} & \quad \text{H}_3C & \quad \text{H} & \quad \text{Br} \\
\text{H}_3C & \quad \text{H} & \quad \text{Br} & \quad \text{H}_3C & \quad \text{H} & \quad \text{Br} \\
\text{H}_3C & \quad \text{H} & \quad \text{Br} & \quad \text{H}_3C & \quad \text{H} & \quad \text{Br}
\end{align*}
\]

\[
\begin{align*}
\text{(2S,3S)} & \quad \text{racemic mixture} & \quad \text{(2R,3R)} \\
\text{S}_2\text{N2-like} & \quad \text{inversion of} \\
& \quad \text{stereochemistry here!}
\end{align*}
\]

**Cyclic-fused epoxides**

\[
\begin{align*}
\text{H}_3C & \quad \text{H} & \quad \text{Br} & \quad \text{H}_3C & \quad \text{H} & \quad \text{Br} \\
\text{H}_3C & \quad \text{H} & \quad \text{Br} & \quad \text{H}_3C & \quad \text{H} & \quad \text{Br} \\
\text{H}_3C & \quad \text{H} & \quad \text{Br} & \quad \text{H}_3C & \quad \text{H} & \quad \text{Br}
\end{align*}
\]

\[
\begin{align*}
\text{trans-product} \\
+ \text{enantiomer}
\end{align*}
\]

 inversion of stereochemistry

or simply :B
Stereochemical/regiochemical issues:

Mechanistic interpretation on the stereochemical/regiochemical outcome under acidic conditions:

In the transition state for the attack of H₂O (H₂O¹⁸ in this case), the nucleophile attacks preferentially the carbon center that can better stabilize a positive character (i.e., the more substituted carbon).
Epoxide-ring opening under basic conditions
A straight S_N2 process at the less-substituted carbon with a **stereochemical inversion**.

Summary of epoxide-ring opening reactions:

**Acidic conditions:** S_N2 like in term of the stereochemical inversion, but at the more substituted C.
  \[ \Rightarrow \text{Ring opening at the more substituted C with the inversion of stereochemistry.} \]

**Basic conditions:** pure S_N2
  \[ \Rightarrow \text{Ring opening at the less substituted C with the inversion of stereochemistry.} \]

1,2-Diaxial opening of cyclohexene oxides

1) \[ \text{H}_3\text{O}^+ \]

2) Because these are cis-fused decalins, these diaxial diols can't invert conformations to become diequatorial diols.
The above examples are quite similar to the bromination reaction of cyclohexene systems.

Problems: Show the structure of the expected major product for each of the following reactions.

(1)

(2)