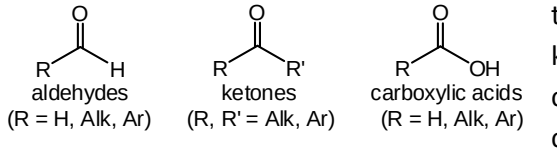
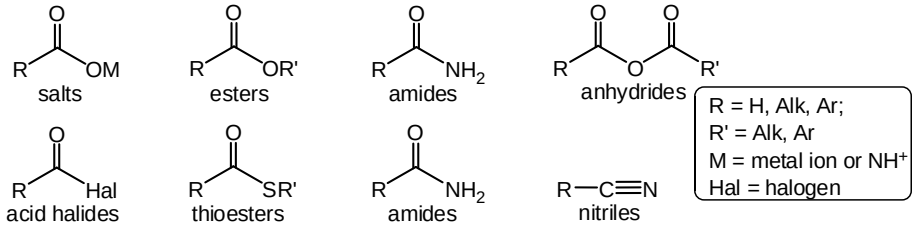
№ 27. CARBONYL COMPOUNDS – CLASSIFICATION, SELECTED REPRESENTATIVES FROM ALDEHYDES, KETONES, AND QUINONES. STRUCTURE AND REACTIVITY OF THE CARBONYL GROUP. CHARACTERISTIC CHEMICAL REACTIONS WITH MEDICO-BIOLOGICAL IMPORTANCE FOR ALDEHYDES, KETONES, AND QUINONES

I. Characteristics and classification The carbonyl compounds contain in their molecule a functional group called carbonyl group **>C=O**. Depending on the substituents at the carbon atom of the carbonyl group, the carbonyl compounds are subdivided into aldehydes, ketones, carboxylic acids, and functional derivatives of carboxylic acids. When one of the substituents on the carbonyl carbon is hydrogen atom, the compounds are named aldehydes.



Aldehydes have functional group –CHO (written always in this specific way in order to show presence of C-H bond and not O-H bond). The group is called aldehyde group. If both substituents on the carbonyl carbon are connected via their carbon atoms, then the compounds are ketones. The functional group of ketones is a carbonyl group (>C=O) and it is called ketone group (keto group). The functional group of carboxylic acids is the carboxyl group (-COOH). All three classes of compounds can be aliphatic or aromatic. Only in the case of ketones there is arylaliphatic subclass (R=Alk and R'=Ar).

The **functional derivatives of carboxylic acids** are their salts, esters, thioesters, acid halides, anhydrides, amides, and nitriles.



The functional group **R–CO–** in all these compounds is called an **acyl group**.

The functional group of nitriles is -C≡N. The product after hydrolysis of all derivatives of carboxylic acids is a carboxylic acid. The product after hydrolysis of a nitrile is also a carboxylic acid. Therefore, the nitriles are considered along with the derivatives of carboxylic acids.

The carbonyl group possesses high reactivity that varies according to the nature of the applied reagent. Due to these varieties the carbonyl compounds have very rich chemistry. For the same reason they are important in living organisms.

II. Selected representatives of aldehydes, ketones, and quinines

II.1. Aldehydes and ketones

$HCHO$ Methanal (trivial name formaldehyde is common; aqueous 40% solution- formalin)

CH_3CHO Ethanal (trivial name acetaldehyde is more common)

C_6H_5CHO Benzaldehyde

CH_3COCH_3 Propanone (trivial name acetone is more common; dimethylketone)

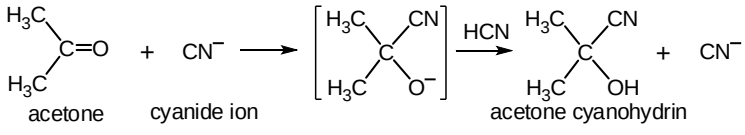
Formaldehyde is the simplest aldehyde. It is an important industrial precursor to many other chemical compounds, especially for polymers. It exhibits most of the chemical properties of other aldehydes but is more reactive. For example it is more readily oxidized by atmospheric oxygen to formic acid. Formaldehyde is a good electrophile, participating in electrophilic aromatic substitution reactions with aromatic compounds. When reacted with phenol (also with urea or melamine) formaldehyde produces hard phenol formaldehyde resin and other resins, which are commonly used in permanent adhesives such as those used in plywood or carpeting. An aqueous solution of formaldehyde can be useful as a disinfectant as it kills most bacteria and fungi (including their spores). Formaldehyde solutions are used as a fixative for microscopy and histology. In view of its widespread use, toxicity and volatility, exposure to formaldehyde is a significant consideration for human health.

Acetaldehyde is one of the most important aldehydes, occurring widely in nature and being produced on a large scale industrially. Because of its small size and its availability as the anhydrous monomer (unlike

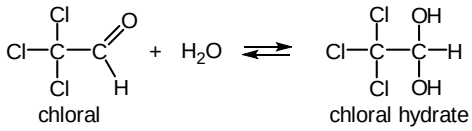
formaldehyde which is gas), it is a common electrophile in organic synthesis. Traditionally, acetaldehyde was mainly used as a precursor to acetic acid. In a synthesis, called Strecker reaction, acetaldehyde condenses with cyanide and ammonia to give, after hydrolysis, the amino acid alanine. Acetaldehyde can condense with amines to yield imines (Schiff's bases) that can react further to valuable compounds. In human metabolism, the enzyme alcohol dehydrogenase oxidizes ethanol in the liver into acetaldehyde, which is then further oxidized into harmless acetic acid.

Benzaldehyde is the simplest aromatic aldehyde and one of the most industrially useful. This colorless liquid has a characteristic pleasant almond-like odor. In fact, benzaldehyde is the primary component of bitter almond oil and can be extracted from a number of other natural sources. On oxidation, benzaldehyde is converted into the odorless benzoic acid. On reduction (by hydrogenation) benzaldehyde gives benzyl alcohol. A common use of benzaldehyde is to confer almond flavor. Benzaldehyde is used chiefly as a precursor to other organic compounds, ranging from pharmaceuticals to plastic additives.

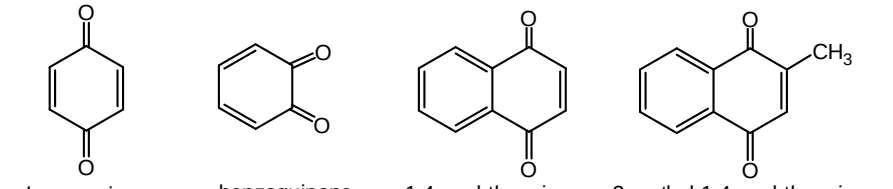
Acetone is the simplest example of the ketones. It is produced industrially in very large amount, mainly as a precursor to polymers. About half of the world's production of acetone is consumed as a precursor to methyl methacrylate (used for making polymers). This application begins with the initial conversion of acetone to its cyanohydrin via a nucleophilic addition reaction. It is a common building block in organic chemistry. Acetone is an important solvent for laboratory or household purposes. Familiar household uses of acetone are as the active ingredient in nail polish remover and as paint thinner and sanitary cleaner. Acetone is naturally produced and disposed of in the human body as a result of normal metabolic processes like decarboxylation of ketone bodies.



Chloral, also known as trichloroacetaldehyde, is with the formula Cl_3CCHO. It reacts with water (similarly to other aldehydes and ketiones by a nucleophilic addition reaction) to form chloral hydrate which was widely used sedative and hypnotic substance.

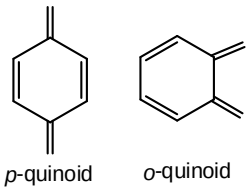


II.2. Quinones belong to a class of organic compounds that are formally derived from aromatic compounds (such as benzene or naphthalene) by exchanging an even number of –CH= groups by –C(=O)– groups, with any necessary rearrangement of double bonds, resulting in a fully conjugated cyclic dione structure. The class includes derivatives of heterocyclic aromatic compounds. Quinones can be viewed as cyclohexadienediones but are named as derivatives of aromatic systems, e.g benzoquinones are derived from benzene, naphthoquinones – from naphthalene etc.



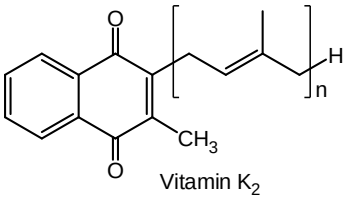
The prototypical member of the class is 1,4-benzoquinone (*para*-quinone), often called simply **quinone** (whence the name of the class). This name should not be mistaken with quinine – the alkaloid with antimalarial and fever-reducing properties. Other important examples are 1,2-benzoquinone (*ortho*-quinone), 1,4-naphthoquinone and 9,10-anthraquinone. Benzoquinone is used in organic chemistry as an oxidizing agent. Stronger quinone oxidizing agents exist; for instance: chloranil (2,3,5,6-tetrachloro-1,4-benzoquinone) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (known as DDQ).

Quinone type of structures are frequently encountered in colored compounds and the structural units are referred to as "quinoid" structures, such as:

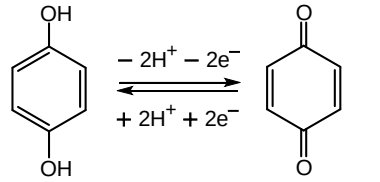


Many quinones and related structures occur in Nature and play important role as microcomponents in living organisms. Two examples are vitamin K and coenzyme Q.

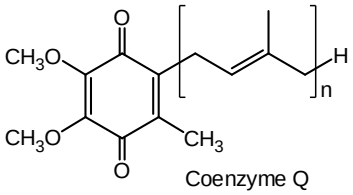
Vitamin K is a group of lipophilic, hydrophobic vitamins that are needed for the posttranslational modification of certain proteins, mostly required for blood coagulation (K stands in the name for "koagulation" in Dannish) but also involved in metabolism pathways in bone and other tissue. They are all related to 2-methyl-1,4-naphthoquinone or to compounds that can be oxidized to it. Some vitamin K is provided by the normal diet, but a large proportion of that required by humans is produced by their intestinal flora.



Vitamin K_2



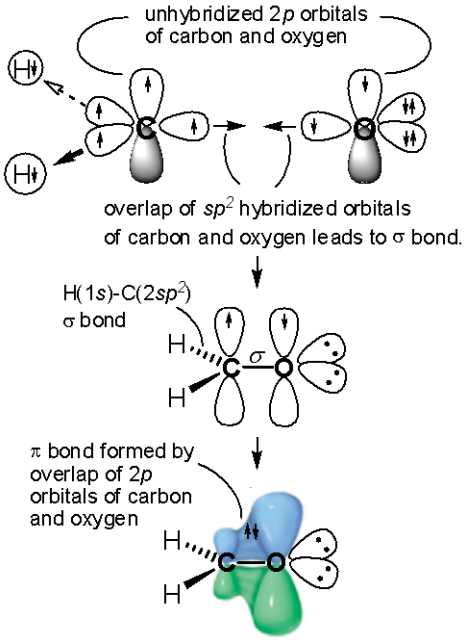
hydroquinone *p*-benzoquinone



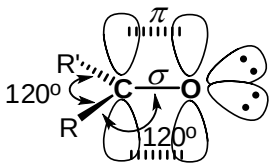
Coenzyme Q

Quinones are related to the corresponding hydrogenated diphenols by an oxidation-reduction process. For instance, the interconversion of hydroquinone and *p*-benzoquinone involves two one-electron transfers. The ready reversibility of this reaction is essential to the role that quinones play in cellular respiration, the process by which an organism utilizes molecular oxygen to convert its food to carbon dioxide, water, and energy. Electrons are not transferred directly from the substrate molecule to oxygen but instead they are transferred by way of an *electron transport chain* involving several redox reactions. A key component of this electron transport chain is the substance known as **Coenzyme Q** (or ubiquinone, where n = 6, 8, or 10). The name "ubiquinone" is shortened from "ubiquitous quinone" that describes the fact that all cells contain CoenzymeQ.

III. Structure and reactivity of the carbonyl group



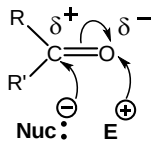
III.1. ***Structure and bonding***. Two of the more notable aspects of the carbonyl group are its geometry and its polarity. The carbonyl group and the atoms attached to it lie in the same plane. **Formaldehyde**, for instance, is a planar molecule. The carbon atom of a carbonyl group is sp^2-hybridized and has trigonal geometry. This carbon atom is bonded to three other atoms (one is oxygen, the others can be hydrogen, carbon, or heteroatoms in carboxylic acid derivatives) through three σ-bonds (sigma-bonds) that are oriented in the same plane at about 120°. Perpendicular to this plane is located the unhybridized *p*-orbital on the carbonyl carbon. This orbital participates in π-bonding (pi-bond) by overlapping with an oxygen unhybridized *2p*-orbital. In a C=O group the oxygen atom is also sp^2-hybridized. The double bond between oxygen and carbon is similar to alkene C=C double bond, except that the carbonyl double bond is shorter and stronger. The C=O bond length is 122 pm, significantly shorter than typical C-O bond distance of 141 pm seen in alcohols and ethers. In any other aldehyde and ketone the bonding pattern is similar.



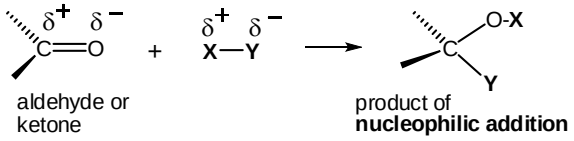
	Type of bond	Length	Energy
in a ketone	C=O	122 pm	745 kJ.mol^{-1}
in an alkene	C=C	134 pm	611 kJ.mol^{-1}

Another difference between the carbonyl and alkene double bonds is the large dipole moment of the carbonyl group. Because of the higher electronegativity of oxygen than carbon, the electron density in both the σ and π components of the carbon-oxygen double bond is displaced toward oxygen. In particular, the less tightly held π electrons are pulled more strongly toward the oxygen atom, as is shown schematically for

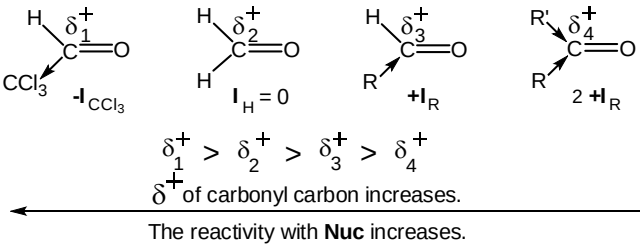
formaldehyde above. The carbonyl group is polarized so that carbon is partially positive and oxygen is partially negative. This polarization plays enormous role in the reactivity of aldehydes and ketones. The positively polarized carbon (that is electrophilic) attracts negatively charged particles or reagents having increased electron density. Such reagents are called **nucleophiles** (**Nu**, Nuc). The negatively polarized oxygen acts on electrophiles that are attracted to increased electron density. Thus, nucleophiles (Nuc:$^-$) react at carbon whereas electrophiles (E^+) react at oxygen.



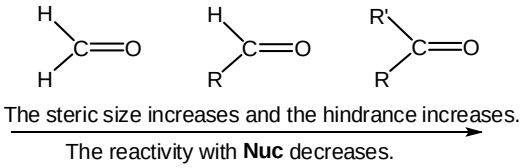
One of the characteristic s of the carbonyl group is its tendency to undergo **nucleophilic addition** reactions of the type represented by the general equation. A negatively polarized atom or group (Y) is transferred to the positively polarized carbon of the carbonyl group in the rate-determining step of these reactions. Many valuable organic synthetic reactions belong to this class. Chloral hydrate was already mentioned. Its formation proceeds via nucleophilic addition of water to chloral, following such mechanism. In a later section, addition of an alcohol to aldehydes will be shown to proceed via the same mechanism.



III.2. ***Influence of substituents***. The reactivity of a carbonyl group toward nucleophiles is governed by electronic and steric factors contributed by the attached substituents.

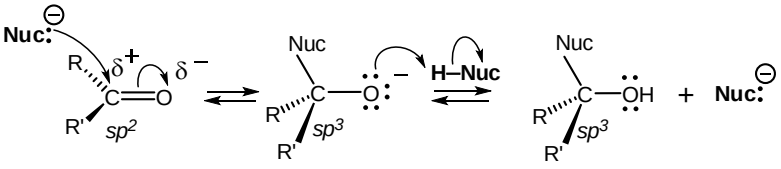


Formaldehyde is usually taken as a reference. Any substituent replacing H atoms in formaldehyde that decreases the electron density at carbonyl carbon will lead to increased reactivity. On the contrary, electron donating substituents that increase the electron density at carbonyl carbon will decrease its reactivity. Therefore, aldehydes are more reactive than ketones which contain two alkyl groups, *vs.* one in aldehydes, that donate electron density (+I effect of an alkyl).



The steric effect is due to larger size of any alkyl group that substitutes hydrogen on a carbonyl carbon. Thus the increased crowding of ketones in respect to aldehydes renders the latter less reactive.

III.3. ***Reactivity***. Aldehydes and ketones undergo many different reactions that give wide variety of new and useful products. Their reactivity arises from the electronegativity of the oxygen and the resulting polarization of the carbon-oxygen double bond. The carbonyl carbon atom, bearing a partial positive charge, attracts and adds nucleophiles. Since that carbon is sp^2 hybridized and has planer arrangement of connected to it atoms, it is relatively unhindered and is open to attack from either face of the double bond. When a nucleophile adds (slow step) to carbonyl group, the hybridization state of carbon changes from sp^2 to sp^3. The electrons of the π bond shift completely to the oxygen atom, giving an intermediate with a full negative charge on oxygen. This oxygen is protonated (fast step) later and the overall reaction is *nucleophilic addition*: the addition of a nucleophile and a proton across the C=O double bond. In principle, two enantiomeric products (non-superimposable mirror images) are possible when the nucleophilic attack occurs with equal probability from both sides of the C=O plane.



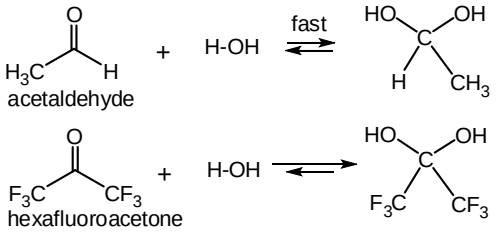
Nucleophilic addition reactions are the most common reactions for aldehydes and ketones. Ketones are less reactive than aldehydes due to the aforementioned electronic and steric effects.

IV. The reaction of aldehydes and ketones with nucleophiles

Both classes of compounds, aldehydes and ketones, form series of characteristic derivatives by *addition reactions* (i.e. reactions from which the molecular formula of a product is sum of the molecular formulae of the reagents) and *condensation reactions* (i.e. reactions in which the combination of the reagents occurs with elimination of water, alcohol or other small molecule). Both of these types of reactions have common initial stages and pathways that commence with nucleophilic attack on the carbonyl carbon.

IV.1. Addition reactions of aldehydes and ketones

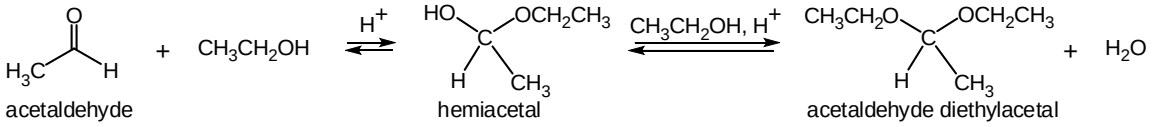
Typical reagents for these reactions are (**H-X** where **X:**$^-$ is a nucleophile and **H**$^+$ - proton): H-OH (water to give hydrates), H-OR (alcohols to give hemiacetals or acetals), H-SR (thiols to give thioacetals), H-CN (hydrogen cyanide to give cyanohydrins), H-NH_2 (ammonia or primary amines to give Schiff's bases), H-OSO_2^- Na^+ (bisulfite anion to give a bisulfite adduct). The fate of the intermediately formed product, R-CH(O**H**)**X**-R', depends on the structure of the starting carbonyl compound, on the nature of the nucleophile, and on the conditions. The formation of the product may be reversible, irreversible or it may lead to elimination of water.



Examples: Addition of water.

A striking example of an electronic effect on carbonyl group is the hydration of hexafluoroacetone. In comparison, acetone is almost negligible hydrated, acetaldehyde is hydrated to about 50% conversion, and hexafluoroacetone is completely hydrated.

Addition of alcohols – formation of hemiacetals, hemiketals, acetals, and ketals. Aldehydes and ketones react by nucleophilic addition mechanism with alcohols to form acetals and ketals (the last term is now dropped from IUPAC nomenclature and the derivatives of ketones are called also acetals). The addition of one mole of alcohol gives intermediates called hemiacetals ("hemi" means half).

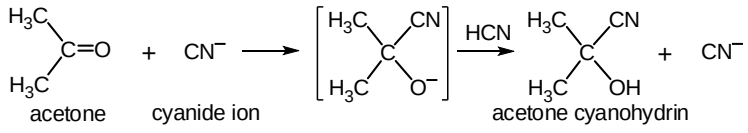


The second half of the reaction converts the hemiacetal into more stable acetal (after elimination of water via a carbocationic intermediate). The properties of acetals from aldehydes and from ketones are similar. Acetal formation is reversible. An equilibrium is established between starting carbonyl compound and the alcohol, and the acetal product. The position of this equilibrium is favorable for most aldehydes, especially when excess alcohol is present as a solvent. For most ketones, the equilibrium position is unfavorable and other methods for preparation are used. Cyclic acetals are produced from diols, e.g. ethylene glycol. These cyclic acetal are valuable in organic synthesis because they "protect" the carbonyl function during reactions at other parts of the molecule. Acetals are susceptible to hydrolysis in aqueous acid. This reaction is simply the reverse of the reaction by which acetals are formed – acetal formation is favored by excess alcohol, acetal hydrolysis - by excess water. Acetal formation and acetal hydrolysis share the same mechanistic pathway but travel this in opposite directions. Acetals are abundant as stable structures in carbohydrate chemistry. Both glucose (an aldehyde) and fructose (a ketone) exist in cyclic forms that carry hemiacetal groups. Other carbohydrates like sucrose (table sugar), lactose (milk sugar) and starch contain acetal groups.

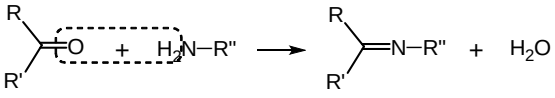
Hemithioacetals and thioacetals are formed similarly to acetals, using thiols instead of alcohols.

Addition of hydrogen cyanide.

The product of addition of hydrogen cyanide to an aldehyde or a ketone contains both a hydroxyl group and a cyano group bonded to the same carbon. Such compounds are called cyanohydrins. The mechanism of the reaction follows the same general pathway outlined above. Initial nucleophilic attack of cyanide ion gives tetrahedral alkoxide ion that

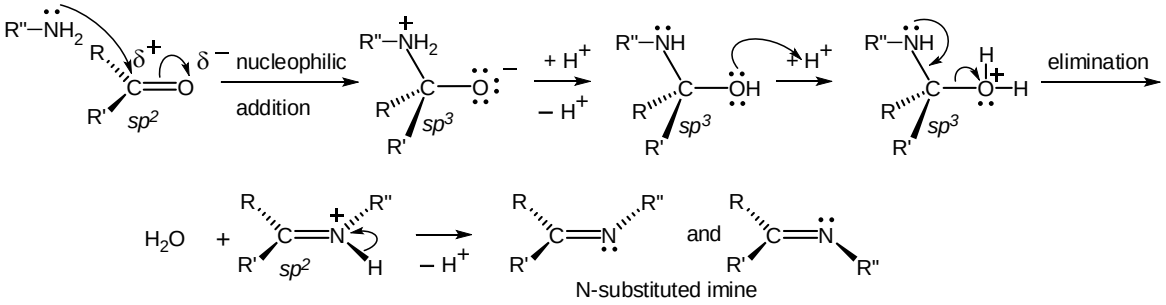


abstracts proton from hydrogen cyanide. Cyanohydrin formation is also reversible, and the equilibrium position depends on the steric and electronic factors. Cyanohydrin formation is a reaction of synthetic value because a new carbon-carbon bond is made by this process and the cyano group may be converted to a carboxylic acid function. Effectively this elongates a chain by one carbon. Historically the reaction has been applied in carbohydrate chemistry.



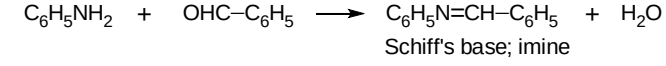
IV.2. Condensation reactions of aldehydes and ketones

A two stage reaction that begins with *nucleophilic addition* to aldehydes or ketones is their reaction with primary amines of type R-NH_2 or Ar-NH_2. The mechanism of this reaction involves initial attack (as discussed above) of nitrogen lone pair on the carbonyl carbon. Under weakly acidic conditions, after deprotonation of N and protonation of O^-, the resulting 1,1-aminoalcohol (carbinolamine) is unstable.

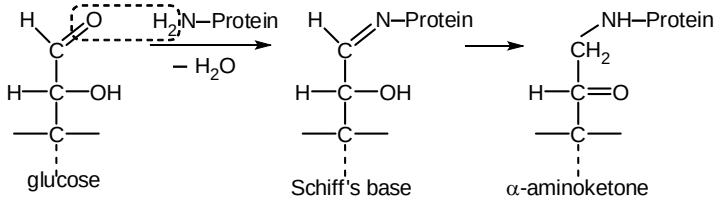


The intermediate undergoes dehydration (*elimination* of water) to yield the product of the reaction, an N-substituted **imine**. The functional group of imines is carbon-nitrogen double bond (C=N). Such compounds are often called Schiff's bases, after the chemist's name who discovered them. Imine formation is reversible reaction where both the addition and elimination phase are accelerated by acid. The products have not only synthetic value but are relevant to biochemical processes. Many biological reactions involve initial binding of a carbonyl compound to an enzyme or a coenzyme by way of imine formation. For instance, the nerve impulse for vision is triggered by a Schiff's base.

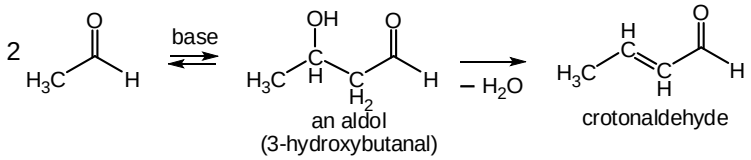
An example of Schiff's base:



Similar condensation process is recognized with pathogenic role in the complications of diabetes. The reaction called **glycation** or **non-enzymatic glycosylation** occurs between a sugar molecule (such as fructose or glucose, mostly in the bloodstream) and a protein or lipid molecule without the controlling action of an enzyme. The first step in glycation reaction is the condensation between the carbonyl group of a reducing sugar and free amino group of lysine residue in a protein. The result is labile Schiff's base that undergoes Amadori rearrangement to form more stable aminoketone.



IV.3. Aldol condensation.

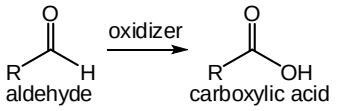


This reaction begins at a carbon adjacent to carbonyl group (the α-carbon) that has more acidic hydrogens and can give an enol. The aldol condensation is a reaction of an enol or an enolate ion that reacts with a carbonyl compound to form a β-hydroxyaldehyde (aldol = **ald**ehyde - alcoh**ol**). This product usually undergoes dehydration to give the unsaturated, conjugated enone. In its usual form, the reaction involves nucleophilic addition of a ketone enolate to an aldehyde. In such cases, the aldehyde should not contain α-hydrogens. The many varieties of aldol reactions have enormous importance in

the organic synthesis because a new carbon-carbon bond is formed. The name aldol condensation is also commonly used in biochemistry, particularly in carbohydrate metabolism.

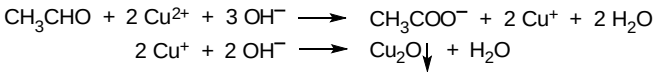
V. Redox reactions

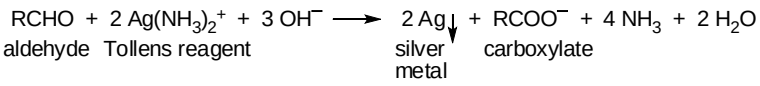
V.1. Oxidation of aldehydes and ketones. Aldehydes are readily oxidized to the corresponding carboxylic acids whereas ketones are not.



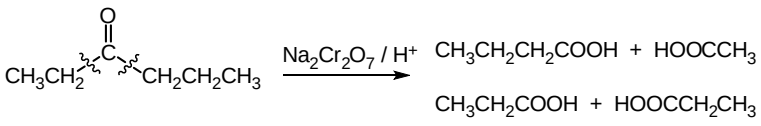
Besides the usual powerful oxidizing agents, such as acidified potassium dichromate, potassium permanganate, and nitric acid, the oxidation of aldehydes can be achieved by a number of relatively weak oxidizers. Fehling's solution (an alkaline solution of copper(II)tartrate complex ion), Benedict's solution (alkaline copper(II)citrate complex), or Tollens' reagent (weakly alkaline diaminosilver ion $[Ag(NH_3)_2]^+$ solution) can all oxidize simple aldehydes with accompanying reduction to copper(I)oxide or metallic silver (the "silver mirror" test for aldehydes and reducing sugars). These three reagents can not oxidize ketones.

Fehling or Benedict tests are positive when precipitation of red cuprous oxide is observed. Fehling complex can be used for test of aliphatic aldehydes, whereas Tollens reagent tests for both aliphatic and aromatic aldehydes.

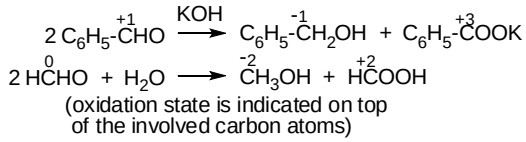




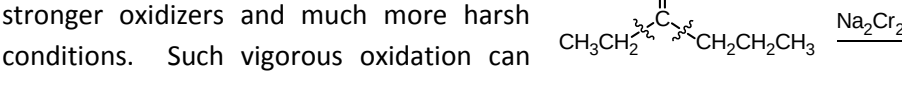
The oxidation of ketones requires stronger oxidizers and much more harsh conditions. Such vigorous oxidation can degrade a ketone by cleaving of C-CO bonds to give a mixture of carboxylic acids with shorter chains.

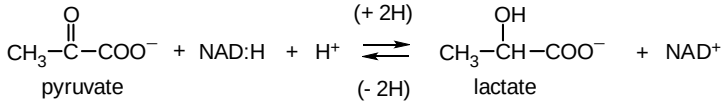


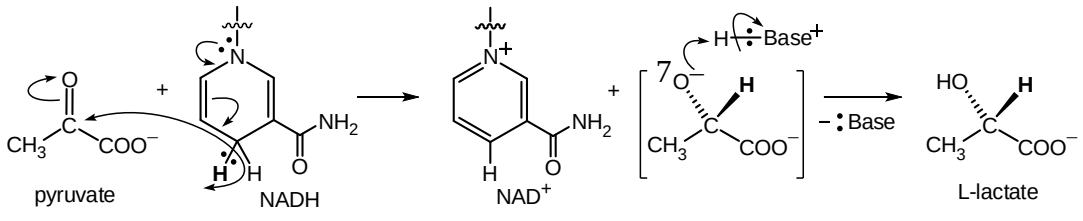
V.2. Disproportionation of aldehydes (Cannizarro reaction). A disproportionation reaction is called such reaction (reversible or irreversible) in which a species is simultaneously reduced and oxidized so as to form two different products. A reactant in disproportionation reaction contains element that can have at least three oxidation states. The reactant contains that element in an intermediate oxidation state whereas one of the products contains that element in higher oxidation state, and a second product has the element in lower oxidation state. Cannizarro reaction is base-catalyzed disproportionation of an aldehyde lacking a hydrogen atom at α-position. The oxidation product is a carboxylic acid, and the reduction product is an alcohol. For aldehydes with α-hydrogens, the preferred reaction is aldol condensation.



V.3. Reduction of aldehydes and ketones. Aldehydes are reduced to primary alcohols and ketones are reduced to secondary alcohols. When hydrogen gas is used for the process, usually in the presence of a catalyst, the reaction is catalytic hydrogenation. Industrially, at elevated temperature and pressure, in the presence of finely divided nickel catalyst, the carbonyl group of an aldehyde or ketone can add hydrogen molecule. Another approach in organic synthesis is to use various donors of hydride ions that attack nucleophilically the carbonyl carbon. Of course, the conditions of both modes of reductions are not compatible with lining cells. However, similar reduction processes occur in living systems. NADH is a reducing agent that donates electrons to a substrate in the form of hydride ion, followed by a proton. NAD^+ is an oxidizing agent - it accepts electrons from

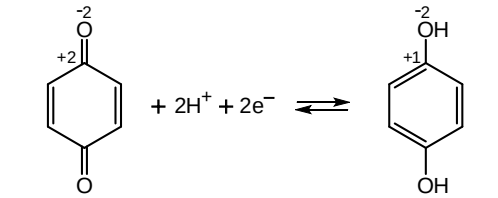






other molecules and becomes reduced to NADH. The electrons are transferred again in the form of a hydride ion followed by a proton. When applied to a carbonyl group, as in pyruvate, both redox reactions have net effect of adding/removing two hydrogen atoms and a pair of electrons. NAD^+ is a coenzyme found in all living cells. The redox reactions involving NAD^+/NADH are of particular importance for release of energy from nutrients. For instance, glycolysis leads to oxidation of glucose, to lactate by way of pyruvate, thereby releasing energy that is transferred to NAD^+ by reduction to NADH. Notice, that the hydride transfer from NADH to pyruvate is **stereoselective**, i.e. it occurs only from one side (face) of the plane of C=O bond. Enzyme catalyzed reductions of carbonyl groups are completely stereoselective. Pyruvate is converted exclusively into L-(+)-lactate by the lactate dehydrogenase - NADH system. The enantiomeric D-(-)-lactate is not formed at all. This is in sharp contrast to the industrial catalytic hydrogenation above, where if special conditions are not applied, both possible enantiomers are produced in equal amount.

V.4. Redox reactions for quinones. Quinones can be reduced by chemical means to the corresponding dihydroxy aromatic compounds. However, the important aspect of this redox system is its electrochemical reversibility. Coenzyme Q and vitamin K are prominent examples of biological redox systems using quinone-hydroquinone interconversion. This redox reaction in coenzyme Q is a key component of the electron transport chain.



p-benzoquinone hydroquinone