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Review

# Coordination chemistry of polyamines and their interactions in ternary systems including metal ions, nucleosides and nucleotides

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**Contents**



**Abstract**

Metal ions and polyvalent organic cations take part in many processes proceeding in living organisms. These processes are associated with the formation of coordination compounds and molecular complexes. An important group of bioligands is made up of biogenic amines, which occur in practically all forms of organisms and their reactions with nucleic acids play an essential role in processes of genetic information transfer. Metals present in cells should be considered as interfering agents, which change the character of interactions. Reactions, including the formation of molecular complexes and metallation of a number of polyamines, have been described. The effectiveness of non-covalent interactions of amines, besides charge, is determined by structural factors (this fact elucidates reaction specificity) and these interactions are of an ion–ion, ion–dipole type, both in binary and ternary systems, that include fragments of nucleic acids (nucleosides, nucleotides) and metal ions, as well. Differences in the character of the interactions can elucidate different biological activity of biogenic amines compared to their analogues, not occurring in living organisms.

Principal metallation sites of discussed bioligands in ternary sysytems, including fragments of nucleic acids, are amino groups of polyamines and endocyclic nitrogen atoms N(1), N(7) and N(3) of purine and pyrimidine rings of nucleosides as well as phosphate groups of nucleotides, respectively.


*Keywords:* Metal ions; Polyamines; Coordination; Nucleosides; Nucleotides; Non-covalent; Interaction

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## 1. Introduction

Biogenic amines: putrescine (Put), spermidine (Spd) and spermine (Spm), belong to the group of aliphatic polyamines (PA) (Fig. 1) and take part in many processes proceeding in living organisms [1–3]. A minor role is played by their structural homologues, concentrations of which in the cells are, however, considerably lower.

The bioligand content in living organisms depends on the nature of tissues and cell age [4–11]. An increased PA level was found in young cells as well as in cancer cells [5,12–20] and this observation is useful for clinical diagnostics and treatment process monitoring [21]. The earliest observation in this subject was the effect of polyamines on biological membranes [22–28]. The high level of polyamines in young cells suggests direct interactions between PA and nucleic acids in proliferation processes [29,30]. Taking into consideration the fact that concentrations of polyamines in cancer cells are higher than those in normal ones, the anti-proliferative agents [31,32] were tested for their capability of retarding the development of cancer cells. The strategy of searching for anti-cancer drugs, consisting in PA depletion, still raises hopes, particularly when using anti-metabolites together with other chemotherapeutic agents [21,31]. The presence of polyamines in living cells is associated with changes in DNA and RNA structures at several organisational levels, which determines their role in processes of genetic information transfer. The high basicity of biogenic amines causes that in physiological conditions they occur as protonated species and in such a form they react with fragments of other biomolecules, e.g. with negative (deprotonated) phosphate groups of nucleotides and endocyclic nitrogen atoms of high electron density of purine and pyrimidine bases [33–37]. Manning polyelectrolyte theory suggests that changes in the structure of molecules depend on reactant charge [38,39]. However, such an approach cannot explain the high specificity of some reactions. In addition to electrostatic interactions, structural factors should also be taken into consideration in order to shed light on the nature of the processes [29,40–52]. Although the interactions between PA and nucleic acids and their effect on

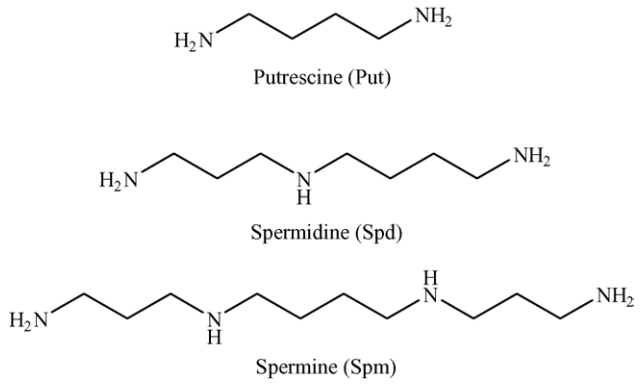


Fig. 1. Biogenic amines.

proliferation and differentiation of cells are unquestionable, the mode and specificity of these interactions, that change the DNA structure, still raise doubts [53].

While analysing these interactions, we cannot neglect the presence of metal ions in living cells. Coordination sites, both in polyamines and nucleosides as well as nucleotides are, at the same time, potential centers of non-covalent interactions. Metal ions, occurring in living organisms, change the character of processes between bioligands and can be considered as interfering agents, competing with polyamine in the reaction with nucleic acid fragments as has been schematically presented in Fig. 2 (single arrows indicate main potential coordination sites and centers of non-covalent interactions).

Many questions concerning the role of metals in living organisms are still far from solved. Their explanation, first of all, needs full recognition of the character of metal–polyamines as well as polyamine–nucleotide interactions in model binary systems, preceding investigation of ternary systems. The results of these observations should yield better insight into intracellular molecular mechanisms of reactions related to metal ions, polyamines and fragments of nucleic acids.

The aim of this work is presentation of current knowledge of such problems as metallation of polyamines, formation of adducts in systems including polyamines and nucleosides or nucleotides, and interactions in ternary

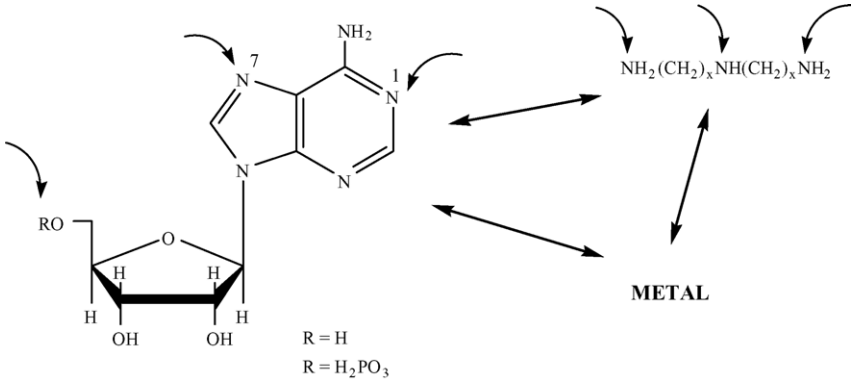


Fig. 2. Scheme of interactions in Nuc(NucP)-PA-metal ternary systems (simple arrows indicate potential donor atoms).

metal/polyamine/nucleotide systems emphasising the role of metals in biological systems.

## 2. Complexes of polyamines with metal ions

### 2.1. Metal/polyamine binary systems

The complexing properties of polyamines (formulas of the amines presented in Scheme 1) depend, of course, on the nature of their $-NH_x$ groups. In coordination systems, the formation of different types of bonds has been observed, from a weak interaction between nitrogen atom and ions of alkali metals and alkaline earth metals to a strong bond between nitrogen and Co(III) and Ru(III) [54,55].

Ethylenediamine (en) belongs to the group of most important and earliest studied chelating ligands. Free ligands can assume *trans* and gauche (*cis*) configurations. Two donor nitrogen atoms combine the central ion with the formation of a five-membered puckered ring. Two enantiomeric conformations are possible in the complex: λ (left-handed helicity) and δ (right-handed helicity) with a low-energy inversion barrier [56,57]. Ethylenediamine is typical chelating ligand, however, it can coordinate in monodentate or bridging mode, as well [58–62]. The number of stereochemical conformations increases in bis(en) systems. If both ligands are in trans arrangement, the following isomers are possible: λλ, δδ and λδ. The first two are energetically equivalent, whereas the third, λδ is less stable by about 4 kJ $mol^{-1}$ [55]. As a result of 1,3-propanediamine (tn) complexation, a six-membered ring is formed and the compounds prefer a chair type coordination, although a twist conformation is also possible, particularly in the case of alkyl derivatives [63]. Linear triamines react with the formation of meridional or facial conformations, while tripodal-type amines: $RC(CH_2NH_2)_3$, where R=H, Me, Et occur only in the facial form, in both the solution [64,65] and solid phase [66,67]. Polyamine chain length clearly affects the character of interactions with metal ions. In solid complexes obtained with Cd(II) nitrate with triamines: dien, 2,3-tri and 3,3-tri of $ML_2$-type stoichiometry, all six nitrogen atoms take part in the coordination. However, in the first of these complexes, the cadmium atom is sandwiched between two ligands with crystallographic $C_2$-symmetry; both triamines adopt exactly the same $g^+g^+tg^+$ conformation. The complex compound of the second polyamine, in contrast to the former one, does not form a sandwiched structure, but is characterized by a distorted octahedral coordination with four equatorial nitrogen atoms and two in axial positions. A 3,3-tri complex is structurally similar to the 2,3-tri compound, however, with a longer *c* parameter. The lengthening of the carbon chain causes relief of the molecular strains and less-distorted octahedral geometry is observed compared to $Cd(2,3\text{-tri})_2$ complex (Fig. 3) [68].

The results of equilibrium studies of metal/amine systems [69–72], including non-aqueous solutions [73], are presented in many papers. The results of kinetic studies [74–78] were also reported. Papers on coordination compounds of amines with metals were reviewed by D.A. House [55], however, only a small number of the references concern studies of complexes of biogenic amines: putrescine, spermidine and spermine.

### 2.2. Metal complexes of biogenic amines (putrescine, spermidine and spermine)

Until recently some authors claimed that putrescine does not form complex compounds with metal ions in solution [79,80]. However, recent spectroscopic and potentiometric studies have clearly shown that Put forms complexes with Cu(II) ions [81–83]. Stability constants of copper (II) complexes with Put, Spd and Spm are listed in Table 1.

At pH about 7, Put forms complexes of a monodentate mode $[CuHPut]^{3+}$. An increase in pH results in the formation of two isomers of the $[Cu(Put)_2(OH)]^+$ type. Two chelate rings occur in one of them, while in the other, both nitrogen atoms of one of the ligands and only one atom of the second ligand are included in the coordination [81]. The reaction of copper(II) with diamines, was confirmed by results of $^{13}C$ NMR studies [88]. The formation of complexes in putrescine-Co(II) systems has been also established [89,90], and in the series of diamine (en, tn, Put) complexes, an increase in the ring size brings about a downfield shift in $^{59}Co$ NMR as a result of ligand field weakening, because in the case of a larger chelate ring, the metal–ligand σ-bond is less overlapped [91]. In studies of a series of platinum complexes, a clear dependence of ring-closing reaction rate and ring size was found [92,93]. Differences in the reactiv-

| | |
|---|---|
| $NH_2(CH_2)_2NH_2$ | en |
| $NH_2(CH_2)_3NH_2$ | tn |
| $NH_2(CH_2)_4NH_2$ | Put |
| $NH_2(CH_2)_2NH(CH_2)_2NH_2$ | dien |
| $NH_2(CH_2)_2NH(CH_2)_3NH_2$ | 2,3-tri |
| $NH_2(CH_2)_3NH(CH_2)_3NH_2$ | 3,3-tri |
| $NH_2(CH_2)_3NH(CH_2)_4NH_2$ | Spd |
| $NH_2(CH_2)_3NH(CH_2)_3NH(CH_2)_3NH_2$ | 3,3,3-tet |
| $NH_2(CH_2)_3NH(CH_2)_4NH(CH_2)_4NH_2$ | Spm |

(in this text, "tri" stands for triamine, "tet" for tetramine; 2,3,4,... signifies the number of $CH_2$ groups between nitrogen atoms, abbreviations for biogenic amines underlined)

Scheme 1.

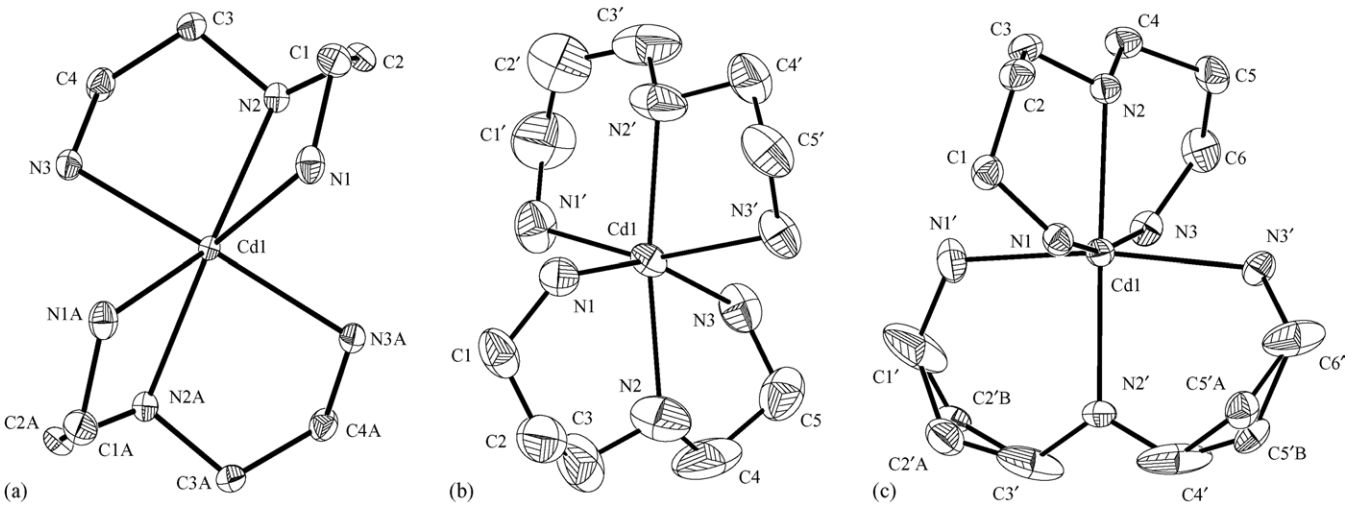


Fig. 3. Crystal structures of Cd(II) complexes with triamines (a): $Cd(dien)_2$, (b): $Cd(2,3\text{-tri})_2$ and (c): $Cd(3,3\text{-tri})_2$.

ity of particular ligands are a consequence of differences in enthalpy of activation rather than entropy of activation. In comparison with putrescine-containing systems, i.e. the formation of a seven-membered ring, the reaction of the eight-membered ring closure in trans-$[Pt(Me_2SO)(N{-}N)Cl_2]$ (N–N = cadaverine) is slower by two orders of magnitude [94]. In some platinum complexes, amines react as bridging ligands [95]. The studies of reactions of bis(platinum) complexes have shown that dimers are kinetically more active than their monomeric analogues [96]. The enthalpy of forming the complex $[Cu(hfaa)_2]$ (hfaa = hexafluoropentane-2-4-dionato) with diamines reflects differences between the energy of a new Cu–N bond in the heteroligand complex and the reduced energy of a Cu–O bond translocated to the axial position [97]. Changes in spectra of ternary complexes $[Co(NH_3)_5\{NH_2(CH_2)_nNH_2\}]^{3+}$ ($n$ = 2–8,10) compared to those of $[Co(NH_3)_5\{NH_2(CH_2)_nNH_3\}]^{4+}$ complexes are ascribed to the formation of charge-transfer bands. This is a result of intramolecular hydrogen bond formation between free amino group and N–H protons of coordinated amines or amino groups [58]. This type of non-covalent interaction plays an important role in processes proceeding in biological systems [98]. Differences in the number of methylene groups of PA influence the hydrophobic character of this species. The alkyl groups of ligands determine the nature of water molecules in their surroundings, including solvating domains in the coordination outer-sphere [89].

Table 1
Overall stability constants[a] [log $\beta$] of $Cu_p(PA)_qH_r$ complexes

| pqr | 110 | 120 | 111 | 121 | 112 | 11-1 | 12-1 |
|---|---|---|---|---|---|---|---|
| Put | 8.62[b] | 13.40[b] | 15.83[b] | | | | 0.065[c] |
| Spd | 11.7[d] | 16.0[d] | 18.9[c] | 26.3[d] | | 1.67[d] | 6.18[d] |
| | 11.70[c] | 17.13[c] | 18.91[c] | | | 2.90[c] | 6.72[c] |
| | 11.61[e] | | 6.83[e,f] | | | 4.48[e,f] | |
| Spm | 14.7[d] | 18.9[d] | | 29.0[d] | 27.8[d] | | |
| | 14.66[c] | | | 29.32[c] | 27.63[c] | | |
| | 14.44[g] | 17.2[g] | 20.4[g] | | | | |
| | 14.70[h] | | 9.99[h,f] | | | | |

[a] For the sake of simplicity statistical parameters were omitted.
[b] 20 °C; $\mu$ = 0.1 ($NaClO_4$) [83].
[c] 20 °C; $\mu$ = 0.1 ($NaClO_4$) [81].
[d] 25 °C; $\mu$ = 0.15 (NaCl) [84].
[e] 25 °C; $\mu$ = 0.15 (NaCl) [87].
[f] Equilibrium constant.
[g] 25 °C; $\mu$ = 0.1 ($KNO_3$) [85].
[h] 25 °C; $\mu$ = 0.1 (NaCl) [86].

After many attempts made preparing 1,ω-diamine complexes with a large ring, a successful isolation of the bis(Put) copper complex was performed [99]. In the solid complex $[Co(Put)_3]Br_3$ obtained, the chair conformation of the seven-membered ring has the absolute configuration of Δ(λλλ) with a coordination environment of the {N6} type, which is trigonally elongated [100–102]. The seven-membered ring is conformationally stabilized in metal complexes; while in a solution, however, this conformation can undergo changes due to the solvation effect and ion pair formation [103]. As the result of reactions between $[Co(H_2O)(NH_3)_5](ClO_4)_3$ or $[CoCl_2(en)_2]Cl$ and diamines $NH_2(CH_2)_nNH_2$, ($n$ = 2–14) in DMSO, a number of coordination compounds can be formed. The yield of the reaction depends mainly on the length of the methylene chain and a medium-size ring remains unstable [104–106]. Putrescine forms monomeric complexes, however, these were not obtained in systems with the longer, naturally occurring, cadaverine. If the number of methylene groups in diamine is higher than 10, monomers are again formed. In systems containing long-chain amines, a tendency for the formation of monomeric species or bridging structures rather than the formation of chelates was observed [106,107]. Bis and tris nickel complexes: $[Ni(Put)_3]Cl_2{\cdot}H_2O$, $[Ni(Put)_2(H_2O)_2]Br_2$, $[Ni(Put)_2](NCS)_2$ have been obtained and a dozen or so of other Ni(II) complexes have been prepared by pyrolysis of the above compounds [108]. All the parent complexes and $[Ni(Put)(NCS)_2]$ are characterized by $O_h$ symmetry, whereas the symmetry of $[Ni(Put)Cl_2]$ is $T_d$.

Moreover, complexes of Zn(II), Cd(II) and Hg(II) halides and pseudohalides with 1,3-diaminopropane, putrescine and cadaverine have been isolated. Diamines behave as bidentate bridging or chelating [109] ligands. However, it has been suggested that $NH_2(CH_2)_nNH_2$ ($n$ = 2–6,8) react with Mo(V) as monodentate ligands and that the diamagnetic character of these compounds points to their dimeric structure [110]. Studies of Cu(II) complexes with linear triamines have shown that the most stable complexes were formed in the case where a sequence of five- and six-membered rings occurred [87,111–113]. In the series of amines, log $K_{CuL}$ values increase in the order: Spm < 3,3,3-tet < 2,2,2-tet < 3,2,3-tet < 2,3,2-tet and depend on ring strain and a capability for assuming the preferred chair or twist-chair conformation. This cannot, however, explain the low stability of spermine complexes [114]. In many systems spermine shows a character different from that of its shorter homologues. When interacting with metal ions, Spm frequently behaves as two independent fragments $NH_2(CH_3)_3NH$-, separated by a long methylene chain [81,87]. This fact clarifies the existence of complexes of this ligand with a coordination environment of the {N2} type, as observed, e.g. in $CuH_2$(Spm) or $PbH_2$(Spm) complexes [81].

The heat of protonated complex formation between spermidine and copper(II) ions is close to that of $[Cu(tn)]^{2+}$, but clearly lower than heats of formation of analogous complexes with five-membered rings. This indicates the formation of a six-membered ring in $[CuHSpd)]^{3+}$, with the protonated nitrogen atom of amino group linked to the tetramethylene chain [115,116]. Analysis of thermodynamic and spectral data leads to the conclusion that the six-membered ring in a $[CuSpd]^{2+}$ complex is fused to a seven-membered ring, with three nitrogen atoms included in the coordination. The latter's enthalpy of formation is about 12.5 kJ higher than that of the protonated complex as well as higher than the enthalpy of formation of $[Cu(en)]^{2+}$, with two nitrogen atoms in the inner coordination sphere. For a series of homologous linear triamines, the low stability of CuL complexes with seven-membered rings is caused by a low enthalpy term (the entropy term is equal), whereas in the case of tetramines, the low stability of compounds parallels the low entropy term. The enthalpy term is advantageous and reflects the high basicity of the ligand [117].

On the grounds of computer-aided analysis of potentiometric data and results of spectral studies, the formation of several complexes in solutions of Cu/Spd and Cu/Spm has been established [81,84,85]. The metallation reaction begins at pH of about 5, with the formation of six-membered anchoring rings in $[CuHSpd]^{3+}$ and $[CuH_2Spm]^{4+}$. A seven-membered ring, which is thermodynamically less advantageous, is formed in subsequent species and is stabilized by the presence of one or two six-membered rings (in Spd and Spm, respectively). The effect of the three-ring chelate manifests itself by increasing the thermodynamic stability of $[CuSpm]^{2+}$ (log $K$ = 14.7), in relation to $[Cu(Spd)]^{2+}$ (log $K$ = 11.7) [84]. The value of $\lambda_{max}$ = 564 nm in the electron spectrum of $[CuSpm]^{2+}$ suggests coordination with the {N4} chromophor. This has been confirmed by crystallographic studies, the results of which indicate formation of a planar-square structure with four nitrogen atoms of the same spermine molecule [118]. A reduction in the strength of the ligand field in $[CuSpd]^{2+}$ ({N3}coordination) leads to a decrease in absorption energy, $\lambda_{max}$ = 626 nm, and then to $\lambda_{max}$ = 655 nm in $[CuHSpd]^{3+}$. Coordination compounds with the involvement of all donor atoms were reported in the Cu(PA) type species, however, compounds, which were characterized by weaker interactions of some nitrogen atoms or even those of monodentate coordination were observed, as well [61,119]. On the other hand, the analysis of results of equilibrium studies shows, that in $Cu(PA)_x$ complexes, coordination with {N4} arrangement and the equatorial location of donor atoms as well as coordination of the {N5} type with one additional nitrogen atom located in the axial position are predominant ones [62,84,119]. These observations were confirmed by the results of studies of complexation reactions of Cu(II), Zn(II) and Co(II) with long-chain polyamines [120,121]. The nature of coordination in the solid phase is similar to that discussed above. Isolated $Cu(Spd)X_2$, (X=Cl,Br,I) complexes have the structure of a square pyramid with three nitrogen atoms in the plane and one halogen atom in the axial position [122]. A six-membered ring assumes a chair conformation, whereas in a seven-membered ring the N–C bond is almost coplanar. In Cu(II) complexes with norspermine, the coordinative polyhedron is close to a square pyramid with four nitrogen atoms in the equatorial plane and a water molecule or sulphate anion in the apical position [123,124]. In solutions of diamines with Hg(II), the stability of complexes formed increases in the series en < tn < Put, therefore compounds having seven-membered rings are more stable than those having five- or six-membered rings. This has been elucidated by the tendency of mercury ions towards linear coordination, in the HgPut complex, therefore, the strain in the largest ring is relatively low [125].

In the series of solid rhodium complexes with tetramines, the shortest ligand 2,2,2-tet forms only the *cis*-α isomer, 2,3,2-tet: *cis*-α and trans, while the complexes of 3,2,3-tet, 3,3,3-tet and the longest of these, i.e. Spm, assume a trans configuration, where differences are associated with steric strain [126]. The size of chelate rings also determines the kinetic character of the complexes. In acidic solution, $[Co(Spd)Cl_3]$ immediately undergoes hydrolysis and an increased lability of coordinated chlorine, with relation to complexes of shorter amines, 2,3-tri and 3,3-tri is observed. In the case of triamines, changes in the rate of reduction of $[Co(PA)(OH_2)_3]^{3+}$ to Co(II) occur in the order: Spd < 3,3-tri < dien and correspond to changes in activation energy [127]. As a result of noncovalent interactions of $ClO_4^-$ and $NO_3^-$ ions, in the processes of forming coordination compounds of spermine with Cu(II) and Zn(II), equilibrium shifts are observed. The formation of outer-sphere complexes is more likely for octahedral copper complexes than for tetrahedral zinc complexes [128].

A number of the new polyamine complexes (including biogenic amines), with platinum(II) and palladium(II), were synthesized in order to develop anti-cancer drugs better than *cis*-DDP or carboplatin, widely used in chemotherapy [129–138]. It is currently well recognized, that the anti-neoplastic properties of platinum compounds are caused by a selective reaction of DNA, with the creation of intrastrand links between guanine/guanine or guanine/adenine adjacent bases, with preferred sites of metallation on N(7) atoms of bases, with the additional possibility of creating bridging structures by N(7) and N(1) atoms [131,139,140]. The adducts formed block processes of replication and transcription [141,142]. The Pt(II) complexes used in clinical practice are unfortunately characterized by high toxicity and show a cytotoxic effect only with relation to some species of neoplasms. Multinuclear complexes of platinum containing bridging polyamines constitute a new class of compounds with a unique feature in comparison with known anti-neoplastic agents [132,136,138,140]. Introduction of biogenic amines into the structure of first generation platinum complexes has a significant impact on their binding character and their cytotoxic properties [138]. Some of them show a high effectiveness against certain neoplasmic species resistant to cisplatin [130,136,143,144]. The activity of bis(platinum) complexes with bridging diamines in some cases surpass that of *cis*-platinum [131]. Dimers have a wider clinical activity range than their monomeric analogues, which is related to their possibility of creating intra- and inter-strand cross-links, which cannot be formed in the case of mononuclear complexes [132,136]. Unlike cisplatin, metallation by bis(platinum) species does not unwind supercoiled DNA [132]. The structural similarities between dinuclear complexes of platinum and polyamines, with respect to charge and separation by a lipophilic polyamine backbone, have been reported [145]. Small differences in polyamine structure lead to significant changes in cytotoxic properties of their complexes with platinum. Besides the structure–activity relationships between biomolecules, the cytotoxic effectivity is also determined by charge, flexibility and non-covalent interactions [136]. The combination of some polyamine analogues with cytotoxic drugs has a synergic effect on certain neoplasmic cells [146]. The results of research on the cytotoxic properties of certain platinum(IV) complexes with polyamines have also recently been reported [135,137,140]. Probably because there is an in vivo reduction of Pt(IV) to Pt(II), the therapeutic activity of Pt(IV) complexes is similar to those of Pt(II). In the search for new cytotoxic patent drugs, a better aqueous solubility for platinum(IV), should be considered [137]. In the course of work on drugs of a cytotoxic nature, compounds of palladium(II) with polyamines have also been synthesized. The $ID_{50}$ values of palladium(II) complexes with putrescine and spermidine are better than those of *cis*-DDP in their action against some cancer cells, however the complexes with spermine have a low anti-proliferative activity [133,134]. These observations correspond to the fact that spermine complexes cannot induce conformational changes in DNA [134].

## 3. Non-covalent interactions in metal-free systems

Recognition of the nature of interactions in metal-free systems was the first step in evaluating the role of metal ions in biological systems, particularly with respect to their effect on reactions of polyamines (PA) with nucleosides (Nuc) and nucleotides (NucP).

The main factor determining non-covalent interaction in binary systems is the high basicity of polyamine donor atoms, which in the physiological medium, causes them to exist in the protonated form [33], thus creating a positive centre of weak interactions.

As far back as some 25 years, NMR and ion-exchange studies have enabled the occurrence of weak interactions in a model system of 5′-adenosine monophosphate, including biogenic amine, where protonated polyamine reacts with negatively charged nucleotide fragments [147,148]. Results of equilibrium studies have shown, that while analysing bonding of polyamines to nucleotides, it is necessary to take into account not only electric charge but also the structural factor. PA can not be considered as a point charge, although such a consideration is possible in the case of the interaction between metal ions, e.g. magnesium(II) and bioligands [148,149].

Taking advantage of the fact that the formation of molecular complexes is accompanied by a shift in the acid-base equilibrium of bioligands, i.e. polyamines and nucleosides or nucleotides, and by hydrogen ion release, the thermodynamic stability of adducts was determined [34,35,150,151]. There is no doubt that the effectiveness of a reaction is related to mutual structural matching of both components of the adduct to the number of donor centres. An increase in the number of interaction sites results in a higher $\log K_e$ of adduct formation (Table 2). At least two reaction centres are indispensable for obtaining a stable adduct. For example, the values of the

Table 2
Equilibrium constants of formation of molecular complexes

| Reaction | $\log K_e$ |
|---|---|
| Ado + $H_2$Put ⇆ Ado$H_2$Put | 1.53 [34] |
| Ado + $H_3$(3,3-tri) ⇆ Ado$H_3$(3,3-tri) | 1.89 |
| Ado + HSpm ⇆ AdoHSpm | 1.03 |
| Ado + $H_2$Spm ⇆ Ado$H_2$Spm | 1.80 |
| Ado + $H_3$Spm ⇆ Ado$H_3$Spm | 1.88 |
| ADP + $H_2$Spm ⇆ ADP$H_2$Spm | 1.69 [153] |
| ADP + $H_3$Spm ⇆ ADP$H_3$Spm | 1.76 |
| ADP + $H_4$Spm ⇆ ADP$H_4$Spm | 2.38 |
| ADP + $H_2$(3,3,3-tet) ⇆ ADP$H_2$(3,3,3-tet) | 2.71 |
| ADP + $H_3$(3,3,3-tet) ⇆ ADP$H_3$(3,3,3-tet) | 3.60 |
| ADP + $H_4$(3,3,3-tet) ⇆ ADP$H_4$(3,3,3-tet) | 4.49 |

calculated equilibrium constants of (Ado)$H_x$(Spm) formation clearly show that the formation of the second centre of the reaction leads to an increase in complex stability, (Table 2) [34].

Changes in electron density, occurring as a result of non-covalent interactions enable determination of interaction sites. Molecular complex formation has brought about shifts in the positions of NMR signals of bioligands involved in the reaction. On the other hand, changes in NMR signals ascribed to atoms that are distant from the reaction centre or in signals observed under conditions in which no adduct is formed, are insignificant (Table 3).

Analysis of results of spectroscopic and equilibrium studies has shown that these interactions are of an ion–dipole and ion–ion type [34–36,150,151,154]. Complexes are formed in a pH range where the nucleoside is already deprotonated and provides a negatively-charged reaction centre, while polyamine is protonated, thus providing a positively charged centre. Deprotonation of polyamines results in the decay of adducts (Fig. 4). Compared to cytidine-containing systems, the range of adduct formation with its analogue, uridine, which is characterized by much higher basicity of the donor nitrogen atom ($\log K^{H}_{Cyd} = 4.5$, $\log K^{H}_{Urd} = 9.2$), is shifted towards higher pH values, associated with a shift in the deprotonation range of the latter nucleoside (Fig. 4a and b) [37]. It is likely that the π-electron system of the heterocyclic ring is also involved in these interactions [152,155]. The presence of an additional centre of interactions, such as the phosphate group in the nucleotide causes a shift in the range of molecular complex formation towards a more acidic medium, (dissociation of the first proton occurs at a lower pH in relation to the nucleoside,) (Fig. 4c) [156]. Surprisingly enough, the phosphate group from AMP is ineffective in non-covalent interactions with spermine, which has been proven by the fact that there are no significant shifts in NMR signals and that values of equilibrium constants for adducts of nucleosides and nucleotides are similar [152]. This inactivity was explained by a competitive involvement of $K^+$ and $Na^+$ ions in the process of adduct formation [153]. The ion–ion, ion–dipole interaction, postulated in Nuc and NucP, polyamine systems, was confirmed through observations of PA interplays with simple cations as well as anions, including $Na^+$ and $Cl^-$, the presence of which changes the interactive nature of bioligands [157–160].

In considering that interactions in these systems are weak and it is difficult to perform observations, the reliability of the results obtained has been proven by comparing the experimental curves with those obtained as the result of computer-aided simulation [34,35,152].

The types of interaction discussed above play an essential role in the molecular recognition and self-organization of biomolecules of living systems [161–164]. Moreover formation of molecular complexes hinders, or at least interferes with, the self-stacking interactions observed in nucleotide systems [150].

Table 3
$^{13}C$ and $^{31}P$ NMR signal position changes (in relation to a single ligand) for Nuc(NucP)/polyamine systems [ppm]

| Species | Interaction centre | pH | Nucleoside or Nucleotide | | | | | | Polyamine | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | C(2) | C(6) | C(5) | C(8) | C(4) | C(5′) | $P_\alpha$ | $P_\beta$ | C(1) | C(2) | C(3) | C(4) | C(5) |
| Ado/Put [35] | No adduct | 2 | 0.000 | 0.000 | 0.000 | 0.020 | 0.000 | | | | 0.000 | 0.000 | | | |
| (Ado)$H_2$(Put) [35] | N(1), N(7), $NH_x^+$ | 4 | 0.500 | 0.680 | 0.230 | 0.370 | 0.015 | | | | 0.240 | 0.150 | | | |
| Ado/Put [35] | No adduct | 11 | 0.030 | 0.020 | 0.080 | 0.050 | 0.030 | | | | 0.000 | 0.020 | | | |
| Ado/Spm [164,152] | No adduct | 2 | 0.002 | 0.001 | 0.005 | 0.003 | 0.005 | 0.002 | | | 0.002 | 0.002 | 0.004 | 0.003 | 0.005 |
| (Ado)$H_4$(Spm) [152] | N(1), N(7), $NH_x^+$ | 6 | 0.438 | 0.337 | 0.242 | 0.125 | 0.070 | 0.003 | | | 0.159 | 0.097 | 0.277 | 0.617 | 0.503 |
| (AMP)$H_2$(Spm) [152] | N(1), N(7), $NH_x^+$ | 10 | 0.245 | 0.745 | 0.714 | 0.189 | 0.003 | 0.010 | 0.012 | | 0.727 | 0.605 | 1.324 | 3.466 | 0.365 |
| (ADP)$H_5$(3,3,3-tet) [153] | N(1), N(7), $-O(PO_3)_2^{2-}$, $NH_x^+$ | 5 | 0.570 | 0.300 | 0.314 | 0.100 | 0.000 | 0.070 | 0.664 | 0.176 | 0.050 | 0.016 | 0.060 | 0.039 | 0.024 |
| Cyd/Spm [152] | No adduct | 2 | 0.001 | 0.004 | 0.004 | | 0.003 | 0.003 | | | 0.001 | 0.003 | 0.004 | 0.005 | 0.007 |
| (Cyd)$H_4$(Spm) [152] | N(3), $NH_x^+$ | 6 | 0.174 | 0.015 | 0.012 | | 0.101 | 0.020 | | | 0.144 | 0.107 | 0.297 | 0.617 | 0.500 |
| (CMP)$H_4$(Spm) [152] | N(3), $-O(PO_3)^{2-}$, $NH_x^+$ | 8 | 0.388 | 0.003 | 0.006 | | 0.104 | 0.161 | 0.114 | | 0.434 | 0.316 | 0.815 | 1.310 | 0.230 |

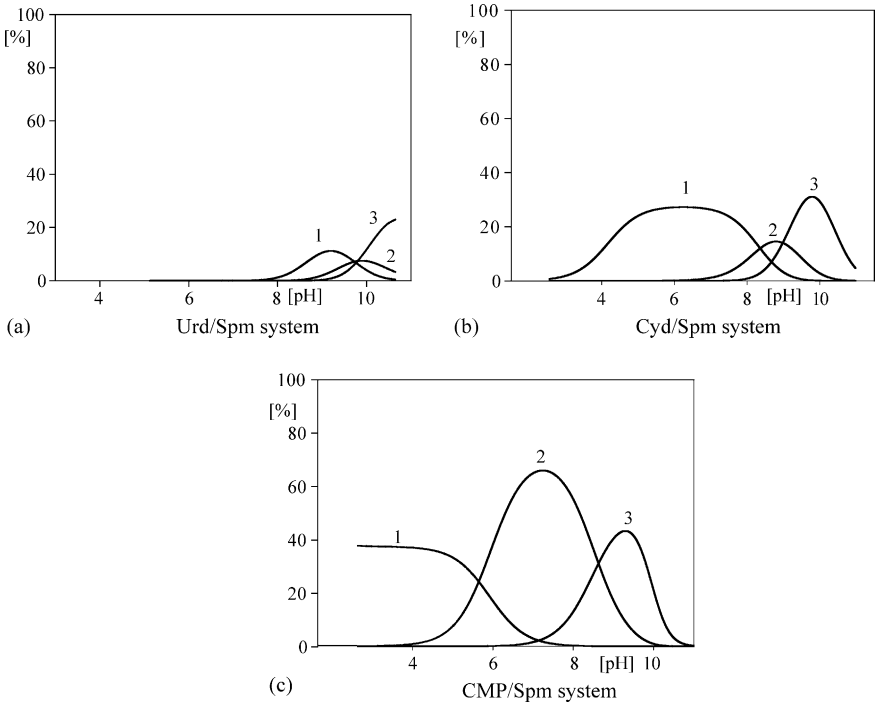


Fig. 4. Distribution diagrams for (a): Urd/Spm, (b): Cyd/Spm, (c): CMP/Spm systems; (a): 1-(Urd)$H_3$(Spm), 2-(Urd)$H_2$(Spm), 3-(Urd)H(Spm) (b): 1-(Cyd)$H_3$(Spm), 2-(Cyd)$H_2$(Spm), 3-(Cyd)H(Spm) (c): 1-(CMP)$H_3$(Spm), 2-(CMP)$H_2$(Spm), 3-(CMP)H(Spm).

## 4. Coordination compounds and polyamine interactions in ternary systems

### *4.1. Coordination sites in polyamines, nucleosides and nucleotides*

The coordination ability of polyamines depends on the number and character of their $-NH_x$ groups. Principal metallation sites of nucleosides are the endocyclic donor N(3) atoms in the case of pyrimidine biomolecules and N(1) and N(7) atoms in purine nucleosides [165–168]. The coordination mode in deoxynucleoside metal complexes is analogous [165]. Although the N(1) atom in adenosine is characterized by a much greater basicity than N(7), the latter is the preferred site of metallation [169]. In nucleotides, phosphate groups are additional effective sites of metal ion binding, although no unequivocal explanation has yet been given with respect to the role of these groups in coordination. Sometimes they are considered as principal or even exclusive coordination sites. In a number of papers the involvement of endocyclic nitrogen atoms of purine or pyrimidine rings was postulated [166,170,171], but the role played by phosphate groups seems to be predominant [172–174].

The results of some studies suggest, however, that in metal–nucleotide–polyamine ternary systems, metal ions bind only endocyclic nitrogen atoms with the possibility of non-covalent interactions of phosphate groups of nucleotides with polyamines present in these systems [175].

Practically, in none of the ternary systems studied, was the involvement of nucleoside carbonyl groups and ribose donor atoms in metallation found [35,36,125,154,176]. In the series of systems studied, the thermodynamic stability of metal complexes with adenosine 5′-triphosphate (ATP) and cytidine 5′-triphosphate (CTP) increases in the order Ni < Co < Cd < Cu < Hg. Ions of Cu(II), Co(II) and Cd(II) form macrochelate compounds with the {N1O1} chromophore. The lower stability of nickel complexes, compared to complexes of other metals, corresponds to different coordination modes and a low effectiveness of the phosphate group, both in purine nucleotides and pyrimidine nucleotides [171,177,178]. The different character of the most stable Hg(II) ion complexes is undoubtedly associated with the tendency of this metal to form linear structures [179].

#### *4.1.1. Coordination dichotomy*

Considering the mode of coordination in systems including purine nucleosides or nucleotides, there is no doubt that the presence of chelate complexes with simultaneous coordination to N(1) and N(7) atoms is impossible for steric reasons. However, in a number of systems, both binary and ternary ones, an occurrence of coordination dichotomy with monodentate metallation of these bioligands was found. Isomers of copper(II) complexes are formed with metal ions coordinated to either N(1) or N(7) atoms [35,150,165,167,177,180]. The occurrence of isomerism has also been found in systems with ions of Ni(II), Co(II), Zn(II), Cd(II) and Hg(II) [103,171,176,177].

In the system Cu/Ado (metallation sites are shown in Fig. 5), N(1)/N(7) isomeric mixing occurs only in an acidic medium (in the basic medium, the N(7) atom is involved in

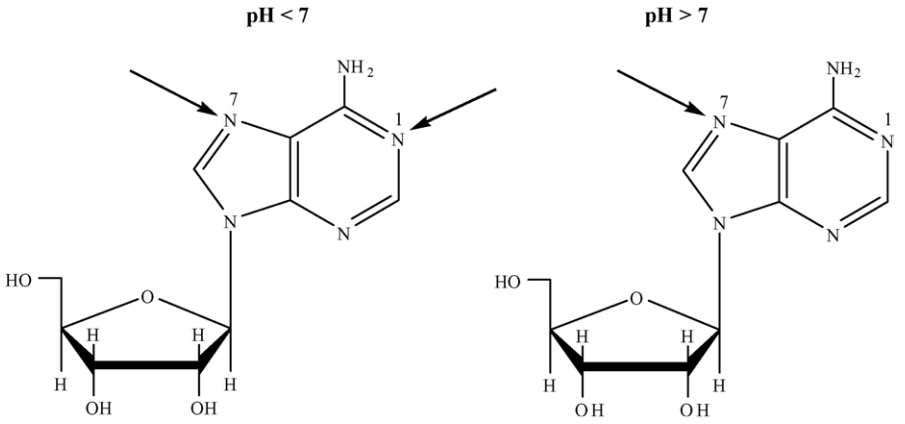


Fig. 5. Sites of metallation of purine nucleotides in acidic and basic media.

the coordination). The introduction of polyamine to a binary system metal/Nuc (or metal/NucP) changes the nature of the coordination dichotomy.

The presence of putrescine or 3,3-tri in the system extends the dichotomy range to the basic medium. On the other hand, the introduction of longer polyamines, such as spermidine or spermine, results in a decay of the dichotomy over the whole pH range [35,150,153]. The effect of polyamines on dichotomy has also been observed in the process of Hg(II)-ADP complexation [176].

### *4.2. Complexes in ternary systems containing metal ions, polyamines and nucleosides*

In ternary systems metal/putrescine/nucleoside {Nuc = adenosine(Ado), cytidine(Cyd), uridine(Urd)} spectroscopic studies have shown the formation of several complexes with {N2}, {N3} and {N2} chromophores, respectively, i.e. both monodentate and bidentate coordination of the polyamine occur. In analogous systems of Put with Cu(II) and Cyd, formation of mixed-ligand complexes has not been observed at all [37,150]. However, within the system with the longer amine–spermidine, a mixed complex Cu(Ado)(Spd)$(OH)_2$ is formed, in which only two nitrogen atoms from Spd are involved in the coordination [34]. Red shift analysis has indicated that complexes having biogenic amines have a tendency to assume a planar-square structure, whereas their homologues, such as tn and 3,3-tri, form complexes with an additional nitrogen atom in the axial position [150]. An increase in chain length of polyamines is usually accompanied by a decrease in the effectiveness of their reactions, despite the higher basicity of donor atoms, compared to their shorter homologues [36]. Spermine, the longest of the biogenic polyamines, has a coordination nature different from that of its shorter homologues. As has already been mentioned, spermine behaves in its interactions as two independent fragments $NH_2(CH_3)_3NH$- (analogously to the chain in 1,3-diaminopropane, tn) separated by a long tetramethylene group, which reduces the coulombic effect and leads to increased effectiveness of interactions with metal ions. The difference in stability constants, $\log \beta$, between Cu(Ado)(Spm) and Cu(Ado)(tn) is 6.29, while between Cu(Cyd) (Spm) and Cu(Cyd)(tn) it is about 6.14. The close value of these differences indicates the same mode of coordination, assuming reliably that in Ado and Cyd, only one nitrogen atom is involved in metallation [152]. Moreover, as follows from a comparison of equilibrium constants of complex formation, all four nitrogen atoms of spermine are involved in the coordination.

In a comparative analysis of equilibrium parameters for mixed complexes of different composition, values of equilibrium constants ($\log K_e$) have been taken into consideration, instead of values of stability constants ($\log \beta$). For instance, the equilibrium constant of Cu(Nuc)(PA) complex formation is: $\log K_e = \log \beta_{CuNucPA} - \log \beta_{CuNuc}$ and this value corresponds to the reaction binding the polyamine to its anchoring Cu(Nuc)

$$Cu(Nuc) + PA \leftrightarrows Cu(Nuc)(PA)$$

The pattern of changes in absorption bands of the complexes formed in Cu/Nuc/Spm systems is in excellent agreement with the dominant ranges of particular complexes. For instance, in a system involving Cyd at pH < 4 (the distribution diagram indicates that the complex in not formed), $\lambda_{max} \approx 830$ nm, in a pH range of about 5–6, $\lambda_{max} \approx 750$ nm, the coordination is {N1} (CuCyd complex), and at pH > 6, $\lambda_{max} \approx 600$ nm, the coordination mode is {N5} (in CuCyd-Spm) with four nitrogen atoms of Spm and one nitrogen atom from Nuc [152]. Shifts in absorption band positions are the result of ligand field changes.

### *4.3. Complexes in ternary systems containing metal ions, polyamines and nucleotides*

The presence of phosphate groups in nucleotides results, of course, in characteristic differences in interactions, compared to those observed in the case of nucleosides, which can particularly clearly be seen in polyamine-containing systems. These differences are presented in Fig. 6 [152,181]. In nucleoside-containing systems, we observe the forma-

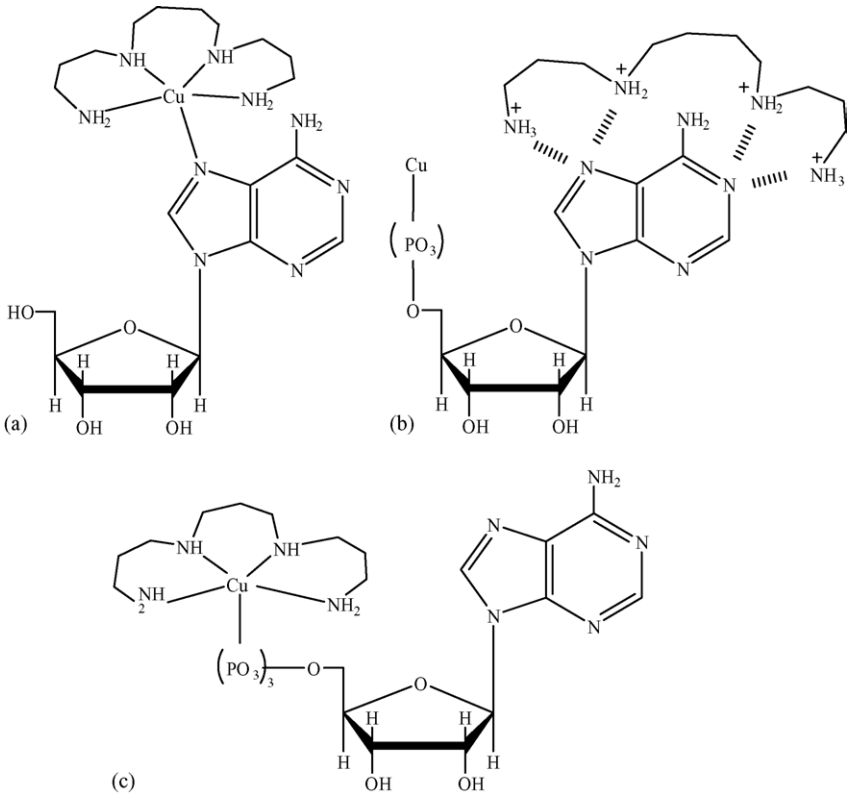


Fig. 6. Differences in the mode of interactions in nucleoside and nucleotide complexes (a): Cu(Ado)(Spm), (b): Cu(AMP)$H_4$(Spm) and (c): Cu(ATP)(3,3,3-tet) complexes.

tion of Cu(Nuc)(Spm) complexes (Nuc = Ado or Cyd) with {N5} type coordination [152], where copper is coordinated to four nitrogen atoms from the polyamine in the equatorial position and a nitrogen atom from Nuc in the axial position (Fig. 6a). Whereas in the Cu(NucP)$H_4$(Spm) complex (NucP = adenosine 5′-monophosphate, AMP or cytidine 5′-monophosphate, CMP), copper ions are bound only to phosphate groups, and spermine interacts non-covalently with nitrogen atoms of high electron density (Fig. 6b). Thus, in the nucleoside-containing system, the metal makes the Spm–Nuc reaction impossible, while in nucleotide-containing system, spermine blocks potential metallation sites [152,181]. The coordinative character of bioligands in metal–polyamine–nucleotide systems is determined by relationships between the effectiveness of interactions of phosphate groups in NucP and the effectiveness of endocyclic nitrogen atoms as well as by the number of polyamine donor atoms and polyamine length. In complexes of the MLL′ type (L = AMP,CMP; L′ = 3,3,3-tet; M = Cu), metallation occurs with the {N4O} chromophore (Fig. 6c) including the nucleotide phosphate group and the amine groups from PA as the bonding sites, whereas no endocyclic nitrogen donor atoms are involved in the coordination [36]. Such an interaction is considerably different from that shown in the analogous spermine-containing complex Cu(AMP)$H_4$(Spm). It is one of many examples taken from our studies, showing that even relatively small differences in polyamine length result in significant changes in interactions and emphasizes the role of the steric factor that determines the specificity of polyamine interactions. Moreover, this factor explains differences in properties of biogenic amines compared to their homologues, which do not occur in living organisms.

The coordination mode in the complexes investigated was determined mainly by analyzing spectroscopic results. With an increasing number of donor centers in chromophores Cu–$N_x$ ($x$ = 1–6) and Cu–$N_xO_y$ ($x$ = 0–4, $y$ = 0–4), a characteristic decrease in $g_{\|}$ and an increase in $A_{\|}$ (determined from EPR spectra) were observed as the result of coordination [62,182]. This analysis was supplemented by observations of the dependence of d–d band positions in the electronic spectra of complexes on the number of donor atoms in the inner coordination sphere. When interpreting changes in NMR signals, limitations of the technique in the case of paramagnetic ions were taken into consideration. In evaluating the interaction mode, an important role was played by a comparative interpretation of the results of equilibrium studies, with the use of information about compositions of complexes and stability constants, calculated by using computer-assisted methods based on analyzing potentiometric titration data [183].

Of course, the nature of coordination in ternary systems containing polyamines and nucleotides depends also on the nature of the metal. Differences between Co(II) and Ni(II) are a typical example. Differences in the coordination between

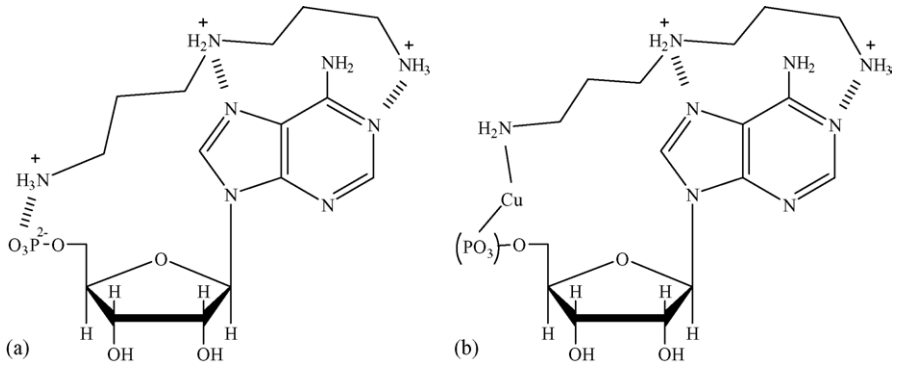


Fig. 7. Interactions in (a): (AMP)$H_3$(3,3-tri) and (b): Cu(AMP)$H_2$(3,3-tri) complexes.

each metal, correspond mainly with the low effectiveness of the phosphate group in the reaction with nickel(II) ions. In cobalt(II) systems an {N1O} type of metallation occurs with the involvement of a phosphate group and an endocyclic nitrogen atom from NucP [177].

### *4.4. The effect of metal ions and polyamines on the mode of interaction*

The introduction of metal ions has a significant influence on the character of the reaction between bioligands. For example, the molecular complex (AMP)$H_3$(3,3-tri) is formed in a metal-free system with interactions of $-NH_x$ groups of the polyamine, phosphate group and high electron density nitrogen atoms N(1) and N(7). The results of spectroscopic and equilibrium studies indicate that metallation leads to elimination of the phosphate groups from non-covalent interactions between bioligands, as schematically shown in Fig. 7 [36].

Another example of the interfering role of metal ions is presented in Fig. 8. The introduction of nickel (II) into an adenosine 5′-monophosphate/Spm system results in a change of the interaction mode between bioligands (Fig. 8) [152,178].

On the other hand, the role of interfering agent is played by the polyamine, as well. Its introduction into the metal/Nuc(NucP) system affects the interaction mode, as has already been discussed, when describing changes in the coordination dichotomy nature in metal/Nuc and metal/NucP (Section 4.1.1). Fig. 9 presents another typical example. In the binary complex Cu(CMP), the phosphate groups of nucleotides and donor atoms N(3) are involved in binding copper(II) ions, whereas following the introduction of polyamine (putrescine) into the system, intramolecular non-covalent interactions occur between the protonated $NH_x$ group of polyamine and high electron density centers of the pyrimidine ring, according to the ion–ion, ion–dipole interaction model. Instead of the N(3) atom, which is excluded from metallation, copper(II) ion is bound to a deprotonated nitrogen atom of putrescine [36].

Analysis of changes in the IR spectra suggest, that in the Cu/UMP system, an unusual case occurs, that involves the carbonyl group from UMP in metallation at pH > 10 in the Cu(UMP)$(OH)_3$ complex. The introduction of spermidine into the system results in a change of coordination and formation of the Cu(UMP)(Spd) (chromophore {N4O}) complex, Fig. 10 [151].

In the series of cytidine 5′-diphosphate-containing systems, which are currently being studied in our laboratory, we have observed a very interesting case (as yet unpublished), which illustrates the dependence of the nature of the interaction upon the conditions of complex formation. In the binary Cu/CDP system, copper(II) is coordinated to a phosphate group and an N(3) atom (analogous to the interaction of the CMP species presented in Fig. 9), whereas in the ternary system Cu(II)/CDP/Spm, the coordination mode has changed. The interfering character of Spm depends on solu-

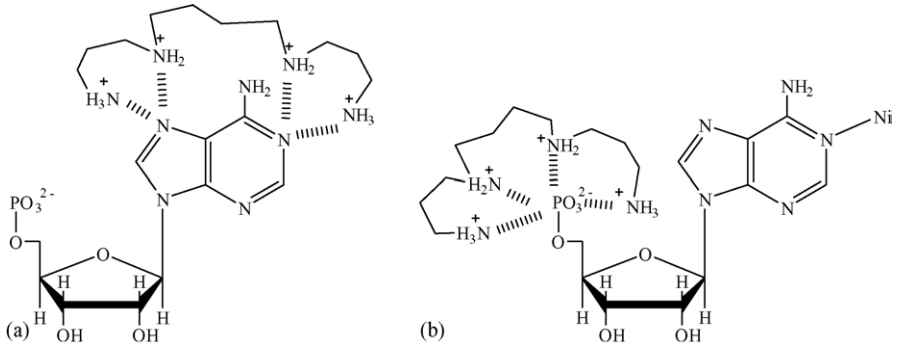


Fig. 8. Interactions in (a): (AMP)$H_4$(Spm) and (b): Ni(AMP)$H_4$(Spm) complexes.

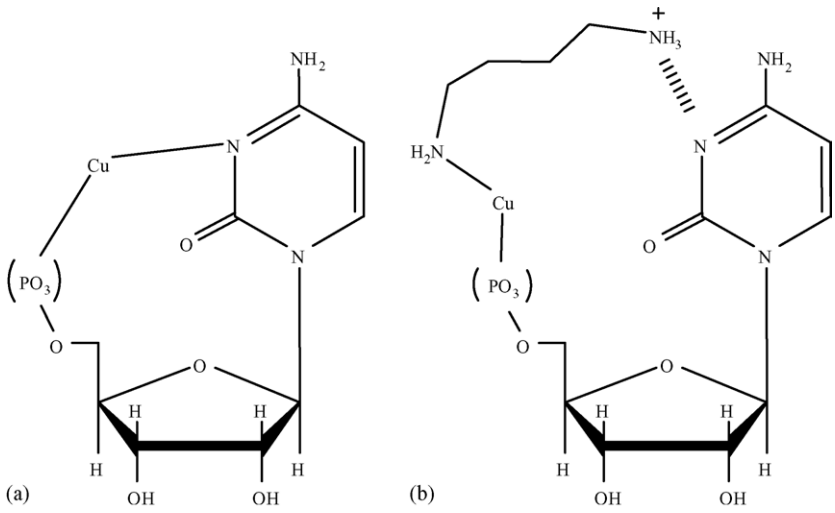


Fig. 9. Mode of interactions in (a): Cu(CMP) and (b): Cu(CMP)H(Put) complexes.

tion acidity. At a low pH, Spm interacts non-covalently with the nucleotide and a Cu(CDP)$H_4$(Spm) complex is formed (Fig. 11a), while with increasing pH, the amine undergoes deprotonation and Cu(CDP)$H_2$(Spm) and Cu(CDP)(Spm) complexes are formed, one after the other (Fig. 11b and c), which involves participation of more and more polyamine nitrogen atoms in coordination.

### 4.5. Intramolecular interactions in the MLL'$H_x$ species

The fact that not all donor atoms of polyamines and nucleotides are involved in bonding with metal ions makes possible the occurrence of non-covalent intramolecular interactions with the participation of protonated amine groups [36,152,153]. The interaction mode in the complex Cu(ATP)$H_3$(Spm) is presented in Fig. 12. In this complex, only the deprotonated nitrogen atom, the phosphate group and N(3) atom coordinate with copper(II) ions, whereas protonated amino groups interact non-covalently with the N(1) center of the nucleotide. An analysis of the equilibrium research data shows that intramolecular interactions of the polyamine with the nucleotide ring bring about additional stabilization in the mixed-ligand complex [153].

Another kind of intramolecular interaction was observed in the complex Ni(AMP)$H_2$(Spm). Due to the low effectiveness of the Ni(II) ion, phosphate group interaction, the above ion coordinates with the endocyclic N(1) atom or N(7) atom of the purine ring and two nitrogen atoms of polyamine (chromophore {N3}). Protonated amino groups of Spm react non-covalently with the AMP phosphate group (Fig. 13) [177].

The non-covalent interactions discussed above play a significant role in processes of molecular recognition within biological systems.

### 4.6. Adducts of the ML···L' type

The stoichiomeric composition of the complex Ni(AMP)$H_4$(Spm) (and similarly, its cobalt-containing analogue), in which all donor atoms of amine are protonated and blocked

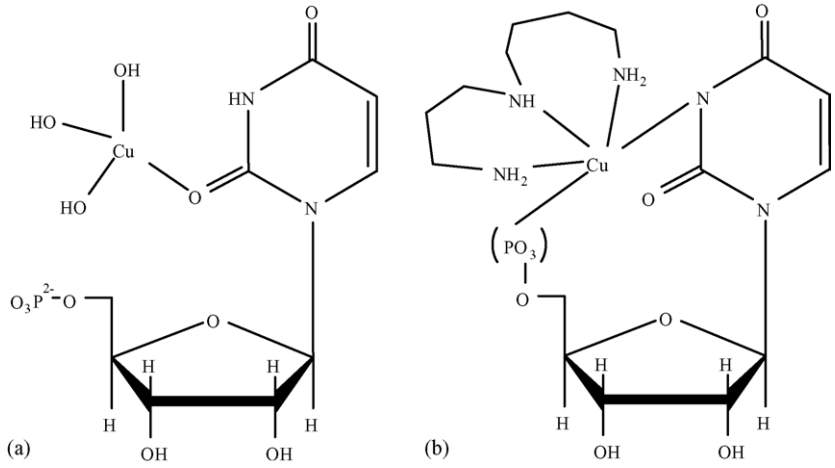


Fig. 10. Mode of interactions in (a): Cu(UMP)$(OH)_3$ and (b): Cu(UMP)(Spd) complexes.

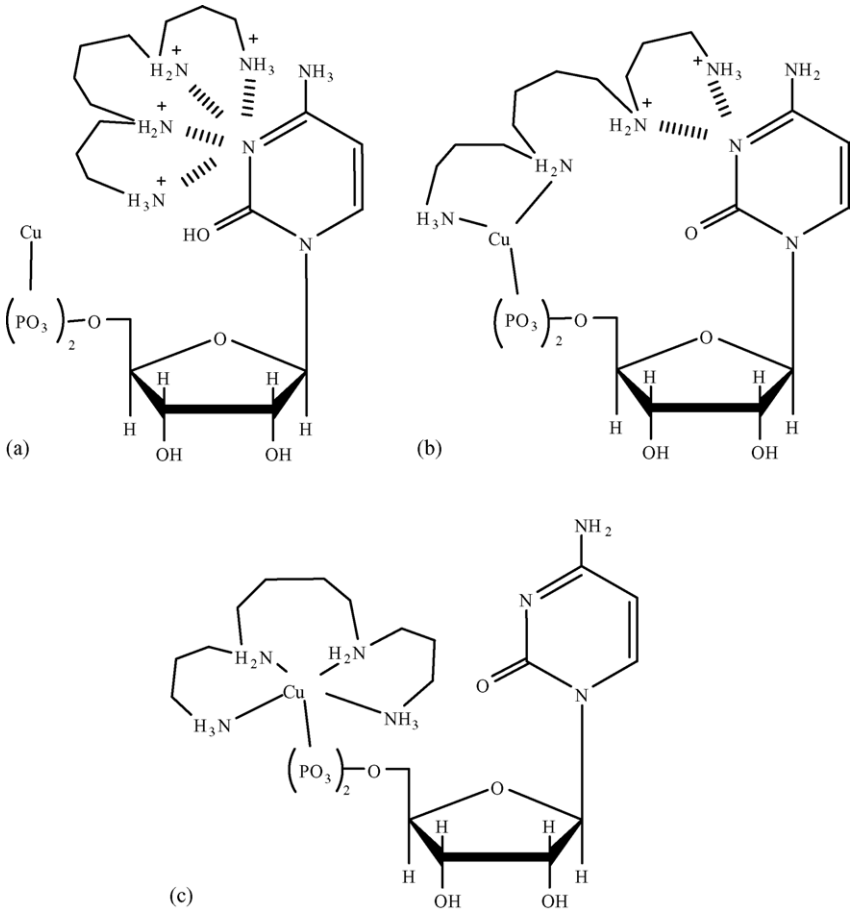


Fig. 11. Influence of pH on the character of interactions in Cu/CDP/Spm system (a): Cu(CDP)$H_4$(Spm), (b): Cu(CDP)$H_2$(Spm) and (c): Cu(CDP)(Spm).

against metallation, as well as the pH range in which the complex exists, indicate that a molecular complex of the ML···L' type is formed as the result of non-covalent, intermolecular interactions of the Ni(AMP) with spermine, the latter remaining in the outer coordination sphere. This is an adduct analogous to that shown in Fig. 6b, i.e. Cu(AMP)$H_4$(Spm). A similar type of non-covalent interaction was found in the Pd(II)/spermidine/amino acid system as was established on the basis of analysis of $^{13}$C NMR and CD data [184]. Conformational changes within the complex are the result of ligand–ligand electrostatic interactions and/or formation of

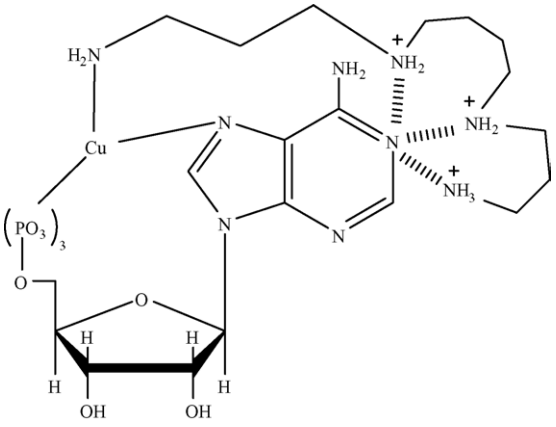

Fig. 12. Effect of stabilization in Cu(ATP)$H_3$(Spm) heteroligand complex.

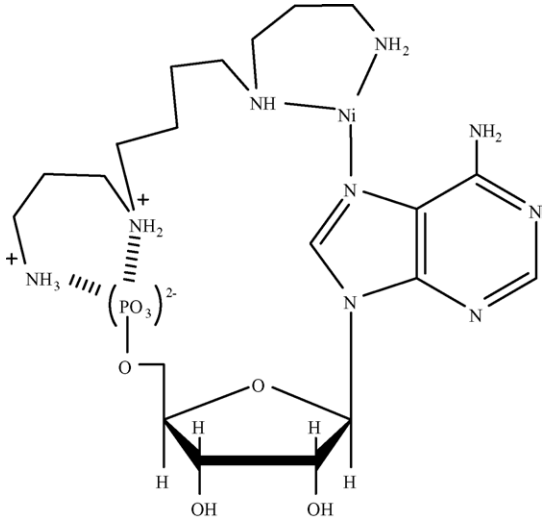

Fig. 13. Effect of stabilization in Ni(AMP)$H_2$(Spm) heteroligand complex.

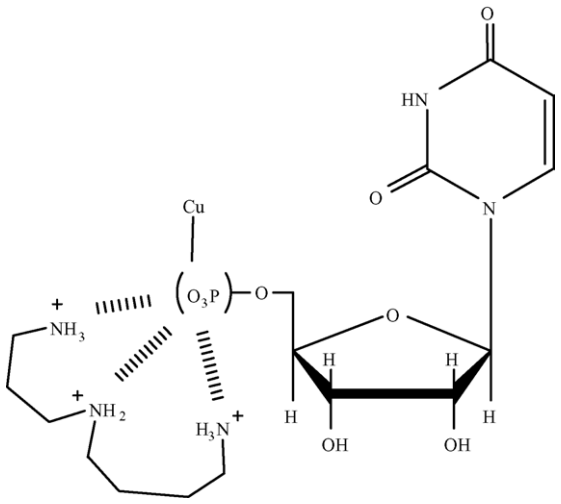


Fig. 14. Untypical interactions in Cu(UMP)$H_3$(Spd) complex.

hydrogen bonds, with the involvement of negatively charged groups from Pd(amino acid)$_2$ and protonated spermidine located in the outer coordination sphere.

This type of molecular complex corresponds to the reaction of zinc fingers with DNA, where intermolecular interactions between the coordination compound and the uncomplexed ligand also occur.

An adduct of an analogous type was found also in the Cu(II)/polyamine/nucleotide systems. Compositions of Cu(ADP)$H_5$(Spm) and Cu(ATP)$H_4$(Spm) species as well as low formation constant values, are an indication of weak interactions between protonated amines and anchoring complexes Cu(ADP) and Cu(ATP). Spectroscopic parameter values clearly show that the metal is bound to the phosphate group in a monodentate mode, whereas protonated polyamine reacts non-covalently with the high electron density centers of the purine ring [153].

A non-typical mode of interaction was found in Cu/spermidine(or spermine)/uridine 5′-monophosphate systems. In the Cu(UMP)$H_4$(Spd) species, a protonated polyamine, located in the outer coordination sphere, interacts non-covalently with an –O–$PO_3$ group bound to the metal ion. The deprotonated phosphate group is thus, at the same time, an efficient coordination and weak interaction site (Fig. 14) [151].

As noted before, both the metal ions and the polyamines involved in complex formation, within systems of biological importance, should be regarded as interference agents in interactions. Taking into consideration the fact, that polyamines interact with nucleic acids (as can be concluded from the observation that inhibition of synthesis of biogenic amines in living cells results in the inhibition of cell proliferation) an analysis of metal ion reactions in ternary systems, including nucleosides, nucleotides and polyamine is essential for the characterization of biochemical reactions, particularly those concerning genetic information transfer. Although our knowledge of the nature of the processes discussed and the roles played by polyamines and metal ions in biological systems is still incomplete, the results so far obtained have made an advance towards explaining the nature of the reaction at the molecular level. The solution of these problems provides further challenges, facing coordination chemistry and bioinorganic chemistry.

## Acknowledgments

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