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ХАРКІВСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ

**Kinetics of biochemical reactions. Chemical equilibrium. The solubility product.**

Methodical instructions for 1st year students’ self-work

in Medical Chemistry

КІНЕТИКА БІОХІМІЧНИХ РЕАКЦІЙ. ХІМІЧНА РІВНОВАГА. ДОБУТОК РОЗЧИННОСТІ.

Методичні вказівки для самостійної роботи студентів 1-го курсу

 з медичної хімії

 Затверджено

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Kinetics of biochemical reactions. Chemical equilibrium. The solubility product: methodical instructions for 1st year students’ self-work in Medical Chemistry / compiled by A.O. Syrovaya, V.N. Petyunina, V.O. Makarov, E.R. Grabovetskaya, S.A. Nakonechnaya, S.V. Andreeva, L.G. Shapoval, L.V. Lukyanova, S.N. Kozub, T.S. Tishakova, O.L. Levashova, E.V. Savelieva, N.V. Kopoteva, N.N. Chalenko – Kharkiv: KhNMU, 2015. – 25 p.

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**Subject** “Kinetics of biochemical reactions. Chemical equilibrium. The solubility product.”

1. **Number of hours** 4

2. **Material and methodological support.**

Tables:

1. Graph structure of the subject.

2. The Michaelis-Menten constant (Km) value for certain enzymes.

3. Kinetics of enzymatic processes.

4. Dependence of enzymatic reactions rate on the concentration of a substrate.

Multimedia support (presentation, educational video).

Educational literature:

1. Medical Chemistry: manual for medical students / I.V. Zavgorodniy, A.O. Syrovaya, E.R. Grabovetskaya et al. – Kharkiv, Ekograf,2011. – 240 p.

2. Medical Chemistry. Self-study guide for the 1st year students (English medium) / A.O. Syrovaya, E.R. Grabovetskaya, L.G. Shapoval et al. – Kharkiv: KhNMU, 2014. – 70 p.

3. Syrovaya A.O. Medical chemistry. Adapted concise course / A.O. Syrovaya, E.R. Grabovetskaya, L.G. Shapoval. - Kharkiv: KhNMU, 2013. – 160p.

4. “Buffer systems, their biological role” - Methodical instructions for I year students' self-work in “Medical Chemistry”

5. Individual tasks for students’ self-control of knowledge in Medical Chemistry / A.O. Syrovaya, L.G. Shapoval, V.N. Petiunina, et al. – Kharkiv: KhNMU, 2014. –50 p.

6. Lecture notes

Laboratory glassware and reagents for laboratory “Kinetics of chemical reactions” (stand rods with burettes, solutions 37,0 g/L Na2S2O3 and H2SO4 (1:200), measuring cylinders, stopwatch, thermometer).

3. **Substantiation of the subject.** The study of chemical reaction kinetics is of great theoretical and practical significance for both chemistry and medicine. The knowledge of factors that affect the rate of the reaction permits to regulate the processes taking place in the organism, to investigate the efficacy of drugs and enzymes. The knowledge of laws that provide the optimal course of the particular process permits to achieve the desired result by creating the right conditions*.* The study of this subject will help to analyze the sequence of competing processes in the organism, to understand causes of metabolic disorders, which take place in the living systems.

4. **The purpose of the subject:**

- general: to be able to explain the basic of kinetic regularities of chemical and enzymatic reactions; interpret the physical nature of chemical equilibrium.

- specific: to analyze the dependence of the reaction rate on the concentration and the temperature, to interpret the dependence of the reaction rate on the activation energy, to analyze peculiarities of catalysts action and explain the mechanism of homogeneous and heterogeneous catalysis, to be able to explain the mechanism of enzymatic action and analyze the effect of enzyme and substrate concentrations on the rate of enzyme-controlled reactions, to analyze chemical equilibrium and to explain its condition fromthermodynamics and kinetics perspective, explain the influence of external factors on chemical equilibrium, to analyze conditions of precipitates formation and dissolution, to explain the role of heterogeneous equilibrium involving salts participation in general homeostasis of the organism;

а) **to know:** basic concepts of chemical kinetics, the rate of chemical reaction, rate constant of chemical reactions, homogeneous and heterogeneous systems;

b) **to be able to:** determine how temperature and concentration of reactants affect the chemical reaction rate, determine kinetic parameters: an order of the reaction, molecularity, interpret the dependence of the rate of the chemical reaction on the activation energy, explain the catalysts action, explain the mechanism of enzymatic action and features of enzymatic catalysis, analyze the chemical equilibrium and explain it from the perspective of thermodynamic and kinetic, explain the influence of external factors on chemical equilibrium, analyze conditions of precipitates formation and dissolution, explain the role of heterogeneous equilibrium involving salts participation in general homeostasis of the organism.

с) **practical skills**:

- to write kinetic equations of simple reactions;

- to determine the rate and direction of the chemical reaction depending on the concentration, temperature and pressure;

- to define the solubility of electrolyte according to the solubility product.

5. **Graph structure of the subject**.

Nature of reacting substances

Molecularity

Mechanism of chemical reaction

Reaction rate

constant

Chemical reaction rate

Chemical equilibrium constant**s**

Optimum conditions for chemical reaction constant

Catalyst

Activation

energy

Arrhenius

equation

Temperature

Van’t-Hoff law

Reagents concentration

Reaction order

Law of mass action

6. **Plan of students’ work**

**Class 1**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| № | Stages | Time(min.) | Training and visual aids | Location |
| 1. | Motivational characteristics and plan of the subject. Answers to the students’ questions | 10 | Text book(work book) | Class room |
| 2. | Students’ individual work with methodical literature, solving of educational tasks | 40 | Methodical instruction for students, lecture notes, text book for students’ self-work, reference data, posters. Manuals, reference materials, tables. |
| 3. | Implementation of the work and writing the report | 20 |
| 4. | Control of knowledge | 15 |  |
| 5. | Analysis and conclusions | 4 |  |
| 6. | Home work | 1 |  |  |

**Class 2**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| № | Stages | Time(min.) | Training and visual aids | Location |
| 1. | Motivational characteristics and plan of the subject. Answers to the students’ questions | 30 | Text book(work book) | Class room |
| 2. | Students’ individual work with methodical literature, solving of educational tasks | 40 | Methodical instruction for students, lecture notes, text book for students’ self-work, reference data, posters. Manuals, reference materials, tables. |
| 3. | Implementation of the work and writing the report | 15 |  |
| 4. | Control of knowledge | 4 |  |
| 5. | Analysis and conclusions | 1 |  |

7. **Tasks for self-work:**

- list of questions to be studied:

1. Basic concepts of chemical kinetics: the chemical reaction rate, the rate constant of chemical reactions, homogeneous and heterogeneous systems.

2. The dependence of the chemical reaction rate on the concentration. Molecularity and order of the reaction. Kinetic equations for first-, second- and zero-order reactions.

3. The dependence of the reaction rate on temperature. Van’t Hoff rule, it features for biochemical processes. Activation energy. Arrhenius equation.

4. Influence of the nature of chemical compounds on the reaction rate. Kinetics of complex reactions: parallel, consecutive, coupled, chain, cyclic.

5. Catalysts and the mechanism of their action.

6. Enzymatic catalysis, its features and kinetics of enzymatic reactions.

7. Chemical equilibrium. Shifting of chemical equilibrium. Le Chatelier’s principle.

8. Heterogeneous equilibrium involving salts participation in general homeostasis of the organism.

9. Preparation of laboratory work.

**1. Main concepts of chemical kinetics.**

The metabolic processes are a number of biochemical reactions taking place at coordinated rates. The same reaction may take place at the different rates depending on the conditions. Thus, glucose burns slowly in the organism in the process of biological oxidation; it is not oxidized in the air, but explodes with liquid oxygen when micro quantities of some salts (catalysts) are added.

Chemical thermodynamics allows to determine the energy of the reactions (including biochemical ones), to predict whether the process will occur depending on the conditions, in case we know Gibbs energy changes. But thermodynamics does not answer the question about the rate of the predicted chemical reaction. For this we should know the mechanism of the reaction. It is chemical kinetics that studies how chemical reactions proceed and determine their rates.

The laws of chemical kinetics are universal for all phenomena, erythrocyte sedimentation, drug digestion, and fermentation.

Chemical reaction rate (*v*) is the change of the amount of a substance during a unit of time per unit of volume for *homogeneous* reactions and per unit of surface for *heterogeneous* reactions:

υ = ∆n / υ∆nτ , mol/m3s– homogeneous reaction,

υ = ∆n / s∆nτ , mol/m3s– heterogeneous reactions

Concentration changes have a positive sign for the reaction products and negative – for the initial reagents. In addition to molar concentration (mol/L), the concentration expressed in mg/100 ml is used for biochemical investigations. For the determination of erythrocyte sedimentation rate (ESR) we measure the height of the column h (mm) of the erythrocytes sediment in the capillary in a period of one hour (mm/h).

**2. Dependence of the chemical reaction rate on the concentration. Molecularity and the reaction order.**

**Kinetic equations for first-, second- and zero-order reactions.**

Main factors that influence the rate of chemical reactions are concentration, temperature, nature of the reacting substances, and presence of a catalyst.

The concentration effect is described by the law of mass action, formulated in 1867 by Norwegians K. Gulberg and P.Vaage: at a constant temperature the rate of the chemical reaction at each moment is directly proportional to the concentration of the reacting substances.

For the reaction (2А + В → products) the dependence of the homogeneous reaction on the concentration of reacting substances can be presented as:

*υ* = *k* [А]2 [В]

where *k* —  constant of the chemical reaction rate. It equals to the rate of the chemical reaction when the concentrations of all reacting substances equals 1, e.g. 1 mol/L. This equation is called kinetic. It is necessary to keep in mind that in kinetic equations only concentrations of substances in gaseous or liquid form are written, because concentrations of solid substances are constant, thus, they are included in the reaction rate constant. E.g. for reactions:

С + О2 = СО2

kinetic equation is:

*υ* = *k* [О2]

The above kinetic reactions are an analytical expression of the law of mass action. They are applicable only to ideal systems, in which the stoichiometric equation reflects the reaction mechanism. When the law of mass action is applied to the real systems, it is necessary to use activities (not concentrations), the exponents of power in the equation are found experimentally.

The rate values cannot be used to compare chemical reactions, because they change over time. The reactions take place under the same conditions can be compared using only their fundamental kinetic parameter, *rate constant*.

In practice the thermochemical equation does not reflect the reaction mechanism. Only a few chemical reactions are accomplished in one stage. The majorities are accomplished in several elementary stages, in which one, two or three molecules are involved. The number of molecules, which react simultaneously at the moment of collision, accomplishing the act of chemical interaction, is called *molecularity* of the reaction.

СН3 — СНО → СН4+ СО – monomolecular

Н2 + І2 → 2НІ – bimolecular

2NO + O2 → 2NO2 – trimolecular

The probability of simultaneous collision of three molecules is 1000 times less than collision of two molecules. Elementary stages of any chemical reaction can be presented as mono- or bimolecular interactions. The rate of multi-stage reactions is controlled by the rate of its slowest stage.

Thus the observed rate of the reaction

2Н2 + О2 = 2Н2О

does not correspond to the rate predicted by the equation:

*υ* = *k* [Н2]2 [О2].

Experiments have shown that this reaction is rather complicated, andaccomplished in several stages following the chain mechanism.

The exponents of power in a kinetic equation are determined using special methods; they are called reaction order with respect to a given substance. The overall order of a reaction equals to the sum of exponents in the rate equation.

It should be noted that the notions of *order and molecularity* do not always coincide. Thus, in one-stage processes, which are accomplished in a gaseous state, the order of the reaction coincides with molecularity, as a rule. In the majority of cases this is not true. The order of complicated reactions changes from 0 to 3, in some cases being an integer value, in some – a fraction. The change of conditions may change the order of the reaction. Molecularity of a reaction remains constant in all conditions and is never a fraction.

Bimolecular reactions frequently comply with the first-order kinetic reactions when they are accomplished with an excessive amount of one reactant. In this case the reaction rate depends on the concentration of molecules which amount is the lowest, because diminishing the number of the molecules of the second kind does not change considerably their concentration, and consequently, the reaction rate. These are reactions of hydrolysis, final stages of enzyme-based processes, reactions of antigens with vitamins, etc.

 The rate of many reactions in the organism does not depend on the concentration of the reacting substances. The rate is constant when all active centers of the enzymes are saturated, so the reaction obeys zero-order rate law.

 The reactions of biochemical processes cannot be higher than second order.

Let us consider how to determine main kinetic characteristics of the reactions using experimental data.

*First-order reactions*. The rate law for a reaction that is first order with respect to a reactant concentration:

υ = – *dc/dτ = k1С*,

its integral expression is:

*k1* = 1/τ∙ln(Со/С) = 2,3∙1/*τ*lg (Со/С)s-1

The rate constant and half-life (τ1/2) of the reaction are useful characteristics of the reaction. The half-life of the reaction is the amount of time during which a half of the initial amount of the substance reacts.

Half-life of first-order reactions is:

τ1/2 = 0, 69/ k1

The physical sense of the reaction rate constant of a first-order reaction is that equal portions of the initial substance react within equal intervals of time. For the first-order reactions a plot of concentration logarithm versus time is linear (Fig. 1a).

*Second order reactions*. The equations of concentration dependence of the time for second-order reactions are considered only for the simplest cases, when the concentrations of reacting substances are equal:

υ = – *dc/dτ = k2 С2*,

*k*2 = 1/*τ*∙ (1/Co – 1/C), d/mol∙s – integral form.

Half-life for second order reactions is:

τ1/2 = 1/*k*2 *C*o

Linear dependence for second-order reactions with equal initial concentrations of the reacting substances is observed for the value of reverse concentration (1/C) versus time (Fig. 1 b).

Fig.1

Linear dependence lgC=φ(τ), 1/C= φ(τ), Co–C=φ(τ) for a ) first-, b) second-, c) zero-order reactions.

*Zero-order reactions.* In zero-order reactions the rate of chemical reactions does not depend on the concentration of the reacting substances. These refractions are mainly catalytical,when the surface of the catalyst is completely covered with molecules of the reacting substances. The further increase in the reagent concentration would not change the reaction rate, because it is located on the surface of the catalyst. E.g. many photochemical reactions (production of HCl from H2 and Cl2), ammonium decomposition on platinum:

2NH3  N2+ 3H2

In general:

*υ* = *k*o or *С* = *С*o —*k*oτ ,

it follows

*k* = (Со –С) / τ

where *С*o —  initial molar concentration, *С* —  concentration at a time  The rate constant of zero-order reactions is measured in mol/L·s, hence the concentration diminishes linearly with the time for zero-order reactions (Fig. 1 c).

For zero-order reactions the time of half-life is proportional to the initial concentration:

τ1/2 = *C*o/2*k*o

In general, the unit of measurement of rate constant for n-order reaction can be determined as follows:

= *k* A*n* mol/L s = k mol/Ln or k = (mol/L) 1-n s-1

The practical implicationsof the above equations and graphs is in their application for the determination the true order of investigated reaction. For this it is necessary to plot a graph of the C0–C or lgC or 1/C value versus the time using experimental data and find the linear dependence. Only in case, when the graph is linear, we can conclude that the studied reaction is zero-, first- or second-order respectively.

Using the experimental data and the values of concentration in different moments of time we calculate the rate constant of the reaction– k. The equation, which gives a constant k value, corresponds to the type of the investigated reaction.

Example. Saponification of methyl ester of acetic acid at 298 K has the following equation:

СН3СООСН3 + NaOH = CH3COONa + CH3OH

The following experimental data were obtained:

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| τ, s | 180 | 300 | 420 | 600 | 900 | 1500 |
| С, mol/L·10–3 | 7,4 | 6,34 | 5,5 | 4,64 | 3,63 | 2,54 |

Со NaOH  = Сo CH3COOCH3 = 0,01 mol/L

Solution: consecutively put the experimental data to the equation of first and second order. We understand that zero order reaction can be only a catalytic process. The investigated reaction is not a catalytic process.

K11 = 1/τln(*Сo/C*)=1/180∙2.3lg(0,01/0,0074)s-1

K21 = 1/1500∙2,3lg(0,01/0,00245)s-1 = 0,0009 s-1

K12 = 1/τln(1*/С –* 1*/Co*)=1/180∙2,3lg(1/0,0074–1/0,01) = 0,196

K22 = 1/1500 (1/0,00245 – 1/*C0,01*) = 0,196 L/mol∙s.

Besides the above analytical method, we can use a graphic method. In this case we plot a dependence graph of lgC or 1/C versus the time and look for linear part of the graph. Thus, for saponification reaction of methyl ester of acetic acid the lgC values were calculated.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| τ, С | 180 | 300 | 420 | … | 1500 |
| lg *C* | -2,1308 | -2,1974 | -2,2596 |  | -2,5952 |
| 1/*C* | 135,1 | 157,7 | 181,8 |  | 393,2 |

 Now let us plot graphs:

We can conclude that methyl ester of acetic acid saponification is the second-order reaction.

**3. Dependence of the reaction rate on the temperature.**

**Van’t Hoff’s rule, its peculiarities for biochemical processes. Activation energy. Arrhenius equation.**

Temperature elevation significantly increases the rate of chemical reactions.

As the temperature increases the number of collision is also increases. In 1879 Van’t Hoff formulated an empirical rule: when the temperature of the system increases by 10 degrees the rate of the chemical reaction increases 2-4 times:

VT2 = VT1 γ∆T/10,

were γ —  temperature coefficient showing how many times the rate increases at temperature elevation by 10 degrees.

Most reactions in the human organisms are enzyme-catalyzed reactions within a narrow range (optimum) of temperature 36-42 degrees. Therefore, the temperature influence on biochemical processes is more considerable and, as a consequence, γ values are equal 7-10 and are taken for a more narrow temperature range - 2, 3, 5 degrees.

As the temperature rises, not every collision results in a chemical reaction. To accomplish it the molecules must have some reserve of energy, which is sufficient to loosen the bonds, which will be reconstructed during the reaction, or they must be able to overcome the energy threshold.

Activation energy (*Е*а)  is the amount of energy (when compared with the mean molecule energy) required for the substances to react. Usually Ea varies from 40 to 200 kJ/mol.

Mathematical dependence of the rate constant on the temperature follows from the theory of active collisions, considering the reaction to be bimolecular and taking place in a gaseous form. The fraction of molecules that have required for the reaction Ea of the total number is determined by heat distribution of Maxwell-Boltzmann (exponential dependence). Hence, the following (Arrhenius equation) is true:

K = Ae – Ea/RT

where *k* – reaction rate constant; *А* – pre-exponential multiplier reflecting the amount of active collisions, it ranges from 0 to 1; Ea - activation energy, J/mol; R – universal gas constant, 8,314 J/mol K; T – absolute temperature; e – natural logarithm base.

The values of activation energy can be determined by measuring the rate constant for the given reaction at two different temperatures using the equation:

Еа = 2,3*RT1T2 / (T2 – T1)*lgk1/k2

Using a graph after taking the logarithm of Arrhenius equation:

ln *k*= –Ea/*RT*+ lnA; tg φ = –*E*a/2,3·*R*;

lg *k*= lgA – *E*a/2,3*RT*; *E*a = – 2,3·*R* tgφ.

Example. At 380 oC the period of half decay of hydrogen peroxide H2O2 (first-order reaction) is 360 minutes. Activation energy for this reaction is 20 kJ/mol. It is necessary to determine the time during when 75% of H2O2 will be destroyed at 450 oC.

Solution: Let us calculate *k* at 380˚С:

*k* =0,69 */ τ*1/2 = 0,69 / 360 = 1,925 ∙ 10-3 min-1

Let us calculate *k* at 450˚C or 723 К:

lg(*kT2/kT1*) = *Ea* / 2,3R(*T2–T1/T2T1*)

*T*1 = 653 K, *k*1 = 1,925·10–3 min–1, *T*2 = 723 К, *Ea* = 200·103 J

lg(*k2/*1,925·10–3) = 200∙10–3 / 2,3∙8,314(723–653/723∙653)

lg(*k2/*1,925·10–3) = 1,5487; *k2/*1,925·10–3 = 35,375; k2 = 6,81∙10-2

Let us calculate the time for 75% transformation of Н2О2, at 723 K. Let Co H2O2 = 1, then Co H2O2 when 75% have reacted is:

6,81∙10-2= 2,3∙1/τlg1/0,25; τ = 6,81∙10-2/2,3∙0,6 ≈ 0,05 min.

**4. Influence of chemical compounds nature on their reaction rate. Kinetics of complicated reactions: parallel, consequent, coupled, chain, cyclic.**

The nature of the reacting substances is also an important factor determining the rate of chemical reactions. The type of the chemical bond plays the decisive role. For organic substances, main types of bonds are nonpolar or low-polar covalent  or  bonds. The reactions with the substances having  bonds are slower than with those having  bonds. Inorganic substances that have ionic or polar covalent bond react faster.

Rate constant and activation energy (*k* and *Ea*) are individual characteristics of the reacting substances and are defined by their nature and type of the chemical bonds. The higher is the Ea value, the lower is the chemical reaction rate. Activation energy is required to break the chemical bond in order for the reaction to occur.

As a rule, chemical and biochemical processes have complicated mechanisms; the described kinetic rules can be applied to separate stages of these processes. The mechanism of complicated processes can be consequent, parallel, coupled or chain.

Consequent processes go through a number of stages: А > В > С. The total rate of this process is determined by the slowest stage. In the organism many processes have a consequent mechanism (e.g., glycogen hydrolysis with ATP).

Parallel reactions are those resulting in formation of several end-products from the initial substance:

In inorganic chemistry an example of a parallel reaction is Berthollet salt decomposition:

Glucose in the organism is oxidized to pyruvic acid through a glycolytic route then oxidation can be accomplished in two ways: Krebs cycle or Pentose Phosphate Cycle.

Coupled reactions follow the scheme:

А + В → М; А + C → N

In this case the first reaction can be independent, while the second one is possible only when it coupled with the first reaction. All endergonic reactions (accomplished with a positive change of Gibbs energy) are coupled with exergonic reactions. They are possible because the energy is provided by exergonic reactions with G01 < 0.

Cyclic processes are important in the process of metabolism, for example Krebs cycle, cycle of urea production, fatty acid oxidation. As the result of cyclic processes some substances are completely turned into final products and excluded from the cycle, the others constantly participate in the cycle. A typical example is any enzymatic reaction in which the enzyme goes through a number of free and coupled forms.

Many reactions such as oxidation, splitting, halogenation, and polymerization have a chain mechanism, which consists of a number of regular elementary acts with participation of very active particles, free radicals. Free radicals can appear due to temperature, radiation, or so-called chain initiators.

Every chain reaction consists of three stages: initiation, propagation and chain termination. Noble prizewinners N.N. Semenov and S.N. Hinshelwood worked out the theory of chain reactions.

Many biological processes have a chain mechanism. In the organism, main source of free radicals at metabolic processes are one-electron processes in oxidation-reduction reactions. They also appear at exposure to radiation.

Many pathological changes in the organism have a chain mechanism, e.g. destruction of the cellular membranes in radiation sickness, tumor development, action of toxins, etc.

Photochemical processes are a type of chain reactions. They proceed in the presence of light: synthesis of hydrogen chloride, ozone synthesis in the upper layers of the atmosphere, process of decomposition of silver salts in photography, isomerization at visual reception, and the most considerable reaction photosynthesis. This is responsible for oxygen and carbon cycle in the nature.

**5. Catalysts and their mechanism of action.**

Catalysts are important regulators of chemical changes. These substances change the rate of the chemical reaction by formation of intermediate compounds with lower activation energy.

The catalysts don’t affect the equilibrium constant. The equilibrium comes faster at the presence of the catalyst as both forward and backward reactions are accelerated. The catalyst cannot change the reaction direction.

There are several theories of catalysis nowadays. The following theories reflect the main ideas about catalysis:

*Theory of intermediate complex formation*: А+К → АК, АК+В → АВ+К. The intermediate compounds are formed on the surface of the catalyst.

*Adsorption theory*. Catalytic activity is due to the ability of the catalyst to adsorb the reagents in the active centers.

*Multiplet theory*. This theory states on formation of the multiplet complex on the active center of the catalyst resulting in release of the energy necessary for splitting the old bonds.

Catalysis is positive when the rate of the reaction is accelerated, and negative if the reaction slows down. If acceleration takes place as a result of catalyst formation during the reaction, the reaction is called autocatalytic.

Catalysis can be homogeneous, heterogeneous or micro-heterogeneous.

**6. Enzyme catalysis, its peculiarities**

**and kinetics of enzymatic reaction.**

All biochemical reactions are catalytic in one-cellular or higher organisms. Enzymes play the role of catalysts. They can be simple and conjugated. Simple ones have only a protein structure, conjugated ones have non-protein components in addition to protein ones. The non-protein part may be a prosthetic group or a co-enzyme.

The size of enzyme molecules is closed to the colloidal particles size. They cannot be considered either homogeneous (which form a homogeneous system with the reacting substances) or heterogeneous (forming their own phase separated from the reacting system by a boundary). Enzymatic catalysis is micro-heterogeneous catalysis.

Peculiarities of enzymatic catalysis

1) High efficiency. Activation energy of biochemical processes 2-3 times less than usual chemical processes Ea, therefore enzymes act 10–3 – 10–6 times faster than non-biological catalysis. This effect is explained, first of all by the concentration factor. The rate of enzyme-catalyzed reaction depends on the concentration of substrate and enzyme. Concentration increases the reaction rate thousands times. It regulates the enzyme activity and so the metabolism. Secondly, enzymes possess an orientation effect, which also increases the rate. It consists of the presence of a stereospecific contact of an active enzyme center with the substrate. This increases sharply the probability of an effective collision, and causes the increase of pre-exponential multiplier A in Arrhenius equation. Thirdly, enzymes possess a polyfunctional effect, i.e. a substrate molecule is simultaneously influenced by several attacking groups of the enzyme.

2) Specificity. A definite enzyme catalyzes only one biological reaction under the given conditions.

3) Soft conditions of the reaction. Biochemical processes in living organisms are accomplished at comparatively low temperatures (36–42 oC), atmospheric pressure and within pH interval of the living organism.

**Kinetics and mechanism of enzymatic actions.**

As mentioned above, enzymes reduce the activation energy. An intermediate product forms between the metabolizing substance S (substrate) and the enzyme (E) – an activated complex (enzyme-substrate complex): S + E > [ES]

This complex is not a chemical compound. The bond that existed initially in the molecules has not disappeared and new chemical bonds have not formed yet. But deformity of electronic clouds of the atoms, which interact to form new bonds, has appeared. In the activated complex enzyme can stretch and weaken the former bonds. An enzyme exhibit a multi-point contact with the substrate that results inthe necessary orientation is achieved and the reacting groups become closer within the active center, which is created by a definite configuration of a protein molecule. According to E. Fisher, the molecule reacting with the enzyme enters this active center, like a key to a lock. The reaction converts from an intermolecular mode to an intramolecular one, which excludes entropic losses.

A high-energy barrier of the non-catalyzed process is broken into two lower ones, because the reacting particles are in close proximity and orientation is optimal

Еа

Еа

′

Еа

′′

S

P

ES

Free energy G

Reaction course

СS

*V*max

*V*

 a b

Fig.2 Enzymatic reaction.

а – energetic diagram of enzyme reaction;

b – dependence of enzyme reaction on the substrate concentration.

in the beginning of the reaction. As a result, the energetic diagram of the reaction has two maximums, corresponding to two different enzyme-substrate complexes and three minimums, corresponding to the substrate, intermediate and products (fig. 2a).

A characteristic feature of enzymatic catalysis is that the rate of enzyme catalyzed reaction increases up to a definite value (vmax). A typical graph of the enzymatic reaction rate vs the substrate concentration Cs (at CF – const) is shown in fig. 2b.

At low substrate concentrations the reaction is first-order with respect to substrate, at high – zero-order and the rate becomes maximal.

In 1913 Michaelis and Menten suggested a theory explaining this dependence. An enzyme process can be presented as:

*k*1 *k*3

 E+S → ES → E+P,

 *k*2

where E and S are enzyme and substrate, P – reaction product, *k*1 – constant of the rate of the intermediate formation, *k*2 – constant of the rate of its decomposition, k3 – constant of the rate of transition of the intermediate complex to reaction product and enzyme.

The rate of all stages of the reaction can be written as follows:

*v*1= *k*1[E][S]; *v*2= *k*2[ES]; *v*3= *k*3[ES]

At equilibrium state:

*v*1= *v*2 + *v*3; *k*1[E][S] = *k*2[ES] + *k*3[ES]

Solving this equation for ES and understanding that the primary rate of the product formation is proportional to concentration of the intermediate complex (*v*0=*k*3[ES]), we will find the expression for the rate of the enzyme reaction:

*v*=  *k3* ([E]∙[S])/(*km*+[S])

Or, using the value of maximum rate, that is the rate at which the enzyme completely exists as a complex [ES]: [E]0 = [ES], we will have:

*v*о= (*v*max∙[S])/(*km*+[S])

where *km*=( *k2*+ *k3*)/ *k1* – Michaelis constant. Its value depends on pH, temperature and the nature of the substrate. In kinetic investigations Michaelis constant is determined experimentally and *equals to the substrate concentration at which the reaction rate equals 1/2 of the maximum rate value*:

The kinetic constant k3 in the equation *v*max = k3[E]0 is called the number of enzyme cycles which shows *the number of the molecules of the substrate turned to the reaction product for a unit of time (second) when all enzymes are [ES] in complex form*. The number of cycles for the majority of enzymes is 0,5.104 s–1. But, for example, for carboanhydrase, one of the most active enzymes, the number of cycles is 0,6.105 s–1. This means that 10–6 M solution of carboanhydrase can catalyze production of 0,6 mol H2CO3 from CO2 and H2O per 1 second, i.e. *v*max=0,6mol/l s.

As it was mentioned above, at lower substrate concentrations the reaction proceeds as a first-order, at higher – zero and the rate becomes maximal. Therefore, for two borderline cases we can write:

*v*= (*v*max/ *km*)[S] – when [S] << Km;

*v* = *v*max – when [S] >> Km

The values of *Michaelis constant, maximum rate and number of cycles* are quantitative characteristics of the reaction for a definite enzyme-substrate system under definite conditions.

**7. Chemical equilibrium. Displacement**

**of chemical equilibrium. Le Chatelier’s principle.**

 All chemical reactions are reversible. As it was mentioned above, in any chemical reaction, collision of the particles results in the formation of an activated complex, which can turn to reaction products but also can decay to the initial reagents. Each stage of a reverse reaction is a conversion of the corresponding stage of the forward reaction.

It is possible to create such a conditions at which any reversible reaction can proceed only in one direction and, hence, will be irreversible. Reactions, which can proceed only in one direction call irreversible. Those that proceed in two opposite directions are reversible.

Let’s discuss the state of chemical equilibrium using the following reaction Н2 + I2 ↔ 2HI as an example. Two reactions, forward and reverse take place simultaneously in the mixture of H2, I2, HI. The rates of the forward and reverse reactions are described by the equations:

*V*forwared = *k*1[Н2] [I2], *V*reverse = k2 [НI]2

When the system reaches the state of chemical equilibrium, at which the rates of the forward and reverse reactions are equal, the following is true:

*k*1[Н2] [I2] = *k*2 [НI]2

It does not mean that there are different amounts of reagents and products in the system. The chemical equilibrium is dynamic in nature, while the thermodynamic equilibrium is static. It is necessary to keep in mind that there is nothing common between a reversible reaction and a thermodynamically reversible process. All real processes, including reversible chemical reactions, are thermodynamically irreversible.

The state of chemical equilibrium is characterized by equilibrium constant (K). It equals to the ratio of the rate constants of forward reaction and reverse (backward) reactions. This is the ratio of concentrations of products and reactants in the power of their stoichiometric coefficients when a reaction is at equilibrium. For the above reaction of HI production:

К = k1/k2 = [HI]2/[H2][I2].

Example.

What is the equilibrium constant for the reaction: СO + С12 = СОС12

if: *С*0 (С)= 0,28 mol/dm3; *C*0(С12) = 0,09 mol/dm3; [CO] = 0,2 mol/dm3

Solution. Keq = [COCl2]/[CO][Cl2]

The following concentrations were reacted СО: 0,28 – 0,2 = 0,08 mol/dm3, the amount of C12 and СОС12 was the similar (according to the reaction equation). Thus, [С12] = 0,09 – 0,08 = 0,01 mol/dm3, а [СОС12] = 0,08 mol/dm3.

Equilibrium constant, being the function of temperature only, can change within a wide range. What is more, *K*eq ≠ 0 і *K*eq ≠ ∞ because at chemical equilibrium partial pressure of any substance cannot be equal either 0 or infinity.

If *K*eq is close to 1 (e.g. 10–2 < *K*p < 102), the reaction is reversible. In this case we can create the initial concentrations of the reacting substances, which will ensure the course of the reaction in one direction or another. If chemical equilibrium constant differs from 1 greatly, it is impossible to create the initial concentrations of the reacting substances, when the reaction moves from right to left at Keq>>>1or from left to right at Keq<<<1. In this case the reaction is near-irreversible. Keq shows how much the reaction has advanced after equilibrium state had been achieved.

It is necessary to remember that equilibrium constant at a constant temperature depends only on the value of standard free energy, which is the thermodynamic state function. Hence, equilibrium constant is also a thermodynamic function depending only on the nature of the reacting substances and can be calculated using reference thermodynamic data: ln *K* = – ∆*G*0/*RT*.

Introduction or elimination one of the reagents at a constant temperature changes the concentration of the reacting substances, but chemical equilibrium constant remains unchanged.

For the reaction HHb + O2 = HHbO2 equilibrium constant at 310 K equals 1300, so the reaction shifts to the right. It is known that hemoglobin can bind with CO producing carboxyhemoglobin (HHbCO). Therefore, addition of CO to the system reduces hemoglobin concentration and results in destruction of oxyhemoglobin. The equilibrium of the reaction of hemoglobin with oxygen will shift to the left. Thus, the changes in the concentration of one substance present in the equilibrium system will cause the changes in all others substances.

The change in conditions (concentration, pressure, temperature) will affect an equilibrium. Le Chatelier’s proposed the following principle: when a stress is applied to a system at equilibrium, the system reacts in such a way to counteract the stress.

Thus, the changes of pressure influence the equilibrium of the reactions accompanied by changes in the volume. For gas systems, a change of pressure is equivalent to the change in the concentration. The process of ammonia synthesis N2 + 3H2 = 2NH3 takes place with volume reduction. If the pressure increases, the concentration of initial substances will increase in greater extent than concentration of products. The reaction will shifts to the side with fewer moles of gas molecules, i.e. to the right.

If the temperature is increased, the equilibrium will shift to the side of the endothermic process. If the temperature is decreased – exothermic.

Catalysts do not shift chemical equilibrium. They accelerate both forward and backward reactions. In this case an equilibrium will be achieved faster.

It is obvious that the equilibrium will shift in one direction, if one of the products is removed from the reaction. There is a very easy rule (Berthollet’s rule) that *chemical interaction in the solutions is almost irreversible if one of the products is gaseous, precipitates or poorly dissociated.*

For example:

NaHCO3 + HCl → NaCl + H2O + CO2↑

Ba(NO3)2 + K2SO4 → BaSO4↓ + 2KNO3

NaOH + HCl  → NaCl +H2O

The first reaction takes place in the stomach, reducing the excess of produced acid. The second reaction is used to make an X-ray contrast substance, barium sulfate. The third example is neutralization reaction producing water and salt. Thus, chemical equilibrium shift is important for biomedical practice.

The laws of preserving and shifting of dynamic equilibrium are true not only for chemical or physical chemical processes. They also have analogues in the living nature. Principle of adaptive reconstructions: any living system being affected reconstructs in such a way which reduces this interaction.

From this point of view, all reactions can be divided into the reactions, the course of which is determined by thermodynamic parameters, and those under kinetic control. For example, dipeptide synthesis in a living cell is characterized by the following: Gibbs’ energy – 17.2 kJ/mol, the power of equilibrium constant 10–3. This process is possible at the presence of external source of free energy that is thermodynamically controlled process. But due to the conjunction with ATP hydrolysis and participation of the enzyme this process is possible in a living cell.

**8. Heterogeneous equilibrium involving salts participation**

 **in the total homeostasis of the organism.**

The discussed cases refer to a homogeneous equilibrium when the process is accomplished in one phase. If the components of the chemical reaction are in different phases, these are heterogeneous processes. In this case the expression for equilibrium constant will include only those components, the concentration of which changes. A solid phase constantly contributes to chemical equilibrium and can be included to equilibrium constant.

An example of heterogeneous equilibrium is dissolution of poorly soluble substances.

Solubility is the amount of substance must be added to a given volume to form a saturated solution. Solubility (s) of the given substance equals its molar concentration in saturated solution and expressed in mol/L. It depends on the nature of the dissolved substance, temperature and ion concentration in the solution. When salts are dissolved in water, the ions are released into the solution. There is a dynamic heterogeneous equilibrium between the solid phase (precipitation) and ions of the electrolyte:

СаSO4 (s.) ↔ Ca2+ + SO42-

The equilibrium constant for this process is:

Ksp =[Ca2+][ SO42-] / [СаSO4]s.

then: [Са2+][SO42–] = [CaSO4]s. · Ksp  = const.

In a saturated solution of a poorly dissolved electrolyte, the product of equilibrium concentration of ions in the power of stoichiometric coefficients is a constant value at the given temperature. It calls the solubility product (Ksp).

Ksp characterizes the ability of the electrolyte to dissolve. For some poorly dissolved salts SP values are given in the table:

|  |  |  |  |
| --- | --- | --- | --- |
| Salt | Ksp | Salt | Ksp |
| AgCl | 1,8·10–10 | Hg | 1,6·10–52 |
| AgBr | 5,3·10–13 | Mg3(PO4)2 | 1,0·10–13 |
| Ag | 8.3·10–17 | Ca3(PO4)2 | 2,0·10–29 |
| BaSО4 | 1,1·10–10 | CaHPO4 | 2,7·10–7 |
| Pb | 2,5·10–27 | Ca3(OH)(PO4)3 | 1,6·10–58 |

Solubility of any soluble electrolyte AxBy (S, mol/L) can be calculated using the following formula:

S =

The change in ion heterogeneous equilibrium is accomplished in accordance to Le Chatelier’s principle. Namely, the changes in the concentration of similar ions can cause the changes in the electrolyte solubility, as the product of solubility is a constant value. Therefore,

a) precipitation is formed if the ion product of its real ions concentrations in the solution (PI) with the account of coefficients in the dissociation equation of electrolyte is more than Ksp for the given temperature;

b) precipitation will dissolve if PI  SP. This can be achieved by the dilution of solution or binding one of the ions to a more stable compound. E.g., a poorly soluble salt of BaCO3 is easily dissolved in hydrochloric acid due to the sharp decrease in concentration of carbonate ion, which decomposes into carbon dioxide and leaves the reaction:

ВаСО3+ 2HCl = BaCl2 + CO2 + H2O

If the mixture of ions is present in the solution, the compound with lesser value of solubility product will precipitate first. According to Le Chatelier’s principle, when a similar ion is added, salt solubility will decrease. Thus, the solubility of AgCl in water is higher than in NaCl solution.

Salt solubility also depends on addition of the electrolytes, which do not have common ions with the solute. This usually improves solubility. The cause of this phenomenon, called salt effect, is due to reduction of activity coefficients of ions of the poorly dissolved salt due to increase of the inter-ion interaction force.

In the human organism, the most important heterogenic processes accomplished with the participation of inorganic ions are associated with formation and dissolution of the mineral base of the bone tissue.

Its main component is hydroxyapatite, calcium hydroxophosphate Ca2(OH)(PO4)3. The bone tissue formation can be written as:

5Са2++ ЗНРО42–+ НОН ↔ Ca5 (OH)(PO4)3 + 4Н+

The equation shows that in acidic medium the bone tissue is destroyed. Bone tissue formation begins from the blood plasma containing the necessary calcium cations as well as dihydro- and hydrophosphate ions. It also contains cations and anions providing the acid-base equilibrium. Calcium cation concentration in the blood plasma is 2,510–3 mol/L, but only its part 110–3 mol/L is in ionized form. Plasma hydrophosphate ion concentration is 2,910–4 mol/L.

It is evident from the table that these concentrations are sufficient for CaHPO4 precipitation (Ksp = 2,7.10–7). As the solution is only slightly oversaturated, crystallization in the plasma results in formation of small amounts of calcium hydrophosphate crystals.

In the bone cells washed by the blood (and microcrystals of calcium hydrophosphate) phosphate ion concentration increases due to enzyme hydrolysis of the phosphoric acid esters. This creates the conditions for greater oversaturation of calcium phosphate solution, which favours the transformation of calcium hydrophosphate to hydroxyapatite. Weak basic medium of the blood plasma also benefits this process. This results in dynamic equilibrium, which is determined by three factors: concentration of phosphate ions and calcium cations as well as the medium acidity. This equilibrium results in daily exchange of 700–800 mg of calcium in the bone tissue.

An increased concentration of free calcium ions and hydrophosphates in the plasma results in precipitation of hydroxyapatite in the bone tissue. Their reduction causes bone dissolution, which can be seen in children with rickets, pregnant, when their bone material is used to form the fetus skeleton, in astronauts due to disorders in activity of enzymes responsible for calcium metabolism.

Increasing the medium acidity also causes hydroxyapatite dissolution. The influence of an acidic medium on the tooth tissue, mineral base of which is composed of hydroxyapatite, provides clear evidence. Anaerobic microorganisms in the oral cavity produce organic acids, which dissolve the tooth hydroxyapatite. This is the cause of caries. Even in the presence of small amounts of protons the bone starts to dissolve giving calcium cations:

Са5(РО4)3OН + 2Н+ → Са4Н(РО4)3 + Са2+ + Н2О.

Further acidification results in complete decay:

Са5(РО4)3OН + 7Н+ → 3Н2РО4 + 5Са2+ + Н2О.

In addition to hydroxyapatite other ions can precipitate in the bone tissue. In the first place, this is fluoride ion. The change of a hydroxyl group to fluoride in the hydroxyapatite results in the formation of less soluble and more mechanically stable fluorapatite Ca5F(PO4)3. The presence of microquantity of fluorapatite in the bone tissue makes it firm. Fluorapatite is especially important as a firm acid–fast covering of the tooth – tooth enamel. The necessity to add fluoride to toothpastes is evident.

Other metals of group 2 (magnesium, beryllium, strontium) can replace calcium in the bone tissue. The presence of the magnesium ions is natural and this can be easily explained by better solubility of magnesium phosphate compared to calcium salts, but the presence of the others is not desirable. Presences of strontium ions in the bone tissue make it fragile (strontium rickets). Radioactive strontium-90 is especially dangerous isotope in case of its presence in the bone tissue. It irradiates the bone marrow and impairs hematopoietic processes. Even small amounts of beryllium in bones cause berylliosis (osteomalacia) – a bone softening. These are typical examples of microelementosis.

Other poorly solved compounds can precipitate in some organs of the human body. Thus, the deposition of calcium carbonate on the vascular walls cause calcinosis.

Urolithiasis is characterized by formation and precipitation of various salts: calcium urate (salt of uric acid, an intermediate substance of nitrogen metabolism), poorly solved calcium phosphates and oxalates. Calculi are formed from colloid particles as the result of coagulation process (see “Disperse systems”). High pH’s in urine also promote their precipitation. One of the causes of death in ethylene glycol poisoning is obstruction of the vessels with poorly soluble calcium oxalate, which precipitates due to the sharp increase in oxalic acid concentration (product of ethylene glycol oxidation).

Cholelithiasis is associated with formation of calcium carbonate as well as calcium bilirubinate.

Treatment of these diseases is based on the effect of the drugs dissolving the calculi, which is achieved using chemicals (chemotherapy) and mineral water.

It is necessary to mention the low solubility of sulfides of a number of d-block metals (mercury, cadmium, and thallium) as well as lead (II) and arsenic (III) cations. The organic substances containing a thiol group (-SH), primarily proteins and enzymes, are firmly bound to such cations. This results in denaturation of proteins and loss of enzymatic activity. It means that these ions are highly toxic. Thus, soluble sulfides capable of reacting with such cations with production of poorly dissolved sulfides can be the simplest antidotes in case of heavy metal poisoning. A so-called hydrogen sulfide drink (sodium sulfide) is used in this case:

Hg2+ + S2– → HgS↓

Organic substances containing thiol group form a large group of antidotes.

Consequently, a heterogenic equilibrium together with the other types of balanced biological processes makes a contribution to the general organism homeostasis.

Precipitation reactions are widely used in clinical, hygienic, and pharmaceutical analysis. They can be used to determine chloride-ion concentration in the blood plasma, urine, gastric juice, and to analyze toxic ions, etc.

Thus, numerous chemical transformations in the living systems are maintained due to a number of equilibrium systems. Understanding the nature of a great number of pathological states and diseases or the consequences of these diseases requires complex analysis of chemical causes from the perspective of impairment in the function of these equilibrium systems. This is true for any anemia associated with impairment of metal-ligand metabolism and radiation exposure causing disorders in the acid-base blood state, for the cases of poisoning with heavy metals, which affects heterogenic equilibrium in the biological environment, for infection diseases such as cholera, the heaviest consequence of which is impairment of water-electrolyte equilibrium in the organism.

- list of laboratory works:

During the classes students perform laboratory experiments “The influence of sodium thiosulfate concentration on the rate of thiosulphuric acid decomposition” and Determination of the temperature coefficient for the reaction of thiosulfuric acid decomposition.

Laboratory work 1. The influence of sodium thiosulfate concentration on the rate of thiosulphuric acid decomposition

Algorithm of the laboratory work

1. Fill tree burettes with following solutions: sodium thiosulfate, sulfuric acid and water.

2. Take two test tubes; pour sodium thiosulfate and water from burettes in one test tube, and sulfuric acid in the other tube. Then combine the contents of test tubes, start a stopwatch and determine the time of the turbidity appearance in the solution (formation opalescent sulfur sediment). Repeat the procedure 5 tames changing volumes of reagents according to the table 1:

The conditional reaction rate (V) is proportional to 1/τ, hence, V1 = 1/τ1, V2 = 1/τ2 , etc.

3. Calculate the salt concentration obtained after dilution: С = (СNa2S2O4VNa2S2O4)/5.

Table 1

|  |  |  |  |
| --- | --- | --- | --- |
| № | Volume, ml | Obtained concentration of Na2S2O4, mol/L | Time of turbidity appearance, sec. |
| H2SO4 | H2O | Na2S2O4 |
| 1 | 2,5 | 2,0 | 0,5 |  |  |
| 2 | 2,5 | 1,5 | 1,0 |  |  |
| 3 | 2,5 | 1,0 | 1,5 |  |  |
| 4 | 2,5 | 0,5 | 2,0 |  |  |
| 5 | 2,5 | 0,0 | 2,5 |  |  |

Plot the graph: V = ·Csalt,make conclusions about the obtained dependence.

Laboratory work 2. Determination of the temperature coefficient for the reaction of thiosulfuric acid decomposition

The algorithm of the laboratory work

1. Pour from burettes 2 cm3 of sodium thiosulfate into one test tube and 2 cm3 of sulfuric acid into another one.

2. Place test tubes into a beaker filled with tap water. Measure the water temperature using a thermometer after 2-3 min.

3. Combine the contents of test tubes (into one), leaving it in a beaker and start a stopwatch to note the time of the opalescence appearance.

All further experiments are carried out with the same volumes of reagents, but the water temperature should be increased by 10o each time. Conduct the experiment 4 times. Record the data in the table, and calculate the temperature coefficient according to the formula: γ = VT+10 / VT.

Table 2

|  |  |  |  |
| --- | --- | --- | --- |
| Temperature, К | Time, s | rate, s-1 | Temperaturecoefficient, γ |
|  |  |  |  |

Calculate the average value of the temperature coefficient of the reaction. Fill the rapport; record your observations and conclusions into “Work book”.

- List of practical skills.

After studying the subject student should be able to write kinetic equations of simple reactions; determine the rate and direction of the chemical reaction depending on the concentration, temperature and pressure; define the solubility of electrolyte according to the solubility product.

8. **Tasks for knowledge control.**

1. Dependence of enzymatic reaction on temperature (T) has optimum temperature range because of:

 А: increase of the reaction rate with the increasing of Т;

 В: increasing the number of effective collisions with an increase in Т;

 С: loss of native structure of the enzyme at high Т.

2. What is the order of enzymatic reactions at high concentration of substrate?

А: zero; В: first; С: second; D: third.

3. 3. In what direction will shift the equilibrium of the following reversible reaction 2PbS(s) + 3O2  2PbS(s) + 2SO(g) if pressure was increased?

А: Towards the formation of products of the reaction;

В: Towards the formation of reagents of the reaction;

С: The equilibrium does not change.

Answers: 1 - С; 2 - А; 3 - А.

9. **Recommendations for the presentation of the results.**

Algorithms for the solving of educational problems of class work and self-work should be recorded in the workbook. Complete a protocol of the laboratory work, write down the conclusions about the effect

10. **Suggested readings**

1. V. Kalibabchuk, V. Halinska, L. Hryschenko, S. Hodzynski, T. Ovsyanikova, V. Samarski. Medical chemistry. –Kyiv AUS Medicine Publishing, 2010, −224p.

**Навчальне видання**

**Кінетика біохімічних реакцій. Хімічна рівновага. Добуток розчінності.**

**Методичні вказівки для самостійної роботи студентів 1-го курсу**

 **з медичної хімії**

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