Reactions of Alcohols

Alcohols are versatile organic compounds since they undergo a wide variety of transformations – the majority of which are either oxidation or reduction type reactions.

Normally: Oxidation is a loss of electrons; Reduction is a gain of electrons.

But in organic terms:

Oxidation:
- loss of H₂;
- addition of O or O₂;
- addition of X₂ (halogens).

Reduction:
- addition of H₂ or H⁻;
- loss of O or O₂;
- loss of X₂.

Neither an oxidation nor reduction:
Addition or loss of H⁺, H₂O, HX.
Oxidation of Alcohols
Primary and secondary alcohols are easily oxidized by a variety of reagents.

Secondary Alcohols
The most common reagent used for oxidation of secondary alcohols to ketones is chromic acid, H₂CrO₄.

\[
\text{OH} \\
\text{R—CH—R'} \\
\text{secondary alcohol} \\
\xrightarrow{\text{Na₂Cr₂O₇/H₂SO₄}} \\
\text{R—C—R'} \\
\text{ketone}
\]

\[\text{Example}\]
\[
\text{H} \\
\text{C₆H₈OH} \\
\text{cyclohexanol} \\
\xrightarrow{\text{Na₂Cr₂O₇/H₂SO₄}} \\
\text{C₆H₈O} \\
\text{cyclohexanone (90%)}
\]

Chromic acid is produced \textit{in situ} by reaction of sodium dichromate, sulfuric acid and water.

\[\text{Na₂Cr₂O₇ + H₂O + 2H₂SO₄} \rightarrow 2 \text{H₂CrO₄} + 2 \text{NaHSO₄}\]
Mechanism of oxidation

The alcohol and chromic acid produce a chromate ester, which then reductively eliminates the Cr species. The Cr is reduced (VI $\rightarrow$ IV), the alcohol is oxidized.

Oxidation of Primary Alcohols
Primary alcohols are easily oxidized just like secondary alcohols, and the INITIAL product of oxidation is an aldehyde.
However, the *aldehyde* can also be easily oxidized to an *acid*, and this ‘over-oxidation’ is a practical problem.

E.g.

\[
\begin{array}{c}
\text{CH}_2\text{OH} \quad \text{Na}_2\text{Cr}_2\text{O}_7, \text{H}_2\text{SO}_4 \quad \rightarrow \\
\text{CO}_2\text{H}
\end{array}
\]

A common reagent that selectively oxidizes a primary alcohol to an aldehyde (*and no further*) is pyridinium chlorochromate, PCC.

\[
\text{N: CrO}_3, \text{HCl}
\]

\[(\text{PCC})\]

E.g.

\[
\begin{array}{c}
\text{H} \quad \text{OH} \quad \text{PCC} \quad \rightarrow \\
\text{aldehyde}
\end{array}
\]

Tertiary Alcohols

These are resistant to oxidation because they have no hydrogen atoms attached to the oxygen bearing carbon (*carbinol* carbon).
Other Oxidizing Reagents
Potassium permanganate is a cheaper but stronger oxidizing agent, and conditions must be controlled carefully.

\[
\text{OH} \quad \xrightarrow{\text{KMnO}_4, \text{base}} \quad \text{CO}
\]

Thermal dehydrogenation is the cheapest method of oxidation but the high temperatures involved limit the applicability of this method.

\[
\text{H} \quad \xrightarrow{\text{CuO, 300}^\circ\text{C}} \quad \text{CO}
\]

Reduction of Alcohols
Normally an alcohol \textit{cannot} be directly reduced to an alkane \textit{in one step}.

\[
\text{H} \quad \xrightarrow{\text{LiAlH}_4} \quad 
\]

The –OH group is a poor leaving group so hydride displacement is not a good option – however the hydroxyl group is easily converted into other groups that are superior leaving groups, and allow reactions to proceed.
One such conversion involves tosyl chloride, and the formation of a tosylate. These compounds undergo substitution and elimination very easily, often more reactive than alkyl halides.

\[
\begin{align*}
\text{OH} & \quad \text{TsCl, pyridine} & \quad \text{OTs} & \quad \text{Nuc}^- \\
\text{C} & \quad (\text{substitution}) & \quad \text{C} & \quad + & \quad \text{OTs} \\
\end{align*}
\]

or elimination:

\[
\begin{align*}
\text{OTs} & \quad \text{H} & \quad \text{C} = \text{C} & \quad + & \quad \text{B} = \text{H} & \quad + & \quad \text{OTs} \\
\text{C} & \quad \text{(elimination)} & \quad \text{B}^- \\
\end{align*}
\]

Cyclohexanol will not reduce with LiAlH\textsubscript{4}, but the corresponding tosylate reduces to cyclohexane very easily.

\[
\begin{align*}
\text{H} & \quad \text{Ts-Cl, py} & \quad \text{H} & \quad \text{O-S} & \quad \text{CH}_3 & \quad \text{LiAlH}_4 & \quad \text{H} \\
\text{C} & \quad \text{Tosyl-} & \quad \text{cyclohexyl tosylate} \\
\end{align*}
\]
Tosylate Esters

Tosylate esters (tosylates) are typically formed from alcohols with reaction with Ts-Cl and pyridine (py).

Tosylate groups undergo a variety of $S_N2$ reactions.

The tosylate is such a good leaving group because it is a stable anion.
The tosylate is such a good leaving group because it is a stable anion.

\[
\text{tosylate ion} = \left[ \begin{array}{c} \text{resonance-stabilized anion} \\ \end{array} \right]
\]

Common S_N2 transformations of Tosylates:

- \( \text{R}^\text{-} \text{OTs} \) → \( \text{R}^\text{-} \text{OH} \)
- \( \text{R}^\text{-} \text{CN} \) → \( \text{R}^\text{-} \text{CN} \)
- \( \text{Br}^- \) → \( \text{R}^\text{-} \text{Br} \)
- \( \text{R}^\text{'} \text{O}^- \) → \( \text{R}^\text{'} \text{OR}^\text{'} \)
- \( \text{NH}_3 \) → \( \text{R}^- \text{NH}_2 \)
- \( \text{LiAlH}_4 \) → \( \text{R}^- \text{H} \)
Alcohols and Hydrohalic Acids
Alkyl halides can also be formed by reaction of alcohols with H-X acids.

\[ \text{R-OH} + \text{H-Br} \rightarrow \text{R-Br} + \text{H}_2\text{O} \]

In acidic media, the alcohol is in equilibrium with its protonated form.

The –OH is a *poor* leaving group, but –OH\(^2+\) is an *excellent* leaving group, and once the -OH is protonated, the molecule may take part in a variety of substitution and/or elimination reactions.

The nature of R determines whether the reactions proceed via \(S_N1\) or \(S_N2\) mechanisms.

If R is primary alkyl \(\rightarrow S_N2\)

If R is bulky tertiary alkyl \(\rightarrow S_N1\).
SN2:

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{C} = \text{O} - \text{H} \quad \xrightarrow{\text{H} - \text{Br}^+} \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{C} = \text{O}^+ - \text{H} \quad \xrightarrow{\text{Br}^-} \quad \text{Br}^+ - \text{C} = \text{H} \quad + \quad \text{H}_2\text{O}
\]

butan-1-ol

1-bromobutane

SN1:

\[
\text{H}_3\text{C} - \text{C} = \text{O} - \text{H} \quad \xrightarrow{\text{H} - \text{Br}^+} \quad \text{H}_3\text{C} - \text{C} = \text{O}^+ - \text{H} \quad \xrightarrow{\text{Br}^-} \quad \text{H}_3\text{C} - \text{C} = \text{H}^+ \quad + \quad \text{Br}^- \quad + \quad \text{H}_2\text{O}
\]

\[
\downarrow
\]

\[
\text{H}_3\text{C} - \text{C} = \text{Br}^+ \quad + \quad \text{H}_2\text{O}
\]
Hydrochloric Acid
H-Cl reacts in the same way, although often Zinc (II) chloride (a Lewis acid) is added to help compensate for the lower nucleophilicity of chloride ion.
The mixture of HCl and ZnCl₂ is called the *Lucas Reagent*.

Secondary and tertiary alcohols react via the Sₙ1 mechanism with the Lucas reagent.

The ZnCl₂ coordinates to the hydroxyl oxygen, and this generates a far *superior* leaving group.

Primary alcohols react in a similar fashion except the free cation is not generated, and the substitution is of Sₙ2 type.
Limitations of use of H-X
1) Only works for H-Cl and H-Br
2) Low chemical yields for primary and secondary alcohols
3) Often observe competing elimination
4) Carbocations can lead to rearranged products

Phosphorous Halides
Phosphorous halides can convert alcohols to alkyl halides.

E.g.
\[
\begin{align*}
3 \text{ R-OH} + \text{PCl}_3 & \rightarrow 3 \text{ R-Cl} + \text{P(OH)}_3 \\
3 \text{ R-OH} + \text{PBr}_3 & \rightarrow 3 \text{ R-Br} + \text{P(OH)}_3 \\
\text{R-OH} + \text{PCl}_5 & \rightarrow \text{R-Cl} + \text{POCl}_3 + \text{HCl}
\end{align*}
\]

PI\textsubscript{3} has to be generated \textit{in situ} via reaction of iodine and phosphorous.

E.g.
\[
\text{CH}_3(\text{CH}_2)_{14}\text{CH}_2\text{-OH} + \text{P/I}_2 \rightarrow \text{CH}_3(\text{CH}_2)_{14}\text{CH}_2\text{-I}
\]

This type of reaction does not work well for \textit{tertiary} alcohols, and also does not lead to \textit{rearranged} products.

These observations are explained by the reaction mechanism.
**Mechanism**
The hydroxyl oxygen displaces a halide (good leaving group) from the Phosphorous.

\[ R-OH + Br^- \xrightarrow{\text{Phosphorous}} R-O^+ + H^+ + Br^- \]

The positively charged oxygen is a good leaving group.

The liberated halide performs an \( S_N2 \) type attack on the back side of the \( R \) group.

\[ R-O^+ + Br^- \xrightarrow{\text{back side}} R-Br + O-P^- \]
Thionyl Chloride
Thionyl chloride (SOCl₂) is the usual method of choice for preparing alkyl chlorides from alcohols.

\[ R-OH + SOCl_2 \rightarrow R-Cl + SO_2 + HCl \]

The mechanism is interesting:
The hydroxyl oxygen attacks the electrophilic Sulfur, and from the tetrahedral intermediate a chloride is ejected.

The chlorosulfite ester rearranges with the breaking of the C-O and S-Cl bonds and the formation of the R-Cl bond and a new S-O bond.

When R is secondary or tertiary, the ionization to a cation probably precedes the Chloride attack, whereas if R is primary the process is probably concerted (Bond breaking and forming at the same time).
Summary of Best Alcohol to Alkyl Halide Transformations

<table>
<thead>
<tr>
<th>Class</th>
<th>Chloride</th>
<th>Bromide</th>
<th>Iodide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>SOCl₂</td>
<td>PBr₃</td>
<td>P/I₂</td>
</tr>
<tr>
<td>Secondary</td>
<td>SOCl₂</td>
<td>PBr₃</td>
<td>P/I₂</td>
</tr>
<tr>
<td>Tertiary</td>
<td>HCl</td>
<td>HBr</td>
<td>HI</td>
</tr>
</tbody>
</table>

Dehydration Reactions of Alcohols
Dehydration of alcohols requires an acidic catalyst to convert the hydroxyl into a good leaving group – this is an equilibrium reaction.

![Chemical Reaction Diagram](image)

It is possible to force the equilibrium to the right (alkene) by removing one or both of the products. This is normally achieved either by distillation (alkene is lower boiling than alkyl halide) or the addition of a dehydrating agent.

Alcohol dehydration usually occurs via the E1 mechanism.
Alcohol dehydration usually occurs via the E1 mechanism.

The first step is the exothermic protonation of the hydroxyl, followed by the slow, endothermic, rate determining ionization to generate the cation. The fast deprotonation is exothermic and produces the alkene.

Since the RDS is the formation of the carbocation, the ease of formation dictates the reaction rates of $3^\circ > 2^\circ > 1^\circ$. 
Rearrangement reactions are common since a free *carbocation* is involved.

**E.g.**

\[
\text{HO-CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 \rightarrow \text{CH}_3\text{CH}=\text{CHCH}_3 + \text{CH}_2=\text{CHCH}_2\text{CH}_3
\]

After butan-1-ol is protonated, the ionization is accompanied by a *hydride shift* to produce a secondary carbocation. There is a choice of protons to be eliminated, and Saytzeff’s rule applies.

**Ch11 Reacns of Alcohols (landscape).docx**

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Bimolecular Dehydration to form Ethers
In certain cases, a protonated primary alcohol may be attacked by another molecule of alcohol. The net result is a dehydration and a formation of an ether.

\[
2 \text{CH}_3\text{CH}_2\text{OH} \xrightarrow{\text{H}_2\text{SO}_4, 140^\circ\text{C}} \text{CH}_3\text{CH}_2\text{O} \text{CH}_2\text{CH}_3 + \text{H}_2\text{O}
\]

Bimolecular dehydration is best used for the synthesis of symmetrical dialkyl ethers from unhindered primary alcohols.
i) Pinacol Rearrangement

\[
\begin{align*}
\text{pinacol} & \quad \xrightleftharpoons[H_2SO_4]{\text{H}_3\text{C}} \quad \text{CH}_3 \\
\text{CH}_3\text{C} & \quad \text{CH}_3 \quad \xrightarrow{\text{H}_2\text{SO}_4} \\
\text{H}_3\text{C} & \quad \text{OH} \quad \text{OH} \\
\text{H}_3\text{C} & \quad \text{CH}_3 \quad + \text{H}_2\text{O}
\end{align*}
\]

The pinacol \textit{rearrangement} is a formal dehydration.

**Mechanism**

The protonation of the hydroxyl is followed by ionization. The tertiary carbocation rearranges with a methyl shift to produce a cation with resonance. The rearranged product is deprotonated to generate the final product.
ii) Cleavage of Glycols
Periodic acid will cleave 1,2 diols to give aldehyde and ketone products.

Periodic acid will cleave 1,2 diols to give aldehyde and ketone products.

(The treatment of an alkene to syn hydroxylation followed by periodic acid cleavage is an alternative to the ozonolysis-reduction procedure described earlier).

Mechanism

The mechanism involves the formation of a cyclic periodate ester, which cleaves to generate to carbonyl groups.
Esterification of Alcohols
Usually the term *ester* means the ester of a carboxylic acid.

In general, an *acid* and *alcohol* generate an *ester* and *water*.

This is called a Fischer esterification.

Acid chlorides provide another route to producing esters.
Esters of Inorganic Acids
Just as alcohols form esters with carboxylic acids, they also form esters with inorganic acids.

\[
R{-}OH + HO-SO\overset{\text{O}}{\text{O}}-\overset{\text{O}}{\text{S}}-\overset{\text{O}}{\text{H}} \rightleftharpoons RO-SO\overset{\text{O}}{\text{O}}-\overset{\text{O}}{\text{S}}-\overset{\text{O}}{\text{H}} + H_2O
\]

p-toluenesulfonic acid
TsOH

p-toluenesulfonate ester
ROTs

\[
R{-}OH + HO-SO\overset{\text{O}}{\text{O}}-\overset{\text{O}}{\text{H}} \rightleftharpoons RO-SO\overset{\text{O}}{\text{O}}-\overset{\text{O}}{\text{H}} + H_2O
\]

sulfuric acid

alkylsulfate
(sulfate ester)

\[
R{-}OH + HO-N\overset{\text{O}}{\text{N}}-\overset{\text{O}}{\text{O}}- \rightleftharpoons RO-N\overset{\text{O}}{\text{N}}-\overset{\text{O}}{\text{O}}- + H_2O
\]
nitric acid

alkyl nitrate ester

Phosphate esters are important in nature since they link the nucleotide bases together in DNA.

\[
R{-}OH + HO-P\overset{\text{O}}{\text{O}}-\overset{\text{O}}{\text{H}} \rightleftharpoons RO-P\overset{\text{O}}{\text{O}}-\overset{\text{O}}{\text{H}} + H_2O
\]

phosphoric acid

alkylphosphate
(phosphate ester)
Reactions of Alkoxides
Alkoxide ions are produced when metals like Na or K are added to alcohols.

\[
\begin{align*}
\text{R–O–H} + \text{Na} & \rightarrow \text{R–O}^- + \text{Na}^+ + \frac{1}{2} \text{H}_2 \\
\text{R–O–H} + \text{K} & \rightarrow \text{R–O}^- + \text{K}^+ + \frac{1}{2} \text{H}_2
\end{align*}
\]

The sodium (or potassium) alkoxides are strong bases and nucleophiles.

Alkoxides can react with primary alkyl halides (or tosylates) to produce ethers.

This is the *Williamson Ether synthesis*, and it involves S_N2 displacement with back side attack of the alkoxide.

\[
\begin{align*}
\text{R–O}^- + \text{Na} & \rightarrow \text{R’–CH}_2–\text{X} \\
\rightarrow & \text{R–O–CH}_2–\text{R’} + \text{NaX}
\end{align*}
\]

Normally this reaction is limited to unhindered primary alkyl halides, otherwise elimination tends to be the preferred mode of reaction.
1) Oxidation (& Reduction & Nuc Addn.)

- Oxidation & Reduction & Nuc Addn.
- Conversion of $\text{–OH (Bad LG)}$ into $\text{Good LG}$, followed by Substn. (or Elimn.)

i) Py, TsCl; then Nuc¯

ii) $\text{H}^+$ and Nuc¯

iii) Lewis Acid and Nuc¯

iv) $\text{SOCl}_2$

v) $\text{PX}_3$

2) Conversion of $\text{–OH (Bad LG)}$ into $\text{Good LG}$, followed by Substn. (or Elimn.)

- $\text{R–OH} \rightarrow \text{R–LG} \rightarrow \text{R–Nuc}$

i) Py, Ts-Cl; then Nuc¯

ii) $\text{H}^+$ and Nuc¯

iii) Lewis Acid and Nuc¯

iv) $\text{SOCl}_2$

v) $\text{PX}_3$

3) Nucleophilic Oxygen reactions ($\text{Oxygen retained in product}$)

- Strong $\text{E}^+$

- $\text{RO–H} \rightarrow \text{RO–E}$

- Weak $\text{E}^+$

- Base

- $\text{RO}$

i) Bimolecular Dehydration

ii) Williamson Ether synth.

iii) Esterification