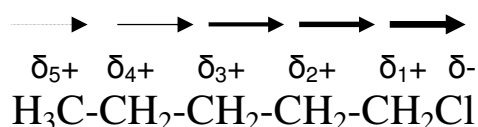# REACTIVITY OF BASIC FUNCTIONAL GROUPS IN ORGANIC COMPOUNDS

Compounds of carbon, in contrast to those of other elements, are extremely numerous and have specific properties that are subject of organic chemistry. Understanding of at least the most basic principles of organic chemistry is the very necessary prerequisite for the further study of biochemistry.

There are some basic universal principles, that allow you to predict properties and reactivity of given organic compound and to understand the reaction mechanism. These are "**Inductive effect**" and "**Mesomeric effect**". Both are related to a shift of electrons along the chemical bond.

Bonds in organic chemistry are typically non-polar, since the electronegativities of carbon and hydrogen (main components of organic compounds) are similar. When hydrogen in given organic compound is substituted by much more electronegative atom (such as oxygen, chlorine, etc.) electrons tend to move towards it (forming partial negative charge δ-, while neighboring carbon gains partial positive charge δ+) and the bond becomes polarized. This is just beginning of a "chain reaction": carbon (No 1) with partial positive charge "posesses less electrons than desired and tries to fix it by stealing electron from its neighbor (carbon No 2)". Carbon No 2 gains partial positive charge and does the same as Carbon No 1 – attracts electrons from carbon No 3. The bigger the distance from "intruder" (in our case chlorine), the weaker effect and the smaller partial charge $(\delta_1 > \delta_2 > \delta_3 > \delta_4 > \delta_5)$.

$$\delta_5+ \quad \delta_4+ \quad \delta_3+ \quad \delta_2+ \quad \delta_1+ \quad \delta-$$
$$H_3C\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2Cl$$

This migration of electrons towards electronegative substituent is called *Negative inductive effect (-I). Positive inductive effect (+I)* would take place when the substituent would be less electronegative (compared with hydrogen) – the direction of "electron flow" would be opposite.
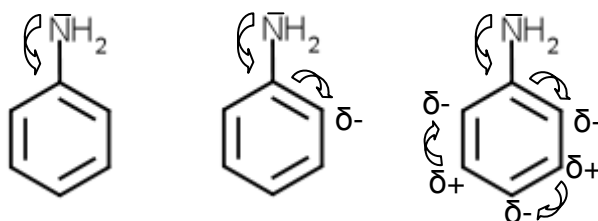
Substituents typically associated with: $-I$ ..... halogens (-X), =O, -OR, -NH$_2$, -NO$_2$
$+I$ ..... alkyles, metals, -O$^-$, -S$^-$

Inductive effect employs σ-electrons (electrons of a single bond) while in case of mesomeric effect, π-electrons (electrons of double bond or free electron pairs) of conjugated system are shifted (conjugated system means that double and single bonds alternate). Mesomeric effect can be either negative (-M, electrons migrate towards substituent – see example of propenoic acid below)

$$H_2C=CH \xrightarrow{\delta-} C \overset{O}{\underset{OH}{\diagdown}}$$
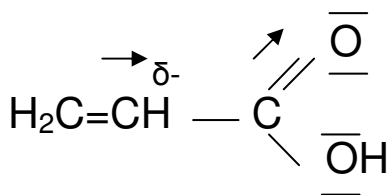
or positive (+M, electrons migrate in the other direction – see aniline below). Positive mesomeric effect in the molecule of aniline leads to delocalization of electrons. Free electron pair of amino group is moved towards carbon No 1. Higher electron density at this

atom affects neighboring double bond – π electrons of double bond between C1 and C2 tend to accumulate close to C2, giving this atom partial negative charge. Again, this charge affects distribution of π electrons of the next double bond, and so on. Finally, aniline molecule has partial positive charges in m- positions (and these atoms would be preferred locations for nucleophilic attacks) and negative ones in o- and p- positions (electrophilic attacks would preferentially take place in these positions).

Substituents typically associated with: -M ..... $-NO_2$, -COOH, -COR, -CN

+M ..... –halogens (-X), $-O^-$, $-S^-$, -OR, $-NH_2$

Note, that the same substituents can exhibit opposite mesomeric and inductive effect (eg halogens have +M, -I). Both effects are combined and the resulting electron shift would be in the direction of the predominant effect for given compound.

Our experiments demonstrate some basic properties of the main functional groups of organic compounds:

Hydroxyl group	–OH	(alcohols, phenols)
Carbonyl group	>C=O	(aldehydes, ketones)
Carboxyl group	–COOH	(carboxylic acids)
Amino group	$-NH_2$	(amines)

Alcohols

Alcohols are aliphatic (non-aromatic) hydrocarbons having hydroxyl (-OH) group bonded to carbon atom. Alcohols are classified as primary (1°), secondary (2°) or tertiary (3°), which refers to the carbon bearing the hydroxyl group.
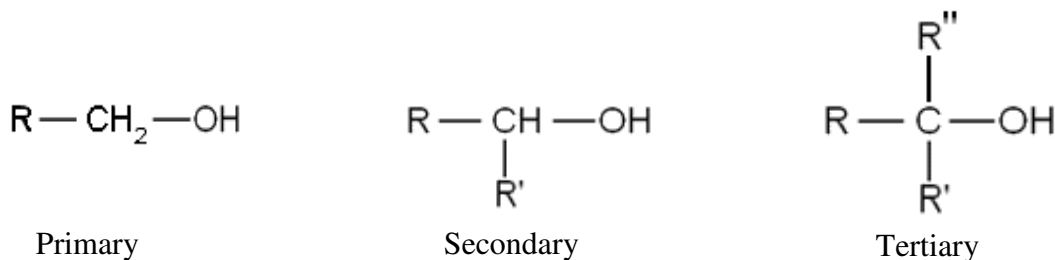
Since the bond between oxygen and hydrogen is polarized (oxygen is partially negative, hydrogen partially positive), proton can be cleaved off and released. Alcohols thus behave like acids (very weak). Due to the positive inductive effect of hydrocarbon chain (we can consider alcohols as derivatives of water, where one of the hydrogen atoms is substituted by –R), the polarization of this bond is ameliorated and the acidity decreases. The longer the R, the stronger +I, the weaker acid it is. It means that methanol behaves as the strongest acid among primary alcohols (but still is weaker than water), secondary alcohols are weaker acids than primary ones, and tertiary are weaker acids than secondary alcohols.

Alcohols are capable of undergoing many different reactions. In this practical lesson, we will focus mainly on their oxidation.

Oxidation of primary as well as secondary alcohols produces carbonyl compounds. Primary alcohols are oxidized to aldehydes, secondary to ketones; while tertiary alcohols are not oxidized at all (a very strong oxidation agent would cleave the hydrocarbon chain and oxidize resulting fragments).
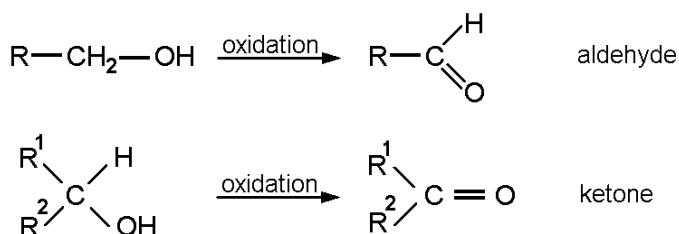

Thus, for instance, methanol is oxidized by chromate to formaldehyde, while chromate is reduced to green chromium(III) sulfate:

$$3\,CH_3OH \; + \; K_2Cr_2O_7 \; + \; 4\,H_2SO_4 \; \rightarrow \; 3\,H_2C{=}O \; + \; Cr_2(SO_4)_3 \; + \; K_2SO_4 \; + \; 7\,H_2O$$
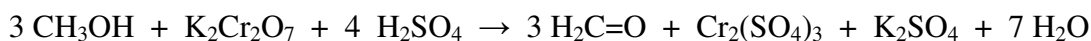
Such reaction can be used to distinguish tertiary alcohol (no reaction) from primary or secondary alcohol (both are oxidized, green chromium (III) sulfate is produced). Alternatively, a milder oxidizing agent can be used – violet potassium permanganate is reduced to brown manganese dioxide. To distinguish primary and secondary alcohol, their oxidation products can be analyzed. Aldehyde (resulting from primary alcohol oxidation) can be detected using Schiff reagent (see chapter Aldehydes, ketones below), while ketone (resulting from secondary alcohol oxidation) does not react.
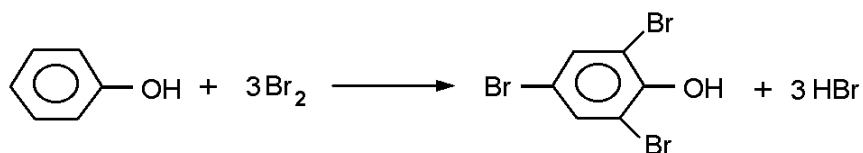
Phenols

In contrast to alcohols, phenols are substances, where the hydroxyl group is bonded directly to an aromatic ring. Solubility of phenols in water is generally poor. In phenols the positive mesomeric effect of oxygen "dumps" its electrons (from free electron pair) towards the aromatic ring. As a result, oxygen "feels electron deprivation" (it lost electrons despite its electronegativity) and "steals" electron from hydrogen atom, increasing the polarity of the O-H bond. Phenols thus tend to dissociate proton, i.e., are stronger acids than alcohols.
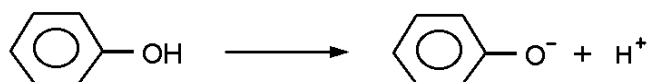
Thus, when dissolving phenols in a hydroxide, phenolate is produced:
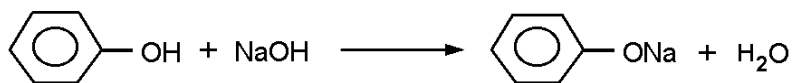
Phenol, C_6H_5-OH, easily undergoes electrophilic substitution of hydrogen atoms on the aromatic ring (due to the positive mesomeric effect, this is most likely to occur in the o- and p- positions). With halogens, phenol yields halogen derivatives, for example tribromophenol after substitution by bromine:

Hydroquinone, as well as other polyfunctional phenols that have hydroxyl groups in -o (1,2) or p- (1,4) position, is very easily oxidized. Oxidation of hydroquinone yields 1,4-benzoquinone:
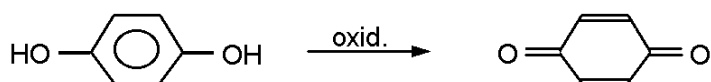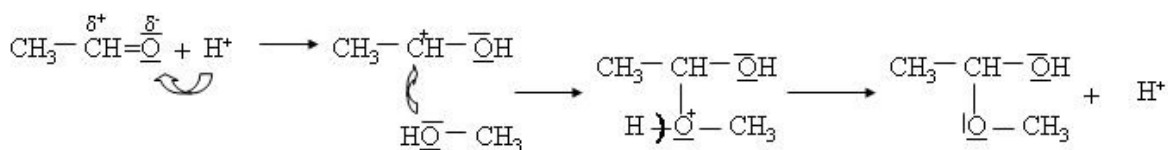

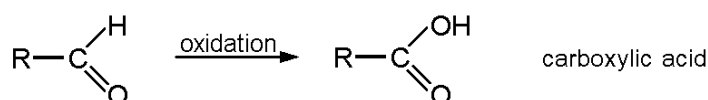Most phenols also form colored coordination complexes with ferric ions in aqueous solutions.

Aldehydes, ketones

Both aldehydes and ketones contain carbonyl group, consisting of oxygen double bonded to carbon atom. Electronegative oxygen attracts π electrons of double bond and gains partial negative charge, whereas carbon atom is partially positively charged. Positively charged carbon is susceptible to nucleophilic additions. Reactivity of carbonyl group is directly proportional to the size of partial charge. When substituents exhibiting positive inductive effect (such as aliphatic hydrocarbons) are located on the carbonyl carbon, partial charge would be lower as well as the reactivity of given compound. The more +I substituents or/and the stronger +I (long hydrocarbon chains show stronger +I than shorter ones), the lower reactivity. Ketones are thus less reactive then aldehydes (ketones have 2 hydrocarbon residues, aldehydes just 1); formaldehyde (having the shortest posible residues: –H) would be the most reactive aldehyde.

Formation of hemiacetal (aldehyde reacts with alcohol at low pH – you will learn more about it in the Saccharides lessons later on) is the typical example of carbonyl reactivity. H^+ (catalyst of the reaction) protonates oxygen of the carbonyl group, which increases the polarity of the bond. Carbonyl carbon is then prone to nucleophilic attack of alcohol (namely, the free electron pair of the oxygen atom) and nucleophilic addition takes place. Product of addition is then stabilized by releasing proton and hemiacetal is formed.

$$CH_3-\overset{\delta^+}{CH}=\overset{\delta^-}{\underline{O}} + H^+ \longrightarrow CH_3-\overset{+}{CH}-\overline{\underline{O}}H \quad\longrightarrow\quad CH_3-CH-\overline{\underline{O}}H \quad\longrightarrow\quad CH_3-CH-\overline{\underline{O}}H \;+\; H^+$$

Aldehydes and ketones can be prepared by oxidation of alcohols (see above), back-reductions of aldehydes and ketones produce corresponding alcohols again. In contrast to ketones, aldehydes can be consecutively oxidized to carboxylic acids easily:

$$R-C\overset{\displaystyle H}{\underset{\displaystyle O}{\big<}} \quad\xrightarrow{\text{oxidation}}\quad R-C\overset{\displaystyle OH}{\underset{\displaystyle O}{\big<}} \qquad \text{carboxylic acid}$$

As aldehydes can be oxidized, we can consider them as reducing agents – several tests used for aldehyde detection are based on the detection of reducing properties (hence non-specific).

Reduction of Fehling´s solution
Dark-blue Fehling′s solution contains ions of copper(II) in soluble complex with sodium-potassium tartrate. It is made just before use by combining Fehling's solution I (copper sulfate) and II (sodium-potassium tartrate in sodium hydroxide) in 1:1 ratio.

When an aldehyde is added and the mixture is heated, the aldehyde is oxidized (eq. above) and reduces blue Cu(II) to copper(I) that appears as an insoluble red precipitate of copper (I) oxide, Cu_2O.

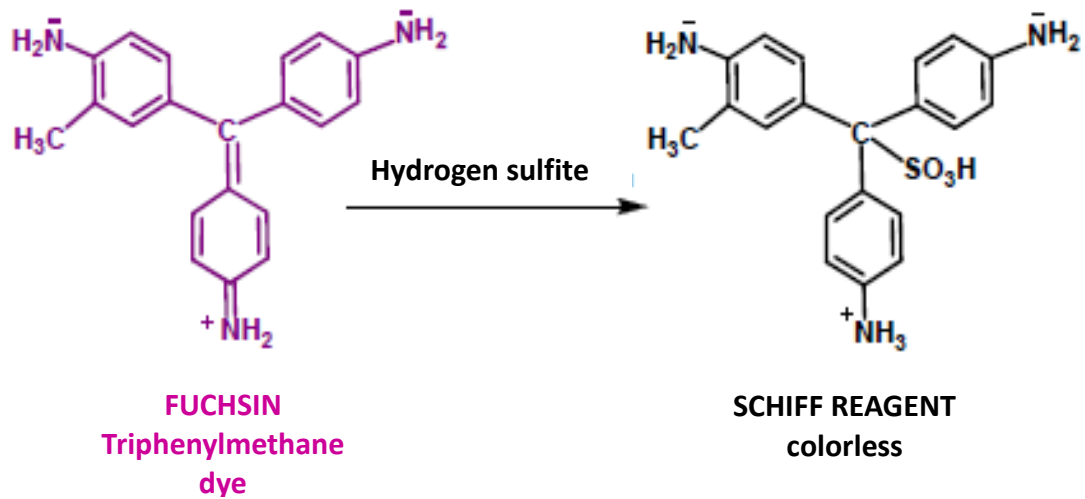### Reduction of Tollens´s solution
The Tollens's reagent is a solution of silver ions in ammonia. It can be used to detect aldehydes or other reducing substances in an analogy to the Fehling's reagent.

In order to prepare this reagent, the same volumes of aqueous $AgNO_3$ and $NaOH$ are combined first. A precipitate of silver oxide Ag_2O results. Aqueous ammonia is then added drop wise until Ag_2O is just dissolved. The resulting solution of $[Ag(NH_3)_2]^+$ is the Tollens's reagent.
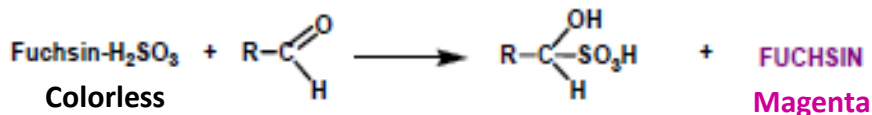
Careful heating of the Tollens's reagent together with an aldehyde gives rise to appearance of reduced, metallic silver as grey-black precipitate or even as silver mirror on the test tube wall.

Schiff´s test as another possibility to detect aldehydes
The Schiff´s reagent is an aqueous solution of purple-red (magenta) fuchsin dye which is decolorized by hydrogen sulfite or sulfite. Hydrogen sulfite reacts with the central carbon atom of fuchsin and disrupts its quinoid structure responsible for the color. Colorless solution of fuchsin-sulfurous acid is generated. After the addition of even small amount of aldehyde, sulfurous acid is released from fuchsin and is bound to aldehyde with much stronger bond. Fuchsin molecule recovers its quinoid structure and the solution turns bright magenta.

FUCHSIN
Triphenylmethane dye

SCHIFF REAGENT
colorless

Reaction with aldehyde

Fuchsin-H_2SO_3 + R–CHO → R–C(OH)(H)–SO_3H + **FUCHSIN**
Colorless → **Magenta**

The reaction with the Schiff´s reagent is frequently used in histology as a PAS staining (Periodic acid-Schiff) to detect polysaccharides such as glycogen in the tissues. Principle of this method is the oxidation of saccharides with periodic acid to aldehydes that are able to react with the Schiff´s reagent to give a purple-magenta color.
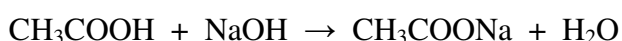
Ketones are detected using Legal´s test

Sodium nitroprusside, $Na_2[Fe(CN)_5NO]$, sodium pentacyanonitrosylferrate, in alkaline medium reacts with ketones to a violet compound. This reaction is employed in some very classical tests for the 'ketone bodies' acetone or acetoacetate in human urine.

$$Na_2[Fe(CN)_5NO] + H_3C\text{-}CO\text{-}CH_3 + NaOH \rightarrow Na_2[Fe(CN)_5N\text{=}CHCO\text{-}CH_3] + H_2O$$
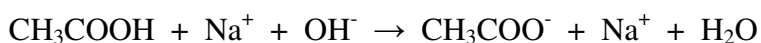$$|$$
$$OH$$
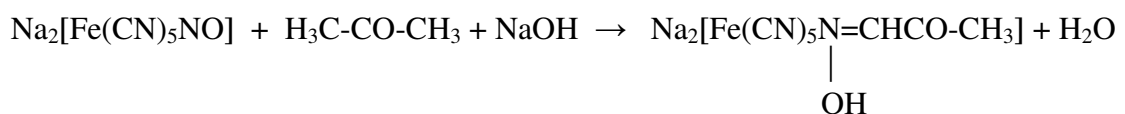
Carboxylic acids

Carboxylic acids are weak or moderately strong acids. Dissociation of the proton from the carboxyl group and its substitution by a metal ion gives salts of carboxylic acids, for instance:

$$CH_3COOH + NaOH \rightarrow CH_3COONa + H_2O$$

In ionic terms:

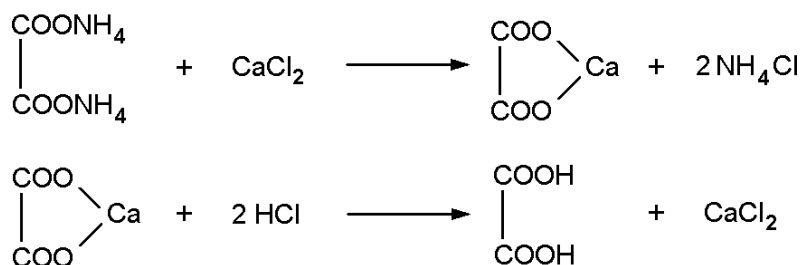$$CH_3COOH + Na^+ + OH^- \rightarrow CH_3COO^- + Na^+ + H_2O$$

The strength of carboxylic acid is, again, dependent of inductive effect. In case of carboxylic acid with long aliphatic chain, polarity of O-H bond in carboxylic group is lowered (electrons are moved from this chain towards COOH – positive inductive effect) and proton is not so "keen" to be dissociated – the acid is weak. Formic acid is thus the strongest unsubstituted monocarboxylic acid. Strength of the acid can be significantly increased by substituting one or more hydrogens in aliphatic residue by electronegative substituent (exhibiting negative inductive effect) – electrons are "drained" from COOH group, polarity of O-H bond increases and proton is readily released. Trichloroacetic acid is thus the strongest carboxylic acid.

Reduction of Tollens's reagent by formic acid

Formic acid, HCOOH, is the simplest and strongest of all monocarboxylic acids. Unlike other homologous monocarboxylic acids, it can be oxidized at carboxylic C atom. It can partially react as an aldehyde – draw its structural formula and you can see it contains both –COOH group (if you hide –H) or –COH group (if you hide –OH). For instance, the Tollens's reagent (solution of silver ions in ammonia, analogy to the Fehling's reagent, see above) is reduced by formic acid.

Formation of calcium oxalate

Oxalic acid is the simplest dicarboxylic acid of formula HOOC-COOH. As it is a diprotic acid, it can give two lines of salts, primary (acidic) and secondary (normal). From the salts of oxalic acid, calcium oxalate is of significance as a component of urinary stones. Calcium oxalate is insoluble in water, but soluble in mineral acids:

$$
\begin{array}{ccccccc}
\text{COONH}_4 & & & & \text{COO} & & \\
| & + & \text{CaCl}_2 & \longrightarrow & | \quad \text{Ca} & + & 2\,\text{NH}_4\text{Cl} \\
\text{COONH}_4 & & & & \text{COO} & &
\end{array}
$$

$$
\begin{array}{ccccccc}
\text{COO} & & & & \text{COOH} & & \\
| \quad \text{Ca} & + & 2\,\text{HCl} & \longrightarrow & | & + & \text{CaCl}_2 \\
\text{COO} & & & & \text{COOH} & &
\end{array}
$$

Formation of esters (esterification)

The carboxylic acids, in general, react with alcohols in the presence of a mineral acid to form **esters**. Thus, reaction of acetic (ethanoic) acid with ethanol produces ethyl acetate (ethyl ethanoate). The sulfuric acid catalyses the esterification, and simultaneously binds water that is formed. Proton attacks oxygen atom in the carboxylic group, generating positive charge on carboxyl carbon, which is prone to nucleophilic attack by hydroxyl group of alcohol. Resulting product is stabilized by releasing proton and water. Reaction mechanism as well as a simplified scheme is shown below. Note that esterification is reversible.

Hydrolysis of esters can be performed under acidic conditions (giving rise to alcohol and acid) or under alkaline conditions (alcohol and salt is formed). Esterification

and hydrolysis of esters belong to the most important reactions in organism. As both reactions are facilitated by enzymes, reaction conditions need not be so extreme.
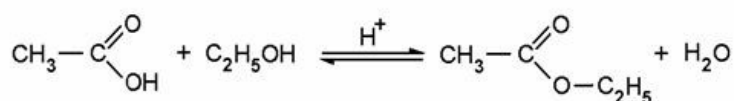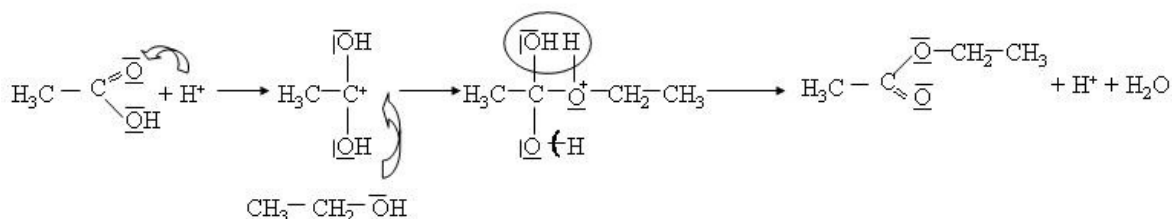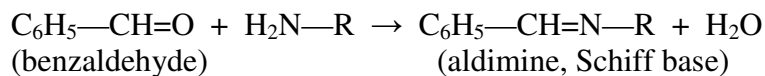

Amines

The amino group is alkaline; therefore, amines give salts of the ammonium type with inorganic acids:

$$R—NH_2 + HX \rightarrow [R\text{-}NH_3]^+ X^-$$
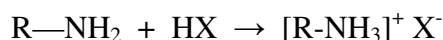
where X^- is an anion of inorganic acid. The salts are usually more water soluble than the free amino bases.

Another characteristic reaction of primary amines is the formation of addition products with carbonyl compounds. The primary addition product eliminates water to produce compound possessing a double bond between carbon atom and nitrogen atom, called **imine (Schiff base)**:

$$C_6H_5—CH=O + H_2N—R \rightarrow C_6H_5—CH=N—R + H_2O$$
(benzaldehyde)   (aldimine, Schiff base)

Such reactions of aromatic (heterocyclic) aldehydes with primary amines are very important, for example, in the metabolic pathways of amino acids.
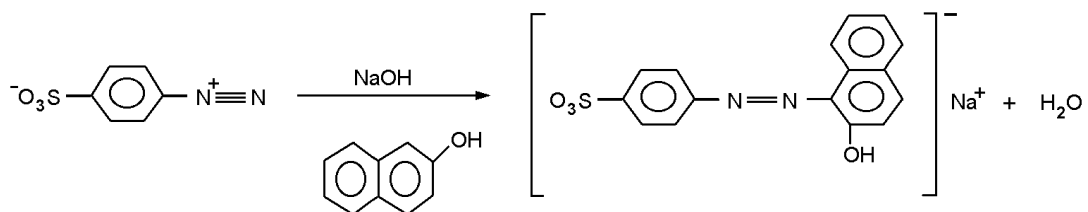
Diazo-coupling reaction

Primary aromatic amines, such as sulfanilic acid $SO_3^-— C_6H_4—NH_3^+$, react with nitrous acid HNO_2 in acidic medium and give a **diazonium** salt:
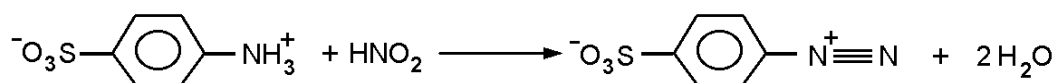
The diazonium derivative of sulfanilic acid, unlike other such compounds, is relatively stable since it forms an internal salt.

In the further reaction called **coupling**, diazonium compound reacts with an aromatic amine or phenol to produce an **azo-compound**. Thus, for instance, diazotized sulfanilic acid and β-naphthol give sodium salt of 2-hydroxynaphthalene-1-azobenzene-4'-sulfonic acid (Orange II):

The azo-compounds are colored and are of great importance as industrially produced synthetic dyes (azodyes). Also, classical tests for bilirubin in urine are based on this diazo-coupling reaction.

According to:
Kraml J. a kolektiv: Návody k praktickým cvičením z lékařské chemie a biochemie. Karolinum, Praha 1999.
Czernek P., Krchňák T., Verlík J.: Názvosloví a základní typy reakcí v organické chemii, Ostrava 2006.