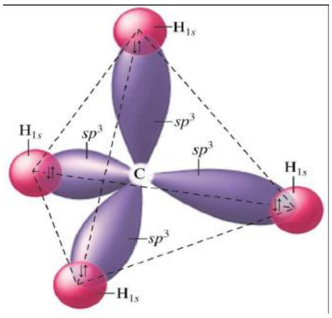
№25. HYDROCARBONS AND HALOGEN DERIVATIVES OF HYDROCARBONS WITH MEDICO-BIOLOGICAL IMPORTANCE. FUNDAMENTAL TYPES OF ORGANIC REACTIONS.

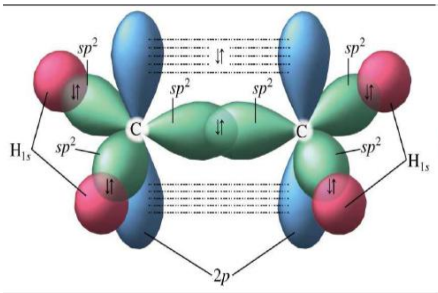
I. Organic chemistry. The term organic compound was used first in about 1777 to describe compounds occurring in or derived from living organisms. Examples of such substances are starch, alcohol and urea. Starch is produced in living plants, alcohol is a product of fermentation caused by microorganisms, and urea is a breakdown product of nitrogen-containing compounds in animals that is excreted in urine. The German chemist Friedrich Wöhler synthesized in 1828 urea from inorganic compound, thus the original meaning of “organic” was no longer applicable. Modern definition of “organic chemistry” is: subdiscipline within chemistry involving the scientific study of the structure, properties, composition, reactions, and preparation (by synthesis or by other means) of carbon-based compounds, hydrocarbons, and their derivatives. These compounds may contain any number of other elements, including hydrogen, nitrogen, oxygen, the halogens as well as phosphorus, silicon and sulfur, some metals. Chemists have produced and characterized in laboratories or industrial plants millions of compounds that are not found in living organisms. The range of application of organic compounds is enormous and we are surrounded by plentiful of products containing organic compounds like plastics, drugs, petrochemicals, food, explosives, paints, etc.. With very few exceptions, organic compounds form the basis of all earthly life processes.

Carbon is a special element:

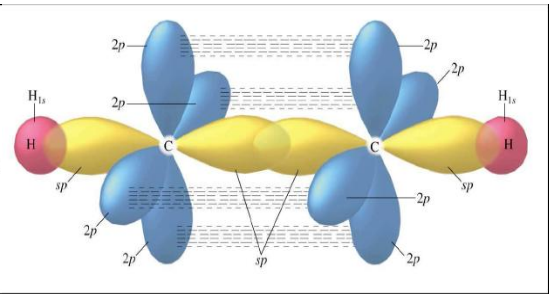
1. Carbon can form strong and short C−C bonds arranged in chains of different length and rings (cycles) of different size.
2. Carbon has no problem bonding to other elements (H, O, N, S, etc.). Given where C is in the periodic table, it typically forms four bonds, with the notable exception of carbon monoxide. Carbon is unlikely to gain or lose four electrons to become a 4- or a 4+ ion. By sharing four more electrons, however, it can achieve an octet in its outermost energy level. Thus, carbon achieves stability by forming four single, covalent bonds. For instance, the infinite size molecule that results from bonding only of C is the very stable diamond (“Girl’s best friend however chemically boring”).
3. Carbon exhibits sp^3-, sp^2- and sp-hybridization of its atomic orbitals. The C-C bond is short enough to allow sideways overlap of the unused p orbitals, resulting in π bonding. Carbon easily forms carbon-carbon double bonds, and even carbon-carbon triple bonds. The geometry of an sp^3-hybridized carbon bonding is tetrahedral (e.g. in ethane C_2H_6), of an sp^2- trigonal (in ethylene, C_2H_4), and of sp- linear (C_2H_2).



Methane



Ethylene

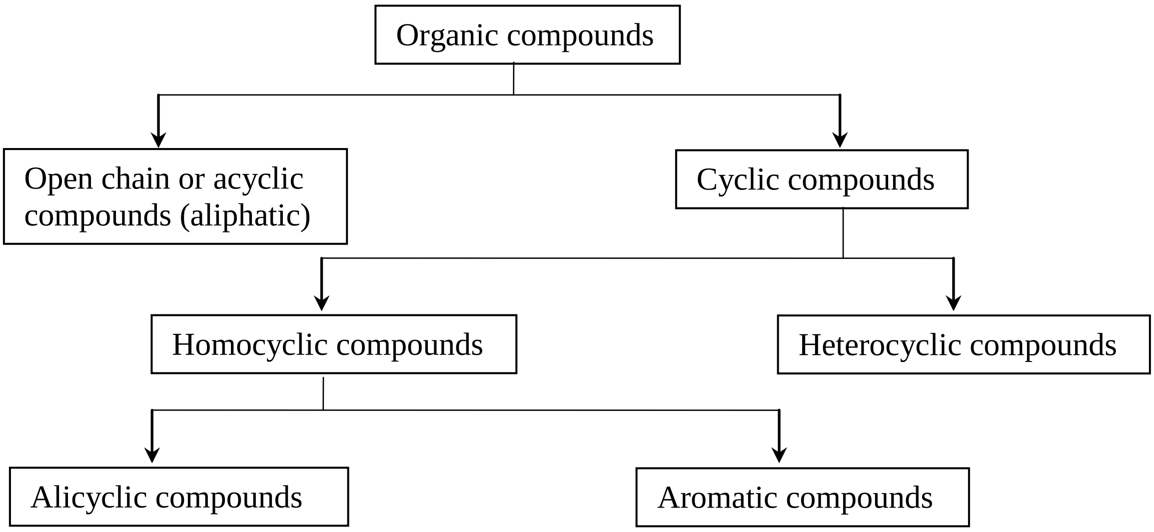


Acetylene

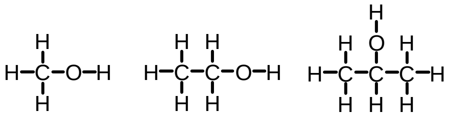
II. Classification of organic compounds

1. Basic classification. Organic compounds can be divided into two major groups. They are **open chain or acyclic (aliphatic)** compounds and **cyclic** compounds. The former group contains carbon atoms that are linked one after the other in a chain whereas the latter includes compounds in which the carbon atoms form rings. Often, the open chain compounds are called aliphatic compounds.

Cyclic compounds are further divided into **carbocyclic or homocyclic** compounds, and **heterocyclic** compounds. Carbocyclic compounds consist of rings made up of only carbon atoms. Their number varies from 3, 4, 5, 6 to even larger number. The remaining valences of the carbon atoms in the ring may be joined with other atoms (C or others) or groups. When the ring contains alternating single and double bonds (following certain rule), we distinguish a large and important group carbocyclic compounds named **aromatic** compounds. Heterocyclic compounds have rings composed, besides of carbon, of one or more atoms different from carbon atoms. Such atoms are known as heteroatoms. Nitrogen, oxygen and sulfur are typical **heteroatoms**.



2. Functional groups. Learning about millions of known organic compounds might seem intimidating. Fortunately, the chemical properties of many organic compounds are very similar, allowing them to be grouped into several classes of compounds. For instance, all compounds below belong to the class of alcohols and have typical properties for alcohols.



Each compound has a specific arrangement of atoms. These arrangements of atoms in a particular way, which give rise to certain chemical properties, are called functional groups. They determine the reactive, structural, or other *functional* characteristics of a molecule. The site of chemical reactivity is the functional group, which in the examples is the hydroxyl group, -OH. The presence of such groups in a molecule gives it the properties which are characteristic of the group. Therefore the study of organic chemistry is essentially the study of a number of characteristic groups – the functional groups. A functional group is an aggregate of one or more atoms in a molecule whose presence confers upon the molecule a unique chemical property, characteristic of the functional group. **Understanding Functional Groups is the secret to learning organic chemistry!**

The next Table II.2.1. contains a listing of the common functional groups with the appropriate prefix and suffix used in a chemical nomenclature name to designate each one.

Table II.2.1. Functional groups and their naming

Group	Prefix	Suffix
-COOH	carboxy-	-oic acid; -carboxylic acid
$-SO_3H$	sulfo-	-sulfonic acid
-COOR	alkoxycarbonyl-	-carboxylate
-COCl	chloroformyl-	-oyl chloride; -carbonyl chloride
$-CONH_2$	carbamoyl-	-amide; -carboxamide
-CN	cyano-	-nitril; -carbonitrile
-CHO	oxo-; formyl-	-al; -carbaldehyde; -carbox aldehyde
>C=O	oxo-; keto-	-one; ketone
-OH	hydroxy-	-ol
-SH	mercapto-	-thiol
$-NH_2$	amino-	-amine

-C≡C-	-	-yne
-C=C-	-	-ene
-Cl	chloro	-chloride

3. Homologous series. Homologous series of compounds is a series in which the members differ from each other only in the number of repeated structural units. Such unit in organic chemistry is most often a methylene group: $-CH_2-$. Examples are alkanes and compounds with alkyl functional groups that differ in the length of their side chain. Members in a homologous series can be represented by general formulae. Individual members can be prepared using similar methods and they show same chemical properties and graded physical properties.

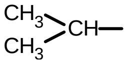
The homologous series of alkanes (paraffins), amines, alcohols, aldehydes, and carboxylic acids are examples shown in Table II.2.2.

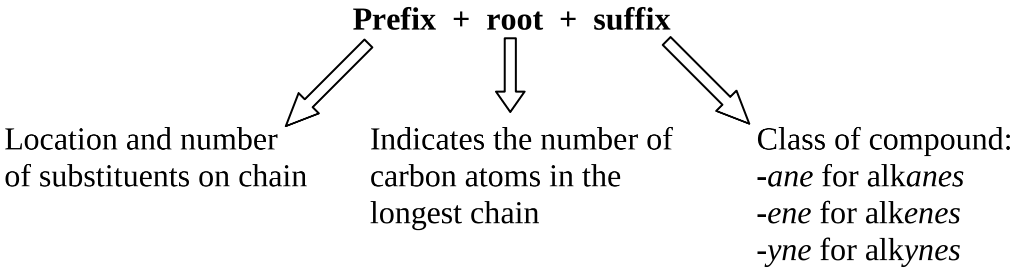
Table II.2.2.

Name of the series	General formulae	Examples of members
Alkanes	C_nH_{2n+2}	CH_4, C_2H_6, C_3H_8, etc.
Alkenes	C_nH_{2n}	C_2H_4, C_3H_6, C_4H_8, etc.
Alkynes	C_nH_{2n-2}	C_2H_2, C_3H_4, C_4H_6, etc.
Amines	$C_nH_{2n+1}NH_2$	CH_3NH_2, $C_2H_5NH_2$, $C_3H_7NH_2$, etc.
Alcohols	$C_nH_{2n+1}OH$	CH_3OH, C_2H_5OH, C_3H_7OH, etc.
Aldehydes	$C_nH_{2n+1}CHO$	CH_3CHO, C_2H_5CHO, C_3H_7CHO, etc.
Carboxylic acids	$C_nH_{2n+1}COOH$ n = a whole number	CH_3COOH, C_2H_5COOH, C_3H_7COOH, etc.

III. Nomenclature of organic compounds. There are two different systems for naming of organic compounds – trivial system and IUPAC system. The trivial system is older and its given names show the origin of a compound or other notable property. Many trivial names continue to be used because their systematic equivalents are considered too cumbersome for everyday use. For example, "tartaric acid", a compound found in wine, has a systematic name of 2,3-dihydroxybutanedioic acid and “lecithin”, the common name for phosphatidylcholine, was originally isolated from egg yolk which in Greek gave the name. In the systematic naming, strict rules are recommended by the commission on the Nomenclature of Organic chemistry at the International Union of Pure and Applied Chemistry.

1. Hydrocarbons

The systematic name of any hydrocarbon or its derivative contain, in principal, prefix, root, and suffix. **The root is based on the longest straight chain.** Compounds with straight chain are designated as normal compounds. If the chain contains branching at the end such as:  $\begin{matrix}CH_3\\CH_3\end{matrix}\!>CH-$ it is known as iso- compound.

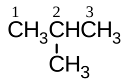


The names of saturated hydrocarbons end on –**ane**. The first four hydrocarbons have unique names; from fifth onward – Greek numerals are used to indicate the number of carbon atoms in the molecule.

Root	Number of carbon atoms	Hydrocarbon normal alkane			Normal alkyl group (as a substituent)	
meth-	1	methane	CH_4		CH_3-	methyl
eth-	2	ethane	C_2H_6	CH_3CH_3	C_2H_5-	ethyl
prop-	3	propane	C_3H_8	$CH_3CH_2CH_3$	C_3H_7-	propyl
but-	4	butane	C_4H_{10}	$CH_3CH_2CH_2CH_3$	C_4H_9-	butyl
pent-	5	pentane	C_5H_{12}	$CH_3(CH_2)_3CH_3$	C_5H_{11}-	pentyl
hex-	6	hexane	C_6H_{14}	$CH_3(CH_2)_4CH_3$	C_6H_{13}-	hexyl
hept-	7	heptane	C_7H_{16}	$CH_3(CH_2)_5CH_3$	C_7H_{15}-	heptyl
oct-	8	octane	C_8H_{18}	$CH_3(CH_2)_6CH_3$	C_8H_{17}-	octyl
non-	9	nonane	C_9H_{20}	$CH_3(CH_2)_7CH_3$	C_9H_{19}-	nonyl
dec-	10	decane	$C_{10}H_{22}$	$CH_3(CH_2)_8CH_3$	$C_{10}H_{21}$-	decyl

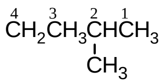
The following rules by IUPAC must be observed when naming organic compounds:

- Rule 1: Organic compounds can be categorized in classes. Each group (not only hydrocarbons) is given a suffix that identifies the group, e.g. **–ol** for alcohols; **-one** for ketones; **–oic acid** for carboxylic acids.
- Rule 2: The root indicates the number of carbon atoms in the main, or longest chain
- Rule 3: Groups containing C and H, attached to the main chain are **alkyl groups** and are considered substituents. They are named using prefixes as in Rule 2 and receive ending **–yl**. If their chain is unbranched, use of *n-* (normal) is allowed. The prefixes *iso-* $(CH_3)_2CH$ at the chain end, *sec-* CH_3CHR- and *tert-* $(CH_3)_3C$- indicate specific branching.
- Rule 4: Atoms or groups of atoms (other than H, such as F-, fluoro, Br-, bromo, Cl-, chloro, NH_2- amino, NO_2- nitro) attached to the main chain are also substituents and are listed before the name of the compound, e.g. 3-bromobutane.
- Rule 5: If the compound contains more than one of the same type of substituent, their number is indicated by a prefix: di-, tri- tetra-, penta-, e.g. dibromomethane.
- Rule 6: The order of substituents in the name is alphabetical (di-, tri-, etc, are not alphabetized, dimethyl- is after triethyl-).
- Rule 7: The position of a substituent on the main chain is indicated by number preceding the substituent's name. **The numbering scheme is chosen in such way as to give smallest number of the main functional group and the chain branches.**



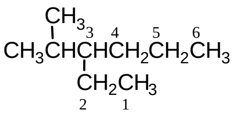
$CH_3\underset{CH_3}{CH}CH_3$

2-methylpropane
(isobutane, common)



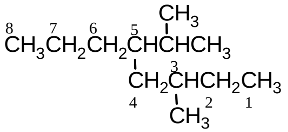
$CH_2CH_3\underset{CH_3}{CH}CH_3$

2-methylbutane
(isopentane,
NOT: 3-methylbutane)



$CH_3\overset{CH_3}{\underset{CH_2CH_3}{CH}}CHCH_2CH_2CH_3$

3-isopropylhexane
(3-ethyl-2-methylhexane)



5-isopropyl-3-methyloctane

The name of the unsaturated hydrocarbons of the alkene series ends on *–ylene* according to the trivial naming system and on *–ene* according to the IUPAC system. The main chain must contain the double bond in alkenes.

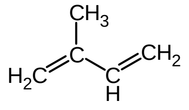
Examples:

$H_2C{=}CH_2$ ethylene (ethene)

$H_2C{=}CH{-}CH_3$ propylene (propene)

$H_2C{=}CH{-}CH_2{-}CH_3$
$H_3C{-}CH_2{-}CH{=}CH_2$ 1-butene

$H_2C{=}CH{-}CH{=}CH_2$ 1,3-butadiene



isoprene
(2-methyl-1,3-butadiene)

The name of triple carbon-carbon bond containing compound of alkyne series ends on *-yne*, as in ethyne (acetylene, C_2H_2).

2. Other compounds.

Simpler alcohols are known by their trivial names. The suffix for alcohols in the IUPAC system is *-**ol***.

CH_3OH - methanol (methyl alcohol); C_2H_5OH - ethanol (ethyl alcohol)

Aldehydes are named by one method after the corresponding acids that are formed after oxidation. According to the IUPAC system class suffix is -***al*** that is added after the hydrocarbon name from which the aldehyde is derived.

HCHO - methanal (formaldehyde, more common name); CH_3CHO - ethanal (acetaldehyde)

The trivial names of first members of carboxylic acid homologous series are:

HCOOH - formic acid; CH_3COOH - acetic acid; CH_3CH_2COOH - propionic acid.

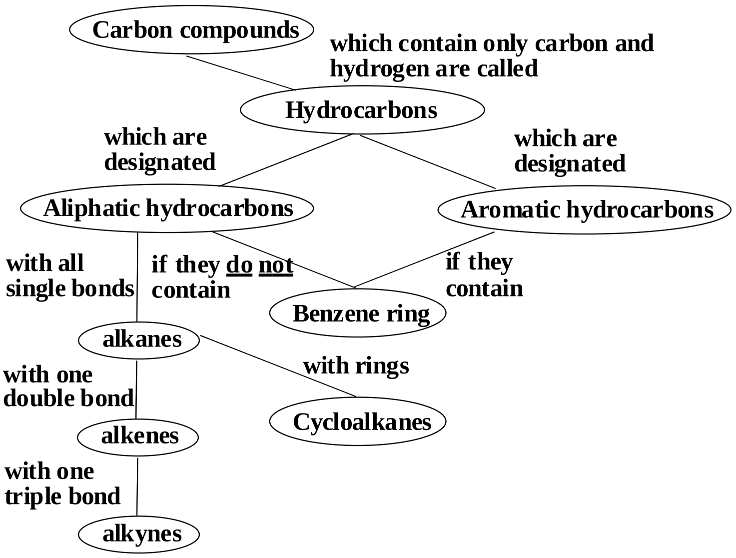
According to IUPAC system, the suffux for monocarboxylic acids is -**oic acid** which is added to the name of the alkane corresponding to the longest chain possessing the carboxy group e.g.:

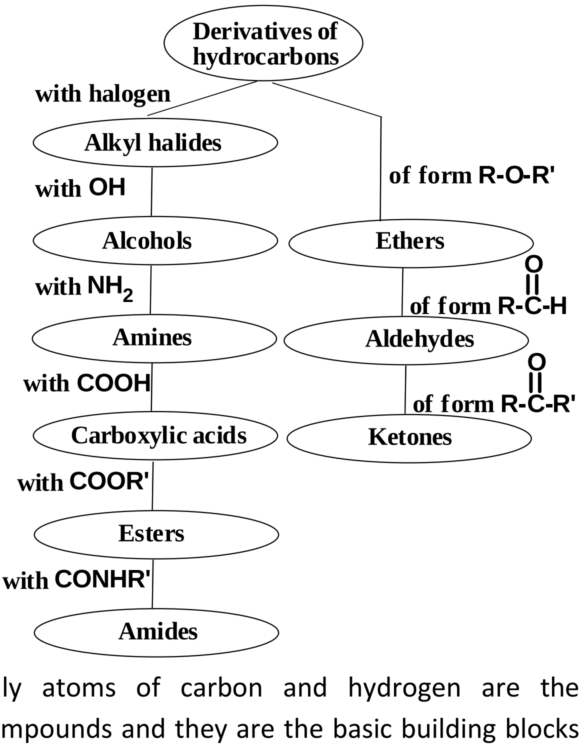
HCOOH - methanoic acid; CH_3COOH - ethanoic acid; CH_3CH_2COOH - propanoic acid.

Details on the nomenclature of organic compounds are given in the “IUPAC Nomenclature of Organic Chemistry” (Blue Book) and on-line “IUPAC Recommendations on Organic & Biochemical Nomenclature, Symbols, Terminology”. The main idea of IUPAC nomenclature is that every compound has one and only one name, and every name corresponds to only one structure of molecules (i.e. a one-one relationship), thereby reducing ambiguity. For ordinary communication, in order to easy the description, the official IUPAC naming recommendations are not always followed except when it is necessary to give a concise definition to a compound. In biochemistry, the trivial names of biomolecules are preferred and almost always used for simplicity and shorter communications.

IV. Hydrocarbons

1. Classification and characteristics





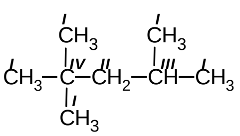
Large class of organic compounds containing only atoms of carbon and hydrogen are the hydrocarbons. The hydrocarbons are the simplest organic compounds and they are the basic building blocks from which all other organic compounds can be formed. The hydrocarbons can be straight-chain, branched-chain, or cyclic compounds. They are the most reduced organic compounds and therefore, they and their residues in more complex substances are rich source of energy. Many hydrocarbons are found in plants, animals and their fossils. The predominant use of hydrocarbons is as a combustible fuel source. Many of them are isolated or produced from crude oil in multimillion ton per year industrial installations.

Hydrocarbon derivatives are formed when there is a substitution by a functional group at one or more of the present carbon atoms.

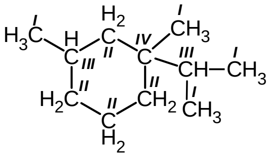
Several types of hydrocarbons have been characterized:

1.1. Alkanes and cycloalkanes. **Alkanes, the saturated hydrocarbons**, contain only single covalent bonds. All of the carbon atoms in a saturated hydrocarbon have *sp*^{3}-hybridization and are bonded to four other carbon atoms or hydrogen atoms. The saturated hydrocarbons' homologous series has general molecular formula C_nH_{2n+2}, where n is an integer and are called, besides alkanes, paraffins (from Latin – having little affinity, or being not very active). The C-C and C-H bonds are quite strong and, therefore, alkanes are generally unreactive.

With the exception of methane, each of the alkanes has a chain of carbon atoms. A carbon atom, bonded to only one other carbon atom is designated as **primary** (′); carbon atom bonded to two other carbon atoms is called **secondary** (″); a carbon connected to three other carbon atoms is **tertiary** (‴); and a carbon bonded to four other carbon atoms is quaternary (^{IV}). For example:



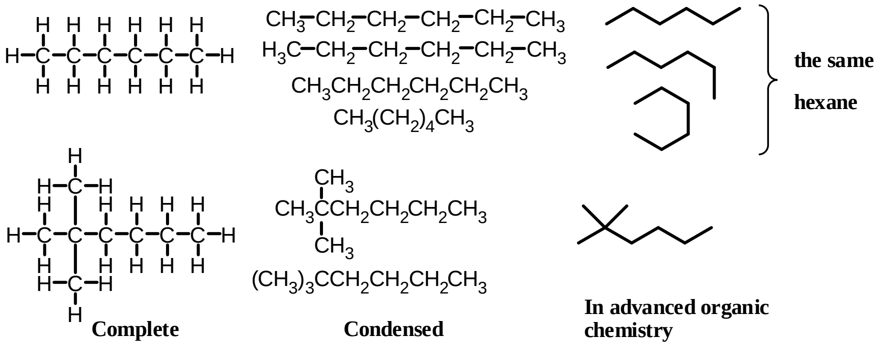
2,2,4-trimethylpentane



1-isopropyl-1,3-dimethyl-cyclohexane

A substituent that contains one hydrogen atom less than the corresponding alkane is called an **alkyl** group. The name of particular alkyl group is obtained by replacing the suffix *–ane* of the alkane name with ending *–yl*. For example methane becomes methyl and ethane – ethyl.

Three usual ways to write structural formulae for any organic compound:



Complete

Condensed
("vertical" and multiple bonds must be shown)

In advanced organic chemistry

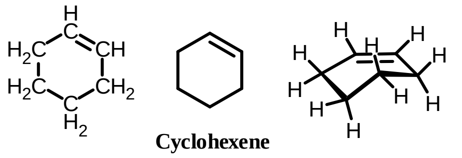
When only lines are used to present a structure, the number of hydrogen atoms at given carbon is "understood" by considering the number of bonds to other carbon atoms or heteroatoms (N, O, S, halogen). The latter symbols can not be omitted.

Compounds of a second homologous series of saturated hydrocarbons have the general molecular formulae C_nH_{2n}, where n is an integer (≥3) and are called cycloalkanes. The name implies that the molecules of these compounds are cyclic (possessing rings). The names are formed by adding prefix *cyclo-* in front of the name of the corresponding normal alkane, e.g. cyclopropane, cyclopentane, cyclohexane etc.

Having in mind different possible kinds of isomerism, for alkanes and cycloalkanes should be considered structural isomerism and conformation.

The chemical reactions of alkanes and cycloalkanes all involve breaking of C–H or C–C single bonds – substitution reactions (often radical), pyrolisis, cracking, and combustion processes.

1.2. Alkenes and cycloalkenes. Hydrocarbons whose molecules contain a double bond are members of the homologous series of alkenes, called also (along with alkynes and arenes) unsaturated hydrocarbons. The general formula of alkenes is C_nH_{2n}. The two carbon atoms linked by a double bond are bound together by two unequal bonds, one stronger σ bond and one, weaker π bond. All other carbon atoms in alkenes involved in single bonds have the usual *sp*^{3}-hybridization, but those in double bonds have *sp*^{2}-hybridization. Therefore, the geometry around these carbon atoms at double bonds is planar trigonal (valence angles of 120°). The cycloalkenes are similar to the cycloalkanes but the former have two carbon atoms linked by a double bond and possess characteristics and reactions of the alkenes. Examples (some alkenes are given above):

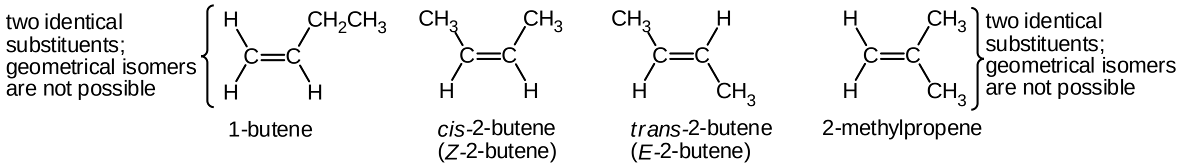


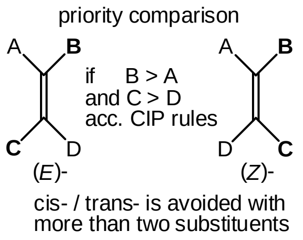
Cyclohexene

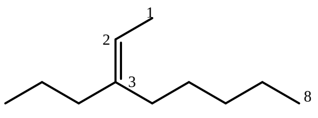
The names of alkenes differ from those of alkanes in two respects:

1. The root chain must contain both C atoms of the double bond. The chain is numbered from the end closer to the C=C bond, and the position of the bond is indicated by the number of the first C atom on it. (Exception in biochemistry of fatty acids – ω-3)
2. The suffix for alkenes is *–ene*.

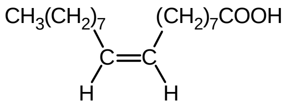
Besides structural (chain) isomerism, alkenes exhibit geometrical (or *cis-/trans-*) isomerism. When two identical (or similar) substituents located on either end of a double bond are on the same side, the stereoisomer is *cis-*, if the substituents are on opposite sides - the isomer is *trans-*. The terms *cis-* and *trans-* specify the **configuration** of the double bond. *Cis-/trans-* stereoisomerism is not possible when one of the doubly bonded carbons bears two identical substituents. The *cis-/trans-* designation is ambiguous for more than two substituents on a double bond. The nomenclature recommends in such cases use of *E- / Z-* system based on priority of groups on a double bond. When atoms of higher atomic number are on the same side, the double bond has *Z*-configuration (from German zusammen); when atoms of higher atomic number are on opposite sides - the double bond has *E*-configuration (from German entgegen).



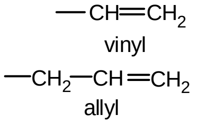




(*Z*)-3-propyl-2-octene (although 9-C chain)



oleic acid (9*Z*-octadec-9-enoic acid *E*- is elaidic acid)

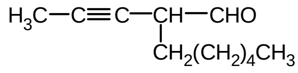


allowed trivial names

Alkenes are relatively stable compounds, but are more reactive than alkanes due to the presence of a carbon-carbon π-bond. The higher reactivity is attributed to the presence of π-electrons in the molecule. These electrons are further apart from the nuclei than in σ-bonds and experience weaker attraction, hence enhanced reactivity at the π-bond. Characteristic reactions of alkenes are associated with rupture of the π-bond and formation of two σ-bonds. Such reactions are called addition reactions, e.g. hydrogenation (addition of H_2), halogenation (of Cl_2, of Br_2), hydrohalogenation (of HCl, of HBr), as well as polymerization, and oxidation.

1.3. Dienes and polyenes. Unsaturated hydrocarbons containing two double bonds are called dienes, and those with more double bonds – polyenes. When the double bonds in these compounds are separated by one single bond they are named conjugated polyenes. If the double bonds are separated by more single bonds then the term for this class is unconjugated polyenes. Rarely two double bonds are connected to the same carbon. Such compounds are cumulenes and contain fragment of sp^2- sp- sp^2 hybridized carbon atoms.

1.4. Alkynes. Alkynes are compounds that contain carbon-carbon triple bond. This bond is formed between two carbons in *sp*-hybrid state and consists of one σ-bond and two π-bonds lying in two mutually perpendicular planes. The general formula of alkynes is C_nH_{2n-2}. The first member's trivial name is acetylene, CH≡CH. Chemically, the alkynes show similar reactivity to that of alkenes, except having two π-bonds, they react even more readily, adding twice as much reagent in addition reactions. Because of higher reactivity acetylenic compounds are relatively rare in Nature but are high volume starting

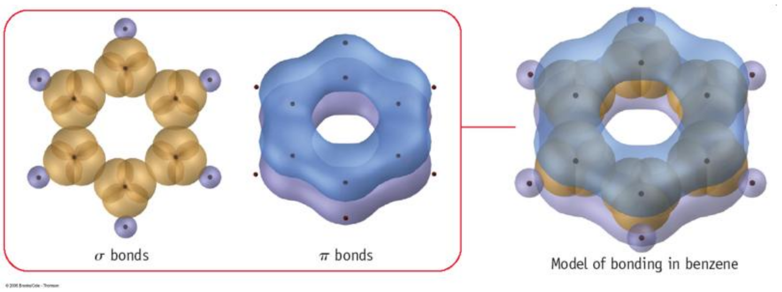


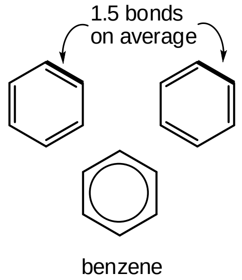
$H_3C{-}C{\equiv}C{-}\underset{CH_2(CH_2)_4CH_3}{\underset{|}{CH}}{-}CHO$

2-hexyl-3-pentynal (the main chain must contain the functional groups - aldehyde and tripple bond; aldehyde carbon is always C-1) materials in industry. Much more common in bioorganic chemistry are derivatives of alkenes. Some of the most aggressive antitumor drugs known contain enyne moiety.

1.5. Aromatic hydrocarbons. An aromatic hydrocarbon or **arene** (or sometimes aryl hydrocarbon) is a hydrocarbon characterized by general alternating double and single bonds between carbons. The term "aromatic" was assigned before the physical meaning of "aromaticity" was discovered, and was derived from the fact that many of these compounds have a sweet scent. The configuration of six carbon atoms in aromatic compounds is known as a benzene ring, after the simplest possible such hydrocarbon, benzene. Aromatic hydrocarbons can be monocyclic or polycyclic (PAH).

Benzene, C_6H_6, is the simplest aromatic hydrocarbon and was recognized as the first aromatic hydrocarbon, with the nature of its bonding first suggested by Friedrich August Kekulé in the 19th century. Each carbon atom in benzene is sp^2-hybridized, located in hexagonal cycle and has four electrons to share. One goes to the hydrogen atom, and one each to the two neighboring carbons. These bonds form the σ framework of benzene molecule. This leaves one electron on unhybridized carbon *p*-orbital that combine with all other *p*-orbitals to form π-bonds. The electrons in the π-bonds are delocalized around the ring with highest electronic density on both sides of ring plane. The electronic structure may be represented equally well with two chemical formulae with alternating single and double bonds around the hexagon. It should be remembered, however, that due to the delocalization all of the carbon-carbon bonds are equivalent. Each bond between two carbons is neither a single nor a double bond, but is equivalent to the others. The structure is also illustrated as a circle inside of the ring to show six π-electrons floating around in delocalized molecular orbitals the size of the ring itself. This also represents the equivalent nature of the six carbon-carbon bonds all of bond order ~1.5 (bond order = (number of bonding electrons – number of antibonding electrons) / 2). The π-electrons are visualized as floating above and below the ring which is flat.





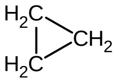
Benzene and other aromatic compounds possess unusual stability. The property that makes aromatic rings especially stable is referred to as **aromaticity** or aromatic character. The π-electrons delocalization is responsible for this stability. Since the π-electrons are delocalized, benzene does not behave like an alkene. For benzene are not typical addition reactions. In order to preserve an aromatic structure, typical reactions for aromatic compounds are electrophilic or nucleophilic substitution reactions in which one or more hydrogens on the aromatic ring are replaced by other atoms or groups.

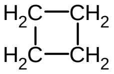
2. Representatives with medico-biological importance

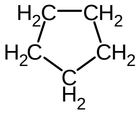
2.1. Alkanes The first 10 members of this homologous series are given above. The C–C and C–H bonds are quite strong and, therefore, alkanes are generally unreactive. Yet, they have a variety of effects on the human body. Gaseous alkanes, as well as vapors from the liquid alkanes, act as anesthetics (anesthesia is the condition of having sensation, including the feeling of pain, blocked or temporarily taken away. This allows patients to undergo surgery and other procedures without the distress and pain). This action is stronger in branched and unsaturated hydrocarbons. Alkanes affect the protective coatings of nerve cells and disrupt the transmission of nerve impulses to and from the brain.

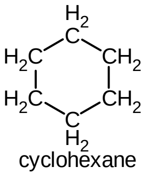
Liquid alkanes (as in gasoline) can do extensive harm if they get into the lungs. They dissolve lipid molecules in the cell membranes of the alveoli, which decreases the ability of the alveoli to expel fluids and leads to pneumonia-like symptoms. Liquid alkanes have similar effect when they contact the skin. Naturally occurring body oils are dissolved by the alkanes, causing the skin to dry out. Higher liquid alkanes have properties more like the naturally occurring body oils. When applied to the skin, mixtures such as mineral oils act as softeners by replacing the natural body oils lost in repeated contact with water or other solvents. Petroleum jelly (vaseline), a mixture of high molecular weight liquid and solid alkanes, is consumed as an ingredient in skin lotions and cosmetics as skin softener and protective film. A good example is the use of petroleum jelly to protect a baby's skin from diaper rash caused by prolonged contact of the baby's skin with urine.

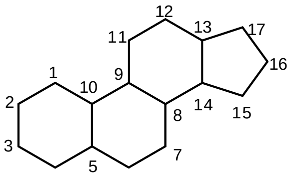
2.2. Cycloalkanes


cyclopropane


cyclobutane


cyclopentane


cyclohexane



sterane skeleton

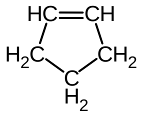
2.3. Alkenes and cycloalkenes

$H_2C=CH_2$
ethylene
(ethene)

$H_2C=CH-CH_3$
propylene
(propene)

$\wr$-$CH=CH_2$
vinyl

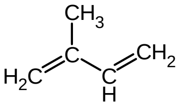
$\wr$-$CH_2-CH=CH_2$
allyl


cyclopentene

2.4. Dienes

$H_2C=CH-CH_2-CH=CH_2$
1,4-pentadiene
(unconjugated)

$H_2C=CH-CH=CH_2$
1,3-butadiene


isoprene
(2-methyl-1,3-butadiene)

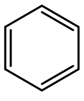
(conjugated dienes)

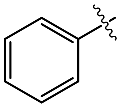
2.5. Alkynes

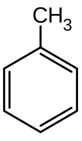
$HC\equiv CH$
acetylene
(ethyne)

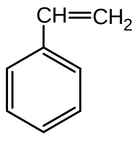
$HC\equiv C-CH_3$
propyne

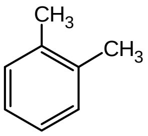
2.6. Aromatic hydrocarbons

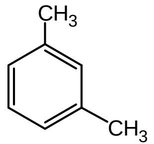

benzene

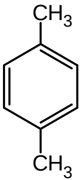

phenyl
group **Ph**

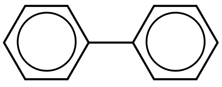

toluene

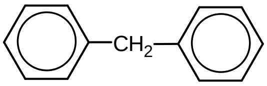

styrene

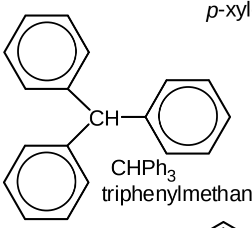

o-xylene

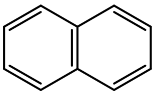

m-xylene

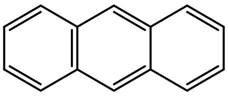

p-xylene

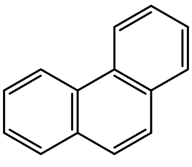

biphenyl

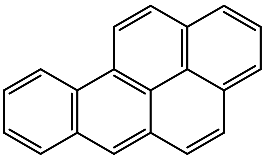

CH_2Ph_2
diphenylmethane


$CHPh_3$
triphenylmethane


naphthalene


anthracene


phenanthrene


benzo[a]pyrene
3,4-benzpyrene

During the industrial revolution many valuable organic compounds, in particular those with fused benzene rings, were obtained from coal tar. The harmful effects of such compounds to humans became evident when workers in coal tar factories developed more often skin cancer. A later study of the chemical components of coal tar concluded that several aromatic fused-ring compounds could cause cancer in mice. Cancer causing chemicals are known as carcinogens. All carcinogenic hydrocarbons in coal tar have similar arrangement of fused benzene rings. One of the most active carcinogens, 3,4-benzpyrene, is a five-ring polycyclic aromatic hydrocarbon (PAH) that is mutagenic. The compound has been discharged earlier in large quantities into the atmosphere from industrial nations because these compounds are formed in the partial combustion of many large organic molecules. This compound is also one of the major carcinogens found in cigarette smoke. Only a very small amount of some PAHs is enough to produce cancer from a metabolic intermediate that intercalates in DNA, covalently bonding to the nucleophilic guanine nucleobases at the N2 position. PAHs are also found in cooked foods, such as grilled meats.

V. Halogen derivatives of hydrocarbons

5.1. Characteristics and classification. The halogen derivatives of hydrocarbons are viewed as formed through substitution of hydrogen atoms with halogen atoms (F, Cl, Br, I). Halogen derivatives are called also **alkyl halides**. Alkyl halides are classified according to the following criteria:

a) type of the halogen atom – F in fluorides, Cl in chlorides, Br in bromides, and I in iodides;

b) number of halogen atoms in the molecule – mono-, di-, tri-, and polyhalogenated derivatives;

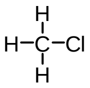
c) type of the hydrocarbon group – derivatives of saturated, unsaturated, and aromatic hydrocarbons. Aromatic halogen derivatives can be of two types: one in which the halogen substitutes the aromatic nucleus and the other in which the halogen is present in the side chain.

d) type of the carbon bearing the halogen – primary, secondary, tertiary alkyl halides.

Alkyl halides are named in two ways:

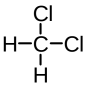
1) in simpler compounds - with the name of the alkyl group followed by the halogen name with –ide ending. For instance: CH_3Cl methyl chloride, CH_3CH_2Br ethyl bromide, $(CH_3)_2CHI$ isopropyl iodide.

2) other naming system uses the halogen atom name as a substituent on alkane main chain and prefixes for the halogens number. For instance: $BrCH_2$-CH_2Br 1,2-dibromoetane. The prefix mono- is usually omitted as well as the number for position of substitution if this does not cause ambiguity, e.g. bromoethane, but 1-bromopropane.



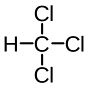
$H-\underset{H}{\overset{H}{C}}-Cl$

chloromethane
(methyl chloride)



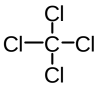
$H-\underset{H}{\overset{Cl}{C}}-Cl$

dichloromethane
(methylene chloride)



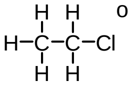
$H-\underset{Cl}{\overset{Cl}{C}}-Cl$

trichloromethane
(chloroform)



$Cl-\underset{Cl}{\overset{Cl}{C}}-Cl$

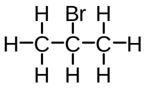
tetrachloromethane
(carbon tetrachloride)



$H-\underset{H}{\overset{H}{C}}-\underset{H}{\overset{H}{C}}-Cl$

often

ethyl chloride



$H-\underset{H}{\overset{H}{C}}-\underset{H}{\overset{Br}{C}}-\underset{H}{\overset{H}{C}}-H$

isopropyl bromide

Halogen derivatives are reactive substances and take part in a variety of reactions due to **the high polarity of the C-X bond**. With this class of compounds are usually demonstrated various mechanisms in organic reactions involving polar species. In substitution reactions, the halogen derivatives react with polar or ionic compounds. The halogen atoms can be replaced by various atomic groups so that new classes of organic compounds are obtained.

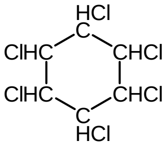
5.2. Properties and representatives with medico-biological importance

Alkylhalogenides are less flammable than alkanes. If they contain more halogen atoms, they might not be flammable at all. As flame retardants, for fire extinguishing, refrigerants, propellants (compressed inert agents in sprays) and solvents they have or had very wide use.

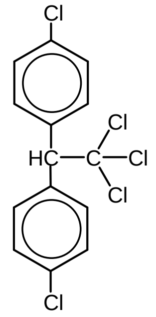
Some haloalkanes (those containing chlorine or bromine) have been shown to have negative effects on the environment such as ozone depletion. They react with ozone in the upper atmosphere, breaking it down to permit vast amounts of UV radiation, causing skin cancer, down to the earth's surface, as shown in a paper in 1974 by Molina and Rowland who shared the 1995 Nobel Prize in Chemistry. The most widely known family within this group is the chlorofluorocarbons (**CFC**s). For example: freons such as **freon 11 (CCl_3F)**, **freon 12 (CCl_2F_2)** are phased out and also use of certain chloroalkanes as solvents for large scale application, such as dry cleaning, have been phased out.

Trichloromethane (**chloroform** is more common name) **$CHCl_3$** and tetrachloromethane (carbon tetrachloride) CCl_4 are colorless liquids used as solvents. Chloroform is used in anesthesiology but it is toxic and its application is already restricted in this field. Tetrachloromethane does not burn and was used to extinguish small fires. Iodoform (triiodomethane) CHI_3 is yellow crystalline compound with iodine odor. It decomposes slowly on air and liberates iodine that kills microorganisms. It is used for wound treatment.

Hexachlorocyclohexane (**hexachlorane**) is an agricultural and household insecticide (lindane, destroying insects, pathogens) and is used also for pharmaceutical treatment for lice

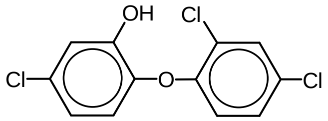


due to its neurotoxicity. Several stereoisomers are known but only one is strong insecticide; the others are inactive. In humans, lindane affects the nervous system, liver and kidneys, and may be a carcinogen, therefore its use is now restricted.

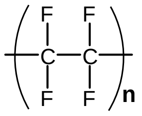

DDT

DDT (from its trivial name, **D**ichloro-**D**iphenyl-**T**richloroethane) is one of the best known synthetic pesticides. It is a chemical with a long, unique, and controversial history. First synthesized in 1874, DDT's insecticidal properties were not discovered until 1939. In the second half of World War II, it was used with great effect among both military and civilian populations to control mosquitoes spreading malaria and lice transmitting typhus, resulting in dramatic reductions in the incidence of both diseases. In the 1970s and 1980s, agricultural use of DDT was banned in most developed countries and later the chemical was outlawed because it is a persistent organic pollutant (very stable in the environment) that bioaccumulates in the food chains and thus is hazardous to animals and humans.

Contemporary inhalational anesthetics often contain halogen derivatives of hydrocarbons that can have also an ether linkage. They replace classical simple but flammable ethers. **Halothane** (or Fluothane, 2-bromo-2-chloro-1,1,1-trifluoroethane, **$CF_3CHClBr$**) is an inhalational general anesthetic. It is the only inhalational anesthetic containing bromine atom. Halothane is a *core* medicine – included in the minimum medical needs for a basic health care system. Desflurane (1,2,2,2-tetrafluoroethyl-difluoromethyl ether, **$CF_3CHF\text{-}O\text{-}CHF_2$**) is used for maintenance of general anesthesia. Enflurane (2-chloro-1,1,2,-trifluoroethyl-difluoromethyl ether, **$CHFClCF_2\text{-}O\text{-}CHF_2$**) is a halogenated ether that was commonly used for inhalational anesthesia during the 1970s and 1980s. Sevoflurane **$(CF_3)_2CH\text{-}O\text{-}CH_2F$** together with desflurane, are replacing isoflurane and halothane in modern anesthesiology. It is often administered in a mixture of nitrous oxide and oxygen.

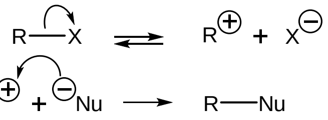

Triclosan

Triclosan (IUPAC name: 5-chloro-2-(2,4-dichlorophenoxy)phenol) is a potent wide spectrum antibacterial and antifungal agent. It is a polychlorinated in benzene rings phenoxy phenol.

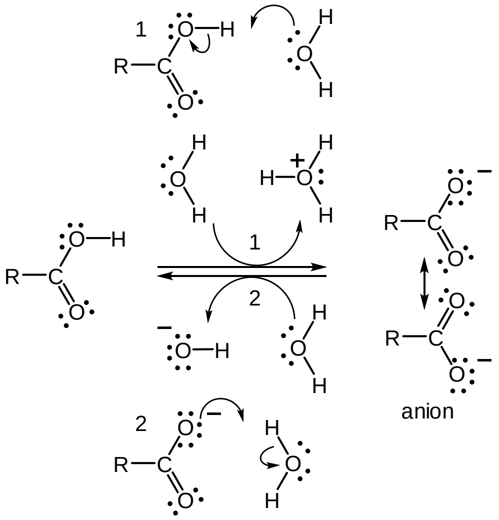


Polytetrafluoroethylene (or polytetrafluoroethene, PTFE) is a synthetic fluoropolymer which finds numerous applications. PTFE is most well known by the DuPont brand name **Teflon**. Water and water-containing substances, and oil and oil-containing substances, like most foods, do not wet PTFE. Due to this property PTFE is used as a non-stick coating for pans and other cookware. It is very non-reactive, partly because of the strength of carbon–fluorine bonds and so it is often used in containers and pipework for reactive and corrosive chemicals. Where used as a lubricant, PTFE reduces friction, wear and energy consumption of machinery. PTFE is biocompatible and is used in medical implants such as grafts to bypass narowed (stenotic) arteries in peripheral vascular disease.

VI. Fundamental types of organic reactions. The halogenated hydrocarbons present the first opportunity to introduce mechanisms of organic reactions and **classify the reactions** in broad classes. A **mechanism of chemical reaction is the sequence of elementary events** (steps) leading from substrate into product. In the context of a reaction mechanism, curly or curved headed arrow show **movement of an electron pair**. Covalent bonds consist of paired electrons; therefore curly arrows illustrate breakage and/or formation of covalent bonds. **Notice**: chemistry is science dealing with formation and breakage of chemical bonds which fundamentally is identical to saying **rearrangement of electron density**. Therefore, indications for transfer (movement) of heavier than electrons particles are incorrect. Their rearrangement follows the rearrangement of electrons. Curly arrows can begin only in areas of high electron density. These are: 1) in the middle of covalent bond; 2) at negative charge; 3) at lone pair of electrons.

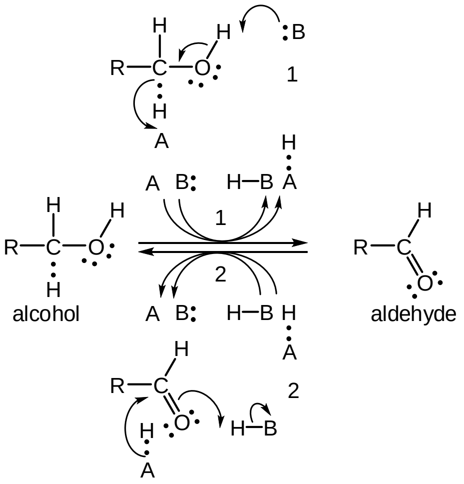


6.1. Acid-base reactions are not associated with change of the oxidation state. An example for use of curly arrows to show the deprotonation of carboxylic acid which transfers a proton to water (a base) describes the actual rearrangement of electron density (1). The oxygen in water lone pair is donated to partially positively charged hydrogen from the carboxylic acid. Simultaneously, the electron pair of O−H bond in the acid moves on the oxygen. This negative charge is not retained only on one of the oxygen atoms of the carboxylate anion but is delocalized on both oxygen atoms. The reversed reaction (2) is protonation of a carboxylate ion (a base) by water molecule serving as an acid. For this mechanism, an electron pair from carboxylate oxygen is transferred to one of water hydrogens and simultaneously the pair of O−H bond in water localizes on the water oxygen to give hydroxide anion.



6.2. Redox reactions proceed with change in the oxidation state. The mechanism, in broad sense, of oxidation of a primary alcohol to aldehyde is shown using curly arrows. In the oxidation (1), the electron pair as one hydride ion (a proton and two electrons) is transferred to the oxidizing agent A; the extra proton from the alcohol O−H group is bound by the catalytic effect of base B. In the reversed, reduction (2) reaction, the donor of hydride is A-H and it is the reducing agent (supplying hydride ion) and the acid H-B is involved as catalyst.

Oxidation is the loss of electrons or an increase in oxidation state by a molecule, atom, or ion.

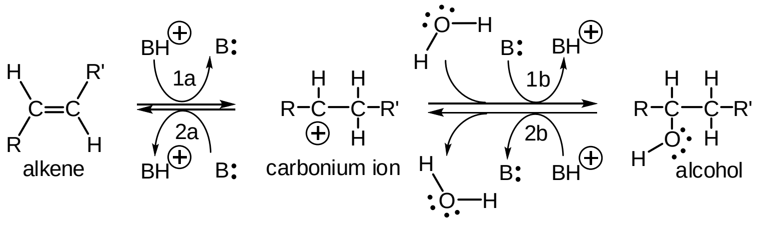


Kinds of Organic Reactions

The classification of the two examples above is based on the outcome of the reaction. In general, we look at what occurs and try to learn how it happens. Using common patterns that describe the changes in transforming a substrate into product there are several basic kinds of organic reactions:

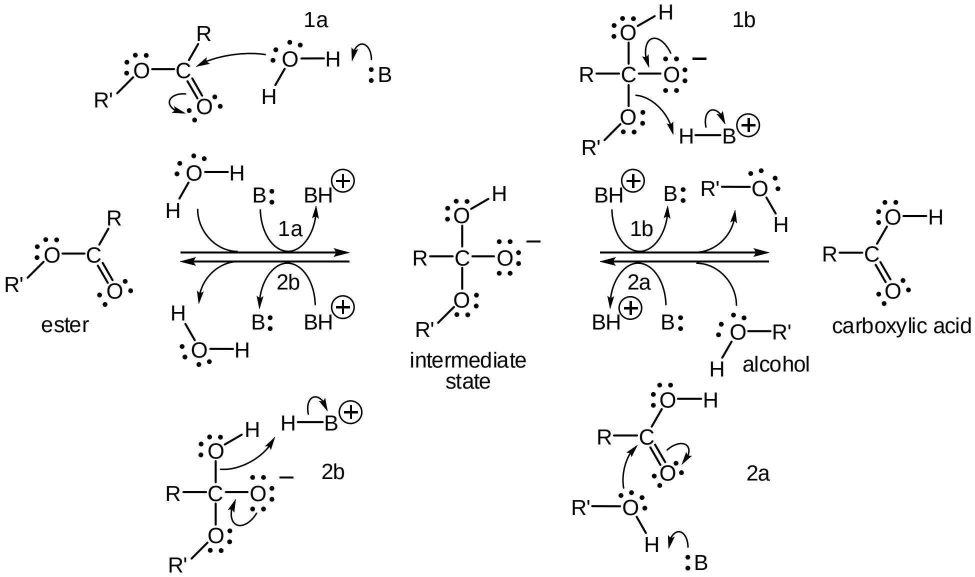
- **Addition reactions** – two molecules combine; the product is "sum" of participating components;
- **Elimination reactions** – one molecule splits into two smaller components;
- **Substitution** – parts, portions from two molecules exchange locations;
- **Rearrangement reactions** – a molecule undergoes changes in the way its atoms are connected.

6.3. Addition/elimination reactions proceed via mechanism involving polar intermediates. For instance, the addition of HBr to alkene is an **electrophilic addition reaction**. An **electrophile** (**E^+**, literally *electron-lover*) is a reagent attracted to electrons that participates in a chemical reaction by accepting an electron pair in order to bond to a **nucleophile**. A **nucleophile** (**Nu^-**, from nucleus and love) is a reagent that forms a chemical bond to its reaction partner (the electrophile) by donating both bonding electrons. Because electrophiles accept electrons, they are Lewis acids. **Most electrophiles are positively charged**, have an atom that carries a partial positive charge, or have an atom that does not have an octet of electrons. The electrophilic addition to alkenes has two mechanistic steps. In the first, the electron rich π-system of the double bond is attacked by electrophile, a proton. The intermediate is called **carbocation** (carbonium ion) and its stability determines the next pathway of the reaction. In the example, the carbonium ion reacts with water molecule to give an



alcohol.

6.4. N**ucleophilic substitution**. Several mechanisms can operate in substitution reactions, depending on the substrate nature. Common for carboxylic acids derivatives are **nucleophilic substitution** reactions. They consist of nucleophilic addition/elimination mechanistic steps. For instance, the conversion of a carboxylic acid into ester (2a, 2b) involves a step in the mechanism that is nucleophilic addition to carbonyl carbon, followed by elimination of leaving group. The nucleophile is an alcohol R’OH, whose oxygen electron pair is attracted to the partially positively charged carbonyl carbon. The intermediate is tetrahedral. It can eliminate water, after protonation from BH^+ to produce the ester. The reversed sequence is the hydrolysis of an ester to carboxylic acid and alcohol (1a, 1b). This mechanism involves also an initial nucleophilic addition of water molecule. Then the intermediate can lose the alcohol residue (R’OH) which gives carboxylic acid. Overall, the reactions of esterification and hydrolysis of ester are reversible.



With the introduction of more highly reactive halogen derivatives, we introduce also two basic mechanisms of a chemical reactions typical for them – **substitution** of the halogen for another functional group. Examples of such substitution reactions where a hydrocarbon halogen derivative is converted into alcohols (by action of alkali hydroxide or water), into amines (with ammonia), into thiols (mercaptan, with hydrogen sulfide), and into esters (with carboxylate ion) all have common mechanis. Included also is Würtz synthesis.

$R\text{-}X + OH^- \longrightarrow R\text{-}OH + X^-$

$R\text{-}X + H_2O \longrightarrow R\text{-}OH + HX$

Hydrolysis of halogen derivatives to alcohols

$R\text{-}X + NaR' \longrightarrow R\text{-}R' + NaX$

Synthesis of alkanes (Würtz synthesis)

$R\text{-}X + :NH_3 \longrightarrow R\text{-}NH_2 + HX$

Synthesis of amines

$R\text{-}X + HS^- \longrightarrow R\text{-}SH + X^-$

Synthesis of thiols

$R\text{-}X + R'COO^- \longrightarrow R'COO\text{-}R + X^-$

Synthesis of esters

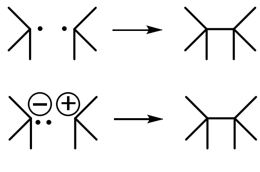
Steps in mechanism. Mechanisms are classified based on the type of elementary steps in a sequence. The following considerations are fundamental in describing a mechanism:

- A step involves either the formation or breaking of a covalent bond;
- Steps can occur individually or in combination with other steps;
- When several steps occur at the same time they are said to be *concerted*;
- When we are **able to characterize a species** (molecule, ion, etc.) along the reaction path, we are concern with an **intermediate** (state at local energy minimum); when such **species is imaginary** in the process of bond formation/breakage – then we speak about **transition state** (state at local energy maximum).

The same basic chemical principles of mechanism are valid for complex biochemical processes.

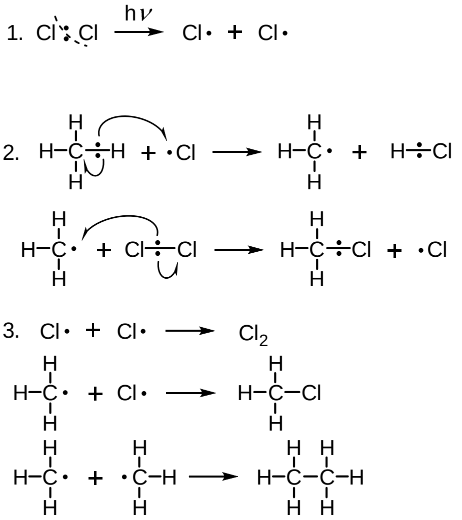
Types of steps in reaction mechanisms:

- Formation of a covalent bond. It can be done by particles donating one electron each (homogenic), or by particles where one of them has a pair of electrons but the has none (heterogenic);
  - **Homogenic or heterogenic**



- Breaking of a covalent bond. It can happen so that each resulting particle retains one electron from the bond (homolytic), or one of the resulting fragments retains both electrons from the bond (heterolytic);
    - **Homolytic or heterolytic**
- Oxidation of a functional group;
- Reduction of a functional group;

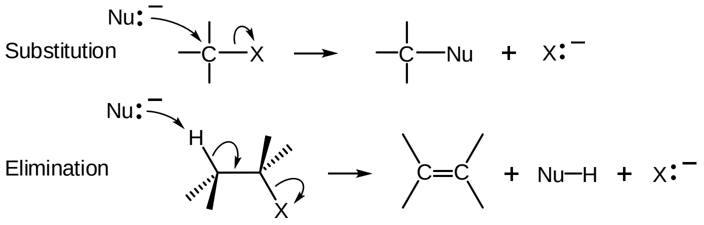
6.5 Free radical chain halogenation. The mechanism of chlorination of alkanes, e.g. methane, in the presence of light proceeds via free radical mechanism. It involves homolytic cleavage of Cl−Cl bond to generate two radicals, each having unpaired electron and therefore, highly are reactive. The step 1) is initiation of the reaction. The steps in 2) are propagation of the chain reaction. Homolytic breakage and homogenic formation of bonds generate new radicals that continue the chain reaction. The reactions in 3) are termination. When two radicals meet and form chemical bond, the chain is interrupted.



Polar reactions and how they occur. Much more often the chemical reactions proceed via polar intermediates or polar reactive species. The basic prerequisites for such mechanisms are:

- molecules can contain local unsymmetrical electron distributions due to differences in electronegativities;
- this causes a partial negative charge on an atom and a compensating partial positive charge on an adjacent atom;
- the more electronegative atom has the greater electron density;
- carbon atom bonded to a more electronegative element has a partial positive charge (δ^+).

When applied to halogen derivatives these principles lead to the conclusion that alkyl halides are strongly polarized at the carbon-halide bond, making the carbon electrophilic (carrying large δ^+ charge). Consequently, nucleophiles (with negative or partial negative charge) will replace the halide in C−X bonds of many alkyl halides (reaction as Lewis base). Nucleophiles that are Brønsted bases produce elimination (loss of HX).

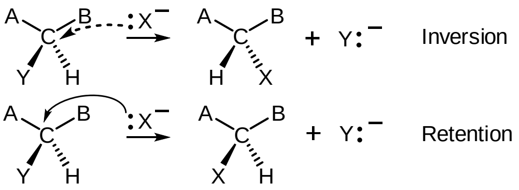


Typical nucleophiles are:

$:OH^-$, H_2O, $:OR^-$, $RCOO^-$, $:CN^-$, $:NH_3$, $:SH^-$

Depending on the structure of alkylhalide, two mechanisms are observable:

- **S_N1 (Substitution Nucleophilic Unimolecular)**. This mechanism includes two steps with carbocation intermediate. It occurs in tertiary, allyl (CH_2=$CHCH_2$-), benzyl ($C_6H_5CH_2$-) halogenides.
- **S_N2 (Substitution Nucleophilic Bimolecular)**. The mechanism has one combined step − without intermediate; Occurs in primary and secondary halides.



The nucleophilic substitution on alkyl halides proceeds with two distinct stereochemical modes:

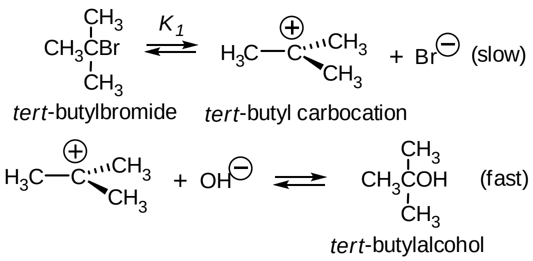
- Substitution with **inversion of configuration**;
- Substitution with **retention of configuration**.

6.6. The S_N1 Reaction.

- Tertiary alkyl halides react rapidly in protic solvents by a mechanism that involves **departure of the leaving group prior to addition of the nucleophile**;
- Called an S_N1 reaction – occurs in two distinct steps while S_N2 occurs with both events in same step;

- If nucleophile is present in reasonable concentration (or it is the solvent), then ionization is the slowest step.

  Typical example is the solvolysis of tertiary butylbromide in alkaline medium which gives *tert*-butanol.



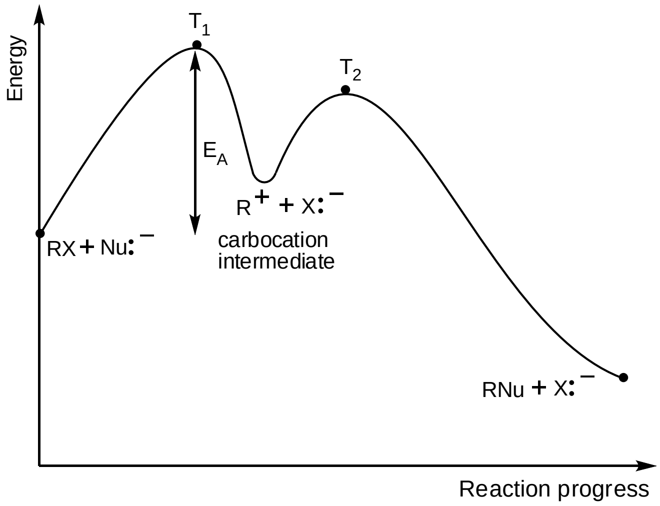
Rate = K_1 [$(CH_3)_3CBr$]

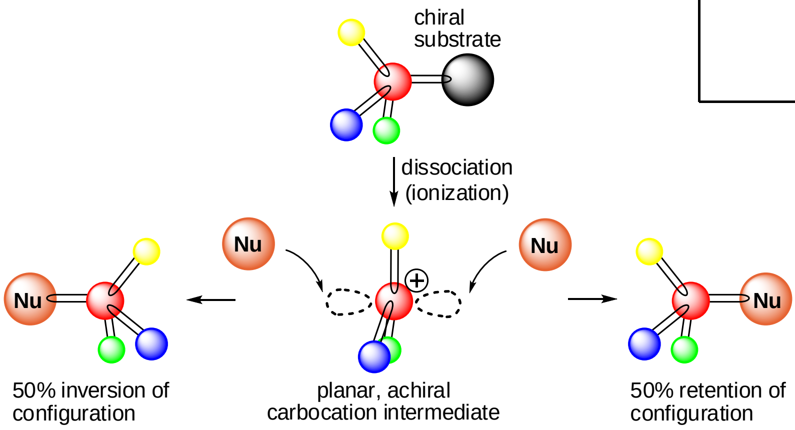
Rate-determining step is the formation of *tert*-butyl carbocation. The S_N1 mechanism is an ionization mechanism. This determines the **first-order rate low**.

The energy diagram illustrating the S_N1 mechanism shows two maxima. The first one is higher, that is the first step is rate-determining step. The local, high energy minimum corresponds to the intermediate carbocation.

Stereochemistry of S_N1 Reaction.

The carbocation is planar (achiral). The planar intermediate leads to loss of chirality, therefore the S_N1 reaction **product is racemic** or has some inversion. **Racemic mixture** is a mixture 1:1 of two enantiomers. The stereochemical outcome of such reaction is due to the almost equal probability of the nucleophile to approach the flat reaction center from either of its two faces.





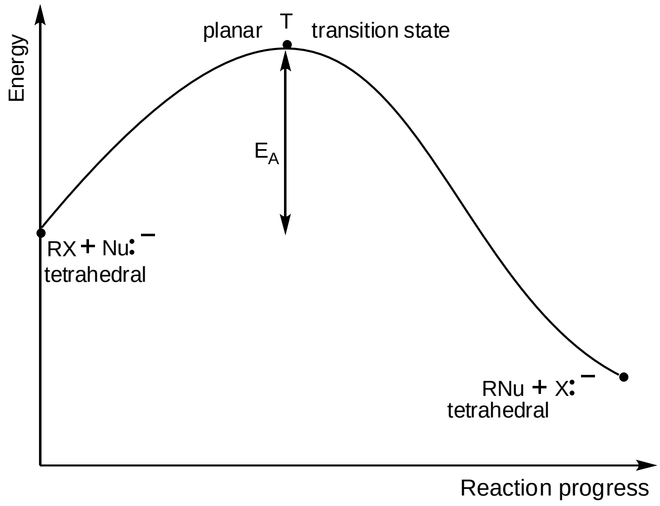
The reactivity of halogen derivatives of hydrocarbons in S_N1 substitutions is governed by the stability of the carbocation. The most stable carbocations are the tertiary, followed by secondary. Therefore, the order of halogenides is tertiary > secondary > primary > methyl.

6.7. The S_N2 Reaction.

Methyl bromide reacts with sodium hydroxide to form methyl alcohol by a nucleophilic substitution reaction. The rate of this reaction is directly proportional to the concentration of both methyl bromide and sodium hydroxide. The reaction follows **second order reaction kinetics**.

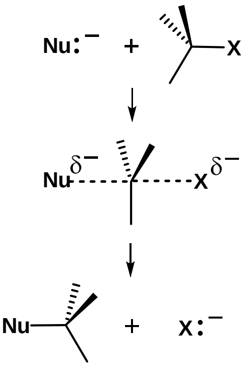
$$CH_3\mathbf{Br} + NaOH \longrightarrow CH_3\mathbf{OH} + NaBr$$

Rate = K_2 [CH_3Br][NaOH]

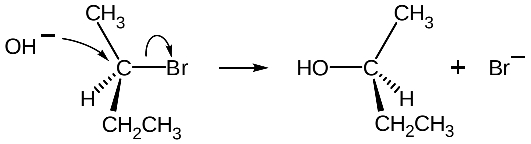


- The reaction involves a transition state in which both reactants are together. The symbol for the mechanism is S_N2 – substitution nucleophilic bimolecular. **The S_N2 mechanism is a concerted process**, that is, a **single step** reaction in which both the alkyl halide and the nucleophile are involved at the transition state. This fact is clearly visible from the energy diagram. Cleavage of the bond between carbon and the leaving group is assisted by formation of a bond between carbon and the nucleophile. In effect, the Nu “pushes off” the leaving group X from its point of attachment.

Therefore, the transition state represents one partially broken (C–X) and one partially formed (C–Nu) bonds. The carbon at which the substitution occurs is planarized at this point. The transition state of an S_N2 reaction has a planar arrangement of the carbon atom and the remaining three groups.



The nucleophile approaches the reaction center from the opposite side of the leaving group. If the substrate is optically active, as shown with 2-bromobutane, then the resulting alcohol has opposite configuration. Substitution reactions that proceed by the S_N2 mechanism lead to inversion of the configuration at the carbon bearing the leaving group.



Characteristics of the S_N2 reaction:

- Very sensitive to steric effects. The more alkyl groups connected to the reacting carbon, the slower the reaction.
- Methyl halides are most reactive. Primary are next most reactive. Secondary might react
- Tertiary are unreactive by this path.

The relative reactivity of nucleophiles has been determined in the following order:

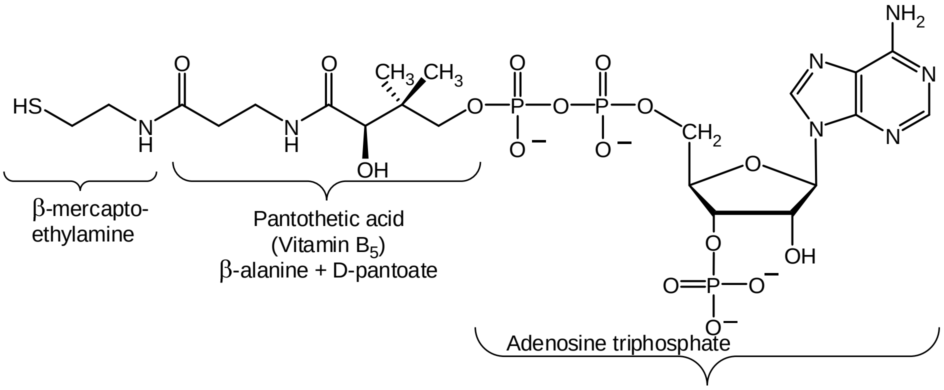
$$CH_3\text{-}Br + OH^{\ominus} \xrightarrow{K} CH_3\text{-}Nu + Br^{\ominus}$$

$$HS^- > CN^- > I^- >> CH_3O^- > OH^- >> Cl^- > NH_3 > CH_3CO_2^- >> H_2O$$

Certain functional groups cannot be displaced by a typical S_N2 reaction. Poor leaving groups are hydroxyl, ether, and amino.

$$\underbrace{R{-}F \quad R{-}OH \quad R{-}OR' \quad R{-}NH_2}_{\text{These compounds do not undergo } S_N2 \text{ reactions}}$$

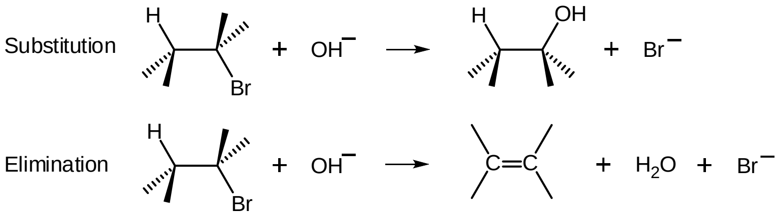
Sulfur is a very good nucleophile. This fact has relevance to biochemical proceses. **Coenzyme A** is, in chemical terms, **a thiol**. It can react with carboxylic acids to form thioesters, thus functioning as an **acyl group carrier**. The reaction is facilitated by the good nucleophilic properties of sulfur. Coenzyme A assists in transferring fatty acids from the cytoplasm to mitochondria. A molecule of coenzyme A carrying an acetyl group is also referred to as **acetyl-CoA**. When it is not attached to an acyl group, the abbreviation usually is 'CoASH' or 'HSCoA'.



6.8. Elimination reaction with alkyl halides.

Nucleophiles react also as Brønsted bases **leading to elimination** in alkyl halides.

- Elimination is an alternative pathway to substitution;
- Elimination is opposite of addition;
- Elimination reaction generates an alkene



- The reaction can compete with substitution and decrease yield, especially for S_N1 processes.

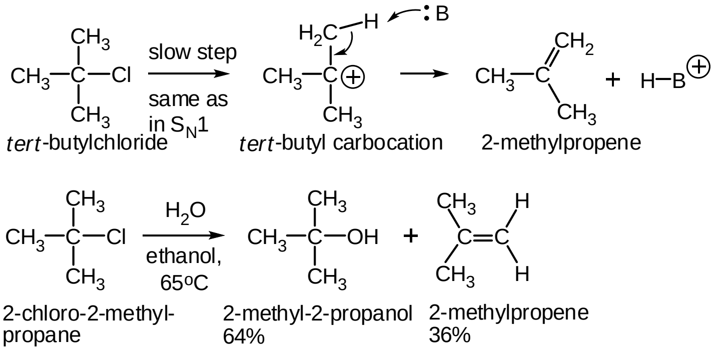
The hydroxide ion in these general examples can substitute the bromine atom but can also act as a base, abstracting first hydrogen atom from the neighboring α-carbon.

Mechanism of elimination reactions. Elimination reactions are accompanied by loss of atoms or atomic groups from a molecule. The resulting product usually contains double, triple bond or a ring. The nomenclature designation of such reactions is with **E**. Two mechanisms are usually considered:

- **E1**: X^- leaves first to generate a carbocation; monomolecular mechanism where a base abstracts a proton from the carbocation;
- **E2**: Concerted transfer of a proton to a base and departure of leaving group; bimolecular mechanism in which the bond to leaving group is broken simultaneously with formation of bond between the proton and the base.

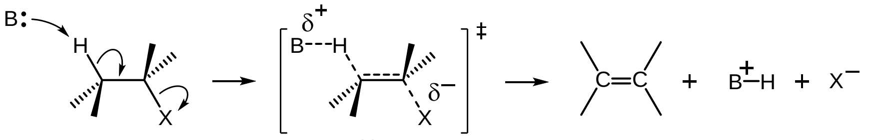
The E1 reaction.

- Competes with S_N1 and E2 at tertiary (3°) centers;
- The rate depends only on the substrate concentration: v = *K* [RX].

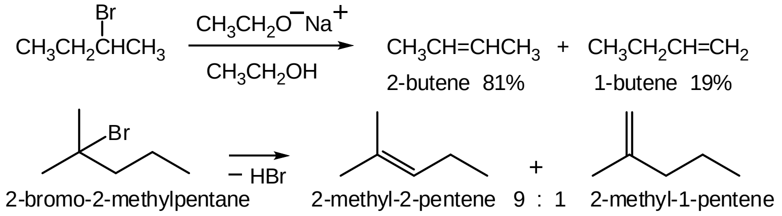


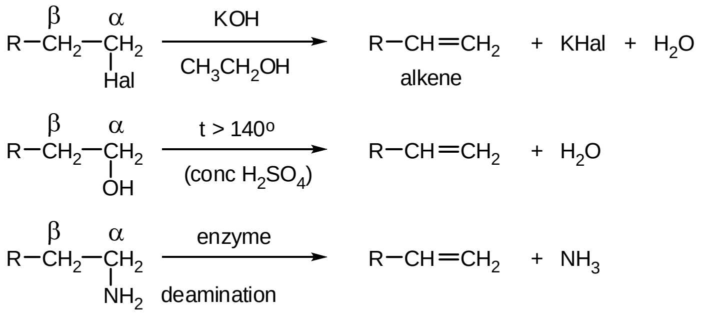
The E2 reaction.

- A proton is transferred to base as the leaving group begins to depart;
- The transition state combines simultaneous leaving of X and transfer of H.

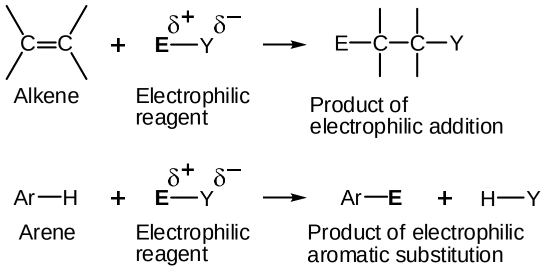

Transition state

- In the elimination of HX from an alkyl halide, the more highly substituted alkene product predominates. This fact is known as Zaitsev rule, as illustrated by elimination of HBr from 2-bromobutane and from 2-bromo2-methylpentane.

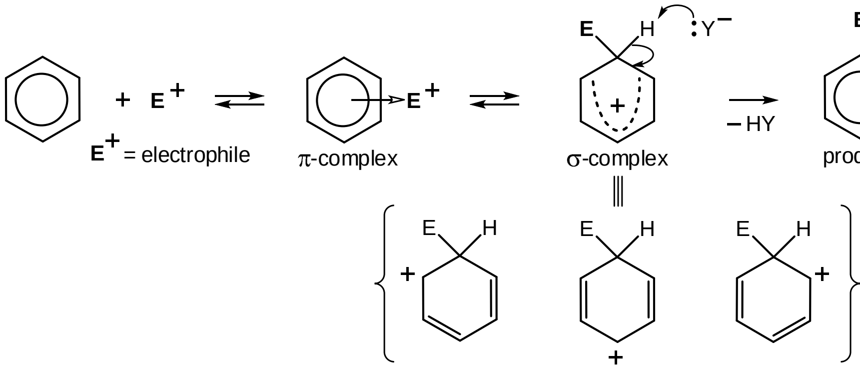




Characteristically, the reagents that react with the aromatic ring of benzene and its derivatives are electrophiles. Just above, it was shown alkenes add electrophilic reagents. A different reaction takes place when electrophiles react with arenes. **Substitution is observed instead of addition**. (The reason for this difference will be explained in the topic concerning stability of aromatic systems.) Representing an arene by the general formula Ar–H, where Ar stands for an aryl group, the electrophilic portion of the reagent replaces one of the hydrogens on the ring.

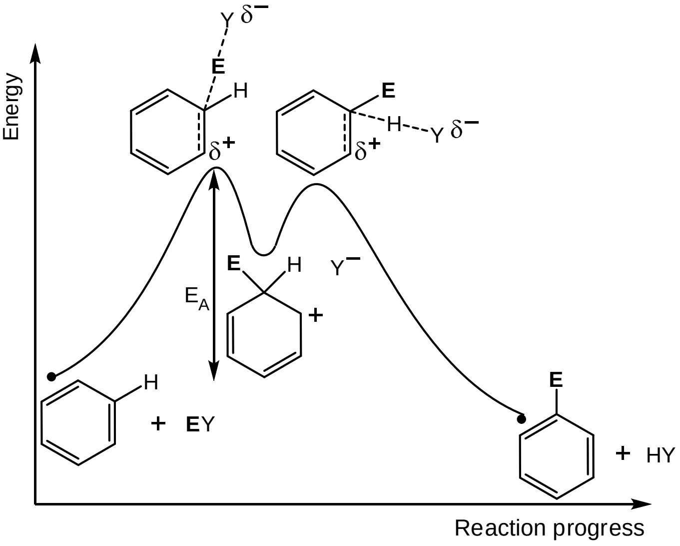


6.9. Such reaction is called **electrophilic aromatic substitution** (S_EAr): an electrophile attacks an aromatic ring and substitutes for one of its hydrogens. The electrophile approaches an aromatic system and combines with it in a π-complex. In the next step the electrophile accepts an electron pair from the π-system of benzene to form a carbocation (σ-complex). This is a high energy species, although the positive charge in it is delocalized on all carbon atoms, in particular on ortho- and para- positions. The cation rapidly suffers deprotonation, resulting in full restoration of the aromaticity of the ring and formation of the product of electrophilic aromatic substitution.



The energy diagram shows that when the ring conjugated system is destroyed, the transition state is with highest energy whereas the next step proceeds easier and faster.

Toluene is more reactive than benzene in an electrophilic aromatic substitution. The reason for this, and for all other groups on benzene ring exhibiting the same effect, is the positive inductive effect of the methyl group. It increases the electron density of the aromatic ring making it more active in S_EAr reaction. Electron-releasing groups are activating the benzene system. On the contrary, electron withdrawing groups (negative inductive effect) decrease the rate of S_EAr reaction.



Using as an example the nitration of toluene, the principle stating that the more stable carbocation is formed faster than a less stable one is illustrated with parts of energy diagrams for nitration of benzene and toluene. The activation by the methyl group is not identical at all possible places for nitration: ortho-, meta-, and para-. The activation energy is smaller for para- and ortho-positions, which isomers are produced faster because the corresponding intermediate carbocations are more stable. This phenomenon in S_EAr reactions is called orientation effect.