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></td>
<td>CH₃OH</td>
<td>methanol</td>
<td>methyl alcohol</td>
</tr>
<tr>
<td></td>
<td>CH₃CH₂OH</td>
<td>ethanol</td>
<td>ethyl alcohol</td>
</tr>
<tr>
<td></td>
<td>CH₃CH₂CH₂OH</td>
<td>1-propanol</td>
<td>n-propyl alcohol</td>
</tr>
<tr>
<td></td>
<td>H₃C-C(CH₂OH)</td>
<td>2-methyl-1-propanol</td>
<td>isobutyl alcohol</td>
</tr>
<tr>
<td></td>
<td>H₃C-C(CH₂OH)</td>
<td>2,2-dimethyl-1-propanol</td>
<td>neopentyl alcohol</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary alcohols (2°-alcohols)</th>
<th>IUPAC names</th>
<th>Common names</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H₃C-C-OH</td>
<td>2-propanol</td>
</tr>
<tr>
<td></td>
<td>H₃C-C-OH</td>
<td>2-butanol</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tertiary alcohols (3°-alcohols)</th>
<th>IUPAC names</th>
<th>Common names</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H₃C-C-OH</td>
<td>2-methyl-2-propanol</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phenols (Ph-OH)</th>
<th>pKa ~10-12</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃CH₂O-CH₂CH₃</td>
<td>diethyl ether</td>
</tr>
<tr>
<td>Ph-O-CH=CH₂</td>
<td>phenyl vinyl ether</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ethers (R-O-R')</th>
<th>IUPAC names</th>
<th>Common names</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃CH₂O-CH₂CH₃</td>
<td>methoxy</td>
<td></td>
</tr>
<tr>
<td>CH₃CH₂O-CH₂CH₃</td>
<td>ethoxy</td>
<td></td>
</tr>
<tr>
<td>PhO-CH=CH₂</td>
<td>phenoxy</td>
<td></td>
</tr>
</tbody>
</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)

\[
\begin{array}{|c|c|c|c|}
\hline
\text{atom} & \text{charge} & \text{oxidation number} \\
\hline
\text{H} & +1 & -1 \\
\text{C} & +2 & 0 \\
\text{O} & -2 & 0 \\
\hline
\end{array}
\]

Therefore,

- The oxidation number of this C is \(-4\).

Other examples of oxidation numbers:

1. 

\[
\begin{align*}
+1 & \quad \text{"reducing agent"} & +1 & \quad \text{"oxidizing agent"} \\
\text{H} & \quad \text{H} & \quad \text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} & \quad \text{H} & \quad \text{H} \\
\end{align*}
\]

2. 

\[
\begin{align*}
0 & \quad \text{Zn} & + & \quad 0 & \quad \text{Br} & - & \quad \text{Br} \\
& & & & & & \quad \text{Br} & \quad \text{Zn} & - & \quad \text{Br} \\
& & & & & & \quad \text{Br} & \quad \text{Zn} & - & \quad \text{Br} \\
\end{align*}
\]

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:

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\end{align*}
\]

For N
\[
3 \times (-1) \text{ from 3 carbon atoms} = -3 \\
+1 \text{ from oxygen atom} = +1 \\
+1 \text{ from the charge} = +1 \\
\]
overall: \(-1\)

For O
\[
-1 \text{ from nitrogen atom} = -1 \\
-1 \text{ from the charge} = -1 \\
\]
overall: \(-2\)

Hydrocarbon oxidation-reduction spectrum:

\[
\begin{align*}
\text{methane} & \quad \text{methanol} & \quad \text{formaldehyde (methanal)} & \quad \text{formic acid (methanoic acid)} & \quad \text{carbonic acid} \\
\text{"reduction" (hydrogenation)} & \quad \text{"oxidation" (oxygen insertion)} & \quad \text{"oxidation" (also: dehydrogenation)} \\
\text{increasing \%O; decreasing \%H} & \quad \text{"oxidation"} & \quad \text{"reduction"} \\
\text{decreasing \%O; increasing \%H} & \quad \text{"oxidation"} & \quad \text{"reduction"} \\
\end{align*}
\]

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

1°-alcohol

\[ \text{RCH}_2\text{OH} \xrightarrow{[\text{ox}]} \text{R-CHO} \xrightarrow{[\text{ox}]} \text{RCOOH} \]

2°-alcohol

\[ \text{R'CCH} \xrightarrow{[\text{ox}]} \text{R'CCHO} \]

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

\[
\begin{align*}
\text{CrO}_3 & \equiv \begin{array}{c}
\text{CrO}_3
\end{array} \\
\text{chromium trioxide (chromic anhydride)}
\end{align*}
\]

"to be oxidized"  

"to be reduced"

\[ \text{RCH}_2\text{OH} + \text{CrO}_3 \xrightarrow{\text{oxidizing agent}} \text{R-CO}_2\text{H} + \text{Cr}^{3+} \]

Balancing the oxidation-reduction reaction

\[
\begin{align*}
3 \times [ R - \text{CH}_2\text{OH} & \equiv R-\text{CO}_2\text{H} + 2\text{H}^+ + 2\text{e}^- ] \quad ("\text{two-electron" oxidation}) \\
2 \times [ \text{Cr}^{6+} + 3\text{e}^- & \equiv \text{Cr}^{3+} ] \\
\text{Overall,} \\
3 \text{ R - CH}_2\text{OH} + 2 \text{Cr}^{6+} & \equiv 3 \text{ R-CO}_2\text{H} + 6\text{H}^+ + 2\text{Cr}^{3+}
\end{align*}
\]

"stoichiometry"
Mechanism for the oxidation with PCC:

1a Chromic acid \[ \text{[CrO}_3^- + \text{H}_2\text{O} \rightarrow \text{H}_2\text{CrO}_4] \] (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. Anhydrous \( \text{Cr}^{+6} \)

- \( \text{CrO}_3 \), pyridine
- pyridinium chlorochromate (PCC): one of the most widely used oxidants!
- pyridinium dichromate (PDC) \( \left[(\text{pyH})_2\text{Cr}_2\text{O}_7\right]^2 \)

oxidation reactions of alcohols using these reagents are carried out in 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:

\[ \text{RCH}_2\text{OH} + \text{CrO}_3 + \text{H}_2\text{SO}_4 + \text{H}_2\text{O} \rightarrow \text{RC} = \text{O} + \text{Cr}^{3+} + 4 \text{H}^+ \]

Often, an ester \(\text{R}-(=\text{O})-\text{OR}\) is a by-product.

Mechanism:
2. Non chromium-based Oxidation Reactions: “greener” methods
   i) Swern oxidation: • usually using dichloromethane (CHCl₃) as the solvent
      • anhydrous (i.e., no water present!), non-acidic conditions
      • 1°-alcohol: stops at an aldehyde; 2°-alcohol: gives a ketone

   Mechanism:

   This is the species in the solution after step 1.

   Note:
   1. \[ \text{H}_3\text{C}=\text{SO}^- \text{CH}_3 \]
   2. \[ :\text{N(CH}_2\text{CH}_3)_3 \]

   Oxidation step!
   "intramolecular process"
IV 2. Non chromium-based Oxidation Reactions: “greener” methods

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](image)

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

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

1. Synthesis

a. Williamson synthesis

\[ \text{S}_\text{N}2 \text{ reaction} \quad \text{R'} - \text{X: alkyl} \text{ halides (usually bromide and iodide, sometimes chloride) or tosylates} \]

\[ \text{R': usually primary; methyl, allyl (CH}_2=\text{CH-CH}_2, \text{ benzyl (PhCH}_2). \]

\[ \text{NaH (1 mol equiv)} \quad \text{I-CH}_2\text{CH}_3 \]

(excess; typically, 1.5 mol equiv)

Mechanism:

\[ \text{H-H (gas)} \quad \text{sodium alkoxide} \]

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

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

Mechanism:

\[ \text{Na} \rightarrow \text{Na} + \text{e}^- \quad \text{anion radical} \]

\[ \text{R-}O\text{-H} + \text{Na} \rightarrow \left[ \text{R-}O\text{-H} \right]^\oplus \text{Na} \]

\[ \text{R-}O:\text{Na}^\oplus + \text{H}^\bullet \]

\[ \text{H}^\bullet + \text{H}^\bullet \rightarrow \text{H}_2 \]

**MO interpretation:**

\[ \sigma^* \quad \text{anti-bonding orbital} \]

\[ \sigma \quad \text{bonding orbital} \]

\[ \text{O-H bond of the anion radical} \]

3 electrons in the O-H bond!

**2º-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. **3º-alkyl halides:** exclusive elimination (E2).

\[ \text{Na}^\oplus \quad \text{H} \quad \text{CH}_3 \quad \text{C} \quad \text{C} \quad \text{CH}_3 \]

(E2!)

\[ \rightarrow \text{OH} + \text{H}_2\text{C}≡\text{CCH}_3 + \text{NaBr} \]

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\text{=}\text{O}).

\[ \text{O-H} \quad \text{1. NaOH} \quad \text{2. } \text{I} \rightarrow \text{PhO}^\ominus \]

80%
VI 2. Cleavage of ethers, pp
In general, difficult to cleave ether C-O bonds (for exceptions, see VIII, pp 10-13).
Can be cleaved by heating with HI (more common) or HBr.
Need a strong Brönsted 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 BBr₃ and AlCl₃ + HSCH₂CH₃.

VII. Intramolecular ether formation
Cyclic ethers: by an intramolecular S_N2 reaction of an alkoxide

\[
\begin{align*}
\text{Cl} & \rightarrow \text{NaOH} \\
\text{H}_2\text{O} & \rightarrow \text{SN2} \\
\text{95%} & + \text{NaCl}
\end{align*}
\]

• 5- and 6-membered cyclic ether formation: fast
• In general, intramolecular reactions are faster than the corresponding intermolecular (bi-molecular) reactions.
• An intermolecular S_N2 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_N2 reaction with the C-Br.

No cyclic ether formation
VIII. Epoxides (or Oxiranes): Special kind of cyclic ethers (3-membered ethers)

Epoxides (or oxiranes):
- The ring is strained; more polarized C-O bonds \( \Rightarrow \) unstable and reactive!

Ethers:
- \( \text{H}_3\text{C} \text{O} \text{C} \text{H}_3 \) (112°) stable

a. Formation:
1. Epoxidation of alkenes with peroxyacids (e.g., \( m \)-chloroperoxybenzoic acid; see Ch. 8)
2. From halohydrin with a base

\[
\begin{align*}
\text{O-H} & \xrightarrow{\text{NaOH}} \text{O-O} \\
\text{C} & \text{H}_3 \text{Cl} & \text{Cl} & \text{Cl} \\
\text{25 °C, 1 hr} & \equiv & \equiv & \equiv \\
\text{H}_2\text{O} & \text{more favored/stable conformer} & \text{C-O and C-Cl} & \text{70%}
\end{align*}
\]

C-O and C-Cl bonds are not oriented for an \( S_N2 \) process to take place.

b. Ring-opening reactions of epoxides: 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

Cyclic-fused epoxides
Note: The mechanism for the ring-opening of epoxides under acidic conditions is quite similar to that of bromination of alkenes.

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\textsubscript{N}2 process at the less-substituted carbon with a 
**stereochemical inversion.**

\[ \text{H}_3\text{C} \cdots \text{O}^\cdot \cdots \text{H} \xrightarrow{\text{H}_3\text{CCH}_2\text{O}^\cdot \text{Na}^\cdot} \text{H}_3\text{C} \cdots \text{O}^\cdot \cdots \text{H} \xrightarrow{\text{H}_3\text{CCH}_2\text{OH}} \]

*less-substituted C; S\textsubscript{N}2 reaction here!*

\[ \begin{align*}
\text{Na}^\cdot & : \text{O}^\cdot \cdots \text{H} \\
\text{H}_3\text{C} \cdots & : \text{O}^\cdot \cdots \text{H} \\
\text{H}_3\text{C} & : \text{OCH}_2\text{CH}_3 \\
\text{H}_3\text{C} & : \text{OCH}_2\text{CH}_3
\end{align*} \]


**Summary of epoxide-ring opening reactions:**

*Acidic conditions:* S\textsubscript{N}2 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\textsubscript{N}2

\[ \Rightarrow \text{Ring opening at the less substituted C with the inversion of stereochemistry.} \]

1,2-Diaxial opening of cyclohexene oxides

1) \[ \begin{align*}
\text{H}_3\text{O}^\cdot & \xrightarrow{\text{H}_3\text{CCH}_2\text{O}^\cdot \text{Na}^\cdot} \text{H}_3\text{CCH}_2\text{OH} \\
\text{H}_3\text{C} & \cdots \text{O}^\cdot \cdots \text{H} \\
\text{H}_3\text{C} & : \text{OCH}_2\text{CH}_3 \\
\text{H}_3\text{C} & : \text{OCH}_2\text{CH}_3
\end{align*} \]

*only 1,2-diaxial transition state feasible for an S\textsubscript{N}2 like process to occur*

2) \[ \begin{align*}
\text{H}_3\text{CCH}_2\text{O}^\cdot \text{Na}^\cdot & \xrightarrow{\text{H}_3\text{CCH}_2\text{OH}} \text{H}_3\text{CCH}_2\text{OH} \\
\text{H}_3\text{C} & \cdots \text{O}^\cdot \cdots \text{H} \\
\text{H}_3\text{C} & : \text{OCH}_2\text{CH}_3 \\
\text{H}_3\text{C} & : \text{OCH}_2\text{CH}_3
\end{align*} \]

*Because these are trans-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)