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Complexes of biogenic amines in their role in living systems

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1 Introduction

Although polyamines (PA) belong to relatively simple aliphatic substances, their role in life processes of animals and plants is of key importance [1]–[5]. The group of the most important amines, called biogenic ones includes:

Spermine (Spm):	$H_2N(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2$
Spermidine (Spd):	$H_2N(CH_2)_3NH(CH_2)_4NH_2$
Putrescine (Put):	$H_2N(CH_2)_4NH_2$.

Of secondary importance are homologues of biogenic amines, occurring in lower contents in living organisms [2, 6–8]:

1,3-diaminopropan:	$H_2N(CH_2)_3NH_2$
Cadaverine:	$H_2N(CH_2)_5NH_2$
Homospermidine:	$H_2N(CH_2)_4NH(CH_2)_4NH_2$
Norspermine (3,3,3-tet):	$H_2N(CH_2)_3NH(CH_2)_3NH(CH_2)_3NH_2$
Thermospermine:	$H_2N(CH_2)_3NH(CH_2)_4NH(CH_2)_4NH_2$
Caldopentamine:	$H_2N(CH_2)_3NH(CH_2)_3NH(CH_2)_3NH(CH_2)_3NH_2$.

The first polyamine discovered in a living organism was tetramine, a spermine crystallised out of sperm in 1678 by Van Leewenkeuk [9]. Putrescine was discovered in the end of the 19th century in microbes and then triamine: spermidine was discovered in the beginning of the 20th century [2]. Later studies have shown that in animal cells spermidine and spermine occur at elevated levels, while in prokaryotes spermidine and putrescine contents are dominant. Putrescine, spermidine, 1,3-diaminopropan, homospermidine, norspermidine, and norspermine have been found in many gram-negative bacteria and algae [7, 10, 11].

Total concentration of PA in living organisms is on the order of millimols, however, the concentration of free polyamines is much lower. A low level of free amines follows from the fact that they are involved in noncovalent interactions with biomolecules occurring in living organisms such as nucleic acids, proteins, or phospholipids. High concentrations of non-bonded polyamines have been detected first of all in young molecules in the process of growth, in particular in rapidly proliferating cancer cells [6, 12]. Elevated levels of free polyamines have been observed, e.g. in breast, colon, lung, prostate, and skin tumours, accompanied by changed levels of enzymes responsible for biosynthesis and catabolism of polyamines. Because of the increased level of free polyamines and a tendency of their interaction with nucleic acids and other bioligands, these compounds have become objects of intense study [1, 13–19]. There is no doubt that the regulation of biosynthesis of polyamines and catabolism is one of the most important pathways in the search strategy for chemoprevention and chemotherapeutic drugs [14, 15, 20–38]. The present state of knowledge of these processes, their significance in biological systems, and their application in medicine are presented in subsequent sections of this chapter.

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2 Polyamines in living systems

Polyamines occur in practically all living organisms, although the level of their concentration depends on the type of species, type of tissue, and first of all on the age of the cells [10, 14, 39–45]. The organ in which the highest concentration of polyamines (2 mM spermidine and 4 mM spermine) has been detected, is the pancreas [10]. High levels of polyamines (spermine and spermidine) have also been detected in the kidneys, spleen, liver, lungs, and in semen [7, 20]. Spermidine and its analogues are also present in high levels in the central nervous system, and that is why spermidine is also called neuridine. It should be pointed out that spermidine is not uniformly distributed in the entire nervous system and occurs in high concentration in the white matter of the brain. Also, an untypical increase in the concentration of spermidine and spermine in the brain has been noted with increasing age of the organism [39, 40]. A similar situation as in the nervous system (different concentration of amine in the same tissue) has been noted in the skin. Measurements with liquid chromatography and fluorescence methods have proved much higher concentrations of spermidine and spermine in the epidermis than in the dermis of the skin. Regular measurements of changes in the PA level in the skin are necessary to control the condition of patients with dermatological diseases [46]. Small amounts of biogenic amines have been found in blood tissues, e.g. 0.01 mM in erythrocytes, and in urine (putrescine and spermidine) [41], in which an increase in their concentration is a symptom of disease.

Increasing concentration of polyamines is also observed in people with cystic fibrosis or mucoviscidosis, most probably spermidine and the products of its metabolic decomposition play an important role in the pathogenesis of dysfunction of cell membranes [47].

Another interesting fact is that polyamines, strongly basic substances, show a high affinity to protons. This affinity increases with an increasing methylene chain of the amine. In physiological conditions, at pH close to 7, biogenic amines are fully protonated. Amines with a methylene chain shorter than three methylene groups in physiological conditions can be partly protonated, which consequently show a lower affinity to polyanions than biogenic amines [48].

From a pharmacological point of view, polyamines are toxic [15], but at appropriate concentrations play various positive roles in living organisms, Figure 1. These compounds interact with entire cells, cellular organelles, and nucleic acids, and participate in many metabolic reactions [5, 49]. Polyamines have been found to catalyse and control biosynthesis of nucleic acids and are directly responsible for macromolecular synthesis taking place upon cell growth (synthesis of DNA is stimulated by spermidine) [44]. Strongly basic polyamines show high affinity to anionic compounds and thus show the ability to bind to nucleic acids. When interacting with phosphate groups of polynucleotides, they prevent denaturation and stabilise the structure of the nucleic acid [6, 10, 50, 51].

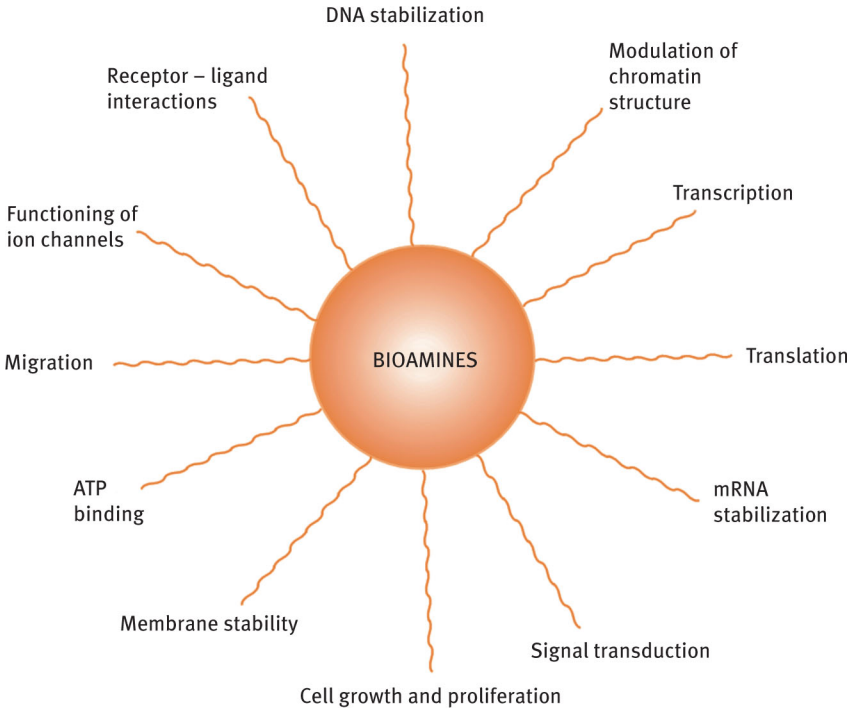

Figure 1: Role of biogenic amines in living organisms.

Polyamines show a tendency towards initiation of t-RNA methylation *in vitro*, prevent enzymatic degradation and radiation-induced damage to ribosomes, and influence synthesis of nucleic acids and proteins [10, 41]. Moreover they affect the degree of DNA packing in a bacteriophage [52, 53].

Biogenic polyamines also influence the functioning of biological membranes (spermine stabilises membrane activity in bacteria), and their effect depends first of all on the positive charge of the amine chain (the greater the charge the better the stabilisation). A very important consequence of attachment of PA to double-layered membranes is protection against lipid peroxidation. Biogenic polyamines also modulate the synthesis of triacylglycerols necessary for membrane construction [24, 26, 27, 43, 49]. Spermidine is also known to exert an antimutagenic effect in bacteria [44].

Some polyamines are precursors of amino acids that are formed by oxidative deamination of amines. One of those amino acids (derivatives of amines) is putreanine, which is a natural component of the brains of vertebrates [42].

The pathway of polyamine biosynthesis has been for the first time defined on the basis of investigation of microorganisms. The later developed scheme of poly-amine biosynthesis for mammals proved almost identical, Figure 2. In bacteria (e.g. in *Escherichia Coli*) and in plants, putrescine is synthesised along two parallel pathways:

1. from ornithine as a result of its decarboxylation in the presence of ornithine decarboxylase
2. from arginine in the process of decarboxylation to agmatine, which is then hydrolysed with involvement of agmatine ureohydrolase directly or through the intermediate product N-carbamyl-1, 4-diaminobutane to putrescine and urea.

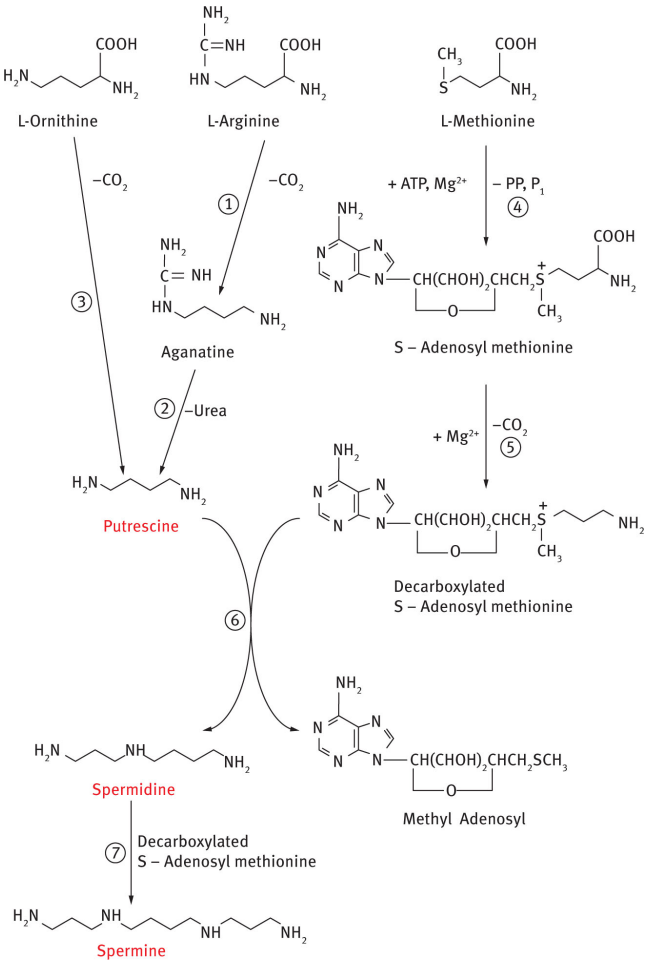

Figure 2: The pathway of polyamine synthesis in living organisms. The enzymes involved are 1 – arginine decarboxylase, 2 – agmatine ureohydrolase, 3 – ornithine decarboxylase, 4 – S-adenosylmethionine synthase, 5 – S-adenosylmethionine decarboxylase, 6 – spermidine synthase, and 7 – spermine synthase.

Catabolism of polyamines in animals has been discovered as a two-stage process controlled by the enzymes spermidine/spermine N1-acetyltransferase (SSAT) [54]–[59]. Thanks to the activity of these enzymes, acetylated polyamines become substrates for further conversion of spermidine to putrescine. SSAT catalyses the formation of N1-acetylspermine or N1-acetylspermidine by a transfer of acetyl group from acetyl-coenzyme

A to the N1 position of spermidine or spermine. In the second stage of this pathway, peroxisomal flavin adenine dinucleotide (FAD) is formed, and its level is directly related to the activity of N1-acetylpolyamine oxidase (APAO) [60]–[65]. APAO is the enzyme that catalyses the cleavage of acetylated polyamines and is responsible for formation of spermidine or spermine, 3-aceto-aminopropanal and H_2O_2 [62, 63, 66–68]. Alternatively, spermine can be oxidised back directly to spermidine with involvement of spermine oxidase (SMO) the enzyme dependent on Flavin adenine dinucleotide (FAD) [67]–[69]. Induction of SMO has been reported to accompany the inflammatory conditions related to the colon and lung cancer, which suggests that SMO may be an attractive target for chemoprevention strategies [70]–[74]. A side effect of the oxidation reaction is generation of toxic hydrogen peroxide (H_2O_2). The molecules of H_2O_2 are known to play an essential role in DNA damage, which leads, among other things, to catabolism of polyamines. Moreover, a significant reduction of the level of intracellular polyamines, which accompany the process of catabolism, is inhibited by an increase in the level of inhibitors of this process [42].

The best recognised transport of polyamines in animals suggests that in the first stage PAs enter the cell through as yet unidentified membrane transporter/ carrier. This process is powered by the membrane potential and then by rapid accumulation of polyamines into polyamine-sequestering vesicles driven by a vacuolar – ATPase pH gradient and proton exchange. This system of transportation permits explanation of the seemingly high total concentration of intracellular poly-amines, although the actual concentration of free PAs is believed to be relatively low [75]–[78]. Another model of polyamines transportation assumes that spermine is bonded to heparin sulphate and glypican 1 (GPC1), which act as agents transporting amine inside the cell [72, 75, 76].

The enzymes and the amines synthesised (especially putrescine) are the direct target of the efforts undertaken to inhibit the synthesis of polyamines in the diseases in which the elevated level of polyamines is observed, particularly in cancer.

3 Polyamines as tumour markers

Neoplastic tumours, along with circulatory system diseases, are the leading causes of death in developed countries [79]. It has been recently established that increased incidence of inflammatory conditions and increased level of synthesis of polyamines are related to the development of intraepithelial neoplasia, which is a risk factor for cancer development. There is ample literature on the relation between the increased level of polyamines concentration and neoplastic diseases, which suggests a relation between induced biosynthesis of PAs and neoplasia [1, 72, 80]. Metabolism of polyamines is an integral component of the mechanisms of carcinogenesis in epithelium tissues. Development of neoplastic disease is a multistage process that involves specific transformations leading to progressive change from healthy normal cells to cancer cells. If the range of inflammatory conditions is irregular, the cell response leads to chronic inflammatory conditions in which the inflammatory focuses are dominated by macrophages and other inflammatory cells. This leads to generation of increased amount of growth agents and cytokines as well as reactive species of oxygen and nitrogen responsible for DNA damage [81, 82].

In persons with neoplastic diseases a considerable increase in the concentration of polyamines in blood and urine is observed; however, no specific values characteristic of the disease could be established because the level of polyamines depends on activity and degree of development of the disease [10, 15, 41, 83–85]. In many types of cancer, e.g. in persons with cancer of the stomach, pancreas, and breast, the concentration of polyamines is practically unchanged (only in 20% and 25% of patients is an increase in the concentration of spermidine and spermine observed, respectively), while an increased level of PAs is observed in about 50% of persons with malignant cancer of the lungs. In persons with cancer of the genital tract, prostate, or bladder, an increased level of PAs is noted in about 90% of patients [20, 45, 74]. Measurements of the concentrations of spermine and spermidine in urine and blood often facilitate diagnosis and evaluation of health conditions and can be used for monitoring the progress of therapy. If the therapy is effective, a significant decrease in the level of polyamines is observed starting from the first week of chemotherapy [15, 45, 86]. However, it has been established that analogues of biogenic amines (spermidine and spermine) inhibit the growth of tumours in model systems and show an antimalarial effect. These types of derivatives are mainly obtained by the Mitsunobu reaction (between alcohol and activated amine, leading to a chiral derivative of polyamine) [87]. In general, cells have well-developed mechanisms regulating the correct intracellular level of PAs, and deregulation of this metabolism (biosynthesis and catabolism) and transport is of key importance for cell growth. An increased level of polyamines (as a consequence of their increased synthesis) is noted as a result of inflammatory conditions or increased proliferation following from rapid growth of cancer cells (PA have pleiotropic effects on cell physiology) [88].

In the 1960s, Russell and Snyder for the first time noted a high level of concentration of ornithine decarboxylase (ODC) accompanying the occurrence of cancer [89]. High activity of ODC and a high level of PAs have been observed to accompany an increase in familial adenomatous polyposis in cases of genetic predispositions for colon cancer related to mutation of adenomatous polyposis coli [90]. Pioneer works aimed at checking correlations between a high level of polyamines and the occurrence of skin cancer have shown that an elevated level of ODC is necessary and often sufficient for triggering cancer in mice [73]. It has been also established that the level of ODC increases in persons with human non-melanoma skin cancer (NMSC) [91]. Induction of ODC and an increase in the level of PAs level have been correlated with breast cancer [16, 92] and prostate cancer [17]. Also other enzymes such as spermidine synthase and spermine synthase are closely related to carcinogenesis. The level of enzymes involved in catabolism is also related to carcinogenesis, e.g. increased activity of SMO is observed in inflammation conditions connected to neoplastic diseases such as infection and the ensuing cancer of alimentary tract (*Heliobacter* pylori) [93]. Infection of gastric epithelial cells provoked by *H*. pylori also leads to deregulation of SMO expression, leading to an increased level of DNA damage and apoptosis. Removal of the source of inflammation has been observed to be correlated with a reduction in SMO expression [94]. A decrease in the level of SMO can bring a reduction in the inflammatory condition caused by *H*. pylori and consequently inhibition of gastric cancer development. An elevated level of SMO expression, relative to its level in healthy prostate tissues, has been also found in tissues from patients with prostatic intraepithelial neoplasia and prostate cancer [95] and ulcerative colitis, the presence of which is related to a high risk of colon cancer [96]. Introduction to the organism of appropriate inhibitors of biosynthesis, e.g. those that inhibit the activity of ornithine decarboxylase, reduces the level of biogenic amines in the organism, Figure 3. Of particular importance is α-difluormethylornithine (DFMO), obtained in 1978, Figure 4. Significant inhibition of cell replication after the introduction of DFMO (or similar inhibitors) suggests a potential therapeutic strategy for the treatment of neoplastic diseases.

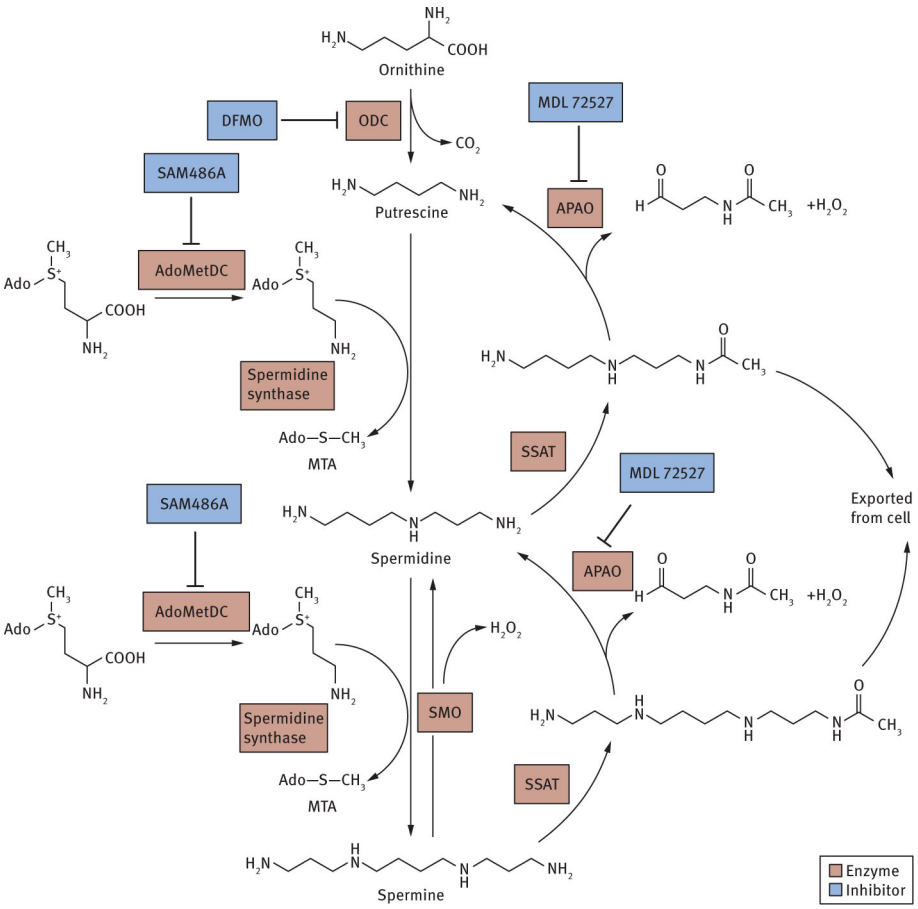

Figure 3: Targets in the polyamine metabolic pathway [72].

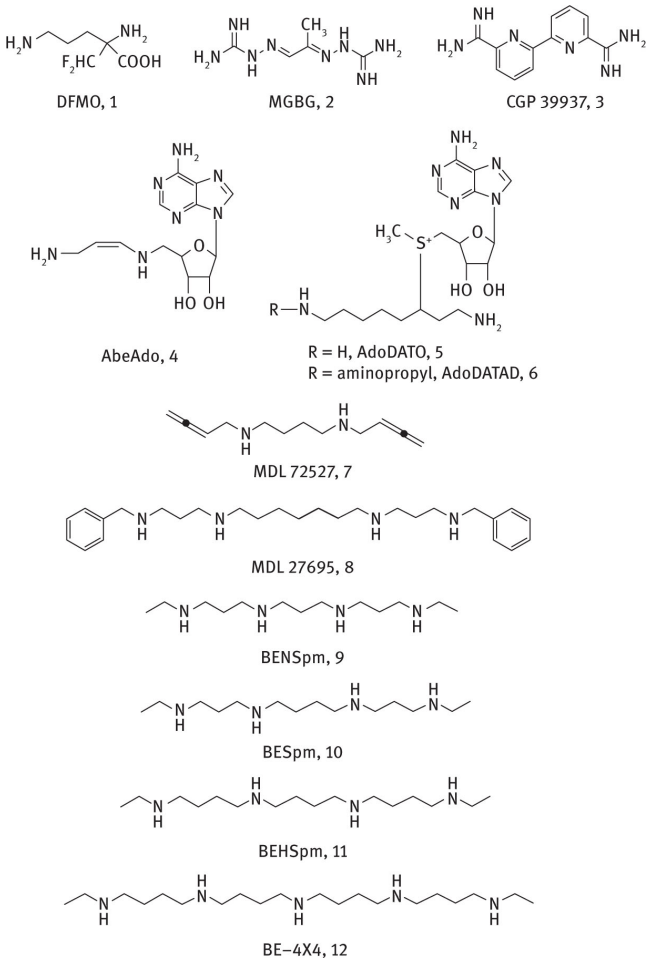

Figure 4: Structures of the classical inhibitors of polyamine biosynthesis [99].

Interference into the metabolism of polyamines through the use of inhibitors of biosynthesis or catabolism seems promising in the treatment of inflammatory conditions bearing substantial risk of cancer development. Clinical trials using DFMO, a selective inhibitor of polyamines synthesis, have shown that after a year of DFMO application the size of enlarged prostates and the amount of serum prostate-specific antigen were reduced by half in persons genetically predisposed to prostate cancer. Similarly, the 3-year application of a combination of DFMO and sulindac, a non-steroid anti-inflammatory drug (NSAID), to persons with stage 1 colon cancer led to a 70% reduction in the amount of cancer cells [1, 97, 98].

4 Weak interactions of polyamines

The most common types of weak noncovalent interactions in biological systems are illustrated in Figure 5.

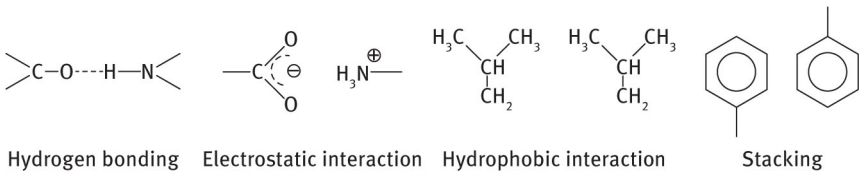

Figure 5: Types of weak interactions.

In the systems of polycations of biogenic amines with other bioligands, the dominant types of interactions are ion–ion or ion–dipole, with involvement of protonated PAs and biomolecules that contain atoms or a group of atoms of negative charge or high electron density [8]. The main factor determining the possibility of occurrence of weak interactions is high basicity of polyamines. In physiological environments, polyamines occur in protonated form [2], and -NH_x^+ groups are potential positive centres of interactions of electrostatic type with other biomolecules such as nucleosides, nucleotides, amino acids, proteins, nucleic acids, or phospholipids [86].

Protonation of primary amine groups in the PA molecule is more exothermic than protonation of secondary groups. Differences in the subsequent ΔH values decrease with increasing length of the chain, which is a consequence of changes in the transmission of inducing effect depending on the number of methylene groups. If the chain is shorter than three methylene groups, at least one pK value is less than seven, and the molecule is partly protonated in the physiological medium [99]–[101]. This explains a low activity of short polyamines in noncovalent interactions in biological systems [48].

Reliable information on the formation of molecular complexes as a result of non-covalent interactions with involvement of protonated polyamines have been published about 40 years ago [102, 103]. As a result of interactions of this type, electron density at the reaction centre changes, which leads to a shift in NMR signals and permits identification of the sites of interactions. On the basis of NMR studies, the protonated -NH_x^+ groups of spermidine and spermine have been found to react with deprotonated phosphate groups and high electron density fragments of AMP, ADP or ATP (5'-adeninomono-, di- and triphosphate, respectively) [102, 104].

According to the polyelectrolytic Manning theory, the main factor determining the mode of interactions is the charge of reagents [105, 106]. However, this approach does not explain the specificity of certain reactions. Analysis of the character of weak interactions of polyamines has revealed that their structure influences the character of the reaction and formation of adducts with other biomolecules. PAs cannot be approximated as a point charge, as has been assumed in analysis of the reaction of biomolecules with metal ions, e.g. magnesium(II) [107]. Spatial matching of polyamine to other bioligands determines the stability of adducts formed. According to the calorimetric studies of polyamine interaction with DNA, much better agreement between theory and experiment is obtained when taking into account the structural actors [108]. Particular improvement in this agreement is obtained for the biogenic amines spermidine and spermine. For biogenic amines the effectiveness of interactions related to structural factors increases in the order Put < Spd < Spm, which corresponds not only to the number of amine groups but also to the length of these PA molecules. As the formation of molecular complexes is accompanied by a shift of the acid-base equilibrium in the reversible process:

$$H_xPA + H_yNuc \leftrightharpoons (Nuc)\,H_{x+y--n}\,(PA) + nH^+PA = \text{polyamine; Nuc} = \text{nucleoside},$$

the liberation of hydrogen cations permits determination of thermodynamic stability of adducts by a potentiometric method with computer analysis of experimental data. Such determinations were performed for a series of binary and ternary systems of polyamines with nucleosides, nucleotides, and amino acids [8, 109–115]. A scheme of the adduct forming in the system of AMP/(3,3-tri), 3,3-tri=$NH_2(CH_2)_3NH(CH_2)_3NH_2$ is presented in Figure 6 [110]. Interestingly, according to NMR results, the longer polyamine, spermine, in the system with the same nucleotide, interacts only with endocyclic nitrogen atoms from AMP (at different spatial arrangement), see Figure 6 [111].

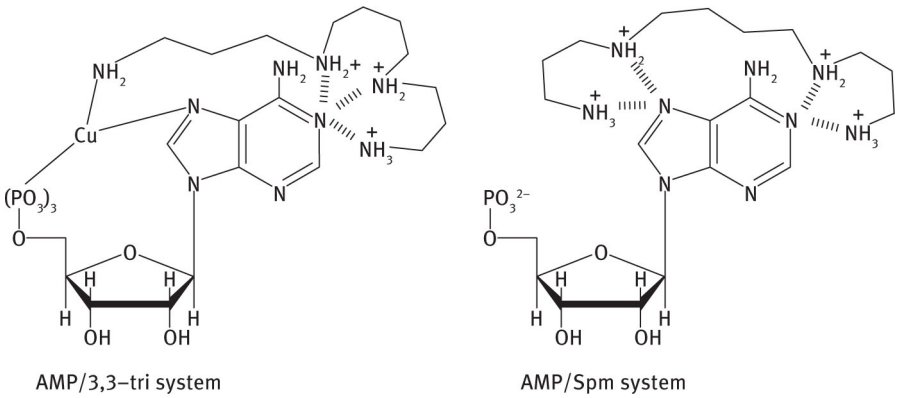

Figure 6: Tentative mode of interactions (noncovalent interaction).

Molecular complexes form in the pH range in which amine is protonated and act as a positive centre of interaction, while the nucleoside (nucleotide, amino acid) is deprotonated and acts as a negative centre of interaction. Dissociation of polyamine leads to adduct decomposition (Figure 7). In comparison to the system with cytidine (Cyd) the pH range of adduct formation in the solution with uridine (Urd) is significantly shifted towards higher pH values, which is a consequence of greater basicity of the endocyclic nitrogen atom from the second nucleoside ($\log K^H_{Cyd} = 4.5$, $\log K^H_{Urd} = 9.2$) and a different pH range of its dissociation (Figure 7a, b) [8, 114, 115].

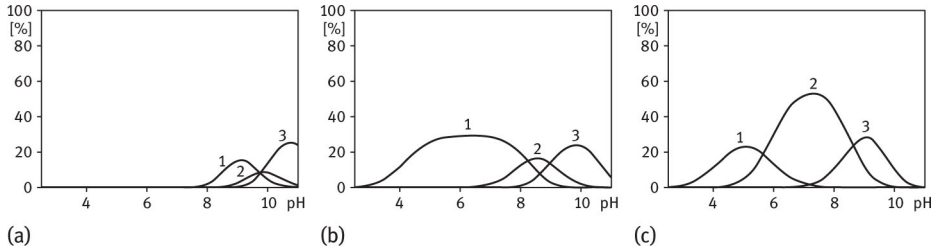

Figure 7: Distribution diagram for (a): Urd/Spm, (b): Cyd/Spm, (c): CMP/Spm systems; (a): 1-(Urd)H_3(Spm), 2 – (Urd)H_2(Spm), 3 – (Urd)H(Spm); (b): 1 – (Cyd)H_4(Spm), 2 – (Cyd)H_3(Spm), 3 – (Cyd)H_2(Spm); (c): 1 – (CMP)H_5(Spm), 2 – (CMP)H_4(Spm), 3 – (CMP)H_3(Spm).

The presence of an additional reaction centre, such as a phosphate group from CMP, causes a shift in the pH range of adduct formation towards higher acidity (Figure 7c). Dissociation of the first proton from the nucleotide takes place at a lower pH than that of the dissociation of nucleoside. Of importance is also the ionic composition of the solution. The presence of Na^+ or K^+ cations weakens the effectiveness of the interactions. The observed formation of complexes of polyamines with inorganic ions and the salt effect changing the acid-base character of the ligands [116]–[118] supports the thesis that formation of adducts of polyamines with other bioligands is of ion-ion and ion-dipole nature. In general, the thermodynamically stable molecular complexes have been found to form only when at least two centres of interaction between the ligands are present [107]. The NMR results have also revealed differences in the types of interactions between different polyamines and ATP molecule. It has been suggested that spermine in contrast to spermidine, prefers pyrimidine base to triphosphate group [119, 120].

Other information provided by NMR results is that in the systems of PA with amino acids the inversion effect takes place. The amine groups from PA can be positive or negative reaction centres depending on the degree of amine protonation [112, 113, 121]. The above discussed type of interactions and noncovalent interactions in the system with metal ions is essential for molecular recognition and self-assembly of biomolecules in living organisms [122, 123].

In the systems with nucleic acids, putrescine polycation at a low concentration locates in and interacts with minor and major DNA grooves, while spermidine and spermine locate only in the major groove. In contrast to putrescine the interaction of spermidine when at high concentrations is much stronger, and this amine is located in major grooves, as indicated by Infrared spectroscopy (IR) results. The authors of [124] suggest the presence of hydrophobic interactions and, apart from them, the presence of electrostatic interactions between polyamines and DNA phosphate groups. The results obtained for the system of DNA and spermine also point to the occurrence of electrostatic interactions [125, 126]. The interactions of spermine polycation in the system with DNA and metal ions have been studied by X-ray diffraction method. The polyamine joins in the crystal lattice the duplexes of nucleic acid through a system of hydrogen bonds between phosphate groups and nitrogen atoms of the bases [127]. Significant differences have been noted between the interaction of biogenic amines and their analogues. The former bind to DNA through major and minor grooves and phosphate groups, while e.g. 1,11-diamine-4,8-diazaundecane (analogue of spermine shorter by one -CH_2 group) binds mainly through the N7 atom from guanine and phosphate groups. Moreover, DNA complexes with analogues of biogenic amines are thermo-dynamically weaker than those with spermine, spermidine, or putrescine. Bonding of amines with DNA leads to partial transformation of B-DNA to A-DNA, which has not been observed for biogenic amines [128]. The study of polyamine interactions with dendrimers has revealed that biogenic amines make more stable complexes than their synthetic analogues and the amine affinity to dendrimers depends on the charge of the polycation [129]. The reactions of a series of polyamines with phytic acid (*myo*-inositolhexakisphosphate acid, IP) were investigated by potentiometric measurements and ^{31}P NMR. As a result of multifunctional noncovalent interactions, stable complexes of the type (IP)H_n(PA) of the molar ratio IP:PA 1:1 and of a different number of protons, are formed in the system. Nonselective interactions in the adducts take place between the positive protonated -NH_x^+ groups from polyamines and negative centres of deprotonated phosphate groups from IP [130, 131]. Biogenic amines have been also found to show antioxidative activity. Spermine is a stronger antioxidant than spermidine, which is suggested to be related to the higher ability of Spm for metal chelation and damage of radicals [132].

The role of polyamines in processes taking place in living organisms has stimulated further studies of this group of ligands. The application of complexes in medicine is described in another part of this chapter. Recently, a number of review papers have been published on the significance of PA in living systems, describing their role as necessary components of biological systems and their negative influence on the health [133]–[136].

5 Complex formation of bioamines

The complexing properties of aliphatic polyamines depend on the number and nature of -NH_2 groups and the length of methylene chains in the molecules. Literature data on the coordination compounds, mainly in binary systems, have been reviewed by D.A. House [137]. One of the most important and earliest studied ligands is ethylene diamine (en), which in metal-free systems assumes *trans* or *cis* (gauche) conformation, the transformation energy is low, close to 4 kJ/mol. Bonding with metal ions usually leads to formation of a five-membered ring. Such species can assume enantiomeric conformations λ (left-handed helicity) or δ (right-handed helicity). The energy barrier of λ D δ inversion is low and equal to about 20 kJ/mol [138]. Although en is a typical chelating ligand, its complexes with monofunctional coordination or the complexes in which it is a bridging ligand are also known [139]–[143]. The number of stereochemical conformations in bis(en) complexes is greater. If the two ligands are *trans* isomers there are λλ, δδ, and λδ possible conformations. The first two are energetically equivalent, while λδ is less stable by about 4 kJ/mol [137].

The simplest triamine, diethylenetriamine (dien), forms six-membered rings with metal ions, and the compounds prefer chair-type coordination, although, particularly in systems with alkyl derivatives, the compounds making twist conformation are also known [139]. Linear triamines react with formation of meridional or facial conformation, while tripodal-type amines, $RC(CH_2NH_2)_3$, where R = H, Me, Et, occur only in the facial form, both in solution [144, 145] and in solid state [146, 147].

The length of a polyamine chain has a significant effect on the character of interaction with metal ions. In solid state complexes, of ML_2 type made by Cd(II) with dien, 2,3-tri and 3,3-tri, all six donor nitrogen atoms are involved in the coordination. In the complex with dien, the cadmium ion is sandwiched between two ligands of crystal-lographic symmetry C_2, in contrast to the complexes with 2,3-tri and 3,3-tri, in which deformed octahedron was detected to be formed, Figure 8 [148].

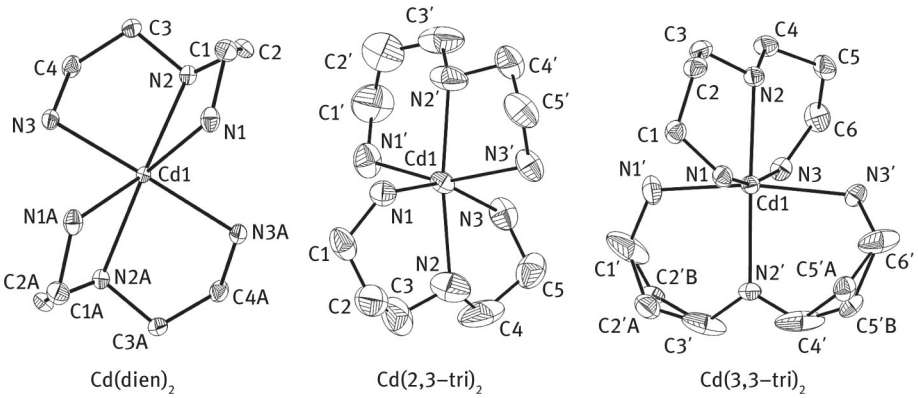

Figure 8: Structures of complexes in Cd(II)/polyamine systems.

Results of the equilibrium studies of metal/amine systems have been presented in a number of papers [8, 137, 142, 149–151], and also of anhydrous systems [152]. Kinetic studies of formation of complexes with polyamines and their analogues have been reported in [153]–[156]. In the formulae of the complexes the charge values have been omitted, unless necessary for understanding of the text.

The literature on metal complexes with biogenic amines: putrescine, spermi-dine, and spermine is rather poor relative to that on metal complexes with other amines, especially in binary systems. Only in the end of the last century was the formation of copper(II) complexes with putrescine finally confirmed, after many years of controversies in this matter [157]. The influence of the size of the ring on processes of chelation has been observed [158]. A larger ring of Put than shorter diamines lead to downfield shift in ^{59}Co NMR signal because of a smaller overlap of metal-ligand σ-bond [159, 160]. In a series of platinum complexes of biogenic amines and their analogues, a clear correlation between the rate of ring-closing and the size of the ring has been found [161]. The differences in reactivity of particular ligands are related rather to enthalpy than entropy of activation. In some platinum complexes amines act as a bridging ligand [162]. Results of the studies of bis(platinum) reactions have proved that dimers are kinetically more active than their monomer analogues [163]. The differences in the spectra of ternary complexes $Co(NH_3)_5[NH_2(CH_2)_nNH_2]$ (n = 2, 8, 10) and $Co(NH_3)_5[NH_2(CH_2)_nNH_3]$ are assigned to the formation of the charge-transfer bands, which is related to the formation of intramolecular hydrogen bonds between free amino groups and protons from coordinated amino groups [140]. After many attempts, 1,ω-diamine copper(II) complex with putrescine was successfully isolated in solid phase [164]. In the solid complex $[Co(PA)_3]Br_3$ the chair conformation of a seven-membered ring with the {N6} coordination geometry, trigonally elongated [165]–[167]. The seven-membered ring is stabilised by the metal ion, although in solution the conformation can change as a result of solvation effect and ion pairs formation [158]. In the systems

with amines of long chains, the tendency to formation of monomeric forms and bridging structures dominates over the formation of chelate complexes [168]–[170]. The series of bis and tris complexes: $[Ni(Put)_3]Cl_2 \cdot H_2O$, $[Ni(Put)_2(H_2O)_2]Br_2$, $[Ni(Put)_2](NCS)_2$, and many products of their pyrolysis are characterised by the symmetry O_h [171]. Also halogen and pseudo-halogen complexes of Zn(II), Cd(II), and Hg(II) with 1,3-dia-minopropane, putrescine, and cadaverine have been isolated. Diamines behave as bridging or chelating ligands [137]. Investigation of copper(II) complexes with linear triamines has shown that the most stable complexes form five- and six-ring sequency [99, 100, 172, 173]. In the series of tetramines, the value of log K increases in the order: Spm < 3,3,3-tet < 2,2,2-tet < 3,2,3-tet < 2,3,2-tet and depends on the tension in the ring and on the ability to assume the chair or twist-chair conformation. It does not explain the low stability of spermine complex, although it correlates with the observation that Spm often behaves as two independent fragments of $NH_2(CH_2)_3NH$ separated by a long methylene chain, which is supported by formation of {N2} type complex with Cu(II) and Spm [111]. A similar behaviour has been reported to occur in the system with Spm analogue 4,9-dioxa-1,12-dodecanediamine. This mode of coordination permits noncovalent interactions with the protonated amine groups from Spm. The heat of formation of protonated complexes of spermidine with copper is similar to that for $Cu(tn)_2$ complex, but much lower than the heat of formation of complexes with five-membered rings, which indicates the formation of six-membered ring in Cu(HSpd) species [174, 175]. As follows from analysis of thermo-dynamic data, in Cu(Spd) the six-membered ring is fused into the seven-membered ring with involvement of three donor nitrogen atoms in the coordination. The enthalpy of Cu(Spd) formation is by 12.5 kJ/mol higher than that of Cu(HSpd) formation. Stability of particular copper(II) complexes forming in the systems with triamines and tetramines is determined by the enthalpy and entropy, respectively [176]. Computer analysis of the potentiometric data in combination with spectroscopic analysis permits the choice of a coordination model, including the stoichiometric composition of the complexes and their thermodynamic stability. Determination of the solution structure in binary systems of metal/polyamine is relatively easy and boils down to finding the number of donor nitrogen atoms from polyamine in the internal coordination zone.

Low stability of the seven-membered ring in the systems with putrescine explains the presence of monofunctional coordination in the complex and formation of the species Cu(HPut) at pH close to 7 [157]. In the systems of copper(II) ions with longer biogenic amines the metalation usually begins at pH close to 5 with formation of the six-membered species Cu(HSpd) and $Cu(H_2Spm)$. The thermody-namically less preferred seven-membered ring is stabilised by the presence of one or two six-membered rings in the Spd and Spm complexes, respectively. The formation of the three-ring chelate corresponds to a high increase in the stability constant of Cu(Spm) complex (log K = 14.70) relative to that of Cu(Spd) (log K = 11.7). Although the absorption bands in electron spectra can differ for different systems, the value λ_{max} = 564 nm suggests the coordination with {N4} chromophore. Decrease in the ligand field strength results in a shift of the absorption energy towards weaker fields, λ_{max} = 626 nm in Cu(Spd), {N3} coordination but λ_{max} = 655 nm in Cu(HSpd), {N2} coordination [13, 177, 178]. For monofunctional coordination, as e.g. in Cu(HPut), λ_{max} = 705 nm [157]. Analysis of these results points to the equatorial geometry of species in {N4} coordination. In the electron spectrum of the complex with {N5} coordination, a red shift appears as a result of localisation of the fifth nitrogen atom in the axial position [142, 177, 179]. The geometry of the complexes is supported by the studies of Cu(II), Zn(II) and Co(II) reactions with long-chain polyamines [180, 181]. The above conclusions on the mode of coordination in solution correlate with the results of a study of the complexes in solid state. The isolated $[Cu(Spd)]X_2$ (X = Cl,Br,I) assume the structure of a square pyramid with one halogen atom at the axial position [182]. The stability of triamine complexes with Hg(II) increases in the series en < tn < Put, which can explain the tendency of this metal ion to linear coordination. The tension in seven-membered ring is relatively the lowest [183]. In the series of solid state complexes of rhodium with tetra-mines, the shortest ligand 2,2,2-tet makes only *cis*-α isomer, while 2,3,2-tet makes *cis*-α and *trans* isomers, and the longer ones 3,2,3-tet, 3,3,3-tet, and Spm assume a *trans* configuration [184]. These differences are related to different tensions in particular rings. The size of the ring also determines the kinetic properties of the complexes. In an acidic medium, $[Cu(Spd)]Cl_3$ immediately undergoes hydrolysis and shows increased lability of the coordinated chlorine ion with respect to the shorter amines 2,3-tri and 3,3-tri. The change in the rate of $Co(PA)(H_2O)_n$ complex reduction to Co(II) increases in the order: Spd < 3,3-tri < dien, which corresponds to the changes in the activation energy [185].

Binary systems were studied mainly in the 1970s and 1980s. Although many problems in bioorganic and bioinorganic chemistry have not been solved yet, the simple structure of amines soon diminished the interest in this group of compounds [186]. At present the research work has been concentrated on more complex, multicomponent model systems that are better approximations of the *in vivo* systems. Much attention has been paid to the interactions and processes related to the transfer of genetic information, mainly to the reactions of polyamines with nucleic acids in the model systems with DNA or RNA fragments (nucleosides, nucleotides) and metal ions [8, 179, 187, 188]. As mentioned above, the interactions of protonated amines stabilise DNA (or RNA) mainly as a result of charge neutralisation. Because of their coordinating abilities, transition metal ions should be treated as factors interfering with the system of noncovalent bonds between the negative fragments

of nucleic acid and the polyamine that is a positive centre. The potential centres of the reaction of polyamine with a nucleotide simultaneously make the metalation sites (Figure 9). In ternary complexes of metal/PA/P-Nuc (PNuc = nucleotides), besides the phosphate residues, the donor atoms N(3) from pyrimidine nucleosides and N(1) and N(7) atoms from purine nucleosides are the preferred sites of metal binding with fragments of nucleic acids.

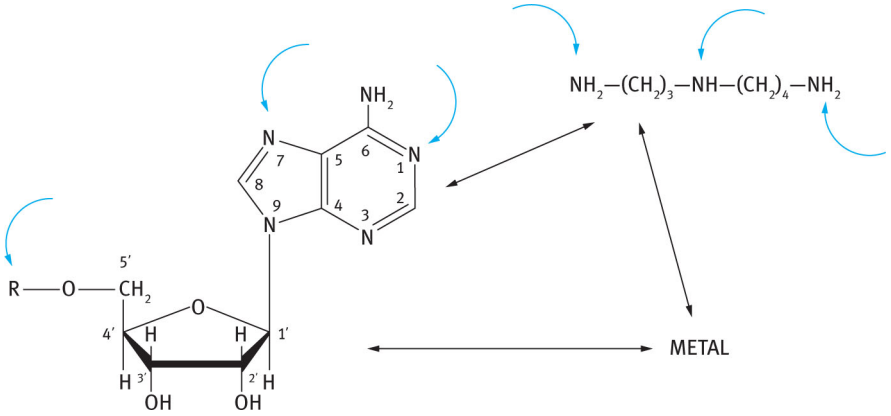

Figure 9: A scheme of interactions in metal/nucleotide/polyamine systems, R = phosphate groups (red arrows indicate potential sites of interactions).

Analysis of the mode of coordination in the systems containing purine nucleosides or nucleotides shows with no doubt that simultaneous bonding of the metal with N(1) and N(7) is impossible for steric reasons. However, in a series of metal/nucleotide and metal/nucleotide/polyamine systems, the coordination dichotomy with monofunctional metalation and formation of a mixture of isomers in which the ions Cu(II), Ni(II), Co(II), Zn(II), Cd(II), Hg(II) were bonded either to N(1) or to N(7) atoms [178, 189–193].

The presence of a phosphate group in nucleotides significantly changes the mode of interaction of this ligand with respect to that of nucleoside. For instance, in the system Cu(II)/Nuc/Spm the complexes with {N5} type coordination are formed, in which the metal ion binds four nitrogen atoms from the polyamine in equatorial position and the nitrogen atom from Nuc in the axial position (Nuc = Ado or Cyd). In the system Cu(II)/PNuc/Spm, (PNuc = AMP or CMP), meta-lation is realised only via the phosphate group, while spermine is engaged in noncovalent interactions with nitrogen atoms of high density from a purine base, Figure 10 [111, 194].

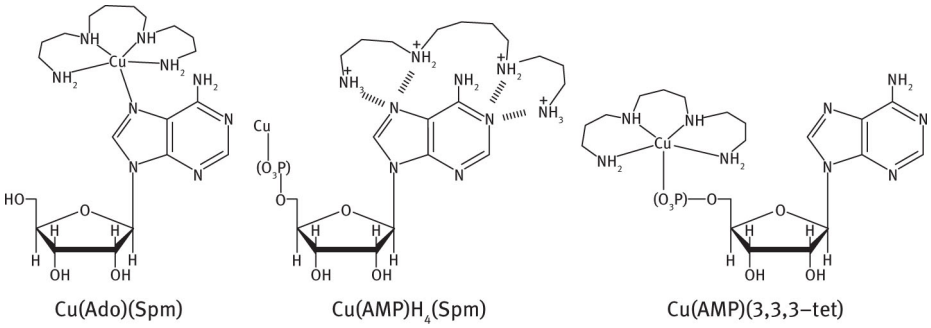

Figure 10: Tentative mode of coordination.

Solution structures presented in Figure 10 are just a few examples from many illustrating that even small differences in the length of polyamines exert significant effects on the character of interactions determining the specificity of the reaction. Of course, also the nature of the metal influences the character of interactions in ternary systems. The effect of metal is best illustrated by the differences between Co(II) and Ni(II). The nickel (II) ions show low effectiveness of binding to phosphate groups from the nucleotide, while cobalt (II) binds both the endocyclic nitrogen atoms and coordinates with involvement of the phosphate groups [189]. In many ternary systems, not all donor atoms from the polyamine are engaged in the metal ions binding in MLL H_x species (L = polyamine, L = nucleotide) that permits the appearance of noncovalent interactions with the protonated $–NH_x^+$ groups from the polyamine, as illustrated in Figure 11. Such an intramolecular interaction has a stabilising effect on the complex [8, 110, 111, 195].

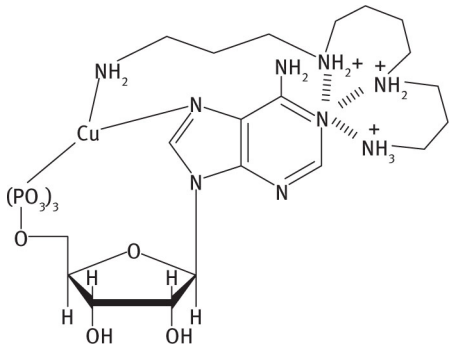

Figure 11: Tentative mode of coordination in Cu(ATP)H_3(Spm).

Also intramolecular interactions between ligands in the inner coordination sphere of the species metal/nucleotide and the polyamine located in the external sphere lead to the formation of molecular complex of ML···L type [196, 197]. The mode of interaction is significantly dependent on the concentration of polyamine [198]. The formation of ML···L type complexes has been also observed in the systems of metal/polyamine/amino acid [112, 113].

The influence of copper ions on the copper srtructure is also illustrated on Figure 12. The introduction of Cu(II) ions to the binary system eliminates the phosphate groups from noncovalent interactions [110].

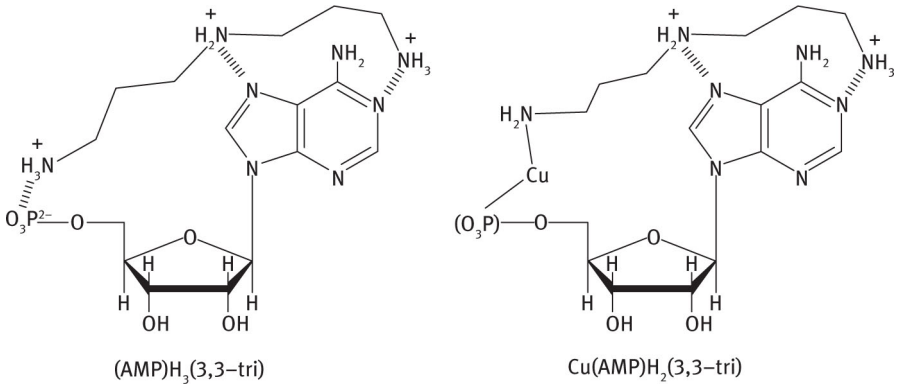

Figure 12: Tentative mode of interaction.

However, polyamine can be treated as an agent interfering into the metal-nucleotide interactions. In the system Cu(II)/CMP, Cu(II) ions bind the phosphate group from the nucleotide and the endocylic N(3) atom. The polyamine introduced into the system blocks N(3) atom as a result of the noncovalent interaction, while the copper ion coordinates to the donor nitrogen atom from putrescine and to the phosphate group from CMP [110]. Moreover, uridine introduced to the ternary system of Cu(II)/ ATP/3,3,3-tet is involved in noncovalent interactions with the purine base from the nucleotide, while the presence of metal ions and the polyamine changes the specific mode of interactions of complementary bases (according to Watson-Crick), observed in the metal-free system, Figure 13 [199].

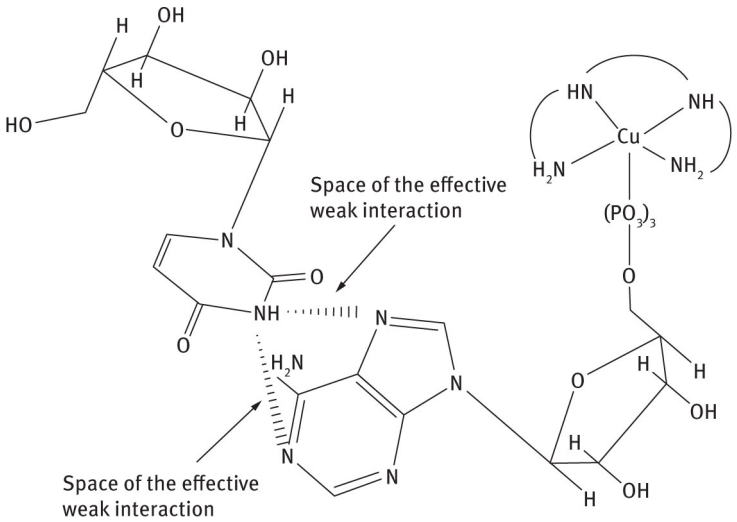

Figure 13: Tentative mode of interaction in Cu(ATP)(3,3,3-tet)H(Urd).

6 Application of polyamine complexes in medicine

The majority of currently used therapeutic drugs are organic compounds, while much less attention has been paid to the effect of inorganic compounds. Metals in coordination or organometallic compounds offer great chemical diversity and thus larger therapeutic use [4]. Inorganic compounds have been shown to be particularly effective in therapy for malignant forms of neoplasms, as their activity is based on the specific interaction with DNA, which leads to cell damage and eventually cell death [200]–[206].

The coordination compounds of platinum have been used for chemotherapy since 1978, when *cis*platin (*cis*-diamminedichloroplatinum (II)) was first introduced in the USA as a component of chemotherapeutic treatment [207]. Although thousands of mononuclear analogues of *cis*platin have been synthesised and tested as potential anticancer drugs, only two compounds, carboplatin and oxaliplatin, have been used in clinical treatment of neoplastic diseases, while other analogues were therapeutically inactive [200, 207–223].

It is known now that the antineoplastic properties of platinum complexes are related to their selective reaction with DNA and possible involvement in the formation of bridging systems with donor nitrogen atoms N(7) and N(1) [210, 224], which affects the processes of replication and transcription. The very promising results of the studies on mononuclear complexes of platinum have aroused interest in the polynuclear platinum complexes containing two or three metallic centres. The polynuclear compounds may be more cytotoxic because they cause considerable irreparable damage to DNA. From among them, the polynuclear platinum complexes containing bridging polyamines make a new class of compounds potentially more effective in antineoplastic diseases therapy than the hitherto used ones, Figure 14 [211, 215, 217, 224]. The introduction of biogenic amines to the first generation platinum complexes has an essential influence on their cytotoxic properties [217].

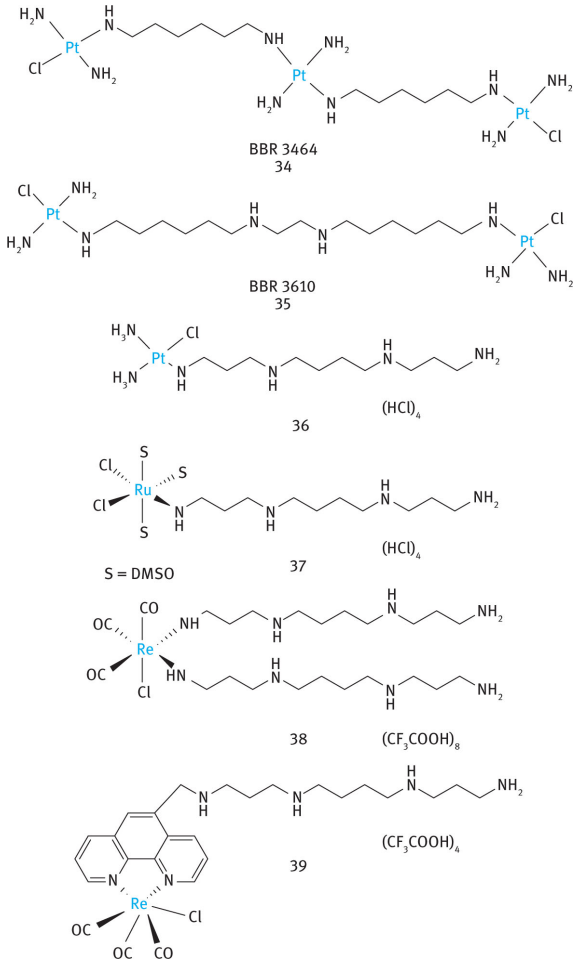

Figure 14: Polyamine–transition metal complexes with antitumour activity [99].

The cytotoxic effect of these compounds is higher than that of *cis*platin [209, 215, 225, 226]. Dimers of this new class of complexes show a wider range of activity than their monomer analogues because of the possibility

of intra- and inter-strand cross-links formation [211, 215]. Small differences in the structure of polyamines were found to lead to considerable changes in the cytotoxic properties of their complexes with platinum. Besides the correlation between the structure and activity, the cytotoxic effectiveness of biomolecules also depends on the charge, flexibility, and noncovalent interactions [206, 215]. One such trinuclear Pt(II) compounds, BBR3464, successfully passed clinical trials, Figure 15 [227]. Also, cytotoxicity of the new complexes of polyamines with platinum (IV) has been tested [224, 228, 229]. Therapeutic possibilities of platinum (IV) complexes are similar to those of platinum (II) because, as has been suggested, *in vivo* the Pt(IV) ions are reduced. In the search for anticancer drugs, the better solubility of platinum (IV) compounds should be taken into account [216]. Many polyfunctional chelates containing di, tri, or tetramines as linkers have been the subject of intense studies [225, 230–236]. Intense studies of anticancer therapeutic drugs of a wide pharmacological spectrum of activity, high therapeutic profile, and low toxicity have shown that polynu-clear platinum complexes are very promising candidates for replacement of *cis*platin and carboplatin in therapeutic applications in which the latter are ineffective. Biogenic amines, putrescine, spermidine, and spermine and their N-alkylated correspondents are used in particular as bridging ligands in the complexes of Pt(II) and Pd(II) [212, 215, 216, 233, 237–251]. The presence of connectivities of this type permits the occurrence of untypical mechanisms of interaction with DNA such as "long-distance" inter- and intrastrand crosslinks inside the DNA helix [252], which contribute to improvement in the anticancer activity shown by some of the complexes, e.g. they give a positive response in the treatment of cancers usually resistant to *cis*platin [253, 254].

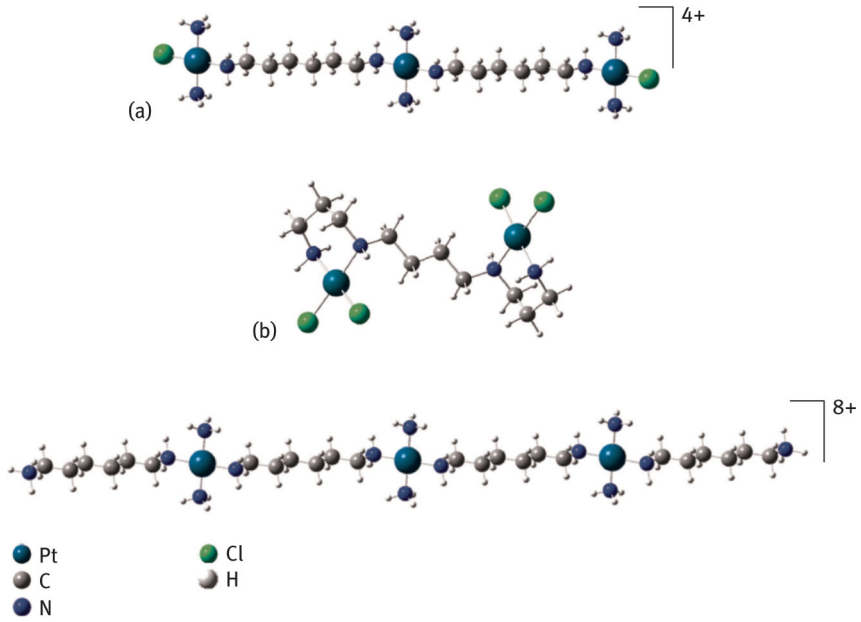

Figure 15: Polyamine-bridged polynuclear Pt(II) complexes: BBR3464 (Triplatin) [254] (a), Pt_2Spm (Spm = spermine) [240] (b), and TriplatinNC [267] (c) [247].

Besides the complexes with platinum, also those with palladium (II) have been tested for cytotoxic activity. The value of ID50 of palladium (II) complexes with putrescine and spermidine is better than for *cis*-DDP, but much worse for the complexes with spermine, which corresponds to the fact that the latter is not able to produce conformational changes in DNA [212, 213]. Higher anticancer activity of the compounds in which Pd(II) has replaced Pt(II) as the central atom, has been already described in literature [255]–[257]. A number of trinuclear complexes of polyamines with Pt(II) and Pd(II) have been synthesised and tested for the structure-activity relationship with regard to their potential cytotoxic properties [258]. Complexes of palladium have been found to reduce the cell activity of the ornithine decarboxylase enzyme more then complexes of platinum [259]. The already recognised functions of polyamines in the processes taking place in living organisms include not only the effect on cell growth and differentiation or cell death, but also the protection of nucleic acids against damage caused by reactive oxidative species (ROS) generated by different substances and also by transition metal ions Cu(II) and Fe(II) [260]–[262]. Moreover, the influence of BBR3464 complex on the shortening of cell lifetimes was much lower than that produced by *cis*platin [253].

The application of polynuclear compounds has brought promising therapeutic effects in the treatment of melanoma, pancreatic, lung, and ovarian cancers [263]–[265]. The cytotoxic effect on the cell lines of human cancer (HSC-3) has been also checked for the dinuclear complex of Pd(II) spermine (Spm) chelate, $(PdCl_2)_2$(Spm) and compared with the effect of the earlier described Pt(II) analogues [215]. The results confirmed higher cytotoxic effect of the compounds with Pd(II) than those with Pt(II) [266].

It is known that Pd(II) complexes are usually very labile and their deactivation by *cis*-trans isomerisation is unlikely. Spermine makes extremely strong chelate bonds with Pd(II) because of a high chelating effect [240]. Spm, while strongly bonded to Pd(II), imposes the *cis* coordination on the labile ligands such as e.g. Cl^-, and prevents such deactivation. Deactivation as a result of interaction with the cell components other than DNA, thanks to the high lability of Pd(II) complexes, is possible.

For the complexes with Pd(II), the range of ligands undergoing exchange is much wider than for the analogous species with Pt(II). It is important that inside the cell, Figure 16, $(PdCl_2)_2$(Spm) undergoes a fast hydrolysis that permits the appearance of hydrated species (e.g. thiols) that interact with cell components other than DNA more strongly and earlier than with DNA. Although the rate of water exchange is 106 times higher for $Pd(H_2O)_4^{2+}$ than $Pt(H_2O)_4^{2+}$ [240, 250], for other systems the Pd(II) and Pt(II) complexes may show the same rate of ligand exchange [268]–[270].

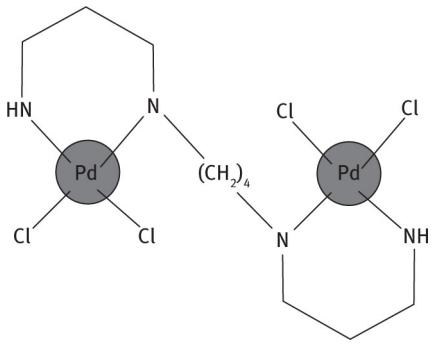

Figure 16: Tentetive mode of coordination in $(PdCl_2)_2$(Spm).

The effect of polyamine analogues, N1,N11-bis(ethyl)norspermine (BENSpm) and N1-cyclo-propylmethyl-N11-ethylnorspermine (CPENSpm), as well as the synthesised dinuclear complexes Pd_2(BENSpm), Pt_2(CPENSpm), and Pd_2(Spm) on the heathy cells of breast epithelial MCF-10A and the breast cancer cell lines JIMT-1 and L56BR-C1, has been studied to evaluate their activities. It has been established that palladination of BENSpm increases cytotoxicity, while platination of CPENSpm leads to its reduction. Moreover, Pd_2(BENSpm) was the most effective compound damaging DNA and reducing the population of bacteria colony. However, Pt_2(CPENSpm) and Pd_2(Spm) show lower toxicity in all tests. Pd_2(Spm) efficiently reduces the level of cell glutathione, which probably causes their metabolic deactivation by linking thiols to their endoge-nic parts. The formation of many cross-link bonds connectivities with DNA leads to distortion of the DNA particle, thus the key biological processes such as DNA replication and transcription are inhibited, which causes inappropriate synthesis of proteins and inhibition of cell proliferation [271, 272]. The problems related to side effects such as neurotoxicity, nephrotoxicity, and development of an acquired resistance to *cis*platin are the main factors limiting the effectiveness of therapy with this drug [271, 272]. Another group of profound interest in experimental cancer research is that of polyamine analogues [273].

Platinum-based therapeutic drugs, such as *cis*platin, are very effective but show undesirable side effects, and their effectiveness is limited to a few types of cancer cells. Therefore, intense research work on development of new drugs of a wider range of activity and lower toxicity is continued. The effectiveness of *cis*platin and its analogues (II generation drugs) as anticancer drugs make them the basis for designing alternative drugs showing other modes of activity and less acute side effects [274]–[277]. The medical use of such metals as Ag, Au, and Cu is well known. Au(III) complexes with porphyrin, dithiocarbamate, and polyamine show *in vitro* high stability constants and much effort has been made to evaluate the anticancer effects of such complexes [278]–[280].

As yet, the main group of inorganic anticancer drugs includes the compounds containing platinum (II) and platinum (IV), palladium (II), gold (I) and gold (III), ruthenium (II) and ruthenium (III), bismuth (III), rhenium (I), and copper (II) as well as gallium (III) and tin (IV). Many of them show *in vitro* much higher cytotoxicity than *cis*platin [281].

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