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The Department of Chemistry

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Bioorganic Chemistry

for 31.05.01"General Medicine" specialty

Manual for Foreign Medical Students

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Bioorganic Chemistry for 31.05.01"General Medicine" specialty. Manual for Foreign Medical Students. – NORTH CAUCASIAN STATE ACADEMY. CHERKESSK, RUSSIA

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Д40 **Джатдоева, Д.Т.** Биоорганическая и медицинская химия: учебно-методическое пособие для обучающихся I курса специальности 35.05.01 «Лечебное дело» / Д.Т. Джатдоева. – Черкесск: БИЦ СКГА, 2022. – 116 с.

В учебно-методическом пособии представлены методические указания для подготовки к каждому занятию курса: цель занятия, вопросы, выносимые на занятие, краткая теоретическая часть, вопросы для самоподготовки и задания для самостоятельной работы. Настоящее учебно-методическое пособие составлено в соответствии с требованиями ФГОС и предназначено для студентов первого курса специальности. 31.05.01 «Лечебное дело» Медицинского института СКГА.

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Contents

Preface

The textbook is based on modern Bioorganic Chemistry chemistry and considers the structure and chemical transformations of organic compounds, especially those that have biological importance. Special attention is given to the chemical reactions that have analogies in living systems. This book conforms to the Federal educational program on Bioorganic Chemistry for medical schools and universities. It is meant for students who study Bioorganic Chemistry during one term. The book may also be useful for teachers and students of specialized secondary schools with instruction conducted in English and colleges, whose main interest is medicine, pharmacy, biology and agriculture.

Dzhatdoeva Diana Tokhtarovna

ABOUT THE AUTHOR

Unit 1. *Basic Theses of Butlerov´s chemical structure theory*

Alexander Mikhailovich Butlerov (1828-1886 gg.), Russian chemist, was one of the outstanding chemists of his time, creator of theory of chemical structure and founder of world famous school of organic chemists.

Study of the synthesis of substances

In 1861, in a published report "On the chemical structure of matter ", the main provisions of the theory of the chemical structure of AM Butlerov were formulated. The scientist described in detail the methods of synthesis and use of different reactions. One of the most important theses of the chemist was his assertion that to each chemical substance there corresponds one formula. Its importance lies in the fact that it characterizes all properties and shows the connection of atoms within molecules.

The Butlerov theory also provided that with the help of controlled reactions, new substances can be produced. In the following years, the famous chemist and his students conducted many experiments to prove this assumption. They were able to synthesize such new substances as isomers of pentane, isobutylene and some alcohols. For their era, these discoveries had a colossal significance, which can only be compared with the importance of defining other elements of Mendeleev (for example, ekabor).

Systematization of chemistry

In the XIX century, the main provisions of Butlerov's theory completely changed the idea of scientists about the structure of chemical elements. In particular, the researcher was the first to suggest that the molecules are not a chaotic cluster of atoms. On the contrary, they have an ordered structure. Atoms are connected to each other in a certain sequence, on which the nature of the entire substance also depends.

Influence of atoms on each other

Butlerov discovered another important regularity. With the formation of chemical bonds, the process of the transition of electrons from one atom to another begins. This changes their density. There are electronic pairs that affect the property of the new forming substance. The scientist studied this phenomenon on the example of hydrogen chloride, where chlorine changes the electronic density of hydrogen bonds.

Chemical bonds

Butlerov believed that the structure of substances can beto study by chemical methods. This position was confirmed by a number of successful experiments of the scientist. Also, the researcher was an advocate of the idea that formulas can be correct only if they reflect the order of the chemical bonds of different atoms. Butlerov was engaged in analyzing this assumption for many years.

He distinguished three types of connections - simple, double andtriple. The scientist was right, but the further development of science has shown that there are other chemical bonds. In particular, now experts can characterize them also with the help of physical parameters.

The development of the Butler theory

Butlerov's theory later developed in two directions. The first was that science was able to determine not only the order of the connection, but also the spatial arrangement of atoms in the molecule. So there was a stereochemistry. This discipline began to explore in detail the spatial structure of molecules. Butlerov himself spoke about this new direction, although he never had time to study this theoretical question.

The second direction in the development of the theory of the scientist wasthe appearance of a doctrine devoted to the electronic structure of atoms. This is not only a chemical, but also a physical discipline. The essence of the mutual influence of atoms was studied in more detail and the reasons for the manifestation of different properties were explained. It was the main provisions of Butlerov's theory that enabled scientists to achieve such successes.

Variety of substances

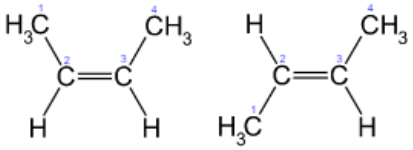
The famous Butlerov's theory is a lot of attentiongives isomerism to a phenomenon consisting in the existence of isomers of substances equal in molecular weight and in atomic composition, which at the same time differ from each other in the arrangement of atoms and in the structure. This feature explains the variety of properties of substances in nature.

Butlerov proved his theory on the example of butane. According to the idea of the scientist, in nature there should exist two kinds of this substance. However, at that time science knew only one butane. Butlerov conducted many experiments and still got a new substance, similar in composition, but different in properties. It was called isobutane.

Isomerism Definition

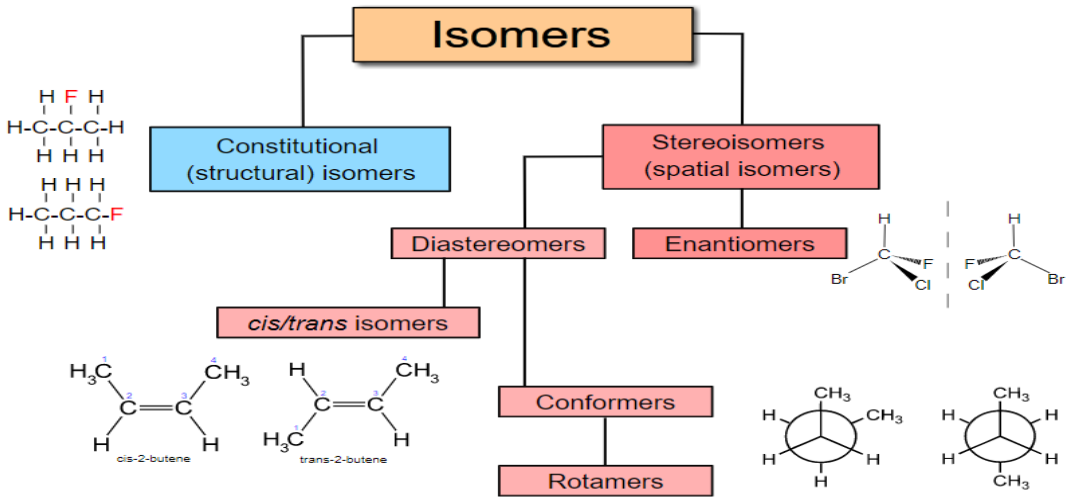
Compounds which have same molecular formula but differ in modes of combination or arrangement of atoms within the molecule are known as isomers and this phenomenon is know as isomerism. Isomers can have different physical or chemical properties.

As for example, the cis and trans isomers of but-2-ene are as follows:



Classification of isomerism

There are two main types of isomerism- structural isomerism and stereoisomerism. These can be further classified as,



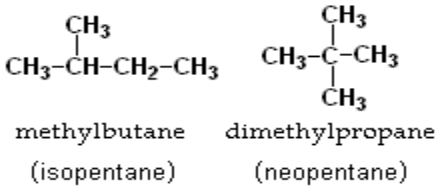
Structural Isomerism

Structural isomerism, or constitutional isomerism, is a type of isomerism where isomers have same molecular formula but have different arrangements of atoms within the molecule.

Structural isomerism can be further classified as:

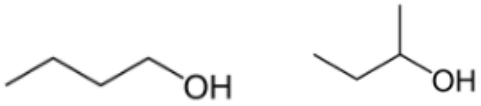
1. Chain isomerism

Chain isomerism is a type of structural isomerism where the isomers have same molecular formula but they differ in the order in which the carbon atoms are bonded to each other. **CH_3-CH_2-CH_2-CH_2-CH_3** -pentane (n- pentane)



2. Position isomerism

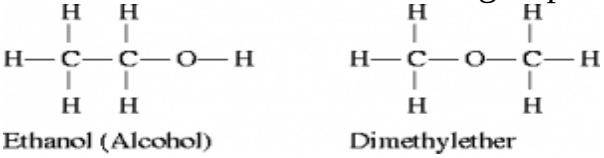
Position isomerism is a type of structural isomerism where the main carbon skeleton are same but they differ in the position of functional group attached to it.



Butan-1-ol Butan-2-ol

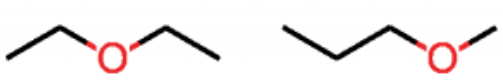
3. Functional group isomerism

Functional group isomerism is a type of structural isomerism where isomers have same molecular formula but differ in functional group.



4. Metamerism

Metamerism is a type of structural isomerism where the isomers have same molecular formula but differ due to the different number of carbon atoms or alkyl groups on either side of functional group (i.e., -O-,-S-, -NH-, -C(=O)-).



Diethyl ether methyl propyl ether

5. Tautomerism is a special type of structural isomerism where the isomers stays in dynamic equilibrium with each other by simple proton transfer in an intramolecular fashion.

2-butanone Keto-form 2-butanol Enol-form

Stereoisomerism

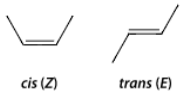
Stereoisomers are isomers that have same molecular formula, same sequence of bonding of atoms but differ in their three dimensional orientation of atoms in space. Stereoisomerism are of two types:

1. Diastereomerism

Diastereomers are a type of stereoisomers where two isomers differ in there configuration and are not mirror image of each other. Two types of diastereomers are possible:

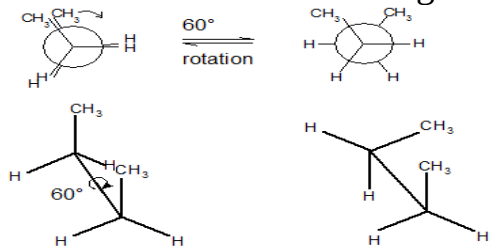
a) Cis-trans isomerism

Geometrical isomerism or cis-trans isomerism arises because of the restricted rotation around the carbon-carbon double bond.



b) Conformational isomerism

Conformational isomerism is a diastereomerism where two isomers differ because of the rotation around the carbon-carbon single bond.



2. Enatiomerism

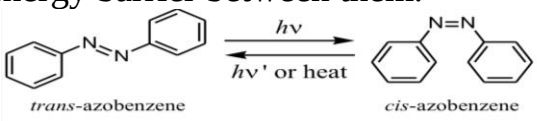
Isomers which are non-superimposable mirror images of each other are known as enantiomers.

These compounds are optically active and can rotate the plane polarized light. Thus it is also known as optical isomerism. The isomer which can rotate the plane polarized light from left to right (or clockwise) is known as dextrorotatory and which can rotate from right to left (or anticlockwise) is known as

laevorotatory. A equal mixture of two enantiomer is known as racemic mixture. Such a mixture is optically inactive as they rotate the plane polarized light in opposite direction and thus cancel each other.

Isomerization

Isomerization is the conversion of one isomer into another. This is also known as rearrangement reaction. The isomers have normally similar bond energy and thus normally exist together in different ratio. So it is possible to convert them easily by crossing the energy barrier between them.



Questions.

1. Give the definition of the isomers.
2. What types of isomerism do you know, give examples?
3. Give the definition of diastereomers.
4. Which isomers are called CIS and TRANS isomers?
5. Give the definition of tautomerism.

Problems. .

1. Name the following chemical compounds:

1) $CH_3-CH_2-CH_2-CH_2-CH_2-CH_3$

2) $CH_3-CH(CH_3)-CH_2-CH_2-CH_3$ 3) $CH_3-CH_2-CH(CH_3)-CH_2-CH_3$ 4) $CH_3-CH(CH_3)-CH(CH_3)-CH_3$ 5) $CH_3-C(CH_3)_2-CH_2-CH_3$

2) 1. Name the following chemical compounds:

Unit 2.Classification and nomenclature of organic compounds.

Organic compounds are divided into 3 large groups: acyclic, carbocyclic and heterocyclic

Acyclic or Open Chain Compounds

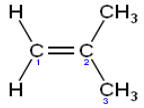
The carbon atoms are present in the form of an open chain. This chain may either be a straight chain or a branched chain. These were initially known as Aliphatic compounds because the compounds of this class were derived from either animal or vegetable fats

- Straight Chain Compounds: The carbon skeleton is in the form of a straight chain. Examples:

n-Propane CH_3-CH_2-CH_3

Propene CH_2=CH-CH_3

- Branched Chain Compounds: The carbon skeleton is in the form of a branched chain. Examples: Isobutylene



The classification can be based on the following principles:

1.the structure of the carbon chain

2.the presence of functional groups

1.Classification of Organic Compounds by the structure of the carbon chain

Organic Compounds

↓ ↓

Cyclic Acyclic

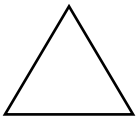
↓ ↓

Heterocyclic Carbocyclic

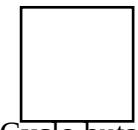
Cyclic or closed-chain compounds: Cyclic compounds contain at least one ring or closed chain of atoms. The compounds with only one ring of atoms in the molecule are known as monocyclic but those with more than one ring of atoms are termed as polycyclic. These are further divided into two subgroups.

Homocyclic or carbocyclic: These are the compounds having a ring or rings of carbon atoms only in the molecule. The carbocyclic or homocyclic compounds may again be divided into two types:

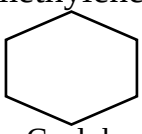
Alicyclic compounds: These are the compounds which contain rings of three or more carbon atoms. These resemble with aliphatic compounds than aromatic compounds in many respects. That is why these are named alicyclic, i.e., aliphatic cyclic. These are also termed as polymethylenes. Some of the examples are,



Cyclopropane

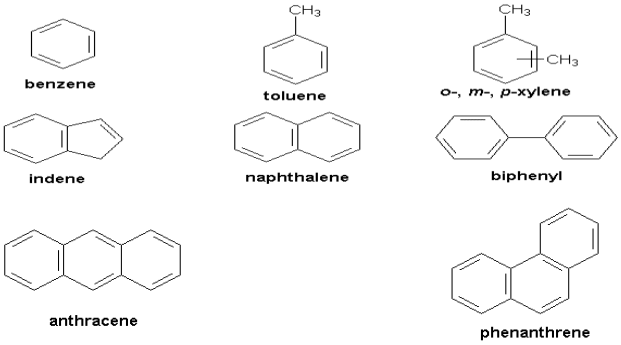


Cyclo butane



Cyclohexane

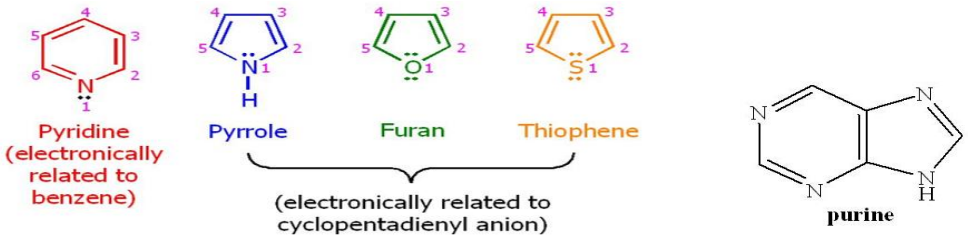
Aromatic compounds: These compounds consist of at least one benzene ring, i.e., a six-membered carbocyclic ring having alternate single and double bonds. Generally, these compounds have some fragrant odour and hence, named as aromatic (Greek word aroma meaning sweet smell).



These are also called benzenoid aromatics.

(b) Heterocyclic compounds: Cyclic compounds containing one or more hetero atoms (e.g. O, N, S etc.) in the ring are called heterocyclic compounds.

Cyclic compounds that include an element other than carbon are called **heterocyclic compounds.**

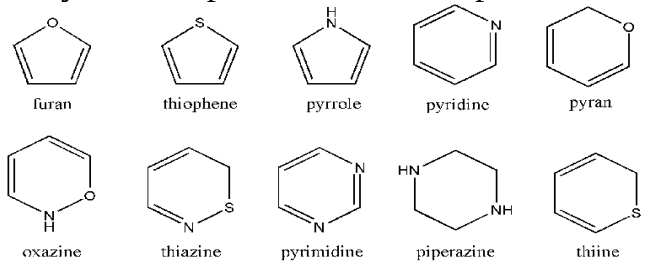


These are of two types:

Alicyclic heterocyclic compounds: Heterocyclic compounds which resemble aliphatic compounds in their properties are called Alicyclic heterocyclic compounds. For example:

Tetrahydrofuran, Piperidine, Oxirane, 1,4-Dioxane and Pyrrolidine

Aromatic heterocyclic compounds: Heterocyclic compounds which resemble benzene and other aromatic compounds in most of their properties are called Aromatic heterocyclic compounds. For example,



2. Classification of Organic Compounds by functional groups

A functional group is an atom or group of atoms in a molecule that gives the molecule its characteristic chemical properties. Double and triple bonds are also considered as functional groups.

All compounds with the same functional group belong to the same class.

These groups of atoms contain oxygen or nitrogen or sometimes sulfur attached to a hydrocarbon skeleton

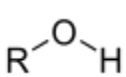
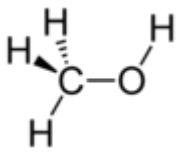
It should be noted that the R in each structure is a wildcard notation for the rest of the molecule's atoms.

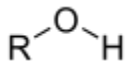
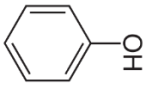
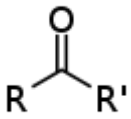
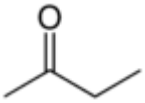
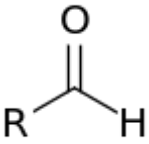
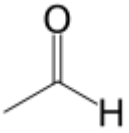
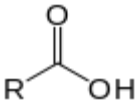
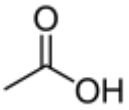
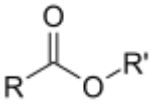
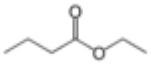
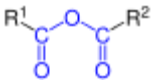
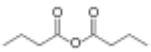
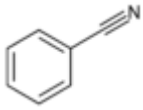
From this it follows:

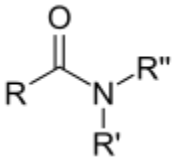
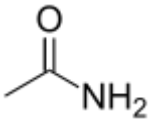
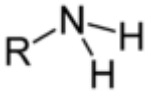
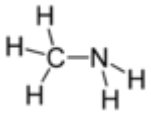
A functional group or moiety is a specific group of atoms within a molecule that is responsible for characteristic chemical reactions of that molecule. No matter what size a molecule is, a functional group participates in chemical reactions in a predictable manner.

Functional groups link to the rest of the molecule via covalent bonds. The group may be neutral or charged.

Monofunctional compounds

Chemical class	Group	Formula	Structural Formula	Prefix	Suffix	Example
Alcohols	Hydroxyl	ROH		hydroxy-	**-ol**	 Methanol

Phenols	Hydroxyl	ROH		hydroxy-	**-ol**	 phenol
Ketones	Carbonyl	RCOR'		-oyl- (-COR') or oxo- (=O)	**-one**	 Butanone *(Methyl ethyl ketone)*
Aldehydes	Aldehyde	RCHO		formyl- (-COH) or oxo- (=O)	**-al**	 Acetaldehyde *(Ethanal)*
Carboxylic acids	Carboxyl	RCOOH		carboxy-	- oic **acid**	 Acetic acid *(Ethanoic acid)*
Esters	Carboalkoxy	RCOOR'		alkanoyloxy- or alkoxycarbonyl	alkyl alkan**oate**	 Ethyl butyrate *(Ethyl butanoate)*
Organic acid anhydride	Carboxylic anhydride	R(CO)O(CO)R'			anhydride	 Butyric anhydride
Nitriles	Nitrile	RCN	R≡N	cyano-	alkane nitrile alkyl cyanide	 Benzonitrile (Phenyl cyanide)
	Isonitrile	RNC	R- N+ ≡ C-	isocyano-	alkane isonitrile alkyl isocyanide	$H_3C\text{-}N^+\equiv C^-$ Methyl isocyanide

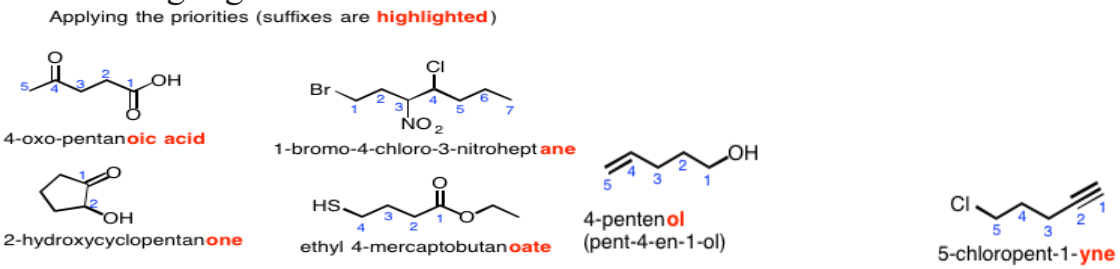
Amides	Carboxamide	RCONR 2		carboxamido- or carbamoyl-	-amide	 Acetamide (Ethanamide)
Amines	Primary amine	RNH2		amino-	-amine	 Methylamine (Methanamine)

Organic compounds of biological importance contain very often not one, but several functional groups. These groups can be identical or different. For example, ethylene glycol, $HOCH_2CH_2OH$, and glycerol, $HOCH_2CH(OH)CH_2OH$, contain two and three hydroxyl groups, respectively. Dicarboxylic acids, such as oxalic, malonic, succinic, have been discussed in the preceding chapter. These compounds are referred to as *polyfunctional* ones.

A significant importance in living systems belongs to *heterofunctional* compounds that involve different functional groups in the same molecule.

Some Examples With Multiple Functional Groups

Here are some examples of applying the order of functional group priorities to solve nomenclature problems. The highest ranked functional group becomes the suffix – it's highlighted in red.



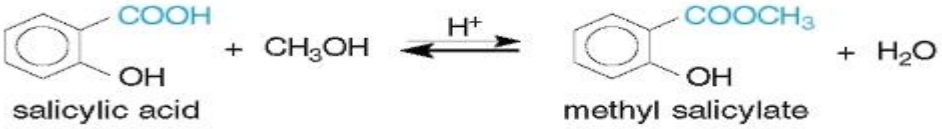
TYPES OF HETEROFUNCTIONAL COMPOUNDS

Hydroxyl, amino, oxo, and carboxyl groups are encountered most widely in heterofunctional compounds. A combination of different functional groups results in the formation of mixed classes of organic compounds, some of them are given in Table 11.1 (other combinations are possible, of course).

Some types of combining functional groups in heterofunctional compounds

Heterofunctional classes	*Functional groups*		*Representatives*	
			formula	*trivial name*
Amino alcohols	NH_2	OH	$H_2NCH_2CH_2OH$	Colamine
Hydroxy carbonyl compounds	OH	$>C=O$	$HOCH_2CHCH{=}O$ OH	Glyceraldehyde
Hydroxy carboxylic acids	OH	COOH	$HOCH_2COOH$	Glycolic acid
Amino acids	NH_2	COOH	H_2NCH_2COOH	Glycine
Oxo acids	=O	COOH	CH_3CCOOH O	Pyruvic acid

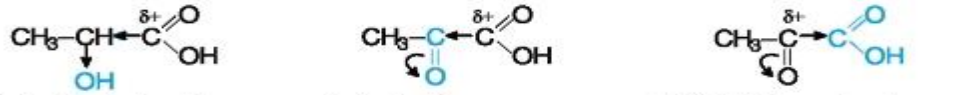
At the first approximation, the chemical behavior of heterofunctional compounds can be represented as a sum of properties of separate monofunctional classes. For instance, pyruvic acid (an oxo acid) can be esterified and transformed into derivatives on its carbonyl group. Salicylic and lactic acids (hydroxy acids) form esters in the reaction with alcohols, as well as their hydroxyl group can be acylated or alkylated. The reaction of salicylic acid with acetic anhydride is used to synthesize aspirin. Esterification of the same acid with methanol results in the formation of methyl salicylate.



salicylic acid methyl salicylate

In consideration of various combinations of functional groups we will mainly attend to new properties arising in such combinations without resort to familiar reactions of individual functional groups. When the functional groups are close to each other their interaction is more sharply pronounced. This may be illustrated by comparing acidic and electrophilic properties of some heterofunctional carboxylic acids.

In the aliphatic series, all groups listed in Table 11.1 are electron-withdrawing substituents, therefore one group has an influence on another. Thus, lactic and pyruvic acids are stronger (pK_a 3.9 and 2.4, respectively) than propionic acid (pK_a4.9) for the reasons that were discussed earlier. The hydroxyl group in lactic acid and the oxo group in pyruvic acid decrease an electron density on the carboxylic carbon (the leftmost and middle structures below).



–*I* effect of the hydroxyl group –*I* effect of the oxo group –*I* effect of the carboxyl group

On the other hand, the inductive effect of the carboxyl group results in a similar increase of δ+ on the atom C-2 as shown for pyruvic acid in the rightmost structure above. Both carbonyl carbons in pyruvic acid are stronger electrophilic sites as compared with monofunctional three-carbon analogues, i. e. acetone and propionic acid. Therefore pyruvic acid reacts with nucleophiles more readily by both nucleophilic addition and nucleophilic substitution reactions.

INTERACTION OF DIFFERENT GROUPS IN HETEROFUNCTIONAL COMPOUNDS

Many functional groups listed in Table can affect each other, especially if one of these groups is a carboxyl or carbonyl group. Two types of interaction are possible: intermolecular or intramolecular; the latter occurs when two functional groups occupy favourable positions for such a reaction.

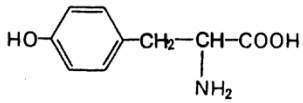
Questions:

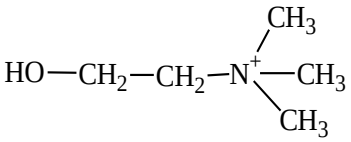
- How would you explain two types of classifications of organic compounds?
- What are the characteristics of organic compounds?
- What are the general characteristics of organic compounds?

- What are some of the shortcomings pertaining to the IUPAC classification of organic compounds?

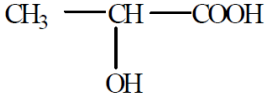
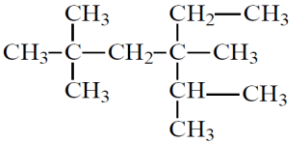
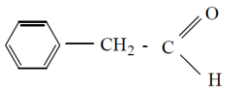
Problems.

1. Name the following chemical compounds:





2. Name the following chemical compounds:

Unit 3. Nomenclature of bioorganic compounds.

Bioorganic chemistry is a rapidly growing scientific discipline that combines organic chemistry and biochemistry. While biochemistry aims at understanding biological processes using chemistry, bioorganic chemistry attempts to expand organic-chemical researches (that is, structures, synthesis, and kinetics) toward biology. When investigating metalloenzymes and cofactors, bioorganic chemistry overlaps bioinorganic chemistry.

Organic compounds are called "organic" because they are associated with living organisms. These molecules form the basis for life. They are studied in great detail in the chemistry disciplines of organic chemistry and bioorganic chemistry. There are four main types or classes of organic compounds that are found in all living things. These are lipids, carbohydrates, proteins, and nucleic acids. In addition, there are other organic compounds that may be found in or produced by some organisms. All organic compounds contain carbon, usually bonded to hydrogen. Other elements may also be present.

Nomenclature of organic compounds.

Nomenclature of organic compounds had been formed during last centuries.

There are:

1. Trivial;
2. Rational;
3. IUPAC (International Union of Pure and Applies Chemistry) nomenclature.

Trivial nomenclature. At first organic compounds were named by chance, for example, because the natural sources of its receiving or their properties (citric acid, formic acid). Many trivial names of organic compounds are used nowadays.

Rational nomenclature. It was the first nomenclature in which the structure of molecule was considered.

CH_4 $CH_3—CH_3$ $CH_3—CH_2—CH_3$

methane methylmethane dimethylmethane

IUPAC nomenclature. The IUPAC system is the most rational and widely used system ofnomenclature in organic chemistry. The most important feature of thissystemis that any molecular structure has only one name. The names of

organic compounds are either systematic, following logically from a set of rules, or nonsystematic, following various traditions.

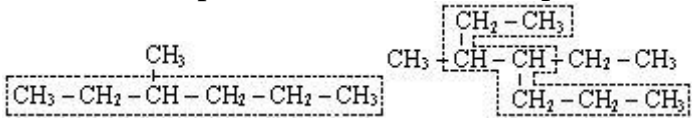
Systematic nomenclature is stipulated by specifications from IUPAC. Systematic nomenclature starts with the name for a parent structure within the molecule of interest. This parent name is then modified by prefixes, suffixes, and numbers to unambiguously convey the structure. Given that millions of organic compounds are known, rigorous use of systematic names can be cumbersome. Thus, IUPAC recommendations are more closely followed for simple compounds, but not complex molecules. To use the systematic naming, one must know the structures and names of the parent structures. Parent structures include unsubstituted hydrocarbons, heterocycles, and mono functionalized derivatives thereof.

General naming principles

I. Rules for IUPAC nomenclature of complex saturated hydrocarbons (Alkanes)

Alkanes which contain a number of branched chains are called complex alkanes. These alkanes are usually named by the IUPAC system according to the following rules:

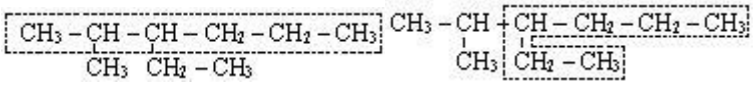
1. Longest chain rule. Find the longest continuous chain of Carbon atoms in the molecule. This is called the parent chain. For example:



Longest chain contains 6 Carbon atoms. Longest chain contains 7 Carbon atoms

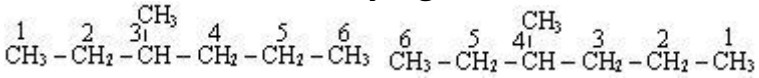
Named as hexane Named as heptane

2. Rule for larger number of side chains. If two different chains of equal lengths are possible, select the one with larger number of side chains or alkyl groups. For example,



Named as hexane with two alkyl substituents (correct) Named as hexane with one alkyl substituent (wrong)

3. Lowest number rule or lowest locant rule. Number the Carbon atoms of the parent chain as 1, 2, 3, 4, … etc. starts from that end which gives the lowest possible number to the Carbon atom carrying the substituents.



Correct wrong

The number that indicates the position of the substituent in the parent chain is called the positional number or the locant. The correct locant for the methyl is 3.

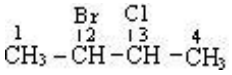
5. Lowest sum rule and lowest set of locants rule. When two or more substituents are present, two rules are generally mentioned. These are:

a) Lowest sum rule. When two or more substituents are present, the numbering of the Carbon atoms of the parent chain is done in such way that the sum oflocants is the lowest. This is called the lowest sum rule.

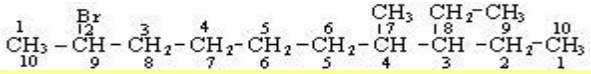
b) Lowest set of locants rule. When two or more substituents are present in the parent Carbon atom chain the lowest set of locants are numbered from all the possible directions.

Organic compound	Word root	Primary suffix	Secondary suffix	IUPAC name
CH_3CH_2OH	Eth	ane	ol	Ethanol
$CH_3CH_2CH_2NH_2$	Prop	ane	amine	Propanamine
$CH_3CH_2CH_2COOH$	But	ane	oic acid	Butanoic acid
CH_3CH_2CN	Prop	ane	nitrile	Propanenitrile
CH_2=CHCHO	Prop	ene	al	Propenol
CH□CHCOOH	Prop	yne	oic acid	Propynoic acid

For example,



2 – Bromo – 3 – chlorobutane



2 – Bromo – 8 – ethyl – 7 – methyldecane

4. Name of the complex alkane. We use prefix to indicate the position of substituent on the parent chain writing the number of the Carbon atom carrying thesubstituent.

5. Alphabetical order of the simple substituents. When two or more simple substituents are present on the parent chain, each prefixes is arranged in alphabetical order before the name of the parent alkane.

6. Numbering of the different substituents in equivalent positions. When two different substituents are present in equivalent positions, the numbering of the parent chain is done in such a way that the subtituent which comes first in the alphabetical order gets the lower number.

7. Naming of the same substituents in different positions. When the same substituents occur more than once on the parent chain at different positions, the positional number of each substituent is separated by commas and suitable numerical prefixes such as di (for two), tri (for three), tetra (for four) etc. are attached to the name of the substituents. However, the prefixes di, tri etc. are not considered while deciding the alphabetical order of the alkyl groups.

In case the same substituent occurs twice on the same Carbon atom, its positional number is also repeated twice.

8. Naming of the complex substituent (or substituted substituent).

a) In the case the substituent on the parent chain is complex (i.e., it has branched chain), it is named as a substituted group by separately numering the Carbon atom of this group attached to the parent chain as 1. The name of such a substituent is always enclosed in brackets to avoid confusion with the numbers of the parent chain.

b) While deciding the alphabetical order of the various substituents, the name of the complex substituent is considered to begin with the first letter of complete name.

c) When the names of two or more substituents are composed of identical words, priority of citation is given to that substituent which has lowest locant at the cited point of difference within the complex substituent.

II. Rules for IUPAC nomenclature of unsaturated hydrocarbons (Alkenes and Alkynes). When naming compounds containing multiple (double and triple) bonds, the following additional rules are followed:

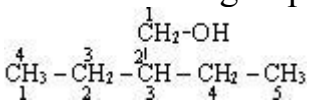
1. The parent chain must contain the multiple bond regardless of the fact whether it also denotes the longest continuous chain of Carbon atoms or not.

2. If both double and triple bonds are present, the numbering of the parent chain should always be done from that end which is nearer to the double or the triple bond.

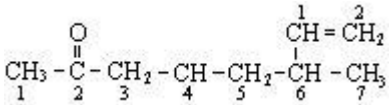
3. If, however, there is a choice in numbering the double bond is always given preference over the triple bond.

Rules for IUPAC nomenclature of compounds containing one functional group, multiple bonds and substituents. While naming organic compounds containing one functional group, double and triple bonds, and substituents, the following additional rules are observed.

1. Parent chain. Select the longest possible chain of Carbon atoms containing the functional group and the maximum number of multiple bonds as **parent chain.**

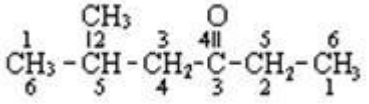


Parent chain contains four rather than five Carbon atoms.



Parent chain contains six rather than seven Carbon atoms.

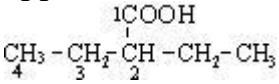
2. Lowest number for the functional group. Number the parent chain in such away that the functional group gets the lowest possible number followed by double and triple bonds even if it violates the **lowest sumrule.**



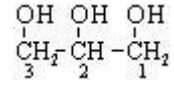
(Wrong) (> C = 0 group gets number 4 which is not lowest)

(Conect) (> C = O group gets lowest number 3)

3. Numbering of the chain terminating functional groups. When achain terminating functional group such as – CHO, - COOH, – COOR, – CONH2, – COCl, –C º N etc. is present, it is always given **number 1.** The locant 1 (unity) for the principal functional group is omitted when there is no ambiguity. But in this chapter, this numericallocant is always included when another numerical locant appears in the same name. For example,

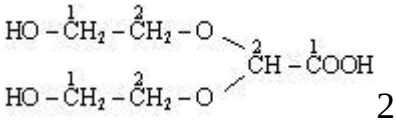


2-ethylbutan-1oic acid



Propane-1, 2, 3-triol

If the organic molecule contains more than one similar complex substituents, then the numerical prefixes such as di, tri, tetra etc. are replaced by bis, tris, tetrakis, etc. For example,



2,2-Bis(2-hydroxyethoxy) ethanoic acid

V. Rules for IUPAC Nomenclature of Polyfunctional Compounds. Organic compounds which contain two or more functional groups are calledpolyfunctionalcompounds. Their IUPAC names are obtained as follows:

1. Principal functional group. When an organic compound contains two or more different functional groups, one of the functional groups is selected as the principal functional groupwhile all other groups (also called the secondary functional groups) are treated as **substituents.** The choice of the principal functional group is made on the basis of the following order of preference.

Sulphonic acids > carboxylic acids > anhydrides > esters > acid chlorides > acid amides > nitriles > aldehydes > ketones > alcohols > amines > ethers > alkenes > alkynes.

All the remaining functional groups such as halo (fluoro, chloro, bromo, iodo), nitroso (– NO), nitro (– NO_2), and alkoxy (– OR) are always treated as substituent groups.

It may be noted that while writing the names of the polyfunctional compounds, the principal functional group is indicated by adding the secondary suffix to the word root while the secondary functional groups are indicated by adding suitable prefixes to the word root.

Table of Functional Groups (descending order of priority)

Class	**Formula**	**Prefix**	**Suffix**
Carboxylic acid	-COOH	carboxy-	-oic acid
Nitrile	-C N	cyano-	-nitrile
Aldehyde	-C- H ‖ O	formyl-	-al
Ketone	-C- ‖ O	oxo-	-one
Alcohol	-OH	hydroxy-	-ol
Thiol	-SH	mercapto-	-thiol
Amine	-NH2	amino-	-amine

Unit 4. The Alkanes

Alkanes are hydrocarbons (i.e. compounds of carbon and hydrogen only). They are called **saturated** hydrocarbons because they contain no double bonds, and so cannot undergo addition reactions. They have the **general formula: CnH2n+2**

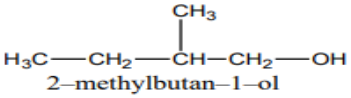
Name	Molecular Formula	Condensed Structural Formula
Methane	CH_4	CH_4
Ethane	C_2H_6	CH_3CH_3
Propane	C_3H_8	$CH_3CH_2CH_3$
Butane	C_4H_{10}	$CH_3(CH_2)_2CH_3$
Pentane	C_5H_{12}	$CH_3(CH_2)_3CH_3$
Hexane	C_6H_{14}	$CH_3(CH_2)_4CH_3$
Heptane	C_7H_{16}	$CH_3(CH_2)_5CH_3$
Octane	C_8H_{18}	$CH_3(CH_2)_6CH_3$
Nonane	C_9H_{20}	$CH_3(CH_2)_7CH_3$
Decane	$C_{10}H_{22}$	$CH_3(CH_2)_8CH_3$
Undecane	$C_{11}H_{24}$	$CH_3(CH_2)_9CH_3$
Dodecane	$C_{12}H_{26}$	$CH_3(CH_2)_{10}CH_3$

Physical Properties

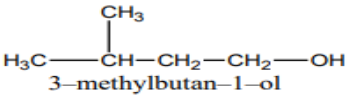
The boiling points of the alkanes increase steadily with the number of C atoms. This is because the van der Waals' forces between the molecules increase with the total number of electrons in the molecule. As the chain length increases, the van der Waals' attractions increase, and the liquid needs to reach a higher temperature before the molecules can acquire enough energy to separate and go into the vapour state. As isomers become more highly branched, boiling points usually fall slightly. This is because the branching means that the molecule has less surface area in contact with its neighbours, thus decreasing the van der Waals attractions.

Isomerism

There are two main types of isomerism: structural isomerism and stereoisomerism. Structural isomers: these have different structural formulae. i.e. the atoms are joined together in a different order. At the most extreme, they may have different functional groups: e.g. C2H6O may be ethanol, CH3CH2OH, or it may be methoxymethane (an ether), CH3OCH3. Alternatively, they may have similar functional groups, but differ in the position of these in the molecule: e.g. propan-1-ol, CH3CH2CH2OH, and propan-2-ol, CH3CH (OH) CH3. Or they may differ only in the hydrocarbon chain (see below):



2–methylbutan–1–ol

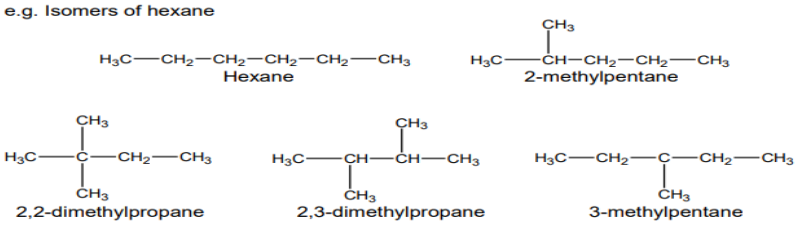


3–methylbutan–1–ol

Stereoisomers. These have the same structural formulae, and differ only by the arrangement of the atoms in space. There are two sorts: cis-trans (or geometrical), and optical.

Isomers of alkanes

Alkanes exhibit structural isomerism.



Chemical properties of alkanes

Alkanes contain carbon-hydrogen bonds, and, from ethane on, carbon-carbon single bonds. These are all non-polar, and the electron density in the σ-bonds is hard to distort (not polarisable), so that alkanes do not react with electrophiles or nucleophiles, or other polar reagents, like acids, alkalis or aqueous oxidising agents.

The bonds can only undergo homolytic bond fission, which occurs when a covalent bond breaks in such a way that each atom takes one electron. This leads to formation of two **free radicals.**

A free radical is an atom, or group of atoms, which have an unpaired electron. It is normally highly reactive, and written with a dot (which does not show an extra electron, simply the unpaired one). e.g. **Cl• or CH3•.**

Alkanes therefore undergo very few reactions: **combustion and cracking a**re the most important. **Reactions of alkanes:**

(a) Combustion

Alkanes burn in a plentiful supply of air or oxygen, to give carbon dioxide and steam:

$$\mathbf{CH_4 + 2O_2 \rightarrow CO_2 + 2H_2O}$$

If air is restricted, carbon monoxide is likely to be formed:

$$\mathbf{CH_4 + 1½\ O_2 \rightarrow CO + 2H_2O}$$

The former reaction gives out much heat, and so alkanes are useful fuels. Methane itself is called **natural gas**, and is used in the home and in modern gas-turbine power stations.

(b) Halogenation

It is possible for the hydrogen atoms in the alkane to be **substituted** by chlorine or bromine. Alkanes react with chlorine or bromine, in the presence of light, or on heating, to form halogenoalkanes and the hydrogen halide:

For example the reaction between methane and chlorine can be represented as follows:

The reaction does not necessarily stop at one substitution, and the reaction between methane and chlorine produces dichloro-, trichloro- and tetrachloro-methane.

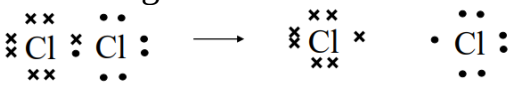
$CH_4 + Cl_2 \rightarrow CH_3Cl + HCl$
$CH_3Cl + Cl_2 \rightarrow CH_2Cl_2 + HCl$
$CH_2Cl_2 + Cl_2 \rightarrow CHCl_3 + HCl$
$CHCl_3 + Cl_2 \rightarrow CCl_4 + HCl$

The process of substitution is random, so all possible products result, though if there is excess methane the main one will be CH_3Cl, while a large excess of chlorine will give mainly CCl_4.

The substitution of a hydrogen atom by a chlorine atom actually takes place in a number of stages. Looking in detail at what happens in each stage of such a reaction is called **the reaction mechanism**. The halogenation of an alkane takes place by a **free radical reaction**.

The reaction between alkanes and these halogens requires an energy source such as ultra violet (u.v.) light.

It can be seen that the Cl-Cl bond requires less energy to break, so this is the bond which is broken by the u.v. light.

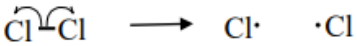


This energy is used to split the halogen molecule to form two chlorine atoms; the chlorine atoms have an unpaired electron – such a species is called free radical. The chlorine radical reacts with a methane molecule. It forms a bond. Looking at the bond enthalpies for the bonds that could be formed;

Curly arrow mechanisms

Reaction mechanisms look at the movement of electrons within and between molecules and ions. The movement of electrons are shown by “curly arrows”, using  for a single electron and  for an electron pair.

The first step in the reaction between methane and chlorine is the formation of the chlorine radical. This is called the **initiation step**. It is shown as follows.



The chlorine radical then attacks the methane molecule.

$CH4 + Cl\bullet \rightarrow CH_3\bullet + HCl$

The methyl radical from this reaction reacts with a chlorine molecule to form chloromethane and a new chlorine radical.

$CH_3\bullet + Cl_2 \rightarrow CH_3Cl + Cl\bullet$

The chlorine radical starts the cycle again and the process continues. These two reactions are called the **propagation stage**.

The propagation stage continues until two radical meet to form a molecule. There are three possibilities for this reaction. Since the ends the sequence it is called the termination stage.

$Cl\bullet + Cl\bullet \rightarrow Cl_2$
$Cl\bullet + CH_3\bullet \rightarrow CH_3Cl$
$CH_3\bullet + CH_3\bullet \rightarrow C_2H_6$

The overall mechanism is called **free radical substitution**.

Note that in the propagation stage the Cl• at the end can go on to attack another CH4 and so the chain can go on for several thousand reactions from one initiation.

The presence of traces of C2H6 in the products shows that CH3• radicals must have been formed. Of course, the Cl• atoms can remove a hydrogen atom from CH3Cl, and so the reaction can go on to CH_2Cl_2, then $CHCl_3$ and finally CCl_4.

Alkanes are **not very reactive** when compared with other chemical species. This is because the backbone carbon atoms in alkanes have attained their octet of electrons through forming four covalent bonds (the maximum allowed number of bonds under the octet rule; which is why carbon's valence number is 4). These four bonds formed by carbon in alkanes are sigma bonds, which are more stable than other types of bond because of the greater overlap of carbon's atomic orbitals with neighboring atoms' atomic orbitals. To make alkanes react, the input of additional energy is needed; either through heat or radiation.

Problems.

1. What hybridization is characteristic of alkanes?
2. What physical properties are characteristic of alkanes?
3. Alkanes are characterized by reactions:

- decompositions,
- substitutions,
- oxidations. Given example.

4. Give the formula of all possible structural isomers C_6H_{14} and name them.
5. Give the formula of conformations of the chair and bath cyclohexane and specify the most favorable.

Unit 5.The Alkenes

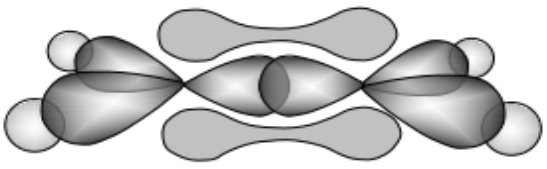
Alkenes are hydrocarbons that contain one double bond. They are **unsaturated** compounds: compounds which are able to undergo addition reactions.

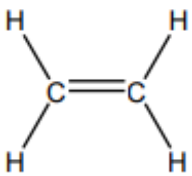
They have the general formula: CnH2n

The double bond in alkenes does not consist of two identical bonds. One of the bonds is a normal bond with the electron cloud lying between to two atoms. **This is called a sigma, σ, bond**.

The other bond has an electron cloud which is placed above and below the two atoms.

This is called **the pi, π**, bond. The electron clouds in ethene can be represented as shown below.



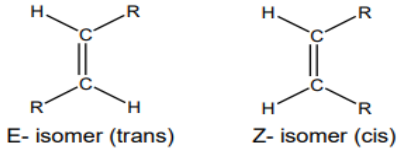


Isomers of alkenes (E-Z Isomerism)

The geometry of the C=C bond is determined by the π-bond, and means that ethene is a rectangular, flat molecule.

The bond angles are at about 120o, and rotation about the C=C axis is restricted, since twisting through 90o would mean the p-orbitals would no longer overlap and **the π-bond** would be broken. The restriction of rotation produces isomers **called E-Z isomers** (geometric isomers or cis-trans isomers)

For E-Z isomerism (cis-trans isomerism) to occur there must be a double bond and two different groups on each of the double bonded carbon atoms

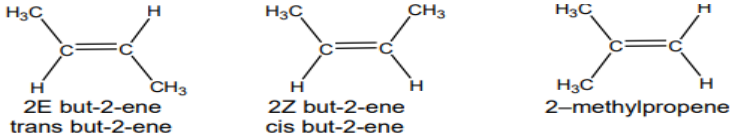


E-Z and cis-trans are different terms for the same type of isomerism.

Trans refers to the isomer where the R groups are on opposite sides of the C=C.

Cis refers to the isomer where the R groups are on the same side of the C=C.

Isomers of butane



The E-Z (cis / trans) isomers will be chemically very similar, though not quite identical, and will have slightly different melting and boiling points.

[Note that a third isomer, 2–methylpropene, which has two methyl groups attached to the same carbon atom, is a structural isomer of these, as is but-1-ene]

E- and Z- vs cis-trans nomenclature The cis trans system breaks down with examples like;

The E-Z naming system is more useful than the cis-trans system.

• The naming of the isomer is determined by priorities.

• Each atom on the double bond is given a priority determined by its atomic number.

• The smaller the atomic number the lower the priority – hydrogen in the example above.

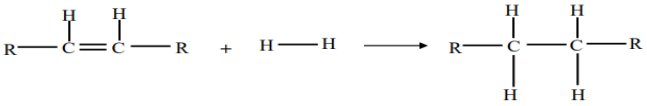
• If atoms with the lowest priority are on the same side on each end of the C=C the isomer is called the Z-isomer. (Z=Zusammen (together)).

• If atoms with the lowest priority are on the same side on each end of the C=C the isomer is called the E-isomer. (E=Entgegen (opposite)

Reactions of alkenes

The alkenes are more reactive than the alkanes because of the C=C bond. It is possible for the double bond to break, allowing each carbon to form a new bond, which is often energetically favourable. Halogens, hydrogen halides, hydrogen and potassium manganate (VII) will **produce addition reactions** with alkenes.

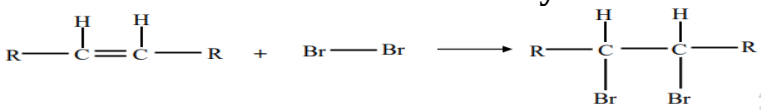
Addition of hydrogen (hydrogenation) Alkenes react with hydrogen in the presence of a nickel catalyst at150oC.



This is important in the hydrogenation of vegetable fats to make margarine. An unsaturated vegetable oil is mixed with a nickel catalyst at 50oC,and hydrogen gas bubbled through. The saturated product has a higher melting point, and is less easily oxidised (longer shelf life).

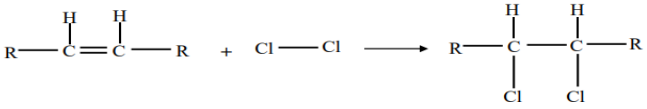
Addition of bromine

Alkenes will decolorise bromine immediately:

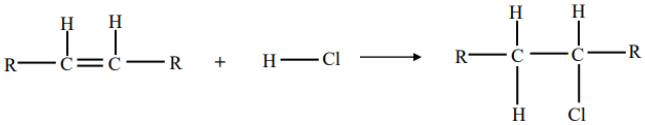


The decolorisation of bromine water is used as a test for the C=C double bond. This reaction occurs in an inert solvent like volasil.

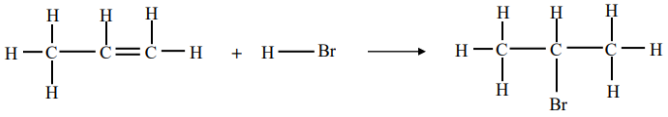
Addition of chlorine



Addition of Hydrogen chloride

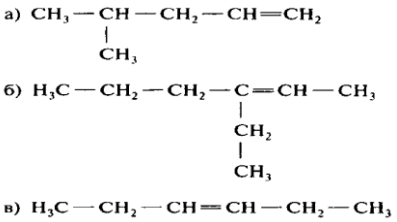


When addition of a hydrogen halide takes place, if the alkene is not symmetrical, the hydrogen adds to the carbon that already has the most hydrogen. This is called Markovnikoff's rule

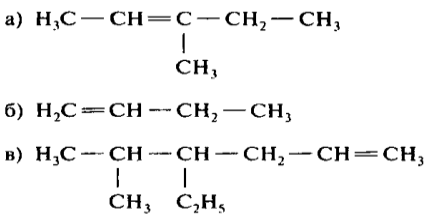


Problems.

1. Name the following hydrocarbons according to THE IUPAC nomenclature:



2.Name the following hydrocarbons according to THE IUPAC nomenclature:



3. What class of hydrocarbons are ethylene hydrocarbons isomeric? Give examples and name all substances.

Unit 6.Alkynes

Alkynes (or acetylene hydrocarbons) are unsaturated hydrocarbons, with the common formula of $\mathbf{C_nH_{2n-2}}$ (n is the number of carbon atoms). Compounds of this type have a triple covalent bond in their structure. The two carbon atoms are in a trouble bond, each of which is in the state of sp-hybridization (this is a special type of overlap of atomic orbitals, when one s and one p-orbital are mixed, and the other two are located perpendicularly and form a p-bond or hold a lone electron pair) – this is why the geometry of this compound of atoms is linear. For example, the simplest alkyne – acetylene C_2H_2 is located on a plane lineally: the angle between carbon atoms in the compound is 180 degrees.

Physical properties

The first three alkynes in their homologous row (in this row substances differ by length – each new hydrocarbon resembles the previous one by its structure, but differs by one structural unit of CH_2) are gases:

- $HC{\equiv}CH$ (C_2H_2 - ethyne, or acetylene);
- $HC{\equiv}C\text{-}CH_3$ (C_3H_4 - propyne);
- $HC{\equiv}C\text{-}CH_2\text{-}CH_3$ (C_4H_6 - butyne).

The principle of addition in the homologous row of homologous difference of CH_2 is clear:

$C_2H_2 + CH_2 = C_3H_4$;

$C_3H_4 + CH_2 = C_4H_6$ (with the addition of CH_2 to the previous alkyne, the next one is obtained)

Isomerism of alkynes

Isomerism is the phenomenon of compounds which are identical in composition but different in structure. For alkynes, there are three types of isomerism:

- **interclass** (alkynes isomerized by alkadienes, hydrocarbons with two double bonds – for example propyne and propadiene – interclass isomers with the formula C_2H_4 (propyne has one triple bond between carbon atoms and one ordinary, while propadiene has two double bonds);
- **isomerism of the position of the triple bond** (in butyne the triple bond may be located at the first and second carbon atom – accordingly, butyne-1 and butyne-2 differ respectively: $CH{\equiv}C\text{-}CH_2\text{-}CH_3$ и $CH_3\text{-}C{\equiv}C\text{-}CH_3$);
- **isomerism of chain** (the structure of the chain in alkynes may differ – for example hexyne-2 $CH_3\text{-}CH{\equiv}C\text{-}CH_2\text{-}CH_2\text{-}CH_3$ is isomerized by 4-methyl pentyne-2 $CH_3\text{-}CH{\equiv}C\text{-}CH_2\ (CH_3)\text{-}CH_3$).

Spatial (geometric) isomerism, in which a compound has identical structure and composition but different location of atoms in space, is not characteristics for alkynes.

Chemical properties of alkynes

Alkynes enter into reactions of substitution, attachment, oxidation and polymerization. The most important and widespread reactions of alkynes are given below.

- **Reactions of oxidation of alkynes**
- Oxidation of alkynes can be complete and incomplete. *In the first case,* the combustion of unsaturated carbon with a triple bond takes place:

$2CH{\equiv}CH + 5O_2 = 4CO_2 + 2H_2O$ (sooty flame).

- *Incomplete combustion* is carried out in the presence of potassium permanganate in a neutral medium, or of potassium dichromate in an acidic medium (for simplicity, atomic oxygen [O] is given in the reaction, as this particular is released in the contact of permanganates or dichromates with organic matter):

CH_3-C≡CH + 3[O] + H_2O = CH_3-COOH + HCOOH

(a mixture of carbonic acids forms – acetic and formic);

CH≡CH + 4[O] = HOOC-COOH (oxalic acid).

- ***Zelinsky's reaction – cyclotrimerization (formation of benzol and its aromatic derivatives):***

3CH≡CH = C_6H_6 (at 500 ^oC or 932 ^oF in the presence of activated charcoal, benzol forms).

- **Reactions of substitution** (characteristic only for alkynes with the group -C≡CH)

On reacting with strong bases, the hydrogen atom in the alkyne is substituted to the metal (insoluble acetylenides form):

CH_3-C≡CH + $[Ag(NH_3)_2]OH$ = CH_3-CH≡CAg + 2NH_3 + 2H_2O.

Addition reactions of alkynes, hydrogenation of acetylene

For alkynes, all addition reactions which affect the double bond are characteristic. For example, a qualitative reaction can be carried out for the double bond – the discoloration of bromine water (as two p-bonds are present, the reaction of complete bromination takes place in 2 stages):

The first one:

CH≡CH + Br_2 = CHBr=CHBr;

The second one:

CHBr=CHBr + Br_2 = $CHBr_2$-$CHBr_2$ (1,1,2,2-tetrabromoethane forms).

With hydrohalogens, the reactions take place according to Markovnikov's rule (hydrogen moves from acid to the most hydrogenated carbon atom, and the halogen to the least). The reaction also has two stages:

The first one:

CH_3-C≡CH + HCl = CH_3-C(Cl)=CH_2;

The second one:

CH_3-C(Cl)=CH_2 + HCl = CH_3-$C(Cl)_2$-CH_3 (product - 2,2-dichlorpropane).

In the presence of acids and salts of bivalent mercury, **Kucherov's** reaction is possible – the reaction of alkynes with water (hydration):

- CH≡CH + H_2O = CH_3-COH (acetaldehyde forms – acetic aldehyde; only in the reaction of acetylene with water);
- CH_3-C≡CH + H_2O = CH_3-C(O)-CH_3 ((with any other alkynes besides acetylene, ketones are formed according to Kucherov's reaction – for example, acetone).

Questions

1. What are the chemical properties of alkyne?
2. What are the differences in chemical properties between alkanes, alkenes and alkynes?
3. What are the properties that alkynes share?

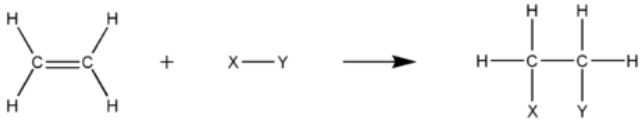
Problems.

1. Is CIS-TRANS isomerism possible for alkynes?

2. Write all possible formulas of hydrocarbon isomers of composition C5H8 belonging to the class of alkynes.

3. Suggest ways to obtain acetylene from inorganic substances. Write the equations of the corresponding reactions.

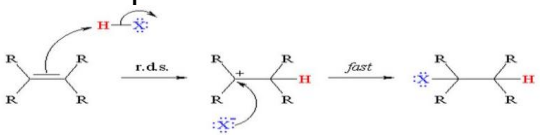
Unit 7. Electrophilic addition

In organic chemistry**, an electrophilic addition** reaction is an addition reaction where, in a chemical compound, a π bond is broken and two new σ bonds are formed. The substrate of an electrophilic addition reaction must have a double bond or triple bond. 

The driving force for this reaction is the formation of an electrophile X^+ that forms a covalent bond with an electron-rich unsaturated C=C bond. The positive charge on X is transferred to the carbon-carbon bond, forming a carbocation during the formation of the C-X bond.

In step 2 of an electrophilic addition, the positively charged intermediate combines with (Y) that is electron-rich and usually an anion to form the second covalent bond.

Step 2 is the same nucleophilic attack process found in an S_N1 . The exact nature of the electrophile and the nature of the positively charged intermediate are not always clear and depend on reactants and reaction conditions.



In Electrophilic addition the electrophile with the positive charge effects the formation of the total structure, which thus bears a positive charge as well, to make up for the new addition, which then results in the intermediate, bearing that positive charge.

In chemistry, a **substrate** is typically the chemical species being observed in a chemical reaction, which reacts with a reagent to generate a product .**Substrate** In this context, a substrate is a base on which a process occurs.

A reagent is a substance that acts on a substrate

Nucleophilic reagents, or nucleophiles, replace the leaving group of a molec ule and provide a pair of electrons for theformation of a new bond. The leaving gro up departs with the pair of electrons that had formed the old bond. Such reactionsar e called nucleophilic substitutions. In the following examples of nucleophilic subst itution, Y is the nucleophile, R is anorganic radical, and X is the leaving group:

$Y:^- + RX \rightarrow RY + X^-$

$Y: + RX \rightarrow RY^+ + X^-$

Nucleophilic reagents comprise negatively charged ions, including **OH^-, CN^-, NO_2^-, OR^-, RS, NH_2, RCO_2, and halogenions (designated Hal**); neutral molecules with a free pair of electrons, for example, H_2O, NH_3, R_3N, R_2S, R_3P, ROH, andRCO_2H; and those organometallic compounds (designated R-Me), that are capable of forming carbanions-that is, those inwhich a bond between a carbon atom and the metal is sufficiently polarized. Nucleophilic substit

ution is characteristic mainlyof aliphatic compounds. Examples of nucleophilic sub stitution include hydrolysis, with the nucleophiles OH^- and H_2O;alcoholysis, in which the nucleophiles are RO^- and ROH; acidolysis, with the nucleophiles RCOO; and RCOOH; amination, involving such nucleophiles as NH_2, NH_3, and RNH_2; and cyanation, with the nucleophile CN^-.

Electrophilic reagents, or electrophiles, replace the leaving group of a mole cule and act as

Electron.pair acceptors in theformation of a new bond. The leaving group de parts as a positively charged species. Electrophilic reagents include positivelycharg ed ions, for example, H^+ and NO_2^+; neutral molecules with an electron deficiency, f or example, SO_3; and highlypolarized molecules, for example: $CH_3CO_2Br^+$. Such polarization is achieved efficiently by complexing with Lewis acids, forexample, H al^+—Hal^-·A, R^+—CL^-A, and RCO^+—Cl

·A, where A = $AlCl_3$, $SbCl_5$, or BF_3. Substitution reactions that involveelectrophile s are called electrophilic substitutions. These include the most important reactions of aromatic hydrocarbons, forexample, nitration, halogenation, sulfonation, and Fri edel-

Crafts alkylation. In the following general formula for electrophilicsubstitution, E^+ = Hal^+, NO_2^+, RCO^+, R^+, or some other electrophile.

Mechanism

The addition of hydrogen halides is one of the easiest electrophilic addition reactions because it uses the simplest electrophile: the proton. Hydrogen halides provide both a electrophile (proton) and a nucleophile (halide). First, the electrophile will attack the double bond and take up a set of π electrons, attaching it to the molecule (1). This is basically the reverse of the last step in the E1 reaction (deprotonation step). The resulting molecule will have a single carbon- carbon bond with a positive charge on one of them (carbocation). The next step is when the nucleophile (halide) bonds to the carbocation, producing a new molecule with both the original hydrogen and halide attached to the organic reactant (2). The second step will only occur if a good nucleophile.

All of the halides (HBr, HCl, HI, HF) can participate in this reaction and add on in the same manner. Although different halides do have different rates of reaction, due to the H-X bond getting weaker as X gets larger (poor overlap of orbitals)s.

Reaction rates

Variation of rates when you change the halogen

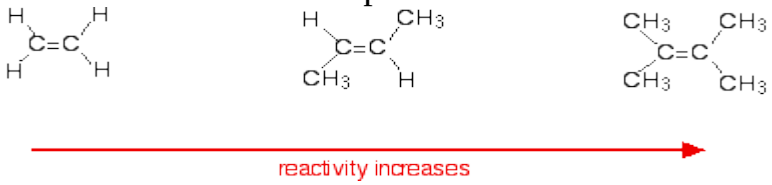
Reaction rates increase in the order HF - HCl - HBr - HI. Hydrogen fluoride reacts much more slowly than the other three, and is normally ignored in talking about these reactions.

When the hydrogen halides react with alkenes, the hydrogen-halogen bond has to be broken. The bond strength falls as you go from HF to HI, and the hydrogen-fluorine bond is particularly strong. Because it is difficult to break the bond between the hydrogen and the fluorine, the addition of HF is bound to be slow.

Variation of rates when you change the alkene

This applies to unsymmetrical alkenes as well as to symmetrical ones. For simplicity the examples given below are all symmetrical ones- but they don't have to be.

Reaction rates increase as the alkene gets more complicated - in the sense of the number of alkyl groups (such as methyl groups) attached to the carbon atoms at either end of the double bond. For example:



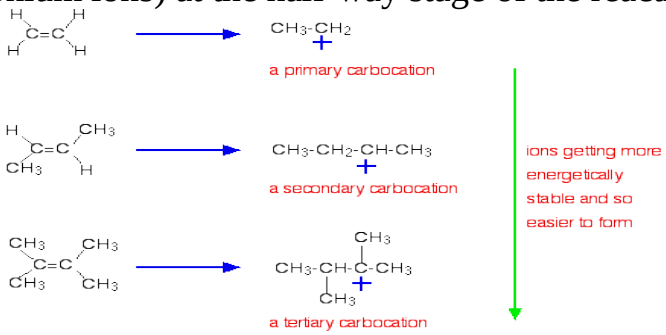
There are two ways of looking at the reasons for this - both of which need you to know about the mechanism for the reactions.

Alkenes react because the electrons in the pi bond attract things with any degree of positive charge. Anything which increases the electron density around the double bond will help this.

Alkyl groups have a tendency to "push" electrons away from themselves towards the double bond. The more alkyl groups you have, the more negative the area around the double bonds becomes.

The more negatively charged that region becomes, the more it will attract molecules like hydrogen chloride.

The more important reason, though, lies in the stability of the intermediate ion formed during the reaction. The three examples given above produce these carbocations (carbonium ions) at the half-way stage of the reaction:



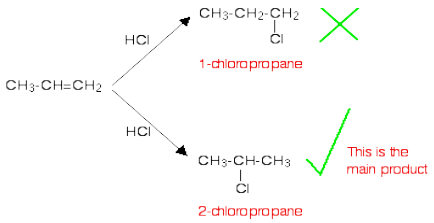
The stability of the intermediate ions governs the activation energy for the reaction. As you go towards the more complicated alkenes, the activation energy for the reaction falls. That means that the reactions become faster.

Addition to unsymmetrical alkenes

What happens? In terms of reaction conditions and the factors affecting the rates of the reaction, there is no difference whatsoever between these alkenes and the symmetrical ones described above. The problem comes with the orientation of the addition - in other words, which way around the hydrogen and the halogen add across the double bond.

Orientation of addition

If HCl adds to an unsymmetrical alkene like propene, there are two possible ways it could add. However, in practice, there is only one major product.



his is in line with Markovnikov's Rule which says:

In this case, the hydrogen becomes attached to the CH_2 group, because the CH_2 group has more hydrogens than the CH group. Notice that only the hydrogens directly attached to the carbon atoms at either end of the double bond count. The ones in the CH_3 group are totally irrelevant.

Conjugation

The word "***conjugation***" is derived from a Latin word that means "to link together". In organic chemistry terms, it is used to describe the situation that occurs when π systems (*e.g.*double bonds) are "linked together".

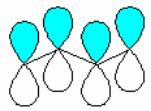
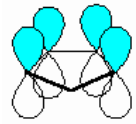
- ***An "isolated"*** π (pi) system exists only between a single pair of adjacent atoms (*e.g.* **C=C**)
- ***An "extended"*** π (pi) system exists over a longer series of atoms (*e.g.* **C=C-C=C** or **C=C-C=O** *etc.*).
- An extended π (pi) system results in a extension of the chemical reactivity.

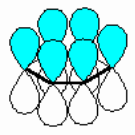
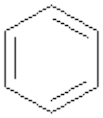
The fundamental requirement for the existence of a conjugated system is revealed if one considers the p orbitals involved in the bonding within the π system.

- **A conjugated** system requires that there is a continuous array of "p" orbitals that can align to produce a π bonding overlap along the whole system.
- If a position in the chain does not provide a "p" orbital or if geometry prevents the correct alignment, then the conjugation is interupted (broken) and therefore lost at that point.

You can investigate these differences by studying the following examples, paying particular attention to the "p" orbitals in the π system. Use the JSMOL models to look at the hybridisations of the atoms in the systems.

The result of conjugation is that there are *extra* π bonding interactions between the adjacent π systems. This extra bonding results in an *overall stabilisation* system. This increased stability due to conjugation is refered to as the **delocalisation energy** or the **resonance energy or conjugation energy**.


1,3-butadiene

1,3-cyclopentadiene


benzene


Problems,

1. explain the term “electrophilic addition reaction,” using the reaction of a protic acid, HX, with an alkene as an example.

2. write the mechanism for the reaction of a protic acid, HX, with an alkene.

3. sketch a reaction energy diagram for the electrophilic addition of an acid, HX, to an alkene.

4. Write reactions

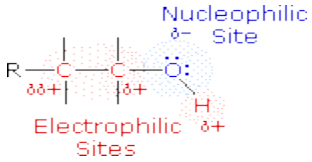
$CH_2=CH_2 + Br_2 \rightarrow$

$CH_2=CH_2 + H_2 \rightarrow$

Unit 8. Alcohols.

Alcohols are some of the most important molecules in organic chemistry.

Alcohols - derivatives of hydrocarbons, in which molecules have one or multiple hydroxyl groups OH. All alcohols are divided into *monatomic* and *polyatomic*. They can be prepared from and converted into many different types of compounds. Alcohols contain the hydroxy functional group (-OH), bonded to a carbon atom of an alkyl or substituted alkyl group. The functional group of an alcohol is the hydroxyl group, –OH. Unlike the alkyl halides, this group has two reactive covalent bonds, the C–O bond and the O–H bond. The of oxygen is substantially greater than that of carbon and hydrogen. Consequently, the covalent bonds of this functional group are polarized so that oxygen is electron rich and both carbon and hydrogen are electrophilic, as shown in the figure below.



Indeed, the dipolar nature of the O–H bond is such that alcohols are much stronger acids than alkanes (by roughly 10^{30} times), and nearly that much stronger than ethers. The most reactive site in an alcohol molecule is the hydroxyl group, despite the fact that the O–H bond strength is significantly greater than that of the C–C, C–H and C–O bonds, demonstrating again the difference between thermodynamic and chemical stability.

Naming Alcohols

Alcohols contain an — OH group attached to a saturated carbon. The common names for alcohols are based on the name of the alkyl group.

CH_3OH	*Methyl alcohol*
CH_3CH_2OH	*Ethyl alcohol*
$CH_3CHOHCH_3$	*Isopropyl alcohol*

The systematic nomenclature for alcohols adds the ending *-ol* to the name of the parent alkane and uses a number to identify the carbon that carries the — OH group. The systematic name for isopropyl alcohol, for example, is 2-propanol.

CH_3OH	*Methanol*
CH_3CH_2OH	*Ethanol*
$CH_3CHOHCH_3$	*2-Propanol*

Solubilities of Alcohols in Water

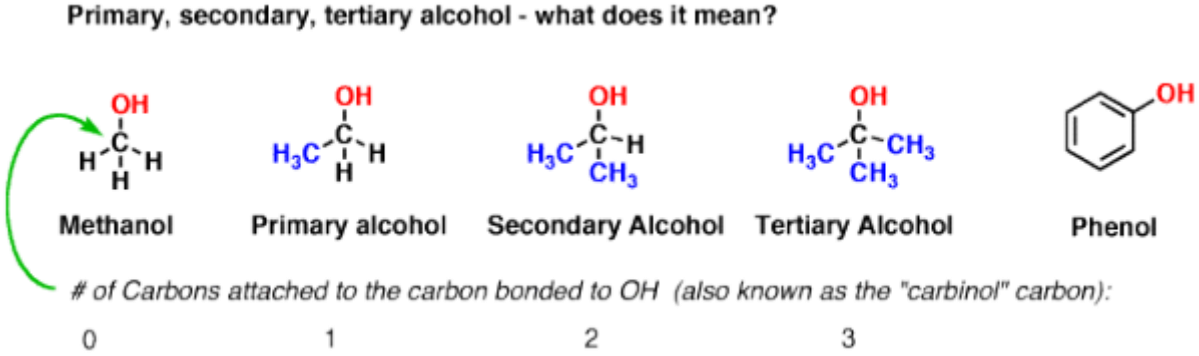
Formula	*Name*	*Solubility in Water (g/100 g)*
CH_3OH	methanol	infinitely soluble
CH_3CH_2OH	ethanol	infinitely soluble

$CH_3(CH_2)_2OH$	propanol	infinitely soluble
$CH_3(CH_2)_3OH$	butanol	9
$CH_3(CH_2)_4OH$	pentanol	2.7
$CH_3(CH_2)_5OH$	hexanol	0.6
$CH_3(CH_2)_6OH$	heptanol	0.18
$CH_3(CH_2)_7OH$	octanol	0.054
$CH_3(CH_2)_9OH$	decanol	insoluble in water

Monatomic alcohols – alcohols that have one hydroxyl group.

There are primary, secondary and tertiary alcohols:

-the primary alcohols have a hydroxyl group near the first carbon atom, the secondary – near the second, etc.



Properties of alcohols, which are isomeric, in many similar, but in some reactions they have differents.

Comparing the relative molecular mass alcohols (Mr) with relative atomic masses of hydrocarbons, it is to notice that the alcohols have a higher boiling point. This is due to the hydrogen bonding between the H atom in the group OH of one molecule and the O atom in the group OH other molecules.

Upon dissolution of the alcohol in the water the hydrogen bonds are formed between molecules of alcohol and water. This explains the decrease of the volume of the solution (it will always be less than the sum of the volumes of water and alcohol separately).

The most prominent representative of the chemical compounds of this class is ethanol. Its chemical formula is C_2H_5-OH. Concentrated ethanol (wine alcohol or ethanol) is prepared from dilute solutions by distillation. It is intoxicating, and in large dose is a poison which destroys living tissue the liver and brain.

It should be noted that ethanol is useful as a solvent, a preservative, a means of lowering the freezing point of any drug. Another equally well-known representative of this class is methyl alcohol (also called wood alcohol or methanol). In contrast to methanol is deadly even in small doses! First, it causes blindness, then just "kills"!

The chemical properties of alcohols may be classified as follows:

Reactions specific to hydrogen of the hydroxyl group.

Reactions specific to the hydroxyl group.

Reactions specific to the carbinol group.

Reactions specific to the whole molecule.

1Reactions specific to hydrogen of the hydroxyl group

Reaction with sodium (Acidity of alcohols): Alcohols have a neutral effect on litmus, but a weak acidic character may appear especially when it reacts with strong active metals, Sodium or potassium which can replace the hydrogen of the hydroxyl group forming metal alkoxide and hydrogen evolves.

$2\ C_2H_5OH_{(l)} + 2Na_{(s)} \rightarrow 2\ C_2H_5ONa_{(l)} + H_{2\,(g)} \uparrow$

Practical experiment

Place 5 ml of ethanol in a test tube then add a small piece of sodium metal, cover the tube opening with your thumb to keep the evolving gas, Observe the effervescence and evolution of hydrogen gas which burns with a pop sound, After the reaction is completed evaporate the solution on water path and observe the formation of a white solid substance which is sodium ethoxide, the sodium ethoxide may be hydrolyzed giving ethanol and sodium hydroxide.

$C_2H_5ONa_{(l)} + H_2O_{(l)} \rightarrow C_2H_5OH_{(aq)} + NaOH_{(aq)}$

$C_2H_5OH_{(aq)} + NaOH_{(aq)} \rightarrow$ No reaction

Esterification

Ester Formation or Esterification (Reaction of alcohols with organic acids in the presence of conc. H_2SO_4): Alcohols react with organic acids to form esters, In this reaction, hydrogen atom is separated from the hydroxyl group of the alcohol molecule and the hydroxyl group is separated from the acid, this was proved by reacting the alcohol containing the heavy oxygen isotope O^{18}, with acetic acid containing the normal oxygen isotope O^{18} by analyzing the oxygen of the formed water, it was found that it is of the normal isotope.

$CH_3COOH + C_2H_5OH \rightarrow CH_3COOC_2H_5 + H_2O$ (R-O-R)

Ester formation is a reversible reaction, so concentrated sulphuric acid H_2SO_4should be added to prevent the reversible reaction and to absorb water, Esterification is the reaction between alcohols and acids in the presence of the dehydrating agent, water is formed from H from alcohol and OH from the acid.

Reactions specific to the hydroxyl group

Because alcohols contain a hydroxyl group, so they react with halogenated acid and conc.sulphuric acid, Ethanol reacts with conc. hydrochloric acid (HCl) in the presence of zinc chloride $ZnCl_2$ as a catalyst (dehydrating agent) to form ethyl chloride, The reaction of HI with alcohol is faster than HBr and HCl, where HI is hydrolyzed easier due to iodine has the largest atomic radius.

$C_2H_5OH_{(l)} + HCl_{(aq)} \rightarrow C_2H_5Cl_{(aq)} + H_2O_{(l)}$

Reactions specific to the carbinol group

Alcohols are easily oxidized by an oxidizing agent such as acidified potassium dichromate or potassium permanganate, the products differ according to the type of alcohol, The action of the oxidizing agents is concerned with the hydrogen atoms attached to the carbinol that converts them to the hydroxyl groups.

We must put into consideration that when two hydroxyl groups are attached to the same carbon atom, the produced compound is unstable and instantaneously loses a water molecule and converted to a stable compound.

Chemicals properties of alcohols

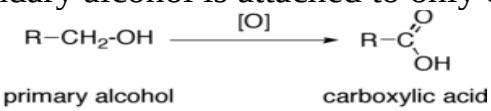
Oxidation

Oxidation in organic chemistry means converting H, which is attached to carbinol, to OH, and it takes place by one of the following reagents "oxidizing agents", $KMnO_4$ acidified with conc. H_2SO_4, or KCr_2O_7 acidified with conc. H_2SO_4 ."Chromic acid", Where atomic oxygen is produced from the reaction.

Oxidation of primary alcohols

The two hydrogen atoms attached to the carbinol are oxidized in two steps, In the first step, the aldehyde is produced, then the acid is produced in the second step, for instance, ethanol is oxidized by hot chromic acid to acetaldehyde then to ethanoic acid.

Primary alcohols are oxidized in two steps while secondary alcohols in one step because the carbinol group of the primary alcohol is attached to two hydrogen atoms while that of secondary alcohol is attached to only one hydrogen atom.



Practical experiment

Put three ml of ethanol in a dry clean test tube, Add the same amount of acidified potassium dichromate $KMnO_4$ "violet" + conc. H_2, Heat the mixture in a water bath for 10 minutes then cool it, we observe that the colour of the solution changed from orange to green colour, The odour of vinegar (ethanoic acid) appears due to the formation of acetic acid.

If we use acidified potassium permanganate as an oxidizing agent, we notice the disappearance of its violet colour due to the oxidation of alcohol into acetaldehyde (odour of green apples), this reaction is used to detect the taking of drivers for liquors.

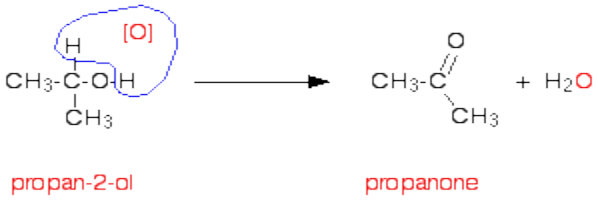
Where the driver blows a balloon through a tube containing silica gel saturated with acidified potassium dichromate, The balloon is left till the exhalation goes out, If the driver is a drinker, The colour of potassium dichromate in the tube changed from orange to green colour.

$CH_3CH_2OH + [O] \rightarrow [CH_3CH_2OOH] \rightarrow CH_3CHOOH \rightarrow CH_3COOH$

Oxidation of primary alcohol is not the ideal method to prepare aldehydes because the aldehyde formed will be oxidized into carboxylic acid, It is not preferred to prepare aldehydes by oxidation of primary alcohols because the reaction does not stop by the formation of the aldehyde but continues forming the organic acid.

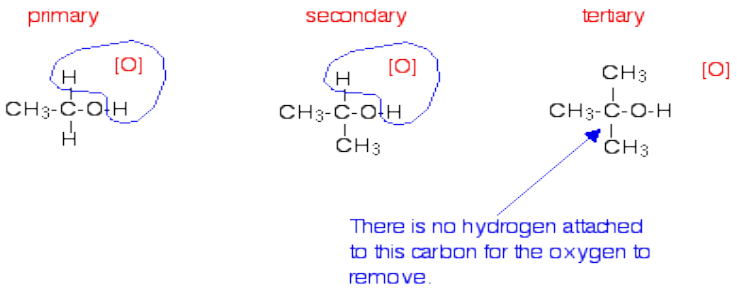
Oxidation of secondary alcohols

The single hydrogen atom attached to the carbinol group is oxidized in one step by the previous method, where ketone is formed, isopropanol is oxidized to acetone (propanone).



Oxidation of tertiary alcohols

Tertiary alcohols are very difficult to be oxidized because the carbinol group in tertiary alcohol is not attached to any hydrogen atoms, The violet colour of the acidified potassium permanganate disappears when it is added to 2-propanol and does not disappear when it is added to 2-methyl-2-propanol because 2-propanol is a secondary alcohol and can be oxidized while 2-methyl-2-propanol is a tertiary alcohol and can't be oxidized.



Reactions specific to the whole molecule

Dehydration means the elimination of H_2O by using conc. H_2SO_4, Alcohols react with concentrated sulphuric acid and the reaction products depend on the number of alcohol molecules as well as the temperature used, when they are heated to 180°C, The water molecule is eliminated from one alcohol molecule to give an alkene.

$CH_3CH_2OH_{(l)} \rightarrow C_2H_{4\,(g)} + H_2O_{(l)}$

All monohydric alcohols (primary- secondary- tertiary) form ethers, If the temperature is 140°C, the conc. sulpheric acid eliminate one molecule of water from every two molecules of the alcohol giving ether.

$2C_2H_5OH_{(l)} \rightarrow C_4H_{10}O_{(g)} + H_2O_{(l)}$

The reaction products of ethanol with sulphuric acid depend on the temperature because at 140°C, the water molecule is removed from two molecules of alcohol forming the corresponding ether while at 180°C, the water molecule is removed from one molecule of the alcohol to form the corresponding alkene.

Action of phosphorus halides:

$3ROH + PCI_3 \rightarrow 3RCI + H_3PO_3$

$ROH + PCI_5 \rightarrow RCI + POCI_3 + HCI$

Similar reactions are obtained by using $P + Br_2$ and $P + I_2$ for alkyl bromide and iodide preparation because of less stable nature of PBr_3 & PI_3

Action of $SOCI_2$:

$$R\text{-}OH + SOCI_2 \xrightarrow{Pyridine} R\text{-}CI + SO_2 + HCI$$

Action of NH_3:

$$CH_3\text{-}OH + NH_3 \xrightarrow[-H_2O]{Al_2O_3} CH_3\text{-}NH_2$$

Action of H_2S:

$$R\text{—}OH + HSH(g) \xrightarrow[\Delta]{ThO_2} \underset{\text{thiols}}{R\text{—}SH} + H_2O$$

Polyatomic alcohols

Polyatomic alcohols – alcohols that have multiple hydroxyl groups OH. Diatomic alcohols are called alcohols containing two hydroxyl groups (OH group); alcohols containing three hydroxyl groups – triatomic alcohols. In their molecules

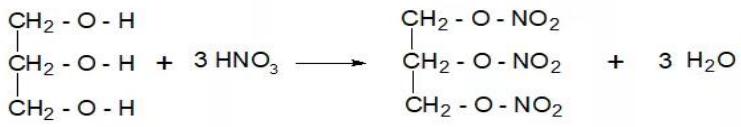
two or three hydroxyl groups never be attached to the same (one) carbon atom. Dihydric alcohols also called *glycol* because they have a sweet taste, is characteristic of all polyatomic alcohols

Polyatomic alcohols with a small number of carbon atoms are a viscous liquids, high alcohols – solid substance. Polyatomic alcohols can be getting by the same synthetic methods as saturated polyatomic alcohols.

As for polyatomic alcohols, they have a sweet taste, but some of them are poisonous. Properties of polyatomic alcohols similar to monoatomic alcohols, with the difference that the reaction is not one-to-hydroxyl group, but several at once.

One of the main distinctions - polyatomic alcohols easily react with copper hydroxide. This gives a transparent solution with bright blue-violet color. This reaction used to reveal the presence of a polyhydric alcohol in any solution.

Interact with nitric acid:



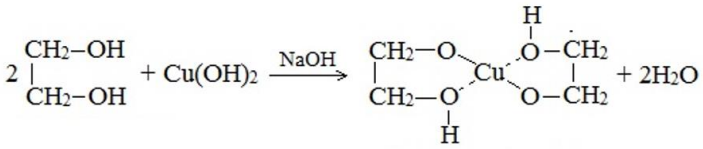
To practical point the greatest interest is the reaction with nitric acid. The resulting *nitroglycerin* and *dinitro Ethyleneglycol* are used as explosives, and *trinitroglycerin* - and even in medicine as a vasodilator.

Glycerin

We've all seen the glycerin. It is sold in pharmacies in the dark bubbles and is a viscous, colorless liquid, sweet taste. Glycerin is a trivalent alcohol. It is very well soluble in water, boils at a temperature 220 ^{0}C.

Chemical properties of glycerin are similar the properties of monoatomic alcohols, but glycerin can react with hydroxides of metals (with copper hydroxide $Cu(OH)_2$), with the formation of glycerate metals are chemical compounds like a salts.

Reaction with copper hydroxide – the typical for glycerin. In the chemical reaction forms a bright blue solution of copper glycerate



Questions:

How does alcohol act as an acid?

Is alcohol acidic or basic?

How do you show that alcohol can act as an acid and a base?

Is alcohol acid or base?

Why is water more acidic than alcohol?

Unit 9. Carboxylic acid.

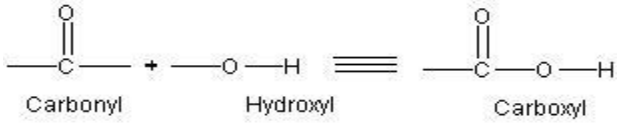
Of the organic compounds that show appreciable acidity, by far the most important are the carboxylic acids.

These compounds contain the carboxyl group attached to hydrogen (HCOOH) an alkyl group (RCOOH), or an aryl group (ArCOOH). These are also named as fatty acids because of some higher members particularly palmitic and

stearic acids, occur in natural fats. The general formula of the carboxylic acids is $C_nH_{2n}O_2$.

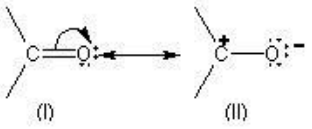
Only the hydrogen atom of the carboxyl group is replaceable by a metal, therefore the fatty acids are mono-basic.

Carboxylic acids are characterized by the presence of carboxyl group. The –COOH group which itself is made up of a carbonyl group (C=O) and a hydroxyl group (¾OH) is called carboxyl group (carb from carbonyl and oxyl from hydroxyl)

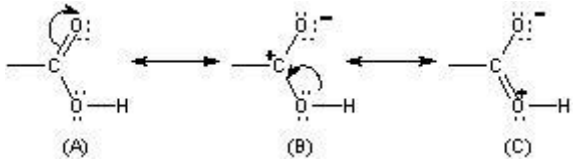


Carboxylic acids may be aliphatic or aromatic

Comparison of resonating structures of carboxylic group and carbonyl group. Carbonyl group has two resonance structures (I and II)

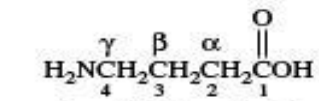


However, for a carboxyl group, three resonance structures (A, B and C) can be written.



In both structures (A) and (C), the C – atom and the two O – atoms have eight electrons in their respective valence shells while in structure (B), C – atom has only six electrons. Therefore, structure (B) is less stable than structure (C), in other words the two important resonance structures of carboxyl group are structures (A) and (C). In both these structures, carboxyl carbon is electrically neutral. However in case of aldehydes and ketones, only one structure i.e. I is electrically neutral. As a result, the carboxyl carbon of the resonance hybrid is less positive and hence less electrophilic than the carbonyl carbon of aldehydes and ketones. However, it may be noted that like carbonyl group, carboxyl group is also polar due to resonance structures (B) and (C)

Nomenclature of Carboxylic Acids



Carboxylic Acid	Common Name
HCOOH	Formic acid [Latin: Fermica = ant]
CH_3COOH	Acetic acid [Latin: acetum = vinegar]
$CH_3–CH_2–COOH$	Propionic acid
$CH_3(CH_2)_2COOH$	Butyric acid
$CH_3(CH_2)_3COOH$	Valeric acid
$CH_3(CH_2)_{14}COOH$	Palmitic acid
$CH_3(CH_2)_{16}COOH$	Stearic acid

Another system of nomenclature, except Formic acid considers acids as acid derivatives of acetic acid

Example:

$CH_3 – CH_2 – COOH$ Methyl acetic acid

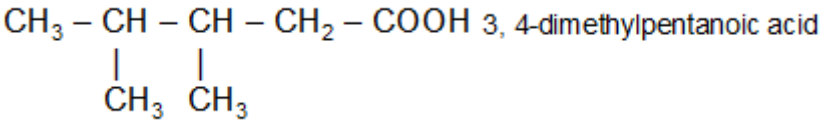
$(CH_3)_3C – COOH$ Trimethyl acetic acid

According to the IUPAC system of nomenclature, the suffix of the monocarboxylic acid is 'oic acid', which is added to the name of the alkane corresponding to the longest carbon chain containing the carboxyl group, e.g.

HCOOH methanoic acid

$CH_3 – CH_2 – CH_2 – COOH$ butanoic acid

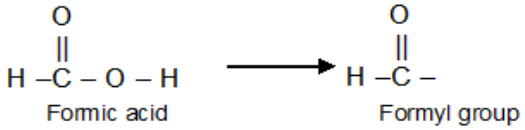
The positions of side-chains (or substituents) are indicated by numbers, the carboxyl group always being given number I.

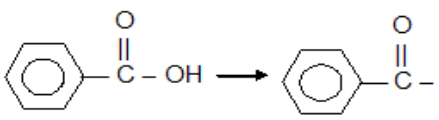


3, 4-dimethylpentanoic acid

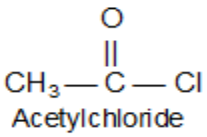
Naming of Acyl Groups; Acid Chlorides and Acid Anhydrides

The group obtained from a carboxylic acid by the removal of the hydroxyl portion is known as an acyl group. The name of an acyl group is created by changing the 'ic' at the end of the name of the carboxylic acid to 'yl', examples:





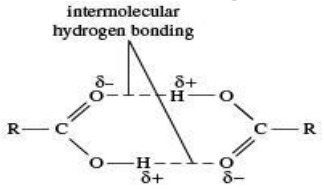
Acid chlorides are named systematically as acyl chlorides.



Acetylchloride

The molecules of carboxylic acids are polar and exhibit hydrogen bonding.

Carboxylic acids exist as dimers (pairs of molecules), not only in the liquid state but even to some extent in the gaseous state.



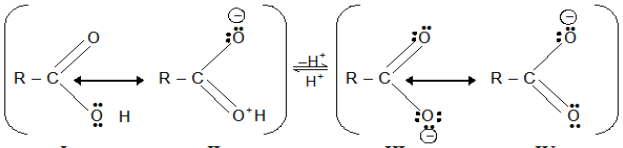
The first four are miscible with water. The higher acids are virtually insoluble. The simplest aromatic acid, benzoic acid, contains too many carbon atoms to show appreciable solubility in water.

Carboxylic acids are soluble in less polar solvents like ether, alcohol, benzene etc.

Carboxylic acids have higher boiling points than alcohols. These very high boiling points are due to the fact that a pair of carboxylic acid molecules are held together not by one but by two hydrogen bonds and exist as dimer. The first three fatty acids are colourless pungent smelling liquids. A study of nitrated spectra of formic acid in the liquid and solid states has provided evidence that this acid, unlike most of the other carboxylic acids, is not dimeric in these states, but is associated as a polymer.

Acidity of Carboxylic Acids

The acidity of a carboxylic acid is due to the resonance stabilization of its anion



Because of the resonance, both the carbon oxygen bond in the carboxylate anion have identical bond length. In the carboxylic acid, these bond lengths are no longer identical.

The acidity of carboxylic acid depends very much on the substituent attached to – COOH group. Since acidity is due to the resonance stabilization of anion, substituent causing stabilization of anion increases acidity whereas substituent causing destabilization of anion decrease acidity. For example, electron withdrawing group disperses the negative charge of the anion and hence makes it more stable causing increase in the acidity of the corresponding acid, on the other hand, electron-releasing group increases the negative charge on the anion and hence makes it less stable causing the decrease in the acidity. In the light of this, the following are the orders of a few substituted carboxylic acids.

a) Increase in the number of Halogen atoms on a-position increases the acidity, eg.
$Cl_3CCOOH > Cl_2CHCOOH > ClCH_2COOH > CH_3COOH$

b) Increase in the distance of Halogen from COOH decreases the acidity e.g.

$CH_3 - CH_2 - CH - COOH > CH_3 - CH - CH_2 - COOH > CH_2 - CH_2 - CH_2 - COOH$

| | |

Cl Cl Cl

This is due to the fact that inductive effect decreases with increasing distance.

c) Increase in the electro negativity of halogen increases the acidity.

$FCH_2COOH > BrCH_2COOH > ICH_2COOH$

Chemical Reactions of Carboxylic Acids

a. lt formation:

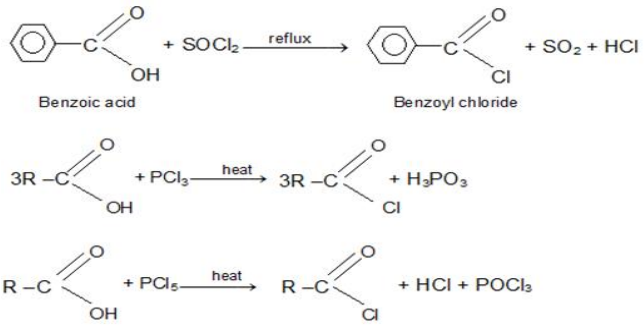
b.

$2CH_3COOH + 2Na \rightarrow 2CH3COO{-}Na^+ + H_2$

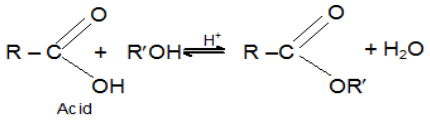
$CH_3COOH + NaOH \rightarrow CH3COO{-}Na^+ + H_2O$

$CH_3COOH + NaHCO_3 \rightarrow CH3COO{-}Na^+ + H_2O + CO_2$

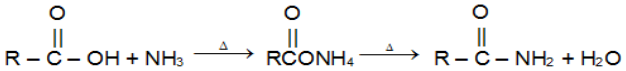
b. Conversion into Acid Chlorides:



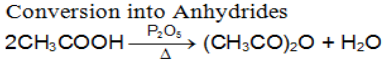
c. Conversion into Esters (Esterification)



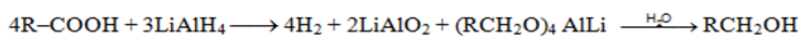
d. Conversion into Amides



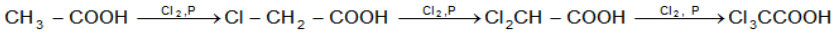
e. Conversion into Anhydrides



f. Reduction:



g. Halogenation:



The qualitative test for carboxylic acids.

S*short-chain carboxylic acids react with iron (III) chloride and yellow - red colour precipitate of basic salts is formed:* $2\,R\text{-}COOH + FeCl_3 + H_2O = (R\text{-}COO)_2(OH)Fe\downarrow + 3\,HCl$

Materials. solution, 10 % sodium hydroxide (NaOH) solution, 1 % iron chloride solution ($FeCl_3$).

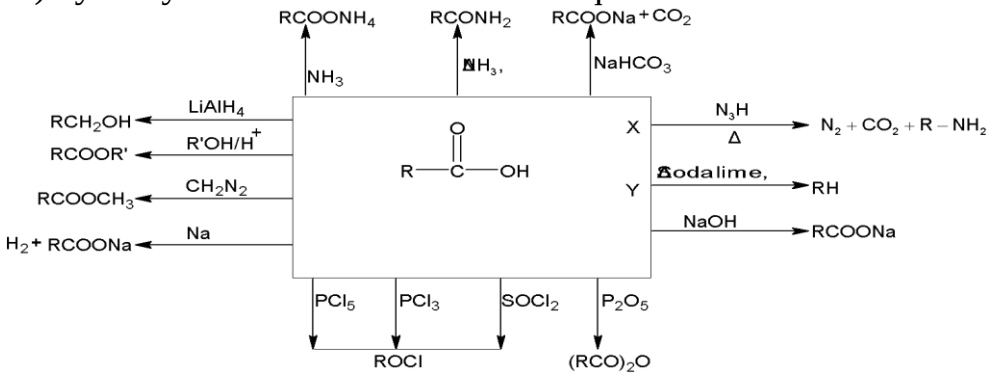
Protocol. Add in tube:

3 drops acetic acid solution,

2-3 drops of 10 % of NaOH solution,

3 drops of iron chloride solution

It is heated this mixture until boiling, after that yellow-red colour precipitate of iron (III) hydroxyl acetate is formed. Write equations of this reaction.



Questions:

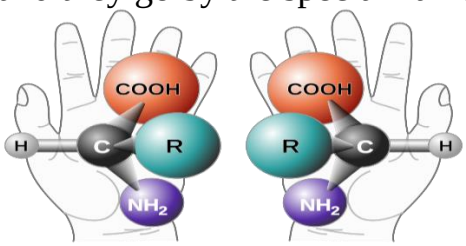
1. What happens when a carboxylic acid is heated?
2. How does carboxylic acid react with HI?
3. Why are carboxylic acids more acidic than phenol?
4. Are carboxylic acids saturated organic compounds?

Unit 10. Stereoisomers.

Generally defined, stereoisomers are isomers that have the same composition (that is, the same parts) but that differ in the orientation of those parts in space. There are two kinds of stereoisomers: enantiomers and diastereomers. Enantiomers are mirror images, like one's hands, and diastereomers are everything else. However, as is stated above, timescale and energy are important. In order to understand these considerations, it is helpful first to consider a special kind of stereoisomer, the conformational isomer.

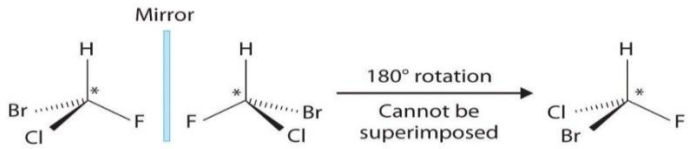
Enantiomers

The left and right hand are mirror images; the left hand is superimposable on the mirror image of the right hand but not on the right hand itself. Some molecules are related to their mirror images in the same manner. Such molecules are, by definition, stereoisomers, and they go by the special name of enantiomers.

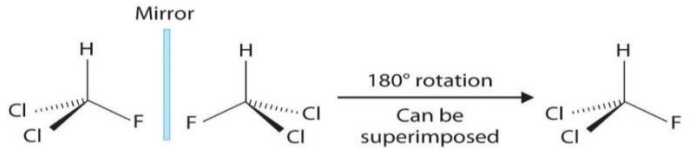


This type of stereoisomer is the essential mirror-image, non-superimposable type of stereoisomer

Note that the gray plane in the middle demotes the mirror plane



(a) Bromochlorofluoromethane



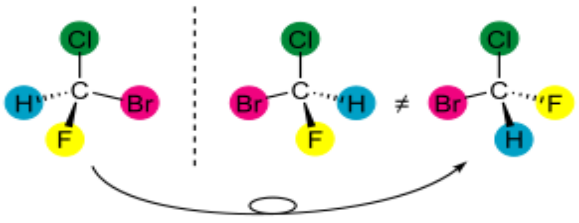
(b) Dichlorofluoromethane

Note that even if one were to flip over the left molecule over to the right, the atomic spatial arrangement will not be equal. This is equivalent to the left hand - right hand relationship, and is aptly referred to as 'handedness' in molecules. This can be somewhat counter-intuitive, so this article recommends the reader try the 'hand' example. Place both palm facing up, and hands next to each other. Now flip either side over to the other. One hand should be showing the back of the hand, while the other one is showing the palm. They are not same and non-superimposable.

This is where the concept of chirality comes in as one of the most essential and defining idea of stereoisomerism.

Chirality

An object that is chiral is an object that can not be superimposed on its mirror image. Chiral objects don't have a *plane of symmetry*. An achiral object has a plane of symmetry or a rotation-reflection axis, i.e. reflection gives a rotated version. Chirality essentially means 'mirror-image, non-superimposable molecules', and to say that a molecule is chiral is to say that its mirror image (it must have one) is not the same as it self. Whether a molecule is chiral or achiral depends upon a certain set of overlapping conditions



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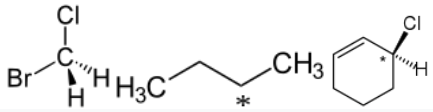
Notice the distinct characteristic of the achiral molecule: it possesses two atoms of same element.

A carbon atom is chiral if it has four different items bonded to it at the same time. Most often this refers to a carbon with three heteroatoms and hydrogen, or two heteroatoms plus a bond to another carbon plus a bond to a hydrogen atom. It can also refer to a nitrogen atom bonded to four different types of molecules, if the nitrogen atom is utilizing its lone pair as a nucleophile. If the nitrogen has only three bonds it is not chiral, because the lone pair of electrons can flip from one side of the atom to the other spontaneously.

Any atom in an organic molecule that is bonded to four different types of atoms or chains of atoms can be considered "chiral".

If a carbon atom (or other type of atom) has four different substituents, that carbon atom forms a *chiral center* (also known as a *stereocenter*). Chiral molecules often have one or more stereocenters. When drawing molecules, stereocenters are usually indicated with an asterisk near the carbon.



Which of the indicated carbon atoms is a stereocenter?

Left: The carbon atom has a Cl, a Br, and 2 CH_3. That's only 3 different substituents, which means this is not a stereocenter.

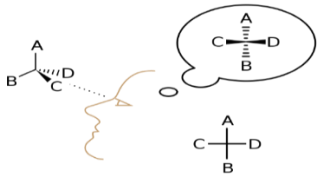
Center: The carbon atom has one ethyl group (CH_{23}), one methyl group (CH_3) and 2 H. This is not a stereocenter.

Right: The carbon atom has a Cl and 1 H. Then you must look around the ring. Since one side has a double bond and the other doesn't, it means the substituents off that carbon are different. The 4 different substituents make this carbon a stereocenter and makes the molecule chiral.

A molecule can have multiple chiral centers without being chiral overall: It is then called a meso compound. This occurs if there is a symmetry element (a mirror plane or inversion center) which relates the chiral centers

Fischer projections

Fischer projections (after the German chemist Hermann Emil Fischer) are an ingenious means for representing configurations of carbon atoms. Considering the carbon atom as the center, the bonds which extend towards the viewer are placed horizontally. Those extending away from the viewer are drawn vertically. This process, when using the common dash and wedge representations of bonds, yields what is sometimes referred to as the "bowtie" drawing due to its characteristic shape. This representation is then further shorthanded as two lines: the horizontal (forward) and the vertical (back), as showed in the figure below:



Operations on Fischer projections]

in a Fischer projection, exchange two substituent positions results in the inversion of the stereocenter rotation by 90° of the Fischer projection results in inversion rotation by 180° of the Fischer projection preserves the configuration

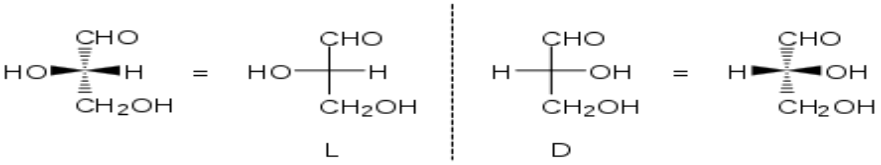
By optical activity: (+)- and (-)-[edit]

An optical isomer can be named by the direction in which it rotates the plane of polarized light. If an isomer rotates the plane clockwise as seen by a viewer towards whom the light is traveling, that isomer is labeled (+). Its counterpart is labeled (-). The (+) and (-) isomers have also been termed d- and l-, respectively (for dextrorotatory and levorotatory). This labeling is easy to confuse with D- and L- and is therefore not encouraged by IUPAC.

The fact that an enantiomer can rotate polarised light clockwise (*d*- or +-enantiomer) does not relate with the relative configuration (D- or L-) of it.

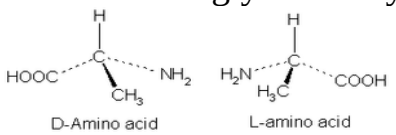
By relative configuration: D- and L-[edit]

Fischer, whose research interest was in carbohydrate chemistry, took glyceraldehyde (the simplest sugar, systematic name 2,3-dihydroxyethanal) as a template chiral molecule and denoted the two possible configurations with D- and L-, which rotated polarised light clockwise and counterclockwise, respectively.

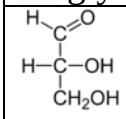
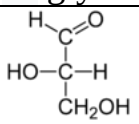
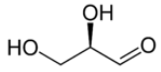
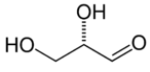


All other molecules are assigned the D- or L- configuration if the chiral centre can be formally obtained from glyceraldehyde by substitution. For this reason the D- or L- naming scheme is called *relative configuration*.

An optical isomer can be named by the spatial configuration of its atoms. The D/L system does this by relating the molecule to glyceraldehyde. Glyceraldehyde is chiral itself, and its two isomers are labeled D and L. Certain chemical manipulations can be performed on glyceraldehyde without affecting its configuration, and its historical use for this purpose (possibly combined with its convenience as one of the smallest commonly-used chiral molecules) has resulted in its use for nomenclature. In this system, compounds are named by analogy to glyceraldehyde, which generally produces unambiguous designations, but is easiest to see in the small biomolecules similar to glyceraldehyde.



One example is the amino acid alanine: alanine has two optical isomers, and they are labeled according to which isomer of glyceraldehyde they come from. Glycine, the amino acid derived from glyceraldehyde, incidentally, does not retain its optical activity, since its central carbon is not chiral. Alanine, however, is essentially methylated glycine and shows optical activity.

D- glyceraldehyde	L- glyceraldehyde
	
	

Nine of the nineteen L-amino acids commonly found in proteins are dextrorotatory (at a wavelength of 589 nm), and D-fructose is also referred to as levulose because it is levorotatory.

By absolute configuration: R- and S-[edit]

Main article: R-S System

The absolute configuration system stems from the Cahn-Ingold-Prelog priority rules, which allow a precise description of a stereocenter without using any reference compound. In fact the basis is now the atomic number of the stereocenter substituents.

The R/S system is another way to name an optical isomer by its configuration, without involving a reference molecule such as glyceraldehyde. It labels each chiral center R or S according to a system by which its ligands are each assigned a priority, according to the Cahn Ingold Prelog priority rules, based on atomic number.

This system labels each chiral center in a molecule (and also has an extension to chiral molecules not involving chiral centers). It thus has greater generality than the D/L system, and can label, for example, an (R,R) isomer versus an (R,S) – diastereomers.

The R/S system has no fixed relation to the (+)/(-) system. An R isomer can be either dextrorotatory or levorotatory, depending on its exact ligands.

The R/S system also has no fixed relation to the D/L system. For example, one of glyceraldehyde's ligands is a hydroxy group, -OH. If a thiol group, -SH, were swapped in for it, the D/L labeling would, by its definition, not be affected by the substitution. But this substitution would invert the molecule's R/S labeling, due to the fact that sulfur's atomic number is higher than carbon's, whereas oxygen's is lower. [Note: This seems incorrect. Oxygen has a higher atomic number than carbon. Sulfur has a higher atomic number than oxygen. The reason the assignment priorities change in this example is because the CH2SH group gets a higher priority than the CHO, whereas in glyceraldehyde the CHO takes priority over the CH2OH.]

Properties of optical isomers

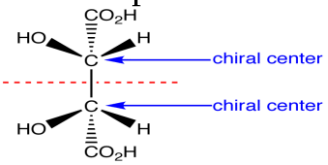
Enantiomers have – *when present in a symmetric environment* - identical chemical and physical properties except for their ability to rotate plane-polarized light by equal amounts but in opposite directions. A solution of equal parts of an optically-active isomer and its enantiomer is known as a racemic solution and has a net rotation of plane-polarized light of zero.

Enantiomers differ in how they interact with different optical isomers of other compounds. In nature, most biological compounds (such as amino acids) occur as single enantiomers. As a result, different enantiomers of a compound may have substantially different biological effects. Different enantiomers of the same chiral drug can have very different pharmological effects, mainly because the proteins they bind to are also chiral.

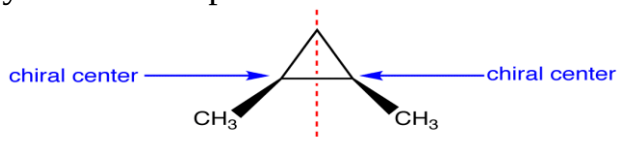
For example, spearmint leaves and caraway seeds respectively contain L-carvone and D-carvone – enantiomers of carvone. These smell different to most people because our taste receptors also contain chiral molecules which behave differently in the presence of different enantiomers.

When a molecule has more than one source of asymmetry, two optical isomers may be neither perfect reflections of each other nor superimposeable: some but not all stereocenters are inverted. These molecules are an example of diastereomers: They are not enantiomers. Diastereomers seldom have the same physical properties. Sometimes, the stereocentres are themselves symmetrical. This causes the counterintuitive situation where two chiral centres may be present but no isomers result. Such compounds are called meso compounds. A meso compound is a molecule with multiple stereocenters that is superimposable on its

mirror image. These particular traits lead to specific qualities that meso compounds do not share with most other stereoisomers. One such quality is the internal mirror plane. All meso compounds have something called an internal mirror plane. This internal mirror plane is simply a line of symmetry that bisects (cuts in half) the molecule. Each half is a mirror image of the other half. Here is an example of a meso compound and its internal mirror plane:



This molecule has a plane of symmetry (the horizontal plane going through the red broken line) and, therefore, is achiral; However, it has two chiral carbons and is consequentially a meso compound.



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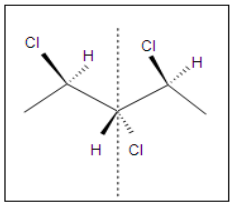
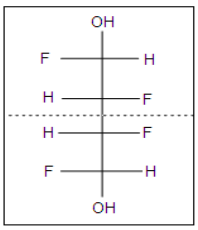
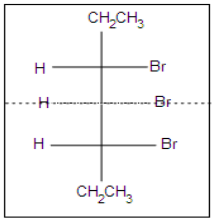
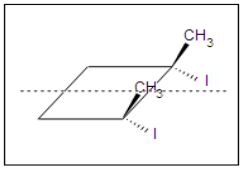
This molecules has a plane of symmetry (the vertical plane going through the red broken line perpendicular to the plane of the ring) and, therefore, is achiral, but has has two chiral centers. Thus, its is a meso compound.









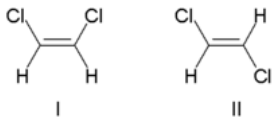
In general, a meso compound should contain two or more identical substituted stereocenters. Also, it has an internal symmetry plane that divides the compound in half. These two halves reflect each other by the internal mirror. The stereochemistry of stereocenters should "cancel out". What it means here is that when we have an internal plane that splits the compound into two symmetrical sides, the stereochemistry of both left and right side should be opposite to each other, and therefore, result in **optically inactive**. Cyclic compounds may also be **meso.**

A mixture of equal amounts of both enantiomers is said to be a racemic mixture.

It is the symmetry of a molecule (or any other object) that determines whether it is chiral or not. Technically, a molecule is achiral (not chiral) if and only if it has an axis of improper rotation; that is, an n-fold rotation (rotation by 360°/n) followed by a reflection in the plane perpendicular to this axis which maps the molecule onto itself.

Cis-trans Isomerism]

Stereoisomerism can occur when a double bond is present, because the pi bond involved prevents that bond from being "twisted" the same way that a single bond can be. A good example is 1,2-dichloroethene: CCl. Consider the two examples below:



The two molecules shown above are *cis*-1,2-dichloroethene and *trans*-1,2-dichloroethene. These two molecules are geometrical isomers because the two carbon atoms cannot be rotated relative to each other, due to the rigidity caused by the pi bond between them. Therefore, they are not "superimposeable" - they are not identical, and cannot take each other's place. Cis/trans isomers have different chemical and physical properties and can exhibit dramatically different biological activity.

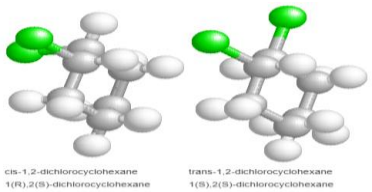
Cis-trans isomerism (Often called geometric isomerism although this term refers to all stereoisomers) is a form of stereoisomerism and describes the orientation of functional groups at the ends of a bond around which no rotation is possible. Both alkenes and cycloalkanes have restricted rotation around certain bonds. In alkenes, the double bond restricts movement and rotation, as does the looped structure of cycloalkanes.

Rotation is possible around the double bond of an alkene but it requires between 60 and 70 kcal of energy. Without the addition of this energy, groups that start on one side of the double bond stay there. This is the basis of cis/trans isomerism.

There are two forms; the cis and trans isomers. The form in which the substituent hydrogen atoms are on the same side of the bond that doesn't allow rotation is called *cis*; the form in which the substituent hydrogens are on opposite sides of the bond is called *trans*. An example of a small hydrocarbon displaying cis-trans isomerism is 2-butene.

Cis isomers and trans isomers of a substance have different physical properties. Trans isomers generally have higher boiling points and lower densities. This is because the trans isomers molecules can line up and fit together better than the cis form. Two isomers with very different properties are maleic acid and fumaric acid. The names are two trivial names for 2-butenedioic acid and repectively the cis and trans isomer.

Cycloalkanes and similar compounds can also display cis-trans isomerism. As an example of a geometric isomer due to a ring structure, consider 1,2-dichlorocyclohexane. These compounds can be named more rigorously using R/S notation



E/Z notation]

Main article: E-Z System

The trans/cis system for naming isomers breaks down when there are more than two different substituents on a double bond. (The cis/trans system should only be used when the carbon atoms involved each have a hydrogen atoms attached). The E/Z notation is unamibiguous. Z (from the German *zusammen*) means together

and usually corresponds to the term *cis*; E (from the German *entgegen*) means opposite and usually corresponds to the term *trans*.

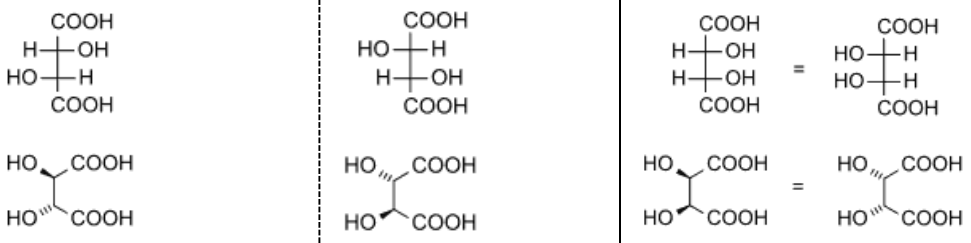
Usually, E isomers are more stable than Z isomers because of steric effects. When two large groups are closer to each other, as they often are with Z, they interfere more with each other and have a higher potential energy than with E, where the large groups are farther apart and interfere less with each other.

Diastereomers with stereocenters

In simple terms, two stereoisomers are diastereoisomers of each other if *only one* chiral center differs between the two stereoisomers. That is to say, if both molecules contain two or more chiral centers, but if only one of the chiral centers in each molecule is different than the other, then the two molecules are diastereoisomers of one another.

If a molecule contains a single asymmetric carbon atom or *stereocenter*, it will have two mirror image forms. If a molecule contains two asymmetric carbons, there are four possible configurations, and it would be mathematically and physically impossible for all four to be mirror images of each other. The more chiral centers in a molecule, the more possibilities there are for different conformers, and therefore the more possible diastereomers exist.

As an example, tartaric acid contains two asymmetric centers, but two of the configurations of the tartaric acid molecule are equivalent to one another – and together they are called meso compounds. This configuration is not optically active, while the remaining two configurations are D- and L- mirror images. For this reason, the meso form of tartaric acid is a diastereomer of the other forms.



(natural) tartaric acid L-(+)-tartaric acid dextrotartaric acid	D-(-)-tartaric acid levotartaric acid	mesotartaric acid
(1:1) DL-tartaric acid "racemic acid"		

The meso form of tartaric acid (right) is a diastereomer of the other forms.

Two common prefixes used to distinguish diastereomers are threo and erythro. When drawn in the Fischer projection the *erythro* isomer has two identical substituents on the same side and the *threo* isomer has them on opposite sites.

Stereoisomers is the isomers that differ arrangement of their atoms in space. Stereoisomers are divided into conformational and configurational ones.

Conformational Isomers

Conformational isomers, or conformers for short, are caused by the rotation around covalent single σ bonds and the three-dimensional (3-D) tetrahedral shape^{3}-hybridized centers.

In larger biomolecules such as proteins and enzymes, the overall conformational shape of the molecule can be necessary for its biological activity.

Two common types of diagrams are used to show conformers. See Figure 3.2. The first is a Sawhorse representation, which is an angled view along the rotating bond. The second is a Newman projection, which is an end-on view along the rotation bond with a circle to represent the front carbon center. Bonding to the front carbon is drawn to the center of the circle. Bonding to the rear carbon are drawn only to the edge of the circle.

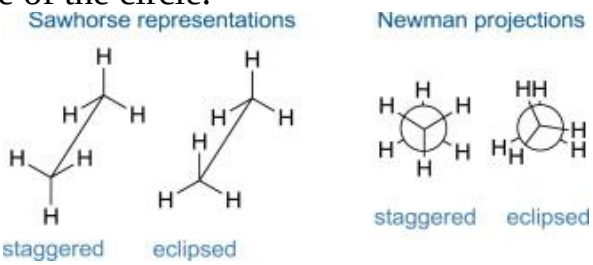


FIGURE 3.2. Extreme conformers of ethane.

For example, in ethane, the energy difference between the two extreme conformers is about 12 kJ/mol. The lower energy staggeredconformer has the C–H bonds rotated as far apart as possible. The higher energy eclipsed conformer has the C–H bonds lined up as shown in Figure 3.2. Because 60–80 kJ is available at room temperature, interconversion over all the possible conformers between these two extremes occurs easily.

Unlike structural isomers, conformers can interconvert easily because the energy for rotation is small compared to the energy in the system under normal conditions. Still, there are small energy differences between conformers, and some are more stable (of lower energy) than others. As seen in Figure 3.3, rotation around the central C–C bond for butane gives two different staggered forms and two different eclipsed forms. This is because two of the hydrogen substituents from the ethane model in Figure 3.2 are now methyl groups.

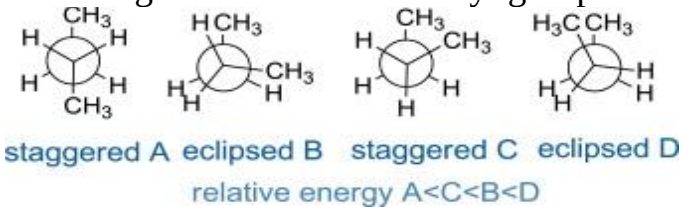


FIGURE 3.3. Staggered and eclipsed conformers for butane.

Conformations in Cycloalkanes

While C–C_5 are nearly planar, rings of six or more carbons have enough flexibility for some rotation around the bonds. Because the bonded centers are ^{3}-hybridized, this leads to conformational changes.

The very common ring shows this feature clearly. There are two extreme conformations that differ by 23 kJ/mol in energy. The lower energy conformer is called a chair, and the higher energy conformer is called a boat. See Figure 3.5.

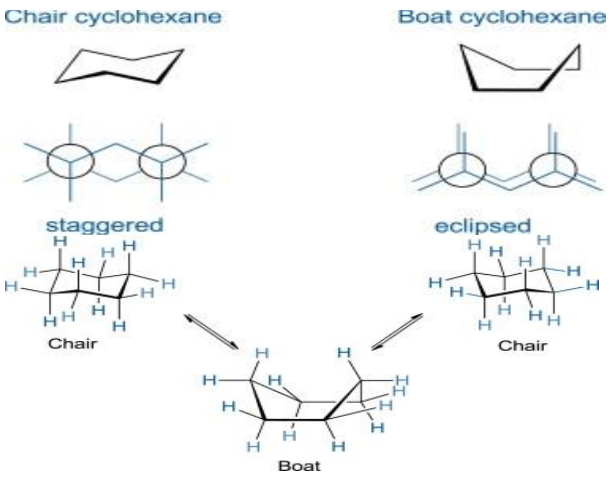
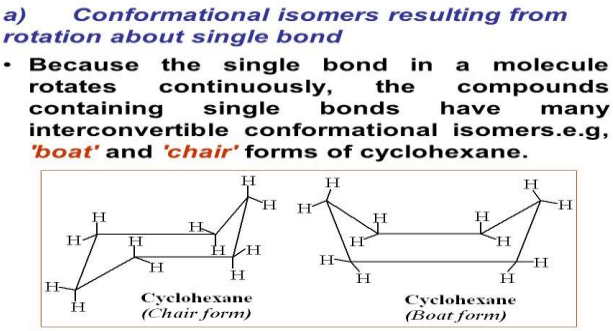


FIGURE 3.5. Cyclohexane conformers.

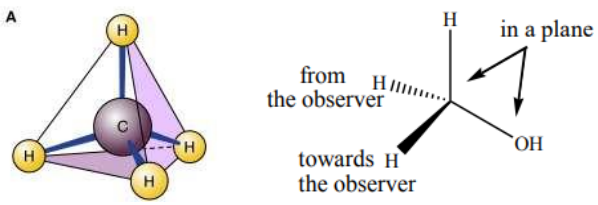
Cyclohexane can easily convert between the two possible lowest energy chair forms. This conversion goes through a boat, and needs about 45 kJ/mol to occur. See Figure



CONFIGURATIONAL ISOMERS

Configuration is a specific spatial arrangement of atoms in the molecule, excluding differences resulting due to rotation about single bonds. Fundamentals of stereoisomerism laid by van't Hoff, who in 1874 formulated the idea that the carbon atom in the sp3 hybridized state has a tetrahedral configuration. To show a tetrahedral configuration of carbon atom on the plane the stereochemical formulas are used. For their illustration the tetrahedral model is oriented in the special way: the carbon atom with its two bonds is arranged in the plane, and then the 3rd bond is arranged in the front of the projection plane, and the 4th is behind the plane. The hydrogens are then located in the surrounding space by wedge with its basis directed towards the viewer (in front of the plane) and hatched (behind the plane) bonds.

CH3OH methanol



tetrahedral configuration of carbon atom stereochemical formula of methanol

Questions:

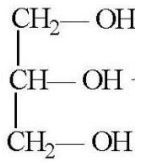
1. What are constitutional isomers?

2. Are conformational isomers stereoisomers? If not then what category of isomers do they belong to, when isomers are categorised as constitution...

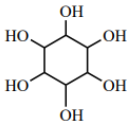
3. What do you mean by constitutional isomers? Is it the other name of structural isomerism?

Unit 11.POLY-AND HETEROFUNCTIONAL COMPOUNDS.

Polyols contain two or more hydroxyl groups. Glycerol and inositol are involved in constructing of lipids.



glycerol

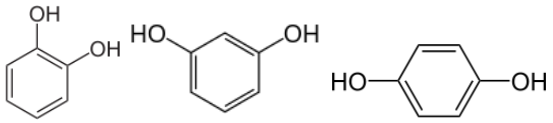


inositol

ethylene glycol

Glycerol and inositol may interact with different acylating reagents. α-Glycerophosphate is formed during the synthesis of phospholipids and triacylglycerols. Ethylene glycol is toxic substance for human body. It is used in the technique for the preparation of antifreeze

Dicarboxylic acids, such as oxalic, malonic, succinic, glutaric, fumaric contain two carboxylic groups (their formulas are presented in chapter 8). Oxalic acid and oxalates are abundantly present in many plants. In humans, the insoluble calcium oxalate may be formed and deposited in the form of kidney stones. Malonic, succinic, glutaric and fumaric acids are the participants of the human metabolism. Catechol, resorcinol and hydroquinone refer to the group of diatomic phenols



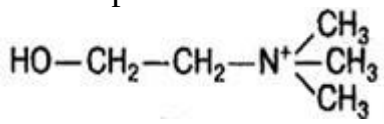
catechol resorcinol hydroquinone

Catechol is a part of the amino acid tyrosine, and catecholamines (dopamine, adrenaline and noradrenaline) which are synthesized from tyrosine with decarboxylation, hydroxylation and methylation reactions. These substances are also known as remedies stimulating adrenoreceptors.

Resorcinol has an antiseptic effect, used as a component of hygiene products. Hydroquinone is a part of coenzyme Q, which involved in the transfer of electrons and protons in the respiratory chain.

Hydroquinone has a variety of uses principally associated with its action as a reducing agent that is soluble in water. It is a major component in most black and white photographic developers for film and paper where, with the compound metol, it reduces silver halides to elemental silver.

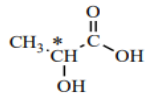
Representatives of aminoalcohols are ethanolamine and choline. They are involved in the construction of lipids.



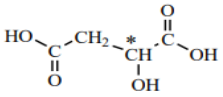
HO- CH_2- CH_2- NH_2

Ethanolamine choline

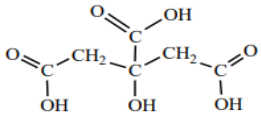
Biologically important hydroxy acids are lactic, malic and citric. Their trivial names are widely used in medicine and biology. Carboxyl group has ionized form at physiological pH value, various compounds having a carboxyl group is often referred to in accordance with the name of their salts.



lactic acid or lactate



malic acid or malate



citric acid or citrate

Lactic acid and malic acid are chiral compounds. They are found in the human body only in the form of L-enantiomers. In humans L-lactate is produced from pyruvate via the enzyme in a process of fermentation during normal metabolism. Industrially, lactic acid fermentation is performed by Lactobacillus bacteria, among others. These bacteria can operate in the mouth; the acid they produce is responsible for the caries. Citric and L-malic acids are participants of Krebs cycle

In decarboxylation, the -COOH or -COONa group is removed and replaced with a hydrogen atom.

$$HOOC\text{-}COOH \xrightarrow{H2SO4} CO_2 + [HOOC] \rightarrow CO_2 + H_2O$$

$$HOOC\text{-}CH_2\text{-}COOH \xrightarrow{H2SO4} CH_3COOH + CO_2$$

MALONIC ACID acetic acid

A hydroxyl, amino, oxo and carboxyl groups are most widely found in heterofunctional compounds. Poly-and heterofunctional compounds have typical reactivity. The compound may react typical for each of the groups present in the compound. Mutual influence of functional groups leads to the appearance of specific properties. In various combinations of functional groups new properties appear. Mutual influence depends strongly on the relative position of functional groups, on their distance. For example, the functional group X may be located in the α, β, γ, δ positions relative to the carboxyl group. When the functional groups are close to each other their interaction is more sharply expressed.

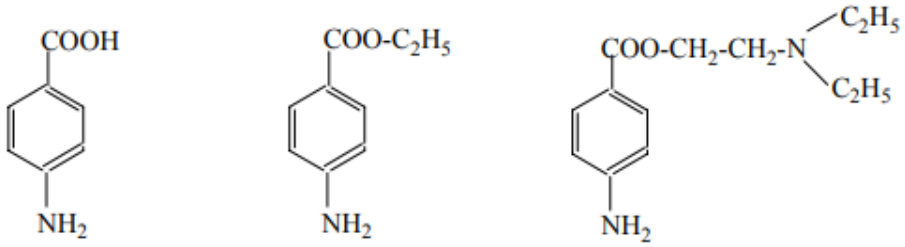
Classification of heterofunctional compounds

Chemical Name	Formula
Lactic acid (2-Hydroxypropanoic acid)	$CH_3\text{-}CH(OH)\text{-}COOH$
Malic acid (Hydroxybutanedioic acid)	$HOOC\text{-}CH_2\text{-}CH(OH)\text{-}COOH$
Tartaric acid	$HOOC\text{-}CH(OH)\text{-}CH(OH)\text{-}COOH$
Citric acid	$HOOC\text{-}CH_2\text{-}C(COOH)(OH)\text{-}CH_2\text{-}COOH$

	OH
Pyruvic acid	CH_3-C-COOH ‖ OH
Acetoacetic acid	CH_3-C- CH_2- COOH ‖ OH
Oxalic acid	HOOC-CH_2–C -COOH ‖ OH

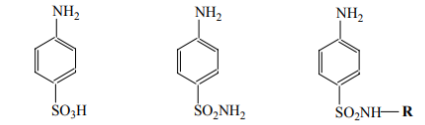
Heterofunctional aromatic compounds

Among them are medicines that contain benzene ring. Let us start to review the benzene ring containing drugs beginning from the derivatives of para-amino benzoic acid (PABA):



PABA **Anesthesine** **Novocain**

Anesthesine and novocain are used as local anesthetics, applied to desensitize a particular region of the body to pain. The introduction of the sulfa drugs in the 1930s hailed the beginning of modern drug therapy. Before their introduction, even a minor bacterial infection could become potentially life threatening. Because no one understood how they worked, at first, people, even physicians, considered sulfa drugs as almost magical. Sulfa drugs are the derivatives of sulfanilic acid, and they are named sulfanilamides. Sulfanilamide was the first drug of this group.



Sulfanilic acid **Sulfanilamide** **General formula of sulfanilamides**

Amino alcohol

Amino alcohols contain both an amine and an alcohol group. Amino alcohol derivatives have been employed as catalysts as well as coupling partners in the synthesis of many compounds. Enantiomerically pure beta-amino alcohols play an increasingly important role in pharmaceutical therapy and as chiral auxiliaries in organic synthesis. Amino alcohol derivatives are currently being studied for their antimicrobial and antifungal activities, and in the modulation of the physiochemical properties of drug molecules. The amino alcohol group is present

in several antibiotics, such as ethambutol for the treatment of tuberculosis. 1,2-Additions, ring-closure reactions, conjugate additions, and α- functionalization of carbonyl compounds are efficiently accomplished by β-amino alcohols as catalysts. The ready availability of β-amino alcohols from a chiral pool (e.g., L-amino acids) makes them an appealing class of versatile promoters to exploit in modern organic synthesis.

Organic compounds of biological importance contain very often not one, but several functional groups. A significant importance in living systems belongs to heterofunctional compounds that involve different functional groups in the same molecule.

Hydroxyl, amino, oxo, and carboxyl groups are encountered most widely in heterofunctional compounds. A combination of different functional groups results in the formation of mixed classes of organic compounds, some of them are given in Table 11.1 (other combinations are possible, of course).

Table 11.1. Some types of combining functional groups in heterofunctional compounds

Heterofunctional classes	*Functional groups*		*Representatives*	
			formula	*trivial name*
Amino alcohols	NH_2	OH	$H_2NCH_2CH_2OH$	Colamine
Hydroxy carbonyl compounds	OH	>C=O	$HOCH_2CHCH{=}O$ (OH)	Glyceraldehyde
Hydroxy carboxylic acids	OH	COOH	$HOCH_2COOH$	Glycolic acid
Amino acids	NH_2	COOH	H_2NCH_2COOH	Glycine
Oxo acids	=O	COOH	$CH_3C(=O)COOH$	Pyruvic acid

Colamine or 2-aminoethanol

Ethanolamine, also called 2-aminoethanol or monoethanolamine (often abbreviated as MEA), is an organic chemical compound that is both a primary amine (due to an amino group in its molecule) and a primary alcohol (due to a hydroxyl group). Like other amines, monoethanolamine acts as a weak base. Ethanolamine is a toxic, flammable, corrosive, colorless, viscous liquid with an odor similar to that of ammonia.

Ethanolamine also refers to a class of antihistamines containing an ethyl-amine group attached to a diphenylmethane structure. Examples of drugs within this class include diphenhydramine (Benadryl), phenyltoloxamine (Percogesic), and doxylamine (Unisom Sleep Tablets). They are one of the oldest classes of antihistamine drugs, yet remain the most effective for treating allergy symptoms, even exceeding the effectiveness of new OTC and prescription antihistamines such as loratadine (Claritin) and Fexofenadine(Allegra). However, all ethanolamines are extremely sedating, even more so than many barbiturates. For this reason, they are not always desirable drugs for treatment, and less-effective drugs are indicated to avoid the substantial drowsiness inherent in ethanolamines

Ethanolamine is **biosynthesized** by decarboxylation of **serine**:

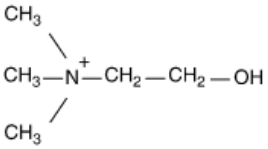
$HOCH_2CH(CO_2H)NH_2 \rightarrow HOCH_2CH_2NH_2 + CO_2$

Ethanolamine is the second-most-abundant head group for Phospholipids substances found in biological membranes (particularly those of prokaryotes);

e.g., phosphatidilethanol. It is also used in messenger molecules such as palmitoylethanolamide, which has an effect on CB1 receptors

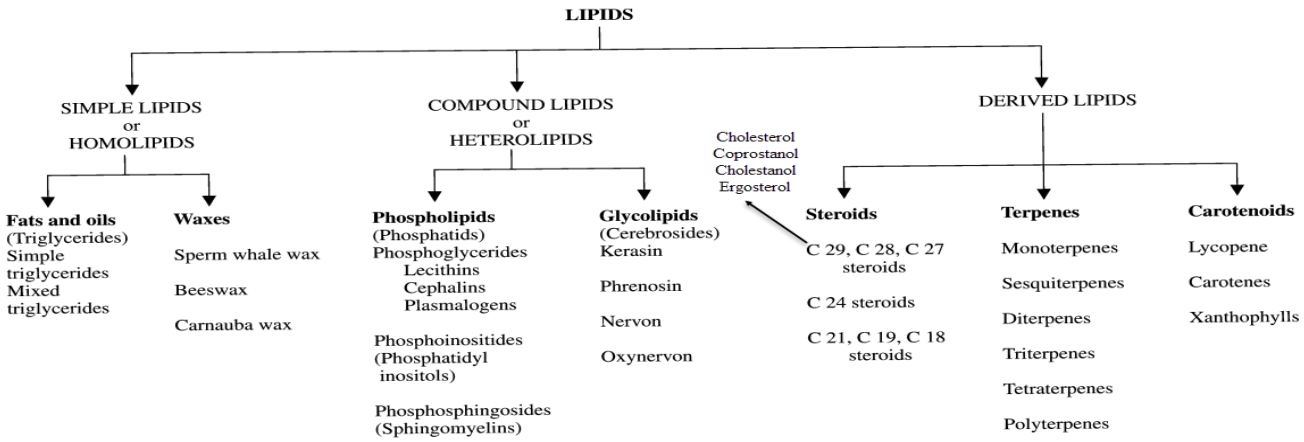
Ethanolamine is commonly called monoethanolamine or MEA in order to be distinguished from diethanolamine (DEA) and triethanolamine (TEA).

Structure of choline



Unit 12.Lipids.

Lipid, any of a diverse group of organic compounds including fats, oils, hormones, and certain components of membranes that are grouped together because they do not interact appreciably with water. One type of lipid, the triglycerides, is sequestered as fat in adipose cells, which serve as the energy-storage depot for organisms and also provide thermal insulation. Some lipids such as steroid hormones serve as chemical messengers between cells, tissues, and organs, and others communicate signals between biochemical systems within a single cell. The of cells and organelles (structures within cells) are microscopically thin structures formed from two layers of phospholipid molecules. Membranes function to separate individual cells from their environments and to compartmentalize the cell interior into structures that carry out special functions. So important is this compartmentalizing function that membranes, and the lipids that form them, must have been essential to the origin of life itself.



Fatty Acids

The common feature of these lipids is that they are all esters of moderate to long chain fatty acids. Acid or base-catalyzed hydrolysis yields the component fatty acid, some examples of which are given in the following table, together with the alcohol component of the lipid. These long-chain carboxylic acids are generally referred to by their common names, which in most cases reflect their sources. Natural fatty acids may be saturated or unsaturated, and as the following data indicate, the saturated acids have higher melting points than unsaturated acids of

corresponding size. The double bonds in the unsaturated compounds listed on the right are all cis (or Z).

FATTY ACIDS

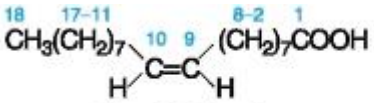
Saturated

Formula	Common Name	Melting Point
$CH_3(CH_2)_{10}CO_2H$	lauric acid	45 ºC
$CH_3(CH_2)_{12}CO_2H$	myristic acid	55 ºC
$CH_3(CH_2)_{14}CO_2H$	palmitic acid	63 ºC
$CH_3(CH_2)_{16}CO_2H$	stearic acid	69 ºC
$CH_3(CH_2)_{18}CO_2H$	arachidic acid	76 ºC

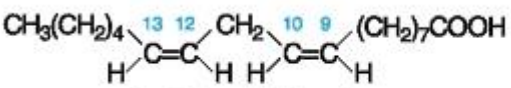
Unsaturated

Formula	Common Name	Melting Point
$CH_3(CH_2)_5CH=CH(CH_2)_7CO_2H$	palmitoleic acid	0 ºC
$CH_3(CH_2)_7CH=CH(CH_2)_7CO_2H$	oleic acid	13 ºC
$CH_3(CH_2)_4CH=CHCH_2CH=CH(CH_2)_7CO_2H$	linoleic acid	-5 ºC
$CH_3CH_2CH=CHCH_2CH=CHCH_2CH=CH(CH_2)_7CO_2H$	linolenic acid	-11 ºC
$CH_3(CH_2)_4(CH=CHCH_2)_4(CH_2)_2CO_2H$	arachidonic acid	-49 ºC

All double bonds in both the acids have the *cis* configuration:



oleic acid ($C_{18:1}$)

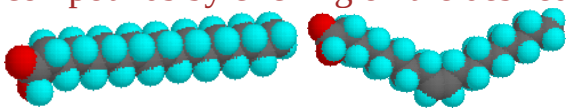


linoleic acid ($C_{18:2}$)

Saturated fatty acids and saturated portions of unsaturated acids exist in more stable staggered conformation because in this conformation the carbon atoms ar as remote from one another as possible. Thus, the preferred conformation of saturated acids is fully extended, whereas a carbon chain in unsaturated acids makes a bend at the position of the *cis* double bond

The higher melting points of the saturated fatty acids reflect the uniform rod-like shape of their molecules. The cis-double bond(s) in the unsaturated fatty acids

introduce a kink in their shape, which makes it more difficult to pack their molecules together in a stable repeating array or crystalline lattice. The trans-double bond isomer of oleic acid, known as elaidic acid, has a linear shape and a melting point of 45 ºC (32 ºC higher than its cis isomer). The shapes of stearic and oleic acids are displayed in the models below. You may examine models of these compounds by clicking on the desired model picture.



stearic acid oleic acid

Two polyunsaturated fatty acids, linoleic and linolenic, are designated "essential" because their absence in the human diet has been associated with health problems, such as scaley skin, stunted growth and increased dehydration. These acids are also precursors to the prostaglandins, a family of physiologically potent lipids present in minute amounts in most body tissues.

Because of their enhanced acidity, carboxylic acids react with bases to form ionic salts, as shown in the following equations. In the case of alkali metal hydroxides and simple amines (or ammonia) the resulting salts have pronounced ionic character and are usually soluble in water. Heavy metals such as silver, mercury and lead form salts having more covalent character (3rd example), and the water solubility is reduced, especially for acids composed of four or more carbon atoms.

$$RCO_2H + NaHCO_3 \longrightarrow RCO_2^{(-)}\,Na^{(+)} + CO_2 + H_2O$$

$$RCO_2H + (CH_3)_3N: \longrightarrow RCO_2^{(-)}\,(CH_3)_3NH^{(+)}$$

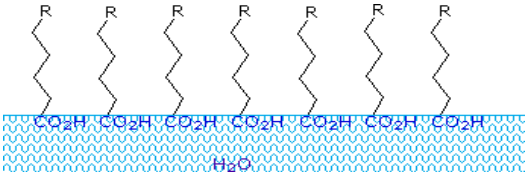
$$RCO_2H + AgOH \longrightarrow RCO_2^{\delta(-)}\,Ag^{\delta(+)} + H_2O$$

Unusual Fatty Acids

Nature has constructed a remarkable variety of fatty acid derivatives

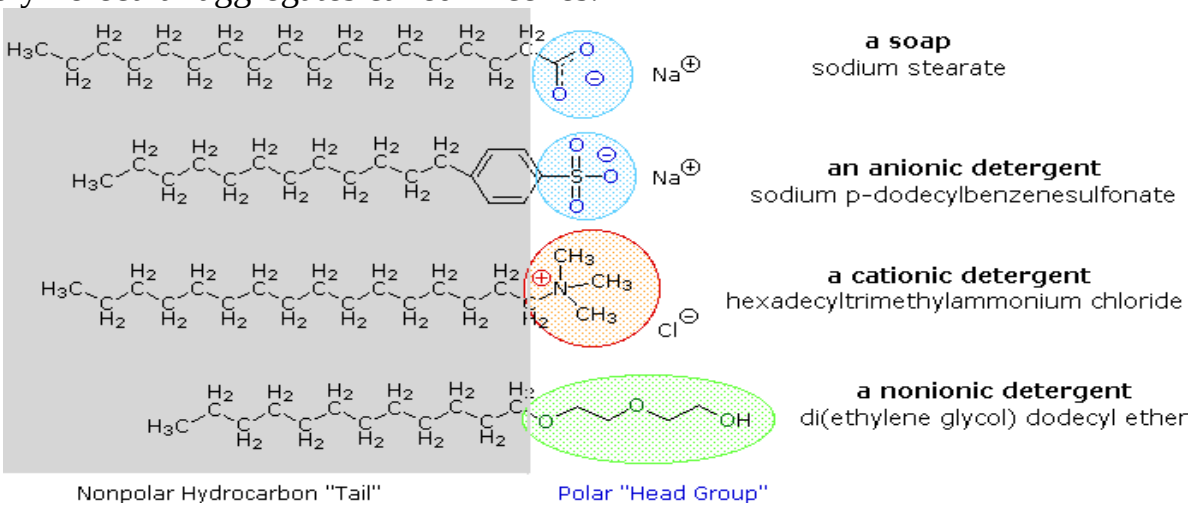
Soaps and Detergents

Carboxylic acids and salts having alkyl chains longer than eight carbons exhibit unusual behavior in water due to the presence of both hydrophilic (CO_2) and hydrophobic (alkyl) regions in the same molecule. Such molecules are termed amphiphilic (Gk. amphi = both) or amphipathic. Fatty acids made up of ten or more carbon atoms are nearly insoluble in water, and because of their lower density, float on the surface when mixed with water. Unlike paraffin or other alkanes, which tend to puddle on the waters surface, these fatty acids spread evenly over an extended water surface, eventually forming a monomolecular layer in which the polar carboxyl groups are hydrogen bonded at the water interface, and the hydrocarbon chains are aligned together away from the water. This behavior is illustrated in the diagram on the right. Substances that accumulate at water surfaces and change the surface properties are called surfactants.



Alkali metal salts of fatty acids are more soluble in water than the acids themselves, and the amphiphilic character of these substances also make them strong surfactants. The most common examples of such compounds are soaps and detergents, four of which are shown below. Note that each of these molecules has a nonpolar hydrocarbon chain, the "tail", and a polar (often ionic) "head group". The use of such compounds as cleaning agents is facilitated by their surfactant character, which lowers the surface tension of water, allowing it to penetrate and wet a variety of materials.

Very small amounts of these surfactants dissolve in water to give a random dispersion of solute molecules. However, when the concentration is increased an interesting change occurs. The surfactant molecules reversibly assemble into polymolecular aggregates called micelles.

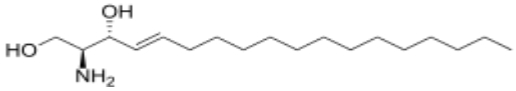


The composition of lipids include:

higher monatomic alcohols (Glycerin is a trivalent alcohol), polyatomic alcohols and amino alcohols

Sphingolipids

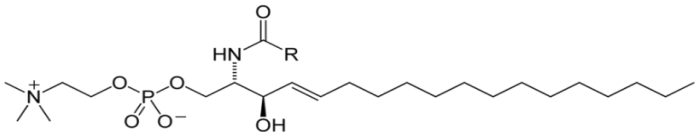
Sphingosine (2-amino-4-trans-octadecene-1,3-diol) is an 18-carbon amino alcohol with an unsaturated hydrocarbon chain, which forms a primary part of sphingolipids, a class of cell membrane that include sphingomyelin, an important phospholipid.



Examples of common sphingolipids include sphingosine and sphingosine 1-phosphate. They are crucial in regulating many cellular processes—such as migration, proliferation, differentiation, and immune responses. These sphingolipids are central for cellular signaling, more knowingly familiar as a bioactive lipid mediator.

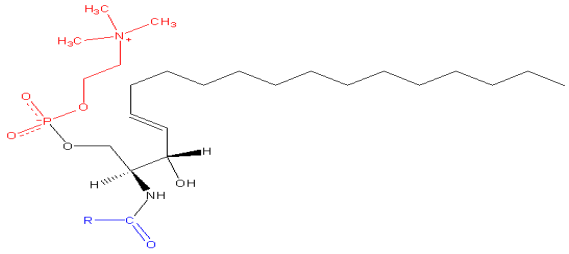
Recent evidences have proven that the signaling function of these sphingolipids indicate association of apoptosis and growth arrest. Sphingosine is capable of directly inhibiting protein kinase C, along with other effects on various protein kinases in vitro.

Sphingomyelin



Sphingomyelin(SPH, ˌsfɪŋgoˈmaɪəlɪn) is a type of sphingolipid found in animal cell membranes, especially in the membranous myelin sheath that surrounds some nerve cell axons. It usually consists of phosphocholine and ceramide, or a phosphoethanolamine head group; therefore, sphingomyelins can also be classified as sphingophospholipids.[1] In humans, SPH represents ~85% of all sphingolipids, and typically make up 10–20 mol % of plasma membrane lipids.

Sphingosine phosphatides occurring in the myelin sheaths of nerves. Found in nervous tissue, brain, and red blood cells. Sphingosine- source of phosphoric acid in body tissue. It is one of the few membrane phospholipids not synthesized from glycerol



Sphingomyelin
Black: Sphingosine
Red: Phosphocholine
Blue: Fatty acid

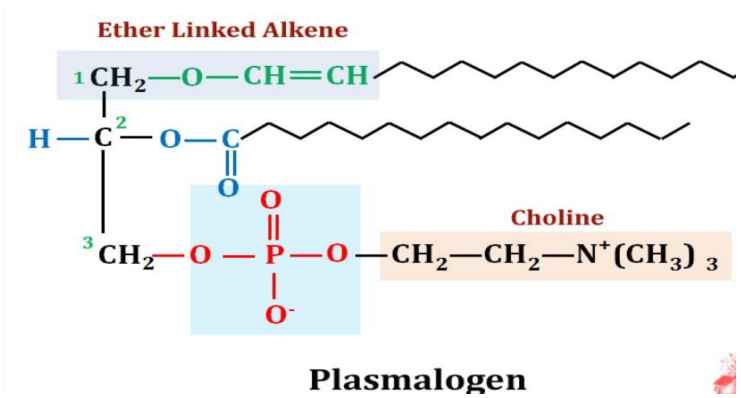
Location

Sphingomyelin is synthesized at the endoplasmic reticulum (ER), where it can be found in low amounts, and at the *trans* Golgi. It is enriched at the plasma membrane with a greater concentration on the outer than the inner leaflet.[6] The Golgi complex represents an intermediate between the ER and plasma membrane, with slightly higher concentrations towards the trans side

Plasmalogens

There are two types of ether phospholipids, plasmanyl- and plasmenyl-phospholipids. Plasmanyl-phospholipids have an ether bond in position sn-1 to an alkyl group. Plasmenyl-phospholipids have an ether bond in position sn-1 to an alkenyl group. The latter are called plasmalogens

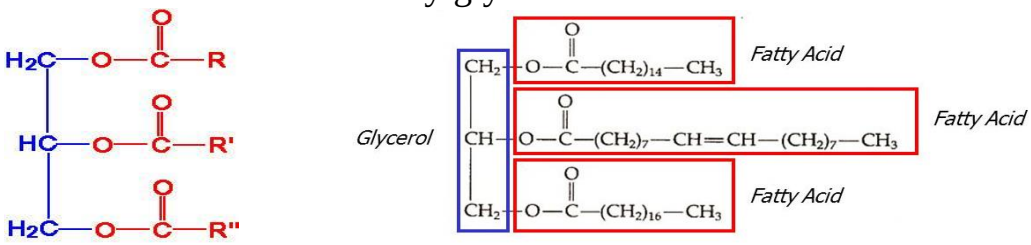
lasmalogens are found in numerous human tissues, with particular enrichment in the nervous, immune, and cardiovascular system. In human heart tissue, nearly 30-40% of choline glycerophospholipids are plasmalogens. Even more striking is the fact that 32% of the glycerophospholipids in the adult human heart and 20% in brain and up to 70% of myelin sheath ethanolamine glycerophospholipids are plasmalogens



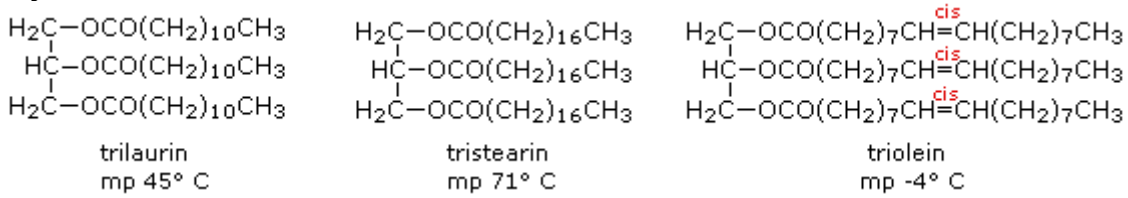
Fats and Oils

Triacylglycerols (Triglycerides)

When all three hydroxyl groups of glycerol are esterified with fatty acids, the structure is called a triacylglycerol:



The triesters of fatty acids with glycerol (1,2,3-trihydroxypropane) compose the class of lipids known as fats and oils. These triglycerides (or triacylglycerols) are found in both plants and animals, and compose one of the major food groups of our diet. Triglycerides that are solid or semisolid at room temperature are classified as fats, and occur predominantly in animals. Those triglycerides that are liquid are called oils and originate chiefly in plants, although triglycerides from fish are also largely oils



Triglycerides having three identical acyl chains, such as tristearin and triolein (above), are called "simple", while those composed of different acyl chains are called "mixed". If the acyl chains at the end hydroxyl groups (1 & 3) of glycerol are different, the center carbon becomes a chiral center and enantiomeric configurations must be recognized.

Waxes

Waxes are esters of fatty acids with long chain monohydric alcohols (one hydroxyl group). Natural waxes are often mixtures of such esters, and may also contain hydrocarbons. The formulas for three well known waxes are given below, with the carboxylic acid moiety colored red and the alcohol colored blue.

spermaceti	beeswax	carnuba wax
$CH_3(CH_2)_{14}CO_2$-$(CH_2)_{15}CH_3$	$CH_3(CH_2)_{24}CO_2$-$(CH_2)_{29}CH_3$	$CH_3(CH_2)_{30}CO_2$-$(CH_2)_{33}CH_3$

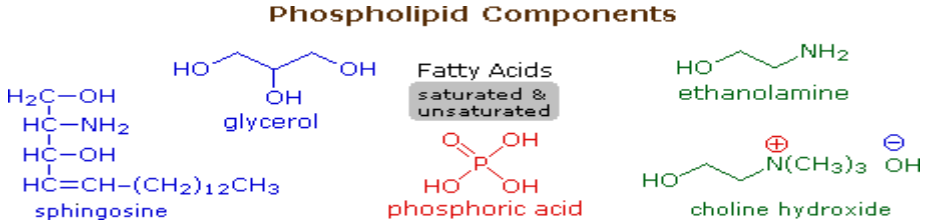
Waxes are widely distributed in nature. The leaves and fruits of many plants have waxy coatings, which may protect them from dehydration and small predators. The feathers of birds and the fur of some animals have similar coatings which serve as a water repellent. Carnuba wax is valued for its toughness and water resistance.

Ceramides are a family of waxy lipid molecules. A ceramide is composed of sphingosine and a fatty acid. Ceramides are found in high concentrations within the cell membrane of eukaryotic cells, since they are component lipids that make up sphingomyelin, one of the major lipids in the lipid bilayer. Contrary to previous assumptions that ceramides and other sphingolipids found in cell membrane were purely supporting structural elements, ceramide can participate in a variety of cellular signaling: examples include regulating differentiation, proliferation, and programmed cell death (PCD) of cells.

The word *ceramide* comes from the Latin *cera* (wax) and *amide*. Ceramide is a component of vernix caseosa, the waxy or cheese-like white substance found coating the skin of newborn human infants.

Phospholipids

Phospholipids are the main constituents of cell membranes. They resemble the triglycerides in being ester or amide derivatives of glycerol or sphingosine with fatty acids and phosphoric acid. The phosphate moiety of the resulting phosphatidic acid is further esterified with ethanolamine, choline or serine in the phospholipid itself. The following diagram shows the structures of some of these components. Clicking on the diagram will change it to display structures for two representative phospholipids. Note that the fatty acid components (R & R') may be saturated or unsaturated.

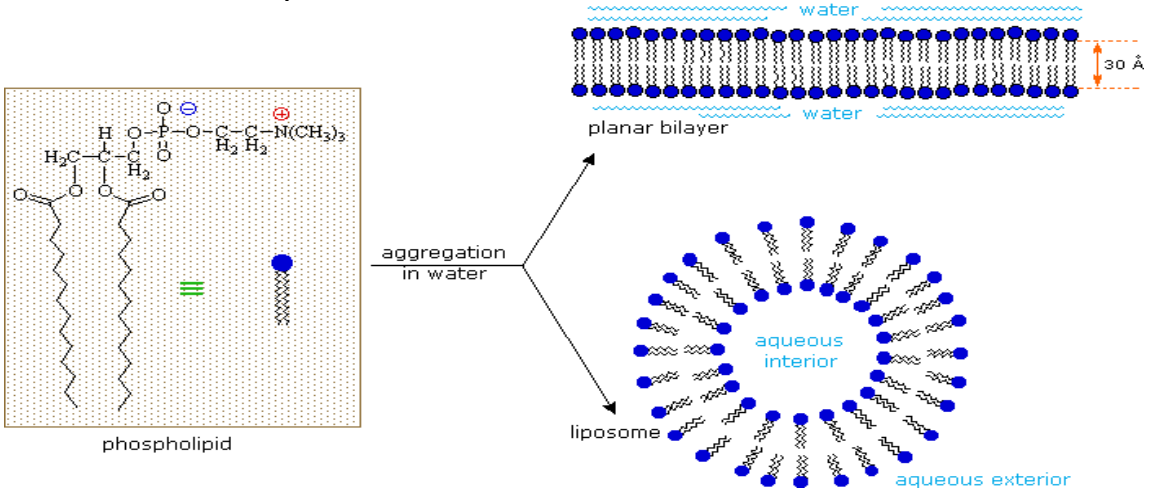


As ionic amphiphiles, phospholipids aggregate or self-assemble when mixed with water, but in a different manner than the soaps and detergents. Because of the two pendant alkyl chains present in phospholipids and the unusual mixed charges in their head groups, micelle formation is unfavorable relative to a bilayer structure.

The phospholipid molecules can move about in their half the bilayer, but there is a significant energy barrier preventing migration to the other side of the bilayer.

This bilayer membrane structure is also found in aggregate structures called liposomes. Liposomes are microscopic vesicles consisting of an aqueous core enclosed in one or more phospholipid layers. They are formed when phospholipids are vigorously mixed with water. Unlike micelles, liposomes have

both aqueous interiors and exteriors.



A cell may be considered a very complex liposome. The bilayer membrane that separates the interior of a cell from the surrounding fluids is largely composed of phospholipids, but it incorporates many other components, such as cholesterol, that contribute to its structural integrity.

The sphingomyelins are also membrane lipids. They are the major component of the myelin sheath surrounding nerve fibers. Multiple Sclerosis is a devastating disease in which the myelin sheath is lost, causing eventual paralysis.

Questions:

1. What are compound lipids?
2. What is the difference between lipids and derived lipids?
3. What is the difference between simple lipids and compound lipids?
4. What are the functions of compound lipids?

Unit 13. Carbohydrates.

Carbohydrates are probably the most abundant and widespread organic substances in nature, and they are essential constituents of all living things.

Carbohydrate, class of naturally occurring compounds and derivatives formed from them. In the early part of the 19th century, substances such as wood, starch, and linen were found to be composed mainly of molecules containing atoms of carbon (C), hydrogen (H), and oxygen(O) and to have the general formula $C_6H_{12}O_6$; other organic molecules with similar formulas were found to have a similar ratio of hydrogen to oxygen. The general formula $C_x(H_2O)_y$ is commonly used to represent many carbohydrates, which means "watered carbon."

Monosaccharides (Glucose, Fructose, Galactose

Disaccharide – Two monosaccharides connected by a glycosidic bond.

Oligosaccharide – 3-20 monosaccharides connected by glycosidic bonds, typically used to move monosaccharides and store them for short times.

Polysaccharide – Many (20+) monosaccharides, usually connected in long chains, used for storage or structural support (Both cellulose and starch are polysaccharides).

Monosaccharides (e.g. glucose) and disaccharides (e.g. sucrose) are relatively small molecules. They are often called sugars. Other carbohydrate molecules are very large (polysaccharides such as starch and cellulose).

Complexity	monosaccharides	Complex Carbohydrates disaccharides, oligosaccharides & polysaccharides			
Size	Tetrose C_4 sugars	Pentose C_5 sugars	Hexose C_6 sugars	Heptose C_7 sugars	etc.
C=O Function	Aldose sugars having an aldehyde function or an acetal equivalent. Ketose sugars having a ketone function or an acetal equivalent.				
Reactivity	Reducing sugars oxidized by Tollens' reagent (or Benedict's or Fehling's reagents). Non-reducing sugars not oxidized by Tollens' or other reagents.				

Monosaccharides

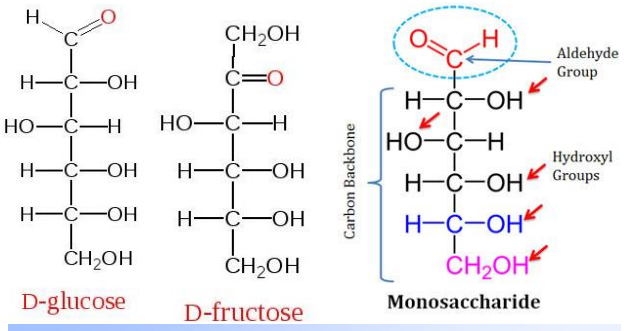
Monosaccharides are the simplest carbohydrates and are often called single sugars. Monosaccharides have the general molecular formula $(CH_2O)_n$, where n can be 3, 5 or 6. They can be classified according to the number of carbon atoms in a molecule:

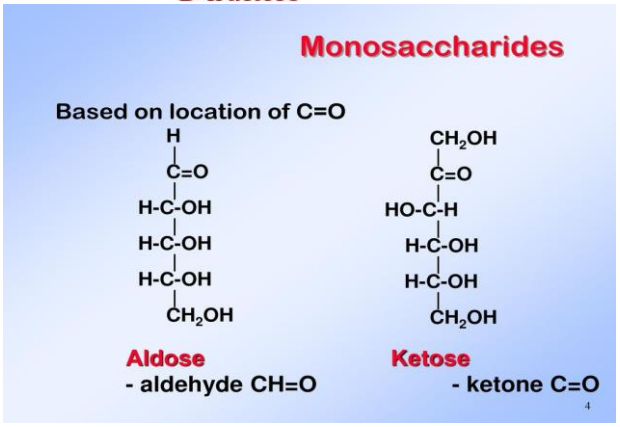
$n = 3$	trioses, e.g. glyceraldehyde
$n = 5$	pentoses, e.g. ribose and deoxyribose ('pent' indicates 5)
$n = 6$	hexoses, e.g. fructose, glucose and galactose ('hex' indicates 6)

There is more than one molecule with the molecular formula $C_5H_{10}O_5$ and more than one with the molecular formula $C_6H_{12}O_6$. Molecules that have the same molecular formula but different structural formulae are called structural isomers.

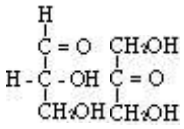
Glyceraldehyde's molecular formula is $C_3H_6O_3$. Its structural formula shows it contains an aldehyde group (-CHO) and two hydroxyl groups (-OH). The presence of an aldehyde group means that glyceraldehyde can also be classified as an aldose

Pentoses and hexoses can exist in two forms: cyclic and non-cyclic. In the non-cyclic form their structural formulae show they contain either an aldehyde group or a ketone group. Further, if the monosaccharide has an aldehyde group, it is called as aldose. A monosaccharide with a keto group is called a ketose.





Monosaccharides are often classified by both their number of carbon atoms and their functional group. A six-carbon monosaccharide with an aldehyde functional group is an aldohexose; a five-carbon monosaccharide with a ketone functional group is a ketopentose. The simplest aldose and ketose are the trioses glyceraldehyde and dihydroxyacetone.



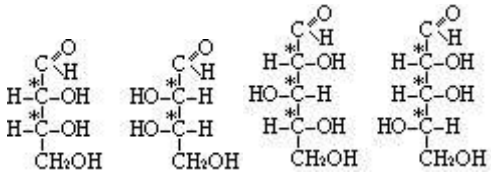
glyceraldehydes dihydroxycaetone

Stereoisomers are isomers whose atoms are connected in the same way but differ in their arrangement in space. The two nonsuperimposable mirror-image forms of a chiral molecule are stereoisomers.

There are two major causes of stereoisomerism: (1) the presence of a chiral center in a molecule, and (2) the presence of "structural rigidity" in a molecule. Structural rigidity is caused by restricted rotation about chemical bonds. It is the basis for cis - trans stereoisomerism, a phenomenon found in some substituted cycloalkanes and some alkenes.

Stereoisomers can be subdivided into two types: enantiomers and diastereomers. Enantiomers are stereoisomers whose molecules are nonsuperimposable mirror images of each other. Left- and right-handed forms of a molecule with a single chiral center are enantiomers.

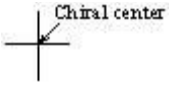
Diastereomers are stereoisomers whose molecules are not mirror images of each other. Cis - trans isomers (of both the alkene and the cycloalkane types) are diastereomers. We will see additional examples of carbohydrate diastereomers in the next section. Stereoisomers that are not enantiomers are diastereomers; they must be one or the other.



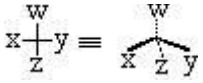
Enantiomers Diastereomers

Fischer Projections. Drawing three-dimensional representations of chiral molecules, can be both time-consuming and awkward. Fischer projections represent a method for giving molecular chirality specifications in two dimensions. A Fischer projection is a two-dimensional notation showing the spatial arrangement of groups about chiral centers in molecules.

In a Fischer projection, a chiral center is represented as the intersection of vertical and horizontal lines. The atom at the chiral center, which is almost always carbon, is not explicitly shown.



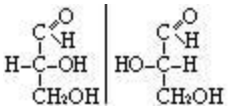
The tetrahedral arrangement of the four groups attached to the atom at the chiral center is governed by the following conventions: (1) Vertical lines from the chiral center represent bonds to groups directed into the printed page. (2) Horizontal lines from the chiral center represent bonds to groups directed out of the printed page.



Fischer projection

Our immediate concern is Fischer projections for monosaccharides. Such projections have the monosaccharide carbon chain positioned vertically with the carbonyl group (aldehyde or ketone) at or near the top.

The smallest monosaccharide that has a chiral center is the compound glyceraldehydes (2,3-dihydroxypropanal). The structural formula and Fischer projections for the two enantiomers of glyceraldehyde are:

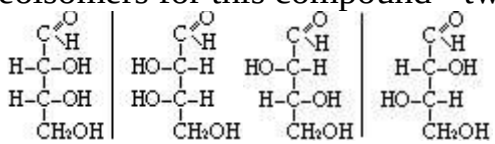


D-glyceraldehyde L-glyceraldehyde

The handedness (right and left) of these two enantiomers is specified by using the designations D and L. The enantiomer with the chiral center - OH group on the right in the Fischer projection is by definition the right-handed isomer (в-glyceraldehyde), and the enantiomer with the chiral center - OH group on the left in the Fischer projection is by definition the left-handed isomer (L-glyceraldehyde).

We now consider Fischer projections for the compound 2,3,4-trihydroxybutanal, a monosaccharide with four carbons and two chiral centers.

There are four stereoisomers for this compound - two pairs of enantiomers.



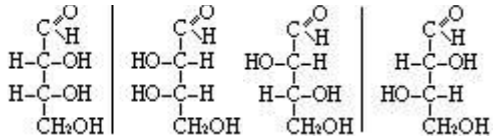
A B C D

First enantiomeric pair Second enantiomeric pair

In the first enantiomeric pair, both chiral center - OH groups are on the same side of the Fischer projection, and in the second enantiomeric pair, the chiral center – OH groups are on opposite sides of the Fischer projection. These are the only – OH group arrangements possible.

The D, L system used to designate the handedness of glyceraldehyde enantiomers is extended to monosaccharides with more than one chiral center in the following manner.

The carbon chain is numbered, starting at the carbonyl group end of the molecule, and the highest-numbered chiral center is used to determine D or L configuration.



A B C D

D- isomer L-isomer D-isomer L- isomer

The D, L nomenclature gives the configuration (handedness) only at the highest-numbered chiral center. The configuration at other chiral centers in a molecule is accounted for by assigning a different common name to each pair of D, L enantiomers. In our present example, compounds A and B (the first enantiomeric pair) are D-erythrose and L-erythrose; compounds C and D (the second enantiomeric pair) are D-threose and L-threose.

A and C are diastereomers, stereoisomers that are not mirror images of each other. Other diastereomeric pairs in our example are A and D, B and C, and B and D. These four pairs are epimers. Epimers diastereomers that differ only in the configuration at one chiral center.

In general, a compound that has n chiral centers may exist in a maximum of 2^n stereoisomeric forms. For example, when three chiral centers are present, at most eight stereoisomers ($2^3 = 8$) are possible (four pairs of enantiomers).

Stereoisomers. 1. Isomers in which the atoms have the same connectivity but differ in spatial arrangement.

2. Stereoisomerism results either from the presence of a chrial center or from structural rigidity caused by restricted rotation about chemical bonds.

Enantiomers. 1. Stereoisomers that are nonsuperimposable mirror images of each other.

2. Handedness (D and L configuration) is determined by the configuration at the highest-numbered chiral center.

3. Enantiomers rotate plane-polarized light in different directions. (+) Enantiomers are dextrorotatory (clockwise), and (-) enantiomers are levorotatory (counterclockwise).

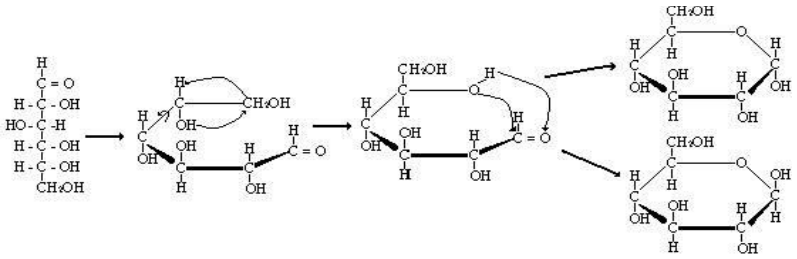
Diastereomers. 1. Stereoisomers that are not mirror images of each other.

2. Epimersdiastereomers whose configurations differ only at one chiral center.

Cyclic forms of monosaccharides. So far in this chapter, the structures of monosaccharides have been depicted as open-chain polyhydroxy aldehydes or ketones. However, experimental evidence indicates that

for monosaccharides containing five or more carbon atoms, such open-chain structures are actually in equilibrium with two cyclic structures, and the cyclic structures are the dominant forms at equilibrium.

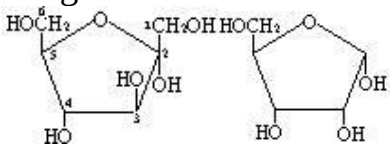
The cyclic forms of monosaccharides result from the ability of their carbonyl group to react intramolecularly with a hydroxyl group. The result is a cyclic hemiacetalor cyclic hemiketal. Such an intramolecular cyclization reaction for D-glucose is shown:



Structure 2 is a rearrangement of the projection formula for D-glucose in which the carbon atoms have locations similar to those found for carbon atoms in a six-membered ring. All hydroxyl groups drawn to the right in the original projection formula appear below the ring. Those to the left in the projection formula appear above the ring.

Structure 3 is obtained by rotating the groups attached to carbon-5 in a counterclockwise direction so that they are in the positions where it is easiest to visualize intramolecular hemiacetal formation. The intramolecular reaction occurs between the hydroxyl group on carbon-5 and the carbonyl group (carbon-1). The –OH group adds across the carbon - oxygen double bond, producing a heterocyclic ring that contains five carbon atoms and one oxygen atom.

Intramolecular cyclic hemiacetal formation and the equilibrium between forms associated with it not restricted to glucose. All aldoses with five or more carbon atoms establish similar equilibria, but with different percentages of the alpha, beta, and open-chain forms. Fructose and other ketoses with a sufficient number of carbon atoms also cyclize; here, cyclic hemiketal formation occurs.
Galactose, like glucose, forms a six-membered ring, but both D-fructose and D-ribose form a five-membered ring.

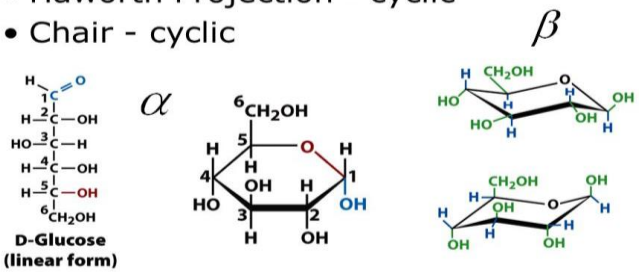


D-fructose D-ribose

D-Fructose cyclization involves carbon-2 (the keto group) and carbon-5, which results in two CH_2OH groups being outside the ring (carbons 1 and 6). D-Ribose cyclization involves carbon-1 (the aldehyde group) and carbon-4.

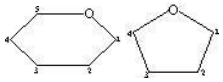
Haworth Projection Formulas.

- Fischer Projection - linear
- Haworth Projection - cyclic
- Chair - cyclic

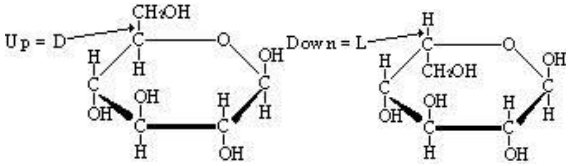


The structural representations of the cyclic forms of monosaccharides found in the previous section are examples of Haworthprojection formulas. A Haworth projection is a of a carbohydrate.

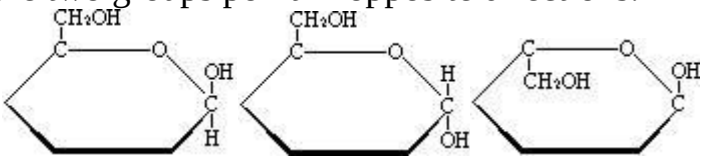
In a Haworth projection, the hemiacetal ring system is viewed "edge on" with the oxygen ring atom at the upper right (six-membered ring) or at the top (five-membered ring).



The D or L form of a monosaccharide is determined by the position of the terminal CH_2OH group on the highest-numbered ring carbon atom. In the в form, this group is positioned above the ring. In the ь form, which is not usually encountered in biological systems, the terminal CH_2OH group is positioned below the ring.

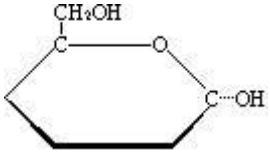


□ or □ configuration is determined by the position of the -OH group on carbon-1 relative to the CHOH group that determines D or L series. In a □ configuration, both of these groups point in the same direction; in an configuration, the two groups point in opposite directions.

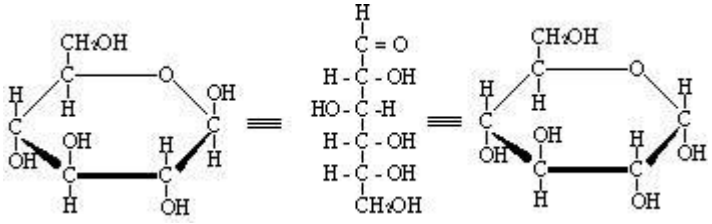


□-D-Monosaccharide □-D-Monosaccharide □-L-Monosaccharide

Where □ or □ configuration does not matter, the -OH group on carbon-1 is placed in a horizontal position, and a wavy line is used as the bond that connects it to the ring.



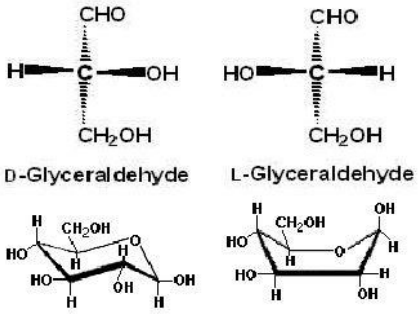
The specific identity of a monosaccharide is determined by the positioning of the other: – OH groups in the Haworth projection. Any - OH group at a chiral center that is to the right in a Fischer projection formula points down in the Haworth projection. Any group to the left in a Fischer projection points up in the Haworth projection. The following is a matchup between Haworth projection and Fischer projection.



□-form □-form

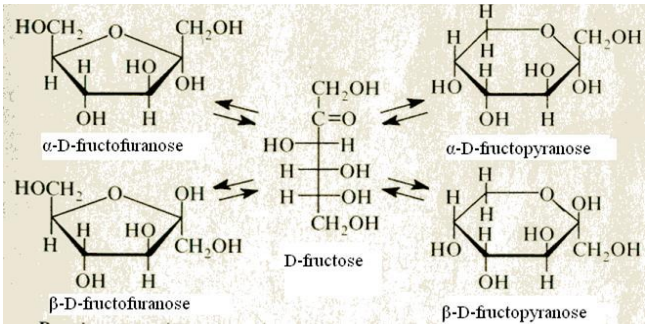
Conformation of Pyranose and Furanose Rings

The six-membered pyranose ring is not planar, because of the tetrahedral geometry of itssaturated carbon atoms. Instead, pyranose rings adopt two classes of conformations, termedchair and boat because of the resemblance to these objects. In the chair form, the substituentson the ring carbon atoms have two orientations: axial and equatorial. Axial bonds are nearly perpendicular to the average plane of the ring, whereas equatorial bonds are nearly parallel tothis plane. Axial substituents sterically hinder each other if they emerge on the same side of the ring (e.g., 1,3-diaxial groups). In contrast, equatorial substituents are less crowded. Thechair form of D-glucopyranose predominates because all axial positions are occupied byhydrogen atoms. The bulkier -OH and -CH2OH groups emerge at the less-hindered periphery. The boat form of glucose is disfavored because it is quite sterically hindered. Thechair form is more stable because of less steric hindrance as hydrogen atoms occupy the axial positions.

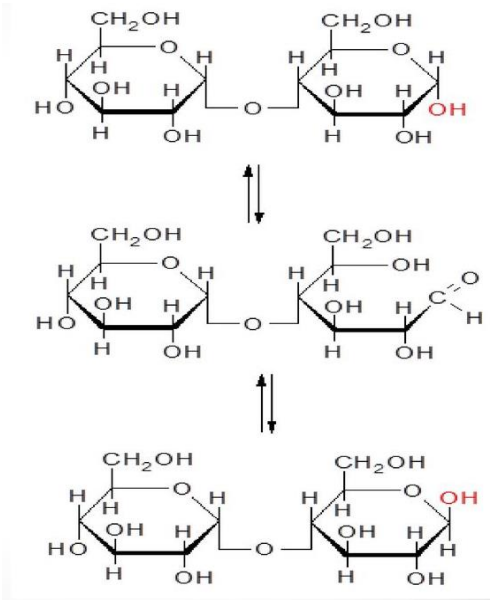


β- D-Glucose (chair form) β-D-Glucose (boat form)

In crystal state monosaccharides have cyclic structure. In water solution monosaccharides have five tautomeric forms – open form, α- and β-pyranose, α- and β-furanose.



This kind of tautomery called cyclo-oxo-tautomery

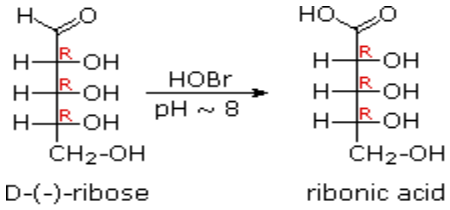


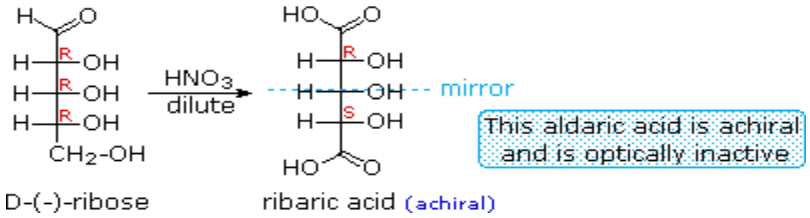
Important Reactions

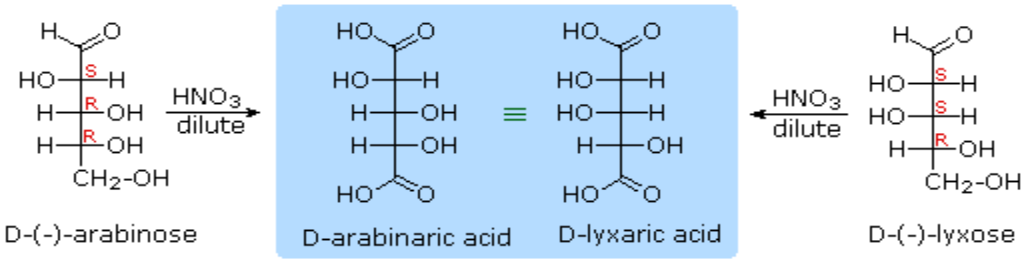
Oxidation

As noted above, sugars may be classified as reducing or non-reducing based on their reactivity **with Tollens', Benedict's or Fehling's reagents**. If a sugar is oxidized by these reagents it is called reducing, since the oxidant ($Ag^{(+)}$ or $Cu^{(+2)}$) is reduced in the reaction, as evidenced by formation of a silver mirror or precipitation of cuprous oxide. The Tollens' test is commonly used to detect aldehyde functions; and because of the facile interconversion of ketoses and aldoses under the basic conditions of this test, ketoses such as fructose also react and are classified as reducing sugars.

When the aldehyde function of an aldose is oxidized to a carboxylic acid the product is called an aldonic acid. Because of the 2º hydroxyl functions that are also present in these compounds, a mild oxidizing agent such as hypobromite must be used for this conversion (equation 1). If both ends of an aldose chain are oxidized to carboxylic acids the product is called an aldaric acid. By converting an aldose to its corresponding aldaric acid derivative, the ends of the chain become identical (this could also be accomplished by reducing the aldehyde to CHOH, as noted below). Such an operation will disclose any latent symmetry in the remaining molecule. Thus, ribose, xylose, allose and galactose yield achiral aldaric acids which are, of course, not optically active. The ribose oxidation is shown in equation 2 below.



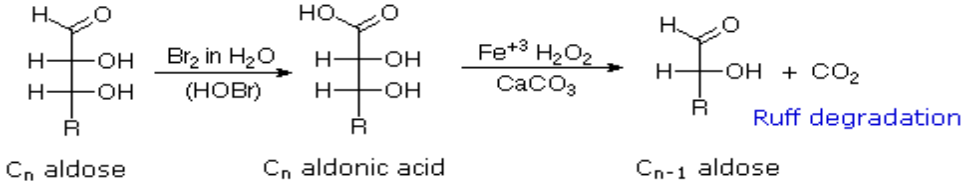


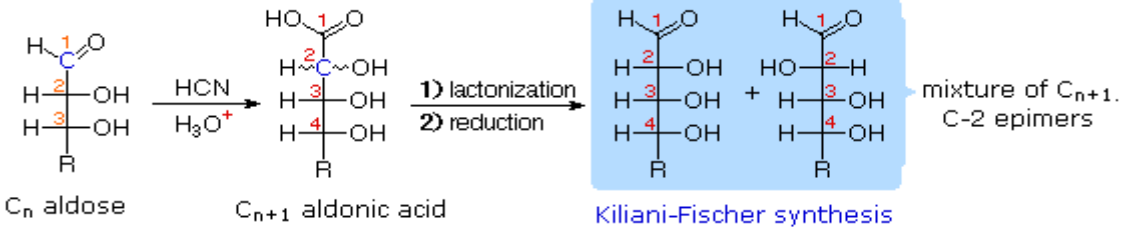


Other aldose sugars may give identical chiral aldaric acid products, implying a unique configurational relationship

Remember, a Fischer projection formula may be rotated by 180º in the plane of projection without changing its configuration.

Chain Shortening and Lengthening

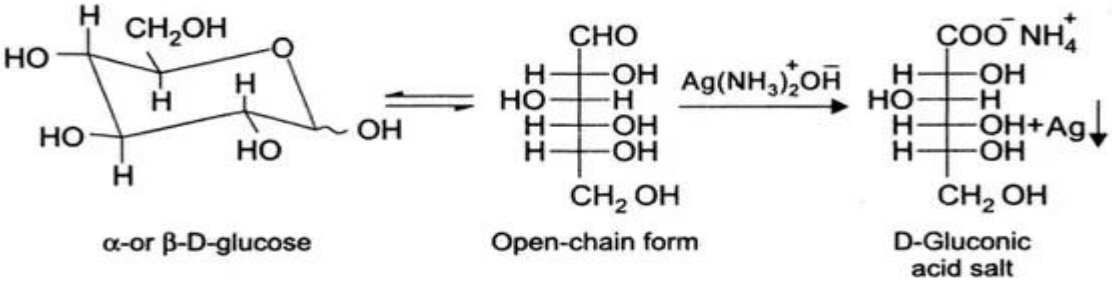




These two procedures permit an aldose of a given size to be related to homologous smaller and larger aldoses

An alternative chain shortening procedure known as the Wohl degradation is essentially the reverse of the Kiliani-Fischer synthesis.

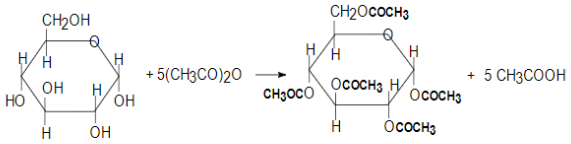
Tollen's test



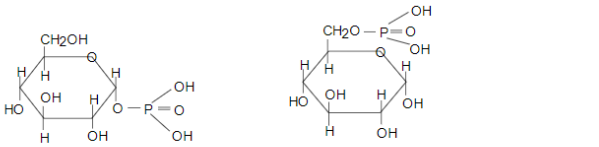
Chemical reactions of –OH groups

Esterification

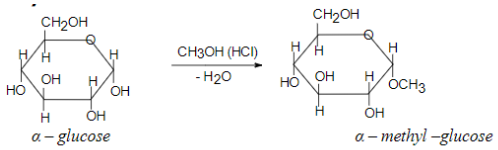
with organic acid



with inorganic acid $-H_3PO_4$



Acylation



Reduction

Sodium borohydride reduction of an aldose makes the ends of the resulting **alditol** chain identical, $HOCH_2(CHOH)_nOH$, thereby accomplishing the same configurational change produced by oxidation to an aldaric acid. Thus, allitol and galactitol from reduction of allose and galactose are achiral, and altrose and talose are reduced to the same chiral alditol. A summary of these redox reactions, and derivative nomenclature is given in the following table.

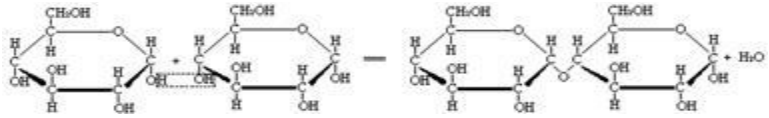
Derivatives of $HOCH_2(CHOH)_nCHO$

HOBr Oxidation	——>	$HOCH_2(CHOH)_nCO_2H$ an Aldonic Acid
Oxidation	——>	$H_2OC(CHOH)_nCO_2H$ an Aldaric Acid
Reduction	——>	$HOCH_2(CHOH)_nCH_2OH$ an Alditol

Benedict's Test

Benedict's Test is used to test for simple carbohydrates. The **Benedict's test** identifies reducing sugars (monosaccharide's and some disaccharides), which have free ketone or aldehyde functional groups Some sugars such as glucose are called reducing sugars because they are capable of transferring hydrogens (electrons) to other compounds, a process called reduction. When reducing sugars are mixed with Benedicts reagent and heated, a reduction reaction causes the Benedicts reagent to change color. The color varies from green to dark red (brick) or rusty-brown, depending on the amount of and type of sugar.

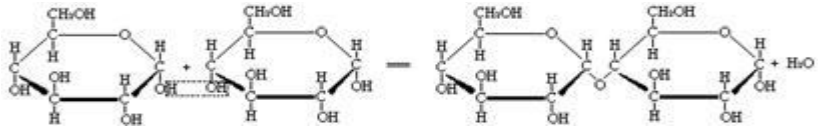
Disaccharides. A monosaccharide that has cyclic forms (hemiacetal or hemiketal) can react with an alcoho1 to form a glycoside (acetal or ketal). This same type of reaction can be used to produce a disaccharide, a carbohydrate in which two monosaccharides are bonded together. In disaccharide formation, one of the monosaccharide reactants functions as a hemiacetal or hemiketal, and the other functions as an alcohol.



Glycosidic linkage

Maltose, often called malt sugar, is produced whenever the polysaccharide starch breaks down, as happens in plants when seeds germinate and in human beings during starch digestion. It is a common ingredient in baby foods and is found in malted milk. Malt (germinated barley that has been baked and ground) contains maltose; hence the name malt sugar.

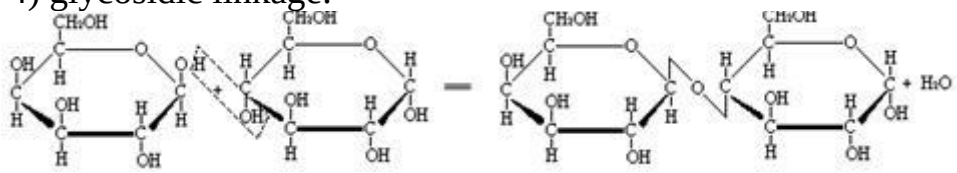
Structurally, maltose is made up of two D-glucose units, one of which must be □-D-glucose. The formation of maltose from two glucose molecules is as follows:



□-D-Glucose □-D-Glucose □-(1-4)-linkage

glycosidic linkage between the two glucose units is called an □(1-4) linkage. The two -OH groups that form the linkage are attached, respectively, to carbon-1 of the first glucose unit (in an a configuration) and to carbon-4 of the second.

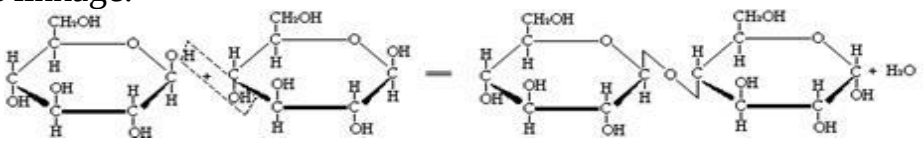
Lactose is made up of a □-D-galactose unit and a D-glucose unit joined by □-(1 - 4) glycosidic linkage.



□-D-galactose □-D-Glucose □(1-4)-linkage

hemiacetal center is unaffected when galactose bonds to glucose in the formation of lactose, so lactose is a reducing sugar (the glucose ring can open to give an aldehyde).

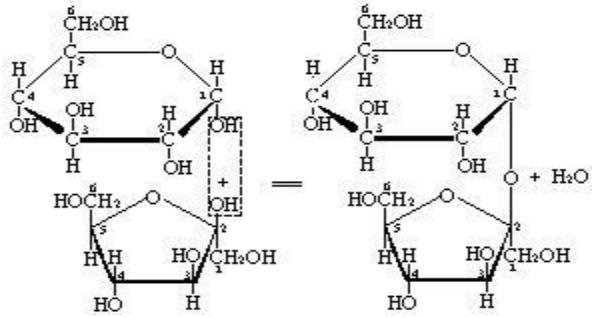
Cellobiose is produced as an intermediate in the hydrolysis of the polysaccharide cellulose. Like maltose, cellobiose contains two D-glucose monosaccharide units. It differs from maltose in that one of D-glucose units – the one functioning as a hemiacetal – must have a configuration instead of the a configuration for maltose. This change in configuration results in a (1 – 4) glycosidic linkage.



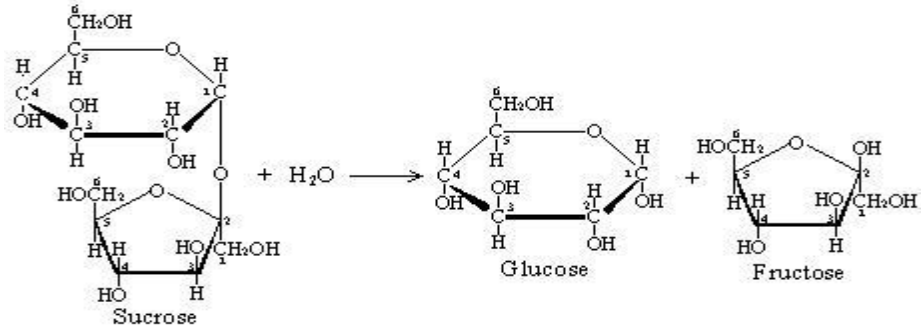
-D-Glucose (1 - 4)-linkage

Like maltose, cellobiose is a reducing sugar, has three isomeric forms in aqueous solution, and upon hydrolysis produces two D-glucose molecules.

Sucrose, common table sugar, is the most abundant of all disaccharides and occurs throughout the plant kingdom. It is produced commercially from the juice of sugar cane and sugar beets. Sugar cane contains up to 20 % by mass sucrose, and sugar beets contain up to 17% by mass sucrose. The two monosaccharide units present in -D-sucrose molecule are -D-glucose and -D-fructose. glycosidic linkage is not a (1-4) linkage, as was the case for maltose, cellobiose, and lactose. It is instead an ,(1-2) glycosidic linkage. The – OH group on carbon-2 of D-fructose (the hemiketal carbon) reacts with the – OH group on carbon-l of D-glucose (the hemiacetal carbon).



Sucrose, unlike maltose, cellobiose, and lactose, is a nonreducing sugar. No helmiacetal or hemiketal center is present in the molecule, because the glycosidic linkage involves the reducing ends of both monosaccharides. Sucrose, in the solid state and in solution, exists in only one form - there are no and isomers, and an open-chain form is not possible. Sucrase, the enzyme needed to break the ,(1 - 2) linkage in sucrose, is present in the human body. Hence sucrose is an easily digested substance. Sucrose hydrolysis (digestion) produces an equimolar mixture of glucose and fructose called invert sugar.



dextrorotatcry

This reaction is also as **inversion of sugar** because the dextrorotatory case sugar is converted into laevorotatory product due to hydrolysis. The mixture of glucose and fructose is called **invert sugar**.

Polysaccharide

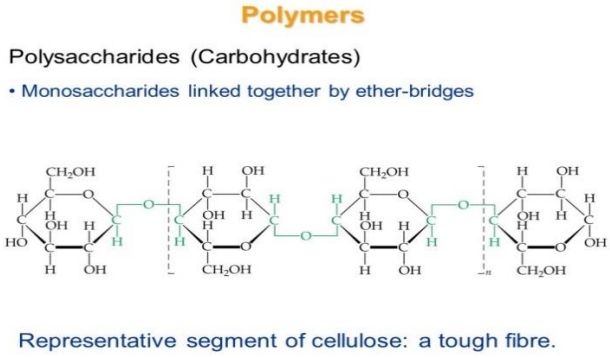
A **polysaccharide (glucans)** contains many monosaccharide units bonded to each other by glycosidic linkages. The number of monosaccharide units varies with the polysaccharide from a few hundred to hundreds of thousands. Polysaccharides are polymers. In some, the monosaccharides are bonded together in a linear (unbranched) chain. In others, there is extensive branching of the chains.

Although there are many naturally occurring polysaccharides, in this section we will focus on only four of them: cellulose, starch, glycogen, and chitin. All play vital roles in living systems - cellulose and starch in plants, glycogen in humans and other animals, and chitin in arthropods.

Polysaccharides may be divided into two classes: **homopolysaccharides**, which are composed of one type of monosaccharide units, and **heteropolysaccharides**, which contain two or more different types of monosaccharide units.

Starch, glycogen and cellulose are homoglycans as they are made of only glucose and are called glucans or glucosans. On the other hand, mucopolysaccharides like hyaluronic acid and chondroitin sulphates are heteroglycans as they are made up of different monosaccharide units.

Cellulose is the most abundant polysaccharide. It is the structural component of the cell walls of plants. Approximately half of all the carbon atoms in the plant kingdom are contained in cellulose molecules. Structurally, cellulose is a linear (unbranched) D-glucose polymer in which the glucose units are linked by □ (1-4) glycosidicbonds.



Representative segment of cellulose: a tough fibre.

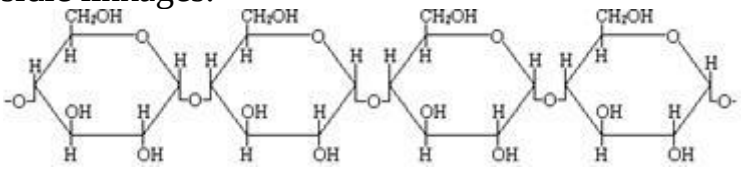
Even though it is a glucose polymer, cellulose is not a source of nutrition for human beings. Humans lack the enzymes capable of catalyzing the hydrolysis of □ (1- 4) linkages in cellulose. Even grazing animals lack the enzymes necessary for cellulose digestion. However, the intestinal tracts of animals such as horses, cows, and sheep contain bacteria that produce cellulose, an enzyme that can hydrolyze □ (1- 4) linkages and produce free glucose from cellulose. Thus grasses and other plant materials are a source of nutrition for grazing animals. The intestinal tracts of termites contain the same microorganisms, which enable termites to use wood as their source of food. Microorganisms in the soil can also metabolize cellulose, which makes possible the biodegradation of dead plants.

Starch, like cellulose, is a polysaccharide containing only glucose units. It is the storage polysaccharide in plants. If excess glucose enters a plant cell, it is converted to starch and stored for later use. When the cell cannot get enough glucose from outside the cell, it hydrolyzes starch to release glucose.

Iodine is often used to test for the presence of starch in solution. Starch-containing solutions turn a dark blue-black when iodine is added. As starch is broken down through acid or enzymatic hydrolysis to glucose monomers, the blue-black color disappears.

Two different polyglucose polysaccharides can be isolated from most starches: amylose and amylopectin. Amylose, a straight-chain glucose polymer, usually accounts for 15%-20% of the starch; arnylopectin, a highly branched glucose polymer, accounts for the remaining 80%-85% of the starch.

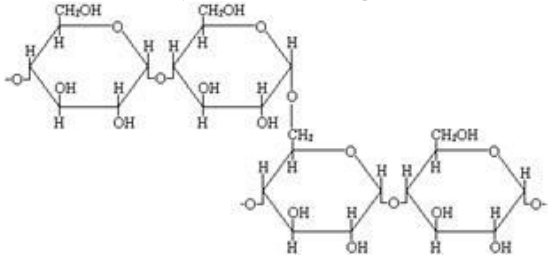
In amylose's structure, the glucose units are connected by (1-4) glycosidic linkages.



Starch (amylose)

The number of glucose units present in an amylose chain depends on the source of the starch; 300 – 500 monomer units are usually present.

Amylopectin, the other polysaccharide in starch, is similar to amylose in that all linkages are a linkages. It is different in that there is a high degree of branching in the polymer. A branch occurs about once every 25 - 30 glucose units. The branch points involve □(1 – 6) linkages:



Starch (amylopectin)

Note that all of the glycosidic linkages in starch (both amylose and amylopectin) are of the type. In amylose, they are all □(1 - 4); in amylopectin, both □(1 -4) and □(1 -6) linkages are present. Because a linkages can be broken through hydrolysis within the human digestive tract (with the help of the enzyme amylase), starch has nutritional value for humans. The starches present in potatoes and cereal grains (wheat, rice, corn, etc.) account for approximately two-thirds of the world' s food consumption.

Glycogen, like cellulose and starch, is a polysaccharide containing only glucose units. It is the glucose storage polysaccharide in humans and animals. Its function is thus similar to that of starch in plants, and it is sometimes referred to as animal starch. Liver cells and muscle cells are the storage sites for glycogen in humans.

Glycogen has a structure similar to that of amylopectin; all glycosidic linkages are of the type, and both (1 - 4) and (1 - 6) linkages are present. Glycogen and amylopectin differ in the number of glucose units between

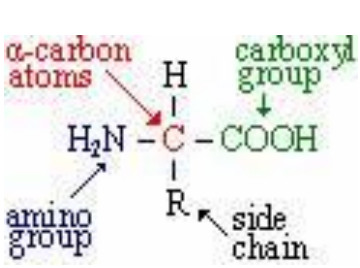
branches and the total number of glucose units present in a molecule. Glycogen is about three times more highly branched than amylopectin, and it is much larger, with a molar mass of up to 3,000,000 amu.

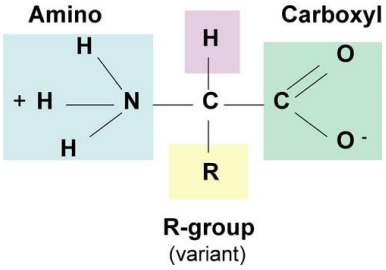
Questions:

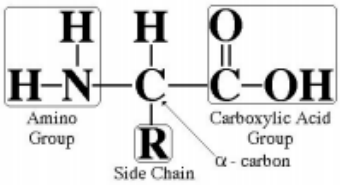
1. What are the best examples of carbohydrates?
2. What are four examples of carbohydrates?
3. What are some examples of complex carbohydrates and simple carbohydrates?

Unit 14. α-AMINO ACIDS, PEPTIDES AND PROTEINS.

An **amino acid** is an organic compound that contains both an amino ($–NH_3$) group and a carboxyl (-COOH) group. The amino acids found in proteins are always α-amino acids - that is, amino acids in which the amino group is attached to the α-carbon atom of the carboxylic acid carbon chain. The general structural formula foran α-amino acid is:

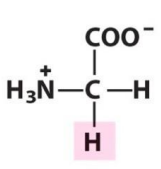
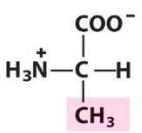
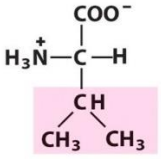
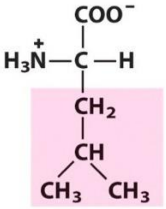
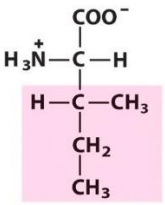


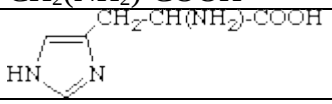
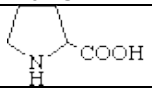
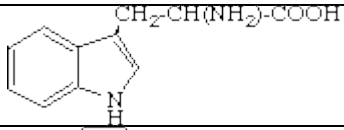
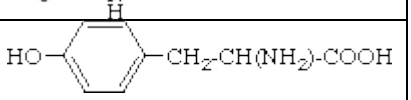




The R group present in an α-amino acid is called the amino acid side chain. The nature of this side chain distinguishes a-amino acids from each other. Side chains vary in size, shape, charge, acidity, functional groups present, hydrogen-bonding ability, and chemical reactivity.

Over 700 different naturally occurring amino acids are known, but only 20 of them, called standard amino acids, are normally present in proteins. A **standard amino acid** is one of the 20 α-amino acids normally found in proteins. The classification of amino acids is based on the chemical structure of their side chains

glycine 	alanine 	Valine 	leucine 	Isoleucine 

Trivial name[a]	**Symbols**[b]		**Systematic name**[c]	**Formula**
Alanine	Ala	A	2-Aminopropanoic acid	CH_3-CH(NH_2)-COOH
Arginine	Arg	R	2-Amino-5-guanidinopentanoic acid	H_2N-C(=NH)-NH-[CH_2]$_3$-CH(NH_2)-COOH
Asparagine	Asn[d]	N[d]	2-Amino-3-carbamoylpropanoic acid	H_2N-CO-CH_2-CH(NH_2)-COOH
Aspartic acid	Asp[d]	D[d]	2-Aminobutanedioic acid	HOOC-CH_2-CH(NH_2)-COOH
Cysteine	Cys	C	2-Amino-3-mercaptopropanoic acid	HS-CH_2-CH(NH_2)-COOH
Glutamine	Gln[d]	Q[d]	2-Amino-4-carbamoylbutanoic acid	H_2N-CO-[CH_2]$_2$-CH(NH_2)-COOH
Glutamic acid	Glu[d]	E[d]	2-Aminopentanedioic acid	HOOC-[CH_2]$_2$-CH(NH_2)-COOH
Glycine	Gly	G	Aminoethanoic acid	CH_2(NH_2)-COOH
Histidine	His	H	2-Amino-3-(1*H*-imidazol-4-yl)-propanoic acid	
Isoleucine	Ile	I	2-Amino-3-methylpentanoic acid[e]	C_2H_5-CH(CH_3)-CH(NH_2)-COOH
Leucine	Leu	L	2-Amino-4-methylpentanoic acid	(CH_3)$_2$CH-CH_2-CH(NH_2)-COOH
Lysine	Lys	K	2,6-Diaminohexanoic acid	H_2N-[CH_2]$_4$-CH(NH_2)-COOH
Methionine	Met	M	2-Amino-4-(methylthio)butanoic acid	CH_3-S-[CH_2]$_2$-CH(NH_2)-COOH
Phenylalanine	Phe	F	2-Amino-3-phenylpropanoic acid	C_6H_5-CH_2-CH(NH_2)-COOH
Proline	Pro	P	Pyrrolidine-2-carboxylic acid	
Serine	Ser	S	2-Amino-3-hydroxypropanoic acid	HO-CH_2-CH(NH_2)-COOH
Threonine	Thr	T	2-Amino-3-hydroxybutanoic acid[e]	CH_3-CH(OH)-CH(NH_2)-COOH
Tryptophan	Trp	W	2-Amino-3-(l*H*-indol-3-yl)-propanoic acid	
Tyrosine	Tyr	Y	2-Amino-3-(4-hydroxyphenyl)-propanoic acid	
Valine	Val	V	2-Amino-3-methylbutanoic acid	(CH_3)$_2$CH-CH(NH_2)-COOH

Nonpolar (hydrophobic) amino acids include all those with alkyl chain R groups (alanine, valine, leucine, and isoleucine), as well as proline, methionine, and two aromatic amino acids, phenylalanine and tryptophan. **Polar (hydrophilic**), uncharged amino acids include glycine, and those amino acids which contain R groups that can form hydrogen bonds with water. The amide groups of asparagine and glutamine, the hydroxyl groups of tyrosine, threonine, and serine, and the sulfhydryl group of cysteine are all good hydrogen bond-forming moieties. **Polar, acidic amino acids** include aspartic acid and glutamic acid. Their R groups contain a carboxyl group, which provides a net negative charge at pH 7. 6

Polar, basic amino acids — histidine, arginine, and lysine have side chains with net positive charges at neutral pH.

Acid - base properties of amino acids. In pure form, amino acids are white crystalline solids with relatively high decomposition points. (Most amino acids decompose before they melt.) Also most amino acids are not very soluble in water because of strong intermolecular forces within their crystal structures. Such properties are those often exhibited by compounds in which charged species are present. Studies of amino acids confirm that they are charged species both in the solid state and in solution.

Both an acidic group (-COOH) and a basic group ($-NH_2$) are present on the same carbon in an α-amino acid.

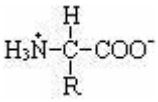
We learned that in neutral solution, carboxyl groups have a tendency to lose protons (H^+), producing a negatively charged species:

$–COOH = – COO^- + H^+$

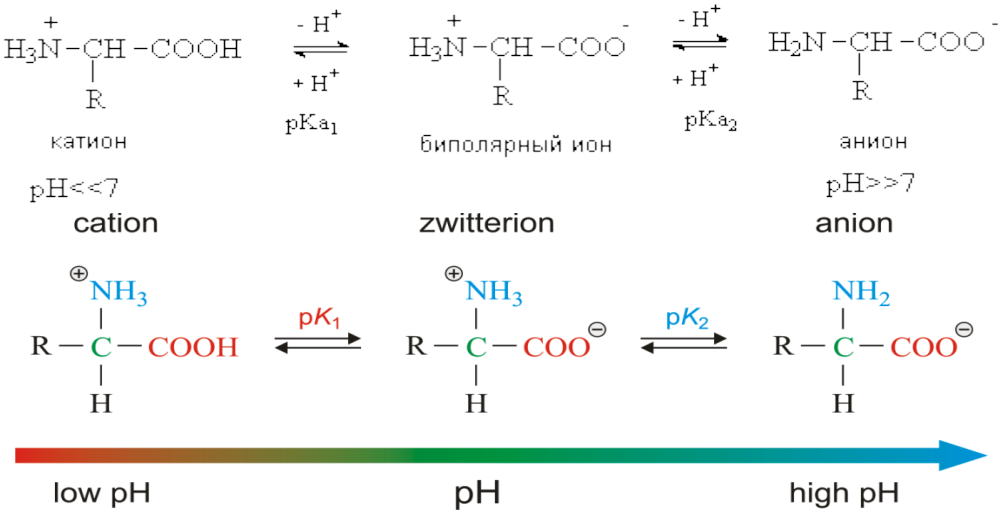
We learned that in neutral solution, amino groups have a tendency to accept protons (H^+), producing a positively charged species:

$–NH_2 + H^+ == –NH_3^+$

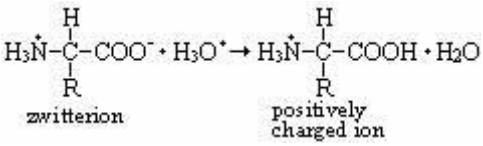
As is consistent with the behavior of these groups, in neutral solution, the –COOH group of an amino acid donates a proton to the $–NH_2$ of the same amino acid. We can characterize this behavior as an internal acid – base reaction. The net result is that in neutral solution, amino acid molecules have the structure



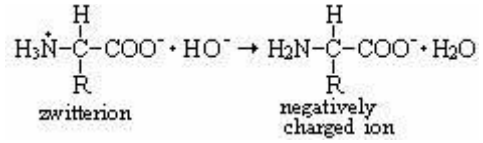
Such a molecule is known as a zwitterion, from the German term meaning "double ion". A **zwitterion** is a molecule that has a positive charge on one atom and a negative charge on another atom. Note that the net charge on a zwitterion is zero even though parts of the molecule carry charges. In solution and also in the solid state, α-amino acids are zwitterions.



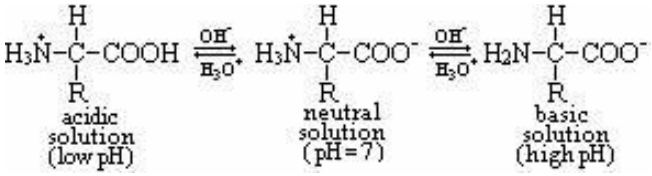
Zwitterion structure changes when the pH of a solution containing an amino acid is changed from neutral either to acidic (low pH) by adding an acid such as HC1 or to basic (high pH) by adding a base such as NaOH. In an acidic solution, the zwitterion accepts a proton (H^+) to form a positively charged ion.



In basic solution, the $-NH_3^+$ of the zwitterion loses a proton, and a negatively charged species is formed.



Thus, in solution, three different amino acid forms can exist (zwitterion, negative ion, and positive ion). The three species are actually in equilibrium with each other, and the equilibrium shifts with pH change. The overall equilibrium process can be represented as follows:



In acidic solution, the positively charged species on the left predominates; nearly neutral solutions have the middle species (the zwitterion) as the dominant species; in basic solution, the negatively charged species on the right predominates.

The previous discussion assumed that the side chain (R group) of an amino acid remains unchanged in solution as the pH is varied. This is the case for neutral amino acids but not for acidic or basic ones. For these latter compounds, the side chain can also acquire a charge, because it contains an amino or a carboxyl group that can, respectively, gain or lose a proton.

Because of the extra site that can be protonated or deprotonated, acidic and basic amino acids have four charged forms in solution.

The existence of two low-pH forms for aspartic acid results from the two carboxyl groups being deprotonated at different pH values. For basic amino acids, two high-pH forms exist because deprotonation of the amino groups does not occur simultaneously. The side-chain amino group deprotonates before the α-amino group.

The ***isoelectric point*** for an amino acid is the pH at which the total charge on the amino acid is zero. Every amino acid has a different isoelectric point. Fifteen of the 20 amino acids, those with nonpolar or polar neutral side chains, have isoelectric points in the range of 4.8 - 6.3. The three basic amino acids have higher isoelectricpoints (His = 7.59, Lys = 9.74, Arg = 10.76), and the two acidic amino acids have lower ones (Asp = 2.77, Glu = 3.22).

A pH below the isoelectric point favors the positively charged form of the amino acid. Conversely, a pH above the isoelectric point favors the negatively charged form of the amino acid.

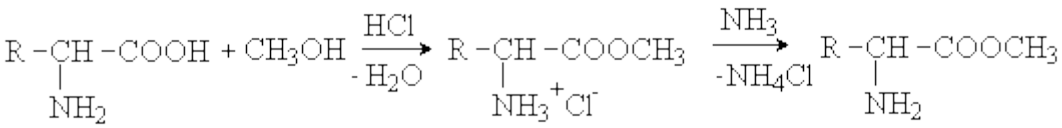
When two electrodes (one positively charged and one negatively charged) are immersed in a solution containing an amino acid, molecules with a net positive charge are attracted to the negatively charged electrode, and negatively charged amino acid molecules migrate toward the positively charged electrode.

The zwitterionform exhibits no net migration toward either electrode. This behavior is the basis for the measurement of isoelectric points. The pH of the solution is adjusted until no net migration occurs.

Mixtures of amino acids in solution can be separated by using their different migration patterns at various pH values. This type of analytical separation is called electrophoresis. **Electrophoresis** is the process of separating charged molecules on the basis of their migration toward charged electrodes.

Reaction of amino acids.

1) Reaction with alcohols(Esterification) – esters formation:

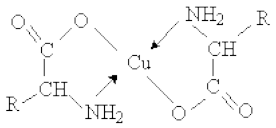


2. Complexation (amino acid chelates)

The compounds to which they attach can affect how well they are absorbed and how available they are for use in the body

a -amino Acids form strong chelate complexes with transition metal ions (Cu, Ni, Co, Cr

and others).

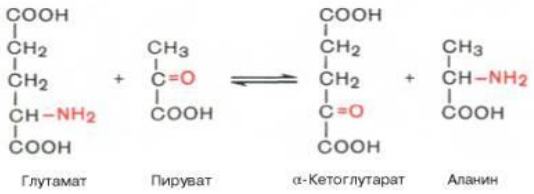


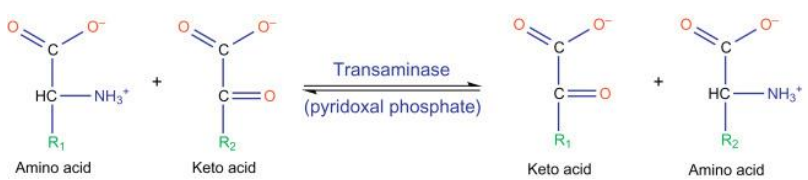
3. Deamination:

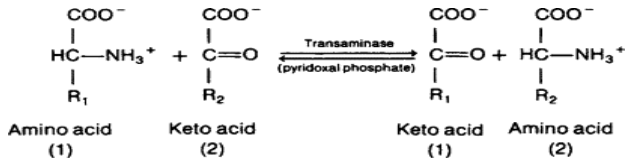
Oxidative Deamination

As in transamination, a Schiff base is formed with a dehydrogenase; more specifically, oxidation turns the amino group into an **imino group (C=N)**. Electron acceptors are the coenzymes NAD^+or $NADP^+$ that are reduced in this process to NADH/H or NADPH/H respectively. By adding water, the imino group is converted into an alpha-keto group which releases ammoniac (NH_3).

Example: Glutamate dehydrogenase reaction with glutamate dehydrogenase: Glutamate – imino acid – alpha-ketoglutarate. In the liver, glutamate from the cytosol is taken into the mitochondrion, where oxidative deamination occurs, under the influence of enzyme **L-glutamate dehydrogenase**, located in the mitochondrial matrix.



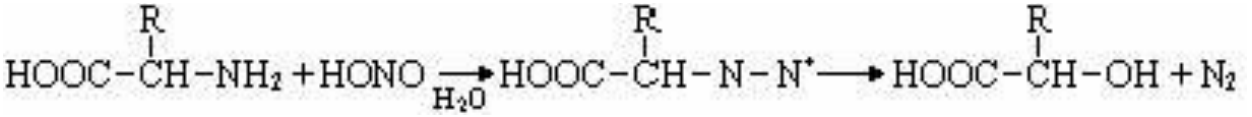




Amino acids react with nitrous acid to give hydroxy acid along with the evolution of nitrogen.

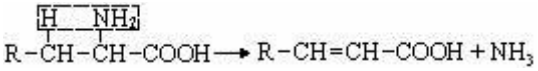
$$RCH(NH_2)COOH + HNO_2 \rightarrow RCH(OH)COOH + N_2 + H_2O$$

или

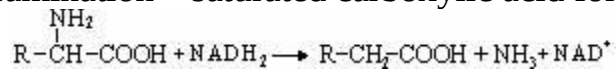


The nitrogen can be collected and measured. Thus this reaction constitutes one of the methods for the estimation of amino acids. The **Van Slyke determination** is a chemical test for the determination of amino acids containing a primary group (**Van Slyke method**)

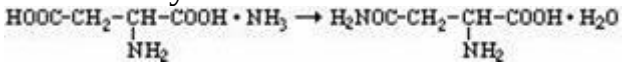
3. intramolecular deamination - unsaturated acids are formed



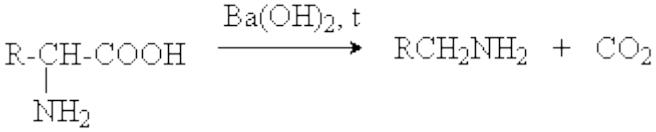
4. redaction deamination – saturated carboxylic acid formation:



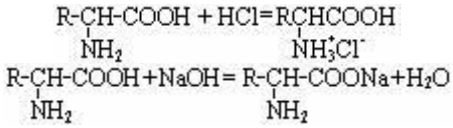
2) Reaction with ammonia – amides formation. The amides of aspartic and glutamic acid acids, asparagine and glutamine, play important role in the transport of ammonia in the body.



3) Decarboxylation. Amino acids may be decarboxylated by heat, acids, bases or specific enzymes to the primary amines:



All amino acids can react with some inorganic acids and bases and form two kind sold:



Transamination of Amino Acids

One of the central reactions of the amino acid metabolism is transamination. As the name suggests, transamination refers to a **transfer amino group**. The process of transamination occurs through aminotransferase enzymes which can be specific for an amino acid or can cater to several amino acids that are similar in their chemical compositions. An amino acid that is currently not needed can be transformed into another amino acid that is currently needed. The reallocation of the amino group occurs via an alpha-keto acid, which basically has an analogous structure to **alpha-amino acids**. Alpha-keto acids only differ from alpha-amino acids in having a keto group, instead of an amino group.

In many organisms, this process is used both to synthesize and to degrade amino acids. One of the primary cellular benefits of the reaction is that it allows the transfer of an amino group without the formation of ammonia, which is a toxic byproduct. In humans, it occurs primarily in the liver, and is also known as aminotransfer. Biochemically, this is an oxidation-reduction reaction that transfers the amino group from an amino acid to an alpha-keto acid. This results in the creation of a new amino acid and a new alpha-keto acid.

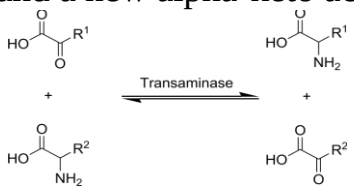
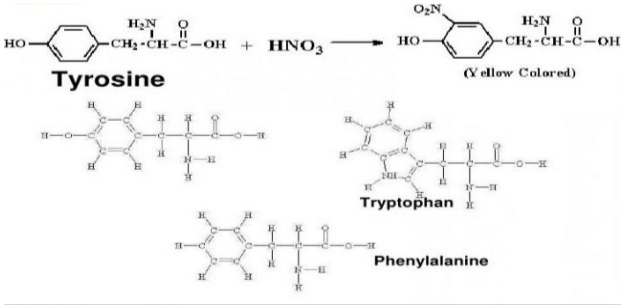


Image: "Aminotransfer Reaction Between an Amino Acid and an Alpha-Keto Acid." by Alcibiades.

Xantoprotein reaction to protein

Not all aminocarboxylic acids can be detected withusing such a sample. The main sign of the xantoprotein protein recognition reaction is the presence of a benzene ring or heterocycle in the amino acid molecule.

Of the protein amino carboxylic acids, two aromatic acids are distinguished, in which there is a phenyl group (in phenylalanine) and a hydroxyphenyl radical (in tyrosine).



What does the xantoprotein reaction mean?

To carry out qualitative analysis of proteins, various methods are used. These include reactions:

biuretovuyu with the appearance of violet staining;

Ninhydrin to form a blue-violet solution;

formaldehyde with the establishment of red coloration;

Fole with precipitation of gray-black color.

There is a xantoprotein reaction to the protein. It is also called Mulder's breakdown. It refers to color reactions to proteins in which aromatic and heterocyclic amino acids are present.

Biuret test. The protein is warmed gently with 10 % solution of sodium hydroxide and then a drop of very dilute copper sulphate solution is added, the formation of reddish - violet colour indicates the presence of peptide link, **–** CO **–** NH **–.** The test is given by all proteins, peptones and peptides. Its name is derived from the fact that the test is also positive for the compound biuret, H_2X –CONH – $CONH_2$ obtained from urea by heating.

It should be noted that dipeptides do not give the biuret test, while all other polypeptides do so. Hence biuret test is important to know whether hydrolysis of proteins is complete or not. If the biuret test is negative, hydrolysis is complete, at least to the dipeptide stage.

Xanthoproteic test. On treatment with concentrated nitric acid, certain proteins give yellow colour. This yellow colour is the same that is formed on the skin when the latter comes in contact with the concentrated nitric acid. The test is given only by the proteins having at least one mole of aromatic amino acid, such astryptophan, phenylalanine, and tyrosine which are actually nitrated during treatment with concentrated nitric acid.

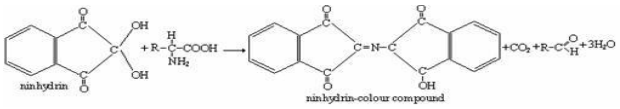
Millon's test. Protein on adding Millon's reagent (a solution of mercuric and mercurous nitrates in nitric acid containing a little nitrous acid) followed by heating the solution give a red precipitate or colour. The test is responded by the proteins having tyrosine. The hydroxyphenyl group of tyrosine is the structure responsible for this test. Moreover, the non-proteinous material having phenolic group also responds the test.

Foll reaction. This reaction reveals the sulfur containing amino acids (cysteine, cystine). Treatment of the sulfur containing amino acids with salt of lead and alkali yields a black sediment.

Adamkevich reaction. This reaction detects the amino acid tryptophan containing indol ring. The addition of the concentrated acetic and sulfuric acids to the solution of tryptophan results in the formation of red-violet ring appearing on the boundary of different liquids.

Ninhydrin test. The ninhydrin colour reaction is the most commonly test used for the detection of amino acids. This is an extremely delicate test, to which proteins, their hydrolytic products, and α-amino acids react. Although the test is positive for all free amino groups in amino acids, peptides, or proteins, the test is much weaker for peptides or proteins because not as many free groups are available as in amino acids. For certain amino acids the test is positive in dilutions as high as 1 part in 100,000 parts of water.

When ninhydrin is added to a protein solution and the mixture is heated to boil, blue to violet colour appears on cooling. The colour is due to the formation of a complex compound.



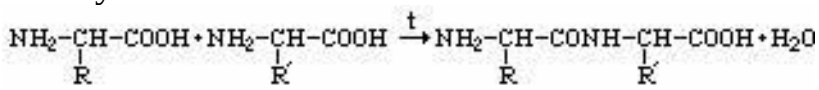
The test is also given by ammonia, ammonium salts, and certain amines. Ninhydrin is also used as a reagent for the quantitative determination of free carboxyl groups in solutions of amino acids.

Nitroprusside test. Proteins containing free -SH groups (of cysteine) give a reddish colour with sodium nitroprusside in ammonical solution.

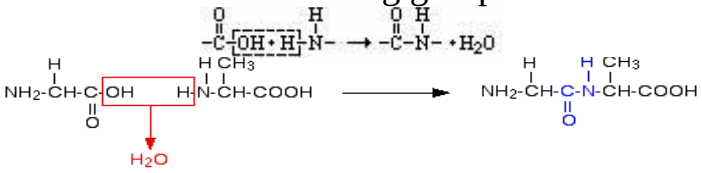
Proteins are polypeptides that contain more than 50 amino acid units. The dividing line between a polypeptide and a protein is arbitrary. The important point is that proteins are polymers containing a large number of amino acid units linked by peptide bonds. Polypeptides are shorter chains of amino acids. Some proteins have molecular masses in the millions. Some proteins also contain more than one polypeptide chain.

The **primary structure of a protein** is the sequence of amino acids present in its peptide chain or chains. Knowledge of primary structure tells us which amino acids are present, the number of each, their sequence, and the length and number of polypeptide chains.

Peptide formation. Two amino acids can react in a similar way - the carboxyl group of one amino acid reacts with the amino group of the other amino acid. The products are a molecule of water and a molecule containing the two amino acids linked by an amide bond.



Removal of the elements of water from the reacting carboxyl and amino groups and the ensuing formation of the amide bond are better visualized when expanded structural formulas for the reacting groups are used.



In amino acid chemistry, amide bonds that link amino acids together are given the specific name of peptide bond. A **peptide bond** is a bond between the carboxyl group of one amino acid and the amino group of another amino acid.

Under proper conditions, many amino acids can bond together to give chains of amino acids containing numerous peptide bonds. For example, four peptide bonds are present in a chain of five amino acids.

Short to medium-sized chains of amino acids are known as peptides. A **peptide** is a sequence of amino acids, of up to 50 units, in which the amino acids are joined together through amide (peptide) bonds. A compound containing two amino acids joined by a peptide bond is specifically called a dipeptide; three amino acids in a chain constitute a tripeptide; and so on. The name oligopeptide is loosely used to refer to peptides with 10 to 20 amino acid residues and polypeptide to larger peptides.

In all peptides, the amino acid at one end of the amino acid sequence has a free H_3N^+ group, and the amino acid at the other end of the sequence has a free COO^-group. The end with the free H_3N^+ group is called the **N-terminal end**, and the end with the free COO^- group is called the **C-terminal end**. By convention, the sequence of amino acids in a peptide is written with the N-trminal end amino acid at the left. The individual amino acids within a peptide chain are called amino acid residues.

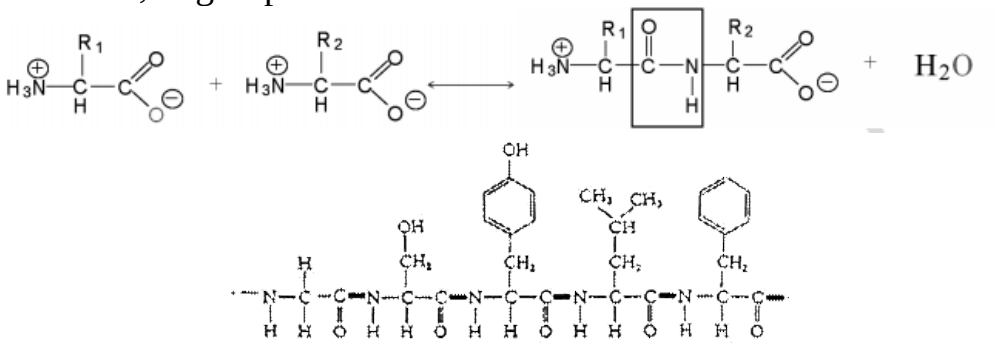
STRUCTURAL ORGANIZATION AND PROPERTIES OF PROTEINS

The architecture of protein molecules is quite complex. Nevertheless, this complexity conforms to the four levels of structural organization.

Primary structure. The primary structure of a protein corresponds to the linear **sequence of amino acids**, or the configuration1 of the polypeptide chain.

The sequence of amino acid residues is encoded in DNA and determines the native threedimensional conformation of the protein.

The primary protein structure is stabilized by peptide bonds, which are formed between α-carboxylic group of one amino acid and the α-amino group of another amino acids.. The continuing pattern of peptide bond is the backbone of protein molecule; R-groups are called the side chains.



Properties of the peptide bond:

Covalent, extremely stable.

Partial double, planar, without possibility of rotation.

Trans-position of O and H atoms provides maximal H-bonding.

Disulfide bonds between cysteine residues also may contribute to the stabilization of primary protein structure. Secondary structure.

Secondary protein structure includes various types of local conformations, which are stabilized by the hydrogen bonding between peptide units; the atoms of side chains are not involved. Three basic types of secondary structure exist: α-helix, β-sheet, and β-turn

Secondary protein structureis a configuration of a polypeptide chain, i.e. means of packaging of a polypeptide chain in certain conformation. This process proceeds not chaotically, but according to the program put in primary frame.

One of the most common type of secondary structure is **a-helix**(fig. 1). Curling of a polypeptide chain happens clockwise. Stability of secondary structure is provided basically by the intramolecular hydrogen bonds which exist between backbone –C=O and H-N- groups. A certain contribution can be made by covalent bonds - peptide and disulfide.

For each protein certain degree of helix is characteristic. Hemoglobin chains are 75% helical, pepsin – are only 30%.

Type of the configuration of polypeptide chains found in proteins of hair, silk, muscles, is called **b-pleated sheet**. This structure is stabilized by intermolecular hydrogen bonds. Segments of a peptide chain settle down in one layer, forming a figure similar to sheet, accordion-like folded. Polypeptide chains can be parallel or antiparallel. b-pleated sheet can be formed also intramolecularly.

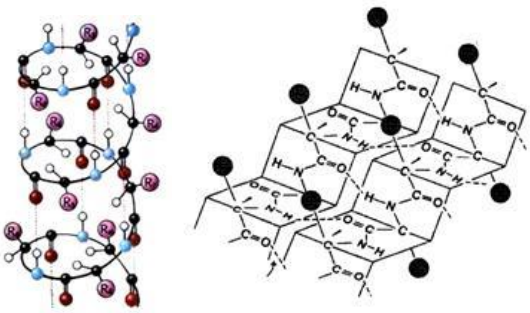


Fig. 1. Secondary structure of protein: a) ***a-helix****, b)* ***b*** *-pleated sheet.*

In nature there are proteins constitution of which does not correspond neither to β- nor a - structure, for example, collagen - the febrile protein of connective tissue in a human body and animals.

Tertiary protein structureis packing of a polypeptide chain in certain volume.

Tertiary structure of proteins is maintained by covalent bonds (disulfide bonds). But the dominant role is played by noncovalent bonds (hydrogen bondes, electrostatic interactions of the charged groups (salt briges), intermolecular Van der Waals forces, hydrophobic interactions etc.).

According to modern knowledge, tertiary protein structure after the end of its synthesis is formed spontaneously. The basic reason is interaction of amino acids radicals with water. Thus non-polar hydrophobic radicals of amino acids are dipped in protein molecule, and polar radicals are oriented towards water. The process of tertiary protein structure formation is called **folding**. In cells there are proteins called **shaperons.** They participate in folding. We know a series of hereditary human diseases the cause of which is infringement of folding process (pigmentosis, fibrosis, Mad Cow Disease).

The **domain** is a compact globular unit in a polypeptide chain (fig. 3). Many proteins are discovered (for example, immunoglobulins), consisting of different in structure and functions domains coded by different genes.

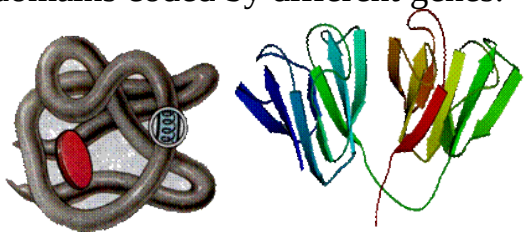


Fig. 2. Myoglobinertiary structure Fig. 3. Globular domains in g- crystallin (protein of human eye crystalline lens)

All biological properties of proteins are bound to safety of their tertiary structure which is called**native**. The protein globule is not an absolutely rigid structure: reversible moves of parts of a peptide chain are possible. These changes do not break the general conformation of a molecule. Conformation of a molecule of protein is influenced by ionic strength of solution, interaction with other substances, pH. Any influences leading to infringement of native conformation of a molecule, is accompanied by particulate or full loss by protein of its biological properties.

Quaternary protein structure. Formation of quaternary protein structure is packing in space of separate polypeptide chains into an organized whole. These chains may have identical or different primary, secondary or tertiary structure.

The protein molecule consisting of several polypeptide chains, is called **oligomer**, and each chain entering it – **monomer**. Oligomer proteins are more often constructed of an even number of monomers, for example, the hemoglobin molecule consists of two a- and two b-polypeptide chains (fig. 4).

About 5% of proteins possess quaternary structure, including hemoglobin, immunoglobulins. The subunit constitution is common with many enzymes.

a chain 1 b chain 1

b chain 2 a chain 2

Fig. 4. Hemoglobin molecule

The protein molecules which are part of the protein quaternary structure, are formed on ribosomes separately and only after the end of synthesis do they form the general supramolecular structure. Protein gets biological activity only after the affiliation of its compositional monomers. Quaternary structure is stabilized by the same types of forces as tertiary, but no covalent bonds.

Some researchers recognize existence of the fifth level of the structural organization of proteins. These are **metabolons** -multifunctional macromolecular complexes of different enzymes catalyzing the whole pathway of metamorphosis of substrate (synthetases of the highest fat acids, pyruvate dehydrogenase complex, and respiratory chain).

The denaturation of protein involves the destruction of its spatial structures while retaining the primary structure. The continuity of the polypeptide chain remains intact. The essence of denaturation is the disintegration of low-energy bonds, which stabilize the spatial structure of the protein. The denaturising factors are primarily: elevated temperature (usually above 58-60°C), organic solvents, acids, alkalis, heavy metal ions (such as Hg2+, Pb2+), concentrated solutions of urea or guanidine hydrochloride. Denatured protein loses its biological activity, e.g. an enzyme loses its catalytic properties, an antibody - its antigen binding ability, collagen the ability to create fibres, and haemoglobin the ability to bind oxygen. The denaturation of protein generally changes its solubility. Soluble protein loses solubility, insoluble protein becomes soluble. Soluble proteins form colloidal or real solutions. The stability of protein solutions mainly depends on the electric charge of the particles, their degree of hydration and temperature. Protein, which as a result of the denaturation agent action lost its colloidal character, usually precipitates from the solution.

Unit 15. Nucleophilic vs Electrophilic Substitution Reaction

Main Difference

Both nucleophilic (**a nucleophile (electron rich molecular species) attacks the nucleophilic centre of a molecule to remove the leaving group**) and electrophilic (**an electrophile (a positive ion or partially positive end of a polar molecule) attacks the electrophilic centre of a molecule whereas, in nucleophilic substitution reaction**) substitution reactions are found in . These substitution reactions are very important in the synthesis of certain compounds. A substitution reaction is a reaction that involves the replacement of an atom or a group of atoms by another atom or a group of atoms. The main difference between nucleophilic and electrophilic substitution reaction is that **nucleophilic substitution reaction involves the displacement of a leaving group by a nucleophile whereas electrophilic substitution reaction involves the displacement of a functional group by an electrophile.**

The Three Stages Of Electrophilic Aromatic Substitution Reactions

Activation. Since halogens (Cl_2, Br_2) don't usually react with aromatic molecules at a reasonable rate, a Lewis acid catalyst (e.g. $FeCl_3$) is added to "activate" the electrophile toward attack

Attack of Electrophile By The Aromatic Ring. The activated electrophile is attacked by the aromatic ring, resulting in a carbocation intermediate (this is the rate determining step, and Step 1 in the generic mechanism of electrophilic aromatic substitution).

Deprotonation. The carbocation intermediate is deprotonated by a weak base, restoring aromaticity (Step 2 in the generic mechanism of electrophilic aromatic substitution).

What is Nucleophilic Substitution Reaction

A nucleophilic substitution reaction is a chemical reaction which involves the displacement of a leaving group by a nucleophile. This leaving group is given that name because it leaves when a nucleophile reacts with the molecule the leaving group is attached to (the whole molecule is called a substrate). The part that the nucleophile is going to be attached is called an electrophile. This electrophile lacks electrons in order to become stable. Therefore, it accepts electrons from a nucleophile. This results in the formation of a covalent bond between nucleophile and electrophile.

Most of the times, the nucleophile is negatively charged. But it can also be a neutrally charged molecule having a free pair of electrons that is ready to be donated. These nucleophilic substitution reactions take place in aliphatic and aromatic organic compounds.

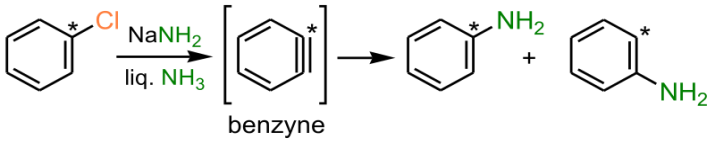


Figure 1: An Example of Nucleophilic Substitution in Aromatic Compounds

In the above example, the benzene ring is attached to a Chlorine (Cl) atom. It is the leaving group in the presence of $NaNH_2$. The nucleophile is $–NH_2$ group.

The carbon atom (with a star mark in the above image) is attacked by the nucleophile and Cl atom is displaced by $–NH_2$ group. This is called a nucleophilic substitution.

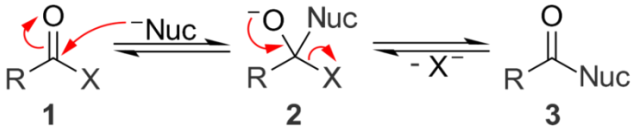


Figure 2: An Example of Nucleophilic Substitution in Aromatic Compounds

In the above example, the nucleophile is indicated by symbol "Nuc". The carbon atom in the center is attacked by the nucleophile and the leaving group "X" is displaced by the nucleophile. It can clearly be seen when considering the difference between the first and the last molecules in the above image.

There are two main types of Nucleophilic substitution reactions categorized according to their mechanism.

S_N1 Reactions

The symbol "S" refers to "substitution" and "N" refers to "Nucleophilic". The number ("1" here) indicates the kinetic order of the reaction. These reactions involve the formation of a carbocation intermediate. Therefore, the reaction occurs in two steps.

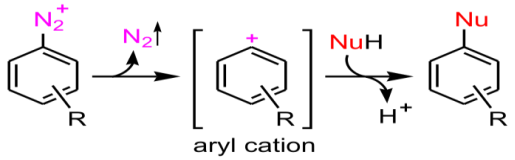


Figure 3: SN1 Reaction Mechanism

In the above example, N_2^+ is the leaving group of the initial molecule. As the first step, the leaving group leaves, forming a carbocation intermediate. The intermediate that is formed here is an aryl cation. Since it is a stable ion, this is the rate determining step of this reaction. As the second step, the nucleophile is attached to the carbocation.

S_N2 Reactions

In the S_N2 reaction, a carbocation is not formed. Therefore the reaction occurs through a single step. Therefore, it is the rate-determining step of the reaction.

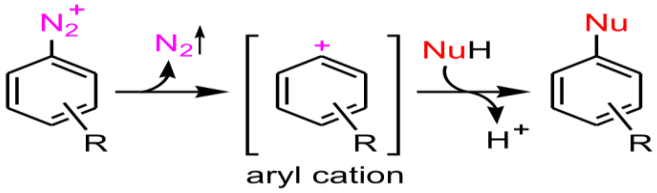


Figure 4: SN2 Reaction Mechanism

The above example shows the leaving of the leaving group ("X" here) and the substitution of the Nucleophile occurring at the same time. Read more: Difference Between S_N1 and S_N2 Reactions.

What is Electrophilic Substitution Reaction

Electrophilic substitution is a chemical reaction that involves the displacement of a functional group by an electrophile. Most of the times, hydrogen atoms are displaced in this manner. Electrophilic substitution reactions are also

found in aliphatic and aromatic compounds. Electrophilic substitution reactions are especially used to make benzene derivatives.

Electrophiles are molecules that are either positively charged or neutrally charged but lacks electrons. Electrophiles accept electrons from nucleophiles in order to neutralize its charge or to obey the octet rule and become stable.

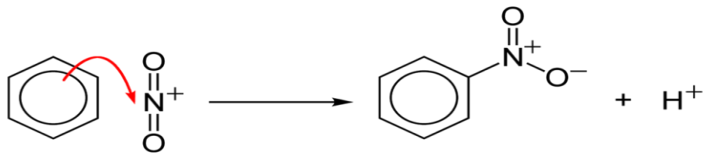


Figure 5: An Example of Electrophilic Substitution Reaction in Aromatic Compounds

In the above example, one hydrogen atom of the benzene ring is displaced by NO_2^+ ion. In this case, NO_2^+ is the electrophile. There is a positive charge in the nitrogen atom. The benzene ring is rich with electrons due to the presence of pi-bonds. Therefore, electrophile attacks the benzene ring and attach with it, making a hydrogen atom the "leaving group".

The Electrophilic substitution reactions are mainly found in two types of mechanisms.

S_E1 Reactions

These S_E1 reactions involve the formation of a carbocation that is stable. Therefore, the rate determining step is the step of the carbocation formation. This indicates that the S_E1 reactions occur in two steps. The attachment of electrophile to the carbocation can also be observed here. But the leaving group is still attached to the carbocation. As the second step, the departure of the leaving group occurs.

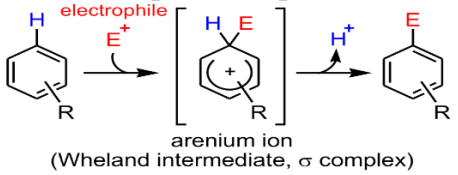


Figure 6: SE1 Reaction Mechanism

S_E2 Reactions

The S_E2 reactions involve only one step. A carbocation is not formed. Therefore the rate determining step is the formation of substituted molecule.

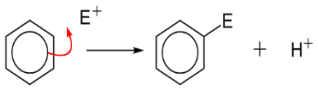


Figure 7: SE2 Reaction Mechanism

Similarities Between Nucleophilic and Electrophilic Substitution Reaction

Both types of reactions are related to electron sharing.

Both reactions result in covalent bonds.

Both reactions result in a displacement of a group present in the substrate molecule.

They produce leaving groups.

Both reaction types are found in chemical reactions related to aliphatic and aromatic compounds.

Difference Between Nucleophilic and Electrophilic Substitution Reaction

Definition

Nucleophilic substitution reaction is a chemical reaction which involves the displacement of a leaving group by a nucleophile.

Electrophilic Substitution Reaction: Electrophilic substitution is a chemical reaction that involves the displacement of a functional group by an electrophile.

Electron Sharing

Nucleophilic Substitution Reaction: In nucleophilic substitution reaction, nucleophile donates its electrons.

Electrophilic Substitution Reaction: In electrophilic substitution reaction, electrophile accepts electrons.

Electrical Charge

Nucleophilic Substitution Reaction: In nucleophilic substitution reactions, the nucleophile is either negatively charged or neutrally charged and the electron accepting molecule is positively charged or neutrally charged.

Electrophilic Substitution Reaction: In electrophilic substitution reaction, the electrophile is either positively charged or neutrally charged and the electron donating molecule is either negatively charged or neutrally charged.

Electrophiles:

Hydronium ion	H_3O^+ (from Bronsted acids)
Boron trifluoride	BF_3
Aluminum chloride	$AlCl_3$
Halogen molecules	F_2, Cl_2, Br_2, I_2

Conclusion.

Electrophic substitution: Most of the electrophilic substitution reactions occur in the benzene ring in the presence of an electrophile (a positive ion)

Nucleophilic Substitution: It involves the reaction between an electron pair donor (the nucleophile) and an electron pair acceptor (the electrophile). The electrophile must have a leaving group for the reaction to take place.

The reaction mechanism occurs in two ways: SN^2 reactions and SN^1. In SN reactions, the removal of the leaving group and the backside attack by the nucleophile occurs simultaneously. In SN reactions, a planar carbenium ion is formed first and then it is further reacted with the nucleophile. The nucleophile has the freedom to attack from either side, and this reaction is associated with racemization.

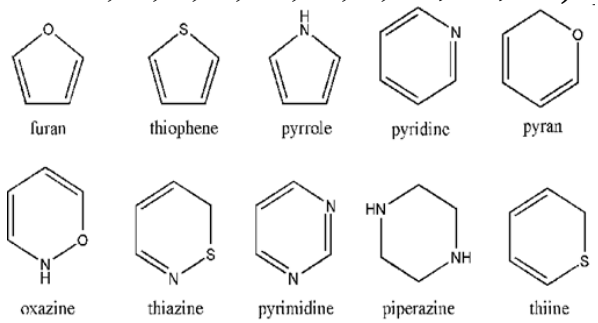
Questions:

1. Which two functional groups are present in an amino acid?
2. What is the order of amino acids?
3. What is the functional group present in methanol acid, and amino acid?

Unit 16. Biologically important heterocyclic compounds.

STRUCTURE, CHEMICAL PROPERTIES OF HETEROCYCLIC COMPOUNDS.

Heterocyclic compounds are compounds, in which molecules cycles, in which structure except atoms Carbon is atoms of other elements – **heteroatoms** (more often N, O, S, B, Al, Si, P, Sn, As, Cu).



Such compounds widespread in the nature (vitamins, antibiotics, enzymes, alkaloid) also can be easily synthesized. Heterocyclic compounds can contain cycles from three to six and more atoms and to contain odes of one to four heteroatoms, but the greatest practical value have five-and hexatomic heterocycles.

Heterocycles are formed by two or more atomscarbon, and also heteroatoms. According to Bayer's theory, stable heterocycles will be only in cases when the deviation of the valences of the atoms forming the cycles is the smallest from the angle of 109 ° 28. "For example, heterocyclic compounds with trinomial heterocycles whose molecules exhibit the greatest deviation of 24 ° 44 "(ethylene oxide, ethylene oxide and ethyleneimine).

Heterocycles are widespread in nature. These include amino acids (tryptophan, carnosine, histidine), imino acids (proline and hydroxyproline), purine (adenine and guanine) and pyrimidine (thymine, uracil and cytosine) bases, biologically important substances of living matter (heme, hemin chlorophyll), alkaloids caffeine and atropine), antibiotics (penicillin, gramicidin C, streptomycin), medications (norsulfazole and caffeine), sulfonamides (norsulfazole, streptocid), organic solvents (pyridine), carbohydrates, nucleic acids, proteins, hormones, vitamins, and many others important substances.

Heterocycles are conveniently grouped into two classes, nonaromatic and aromatic

Classification of chemical compounds

The classification is based on the structureheterocycles in whose molecule carbon atoms are bound to a heteroatom (heteroatoms) and hydrogen atoms. Heterocycles and their derivatives are divided into groups depending on the number of atoms forming the cycle (three-, four-, five-, six-membered, etc.). In each such group there are subgroups with one, two, and three heteroatoms.

Heterocyclic compounds in mostcases are named according to the historical nomenclature (pyridine, pyrrole, acridine). From the historical names, the names of their derivatives are formed (pyridine-4-carboxylic acid, methylpyridine). To denote the position of substituents, the atoms of heterocycles are numbered. The numbering is carried out from a heteroatom or denoted by the letters of the Greek

alphabet, starting from the carbon atom adjacent to the heteroatom - alpha, beta, gamma, etc.

Heterocyclic compounds: nomenclature

When naming heterocyclic compoundsaccording to the IUPAC nomenclature, the number of atoms in the heterocycle, its structure, placement of substituents and other features (for example, furfural has a systematic name furan-2-carbaldehyde) is taken into account. The names of heterocyclic compounds are indicated in the description of the methods for their preparation, properties and values.

The stability of the previously considered heterocycles depends on the number of carbon atoms in the molecule of the heterocycle, the heteroatom itself and its location in the heterocycle. The least stable are heterocyclic compounds, consisting of three and four cycles, which are easily broken and become acyclic compounds. There are many heterocyclic compounds, the cycles of their molecules are stable, similar to the cycle of the benzene nucleus. They are the main structural element of many bio-compounds that are of great importance for industry, medicine and veterinary medicine.

By size of ring:

Three-membered

Four-membered

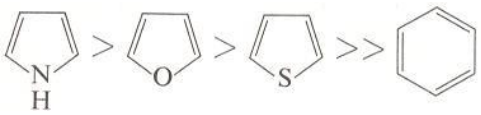
Five-membered

Six-membered

Chemistry of heterocyclic compounds

The chemical properties of five-membered (thiophene and itsderivatives) of heterocycles are due to the presence of a pi-excess electron system in their molecule, which increases their aromaticity. Compared with benzene, thiophene more easily enters the electrophilic substitution reaction.

The typical reaction of furan, pyrrole, and thiophene is electrophilic substitution. All three heterocycles are much more reactive than benzene. The reactivity order being is:

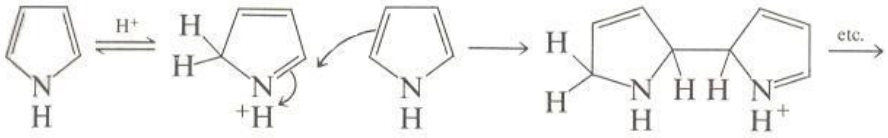


To give some idea of the magnitude of this reactivity order, partial rate factors (activities related to benzene) for tritium exchange with fluoroacetic acid.

Reciprocal transformation of furan, pyrrole, thiophene (Yurie`s cycle reactions)

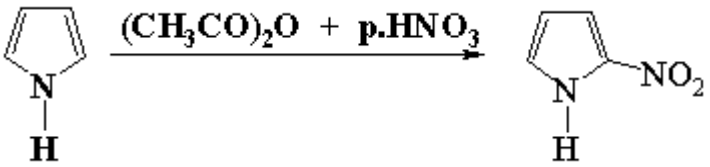
1. Interaction with dilute mineral acids

Pyrroles are polymerized by even dilute acids by a mechanism such as the following .



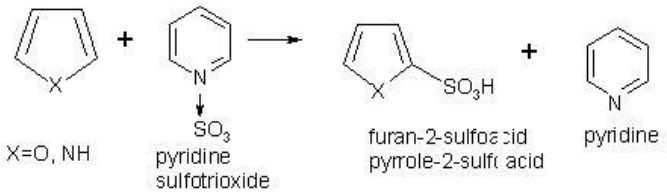
Reactions of electrophilic substitution:

This orientation is understandable in terms of the mechanism of electrophilic aromatic substitution.

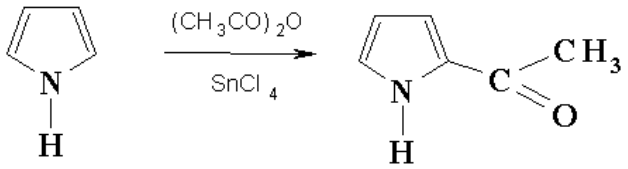


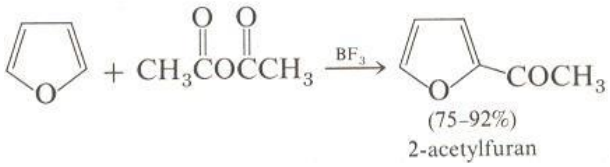
Nitration

Sulfonation

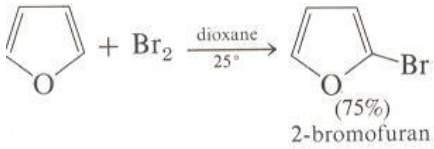


Acylation

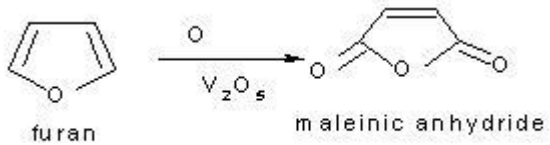


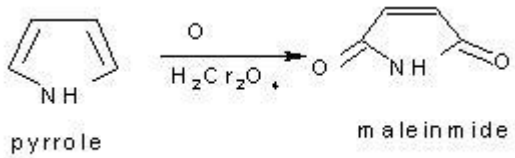


Halogenation



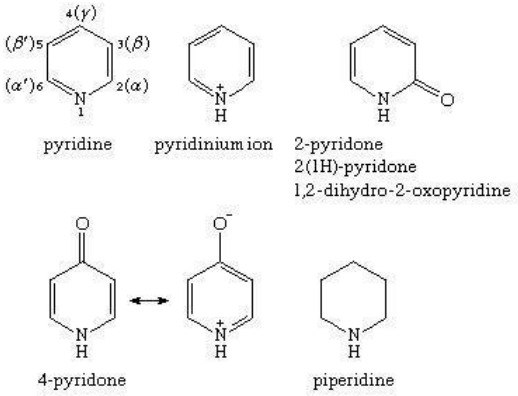
Reactions of oxidation



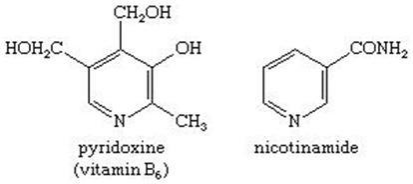


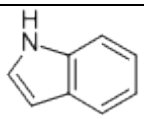
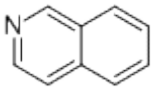
Six-membered rings with one heteroatom

The pyridones are aromatic compounds because of contributions to the resonance hybrid from charged resonance forms such as that shown for 4-pyridone.

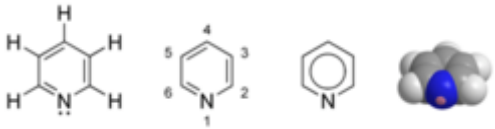


Pyridine derivatives are also of great biological importance. For example, nicotinic acid is more commonly known as the B-complex vitamin niacin; a nutritionally equivalent form of niacin is nicotinamide, or niacinamide. Pyridoxine is another member of the B complex, vitamin B6. The structures of pyridoxine and nicotinamide are:



Indole 		Isoquinoline 		

Pyridine



Pyridine is one of the simplest heterocycle known since its discovery in 1849 by Scottish chemist Thomas Anderson. It closely resembles with benzene structure, where a benzene methine (=CH-) group is occupied by “N” to form a six membered aromatic heterocycle of formula C5H5N. It is a room temperature colorless, water-soluble liquid with the distinctive pungent smell. The presence of electronegative “N” in ring structure is the sole cause of new properties induced in pyridine differentiating it markedly from benzene. The “N” presence in ring prevents the electron density be distributed evenly over the ring owing to its negative inductive effect, which also causes the weaker resonance stabilization (117 kJmol−1) than benzene (150 kJmol−1). This is evident from the shorter C-N bond distance (137 pm) compare to 139 pm of the C-C bond. The other bond lengths satisfy typical aromatic nature of the pyridine ring. Similar to benzene all the pyridine ring atoms are sp2 hybridized and involve in the π electron resonance. The sp2 “N” involvements in resonance come through its unhybridized p-orbital rather than involving its lone pair. The lone pair thus in sp2 orbital remain directed

outward of the ring in the same plane without contributing to the aromatic behavior of pyridine but greatly influence the chemical environment of the ring. The available “free” lone pair thus could be utilized by “N” in several ways suiting for chemical reactions either on pyridine ring or as Lewis base to form coordinate bond with Lewis acids (Figure 1). It is a weak base reacts with acids to get protonated to pyridinium salt with pKa of conjugate acid (pyridinium cation) is 5.25. For an illustrative example the pyridine reacts with p-toluenesulfonic acid and gets protonated to pyridinium p-sulfonate salt. The protonated pyridine thus produced is isostructural and isoelectronic with benzene. Pyridine has a conjugated system of six π electrons that are delocalized over the ring. The molecule is planar and, thus, follows the Hückel criteria for aromatic systems. In contrast to benzene, the electron density is not evenly distributed over the ring, reflecting the negative inductive effect of the nitrogen atom. For this reason, pyridine has a dipole moment and a weaker resonant stabilization than benzene

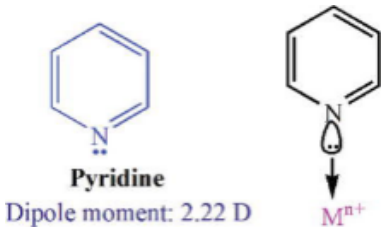


Figure 1.Structure of pyridine and its ligation to metal.

In organic reactions, pyridine behaves as a tertiary amine with protonation, alkylation, acylation and N-oxidation at the nitrogen atom. It also behaves as an aromatic compound with nucleophilic substitutions.

Pyridine is a good nucleophile (with a donor). It is easily attacked by alkylating agents to give N-alkylpyridinium salts.

Nucleophilic aromatic substitution takes place at C2 and C4 for example in the Chichibabin reaction of pyridine with sodium amide to 2-aminopyridine. In the **Emmert reaction** pyridine is reacted with a ketone in presence of aluminium or magnesium and mercuric chloride to the carbinol also at C2

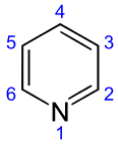
Pyridine reactions:

Electrophilic substitution reactions $\mathbf{S_E}$.

Nucleophilic substitution reactions **S N.**

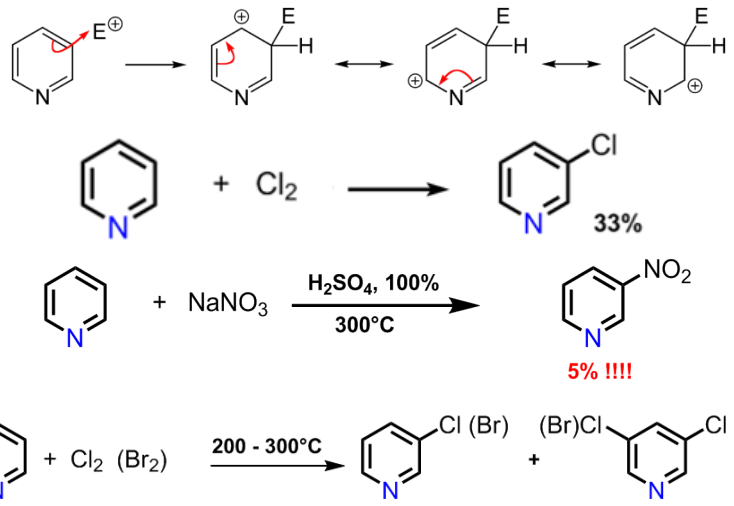
Reduction.

Oxidation.



Electrophilic substitution reactions $\mathbf{S_E}$

Because of the electronegative nitrogen in the pyridine ring, the molecule is relatively electron deficient. It, therefore, enters less readily into electrophilic aromatic substitution reactions than benzene derivatives. Skeletal formulae depicting the addition of an electrophile to pyridine in the 3 position, and the resonance structures of the intermediate formed

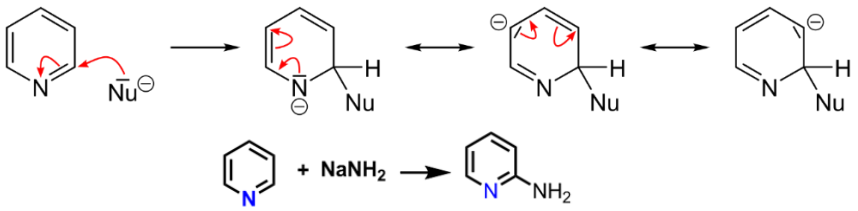


Nucleophilic substitution reactions **S N.**

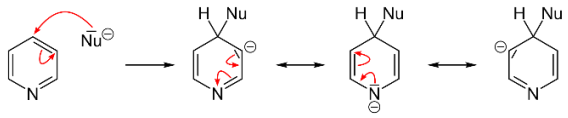
Pyridine is more prone to nucleophilic substitution

With nucleophiles, pyridine reacts at positions 2 and 4 and thus behaves similar to imines and carbonyls.

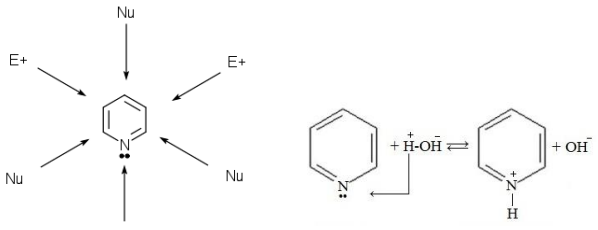
Addition of a nucleophile to pyridine at position 2, including all resonance structures.



Addition of a nucleophile to pyridine at position 4, including all resonance structures

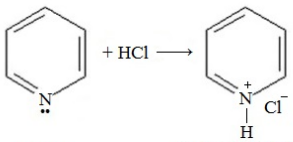


The nitrogen center of pyridine features a **basic lone pairelectrons**. This lone pair does not overlap with the aromatic π-system ring, consequently pyridine is a **basic**, having chemical properties similar to those of tertiary amines.

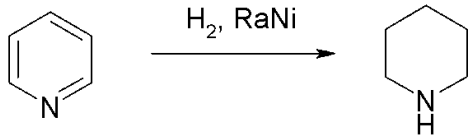


ion pyridine

The pyridine reacts with hydrogen chloride results in the formation of pyridinium chloride



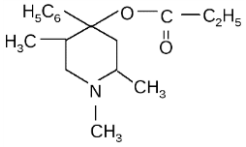
Reduction.



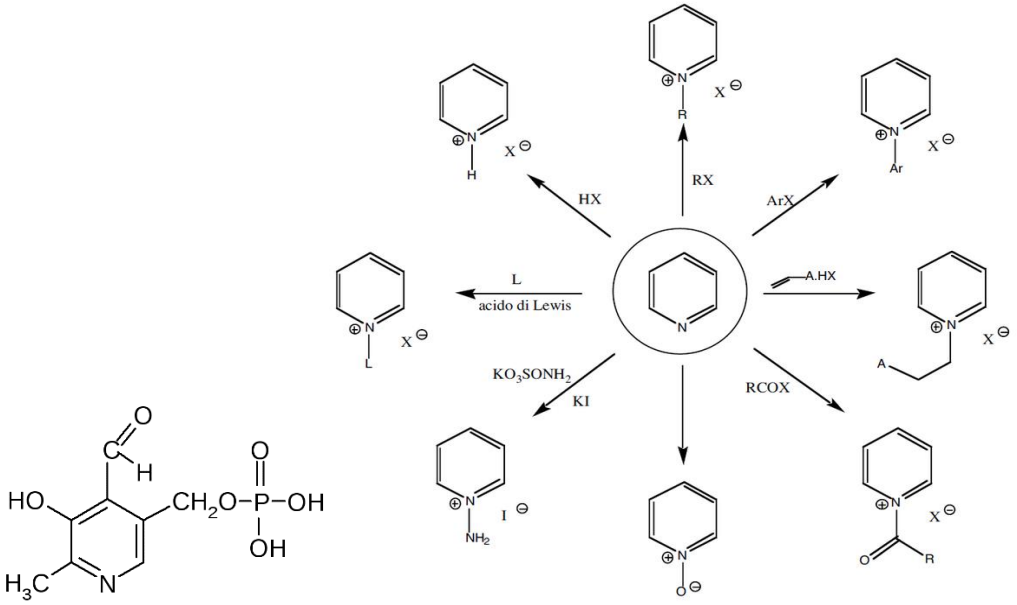
Piperidine

Piperidine is best known as a representative structure element within many pharmaceuticals

Promedol is a synthetic derivative of piperidine.

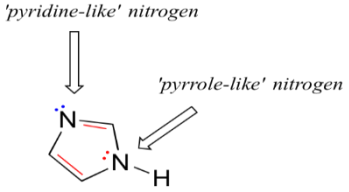


Pyridoxal phosphate the active form of vitamin B_6, is a coenzyme in a variety of enzymatic reactions.

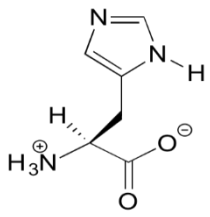


Five-membered heterocycles with two nitrogen atoms

Imidazole is another important example of an aromatic heterocycle found in biomolecules - the side chain of the amino acid histidine contains an imidazole ring.



imidazole

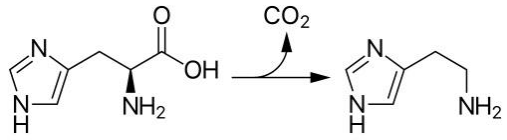


histidine

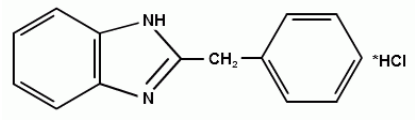
In imidazole, one nitrogen is 'pyrrole-like' (the lone pair contributes to the aromatic sextet) and one is 'pyridine-like' (the lone pair is located in an orbital, and is *not* part of the aromatic sextet).

Histidine is an essential amino acid found in most animal proteins. hat is; histidine is important in tissue growth and repair while the body releases

histidine during allergic reactions. Histidine serves as the precursor for the synthesis of histamine in a biochemical reaction known as decarboxylation.



Histamine is involved in local immune responses as well as regulating physiological functions in the gut and acting as a neurotransmitter for the brain, spinal cord. Histamine is involved in the inflammatory response and has a central role as a mediator of itching in allergic reactions, like a defensive reaction

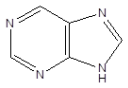


Dibazolum.

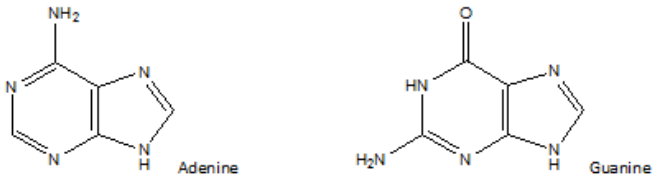
Apply For elimination of spasms of blood vessels

Purine

Purine is an aromatic organic compound. It is a heterocyclic compound containing nitrogen. In purine, a pyrimidine ring and a fused imidazole ring are present. It has the following basic structure.



Purines and their substituted compounds are widely distributed in nature. They are present in nucleic acid. Two purine molecules, adenine and guanine, are present in both DNA and RNA. Amino group and a ketone group are attached to the basic purine structure to make adenine and guanine. They have the following structures.



In nucleic acids, purine groups make hydrogen bonds with complementary pyrimidine bases.

Xanthine (3,7-dihydropurine-2,6-dione), is a purine base found in most human body tissues and fluids and in other organisms. A number of are derived from xanthine, including caffeine and theobromine

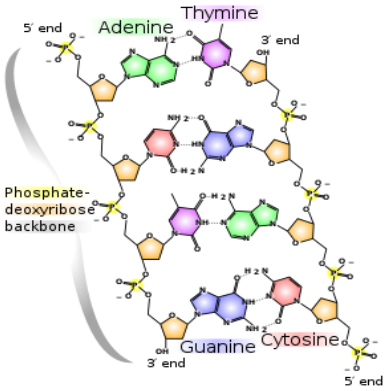
Hypoxanthine is a naturally occurring derivative. It is occasionally found as a constituent of nucleic acids, where it is present in the anticodontRNA in the form of its nucleoside inosine. It has a tautomer known as 6-hydroxypurine.

Hypoxanthine is a necessary additive in certain cell, bacteria, and parasite cultures as a substrate and nitrogen source.

Uric acid is a heterocyclic compoundcarbon, nitrogen, oxygen, and hydrogen with the formula C5H4N4O3. It forms ions and salts known as urates and acid urates, such as ammonium acid urate. Uric acid is a product of the metabolic breakdown of purine nucleotides, and it is a normal component of urine. High blood concentrations of uric acid can are associated with other medical conditions, including diabetes and the formation of ammonium acid urate kidney stones.

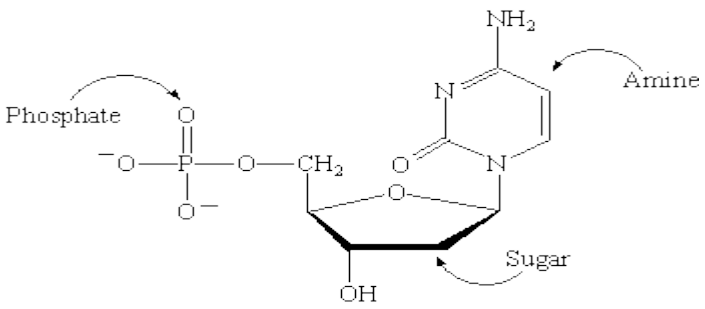
1. Why is pyrrole more reactive than benzene?
2. Why are pyrrole and furan more reactive for electrophilic substitution at the C2 and C5 positions?
3. Why does pyridine not undergo an electrophilic substitution reaction?

Unit 17. Nucleic acid

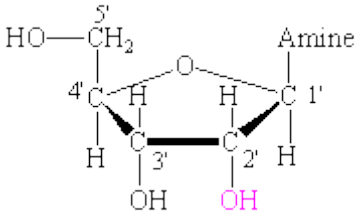


DNA was first isolated by Friedrich Miescher in 1869.

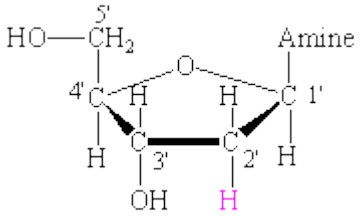
In 1944 Oswald Avery presented evidence that nucleic acids were involved in the storage and transfer of the genetic information needed for the synthesis of proteins. In 1954, James Watson and Francis Crick proposed a structure for DNA that explained how DNA could be used to store genetic information. The nucleic acids are polymers with molecular weights as high as 100,000,000 grams per mole. They can be broken down, or digested, to form monomers known as **nucleotides**. Each nucleotide contains three units: a sugar, an amine, and a phosphate, as shown in the figure below.



Nucleic acids are divided into classes on the basis of the sugar used to form the nucleotides. **Ribonucleic acid** (**RNA**) is built on a □-D-ribofuranose ring. **Deoxyribonucleic acid** (**DNA**) contains a modified ribofuranose in which the -OH group on the second carbon atom has been removed, as shown in the fiugre below.



D-ribofuranose found in DNA



D-deoxyribofuranose found in DNA □

Views about the role of DNA in inheritance changed in the late 1940's and early 1950's.

By conducting a careful analysis of DNA from many sources, Erwin Chargaff found its composition to be species specific. In addition, he found that the amount of adenine (A) always equaled the amount of thymine (T), and the amount of guanine (G) always equaled the amount of cytosine (C), regardless of the DNA source.

Building Blocks of Nucleic Acids

Nucleic acids are bio polymers composed of monomer units called as nucleotides, thus they are the building blocks of all nucleic acids. Each nucleotide has three components which are bonded together in a certain manner to form complete unit. These components are as follow.

1. Nitrogen-containing "base"

There are two type of nitrogenous base present in nucleotides, **pyrimidine (one ring) or purine (two rings)**which are quite differ from each other in there structures.

(a) Purine

There are two purine base commonly found in nucleic acid, **Adenine (A) and guanine (G)**.
Both purine bases bonded with sugar through the N9 of base with C_1 of the sugar.

(b) Pyrimidine

There are three pyrimidine base, **Thymine (T) and cytosine(C) present in DNA and Uracil (U)**.

2. Five carbon sugar

Two pentose sugars are present in nucleic acids, **ribose or deoxyribose sugar**.
DNA contains Î²-D-2-deoxyribose sugar while RNA contains Î²-D-ribose sugar. Both sugars are differing only in the presence of one oxygen atom at C position.

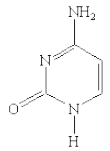
In any nucleotide, the combination of these two components, a base and sugar is known as a nucleoside.

The bonding between nucleosides and phosphoric acid molecules results the formation of nucleotides.

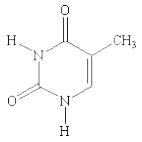
In nucleosides, the 1-position of pyrimidine and 9-position of purine

bonded with C_1 of the sugar molecule through a Î²-linkage also known as **N-glycosidic linkage**.

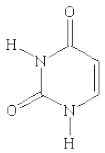
Purines and Pyrimidines. The amines that form nucleic acids fall into two categories: **purines** and **pyrimidines**. There are three pyrimidines — cytosine, thymine, and uracil — and two purines — adenine and guanine, as shown in the figure below.



Cytosine

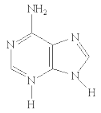


Thymine

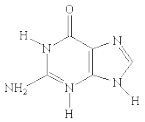


Uracil

PYRIMIDINES



Adenine

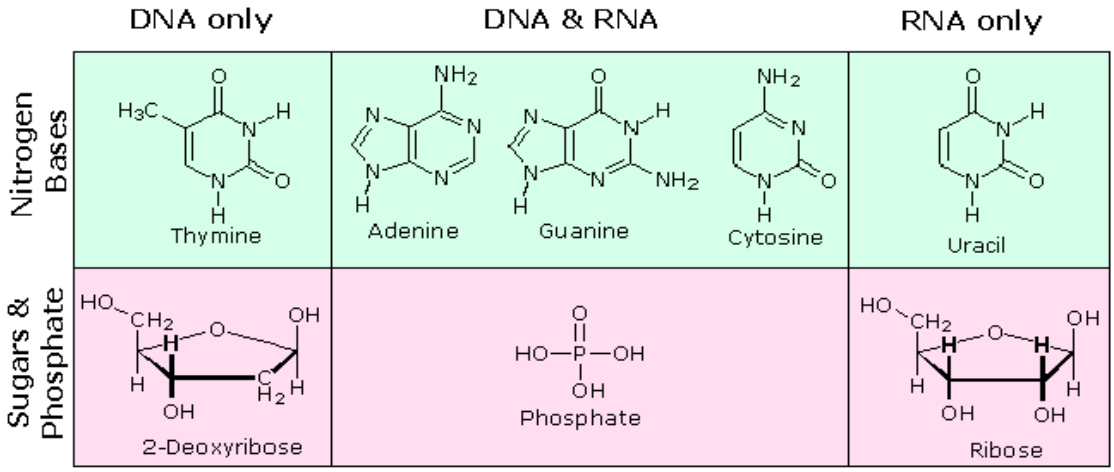


Guanine

PURINES

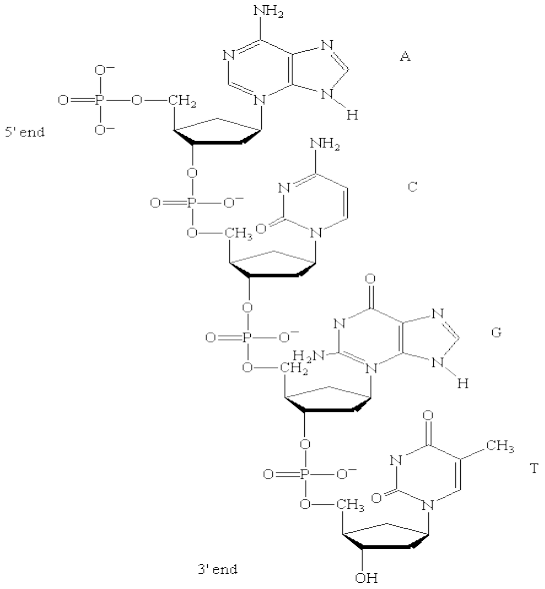
DNA and RNA each contain four nucleotides. Both contain the same purines — adenine and guanine — and both also contain the pyrimidine cytosine. But the fourth nucleotide in DNA is thymine, whereas RNA uses uracil to complete its quartet of nucleotides.

Components of Nucleic Acids



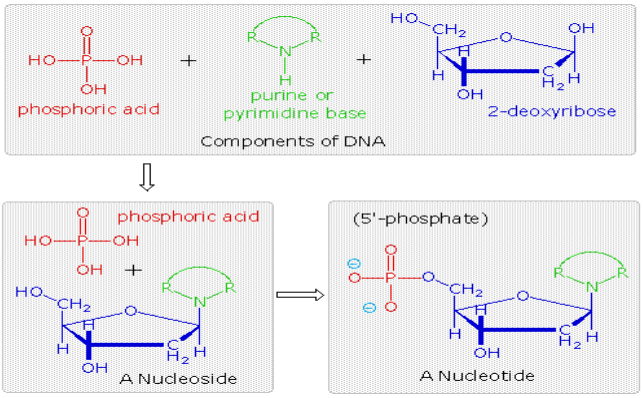
Polynucleotides

The carbon atoms in the sugar at the center of a nucleotide are numbered from 1 to 5. The -OH group on the 3 carbon of one nucleotide can react with the phosphate attached to the 5 carbon of another to form a dinucleotide held together by phosphate ester bonds. As the chain continues to grow, it becomes a **polynucleotide**. A short segment of a DNA chain is shown in the figure below.

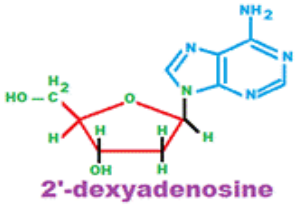
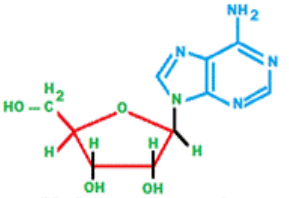


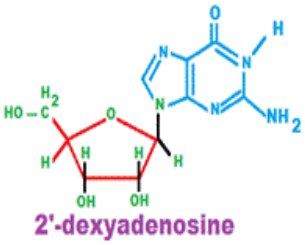
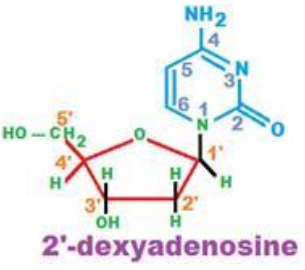
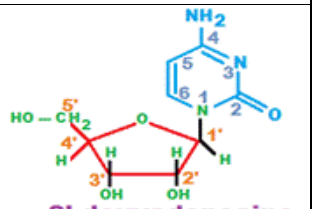
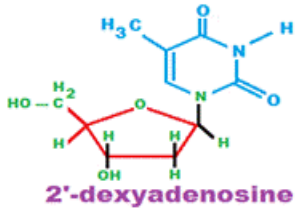
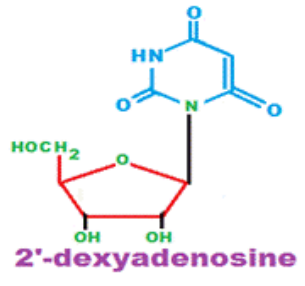
this DNA segment contains the following sequence of amine substituents: adenine (A), cytosine (C), guanine (G), and thymine (T).

When the phosphate group of a nucleotide is removed by hydrolysis, the structure remaining is called a nucleoside.



On the basis of five different bases, there are five nucleosides are possible in DNA and RNA.

Abbreviation	Base	Nucleoside	Nucleic Acid	Structure of nucleoside
A	Adenine	Deoxyadenosine	DNA	 2'-dexyadenosine
		Adenosine	RNA	 2'-dexyadenosine

G	Guanine	Deoxyguanosine	DNA	
		Guanosine	RNA	
C	Cytosine	Deoxycytidine	DNA	
		Cytidine	RNA	
T	Thymine	Deoxythymidine (thymidine)	DNA	
U	Uracil	Uridine	RNA	

In addition to its role as a stable informational library, chromosomal DNA must be structured or organized in such a way that the chemical machinery of the cell will have easy access to that information, in order to make important molecules such as polypeptides. Furthermore, accurate copies of the DNA code must be created as cells divide, with the replicated DNA molecules passed on to subsequent cell generations, as well as to progeny of the organism. The high molecular weight nucleic acid, DNA, is found chiefly in the nuclei of complex

cells, known as **eucaryotic cells**, or in the nucleoid regions of **procaryotic cells**, such as bacteria. It is often associated with proteins that help to pack it in a usable fashion. In contrast, a lower molecular weight, but much more abundant nucleic acid, **RNA**, is distributed throughout the cell, most commonly in small numerous organelles called **ribosomes**. Three kinds of RNA are identified, the largest subgroup (85 to 90%) being ribosomal RNA, **rRNA**, the major component of ribosomes, together with proteins. The size of rRNA molecules varies, but is generally less than a thousandth the size of DNA. The other forms of RNA are messenger RNA, **mRNA**, and transfer RNA, **tRNA**. Both have a more transient existence and are smaller than rRNA.

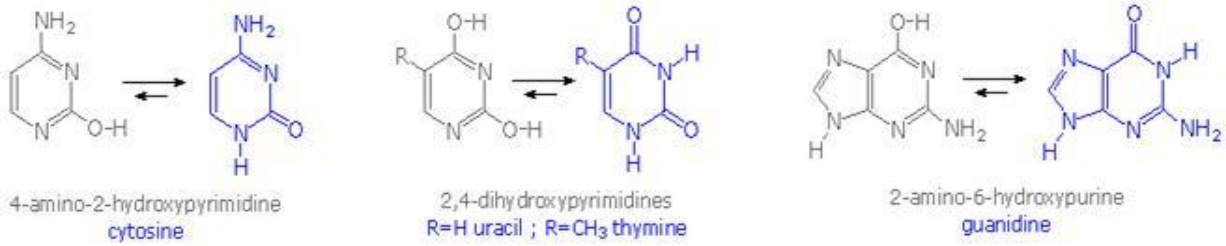
The RNA's play a vital role in the transfer of information (transcription) from the DNA library to the protein factories called ribosomes, and in the interpretation of that information (translation) for the synthesis of specific polypeptides. These functions will be described later.

The Secondary Structure of DNA

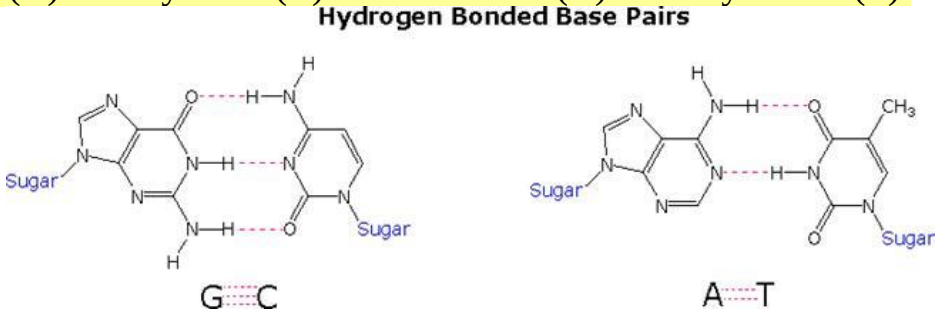
Rosalind Franklin, working at King's College, London, obtained X-ray diffraction evidence that suggested a long helical structure of uniform thickness. Francis Crick and James Watson, at Cambridge University, considered hydrogen bonded base pairing interactions, and arrived at a double stranded helical model that satisfied most of the known facts, and has been confirmed by subsequent findings.

Base Pairing

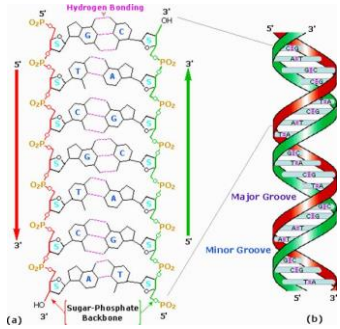
Careful examination of the purine and pyrimidine base components of the nucleotides reveals that three of them could exist as hydroxy pyrimidine or purine tautomers, having an aromatic heterocyclic ring. Despite the added stabilization of an aromatic ring, these compounds prefer to adopt amide-like structures. These options are shown in the following diagram, with the more stable tautomer drawn in blue.



Once they had identified the favored base tautomers in the nucleosides, Watson and Crick were able to propose a complementary pairing, via hydrogen bonding, of guanosine (G) with cytidine (C) and adenosine (A) with thymidine (T).



Complementary primary nucleotide structures for each strand allowed intra-strand hydrogen bonding between each pair of bases.



Deoxyribonucleic acid (DNA) consists of covalently linked chains of deoxyribonucleotides, and ribonucleic acid (RNA) consists of chains of ribonucleotides.

Thus the backbone of both DNA and RNA consists of alternating phosphate and pentose groups, in which phosphodiester bridges provide the covalent continuity. The purine and pyrimidine bases of the nucleotide units are not present in the backbone structure but constitute distinctive side chains, just as the R groups of amino acid residues are the distinctive side chains of polypeptides. In addition to the nuclear DNA, diploid eukaryotic cells also contain very small amounts of DNA in the mitochondria; it differs in its base composition and molecular weight from nuclear DNA. Most cells contain 2 to 8 times as much RNA as DNA.

DNA

Deoxyribonucleic acid, or DNA, is a biological macromolecule that carries hereditary information in many organisms. DNA is necessary for the production of proteins, the regulation, metabolism, and reproduction of the cell. Large compressed DNA molecules with associated proteins, called chromatin, are mostly present inside the nucleus. Some cytoplasmic organelles like the mitochondria also contain DNA molecules.

DNA is usually a double-stranded polymer of nucleotides, although single-stranded DNA is also known. DNA usually occurs as linear chromosomes in eukaryotes, and circular chromosomes in prokaryotes. The set of chromosomes in a cell makes up its genome; the human genome has approximately 3 billion base pairs of DNA arranged into 46 chromosomes.[109] The information carried by DNA is held in the sequence of pieces of DNA called genes. Transmission of genetic information in genes is achieved via complementary base pairing. For example, in transcription, when a cell uses the information in a gene, the DNA sequence is copied into a complementary RNA sequence through the attraction between the DNA and the correct RNA nucleotides. Usually, this RNA copy is then used to make a matching protein sequence in a process called translation, which depends on the same interaction between RNA nucleotides. In alternative fashion, a cell may simply copy its genetic information in a process called **DNA replication.** When a double-stranded

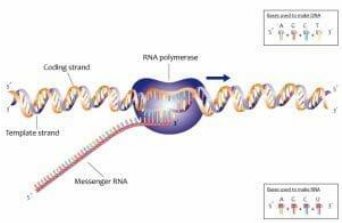
DNA molecule needs to be **replicated**, the first thing that happens is that the two strands separate along a short stretch, creating a bubble-like structure. In this transient single-stranded region, a number of enzymes and other proteins, including DNA polymerase work to create the complementary strand, with the correct nucleotide being chosen through hydrogen bond formation. These enzymes continue along each strand creating a new polynucleotide molecule until the entire DNA is replicated.

Life begins from a single cell. For humans, this is the zygote formed by the fertilization of an egg by a sperm. After this, the entire dazzling array of cells and types are produced by cell division. Even the maintenance of normal functions in an adult requires constant mitosis. Each time a cell divides, nuclear genetic material is duplicated. This implies that nearly 3 billion nucleotides are accurately read and copied. High-fidelity DNA polymerases and a host of error repair mechanisms ensure that there is only one incorrectly incorporated nucleotide for every 10 billion base pairs.

Transcription

The second important function of genetic material is to direct the physiological activities of the cell. Most catalytic and functional roles in the body are carried out by peptides, proteins and RNA. The structure and function of these molecules is determined by nucleotide sequences in DNA.

When a protein or RNA molecule needs to be produced, the first step is transcription. Like DNA replication, this begins with the transient formation of a single-stranded region. The single-stranded region then acts as the template for the polymerization of a complementary polynucleotide RNA molecule. Only one of the two strands of DNA is involved in transcription. This is called the template strand and the other strand is called the coding strand. Since transcription is also dependent on complementary base pairing, the RNA sequence is nearly the same as the coding strand.



In the image, the coding strands and the template strands are depicted in orange and purple respectively. RNA is transcribed in the 5’ to 3’ direction.

Messenger RNA contains only the four major bases. It is synthesized in the nucleus during the process of transcription, in which the sequence of bases in one strand of the chromosomal DNA is enzymatically transcribed in the form of a single strand of mRNA; some mRNA is also made in the mitochondria. The sequence of bases of the mRNA strand so formed is complementary to that of the DNA strand being transcribed. Each of the thousands of different proteins synthesized by the cell is coded by a specific mRNA or segment of an mRNA molecule.

Transfer RNAs

Transfer RNAs are relatively small molecules that act as carriers of specific individual amino acids during protein synthesis on the ribosomes. Each of the 20 amino acids found in proteins has at least one corresponding tRNA, and some have multiple tRNAs

Ribosomal RNA

Ribosomal RNA (rRNA) constitutes up to 65 percent of the mass of ribosomes. Although rRNAs make up a large fraction of total cellular RNA, their function in ribosomes is not yet clear. A few of the bases in rRNAs are methylated.

Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) are chainlike macromolecules that function in the storage and transfer of genetic information They are major components of all cells, together making up from 5 to 15 percent of their dry weight.

Just as the amino acids are the building blocks, or monomeric units, of polypeptides, the nucleotides are the monomeric units of nucleic acids.

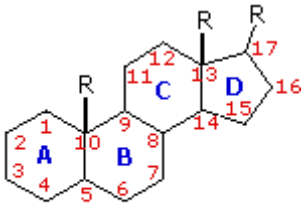
Questions:

1. What are the characteristics of nucleic acids?
2. What are two types of nucleic acids and their functions?
3. What is the biological importance of nucleic acids?

Unit 18. Low molecular weight bioregulators

Steroids

The important class of lipids called **steroids** are actually metabolic derivatives of terpenes, but they are customarily treated as a separate group. Steroids may be recognized by their tetracyclic skeleton, consisting of three fused six-membered and one five-membered ring, as shown in the diagram to the right. The four rings are designated A, B, C & D as noted, and the peculiar numbering of the ring carbon atoms (shown in red) is the result of an earlier misassignment of the structure. The substituents designated by R are often alkyl groups, but may also have functionality. The R group at the A:B ring fusion is most commonly methyl or hydrogen, that at the C:D fusion is usually methyl. The substituent at C-17 varies considerably, and is usually larger than methyl if it is not a functional group. The most common locations of functional groups are C-3, C-4, C-7, C-11, C-12 & C-17. Ring A is sometimes aromatic. Since a number of tetracyclic triterpenes also have this tetracyclic structure, it cannot be considered a unique identifier.

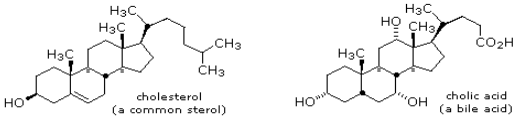


The Steroid
Carbon Skeleton

Steroids are widely distributed in animals, where they are associated with a number of physiological processes. Examples of some important steroids are

shown in the following diagram. Different kinds of steroids will be displayed by clicking the "Toggle Structures" button under the diagram. Norethindrone is a synthetic steroid, all the other examples occur naturally. A common strategy in pharmaceutical chemistry is to take a natural compound, having certain desired biological properties together with undesired side effects, and to modify its structure to enhance the desired characteristics and diminish the undesired. This is sometimes accomplished by trial and error.

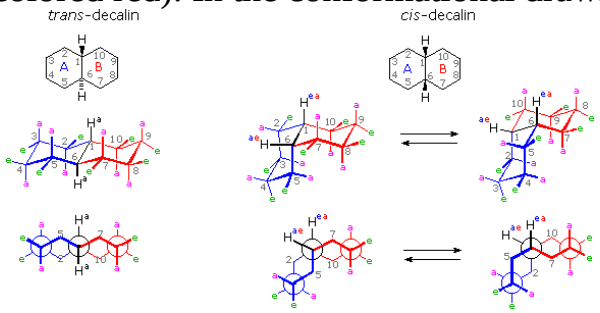
The generic steroid structure drawn above has seven chiral stereocenters (carbons 5, 8, 9, 10, 13, 14 & 17), which means that it may have as many as 128 stereoisomers. With the exception of C-5, natural steroids generally have a single common configuration. This is shown in the last of the toggled displays, along with the preferred conformations of the rings. Steroids are complex ethers of cyclic spirits *sterols* and fatty acids.



Typical Animal Steroids

Chemical studies of the steroids were very important to our present understanding of the configurations and conformations of six-membered rings. Substituent groups at different sites on the tetracyclic skeleton will have axial or equatorial orientations that are fixed because of the rigid structure of the trans-fused rings. This fixed orientation influences chemical reactivity, largely due to the greater steric hindrance of axial groups versus their equatorial isomers. Thus an equatorial hydroxyl group is esterified more rapidly than its axial isomer.

It is instructive to examine a simple bicyclic system as a model for the fused rings of the steroid molecule. Decalin, short for decahydronaphthalene, exists as cis and trans isomers at the ring fusion carbon atoms. Planar representations of these isomers are drawn at the top of the following diagram, with corresponding conformational formulas displayed underneath. The numbering shown for the ring carbons follows IUPAC rules, and is different from the unusual numbering used for steroids. For purposes of discussion, the left ring is labeled A (colored blue) and the right ring B (colored red). In the conformational drawings the ring fusion

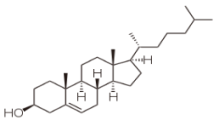


and the angular hydrogens are black.

The most generally abundant steroids are sterols, which occur in all tissues of animals, green plants, and fungi such as yeasts.

A sterol is a particular type of lipid that consists of four fused rings with one molecule at the end. The prototypical sterol is cholesterol, which has been highly studied for its health effects.

Cholesterol is a sterol that is very important for normal cellular functioning. It is a vital component of animal cellular membranes and is necessary for their stability and fluidity. Also, it is the precursor molecule for many other compounds, including steroid hormones like estrogen, testosterone, and cortisol. Vitamin D is made from cholesterol, and the activated form of Vitamin D is a sterol.



Cholesterol

Bile acids

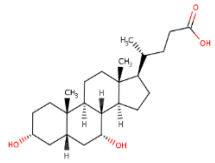
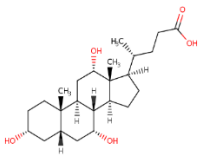
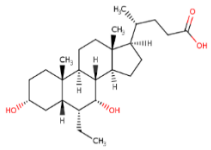
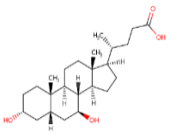
Bile acids (BAs) are a family of steroidal molecules derived from cholesterol and biosynthesised in the pericentral hepatocytes of the liver. Structurally they may be regarded as consisting of two components, a rigid steroid nucleus and a short aliphatic side chain terminating in an alcohol or carboxyl group. Bile acids are synthesized from cholesterol in the liver and actively secreted along with cholesterol and phospholipids into the bile.

Bile flowing from the liver is concentrated in the gallbladder and, in response to a meal, released into the upper intestine. The primary bile acids synthesized in the liver are cholic and chenodeoxycholic acid which are typically conjugated to glycine or taurine before secretion. In the intestine, the primary bile acids are often converted by colonic bacteria to the secondary bile acids. The major components of the bile acid pool are cholic and chenodeoxycholic acid with lesser amounts deoxycholic and lithocholic acid and minor amounts of ursodeoxycholic acid.

Bile acids also act as signaling molecules and are important in regulation of their own synthesis, uptake and secretion as well as control of cholesterol synthesis and regulation of lipid and glucose metabolism. Bile acid levels are increased in the serum and liver in patients with obstructive jaundice or cholestasis and, perhaps because of their inherent detergent activities, can cause hepatocyte injury.

CHEMICAL FORMULAS AND STRUCTURES

Bile Acids

MOLECULAR FORMULA STRUCTURE	**MOLECULAR FORMULA STRUCTURE**	**MOLECULAR FORMULA STRUCTURE**	**MOLECULAR FORMULA STRUCTURE**
Chenodiol  C24-H40-O4	Cholic Acid  C24-H40-O5	Obeticholic Acid  C26-H44-O4	Ursodiol  C24-H40-O4

Questions:

1. What are some trace elements found in organic compounds?
2. What are the main properties of simple molecular compounds?
3. What are the examples of high molecular compounds?

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БИООРГАНИЧЕСКАЯ И МЕДИЦИНСКАЯ ХИМИЯ

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