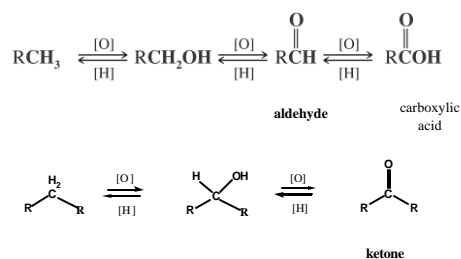


Chapter 12- part 1

Alcohols from Carbonyl Compounds: Oxidation-Reduction

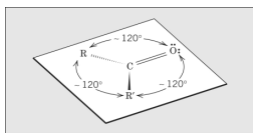
Solomons – pp. 513-526

Central linking role of alcohols and carbonyls



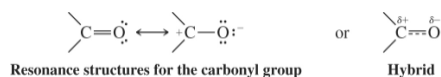
[O] and [H] are generic symbols for oxidation and reduction

Structure of Carbonyl Group



Carbonyl carbon = sp^2 hybridized and trigonal planar
All three atoms attached to the carbonyl group lie in one plane

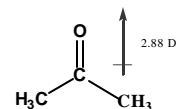
Carbonyl bond is highly polar



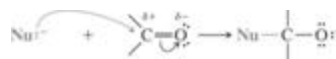
Substantial $\delta+$ charge on the carbon !

Dipole Moments (Debyes)

Water	1.85
Methanol	1.70
Acetone	2.88



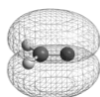
Carbonyls react with nucleophiles



- ◆ The nucleophile adds to the $\delta+$ carbon
- ◆ The p electrons shift to the oxygen
- ◆ The carbon becomes sp^3 hybridized (tetrahedral!)

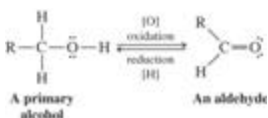
- ◆ Several chapters in Organic II
- ◆ For now, two nucleophiles that convert carbonyls to alcohols:
 - Hydride ions (H^-)
 - Carbanions (R^-) – second half of Ch. 12 (first topic Jan/08)

p -orbital of formaldehyde



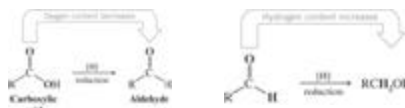
◆ Carbonyl groups and alcohols can be interconverted by oxidation and reduction reactions

◆ Alcohols can be oxidized to aldehydes; aldehydes can be reduced to alcohols



Organic Oxidations and Reductions

◆ Reduction: increasing the hydrogen content or decreasing the oxygen content of an organic molecule



◆ Oxidation: increasing the oxygen content or decreasing the hydrogen content of an organic molecule



Reduction by addition of two hydrogens

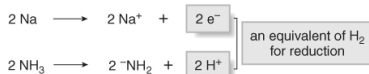
Three types of reductions: differing in how H₂ is added.

1. Simplest reducing agent is molecular H₂. Reductions using H₂ require a metal catalyst.

- Used for alkenes or alkynes, less for carbonyl groups

2. Add two protons and two electrons to a substrate—that is, H₂ = 2H⁺ + 2e⁻.

- Dissolving metal reductions use alkali metals as source of electrons, and liquid ammonia as source of protons.



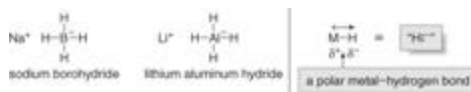
- Used to convert alkynes to trans alkenes

The Third Way

• 3. Add hydride (H⁻) and then a proton (H⁺). (=H₂)

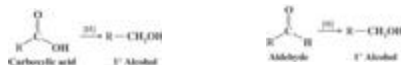
- The most common hydride reducing agents contain a hydrogen atom bonded to boron or aluminum.

- NaBH₄ and LiAlH₄ deliver H⁻ to the substrate, and then a proton is added from H₂O or an alcohol.

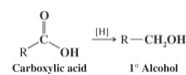


Reductions of carbonyls to alcohols

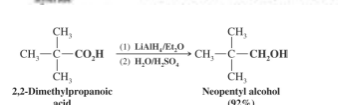
Several carbonyl compounds can be reduced to alcohols



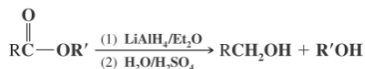
Carboxylic acids can be reduced to primary alcohols



A difficult reduction, requires the powerful reducing agent such as lithium aluminum hydride (LiAlH₄, also abbreviated LAH)



- ◆ Esters are also reduced to primary alcohols
 - LAH or high pressure hydrogenation can accomplish this transformation



Aldehydes and ketones are reduced to 1° and 2° alcohols respectively



- ◆ Aldehydes and ketones are reduced relatively easily; the mild reducing agent sodium borohydride (NaBH₄) is typically used
- ◆ LAH or hydrogenation with a metal catalyst can also be used



Key step is reaction of hydride with carbonyl carbon



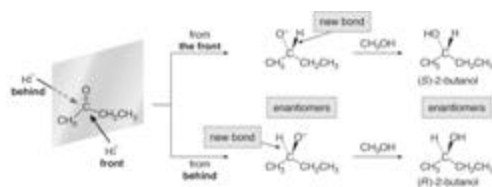
- ◆ Carboxylic acids and esters are less reactive to reduction than aldehydes and ketones and require the use of LAH



- ◆ Lithium aluminium hydride is very reactive with water and must be used in an anhydrous solvent such as ether
- ◆ Sodium borohydride is considerably less reactive and can be used in solvents such as water or an alcohol

Stereochemistry of Carbonyl Reductions

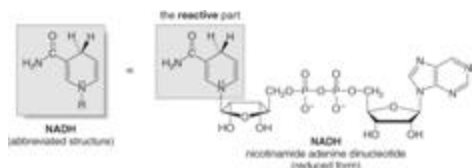
- Hydride converts a planar sp² hybridized carbonyl carbon to a tetrahedral sp³ hybridized carbon.



Conclusion: with achiral reducing agents, racemic mixture is produced

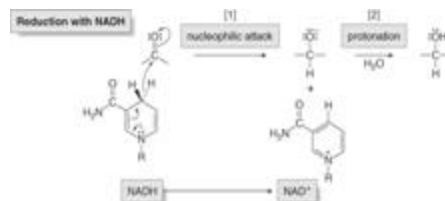
Enantioselective Carbonyl Reductions

- Biological reductions that occur in cells always proceed with complete selectivity, forming a single enantiomer.
- In cells, a common reducing agent is NADH.
- NADH is a coenzyme—an organic molecule that can function only in the presence of the enzyme.

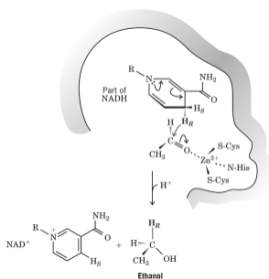


Enantioselective Carbonyl Reductions

- The active site of the enzyme binds both the carbonyl substrate and NADH, keeping them in close proximity.
- NADH then donates H⁻ in much the same way as a hydride reducing agent.

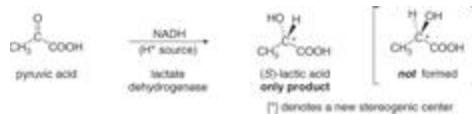


Partial active site of alcohol dehydrogenase with NADH



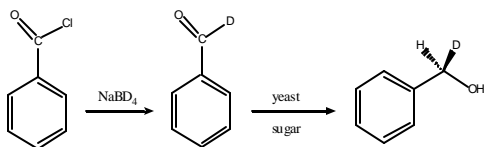
Enantioselective Carbonyl Reductions

- The reaction is completely enantioselective. Reduction of pyruvic acid with NADH catalyzed by lactate dehydrogenase affords solely the S enantiomer.
- NADH reduces a variety of different carbonyl compounds in biological systems. The configuration of the product (*R* or *S*) depends on the enzyme used to catalyze the process.



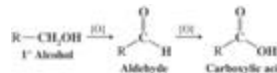
Enantioselective Carbonyl Reductions

- A personal example – preparation of chiral benzyl alcohol.



Oxidation of Alcohols

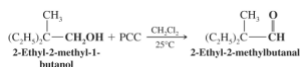
- Primary alcohols can be oxidized to aldehydes or to carboxylic acids
- The oxidation is difficult to stop at the aldehyde stage and usually proceeds on to the carboxylic acid



Oxidation of Alcohols

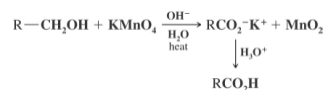
To stop at the aldehyde stage, use pyridinium chlorochromate (PCC)

- PCC is made from chromium trioxide under acidic conditions
- It is used in organic solvents such as methylene chloride (CH_2Cl_2)



Oxidation of Primary Alcohols to Carboxylic Acids

Potassium permanganate (KMnO_4) is a typical reagent used for oxidation of a primary alcohol to a carboxylic acid

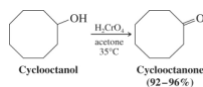


- The reaction is generally carried out in aqueous solution; purple of MnO_4^- becomes the brown precipitate of MnO_2

Oxidation of Secondary Alcohols to Ketones

Oxidation of a secondary alcohol produces a ketone

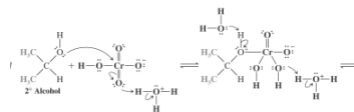
- Many oxidizing agents can be used, including chromic acid (H_2CrO_4), KMnO_4 , or Jones reagent (CrO_3 in acetone)



Example of oxidation mechanism

Mechanism of Chromate Oxidation

- Step 1: A chromate ester is formed from the alcohol hydroxyl**

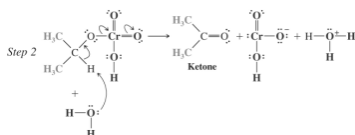


Alcohol adds to chromate



and a water molecule departs

Step 2: An elimination reaction occurs by removal of a hydrogen atom from the alcohol carbon and departure of the chromium group with a pair of electrons.



Cr atom departs with pair of electrons originally on the alcohol oxygen

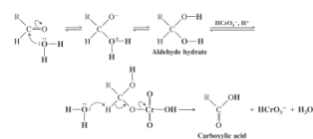
Hence organic compound is oxidized

Oxidation state of chromium is reduced from +6 to +4

Why stopping oxidation of P ROH at aldehyde is difficult

Aldehydes form hydrates in water (an equilibrium)

- An aldehyde hydrate is a diol and can react by the same mechanism to produce a carboxylic acid



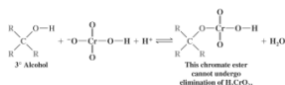
Pyridinium chlorochromate (PCC) reactions are run in anhydrous methylene chloride and the aldehyde cannot form a hydrate

- The oxidation of a primary alcohol therefore stops at the aldehyde stage

Tertiary alcohols are not oxidized

- Tertiary alcohols can form the chromate ester but cannot eliminate because they have no hydrogen on the alcohol carbon

- Tertiary alcohols are therefore not oxidized



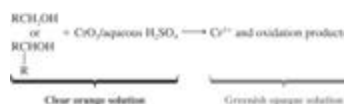
Identification of the hydroxy group

- Spectroscopic Evidence for Alcohols**

- Alcohol O-H infrared stretching absorptions appear as strong, broad peaks around 3200-3600 cm^{-1}

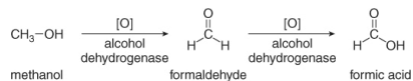
- A Chemical Test for Primary and Secondary Alcohols**

- Chromium oxide in acid has a clear orange color which changes to greenish opaque if an oxidizable alcohol is present



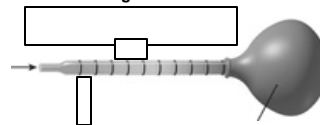
The Oxidation of Ethanol in the body

- Ingested ethanol is oxidized in the liver first to CH_3CHO (acetaldehyde), and then to CH_3COO^- (the acetate anion).
- This oxidation is catalyzed by alcohol dehydrogenase.
- If more ethanol is ingested than can be metabolized, the concentration of acetaldehyde increases. Acetaldehyde, which is toxic, is responsible for the feelings associated with a hangover.



Oxidation of 1^o Alcohols - breathalyzers

- Early breathalyzers were based on Cr^{6+} oxidations, as the red-orange Cr^{6+} reagent is reduced to green Cr^{3+} .



- Individual blows into a tube containing $\text{K}_2\text{Cr}_2\text{O}_7$, H_2SO_4 .
- The higher the concentration of $\text{CH}_3\text{CH}_2\text{OH}$ in the breath, the farther the green Cr^{3+} color extends down the sample tube.
- This extent of the green color is then correlated with blood alcohol levels.