MINISTRY OF HEALTH OF UKRAINE
ODESA NATIONAL MEDICAL UNIVERSITY
Department of Medical Biology and Chemistry

CONFIRMED by
Vice-rector for scientific and pedagogical work
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METHODOLOGICAL DEVELOPMENT
TO THE LECTURES ON EDUCATIONAL DISCIPLINE
"MEDICAL CHEMISTRY"

Department, course **International faculty, 1st course**

Specialty: **222 «Medicine»**

Discipline **Medical chemistry**

The program was approved:
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Lecture № 1

***Topic*: «Chemistry and medicine. Biogenic elements, their role in life processes.»**

Actuality of theme: Medicinal chemistry studies the structure and reactivity of the most important biologically active molecules, the theory of chemical bonding in complex compounds of biometals with bioligands, and the role of biogenic elements in the vital activity of the body. It investigates the processes that take place at the molecular and submolecular levels, and it is precisely here that the causes of the occurrence of various forms of diseases and the specificity of hereditary characteristics should be sought.

Aims: show the value of chemistry for the development of modern medicine, the interrelationship of the biological action of elements depending on their location in the periodic table in accordance with the electronic classification of s -, p-, d -, f- blocks of elements. To acquaint students with the structure and content of the "Medical Chemistry" course. Pay attention to safety rules when working in a chemical laboratory. Trace the relationship between the biological activity of chemical elements and the electronic structure of their atoms. Consider different types of classifications of biogenic elements.

Basic concepts: atomic structure, biogenic elements, s-, p-, d-elements, classification of biogenic elements.

Plan and organizational structure of the lecture:

1. relationship between chemistry and medicine.
2. Classification of biogenic elements.
3. Biogenic s-elements. Biological role.
4. Biogenic p-elements. Biological role.
5. Biogenic d-elements. Biological role.

Content of lecture material (lecture text)

For modern physicians and pharmacists, the study of inorganic chemistry is of great importance because many drugs are inorganic in nature. Therefore, physicians must clearly know their properties: solubility, mechanical strength, reactivity, impact on humans and the environment.

Modern medicine has extensively studied the relationship between the content of chemical elements in the body and the occurrence and development of various diseases. It turned out that the body is particularly sensitive to changes in its concentration of trace elements, i.e. elements present in the body in an amount less than 1 g per 70 kg of human body weight. Such elements include copper, zinc, manganese, molybdenum, cobalt, iron and nickel.

Of the non-metalloids, atoms of hydrogen, oxygen, nitrogen, carbon, phosphorus and sulfur in organic compounds and atoms of halogens and boron both as ions and as part of organic particles can almost always be found in living systems. Deviations in the content of most of these elements in living organisms often lead to quite severe metabolic disorders.

Most diseases are caused by a deviation of concentrations of any substance from the norm. This is due to the fact that a huge number of chemical transformations within the living cell occurs in several stages, and many substances are important to the cell not by themselves, they are only intermediaries in a chain of complex reactions, but if any link is broken, then the whole chain as a result often ceases to perform its transfer function; stops the normal work of the cell for the synthesis of necessary substances.

Changes in zinc concentrations have been proven to be associated with the course of cancer, cobalt and manganese with heart muscle diseases, and nickel with blood clotting processes. Determination of the concentration of these elements in the blood can sometimes detect early stages of various diseases. Thus, changes in zinc concentrations in blood serum are associated with the course of liver and spleen diseases, and concentrations of cobalt and chromium - with some cardiovascular diseases.

The role of organic molecules in maintaining the normal vital functions of the body is very great. They can be divided into three groups according to the principles inherent in their design: biological macromolecules (proteins, nucleic acids and their complexes), oligomers (nucleotides, lipids, peptides, etc.) and monomers (hormones, antibiotics, vitamins and many other substances).

It is especially important for chemistry to establish the connection between the structure of a substance and its properties, in particular its biological action. For this purpose, many modern methods from the arsenal of physics, organic chemistry, mathematics, and biology are used.

In modern science, many new sciences have emerged on the boundary of chemistry and biology, which differ in their methods, goals, and objects of study. All these sciences are commonly grouped under the term "physicochemical biology". This field includes:

a) Chemistry of natural compounds (bioorganic and bioinorganic chemistry bioorganic chemistry and inorganic biochemistry, respectively);

b) biochemistry;

c) biophysics;

d) molecular biology;

e) molecular genetics;

f) pharmacology and molecular pharmacology and many related disciplines.

The scientific substantiation of the doctrine of chemical elements was obtained in academic Vladimir Vernadsky works, who showed a close relationship between the chemical composition of the Earth's crust, oceans and living organisms. He believed that living organisms and the Earth's crust form a single system, and living organisms are involved in the geochemical processes of the distribution of chemical elements in the Earth's crust.

The shell of the Earth, within the boundaries of which organisms live, is called the *biosphere*.

The most important studies of the biosphere were carried out by the first president of the Ukrainian Academy of Sciences V.I. Vernadsky (1863-1945). Studying geochemical transformations in the Earth's crust, V.I. Vernadsky established that the changes occurring in its upper layers in a certain way affect the chemical composition of living organisms. Studies of the chemical composition of the Earth's crust, soil, sea water, plants, animals, and humans have shown that living organisms, including the human one, contain almost all the elements that exist in the Earth's crust and sea water. V.I. Vernadsky believed that living organisms and the earth's crust make up one system.

Studying the movement (migration) of elements, V.I.Vernadsky established that migration, dispersion and concentration of elements depend on the atomic mass of the chemical element, the atomic and ionic radius, and also on the ability of the elements to form chemical compounds.

All chemical elements that take part in the biological processes of living organisms are called *biogenic elements*.

The quantitative content of chemical elements in living matter (living matter is the totality of all living organisms) is inversely proportional to their numbers in the periodic system of elements, i.e. the quantitative chemical composition of living matter is a periodic function of the element number. However, this regularity is violated for elements of the main subgroups of I, II, and VII groups.

Violation of this pattern depends on the nature of the chemical bond between the atom of the element in question and other atoms included in the molecules of bioorganic compounds.

The quantitative content of covalently bound atomic elements decreases with increasing charge of atoms in the group (for example, N, P, As, Sb), and the elements that are in the body in the form of ions (S-elements of I and II groups, p-elements of group VII) - increases (to the optimum ionic radius), and then decreases. For example, when switching from beryllium to calcium, the content of an element in a living organism increases, and then decreases; during the transition from fluorine to chlorine, it also increases, and then decreases (table 1).

Table 1. The dependence of the quantitative content of chemical elements on the nuclear charge

Element	Content, mass fraction, %	Element	Content, mass fraction, %
$_{4}Be$	10^{-7}-10^{-4}	$_{9}F$	10^{-5}
$_{12}Mg$	$2,7 . 10^{-2}$	$_{17}Cl$	$1 \cdot 10^{-1}$
$_{20}Ca$	2,0	$_{35}Br$	10^{-4}-10^{-3}
$_{38}Sr$	10^{-3}-10^{-2}	$_{53}I$	10^{-5}-10^{-3}
$_{56}Ba$	10^{-5}-10^{-4}		

There are several classifications of chemical elements contained in the human body.

So, V.I.Vernadsky, depending on the average content in living organisms, divided the elements into three groups:

1. Macroelements. These are elements which content in the body is above 10^{-2}%. These include C, H, O, N, P, S, Ca, Mg, Na, and Cl.

2. Microelements. These are elements whose content in the body ranges from 10^{-2} to 10^{-12}%. These include I, Cu, As, F, Br, Sr, Ba, Co.

3. Ultramicroelements. These are elements whose content in the body is below 10^{-12}%. These include Hg, Au, U, Ra, etc.

Biogeochemistry was further studied in the Academician A.P. Vinogradov works.

In the process of evolution from inorganic substances to bioorganic basis for the use of certain chemical elements in the creation of biosystems is natural selection. As a result of this selection, only six elements form the basis of all living systems: C, H, O, N, P, S, called organogens. Their content in the body reaches 97.4%.

From the point of view of chemistry, the natural selection of organogen elements can be explained by their ability to form chemical bonds: on the one hand, they are strong enough, that is, energy-intensive, and on the other hand, quite labile, which could easily give in to hemolysis, heterolysis, and cyclic redistribution.

The number one organogen is undoubtedly carbon. Its atoms form strong covalent bonds between themselves or with atoms of other elements. These bonds can be ordinary or multiple, thanks to such bonds, carbon can form conjugate or cumulated systems in the form of open or closed chains, cycles. Unlike carbon, organogen elements do not form hydrogen and oxygen labile bonds, but their presence in an organic, including bioorganic, molecule determines its ability to interact with a bio-solvent - water. In addition, hydrogen and oxygen are carriers of the redox properties of living systems, they ensure the unity of redox processes. The remaining three organogens - N, P and S, as well as some other elements - Fe, Mg, which make up the active centers of enzymes, like carbon, are able to form labile bonds. A positive property of organogens is that they, as a rule, form compounds that are readily soluble in water and therefore are concentrated in the body.

Of all the biogenic elements, eleven (O, H, N, S, Ca, Mg, K, Na, Cl, P, C) make up 99.5% of the body mass. The content of all other elements is less than 0.5%.

The natural selection of elements was due to such factors:

- the ability to form strong (energy-intensive) bonds;
- the ability to form chains;
- lability of bonds;
- “lability” of atoms, for example, S, P, Fe /according to J. Bernal /;
- the formation of compounds readily soluble in water, which contributed to their concentration in the body;
- the tendency to form stable coordination compounds with biological molecules.

Human organs differently concentrate various chemical elements in themselves, that is, micro and macro elements are unevenly distributed between different organs and tissues. Most trace elements accumulate in the liver, bone and muscle tissue. These tissues are the main depot (reserve) for many trace elements.

It is known that Cu is concentrated in the liver, Zn - in the pancreas; I - in the thyroid gland; F - in tooth enamel; Al, As accumulate in the hair and nails; Cd, Hg, Mn - in the kidneys; Sr - in the prostate gland; Ba - in the retina.

Developing the ideas of V.I. Vernadsky on the role of the elemental composition of the soil in the evolution of organisms, A.P. Vinogradov developed the doctrine of biogeochemical provinces - areas with an increased or decreased content of an element in them - and endemic diseases caused by the associated content of elements in the human body.

Diseases associated with a deficiency or excess of elements in the human body have been identified. So, with rickets, there is a violation of phosphorus-calcium metabolism, which leads to a decrease in calcium content. With jade, due to a violation of electrolyte metabolism, the content of calcium, sodium, chlorine decreases and the content of magnesium and potassium in the body increases. Cuprum deficiency is one of the causes of cancer. In some cases, doctors associate lung cancer with elderly people with an age-related decrease in the content of cuprum in the body. However, an excess of cuprum in the body leads to mental disorders and paralysis of some organs (Wilson's disease). Only relatively large amounts of cuprum compounds are harmed. Such patterns are due to the fact that in the human body a balance of optimal concentrations of nutrients is maintained - chemical homeostasis. Violation of this balance can lead to various diseases.

Nowadays it has been firmly established that the lack of certain chemical elements in the soil leads, respectively, to a lower level of these elements in the body of people living in a given area, and to certain diseases.

So, in Ukraine, the Carpathians and Crimea there are geochemical provinces with a low iodine content, and the Kropyvnytskyi region – there is a high content of uranium.

Information on the content of one or another chemical element in the human body is important both for the diagnosis of the disease and for the direction of its treatment. Deficiency of chemical elements in the human body is characterized by certain symptoms (table 2).

Table 2. Characteristic symptoms of chemical elements deficiency in the human body

Element deficiency	Typical symptom
Ca	Skeletal growth retardation
Mg	Muscle cramps
Fe	Anemia, a violation of the immune system
Zn	Skin damage, growth retardation, sexual maturation retardation
Cu	Arterial weakness, impaired liver function, secondary anemia
Mn	Infertility, skeletal growth impairment
Mo	Slowing down cell growth, caries tendency
Co	Pernicious anemia
Ni	Increased depression, dermatitis
Cr	Diabetes Symptoms
Si	Skeletal growth impairment
F	Tooth decay
I	Disruption of the thyroid gland, slowing down metabolism
Se	Muscular (particularly heart) weakness

The rapid technical development of civilization has led not only to the creation of modern technologies, but also to the appearance of environmental problems.

The environment is polluted in two ways: natural or man-made, i.e. due to human activity. Natural disasters - earthquakes, volcanic eruptions, etc. - strongly pollute the environment. But nature over many years has adapted to most natural pollution and learned to neutralize it.

Over the years of technological progress, man-made disasters have become more frequent. For example, on April 26, 1986, the largest nuclear accident occurred. Radioactive substances from the reactor entered the atmosphere and formed a radioactive cloud, which was 30 km wide and 100 km long. Ukraine experiences the consequences of this disaster even after 30 years.

Significant amounts of SO_2, NO, CO, CO_2 accumulate in the atmosphere as a result of human industrial activity and, together with the air we breathe, enter our body, which negatively affects our health. In recent years, the CO_2 content in the atmosphere has increased dramatically, which, according to scientists, has led to a 1 degree increase in temperature on the planet over the past 100 years. In 1997, in Kyoto at the International Conference, the developed countries of the world signed an agreement, according to which a limit was set for emissions of industrial gases into the atmosphere.

In the practice of sanitary-hygienic, biochemical, clinical and analytical laboratories for the study of the quality of drinking and wastewater, food, air, soil, methods of qualitative analysis occupy a leading place. In clinical and biochemical laboratories, these methods are used to study the chemical composition of individual organs and tissues, metabolism in humans and animals in normal and pathological conditions. A chemical analysis of blood, urine, gastric juice and other biological fluids facilitates the diagnosis of the disease and makes it possible to monitor the course of the disease in dynamics.

V.V. Kowalski created the doctrine of geochemical ecology - biochemical and physiological adaptations of the body to the chemical elements of this environment. According to Kowalski, most organisms adapt to the unusual content of certain elements and develop normally. And only 5 to 20% of organisms in these conditions suffer from endemic diseases. He, based on the degree of importance of chemical elements for human life, divided them into three groups:

Irreplaceable elements. They are constantly in the human body, are part of its inorganic and organic compounds. These are H, O, Ca, N, K, P, Na, S, Mg, Cl, C, I, Mn, Cu, Co, Zn, Fe, Mo, V. A deficiency in the content of these elements leads to a disruption in the normal functioning of the body.

Impurity elements. These elements are constantly found in the human body, but their biological role has not always been clarified or little studied. These are Ga, Sb, Sr, Br, F, B, Be, Li, Si, Sn, Cs, As, Ba, Ge, Rb, Pb, Ra, Bi, Cd, Cr, Ni, Ti, Ag, Th, Hg Ce. Se.

Microimpurity elements. They are found in the human body, but there is no information about the quantitative content or the biological role. These are Sc, Tl, In, La, Sm, Pr, W, Re, Tb, etc.

A.I. Venchikov believed that chemical elements, regardless of their quantitative content, should be given the name of biotic elements if their physiological activity is proven. By A.I. Venchikov, biotics are chemical elements of exogenous origin that are part of the biochemical structures and systems of the body, participating in biochemical and physiological processes and capable of increasing the body's resistance to the action of harmful agents on it. It follows from this definition that both macro- and microelements that are part of vitamins, enzymes and other substances that are necessarily involved in metabolic processes can be classified as biotics. In accordance with this classification, elements playing the role of plastic material in the body, as well as creating physical and chemical conditions for physiological processes (pH of the medium, osmotic pressure, etc.) to this group, except C, N, O, H can be attributed macroelements Na, Ca, K, Mg, Cl, P. The next group includes elements involved in metabolic processes. These are biocatalytic elements (Fe, Cu, Mn, etc.). They activate the enzymatic processes of the body or enter the structure of enzymes (Zn), vitamins (Co), hormones (I).

The third group includes the so-called reticuloendothelial elements (As, Hg, Sb, etc.), which contribute to the reticuloendothelial system of the formation of substances that inhibit the vital activity of microbes.

A.P. Vinogradov proposed a fundamentally new classification, based on which the biological role of elements was made dependent on the electronic structure of their atoms, i.e. it was depended on the position in the periodic system of elements D.I. Mendeleev.

Based on the electronic structure of atoms, elements of s, p, d - blocks are referred to biogenic elements. The electronic structure of an atom determines the features of its behavior in chemical reactions, and affects the types of chemical bonds formed by it in compounds.

S-BLOCK BIOGENIC ELEMENTS

S-ELEMENTS OF GROUP I

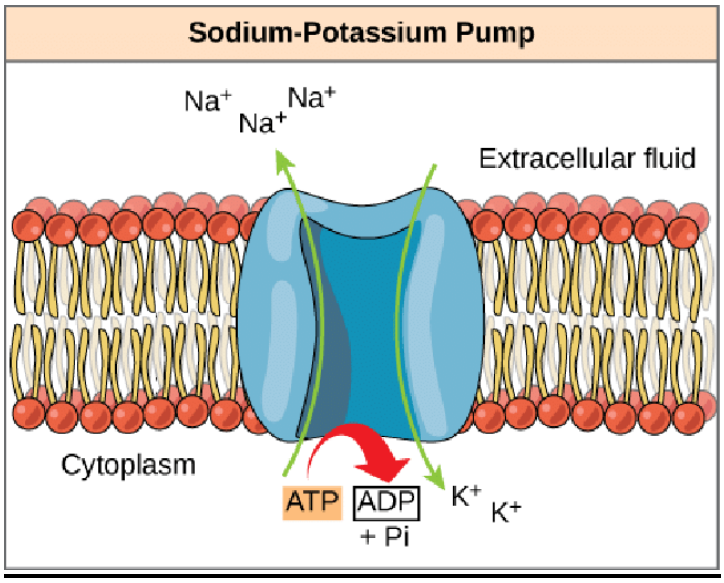
In the periodic system of chemical elements of D.I. Mendeleev, biogenic s-elements are included in the main subgroups of I and II groups. They are located at the beginning of periods and are typical metals.

s-Elements are characterized by small values of ionization potentials at sufficiently large values of the radii of atoms and ions. Group I s-elements, as a rule, form compounds with an ionic type of bond, group II s-elements in this respect are somewhat inferior to them. These properties make them physiologically active, and such elements as K, Na, Ca, Mg are vital and exhibit unique properties in the body. Most biogenic s-elements are macroelements. Their high concentration in the body is associated with the formation of compounds that are readily soluble in biological fluids (s-elements of group I), and hardly soluble salts involved in the formation of bone tissue (s-elements of group II). The biogenic elements of group I are necessary for the normal living organism functions. First of all, these are macroelements - hydrogen, potassium and sodium.

Macroelements potassium and sodium are distributed throughout the body. According to A. Webb, in all organs except the kidneys, the potassium content is greater than sodium. By chemical properties, potassium differs markedly from sodium. This is largely due to the presence of free d-orbitals in potassium and its analogues, which have energy close to the energy of ns - sublevels. The difference in properties possibly determines their different behavior in living organisms. The main difference is that sodium ions are part of intercellular fluids, and potassium ions are intracellular; sodium cations suppress the activity of muscle functions and are therefore necessary for their contraction; potassium cations help to relax the heart muscles between contractions.

A different concentration of potassium and sodium cations inside and outside the nerve cell and its axon and the greater ease of passage of K^+ ions through the membrane than Na^+ leads to the appearance of a potential difference in the cell body of the order of 60-90 mV, while the inner surface of the cell membrane is negatively charged with

respect to the outside. A peculiar - Na^+ - K^+ - pump is formed. When excited, biochemical processes occur that lead to a change in the permeability of the cell membrane. As a result, sodium ions penetrate into the cell, causing local damping of the negative charge and its change to a positive one. The so-called action potential arises. The restoration of the initial potential occurs not as a result of the reverse movement of sodium ions, but as a result of the release of an equivalent amount of potassium ions from the cell.



S - Elements of group II

The biogenic S-elements of group II include macrocells magnesium and calcium, which, according to the classification of A.I. Venchikova belong to the group of biotics, playing the role of plastic material, as well as creating physico-chemical conditions for physiological processes, and trace elements of beryllium and strontium; the role of the remaining micro- and ultramicroelements (barium and radium) in the body is not well understood.

Magnesium and calcium are vital elements. Calcium is the main structural element of living organisms; Magnesium is a part of a large number of enzymes and is an activator of many biochemical processes.

The calcium atom is larger in size than the magnesium atom; therefore, its ability to form hydrates, as well as the solubility of its carbonates and phosphates in water, is

significantly lower compared to magnesium compounds. Calcium carbonates and phosphates are the main material that forms bone and dental tissue.

A quantitative characteristic of the solubility of compounds is the solubility product (SP). Its meaning becomes clear if we consider the equilibrium processes that occur in heterogeneous systems. In such systems — saturated solutions of sparingly soluble substances — the solid phase is in equilibrium with the hydrated ions in solution. In general:

$$K_mA_n \rightarrow mK^{n+} + nA^{m-}$$

precipitate → solution

This state is characterized by the equilibrium constant, which is obtained using the law of mass action, and is called the solubility product:

$$SP = [K_p^{n+}]^m \cdot [A_p^{m-}]^n \quad (1)$$

For a saturated solution of $Mg(OH)_2$ in equilibrium with the precipitate:

$$Mg(OH)_2 \leftrightarrow Mg^{2+} + 2OH^-$$

precipitate solution

the expression for the solubility product is:

$$SP\ (Mg(OH)_2) = [Mg^{2+}] \cdot [OH^-]^2$$

Thus, in a saturated solution of a sparingly soluble compound, the product of the concentrations of its ions in degrees of stoichiometric coefficients at a given temperature is a constant value (table 3).

Table 3. The solubility product of some sparingly soluble electrolytes in water, t = 25°C.

Compound	**SP**	***p*SP = -lg SP**
$CaCO_3$	$4,8 \times 10^{-9}$	8,32
$Ca_3(PO_4)_2$	$2,0 \times 10^{-29}$	28,70
CaF_2,	$4,0 \times 10^{-11}$	10,40
$Mg(OH)_2$	$5,5 \times 10^{-12}$	11,26
$BaSO_4$	$1,8 \times 10^{-10}$	9,75

It is likely that the elements involved in the formation of bone tissue should satisfy the basic requirements: to be macroelements, have high energy for the formation of chemical bonds, form poorly soluble compounds; easily absorbed by a living organism. Calcium phosphate and calcium carbonate meet these requirements. Calcium, phosphorus, carbon and oxygen are macrocells; the binding energy of oxygen with phosphorus and carbon, through which calcium binds to them, is quite high; calcium phosphate and calcium carbonate sparingly soluble compounds; all these elements are easily absorbed by the body, since in nature they exist in easily accessible forms for assimilation. Magnesium, which is also a macronutrient, forms poorly soluble phosphates and basic carbonates, but they are more soluble than calcium.

Precipitation formation and dissolution conditions

As is known, the solubility product at constant temperature is a constant value. According to the rule of the solubility product, at the moment when the product of the ion concentration (ion product) of the sparingly soluble electrolyte reaches the value of its solubility product at a given temperature, the solution becomes saturated relative to this electrolyte.

If the product of the molar concentration of ions in the solution is greater than the product of solubility, then such a solution is supersaturated. From a supersaturated solution, sooner or later, a part of the dissolved substance will be released in the form of a solid phase (precipitate). Thus, denoting the product of molar concentrations of ions in solution through PC, the condition for the possible formation of a precipitate can be written as the inequality pK > SP.

If the ionic product is less than the solubility product (pK <SP), then the solution is unsaturated and no precipitate is formed.

For example, for $CaCO_3$, the following ratios of pK and SP are observed:

$CaCO_3 \leftrightarrow Ca^{2+} + CO_3^{2-}$

$SP = [Ca^{2+}][CO_3^{2-}]$

a) in unsaturated solution: $C(Ca^{2+}) \cdot C(CO_3^{2-}) < SP\ (CaCO_3)$;

b) in saturated solution: $C(Ca^{2+}) \cdot C(CO_3^{2-}) = SP\ (CaCO_3)$;

c) in a supersaturated solution: $C(Ca^{2+}) \cdot C(CO_3^{2-}) > SP\ (CaCO_3)$.

Alkaline earth metals often compete with each other. For example, Ca^{+2} ions inhibit the activity of enzymes activated by Mg^{+2} ions (magnesium is an activator of more than 15 enzymes). Mg^{2+} in turn inhibits the action of myosin adenosine triphosphatase, which is activated by Ca^{2+} ions. Mg^{2+} ions are necessary for the transmission of nerve impulses, muscle contraction and carbohydrate metabolism. Together with calcium ions, magnesium ions are part of many cellular structures. Magnesium is more of an intracellular ion, while the calcium inside the cell is much less than outside it. Based on this, one can expect the presence of a magnesium - calcium pump between the intracellular and intercellular fluid. Moreover, in all cells, the separation of Ca^{2+}, Mg^{2+}, Na^{+}, K^{+} is strictly controlled.

BIOGENIC ELEMENTS OF THE D-BLOCK

More than 30 d-elements are known, which in the periodic system form three complete insert decades (Sc - Zn, Y - Cd, La - Hg) and several elements of the fourth decade. The electron filling of the d sublevel occurs in accordance with the Gund rule, i.e. the total value of spin numbers should be maximum. At the external level of d-element atoms, there are one or two electrons of the s-state (with the exception of palladium atoms for which there are no s-electrons of the external level), which can be explained on the basis of the principle of least energy. A decrease in the number of s-electrons at the external level to one or their absence in palladium atoms occurs due to the “dip” (or slip) of electrons from the s-external to the d-pre-sublevel, due to which a more stable state with a smaller energy reserve is achieved. For example, in the atoms of the elements of chromium, molybdenum, niobium, cuprum, argentum, aurum, etc. there is a “dip” of one external s-electron, and in the atoms of the element of palladium - two external s-electrons.

For atoms of transition metals, two especially stable states are characteristic: in the first, the orbitals of the anterior d-sublevel are half filled (nd^5); in the second, d-orbitals are completely filled (nd^{10}).

Due to the high charge of the nucleus and the presence of free electronic orbitals, they are part of biologically active compounds (enzymes, hormones, vitamins, pigments, etc.) and have a high specificity of action.

THE BIOLOGICAL ROLE OF D-ELEMENTS AND THEIR COMPOUNDS

Organisms selectively assimilate necessary chemical elements from the external environment, concentrating them in certain organs and tissues. The source of income is food and water, and for some chemical elements, and air. The mass fraction of various elements is not the same and varies widely.

The main factors determining the accumulation of chemical elements in the human body are the following: quantitative content in the external environment, properties of chemical elements, atomic mass and atomic nucleus charge, solubility of natural compounds, ability to complexation, etc. Complexation is a specific property of d-block elements. Most biogenic d-elements are trace elements. In the human body, as components of enzymes, hormones, vitamins and other biologically active substances, they participate in the processes of reproduction, growth, metabolism of proteins, lipids, carbohydrates, etc. Complex compounds in which the central ion is the elements of inserted decades, and the ligands are amino acids, proteins, etc., are easily soluble in water and well absorbed by living organisms. In the human body, proteins, amino acids and their derivatives, nucleic acids, nucleoproteins, nitrogen bases, peptides, fatty acids, carbohydrates, vitamins, enzymes, hormones, bile acids and other compounds are included in biological complexes as ligands. Among the numerous complex compounds in biosystems, biological complexes of metals with a porphyrin system should be distinguished: iron porphyrin complex (Fe ~ * ion is a complexing agent), cobaltoporphyrin complex (Co ion is a complexing agent). It is generally accepted that both living and non-living nature is more complex than other chemical compounds.In all

of the above compounds, the molecules usually contain several functional groups of different types that can coordinate metal ions s, including the transient, i.e. d-block elements.

General material and educational and methodological support of the lecture:

- Working program of the discipline
- Silabus
- Methodical recommendations for independent work of higher education applicants
- Multimedia presentations
- Situational tasks

Recommended literature

Basic literature:

1. Medical Chemistry: textbook / V.Y. Tsuber, A.A. Kotvytska, K.V. Tykhonovych et al. - – Kyiv, AUS Medicine Publishing, 2022. – 392 p.

2. Medical chemistry: a textbook for universities / V. O. Kalibabchuk, I. S. Chekman, V. I. Galynska and others; for ed. Prof. V. O. Kalibabchuk – 4th ed. – K. VSV "Medicine", 2019 – 336 p.

3. Medical chemistry / V.O. Kalibabchuk, V.I. Halynska, L.I. Hryshchenko et al. – Kyiv, AUS Medicine Publishing, 2020. – 224 p.

4. General and Inorganic Chemistry: textbook / V.O. Kalibabchuk, V.V. Ohurtsov, V.I. Halynska et al. – Kyiv, AUS Medicine Publishing, 2019. – 456 p.

Additional literature:

1. Medical chemistry: a textbook / V. P. Muzychenko, D. D. Lutsevich, L. P. Yavorska; for order. B. S. Zimenkovsky. – 3rd ed., Ed. – K.: BCB «Medicine», 2018. – 496 p.

2. Mironovich L. M. Medical Chemistry: A Textbook. – Kyiv: Karavella, 2008. – 159 p.

3. Moroz A. S. Medical chemistry: a textbook / D. D. Lutsevich, L. P. Yavorska. – Vinnytsia: New book, 2006. – 776 p.

4. Gotsulyak L. O., Mardashko O. O., Yerigova S. G., Kuzmenko G. I., Kuzmina A. V., Zhilinskaya K. I. Bioinorganic, physicoloid and bioorganic chemistry. Teaching. manual. Odessa. Odessa State Medical University 1999. – 248 p.

5. Textbook of Medicinal Chemistry / V. Alagarsamy // CBS Publishers & Distributors Pvt Ltd, India; 3rd edition, 2018 – 584 p.

6. Richard Post. Chemistry: Concepts and Problems / Richard Post, Chad Snyder, Clifford C. Houk // A Self-Teaching Guide, Jossey-Bass, 2020. – 432 p.

Lecture № 2

***Topic*: «Complexation in biological fluids. Basics of chelation therapy.»**

Actuality of theme: The ability to form complex compounds is one of the important features of transition metals. These compounds are common in the mineral composition of plants and animal organisms. They perform numerous functions. Most biologically important substances are complex compounds in which complex organic substances are connected with metal ions.

Goal: Summarize knowledge about the structure, nomenclature and properties of coordination compounds, their use in medical practice, get acquainted with bioligands, understand their biological role, as well as the application of the basic provisions of coordination compounds to living organisms.

Basic concepts: inner sphere, outer sphere, ligand, coordination number, nomenclature of complex compounds, chelate complex.

Plan and organizational structure of the lecture:

1. Werner's coordination theory.
2. Structural components of complex compounds.
3. Nomenclature of complex compounds.
4. Classification of complex compounds.
5. Ionic equilibria in solutions of complex compounds.
6. Biological role of complex compounds.

Content of lecture material (lecture text)

Werner Coordination Theory

By the 90s of the XIX century, a great deal of material had been accumulated on a special group of molecular compounds, the composition of which cannot be explained from the standpoint of the classical theory of valency.

Compounds of **the first order** or valence-saturated compounds are compounds of the type BF_3, CH_4, NH_3, CO_2, etc., in which the element exhibits its usual maximum valency.

Higher-order compounds, valence-unsaturated, are compounds that are obtained by the interaction of first-order compounds with each other.

$$CoCl_3 + 6NH_3 = CoCl_3 \cdot 6NH_3 = [Co(NH_3)_6]Cl_3$$

$$Fe(CN)_3 + 3KCN = Fe(CN)_3 \cdot 3KCN = K_3[Fe(CN)_6]$$

The Swiss chemist Alfred Werner, one of the founders of the chemistry of complex compounds, Nobel Prize Laureate, in 1893 proposed a theory of higher-order compounds, which made it possible to understand the structure and some properties of complex compounds. The forces of attraction exist not only between atoms, but also between molecules. Complex, are called compounds in the crystal nodes of which are complexes capable of independent existence in solution.

The role of complexing agents can play any element of the periodic system.

$K[PF_6]$; $K_3[PO_4]$; $K_3[PS_4]$

Ligands can occupy one or more places in the coordination sphere, i.e. connect to the central atom through one or more atoms.

Werner classified the most stable compounds of the highest order as complex compounds. Werner suggested that any element, after saturating its usual valencies, is also able to exhibit an additional valency - coordination, due to which higher-order compounds are formed.

The basis of Werner's coordination theory:

1) The central place in the complex compounds is occupied by the complexing agent - usually a positively charged ion (most often metal)

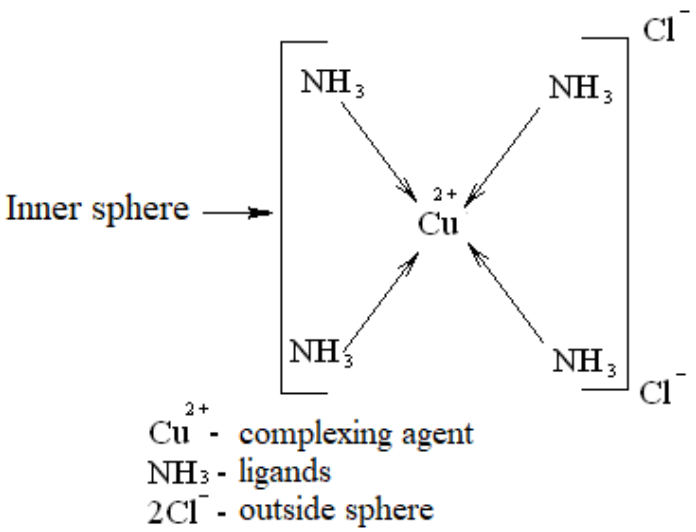
2) Ligands are located or coordinated around the complexing agent, i.e. ions of the opposite sign or neutral molecules.

3) The complexing agent and ligands form the internal sphere of the complex compound.

4) Ions that are not included in the inner sphere constitute the outer sphere of complex compounds.

According to generally accepted notation, the inner sphere when writing is separated from the outer by square brackets.

So the compound [**$Cu(NH_3)_4]Cl_2$** can be depicted:

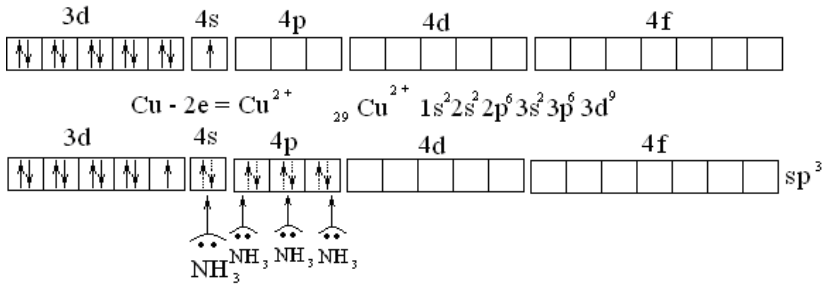


Let us consider the structure of the complex ion **$[Cu(NH_3)_4]^{2+}$** from the point of view of the valence bond method:

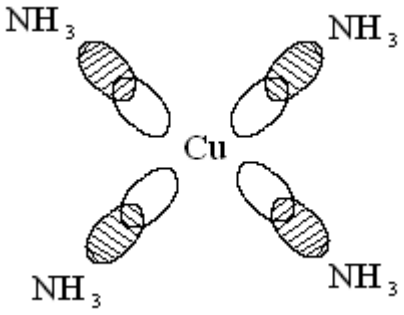
1) electronic formula of copper atom and ion

$$_{29}Cu \quad 1s^2 2s^2 2p^6 3s^2 3p^6 3d^{10} 4s^1$$

2) electronic diagram of copper atom and ion



Within the valence layer, the cuprum ion has empty orbitals, which play the role of acceptors of electron pairs. The 4s and 4p orbitals of the Cu^{+2} ion form 4 hybrid sp^3 orbitals. The overlapping of the orbits of the central atom with the orbitals of ammonia molecules can be simplified as follows:



Most often, the role of complexing agents is played by transition metal cations (d-elements, f-elements, less often s and p).

Ligands that form only one bond with the complexing agent are monodentate ligands: **NH_3, H_2O, CN^-, NO_2^-, Cl^-, CO,** etc.

Bidentate ligands are capable of forming two bonds with the complexing agent: **oxalate ion $^-OOC\text{-}COO^-$, CO_3^{2-}, SO_4^{2-},** 1,2-diaminoethane $H_2N\text{-}CH_2\text{-}CH_2\text{-}NH_2$.

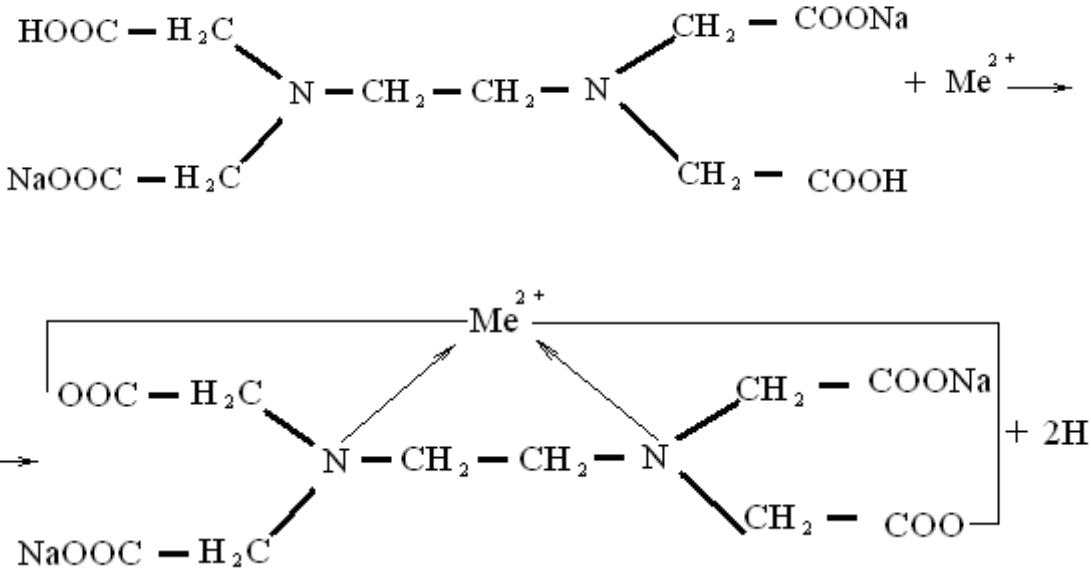
Multidentate ligands can form more than two bonds with the complexing agent. Complexes with multidental ligands are called chelating. The formation of chelate complexes is used to soften hard water and dissolve kidney stones. The most important role is played in analytical practice, metal production.

Many complex compounds containing multidental ligands are chelates. Ligands capture the complexing agent like a claw of cancer (Greek: *Chele - claw*).

The ligand joins the complex-forming agent simultaneously by two types of bonds — ionic and covalent, arising by the donor-acceptor mechanism (arrow from donor to

acceptor). The complexing agent, as it were, is pulled into the ligand, covered by bonds like a claw of cancer, hence the name (chelate).

An example of a chelate is the disodium salt of ethylenediaminetetraacetic acid, known as Trilon B (or complexone III):



Formation by complexone III of an intracomplex compound with some doubly charged cation occurs by metal substitution of the hydrogen atoms of the carboxyl groups and simultaneous interaction of the cation with the nitrogen atoms of the amino group (due to the coordination bond).

Complexon III was widely used in chemical analysis because it forms intracomplex salts with divalent metal cations (Ca^{2+}, Mg^{2+}, Ba^{2+}) which are very difficult to transfer to complex compounds in other ways. The method of quantitative determination of metals by complexones is called complexometry.

Chelating compounds include such important substances for life as **chlorophyll and hemoglobin.**

The coordination number can vary from 2 to 12. The most common coordination numbers are 4 and 6.

The coordination number is determined by the nature of the complexing agent and ligands, as well as the external conditions:

1) The larger the size of the complexing agent, the higher its c.n.

Compound	Coordination Number
$[BF_4]^-$	4
$[AlF_6]^{3-}$	6

2) The smaller the ligand size is, the higher the c.n complexing agent has.

Compound	Coordination Number
$[AlCl_4]^-$	4
$[AlF_6]^{3-}$	6

3) The greater the charge (oxidation degree) of the complexing agent, the higher its c.n.

Compound	Oxidation Number	Coordination Number
$[Ag(NH_3)_2]Cl$	+1	2
$[Cu(NH_3)_4]SO_4$	+2	4
$[Cr(H_2O)_6]Cl_3$	+3	6

In most cases, the rule is met: **The coordination number of the complexing agent is twice its charge.**

4) With increasing temperature c.n. goes down.

Coordination numbers of some complexing ions:

Cu^+ Ag^+ Au^+ 2

Cu^{+2} Hg^{+2} Cd^{+2} Au^{+2} 4

Fe^{+2} Fe^{+3} Co^{+2} Cr^{+3} Al^{+3} Pt^{+4} 6

Ca^{+2} Sr^{+2} Ba^{+2} 8

Nomenclature of complex compounds

When writing the name of the complex compounds should be guided by the following rules:

1. Complex compounds are called from the end of the formula, that is, from right to left. In other words, the anion is first called, then the cation.

2. The name of the complex ion:

1) ligands are first called, denoting their number using Greek numerals: mono − 1, di − 2, three − 3, tetra − 4, penta − 5, hexa − 6, etc .;

2) in mixed complexes, anions are first called, adding the ending “-o” to the Latin name, then − neutral ligands starting from NH_3.

H_2O – aqua	CN^- – cyano	NO_2^- – nitro (bond with N)
NH_3 – ammin	NO_3^- – nitrato	ONO^- – nitrito (bond with O)
CO – carbonyl	SO_4^{2-} – sulfato	SCN^- – thiocyanato
OH^- – hydroxo	SO_3^{2-} – sulfito	CH_3COO^- – acetato
F^- – fluoro	CO_3^{2-} – carbonato	$C_2O_4^{2-}$ – oxalato

3) the last to be called complexing agent, indicating its charge in Roman numerals in parentheses.

If the complexing agent is part of the complex cation, then the name of the metal is given.

If the complexing agent is part of the complex anion, then in its Latin name the suffix "-um" is replaced by the suffix "-at".

Fe – ferrate	Cr – chromate	Co – cobaltate
Pt – platinate	Cu – cuprate	Hg – mercurate

3. The name of the cation of the outside sphere is given in the genitive case:

$K_3[Fe(CN)_6]$ – potassium hexacyanoferrate (III),

$[Pd(H_2O)(NH_3)_2Cl]Cl$ – chlorodiamminemonoaquapalladium (II) chloride,

$NH_4[Cr(NH_3)_2(SCN)_4]$ – ammonium tetratiocyanatodiamminechromate (III),

$H_2[PtCl_6]$ – hydrogen hexachloroplatinate (IV) or hexachloroplatinic acid.

The names of complex compounds without an external sphere consist of one word, without indicating the charge of the complexing agent:

$[Ni(CO)_4]$ – tetracarbonylnickel,

$[Pt(NH_3)_2Cl_2]$ – diammindichloroplatinum.

The nature of the chemical bond in complex compounds

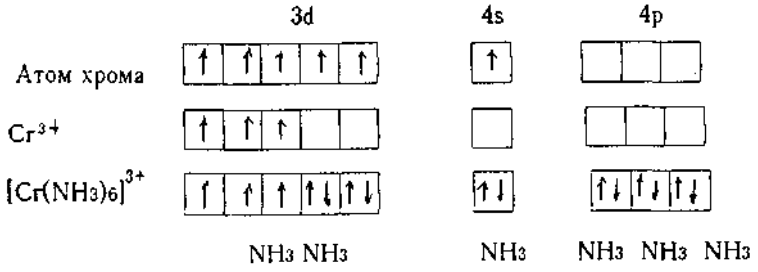
There are several theoretical approaches that explain the chemical structure of complex compounds. One of them is the valence bond (VB) method, which allows, in particular, to come to the following points:

1) Between the inner and outer spheres of the CS, the bond is mainly ionic, and between the complexing agent and ligands, it is covalent, formed by the donor-acceptor mechanism. Most often, ligands are donors of electron pairs, and complexing agents are acceptors.

2) The complexing agent orbitals involved in the formation of communication undergo hybridization. The geometry of the complex ion depends on the type of hybridization.

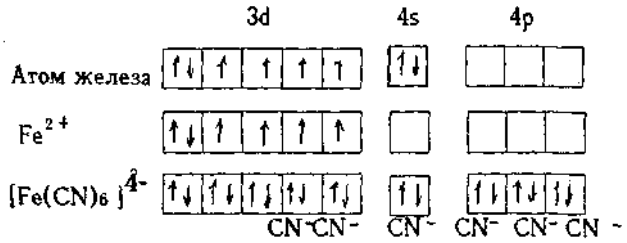
3) The population of the orbitals by electrons determines the magnetic properties of the complex compound. In the presence of unpaired electrons, the complex compound is paramagnetic, and in their absence, diamagnetic.

Consider examples illustrating the theory of valence bonds. For example, the complex $[Cr(NH_3)_6]^{3+}$. In this complex, the oxidation state of chromium is +3:



Six pairs of electrons of NH3 molecules occupy the vacant orbitals of the chromium ion. The molecule is octahedral. The complex contains three unpaired electrons and is paramagnetic.

Consider the complex $[Fe(CN)_6]^{4-}$. The complex is diamagnetic, because no unpaired electrons as shown below:



CLASSIFICATION OF COMPLEX COMPOUNDS

I. Classification by charge of complex ions.

Name	Composition	Example
1. Cationic	complex cation is composed	$[Cu(NH_3)_4]SO_4$
2. Anionic	complex anion is composed	$H_2[PtCl_4]$
3. Neutral	consist only of an internal sphere and do not have an external sphere	$[Pt(NH_3)_2Cl_2]$
4. Cationic anionic	include a complex cation and a complex anion	$[Cu(NH_3)_4][PtCl_4]$

II. Classification by the nature of ligands.

Name	Ligand	Example
1. Aquacomplexes (hydrates)	H_2O	$[Cu(H_2O)_6]Cl_2$
2. Ammonia (Amines)	NH_3	$[Cu(NH_3)_4]SO_4$
3. Hydroxocomplexes	OH^-	$K_2[Zn(OH)_4]$
4. Acid complexes	acid residue (NO_2^-, $C_2O_4^{2-}$ and else)	$K_4[Fe(CN)_6]$ $K_2[HgI_4]$
5. Mixed	various	$[Co(NH_3)_4Cl_2]Cl$
6. Chelate	bi-and poly-dentat	$[Co(NH_2CH_2CH_2NH_2)_3]Cl_3$

ISOMERIA OF COMPLEX COMPOUNDS

Isomers are called chemical compounds of the same composition, but differing in structure and properties. The existence of isomers is an important argument in constructing a theory of chemical structure. An important step in the development of coordination theory was the interpretation of the spatial arrangement of atoms in complex compounds. All types of isomerism are divided into two groups.

A. Structural isomers.

B. Stereoisomers.

1. STRUCTURAL ISOMERIA

Isomers having the same molecular formula but different arrangement of atoms around the complexing agent are called structural isomers.

Ionization isomerism. In this type of isomerism, differences arise in the exchange of groups within and outside the coordination sphere. Ionization isomerism is inherent only to cationic complexes. These isomers form various ions in solution.

For example, the structural structure of two compounds:

$[Co(NH_3)_5Br]SO_4$ pentaamminebromocobalt (III) sulfate (red-violet)

$[Co(NH_3)_5SO_4]Br$ pentaamminesulfatocobalt (III) bromide (red)

Other compounds demonstrating this type of isomerism:

$[Co(NH_3)_4Cl_2]NO_2$ $[Co(NH_3)_4Cl(NO_2)]Cl$

$[Pt(NH_3)Cl_2]Br_2$ $[Pt(NH_3)_4Br_2]Cl_2$

Hydrated isomerism. This type of isomerism is similar to ionization isomerism. The difference in the structure of hydrated isomers is the unequal arrangement of water molecules. In one case, it enters the internal sphere of the complex, and in others, part of the water molecules is crystallized. A classic example of hydrated isomerism is chromium (III) chloride hydrates. There are isomers with a molecular formula $CrCl_3 \cdot 6H_2O$:

$[Cr(H_2O)_6]Cl_3$ purple

$[Cr(H_2O)_5Cl]Cl_2 * H_2O$ blue-green

$[Cr(H_2O)_4Cl_2]Cl * 2H_2O$ green

They differ from each other in physical and chemical properties.

Coordination isomerism. This isomerism occurs when the cation and anion are complexes. For example, coordination isomers, the central atoms of which are different.

$[Co(NH_3)_6][Cr(CN)_6]$ and $[Cr(NH_3)_6][Co(CN)_6]$

$[Pt(NH_3)_4][PdCl_4]$ and $[Pd(NH_3)_4][PtCl_4]$

This type of isomerism can also be represented by compounds in which the same metal ion is included in both the anionic and cationic complexes. For example,

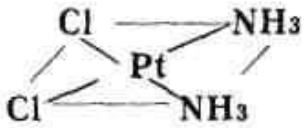
$[Cr(NH_3)_6][Cr(CN)_6]$ and $[Cr(NH_3)_4(CN)_2][Cr(NH_3)_2(CN)_4]$

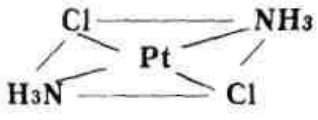
$[Pt(NH_3)_4][PtCl_4]$ and $[PtCl(NH_3)_3][PtCl_3(NH_3)]$

STEREOISOMERIA

Stereoisomers are those isomers that have the same arrangement of atoms or groups, but their different spatial arrangement around the central atom.

Geometric isomerism. This type of isomerism appears if the ligands occupy different places around the central atom. There are only two symmetrical geometric figures that can reflect the structure of complex compounds with a coordination number of 4. This is a flat square and a tetrahedron. Based on the existence of platinum (II) diammine dihalide complexes in two isomeric forms, Werner came to the conclusion that platinum (II) complexes have a square-square structure. The complex $[Pt(NH_3)_2Cl_2]$ exists in the form of two geometric isomers (cis and trans). They differ in color, solubility, and with respect to certain chemicals. Later, the difference was found in their biological activity.





Cis-(light yellow) Trans-(dark yellow)

Optical isomerism. Molecules of a tetrahedral type with an asymmetric atom

located in their center are capable of forming isomers that rotate the plane of polarized light in different ways. Such isomers are called optical. Optical isomers (antipodes) have equal in magnitude and opposite in sign rotation. Optical isomerism for complexes with a coordination number of 4 is not characteristic. Werner's coordination theory predicted the existence of optical isomers for complex compounds of the octahedral type. Optical isomers are possible for the complex compound $[Co(En)_2NH_3Cl]Cl$ cis configuration. Complexes such as $[Co(En)_3]$ and $[Cr(C_2O_4)_3]^{3-}$ exist as optical isomers. Currently, a large number of optically active complex compounds of the octahedral type are known. Typically, these compounds contain cyclic ligands.

Ionic equilibria in solutions of complex compounds

In aqueous solutions, complex compounds dissociate stepwise. Distinguish between primary and secondary dissociation.

Primary dissociation is the dissociation of a complex compound into a complex ion and the outer sphere:

$$K_4[Fe(CN)_6] \rightarrow 4K^+ + [Fe(CN)_6]^{4-}.$$

The primary dissociation proceeds completely, this is the dissociation of a strong electrolyte.

Secondary dissociation proceeds to a very small extent due to the high strength of the complex ion:

$$[Fe(CN)_6]^{4-} \rightleftarrows Fe^{2+} + 6CN^-$$

The chemical equilibrium constant for the secondary dissociation reaction is called **the instability constant** of the complex ion:

$$K_{inst} = \frac{[Fe^{2+}] \cdot [CN^-]^6}{[[Fe(CN)_6]^{4-}]} \quad (1)$$

The inverse of the instability constant is called **the stability constant** of the complex ion:

$$K_{stab} = \frac{1}{K_{inst}} \quad (2)$$

The values of the instability and stability constants can be a measure of the thermodynamic strength of a complex ion.

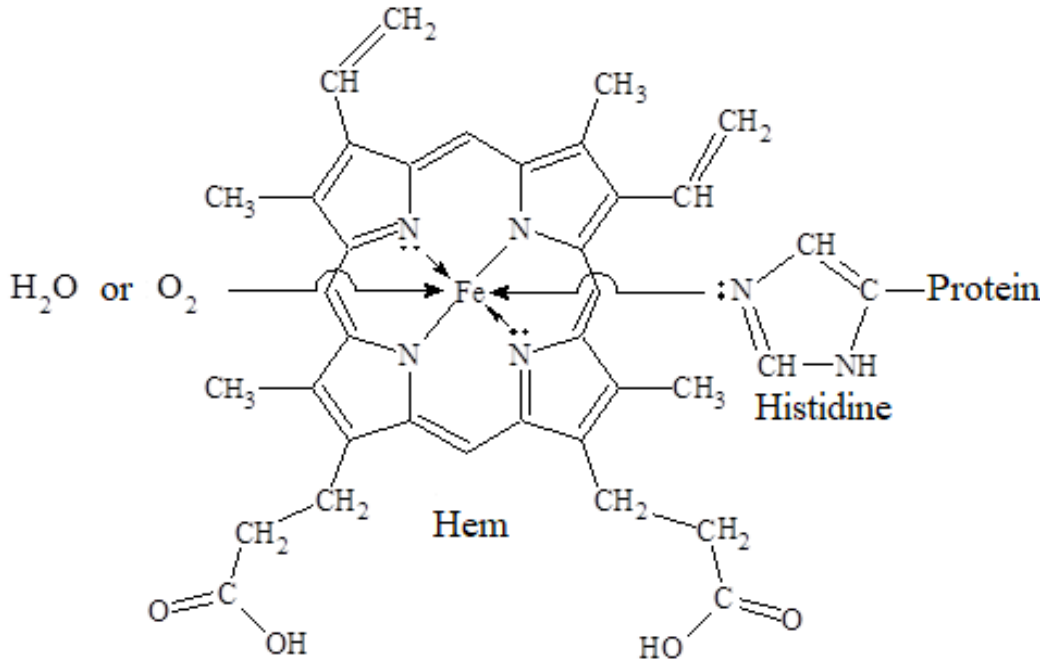
The biological role of complex compounds

The complex compounds considered by us above contained ligands, mainly of an inorganic nature. However, complex biological systems play an important role in biological systems, in which complex organic molecules possessing polydentate properties (i.e., are capable of forming several bonds with a complexing agent) act as ligands.

Metalloproteins

Metalloproteins include biopolymers, which, in addition to protein, contain a prosthetic group (non-protein component), including metal ions.

A separate group of metalloproteins is hemoproteins containing ferrum compounds as a prosthetic group. One of the most important hemoproteins is hemoglobin. It consists of protein (globin) and a complex of ferrum with porphyrin (heme). In heme, the Fe^{2+} ion (complexing agent) is bonded to two nitrogen atoms belonging to the porphyrin ring, a covalent bond, and two more coordination bonds. The coordination number of Fe^{2+} is six: in the porphyrin complex, the fifth coordination place is occupied by the histidine group of the protein, forming the coordination bond of the nitrogen atom with Fe2 +. In the absence of oxygen, the sixth ligand is water. When water is replaced by oxygen, oxyhemoglobin is formed. In addition to water and oxygen, the Fe^{2+} ion can bind some other ligands, for example, CO, CN^-, and nitrogen oxides. Thus, hemoglobin forms carboxyhemoglobin with carbon monoxide molecules, and methemoglobin containing Fe^{3+} ions with nitrogen oxides. The accumulation of these types of hemoglobin in the blood leads to a decrease in blood supply to the tissues.



Hemoglobin bonding scheme

Hem in the form of heme-porphyrin is a prosthetic group of hemoglobin derivatives**: myoglobin, catalase, peroxidase and cytochromes.**

A distinctive feature of hemoglobin (myoglobin) is the constant oxidation state of ferrum Fe^{2+}. Equilibrium:

$$O_2 + \text{hemoglobin} \rightleftarrows \text{oxyhemoglobin}$$

in the lungs it is shifted to the right, and in the cells - to the left.

Thus, hemoglobin (myoglobin) is a carrier of molecules (H_2O, O_2).

Transport functions are also performed by cytochromes, in which the connection between the heme and the polypeptide chain is carried out using cysteine residues of the protein chain.

However, unlike hemoglobin and myoglobin, the mechanism of their action is based on a change in the oxidation state of ferrum:

$$Fe^{2+} - \bar{e} \rightarrow Fe^{3+},$$

$$Fe^{3+} + \bar{e} \rightarrow Fe^{2+}.$$

By transferring electrons from cytochrome b to cytochrome oxidase, ferrum ions are involved in oxidative phosphorylation.

Cytochromes do not interact with oxygen and CO.

Vitamins

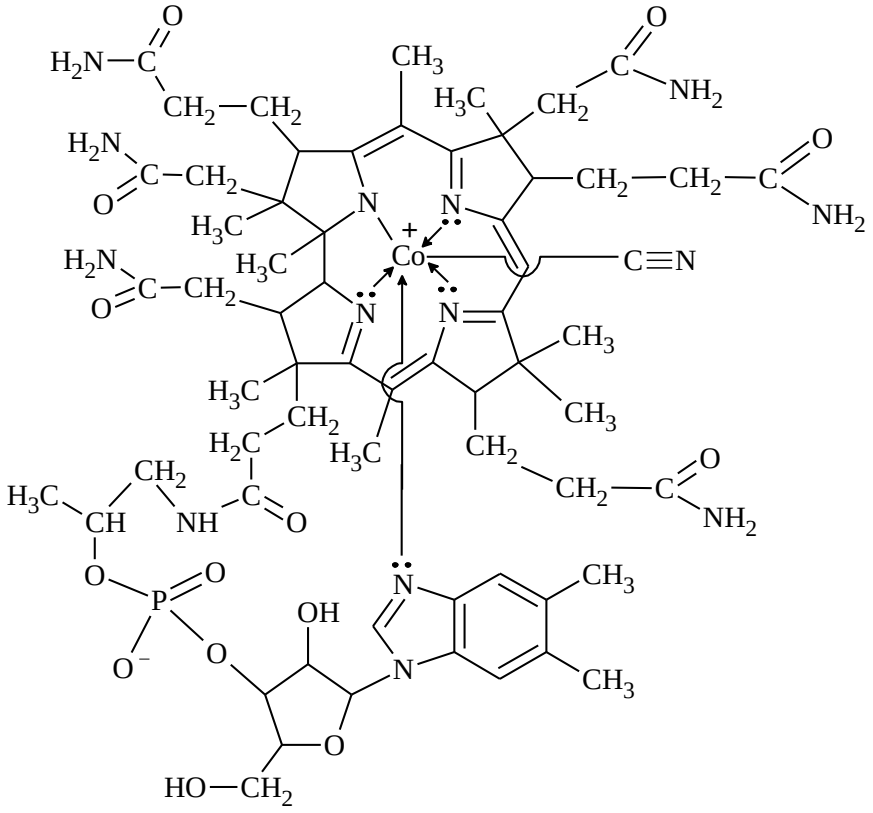
The only vitamin containing metal in its structure is **vitamin B_{12} (cobalamin)**.

It includes the Co^{3+} ion, which is located in the center of the planar corrine system (similar to the porphyrin) and is bonded to the nirogen atoms of the reduced pyrrole rings. Perpendicular to the plane of the corrine system is a nucleotide ligand consisting of 5,6-dimethylbenzimidazole and ribose with a phosphoric acid residue. Finally, the sixth ligand is the cyanide ion.

Vitamin B_{12} is contained in enzyme systems in the form of B_{12}-co-enzymes or cobamide coenzymes methylcobalamin containing an additional methyl group, and deoxyadenosine-cobalamin containing 5-deoxyadenosine cobalamin.

So, methyl-cobalamin acts as a carrier of the methyl group in the methionine synthesis reaction. In addition, vitamin B_{12} is required for the formation of red blood cells.

A lack of vitamin B_{12} leads to disorders of the nervous system and causes a sharp decrease in the acidity of the gastric juice.



Vitamin B_{12} (cobalamin) bonding scheme

ENZYMES

Enzymes are a class of substances of protein nature that catalyze a large number of chemical reactions. Enzymes provide the realization of genetic information, as well as the metabolism and energy. Enzymes differ from inorganic catalysts in significantly greater activity and high specificity of action: one enzyme, as a rule, catalyzes only one chemical reaction.

The active principle of the carboxypeptidase enzyme that catalyzes the hydrolysis processes is Zn^{2+} ion. Zinc ion draws on itself the electrons of the carbonyl group C = O in the peptide (– CO – NH –), as a result, the C = O bond is even more polarized, which facilitates the hydrolysis and breaking of the C–N bond.

Zinc ions are also a part of the carbonic anhydrase enzyme, which catalyzes the hydration of CO_2, i.e., the formation of the HCO_3^- ion, and at the same time participates in the catalytic decomposition of HCO_3^-, which is accompanied by the release of CO_2. The first reaction proceeds in the alveoli of the lungs, the second (reverse) – in the cells.

Some other metal complex compounds that play a specific biological role are shown in the table.

Table. Biologically important metal complexes

Metal	Type of Biomolecule	Ligands	Biological Function
Cu^{2+}	Cytochrome oxidase, ceruloplasmin, etc.	Nitrogen bases	Oxidation, deposition and transport of cuprum
Mn^{2+}	Arginase, decarboxylase of amino acids, phosphotransferase, etc.	Phosphate, imidazole	Decarboxylation, phosphate transfer
Mo^{2+}	Nitrogenase, nitrate reductase, xanthine oxidase	Not identified	Reduction of N2 to NH3, Purine Oxidation

Mg^{2+}	Chlorophyll	Porphyrin	The conversion of light energy into energy of chemical bonds
Cr^{3+}	Yeast	Niacin, amino acids	Participation in carbohydrate metabolism, increased action of insulin

Toxicological role of complexation

The toxic effect of most heavy metals (mercury, lead, thallium, etc.) is explained by the ability of ions of these metals to form strong complexes with proteins, enzymes and amino acids. As a result, enzyme activity is suppressed and protein coagulation occurs.

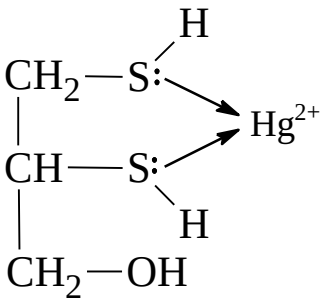
For example, Hg^{2+} mercury ions form strong complexes with proteins that have SH groups in their composition. Thus, mercury is concentrated in tissues and organs rich in these proteins, namely in the kidneys, brain, and oral mucosa.

Lead is retained by red blood cell proteins, then enters the blood plasma in the form of complexes with gamma globulin and, finally, reaches the kidneys, liver and other organs. Lead also builds up in bone tissue.

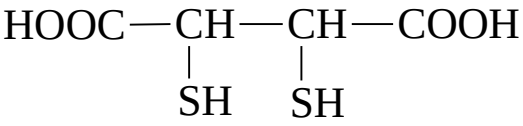
Some agents capable of forming strong complexes with metal ions are used as antidotes for household and professional poisoning with heavy metal compounds, as well as for chronic intoxications caused by overdose of drugs.

So, the intravenous administration of EDTA allows you to remove excess Ca^{2+} ions from the body in the form of a durable complex, which reduces the likelihood of stone formation in the kidneys and gall bladder.

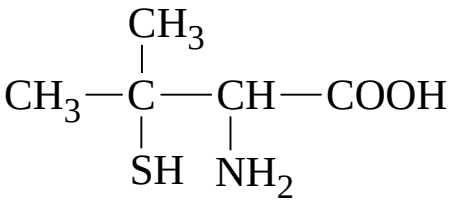
In case of poisoning with compounds of mercury, antimony and arsenic, dimercaprol (2,3-dimercaptopropanol-1) is administered intravenously, which not only reduces the toxic effect of these elements, but also removes them from the body in the form of complexes:



Later, 2,3-dimercaptosuccinic acid was administered, which is administered orally:



For poisoning with copper compounds, penicillamine is used:



The complex of copper with penicillamine is excreted with urine.

General material and educational and methodological support of the lecture:

- Working program of the discipline
- Silabus
- Methodical recommendations for independent work of higher education applicants
- Multimedia presentations
- Situational tasks

Recommended literature

Basic literature:

1. Medical Chemistry: textbook / V.Y. Tsuber, A.A. Kotvytska, K.V. Tykhonovych et al. - – Kyiv, AUS Medicine Publishing, 2022. – 392 p.

2. Medical chemistry: a textbook for universities / V. O. Kalibabchuk, I. S. Chekman, V. I. Galynska and others; for ed. Prof. V. O. Kalibabchuk – 4th ed. – K.

VSV "Medicine", 2019 – 336 p.

3. Medical chemistry / V.O. Kalibabchuk, V.I. Halynska, L.I. Hryshchenko et al. – Kyiv, AUS Medicine Publishing, 2020. – 224 p.

4. General and Inorganic Chemistry: textbook / V.O. Kalibabchuk, V.V. Ohurtsov, V.I. Halynska et al. – Kyiv, AUS Medicine Publishing, 2019. – 456 p.

Additional literature:

1. Medical chemistry: a textbook / V. P. Muzychenko, D. D. Lutsevich, L. P. Yavorska; for order. B. S. Zimenkovsky. – 3rd ed., Ed. – K.: BCB «Medicine», 2018. – 496 p.

2. Mironovich L. M. Medical Chemistry: A Textbook. – Kyiv: Karavella, 2008. – 159 p.

3. Moroz A. S. Medical chemistry: a textbook / D. D. Lutsevich, L. P. Yavorska. – Vinnytsia: New book, 2006. – 776 p.

4. Gotsulyak L. O., Mardashko O. O., Yerigova S. G., Kuzmenko G. I., Kuzmina A. V., Zhilinskaya K. I. Bioinorganic, physicoloid and bioorganic chemistry. Teaching. manual. Odessa. Odessa State Medical University 1999. – 248 p.

5. Textbook of Medicinal Chemistry / V. Alagarsamy // CBS Publishers & Distributors Pvt Ltd, India; 3rd edition, 2018 – 584 p.

6. Richard Post. Chemistry: Concepts and Problems / Richard Post, Chad Snyder, Clifford C. Houk // A Self-Teaching Guide, Jossey-Bass, 2020. – 432 p.

Lecture № 3

***Topic*: «Chemical thermodynamics and theoretical foundations of bioenergetics.»**

Actuality of theme: During biochemical processes, chemical and physical phenomena, which are studied by physical chemistry, are closely related. Studying the course of physical and colloidal chemistry will allow the future specialist to acquire knowledge in the field of manufacturing, quality control and storage of medicines, as well as their biotransformation in the human body.

Goal: on the basis of the laws of thermodynamics, study the interconversion of various types of energy in chemical and physicochemical processes, apply the laws and principles of thermochemical calculations to form a holistic approach to the study of chemical and biological processes.

Basic concepts: thermodynamic system, thermodynamic process, phase, component, thermodynamic parameters, system state functions, heat, work, internal energy, enthalpy.

Plan and organizational structure of the lecture:

1. Basic concepts and definitions of chemical thermodynamics.
2. The first law of thermodynamics.
3. Fundamentals of thermochemistry. Hess's law. Thermochemical calculations

Content of lecture material (lecture text)

Thermodynamics is a science that studies the general laws of transformation of different types of energy in a system. It describes changes and transformations without considering the structure of the bodies of the system.

Knowledge of energy changes is crucial for understanding the most important biological processes.

From the point of view of bioenergy, all living things are divided into autophores, which accumulate energy in organisms due to biochemical processes (for example, plants) and heterophores, which produce it as a result of oxidation of nutrients - fats and carbohydrates. Animal organisms are heterophores.

Basic concepts

A thermodynamic system is a body or a group of bodies that are in energy interaction and are mentally or physically separated from the surrounding bodies, which are called the external or surrounding environment.

System classification:

1) if possible heat and mass transfer: isolated, closed, open. **An isolated system** does not exchange matter or energy with the environment. The concept of an isolated system is used in theoretical chemistry as a theoretical one. **A closed system** exchanges energy with the environment, but does not exchange matter. **An open system** exchanges with the environment and matter and energy. *Living organisms are open thermodynamic systems. An integral sign of a living organism is exchange with the environment: the ingestion of food products and oxygen with air and the release of metabolic products from it.*

2) by internal structure and properties: homogeneous and heterogeneous. **A homogeneous system** is called a system inside which there are no surfaces dividing the system into parts that are different in properties or chemical composition. Examples of homogeneous systems are aqueous solutions of acids, bases, salts; gas mixtures; individual pure substances. **Heterogeneous systems** contain natural surfaces within themselves. Examples of heterogeneous systems are systems consisting of substances of a different state of aggregation: metal and acid, gas and a solid substance, two liquids insoluble in each other.

A phase is a homogeneous part of a heterogeneous system, having the same composition, physical and chemical properties, separated from other parts of the system by a surface. The phases are solid, liquid and gaseous. A homogeneous system always consists of one phase, but a heterogeneous system consist several phases.

The properties of the system in physical chemistry can be described by setting the **system parameters**. The parameters most often are temperature (T), pressure (P), volume (V), amount of substance (ν) and others.

If the parameters of the system are constant, they say that the system is in a state of **equilibrium.**

The processes can be **isothermal** (occur at T = const), **isobaric** (P = const), **isochoric** (V = const), **adiabatic** (proceed without heat exchange with the environment). Of greatest importance in chemical thermodynamics are **isobaric-isothermal** (P, T = const) and **isochoric-isothermal** (V, T = const) processes. It is under such conditions that all chemical reactions occur.

The state of the system changes with at least one of its parameters.

For example, the Mendeleev-Clapeyron equation

$$P \cdot V = \frac{m}{M} RT$$

is the equation of state of an ideal gas.

For most systems, the thermodynamic description uses state functions that can be uniquely determined through the parameters (T, P, V).

A function of the state of a system is a function whose change depends only on the initial and final states of the system and does not depend on the path of the system from the initial to the final state.

State Functions:

- *E is the total energy of the system*
- *U - internal energy*
- *H - enthalpy*
- *S - entropy*
- *G - Gibbs free energy*

- *F - Helmholtz free energy.*

Internal energy (**U**) is the energy reserve of the system. It includes all types of energy associated with the structure of the system, and does not include the kinetic and potential energy of the system as a whole. Since there is no absolute knowledge of the structure of matter, the absolute value of internal energy cannot be found.

Enthalpy is the energy reserve of a system in the form of heat. Internal energy, enthalpy, heat, and work are measured in J / mol.

Entropy (**S**) is a thermodynamic function that quantifies the degree of disorder in a system. It is a function of the state of the system, measured in J/mol·K.

Helmholtz energy (**F**) is a function of the state of a system that characterizes the flow of chemical processes under isochoric-isothermal conditions.

Gibbs energy (**G**) is a function of the state of a system that characterizes the occurrence of chemical processes under isobaric-isothermal conditions. Helmholtz and Gibbs energies are measured in kJ/mol.

The total energy (**E**) is a fundamental function of the state of the system:

$$\mathbf{E = K + P + U}$$

where K is the kinetic energy of moving particles of the system;
P is potential energy of influence on the system of external force fields;
U is the internal energy of the system.

In thermodynamics, it is assumed that the system is in relative peace (K = 0), and the influence of external power (gravitational, electromagnetic, and other forces) on the system can be neglected (P = 0).

Under the given limiting conditions it will take the form:

$$\mathbf{E = U}$$

The internal energy of the U system is the total energy reserve, which consists of the kinetic energy of the translational and rotational motion of molecules, the energy of attraction and repulsion of particles, the energy of electronic excitation, internuclear and intranuclear interaction, etc.

Accounting for all these components is impossible, but for thermodynamic analysis it is enough to know only the change in internal energy during the transition from one state to another.

The first law of thermodynamics is a special case of one of the most important laws of natural science - the law of conservation and transformation of energy. **The heat absorbed by the system is expended on the change in internal energy and the completion by the system of work:**

$$\Delta Q = \Delta U + A$$

If the only type of work is the work of expansion forces, then

$$\Delta Q = \Delta U + P\Delta V$$

$A = p \cdot \Delta V$ – mathematical expression of the I-th law of thermodynamics

The body receives the energy necessary for the course of life processes with food in the form of the energy of the bonds of macromolecular compounds. In the body, these substances are oxidized to simpler ones. The released energy is converted into other types of energy, mainly into the heat necessary to maintain body temperature, as well as into work during various movements, including labor processes. At the same time, new complex ones are formed in the human body with partial absorption of the released energy, for example, in the muscles, which are the main source of heat production.

In the body there are fluctuations in the internal energy contained in its various parts. However, over a rather long period, for example, a day, all these fluctuations are mutually balanced, i.e. a constant state of the body is maintained. Therefore, when compiling, for example, the daily energy balance of an organism, we can assume that its internal energy remains on average unchanged.

As applied to a living organism, the law of conservation of energy (or the first law of thermodynamics) can be formulated as follows:

The amount of heat Q released in the body during the assimilation of food is spent on compensating for the loss of heat q in the environment and the body performing work A, i.e. $Q = q + A$.

This equation is the equation of the energy balance of the human body, on the basis of which the necessary energy value (calorie content) of the diet is determined. Food is also spent on the restoration and growth (at a young age) of body tissues, the formation of reserves (fat deposition), etc.

In general, it is believed that heat loss of the human body in a temperate climate averages 7,100 kJ per day. If we add to this A = 2500 - 3340 kJ, equivalent to the mechanical work performed by the body (for people who do not have physical activity), then we get the daily energy expenditure of the order of 9600 - 10400 kJ. When performing physical work, costs increase to 25,000 kJ per day. These energy costs should be replenished by food.

Foods include mainly fats, proteins, carbohydrates, mineral salts, vitamins, water. The body receives energy mainly due to the first three groups of substances. From the point of view of energy, the most valuable are fats - 39 kJ / g, carbohydrates (18 kJ/g) and proteins (18 - 22 kJ/g) are less valuable.

For the energy characteristics of such processes, we introduce a new function (H) - enthalpy, or heat content. The enthalpy of the system is equal to the sum of the internal energy and the work of expansion.

$$\mathbf{H = U + A}$$

Since the work of the isobaric-isothermal process

$$\mathbf{A = p \cdot \Delta V}$$

then the change in enthalpy during the transition of the system from the initial state to the final

$$\boldsymbol{\Delta H = \Delta U + p \cdot \Delta V}$$

Because it is impossible to calculate U and, therefore, it is impossible to calculate H, but only their change.

Those the change in enthalpy is equal to the sum of the change in the internal energy of the system and the perfect system work.

Enthalpy is equivalent to the internal energy of the system at constant pressure.

$\Delta H < 0$ - exothermic reaction

$\Delta H > 0$ - endothermic reaction.

If an isochoric process is carried out, for example

$$Zn_{тв} + S_{тв} = ZnS_{тв} + Q_V$$

then in this case V = const, the reaction proceeds in the solid phase, and the work of expansion is absent:

$$\boldsymbol{Zn_{тв} + S_{тв} = ZnS_{тв} + Q_V}$$

$$\boldsymbol{U_1 \qquad U_2 \qquad \Delta U}$$

$$\boldsymbol{\Delta U = U_2 - U_1}$$

$$\boldsymbol{\Delta U = - Q_V}$$

For an isochoric process, a change in internal energy is equal to the thermal effect taken with the opposite sign.

The change in the internal energy of the system or enthalpy is usually attributed to the standard state of the starting materials and reaction products. The standard state of a substance at a given temperature is its state in the form of a pure substance at p = 101,325 kPa and t = 25^0C (298 K).

Changes in the corresponding quantities referred to standard conditions are called standard and are denoted by ΔH^0 and ΔU^0.

The standard heat of formation of a substance is the standard enthalpy of formation of 1 mole of a substance from simple substances (kJ / mol).

Enthalpy of formation of simple substances = 0.

If the element forms several simple substances, then the standard state is the state of the element in the form of the most stable under the given modification conditions and for it $\Delta H^0 = 0$.

The study of thermal changes in chemical reactions involved in thermochemistry.

Chemical equations that indicate the thermal effects of the reaction are called thermochemical.

There is a form for writing the equation:

$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O + 674$ *kcal*

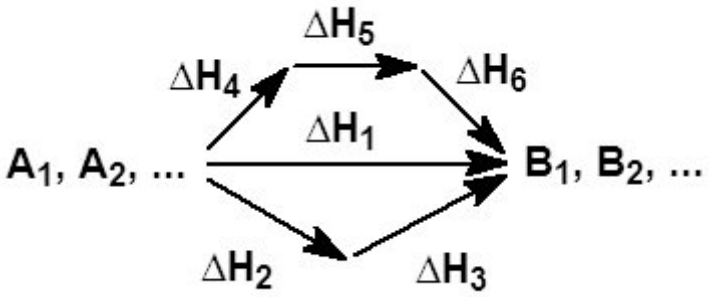
$\Delta H^0 = -674$ kcal

Exothermic reaction

Internal energy (U) and enthalpy (H) are functions of the state of the system; therefore, ΔU and ΔH depend only on which substances react under given conditions and which products are obtained, but do not depend on the path of the chemical process. This provision is known as the law of Hess (1810):

The thermal effect of a chemical reaction that proceeds at constant pressure or at a constant volume does not depend on the number of intermediate stages, but is determined only by the initial and final state of the system.

Hess law has a graphical representation in the form of a diagram:



$$\Delta H_1 = \Delta H_2 + \Delta H_3 = \Delta H_4 + \Delta H_5 + \Delta H_6 \qquad (11)$$

The practical value of the Hess law is that it allows you to calculate the thermal effects of chemical processes.

In thermochemical calculations, a number of consequences from the Hess law are usually used:

1. The thermal effect of the direct reaction is equal in magnitude and opposite in sign to the thermal effect of the reverse reaction.

$2H_{2(g)} + O_{2(g)} \rightarrow 2H_2O_{(l)}$; $\Delta H^0 = -136{,}6$ kcal < 0

Exothermic reaction

$2H_2O_{(l)} \rightarrow 2H_{2(g)} + O_{2(g)}$, $\Delta H^0 = 136{,}6$ kcal > 0

Endothermic reaction

2. The thermal effect of the chemical reaction is equal to the difference in the sums of the heats of formation of the reaction products and the process inputs, multiplied by stoichiometric coefficients.

$$\Delta H = \Sigma (\nu_i \Delta H_f)_{products} - \Sigma (\nu_i \Delta H_f)_{process\ inputs} \quad (12)$$

3. The thermal effect of a chemical reaction is equal to the difference in the sums of the heats of combustion of the starting materials and reaction products, multiplied by stoichiometric coefficients.

$$\Delta H = \Sigma (\nu_i \Delta H_c)_{process\ inputs} - \Sigma (\nu_i \Delta H_c)_{products} \quad (13)$$

Application - dietetics - calculation of calorie content of food products.

When studying all processes, they want to get an answer to 2 questions:

1. How complete is the process?

2. How quickly will equilibrium come?

In 1867, Bartlo formulated the principle according to which: all spontaneous processes are exothermic:

$$CaO + H_2O_{(l)} \rightarrow Ca(OH)_2 \; ; \Delta H < 0$$

But it turned out that there are a large number of physical and chemical phenomena occurring spontaneously and with heat absorption.

$$KCl_{(тв)} \rightarrow KCl_{(ж)} \; , \Delta H > 0$$

Those ΔH does not play a role in determining the spontaneous course of the process.

In all cases considered, it is logical to talk about a change in entropy - S - the state function of the system.

S is a quantitative measure of system disorder [J / mol · K]

The second law of thermodynamics determines the conditions for the occurrence of spontaneous processes. Clausius postulate: **spontaneous transfer of heat from a less heated body to a hotter body is impossible.**

All spontaneous processes occur with an increase in entropy in the system.

If ΔS > 0 – spontaneous process is thermodynamically possible;

If ΔS < 0 – process is impossible;

If ΔS = 0 – the process is reversible.

$$S_{cr} < S_l < S_g$$

An important conclusion follows from the second law of thermodynamics:

The total change in entropy necessary for the formation of the human body and the maintenance of its life or the existence of any other living system is always positive.

The second law of thermodynamics allows us to determine the direction of chemical reactions and the conditions for establishing chemical equilibrium.

The stability of the system is determined by the ratio of enthalpy and entropy factors. The enthalpy factor characterizes the system's desire for ordering, because accompanied by a decrease in internal energy, and the second factor reflects a tendency to disorder, because this condition is most likely. It was advisable to introduce a state function that takes into account the combined influence of both factors.

In thermodynamics, there are two functions that reflect both the change in the internal energy (enthalpy) of a given process and its inherent probability (entropy).

This is the isochoric-isothermal potential F (Helmholtz free energy) and the isobaric-isothermal potential G (Gibbs free energy).

$$\boldsymbol{\Delta G^0 = \Delta H^0 - T\Delta S^0}$$

ΔG^0 – Gibbs free energy – isobaric-isothermal potential (P,T = const).

$$\boldsymbol{\Delta F^0 = \Delta U^0 - T\Delta S^0}$$

ΔF^0 – Helmholtz free energy – isochoric-isothermal potential (V,T = const).

The value of ΔG determines the possibility of a spontaneous process:

ΔG = 0 – the process is equilibrium;

ΔG < 0 – the process is spontaneous, the system spontaneously passes from one state to another;

ΔG > 0 – the process cannot run spontaneously in the forward direction under standard conditions.

Let us analyze the ratio:

1. If $\Delta H < 0$ (exothermic process), and $\Delta S > 0$, then $\Delta G < 0$ at any temperature, i.e. the isobaric process in the case of an exothermic reaction proceeds spontaneously at any temperature.

2. If $\Delta H > 0$ (endothermic process), then $\Delta G < 0$ if $|\Delta H| < |T\Delta S|$ and $T\Delta S > 0$. This is done if the reaction proceeds at very high temperatures or in the gas phase, when the entropy increases significantly, i.e. in the case of an endothermic reaction, the process proceeds spontaneously only at very high temperatures.

3. If $\Delta H > 0$ and $|\Delta H| > |T\Delta S|$, then $\Delta G > 0$ and a spontaneous process is impossible, i.e. a process that is accompanied by a simultaneous increase in enthalpy and a decrease in entropy at a constant value of pressure and temperature is impossible.

As follows from relations (14) and (15), spontaneous flow of the process is possible both with increasing and decreasing entropy (under the conditions P=const or V=const), which distinguishes the systems under consideration from the isolated ones in which the spontaneous process is always accompanied increase in entropy.

So, based on the second law of thermodynamics, we can conclude that in a system in which constant pressure and temperature are maintained, the processes proceed with a decrease in G. The change in entropy can be either positive or negative (there is no contradiction to the principle of increasing entropy, which follows from the second law of thermodynamics and refers to isolated systems). In accordance with this principle, if a process occurs in the system with a decrease in entropy, then in the environment, which can be considered together with the system as a united isolated system, a compensating increase should occur.

In addition, the negative sign ΔG only indicates the possibility of a spontaneous process under standard conditions. Whether this process will actually go on depends on specific conditions and other factors.

FREE ENERGY AND EQUILIBRIUM CONSTANT

The direction of a chemical reaction, like any other process, at a given pressure and temperature is determined by the change in the Gibbs energy of the system as a result of the reaction.

The minimum value of the Gibbs total energy indicates that chemical equilibrium has occurred in the system (the condition for the minimum of a function is that its derivative is equal to zero).

$$\Delta G = \Delta G^0 + RT\ln K \quad (16)$$

if $\Delta G=0$

$$\Delta G^0 + RT\ln K = 0$$

$$\Delta G^0 = - RT\ln K$$

$$\Delta G^0 = -2{,}303\, RT\lg K \quad (17)$$

where K – equilibrium constant*;* ΔG^0 *– Gibbs free energy.*

From the relation follows:

1. The process is carried out as spontaneous in the forward direction, if $K > 1$*, then* $\lg K > 0$ *and* $\Delta G < 0$*;*

2. If $K < 1$*, then* $\lg K < 0$ *and* $\Delta G > 0$*, that is, there will be a spontaneous process of converting products into starting materials;*

3. If $K = 1$*,* $\Delta G = 0$ *- the process is equilibrium.*

ON THE APPLICABILITY OF THE THERMODYNAMICS OF EQUILIBRIUM PROCESSES TO BIOLOGICAL SYSTEMS

The considered laws of classical and chemical thermodynamics are the criteria for the possibility of a spontaneous process and the conditions for the implementation of the equilibrium process. Moreover, the universal criterion for any process is the change in Gibbs free energy. However, quite often, when $\Delta G > 0$ and a spontaneous flow of the process is impossible, this reaction is combined with another so that the total reaction turns out to be spontaneous. The combination of two or more reactions plays an important role in biochemical systems. For example, many reactions in the body are carried out only because they are combined with reactions that occur spontaneously with the release of energy. Thus, the release of energy from food during metabolism is the primary source of necessary free energy. For example, spontaneous oxidation of glucose in the body by the reaction:

$$C_6H_{12}O_6 + 6\ O_2 = 6\ CO_{2\ г} + 6\ H_2O_{(l)}$$

is characterized by the release of a significant amount of energy: $\Delta H° = -2800$ kJ/mol, $G° = -2880$ kJ/mol.

This energy is expended by the body to do useful work (converting ADP to ATP, maintaining a constant body temperature, etc.)

The transformation of energy in living systems, its formation and deposition is the subject of bioenergy. As the molecular mechanism of many biological and biochemical processes is clarified, scientists are trying to apply thermodynamic concepts in studies of living systems. Living organisms are open systems, their state is defined as stationary, rather than equilibrium. Under stationary understand the equilibrium state with a constant concentration of particles, which is maintained by the influx and outflow of matter from the system. In fact, any cell in equilibrium is already a dead cell. The study of open systems requires methods of thermodynamics of irreversible processes. So far, such methods have not been developed. Therefore, at present, there are different opinions on the value of equilibrium thermodynamics for solving biological problems. Nevertheless, there are certain biochemical issues in which classical thermodynamics methods are very effective. For example, thermodynamic calculations are based on the assessment of the energy value of food products, which underlies dietetics, the assessment of the energy intensity of biochemical processes, the effectiveness of many macroergic drugs (ATP, cocarboxylase, vitamin B_{12}, etc.), the modeling of biological structures and processes.

General material and educational and methodological support of the lecture:

- Working program of the discipline
- Silabus
- Methodical recommendations for independent work of higher education applicants
- Multimedia presentations
- Situational tasks

Recommended literature

Basic literature:

1. Medical Chemistry: textbook / V.Y. Tsuber, A.A. Kotvytska, K.V. Tykhonovych et al. - – Kyiv, AUS Medicine Publishing, 2022. – 392 p.

2. Medical chemistry: a textbook for universities / V. O. Kalibabchuk, I. S. Chekman, V. I. Galynska and others; for ed. Prof. V. O. Kalibabchuk – 4th ed. – K. VSV "Medicine", 2019 – 336 p.

3. Medical chemistry / V.O. Kalibabchuk, V.I. Halynska, L.I. Hryshchenko et al. – Kyiv, AUS Medicine Publishing, 2020. – 224 p.

4. General and Inorganic Chemistry: textbook / V.O. Kalibabchuk, V.V. Ohurtsov, V.I. Halynska et al. – Kyiv, AUS Medicine Publishing, 2019. – 456 p.

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Richard Post. Chemistry: Concepts and Problems / Richard Post, Chad Snyder, Clifford C. Houk // A Self-Teaching Guide, Jossey-Bass, 2020. – 432 p.

Lecture № 4

***Topic*: «Kinetic patterns of biochemical processes»**

Actuality of theme: Chemical kinetics is a branch of physical chemistry that studies the concepts of speed and mechanisms of chemical reactions, as well as the factors affecting them. It is extremely important to understand the mechanisms of reactions, to control the process at a quantitative level. The laws of chemical kinetics are used to explain the mechanisms of biochemical reactions (normal and malignant tissue growth), kinetic assessment of treatment effectiveness, achieving the maximum yield of reaction products, studying the distribution of drugs introduced into the body and their half-life from the body. Nowadays, chemical kinetics has become one of the effective "tools" for the study of catalytic reactions, including enzymatic ones, occurring in the human body. It is not for nothing that the expression appeared among scientists: all processes in chemistry and biochemistry are divided into catalytic and those where the fact of catalysis has not yet been discovered.

Goal: get acquainted with the most important concepts and laws of chemical kinetics; analyze the influence of various factors (concentration, pressure, temperature) on the speed of a chemical reaction; to classify types of chemical processes by kinetic feature; interpret the influence of catalysts on the speed of chemical processes and explain the mechanism of their action; to know the features of enzymatic catalysis.

Basic concepts: rate of chemical reaction, molecularity, the reaction order, the effect of temperature, activation energy, catalysis, chemical equilibrium.

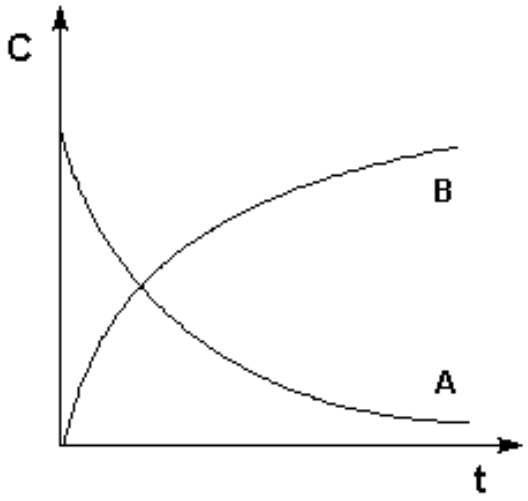
Plan and organizational structure of the lecture:

1. THE IMPORTANT FACTORS THAT AFFECT THE RATE OF REACTION
2. METHODS FOR DETERMINING THE REACTION ORDER.
3. THE CONCEPT ABOUT ACTIVE PARTICLES
4. ENZYMATIC CATALYSIS.
5. ACID-BASIC CATALYSIS
6. CHEMICAL EQUILIBRIUM

Content of lecture material (lecture text)

Chemical thermodynamics gives information about the possibility of a reaction, but it is important to know the speed of a process. Chemical kinetics is the doctrine of the speed of chemical reactions, their mechanism and patterns of flow over time. To determine the speed of a chemical reaction, it is necessary to know not only the initial and final state of the system, but also the path along which the reaction proceeds; therefore, it is much more difficult to obtain kinetic laws than thermodynamic ones.

The rate of a chemical reaction shows the number of chemical interactions leading to the formation of reaction products per unit time in a unit volume (for a liquid medium) or on a unit surface, if the process involves a solid substance. The ratio of changes in the concentration of reacting substances to the final (measured) period of time is called the average speed: $V_{av} = \pm \Delta C / \Delta t$, mol/(L·s).



True rate is the ratio of changes in the concentration of reacting substances to an infinitely small period of time: $V_{trr} = \pm dC / dt$, mol/(L·s) – in SI system.

In medicine, other units of measurement of the reaction rate are also used, for example, ESR - the erythrocyte sedimentation rate. It is measured by the height of the column of red blood cells that have settled in the capillary per hour (normal ≈ 5 mm / hour). Pharmacokinetics is a special discipline which is based on the kinetic laws of the distribution of drugs in the body. It studies the distribution of drugs over time, the

processes of absorption, the time of metabolism (withdrawal), the relationship between concentration and the magnitude of the therapeutic effect.

THE IMPORTANT FACTORS THAT AFFECT THE RATE OF REACTION

The factors are :

1) The nature of the reactants;
2) Concentration of reactants or pressure (for gases);
3) Temperature;
4) The presence of a catalyst in a system.

1. The nature of the reactants

$$H_2SO_{4(dilute)} + Zn = ZnSO_4 + H_2\uparrow (V_1)$$

$$2CH_3COOH + Zn = (CH_3COO)_2Zn + H_2\uparrow (V_2)$$

$V_1 > V_2$ as H_2SO_4 is more strong electrolyte

2. The effect of concentration on the rate of a chemical reaction.

The effect of concentration on the rate of a chemical reaction is determined by the law of mass action - at a constant temperature, the speed of this reaction is directly proportional to the product of the concentrations of the reacting substances, taken in degrees equal to their stoichiometric coefficients.

$$aA + bB \leftrightarrow cC + dD$$

$$V_f = k_f \cdot [A]^a \cdot [B]^b$$

k **-** reaction rate constant shows the number of effective collisions (those that led to the reaction) per 1 mol of reacting substances. k depends on the temperature and nature of the substance, but does not depend on the concentration.

In the equation of the law of acting masses, the most difficult to determine the reaction rate constant. To determine it, you need to know the following concepts: reaction order and molecularity.

Molecularity is determined by the number of molecules whose simultaneous interaction at the time of the collision is a chemical transformation.

Monomolecular: $C_2H_5OH \rightarrow C_2H_4 + H_2O$; $N_2O_4 \rightarrow 2NO_2$

Bimolecular: $2NO=N_2O_2$; $N_2 + O_2 = 2NO$

Trimolecular: $Cl_2+ 2NO= 2NOCl$

Most often, chemical processes consist of mono and bimolecular stages.

When conducting a chemical reaction, one of the most significant is the question of how quickly the studied transformation occurs. The answer to this question is given by the dependence of the concentration of the determined component on time, i.e. equation of the kinetic curve of the accumulation or expenditure of this component.

The exponent is called the order for a given component or private *order*. The sum of the partial orders for all components is the general or formal order of the reaction.

For example, reaction $N_2 + O_2 = 2NO$

$$V = k\, C_{N2}\, C_{O2}$$

It is a second order reaction, but it is also a first order reaction with respect to the N_2 component, as well as the O_2 component.

The true order of the reaction can only be determined experimentally. It can be integer, zero or fractional.

The reaction order, which is established experimentally, makes it possible to establish its possible mechanism.

METHODS FOR DETERMINING THE REACTION ORDER

Carrying out the reaction under conditions when the concentration of one of the reagents is much lower than the concentration of the other (others) and the reaction rate depends on the concentration of only this reagent, is used to determine the particular order of the reaction. This is the so-called excess concentration method or *Ostwald* isolation method. The reaction order for this substance is determined by one of the methods listed below.

The graphical method consists in constructing a graph of the dependence of the concentration of the reagent on time in various coordinates. For various private orders, these dependencies have the following form:

Reaction order	Concentration versus time
1	$lnC = lnC_o - k\tau$
2	$\frac{1}{C} = k\tau + \frac{1}{C_o}$
3	$\frac{1}{C^2} = k\tau + \frac{1}{C_o^2}$

If we plot these dependencies on the basis of experimental data, then only one of them will be a straight line. If, for example, a graph constructed from experimental data turned out to be straightforward in the coordinates **lnC = f(t)**, then the particular reaction order for this substance is equal to unity.

The method of selecting the kinetic equation consists in substituting experimental data for studying the dependence of the concentration of a substance on time in kinetic equations of various orders. Substituting the values of the reagent concentration at different instants of time in the table of equations, the values of the rate constant are calculated. The particular order of the reaction for a given substance is equal to the order of the kinetic equation for which the value of the rate constant remains constant in time.

Reaction order	Expression for the rate constant
1	$k = \frac{1}{\tau} ln \frac{C_0}{C}$
2	$k = \frac{1}{\tau}\left(\frac{1}{C_o} - \frac{1}{C}\right) = \frac{1}{\tau}\frac{C_o - C}{C_o C}$
3	$k = \frac{1}{\tau}\frac{C_o^2 - C^2}{2C_o^2 C^2}$

The method for determining the half-conversion time is to determine $t_{1/2}$ for several initial concentrations. As can be seen from the equations given in the table, the half-reaction time for the first-order reaction does not depend on C_o, for the second-order

reaction it is inversely proportional to C_o, and for the third-order reaction it is inversely proportional to the square of the initial concentration.

Reaction order	Expression for period of semi-transformation
1	$\tau_{1/2} = \frac{ln2}{k}$
2	$\tau_{1/2} = \frac{1}{k} \cdot \frac{1}{C_o}$
3	$\tau_{1/2} = \frac{1}{k} \cdot \frac{3}{2C_o^2}$

By the nature of the dependence of $t_{1/2}$ on C_o, it is not difficult to conclude on the reaction order for this substance. This method, unlike the ones described above, is also applicable for determining fractional orders.

Molecularity and order coincide only in single-stage processes. They do not coincide when one of the reacting substances is taken in excess and therefore does not participate in determining the order.

For example:

$$CH_3COOC_2H_5 + H_2O_{excess} \leftrightarrow CH_3COOH + C_2H_5OH,$$

$V_{forw} = K_{forw} \cdot [CH_3COOC_2H_5] \cdot [H_2O]$, first-order bimolecular reaction.

If the reaction is carried out by sequentially proceeding stages (not necessarily all of them are chemical) and one of these stages requires much longer time than the others, that is, it goes much slower, then this stage is called *limiting*. It is this very slowest stage that determines the speed of the whole process.

The effect of temperature on the rate of a chemical reaction.

This influence is determined by the Vant-Hoff rule: with an increase in temperature by 10 ° C, the rate of a homogeneous chemical reaction increases by 2–4 times.

$$V(t_2) = V(t_1) \cdot \gamma^{(\Delta t/10)}$$

$V(t_2)$ and $V(t_1)$ – reaction rates at temperature t_2 and t_1.

γ – temperature coefficient = 2 ÷ 4, shows how many times the reaction rate increased with increasing temperature by 10^0C.

$$\Delta t = t_2 - t_1.$$

For biochemical reactions, the temperature coefficient with increasing temperature by 10^0C cannot be received, but only at 5^0C, and γ= 1,1 ÷ 1,8 times.

Vant Hoff rule works at temperatures from 0^0C to 100^0C.

For higher temperatures the Arrhenius rule is used. Arrhenius suggested that not every collision of molecules leads to chemical interaction. Only a small fraction of the total number of molecules that have the necessary or large energy reserve for the reaction to enter the reaction. ***Activation energy – E_a*** – is excess energy compared to the average value that a molecule must possess at the moment of collision in order to be capable of chemical interaction. The lower the activation energy leads to the higher the reaction rate.

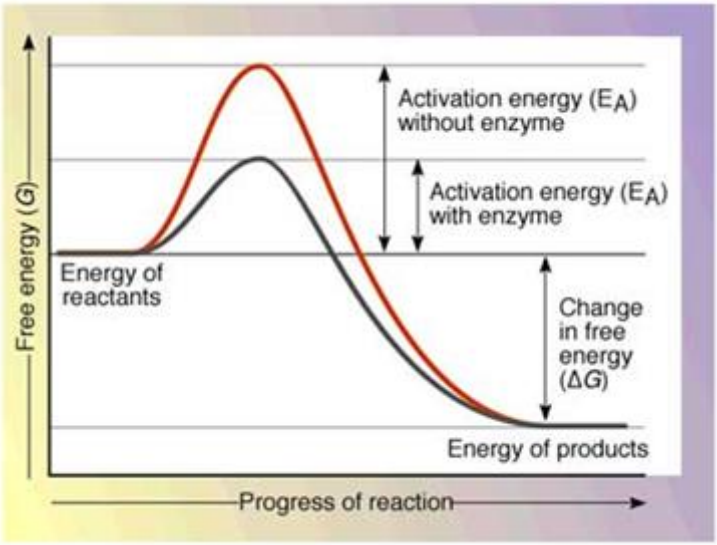


Fig.1. Activation Energy.

Activation energy is spent on weakening the bonds between atoms in the molecules of the reacting substances. In this case, the substances pass into an unstable intermediate state called the activated complex.

Arrhenius equation for calculating the activation energy:

$$k = Ae^{-\frac{E_a}{RT}} \quad or \quad ln\ k = -\frac{E_a}{RT} + ln\ A$$

Where:

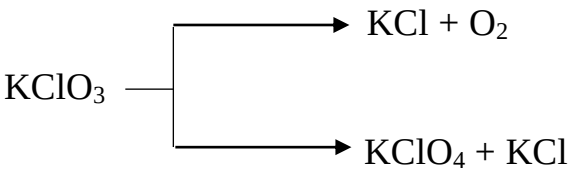
k =	Chemical Reaction Rate
A =	Pre-exponential Factor
E_a =	Activation Energy
R =	Gas Constant
T =	Temperature in Kelvin

A high value of the activation energy of the reaction is undesirable, as this means that a high energy barrier stands in the way of its implementation. For most of the biochemical reactions, E_a is 2–3 times lower than for chemical ones, since they proceed in the presence of enzymes that lower E_a. However, the activation energy for the destruction of biological structures is very high, which helps protect cells from damage. The reaction rate can be increased by reducing the activation energy, which is carried out by introducing a catalyst into the reaction medium.

Complex reactions belong to three main types:

1**. Parallel reactions** - a related system of reactions in which different products can be obtained from the same starting materials.

For example,



2. **Sequential reactions** - a connected system of reactions in which the products of the previous stages are the starting materials for the subsequent ones.

For example, the reaction of sulfuric acid and sodium thiosulfate is carried out sequentially:

First stage: $Na_2S_2O_3 + H_2SO_4 \rightarrow Na_2SO_4 + H_2S_2O_3$

Second stage: $H_2S_2O_3 \rightarrow H_2O + S + SO_2$

Summary: $Na_2S_2O_3 + H_2SO_4 \rightarrow Na_2SO_4 + H_2O + S + SO_2$

3. **Conjugated reactions** are reactions of the type A + B → M, A + C → D, of which one, for example the second, proceeds only together with the first. In such reactions, substance B is an inducer of another reaction.

An example of such a reaction is the oxidation of ferrum (II) sulfate and iodohydrogen with hydrogen peroxide.

$$FeSO_4 + H_2O_2 \rightarrow Fe_2(SO_4)_3 + H_2O$$

$$HI + H_2O_2 \rightarrow I_2 + H_2O$$

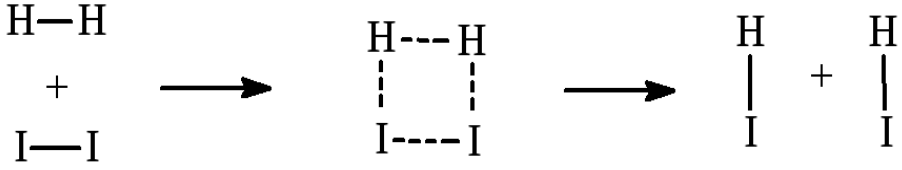
Ferrum sulfate is oxidized by hydrogen peroxide, regardless of the presence of iodohydrogen, but iodohydrogen by hydrogen peroxide is not oxidized if there is no ferrum (II) sulfate. In this reaction, the inducer is ferrum (II) sulfate.

The kinetics of conjugated reactions is very complex.

THE CONCEPT ABOUT ACTIVE PARTICLES

To explain the laws of the chemical reaction and calculate the rate constants, two theories were proposed: Arrhenius theory of active collisions (we considered it earlier) and Eyring and Polyany theory of the transition state.

The theory of the transition state makes it possible to more accurately calculate the E_{act} and rate constants. It was proposed in the 30s of the twentieth century. According to this theory, the condition for the course of the reaction is the formation of a fragile (metastable) intermediate complex due to the redistribution of bonds in the reacting molecules. The intermediate complex, in turn, can be formed only if the reacting particles have energy no less than the activation energy of the transition state. For example, a system of H_2 and I_2 forms HI if H_2 and I_2 molecules have sufficient energy to form an intermediate complex:



The theory of the transition complex complements the theory of active collisions. The structure of the transition complex is of great importance, because the rate constant

in the kinetic equation depends on the equilibrium constant of transition complex formation:

$$A + BC \underset{k_{-1}}{\overset{k_1}{\leftrightarrow}} A\ldots B\ldots C \xrightarrow{k_2} AB + C$$

The formation of an active complex requires a certain activation energy, but its decay is spontaneous. Therefore, the reaction rate is equal to the number of active complexes that pass through the energy barrier per unit time in the direction of the reaction.

Catalysis is the process of changing the rate of a chemical reaction by introducing a catalyst into the reaction medium.

A *catalyst* is a substance participating in the course of a chemical reaction and changing its speed, but remaining unchanged after the reaction.

There are *positive catalysis* (the reaction rate increases), *negative catalysis* (the reaction rate decreases), *autocatalysis* (the catalyst is formed during the chemical reaction), homogeneous catalysis (the catalyst is in the same state of aggregation with the reacting substances),

$$2SO_2 + O_2 \xrightarrow{NO,\ NO_2} 2SO_3$$

heterogeneous catalysis (the catalyst is in a different state of aggregation than reactants).

$$N_2 + 3H_2 \xrightarrow{Fe_{(s)}} 2NH_3$$

Some features of homogeneous and heterogeneous catalysis are common:

1. The catalyst takes part in the chemical process, but is not part of the products.

2. The interaction of the catalyst with the starting materials is not stoichiometric (one mass part of the catalyst can cause the conversion of millions of mass parts of the starting materials).

3. The catalysts do not affect the value of the equilibrium constant, i.e. equally change the speed of direct and reverse reactions.

4. The activity of the catalyst depends on the presence of certain foreign substances - activators (promoters).

5. Most catalysts have selectivity.

The mechanisms of catalytic reactions are complex, diverse, and very rarely firmly established. For homogeneous catalysis, a quantitative theory of intermediate compounds has been developed:

6. First, a metastable intermediate compound of the catalyst and reagent is formed.

7. Formation proceeds at high speed.

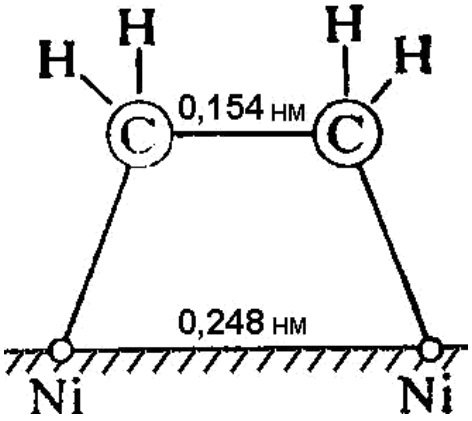
8. The decomposition of the intermediate is a limiting step.

There is no single theory regarding heterogeneous catalysis. A feature of heterogeneous catalysis is the formation of chemisorbed complexes at the active centers that are incapable of independent existence. The nature of chemisorption depends on the electronic nature of the solid catalyst. Active metals give strong adsorption complexes; therefore, they are inactive catalysts. Conversely, inactive metals (and semiconductors) form fragile chemisorbed complexes and exhibit catalytic activity.

A.A.BALANDIN `s MULTIPLET THEORY OF HETEROGENEOUS CATALYSIS

It is assumed that the formation of a surface active complex to accelerate this reaction involves groups of active atoms - multiplets - that satisfy the principles of geometric and energy correspondence.

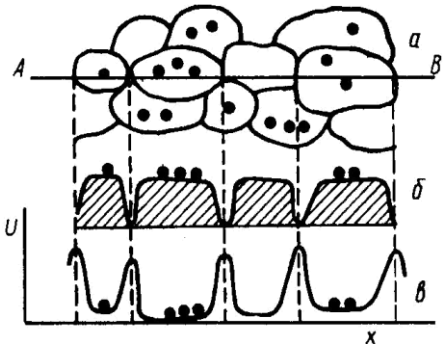
According to the principle of geometric correspondence, the multiplet must geometrically correspond to the molecules of the reacting substances.



For example, in the hydrogenation reaction of ethylene on nickel with the formation of ethane $C_2H_4 + H_2 \rightarrow C_2H_6$, carbon atoms are bonded to nickel atoms, while the double bond between the carbons turns into a single bond, and both carbon atoms join two atoms of the nickel multiplet (doublet) with free valencies.

The principle of energy correspondence requires that the energy level of the multiplet be located approximately in the middle between the levels of the initial molecules and reaction products, and the energies of its formation and decay should be minimal.

N.I. KOBOZEV`s THEORY OF ACTIVE ENSEMBLES



For adsorption catalysts (whose atoms are statistically (amorphously) distributed over the surface of a solid), only sets (ensembles) of catalyst atoms with a certain number of atoms within the migration region (a region that the catalyst atoms cannot leave due to thermal motion) will be active ensembles.

The surface of anything consists of a large number of such areas separated by energy and mechanical barriers.

The number of atoms in the active ensemble is determined experimentally from the dependence of the activity of the catalyst on the average number of atoms in one region.

ROGINSKY`s ELECTRON-CHEMICAL THEORY

This theory assumes that the adsorption of molecules that react on a catalyst depends on the distribution of electrons on the surface and inside the catalyst. By the nature of the interaction of the catalyst and reacting substances, catalytic reactions are divided into redox reactions in which electrons and acid-base transfer to the catalyst and from the catalyst if protons are transferred.

An important feature of the catalysis process is the reduction of activation energy. The catalyst, getting into the reaction medium, forms an activated complex with one of the reacting substances. Then, the activated complex reacts with other reacting substances, forming reaction products and a catalyst. The action of the catalyst is reduced to the discovery of a new reaction path in which the catalyst directly interacts with at least one of the reacting substances, while the energy of formation of the activated complex is much lower.

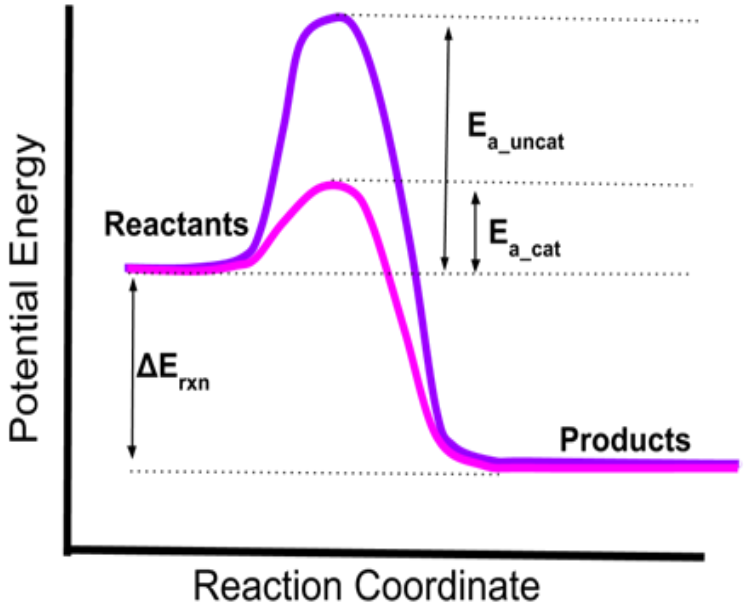


Fig.2. Activation energy in the presence of a catalyst.

ENZYMATIC CATALYSIS

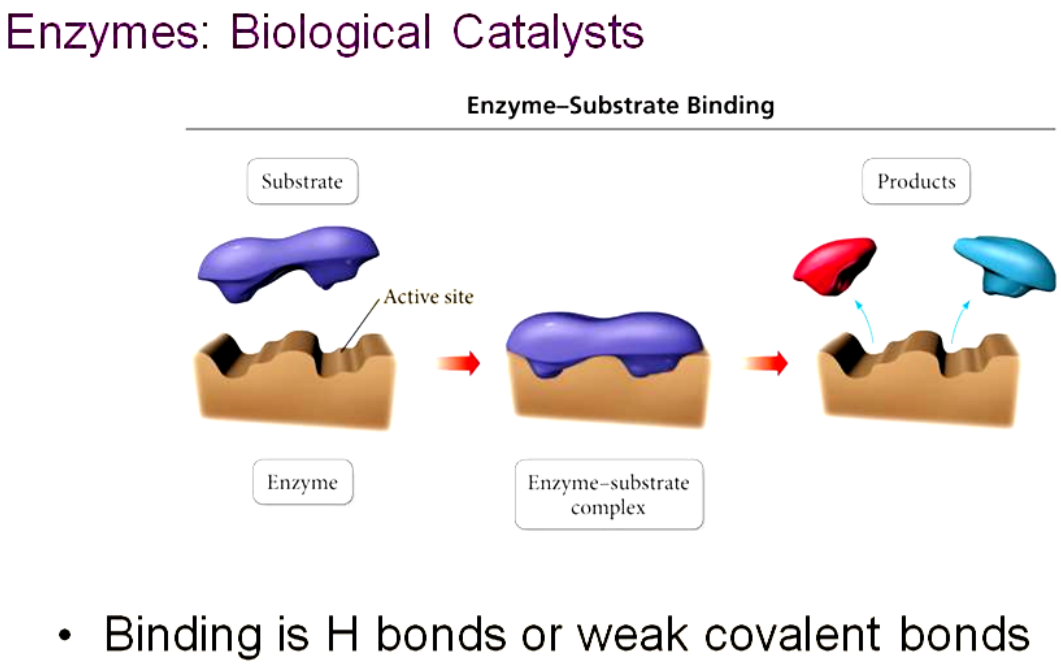
The role of catalysts in the body is given to enzymes. Enzymatic catalysis has a number of features:

1. High catalytic activity. Enzymes are millions of times superior in their activity to chemical catalysts, so very few are needed for reactions.

2. High specificity. Each enzyme acts on a strictly defined reaction or group of reactions.

3. Enzymes are active at a strictly defined pH.

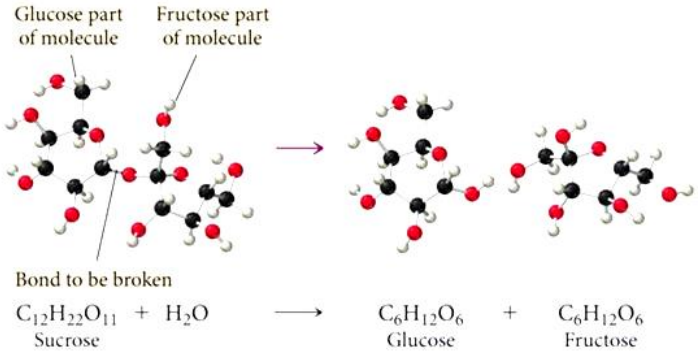
4. Enzymes are most active at a temperature of 37^0C ÷ 40^0C, at a lower temperature, the enzymes become less active, and at a higher temperature, enzymes are denatured.



Enzymatic Hydrolysis of Sucrose

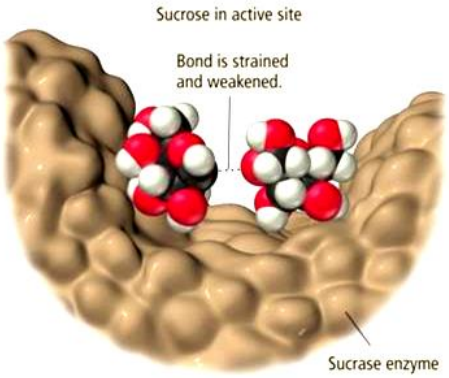
$E + S \rightleftharpoons ES$ Fast

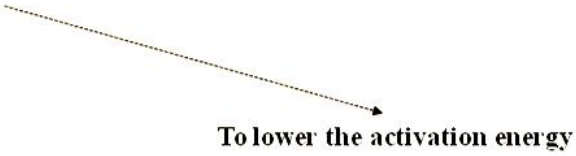
$ES \longrightarrow E + P$ Slow, rate limiting



$C_{12}H_{22}O_{11} + H_2O \longrightarrow C_6H_{12}O_6 + C_6H_{12}O_6$

Sucrose — Glucose — Fructose



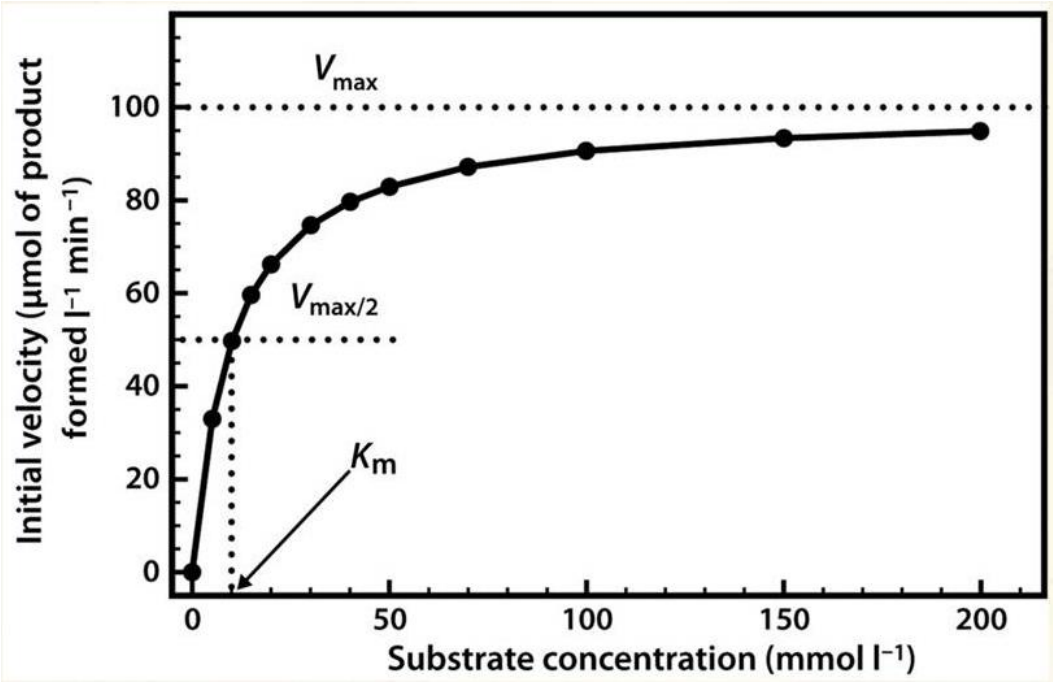


Leonor Michaelis and Maud Menten – first researchers who explained the shape of the rate curve (1913)

During reaction enzyme molecules, E, and substrate molecules, S, combine in a reversible step to form an intermediate enzyme-substrate (ES) complex

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} E + P$$

k_1, k_{-1}, k_2, k_{-2} – rate constant – indicate the speed or efficiency of a reaction



The Michaelis-Menten Equation

The basic equation derived by Michaelis and Menten to explain enzyme-catalyzed reactions is

$$v_o = \frac{V_{max}[S]}{K_m + [S]}$$

K_m - Michaelis constant;

V_o - initial velocity caused by substrate concentration, [S];

V_{max} - maximum velocity

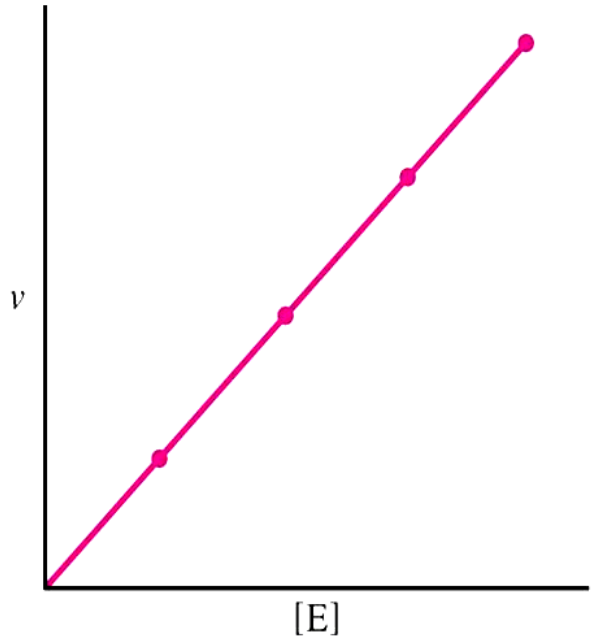
_ At a fixed enzyme concentration [E], the initial velocity Vo is almost linearly proportional to substrate concentration [S] when [S] is small but is nearly independent of [S] when [S] is large

- Rate rises linearly as [S] increases and then levels off at high [S] (saturated)

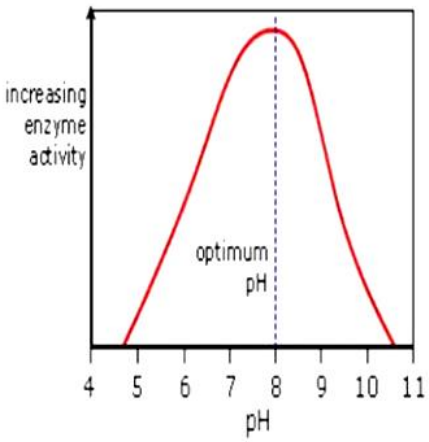
Effect of enzyme concentration [E] on velocity (v)

In fixed, saturating [S], the higher the concentration of enzyme, the greater the initial reaction rate

This relationship will hold as long as there is enough substrate present



Effect of pH on enzyme activity



- Hydrogen ion concentration also have an influence on enzyme activity.
- For most enzymes, the effective pH range is 4.0-9.0.
- Beyond these limits, denaturation of enzymes take place.
- Optimum pH for pepsin is 2.0 and for trypsin 8.0

ACID-BASIC CATALYSIS

According to the proton theory of acids by Bronsted and Lowry, an acid is a substance that can give off a proton, and a base is a substance that can attach it. (Note

that according to the aprotic theory of Lewis acids, an acid is an acceptor of a lone pair of electrons, and a base is a substance that is a donor of an electron pair in the formation of a compound with a donor-acceptor bond BF_3 (acid) + NH_3 (base) ⇔ $F_3B{-}NH_3$.

Typical Lewis aprotic acids are ($AlBr_3$, $FeCl_3$, BF_3)

The following types of reactions are distinguished in acid-base catalysis.

1) Specific acidic and basic catalysis.

The former include reactions in which the activation of the substrate is carried out only by hydrogen ions, and to the second, only by hydroxyl ions. The simplest mechanisms of these reactions include the reversible interaction of the substrate (S) with the catalytic particle and the conversion of the resulting complex into a product:

$$S + H^+ \underset{k-1}{\overset{k_1}{\leftrightarrow}} SH^+ \xrightarrow{k_2} P + H^+$$

specific acidic catalysis

$$SH + OH^- \underset{k-1}{\overset{k_1}{\leftrightarrow}} S^- + H_2O \xrightarrow{k_2} P + OH^-$$

specific basic catalysis

2) General acid and basic catalysis - reactions with activation of the substrate by any proton donor, except for hydrogen ions, i.e. under the influence of generalized Bronsted acids; and reactions with activation by any proton acceptor other than OH^-, i.e. the generalized Bronsted base, respectively:

$$S + HA \underset{k-1}{\overset{k_1}{\leftrightarrow}} SH^+ + A^- \xrightarrow{k_2} P + HA$$

general acidic catalysis

$$SH + B \underset{k-1}{\overset{k_1}{\leftrightarrow}} S^- + BH^+ \xrightarrow{k_2} P + B$$

general basic catalysis

CHEMICAL EQUILIBRIUM

For a reversible reaction

$$aA+bB \rightleftarrows cC+dD$$

we write the kinetic equations for the forward and reverse reactions:

$$V_{forw} = k_{forw} \cdot c(A)^a \cdot c(B)^b$$

$$V_{rev} = k_{rev} \cdot c(C)^c \cdot c(D)^d$$

For a given state of the system, ΔG = 0. No visual changes are visible.

Since both direct and reverse reactions proceed in a state of chemical equilibrium, this equilibrium is called dynamic or mobile equilibrium, i.e. its establishment does not mean termination of the reaction. The concentrations of all participants in the reaction remain constant, are called equilibrium and are denoted by [A], [B], etc., the dimension of these quantities is mol / L.

Since at the moment of equilibrium the rates of direct and reverse reactions are equal, we can write:

$$V_{forw} = V_{rev}$$

$$k_{forw} \cdot [A]^a \cdot [B]^b = k_{rev} \cdot [C]^c \cdot [D]^d$$

The ratio of the rate constants of direct and reverse reactions is called the equilibrium constant:

$$K_{eq} = \frac{k_{forw}}{k_{rev}} = \frac{[C]^c[D]^d}{[A]^a[B]^b}$$

This expression is called the law of mass action for a system in a state of chemical equilibrium. The value of the equilibrium constant expressed in terms of the concentration of the participants in the reaction will be denoted by K_{eq}. K_{eq} is a thermodynamic quantity that does not depend on the path of the process. The value of the equilibrium constant indicates the direction of the process: if $K_{eq} \rightarrow \infty$, then the reaction products prevail in the reaction mixture, therefore, a direct reaction proceeds mainly (the equilibrium is shifted to the right).

For example,

$$N_{2(g)} + 3H_{2(g)} \leftrightarrow 2NH_{3(g)}$$

$$K_{eq} = \frac{[NH_3]^2}{[N_2][H_2]^3}$$

The equilibrium constant depends on the temperature and nature of the reacting substances, but does not depend on the concentration of substances. The catalyst does not affect the value of the equilibrium constant, since it equally increases the rate of both direct and reverse reactions.

The expression for the equilibrium constant of a heterogeneous reaction includes only the concentrations of substances in solution or in the gas phase, since the concentrations of solid and liquid substances agreed to be considered constant (equal to 1).

CHEMICAL EQUILIBRIUM SHIFT

The state of chemical equilibrium is maintained as long as the thermodynamic parameters at which it is established remain unchanged. When conditions (*temperature, pressure, concentrations of substances involved in the reaction*) change, the rates of the forward and reverse reactions change, as a rule, differently and the equilibrium is disturbed. As a result, after a while the state of a new chemical equilibrium is established in the system, which is characterized by new equilibrium concentrations of all substances

The process of transition from one equilibrium state to another is called a shift in chemical equilibrium. The direction of this displacement obeys the principle of **Le Chatelier** (1884):

If a system in a state of chemical equilibrium is exposed to external influences, then the equilibrium is shifted in such a way that this effect decreases.

Factors Affecting Chemical Equilibrium

Change of conditions		Equilibrium offset direction
Temperature	increases	Towards the endothermic reaction
	decreases	Towards exothermic reaction
Pressure	Increases	Towards reducing the volume of gaseous substances

	decreases	Towards increasing the volume of gaseous substances
The reactants concentration	increases decreases	Towards direct reaction Towards the reverse reaction
The products concentration	increases decreases	Towards the reverse reaction Towards direct reaction
Catalysts		Balance does not shift

DEPENDENCE OF K_{eq} FROM TEMPERATURE

Equilibrium is the central concept of thermodynamics. Therefore, the equilibrium constant is uniquely related to the corresponding thermodynamic functions. For a gaseous system, the relationship between the equilibrium constant and the change in the isobaric reaction potential ΔG is expressed by the following equation:

$$\Delta G = -RT\ln K_{eq}$$

If $\Delta G^0 << 0$, then $K_{eq} >> 1$, the equilibrium is shifted to the right (the direct reaction is almost irreversible under standard conditions). **This concerns the definition for practically irreversible reactions.**

If $\Delta G^0 >> 0$, then $K_{eq} << 1$, the equilibrium is shifted to the left **(the reverse reaction is almost irreversible).**

With increasing temperature, the equilibrium constant decreases for the exothermic reaction, and increases for the endothermic reaction. With a decrease in temperature - vice versa.

General material and educational and methodological support of the lecture:

- Working program of the discipline
- Silabus
- Methodical recommendations for independent work of higher education applicants
- Multimedia presentations
- Situational tasks

Recommended literature

Basic literature:

1. Medical Chemistry: textbook / V.Y. Tsuber, A.A. Kotvytska, K.V. Tykhonovych et al. - – Kyiv, AUS Medicine Publishing, 2022. – 392 p.

2. Medical chemistry: a textbook for universities / V. O. Kalibabchuk, I. S. Chekman, V. I. Galynska and others; for ed. Prof. V. O. Kalibabchuk – 4th ed. – K. VSV "Medicine", 2019 – 336 p.

3. Medical chemistry / V.O. Kalibabchuk, V.I. Halynska, L.I. Hryshchenko et al. – Kyiv, AUS Medicine Publishing, 2020. – 224 p.

4. General and Inorganic Chemistry: textbook / V.O. Kalibabchuk, V.V. Ohurtsov, V.I. Halynska et al. – Kyiv, AUS Medicine Publishing, 2019. – 456 p.

Additional literature:

1. Medical chemistry: a textbook / V. P. Muzychenko, D. D. Lutsevich, L. P. Yavorska; for order. B. S. Zimenkovsky. – 3rd ed., Ed. – K.: BCB «Medicine», 2018. – 496 p.

2. Mironovich L. M. Medical Chemistry: A Textbook. – Kyiv: Karavella, 2008. – 159 p.

3. Moroz A. S. Medical chemistry: a textbook / D. D. Lutsevich, L. P. Yavorska. – Vinnytsia: New book, 2006. – 776 p.

4. Gotsulyak L. O., Mardashko O. O., Yerigova S. G., Kuzmenko G. I., Kuzmina A. V., Zhilinskaya K. I. Bioinorganic, physicoloid and bioorganic chemistry. Teaching. manual. Odessa. Odessa State Medical University 1999. – 248 p.

5. Textbook of Medicinal Chemistry / V. Alagarsamy // CBS Publishers & Distributors Pvt Ltd, India; 3rd edition, 2018 – 584 p.

Richard Post. Chemistry: Concepts and Problems / Richard Post, Chad Snyder, Clifford C. Houk // A Self-Teaching Guide, Jossey-Bass, 2020. – 432 p.

Lecture № 5

***Topic*: «Solutions. Acid-base equilibria in biosystems.»**

Actuality of theme: Solutions are one of the most important states of matter, which is of great importance in human life and practical activities. The processes of assimilation of food by humans and animals are related to the transfer of nutrients into a solution. The solution is all the most important biological fluids (blood, lymph, etc.). The composition of the solution can be expressed in different ways, both with the help of dimensionless units and with the help of dimensional units - concentration. Knowledge of how to express the concentration of solutions and the ability to prepare solutions of a certain concentration are necessary for students to study biochemistry, hygiene, pharmacology, and doctors for the correct interpretation of laboratory analysis data, calculation of drug dosages.

Goal: To form systematic knowledge about the concepts: solutions, solubility, properties of solutions. Know different ways of expressing the concentration of solutions and the relationship between them. Familiarize yourself with the methods of determining pH; learn how to calculate the degree and constant of dissociation; pH of the solution. Explain the mechanism of action of buffer systems and their role in maintaining acid-base balance in biosystems.

Basic concepts: electrolyte solution, strong electrolytes, weak electrolytes, Ionic product of water, dissociation constant , pH, buffer systems.

Plan and organizational structure of the lecture:

1. Arrhenius Theory of Electrolytic Dissociation
2. Factors affecting the degree of dissociation
3. Weak electrolytes. Dissociation constant.
4. Ionic product of water. pH
5. Biological role of pH.
6. Buffer systems.
7. Blood buffer systems

Content of lecture material (lecture text)

Arrhenius Theory of Electrolytic Dissociation

Most natural chemical systems and biological objects are **electrolyte solutions.**

Electrolytes	Substances that in solutions or melts decay into ions, and therefore conduct an electric current. Almost all acids, bases, salts belong to electrolytes.
Non-electrolytes	Substances that in solutions or melts do not decay into ions and do not conduct electric current. These include most organic compounds (sugar, benzene), oxides, simple substances.

The ability of electrolyte solutions to conduct electric current was explained by the theory of electrolytic dissociation, proposed by the Swedish chemist Svante Arrhenius (1883 - 1887), which is based on the postulates:

- *Electrolytes, when dissolved in water or melted, decompose into positive and negative ions.*

Electrolytic dissociation is the decomposition of electrolyte molecules into ions by the action of polar solvent molecules (water).

Under the influence of an electric current, the ions acquire directional motion: positively charged move to the cathode and are called cations, and negatively charged to the anode and are called anions.

For example,

$$HCl \leftrightarrow \underset{\text{cation}}{H^+} + \underset{\text{anion}}{Cl^-}$$

- *The dissociation of molecules into ions is incomplete and is characterized by the degree of dissociation* $\boldsymbol{\alpha}$.

The degree of dissociation is the ratio of the number of molecules disintegrated into ions (n) to the total number of molecules (N)

$$\boldsymbol{\alpha} = \frac{\boldsymbol{n}}{\boldsymbol{N}} \cdot 100\%$$

Factors affecting the degree of dissociation:

- the nature of the electrolyte;
- the nature of the solvent;

- degree of dilution.

Depending on the degree of dissociation, Arrhenius divided all electrolytes into 3 groups - strong, weak and medium strength:

1. **Strong electrolytes -** when dissolved in water, they dissociate almost completely. The degree of dissociation is greater than 30% (α> 30%). These include almost all soluble salts, strong acids, alkalis:

HCl, HNO_3, H_2SO_4, $HMnO_4$ – acids;

NaOH, KOH, LiOH, $Ba(OH)_2$ – base (alkali);

NaCl, K_2SO_4, KNO_3, $KMnO_4$ – salts.

2. **Weak electrolytes -** when dissolved in water, they partially dissociate. The degree of dissociation is less than 3% (α <3%). These include covalent compounds that undergo partial dissociation in water. These are weak acids (H_2S, H_2CO_3, HCN) and weak bases (NH_4OH), sparingly soluble salts, H_2O; almost all organic acids (CH_3COOH), phenols, amines.

3. **Electrolytes of medium strength** - degree of dissociation 3% <α <30%. These include H_2CrO_4, H_2SO_3, H_3PO_4, HI.

- *The forces of interaction between ions are absent and electrolyte solutions behave like ideal gas systems. This position was not expressed directly, but it underlies all the quantitative relations obtained by the authors of the theory of electrolytic dissociation.*

The theory of electrolytic dissociation made it possible to explain many features of the chemical properties of electrolytes, however, the Arrhenius theory had a number of drawbacks, in particular, it did not take into account the interaction between ions in solution caused by their electric charges.

Weak electrolytes. Dissociation constant

Strong electrolytes exist in solutions only in the form of ions, and in solutions of weak electrolytes there are ions and molecules between which dynamic equilibrium is established at a given temperature:

$$CtAn \Leftrightarrow Ct^{+} + An^{-}$$

Because weak electrolytes obey the law of acting masses; this equilibrium can be quantitatively characterized by an equilibrium constant, which in this case is called the dissociation constant.

Dissociation constant is the ratio of the product of the concentration of electrolyte ions to the concentration of undissociated molecules:

$$K_{diss} = \frac{[Ct^+][An^-]}{[CtAn]}$$

where: $[Ct^+]$ - the concentration of cations;

$[An^-]$ - the concentration of anions.

For example, for acetic acid:

$$CH_3COOH \Leftrightarrow H^+ + CH_3COO^-$$

$$Kd_{iss} = \frac{[H^+][CH_3COO^-]}{[CH_3COOH]}$$

If the degree of dissociation is known, the dissociation constant (Cd) is calculated from the Ostwald dilution law:

$$K_d = \frac{\alpha^2 c}{1-\alpha},$$

where c is the electrolyte concentration, mol/L.

4. Ionic product of water. pH

Water, being a very weak electrolyte, dissociates into ions to a very small extent:

$$H_2O \leftrightarrow H^+ + OH^-$$

We apply the law of the acting masses to this reversible process.

$$K = \frac{[H^+]\cdot[OH^-]}{[H_2O]},$$

where K is the dissociation constant of water, which can be calculated, for example, using the values of electrical conductivity.

At 22°C $K = 1{,}8\cdot10^{-16}$.

Since water dissociates extremely little, in the equation the concentration of water $[H_2O]$ can be considered as a constant value. Numerically $[H_2O]$ = =1000/18= 55,56 mol/L. The equation can be rewritten as following:

$$K \cdot [H_2O] = [H^+][OH^-] = K_w.$$

K_w – a constant value - is called the ionic product of water. Substituting the values of K and $[H_2O]$ in the equation, we obtain the numerical value of the ionic product of water at 22 °C:

$K_w = [H^+]\,[OH^-] = 1{,}8 \cdot 10^{-16} \cdot 55{,}56 = 10^{-14}$.

Then, $K_w = [H^+][OH^-] = 10^{-14}$,

Where K_w is constant value at constant temperature.

The medium of aqueous solutions is determined by the ratio of the concentrations of two ions H^+ and OH^-, which are always present in water and in an aqueous solution of any substance.

1) *neutral medium*

For pure water, the concentration of hydrogen ions is equal to the concentration of hydroxide ions, since one mole of H^+ ions and one mole of OH^- ions are formed from one mole of water. Consequently, the concentration of these ions at 22°C $[H^+] = [OH^-] = 10^{-7}$ mol/L.

2) *acidic medium*

if acid is added to pure water, then $[H^+] > [OH^-]$ and $[H^+] > 10^{-7}$ mol/L.

3) *alkaline medium*

if alkali is added to pure water, then $[H^+] < [OH^-]$ and $[H^+] < 10^{-7}$ mol/L.

To avoid the inconvenience associated with the use of numbers with negative exponents, the concentration of hydrogen ions is usually expressed in terms of the hydrogen index and denoted by the pH symbol.

pH is the decimal logarithm of the concentration of hydrogen ions, taken with the opposite sign:

$$pH = -\lg[H^+] \quad \text{или} \quad [H^+] = 10^{-pH},$$

where $[H^+]$ – hydrogen ion concentration, mol/L.

The concept of "hydrogen indicator" was introduced by the Danish chemist Zørensen in 1920: the letter "p" is the initial letter of the Danish word potenz is a mathematical degree, the letter H is the symbol of hydrogen.

Using pH, the reaction of solutions is characterized as follows:

neutral pH = 7,

acidic pH <7,

alkaline pH> 7.

Qualitatively, the nature of the medium is determined using indicators - weak organic acids and bases, which change their color depending on the medium of the solution, i.e. pH of the solution. For example, colour of litmus in an acidic medium - red, in an alkaline - blue, it is not used to determine neutral; phenolphthalein: in an acidic medium is colorless, in an alkaline - raspberry.

In addition, the hydrogen indicator can be simply and conveniently determined using indicator paper - strips of special paper containing a number of indicator paints. If you wet a strip of such paper with the test solution, then it acquires a characteristic color, which is compared with pH color standards (scale).

The true pH value is determined using pH meter instruments using by the potentiometric method.

BIOLOGICAL ROLE OF pH

The pH value is of great importance in chemical and biological processes, because depending on the nature of the medium, these processes can proceed at different speeds and in different directions.

Therefore, the determination of the pH of solutions is very important in medicine, science, technology, agriculture.

All body fluids in a living organism have constant pH values. Changing the pH of blood or gastric juice is a diagnostic test in medicine. Deviation of pH from normal values even by 0.01 units indicates pathological processes in the body.

For example, some pH values:

Gastric juice	1,0 — 2,0
Coca-Cola	2,1 — 2,4

Lemon juice	2,5±0,5
Vinegar	2,9
Apple juice	3,5±1,0
Coffee	5,0
Shampoo	5,5
Tea	5,5
Healthy skin	~ 6,5
Saliva	6,35 — 6,85
Milk	6,6 — 6,9
Blood	7,36 — 7,44
Sea water	8,0
Baking soda solution	8,5
Hand soap	9,0 — 10,0
Ammonia	11,5

BRØNSTED-LOWRY ACID BASE THEORY

Arrhenius theory is valid only for aqueous solutions.

Bronsted and Lowry in 1923 proposed the proton theory of acids and bases. According to this theory, acids are substances that can be proton donors, and bases are substances that can attach protons (proton acceptors):

$$ACID \leftrightarrow H^+ + BASE$$

Here are a few examples showing the Bronsted-Lowry definition:

ACID				**BASE**
HNO_3	→	H^+	+	NO_3^-
NH_4^+	→	H^+	+	NH_3
HSO_4^-	→	H^+	+	SO_4^{2-}

$$HCl \rightarrow H^+ + Cl^-$$

The same compound may exhibit acid or base properties, under conditions are changed. For example,

$$\mathbf{H_2O \rightarrow H^+ + OH^-}$$

acid

$$\mathbf{H_2O + H^+ \rightarrow H_3O^+}$$

base

In the total equation:

$$\mathbf{H_2O + H_2O \rightarrow OH^- + H_3O^+}$$

acid 1 base 2 base 1 acid 2

Because there are no free protons in solutions, then the interaction of acids with bases can be represented by the general scheme:

Acid 1 + Base 2 → Base 1 + Acid 2

Such pairs of acids and bases are called conjugated. So, in the equations below, pairs acid 1 and base 1, acid 2 and base 2 are conjugated.

Acid 1		**Base 2**		**Base 1**		**Acid 2**
H_2O	+	H_2O	→	OH^-	+	H_3O^+
H_2O	+	NH_3	→	OH^-	+	NH_4^+
HCl	+	NH_3	→	Cl^-	+	NH_4^+
H_3O^+	+	$[Co(NH_3)_5OH]^{2+}$	→	H_2O	+	$[Co(NH_3)_5H_2O]^{3+}$

Therefore, the acid and base can be any molecules or ions capable of cleaving or attaching a proton, and reactions of this type are called protolytic.

LEWIS ELECTRONIC THEORY

However, there are substances that have strongly pronounced acidic and basic

properties, but they cannot be attributed to Bronsted acids and bases due to the absence of a proton. A more general idea of acids and bases was given by D. Lewis (1923).

An acid is a particle capable of attaching an electron pair (electron acceptor); A base is a particle capable of donating an electron pair (electron donor). According to Lewis, the acid and base interact with each other with the formation of a donor-acceptor bond.

$$Ag^+ + 2NH_3 \rightarrow [Ag(NH_3)_2]^+$$

The reaction between neutral molecules:

$$(CH_3)_3N : + BF_3 \rightarrow (CH_3)_3N:BF_3$$

The neutralization reaction in the Lewis theory is considered as the addition of an electron pair of a hydroxide ion to a hydrogen ion, which provides a free orbital for placing this pair:

$$H[]^{1+} + :OH^{1-} = H:OH$$

Lewis bases include halide ions, ammonia, amines, oxygen-containing organic compounds. Lewis acids include halides of boron, aluminum, silicon, and tin.

BUFFER SYSTEMS

Buffer systems are a combination of several substances in a solution, giving it buffering properties, i.e. ability to withstand changes in the active reaction of the medium (pH) upon dilution, concentration of the solution or when small amounts of strong acid or alkali are added to it.

Buffer systems are widespread in nature: they are found in the waters of the oceans, soil waters, and especially in living organisms, where they act as regulators that support the active reaction of the environment under certain conditions necessary for the normal course of life processes. Buffer systems provide the state of acid-base equilibrium corresponding to the norm - protolytic homeostasis. The shift of protolytic equilibrium to the acidic region causes acidosis, to alkaline - alkalosis. The constancy of the pH of biological fluids, tissues and organs is due to the presence of several buffer

systems that make up these bioobjects. Buffer systems exhibit their buffer properties in a certain range of pH values (≈2 units) - called the buffer action zone.

Buffer solutions are solutions that maintain a constant pH when diluted with water or when acids and alkalis are added to them.

Typically, buffer solutions are solutions containing:

1) a weak acid and its salt formed by a strong base;

2) a weak base and its salt formed by a strong acid.

We consider the mechanism of the buffer action using the acetate buffer solution $CH_3COOH + CH_3COONa$ as an example.

The following processes take place in this solution and equilibrium is established:

$$CH_3COOH \Leftrightarrow CH_3COO^- + H^+$$

$$CH_3COONa \Leftrightarrow CH_3COO^- + Na^+$$

a) When a strong acid (for example, HCl) is added, the CH_3COONa salt will counteract the change in acidity.

An exchange reaction occurs, as a result, strong acid (HCl) is replaced by weak acid (CH_3COOH) and the pH remains almost unchanged:

$$CH_3COONa + HCl \rightarrow NaCl + CH_3COOH$$

b) When a small amount of alkali (NaOH) is added, the pH also does not change significantly, because alkali reacts with acetic acid (neutralization reaction), as a result of which OH^- - ions combine with H^+ ions to form an H_2O molecule:

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

These processes lead to a shift in the dissociation equilibrium towards the formation of new ions and thereby restore the pH value.

Each of the buffer mixtures is characterized by a certain concentration of hydrogen ions, which the buffer system seeks to preserve when acid or alkali is added to it.

Let us consider how the pH of buffer systems is determined by the example of acetate buffer. It consists of acetic acid (weak electrolyte) and its salt - sodium acetate (strong electrolyte). The acid dissociates partially, and the salt completely.

$$CH_3COOH \leftrightarrow CH_3COO^- + H^+ \qquad (1)$$

$CH_3COONa \leftrightarrow CH_3COO^- + Na^+$ (2)

In such a system, the pH is determined by acid dissociation. We apply the law of acting masses to equation (1) and write the expression for the dissociation constant:

$K_d = [CH_3COO^-][H^+] / [CH_3COOH]$ (3)

Where

$[H^+] = K_d \cdot [CH_3COOH] / [CH_3COO^-]$ (4)

That is, the concentration of H^+ ions depends on the dissociation constant of a weak acid and the ratio of the concentrations of acid molecules and its anions.

However, in the buffer solution, the concentration of anions is determined mainly by the concentration of the salt, which completely dissociates. In this case, a salt with the ion of the same name completely suppresses acid dissociation. Therefore, we can assume that the concentration of anions is equal to the concentration of salt, and the concentration of acetic acid molecules is equal to the initial acid concentration.

$[CH_3COO^-] = [Na^+] = [salt]$ (5)

$[CH_3COOH] = [acid]$ (6)

Substituting (5) and (6) into (4), we can write

$$[H^+] = K_d \frac{[acid]}{[salt]}$$

Or in logarithmic form

$$-\lg[H^+] = -\lg K_d - \lg \frac{[acid]}{[salt]}$$

By using the notation, we obtain

$$pH = pK_A - \lg \frac{[acid]}{[salt]} \quad (7)$$

or $$pH = pK_A + \lg \frac{[salt]}{[acid]} \quad (8)$$

Equations (7) and (8) are called **the Henderson-Hasselbach equations**.

According to the Bronsted theory, the anion of an acid is its conjugate base, therefore, in general terms, the Henderson-Hasselbach equation takes the form:

$$pH = pK_A + \lg \frac{[conjugated\ base]}{[acid]} \quad (9)$$

It follows from (7) and (8) that the pH of the buffer solution is determined by the ratio of the concentrations of the components and the dissociation constant of the weak acid that is part of this buffer.

Consider the mechanism of action of the main buffer on the example of ammonia buffer solution.

The following processes take place in this solution and equilibrium is established:

$$NH_4OH \Leftrightarrow NH_4^+ + OH^-$$

$$NH_4Cl \Leftrightarrow NH_4^+ + Cl^-$$

a) When a strong acid is added (e.g. HCl):

$$NH_4OH + HCl \rightarrow NH_4Cl + H_2O$$

The neutralization reaction takes place and the pH practically does not change.

b) When a small amount of alkali (NaOH) is added, the pH also does not change significantly:

$$NH_4Cl + NaOH \rightarrow NH_4OH + NaCl$$

Buffer capacity (*B*) is the amount of equivalent substance (N) of a strong acid or strong base that needs to be added to 1 liter of buffer solution so that its pH changes by one:

$$B = \frac{N}{pH_2 - pH_1},$$

where N is the amount of an equivalent substance of a strong acid (or strong base);

pH_1 is pH before adding a strong acid or base;

pH_2 is pH after adding strong acid or alkali.

The buffer capacity is determined by two factors:

1. The concentration of the acid-base pair - the higher the concentration of the acid-base pair, the higher the buffer capacity.

2. The ratio of the concentrations of the components.

The buffer capacity is higher, the higher the concentration of the components (acid and its salt or alkali and its salt). The solution with the same concentration of components has the highest buffer capacity.

BLOOD BUFFER SYSTEMS

BLOOD PLASMA

The normal blood pH is 7.40 ± 0.05, i.e. $[H^+] \approx 3.7 \cdot 10^{-8} – 4 \cdot 10^{-8}$ mol/L. The constancy of these values is ensured by the simultaneous action of hydrocarbonate ($H_2CO_3/NaHCO_3$), phosphate (NaH_2PO_4/Na_2HPO_4), protein (PrCOOH/PrCOONa) and amino acid buffer systems.

1. Hydrocarbonate.

The peculiarity of this system is that one of the components of the system – H_2CO_3 is formed during the interaction of CO_2 with H_2O.

$$CO_{2(ð-ð)} + H_2O \rightleftharpoons H_2CO_3$$

In turn, the concentration of CO_2 is determined by the equilibrium

$$CO_{2(ãàç)} \rightleftharpoons CO_{2(ð-ð)},$$

which is described by Henry's law

$$CO_{2(ð-ð)} = \mathbf{s} \cdot \mathbf{P}(CO_2)$$

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equilibrium is established in the blood:

$$CO_{2(ð-ð)} + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

In accordance with equation 1, the pH of the hydrocarbonate buffer is ultimately determined by the concentration of HCO_3^- and the partial pressure of CO_2:

$$pH = p\mathbf{K_{a1}} + \lg\frac{\mathbf{C}(HCO_3^-)}{\mathbf{s}\cdot\mathbf{P}(CO_2)}$$

$$p\mathbf{K_{a1}} = 6.1 \Longrightarrow \frac{\mathbf{C}(HCO_3^-)}{\mathbf{C}(H_2CO_3)} = 10^{1.3} = 20$$

Between CO_2 in the alveoli and bicarbonate buffer in blood plasma, equilibrium is established:

$$\text{Àòì î ñôåðà} \rightleftharpoons CO_{2(\text{ãàç})} \overset{1}{\rightleftharpoons} CO_{2(\text{ð-ð})} \underset{-\,H_2O}{\overset{2}{\rightleftharpoons}} H_2CO_3 \overset{3}{\rightleftharpoons} H^+ + HCO_3^-$$

When proton donors enter the bloodstream, equilibrium 3 shifts toward H_2CO_3. At the same time, the concentration of H_2CO_3 increases, and the concentration of HCO_3^- decreases. This leads to a shift of equilibrium 2 to the left, as a result of which equilibrium 1 shifts towards the formation of gaseous CO_2, which leads to an increase in CO_2 pressure in the lungs and its removal due to increased pulmonary ventilation.

Upon receipt of proton acceptors, the equilibrium shifts in the opposite direction, which leads to the dissolution in the blood plasma of an additional amount of CO_2 contained in the lungs.

As a result of the described processes, the hydrocarbonate buffer system effectively ensures a constant pH of blood plasma. This system is also found in red blood cells and kidney tissue.

2. Phosphate buffer system

$$pH = p\mathbf{K_a}(H_2PO_4^-) + \lg\frac{\mathbf{C}(HPO_4^{2-})}{\mathbf{C}(H_2PO_4^-)}$$

$$\frac{\mathbf{C}(HPO_4^{2-})}{\mathbf{C}(H_2PO_4^-)} \approx 4:1$$

The phosphate buffer system is less powerful than bicarbonate, due to the low content of phosphates in the blood plasma.

The phosphate system is also found in tissues, kidneys, and red blood cells.

3. Protein buffer system.

It is a combination of albumin and globulin.

4. Aminoacid buffer systems.

Almost all amino acids have pH values significantly different from 7.4 and their power is small.

Thus, the power of the blood plasma buffer systems decreases in the series H_2CO_3/HCO_3^- >proteins> $H_2PO_4^-/HPO_4^{2-}$ > aminoacids.

RED BLOOD CELLS

Normal erythrocyte pH is 7.25 ± 0.05. There are hydrocarbonate and phosphate buffer systems. Their power is small compared with the power in blood plasma. The hemoglobin - oxyhemoglobin system plays an important role, which accounts for about 80% of the whole buffer capacity of whole blood. Hemoglobin is a weak acid (pK_a = 8.2), dissociates according to the scheme:

$$HHb \rightleftharpoons H^+ + Hb^-$$

The undissociated part is bigger, i.e. $\frac{C(Hb^-)}{C(HHb)} \approx \frac{1}{9}$.

In the lungs HHb reacts with O_2,

$$HHb + O_2 \rightarrow HHbO_2$$

forming oxyhemoglobin, which is carried by the blood to the capillary vessels, from where O_2 enters the tissue. $HHbO_2$ is a weak acid –pKa ($HHbO_2$) = 6.95. Therefore, under the action of proton donors, they will be neutralized first of all by the Hb^- anion

$$H^+ + Hb^- \rightarrow HHb,$$

because has a greater affinity to H^+.

But under the action of bases - proton acceptors - oxyhemoglobin will primarily react:

$$HHbO_2 + OH^- \rightarrow HbO_2^- + H_2O$$

The $HHbO_2$ / HbO_2^-system also protonates the HCO_3^- ions, followed by the release of CO_2 through the lungs:

$$HCO_3^- + HHbO_2 \rightleftarrows HbO_2^- + CO_2 + H_2O$$

It should also be noted the participation of phosphoric acid esters in maintaining a constant pH. Phospholipids are weak acids. pK_a dissociations of polar phosphate groups are in the range of 6.8–7.2. Therefore, at a physiological value of pH = 7.25, the phospholipids of the erythrocyte membranes are in both ionized and non-ionized forms. The ratio of ionized to non-ionized forms is approximately 3:1.

Conclusion - the erythrocyte membrane itself has a buffering effect, maintaining a constant pH of the internal environment of red blood cells.

Summary - the combined effect of several buffer systems provides acid-base homeostasis in the body.

General material and educational and methodological support of the lecture:

- Working program of the discipline
- Silabus
- Methodical recommendations for independent work of higher education applicants
- Multimedia presentations
- Situational tasks

Recommended literature

Basic literature:

1. Medical Chemistry: textbook / V.Y. Tsuber, A.A. Kotvytska, K.V. Tykhonovych et al. - – Kyiv, AUS Medicine Publishing, 2022. – 392 p.

2. Medical chemistry: a textbook for universities / V. O. Kalibabchuk, I. S. Chekman, V. I. Galynska and others; for ed. Prof. V. O. Kalibabchuk – 4th ed. – K. VSV "Medicine", 2019 – 336 p.

3. Medical chemistry / V.O. Kalibabchuk, V.I. Halynska, L.I. Hryshchenko et al.

– Kyiv, AUS Medicine Publishing, 2020. – 224 p.

4. General and Inorganic Chemistry: textbook / V.O. Kalibabchuk, V.V. Ohurtsov, V.I. Halynska et al. – Kyiv, AUS Medicine Publishing, 2019. – 456 p.

Additional literature:

7. Medical chemistry: a textbook / V. P. Muzychenko, D. D. Lutsevich, L. P. Yavorska; for order. B. S. Zimenkovsky. – 3rd ed., Ed. – K.: BCB «Medicine», 2018. – 496 p.

8. Mironovich L. M. Medical Chemistry: A Textbook. – Kyiv: Karavella, 2008. – 159 p.

9. Moroz A. S. Medical chemistry: a textbook / D. D. Lutsevich, L. P. Yavorska. – Vinnytsia: New book, 2006. – 776 p.

10. Gotsulyak L. O., Mardashko O. O., Yerigova S. G., Kuzmenko G. I., Kuzmina A. V., Zhilinskaya K. I. Bioinorganic, physicoloid and bioorganic chemistry. Teaching. manual. Odessa. Odessa State Medical University 1999. – 248 p.

11. Textbook of Medicinal Chemistry / V. Alagarsamy // CBS Publishers & Distributors Pvt Ltd, India; 3rd edition, 2018 – 584 p.

12. Richard Post. Chemistry: Concepts and Problems / Richard Post, Chad Snyder, Clifford C. Houk // A Self-Teaching Guide, Jossey-Bass, 2020. – 432 p.

Lecture № 6

Topic: **«Physico-chemistry of surface phenomena. Basics of adsorption therapy. Chromatography.»**

Actuality of theme: Surface phenomena are processes that occur at the boundary of two phases and depend on the features and structure of their surface. Biological objects are heterogeneous systems that consist of several phases and are separated from each other by interfaces. Any living organism contains a huge number of heterogeneous systems, on the distribution surface of which the most important biochemical processes take place. All surface phenomena are characterized by a small activation energy. That is why biochemical reactions take place on the surface of the distribution at a high speed according to the ambient temperature.

Aims: To form systematic knowledge about sorption processes. Find examples of practical application of sorption processes in professional activities and in life. To evaluate the surface properties of substances based on the structure of their molecules, to be able to explain the behavior of biologically active substances from the point of view of surface activity, to interpret the use of adsorbents for analytical and medical purposes.

Basic concepts: **s**urface phenomena**, s**urface energy**, b**iological role of adsorption**,** adsorption of electrolytes, chromatography.

Plan and organizational structure of the lecture:

1. Surface phenomena. Surface energy.
2. Surface tension of liquids. Surface activity.
3. Adsorption at the L-G and L-L boundaries.
4. Langmuir adsorption isotherm equation. "Langmuir Circle". Structure of biological membranes. Polymolecular adsorption.
5. Biological role of adsorption in medical practice.
6. Adsorption of electrolytes.
7. Chromatography.

Content of lecture material (lecture text)

Surface effects include those effects and behavior of substances that are observed on the interface. The cause of surface phenomena is the special state of molecules in the layers of liquids and solids directly adjacent to the interface. These layers sharply differ in many physicochemical characteristics (specific energy, density, viscosity, etc.) from the properties of phases in the depth of the volume. The differences are associated with a certain orientation of the molecules in the surface layers and their different energy state in comparison with the molecules in the bulk.

The importance of surface phenomena for medicine is determined by the fact that most dosage forms are dispersed systems with a large specific surface: powders, ointments, suspensions, emulsions, etc.

Sorption processes are those that occur on PRF in heterogeneous systems.

The absorption of substances by solids or liquids is called sorption.

There are such sorption processes:

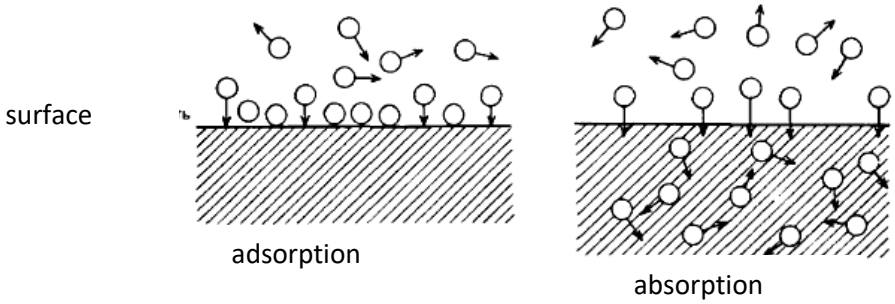
- absorption;

- adsorption;

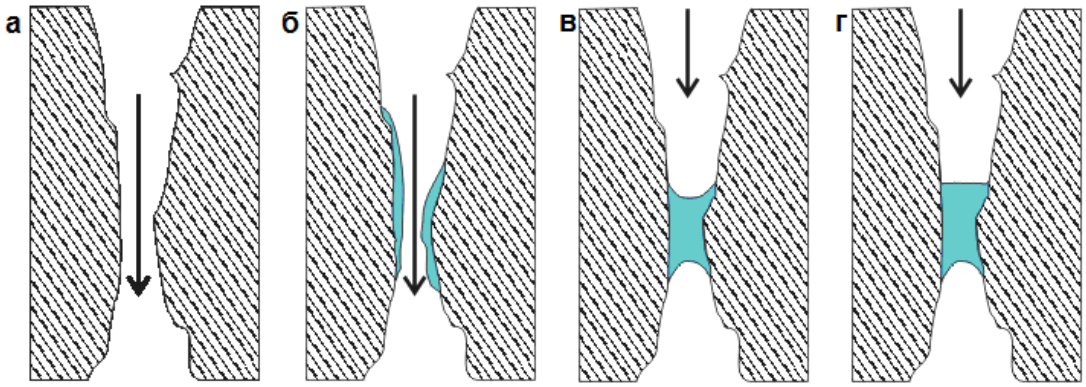
- capillary condensation.

Absorption is the absorption of gas by the entire volume of a solid or liquid. During absorption, the distribution of gas molecules in the solid or liquid phase occurs mainly as a result of diffusion. For example, the absorption of hydrogen by palladium, carbon dioxide and ammonia by water.

Adsorption – spontaneous concentration of a substance on a solid or liquid PRF. The liquid or solid phase, which serves as an absorber, is called an adsorbent. An adsorbed substance (gas, liquid, dissolved substance) is called an adsorbent, and an already adsorbed substance is called an adsorbate.



Capillary condensation is the condensation of gaseous substances in the pores of solids (for example, in the pores of silica gel, alumina gel) under the action of sorption forces. The cause of capillary condensation is a reduced vapor pressure above the liquid located in the pores of solids.



Depending on the type of interaction between the adsorbent and the adsorbate, physical and chemical adsorption are distinguished.

SORPTION

Physical adsorption	**Chemical adsorption(chemosorption)**
-Molecules retain their individuality; -reversible; -decreases with temperature; -quantity of heat 8 – 25 kJ/mole	-Molecules lose their identity; -nonreversible; -increases with temperature; -quantity of heat more than 80 kJ/mole

Adsorption forces

Physical (orientational, induction) PHYSICAL ADSORPTION	**Chemical** (ionic, covalent, coordination) CHEMOSORPTION
1) reversible; 2) non-specific; 3) low heat of adsorption.	1) nonreversible; 2) specific; 3) heat of adsorption are comparable in magnitude with the heats of chemical reaction.

Physical or van der Waals adsorption is the result of cohesive and adhesive forces. During physical adsorption, there is no chemical interaction between the adsorbent and the adsorbate; therefore, the adsorbate molecules do not lose their individuality. The equilibrium during physical adsorption is established quickly, and it is always reversible:

Adsorption ↔ desorption.

With increasing temperature, physical adsorption always decreases.

Chemical adsorption or chemisorption is due to the action of valence (chemical) forces, and is always accompanied by the formation of surface chemical compounds, but without the formation of a new bulk phase. Chemisorption in some cases proceeds rather slowly; it is usually irreversible. With increasing temperature, chemisorption tends to increase.

The adsorption value is measured by the number of moles of adsorbate, which per unit surface or per unit mass of adsorbent. The units of adsorption are mol/m^2 or mol/g.

THEORY OF MONOMOLECULAR ADSORPTION OF LANGMUIR

The first theoretical equation for the adsorption isotherm was obtained by the American scientist Langmuir in 1915.

The main points of the theory are as follows:

1. Adsorption is localized and is caused by forces close in nature to chemical forces. These forces act at short distances.

2. Adsorption occurs on the active centers of a solid surface, where there are particles with uncompensated intermolecular forces. Active centers are located mainly on convex surface areas: protrusions, ribs, corners.

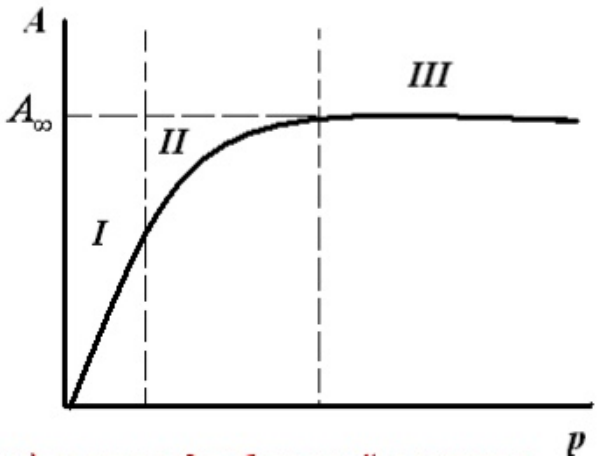
3. Only a monomolecular adsorbate layer can form on the surface of the adsorbent.

4. The adsorption process is in dynamic equilibrium with the desorption process.

5. The forces of interaction between the adsorbed molecules are neglected.

Langmuir isotherm equation

Based on the foregoing, Langmuir derived the equation of the adsorption isotherm for the gas – solid interface



I – at a low pressures ($p \rightarrow 0$, $K_{eq} << 1$) the adsorption increases linearly with increasing concentration.

$$\mathbf{A = A_\infty * K_{eq}}$$ – Henry`s equation

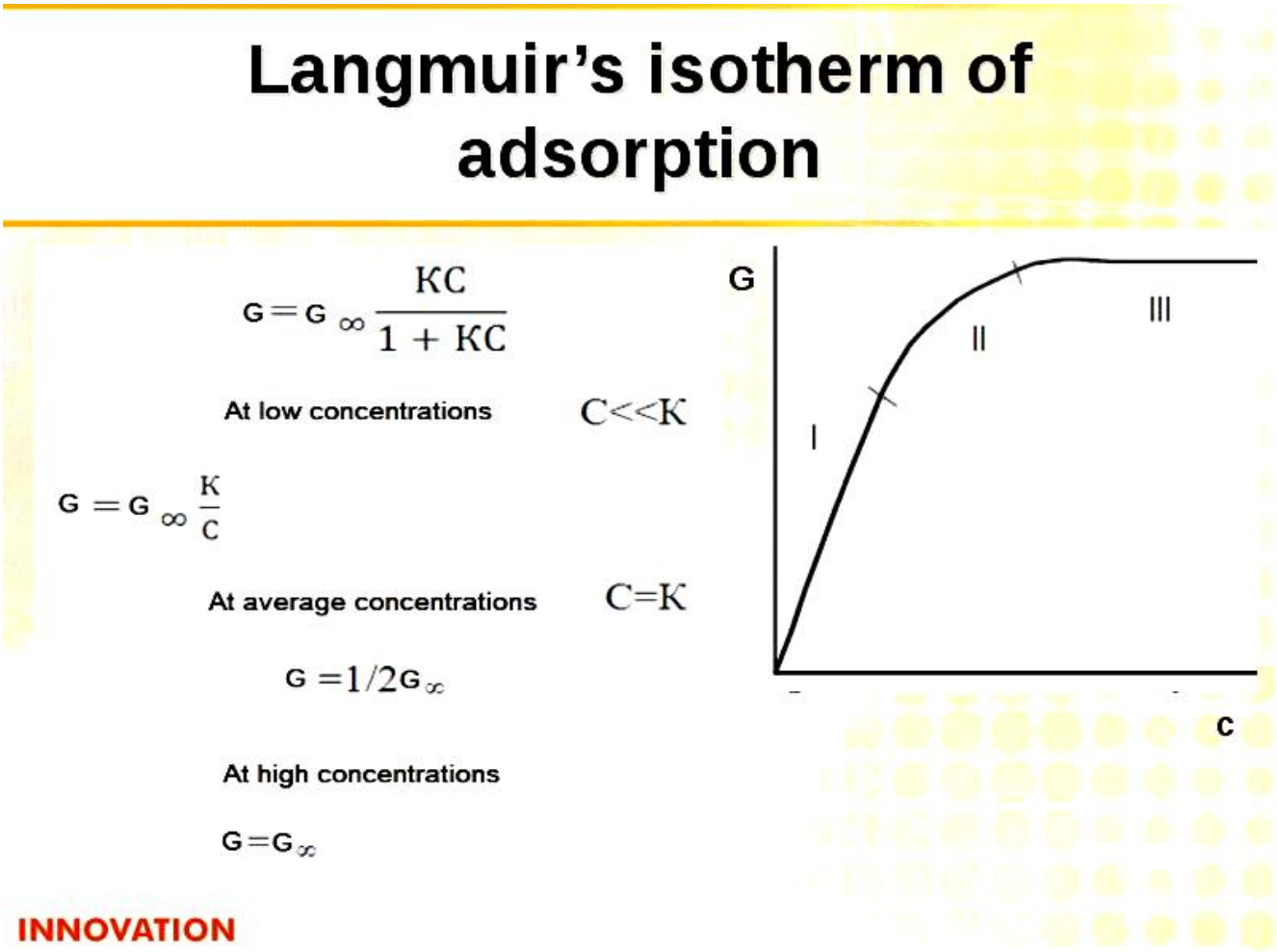
II – at a middle pressures:

$$\mathbf{A = A_\infty \frac{kP}{1+kP}}$$

III – at high pressures ($K_{eq} >> 1$) the entire surface is occupied by adsorbate molecules:

$$\mathbf{A = A_\infty}$$

The Langmuir adsorption isotherm equation can also be used to describe adsorption for the solution – solid interface:



$$A = A_\infty \frac{kC}{1+kC}$$

Where C is the equilibrium concentration of the adsorbent.

FREINDLICH ISOTHERM ADSORPTION EQUATION

This empirical equation is used more often than other isotherms, because was derived based on experimental data.

$$A = \Gamma = \frac{x}{m} = k \cdot p^{1/n}$$

Where x is the amount of adsorbed substance;

m is the mass of the adsorbent;

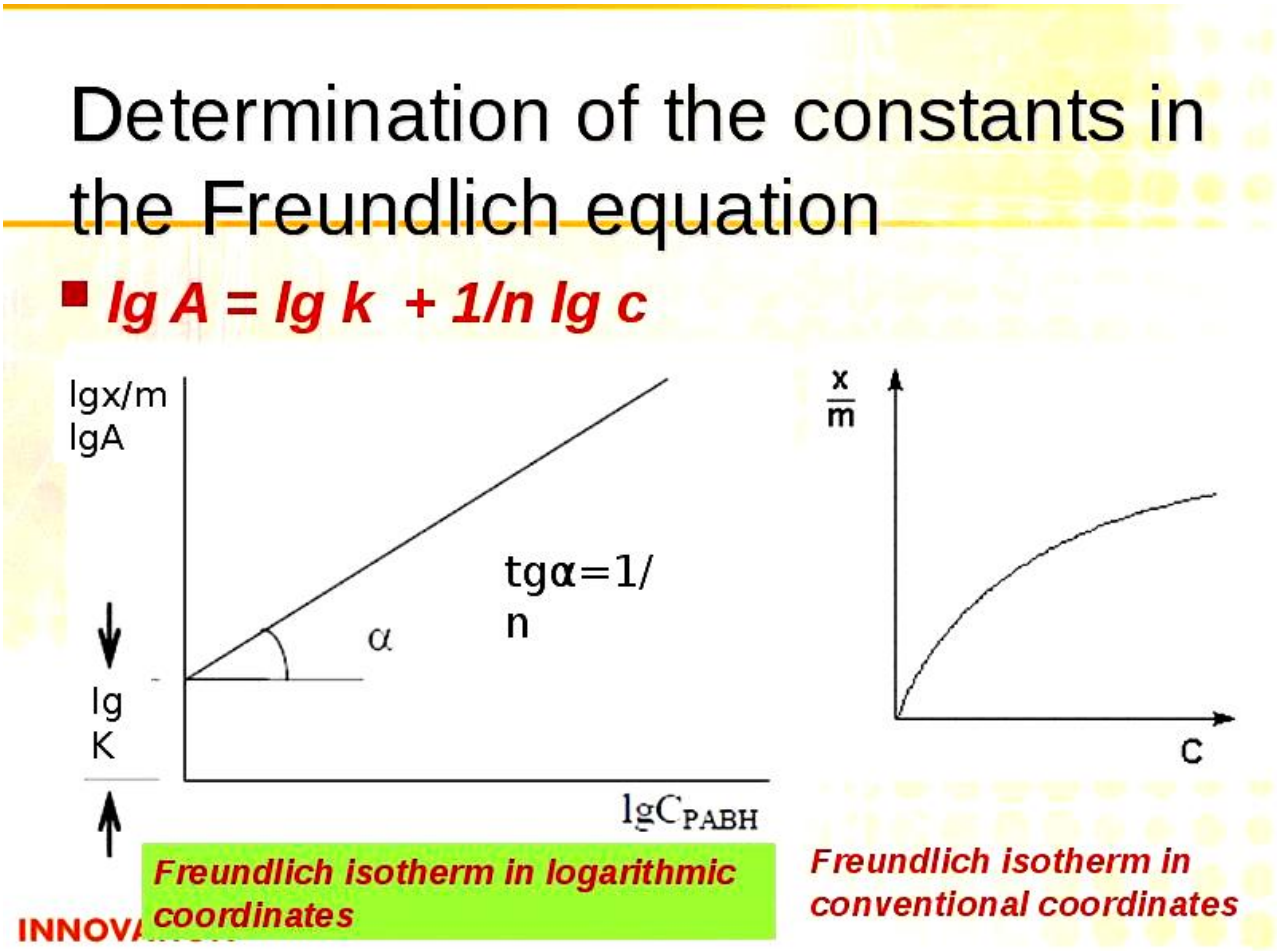
p is the equilibrium gas pressure in the system;

k and 1/n are constants.

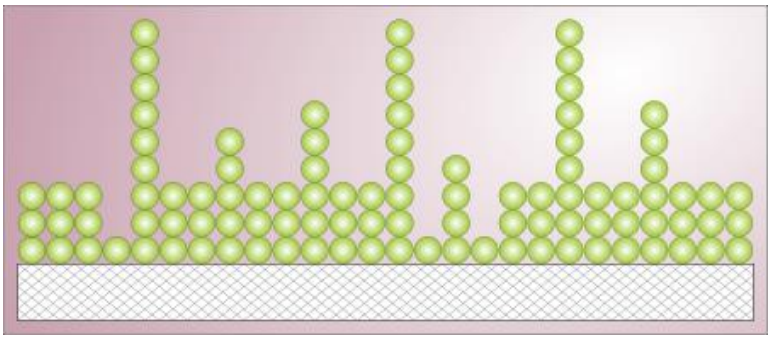
For adsorption from a solution on a solid adsorbent, the Freindlich equation has the form:

$$A = \Gamma = \frac{x}{m} = k \cdot c^{1/n}$$

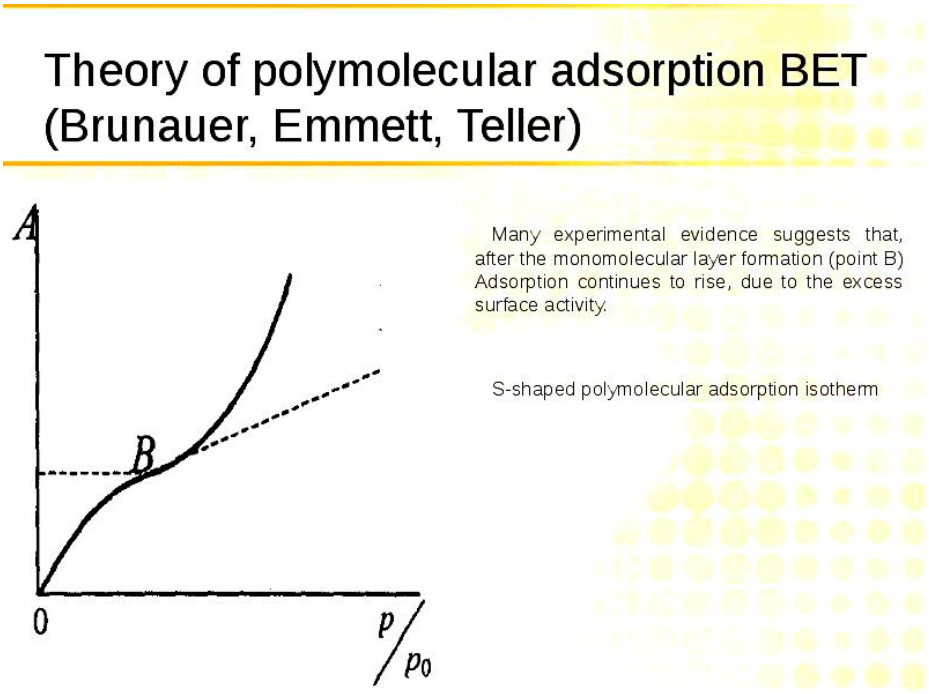
Where c is the equilibrium concentration of the solution.



BET POLYMOLECULAR ADSORPTION THEORY

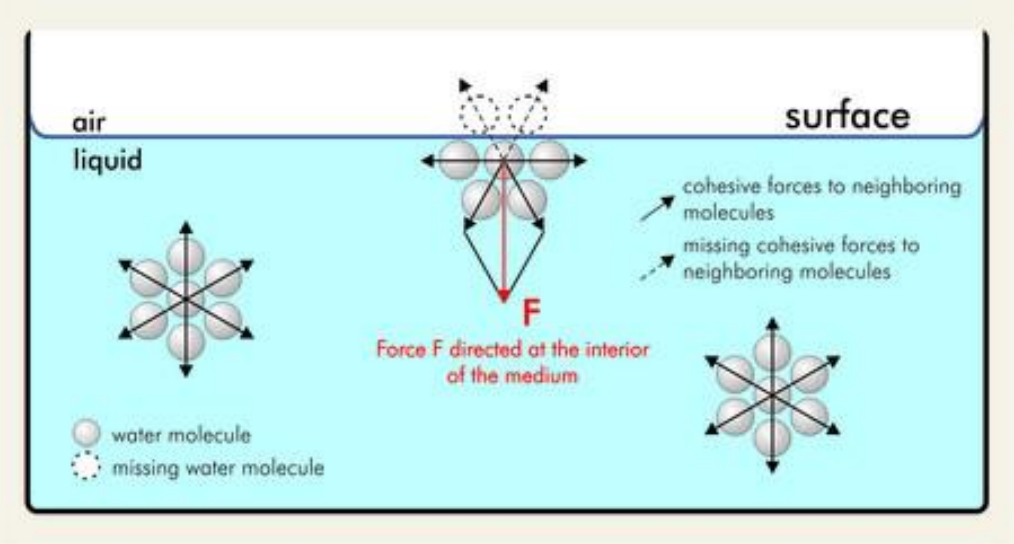


In most cases, the monomolecular adsorption layer does not compensate for the completely excess surface energy and therefore there remains the possibility of the influence of surface forces on the second, third and subsequent adsorption layers. This possibility is realized when gases and vapors are adsorbed at temperatures below the critical temperature, i.e., polymolecular layers of matter are formed on the surface of the adsorbent, which can be represented as forced condensation of vapor under the influence of surface forces. As a result, if in the region of the formation of the monomolecular layer the adsorption substantially slows down its growth with increasing vapor pressure, then in the region of pressures close to the saturated vapor pressure, it begins to increase sharply.



This isotherm is described by the theory of BET polymolecular adsorption, named after the initial letters of the names of its authors (Brunauer, Emmett, Teller).

SURFACE TENSION OF SOLUTIONS



The properties of molecules in the surface layer and in the volume of the system differ significantly from each other. The molecules inside the liquid experience the same effect from all sides, as a result of the attractive forces are compensated and their resultant is zero. Looking at the surface between the liquid and the air, it can be seen that the liquid molecules in the surface layer experience unequal attraction from the liquid and from the gaseous phases.

Since the density of the gas is less than the density of the liquid, the resultant of all attractive forces will be directed inside the liquid perpendicular to its surface. Thus, surface liquid molecules are always under the action of a force tending to draw them in, i.e. the surface of the liquid always tends to contract. This explains the spherical shape of the drop (the ball has a minimal surface).

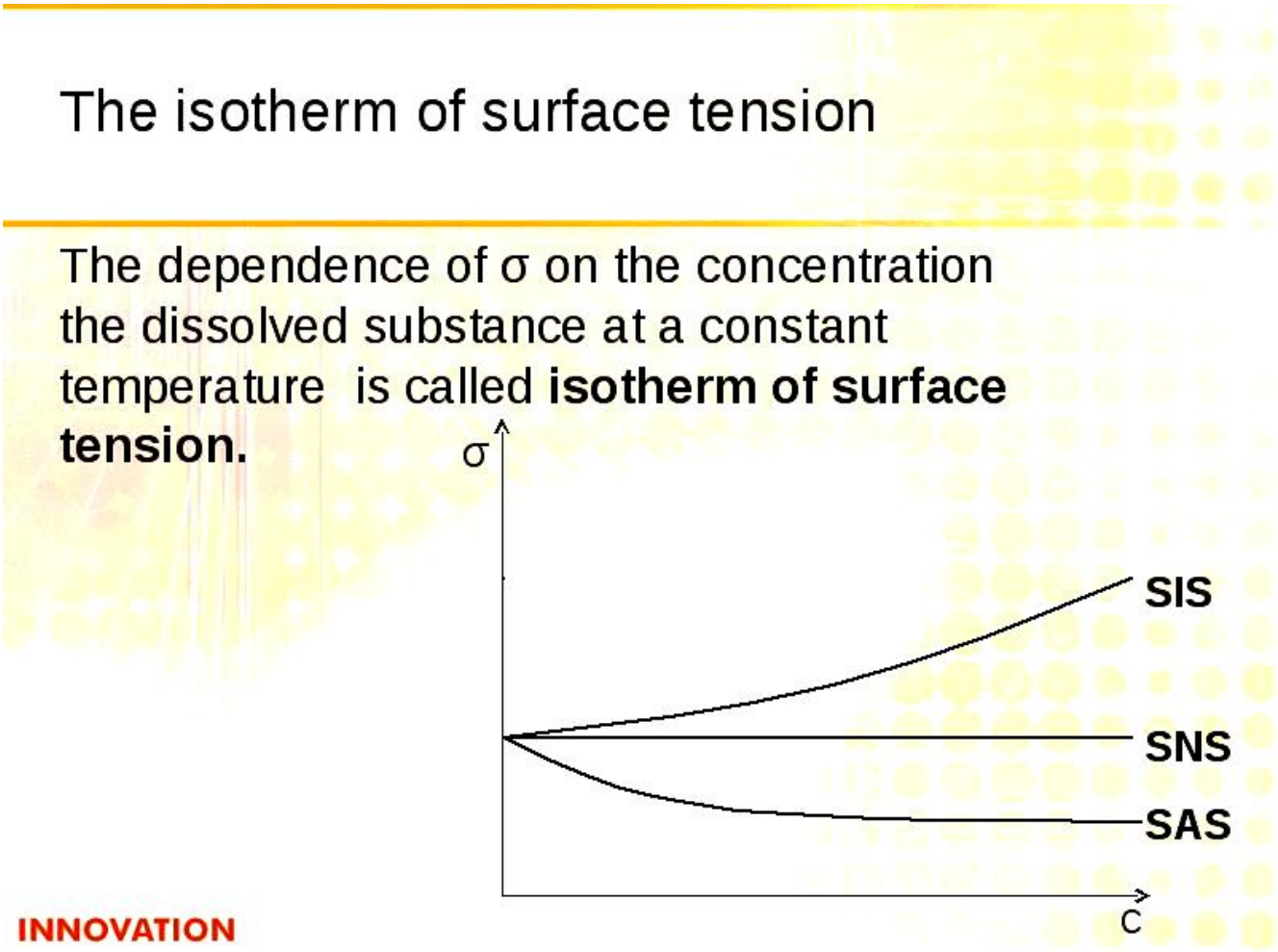
Every surface is characterized by a supply of energy called surface energy. It depends on the surface tension σ and the surface area A.

Surface tension is surface energy referred to a unit of surface: $\boldsymbol{\sigma = F/A}$

It is measured in N/m^2.

Adsorption of the solute at the gas-gas interface is associated with a change in the free surface or surface tension.

The dependence of surface tension on the concentration of the solute can be represented by the following curves:

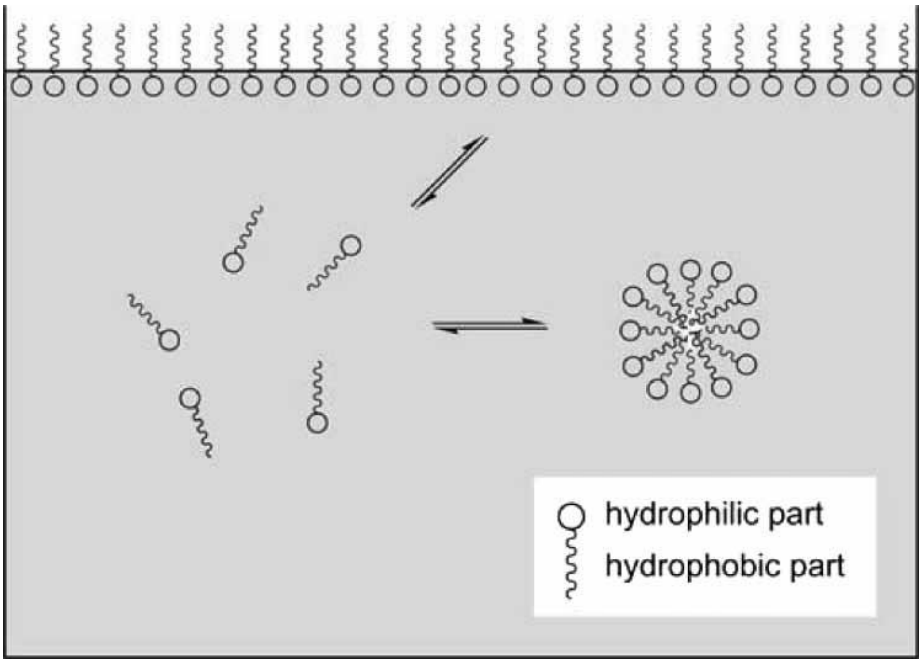


SAS are substances that lower the surface tension of a solvent when dissolved. If the force field of the molecules of the dissolved substance is weaker than the force field of the solvent, then the surface tension of the solution (σ) is less than the surface tension of the solvent. For example, soaps, alkyl sulfates, alkyl benzene sulfonates.

SIS - substances that increase the surface tension of a solvent upon dissolution. If the force field of the molecules of the dissolved substance is stronger than the force field of the solvent molecules. For example, inorganic acids, salts, bases.

SNS - substances that do not change the surface tension of the solvent upon dissolution. For example, glucose, sucrose, etc.

A characteristic feature of the structure of surfactant molecules is their diphilic structure, which manifests itself in the presence of hydrophilic and hydrophobic parts of the molecule, i.e. polar group and non-polar hydrocarbon radical.



The polar groups include –OH, –COOH, $–NH_2$. A hydrocarbon radical is a non-polar tail.

The diphilic nature of the surfactant nature promotes their spontaneous concentration at the phase boundary, where each part of the molecule can interact with the phase to which it has the highest affinity.

Surfactants are classified according to various criteria. So, in terms of their ability to dissolve in water, surfactants are water-soluble and fat-soluble.

The ability of water-soluble surfactants to dissociate into ions distinguishes ionic (non-dissociating to ions) and non-ionic (non-dissociating to ions) surfactants.

Ionogenic can be:

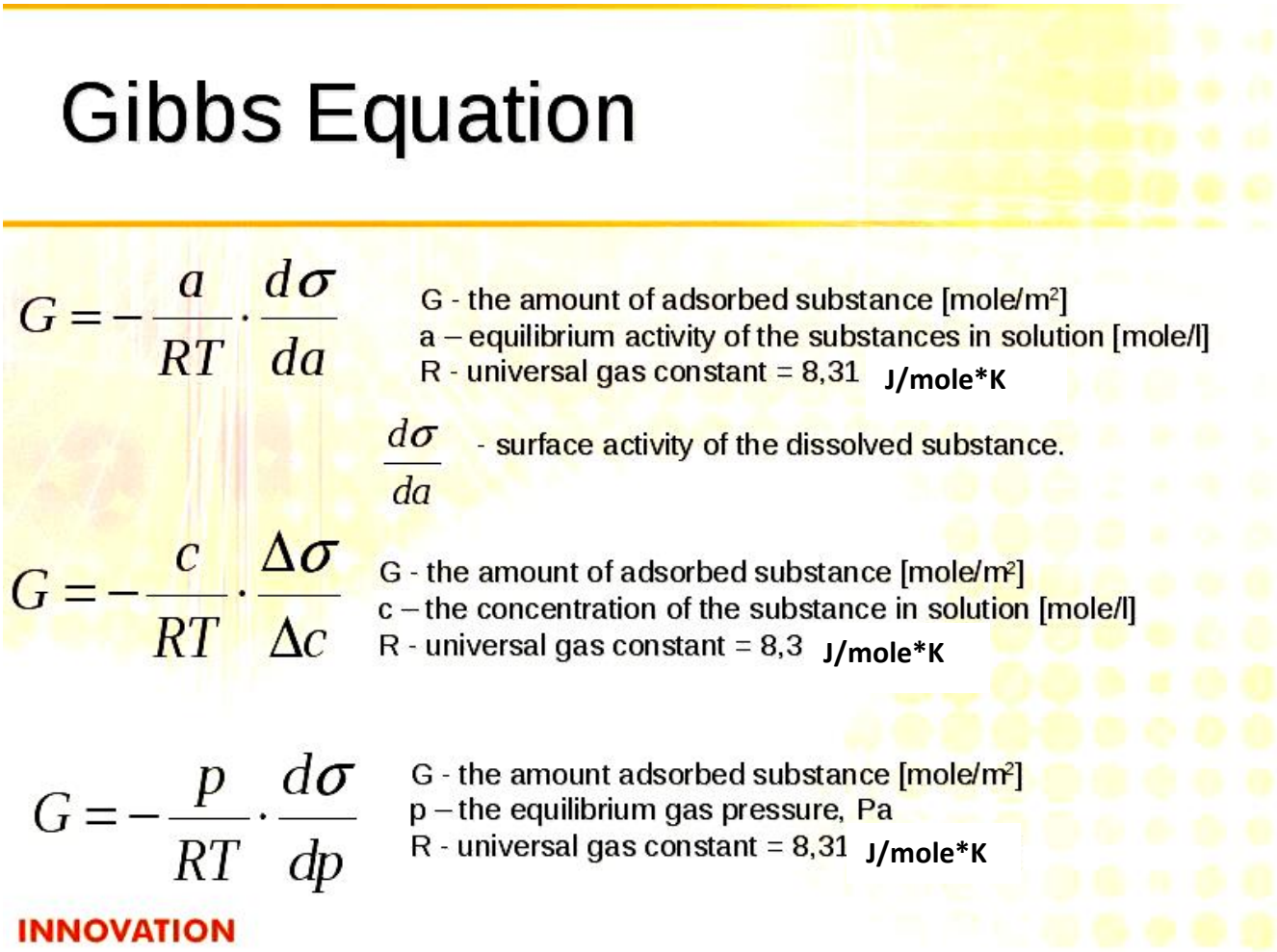
1) Anionic (surface-active ions are negatively charged). For example, soaps are alkaline salts of fatty acids of the RCOOMe type, alkyl sulphates are alkaline salts of sulfoesters of higher alcohols of the $ROSO_3Me$ type;

2) Cationic (surfactant ions are positively charged), for example, salts of amines of the type $[RNH_3]^+ Cl^-$, quaternary ammonium bases of the type $[R (CH_3) 3N]^+ Cl^-$;

3) Ampholytic (depending on the pH of the medium can be either anionic or cationic surfactants). For example, amino acids containing acidic (carboxylic) and basic (amine) groups.

GIBBS ADSORPTION ISOTHERM EQUATION

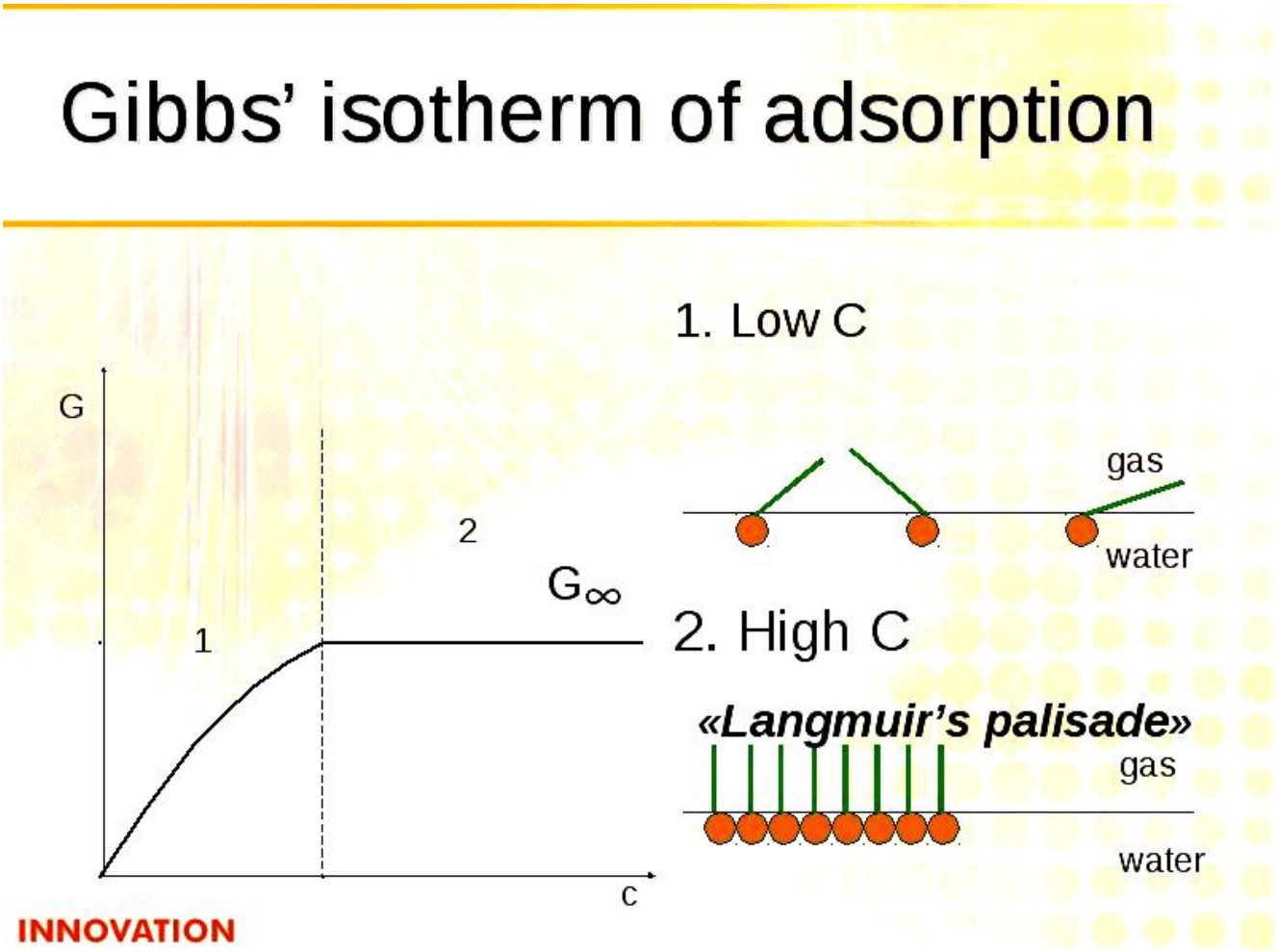
When dissolved in water, surfactants accumulate in the surface layer, and TIDs are concentrated in the volume of the solution. In 1878 american scientist Gibbs proposed an equation linking the adsorption value with the solution concentration and surface tension at the interface between the liquid and gas phases.



$$\Gamma = -\frac{C}{RT} \cdot \frac{d\sigma}{dC}$$

Where C is the concentration of the solution; σ is the surface tension of the solution, R is the universal gas constant; T is the temperature.

The equation is called the adsorption isotherm.

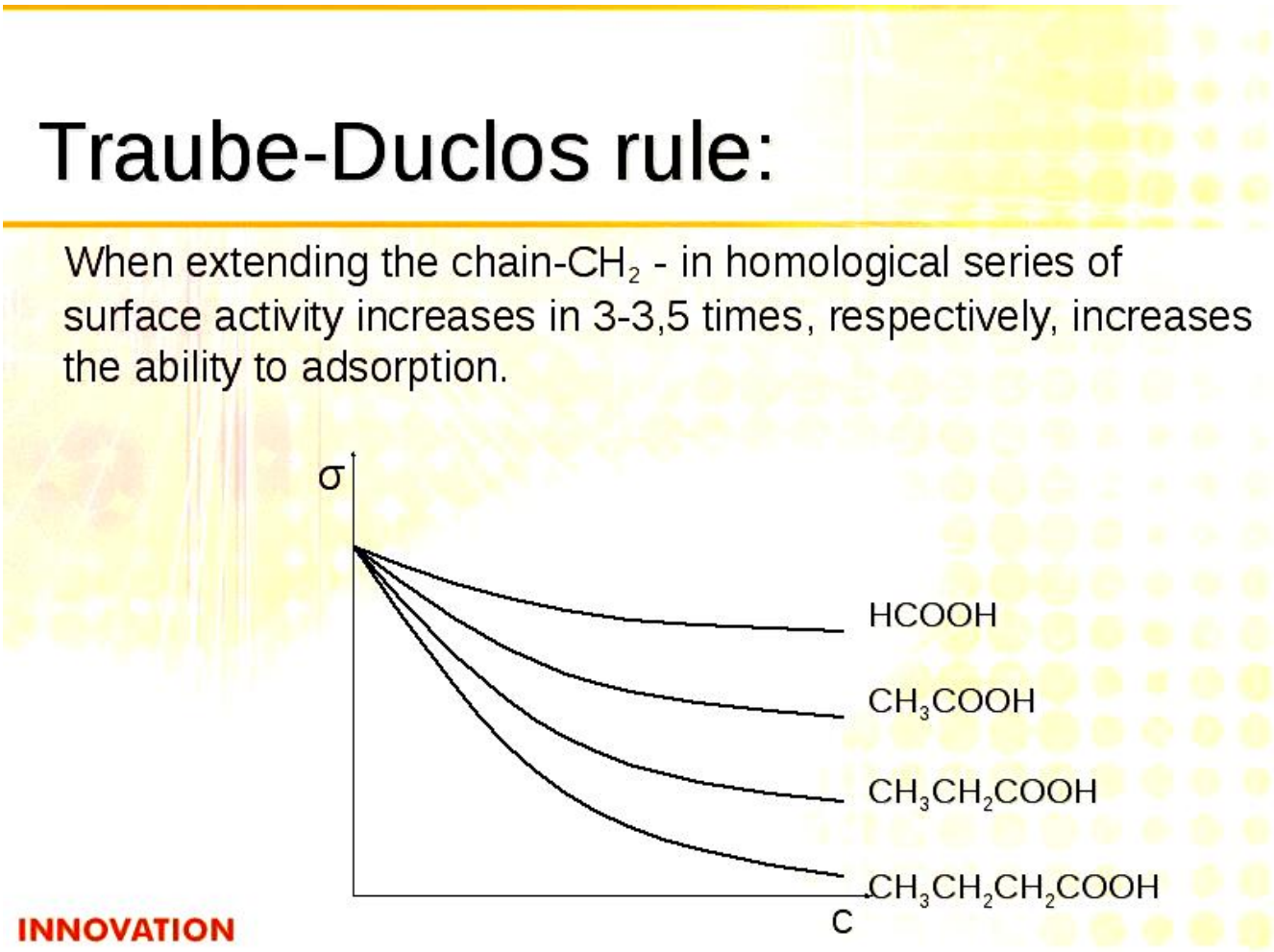


DUKLOS-TRAUBE RULE

It was experimentally established that the surface activity $(\frac{d\sigma}{dC})$ of water-soluble surfactants, as a rule, increases with decreasing polarity of the substance. For molecules with a large number of polar groups, surface activity is low.

Based on a large amount of experimental material, Duclos and Traube formulated the rule:

The surface activity in the series of homologs increases by 3–3.5 times with chain elongation by one CH_2- group (only at 200 ° C).



ADSORPTION OF STRONG ELECTROLYTES

As a result of the fact that strong electrolytes in solution are completely dissociated into charged particles, when considering the adsorption of electrolytes, it is necessary to take into account both specific adsorption and electrostatic forces.

ADSORPTION OF ELECTROLYTES

Adsorption from aqueous solution of electrolytes occurs so that mainly ions of the same type are adsorbed on a solid adsorbent. Predominant adsorption from a solution of either an anion or a cation is determined by the nature of the adsorbent and ions. The mechanism of adsorption of ions from electrolyte solution can be different: distinguish between exchange and selective adsorption of ions.

Ions, as a rule, are adsorbed on polar adsorbents. The adsorption of ions is characterized by high selectivity and is exchange in nature.

The selectivity, or specificity, of ion adsorption consists, first of all, in the accumulation on a solid adsorbent of predominantly either cations or anions.

Selective Adsorption Factors:

1) The nature of the adsorbent (sign of its charge);

2) The nature of adsorbed ions (their charge, radius, degree of hydration).

Since electrostatic forces play a leading role in ion adsorption processes, predominantly cations are adsorbed on negatively charged adsorbents, and anions on positively charged ones.

The rule of selective adsorption by Peskov-Fajans-Paneth

On a solid crystalline surface, ions are predominantly adsorbed, which are either part of the crystal lattice or isomorphic to it.

$$BaCl_2 + Na_2SO_4 \rightarrow BaSO_4\downarrow + 2NaCl$$

On the $BaSO_4$ precipitate, Ba^{2+} and SO_4^{2-} ions will be adsorbed, but not Na^+ or Cl^- ions.

The adsorption of ions depends on many factors:

1) The larger the charge of an ion, the greater its adsorption capacity

$$Pb^{4+} > Al^{3+} > Ca^{2+} > K^+$$

2) For ions having the same charge, the adsorption capacity depends on their radius and degree of hydration. The larger the radius and the lower the degree of

hydration, the better they are adsorbed on a solid surface. The hydration shell interferes with adsorption forces.

$$Cs^+ > Rb^+ > K^+ > Na^+ > Li^+$$

$$Ba^{2+} > Sr^{2+} > Ca^{2+} > Mg^{2+}$$

$$CNS^- > I^- > Br^- > Cl^-$$

Such series are called lyotropic or Hofmeister series.

BASES OF ADSORPTION THERAPY

The development of civilization, primarily the growth of industrial production, the chemicalization of agriculture and everyday life, the intensive use of fossil fuels, has led to the appearance in the environment of many toxic substances for human health. Tens of thousands of foreign compounds fall into the internal environment of the human body. That is why in recent decades a new direction has appeared in medicine, which is developing intensively - efferent medicine (from Latin. Efference - to derive). Unlike traditional methods of treatment based on the introduction of drugs into the body, efferent medicine allows you to remove harmful and toxic substances from it - to protect the internal environment of the body with sorbents. It should be noted that the methods of efferent medicine dates the ability to cleanse the body not only of toxic substances that enter from the external environment, i.e. toxins of exogenous origin, but also from toxins of endogenous origin (toxic substances that form and accumulate in the body, for example, during burns, radiation sickness, kidney and liver failure, etc.)

Hemosorption is a direct blood purification method in which blood is released from toxins by passing it through an adsorbent column connected to a blood circulation system.

Hemosorption is an effective treatment for seriously ill patients with endogenous and exogenous intoxications of various origins. Currently, it is successfully used in the treatment of patients with exogenous poisoning, liver and kidney failure, autoimmune and allergic diseases, surgical patients with severe endotoxemia, patients with toxic

forms of schizophrenia. According to clinicians, the use of hemosorption is most appropriate in the first stages of poisoning, when the maximum amount of poison circulates in the blood.

Plasma sorption is an effective method of detoxification of the body, the essence of which is the passage of plasma, previously separated from the formed elements of the blood, through a column with a sorbent, after which the purified plasma combines with the formed elements and returns to the vascular bed.

Plasma sorption is used in the treatment of patients with severe forms of poisoning with organophosphorus insecticides, barbiturates, antidepressants, chlorinated hydrocarbons, etc.

Lymphosorption is a type of sorption detoxification of the body, which consists in passing lymph removed from the body through the thoracic lymphatic flow on the neck, through a column with sorbent and then introducing lymph free of toxic substances into the vascular system of the patient.

Lymphosorption is the most effective way to detoxify the body when toxic substances of exogenous origin, such as pale toadstool alkaloids, carbon tetrachloride, etc. enter it. The advantages of the method include its relative non-injuries (absence of damage to blood cells, disturbances in the blood coagulation process, changes in the cardiovascular system). However, the widespread use of lymphosorption is limited by the insufficient rate of formation and outflow of lymph.

Liquorosorption is a type of detoxification of the body in which cerebrospinal fluid is passed through a layer of sorption material, and then returned to the cerebrospinal canal.

Application sorption is one of the types of sorption detoxification, which helps to heal infected wounds and burns, restore the integrity of the skin, as well as the mucous membranes by sorption absorption of toxins from the wound or burn zone.

The use of application therapy contributes to the intensification of tissue regeneration processes, since with the help of applications, the wound is more quickly

released from protein decomposition products. At the same time, the general intoxication of the body decreases.

The essence of application therapy consists in applying a gauze napkin with granular sorbent or dressings made of carbon fiber material to a wound or burn area. After application, the material is easily regenerated and therefore can be used repeatedly.

Enterosorption is a type of sorption detoxification of the body, in which the sorbent enters the oral cavity, after which, passing at different speeds through the digestive system, it adsorbs toxic substances and metabolic products.

The method is based on the idea that a decrease in the amount of toxic substances in one of the parts of the body (in this case, in the stomach and intestines) causes a decrease in their concentration throughout the body. Due to the absorption of toxins by sorbents in the intestine, their content in the blood decreases, the load on organs such as the liver, kidneys, etc. decreases.

Chromatography is a physicochemical method for analyzing and separating mixtures of substances based on their different distribution between two phases, one of which is stationary (solid or liquid), and the other mobile (gas or liquid), which is filtered through the stationary.

From the history of chromatography

Birthday of chromatography – 21.03.1903

The report of M.S. Tsvet "A new category of adsorption phenomena and their application to biochemical analysis"
His method of M.S. Tsvet called - "chromatography" (written by color)

Mikhail Semenovich Tsvet
(1872—1919)

Richard Kuhn (Institute of Basic Medicine , Heidelberg) (1938, Nobel Prize in Chemistry for the suggested color adsorption chromatography carotenoids and vitamins)
Alfred Vintershtayn (1915, Nobel Prize in Chemistry for his research of chlorophyll)
Archer Martin Porter , Richard Laurence Millington Singe (1938, first countercurrent extractor using water and chloroform to separate oligopeptides ; 1940. Using liquid-liquid chromatography for separation of amino acids ; November 19 , 1941. The article " A new form of use of the two liquid phases for chromatography " in «Biochemical journal»;1952 . Nobel Prize for the discovery of partition chromatography
Archer Porter Martin , Anthony James Trafford (50s first gas chromatograph)
Izmailov, Schreiber (1938g. first work on thin-layer chromatography)
Stahl (1956 Using thin-layer chromatography as an analytical method)

INNOVATION

The discovery of chromatography is a merit of the Russian botanist M.S. Colors (1903), which passed an alcoholic extract of chlorophyll through a column filled with calcium carbonate, received eight colored bands on an adsorbent, each of which corresponded to a particular pigment. Taking into account the color of the zones, M.S. Tswet called the resulting picture of the distribution of pigments a chromatogram (from Greek chromos - color). Therefore, the method he founded was called chromatography. It should be noted that the author of the method also provided for the fundamental possibility of separating mixtures and colorless components.

Thanks to technological progress, chromatography has become a unique method of analysis (analytical chromatography) and separation (preparative chromatography) of mixtures of any substances and - most importantly - substances that are very similar in structure and properties.

General material and educational and methodological support of the lecture:

- Working program of the discipline
- Silabus
- Methodical recommendations for independent work of higher education applicants
- Multimedia presentations
- Situational tasks

Recommended literature

Basic literature:

1. Medical Chemistry: textbook / V.Y. Tsuber, A.A. Kotvytska, K.V. Tykhonovych et al. - – Kyiv, AUS Medicine Publishing, 2022. – 392 p.

2. Medical chemistry: a textbook for universities / V. O. Kalibabchuk, I. S. Chekman, V. I. Galynska and others; for ed. Prof. V. O. Kalibabchuk – 4th ed. – K. VSV "Medicine", 2019 – 336 p.

3. Medical chemistry / V.O. Kalibabchuk, V.I. Halynska, L.I. Hryshchenko et al. – Kyiv, AUS Medicine Publishing, 2020. – 224 p.

4. General and Inorganic Chemistry: textbook / V.O. Kalibabchuk, V.V. Ohurtsov, V.I. Halynska et al. – Kyiv, AUS Medicine Publishing, 2019. – 456 p.

Additional literature:

1. Medical chemistry: a textbook / V. P. Muzychenko, D. D. Lutsevich, L. P. Yavorska; for order. B. S. Zimenkovsky. – 3rd ed., Ed. – K.: BCB «Medicine», 2018. – 496 p.

2. Mironovich L. M. Medical Chemistry: A Textbook. – Kyiv: Karavella, 2008. – 159 p.

3. Moroz A. S. Medical chemistry: a textbook / D. D. Lutsevich, L. P. Yavorska. – Vinnytsia: New book, 2006. – 776 p.

4. Gotsulyak L. O., Mardashko O. O., Yerigova S. G., Kuzmenko G. I., Kuzmina A. V., Zhilinskaya K. I. Bioinorganic, physicoloid and bioorganic chemistry. Teaching. manual. Odessa. Odessa State Medical University 1999. – 248 p.

5. Textbook of Medicinal Chemistry / V. Alagarsamy // CBS Publishers & Distributors Pvt Ltd, India; 3rd edition, 2018 – 584 p.

6. Richard Post. Chemistry: Concepts and Problems / Richard Post, Chad Snyder, Clifford C. Houk // A Self-Teaching Guide, Jossey-Bass, 2020. – 432 p.

Lecture № 7

Topic: «Dispersed systems. Colloidal solutions and their physical and chemical properties.»

Actuality of theme: Blood, protoplasm, muscle and nerve cells, biological membranes, fibers, genes, viruses are colloid formations. Colloid-chemical processes are the basis of nutrition, growth and development of plant and animal organisms, as well as humans. The study of the properties of colloidal systems and the methods of their preparation allows us to understand the complex processes of life of organisms. The study of methods of cleaning colloidal solutions contributed to the introduction into medical practice of such methods of diagnosis and treatment as electrophoresis, compensatory dialysis, vividialysis, as well as the "artificial kidney" device.

Goal: Formulate systematic knowledge about the basic laws of colloidal chemistry, their close connection with the vital activity of biological systems; consideration of colloidal and chemical aspects of molecule-cell-organism transformations; disclosure of the content of the main laws, to understand their fundamental possibilities when solving specific tasks; increasing the level of theoretical training of students.

Basic concepts: colloidal systems, dispers systems, micella, DEL, electrophoresis, electroosmosis, coagulation of colloidal solutions.

Plan and organizational structure of the lecture:

1. General characteristics of colloidal systems.
2. Methods of obtaining colloidal systems.
3. Methods of cleaning colloidal systems.
4. Molecular-kinetic properties of dispersed systems. Optical properties of colloidal systems.
5. The structure of a colloidal particle.
6. Electrokinetic properties. Electrophoresis. Electroosmosis

Content of lecture material (lecture text)

Dispersed systems are extremely diverse; almost every real system is dispersed. Dispersed systems are classified primarily by the size of the particles of the dispersed phase (or degree of dispersion); in addition, they are divided into groups that differ in nature and state of aggregation of the dispersed phase and the dispersion medium.

Colloidal systems refer to disperse systems - systems where one substance in the form of particles of various sizes is distributed in another.

Particle Size Classification:

Coarse dispersed systems are systems whose particle size of the dispersed phase exceeds 10^{-7} m. These include suspensions and emulsions, for example, a suspension of clay in water, an emulsion of fat in water (milk), etc.

Colloidal systems are systems whose particle size of the dispersed phase is 10^{-7} - 10^{-9} m. Colloidal systems are characterized by heterogeneity, i.e. the presence of phase interfaces and a very large value of the specific surface of the dispersed phase. This leads to a significant contribution of the surface phase to the state of the system and leads to the appearance in colloidal systems of special properties inherent only to them. Their particles do not settle under the influence of gravity, pass through paper filters, but are retained by plant and animal membranes (parchment, membrane from a bull's bubble, etc.). For example, soil colloids, aqueous solutions of silver, gold-sulfur, metal sulfides.

True solutions are homogeneous single-phase dispersed systems. The dissolved substance is in the form of molecules or ions, for example, solutions of sugar, alcohol, urea in water, solutions of electrolytes, etc. The particle size is 10^{-10} – 10^{-14} m.

Colloidal systems, in turn, are divided into two groups that differ sharply in the nature of the interactions between the particles of the dispersed phase and the dispersion medium — lyophobic colloidal solutions (sols) and solutions of high molecular compounds (HMC). Lyophobic colloids include systems in which particles of a dispersed phase interact weakly with a dispersion medium; these systems can be obtained only with the expenditure of energy and are stable only in the presence of stabilizers.

HMC solutions are formed spontaneously due to the strong interaction of the particles of the dispersed phase with the dispersion medium and are able to maintain stability without stabilizers. Lyophobic colloids and HMC solutions also differ in the structure of the particles that make up the dispersed phase. For lyophobic colloids, the unit of structure is a complex multicomponent aggregate of variable composition - a micelle, for HMC solutions - a macromolecule.

Methods for producing lyophobic colloids

Colloidal systems in terms of degree of dispersion occupy an intermediate position between true solutions (molecular or ion-dispersed systems) and coarsely dispersed systems. Therefore, colloidal solutions can be obtained either by association (condensation) of the molecules and ions of the true solutions, or by further fragmentation of the particles of the dispersed phase of coarsely dispersed systems.

Methods for producing colloidal solutions can also be divided into two groups: condensation and dispersion methods.

Dispersion methods are based on the fragmentation of solids into colloidal particles and thus the formation of colloidal solutions. The dispersion process is carried out by various methods: mechanical grinding of the substance in the so-called colloid mills, electric arc spraying of metals, crushing substances using ultrasound.

Condensation methods

A substance in a molecularly dispersed state can be converted to a colloidal state when one solvent is replaced by another - the so-called solvent replacement method. An example is the production of a rosin sol, which is not soluble in water but readily soluble in ethanol. With the gradual addition of an alcoholic solution of rosin to water, a sharp decrease in the solubility of rosin occurs, resulting in a colloidal solution of rosin in water. Similarly, a hydrosol of sulfur can be obtained.

Colloidal solutions can also be obtained by chemical condensation, based on chemical reactions, accompanied by the formation of insoluble or sparingly soluble substances. For this purpose, various types of reactions are used - decomposition, hydrolysis, redox, etc. So, a red gold sol is obtained by reducing the sodium salt of a golden acid with formaldehyde:

$$2NaAuO_2 + 3HCOH + NaCO_3 \rightarrow 2Au + 3\ HCOONa + H_2O + NaHCO_3$$

In a similar manner, a silver sol is obtained from dilute solutions of silver nitrate. Sulfur sol can be obtained by oxidation of hydrogen sulfide with oxygen in an aqueous solution, the action of sulfur dioxide on hydrogen sulfide, or the decomposition of thiosulfuric acid:

$$H_2S + O_2 \rightarrow S + H_2O$$

$$H_2S + SO_2 \rightarrow S + H_2O$$

Sols can also be obtained as a result of ion exchange reactions, as a result of which an insoluble salt is released, which forms a colloidal solution under certain conditions; in this way, for example, a sol of silver iodide is obtained.

$$AgNO_3 + KI \rightarrow AgI + KNO_3$$

The hydrolysis of various salts can lead to the formation of colloidal solutions of insoluble hydroxides or acids; in this way, for example, a ferrum (III) hydroxide sol is obtained having the following structure:

$$FeCl_3 + 3H_2O \rightarrow Fe(OH)_3 + 3HCl$$

Regardless of the method used, the following conditions are necessary to obtain stable colloidal solutions (sols):

- the presence of two mutually insoluble or sparingly soluble components;

- achieving a colloidal degree of dispersion (10^{-7} - 10^{-9} m) of particles of the dispersed phase;

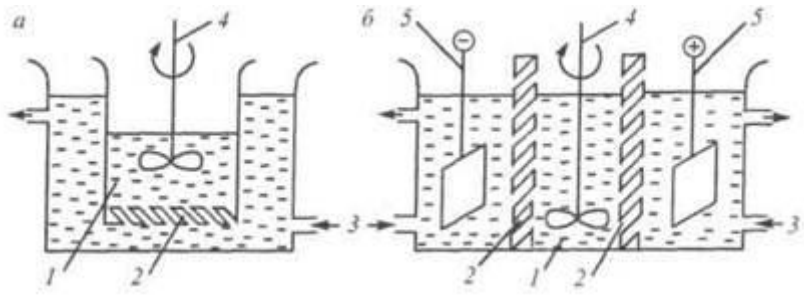
- the presence of a stabilizer, which gives the system a certain stability.

Upon receipt of colloidal solutions by one method or another, especially with the help of chemical reactions, it is practically impossible to accurately predict the necessary quantitative ratio of the reactants. For this reason, an excess of electrolytes may be present in the formed sols, which reduces the stability of colloidal solutions. To obtain highly stable systems and to study their properties, sols are subjected to purification both from electrolytes and from other low molecular weight impurities.

Methods of colloidal solution purification

Colloidal solutions can be cleaned either by dialysis or ultrafiltration.

Dialysis involves the removal of low molecular weight substances from sols with a pure solvent using a membrane. Changing the solvent in the dialyzer, you can almost completely remove impurities of electrolytes and low molecular weight non-electrolytes. But this method is quite lengthy.



Schemes of the dialyzer (a) and the electrodialyzer (b):

1 - dialyzable colloidal solution; 2 - membrane; 3 - supply of the solvent; 4 - mixer; 5 – electrodes.

Electrodialysis is an accelerated dialysis process using electric current. A device for its implementation is called an electrodialyzer. Under the influence of an electric current, ions are transferred from the middle chamber to the anode and cathode

chambers, into which the corresponding electrodes are immersed. Sol in the middle chamber for a short time (minutes, hours) can be purified from dissolved salts.

Compensatory dialysis and vividialysis are methods developed for the study of biological fluids – colloids. The principle of the compensation dialysis method is that instead of a pure solvent, solutions of different concentrations of the substance to be determined are used in the dialyser. For example, to determine the free sugar in the blood serum, it is dialyzed against isotonic saline containing various concentrations of sugar. In that salt solution, where the sugar concentration is equal to the concentration of free sugar in the blood serum, the dialysis concentration does not change the sugar concentration.

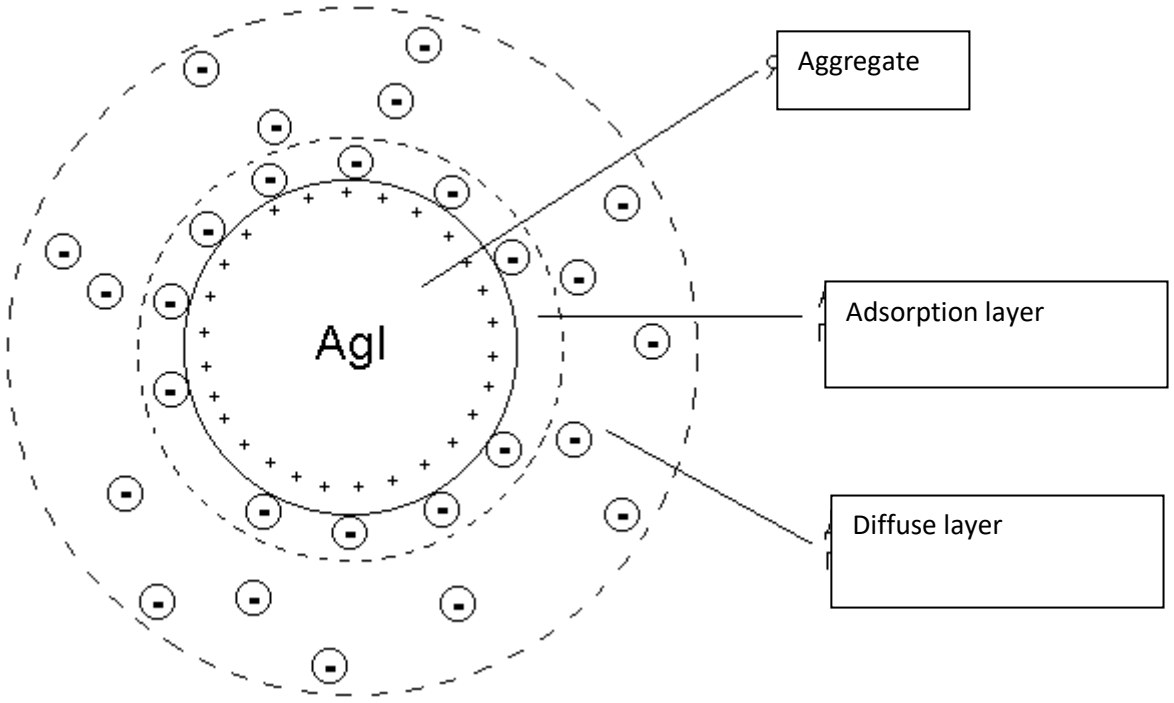
The method of **vividialysis** (intravital dialysis), which is used to determine low molecular weight substances in the blood, is close to this method.

The principle of compensatory vividialysis was used to create the "artificial kidney" apparatus, which makes it possible to cleanse the blood of metabolic products.

Ultrafiltration is the filtration of a colloidal solution through a semipermeable membrane that passes a dispersion medium with low molecular weight impurities and traps particles of a dispersed phase or macromolecule. To accelerate the process, ultrafiltration is carried out with a pressure drop on both sides of the membrane, which is ensured by connecting the device to a vacuum pump. The membrane is made of parchment, cellophane, asbestos, ceramics, and other materials. By ultrafiltration, you can obtain a concentrated colloidal solution, as well as conduct a preparative separation of dispersed systems.

The structure of the lyophobic sol particle

The structural unit of the lyophobic sol is a micelle. Selective adsorption is realized in accordance with Peskov-Fajans-Paneth rule. On a solid crystalline surface, ions are predominantly adsorbed, which are either part of the crystal lattice or isomorphic to it.



For example $\mathbf{K_3PO_4 + 3AgNO_3 \rightarrow Ag_3PO_4 \downarrow + 3KNO_3}$

excess

30mL K_3PO_4 + 1mL $AgNO_3$ → colloidal solution

$K_3PO_4 \rightarrow 3K^+ + PO_4^{3-}$

$\{m\ Ag_3PO_4\ n\ PO_4^{3-} | (3n-x)\ K^+\}^{x-}\ xK^+$

PDI CI diffusion

aggregate layer

nucleus

granule

micelle

The charge of the granule always coincides with the charge of the PDI, but always less than its value.

Consider the structure of the second micelle.

$AgNO_3 \rightarrow Ag^+ + NO_3^-$

E ξ

$\{m\ Ag_3PO_4\ n\ Ag^+(n-x)\ NO_3^-\}^{x+} x\ NO_3^-$

After adsorption of PDI on the micelle core, an E-potential or electrodynamic potential arises.

The charge between the granule and the diffusion layer is the zeta-potential or electro kinetic potential. Its value indicates the stability of the colloidal solution.

The structure of the double electric layer

When considering the structure of the micelle, it was shown that a double electric layer forms on the surface of lyophobic colloids. The first theory of the structure of DEL was developed by Helmholtz and Perrin; in their view, the double electric layer is similar to a flat capacitor, the inner lining of which is in the solid phase, and the outer one is in the liquid parallel to the surface of the nucleus at a distance of the order of the diameter of the ion. In this case, the electric field potential inside the DEL φ decreases linearly with increasing distance r from the surface (Fig. A.).

Guye and Chapman later proposed another model, according to which counter ions, due to thermal motion, form a diffuse ionic atmosphere near the solid surface of the nucleus. In this case, the decrease in the electric potential of the DEL φ with increasing distance r occurs nonlinearly (Fig. B).

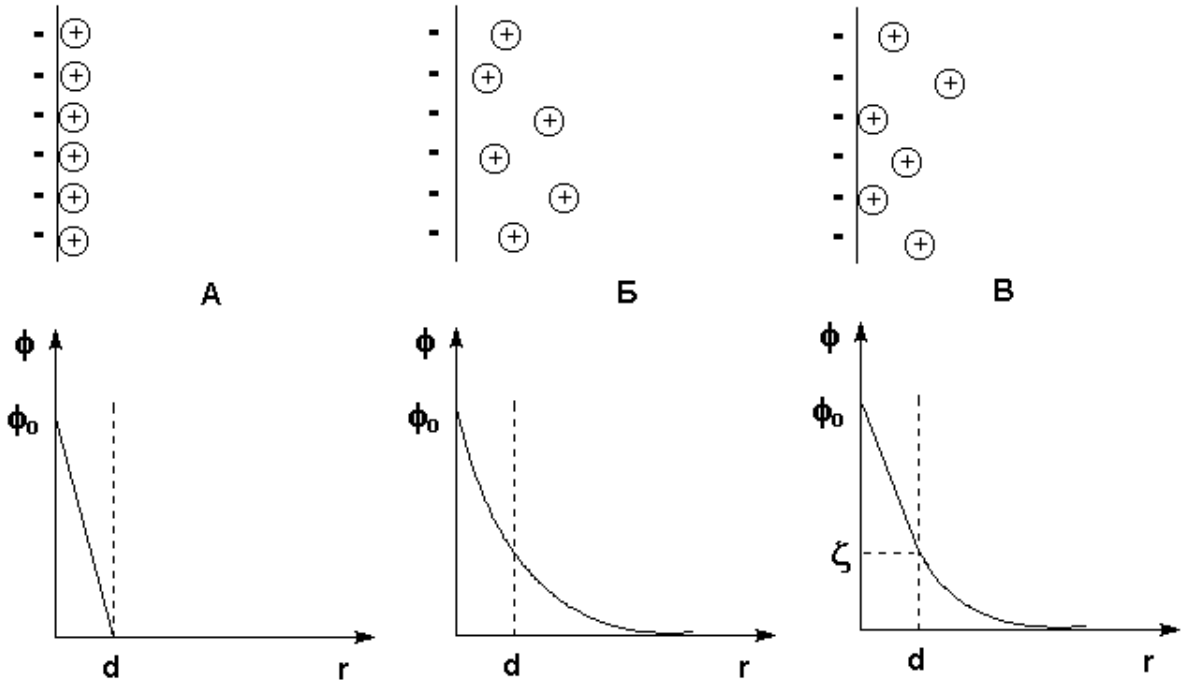


Fig.2. The structure of DEL:

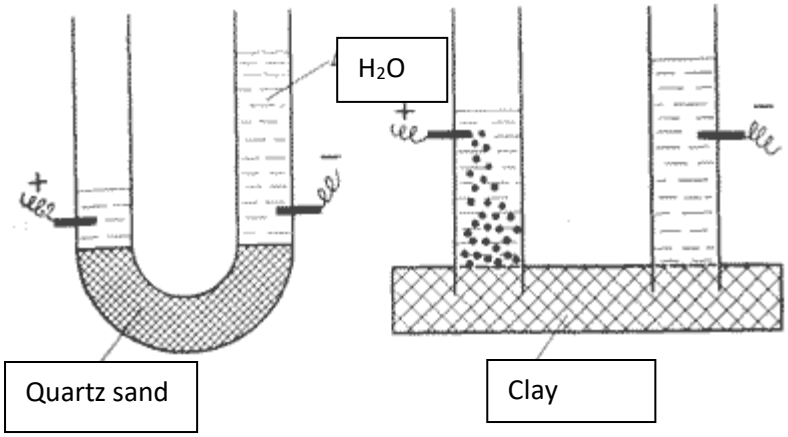
a) - according to Helmholtz and Perrin,

b) - according to Guy and Chapman,

c) - according to Stern. Above is the arrangement of counter ions, below is the dependence of the potential on the distance

The structural model of the DEL proposed by Stern combines the early models, taking into account both the adsorption of counter ions and their thermal motion. According to this model, which is now generally accepted, some of the counter ions are assigned to the PDI, and the other part is free to move.

Electrical properties of disperse systems



The movement of the dispersed phase and dispersion medium was first studied by Professor of Moscow University F.F. Reuss (1807). He stuck two glass tubes into the crude clay, poured a little sand into them, poured water to the same level and lowered the electrodes, connecting them to a direct current source. After some time, clouding appeared in the anode tube and the water level dropped. In the cathode, there was no turbidity, but the liquid level increased (Fig.)

This phenomenon was explained by the fact that clay particles have a negative charge. It turned out that the ability of the dispersed phase and the dispersion medium to move under the action of an electric current is characteristic of all colloidal solutions.

The movement of the particles of the dispersed phase relative to the dispersion medium in an electric field towards the oppositely charged electrode is called electrophoresis.

The movement of a dispersion medium in an electric field is called electroosmosis. Under the influence of an electric field, a deformation of a double electric layer occurs; a particle with an adsorption layer moves to one electrode, and diffuse layer ions move to another.

The direction of motion of the particles gives an answer to the question about the sign of their charge, and the speed of movement - about its magnitude. The absence of

movement indicates that the particle is in an isoelectric state (i.e., lack of charge). This can happen when all the ions of the diffuse layer are moved to the adsorption one.

The velocity of particles of the dispersed phase in an electric field depends on the value of ξ - potential. This dependence is expressed by the ratio:

$$V = \frac{\xi \cdot H \cdot E}{4\pi \cdot \eta}$$

where V is the electrophoretic speed;

H is the electric field strength;

E is the dielectric constant;

η is the viscosity;

ξ is the zeta potential

Thus, the electrophoretic speed is directly proportional to the ξ potential and inversely proportional to the viscosity of the solution, i.e. particle size.

Transforming the equation, we obtain

$$\xi = \frac{4\pi \cdot \eta \cdot V}{H \cdot E}$$

In 1937, Tiselius proposed the use of electrophoresis as a new method for the separation and analysis of a mixture of proteins. Electrophoresis of human serum proteins revealed five components: albumin and four globulins. Serum albumin predominated quantitatively, serum globulins were divided into four components in order of decreasing electrophoretic mobility: α_1, α_2, β, and γ.

Thus, the electrophoresis method allows one to separate protein mixtures and determine the molecular weights of individual components. In addition, electrophoresis along with iontophoresis is used in medical practice for the introduction of various medicinal substances into the body.

Optical properties of colloidal systems

The special optical properties of colloidal solutions are due to their main features: dispersion and heterogeneity. The optical properties of dispersed systems are greatly affected by particle size and shape. The passage of light through a colloidal solution is accompanied by such phenomena as absorption, reflection, refraction and scattering of light. The predominance of any of these phenomena is determined by the ratio between the particle size of the dispersed phase and the wavelength of the incident light. In coarsely dispersed systems, reflection of light from the surface of particles is mainly observed. In colloidal solutions, the particle sizes are comparable to the wavelength of visible light, which determines the scattering of light due to diffraction of light waves.

Light scattering in colloidal solutions is manifested in the form of opalescence - a dull glow (usually bluish tones), which is clearly visible against a dark background with side illumination of the sol. The cause of opalescence is the scattering of light by colloidal particles due to diffraction. The opalescence is associated with the phenomenon characteristic of colloidal systems - the Tyndall effect: when a light beam passes through a colloidal solution from directions perpendicular to the beam, a luminous cone is formed in the solution.

The process of diffraction light scattering by particles whose size is much smaller than the wavelength is described by the Rayleigh equation relating the intensity of the light scattered by a unit volume of light I with the number of particles per unit volume ν, particle volume V, wavelength λ and amplitude A of the incident radiation and the refractive indices of the dispersed phase and dispersion environments n_1 and n_2, respectively:

$$\mathbf{I} = \frac{24\nu\pi^2 V^2 A^2}{\lambda^4}\left(\frac{n_1^2 - n_2^2}{n_1^2 + n_2^2}\right)$$

It can be seen from the equation that the shorter the wavelength of the incident radiation, the greater the scattering. Therefore, if white light falls on a particle, the blue and violet components will experience the greatest scattering. Therefore, in transmitted

light, the colloidal solution will be painted in reddish color, and in the lateral, reflected - in blue.

A method for determining the concentration or degree of dispersion of a sol, called nephelometry, is based on a comparison of the light scattering intensity of sols, one of which has a known concentration (degree of dispersion). An ultramicroscopy is based on the use of the Tyndall effect - a device that allows you to observe colloidal particles larger than 3 nanometers in scattered light (in a conventional microscope, particles with a radius of at least 200 nm can be observed due to limitations associated with the resolution of the optics).

Stability and coagulation of colloidal solutions

The ability of a dispersed system to maintain a structure (dispersion and uniform distribution of a dispersed phase in a dispersion medium) is called the stability of a dispersed system.

In 1920, the scientist Peskov proposed distinguishing between 2 types of stability:

1. Sedimentation - stability of a dispersed system with respect to gravity.

The basic conditions for the existence of this stability are high dispersion and the participation of particles of the dispersed phase in the Brownian motion.

2. Aggregate stability is the ability of a dispersed system to maintain a certain degree of dispersion, i.e. dispersed phase particles do not combine into larger aggregates due to their collision.

In real systems, aggregative stability is due to the simultaneous action of several factors. In this case, the main role belongs to electrostatic and adsorption-solvate factors.

The electrostatic factor contributes to the creation of electrostatic repulsive forces, increasing with increasing surface potential and especially the electro kinetic potential of the particles of the dispersed phase.

The adsorption-solvation factor leads to a decrease in interfacial tension and a decrease in the Gibbs energy of the interface.

Different colloidal systems are characterized by varying degrees of stability. However, a common property for all colloidal systems is their desire to lower free surface energy by reducing the interface. One way to reduce this is to enlarge the particles,

The process of combining colloidal particles into larger aggregates is called coagulation.

A study of the coagulation of hydrophobic sols allowed us to develop a modern theory of coagulation, according to which colloidal particles can move freely up to a distance of 10^{-7} m during Brownian motion. Further convergence of these particles leads to the fact that the diffuse layer of each particle with polar water molecules that surround ions in a thin layer of liquid condense, acquiring the properties of a solid (increased elasticity, viscosity, higher boiling point, etc.), which prevents the adhesion of colloidal particles.

Between colloidal particles there is an excess, the so-called proppant pressure. If the particles have enough energy to overcome the “wedging pressure”, then at a distance of about 10^{-7} - 10^{-9} m intermolecular attraction forces begin to prevail and the particles combine. The greater the ξ potential, the more stable the colloidal system. Colloidal systems possess the least stability at $\xi = 0$, i.e., in the isoelectric state.

Coagulation of sols can be caused by various factors: the addition of electrolytes, heating or freezing, mechanical stress, etc. The most important and studied factor in the coagulation of hydrophobic colloids is the effect of electrolyte solutions on them.

A series of empirical laws have been established for coagulation of sols with electrolytes.

1. To start coagulation of the sol, a certain minimum concentration of electrolyte is required, called the coagulation threshold γ.

2. The one of the electrolyte ions has a coagulating effect, the charge of which is opposite to the charge of colloidal particles, and the coagulating effect of the ion is stronger, the greater its charge (Schultze-Hardy rule). In accordance with the Schultze-Hardy rule, coagulation thresholds for single, double, and triple charged ions are referred to as 729: 11: 1, i.e., a triple charged coagulation ion requires 729 times less than a single charged one.

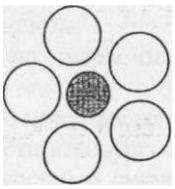
3. In the ranks of inorganic ions with the same charges, the coagulating effect increases with decreasing hydratation ability of the ions; for example, in a series of singly charged alkali metal cations, the coagulating effect increases from lithium to rubidium:

$$\gamma\ (Li^+) > \gamma\ (Na^+) > \gamma\ (K^+) > \gamma\ (Rb^+)$$

Rows in which ions with the same charge are grouped in increasing or decreasing coagulating action are called lyotropic series.

When electrolytes are added, the diffuse layer is compressed and the ξ potential decreases, which reduces the stability of the colloidal system.

The addition of certain substances to the colloidal system can increase its stability. This effect is caused by some surfactants and macromolecular compounds. The addition of a high molecular weight compound in the case of sufficient concentration leads to the fact that the high molecular weight compound is adsorbed on the micelle, forming a large aggregate with hydrophilic properties / stabilization of the colloidal particle is observed /. This phenomenon is called the “protection” of the colloidal solution with a high molecular weight compound.



With an excess of actually colloidal particles in the mixture, the latter, in turn, can be adsorbed on the surface of the HMC, forming a large aggregate of low stability. This phenomenon is called astabilization.

The phenomenon of colloidal "protection" has great physiological significance: many hydrophobic colloids, blood particles and biological fluids are "protected" by high molecular weight compounds - proteins that have the most powerful protective effect.

Blood proteins increase the solubility of $CaCO_3$ by five times, and also “protect” droplets of fat, cholesterol, etc. from coagulation. Reducing this "protection" leads to the deposition of cholesterol and calcium salts on the walls of blood vessels / atherosclerosis and calcification /. It is believed that the hydrophilicity of human blood proteins decreases with age and, accordingly, the ability to "protect" decreases. The consequence of this is atherosclerosis - an essential factor in the aging of the body.

The decrease in the protective properties of proteins and other hydrophilic compounds also leads to the deposition of uric acid salts / urates /, the formation of stones in the kidneys, liver, and ducts of the digestive glands.

The phenomenon of "protection" is used in the preparation of pharmacological preparations; were proposed "protected" by proteins metal sols / collargol and others /.

General material and educational and methodological support of the lecture:

- Working program of the discipline
- Silabus
- Methodical recommendations for independent work of higher education applicants
- Multimedia presentations
- Situational tasks

Recommended literature

Basic literature:

1. Medical Chemistry: textbook / V.Y. Tsuber, A.A. Kotvytska, K.V. Tykhonovych et al. - – Kyiv, AUS Medicine Publishing, 2022. – 392 p.

2. Medical chemistry: a textbook for universities / V. O. Kalibabchuk, I. S. Chekman, V. I. Galynska and others; for ed. Prof. V. O. Kalibabchuk – 4th ed. – K. VSV "Medicine", 2019 – 336 p.

3. Medical chemistry / V.O. Kalibabchuk, V.I. Halynska, L.I. Hryshchenko et al. – Kyiv, AUS Medicine Publishing, 2020. – 224 p.

4. General and Inorganic Chemistry: textbook / V.O. Kalibabchuk, V.V. Ohurtsov, V.I. Halynska et al. – Kyiv, AUS Medicine Publishing, 2019. – 456 p.

Additional literature:

1. Medical chemistry: a textbook / V. P. Muzychenko, D. D. Lutsevich, L. P. Yavorska; for order. B. S. Zimenkovsky. – 3rd ed., Ed. – K.: BCB «Medicine», 2018. – 496 p.

2. Mironovich L. M. Medical Chemistry: A Textbook. – Kyiv: Karavella, 2008. – 159 p.

3. Moroz A. S. Medical chemistry: a textbook / D. D. Lutsevich, L. P. Yavorska. – Vinnytsia: New book, 2006. – 776 p.

4. Gotsulyak L. O., Mardashko O. O., Yerigova S. G., Kuzmenko G. I., Kuzmina A. V., Zhilinskaya K. I. Bioinorganic, physicoloid and bioorganic chemistry. Teaching. manual. Odessa. Odessa State Medical University 1999. – 248 p.

5. Textbook of Medicinal Chemistry / V. Alagarsamy // CBS Publishers & Distributors Pvt Ltd, India; 3rd edition, 2018 – 584 p.

6. Richard Post. Chemistry: Concepts and Problems / Richard Post, Chad Snyder, Clifford C. Houk // A Self-Teaching Guide, Jossey-Bass, 2020. – 432 p.