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Biological Activities of Semicarbazone, Thiosemicarbazone - Metal Complexes and Their Stability Constant

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ABSTRACT

Semicarbazone and thiosemicarbazones are one of the most widely used organic compounds that can interact with metal to form complexes. Their complexes exhibit a broad range of biological activities, including antiviral, fungicidal, antiparasital, antibacterial, antitumor and antimalarial activities. Stability constant is an important determinant factor for the properties of metal-ligand interactions in biological system. Protonation constants which are important physicochemical parameters can provide critical information about semicarbazone and thiosemicarbazone metal complexes as drug properties such as solubility, lipophilicity, acidity, basicity, transport behavior, bonding to receptors, and permeability natures. This review summarizes recent works on the biological activities of semicarbazone and thiosemicarbazone metal complexes and their stability constant.

Keywords: Semicarbazone , Thiosemicarbazone, Metal Complexes, Biological Activities, Stability constant

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INTRODUCTION

Semicarbazone and thiosemicarbazones are Schiff base ligands which have gained importance over the decades as potential drug candidates. The introduction of metal ions or metal ion binding components into a biological system for the treatment of diseases is one of the main subdivisions in the field of bioinorganic chemistry [1]. Semicarbazone and Thiosemicarbazones and their metal complexes were interestingly studied because they have a wide range of actual or potential medical applications which include notably antiviral [1], Fungicidal [2] antiparasital, antibacterial, antitumor and antineoplastic activities [3].

Stability constant is well known tool for solution chemist, biochemist, and chemist to help for the determination of the properties of metal-ligand reactions in water and biological system [4]. Protonation constants which are important physicochemical parameters can provide critical information about semicarbazone and thiosemicarbazone metal complexes as drug properties such as solubility, lipophilicity, acidity, basicity [4], transport behavior, bonding to receptors, and permeability [5]. Hence, the relationship between the protonation constants and structure in drug design studies is important [6]. Protonation constants are also important parameters for the selection of the optimum conditions in the development of analytical methods [7] and choosing a suitable pH value for carrying out spectrophotometric quantitative analyses of drugs. Additionally, knowledge of the protonation constants of some compounds is necessary for the calculation of the concentration of each ionized species at any pH, which is important for the complete understanding of the physiochemical behavior of molecules [8] and provides also information about the stereo chemical and conformational structures of active centers of enzymes [9, 10]. In spite of the large interest shown in the coordination properties of semicarbazone, thiosemicarbazone ligands and the attention paid in recent years to the possible variable biological activities of their metal complexes, reviews dealing about bioactivities, stability constant, protonation constant and complex formation equilibria of semicarbazone, thiosemicarbazones and their complexes are still very rare.

LITERATURE REVIEWS

Semicarbazone and thiosemicarbazone

Semicarbazones and thiosemicarbazones are a class of compounds obtained by condensation of Semicarbazides with suitable aldehydes or ketones. Semicarbazone is a derivative of semicarbazide which contains an additional ketone functional group. These Schiff base ligands are synthesized by condensation reactions between primary amines and aldehydes or ketones (R''CR'=NR where R and R' and R" represent alkyl and/or aryl substituents).Their structures are given bellow: [11].

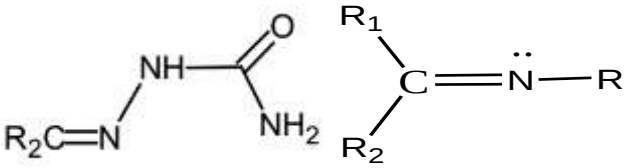
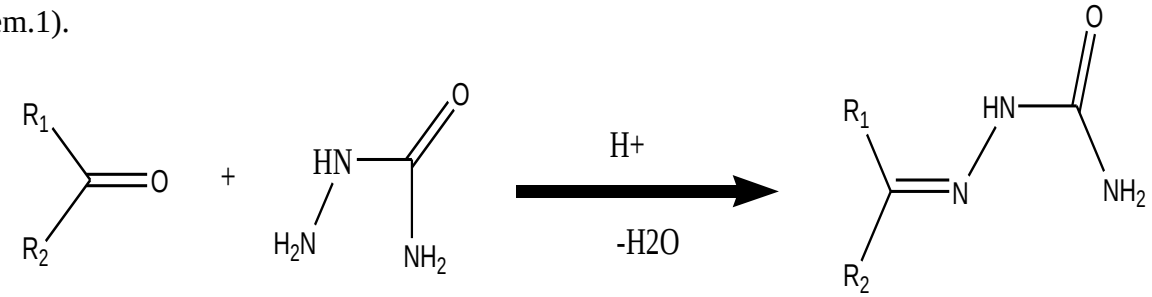


Figure 1: Structure of semicarbazone analogues and structure of Schiff base

The semicarbazone is formed when ammonia related a compound (nucleophiles) such as semicarbazide is added to the carbonyl group (=CO), they form imine like derivatives (schem.1).



Scheme-1: Synthesis of semicarbazone analogues

Thiosemicarbazone is a derivative of semicarbazone which contain sulfur atom in place of oxygen as shown in fig.2.

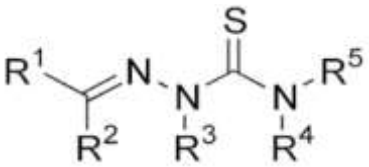
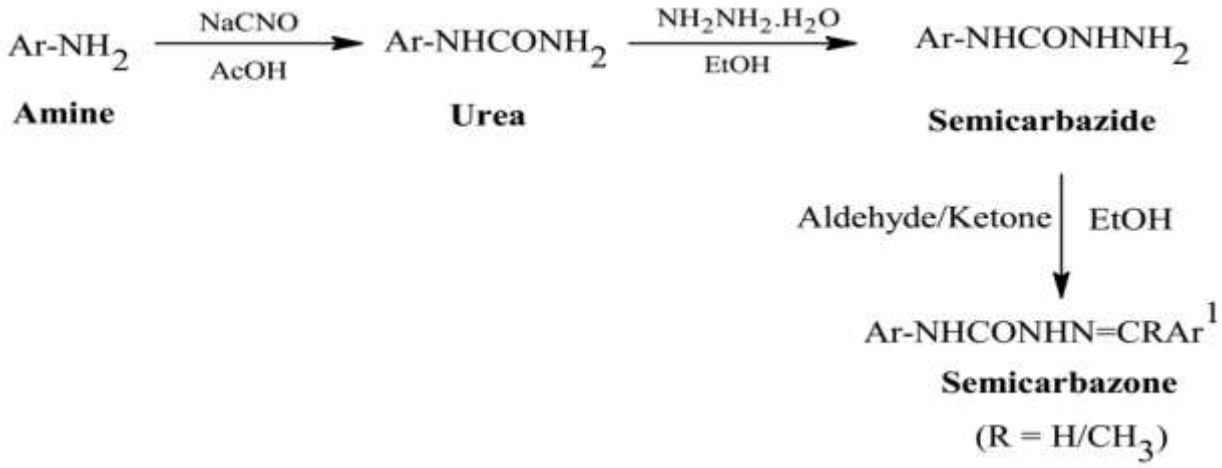


Figure 2: General Structure of Thiosemicarbazones, R^1, R^2, R^3, R^4, R^5 = H, or any organic substituent

The general method for the synthesis of semicarbazone analogues is presented in Schem-2.



Scheme 2: General Method for the synthesis of semicarbazone analogues

Semicarbazone and thiosemicarbazone metal complexes

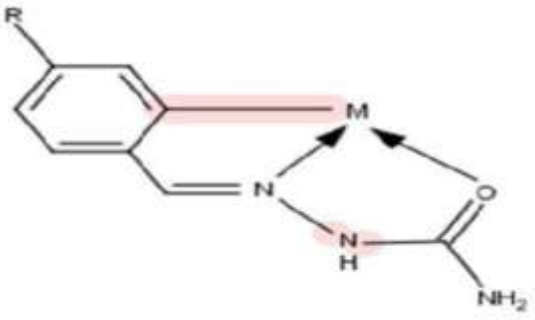
Interestingly, semicarbazone show a variety of coordination modes with transition metals, the coordination mode is influenced by the number and type of substituent [12]. That is due to the active donor sites of ligand vary depending upon the substituent. They are very versatile ligands which can coordinate to metal as neutral molecules or after deprotonation as anionic ligands and can adopt a variety of different coordination modes.

Semicarbazones and Thiosemicarbazones act as ligands because

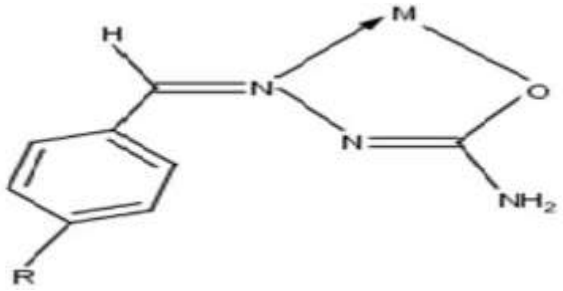
1. They have better co-ordination tendency.
2. They form more stable complexes.
3. They have better selectivity.
4. They may form macrocyclic ligands
5. They have the ability to produce some new and unique complexes with enhanced biological activities [12].

Aromatic substituent on semicarbazone skeleton can further enhance the delocalization of electron charge density. These classes of compounds usually react with metallic cations giving complexes in which the semicarbazone behave as chelating ligands upon coordination to a metal center; the delocalization is further increased through the metal chelate rings. The coordination possibilities are further increased if the substituent has additional donor atoms.

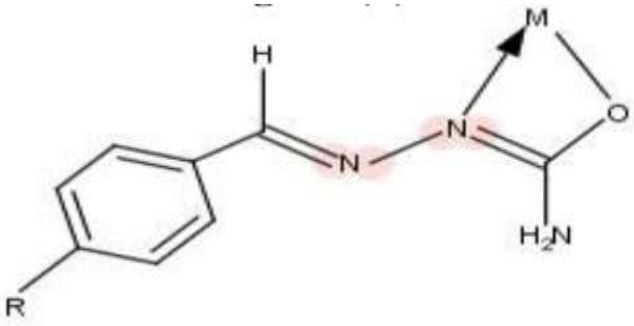
The different coordination mode of substituted benzaldehyde semicarbazone is given as;



C, N, O-tricoordination



N, O-coordination forming five membered chelate



Four member chelate formation N, O-donor

Figure 3: Different coordination modes of semicarbazone derivatives with metals

Biological activities of semicarbazones , thiosemicarbazones and their metal complexes

Semicarbazones and thiosemicarbazone presents a wide range of bioactivities, and their chemistry and pharmacological applications have been extensively investigated. The biological properties of semicarbazones are often related to metal ion coordination. Firstly, lipophilicity, which controls the rate of entry into the cell, is modified by coordination [13]. Also, the metal complex can be more bioactive than the free ligand [13].

The mechanism of action can involve binding to a metal *in vivo* or the metal complex may be a vehicle for activation of the ligand as the cytotoxic agent. Moreover, coordination may lead to significant reduction of drug-resistance [14]. The semicarbazone and thiosemicarbazone usually behave as chelating ligands and usually react with metallic cations giving complexes. Some complexes with semicarbazones and thiosemicarbazones have received much attention due to their wide range of applications as an antiviral, antibacterial and antimicrobial, antifungal activities [14]. These Schiff bases are characterized by an imine group **–N=CH-**, which helps to clarify the mechanism of transamination and racemization reaction in biological system [15].

It exhibits antibacterial and antifungal effect in their biological properties [16, 17]. Metal-imine complexes have been widely investigated due to antitumor and herbicidal use. They can work as models for biologically important species [17]. Schiff bases are identified as promising antibacterial agents. For example, N-(Salicylidene)-2-hydroxyaniline (Fig.4) is active against Mycobacterium tuberculosis [18].

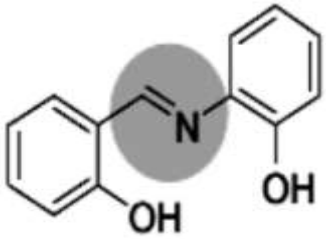
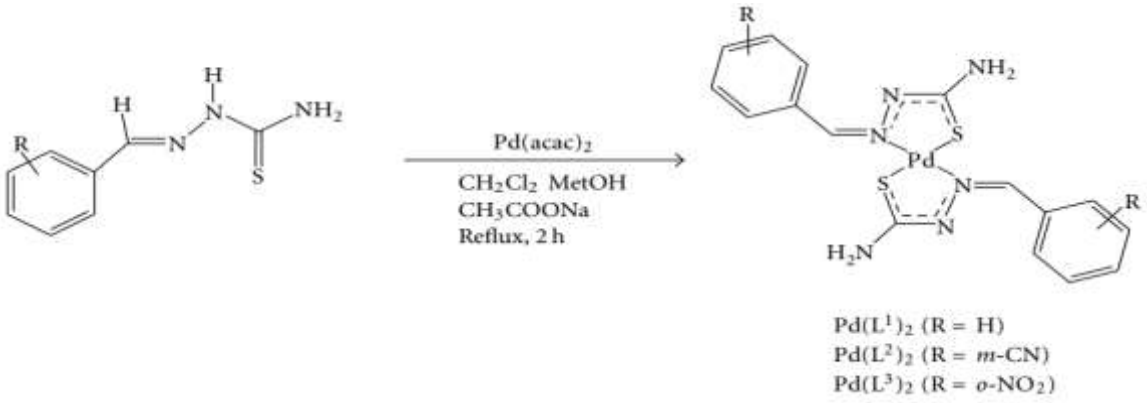


Figure 4: N-(Salicylidene)-2-hydroxyaniline as the example of bioactive Schiff base

Benzaldehyde Thiosemicarbazone Derivatives metal complex as bioactive species

The complex $Pd(L^2)_2$[HL_2 = *m*-CN-benzaldehyde thiosemicarbazone] shows a square-planar geometry with two deprotonated ligands (L) coordinated to Pd^{II} through the nitrogen and sulphur atoms in a *trans* arrangement [19].

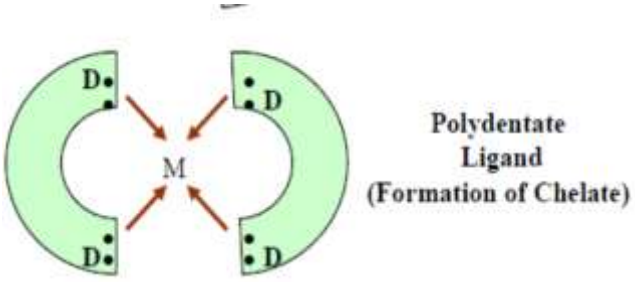


Scheme 3: Synthesis of the palladium (II) bis-chelate complexes

Mostly this compound is toxic for host cell of microorganism and can act as antiviral and antibacterial activities as reported [19].

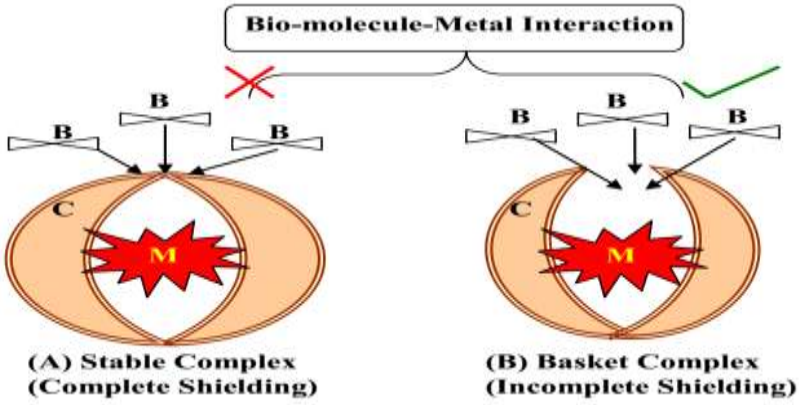
Stability constants of the semicarbazone and thiosemicarbazone metal complexes

Stability constant is well known tool for solution chemist, biochemist, and chemist to help for determination of the properties of metal-ligand reactions in water and biological system [20]. In the study of coordination compound in solution, first and foremost requirement is the knowledge of stability constant of complex. For correct interpretation of complex, the knowledge of stability constant is essential. Reliable information of stability constant is of great importance in analytical and separation procedure. To remove undesirable and harmful metals from living organism, chelating agents are very much useful in biological systems. This gives importance to the study of determination of stability constant of metal complexes. A suitable multidentate ligand can satisfy all the coordination positions of the metal ion that would be ideally suited in the elimination of the toxic metal ion. So that the chelated metal ion cannot bind to any binding sites of enzymes and proteins e.g. **EDTA** is the most familiar example of chelating agents used in chelation therapy.



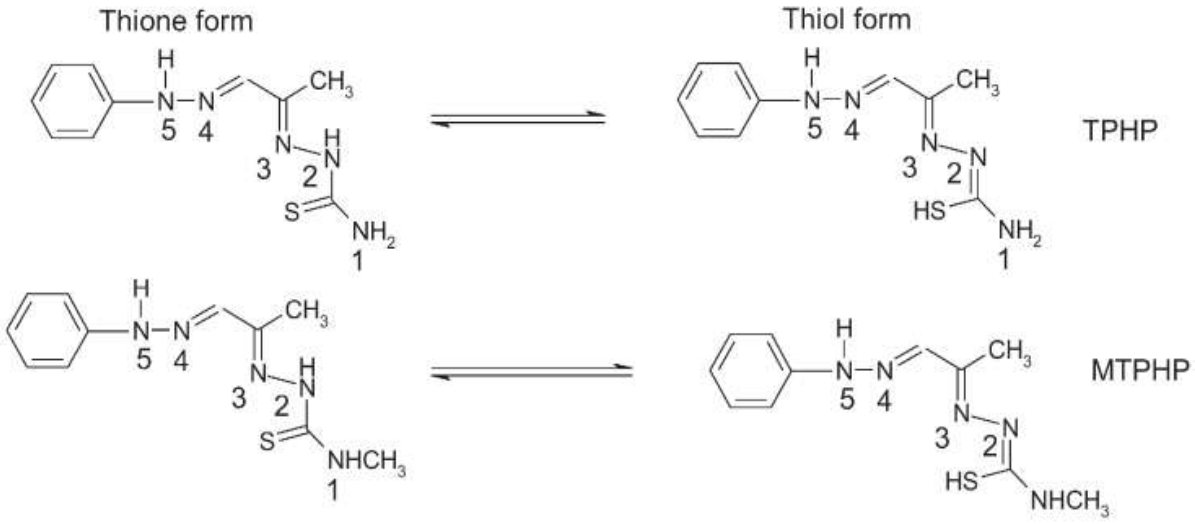
Structure of the two different complexes of metals with chelating agents below also shows the importance of stability constant for chelation therapy.

Symbols used: B- Bio-molecules; **C**-Chelating agent; **M**- Metal



Many workers study the effect of transition metal on a stability of complex by pH metrically [21-23]. The most important characteristics of the central metal atom which influence the stability of complex compounds are the degree of oxidation, the radius and electronic structure. The strength of binding of ligand to the central metal ion is depending on structure of ligand molecule or ions [24-26]. The stability of complexes is dependent upon the size and number of chelating rings also. The structure of chelating agent determines the size of the chelating rings and the number of rings formed on chelation. It has concluded that five and six member rings of amino acid chelates are the most stable [27, 28].

The stoichiometric stability constants of M (II) complexes of the thiosemicarbazone ligands were determined in 50 % DMSO-water mixture at different temperatures and different constants are obtained in different temperatures [29]. Specific example, the high stability of M(II)-MTPHP complexes than M(II)-TPHP complexes can be attributed to the presence of -CH_3 group in the thiosemicarbazide moiety which is in agreement with the basicity of these ligands. This is quite reasonable because the presence of the above —CH_3 group (i.e. an electron-donating group) will enhance the electron density by their high positive inductive effect, whereby stronger chelation is formed. Different studies indicated that alkylation of the N terminal of thiosemicaarbazone has a highest effect on the stability of the formed complexes [29].



Scheme 4: Molecular structure of TPHP and MTPHP thiosemicarbazone compounds

The formation of bio ligand complexes of some semicarbazone and thiosemicarbazone medicinal drugs with Co (II), Ni (II) and Cu (II) ions were mainly investigated.

Protonation constants of semicarbazone and thiosemicarbazone ligands

The protonation constants for monoprotic acid HL:

When the ligands involved may be considered as a monobasic acid having only one dissociable H^+ ion from thiolic -SH group and it can therefore, be represented as HL. The dissociating equillibria can be shown as.

$$HL \rightleftharpoons H^+ + L$$

By the law of mass action; $k = \frac{[H^+][L^-]}{[HL]}$

Where, the quantities in bracket denote the activities of the species at equilibrium.

The protonation constants of semicarbazone and thiosemicarbazone ligands under experimental variables depend on both ionic strength and temperature. The acid dissociative constant P**Ka** of ligands can be determined from the resulting $[H^+]$ in solution. The activity determined is converted to $[H^+]$ using equations [31]:

$$\partial_{H+} = \gamma [H^+] \quad \text{.....1}$$

$$P^H = -\text{Log } \partial_{H+} \quad \text{.....2}$$

Rearranging and substituting into equation (2) gives;

$$\text{Log } [H^+] = - P^H - \text{Log } \gamma \quad \text{.....3}$$

The constant; Log γ may be obtained from the expression given by Debye and Hückel, the activity coefficient, γ_i, of an ion of valence z_i is given by the expression;

$$\log\gamma_i = -AZi^2\sqrt{\mu} \quad \text{.....4}$$

Where Z_1 and Z_2 are the charges +1 or -1 which are H^+ and NO_3^- respectively. This equation yields a satisfactory measure of the activity coefficient of an ion species up to an ionic strength, **μ**, of about 0.02. For water at 25°C, ***A*** is a factor that depends only on the temperature and the dielectric constant of the medium, is approximately equal to 0.51. The values of ***A*** for various solvents of pharmaceutical importance are found in tables.

The ionic strength, μ of the solution is given as [32]:-

$$\mu = \tfrac{1}{2} \sum c_i z_i^2 \quad \text{.....5}$$

(Where C_1 is the molar concentration and Z_1 is its charge).

The expression for the acid dissociation constant for the reaction is given by;-

$$HA \leftrightarrow H^+ + A^-$$

$$ka = \frac{[H^+][A^-]}{[HA]} \quad \text{.....6}$$

Where (H^+) is from equation (3) while (HA) and (A^-) are known concentration. The calculated PKa of semicarbazone and thiosemicarbazone at specified temperature can be determined. The higher values of stability constants suggest good stable complexes as usual trend of divalent transition metal complex with the ligand such as azoles [33, 34].

The values of $\bar{n}_A$ for metal – ligand systems represent is the average number of coordination number of the ligands to the metal ions .Typically as ligand is added to the solution of the metal ions ML_1 is first formed more rapidly than ML_2. If no precipitate was observed in the titration vessels, it indicates that the possibility of formation of metal hydroxide can be excluded. The pH metric analysis may show that the complexes having 1:2 (metal-ligand) stoichiometry, is a common feature in the first row transition metals [35].

Calculations of $\bar{n}_A$ and $\bar{n}$

The value of $\bar{n}_A$ (the degree of formation of the proton complex) was calculated by employing the following equation (7): [36].

$$\bar{n}_A = Y + \frac{(V' - V'')(N + E^0)}{(V^0 + V')T_{L_0}} \quad \text{.....7}$$

Where Y = number of replaceable hydrogen ion, V^o = total volume 50 ml, V' = volume of alkali used by acid, V'' = Volume of alkali used by acid and ligand, N = concentration of alkali, E^o = total strength of acid, T_{Lo} = total concentration of ligand.

The proton ligand formation curves can be obtained by plotting the degree of formation $\bar{n}_A$ of the proton complex against pH values. The values of $\log K_1 H$ can be obtained from the curves

corresponding to $\bar{n}$ - values of 0.5. The stability constants at different temperatures can be calculated. The values of $\bar{n}$ (average number of ligand molecules attached per metal ion) are calculated using equation (8).

$$\bar{n} = \frac{(V''' - V'')(N + E^0)}{(V^0 + V')\bar{n}_A T_{M^0}} \quad \ldots\ldots 8$$

Where V''' = volume of alkali used for acid + ligand + metal ion, $T_M{}^o$ = total concentration of the metal ion, rest of term symbols are as given in equation (7).

Effect of ionic strength on the protonation constants of thiosemicarbazone compounds

The effect of variation of ionic strength on the protonation constants of thiosemicarbazone compounds are investigated and reported. The proton ligand protonation constants of the ligand have been evaluated at different ionic strengths (example- 0.05, 0.10, 0.15, 0.20 and 0.25 M) using sodium nitrate as a supporting electrolyte at constant temperature (298 K). It was reported that the protonation constants of the thiosemicarbazone decrease with increase in the ionic strength of the medium which is in good agreement with the Debye-Hückel equation [37, 38]. Log $K_{\text{Protonation}}$ values were plotted vs. square root of μ as per the Debye-Huckel equation. The plots of logK vs $\sqrt{\mu}$ for all systems were found to be linear with correlation coefficient ranges from 0.98–0.99.

The relationship between the properties of central metal ion and stability of complexes

Definitions of stability constants of complexes: - for metal -ligand complexes their stability constants are given as; -

$$K_{ML} = [ML]/ [M][L]$$

$$K_{MHL} = [MHL]/ [ML][H]$$

(L = thiosemicarbazone ligands); (Charges are omitted for simplicity).

In order to explain why a given ligand prefers binding to one metal instead of another metal, it is important to link the relationship between the stability constants of metal complexes and properties of the metal ions, such as the atomic number, ionic radius, ionization potential and electronegativity. It was reported that, the formation constants of M^{II}- complexes of some transition metal ions with thiosemicarbazones obeyed this arrangement: - $Mn^{2+} < Co^{2+} < Ni^{2+} < Cu^{2+}$ which is consistent with Irving Williams' order [39].

The relation between the $\log K_{ML}$ and reciprocal of the ionic radii (1/r) of transition metal ions represents nearly a linear relationship. Additionally, a linear relation has been noticed between $\log K_{ML}$ and the electro negativities of the metal ions under different investigations [40]. This is consistent with the fact that the increase in the electronegativity of metals (Mn^{2+} (1.55) < Co^{2+} (1.88) < Ni^{2+} (1.91) < Cu^{2+} (2.0)) will reduce the difference in electronegativity between

the metal atom and the donor atom of the ligand. Therefore, the metal-ligand bond should have more covalent character, leading to increase the degree of stability of complexes.

A good linear correlation is obtained between the stability constants of metal complexes and the second ionization potential of the metal ions under different investigations. Generally, it is observed that the stability constant of the Cu^{2+} complex is larger in comparison to the other metals. The ligand field had given Cu^{2+} further stability as a result of tetragonal distortion of the octahedral symmetry [41].

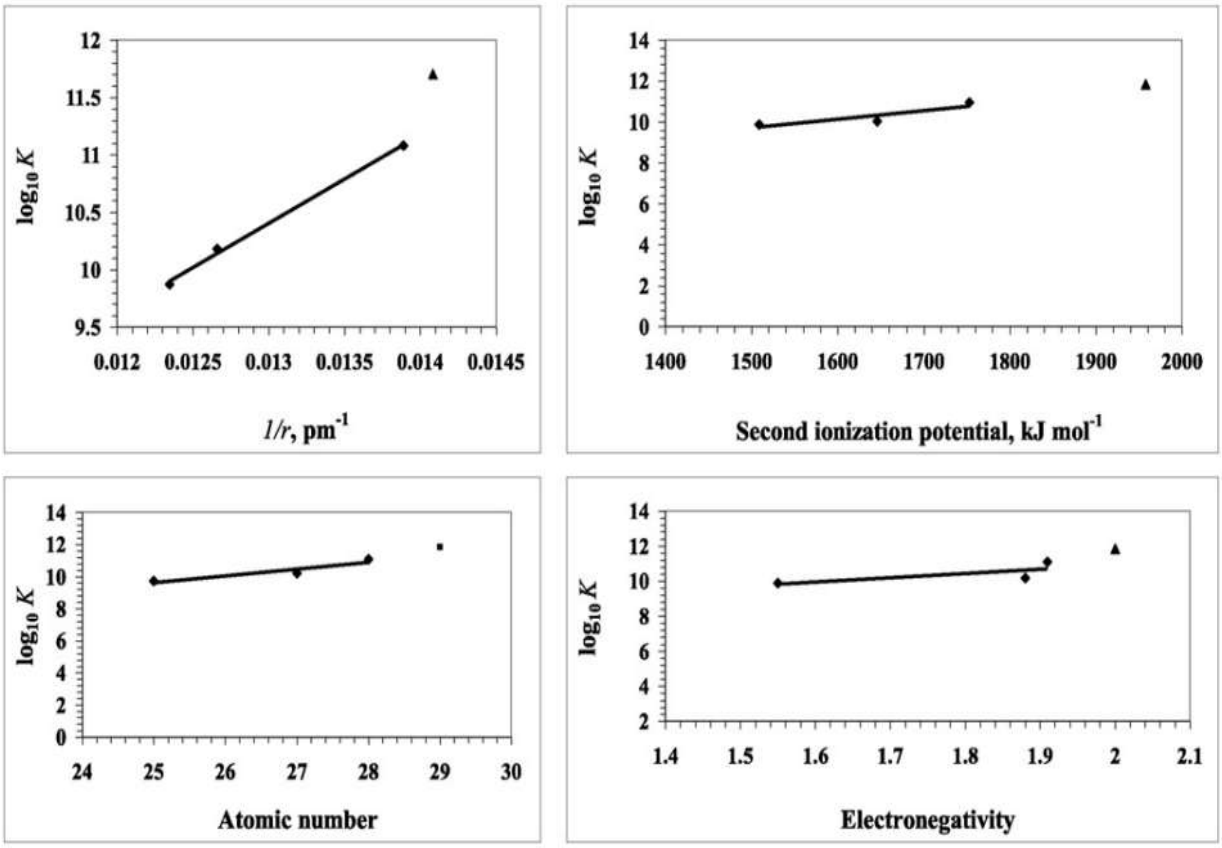


Figure 5: **Variation of the stability constants for the M (II) - complexes with properties of the metal(II) ions.**

Thermodynamic and kinetic stability of semicarbazone and thiosemicarbazone complexes

The thermodynamic stability of a species is the measure of extent of its formation under a particular set of conditions. In the language of thermodynamics, the equilibrium constant of a reaction is the measure of the heat expelled from the reaction system and entropy change during the reaction. The entropy of a system is the measure of the amount of disorder. The greater the amount of disorder in the products of a reaction relative to the reactants, the greater will be the increase in entropy during the reaction and higher is the stability of products [42].

The determination of stability constant of metal complexes is an important factor in the estimation of the thermodynamic functions ΔH, ΔG and ΔS. In order to estimate these factors,

a plot of the confirmed stability constants against the reciprocal of temperatures and the slope of the plot gave the values the enthalpy, ΔH. The negative values of ΔH shows that the dissociation constants are accompanying by liberation of heat and the process is exothermic.

The overall changes in energy (ΔG^o) and entropy (ΔS^o) accompanying complexation have been determined using temperature and Gibb's Helmholtz equation. The value of ΔG^o is obtained from the equation [42]:

$$\mathbf{\Delta G^o = -RTlnK \text{ or } \Delta G^o = -2.303RTlogK}.$$

The value of ΔS^o is calculated by using the following equation;

$$\mathbf{\Delta S^0 = \frac{\Delta H^0 - \Delta G^o}{T}}$$

The free energies of formation ΔG of metal complexes having negative values indicating spontaneity of the reaction process. However, as the temperature increases, the stability of complex decreases. This also confirms the irreversibility of the metal complexes. The negative value of ΔS is due to the increased order as a result of salvation process.

The thermodynamic stability of metal ions with semicarbazone and thiosemicarbazone are denoted by stepwise formation constants as shown in equations bellow as (charges omitted for simplicity) [43].

$M + L \rightleftharpoons ML \qquad K_1 = \frac{[ML]}{[M][L]}$

$ML + L \rightleftharpoons ML_2 \qquad K_2 = \frac{[ML_2]}{[ML][L]}$

$ML_2 + L \rightleftharpoons ML_3 \qquad K_3 = \frac{[ML_3]}{[ML_2][L]}$

Overall stability constants as:-

$M + L \rightleftharpoons ML \qquad \mathbf{b_1} = \frac{[\boldsymbol{ML}]}{[\boldsymbol{M}][\boldsymbol{L}]}$

$M + 2L \rightleftharpoons ML_2 \qquad b_2 = \frac{ML}{[M][L]^2}$

$M + 3L \rightleftharpoons ML_3 \qquad b_3 = \frac{ML}{[M][L]^3}$

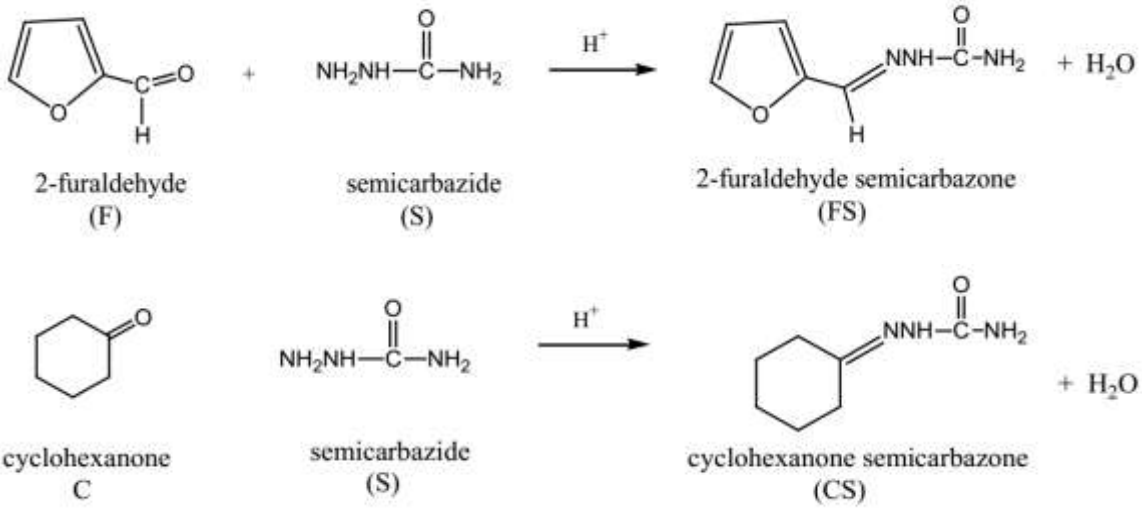
The equation relating the stepwise and overall stability constants is indicated by equation:-

$$\beta_n = K_1 K_2 \ldots K_n$$

In biological systems, many factors affect metal–ligand complex formation. A hard– soft acid–base consideration is one basic factor [44]. Concentrations of the metal and ligand at the site of complexation are determined locally through concentration gradients, membrane permeability to metals and ligands, and other factors. Various competing equilibria-solubility products, complexation, and/or acid–base equilibrium constants-sometimes referred to as ''metal ion

speciation,'' all affect complex formation [45]. Ion size and charge, preferred metal coordination geometry, and ligand chlelation effects all affect metal uptake. To better measure biological metal–ligand interactions, an ''uptake factor'' is defined as $K_{ML}[M]$, where K_{ML} is the stability constant K_1 and [M] is the concentration of metal ion. Great selectivity for metal species is necessary to concentrate the necessary ions at sites where they are needed. Differentiating ligands are those preferred by the cation in question. The more stable product is called the thermodynamically controlled product. The product formed by way of the lower energy of activation pathway forms faster and is referred to as the kinetically controlled product.

Kinetically controlled product (the one formed faster) and the thermodynamically controlled product (the more stable one) are the same. The more stable product is formed faster [46].



The product of this reaction is the one that forms faster. The other reaction is thermodynamically controlled. The product of this reaction is the more stable product.

For this pair of reactions, the thermodynamically controlled product is not the same as the kinetically controlled product. One of the products, either FS or CS, will be the kinetically controlled product. The other product will be the thermodynamically controlled product [47].

Effect of temperature and thermodynamics

The values of thermodynamic parameters that are related to the protonation of thiosemicarbazones and their metal (II) complexes have been calculated from the temperature dependent data values. Values of ΔH and ΔS can be obtained by drawing the relationship between the values of equilibrium constants (lnK) versus reciprocal of temperature (1/T) Or ($\mathbf{lnk = \frac{\Delta S}{R} - \frac{\Delta H}{RT}}$) leading to an intercept ΔS/R and a slope –ΔH/R. Main concepts can be summarized as follows:

1. The protonation reaction of the semicarbazone and thiosemicarbazones are exothermic with a net negative ΔG.

2. Often, the color of the solution after formation of the complex differs from the color associated with the free ligand at the same pH.
3. Formation constants of metal complexes at different temperatures was calculated and discussed as follows:

A. These values decrease with rising of temperatures, proposing that the process of complex formation is favored at low temperature.

B. $LogK_1$ is larger than $logK_2$. This is due to the fact that the interaction of a second bulky ligand molecule is usually weaker than the first ligand, i.e., the ML_2 (1:2) species is not formed until complete formation of the ML (1:1) species. This can be ascribed to:

- The increase in the Lewis acidity of the free metal ion (M^{+n}) as compared to the 1:1 chelated ion ($ML^{+\,n-1}$) and
- The steric hindrance caused by the addition of a second bulky ligand molecule on the $ML^{+\,n-1}$ chelated ion.

A. For the same ligand at constant temperature, the stability of the chelates increases in the order $Cu^{2+} > Ni^{2+} > Co^{2+} > Mn^{2+}$ [48, 49]. This order largely reflects that the stability of Cu^{2+} complexes is considerably larger than those of other metals of the 3d series. Under the influence of both the polarizing ability of the metal ion [50] and the ligand field [51], Cu^{2+} will receive some extra stabilization due to tetragonal distortion of octahedral symmetry in its complexes. The greater stability of Cu^{2+} complexes is produced by the well-known Jahn-Teller effect [51].

Stability constant determination for complexes

The stepwise formation of mononuclear, binary and ternary complexes can be described by a set of equilibrium constants. The law of mass action strictly determines the concentration relation of the reactants and products in every reversible chemical reaction.

The numerical values of the equilibrium constants depend on the concentration scale applied. According to [52] Bjerrum[1] and Martell et al[2], the formation of complex ML_N is in general a stepwise process and one has to deal a series of equilibria of the type:

$$M + L \rightleftharpoons ML \quad \text{.....(a)}$$

$$ML + L \rightleftharpoons ML_2 \quad \text{.....(b)}$$

$$ML_2 + L \rightleftharpoons ML_3 \quad \text{.....(c)}$$

$$ML_{N-1} + L \rightleftharpoons ML_N \quad \text{.....(d)}$$

[The charges on a metal ion are neglected]

According to law of mass action-

$$K_1 = [ML] / ([M][L]) \quad \text{.....(e)}$$

$$K_2 = [ML_2] / ([ML] [L]) \quad \text{.....(f)}$$

$K_3 = [ML_3] / [ML_2] [L]$ ……(g)

$K_N = [ML_N] / [ML_{N-1}] [L]$ ……..(h)

Where, K_1, K_2, K_3 and K_N are equilibrium constants.

These equilibrium constants characterize the stability of complexes and are usually called as 'stability constants'. The law of mass action is strictly valid only when activities are used instead of concentrations, because the activity of species is equal to the product of its concentration and the activity coefficient [52]. The complex is governed by N equilibrium constants, each defined as ;

$$\mathbf{K_{i(T)} = a_{MLi} / (a_{MLi-1}.a_L)} \text{ ……..(i)}$$

$$\mathbf{K_{i(T)} = K_1 \gamma M_{Li-1} \gamma_L / V_{MLi}} \text{ ……..(j)}$$

Where $K_{i(T)}$ is called as i^{th} thermodynamic metal-ligand stability constant or formation constant and "a" represents the activity and "y" represents activity coefficient of constituents.

The overall stability constant (b_N) for the equilibrium process, is the product of various stepwise formation constants and may be written as:

$$M + NL \rightleftharpoons ML_N$$

$\mathbf{b_N = K_1.K_2.K_3}$ ..... $K_N = \frac{a_{ML_N}}{(a_{Ma_{L)N}})}$

The degree of formation or ligand number n is expressed by Bjerrum as -

$$\bar{n} = \frac{T_L - [L]}{T_M}$$

Where T_L is the concentration of ligand in all forms, [L] is the concentration of free chelating species and T_M is the total concentration of metal ion (bound or free).

Applications of stability constant for biological activity

Stability constant values are exploited in a wide variety of applications. Chelation therapy is used in the treatment of various metal-related illnesses, such as iron overload in β-thalassemia sufferers who have been given blood transfusions. The ideal ligand binds to the target metal ion and not to others, but this degree of selectivity is very hard to achieve. The synthetic drug deferiprone achieves selectivity by having two oxygen donor atoms so that it binds to Fe^{3+} in preference to any of the other divalent ions that are present in the human body, such as Mg^{2+}, Ca^{2+} and Zn^{2+}. Excess copper in Wilson's disease can be removed by penicillamine or Triethylene tetramine (TETA). DTPA has been approved by the U.S. Food and Drug Administration for treatment of plutonium poisoning [53]. DTPA is also used as a complexing agent for gadolinium in MRI contrast enhancement. The requirement in this case is that the complex be very strong, as Gd^{3+} is very toxic. The large stability constant of the octadentate ligand ensures that the concentration of free Gd^{3+} is almost negligible, certainly well below

toxicity threshold [54]. EDTA forms such strong complexes with most divalent cations that it finds many uses. For example, it is often present in washing powder to act as a water softener by sequestering calcium and magnesium ions. The selectivity of macrocyclic ligands can be used as a basis for the construction of an ion selective electrode. For example, potassium selective electrodes are available that make use of the naturally occurring macrocyclic antibiotic valinomycin[54].

SUMMERY

Semicarbazone and thiosemicarbazone are an important structural motif that has the potential to display chemical functionality in biologically active molecules. Optimization of this structure can result in groundbreaking discovery of new class of bioactive compounds. the success of semicarbazone and thiosemicarbazone based complexes as antiviral, fungicidal, antiparasital, antibacterial, antitumor and antineoplastic agents is largely depend on the possibility of enhancement in activity is obtained by the modifications in their structures and as a consequence, their better acceptability and solubility *in vivo*. Semiarbazone show a variety of coordination modes with transition metals, the coordination mode is influenced by the number and type of substituent. That is due to the active donor sites of ligand vary depending upon the substituent. They are very versatile ligands which can coordinate to metal as neutral molecules or after deprotonation as anionic ligands and can adopt a variety of different coordination modes. The stability constant of the transition metal complexes with some medicinally important semicarbazone compounds was reported by Chudhari. He concludes that determination of stability constants of biologically active metal complexes plays crucial role for the physiochemical properties of the drugs. The formation of bioligand complexes of some semicarbazone and thiosemicarbazone medicinal drugs with metal ions were also investigated with their respective stability constant.

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