BIOLOGICAL AND MEDICAL SIGNIFICANCE OF CHEMICAL ELEMENTS

Irena Kostova

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Biological and Medical Significance of Chemical Elements

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PREFACE

This book attempts to highlight the current knowledge of the biological role of chemical elements of the periodic table in organisms' life. The first part covers the occurrence in the body and the environment, the chemical properties, and biological functions of all the chemical elements of the periodic table in detail. The second part focuses on the effects of chemical elements on human health. It describes the beneficial effects of the incorporation of chemical elements in drugs including the latest trends in the development of new pharmaceuticals. Essential elements useful in diagnosis and therapyand notable features in their chemistry related to their biological activity are emphasized.

The book deliberates the importance of chemical elements in the lifecycle from both chemical and biological perspective and their role in biological pathways. The biochemistry of the essential non-metals oxygen, nitrogen, carbon, hydrogen, sulfur, and phosphorus is well studied, but all other elements in the periodic table have multiple functions and a serious influence on life processes despite their lower amounts in the body. Their biological role is of great importance and should be considered, especially the functions of the biogenic metals Na, K, Mg, Ca, Cu, Zn, Fe, Co, Mn, and Mo. Many other chemical elements, though non-essential, are present in biological systems and some of them are in higher amounts than some essential ones. However, non-essential elements are bioactive, having either beneficial (healthy) or harmful (toxic) effects depending on concentration. Each element is buffered in a certain range of quantities in order to minimize interference with the other elements or biomolecules and to obtain its required specificity of action. Many transition and trace metal ions and some biometalloids are constituents of naturally occurring metal-based biomolecules with fundamental biological roles in enzyme catalysis, in the structures and interactions of macromolecules of the body, in the regulation of metabolic pathways, in biomineralization processes, etc.

A periodic table of the elements, required for life, commonly includes all the elements observed in life functions for human, animal, and plant health. Although the journey through the periodic table illustrates the specific functions of biogenic elements, there are some elements whose functions in living systems are poorly understood. Research demonstrates that we need to know more about all elements and address their functions, even those that are considered non-essential. Inorganic compounds have been used in medicine for many centuries, but often only in an empirical way with little or no understanding of the molecular basis of their mechanisms of action and in many cases with little experience in designing targeted biologically active compounds. Diagnostic and therapeutic nuclear medicine uses many elements representing a large part of the periodic table. For many of them, it is necessary to find out in more detail the negative side effects. The information about the complex pathways of biological processes where various elements of the periodic table play important roles will help in understanding various diseases and treatment options.

Moreover, the duality that exists in the biology of the elements in the groups of the periodic table is also of great importance for the protection against the biochemical mimicry and competition of chemically similar elements. Conditions of overload and deficiency pose a risk of accumulating, toxicity or various disease obstructions. Many drug molecules and metal-based complexes have been discovered in recent years for diagnostic and therapeutic purposes, which also highpoint the importance of metal ions and the synergistic functions of elements in humans and other organisms. Many exciting challenges remain in this field. The aim of the current book is to give a comprehensive, authoritative, critical, and appealing account of general interest to the chemistry community.

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CHAPTER 1

Occurrence and Classification of Chemical Elements

OCCURRENCE OF CHEMICAL ELEMENTS IN NATURE

The study of the influence of various chemical elements on the body of animals and humans, as well as the study of chemical elements as permanent components of tissues and biological fluids of living organisms began in the second half of the XIX century. Since then, a lot of scientific literature has appeared concerning the distribution of chemical elements and their biological role.

The chemical elements found in nature are elements with atomic numbers from 1 through 98, however around ten of them occur in extremely small quantities, especially the elements with atomic numbers 93-98. Although many elements of the periodic table occur in nature, they might not exist in pure or native form [1, 2]. The only pure native elements in nature are the noble gases, noble metals (gold, silver), and carbon, nitrogen, and oxygen from nonmetals. Most of the elements that occur naturally are not in pure form and can be found in their chemical compounds.

Studying the geochemical transformations in the earth's crust, it has been established that the changes occurring in the upper layers of the earth's crust have a certain effect on the chemical composition of living organisms and the development of bioreactions in them [3 - 5]. Living organisms, in turn, cause regular migrations of chemical elements in nature. The science that studies the role of living organisms in the geochemical processes of migration, distribution, scattering, and concentration of chemical elements in the shells of the biosphere is called biogeochemistry.

The biosphere is a shell of the Earth, containing the entire set of living organisms and that part of the planet's matter that is in continuous exchange with these organisms. The biosphere covers the lower part of the atmosphere, the hydrosphere, and the upper part of the lithosphere (up to a depth of 5 km).

The atmosphere is the lightest shell of the Earth, which borders outer space, through the atmosphere, there is an exchange of matter and energy with the cosmos. The atmosphere has high mobility, variability of its constituent

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components, and uniqueness of physical and chemical processes. The thermal regime of the Earth's surface is determined by the state of the atmosphere. The ozone layer in the atmosphere protects our planet from the effects of ultraviolet radiation from the Sun. As a result of the activity of living organisms, geochemical phenomena, and human economic activity, the composition of the atmosphere is in a state of dynamic equilibrium. The main components of the atmosphere are nitrogen (78%), oxygen (21%), argon (0.9%), and carbon dioxide (0.04%) - in the surface layer [1 - 5]. The atmosphere includes the troposphere, stratosphere, and ionosphere. The troposphere and stratosphere are usually combined into the lower layers of the atmosphere (height 9-17 km), which differ significantly in composition from the upper layers (ionosphere). In the lower layers of the atmosphere, about 80% of the gases and all water vapor are concentrated.

The troposphere is a non-equilibrium chemically active system. As a result of geological and biological processes and human activities, most of the gaseous impurities released from the Earth's surface into the troposphere are in reduced form or in the form of some oxides: NO, NO_2, H_2S, NH_3, CO, CH_4, SO_2, *etc*. Impurities returned to the Earth's surface turn into compounds with a high degree of oxidation - H_2SO_4, HNO_3, sulfates, nitrates, CO_2, *etc*. Thus, the troposphere plays the role of a global oxidative reservoir on the planet.

The hydrosphere is the water shell of the Earth. Water penetrates everywhere into various natural formations, and even the purest atmospheric water contains 10-50 mg/l soluble substances. In the hydrosphere, 96.54% of the mass is oxygen and hydrogen, and 2.95% is chlorine and sodium [1 - 5].

The lithosphere is the outer solid shell of the Earth, consisting of sedimentary and igneous rocks. The surface layer of the lithosphere, in which the interaction of living matter with mineral (inorganic) matter occurs, is the soil. The remains of organisms after decomposition passes into the humus (fertile part of the soil). In the lithosphere, oxygen is the most common (47% of its mass), followed by silicon (29.5%), aluminum (8.05%), iron (4.65%), calcium (2.96%), sodium (2.50%), potassium (2.50%) and magnesium (1.65%). These eight elements account for more than 99% of the mass of the lithosphere [1 - 6]. In nature, there is always a cycle of chemical elements, where living organisms play a large role. Living organisms continuously cause the movement of chemical elements - this is their geochemical function. Any movement of chemical elements in the Earth's crust is called the migration of chemical elements. When this migration occurs with the participation of living organisms, it is called biogenic migration. Among the most important tasks of biogeochemistry are the exchange of substances between living matter and matter of the planet, biogenic migration of chemical elements in the biosphere, biogenic properties of elements, biogenic concentrations of chemical elements that determine the normal conditions for the development of organisms [6].

It is estimated that 98% of the body mass of men is made up of nine nonmetallic elements. In the average chemical composition of a living being, the part of oxygen, carbon, hydrogen, and nitrogen, makes up most of its mass [7]. The important feature of these chemical elements is their greater reactivity. These four elements have one property: they easily form covalent bonds typical for biosystems. In addition, carbon, nitrogen, and oxygen form single and double bonds, thanks to which they can give a wide variety of chemical compounds. Carbon atoms are also capable of forming triple bonds with both other carbon atoms and nitrogen atoms. This explains the great diversity of carbon compounds in nature. Phosphorus, sulfur, chlorine, bromine, iodine, calcium, sodium, potassium, magnesium, *etc*. are also strongly captured and accumulated by organisms. Approximate percentages by weight of some chemical elements in the hydrosphere, lithosphere and in the human body are given in Table **1**.

Table 1. Percentages of biogenic elements in the hydrosphere, lithosphere, and in the human body and their biological importance.

Chemical element	Hydrosphere	Lithosphere	Human body	Biological importance
Oxygen	85.82	47.20	62.40	O plays a crucial role in respiration, immune function, and photosynthesis in living organisms. H forms H-bonds, crucial for the life-supporting properties of water and the operation of enzymes; controls protein folding, and opening of active sites in hydrophilic and hydrophobic environments. N - the essential constituent of proteins, enzymes, DNA, RNA; N-fixation by plants is the key reaction in the nitrogen cycle; N-based biocompounds. C plays a key role in the formation of organic molecules; CO_2 in photosynthesis; respiration supplies O_2 for the conversion of carbohydrates and other organic compounds back to CO_2. P creates a bridge between sugar units in DNA and RNA for cell replication; ATP - the major source of energy in all biological processes. S - important constituents of plant and animal proteins holding amino acids - cysteine, cystine, methionine involved in metabolic reactions.
Hydrogen	10.72	0.15	9.80	
Nitrogen	$1 \cdot 10^{-5}$	0.01	3.10	
Carbon	$2 \cdot 10^{-3}$	0.10	21.15	
Phosphorus	$5 \cdot 10^{-6}$	0.08	0.95	
Sulfur	0.09	0.09	0.25	
Chlorine	1.89	0.045	0.15	
Calcium	0.04	3.60	1.50	
Sodium	1.06	2.64	0.15	
Potassium	0.04	2.60	0.35	
Magnesium	0.14	2.10	0.05	

CHAPTER 2

Biological Functions of Elements of Main Groups

GENERAL CHARACTERISTICS OF s-ELEMENTS AND THEIR COMPOUNDS

s-Elements are placed in IA and IIA groups of the periodic table (except for helium, which is in the VIIIA group). At the external electronic level, they have one or two electrons for s^1- and s^2-elements that their atoms give up easily, producing one- and two-charged cations. As the amount of valence electrons increases at the energy level, the ionization energy of atoms increases (ionization energy is the energy needed to separate the least bound electron from an atom), and consequently, the reducing properties of atoms decrease. Therefore, s^2-elements are weaker reducing agents than s^1-elements. In the group, the reducing activity of s-elements increases from the top to the bottom, as the number of electron layers in atoms increases and the ionization energy decreases in the same direction [3, 4].

The radii of ions in the subgroups from the top to the bottom increase, and in the period moving from s^1 to s^2-elements, the radii decrease. The regularities of the radius changes of s-element ions in the group and period and the structure of their electron shells affect the nature of the relationship between the anions and cations of s-elements and the solubility of their salts. Since the ions of s-elements have a stable electron configuration such as that of inert gases, they have a small ability to polarize and are themselves weak polarizers. Polarization is the displacement of the electron cloud of an anion (polarized anion) under the influence of a positive charge of the ion.

The polarizing capacity (ρ) of the ion *(i.e.*, its ability to deform the electron cloud of the anion) depends on the charge of the cation and its size is proportional to the charge density on the ion: ρ is equal to the charge of the cation divided by the radius of the cation. From this relationship, it can be seen that the greater the charge of the ion and the smaller its radius, the greater the polarizing effect of the ion and the less it is capable of polarization.

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The polarizing power of cations of s-elements decreases moving from Li^+ to Cs^+ in the IA group. Due to the high polarizing power of the Li^+ cation, lithium compounds have the least pronounced ionic character compared to the same type of compounds of other alkali metals. With an increase in the polarizing properties of cations, the bond strength with the anion rises and the solubility of the compounds decreases. If the s^1-elements have the lowest charge (+1) and the greatest radius in their period, so cations do not polarize themselves and have a low polarizing ability. Most of their salts are water-soluble due to the high polarity of the bond, which is close to ionic, because possible precipitation can be formed only with large, easily polarized anions [3, 4].

Sodium and potassium are vital biogenic metals and their biochemical behavior is similar, though Na^+ and K^+ cations are different based on their hydration enthalpies and ionic radius. In cell membranes, the specific protein pumps for these cations (Na/K ATPases) maintain their concentration gradient in the plasma and in the intracellular matrix which helps in generating the electro-potential gradients important for the nerve impulses.

When moving to cations of s^2-elements, the polarizing properties are enhanced as the charge (+2) increases and the radius of the ion decreases. This leads to an increase in the bond strength (the bond approaches covalent), and the solubility of the salts decreases. Cations of s^2-elements form insoluble precipitates of chromates, carbonates, sulfates, oxalates, *etc.,* which are of analytical importance and are used to separate and detect individual cations of s^2-elements.

Like sodium and potassium, magnesium and calcium are also plentiful elements in the body [7 - 10]. Bones, teeth, skeletal muscles, and soft tissues hold around 95% of the total Ca^{2+} and Mg^{2+} ions existing in the body. Mg^{2+} ion, representing 1% in extracellular fluid, acts as a vital cofactor activating many enzymes involved in transcription, replication, and translation processes. Both Ca^{2+} and Mg^{2+} ions participate in the stabilization of nucleic acids, lipid membranes and in the regulation of the contractions of skeletal and cardiac muscles. Dysregulation of calcium and magnesium leads to many disease conditions including gastrointestinal, coronary heart disease, diabetes, osteoporosis, and neurological indications.

In water, the cations of s-elements are hydrated and form aqua-complexes ($[Ca(H_2O)_6]^{2+}$) due to the electrostatic attraction of water dipole molecules. Since the electron shell of the ions of s-elements has a stable configuration of inert gases and ligands (water molecules) have a little effect on the state of electrons, all of them in aqueous solutions are colorless [3, 4].

Looking at the dependence of hydration enthalpies of the cations of s-elements on their size, it can be seen that with an increase in the charge of ions, the energy of their hydration increases, and with an increase in the size of the ions, it decreases.

Ions of s-elements in aqueous solutions form coordination compounds with inorganic and organic ligands, for example, with 8-oxyquinoline (LiOx, $MgOx_2$, $BaOx_2$) and with ammonia $[Mg(NH_3)_4]Cl_2$. Nevertheless, the stability of these complexes is small, since s-elements form a bond with the ligands, which is approaching the ionic bond. The least stability of complex compounds is observed in cations with a large radius and a small charge (s^1-elements). In the cations of s^2-elements with a decrease in radius and an increase in charge, the stability of the complexes increases.

The variation in the radius of the ion has a great influence on its basic properties. Hydroxides of s-element cations have pronounced basic properties (except for $Be(OH)_2$), which are explained by the fragility of the ionic bond E-OH. That is why s-elements are called alkaline and alkaline earth metals. The basic properties of hydroxides increase with an increase in the ion radius, since this weakens the mutual attraction of metal and hydroxide ions, which facilitates the process of ionization of the compound [3, 4]. Therefore, in the group, the basic character of s-element hydroxides increases from the top to the bottom (for example, from LiOH to CsOH), and in the period, it increases with the transition from s^2- to s^1-element. Thus, in the second period, LiOH is a strong base, $Be(OH)_2$ is amphoteric; in the third period, NaOH is a strong base; $Mg(OH)_2$ is a medium-strength base; in the fourth period, KOH is a strong base, $Ca(OH)_2$ is a strong base with less pronounced basic properties than that of KOH.

The solubility of s-element hydroxides is also associated with the change in the radius of the ion. With an increase in the polarizing capacity of the cation, the bond strength of the ion with the hydroxide anion increases and the solubility of the base decreases. Therefore, the hydroxide of the s^2-element cation has a lower solubility than the hydroxide of the cation of s^1-elements of the same period.

Salts of s-elements undergo hydrolysis when the salt is obtained by a strong base (alkaline and alkaline earth metals) and a weak acid. When such a salt is dissolved in water, the cations undergo strong hydration and the salt completely dissociates. The resulting anions of a weak acid, being a strong base, are protonated by water molecules, forming a weak acid and hydroxide ions:

$A^- + HOH \rightleftarrows HA + OH^-$

CHAPTER 3

Biological Functions of d- and f- Block Elements

GENERAL CHARACTERISTICS OF d-ELEMENTS AND THEIR COMPOUNDS

In the periodic table of elements, there are currently 40 d-elements: each of the fourth, fifth, sixth, and seventh periods contains 10 d-elements. They are located between s- and p-elements.

d-Elements are in the group the trace microelements [11 - 13]. Transition metals have some common features:

1. d-elements are rather common in nature and thus available for absorption from the soil;
2. d-elements have high affinity to various donor atoms;
3. d-elements have various stable oxidation states and easily change their oxidation states.

These microelements take part in the most important life processes:

1. Enzymatic catalysis of synthetic reactions and cellular energy processes;
2. Electron transfer, transfer of ions, biomolecules, and molecular enzymes;
3. Regulating the activity of cellular mechanisms and biosystems.

Free ions of transition metals cannot exist in the organism. In biochemical interactions, most often d-elements participate in the form of metal-based bioinorganic complexes [3,11-13].

A characteristic feature of d-elements is that in their atoms, the orbitals are filled not with the outer shell (as in s- and p-elements), but with the pre-external shell. In d-elements, the valence orbitals are the energetically close nine orbitals: one ns-orbital, three np-orbitals, and five (n - 1)d-orbitals.

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At the external level, the atoms of d-elements usually have two s^2 electrons. However, nine d-elements (Nb, Rh, Cr, Mo, Ru, Pt, Cu, Ag and Au) have a half-filled 4s subshell. In the palladium atom, there is a “double dip”, and its outer level does not contain electrons. This structure of the electron configuration of the atoms of d-elements determines a number of their common properties [3,4,11-13]. All d-elements are metals, but their metallic properties are less pronounced than those of s-elements. In each large period, d-elements form families of 10 d-elements consisting of two subfamilies (s^2d^1 - s^2d^5 and s^2d^6 - s^2d^{10}).

d-Elements are characterized by a large set of oxidation states and, as a consequence, changes in acid-base and redox properties within wide limits. Since part of the valence electrons reside in s-orbitals, the lower oxidation state exhibited by them is usually +2. The exceptions are elements whose ions E^{+3} and E^+ have stable electron configurations d^0, d^5 and d^{10}, such as Sc^{+3}, Fe^{+3}, Cr^+, Cu^+, Ag^+, Au^+. Compounds in which d-elements are in their lowest oxidation state form ionic crystals, exhibit basic properties in chemical interactions and are, in general, strong reducers [4,9-13]. All d-elements, except for Zn, Cd, Sc, Y, and Ag, exhibit variable oxidation states. For almost all d-elements, the oxidation states of +2 and +3 are possible.

d-Elements from IIIB to VIIB groups in the higher oxidation states are comparable in properties to the corresponding p-elements. Thus, in the higher oxidation states, Mn(VII) and Cl(VII) are electron analogues. The resemblance of their electronic configurations (s^2p^5) leads to similar properties of Mn(VII) and Cl(VII) compounds. Mn_2O_7 and Cl_2O_7 under standard conditions are unstable liquids, anhydrides of strong acids with the general formula HEO_4. In the lower oxidation states, Mn and Cl have different electronic structures, which causes a difference in the chemical properties of their compounds [3,4,9-13]. Cl_2O is a gaseous compound, an anhydride of HClO, while MnO is a solid crystalline substance of a basic nature. The similar properties of d-elements with those of the main groups elements is fully demonstrated in the elements of the III groups ns^2np^1 and $(n-1)d^1ns^2$. With increasing the number of the group, this similarity decreases. Elements of the VIIIA group are gases, these of VIIIB are metals. The similarity is also typical for the first and second groups.

From a chemical point of view, d-elements are characterized by three main features: a tendency to exhibit oxidation-reduction properties; acid-base and amphoteric properties; high ability to complexation reactions.

TENDENCY TO EXHIBIT OXIDATION-REDUCTION PROPERTIES

All d-elements, like all metals, are reducing agents. Their reducing capacity is determined both by the structure of the electronic configurations and the size of ions. In the period with the increasing of Z, the reducing properties of metals decrease, reaching a minimum in the elements of group IB. Heavy metals of VIIIB and IB groups are termed noble for their inertness. Due to the negative values of the standard electrode potential, all d-elements, except copper, must dissolve in diluted solutions of acid with the release of hydrogen [3,4,11-13].

Metals with negative potentials are oxidized in the air; metals with positive potentials are oxidized much more slowly or practically not oxidized at all (Pt, Au).

Compounds of d-elements in their highest oxidation state have strong oxidative properties [11 - 13]. For example, chromium(VI) compounds are strong oxidizing agents and in oxidation-reduction processes pass into chromium(III) derivatives in acidic and alkaline environments:

$Cr_2O_7^{2-} + 14H^+ + 6\bar{e} \rightleftarrows 2Cr^{3+} + 7H_2O$

$CrO_4^{2-} + 4H_2O + 3\bar{e} \rightleftarrows Cr(OH)_3 + 5OH^-$

The greatest oxidative activity of chromium(VI) compounds is observed in acidic solutions.

Chromate ions CrO_4^{2-} are able to pass into dichromate ions $Cr_2O_7^{2-}$ and vice versa:

$2CrO_4^{2-} + 2H^+ \rightleftarrows H_2O + Cr_2O_7^{2-}$

$Cr_2O_7^{2-} + 2OH^- \rightleftarrows H2O + 2CrO_4^{2-}$

Chromates and dichromates have the same oxidation state of chromium equal to +6, but dichromate ions $Cr_2O_7^{2-}$ exist in an acidic environment, and chromate ions CrO_4^{2-} in an alkaline.

Strong oxidizing properties are also possessed by the salts of $HMnO_4$, permanganate salts. The most widely used is $KMnO_4$. Depending on pH, the reduction of permanganates can occur with the formation of various final products [4,11-13]. In an acidic medium, the reduction reaches manganese ions Mn^{2+}, in a neutral environment, the final product is usually the hydrated manganese oxide MnO_2, and in a highly alkaline medium, a fragile manganate MnO_4^{2-} is formed:

$2KMnO_4 + 5Na_2SO_3 + 3H_2SO_4 = 2MnSO_4 + 5Na_2SO_4 + K_2SO_4 + 3H_2O$

$2KMnO_4 + 3Na_2SO_3 + H_2O = 2MnO_2 + 3Na_2SO_4 + 2KOH$

$2KMnO_4 + Na_2SO_3 + 2KOH = 2K_2MnO_4 + Na_2SO_4 + H_2O$

CHAPTER 4

Application of Main Group Elements and Their Compounds in Medicine

THE USE OF S-ELEMENTS AND THEIR COMPOUNDS IN MEDICINE

Hydrogen

In medical practice, distilled water is used to prepare solutions and water for injection (a pyrogenic). A 30% hydrogen peroxide solution is used for the treatment of purulent wounds [22]. The 3% solution of hydrogen peroxide is used as a disinfectant for wound washing and rinsing in inflammatory diseases of the mucous membranes (stomatitis, sore throats), for the treatment of purulent wounds, stopping nosebleeds, *etc.*

Even though most of the naturally occurring hydrogen is protium ^1H (99.9885%), with a small quantity of the heavier isotope deuterium ^2H (0.0115%) in almost everything people consume and drink. The deceleration of biochemical reactions including the heavier isotopes of elements has been studied [327]. Organisms can integrate lighter isotopes favorably, which may have significance for evolution processes [328]. Deuterium ^2H is widely used in the pharmaceutical industry [329]. In medicine, the isotope of hydrogen (deuterium) is used as a label in studies of the pharmacokinetics of drugs [16, 329]. Radioactive isotope tritium ^3H with a half-life of 12.3 years is used in radioisotope diagnostics as a radiotracer, being a $\beta-$emitter. Tritium is also used in the study of biochemical metabolic reactions. Apparently, elemental hydrogen H_2 is not utilized by human bodies, but it is used by various bacteria species (nitrogen-fixing bacteria, cyanobacteria, *Salmonella* and *Escherichia coli*, photosynthetic bacteria species, *etc.*) as a significant reducing agent in enzyme hydrogenase.

Lithium

Lithium ions Li^+, affecting the activity of certain enzymes, regulate the ionic Na^+ - K^+ balance of cells of the cerebral cortex. The symptoms of Li deficiency in humans are supposed to be manifested mainly as behavioral anomalies [24 - 26]. A connection between low Li intake and changed behavior and aggressiveness has been elucidated [330]. That is why lithium-containing drugs are widely used in

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psychiatric clinics in the therapy of manic depression (bipolar disorder) [331 - 333]. For example, lithium carbonate Li_2CO_3 is used to treat manic arousal in various mental illnesses. Lithium salts are orally administered in some controlled doses per day. Problems in the treatment result from the toxicity of Li at higher amounts. Solutions of lithium chloride or lithium bromide are used in air conditioning installations, because the solutions of these salts are able to absorb ammonia, amines, and other impurities from the atmosphere.

Sodium

In the body, sodium comes primarily in the form of NaCl (table salt). The daily need of the body for sodium is 1 g. Depending on the concentration of sodium chloride, isotonic (physiological), and hypertonic solutions are known. Isotonic is a 0.9% solution of NaCl, since its osmotic pressure corresponds to the osmotic pressure of the blood plasma (7.7 atm) [28]. Isotonic solution is used as a plasma-substituting solution for dehydration of the body, for dissolving medicinal substances, *etc.* Hypertonic solutions (3-, 5-, 10%) are used externally in the form of compresses and lotions for the treatment of purulent wounds.

Sodium hydroxide NaOH (caustic soda) is used in soap, tannery, pharmaceutical, textile industry, and agriculture. A 10% solution of NaOH is part of the silamine used in orthopedic practice for casting refractory models.

Sodium bicarbonate $NaHCO_3$ (drinking soda) is used for increased acidity of stomach juice, peptic ulcer of the stomach, and duodenum. The introduction of sodium bicarbonate into the stomach leads to the rapid neutralization of hydrochloric acid in gastric juice:

$$NaHCO_3 + HCl = NaCl + H_2O + CO_2$$

Too large doses of $NaHCO_3$ lead to alkalosis, which is no less harmful than acidosis.

$NaHCO_3$ is used in the form of rinses for inflammatory diseases of the eyes, and mucous membranes of the upper respirational tract [3, 4, 10]. The action is based on hydrolysis, as the solution has a slightly alkaline environment:

$$NaHCO_3 + H_2O \leftrightarrow NaOH + H_2CO_3$$

When alkalis are exposed to microbial cells, cellular proteins are deposited and, consequently, the death of microorganisms occurs.

Sodium sulfate decahydrate ($Na_2SO_4.10H_2O$, Glauber's salt) is used as a laxative [3, 4, 10, 12 - 15]. This salt is slowly absorbed from the intestines, which leads to an increase in osmotic pressure and the accumulation of water in the intestine, its contents are liquefied, and feces are quickly excreted from the body.

Sodium tetraborate decahydrate $Na_2B_4O_7 \cdot 10H_2O$ (borax) is used externally as an antiseptic agent for douching, rinsing, and lubrication [3, 4, 10, 12-15]. In aqueous solutions, borax is easily subjected to hydrolysis:

$$Na_2B_4O_7 + 7H_2O \leftrightarrow 4H_3BO_3 + 2NaOH$$

Formed during hydrolysis, boric acid has an antiseptic effect.

Sodium and potassium iodides (NaI and KI) are used as iodine medications for thyroid diseases [3, 4]. Sodium and potassium bromides (NaBr, KBr) are used as sedative agents [3, 4, 10]. Sodium fluoride (NaF) is used in dentistry (2% solution) and for the prevention of dental caries in children.

Sodium nitrite ($NaNO_2$) is prescribed orally, subcutaneously, and intravenously (in the form of 1% solution) as a coronary dilator agent for angina pectoris [3, 4].

Sodium thiosulfate ($Na_2S_2O_3$) is used as an antidote and a desensitizing agent [3, 4, 10, 193]. In case of cyanide poisoning, less toxic thiocyanates are formed after ingestion of sodium thiosulfate:

$$KCN + Na_2S_2O_3 \rightarrow KNCS + Na_2SO_3$$

Solutions of sodium citrate are used for blood preservation purposes [3, 4, 10].

The complex sodium nitroprusside $Na_2[Fe(CN)_5NO]$, (Fig. **11**), serves as an agent for lowering blood pressure, since it relaxes the muscles of blood vessels [334, 335].

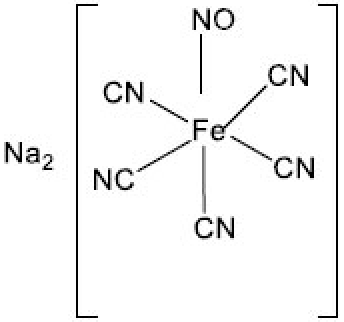

Fig. (11). Structure of sodium nitroprusside.

CHAPTER 5

Application of d- and f- Block Elements and Their Compounds in Medicine

THE USE OF D-ELEMENTS AND THEIR COMPOUNDS IN MEDICINE

The Medical and Biological Significance of d-elements of the IB Group

Copper

The therapeutic use of copper, silver, and gold was discovered in the earliest in the field of medicine to treat syphilis and other disease conditions. Copper is an important trace element necessary for the normal functioning of organisms [195]. Complex compounds of copper(II) with bioligands are involved in many metabolic processes, especially in redox reactions.

Compounds of copper are extensively used in medical practice as medicines. Of the copper compounds in medicine, copper(II) sulfate pentahydrate $CuSO_4{\cdot}5H_2O$ has an antimicrobial effect. It is used as an astringent and antiseptic externally in the form of solutions (dilute solution for lubricating the burning surface of the skin, eye drops). The 5% solution of $CuSO_4$ is used to treat white phosphorus burns. Copper sulfate is included in vitamin-mineral complexes as a source of trace element copper [195 - 199]. $CuSO_4.5H_2O$ is used as a fungicide and for the extermination of certain algae. The diluted solution of copper(II) sulfate (2% solution) may be used internally as an antidote for rare white P intoxication or burns because it transforms P into insoluble Cu(II) phosphide Cu_3P_2. Cu(II) sulfate is used for the preparation of the Benedict reagent containing Cu^{2+}-chelate and used for the analysis of compounds, which reduce the Cu(II) chelate to insoluble Cu(I) oxide Cu_2O or copper(I) hydroxide CuOH. Copper is an integral component of the filling material "Hallodent M" and a liquid (an alloy of gallium and tin) for the manufacture of metal fillings. Cu(I) and Cu(II) oxides are parts of microbicidal phosphate cement used as filling materials. Glass ionomeric cement is a "powder-liquid" system. Glass ionomeric cement are used for dental restoration.

Copper coordination compounds are currently found to exhibit antineoplastic activity with a different mechanism of action compared to that of Pt(II) complexes

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[475]. Additionally, there are many reports on the SOD-mimic, anti-Alzheimer's, antioxidant, anti-inflammatory, antifungal, *etc.* properties of copper(II) complexes [476].

Silver

The biological role of silver has not been completely established. It is classified as a potentially toxic element with a suspected carcinogenicity. Excessive amounts of silver that enter the human body are deposited in the subepithelial layers of the skin, causing the appearance of gray and brown spots (argyrosis). It has been proven that both Ag and its compounds have antibacterial effects that havee been used for water disinfection and wound management [477 - 480].

All medications of silver used in medical practice are preparations for external use, based on its binding, cauterizing, and antibacterial properties. Between its inorganic compounds, silver nitrate $AgNO_3$ is extensively used for these purposes. In small concentrations, silver nitrate has an astringent, antiseptic, and anti-inflammatory effect, and in concentrated solutions, it cauterizes tissues. It was employed in the treatment of ulcers and Ag(I) cations were recognized as antimicrobic agents [477 - 479]. For preventive purposes, $AgNO_3$ (lapis) can be dropped into the eyes of newborns to prevent inflammation caused by gonococci. Ag(I) nitrate has an astringent and anti-inflammatory effect. Externally, it is used in the form of 1-10% of solutions or ointments, and internally as 0.05% solution to treat stomach ulcers and gastritis. Silver nitrate is used in pediatric dentistry for conservative treatment of caries in children. An ammonia solution of silver oxide, obtained from silver nitrate, and a 10% formalin interact. The chemistry of this process can be expressed as follows:

$$2AgNO_3 + 2NH_4OH \rightarrow Ag_2O + 2NH_4NO_3 + H_2O$$

$$Ag_2O + HCHO \rightarrow 2Ag + HCOOH$$

The resulting silver film has a bactericidal effect. Solutions of $AgNO_3$ and AgCl are used to impregnate the dressing materials - paper, cotton wool, and gauze.

In medical practice, along with silver nitrate, colloidal silver preparations are used - collargol and protargol, in which the metal is in solution in the form of the smallest solid particles. Collargol and protargol in the form of aqueous solutions and ointments are used to lubricate the inflamed mucous membranes of the upper respiratory tract, to wash purulent wounds, in eye drops, in erysipelas, *etc.* Silver nitrate in combination with a sulfonamide antibiotic, produces silver sulfadiazine, a local antimicrobial agent for burn treatment [477].

Nowadays many silver-containing medical products are available, as dressings for burn wounds, catheters, wound-care products, and as dental implants. [478]. Silver wound dressings are applied rather than antibiotics due to the development and increase of antibiotic-resistant microorganisms [479]. Ag-based nanoparticles have been assessed as antiviral agents [200, 480]. Alloys of Au, Ag, and Cu in small amounts are widely used in dental practice for prosthetics. Silver is a part of silver-palladium alloys and of powder (an alloy of silver, tin, and copper) used for the manufacture of silver amalgam (AC-2) used in metal fillings. It has to be mentioned that confusion exists over the benefits and hazards associated with silver compounds and alloys.

Gold

For many centuries, it was supposed that gold has medicinal and strong therapeutic value [201, 481-491]. Metallic gold as foil or sand was used as medicine for different diseases in older times. Such elementary Au is relatively ineffective. Alchemists identified that metal Au dissolves in royal water and can be reduced back to Au^0 as a stable colloid (Au ash), the color of which is dependent on the particle sizes and varies from blue to purple. Neutralized solutions “aurum potabile” were extensively used in the Middle Ages, although their actual value is questionable. During the XIX century, gold was called a panacea, a cure for all diseases. The rational use of Au compounds in medical practice dates back to the early XXth century, when microbiologist Robert Koch revealed that $K[Au(CN)_2]$ killed tuberculosis bacteria. Like various other Au(I) complex compounds, $[Au(CN)_2]^-$ contains linear fragments of two-coordinated gold bound to carbon atoms of cyanide ions $[NC\text{-}Au\text{-}CN]^-$. Complexes of three-coordinated Au(I) and tetrahedral complexes of four-coordinated Au(I) are identified but less studied. Gold(I) belongs to class “b”, *i.e.,* to the “soft” ions, thus the most stable compounds should contain heavier bioligands. Thus, P and S are preferable than N and O. Aqua-cation of Au(I) $[Au(H_2O)_x]^+$ is unidentified. Gold(I) stabilizes by π-acceptor ligands. In biosystems, the most favored ligand for gold(I) is the S-atom of thiol (Cys in protein molecules). The attraction of gold(I) to DNA is very small.

Weak gold(I)- gold(I) interactions are often found in the molecules of the gold(I) complexes, which are perpendicular to the axis of linear coordination. The Au-Au bonds are much shorter than the sum of the van der Waals radii. This attraction of Au cations to each other is called “aurophilicity”, which may be due to the strong impact of the relativistic effect in Au chemistry (the inner shell electrons, moving at close to the speed of light, cause the shell to contract). Unlike copper, also found in the IB group, Au^{+2}, is not stable. Square planar complexes of Au^{+3} can be easily obtained, but are predisposed to reduction in biosystems (up to Au^+ or Au^0).

CHAPTER 6

REFERENCES

CONCLUDING REMARKS

The book titled "BIOLOGICAL AND MEDICAL SIGNIFICANCE OF CHEMICAL ELEMENTS" is devoted to the chemistry and biological role of biogenic essential and trace elements. It deals with issues related to the prevalence of chemical elements in nature, the ratio of the chemical elements and their compounds in living organisms and the environment, the biological role of elements depending on their position in the periodic table of elements, the use of compounds of s-, p-, d- and f-elements in medicine, and environmental aspects of the action of their compounds.

Chemical elements are present in different forms in nature, and these elements are very essential for the body to perform different functions. It is known that the human body contains nearly all the elements of the periodic table, many of which go into the body from the environment and can participate in biochemical processes in health and disease. When considering the chemistry of biogenic elements on the basis of the periodic law, an approach is used to find out which properties and features of the elements are responsible for their different amounts in living organisms, which determines the specific role of elements in biological systems. The study of chemical and biological properties provides information about the patterns of individual properties of chemical elements and their compounds. Here an element-by-element journey through the periodic table is made, starting with the main groups IA-IIA (s-elements: hydrogen, alkali and alkaline earth metals), IIIA-VIIIA (p-block elements, mostly non-metals, metalloids, and noble gases), followed by groups IB-VIIIB, including d- and f-elements such as transition metals, lanthanides, and actinides.

Special attention in the book is paid to the chemistry and biology of the essential biogenic elements and their compounds. However, the periodic table also offers potential for novel therapeutic and diagnostic agents, based on not only essential elements, but also non-essential elements, and on radionuclides, which provide new challenges in biology, bioinorganic chemistry, and medicine. Future advances in the design of inorganic, organic, organometallic, metal-based coordination compounds, and supramolecular drugs require more knowledge of their mechanism of action, including target sites and metabolism.

The most characteristic patterns of modern human beings are the deficiency of essential elements and the excess of toxic trace elements. The accumulation or

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deficiency of the elements may stimulate an alternate pathway that might cause diseases. Chronic toxicity, acute intoxication, and their effects on the living body have also been considered.

This book highlights the current knowledge of essential biogenic elements, trace elements useful in diagnosis and therapy, and notable features in their chemistry which relate to their biological activity. The book may be of interest to researchers working in the field of bioinorganic and medicinal chemistry, as well as in medicine and biology.

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SUBJECT INDEX

Irena Kostova

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Prof. Irena Kostova is one of the World's Top 1% of scientists with the greatest contribution to modern science according to Stanford University's ranking of scientists. She graduated from Mendeleev University in Moscow. She completed her Ph.D. and DSc theses at MU-Sofia where she is currently a full professor in the chemistry department. She did her second specialization in "Medical chemistry". Her research interests include developmental work in theoretical and coordination chemistry, vibrational spectroscopy, biologically active compounds, etc. She is an author of about 200 publications with high impact factor and h-index, several textbooks, education book materials, and monographs with around 7000 citations in indexed journals. She has been a lecturer at renowned universities. She is also a member of the organizing committees of over 30 international conferences, an editor of 7 prestigious international scientific journals, an editorial board member of over 25 international journals and a reviewer for numerous high-ranking journals and international projects. She has created and maintained collaborations with a number of European universities under European programs.