Chapter

# Correlation between HSAB Principle and Substitution Reactions in Bioinorganic Reactions

*Tanja Soldatović*

## Abstract

Substitution reactions are a type of reactions where one functional group or ligand is substituted by another. They could be electrophilic or nucleophilic, depending upon whether the reagent is involved. Complex compounds could be involved in a number of substitution reactions such as ligand exchange, solvent exchange, complexation or anation reactions, solvolysis, acid and base hydrolysis, inter- and intramolecular isomerization, racemization, and metal ion reaction. Hard-soft acid–base principle (HSAB) contributes to better understanding of the mechanism of nucleophilic substitution reactions of transition metal complexes. Metal–ligand bonds in transition metal compounds are closely related to the HSAB nature of metals and their preferred ligands. Also, the principle is qualitatively useful to predict the preference of the metal for the ligand in bioinorganic reactions.

**Keywords:** substitution, complexes, hard-soft acid–base principle, metal–ligand bonds, bioinorganic reactions

## 1. Introduction

The aim of this chapter is to present connection between hard-soft acid–base principle with bioinorganic substitution reactions. Bioinorganic chemistry is an interdisciplinary field which connects inorganic chemistry with different types of chemistries, physics, medicine, biology, physiology, etc. This field includes studies of kinetic and thermodynamic of substitution reactions of transition metal ion coordination compounds and biomolecules such as enzymes, nucleic acids, proteins, peptides, amino acids, and others.

Ligand substitution reactions are the most fundamental type of chemical reaction that can occur when a metal complex is dissolved in solution in the presence of other nucleophiles. Acid–base properties of central metal ions and ligands are very important for understanding the mechanism of interactions between metal ions (Lewis acids) and various biomolecules (Lewis bases) with different donor atoms. HSAB principle is qualitatively useful to predict the preference of the metal for the ligand and to predict the stability of M-L bonds. Hard-hard or soft-soft bonds of acid and base contribute to the stabilization and strength of the bonds between donor and acceptor. These factors also include the charges and sizes of the cation and donor atom, their electronegativities, and the orbital's overlap between them.

## 2. Hard and soft metal centers and ligands

From the theory we know that Lewis acid is an electron acceptor and a Lewis base is an electron donor. In coordination chemistry, we consider the central metal ions as a Lewis acid which are coordinated (bonded) by one or more molecules or ions (ligands) which act as Lewis bases. The formed coordinated bonds between the central atom or ion with ligands have covalent character, which are known under the name coordinate covalent bond or simple coordinate bond. The acceptor properties of metal ions toward ligands could be divided into two classes. These two classes are "hard" acids or class (a) cations and "soft" acids or class (b) cations. Similar patterns were found for other donor atoms: ligands with O- and N-donors form more stable complexes with class (a) cations, while those with S- and P-donors form more stable complexes with class (b) cations.

The terms "hard" and "soft" acids arise from a description of the polarizabilities of the metal ions. Hard acids are typically either small monocations with a relatively high charge density or are highly charged, again with a high charge density. These ions are not very polarizable and show a preference for donor atoms that are also not very polarizable, e.g., O. Such ligands are called hard bases. Soft acids tend to be large monocations with a low charge density, e.g., $Pd^{2+}$, and are very polarizable. Soft metal ions prefer to form coordinate bonds with donor atoms that are also highly polarizable, e.g., P. Such ligands are called soft bases. Pearson's classification of hard and soft acids comes from a consideration of a series of donor atoms placed in order of electronegativity:

$$F > O > N > Cl > Br > C \sim I \sim S > Se > P > As > Sb$$

A hard acid is one that forms the most stable complexes with ligands containing donor atoms from the left side of the series. The reverse is true for a soft acid. This classification is listed in **Table 1**.

The applications of the HSAB principle are useful to predict thermodynamically stable M-L bonds. For example:

- Fe(III) belongs to a class of hard acids and prefers the hard bases, e.g., O. Thus, it is understandable why the concentration of Fe(III) ions in the body is controlled by $OH^-$, $O^{2-}$, and $RO^-$ species. In ferritin protein that stores iron and releases it in a controlled fashion, Fe(III) ions are bound by the phenolate group –OPh.

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

**Table 1.**
*Selected hard and soft metal centers (Lewis acids) and ligands (Lewis bases) and those that exhibit intermediate behavior.*

- Pt(II) a soft acid prefers soft bases S-donor instead of N-donor ligands. Antitumor activity of platinum(II)-based drugs is explained by the assumption that they firstly react with S-donor biomolecules, which is kinetically more favorable and then comes to form thermodynamically more stable Pt-DNA adducts.

Ligands with hard N- or O-donor atoms form more stable complexes with s- and p-block metal cations (e.g., $Na^+$, $Mg^{2+}$), early d-block metal cations (e.g., $Co^{3+}$, $Cr^{3+}$), and f-block metal ions (e.g., $Th^{4+}$). On the other hand, ligands with soft P- or S-donors have a preference for heavier p-block metal ions (e.g., $Tl^+$) and later d-block metal ions (e.g., $Pd^{2+,}$ $Ag^+$).

Complex formation involves ligand substitution. If we suppose that metal ion is a hard acid, the hard-hard bond with ligands is favorable. If ligand is a soft base, ligand substitution will not be favorable. If metal ion is a soft acid and ligand is a soft base, soft-soft interaction is favorable.

Although successful, the HSAB principle initially lacked a satisfactory quantitative basis. Today it is possible to use DFT theory to derive electronic chemical potential values (electronic chemical potential) and chemical hardness values [1].

## 3. Substitution reactions in transition metal coordination chemistry

Substitution reactions of complexes are divided on electrophilic ($S_E$) or nucleophilic ($S_N$) depending on the replacement of either central metal ion or ligand. If the metal ion is substituted during the reaction, i.e., electrophile, the reactions are electrophilic substitution (Eq. (1)); otherwise if a ligand is replaced, that is nucleophilic substitution reaction (Eq. (2)) [2, 3]:

$$[ML_n] + M' \rightleftharpoons [M'L_n] + M \quad (1)$$

$$[ML_n] + X \rightleftharpoons [ML_{n-1}X] + L \quad (2)$$

Ligand substitution reactions in metal complexes can occur in two ways, either by a combination of solvolysis and substitution by ligand or simple exchange in which there is a replacement of one ligand by another without the direct inclusion of solvent. The direct substitution is more relevant for the square-planar complexes with regard to octahedral complexes. For other complex geometries, both routes are used [4].

Nucleophilic substitution reactions, according to Langford and Gray, are carried out in three different mechanisms: dissociative (D), associative (A), or interchange mechanism (I) (**Figure 1**) [2].

In the dissociative mechanism (D), the first step of the reaction is dissociation of the one ligand L from the inner coordination sphere, whereby an intermediate with a decreased coordination number forms. In the next step, the entering ligand X binds to the central metal ion. Since the first step of the reaction is slower, it determines the overall rate of the substitution reaction.

In the associative mechanism (A), in the first step, the entering ligand X binds to the central metal ion, forming an intermediate with an increased coordination number, and then, in the second step, the leaving ligand L leaves the coordination sphere of the complex. The formation of an intermediate with an increased coordination number is slower, and it determines the rates of this substitution process.

When an intermediate cannot be detected by kinetic, stereochemical, or product distribution studies, the so-called interchange mechanisms (I) are invoked. Associative interchange mechanisms ($I_A$) have rates dependent on the nature of the

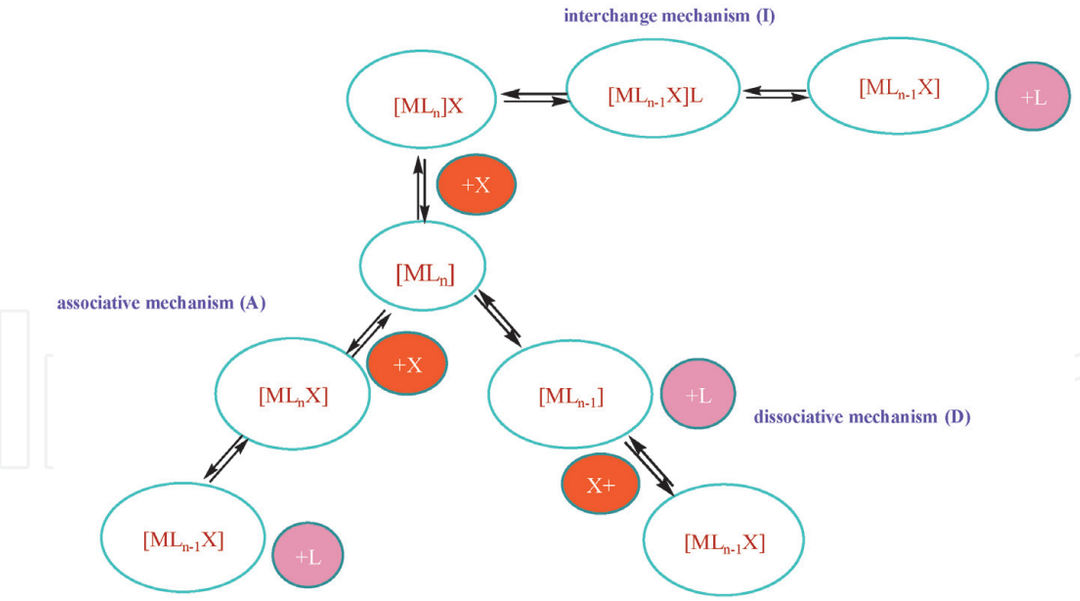


**Figure 1.**
*Schematic representation of the mechanisms for substitution reactions.*

entering group, whereas dissociative interchange ($I_D$) mechanisms do not. If the process of breaking the bond between the central metal ion and the outgoing ligand L has a greater impact on the rate of reaction, the mechanism is $I_D$, and if forming a new bond between the central metal ion and the entering ligand X has a greater impact on the chemical reaction rate, the mechanism is marked with $I_A$ [2, 3].

The associative mechanism is well-known and preferred for four-coordinated square-planar complexes. Dissociative mechanisms are more common for six-coordinated octahedral complexes. Five-coordinated complexes could react in both mechanisms [4]. For investigations of complex-ligand substitution reactions, experimental techniques such as spectroscopic techniques (UV–Vis, NMR, Mössbauer, IR, Raman, EPR spectroscopy, MS), rapid cryogenic X-ray structure determinations of reactive intermediates, matrix isolation of reactive intermediates, fast kinetic techniques, low-temperature kinetics, high-pressure kinetic and thermodynamic techniques to construct volume profiles as compared to energy profiles, and theoretical methods to analyze and predict reaction mechanisms are widely used [2–4].

### 3.1 Bioinorganic reactions

Under the classification of bioinorganic reactions, we consider the interactions of metal ions with biomolecules under physiological conditions. Ligand affinity and possible coordination geometries of the metal center are important bioinorganic principles. Metal–ligand bonds are closely related to the HSAB nature of metals and their preferred ligands. Many factors could affect metal–ligand complex formation including the formation of competing equilibria-solubility products, complexation, and/or acid–base equilibrium constants—sometimes referred to as "metal ion speciation" which all affect the complex formation. Ion size and charge, preferred metal coordination geometry, and ligand chelation effects all affect metal uptake. In biological systems, as in all others, metal ions exist in an inner coordination sphere with ligands binding directly to the metal. The bioinorganic reaction mechanism includes investigation of all processes which occur during applications of metal-based drugs. Thus, the determination of mechanism helps to clarify what will happen after administrations of the drugs and helps to improve medical characteristics of them.

## 4. Substitution reactions of platinum(II) and zinc(II) complexes with biomolecules in correlation with HSAB principle

### 4.1 Substitution reactions of platinum(II) complexes

Platinum complexes are in medical use worldwide. Cisplatin or *cis*-diamminedichloridoplatinum(II), *cis*-DDP is the first generation of antitumor metal-based complex. Many years of research indicated that preference platinum(II) as soft acid toward soft bases is responsible for the negative side effect of this drug. From the moment of injection of the drugs in the body to their binding to DNA molecules, a large number of secondary processes happen that are responsible for the occurrence of toxic effects [5, 6]. Thus, platinum(II) possesses high affinity to the sulfur and in the blood plasma itself reacts immediately with albumin or other biomolecules that contain sulfur (proteins or peptides in which L-cysteine or L-methionine). Considering that the concentration of thiol, including L-cysteine and glutathione, in intracellular fluid is about 10 mM, it is presumed that the platinum(II)-based antitumor reagents first react with sulfur donor nucleophiles, which is kinetically favored and after that form thermodynamically more stable Pt-DNA compounds.

The monofunctional complexes represent a good model for investigations of platinum(II) interactions with various biomolecules which contains sulfur and nitrogens. The structures of complexes disable the bifunctional coordination to the DNA, because of that, they do not exhibit antitumor properties, but simplify investigation of substitution reactions of these complexes.

The most studied monofunctional complexes are $[PtCl(terpy)]^+$ and $[PtCl(dien)]^+$ and their aqua analog in different reaction conditions. *Dien* (diethylenetriamine or 1,5-diamino-3-azapentane) or *terpy* (2,2′:6′,2″-terpyridine) are tridentate ligands, while the fourth coordination place is occupied with labile ligand, mostly chlorido ligand. *Terpy* ligand affects nucleophilic substitution reactions which are controlled by strong π-acceptor ability of the tridentate chelate 2,2′:6′,2″-terpyridine. The electronic communication between three pyridine rings causes a decrease in electronic density on the platinum center due to additional formation of π-back bond and makes it more electrophilic and more reactive.

Considering that platinum as soft acid prefers soft bases such as sulfur-coordinated biomolecules, we have studied kinetics for the complex formation of $[PtCl(terpy)]^+$ with guanosine-5′-monophosphate (5'-GMP) in the presence and absence of glutathione (GSH) at pH ca. 6, with concentration $[Pt(terpy)Cl]^+$:GSH: 5'-GMP ratio of 1:2:10 [7].

The observed pseudo-first-order rate constants, $k_{obs}$, as a function of the total concentration of nucleophile are described by Eq. (3):

$$k_{obs} = k_1 + k_2\,[\text{nucleophile}] \tag{3}$$

A least-squares fit of the data according to Eq. (3) resulted in values for the forward anation rate constants, $k_2$, and the reverse equation rate constant, $k_1$ [2]. The substitution reactions are characterized by almost zero values for $k_1$. Thus, the complex formation reaction for the GSH goes almost to completion. Linear plots of the observed *pseudo*-first-order rate constants $k_{obs}$ versus the total concentration of the GSH pass almost through the origin (**Figure 2**).

The intercept is very small within the experimental error limits (**Figure 2**), illustrating that the solvent cannot effectively displace the coordinated nucleophile. Thus, no significant solvent or reverse reaction path was observed in the present systems, such that direct nucleophilic substitution is the major observed reaction pathway under the selected conditions. The following rate law can be formulated:

$$k_{obsd} = k_2\,[\text{nucleophile}] \quad (4)$$

where $k_2$ is a *second*-order rate constant for the forward reaction. The rate low indicates that the reactions proceed via a direct nucleophilic substitution pathway. The second-order rate constants are obtained from the linear least-squares analysis of the kinetic data.

Obtained data clearly point to a kinetic preference $[PtCl(terpy)]^+$ toward the GSH at pH *ca.* 6. 5'-GMP is also a very good nucleophile for Pt(II) complexes but at neutral pH cannot compete with GSH. The second-order rate constant for GSH is $10^2$ times higher for GSH than for the 5'-GMP. This is also reflected in the competition reactions utilizing mixtures of the GSH and GMP. Also, proton and $^{195}Pt$ NMR data did not show any N7 coordination of GMP, in spite of its excess, in the presence of thiols [8].

However, at or near neutral pH, although less than 10% of thiols are deprotonated, the N-bonding bases cannot compete with the thiol-containing amino acids and peptides [8, 9]. Therefore, binding primarily takes place through the sulfur donor sites.

According to the HSAB principle, the platinum prefers sulfur donor biomolecules as soft base, but with nitrogen donors, biomolecules (intermediate) build thermodynamically very stable complexes. The interactions of anticancer platinum-based drugs with sulfur thioether biomolecules are more favorable. According to this we have investigated the competitive reactions of $[PtCl(dien)]^+$ (10 mM) with L-methionine 5'-GMP in a molar ratio: $[PtCl(dien)]^+$:L-methionine:5'-GMP = 1:1:3 [10, 11]. In the initial stage of the reactions (<40 h), $^1H$ NMR peak for the free L-methionine (δ 2.142 ppm) decreases in intensity, and new peak of the [Pt(dien)(*S*-meth)]$^{2+}$ appeared in the spectrum (δ 2.544 ppm), whereas a little of the 5'-GMP reacted. In the later stages (72 h), the peaks for the bounded L-methionine and free 5'-GMP (δ 8.208 ppm) decreased in intensity, whereas those for free L-methionine increased in intensity, as did those assignable to bound 5'-GMP in [Pt(dien)(*N7*-GMP)]$^{2+}$ (δ 8.624 ppm) as shown in **Figure 3** [10].

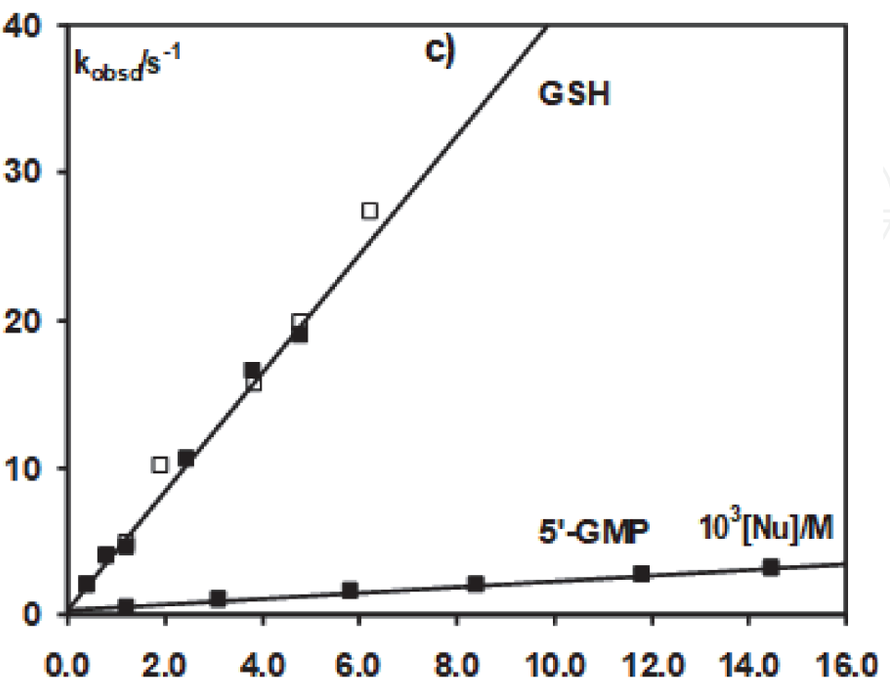


**Figure 2.**
*Observed* pseudo-*first-order rate constants,* $k_{obs}$*, as a function of nucleophile concentration at 37°C for 5'-GMP and GSH without 5'-GMP (open square) and in the presence of excess of 5'-GMP (full square) [7].*

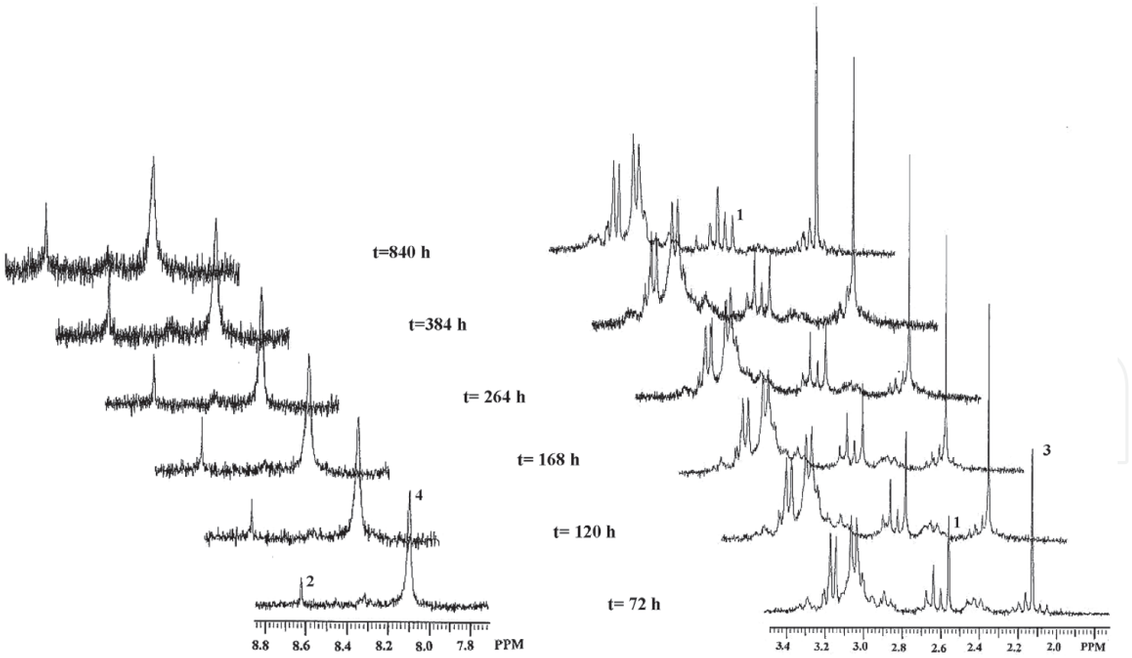


**Figure 3.**
*$^1$H NMR spectra of the reactions of [PtCl(dien)]$^+$ (10 mM) with mixture of L-methionine and 5'-GMP in the ratio 1:1:3 (where **1** is the signal for the [Pt(dien)(S-meth)]$^{2+}$, **2** is the signal for the [Pt(dien)(N7-GMP)]$^{2+}$, **3** is the signal for the free L-methionine, and **4** is the signal for the free 5'-GMP [10].*

In separated experiments we confirmed that the reactions of [PtCl(dien)]$^+$ with L-methionine is relatively fast, and the complex [Pt(dien)(*N7*-GMP)]$^{2+}$ can be formed from [Pt(dien)(*S*-meth)]$^{2+}$ in direct displacement of coordinated L-methionine by 5'-GMP. Moreover, the 5'-GMP proton signals of the end product are identical to those belonging to [Pt(dien)(*N7*-GMP)]$^{2+}$ formed by direct reactions of 5'-GMP and [PtCl(dien)]$^+$ complex [10].

As could be seen, initially there is rapid formation of [Pt(dien)(*S*-meth)]$^{2+}$ followed by displacement of L-methionine by 5'-GMP (**Figure 4**). In the later stages, the concentration of [Pt(dien)(*N7*-GMP)]$^{2+}$ is predominant [10].

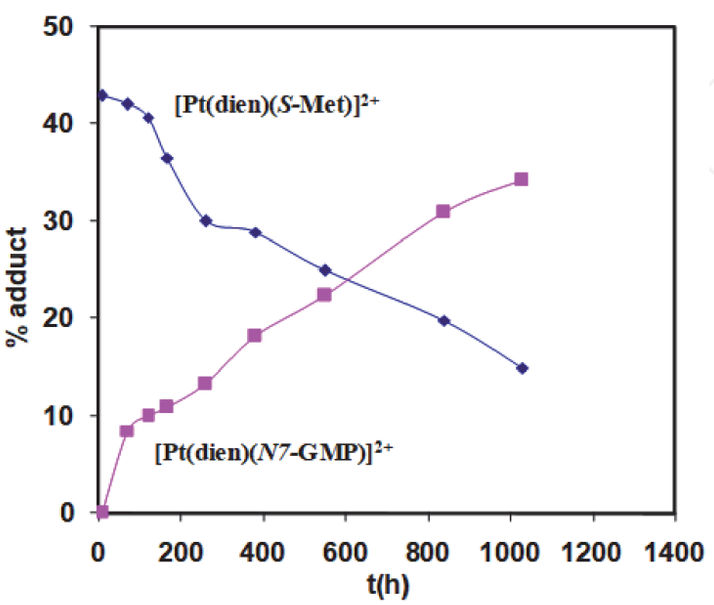


**Figure 4.**
*Observed product formation during the competition reaction of [PtCl(dien)]$^+$ with L-methionine and 5'-GMP in molar ratio [PtCl(dien)]$^+$: L-methionine:5'-GMP = 1:1:3 [10].*

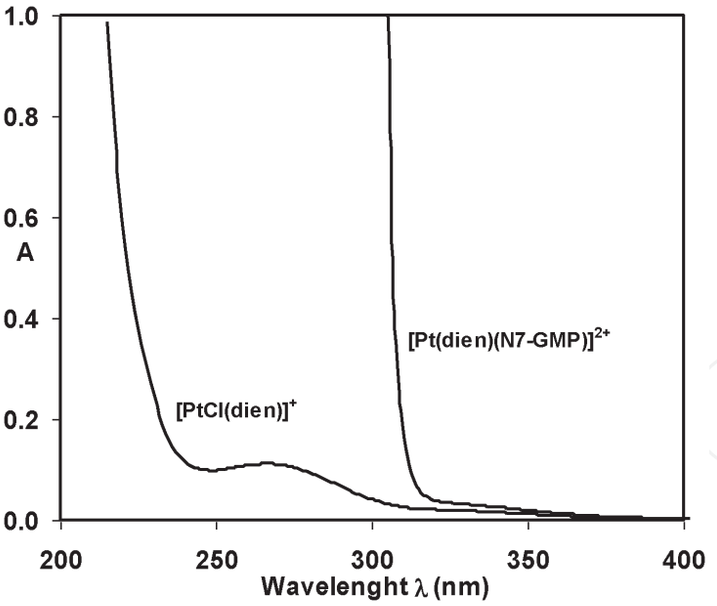


**Figure 5.**
*Electronic spectra for the starting complex, [PtCl(dien)]$^{+}$, and for the final product, [Pt(dien)(N7-GMP)]$^{2+}$ [10].*

The spectra of the starting complex, [PtCl(dien)]$^{+}$ and the final reaction product is presented in **Figure 5** [11].

In these experiments we confirmed that the mechanism of interactions of platinum(II) complexes as soft acid with soft sulfur bases originating from thiols and thioethers differs in the presence of an excess intermediate nitrogen bases (e.g., DNA constituent), depending on biomolecules that will react. If sulfur is from the thioether molecule, the resulting Pt-S(thioether) bond may be interrupted in the presence of the DNA molecule, i.e., the N7 atom from the guanosine-5′-monophosphate may substitute the molecule of thioether from the resulting complex. Also, the thiol molecule may substitute the thioether from compound. However, the bond between the platinum complex and the molecule containing the thiol group is not favorable. The compounds are extremely stable and nonselective. The Pt-S(thioether) products are "platinum reservoirs" in the organism; they are suitable intermediates in platinum complex(II) and DNA molecule reactions, while Pt-S(thiol) compounds completely deactivate complexes forming the compounds responsible for toxic effects.

## 4.2 Substitution reactions of zinc(II) complexes

Transition metal compounds play crucial roles in bioinorganic reactions as cofactors in metalloproteins; they act mainly as a Lewis acid. The electronic properties of Zn(II), such as intermediate Lewis acidity, redox inertness, and flexible coordination geometry, render it a suitable cofactor in several proteins that perform essential biological functions. Zinc(II) ions are essential cellular components involved in several biochemical processes.

Zinc is a good Lewis acid, especially in complexes with lower coordination numbers; it lowers the p$K_a$ of coordinated water and is kinetically labile, and the inter conversion among its four-, five-, and six-coordinate states is fast [12]. The utilization of zinc(II) for synthesis of novel antitumor non-platinum drugs could be beneficial. The non-platinum antitumor complexes could be alternatives to platinum-based drugs due to their better characteristics and less negative side effects.

We investigated the kinetics and mechanism of ligand substitution reactions between [$ZnCl_2$(terpy)] and biomolecules [13, 14].

Kinetics and mechanism of the substitution processes of [$ZnCl_2$(terpy)] complex with tripeptide GSH were investigated under *pseudo*-first-order conditions with respect to the complex concentration. Whatever system is considered, the absorbance always shows an exponential growth or downtrend versus time indicating the first-order kinetics with respect to the nucleophile ($\nu = -d[Nu]/dt = k_{obsd}[Nu]$) [2]. The kinetics traces showed two reaction steps, but different reaction mechanism for substitution reactions between [$ZnCl_2$(terpy)] complex and glutathione has been obtained (**Figure 6**).

For the substitution reactions between [$ZnCl_2$(terpy)] and glutathione, *first*-order linear dependence, $k_{obs1}$, on the complex concentration at low concentration was observed. At higher concentration, saturation kinetics was obtained. These could be explained by considering that the first step is a very fast pre-equilibrium formation of intermediate (*pseudo*-octahedral complex), followed by rearrangement to final complex, whereas one chloride is substituted by GSH (**Figure 7**) [13].

The value of rate second-order constant $k_2$ which described the substitution of the one chloride and pre-equilibrium constant $K_1$ could be determinate using Eq. (5).

$$k_{obs1} = \frac{k_2 K_1 [Zn^{II}]}{1 + K_1 [Zn^{II}]} \tag{5}$$

The value of pre-equilibrium constant was found to be $K_1 = 1831\ mol^{-1}\ L$. The second substitution step is independent of glutathione concentration $k_{obs2} = k_{2'}$, which indicates that chelation process takes place (**Figures 6** and 7). At pH 7.38 GSH is deprotonated [15], the formation of five-membered chelate ring is possible via O-carboxylate and N-ammine group from γ-glutamyl residue [16]. Five-coordinate metal centers Zn(II) according hard-soft acid nature of metals prefer O-carboxylate bioligands [17, 18].

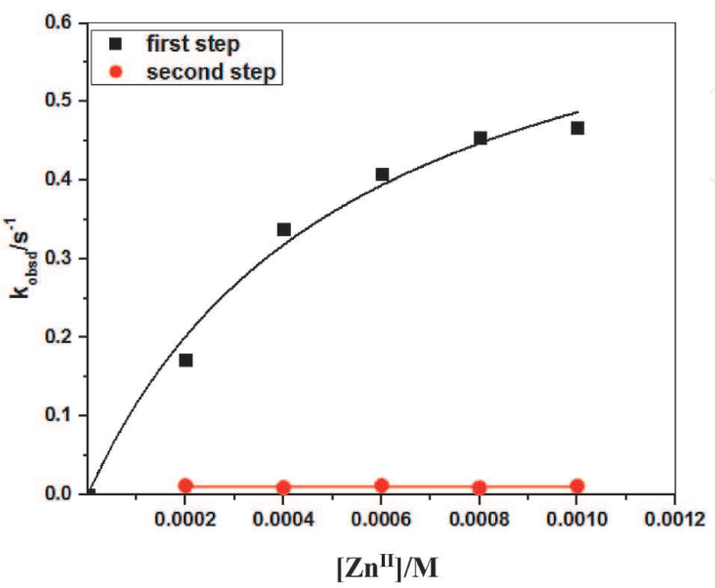


**Figure 6.**
Pseudo-*first-order rate constants as a function of complex concentration for the first and second substitution reactions of the [$ZnCl_2$(terpy)] and complex with glutathione at pH 7.38 (0.005 M phosphate buffer) in the addition of 0.010 M NaCl at 22°C [13].

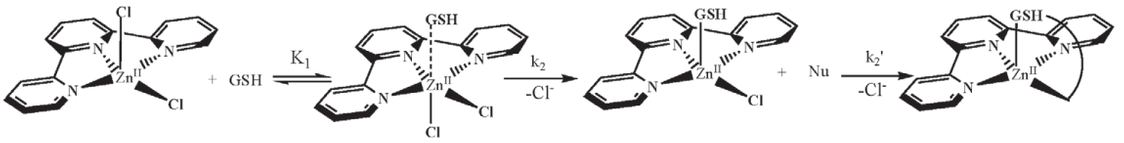


**Figure 7.**
*The proposed reaction pathways for the reaction of [$ZnCl_2$(terpy)] complex and glutathione [13].*

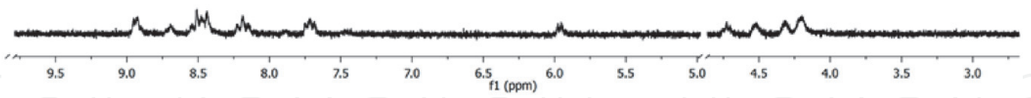


**Figure 8.**
*NMR spectra of the reaction between [$ZnCl_2$(terpy)] and 5'-GMP at 295 K, pD 4.5 in $D_2O$ after 1 minute [14].*

The nature of the ligand in inner coordination sphere is expected to play an important role in the binding of the metal complexes to biomolecules and in their cytotoxic effect. We have made an attempt to the mechanism of substitution between DNA constituent 5'-GMP and square-pyramidal [$ZnCl_2$(terpy)] complex by $^1$H NMR method [14]. The reaction reached completion for less than 1 min, which was visible in NMR tube. The color of the solution after addition of 5'-GMP in molar ratio 1:1 turns white. $^1$H NMR spectra were recorded after 24, 48 h, and during several weeks, but changes in spectrum have not been observed (**Figure 6**).

The singlet of H8 proton of the coordinated 5'-GMP appeared at 8.70 ppm, while the doublet of the H1' proton was at 5.97 ppm. Corresponding to terpy ligand in the spectrum, six proton patterns have been observed. The doublet of 6,6″ appeared at 8.95 ppm, the multiplet formed by covered signals of 3′,5′ protons, from middle pyridine; 4,4″ protons appeared in the range 8.49–8.42 ppm, the triplets of 4′ proton from middle pyridine ring; and 5,5″ protons were at 8.19 and 7.71 ppm, respectively. The doublet of 3,3″ protons seems to be at the same position as H8 proton of 5'-GMP (the signal was broadened) (**Figure 8**) [17]. The protons in the aromatic region of the spectra all correspond to signals from known terpy ligand coordinated to metal ions as is expected [19, 20].

As mentioned before, [$ZnCl_2$(terpy)] reacted immediately with DNA constituent; the rate of nucleophilic substitution reaction is controlled by strong $\pi$-acceptor ability of the tridentate chelate 2,2′:6′,2″-terpyridine. The electronic communication between three pyridine rings causes a decrease in electronic density on the zinc center due additional formation of $\pi$-back bonding and makes it more electrophilic and more reactive. The final product [ZnCl(terpy)(*N7*-GMP)] is also characterized by DFT calculation in combination with experimental NMR technique. The results are in good agreement; it confirmed coordination via N7 donor (intermediate Lewis base) [14].

In order to confirm the geometry around the coordinated center, structural index $\tau$ [21] was calculated for both [ZnCl(terpy)(*N7*-GMP)] and [ZnCl(en)(*N7*-GMP)] complexes. For five-coordinated Zn(II) complex, the structural index $\tau5 = (\beta - \alpha)/60°$ ($\alpha$ and $\beta$ are the two largest angles around the central atom) [21], which represents the relative amount of trigonality (square-pyramid, $\tau5 = 0$; trigonal-bipyramid, $\tau5 = 1$) is 0.32. The coordination geometry around zinc ion could be best described as somewhat between square-pyramidal and trigonal-bipyramidal, more like leaned toward distorted square-pyramidal geometry. Reported structures of three $ZnN_3S_2$ complexes, namely, [Zn(terpy)$(iPrO)_2PS_2]_2$ [22], [Zn(BMIP)] [23], and [Zn(BMAP)] [24], have similar position of the donor atoms in the ligands resulting in distorted trigonal-bipyramidal geometry of complex with minor distortion due to the bulky groups.

## 5. Conclusions

The theory of hard and soft acids and bases (HSAB) has proven to be a useful tool in predicting the outcome of bionorganic substitution reactions. According to this principle, electrophile such as complex compounds of transition metal ions reacts preferentially with donor atoms of biologically relevant nucleophiles of similar hardness or softness. Strong bonds are forming between hard acids and hard bases, soft acids and soft bases or borderline acids with borderline. Thus, platinum (II) belong to soft acid, and prefer soft bases. Kinetically are preferred reactions with sulfur donor biomolecules but more thermodynamically stable are Pt-N products. On other hand zinc(II) is borderline hard/soft ions and readily complexes with ligands containing a range of donor atoms, e.g., hard O-, intermediate N- and soft S-donors according to coordination numbers.

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## Conflict of interest

The author declares no conflict of interest.

## Author details

Tanja Soldatović
Department of Chemical-Technological Sciences, State University of Novi Pazar, Novi Pazar, Serbia

*Address all correspondence to: tsoldatovic@np.ac.rs

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