Chapter 7

Mechanism of Interactions of Zinc(II) and Copper(II) Complexes with Small Biomolecules

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.79472

Abstract

Over the past few decades, transition metal complexes have attracted considerable attention in medicinal inorganic chemistry, especially as synthetic metallonucleases and metal-based anticancer drugs that are able to bind to DNA under physiological conditions. The use of metal-based drugs presents the most important strategy in the development of new anticancer and antimicrobial agents. Negative side effects during treatment (such as vomiting, resistance, nephrotoxicity, ototoxicity, neurotoxicity and cardiotoxicity) prompted researchers to design new classes of DNA and protein targeting metal-based anticancer agents with potential in vitro selectivity and less toxicity. Knowledge of mechanism of the interaction zinc(II) and copper (II) ions with biomolecules and other relevant ligands is essential for understanding the cellular biology of delivery complexes to DNA and proteins. Results obtained from investigations provide useful information for the future design of potential zinc- and copper-based anticancer drugs. Different mechanism of interactions with selected biomolecules compared to platinum-based drugs has been observed.

Keywords: transition metal complexes, kinetics, mechanism of interactions, metal-based drugs, biomolecules, antitumour activity

1. Introduction

The aim of this chapter is to present fundamental chemical properties and new investigations of coordination compounds of some transition metal ions with an overview of medicinal applications. Transition metals appear in almost every facet of our day-to-day life, from industrial uses such as the manufacture of construction and building materials, tools, vehicles, up to cosmetics, paints and fertilizers. Their reactions are in general important in many

technical processes such as catalysis, materials synthesis, photochemistry, as well as, in biology and medicine.

It is known that metal ions play an important role in the biological and biomedical processes. Namely, many processes such as breathing, metabolism, photosynthesis, growth, reproduction, muscle contraction cannot imagine without the presence of some metal ions. It is currently believed that about 24 elements are essential for the life of mammals, which are: H, C, N, O, F, Na, Mg, Si, P, S, Cl, K, Ca, V, Mn, Fe, Co, Ni, Cu, Zn, Se, Mo, Sn and I.

The field of inorganic coordination chemistry, among other thing, is concerned with the study of the use of compounds of essential and non-essential elements in medicine, as well as, of the interaction of given compounds with the present biomolecules within the organism. Now many inorganic coordination compounds are widely used in medicine for the treatment of many diseases, including various cancers, Alzheimer's disease, diabetes, rheumatoid arthritis and others. In this chapter, among other things, we are focused on coordination compounds zinc(II) and copper(II) and on investigation of the mechanism of interactions with biologically relevant molecules.

2. Transition metal ions chemistry

2.1. Lewis acid base theory

Although, in this chapter, we mainly discuss the coordination compounds of transition metal ions, it is very important to explain some of the basic characteristics of complex compounds such as are definition of Lewis acids and bases.

A Lewis acid is an electron acceptor and a Lewis base is an electron donor. In a coordination complex, the central metal ions act as a Lewis acid and are coordinated (bonded) by one or more molecules or ions (ligands) which act as Lewis bases. Formed coordinated bonds between central atom or ion with ligands have covalent character and are known under name *coordinate covalent bond* or simple *coordinate bond*. Atoms in the ligands that are directly bonded to the central atom or ion are donor atoms.

2.2. Hydration or hydrolysis of metal ions?

When a metal salt is dissolved in water, the ionic bond is interrupted, the cations and anions are hydrated. For example, when NaCl is dissolved in water, the inner hydration shell around Na^+ is formed. The $Na^+ \cdots O$ interaction can be described in terms of an ion-dipole interaction, while the solvation of the anion can be described in terms of the formation of hydrogen bonds between Cl^- and H atoms of surrounding H_2O molecules (**Figure 1**).

Hydration is solvation when the solvent is water. If the metal-oxygen bond possesses covalent character, there is also an ionic contribution to the bonding interaction. Each O atom donates a pair of electrons to the metal M^{z+} ion, and each H_2O molecule acts as a Lewis base while the metal ion acts as a Lewis acid. The M-O interaction is covalent, in contrast to the case for Na^+.

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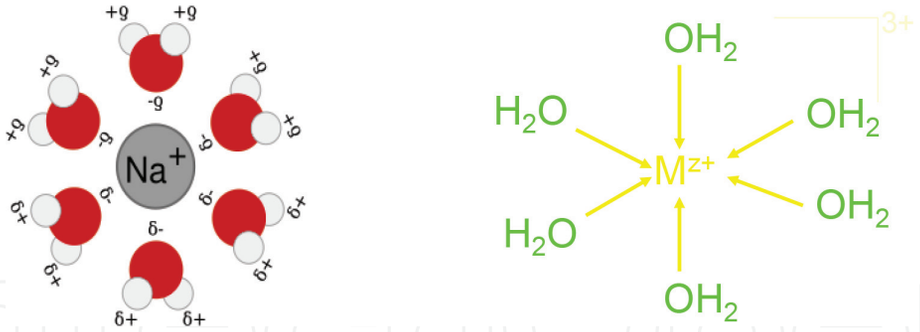


Figure 1. Left: the first hydration shell of an Na^+ ion; ion-dipole interactions between the Na^+ ion and the H_2O molecules; Right: bonding of metal ions and H_2O molecules.

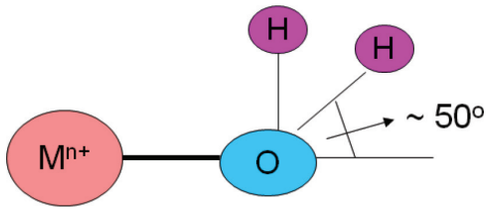


Figure 2. The plane of the water molecule in the direction M^{z+}·····O axis.

In practice, the character of the metal-·oxygen interaction varies with the nature of the metal ion and relevant to this is the electroneutrality principle (**Figure 1**).

In concentrated solutions, the plane of the water molecule makes an angle of up to 50° degree with the M^{z+}·····O axis (**Figure 2**) implying interaction of the cation with a lone pair of electrons rather than an ion-dipole interaction, it suggests that the metal-oxygen interaction involves the use of an oxygen lone pair. Metal cations are equated with the formula $[M(H_2O)_n]^{z+}$, where z is 1, 2 or 3, and they tend to hydrolyze [1].

2.3. Transition metal ions as Brønsted acids

Metal ions in aqueous solution behave as Lewis acids. The positive charge on the metal ion draws electron density from the O-H bond in the water. This increases the bond's polarity making it easier to break. When the O-H bond breaks, an aqueous proton is released producing an acidic solution. Hydrolysis refers to the reversible loss of H^+ from an aqua species.

Transition metal ions can act as Brønsted acids by loss of H^+ from a coordinated water molecule. Small cations such as Li^+, Mg^{2+}, Al^{3+}, Fe^{3+} and Ti^{3+} possess high charge densities, cannot be Brønsted acids by themselves. Water molecules covalently bound to one of these metal ions are more acidic than normal, the H atoms carry significant positive charge. Thus, reactions such as the following occur.

$$[Fe(H_2O)_5(OH)]^{2+} + H_2O \rightleftharpoons [Fe(H_2O)_4(OH)_2]^{+} + H_3O^{+}$$

$$pK_{eq}\,([Fe(H_2O)_6]^{3+}) \sim pK_a\,(HNO_2)$$

The characteristic colour of the $[Fe(H_2O)_6]^{3+}$ ion is purple, but aqueous solutions appear yellow due to the formation of the hydroxo species $[Fe(H_2O)_5(OH)]^{2+}$ and $[Fe(H_2O)_4(OH)_2]^{+}$.

The equilibrium constant K_{eq} for the hydrolysis of a hydrated cation is analogous to the K_a for the ionization of a weak acid. Generally, hydrolysis constants for cations are signed as $-\log K_a$. These hydrolysis constants are averages of different experimental measurements. If we compare the value of constant for previous reaction with K_a of weak acids, it can be seen that pK_{eq} of $[Fe(H_2O_6)]^{3+}$ correspond to pK_a of weak nitrous acid.

2.4. Stability constants of coordination complexes

Metal ions in aqueous solution are hydrated; the aqua species may be accounted as $M^{z+}_{(aq)}$ where this often represents the hexaaqua ion $[M(H_2O)_6]^{n+}$. Addition of a neutral ligand L to the solution leads the formation of a series of complexes $[M(H_2O)_5L]^{n+}$, $[M(H_2O)_4L_2]^{n+}\ldots[ML_6]^{n+}$. The stepwise displacements of coordinated H_2O by L are represented by Eqs. (1) and (2).

$$[M(H_2O)_6]^{z+} + L \underset{}{\overset{K_1}{\rightleftharpoons}} [M(H_2O)_5L]^{z+} + H_2O$$

$$K_1 = \frac{[M(H_2O)_5L]^{z+}}{[M(H_2O)_6]^{z+}\,[L]} \tag{1}$$

$$[M(H_2O)L_5]^{z+} + L \overset{K_6}{\rightleftharpoons} [ML_6]^{z+} + H_2O$$

$$K_6 = \frac{[ML_6]^{z+}}{[M(H_2O)L_5]^{z+}\,[L]} \tag{2}$$

In step-wise formation of complex $[ML_6]^{+}$ from $[M(H_2O)_6]^{z+}$, each displacement of a coordinated water molecule by ligand L has a characteristic *stepwise stability constant*, K_1, K_2, K_3, K_4, K_5 or K_6. Alternatively, we may consider the overall formation of $[ML_6]^{z+}$ (Eq. (3)).

$$[M(H_2O)_6]^{z+} + 6L \rightleftharpoons [ML_6]^{z+} + 6H_2O$$

$$\beta_6 = \frac{[ML_6]^{z+}}{[M(H_2O)_6]^{z+}\,[L]^6} \tag{3}$$

The constant β_6 we call as *cumulative stability constant.* The connection between values of stepwise formation stability constant and overall stability constant is given by expression: $\beta_6 = K_1K_2K_3K_4K_5K_6$ or $\log\beta_6 = \log K_1 + \log K_2 + \log K_3 + \log K_4 + \log K_5 + \log K_6$. Determinations of stability constants can be made by polarographic or potentiometric measurements (if a suitable reversible electrode exists), by pH measurements (if the ligand is the conjugate base of a weak acid) or by ion-exchange, spectrophotometric (i.e. observation of electronic spectra and use of the Beer–Lambert Law), NMR spectroscopic or distribution methods [1].

Hard (acids)	**Intermediate (acids)**	**Soft (acids)**
Li^+, Na^+, K^+, Rb^+, Be^{2+}, Mg^{2+}, Ca^{2+}, Sr^{2+}, Sn^{2+}, Mn^{2+}, Al^{3+}, Ga^{3+}, In^{3+}, Sc^{3+}, Cr^{3+}, Fe^{3+}, Co^{3+}, Y^{3+}, Th^{4+}, Pu^{4+}, Ti^{4+}, Zr^{4+}, $[VO]^{2+}$, $[VO_2]^+$	Pb^{2+}, Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Os^{2+}, Ru^{3+}, Rh^{3+}, Ir^{2+}	Zero oxidation state metal centres, Tl^+, Cu^+, Ag^+, Au^+, $[Hg_2]^{2+}$, Hg^{2+}, Cd^{2+}, Pd^{2+}, Pt^{2+}, Ru^{2+} Tl^{3+}
Hard (bases)	**Intermediate (bases)**	**Soft (bases)**
F^-, Cl^-, H_2O, ROH, R_2O, $[OH]^-$, $[RO]^-$, $[RCO_2]^-$, $[CO_3]^{2-}$, $[NO_3]^-$, $[PO_4]^{3-}$, $[SO_4]^{2-}$, $[ClO_4]^-$, $[ox]^{2-}$, NH_3, RNH_2	Br^-, $[N_3]^-$, py, $[SCN]^-$ (*N*-bound), $ArNH_2$, $[NO_2]^-$, $[SO_3]^{2-}$	I^-, H^-, R^-, $[CN]^-$ (*C*-bound), CO (*C*-bound), RNC, RSH, R_2S, $[RS]^-$, $[SCN]^-$ (*S*-bound), R_3P, R_3As, R_3Sb, alkenes, arene

Table 1. Selected hard and soft metal centres (Lewis acids) and ligands (Lewis bases) and those that exhibit intermediate behaviour.

2.5. Hard and soft acid base principle

Based on acceptor properties of metal ions towards ligands (i.e. Lewis acid-Lewis base interactions), two classes of metal ion can be identified, although the distinction between them is not clear-cut. The terms "hard" and "soft" acids arise from a polarizabilities of the metal ions. Hard acids are typically either small monocations with a relatively high charge density or are highly charged, again with a high charge density. These ions are not very polarizable and show a preference for donor atoms that are also not very polarizable, for example, F^-. Such ligands are called hard bases. Soft acids tend to be large monocations with a low charge density, for example, Au^+, and are very polarizable. They prefer to form coordinate bonds with donor atoms that are also highly polarizable, for example, I^-. Such ligands are called soft bases [1]. Hard acids (hard metal cations) form more stable complexes with hard bases (hard ligands), while soft acids (soft metal cations) show a preference for soft bases (soft ligands). The list of hard and soft acids and bases with included intermediates is shown in **Table 1**.

The hard and soft acid base (HSAB) principle is qualitatively useful, the hard-hard or soft-soft matching of acid and base represents a stabilization that is additional to other factors that contribute to the strength of the bonds between donor and acceptor. These factors include the sizes of the cation and donor atom, their charges, their electronegativities and the orbital overlap between them.

Complex formation usually involves ligand substitution. If we suppose that M^{z+} is a hard acid. It is already associated with hard H_2O ligands, and hard-hard interaction is a favourable. If L is a soft base, ligand substitution will not be favourable. If M^{z+} is a soft acid, ligand substitution will be favourable [1].

3. Medicinal application of inorganic complexes (metal-based drugs)

3.1. Medicinal inorganic chemistry

Medicinal inorganic chemistry is a part of bioinorganic chemistry that occupies a significant place in the field of therapeutic and diagnostic medicine. Inorganic coordination compounds are now used in medicine for the treatment of numerous diseases.

Today, it is well known that some metal ions are required for normal functions of organism. Lack of zinc, iron, copper, ions and so on can induce disease. Some metal ions such as arsenic, cadmium, chromium, lead and mercury can induce toxicity in humans. Even essential metal ions can be toxic when present in excess. An important aspect of medicinal bioinorganic chemistry is ability to understand all this in the molecular level and treat diseases caused by inadequate metal ion function constitutes.

Medicinal inorganic chemistry is a multidisciplinary field combining elements of chemistry (synthesis and reactivity), pharmacology (pharmacokinetics and toxicology), biochemistry (targets, structure and conformational changes) and medicinal chemistry (therapeutics, pharmacodynamics and structure-activity relationships). The main focus of this field is to design of novel therapeutic and diagnostic agents and to investigate the mechanism of medicinal action, as improvement of the action of many organic compounds used in medicine by activation or biotransformation by metal ions [2–4].

3.2. Metal complexes as drugs

In order for the coordination complexes to be approved as drugs, it is necessary to detailed examination of the fundamental aqueous chemistry of the proposed drug, including its pharmacokinetics, the metabolic processes in blood and intracellularly, and the effects of the drug on the target of choice. Inorganic coordination chemistry offers a wide variety of synthesis of coordination compounds with different coordination spheres, including ligand designs, oxidation states and redox potentials of transition metal ions, thus gives the ability to systematically alter the kinetic and thermodynamic properties of the complexes towards biological receptors. Well-known metal ions and their coordination complexes that have found usage in medicine can be divided into:

1. Platinum anticancer agents (e.g., cisplatin, *cis*-$[PtCl_2(NH_3)_2]$)
2. The gold(I)-containing antiarthritic drugs (e.g. auranofin)
3. Metal-mediated antibiotics like bleomycin, which requires iron or other metals for activity
4. Technetium-99 m and other short-lived isotopes (rhenium-186, rhenium-188 and gallium-68) used as radiopharmaceuticals in disease diagnosis and treatment
5. Magnetic resonance imaging (MRI)-enhancing gadolinium(III) compounds
6. Antibacterials, antivirals, antiparasitics and radiosensitizing agents

Platinum complexes are now among the most widely used drugs for the treatment of cancer. Thanks to the successful and widespread use of cisplatin a large number of analogous compounds were synthesized. All these compounds have several common characteristics:

1. bifunctional complex compounds with *cis*-geometry
2. the general formula of these compounds is *cis*-$[PtA_2X_2]$ where A_2 are two inert monodentate nitrogen donor ligands or one inert bidentate nitrogen donor ligand, while with X_2 are two labile monodentate or one labile bidentate ligand

http://dx.doi.org/10.5772/intechopen.79472

3. the oxidation state of platinum in the complexes is +2 or +4

4. nitrogen-donor ligands have to contain at least one NH bond.

Figure 3 presents some of platinum complexes that are in the medicinal use worldwide.

The second-generation platinum(II) antitumour complexes are carboplatin, oxaliplatin, nonplatinum, zenithplatin, enloplatin, NK121, CI-973 and others. Instead of labile chloride ligands, they contain bidentate ligands such as 1,1-cyclobutanedicarboxylate, glycolate, and complexes with 1,2-diaminocyclohexane as an inert ligand, while the labile ligands are sulphates, malonates and other ligands [5]. The second-generation complexes based on the cisplatin structure were developed to improve toxicity and/or expand the range of useful anticancer activity. The third-generation platinum antitumour complexes are octahedral platinum(IV) coordination compounds with general formula *cis*-$[PtA_2X_2Y_2]$, where two labile monodentate or one labile bidentate ligand is labeled as Y_2. The platinum(IV) drugs are orally administrated to patients. In the presence of various biomolecules such as cysteine or ascorbic acid, the redaction to Pt(II) occurred by leaving the axial ligands Y_2. In addition, this group includes new complexes with a *trans*-geometric structure, polynuclear platinum complexes (BBR3464) and complexes containing a ligand with an asymmetric carbon atom [6].

The mechanism of the antitumour effects of platinum complexes consists in their binding to DNA molecules, thereby preventing replication and transcription of DNA, that is, preventing the process of uncontrolled cell growth [7–9]. From the moment of injection of the drugs in the body to their binding to DNA molecules, a large number of secondary processes happen that

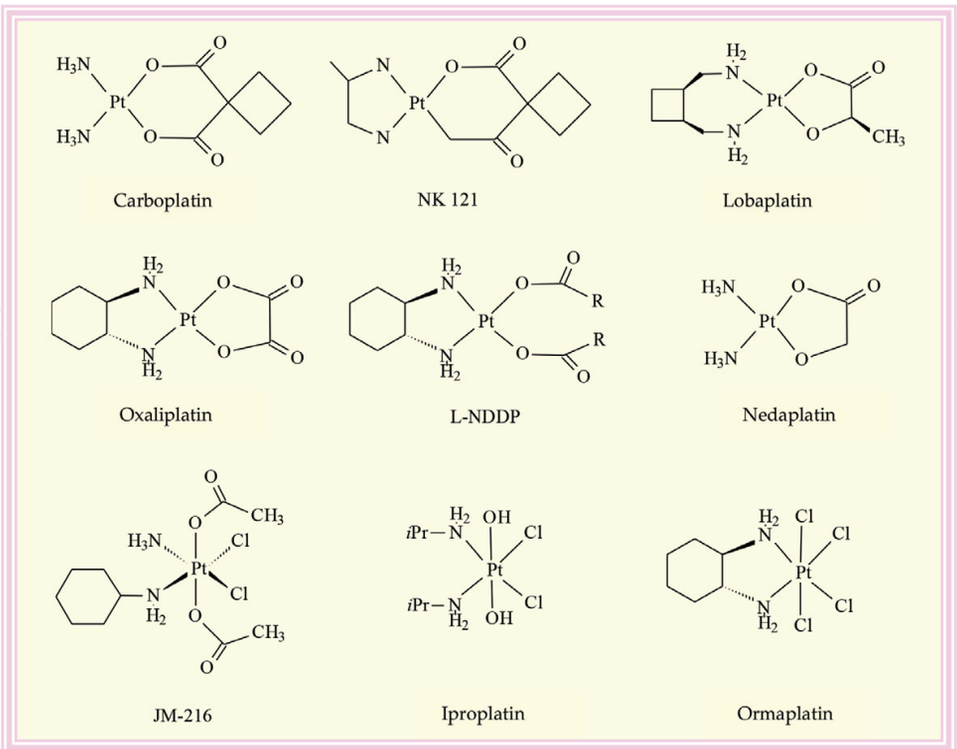


Figure 3. Platinum antitumour complexes with adopted commercial names.

are responsible for the occurrence of toxic effects [8, 9]. Hydrolysis of Pt(II) drugs in the body occurs as a result of a different concentration of chloride ions in and out of the cell. Namely, the high concentration of Cl^- ion in the extracellular fluid (104 mM) suppresses the hydrolysis process, while in the intracellular low concentration of about 4 mM, it is suitable for the hydrolytic reactions of platinum(II) antitumour drugs [10, 11]. The antitumour platinum(II) agents must not be either too reactive or too inert, since in both cases their toxicity is increasing [10]. On the other hand, the essential characteristic of these compounds must be selectivity towards certain biomolecules [12]. High affinities for the platinum complexes show the biomolecules that contain sulphur, as the thiols and the thioethers, as soft acid platinum(II) drugs form very stable compounds with sulphur donor biomolecules, for example, soft bases. The resulting compounds are responsible for negative side effects during treatment (such as vomiting, resistance, nephrotoxicity, ototoxicity, neurotoxicity and cardiotoxicity).

During the recent years, many ruthenium complexes with oxidation state +2 or +3 found to have anticancer activity. Antitumour activities of Ru(II) and Ru(III) complexes take place in a different manner in comparison with platinum(II) drugs, what is linked with geometrical structures and reversible redox potential of ruthenium. The real revolution among the ruthenium complexes was initiated by two isostructural complexes Ru(III): [ImH]*trans*-[$RuCl_4(Im)_2$] and [IndH]*trans*-[$RuCl_4(Ind)_2$], better known by the names ICR and KP1019, respectively (Im = imidazole and Ind = indazole) and [Na]*trans*-[$RuCl_4$(Im)(dmso-*S*)] or NAMI-A (dmso-*S* = dimethyl sulphoxide coordinated through sulphur), which is a structural analogue to the previously synthesized ICR complex (**Figure 4**). Apart from the fact that these complexes have shown activity to several different types of tumours, it is particularly interesting that they are active against tumours resistant to platinum complexes. The mechanism of action of this compound is not related to DNA binding; rather, it is an antimetastatic agent [13]. Metastasis (the process whereby tumour growth occurs distant from the original or primary tumour site)

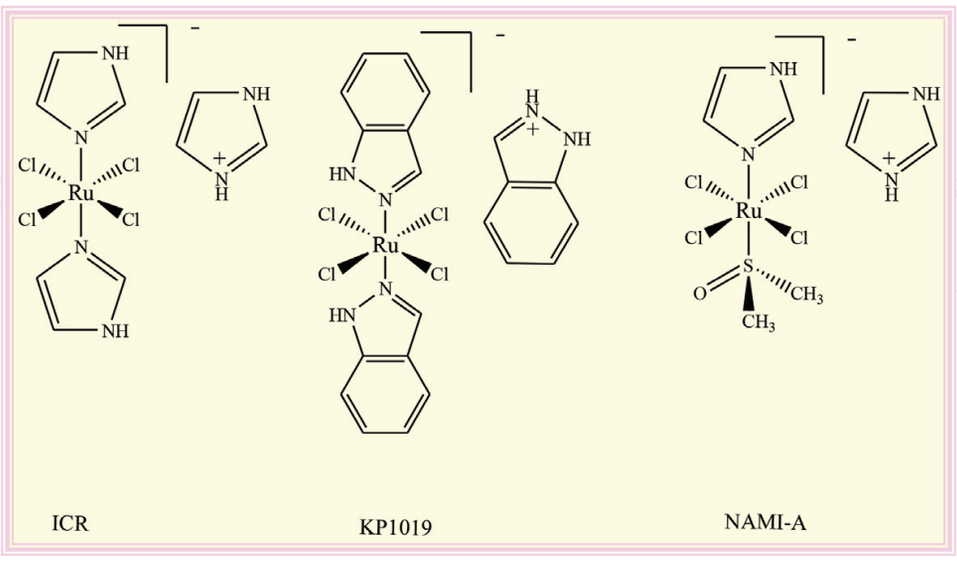


Figure 4. The structures of the ruthenium(III) complexes: [ImH]*trans*-[$RuCl_4(Im)_2$] or ICR; [IndH]*trans*[$RuCl_4(Ind)_2$] or KP1019 and ([ImH]*trans*-[$RuCl_4$(Im)(dmso-*S*) or NAMI-A.

is linked with angiogenesis, the dynamic process that involves new blood vessel formation. Antitumour activity of ruthenium complexes is related with interaction with proteins in cell membrane or collagen in extracellular fluid.

The ruthenium(II) complexes types $[Ru(II)(\eta^6\text{-arene})(en)X]^+$ ($X = Cl^-$ or I^-, arene = p-cumene or biphenyl, en = ethylenediamine) characterize higher stability to hydrolysis and get in cytoplasm in unchanged form. They are supposed to act as catalysts for glutathione oxidation, which contribute to the increase in cellular oxidative stress and programmed cell death, i.e. apoptosis. Ru(III) complexes tend to be more biologically inert than related Ru(II) complexes, like several other metal ions, can be delivered to cells *via* the iron transport protein transferrin.

The coordination compounds of other metal ions such as Au(I), Au(III), Ti(IV), Cu(II) or MnSOD (manganese-based superoxide dismutase mimics) are on clinical trial. The enzyme superoxide dismutase (SOD), either as the manganese containing MnSOD (present in the mitochondrion) or the dinuclear Cu/Zn-SOD (present in the cytosol and extracellular space), performs the role of superoxide detoxification in normal cells and tissue [14].

Polyoxometallates of the Keggin type such as $[NaW_{21}Sb_{29}O_{86}][NH_4]_{17}$ and $K_{12}H_2[P_2W_{12}O_{48}]\cdot 24H_2O$ have potential in the anti-HIV field, they bind to viral envelope sites on cell surfaces and interfere with virus adsorption [3]. Metal-chelating macrocyclic bicyclam ligands are among the most potent inhibitors of HIV ever described, and there is considerable interest in the role of Zn proteins in the viral life cycle. Metal ions are required for the activity of anti-HIV G-quartet oligonucleotides (antisense oligonucleotides) such as T30177, a potent inhibitor of the enzyme HIV-1 integrase [3].

Bismuth compounds have been used for their antacid and astringent properties in a variety of gastrointestinal disorders [15, 16]. The effectiveness of bismuth is due to its bacteriocidal action against the Gram-negative bacterium, *Helicobacter pylori*. Usually, the bismuth preparations are obtained by mixing an inorganic salt with a sugar-like carrier.

Injectable Au(I) thiolates and an oral Au(I) phosphine complex are widely used for the treatment of rheumatoid arthritis. Proteins appear to be the targets for gold therapy, including albumin in blood plasma and enzymes in joint tissues. The detection of $[Au(CN)_2]$ in the blood and urine of patients undergoing gold therapy (chrysotherapy) raises the possibility that this is an active metabolite. Cyanide could be involved in the metabolic pathways for other metal ions (both natural and therapeutic) in the body since it can be synthesized by some cells. The recent discovery that oxidation of administered Au(I) compounds to Au(III) may be responsible for some of the side effects of gold therapy has highlighted interests in the biological redox chemistry of gold, including possible stabilization of Au(III) complexes by peptides and proteins, which now is main target for developing antitumour Au(III) drugs [3, 4, 6].

Peroxovanadate complexes can inhibit insulin receptor-associated phosphotyrosine phosphatase and activate insulin receptor kinase, and both V(IV) and V(V) compounds offer promise as potential insulin mimics [4, 6]. Lithium compounds are kinetically labile and are used for the treatment of bipolardisorders, and Li(I) inhibition of Mg(II)-dependent inositol monophosphatase enzymes leads to interference with Ca(II) metabolism [4]. Newer uses have appeared in

the treatment of viral diseases including AIDS, alteration of the immune response and cancer. The lithium salt of linolenic acid (LiGLA) has a significant anticancer effect against certain cancers [6].

Less labile metal ions can be used to control the levels of biologically active ligands in the body. Thus, Fe(III) in sodium nitroprusside delivers NO to tissues and is used for the treatment of hypertension and control of blood pressure. The possibility arises of utilizing Ru(III) to scavenge NO in the treatment of septic shock. As is mentioned, the injection of gram quantities of Gd(III) complexes to provide contrast magnetic resonance images (MRI) of the body illustrates how the toxicity of metal ions and tissue targeting can be controlled by the appropriate choice of ligands [4]. The importance of metal complexes as imaging agents for various diseases including heart disease and brain disorders have also been recognized. They are able to determine specific aspects of disease such as tissue hypoxia, and can detect molecular phenomenon such as multidrug resistance [3]. Metal centres, being positively charged, favourably bind to negatively charged biomolecules (proteins and nucleic acids) and offer excellent tools for understanding of more specific biological processes including the formation of thrombi and the imaging of infection, and so on. By means of scanning techniques viz. gamma scintigraphy, positron emission tomography (PET) and magnetic resonance imaging (MRI), tissues and organs with radiolabelled compounds can be visualized and such visualization facilitates the detection of abnormalities in their function. Radionuclide complexes are used for diagnosis, as contrast media and as therapeutic agents. A ^{99m}Tc radiopharmaceutical (^{99m}Tc–SESTAMIBI), known as cardiolite, is an established radiopharmaceutical for myocardial perfusion imaging [3, 4]. A wide variety of coordinated spheres, oxidation states and redox potentials of metal ions in coordinated and organometallic compounds give possibility of design and synthesis of new metal complexes with selected kinetic and thermodynamic properties towards biological receptors [3, 4, 6].

Many Cu-complexes of anti-inflammatory drugs have been found more active in animal models than either their parent Cu(II) salt or NSAID (nonsteroidal anti-inflammatory drugs). Cu(II) complex of salicylate has been found about 30 times more effective than aspirin as an anti-inflammatory agent. The pharmacological activity of these complexes has been proposed to be due to its inherent physico-chemical properties of the complex itself rather than that of its constituents [17].

The amount of metals present in the human body is approximately 0.03% of the body weight. Low metal ion concentrations may be harmful for the body. It has been reported that in various cancers the concentrations of Cd, Cr, Ti, V, Cu, Se and Zn were found to be at a lower level than in normal conditions of body [18]. Ligands having electron donor atoms like N, O, S and P may form coordination bond with metal ion. Chelation causes drastic changes in biological properties of ligands as well as metal moiety and in many cases it causes synergistic effect of metal ion and ligand both [19]. On the other hand, the presence of metals such as lead, mercury, arsenic, uranium and plutonium induces metal poisoning. In order to remove these metals medical procedure, chelation therapy is performing. The medical procedure involves the administration of chelating agents to remove heavy metals from the body. Some common chelating agents are ethylenediaminetetraacetic acid (EDTA), 2,3-dimercaptopropanesulphonic acid (DMPS) and thiamine tetrahydrofurfuryl disulphide (TTFD).

http://dx.doi.org/10.5772/intechopen.79472

4. Investigation of the interactions of zinc(II) and copper(II) complexes with small biomolecules

4.1. Substitution mechanisms in complex compounds

Complex compounds are involved in a number of substitution reactions such as ligand exchange, solvent exchange, complexation or anation reactions, solvolysis, acid and base hydrolysis, inter- and intramolecular isomerization, racemization and metal ion exchange [20]. Substitution reactions of complexes can be electrophilic (SE) or nucleophilic (SN) depending on the replacement of either central metal ion or ligand. If the metal ion is substituted during the reaction, that is, electrophile, the reactions are electrophilic substitution (Eq. (4)), otherwise if a ligand is replaced that is nucleophilic substitution reaction (Eq. (5)) [21, 22].

$$[ML_n] + M' \rightleftharpoons [M'L_n] + M \quad (4)$$

$$[ML_n] + X \rightleftharpoons [ML_{n-1}X] + L \quad (5)$$

Nucleophilic substitution reactions, according to Langford and Gray, are carried out in three different mechanisms: dissociative (D), associative (A) or interchange mechanism (I) [22]. In the dissociative mechanism (D), the first step of the reaction is dissociation of the one ligand L from the inner coordination sphere, whereby an intermediate with a decreased coordination number forms. In the next step, the entering ligand X binds to the central metal ion. Since the first step of the reaction is slower, it determines the overall rate of the substitution reaction. In the associative mechanism (A), in the first step, the entering ligand X binds to the central metal ion, forming an intermediate with an increased coordination number, and then, in the second step, the leaving ligand L leaves the coordination sphere of the complex. The formation of an intermediate with an increased coordination number is slower and it determines the rates of this substitution process. When an intermediate cannot be detected by kinetic, stereochemical or product distribution studies, the so-called interchange mechanisms (I) are invoked. Associative interchange mechanisms (I_A) have rates dependent on the nature of the entering group, whereas dissociative interchange (I_D) mechanisms do not. If the process of breaking the bond between the central metal ion and the outgoing ligand L has a greater impact on the rate of reaction, the mechanism is I_D, and if the forming a new bond between the central metal ion and the entering ligand X has a greater impact on the chemical reaction rate, the mechanism is marked with I_A [21, 22].

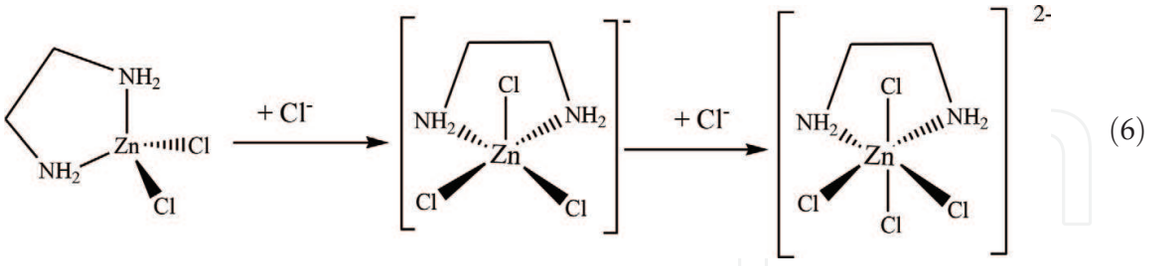
Factors affecting metal ion lability include size, charge, electron configuration and coordination number. The associative mechanism is well known and preferred for four-coordinated square-planar complexes. Dissociative mechanisms are more common for six-coordinated octahedral complexes. Five-coordinated complexes could react in both mechanisms [23]. The study of kinetics and mechanism of the reactions of transition metal complexes expanded with development of organometallic and bioinorganic chemistry, as well as, with the development of new experimental techniques (UV-Vis spectrophotometry, NMR spectroscopy, "stop-flow" spectrophotometry, HPLC, EPR spectroscopy, etc.). The main aims of study are determination of rates of substitution processes, investigation of the influence of different parameters (change

of reactant concentration, pH, temperature and pressure change, introduction catalyst, etc.), investigation of interactions between potential antitumour metal-based drugs and biologically relevant molecules [20–24].

4.2. The bioinorganic chemistry of zinc(II) and copper(II) complexes

Transition metal compounds play crucial roles as cofactors in metalloproteins; they act mainly as a Lewis acid. Two essential metal ions, namely zinc and copper ions, modulate enzymes activities, catalytic and regulatory functions, oxidative-reductive processes, etc. [4, 24]. Zinc has a specific role in bioinorganic processes because of the peculiar properties of the coordination compounds of the zinc(II) ion, easily can be four-, five- or six-coordinate, without a marked preference for six coordination [24]. The most studied metalloproteins in which zinc serves a structural role belong to the zinc-finger family, which is involved in control of nucleic acid replication, transcription and repair [25]. In zinc-finger proteins, zinc is tetrahedrally coordinate to histidines and/or cysteines, the coordination of aspartic acid and glutamic acid residues to the metal, also has been found in metalloenzymes [26].

Zinc is a good intermediate Lewis acid, especially in complexes with lower coordination numbers; it lowers the pK_a of coordinated water and is kinetically labile, and the inter conversion among its four-, five- and six-coordinate states is fast [27]. The theoretical studies have shown that zinc does not have a strong preference for a particular number of water molecules in its first coordination layer and can accommodate four, five or six water ligands; the calculated energy differences between isomeric $[Zn(H_2O)_6]^{2+}$, $\{[Zn(H_2O)_5],(H_2O)\}^{2+}$ and $\{[Zn(H_2O)_4],(H_2O)_2\}^{2+}$ complexes differ by only a few kilocalories per mole [28]. Moreover, dynamic conversion of structural zinc into a transient catalytic centre may be a mechanism for nucleic acid cleavage [29]. Recently, we determined the metal–ligand stoichiometry between $[ZnCl_2(en)]$ (where en = 1,2-diaminoethane or ethylenediamine) complex and chloride at pH 7.2. In the presence of an excess of chloride (0.010 M NaCl), the octahedral $[ZnCl_4(en)]^{2-}$ formed in solution at pH 7.2 [30] (Eq. (6)).



(6)

Also, we have investigated the mechanism of interaction between biologically relevant nucleophiles and $[ZnCl_2(terpy)]$ (where terpy = 2,2′:6′,2″- terpyridine) complex in the presence of NaCl [31, 32]. The excess of chloride did not affect coordination geometry of complex [32]. The result of the metal–ligand stoichiometry between $[ZnCl_2(terpy)]$ complex and imidazole implied formation of the five-coordinate specie $[Zn(terpy)(imidazole)_2]$ [31] (**Figure 5**).

Promising anticancer agents could be the zinc-based compounds, especially because zinc is implicated as an important cytotoxic/tumour suppressor agent in several cancers [33].

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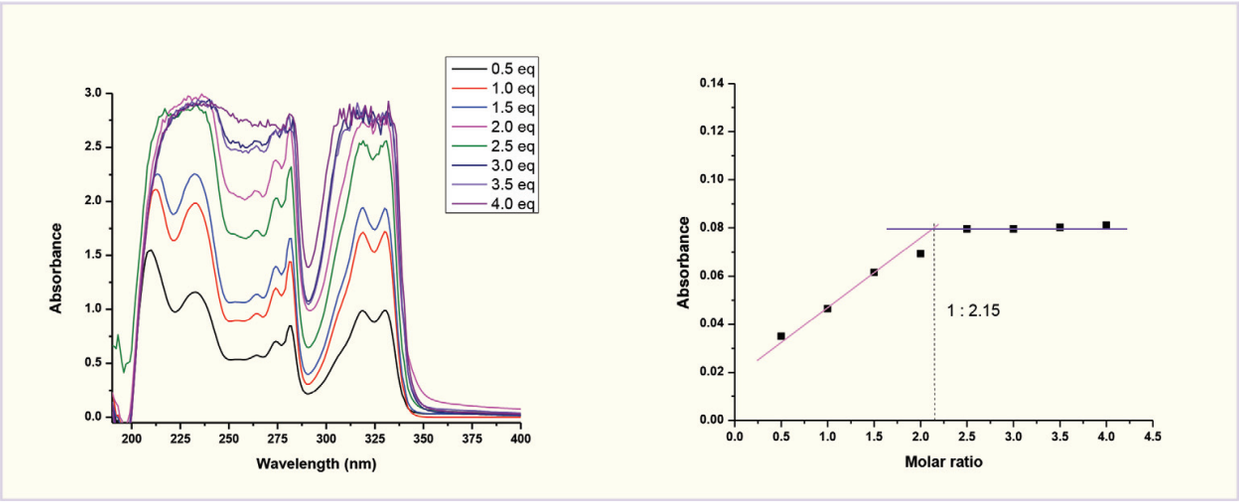

Figure 5. Titrations of $[ZnCl_2(terpy)]$ with imidiazole as monitored by UV-vis spectra. Left: $[ZnCl_2(terpy)]$-imidiazole, right: cross-section of UV-vis spectra at 350 nm in the presence of 0.001 M NaCl [31].

The mechanism of potential anticancer activity of zinc(II) complexes is assumed to be connected with: (i) fast inter conversion among its four-, five- and six-coordinate states; (ii) preference of the variable coordination geometries (tetrahedral, five-coordinate and octahedral) that zinc(II) is able to adopt, towards diverse donor site of relevant nucleophiles [27]. Knowledge of mechanism of the interaction zinc(II) ions with biomolecules and other relevant ligands is essential for understanding the processes in the cells during delivery of complexes to DNA and proteins.

On the other hand, copper(II) controls cancer development. It serves as a limiting factor for multiple aspects of tumour progression, growth, angiogenesis and metastasis [34–36]. Copper(II) complexes offer various potential advantages as antimicrobial, antiviral, anti-inflammatory, antitumour agents, enzyme inhibitor, chemical nucleases, and they are also beneficial against several diseases like copper rheumatoid and gastric ulcers [37, 38]. It has been shown recently that metal complexes of imidazole terpyridine (itpy) have potential applications in chemotherapy [39]. Changing the ligand environment towards the specific target is a possible way of tuning the selectivity of a drug molecule. The nature of the ligands plays an important role in the binding of a metal complex to a biomolecule such as DNA or protein [39, 40].

The chemistry of copper is dominated by the +2 oxidation state, for example, copper(II) complex ions. In comparison with other divalent first-row transition-metal aqua ions, the $[Cu(H_2O)_6]^{2+}$ ion is extremely labile [41, 42]. This effect is a consequence of Jahn-Teller distortion. As a result of the d^9 electronic configuration, an elongation of the axial-bound solvent molecules is weakly coordinated. Due to this distortion the axial water molecules are weaker bound to the central atom and therefore can be more easily substituted. The strong ligand field forces the metal ion into a different geometry, for example, 2,2′,2″-triaminotriethylamine ligands (tren) will restrict the degree and rapidity of distortion of the $[Cu(tren)H_2O]^{2+}$ complex and remove the dynamic Jahn-Teller effect as stabilizing effect [43]. The bulk of five-coordinate {Cu(terpy)(bipy)} and {Cu(terpy)(phen)} (terpy = 2,2′:6′,2″- terpyridine or derivative, bipy = 2,2′-bipyridine or derivative, phen = 1,10-phenanthroline or derivative) complexes

exhibiting ostensibly square-based pyramidal geometries also shows an additional interaction in the remaining axial site leading to a better description as their being six-coordinate [44].

4.3. Study on the kinetics and mechanism of the reactions of zinc(II) and copper(II) complex compounds with relevant biomolecules

Clear understanding of complex formation reactions between zinc(II) and copper(II) complexes and biorelevant nucleophiles is still largely missing. Substitution behaviour of Zn and Cu-complex compounds at physiological conditions is very complex due to the rather high molecular mobility, distortions of complex compound and facile interconversion of four- to five-, six-coordinate complexes. Adopted geometry of complex compounds conditionals different preferences towards bio-ligands. Thus, the square pyramidal structure of Zn(II) and Cu(II) in biological systems prefers *O*-carboxylate or carbonyl and *N*-imidazole donor bio-ligand, while tetrahedral prefers *S*-thiolate or thioether, *N*-imidazole [4]. Investigation of mechanism of the interaction between zinc(II) and copper(II) ions and biomolecules and other relevant ligands is essential for understanding the mechanism of action of the potential zinc- and copper-based antitumour drugs.

Recently, we have investigated by different methods (UV-Vis, EPR, HPLC-MS, density-functional calculations, mole-ratio, etc.) the kinetics and mechanism of the reactions between tetrahedral and square-pyramidal Zn(II) or Cu(II) complex compounds (i.e. [$ZnCl_2$(en)], [$CuCl_2$(en)], [$CuCl_2$(terpy)] and [$ZnCl_2$(terpy)]) with bio-nucleophiles as a function of entering nucleophile concentrations and temperature at pH 7.2–7.4 [30–32, 45]. The kinetics showed that the substitution reactions involve the consecutive displacement of both chloride ligands for every complex. Higher reactivity of [$CuCl_2$(terpy)] complex then [$ZnCl_2$(terpy)] was obtained. The order of reactivity of the investigated biomolecules for the first reaction step is: glutathione (GSH) >> DL-aspartic acid (DL-Asp) > guanosine-5′-monophosphate (5′-GMP) > inosine-5′-monophosphate (5′-IMP) > L-methionine (L-Met) (for [$CuCl_2$(terpy)]), while for [$ZnCl_2$(terpy)] order is: DL-Asp > GSH > 5′-GMP > 5′-IMP >> L-Met. Chelate formation and pre-equilibrium were obtained for the substitution process between [$ZnCl_2$(terpy)] complex and glutathione [32]. The π-acceptor properties of the tridentate N-donor chelate (terpy) predominantly control the overall reaction pattern [31, 32, 45]. Based on energetic stability of complexes, it can be concluded that both complexes make hydrates very easy, but the bond between water molecule and metal ion is pretty weak. In addition, there is a very good agreement between experimental and calculated spectra obtained for hydrated and non-hydrated complexes in aqueous solution. During formation of monohydrate, Zn(II) and Cu(II) complexes obtain little shaped octahedral geometry, with three nitrogen and chloride atom in the central plane, and with water molecule and the other chloride atom on the line almost normal to the plane [32]. The presence of various concentration of chlorides has significant impact on rate constants of substitution processes of the [$ZnCl_2$(terpy)] complex by nucleophiles [31].

As we mentioned in Section 4.2, the mole-ratio method was used for determining the metal-ligand stoichiometry between [$ZnCl_2$(en)] and chloride at pH 7.2. The results have shown stepwise formation of 1:1 and 1:2 complexes, and indicate additional coordination of chlorides in the first coordination sphere (Eq. (6)) [30]. The kinetics of ligand substitution reactions of this

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complex and biological relevant nucleophiles such as 5′-IMP, 5′-GMP, L-Met, GSH and DL-Asp was followed under *pseudo*-first-order conditions by UV-Vis spectrophotometry. In the presence of an excess of chloride the octahedral complex anion $[ZnCl_4(en)]^{2-}$ has been formed. The first step of the substitution reactions could be interpreted as substitution of the axial chlorido ligands in *cis* position towards bidentate ethylenediamine by the biologically relevant nucleophiles, while the second step is substitution of the equatorial chlorido ligand. The order of reactivity of the investigated nucleophiles for the first reaction step is 5′-IMP > GSH > L-Met > DL-Asp > 5′-GMP, while for the second reaction step is GSH > L-Met > 5′-IMP > DL-Asp > 5′-GMP [30].

In the presence of an excess of chloride, the square-planar complex $[CuCl_2(en)]$ exists as a *pseudo* octahedral complex with two axially and weakly-bound solvent ligands, these ligands are rapidly replaced/substituted by chloride ions to form $[CuCl_4(en)]^{2-}$ as a pre-equilibrium intermediate, while equilibrium reaction was observed for $[CuCl_2(terpy)]$ [45]. The order of reactivity of the investigated bio-relevant nucleophiles towards $[CuCl_4(en)]^{2-}$ complex is: GSH > 5′-GMP > 5′-IMP > DL-Asp > L-Met, while towards $[CuCl_2(terpy)]$ the order of reactivity is: DL-Asp > L-Met > GSH > 5′-GMP > 5′-IMP, for the first reaction step. Different order of reactivity of biomolecules towards $[CuCl_2(en)]$ and $[CuCl_2(terpy)]$ complexes could be explained by different geometrical structures of complexes (octahedral and square-pyramidal, respectively) in the presence of chloride and their different preferences towards donor atoms of biomolecules. Mass spectrum of $[CuCl_2(terpy)]$ in Hepes buffer has shown two new signals at m/z = 477.150 and m/z = 521.00, assigned to $[CuCl(terpy)]^+$ − Hepes fragments of coordinated Hepes buffer. These signals also appear in mass spectra of ligand-substitution reactions between $[CuCl_2(terpy)]$ and biomolecules in molar ratio 1:1 and 1:2. According to EPR data, L-Met forms the most stable complex with $[CuCl_2(en)]$ among the ligands considered (**Figure 6**), while $[CuCl_2(terpy)]$ complex did not show significant changes in its square-pyramidal geometry in the presence of the buffer or bio-ligands [45].

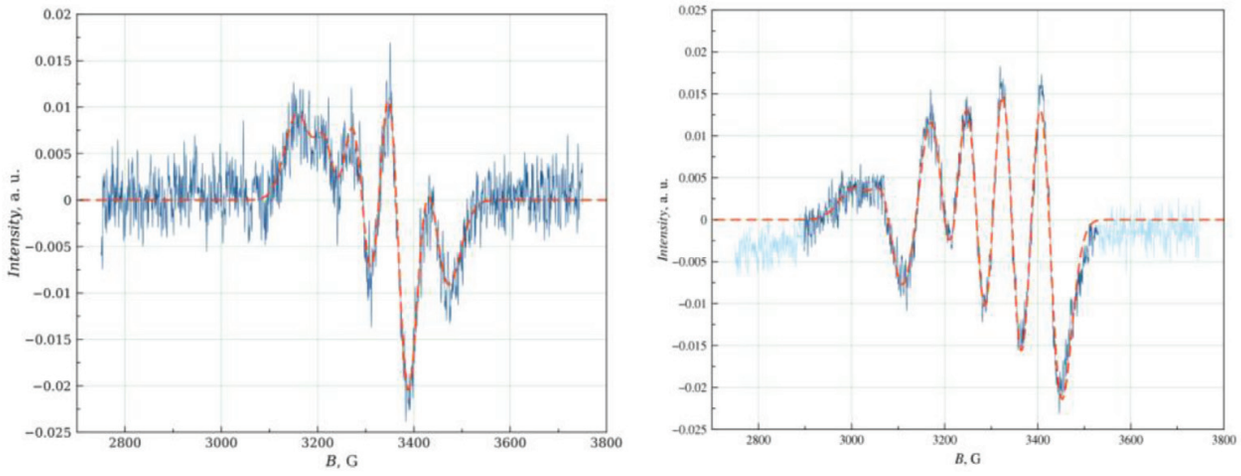

Figure 6. Left: EPR spectrum of 0.0001 M $[CuCl_2(en)]$ complex solution in 0.010 M NaCl 0.025 M Hepes buffer, pH 7.4, at 300 K. Right: EPR spectrum of 0.0001 M equimolar $[CuCl_2(en)]$ − L-Met solution in 0.0010 M NaCl 0.025 M Hepes buffer, pH 7.4, at 300 K [45].

5. Conclusions

Detailed knowledge of chemical properties of complex compounds could be very useful for the future investigations of new pharmacological agents. Although recent studies are trying to obtain more mechanistic information, and results provide very useful information for the future design of potential zinc- or copper-based anticancer drugs, it is evident that, up to now, this field is not investigated enough. In general, attempts to correlate the antitumour activity of zinc(II) and copper(II) compounds with coordination number and geometry could be very promising for discovery of the alternative tumour treatment.

Acknowledgements

The author gratefully acknowledges financial support from State University of Novi Pazar, and Ministry of Education, Science and Technological Development, Republic of Serbia (Projects No. 172011).

Conflict of interest

No potential conflict of interest was reported by the author.

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