Seminar_6

1. **Nomenclature of Aldehydes and Ketones**
2. **Synthetic Preparation of Aldehydes and Ketones**
3. **Reactions of Aldehydes and Ketones**
    - **Reversible Addition Reaction**
    - **Irreversible Addition Reactions**
    - **Other Carbonyl Group Reactions**
4. **Carbohydrates**
    - **Aldose and Ketose**
    - **Cyclic Forms of Monosaccharides**
    - **Polysaccharides**

TEST - Aldehydes and ketones. Carbohydrates.

- Give the names
- Aldehydes Reactions
- Write isomeric compounds of aldohexose
- Cyclic Forms of Monosaccharides

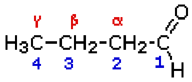
Nomenclature of Aldehydes and Ketones

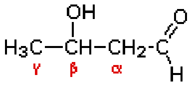
Aldehydes and ketones are organic compounds which incorporate a **carbonyl functional group**, C=O. The carbon atom of this group has two remaining bonds that may be occupied by hydrogen or alkyl or aryl substituents. If at least one of these substituents is hydrogen, the compound is an **aldehyde**. If neither is hydrogen, the compound is a **ketone**.

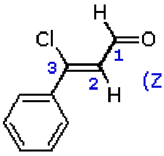
The IUPAC system of nomenclature assigns a characteristic suffix to these classes, **al** to aldehydes and **one** to ketones. For example, $H_2C=O$ is methanal, more commonly called formaldehyde. Since an aldehyde carbonyl group must always lie at the end of a carbon chain, it is by default position #1, and therefore defines the numbering direction. A ketone carbonyl function may be located anywhere within a chain or ring, and its position is given by a locator number. Chain numbering normally starts from the end nearest the carbonyl group. In cyclic ketones the carbonyl group is assigned position #1, and this number is not cited in the name, unless more than one carbonyl group is present.

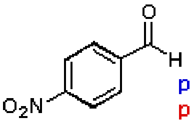
Examples of IUPAC names are provided (in blue) in the following diagram. Common names are in red, and derived names in black. In common names carbon atoms near the carbonyl group are often designated by Greek letters. The atom adjacent to the function is alpha, the next removed is beta and so on. Since ketones have two sets of neighboring atoms, one set is labeled α, β *etc.*, and the other α', β'.

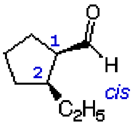
Aldehydes


butanal
butyraldehyde


3-hydroxybutanal
β-hydroxybutyraldehyde
or aldol

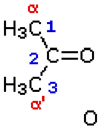

(Z)-3-chloro-3-phenyl-2-propenal

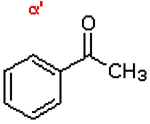

p-nitrobenzenecarbaldehyde
p-nitrobenzaldehyde

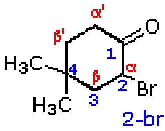

cis-2-ethylcyclopentanecarbaldehyde

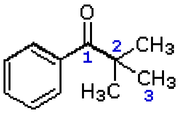

pentanedial
glutaraldehyde

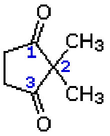
Ketones

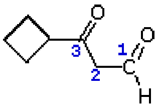

propanone
acetone


phenylethanone
acetophenone
methyl phenyl ketone


2-bromo-4,4-dimethylcyclohexanone

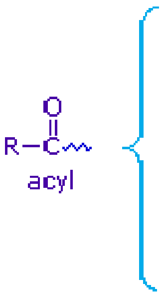

2,2-dimethyl-1-phenylpropanone
t-butyl phenyl ketone

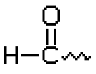

2,2-dimethyl-1,3-cyclopentanedione

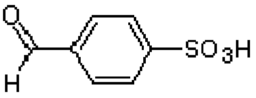

3-cyclobutyl-3-oxopropanal

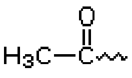
Very simple ketones, such as propanone and phenylethanone (first two examples in the left column), do not require a locator number, since there is only one possible site for a ketone carbonyl function. Likewise, locator numbers are omitted for the simple dialdehyde at the bottom left, since aldehyde functions must occupy the ends of carbon chains. The hydroxy butanal and propenal examples (2nd & 3rd from the top, left column) and the oxopropanal example (bottom right) illustrate the nomenclature priority of IUPAC suffixes. In all cases the aldehyde function has a higher status than either an alcohol, alkene or ketone and provides the nomenclature suffix. The other functional groups are treated as substituents. Because ketones are just below aldehydes in nomenclature suffix priority, the "oxo" substituent terminology is seldom needed.

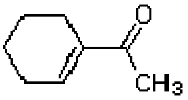
Simple substituents incorporating a carbonyl group are often encountered. The generic name for such groups is **acyl**. Three examples of acyl groups having specific names are shown below.

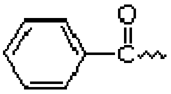

acyl

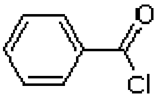

formyl


4-formylbenzenesulfonic acid


acetyl


1-acetyl-1-cyclohexene


benzoyl

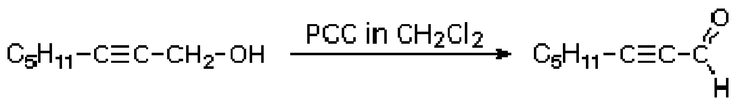

benzoyl chloride

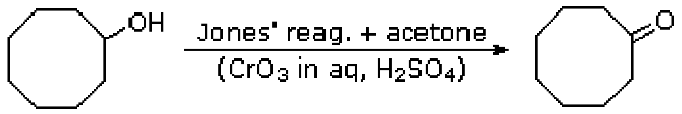
Synthetic Preparation of Aldehydes and Ketones

Aldehydes and ketones are obtained as products from many reactions discussed in previous sections of this text. The following diagram summarizes the most important of these.

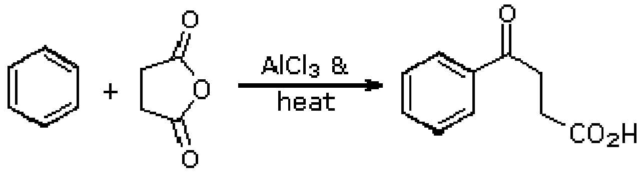
With the exception of Friedel-Crafts acylation, these methods do not increase the size or complexity of molecules. In the following sections of this chapter we shall find that one of the most useful characteristics of aldehydes and ketones is their reactivity toward carbon nucleophiles, and the resulting elaboration of molecular structure that results. In short, aldehydes and ketones are important intermediates for the assembly or synthesis of complex organic molecules.

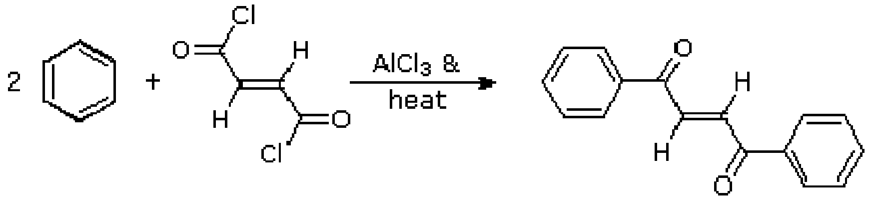
1. Oxidation of 1° & 2° Alcohols

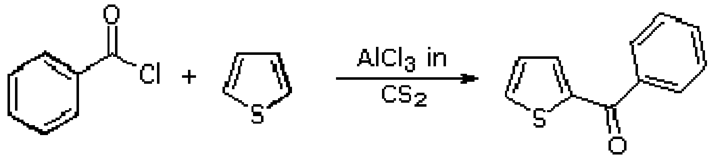




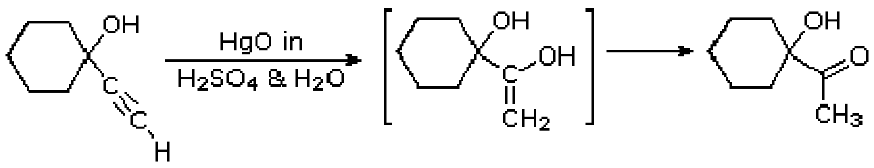
2. Friedel-Crafts Acylation

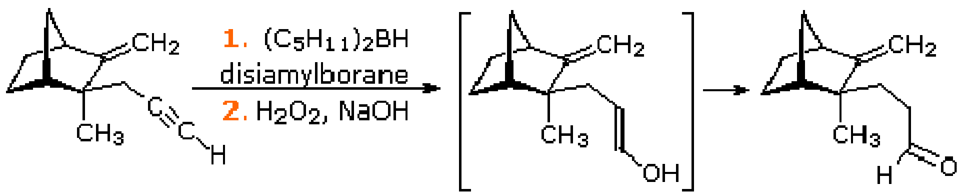




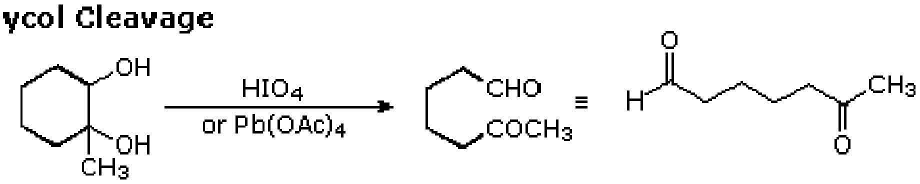


3. Hydration of Alkynes

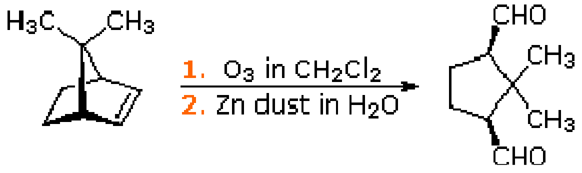




4. Glycol Cleavage



5. Ozonolysis of Alkenes



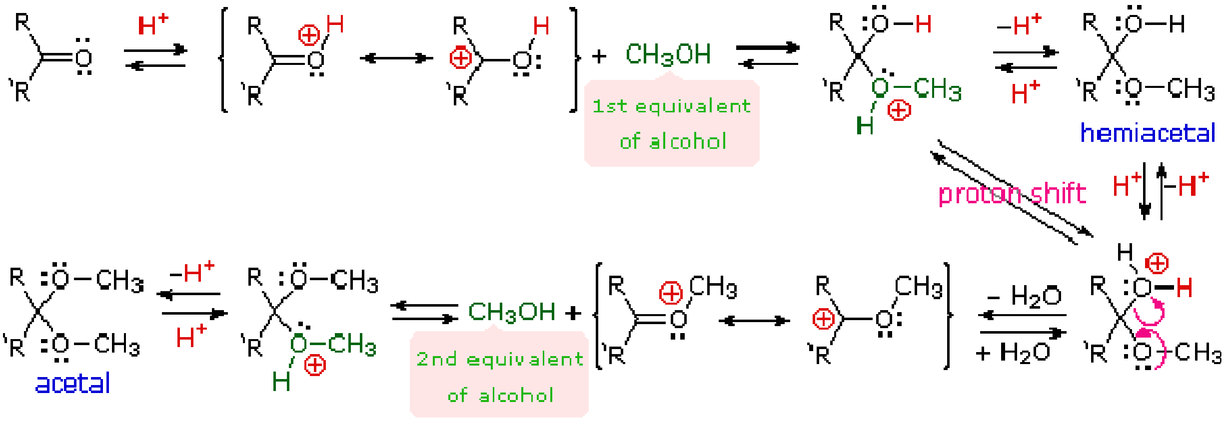
Reactions of Aldehydes and Ketones

Reversible Addition Reactions

ACETAL FORMATION

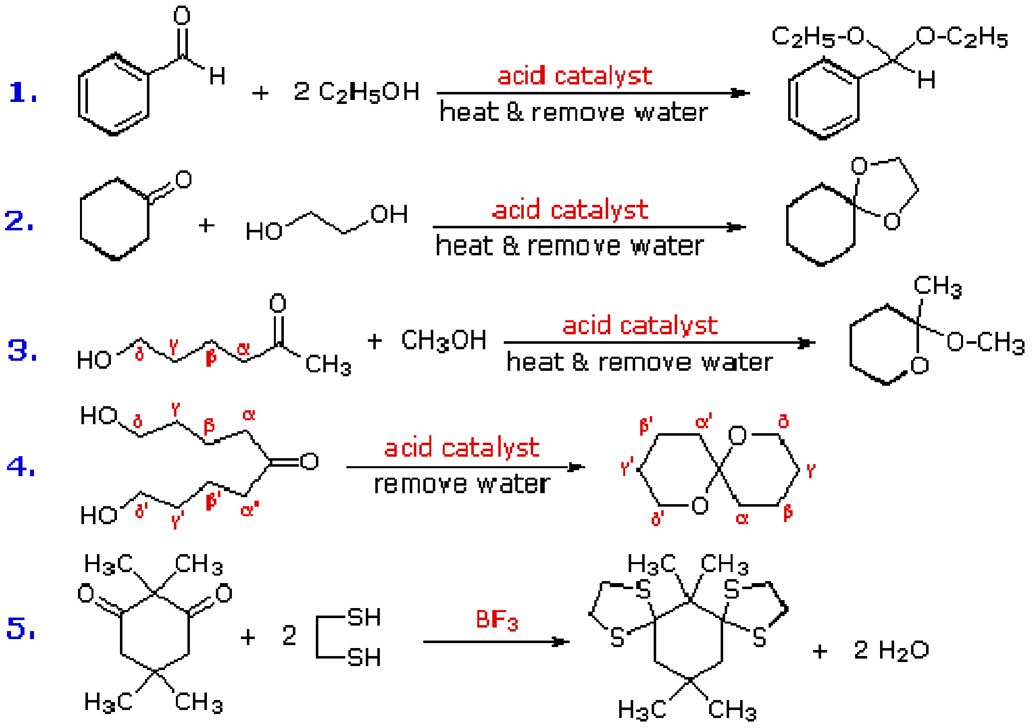
Acetals are geminal-diether derivatives of aldehydes or ketones, formed by reaction with two equivalents of an alcohol and elimination of water. Ketone derivatives of this kind were once called ketals, but modern usage has dropped that term. The following equation shows the overall stoichiometric change in acetal formation, but a dashed arrow is used because this conversion does not occur on simple mixing of the reactants.

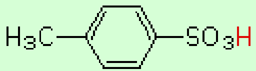
$$R_2C{=}O \;+\; 2\,R'OH \dashrightarrow R_2C(OR')_2 \;+\; H_2O \quad \text{(an acetal)}$$



In order to achieve effective acetal formation two additional features must be implemented. First, an acid catalyst must be used; and second, the water produced with the acetal must be removed from the reaction. The latter is important, since acetal formation is reversible. Indeed, once pure acetals are obtained they may be hydrolyzed back to their starting components by treatment with aqueous acid. The mechanism shown here applies to both acetal formation and acetal hydrolysis by the principle of microscopic reversibility.

Some examples of acetal formation are presented in the following diagram. As noted, p-toluenesulfonic acid (pK_a = -2) is often the catalyst for such reactions. Two equivalents of the alcohol reactant are needed, but these may be provided by one equivalent of a diol (example #2). Intramolecular involvement of a gamma or delta hydroxyl group (as in examples #3 and 4) may occur, and is often more facile than the intermolecular reaction. Thiols (sulfur analogs of alcohols) give thioacetals (example #5). In this case the carbonyl functions are relatively hindered, but by using excess ethanedithiol as the solvent and the Lewis acid BF_3 as catalyst a good yield of the bis-thioacetal is obtained. Thioacetals are generally more difficult to hydrolyze than are acetals.



The acid often used to catalyze acetal formation is p-toluenesulfonic acid 

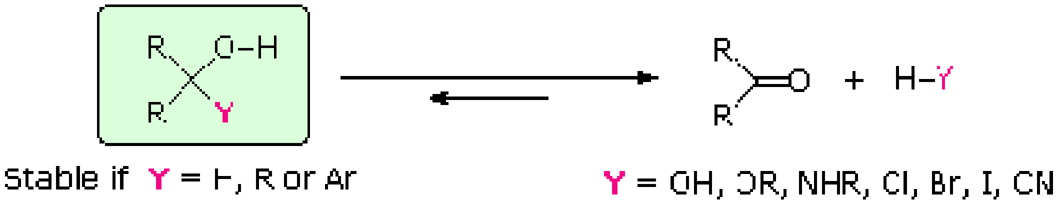
Toluene is usually the solvent, and water is removed azeotropically by distillation

The importance of acetals as carbonyl derivatives lies chiefly in their stability and lack of reactivity in neutral to strongly basic environments. As long as they are not treated by acids, especially aqueous acid, acetals exhibit all the lack of reactivity associated with ethers in general.

Among the most useful and characteristic reactions of aldehydes and ketones is their reactivity toward strongly nucleophilic (and basic) metallo-hydride, alkyl and aryl reagents (to be discussed shortly). If the carbonyl functional group is converted to an acetal these powerful reagents have no effect; thus, acetals are excellent protective groups, when these irreversible addition reactions must be prevented.

Irreversible Addition Reactions

The distinction between reversible and irreversible carbonyl addition reactions may be clarified by considering the stability of alcohols having the structure shown below in the shaded box.

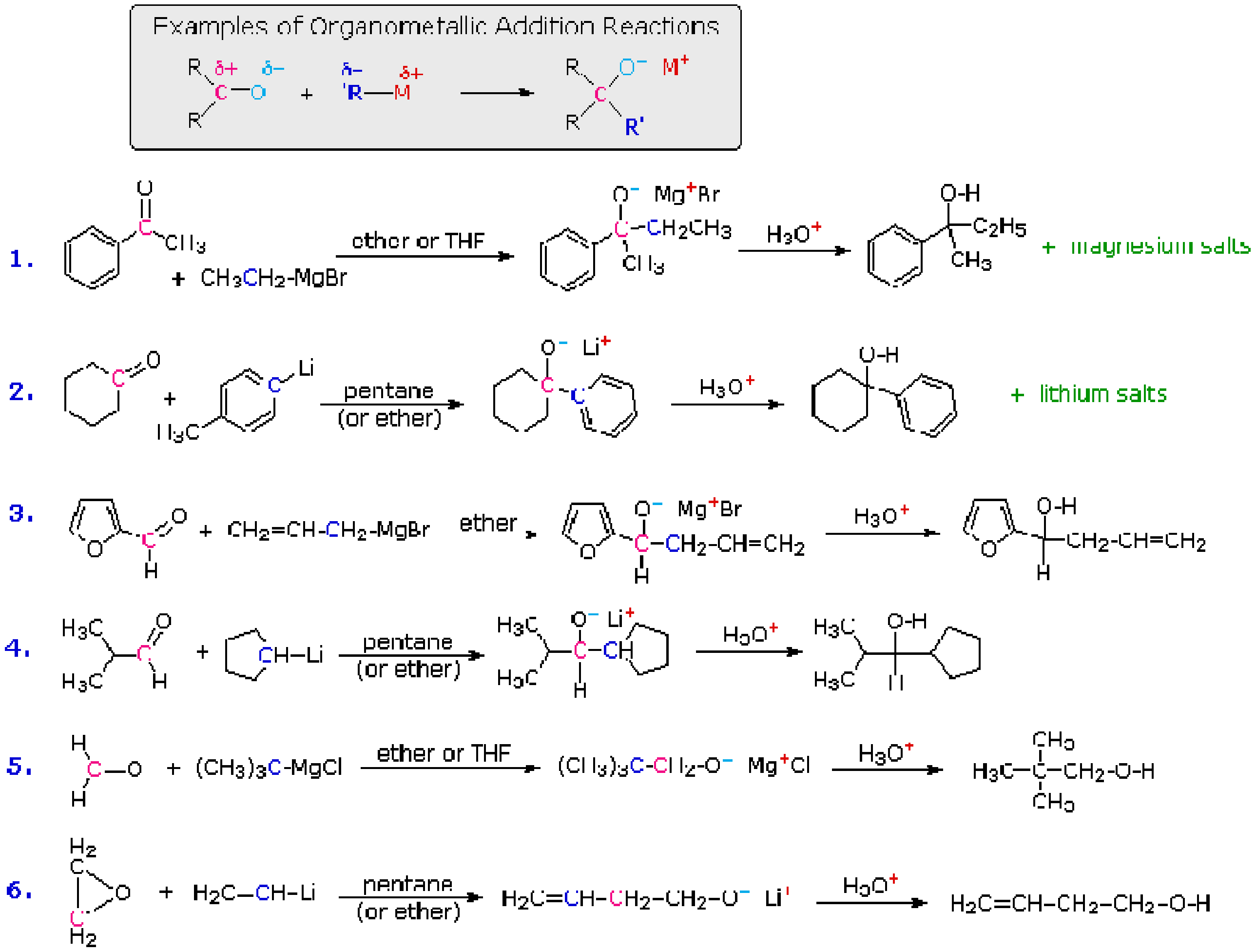


If substituent Y is not a hydrogen, an alkyl group or an aryl group, there is a good chance the compound will be unstable (not isolable), and will decompose in the manner shown. Most hydrates and hemiacetals (Y = OH & OR), for example, are known to decompose spontaneously to the corresponding carbonyl compounds. Aminols (Y = NHR) are intermediates in imine formation, and also revert to their carbonyl precursors if dehydration conditions are not employed. Likewise, α-haloalcohols (Y = Cl, Br & I) cannot be isolated, since they immediately decompose with the loss of HY. In all these cases addition of H–Y to carbonyl groups is clearly reversible.

If substituent Y is a hydrogen, an alkyl group or an aryl group, the resulting alcohol is a stable compound and does not decompose with loss of hydrogen or hydrocarbons, even on heating. It follows then, that if nucleophilic reagents corresponding to H:(–), R:(–) or Ar:(–) add to aldehydes and ketones, the alcohol products of such additions will form irreversibly. Free anions of this kind would be extremely strong bases and nucleophiles, but their extraordinary reactivity would make them difficult to prepare and use. Fortunately, metal derivatives of these alkyl, aryl and hydride moieties are available, and permit their addition to carbonyl compounds.

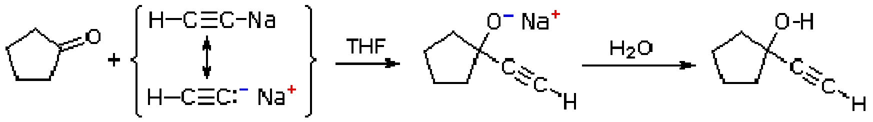
Addition of Organometallic Reagents

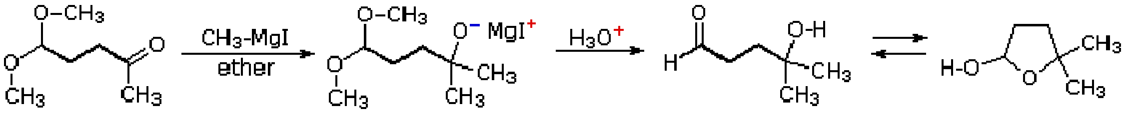
The two most commonly used compounds of this kind are alkyl lithium reagents and Grignard reagents. They are prepared from alkyl and aryl halides. These reagents are powerful nucleophiles and very strong bases (pKa's of saturated hydrocarbons range from 42 to 50), so they bond readily to carbonyl carbon atoms, giving alkoxide salts of lithium or magnesium. Because of their ring strain, epoxides undergo many carbonyl-like reactions. Reactions of this kind are among the most important synthetic methods available to chemists, because they permit simple starting compounds to be joined to form more complex structures. Examples are shown in the following diagram.



A common pattern, shown in the shaded box at the top, is observed in all these reactions. The organometallic reagent is a source of a nucleophilic alkyl or aryl group (colored blue), which bonds to the electrophilic carbon of the carbonyl group (colored magenta). The product of this addition is a metal alkoxide salt, and the alcohol product is generated by weak acid hydrolysis of the salt. The first two examples show that water soluble magnesium or lithium salts are also formed in the hydrolysis, but these are seldom listed among the products, as in the last four reactions. Ketones react with organometallic reagents to give 3º-alcohols; most aldehydes react to produce 2º-alcohols; and formaldehyde and ethylene oxide react to form 1º-alcohols (examples #5 & 6). When a chiral center is formed from achiral reactants (examples #1, 3 & 4) the product is always a racemic mixture of enantiomers.

Two additional examples of the addition of organometallic reagents to carbonyl compounds are informative. The first demonstrates that active metal derivatives of terminal alkynes function in the same fashion as alkyl lithium and Grignard reagents. The second example again illustrates the use of acetal protective groups in reactions with powerful nucleophiles. Following acid-catalyzed hydrolysis of the acetal, the resulting 4-hydroxyaldehyde is in equilibrium with its cyclic hemiacetal.





Other Carbonyl Group Reactions

Reduction

The metal hydride reductions and organometallic additions to aldehydes and ketones, described above, both decrease the carbonyl carbon's oxidation state, and may be classified as reductions. As noted, they proceed by attack of a strong nucleophilic species at the electrophilic carbon. Other useful reductions of carbonyl compounds, either to alcohols or to hydrocarbons, may take place by different mechanisms. For example, hydrogenation (Pt, Pd, Ni or Ru catalysts), reaction with diborane, and reduction by lithium, sodium or potassium in hydroxylic or amine solvents have all been reported to convert carbonyl compounds into alcohols. However, the complex metal hydrides are generally preferred for such transformations because they give cleaner products in high yield.

The reductive conversion of a carbonyl group to a methylene group requires complete removal of the oxygen, and is called deoxygenation. In the shorthand equation shown here the [H] symbol refers to unspecified reduction conditions which effect the desired change. Three very different methods of accomplishing this transformation will be described here.

$$R_2C{=}O \; + \; [H] \longrightarrow R_2CH_2 \; + \; H_2O$$

Oxidation

The carbon atom of a carbonyl group has a relatively high oxidation state. This is reflected in the fact that most of the reactions described thus far either cause no change in the oxidation state (e.g. acetal and imine formation) or effect a reduction (e.g. organometallic additions and deoxygenations). The most common and characteristic oxidation reaction is the conversion of aldehydes to carboxylic acids. In the shorthand equation shown here the [O]symbol refers to unspecified oxidation conditions which effect the desired change. Several different methods of accomplishing this transformation will be described here.

$$RCH{=}O \; + \; [O] \longrightarrow RC(OH){=}O$$

In discussing the oxidations of 1° and 2°-alcohols, we noted that Jones' reagent (aqueous chromic acid) converts aldehydes to carboxylic acids, presumably via the hydrate. Other reagents, among them aqueous potassium permanganate and dilute bromine, effect the same transformation. Even the oxygen in air will slowly oxidize aldehydes to acids or peracids, most likely by a radical mechanism. Useful tests for aldehydes, Tollens' test,Benedict's test & Fehling's test, take advantage of this ease of oxidation by using Ag(+) and Cu(2+) as oxidizing agents (oxidants).

$$\mathbf{RCH{=}O \quad + \quad 2\,[Ag(+)\ OH(-)] \quad \longrightarrow}$$

$$\mathbf{RC(OH){=}O \quad + \quad 2\ Ag\ (metallic\ mirror) \quad + \quad H_2O}$$

When silver cation is the oxidant, as in the above equation, it is reduced to metallic silver in the course of the reaction, and this deposits as a beautiful mirror on the inner surface of the reaction vessel. The Fehling and Benedict tests use cupric cation as the oxidant. This deep blue reagent is reduced to cuprous oxide, which precipitates as a red to yellow solid. All these cation oxidations must be conducted under alkaline conditions. To avoid precipitation of the insoluble metal hydroxides, the cations must be stabilized as complexed ions. Silver is used as its ammonia complex, $Ag(NH_3)_2(+)$, and cupric ions are used as citrate or tartrate complexes. Saturated ketones are generally inert to oxidation conditions that convert aldehydes to carboxylic acids. Nevertheless, under vigorous acid-catalyzed oxidations with nitric or chromic acids ketones may undergo carbon-carbon bond cleavage at the carbonyl group.

Carbohydrates

The Latin word for sugar* is saccharum, and the derived term saccharide is the basis of a system of carbohydrate classification. A monosaccharide is a simple carbohydrate, one that on attempted hydrolysis is not cleaved to smaller carbohydrates. Glucose ($C_6H_{12}0_6$), for example, is a monosaccharide. A disaccharide on hydrolysis is cleaved to two monosaccharides, which may be the same or different. Sucrose--common table sugar--is a disaccharide that yields one molecule of glucose and one of fructose on hydrolysis.

$$\text{Sucrose } (C_{12}H_{22}O_{11}) + H_2O \longrightarrow \text{glucose } (C_6H_{12}O_6) + \text{fructose } (C_6H_{12}O_6)$$

An oligosaccharide (oligos is a Greek word that in its plural form means "few") yields two or more monosaccharides on hydrolysis. Thus, the IUPAC classifies disaccharides, trisaccharides, and so on as subcategories of oligosaccharides. Polysaccharities are hydrolyzed to "many" monosaccharides. The IUPAC has chosen not to specify the number of monosaccharide components that separates oligosaccharides from polysaccharides. The standard is a more practical one; it notes that an oligosaccharide is homogeneous. Each molecule of a particular oligosaccharide has the same number of monosaccharide units joined together in the same order as every other molecule of the same oligosaccharide. Polysaccharides are almost always mixtures of molecules having similar, but not necessarily the same, chain length. Cellulose, for example, is a polysaccharide that gives thousands of glucose molecules on hydrolysis but only a small fraction of the cellulose chains contain exactly the same number of glucose molecules.

Aldose and Ketose

C=O Function

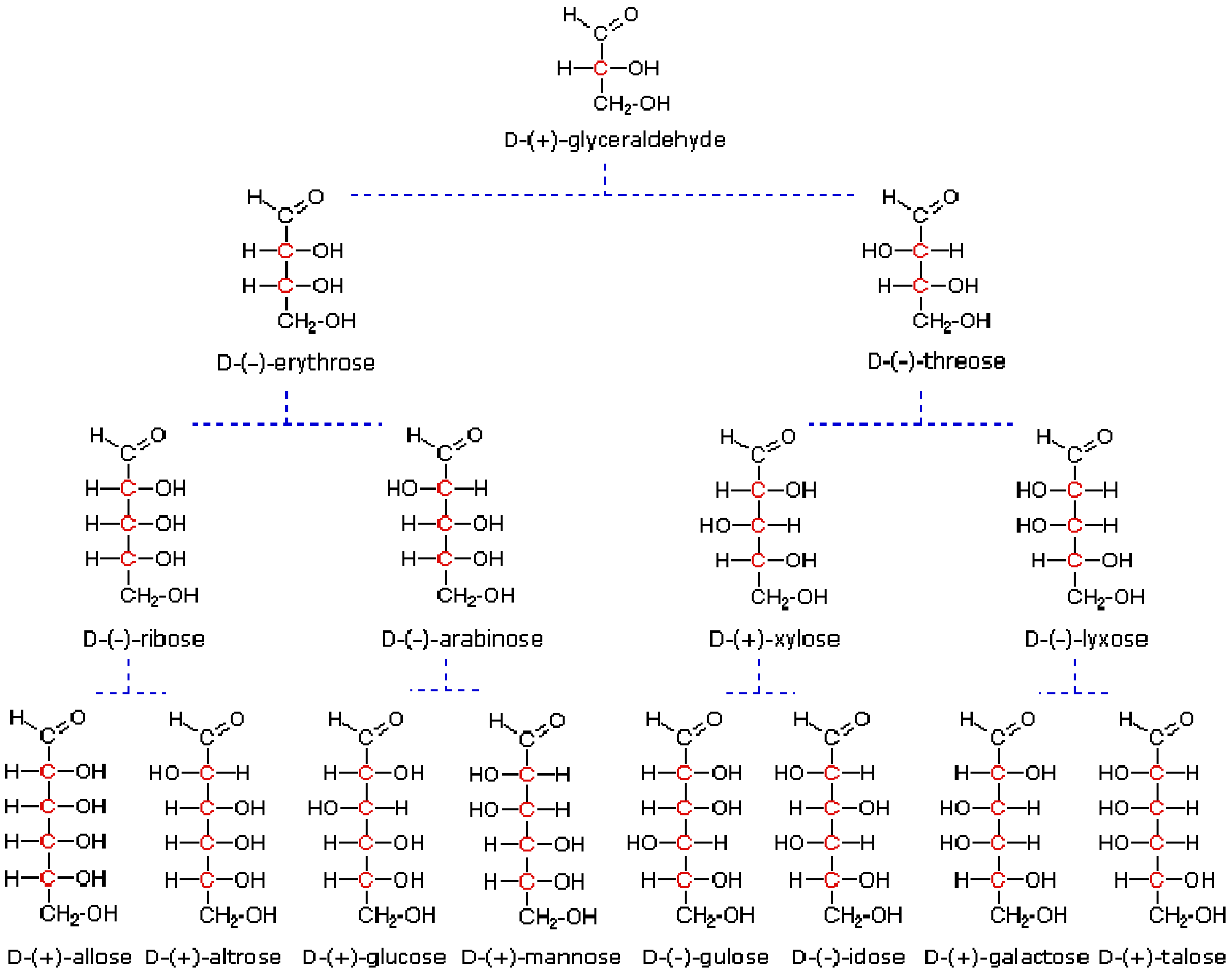
Aldose

sugars having an aldehyde function or an acetal equivalent.

Ketose

sugars having a ketone function or an acetal equivalent.

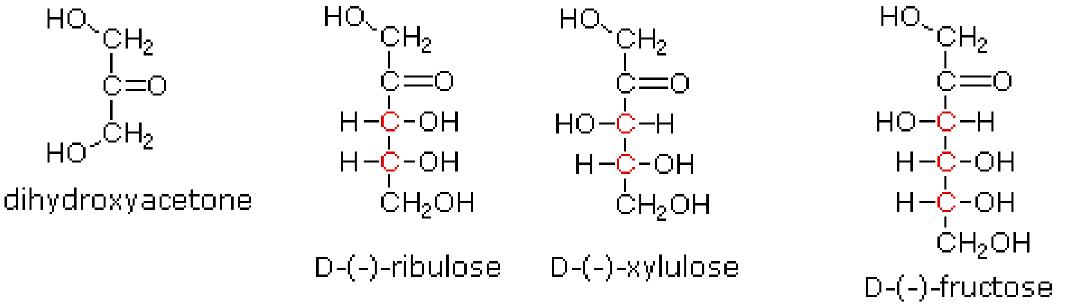
It is important to recognize that the sign of a compound's **specific rotation** (an experimental number) does not correlate with its configuration (D or L). It is a simple matter to measure an optical rotation with a polarimeter. Determining an absolute configuration usually requires chemical interconversion with known compounds by stereospecific reaction paths.



If a monosaccharide has a carbonyl function on one of the inner atoms of the carbon chain it is classified as a ketose. Dihydroxyacetone may not be a sugar, but it is included as the ketose analog of glyceraldehyde. The carbonyl group is commonly found at C-2, as illustrated by the following examples (chiral centers are colored red). As expected, the carbonyl function of a ketose may be reduced by sodium borohydride, usually to a mixture of epimeric products. D-Fructose, the sweetest of the common natural sugars, is for example reduced to a mixture of D-glucitol (sorbitol) and D-mannitol, named after the aldohexoses from which they may also be obtained by analogous reduction. Mannitol is itself a common natural carbohydrate.

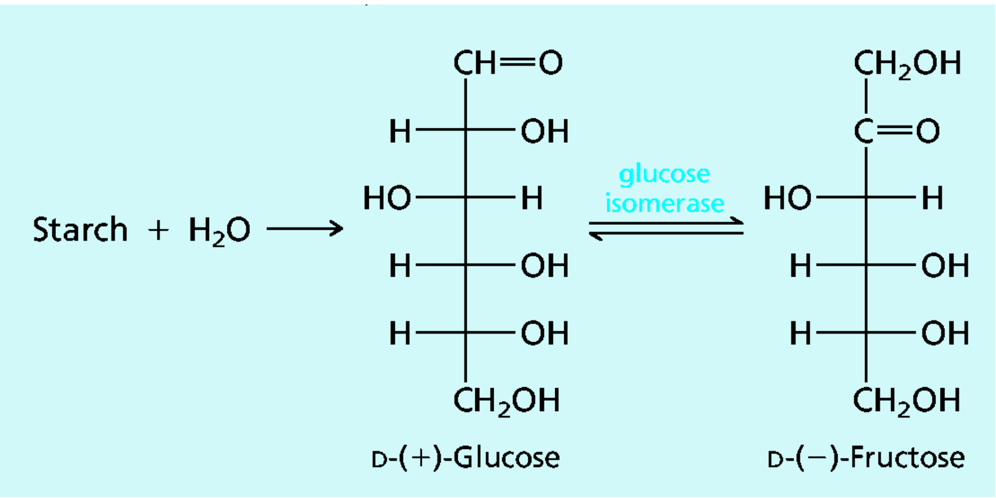
Although the ketoses are distinct isomers of the aldose monosaccharides, the chemistry of both classes is linked due to their facile interconversion in the presence of acid or base catalysts. This interconversion, and the corresponding epimerization at sites alpha to the carbonyl functions, occurs by way of an enediol tautomeric intermediate.

Ketose Examples



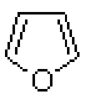
There is no shortage of compounds, natural or synthetic, that taste sweet. The most familiar are naturally occurring sugars, especially sucrose, glucose, and fructose. All occur naturally, with worldwide production of sucrose from cane and sugar beets exceeding 100 million tons per year. Glucose is prepared by the enzymatic hydrolysis of starch, and fructose is made by the isomerization of glucose.

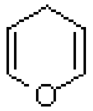
Among sucrose, glucose, and fructose, fructose is the sweetest. Honey is sweeter than table sugar because it contains fructose formed by the isomerization of glucose as shown in the equation.

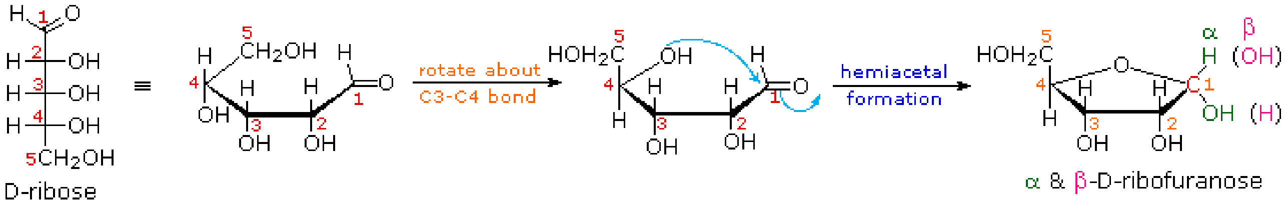


Cyclic Forms of Monosaccharides

As noted above, the preferred structural form of many monosaccharides may be that of a cyclic hemiacetal. Five and six-membered rings are favored over other ring sizes because of their low angle and eclipsing strain. Cyclic structures of this kind are termed **furanose** (five-membered) or **pyranose** (six-membered), reflecting the ring size relationship to the common heterocyclic compounds furan and pyran shown on the right. Ribose, an important aldopentose, commonly adopts a furanose structure, as shown in the following illustration. By convention for the D-family, the five-membered furanose ring is drawn in an edgewise projection with the ring oxygen positioned away from the viewer. The anomeric carbon atom (colored red here) is placed on the right. The upper bond to this carbon is defined as beta, the lower bond then is alpha.

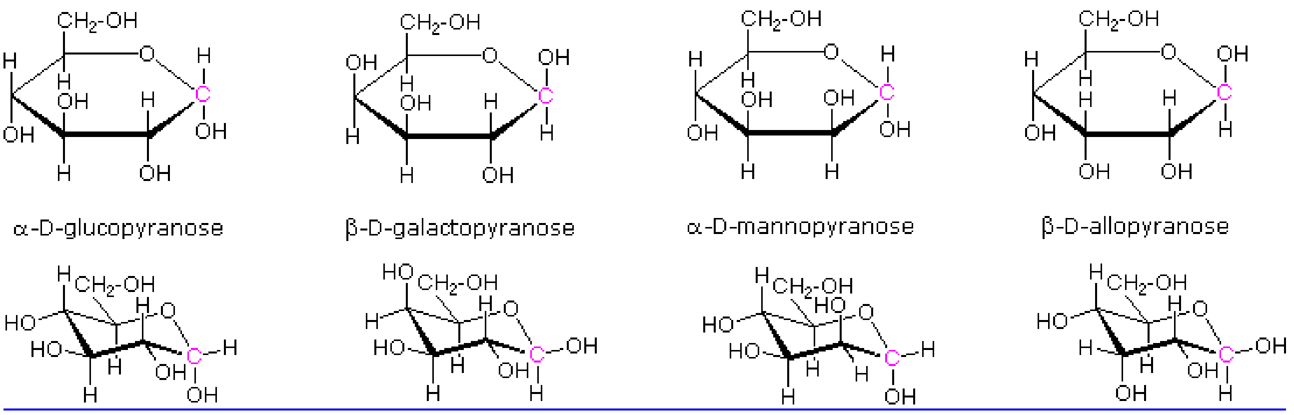

furan

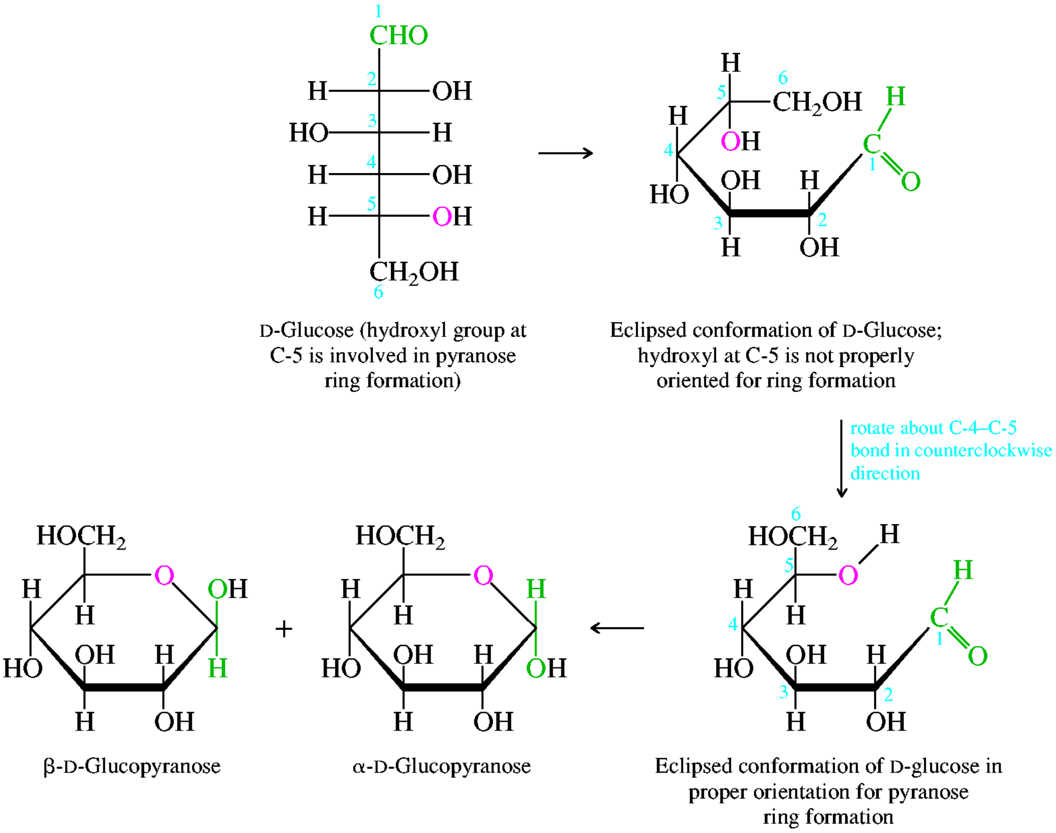

pyran



The cyclic pyranose forms of various monosaccharides are often drawn in a flat projection known as a Haworth formula, after the British chemist, Norman Haworth. As with the furanose ring, the anomeric carbon is placed on the right with the ring oxygen to the back of the edgewise view. In the D-family, the alpha and beta bonds have the same orientation defined for the furanose ring (beta is up and alpha is down). These Haworth formulas are convenient for displaying stereochemical relationships, but do not represent the true shape of the molecules. We know that these molecules are actually puckered in a fashion we call a **chair conformation**. Examples of four typical pyranose structures are shown below, both as Haworth projections and as the more representative chair conformers. The anomeric carbons are colored red.

Examples of Some Pyranose Forms of Hexoses


α-D-glucopyranose β-D-galactopyranose α-D-mannopyranose β-D-allopyranose



D-Glucose (hydroxyl group at C-5 is involved in pyranose ring formation)

Eclipsed conformation of D-Glucose; hydroxyl at C-5 is not properly oriented for ring formation

β-D-Glucopyranose

α-D-Glucopyranose

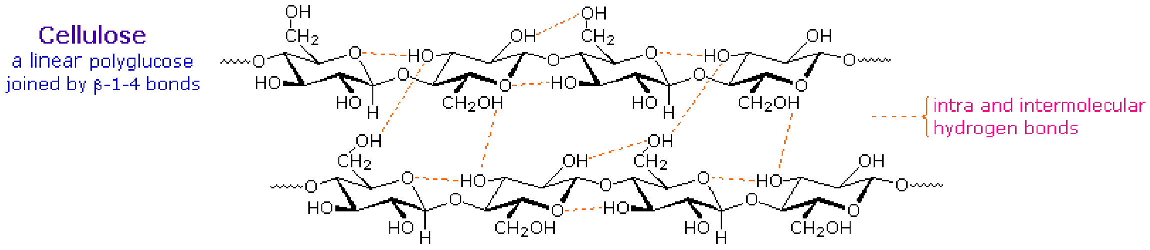
Eclipsed conformation of D-glucose in proper orientation for pyranose ring formation

POLYSACCHARIDES

As the name implies, polysaccharides are large high-molecular weight molecules constructed by joining monosaccharide units together by glycosidic bonds. They are sometimes called glycans. The most important compounds in this class, cellulose, starch and glycogen are all polymers of glucose. This is easily demonstrated by acid-catalyzed hydrolysis to the monosaccharide. Since partial hydrolysis of cellulose gives varying amounts of cellobiose, we conclude the glucose units in this macromolecule are joined by beta-glycoside bonds between C-1 and C-4 sites of adjacent sugars. Partial hydrolysis of starch and glycogen produces the disaccharide maltose together with low molecular weight dextrans, polysaccharides in which glucose molecules are joined by alpha-glycoside links between C-1 and C-6, as well as the alpha C-1 to C-4 links found in maltose. Polysaccharides built from other monosaccharides (e.g. mannose, galactose, xylose and arabinose) are also known, but will not be discussed here.

Over half of the total organic carbon in the earth's biosphere is in **cellulose**. Cotton fibers are essentially pure cellulose, and the wood of bushes and trees is about 50% cellulose. As a polymer of glucose, cellulose has the formula $(C_6H_{10}O_5)_n$ where n ranges from 500 to 5,000, depending on the source of the polymer. The glucose units in cellulose are linked in a linear fashion, as shown in the drawing below. The beta-glycoside bonds permit these chains to stretch out, and this conformation is stabilized by intramolecular hydrogen bonds. A parallel orientation of adjacent chains is also favored by intermolecular hydrogen bonds. Although an individual hydrogen bond is relatively weak, many such bonds acting together can impart great stability to certain conformations of large molecules. Most animals cannot digest cellulose as a food, and in the diets of humans this part of our vegetable intake functions as roughage and is eliminated largely unchanged. Some animals (the cow and termites, for example) harbor intestinal microorganisms that breakdown cellulose into monosaccharide nutrients by the use of beta-glycosidase enzymes.

Cellulose is commonly accompanied by a lower molecular weight, branched, amorphous polymer called hemicellulose. In contrast to cellulose, hemicellulose is structurally weak and is easily hydrolyzed by dilute acid or base. Also, many enzymes catalyze its hydrolysis. Hemicelluloses are composed of many D-pentose sugars, with xylose being the major component. Mannose and mannuronic acid are often present, as well as galactose and galacturonic acid.



Starch is a polymer of glucose, found in roots, rhizomes, seeds, stems, tubers and corms of plants, as microscopic granules having characteristic shapes and sizes. Most animals, including humans, depend on these plant starches for nourishment. The structure of starch is more complex than that of cellulose. Starch is a soft, white, tasteless powder that is insoluble in cold water, alcohol, or other solvents. The basic **chemical formula** of the starch molecule is $(C_6H_{10}O_5)_n$. Starch is a **polysaccharide** comprising glucose monomers **joined in *α* 1,4 linkages**. The simplest form of starch is the linear polymer; *amylopectin* is the branched form.