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Alcohol , Oxidation and Toxicity to Human

5th lecture in Medical Chemistry
Faculty of Medicine
University of Diyala

by
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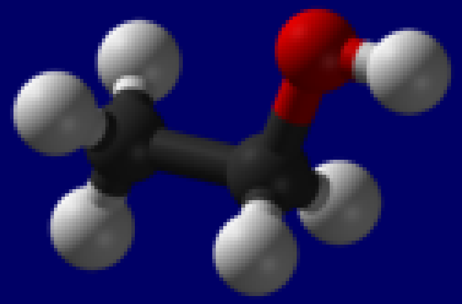
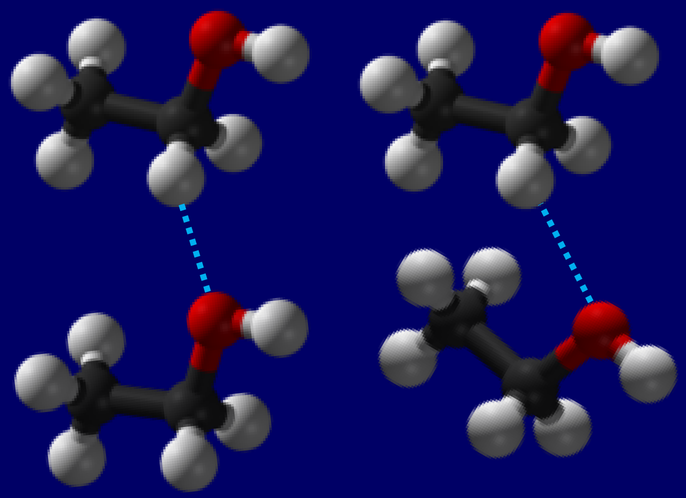
Alcohols: Structure and Physical Properties

- An organic compound containing a hydroxyl group attached to an alkyl group
- Alcohols have the general formula R-OH
- Hydroxyl group is very polar.
- Hydrogen bonds can form readily.
- Alcohols have abnormally high boiling points. relative to their molecular weights due to their ability to hydrogen bond





Solubility

- Low molecular weight alcohols (up to 5-6 carbons) are soluble in water (very polar)

CH_3CH_2OH very soluble

CH_3OCH_3 barely soluble

$CH_3CH_2CH_2CH_2OH$ 7g per 100

$HOCH_2CH_2CH_2CH_2OH$ is very soluble (two OH groups)

- As molecular weight increases, alcohols become insoluble in water still polar but, the ratio of hydroxyl groups to carbons in the chain determines solubility.

- Diols and triols are more soluble than those with only a single hydroxyl group

Alcohols: Nomenclature

IUPAC: based on the longest chain containing the OH carbon

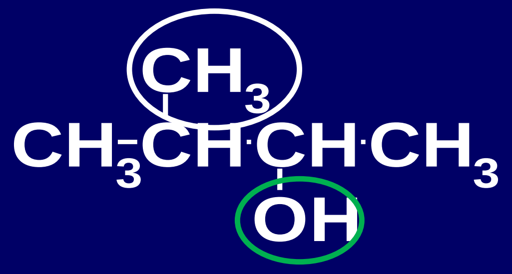
The -*e* of the alkane name is replaced with -*ol*

The chain is numbered from the end giving the -OH carbon the lower number

The name is prefixed with the number indicating the position of the OH group

For cyclic alcohols, the OH is at C-1

Ex.



1. Name the parent compound – 4 carbons = butane
2. Replace the –e with –ol = butanol
3. Number the parent chain to minimize number of carbon with the –OH group = number from right to left

3-methyl-2-butanol

1. Identify, name, and number all substituents = methyl on C-3

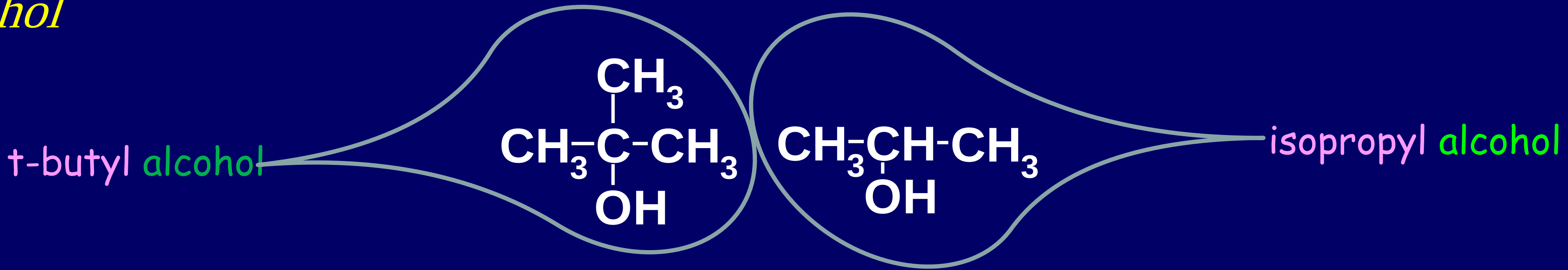
3-methylcyclohexanol

OH must be at C-1

1. Name the parent compound – 6 carbon ring = cyclohexane
2. Replace the –e with –ol = cyclohexanol
3. Number the ring to minimize number of carbon with the –OH group = number counterclockwise
4. Identify, name, and number all substituents = methyl on C-3

Common Names of Alcohols

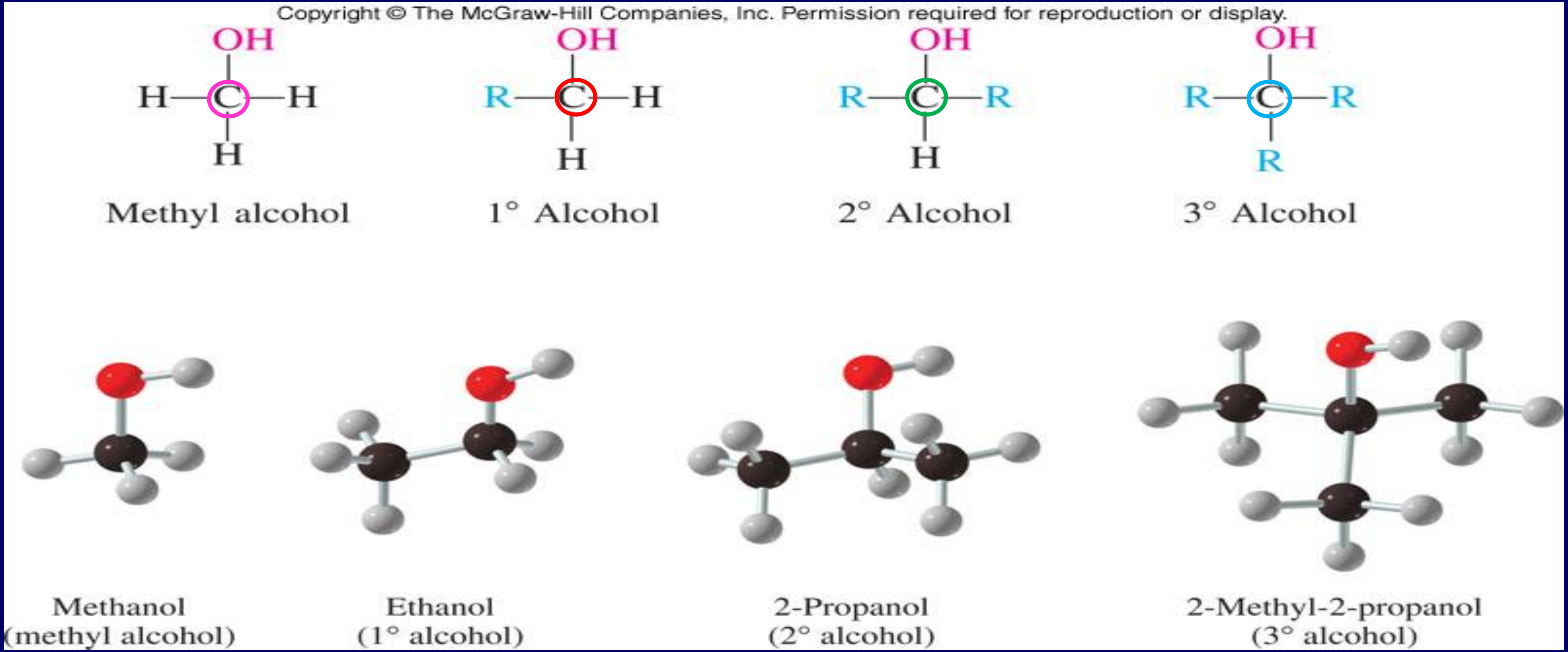
The common names for alcohols consist of the alkyl group name, a space, and the word *alcohol*



Classification of Alcohols

Alcohols, depending on the number of alkyl groups attached to the carbinol carbon, are classified as Primary , Secondary and Tertiary

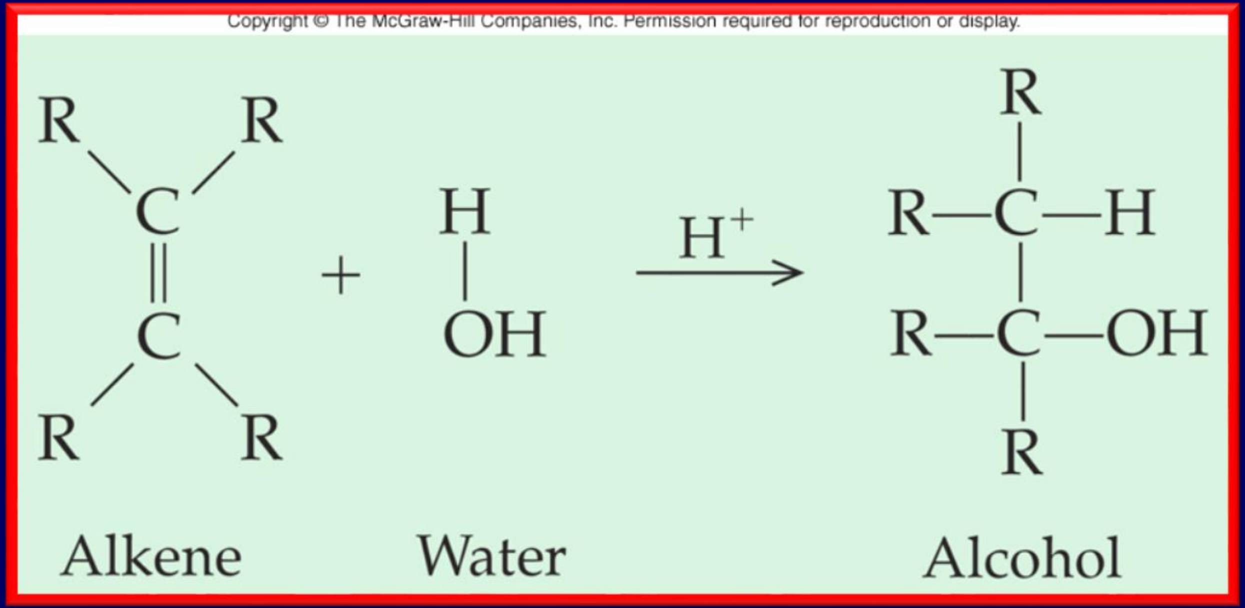
Carbinol carbon is the carbon bearing the hydroxyl group



Preparation of Alcohols

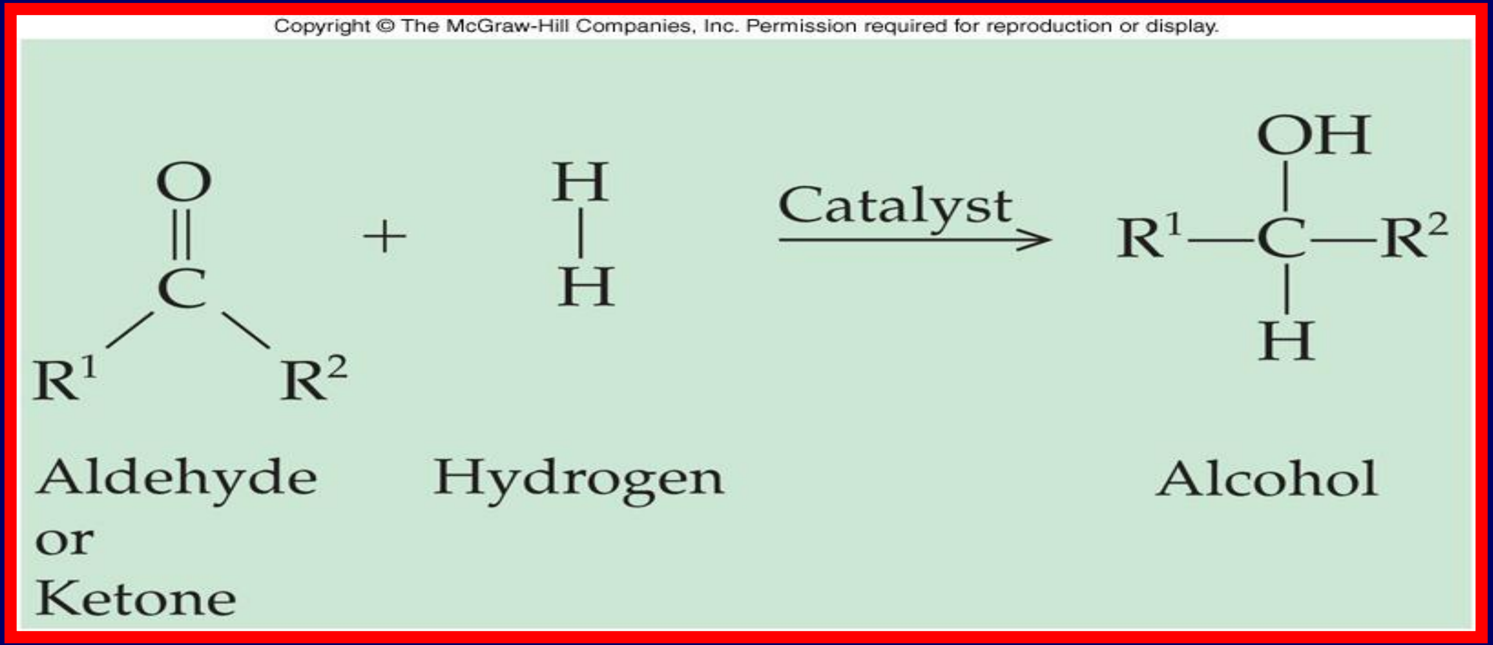
1. Hydration

- Addition of water to the carbon-carbon double bond of an alkene produces an alcohol
- A type of addition reaction called ***hydration***
- Requires a trace of acid as a catalyst



2. Hydrogenation (reduction)

Addition of water to the carbon-oxygen double bond of an aldehyde or ketone produces an alcohol
A type of addition reaction
Also considered a reduction reaction
Requires Pt, Pd, or Ni as a catalyst



Source of Ethanol

- Ethanol is an odorless and colorless liquid widely used as a solvent.
- The alcohol in alcoholic beverages derived from fermentation of carbohydrates

$$C_6H_{12}O_6 \xrightarrow[\text{enzyme action}]{\text{Several steps involving}} 2CH_3CH_2OH + 2CO_2$$

Sugar (glucose) — Ethanol (ethyl alcohol)

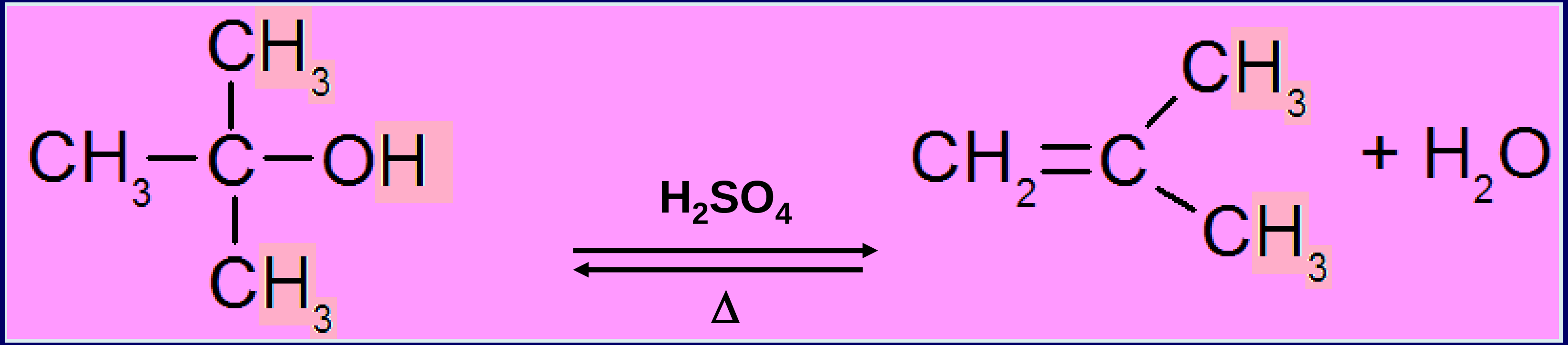
Reactions of Alcohols

- Alcohols can be converted into many other functional groups, including
  - alkenes
    Dehydration
  - alkyl halides
    Substitution
  - alkanes
    by reduction
  - aldehydes or ketones
  - carboxylic acids
  - esters
  - ethers

  } by oxidation

1. Dehydration

Removal of water, forming an alkenes

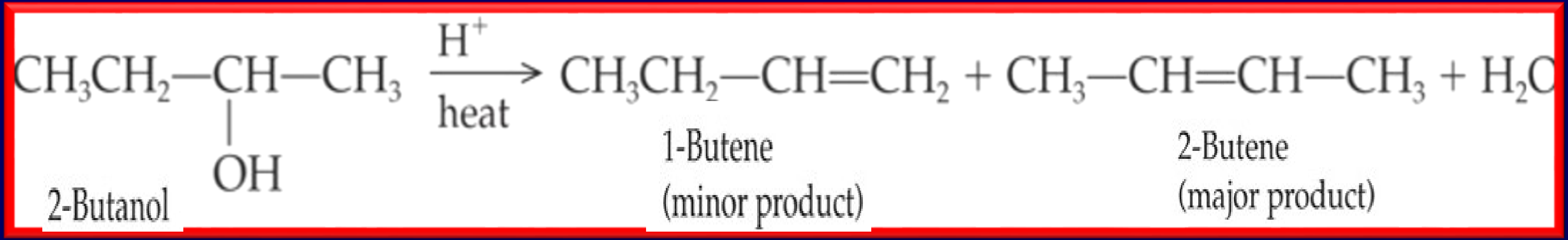


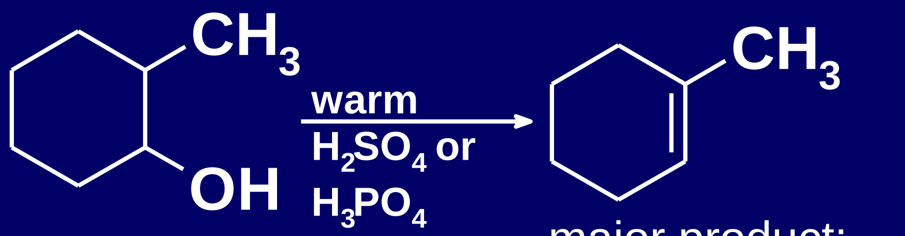
Typical reaction conditions

- ✓ Acid catalyst conc. H_2SO_4 Or conc. H_3PO
- ✓ Heat
- ✓ Zaitsev's Rule

Zaitsev's Rule

- Some alcohol dehydration reactions produce a mixture of products.
- Zaitsev's rule states that in an elimination reaction the alkene with the greatest number of alkyl groups on the double bonded carbon is the major product of the reaction.



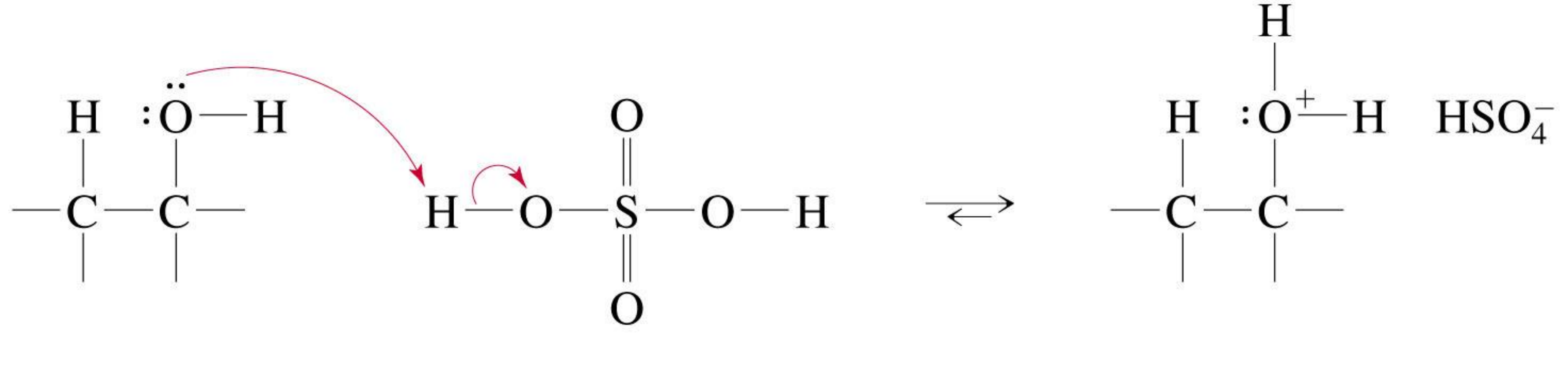


major product:
more substituted
alkene

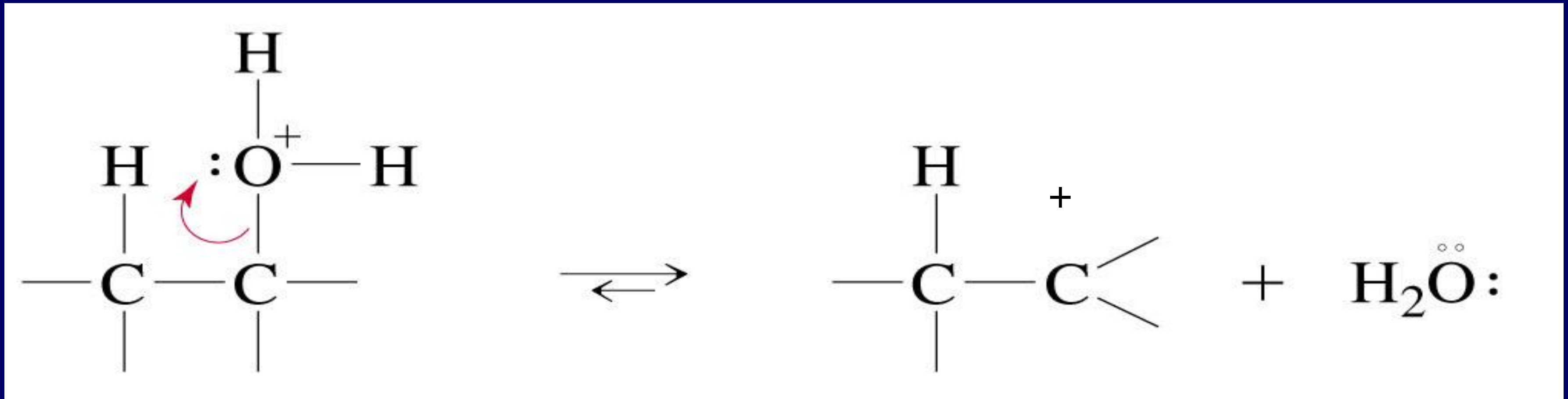
What are the major and minor products when 3-methyl-2-butanol is dehydrated?

Mechanism of Dehydration (E1)

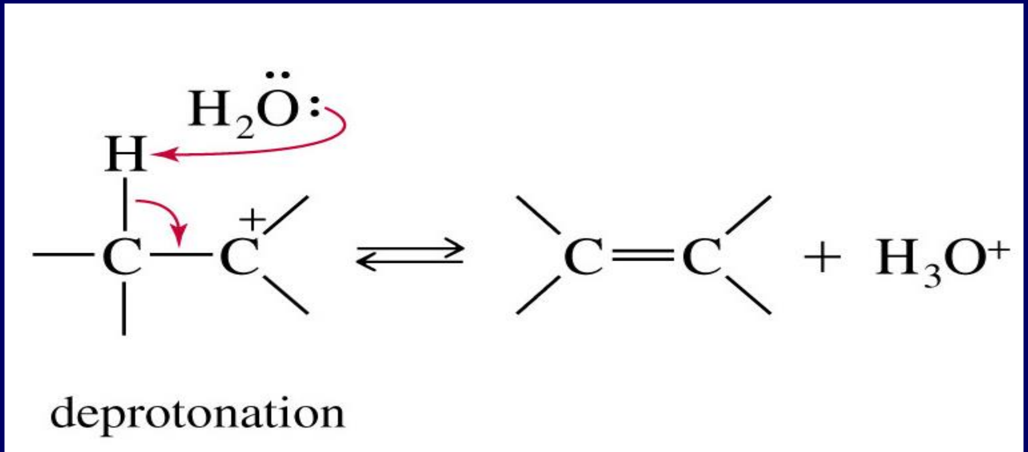
Step 1: Protonation of the hydroxyl group (fast)



Step 2: Ionization (RDS)



Step 3: Deprotonation to form alkene



2. Reaction with alkyl halide

S_N2 reaction between an alkoxide ion and an alkyl halide to form an ether.

$$ROH + NaOH \longrightarrow RO^- Na^+ + H2O$$

$$RO^- Na^+ + R'CH_2X \longrightarrow ROCH_2R'$$

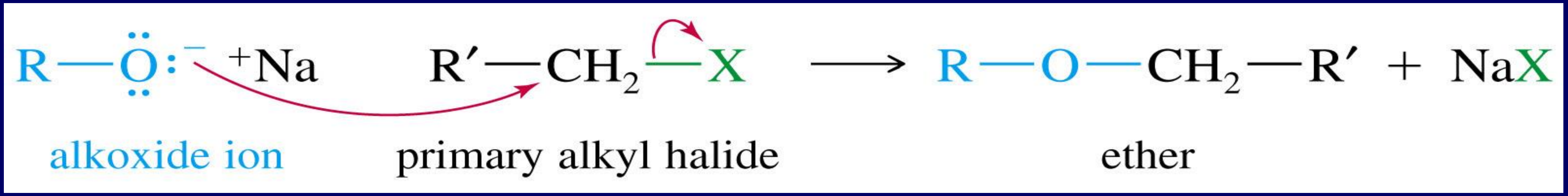
$$CH_3CH_2O^- Na^+ + CH_3I \longrightarrow CH_3CH_2OCH_3$$

$$RCH_2\text{-}X > R_2CH\text{-}X >>>>>>>>> R_3C\text{-}X$$

Steric effect around the carbinol

This reaction called Williamson reaction

Williamson Ether Synthesis Mechanism as fellow



3. Oxidation of Alcohols

Primary and secondary alcohols are easily oxidized by a variety of oxidizing agents.

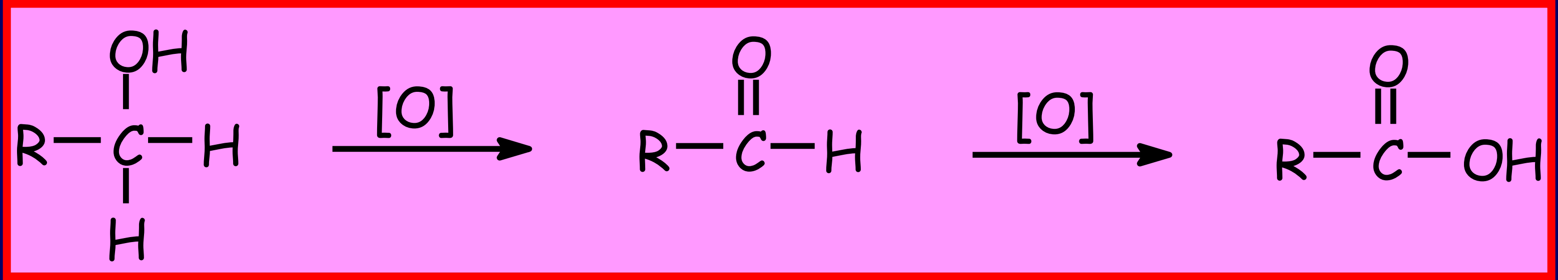
Substances that cause another to be oxidized

Some of the common oxidizing agents for organic compounds include:

- Chromium reagents
- PCC (pyridinium chlorochromate)
- $KMnO_4$
- HNO_3
- NaOCl

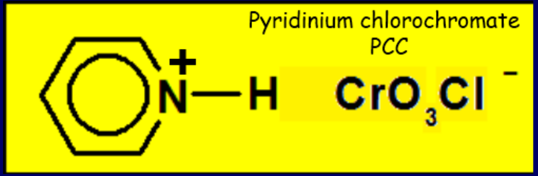
Oxidation of 1º and 2º Alcohols

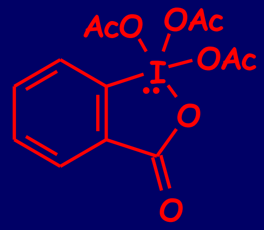
- Depending on the oxidizing agent used, primary alcohols can be oxidized to either aldehydes or carboxylic acids



- The aldehyde that forms initially is easily oxidized to the carboxylic acid by many reagents

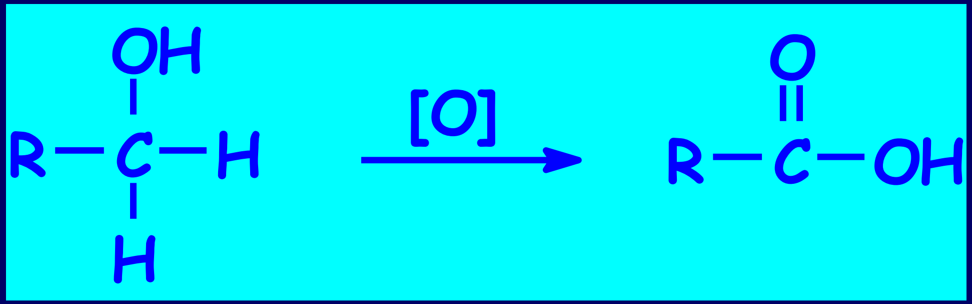
- The following reagents convert a primary alcohol to the aldehyde and secondary alcohol to ketone without further oxidation.
  Pyridinium chlorochromate (PCC)
  Swern's oxidation
  Dess-Martin Periodinane (DMP)





DMP

Oxidation of 1º Alcohols to Carboxylic Acids



Common Reagents: Chromic acid reagent $Na_2Cr_2O_7/H_2SO_4$ or $K_2Cr_2O_7/H_2SO_4$

CrO_3 or NaOCl (aq)

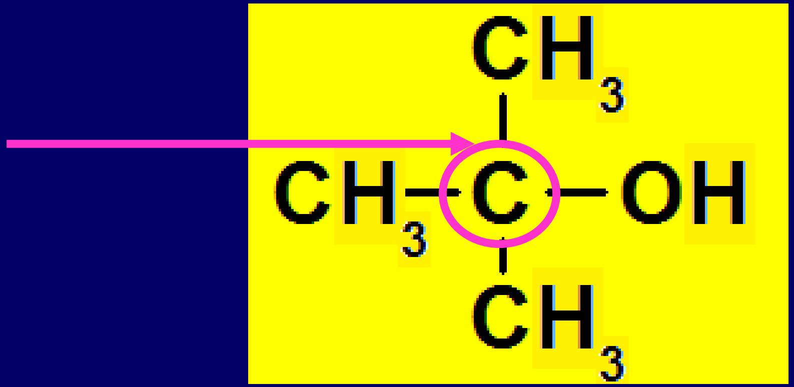
Other oxidizing agents can also be used to oxidize alcohols:

$KMnO_4$ (aq), OH^-

Cold HNO_3

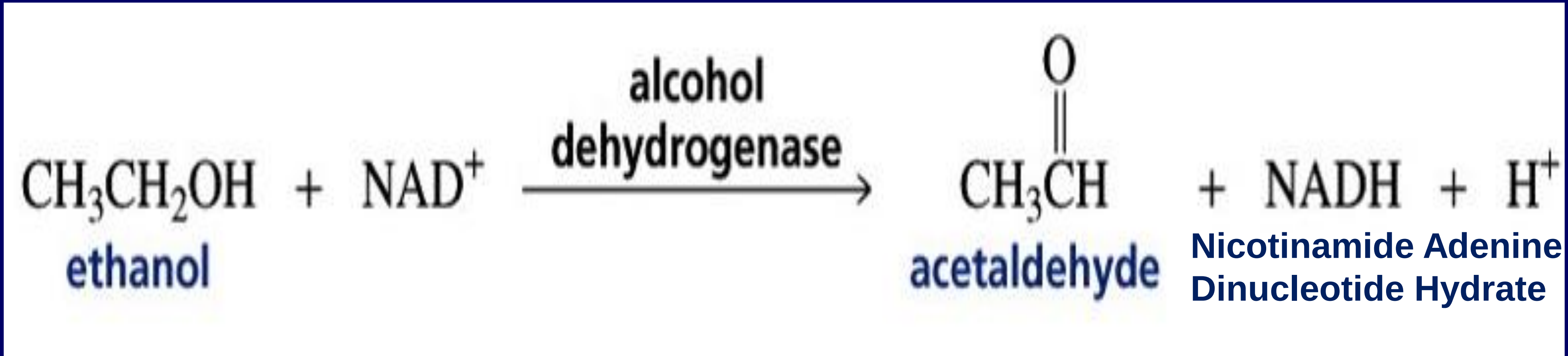
Must be carefully controlled because they can also cleave C-C bonds.

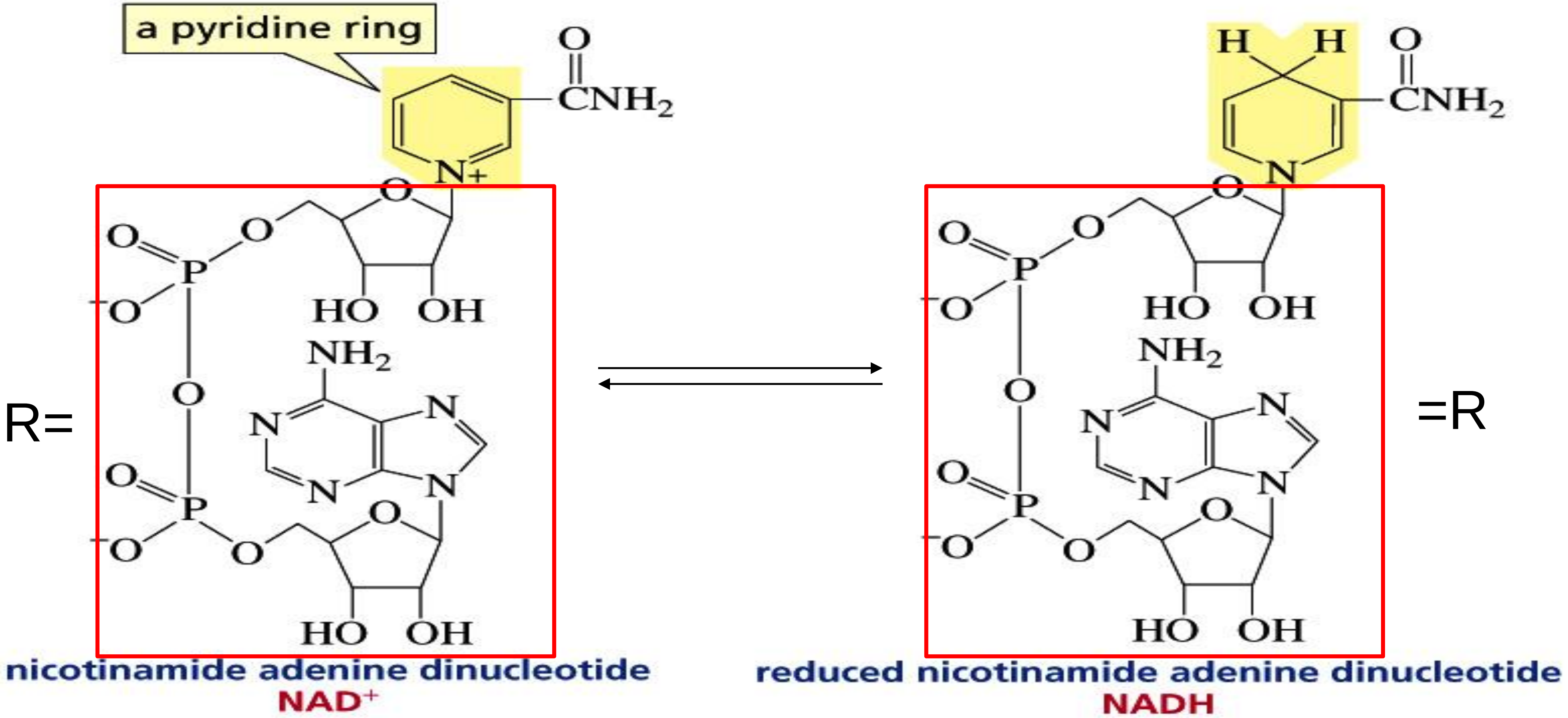
Tertiary alcohols cannot be oxidized easily.
No hydrogen present on carbinol carbon
Oxidation would require breaking C-C bond
severe conditions required



Biological Oxidation-Reduction

- Oxidoreductases catalyze biological redox (reduction oxidation) reactions.
- Coenzymes (organic molecules) are required to donate or accept hydrogen.
- NAD^+ (Nicotinamide Adenine Dinucleotide) is a common coenzyme.
- NAD^+ oxidizes ethanol by accepting a hydride ion.

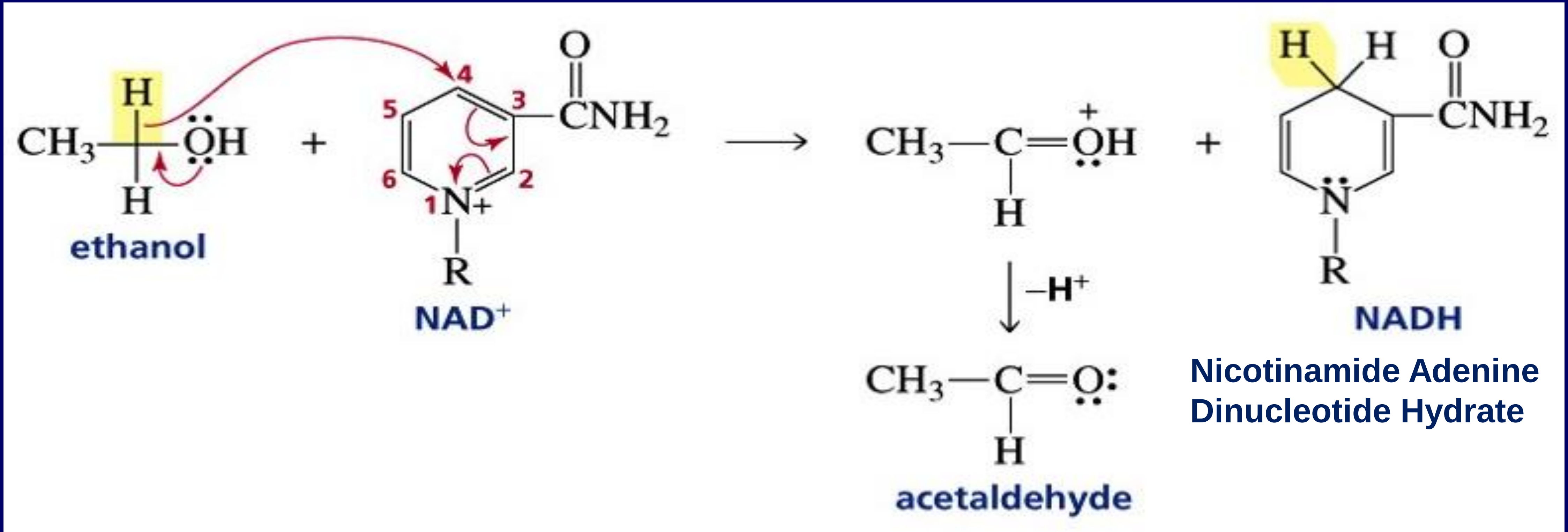




Nicotinamide Adenine Dinucleotide Hydrate

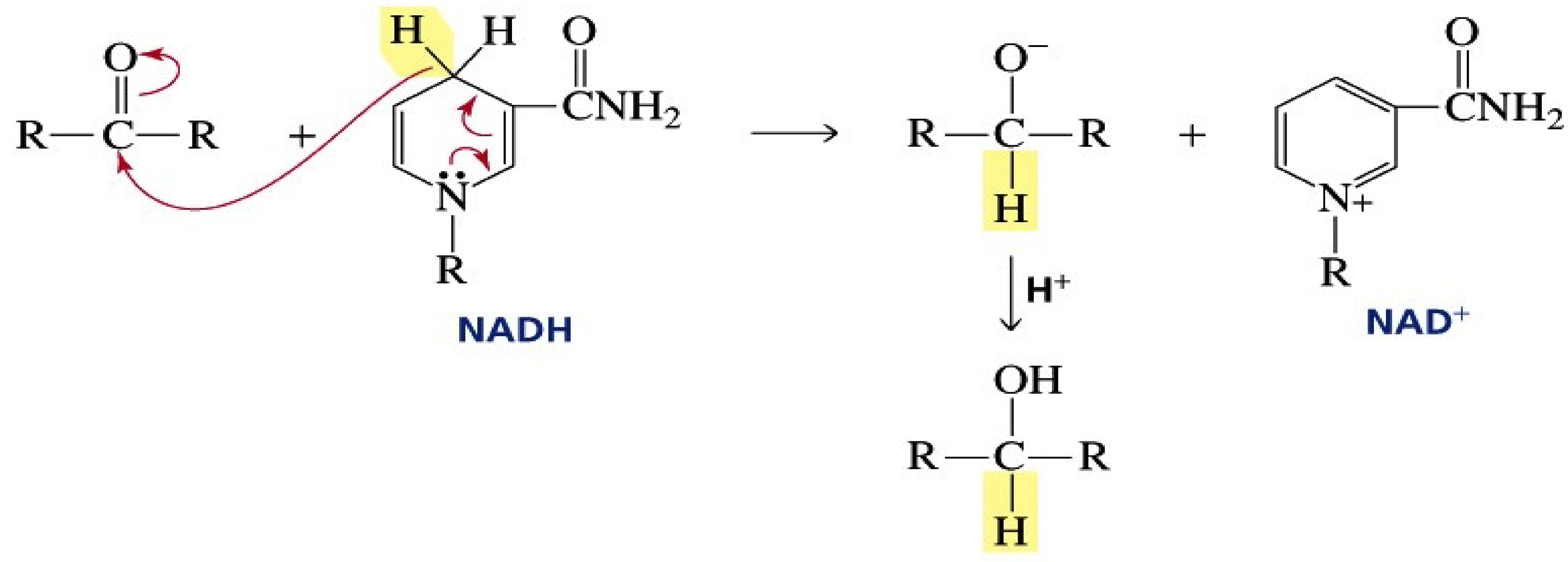
Mechanism of the biological oxidation of ethanol

- NAD^+ oxidizes ethanol by accepting a hydride ion



Mechanism of the biological redaction of carbonyl compounds

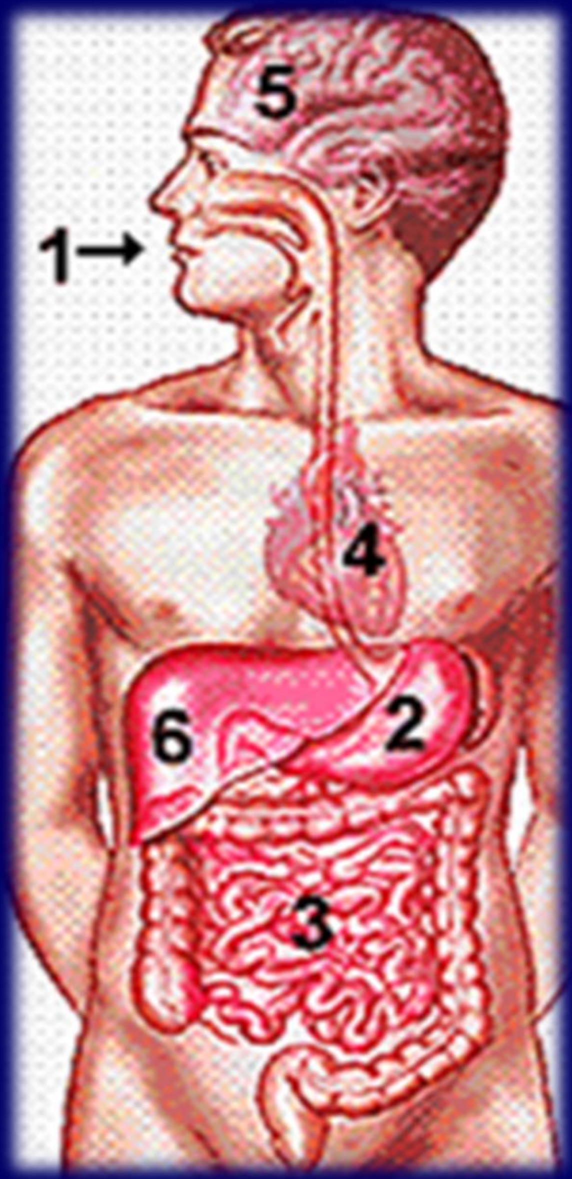
- NADH reduces a carbonyl compound by donating a hydride ion



Pathway of Alcohol

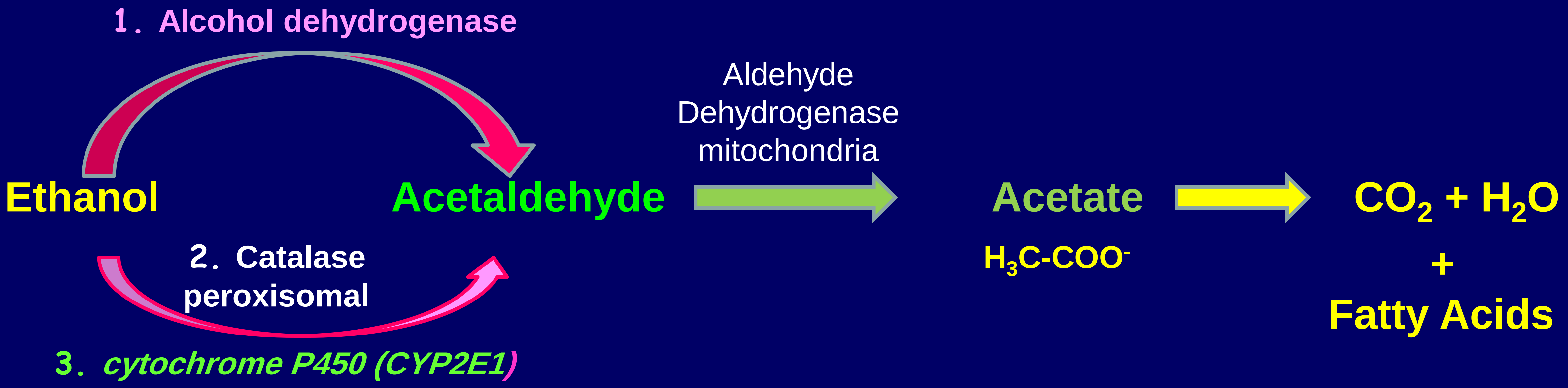
The route taken by alcohol during consumption is as follows:

1. Mouth & Esophagus – alcohol is diluted by saliva before being swallowed. Some is immediately absorbed
2. Stomach – more alcohol is absorbed here, irritating the lining of the stomach and increasing the acidity.
3. Small Intestine – any remaining alcohol is passed here and is the site of most alcohol absorption
4. Bloodstream – alcohol quickly diffuses through the body, affecting almost all cells
5. Brain - these cells are more susceptible because they are usually protected from toxins by the blood-brain barrier.
6. Liver – blood-alcohol is metabolized in two stages and then respired into CO_2, H_2O, and fatty acids.
7. Excretion via urine, the lungs, and sweat.



Processing of Ethanol

1. Oxidative pathway



1. Alcohol arrives at the liver via the bloodstream
2. Alcohol turns (oxidized) into acetaldehyde via:

- ✓ **Alcohol dehydrogenase**
- ✓ **Catalase peroxisomal**
- ✓ **Cytochrome P450 2E1 (CYP2E1)**

} This is the “bad” version

3.ALDH (Aldehyde Dehydrogenase) converts acetaldehyde into acetate

This is the "good" version that can be broken down

4. Acetate is converted into CO_2 + H_2O and fatty acids by liver cell mitochondria.

If fatty acids accumulate too fast, cirrhosis can occur

Oxidative Pathways

1. Alcohol dehydrogenase ADH.

- The major pathway of oxidative metabolism of ethanol in the liver involves ADH (present in the fluid of the cell [i.e., cytosol])

- Metabolism of ethanol with ADH produces acetaldehyde, a highly reactive and toxic byproduct that may contribute to tissue damage and, possibly, the addictive process

- This oxidation process involves an intermediate carrier of electrons, nicotinamide adenine dinucleotide (NAD^+), which is reduced by two electrons to form NADH. (see slide 23)

2. Cytochrome P450

- The cytochrome P450 isozymes, including CYP2E1,1A2, and 3A4
- Present predominantly in the microsomes, or vesicles, of a network of membranes within the cell known as the endoplasmic reticulum,
- Also contribute to alcohol oxidation in the liver. CYP2E1 is induced by chronic alcohol consumption and assumes an important role in metabolizing ethanol to acetaldehyde at elevated ethanol concentrations
- In addition, CYP2E1 dependent ethanol oxidation may occur in other tissues, such as the brain, where ADH activity is low.

3. Catalase

Catalase, located in cell bodies called peroxisomes, is capable of oxidizing ethanol in vitro in the presence of a hydrogen peroxide H_2O_2 generating system

$$CH_3CH_2OH + H_2O_2 \rightarrow CH_3CHO + 2H_2O$$

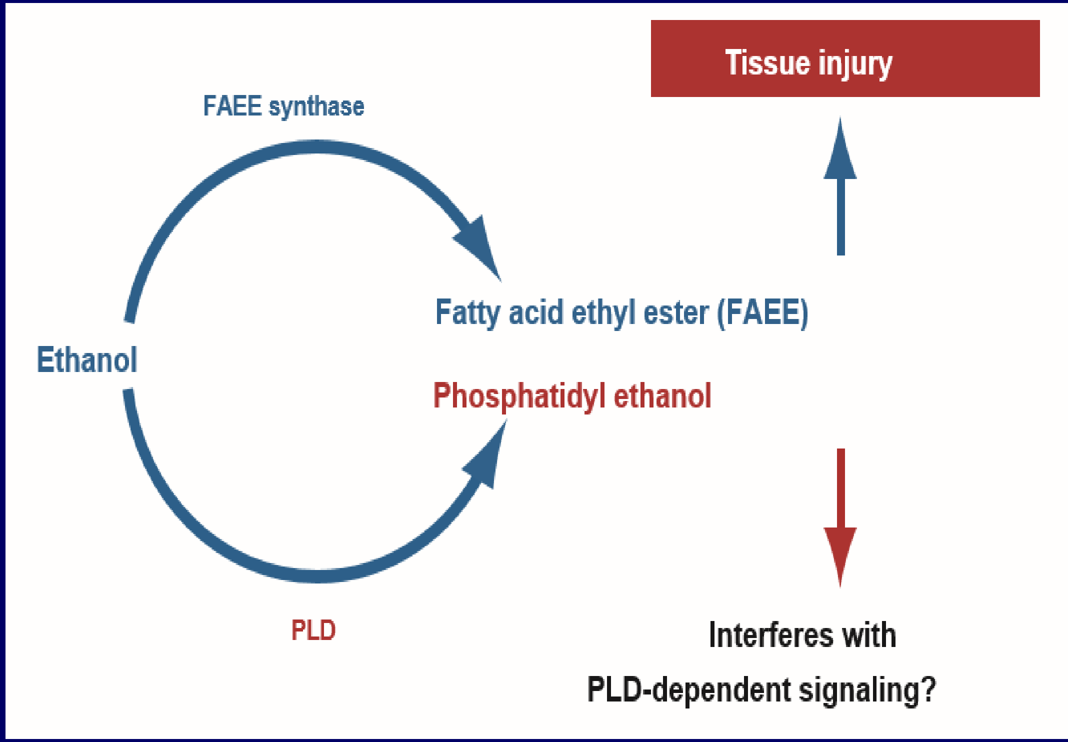
It is considered a minor pathway of alcohol oxidation

2. Non-oxidative Pathways

- The non-oxidative metabolism of alcohol is minimal.
- Alcohol is non-oxidatively metabolized by at least two pathways:-

First pathway leads to formation of:

1. Molecules called fatty acid ethyl esters (FAEEs) from the reaction of alcohol with fatty acids **(catalyzed by FAEE synthase)** .
2. A type of fat molecule containing phosphorus known as phosphatidyl ethanol.



The second pathway requires the enzyme phospholipase D (PLD) which breaks down phospholipids (primarily phosphatidylcholine) to generate phosphatidic acid (PA). This pathway is a critical component in cellular communication.

The relation between oxidative and non-oxidative pathways

Oxidative and nonoxidative pathways of alcohol metabolism are interrelated. Inhibition of ethanol oxidation by compounds that inhibit ADH, CYP2E1, and catalase results in an increase in the nonoxidative metabolism of alcohol and increased production of FAEEs in the liver and pancreas

Consequences of Alcohol Metabolism

The different pathways of ethanol metabolism described have numerous detrimental consequences that contribute to the tissue damage and diseases seen in alcoholic patients. **These consequences include**

1. Oxygen deficits (hypoxia) in the liver

- The main pathway of alcohol metabolism, which involves ADH and ALDH, results in the generation of NADH.
- The NADH then is oxidized by a series of chemical reactions in the mitochondria (i.e., the mitochondrial electron transport system, or respiratory chain), resulting in the transfer of electrons to molecular oxygen (O_2), which then binds protons (H^+) to generate water (H_2O).
- To have enough oxygen available to accept the electrons, the hepatocytes must take up more oxygen than normal from the blood.
- However, not enough oxygen may be left in the blood to adequately supply other liver regions with oxygen.

2. Interaction between alcohol metabolism byproducts and other cell components, resulting in the formation of harmful compounds (i.e., adducts)

- Acetaldehyde interacts with certain amino acids in proteins (e.g., lysine, cysteine, and some of a group of amino acids called aromatic amino acids).
- These adducts can indirectly contribute to liver damage because the body recognizes them as “foreign” and therefore generates immune molecules (i.e., antibodies) against them.
- The antibodies bind to the adducts and induce the immune system to destroy the hepatocytes containing these adducts. This process is known as **immune-mediated**

3. Formation of highly reactive oxygen-containing molecules (i.e., reactive oxygen species [ROS]) that can damage other cell components

- ROS, including superoxide ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), hypochlorite ion (OCl^-), and hydroxyl ($^{\bullet}OH$) radicals

- ROS act by “stealing” hydrogen atoms from other molecules

- Thereby converting those molecules into highly reactive free radicals. Alternatively, ROS can combine with stable molecules to form free radicals.

- Through both of these mechanisms, ROS play an important role in cancer development (i.e., carcinogenesis), atherosclerosis, diabetes, inflammation, aging, and other harmful processes

4. Changes in the ratio of NADH to NAD^+ (i.e., the cell's redox state).

- NADH and NAD^+ are involved in many important cellular reactions,
- The ratio of NADH to NAD^+ frequently fluctuates in response to changes in metabolism.
- Ethanol oxidation, as mentioned before, results in a significant increase in the hepatic $NADH/NAD^+$ ratio in both the cytosol and mitochondria

- In addition to its many effects on biochemical reactions, the $NADH/ NAD^+$ ratio also may affect the activity (i.e., expression) of certain genes.


Thank you for your attention