№26. ALCOHOLS AND PHENOLS, THIOLS, ETHERS, AMINES, AND THEIR DERIVATIVES. REPRESENTATTIVES. CHARACTERISTIC CHEMICAL REACTIONS WITH MEDICO-BIOLOGICAL IMPORTANCE

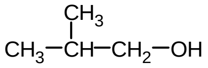
I. Oxygen derivatives.

I.1. Hydroxy derivatives – alcohols and phenols. The characteristic functional group of alcohols and phenols is –OH group (hydroxyl group). The class suffix according to the IUPAC nomenclature is **–ol** and the class prefix is **hydroxy-**. Hydroxyl groups can be attached to all types of carbon chains and rings.

1. Alcohols are the hydroxyl derivatives of aliphatic and alicyclic hydrocarbons. Alcohols can be divided into three types depending on the placement of the hydroxyl group in the molecule. Primary alcohols have the hydroxyl group attached to a primary carbon, that is a carbon bonded to only one other carbon atom. Secondary alcohols have the hydroxyl group attached to a secondary carbon that has two other carbons bonded to it. Tertiary alcohols have the hydroxyl group connected to a tertiary carbon that is bonded to three other carbon atoms. Examples:

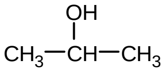
$CH_3-CH_2-CH_2-OH$

1-propanol
(primary alcohol)



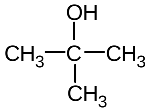
$CH_3-CH(CH_3)-CH_2-OH$

2-methylpropan-1-ol
(primary alcohol)
isobutanol



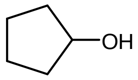
$CH_3-CH(OH)-CH_3$

2-propanol
(secondary alcohol)
isopropanol

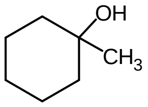


$CH_3-C(OH)(CH_3)-CH_3$

2-methyl-2-propanol
(tertiary alcohol)
tert-butanol

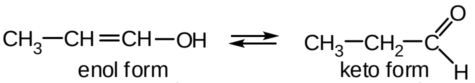


cyclopentanol
(secondary alcohol)



1-methylcyclohexanol
(tertiary alcohol)

In some compounds the hydroxyl group can be attached to a carbon that is bonded to another carbon by double bond. Such compounds are called enols. They are usually less stable and rapidly interconvert with the corresponding more stable carbonyl compounds. The process is known as keto-enol tautomerization and the concept of tautomerizations is called **tautomerism**. Tautomerism is a special case of structural isomerism and can play an important role in base pairing in DNA and RNA molecules.



enol form
1-propenol

keto form
propanal

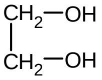
Alcohols can be grouped also according to the number of hydroxyl groups present in their molecules. Alcohols containing one hydroxyl group are called monohydric, those containing two and three hydroxyl groups are termed dihydric and trihydric, respectively. Alcohols with more than one OH group are named also polyhydric alcohols – usually encountered in carbohydrates (sugars).

CH_3-OH

methanol
(monohydric)

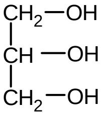
CH_3-CH_2-OH

ethanol
(monohydric)



$HOCH_2-CH_2OH$

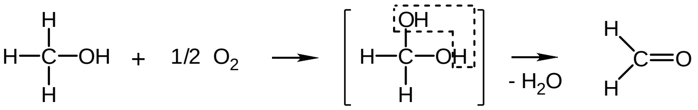
ethylene glycol
ethane-1,2-diol
(dihydric)



$HOCH_2-CH(OH)-CH_2OH$

glycerol
propane-1,2,3-triol
(trihydric)

Diols having both –OH groups on the same carbon (geminal diols) are usually unstable. They are considered hydrates of aldehydes or ketones and lose water molecule to convert into these carbonyl compounds, e.g.:



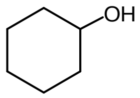
unstable
compound

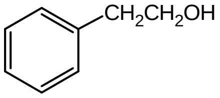
formaldehyde

According to the type of the hydrocarbon residue, the alcohols are classified as saturated, unsaturated, alicyclic, and aromatic. The latter contain aromatic ring that is not substituted with OH group.

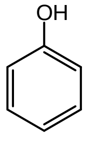
CH_3-CH_2-OH
ethanol
(saturated)

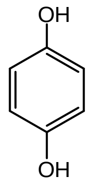
$CH_2=CH-CH_2-OH$
allyl alcohol; 2-propen-1-ol
(unsaturated)

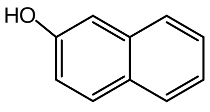

cyclohexanol
(alicyclic)


2-phenyl ethanol
(aromatic)

2. Phenols are a class of chemical compounds consisting of a hydroxyl group (-OH) bonded directly to an aromatic hydrocarbon group. Although similar to alcohols, phenols have unique properties and are not classified as alcohols (since the hydroxyl group is not bonded to a *saturated* carbon atom). The simplest of the class is phenol, C_6H_5OH, (do not mistake the *compound name* phenol with phenyl that is the *name of group* from benzene when present in more complex compound and named as a substituent).


phenol


hydroquinone
(1,4-benzenediol)

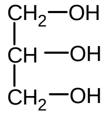

β-naphthol

3. Representatives of alcohols and phenols with medico-biological importance

Methanol (**CH_3OH**), called also wood alcohol, was first isolated in 1661 by dry distillation. Nowadays the largest use of methanol by far is in making other chemicals. About 40% of methanol is converted to formaldehyde, and from there into products as diverse as plastics, plywood, paints, explosives, and textiles. Methanol is used as fuel for vehicles. Methanol is produced naturally in the anaerobic metabolism of many varieties of bacteria. Methanol is poisonous. It has a high toxicity in humans. If ingested, as little as 10 mL can cause permanent blindness by destruction of the optic nerve, and 30 mL is potentially fatal dose.

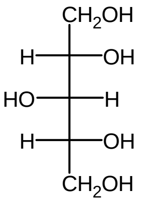
Ethanol (**CH_3CH_2OH**). The fermentation of sugar into ethanol is one of the earliest organic reactions employed by humanity. The intoxicating effects of ethanol consumption have been known since ancient times. In modern times, ethanol intended for industrial use is also produced from by-products of petroleum refining. This compound has widespread use as a solvent of substances intended for human contact or consumption: scents, flavorings, colorings, and medicines. In chemistry, it is both an essential solvent and a feedstock for the synthesis of other products. Currently ethanol is an additive to gasoline that poses a serious question – should food-stuff (corn) be used for fuel or to feed the hungry.

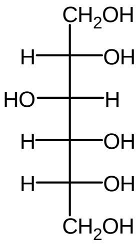
Ethylene glycol (**$HOCH_2CH_2OH$,** IUPAC name ethane-1,2-diol) is an organic compound widely used as an automotive antifreeze and a precursor to polymers. In its pure form, it is an odorless, colorless, syrupy, sweet-tasting liquid. Ethylene glycol is toxic, and ingestion can result in death.



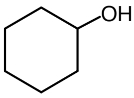
$$\begin{array}{l} CH_2-OH \\ | \\ CH-OH \\ | \\ CH_2-OH \end{array}$$

Glycerol is a simple polyol compound, available from hydrolysis of fats. It is a colorless, odorless, viscous liquid that is widely used in pharmaceutical formulations. Glycerol has three hydrophilic hydroxyl groups that are responsible for its solubility in water and its hygroscopic nature. The glycerol backbone is central to all lipids known as *triglycerides*. Glycerol is sweet-tasting but contrary to glycol has low toxicity. In foods and beverages, glycerol serves as solvent and sweetener, and may help preserve foods. As a sugar substitute, it has about the same food energy per unit mass as table sugar but it does not raise blood sugar levels, nor does it feed the bacteria that form plaques and cause dental cavities.


D-xylitol

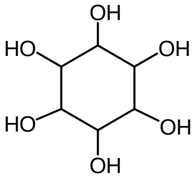

D-sorbitol

Xylitol and **sorbitol** are sugar alcohols, polyols. They are used as sweeteners and sugar substitutes in various foods. Xylitol is considered safe for diabetics and individuals with hyperglycemia (high glucose levels in blood plasma).



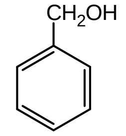
cyclohexanol

Cyclohexanol is one of the major members of the alicyclic alcohols family. The molecule has a cyclohexane ring and can be viewed as obtained from cyclohexane by replacement of one hydrogen atom by a hydroxyl group. Thus it is a secondary alcohol. Billions of kilograms are produced annually, mainly as a precursor to Nylon. Cyclohexanol is an important feedstock in the polymer industry and it is also used as plasticizer and as a solvent.



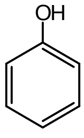
inositol

Inositol (cyclohexane-1,2,3,4,5,6-hexol) is a sixfold alcohol (polyol) of cyclohexane that has several possible stereoisomers, of which the most prominent form, widely occurring in nature, is ***myo*-inositol**. Inositol is a carbohydrate, though not a classical sugar. It is almost tasteless, with a small amount of sweetness. *Myo*-inositol plays an important role as the structural basis for a number of secondary messengers in eukaryotic cells, including inositol phosphates, phosphatidylinositol and phosphatidylinositol phosphate lipids. Inositol or its phosphates and associated lipids are found in many foods, in particular, in cereals, nuts, beans, and fruit, especially melons and oranges.

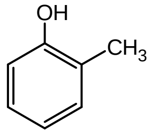


benzyl alcohol

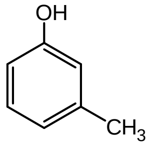
Benzyl alcohol ($PhCH_2OH$) is denoted BnOH since the benzyl group $PhCH_2$- is often abbreviated "Bn". Benzyl alcohol is a colorless liquid with a mild pleasant aromatic odor. It is a useful solvent due to its polarity, low toxicity, and low vapor pressure. Benzyl esters are popular protecting groups because they can be removed by mild hydrogenolysis (cleavage with hydrogen), in particular, in peptide synthesis. Benzylic centers have special reactivity, e.g. the benzyl carbocation has the formula $C_6H_5CH_2^+$ and the benzyl carbanion has the formula $C_6H_5CH_2^-$. None of these species have significant existence under normal conditions, but they are relatively stabilized by the phenyl ring and are useful references for discussion of mechanisms.



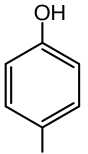
phenol



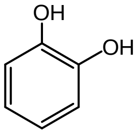
o-cresol



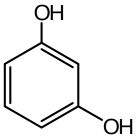
m-cresol



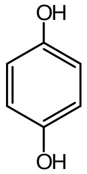
p-cresol



catechol



resorcinol

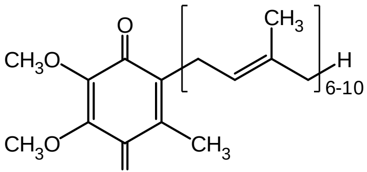


hydroquinone

Phenol, also known as **carbolic acid**, is a crystalline colorless solid at room temperature. It is produced on a large scale (about 7 million ton/year) as a precursor to many materials and useful compounds. It is only mildly acidic but requires careful handling due to its toxicity and its propensity to cause severe burns. Condensation with formaldehyde gives phenolic resins, the most famous of which is Bakelite - one of the first synthetic plastics. The major uses of phenol involve its conversions to plastics or related materials.

Cresols are methylphenols. There are three forms of cresols that are only slightly different in their chemical structure: ***ortho*-cresol** (*o*-cresol), ***meta*-cresol** (*m*-cresol), and ***para*-cresol** (*p*-cresol). These forms occur separately or as a mixture. Cresols are used to dissolve other chemicals, as disinfectants and deodorizers, and to make specific chemicals that kill insect pests. Cresol solutions are used as household cleaners and disinfectants, perhaps most famously under the trade name Lysol. They are less toxic than phenol.

Catechol (1,2-benzenediol), **resorcinol** (1,3-benzenediol), and **hydroquinone** (1,4-benzenediol) have two hydroxyl groups that substitute on a benzene ring and these compounds are classified as polyphenols. Catechol is produced industrially in large amounts as a precursor to pesticides, flavors and fragrances. Small amounts of catechol occur naturally in fruits and vegetables, but the catechol skeleton fragment is found widely in a variety of natural products. Resorcinol is used externally as an antiseptic and disinfectant, and also as a chemical intermediate for the synthesis of pharmaceuticals and other organic compounds. Resorcinol is an analytical reagent for the qualitative determination of ketoses (Seliwanoff's test). Both hydroquinone and catechol have been used as film developing chemicals. The use of hydroquinone for film developing is common (through reducing Ag^+ to metallic Ag). Hydroquinone can undergo mild oxidation to convert to the compound *para-benzoquinone*, $C_6H_4O_2$, often called *p*-quinone or simply quinone. Reduction of quinone reverses this reaction back to hydroquinone. Some biochemical compounds in nature have this sort of hydroquinone or quinone portion in their structures and can undergo similar redox interconversions. Hydroquinone has a variety of uses principally associated with its action as a reducing agent which is soluble in water.


Coenzyme Q

Coenzyme Q (Coenzyme Q10, also known as ubiquinone, CoQ10 – pronounced like "kou-cjue-ten“) is a 1,4-benzoquinone, Q = quinone and 10 = number of isoprenyl subunits. This oil-soluble substance is present in most eukaryotic cells, primarily in the mitochondria. It is a component of the electron transport chain and participates in aerobic cellular respiration, generating energy in the form of ATP. Those organs with the highest energy requirements—such as the heart and the liver—have the highest CoQ10 concentrations.

I.2. Ethers, hydroperoxides and dialkyl peroxides

1. Ethers are compounds containing the fragment **R—O—R’**, where **R** and **R’** can be alkyl or aryl (aromatic residues) groups. Like alcohols, ethers can be viewed as relatives of water with alkyl groups replacing hydrogen atoms. The difference is that in alcohols one alkyl group replaces one hydrogen, whereas in ethers two alkyl groups replace both hydrogens, as in:

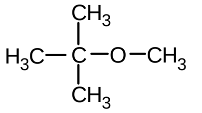
H—O—H	R—O—H	R—O—R'	H—O—O—H	R—O—O—H	R—O—O—R'	R—O—⌇
water	alcohol	ether	hydrogen peroxide	hydroperoxide	peroxide	alkoxy group

The hydrogen peroxide’s hydrogens (H_2O_2) can also be replaced by one or two alkyl groups to give organic hydroperoxides or peroxides, respectively. The residue after removing the hydrogen from an aliphatic alcohol R-OH is named alkoxy group (R-O—), e.g. methoxy ($-OCH_3$), ethoxy ($-OC_2H_5$), etc..

Examples of ethers:

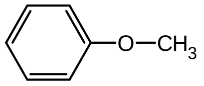
$CH_3CH_2—O—CH_2CH_3$

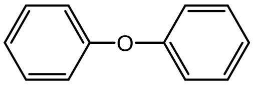
diethyl ether (ethoxyethane)



$H_3C—C(CH_3)_2—O—CH_3$

methyl *tert*-butyl ether (MTBE)


methyl phenyl ether (methoxybenzene, anisole)


diphenyl ether

Nomenclature naming: simple ethers’ names are formed by using both names of the present hydrocarbon residues ending on -yl followed by “ether”, e.g. methyl *tert*-butyl ether. In more complex compounds the ether group – alkoxy group is a substituent. Then the prefix for an ether group is alkoxy, e.g. 3-propoxyoctane.

Diethyl ether (called simply “ether”) is the oldest known ether synthesized in 16th century under the name "sweet oil of vitriol" which reflects the fact that it is obtained by distilling a mixture of ethanol and sulfuric acid (vitriol). At about the same time Paracelsus (known for his pioneering contributions on the use of chemicals and minerals in medicine and the phrase "All things are poison and nothing is without poison, only the dose permits something not to be poisonous" or, more commonly, "The dose makes the poison.") discovered ether's analgesic properties. Many tons of diethyl ether are produced annually using sulfuric acid catalyst. Ether is a common solvent for reaction medium and for extractions, and was once used as a general anesthetic. Now desflurane, isoflurane and sevoflurane are the most widely used volatile general anaesthetics today. They are often combined with nitrous oxide (N_2O).

Some compounds, like monensin, containing many ether linkages (polyethers) have shown antibiotic properties.

Methyl *tert*-butyl ether (**MTBE**) is gasoline additive, used to “oxygenate” fuel and to raise the octane number. Its use leads to environmental concerns because it easily pollutes large quantities of groundwater when gasoline with MTBE is spilled or leaked. MTBE in organic chemistry as a relatively inexpensive solvent with properties comparable to diethyl ether but with a higher boiling point and lower solubility in water. As a solvent, MTBE possesses one distinct advantage over most ethers - it has a much lower tendency to form explosive organic peroxides.

Anisole (methoxybenzene) is relatively non-toxic ether with a smell reminiscent of anise seed, and in fact many of its derivatives are found in natural and artificial fragrances. Anise-flavored (with anethole) liqueurs and spirits, such as mastika, raki, arak, and absinthe, form a milky oil-in-water microemulsions –ouzo effect when diluted with water. The compound is mainly made synthetically and is a precursor to other synthetic compounds.

2. Hydroperoxides and dialkyl peroxides

Organic peroxides are compounds with a specific functional group (-O-O-) or a molecule containing an oxygen-oxygen single bond (R-O-O-R'). When the other oxygen bears a hydrogen, it is called a hydroperoxide (R-O-O-H). The radical HOO· is known as hydroperoxide radical, and is thought to be involved in combustion of hydrocarbons in air. Organic peroxides tend to decompose easily to free radicals of the form RO·. This property means that organic peroxides can accidentally initiate explosions. Some dialkyl ethers, when exposed to oxygen for long time form hydroperoxides and peroxides and can become shock sensitive. Extreme care must be taken with liquid ether samples showing signs of crystal growth or precipitates.

II. Sulfur containing derivatives - thiols, sulfides, disulfides

II.1. Characteristics.

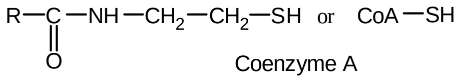
H—S—H	R—S—H	R—S—R'	R—S—S—R'
hydrogen sulfide	thiol mercaptan (-SH thiol, sulfhydryl group)	thioether (sulfide)	disulfide

Thiols, sulfides, and disulfides are hydrocarbon derivatives that are sulfur analogs of alcohols, ethers, and peroxides, respectively. In the general formulae above, R and R’ are alkyl groups. The functional group HS- is called also sulfhydryl group or mercapto group and thiols are called mercaptanes. In protein structures, the group -S-S- is called disulfide bridge, or disulfide bond, or linkage. Nomenclature:

- The preferred (IUPAC) method is to add the suffix *-thiol* to the name of the alkane. The method is nearly identical to naming an alcohol (*-ol*). Examples: CH_3SH methanethiol, CH_3CH_2SH ethanethiol.
- An older method, the word *mercaptan* replaces *alcohol* in the name of the equivalent alcohol compound, e.g. isopropyl alcohol and isopropyl mercaptan
- As a prefix, the term *mercapto* (or *sulfanyl*) are used. Example: mercaptopurine, 2-mercaptoethanol.

II.2. Representatives

$CH_3—SH$	$CH_3—CH_2—SH$	$HO—CH_2—CH_2—SH$
methanethiol (methyl mercaptan)	ethanethiol (ethyl mercaptan)	2-mercaptoethanol



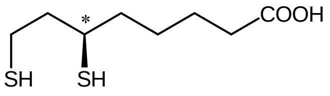
$$R—\overset{}{\underset{\underset{O}{\|}}{C}}—NH—CH_2—CH_2—SH \text{ or } CoA—SH$$

Coenzyme A

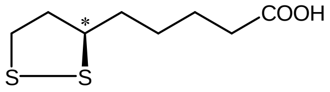
The term “thiol” brings about first association: “very bad, unbearable smell”. The odor of thiols is often strong and repulsive, particularly for those of low molecular weight, like garlic. Volatile thiols are added to natural gas in order to detect leaks, because often the human nose detection threshold is much lower then the toxicity level. Thiols are also responsible for a class of wine and beer faults due to bacteria. Skunk spray is composed mainly of low molecular weight thiol compounds. These compounds are detectable by the human nose at concentrations of only 10 parts per billion. The odor of thiols weakens as the number of carbons increases, due to lower volatility and lower sulfur content. Not all thiols have unpleasant odors, e.g. grapefruit mercaptan, is responsible (only in low concentration) for the characteristic scent of grapefruit.

2-Mercaptoethanol (also **β-mercaptoethanol)** is used to reduce disulfide bonds and can act as a biological antioxidant by scavenging hydroxyl radicals. Some proteins can be denatured by 2-mercaptoethanol via its ability to cleave disulfide bonds. The dimercapto derivative of glycerol (BAL) was used as an antidote for the poison Lewisite that is now obsolete arsenic-based chemical warfare agent. Today BAL is used medically in treatment of arsenic, mercury, gold and lead, and other toxic metal poisoning due to its chelating properties.

Coenzyme A. Many cofactors (non-protein-based helper molecules), contain thiol group (sulfur is a good nucleophile). The biosynthesis and degradation of fatty acids and related long-chain hydrocarbons is conducted using a mechanism that anchors the growing chain through a thioester derived from the thiol Coenzyme A. It has role in the synthesis and oxidation of fatty acids, and the oxidation of pyruvate in the citric acid cycle. Many enzymes use coenzyme A as a substrate.



dihydrolipoic acid
(6,8-dimercaptooctanoic acid)



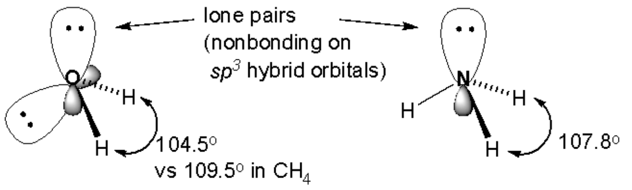
lipoic acid

Natural **lipoic acid** (LA) is an essential cofactor of four mitochondrial enzyme complexes. Biochemically synthesized LA is essential for life and aerobic metabolism; it can be supplemented with food. Although the intracellular medium is strongly reducing, both free LA and its reduced form, dihydrolipoic acid (DHLA) have been detected within cells. (The cytosolic and mitochondrial redox state is maintained in a reduced state relative to the extracellular matrix and plasma due to high concentrations of glutathione). The antioxidant effects of LA have been shown (similar to vitamin C and vitamin E). Lipoic acid is reduced intracellularly to dihydrolipoic acid.

III. Nitrogen containing compounds - amines

III.1. Characteriscits, types and names

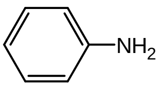
Amines can be viewed as ammonia whose hydrogen atoms are replaced by one, two, or three hydrocarbon residues. Recall the relationship electronic configuration – properties of water and ammonia.



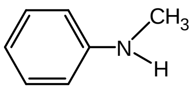
Amines are classified by the type of hydrocarbon residues: aliphatic (saturated or unsaturated), aromatic, and mixed. Examples of aliphatic (ethylamine), aromatic (aniline) and mixed amines:

$CH_3—CH_2—NH_2$

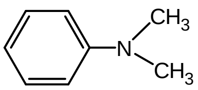
ethylamine
(aminoethane)



aniline
(aminobenzene)



N-methylaniline



N,N-dimethylaniline

The letter N in the name indicates that the substituent group R is attached to the nitrogen atom.

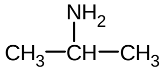
Nomenclature. The names of amines are formed in two ways:

- ☐ as derivatives of NH_3 with **suffix –amine**: methylamine; ethylamine; N-methylpropylamine
- ☐ as derivatives of hydrocarbons with **prefix amino-**: aminobutane, N-methylaminobutane, aminocyclohexane

Amines are also subdivided into primary, secondary, tertiary, and quaternary ammonium salts (quats) depending on the number of hydrocarbon residues attached to the nitrogen atom (this division is different than in alcohols). Thus the functional group for primary amines is $-NH_2$, for secondary amines is -NHR, for tertiary is tertiary nitrogen atom $-NR_2$, and for quaternary ammonium salts - quaternary N^+ atom.

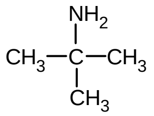
$CH_3—CH_2—CH_2—NH_2$

n-propylamine
(primary amine)
1-aminopropane



$CH_3—\overset{NH_2}{\overset{|}{CH}}—CH_3$

isopropylamine
(primary amine)
2-aminopropane

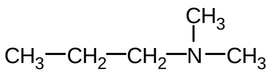


$CH_3—\underset{CH_3}{\underset{|}{\overset{NH_2}{\overset{|}{C}}}}—CH_3$

tert-butylamine
(primary amine)

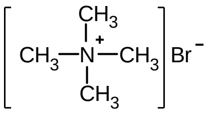
$CH_3—CH_2—CH_2—NH—CH_3$

N-methylpropylamine
(secondary amine)



$CH_3—CH_2—CH_2—\overset{CH_3}{\overset{|}{N}}—CH_3$

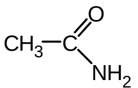
N,N-dimethylpropylamine
(tertiary amine)



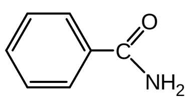
$\left[CH_3—\underset{CH_3}{\underset{|}{\overset{CH_3}{\overset{|}{N^+}}}}—CH_3\right]Br^-$

tetramethylammonium bromide
(quaternary ammonium salt)

Depending on the number of amino groups in their molecule, the amines may be monoamines, diamines, polyamines.



acetamide

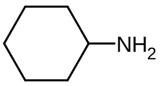


benzamide

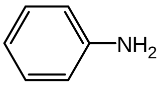
In order to avoid confusion later, a distinction should be made now between amines and carboxylic acid derivatives in which amino group NH_2- replaces the hydroxyl group HO- in COOH. Such compounds are acid **amides** and not amines. They have quite different properties in comparison with amines.

$CH_3—NH_2$
methylamine

$CH_3—CH_2—NH_2$
ethylamine



cyclohexylamine



aniline

Methylamine is a good nucleophile as it is highly basic and unhindered, though, as an amine it is considered a weak base. Its use in organic chemistry is pervasive, very broad. Some reactions involving simple reagents are used in multiton production processes. Representative commercially significant chemicals produced from methylamine include the pharmaceuticals ephedrine and theophylline, some important pesticides, and the solvents N-methylformamide and N-methylpyrrolidone. The preparation of some surfactants and photographic developers require methylamine as a building block. **Ethylamine** is also widely used in chemical industry and organic synthesis, e.g. as a precursor to many herbicides. It is found in rubber products as well. **Cyclohexylamine** is used as an intermediate in synthesis of some herbicides, antioxidants, pharmaceuticals (e.g., analgesics, and bronchodilators), corrosion inhibitors, some sweeteners (the most notable one being cyclamate), etc. **Aniline** was first isolated from the destructive distillation of indigo in 1826 and later, from coal tar. The great commercial value of aniline was due to the readiness with which it yields, directly or indirectly, dyestuffs. The principal use of aniline in the dye industry is as a precursor to indigo, the blue of blue jeans. Aniline is poisonous and some of its derivatives are carcinogenic. Many pharmaceuticals, however, contain fragment of aniline.

Amines as natural products. The easy with which amines are extracted into aqueous acid, combined with their regeneration on treatment with a base, makes it a simple matter to separate amines from other plant materials, and nitrogen-containing natural products were among the earliest organic compounds to be studied. Their basic properties led amines obtained from plants to be called **alkaloids**. The number of known alkaloids exceeds 5000. They are of special interest because most are characterized by a high level of biological activity. Some examples include *morphine, cocaine, quinine, nicotine*. Several naturally occurring amines mediate the transmission of nerve impulses and are referred to as neurotransmitters, like **epinephrine** and **serotonin**.

$H_2N—(CH_2)_4—NH_2$
putrescine
(tetramethylenediamine)

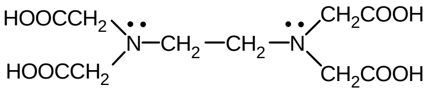
$H_2N—(CH_2)_4—NH—(CH_2)_3—NH_2$
spermidine

$H_2N—(CH_2)_5—NH_2$
cadaverine
(pentamethylenediamine)

$H_2N—(CH_2)_3—NH—(CH_2)_4—NH—(CH_2)_3—NH_2$
spermine

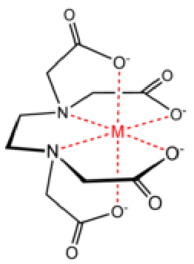
Among the more important amine derivatives found in the body are a group of polyamines, which contain two to four nitrogen atoms separated by several methylene units. These compounds are present in almost all mammalian cells, where they are involved in cell differentiation and proliferation. Putrescine and cadaverine are produced by the breakdown of amino acids in living and dead organisms and both are toxic in large doses. The two compounds have foul odor of putrefying (rotten, decaying) flesh. They are also found in semen and some microalgae, together with related molecules like spermidine and spermine. The last are polyamines involved in all eukaryotic cell metabolism.

$H_2N—CH_2—CH_2—NH_2$
ethylenediamine
(1,2-diaminoethane)



$$(HOOCCH_2)_2\ddot{N}—CH_2—CH_2—\ddot{N}(CH_2COOH)_2$$

ethylenediaminetetraacetic acid
(EDTA)



Ethylenediamine is a large scale industrial chemical that is building block for pharmaceuticals and agrochemicals; precursor of chelating agents (chelating ligands such as EDTA). Nylon6-6 is produced from another diamine - hexamethylenediamine.

EDTA contains two tertiary N atoms and four carboxylic acid groups. The compound is widely used in coordination chemistry. $EDTA^{4-}$ is a polydentate ligand that usually binds to a metal cation through its two amines and four carboxylates. Many of the resulting coordination compounds adopt octahedral geometry as shown in the graphics above. Especially strong complexes are formed with Mn(II), Cu(II), Fe(III), Pb (II) and Co(III). EDTA is used in textile, pulp and paper industry; it is added to foods to prevent catalyzed by metal ions oxidation; also is added to cosmetics. In medicine EDTA is applied in chelation therapy, e.g. treating lead poisoning. In clinical laboratory, EDTA is used extensively in analysis of blood, e.g. for complete blood count; in dentistry – for preparation of root canal.

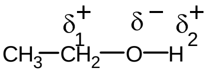
The term **biogenic amine** describes a biochemically relevant compound that contains an amino group – acetylcholine (quat salt), histamine, serotonin, norepinephrine, epinephrine, dopamine, tryptamine etc.

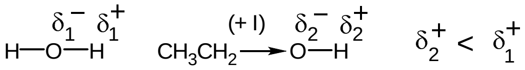
IV. Characteristic chemical reactions with medico-biological importance

1. Acidic and basic properties

1.1. Alcohols and phenols. When comparing the acid-base properties of alcohols, phenols, thiols, and amines these compounds are considered in light of Brønsted-Lowry concept of acids. Remember that two acid/base pairs: (acid1/base1) and (acid2/base2), are necessary in order for a proton transfer to occur. If a compound is to behave as an acid1, donating a proton, there must be a base2 to accept the proton, therefore the relative strength determines if a compound will react as an acid or a base. Unfamiliar till now strong bases may render some organic compounds acidic. Examples of bonds and corresponding acids in organic chemistry:

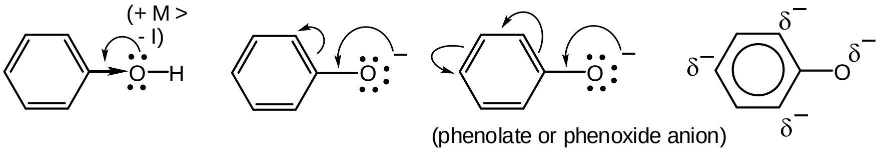
- O-H acids (familiar from common inorganic acids, like phosphoric)
- S-H acids
- N-H acids
- C-H acids (these require very strong bases, indeed, if not activated)

The oxygen atom is more electronegative than the carbon and the hydrogen atoms, as well as the N, and S are more electronegative than H, thus the O-H (or N-H, S-H) bond is polar. The oxygen atom is partially negatively charged whereas the hydrogen atoms bear partially positive charge. Such not full but partial charge is denoted by the Greek letter δ, as in:  $\overset{\delta_1^+}{CH_3}-\overset{}{CH_2}-\overset{\delta^-}{O}-\overset{\delta_2^+}{H}$ The hydrogen atom of the hydroxyl group in alcohols, similarly to the hydrogen atoms in water molecule, is ionizable, i.e. heterolytically cleavable to give ions. In comparison with a hydrogen atom in water molecule, the hydrogen in alcohols is less mobile due to the positive inductive effect of the alkyl group. This effect moves electron density towards the oxygen, thus increases the electron density of O-H bond and it is more difficult to break this bond.


$H-\overset{\delta_1^-}{O}-\overset{\delta_1^+}{H}$ $CH_3CH_2\xrightarrow{(+I)}\overset{\delta_2^-}{O}-\overset{\delta_2^+}{H}$ $\delta_2^+ < \delta_1^+$

As a result, the hydrogen atom of ethanol molecule is less ionizable (less mobile) than the hydrogen atoms in water molecule. The degree of ionization of O-H bond in ethanol is smaller than in water O-H, therefore ethanol is weaker acid than water.

The most characteristic property of phenols is their acidity. Phenols are more acidic than alcohols.



(phenolate or phenoxide anion)

One lone electron pair on the oxygen atom in phenol molecule is conjugated with the π-electrons of the phenyl ring, and electron density is shifted towards it (+M effect). Although the hydroxyl group has negative inductive effect (-I), the polarity of O-H increases in comparison to that in alcohols. Even more important is the relative stability of the corresponding anions obtained after ionization of an alcohol and phenol. In the former, the alkyl group donates electron density and the negative charge is localized on oxygen. In the phenolate (phenoxide) anion, the charge is stabilized by electron delocalization into the aromatic ring. The negative charge is shared by the oxygen and the carbons that are *ortho* and *para* to it. This delocalization greatly stabilizes phenoxide anion. Thus, the degree of ionization of O-H bond in phenol is higher than in water or alcohol. Phenol is stronger acid than an alcohol.

$$\text{Stronger acid 1} + \text{stronger base 2} \xrightleftharpoons{K > 1} \text{weaker base 1} + \text{weaker acid 2}$$

$$R-O-H < H-O-H < R-S-H < Ar-O-H < Ar-S-H$$

$R-O-H$	$H-O-H$	$R-S-H$	$Ar-O-H$	$Ar-S-H$
pK_a $R=CH_3$ 15.5 *i*-Pr 16.5 *t*-Bu 17.0 however $(CF_3)_2CH$ 9.3	15.7	10-11	10 for PhOH	7.2 for PhSH

In any proton transfer process the position of equilibrium favors formation of the weaker acid and the weaker base. When alcohols are dissolved in water, they exist mostly in unionized form. When phenol is dissolved in water, it is significantly ionized, i.e. the solution is acidic. The acid strength is expressed quantitatively with pK_a – the larger the value of pK_a, the weaker is the acid. Notice, that when an alcohol contains electron withdrawing substituents, like fluorine atoms in hexafluoro 2-propanol, its acidity increases. Tertiary alcohols are weaker acids than secondary which are weaker acids than primary due to summation of +I effects.

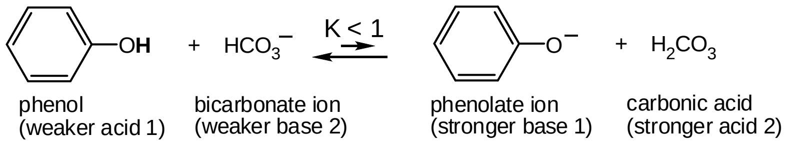
The relationship between acidity constants explains why alcohols react only with active metals whereas phenols react with active metals and hydroxides but do not react with carbonate or bicarbonate ion (the latter are not strong enough bases to accept the phenol OH proton).

$$2\,CH_3CH_2OH + 2\,Na \longrightarrow 2\,CH_3CH_2O^-Na^+ + H_2$$

$$2\,C_6H_5OH + 2\,Na \longrightarrow 2\,C_6H_5O^-Na^+ + H_2$$

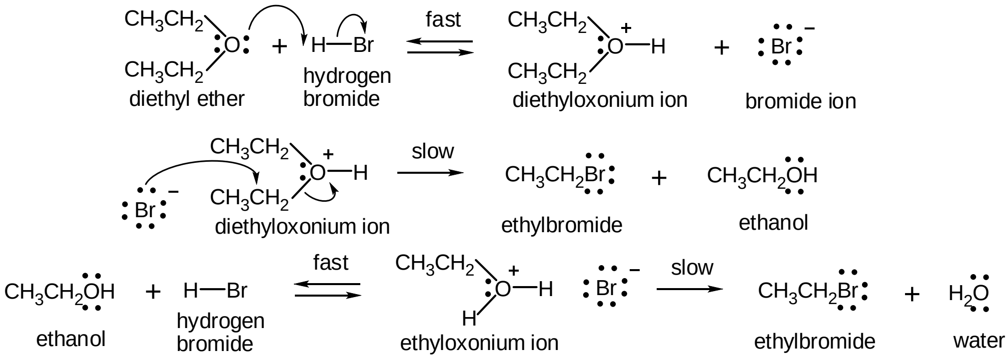
$$\underbrace{C_6H_5O^- + H^+} + \underbrace{Na^+ + OH^-} \rightleftharpoons \underbrace{C_6H_5O^- + Na^+}_{\text{sodium phenolate}} + H_2O$$

The product of these reactions is called an alcoholate (RO^-) or phenolate (PhO^-).

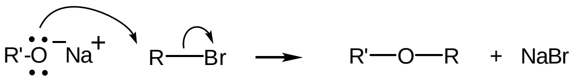


1.2. Ethers

Ethers do not have polar O-H bond and cannot act as Brønsted-Lowry acids, but exhibit basic character due to lone electron pairs. Strong acids protonate the oxygen to give "onium ions" $[RO(H)CH_3]^+Br^-$. A protonated ether can undergo substitution or elimination with removal of a stable alcohol molecule. Ethers are inert toward bases but they can react under strongly acidic conditions. Ethers are cleaved with HI and HBr because these two reagents are sufficiently acidic to protonate the ether, whereas the iodide or bromide ions are good nucleophiles for the substitution. The conditions for this reaction are harsh and the molecule must not contain other functional groups that are sensitive to strong acid. The reaction has application in carbohydrate chemistry. The mechanism is:



Symmetrical ethers are formed by acid catalyzed dehydration of primary alcohols; unsymmetrical – by Williamson ether synthesis (an S_N2 reaction).



1.3. Thiols

Oxygen is more electronegative than sulfur, but the latter has larger atom's radius (electrons are away from nucleus) and is with higher polarizability, thus tendency for delocalization of negative charge ($\chi_S < \chi_N < \chi_O$). For this reason, although the S-H bond is less polar than the O-

$$\underset{\substack{\text{ethanethiol}\\ \text{(stronger acid } pK_a\text{=10)}}}{CH_3CH_2SH} + \underset{\substack{\text{hydroxide ion}\\ \text{(stronger base)}}}{OH^-} \longrightarrow \underset{\substack{\text{ethanethiolate ion}\\ \text{(weaker base)}}}{CH_3CH_2S^-} + \underset{\substack{\text{water}\\ \text{(weaker acid } pK_a\text{=15.7)}}}{H_2O}$$

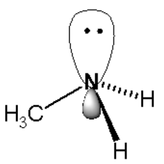
$$C_2H_5SH + NaOH \rightleftharpoons C_2H_5S^-Na^+ + H_2O$$

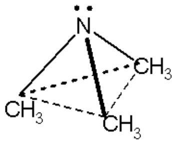
$$\underbrace{C_2H_5S^- + H^+} + \underbrace{Na^+ + OH^-} \rightleftharpoons \underbrace{C_2H_5S^- + Na^+}_{\text{sodium ethanethiolate}} + H_2O$$

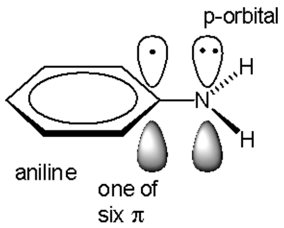
H bond, thiols are more acidic than alcohols. Typical alcohols' pK_a values are 16-17, whereas thiols have $pK_a \approx$ 10-11. The significance of this difference is that a thiol can be quantitatively converted into its conjugate base (called alkanethiolate ion, RS^-) by the action of alkali hydroxide. This chemical reaction in general form and using sodium hydroxide is expressed above with molecular and complete ion equations. For the same reasons as in phenols, thiophenols are even stronger acids than thiols, $pK_a \approx 7$.

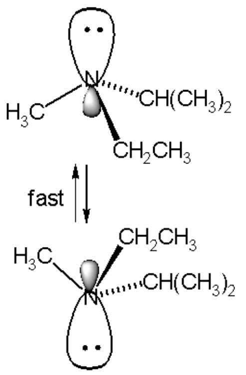
1.4. Amines

The nitrogen atom in ammonia molecule and in molecules of aliphatic amines is in *sp*^{3}-hybrid state. Unshared electron pair occupies one of the *sp*^{3}-orbitals. In methylamine the valence angle CNH is 112° (slightly larger than tetrahedral 109°) and the angle HNH is 106° (slightly smaller). The molecule of trimethylamine is considered as triangular pyramid with nitrogen atom at the top. The nitrogen atom in an aromatic amine, such as aniline, is in *sp*^{2}-hybrid state. The non-hybrid *p*-orbital is occupied by the unshared electron pair. The angles CNH and HNH are about 120° and the molecule of aniline is planar, trigonal around the nitrogen.


methylamine

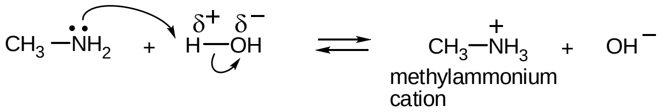

trimethylamine





Amines undergo pyramidal inversion as shown (resembles umbrella inversion in strong wind). This interconversion is extremely fast at room temperature process because the energy barrier is low. Even if all three substituents on the nitrogen in an amine are different, the nitrogen atom cannot become a permanent chiral center due to rapid inversion (like a conformational change).

The lone electron pair at the nitrogen atom (similarly to ammonia) is the cause for the basic character of all amines. There are unshared electron pairs on the oxygen atom in water and alcohol molecules as well. They also determine the basic character of these compounds. However, the oxygen atom is more electronegative than the nitrogen atom and attracts its electrons with greater strength. Thus, the basic character of water and alcohols is weakly expressed. Yet, there are stable trialkyloxonium salts. Aliphatic amines are organic bases of moderate strength. Similarly to ammonia, in aqueous solutions amines are reversibly ionized to alkylammonium cations and hydroxide anions. Therefore the medium has alkaline character, pH>7. Compared to alkali metal hydroxides, amines are reasonably weak.



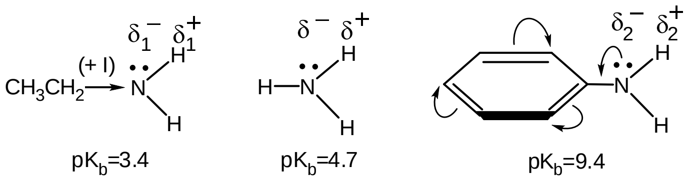
$$CH_3-\ddot{N}H_2 + \overset{\delta+}{H}-\overset{\delta-}{OH} \rightleftharpoons CH_3-\overset{+}{N}H_3 + OH^-$$

methylammonium cation

The basicity of amines depends on:

- The electronic properties of the substituents (alkyl groups enhance the basicity, aryl groups diminish it).
- Steric hindrance from the size of groups on nitrogen.
- The degree of solvation of the protonated amine.

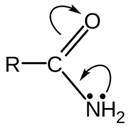
The electron density on the nitrogen atom is greater in the molecules of aliphatic amines than in the molecule of ammonia due to the positive inductive effect of an alkyl group that donates, gives away electron density. Therefore, amines are stronger bases than ammonia. The influence of a benzene ring is opposite to the influence of alkyl groups. The lone electron pair in aromatic amines is conjugated with the π-electrons of the benzene ring and this pair is not readily available for donation to a proton. This effect dominates over the negative inductive effect of the amino group. The sum of these two effects causes a decrease of electron density on the nitrogen atom in aniline and other aromatic amines. Because of decreased electronic density on N aromatic amines are weak bases – weaker than ammonia. The strength of a base is expressed quantitatively with pK_b – the larger the value of pK_b, the weaker is the base (and stronger is the corresponding conjugate acid, i.e the protonated amine). Aqueous solution of aniline has neutral reaction (pH≈7) and does not change the violet litmus color.



$\delta_1^- > \delta_{NH_3}^- > \delta_2^-$

The aromatic amines react with strong acids only. $C_6H_5-\ddot{N}H_2 + HCl \longrightarrow C_6H_5-\overset{+}{N}H_3Cl^-$

Amines possess basic nitrogen atom but all N-H bond are polar because the nitrogen is more electronegative than hydrogen which bears partial positive charge. The polar N-H bond is responsible for weak acidic properties of amines. For example, diisopropyl amine can act as a weak acid giving common strong organic base, diisopropylamide anion, $[(CH_3)_2CH]_2NH^-$ (pK_a=36).



The participation of an amine lone pair in protonation reaction should not be mixed with acid-base properties of an amide. Compared to amines, amides are very weak bases. Therefore amides don't have as clearly noticeable acid-base properties in water. This lack of basicity is explained by the electron-withdrawing nature of the carbonyl group where the lone pair of electrons on the nitrogen is delocalized over the amide group. The proton of a primary or secondary amide does not dissociate readily under normal conditions. Amides are weak acids as well but stronger than amines.

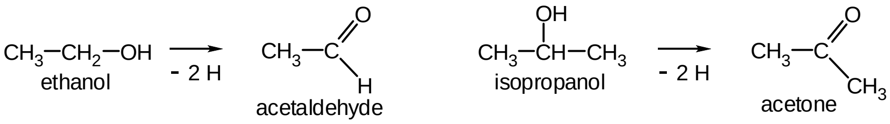
The order of relative strength of organic acids is: C-H acid < N-H acid < O-H acid < S-H acid.

2. Typical reactions for alcohols, phenols, thiols and amines

2.1. Redox reactions

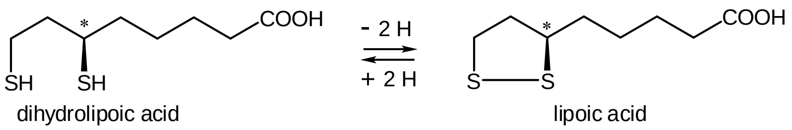
Oxidation processes are of particular importance for biochemistry, especially through dehydrogenation:

Primary alcohols are dehydrogenated into aldehydes. Secondary alcohols are oxidized to ketones.



The dehydrogenation of thiols is a reversible process: $2\ R-SH \underset{+2\,H}{\overset{-2\,H}{\rightleftharpoons}} R-S-S-R$

Thiols give disulfides and dithiols furnish cyclic disulfides, as in lipoic acid.



Similar process is responsible for the formation of disulfide bridges in folded proteins, due to cycteine conversion into cyctine.

2.2. Other reactions

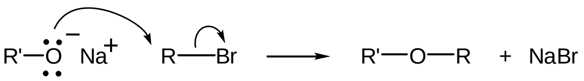
For hydroxyl derivatives: a) Alcohols can form ethers by bimolecular dehydration:

$$2\ CH_3CH_2OH \xrightarrow{H_2SO_4,\ 140^oC} CH_3CH_2{-}O{-}CH_2CH_3 + H_2O$$

ethanol diethyl ether

This reaction is used for industrial preparation of diethyl ether and for synthesis of symmetrical ethers.

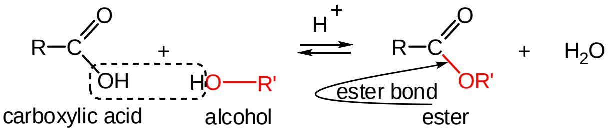
For unsymmetrical ethers is applied a reaction between alcoholate ion and alkyl halide (Williamson ether synthesis, an S_N2 reaction):

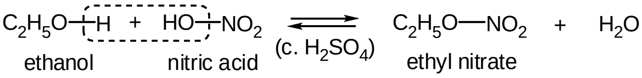


b) Alcohols can eliminate water at higher temperature and acid catalysis to give an alkene, a unimolecular intramolecular dehydration: $CH_3CH_2OH \xrightarrow{H_2SO_4,\ 180^oC} CH_2{=}CH_2 + H_2O$

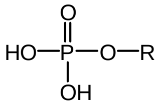
ethanol ethylene

c) Esterification of carboxylic acids with alcohols:





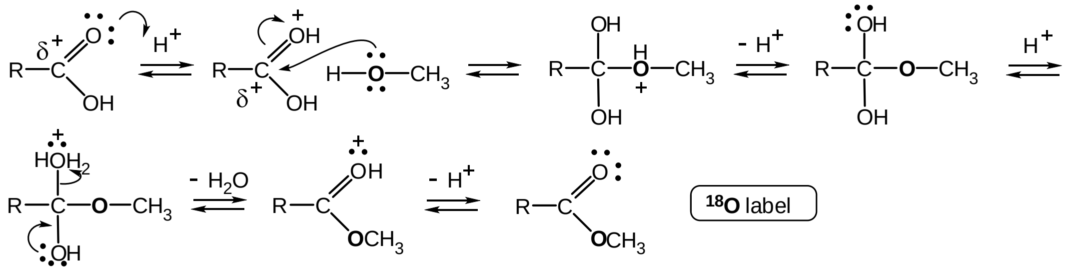
Esterification is the general name for a chemical reaction in which two reactants (typically an alcohol and an acid – inorganic, like phosphoric and nitric, or carboxylic) form an ester and water as reaction products.



$HO-P(=O)(OH)-O-R$

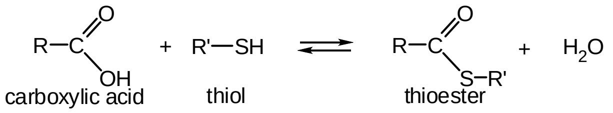
Ester of phosphoric acid

Esters are common in organic chemistry and as biologically significant molecules, and often have a characteristic pleasant, fruity odor. The reaction of cleavage of an ester by water is called hydrolysis. When the ester is of a carboxylic acid and the process is catalyzed by base, the term is saponification. The esterification mechanism involves attack by the nucleophilic alcohol (nucleophilic addition) on the carbonyl carbon of the carboxylic acid, followed by elimination of water. Classical conditions are with acidic catalysis where the mechanism is proven by use of isotopically labeled with ^{18}O alcohol.

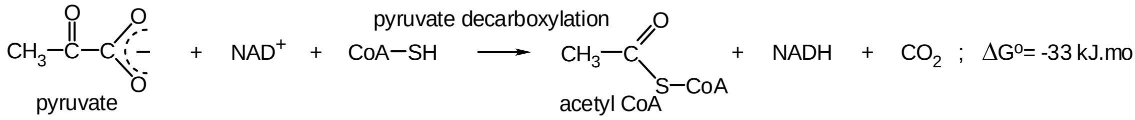


Isotopic labeling is a technique for tracking the passage of a substance through a system, e.g. series of (bio)chemical transformations. The substance is 'labeled' by including unusual isotopes, that have different than the natural abundance. If these unusual isotopes are later detected in a certain part of the system, they must have come from the labeled substance. **Radioisotopic labelling** is based on radioactive nuclides, included in the chemical composition of a substance. When these decay, their presence can be determined by detecting the radiation emitted by them. An *isotopic tracer* (isotopic marker or isotopic label) is used in chemistry and biochemistry to help understand chemical reactions and interactions. The label behaves in almost exactly the same way chemically as other atoms in the compound but can be detected by mass-spectroscopy, nuclear magnetic resonance spectroscopy, radiation emission etc. Common isotope labels are ^{2}D,^{15}N, ^{13}C, and ^{31}P.

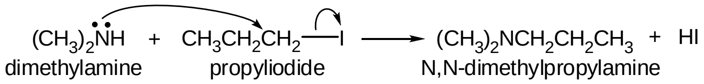
For thiols: A thioester is an ester formed from a carboxylic acid and a thiol.



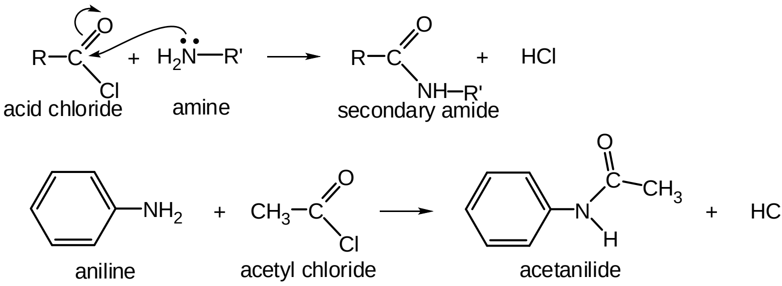
Thioesters are much more reactive toward nucleophilic acyl substitution than esters of alcohols. For this reason thioesters are widespread in biochemistry. The best known derivative is acetyl coenzyme A (acetyl-CoA). It is a typical thioester formed by pyruvate decarboxylation reaction in living cells. This transformation is far from equilibrium biochemical reaction that uses pyruvate to form acetyl-CoA, releasing NADH, a reducing equivalent, and carbon dioxide via decarboxylation. It is known as the link reaction because it forms an important link between the metabolic pathways of glycolysis and the citric acid cycle (Krebs cycle) where acetyl-CoA enters.



For amines: Amines act as nucleophiles and can be alkylated by alkyl halides in an S_N2 reaction.

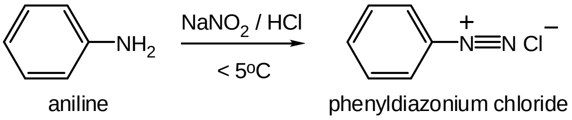


Primary and secondary amines can be acylated by acid halides. The mechanism is similar to that of esterification – nucleophilic addition of the amine to electron-deficient carbonyl carbon, followed by elimination of chloride ion.



The reaction has importance in peptide synthesis and manufacturing of various substances.

Acylation reactions. An acylation reaction is the process of adding an **acyl group** (**RCO**–) to a compound. The compound providing the acyl group is called the acylating agent. Acyl halides and anhydrides of carboxylic acids are better acylating agents than acids themselves used to acylate amines to form amides or acylate alcohols to form esters. The amines and alcohols are nucleophiles; the mechanism is nucleophilic addition-elimination. The advantage of acyl halides and anhydrides over carboxylic acids in such reactions is that the conversion is almost complete whereas the reaction with acids is reversible and reaches an equilibrium with some starting reagents present.



Aromatic amines react with nitrous acid to give diazonium salts. They are unstable compounds that react readily with other aromatic nucleus to produce azo compounds. These are widely used as dyes.

Both aliphatic and aromatic primary amines react with aldehydes or ketones to from a Schiff base. A Schiff base (called also imine or azomethine) contains as a functional group carbon-nitrogen double bond with the nitrogen atom connected to an aryl or alkyl group—but not hydrogen. Schiff bases are of the general formula $R_1R_2C=N-R_3$, where R_3 is an aryl or alkyl group that makes a stable imine.