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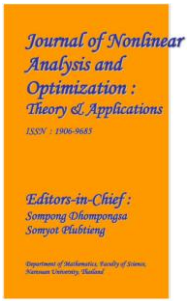

PHYSIOCHEMICAL AND BIOLOGICAL STUDY OF SOME TRANSITION METAL COMPLEXES

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Abstract
This paper examines and focuses on the proposed work deals with the study of transition metal complexes with drugs. By keeping in view the scope and importance of transition metal complexes of Ca(II), Cu(II) and Cr(III) with Alfuzosin, Lamivudine, Ketamine, Phenibut Metoprolol and Sitagliptin solution of theses drug molecules and amino acids and their stability in the biological system.

Introduction

The biologically important compounds and synthetic drugs which are medicinal drug molecules possesses nitrogen, oxygen and sulphur hetero atomic moiety in their functional groups. This hetero atomic moiety has significant property to form a complex compound with biologically important metal ions and act as strong chelating ligands to form stable five or six member chelate rings. The coordination behavior of drugs with metal ions in presence of other competing ligands which are biologically importance can be examined in vitro. Chemistry of drugs and its metal complexes attracts many researchers because of its tremendous application in medicinal field. Coordination compound has a 150-year history. Alfred Werner[1] et al. described the nature and production of coordination compounds in 1975. Jannik Bjerrum published his findings on determining the stability constant in 1941.[2] Co-ordination compounds have been a challenge to the inorganic chemist right from the time these were identified in the nineteenth century. Complexes play essential roles in the industry ranging from anti-corrosion and soil treatment agents to medicinal agents, which testify to their significance in contemporary life.[3] The complex formation has played a vital role in the field of therapeutic and biological sciences.[4] The versatile field of study found its seed in the work of Alfred Werner, a renowned chemist of 19th century who was attracted to the study of colourful compounds of cobalt and later awarded the prestigious Nobel Prize in chemistry in 1913.[5] Co-ordination compounds are formed by the interaction of a metal ion and ligands molecules and retain their identity in solution. The theory of co-ordination compounds was modified and developed from time to time by Lewis, Pauling, Bethe, Van-Vleck, Jannik Bjerrum and Cartdge.[6 7–10] Stability constants are fundamental to understanding the behavior of metal ions in aqueous solution. Such understanding is important in a wide variety of areas, such as metal ions in biology, biomedical applications, metal ions in the environment, extraction metallurgy, food chemistry, and metal ions in many industrial processes. Despite this importance, it appears that many inorganic chemists have lost an appreciation for the importance of stability constants, and the thermodynamic aspects of complex formation, with attention focused over the last thirty years on newer areas. The coordination chemistry has played a paramount role in the field of medicinal, environmental and biological sciences. The role of transition metal ions and their complexes in metabolism, transportation, detoxification and catalytic processes are very important. The stability constant of metal complexes with drugs are useful to know the proper dose of drug, their effect on other components and to study the effectiveness of metal ligand bonds. It also helps to elucidate the mechanism of action of drugs. The complexes of drugs are more potent than drug. The amino acids are very important basic structural units of proteins and plays very important role in the cell structure and its functions. Metal ligand complexes are extensively used in the treatment of various diseases for example Cisplatin is being used as anticancer agent. The effectiveness of any molecule as drug depends on its coordinating behavior at the body temperature and extra cellular fluid pH condition. It is now understood that different trace elements serve many

important roles in the living body at a molecular level. To explain the mechanism of drug development there must have to knowledge about molecular mechanism of drug.

Objectives

1. To Study the Calvin- Bjerrum as modified by Irvin-Rossoti titration techniques methods from literature.
2. To screen the required drug molecules for the present work.
3. To study the binary complexes titration analysis.
4. To study the co-ordination behaviour of metal ions with ligands.
5. To study the nature of stability of Complexes.
6. To study the effect of organo-aqueous solvent on complex formation.
7. Compilation of the data and scientific discussion of results obtained throughout the study.

Materials and Methods

The most generally utilized and probably the more accurate, simple, easier and reliable method for the determination of stability constant of metal complexes in solution is based on the potentiometric measurement of hydrogen ion concentration. This depends on the fact that pH of the solution is directly affected by complex formation, which is accompanied by the displacement of a proton from the acidic ligand. Potentiometric titration is well known for simple electro analytical technique for determination of stability constants metal complexes which was applied for current research work.

- Stability constant of binary and ternary complexes were determined PH metrically or Potentiometrically by using Calvin-Bjerrum PH metric titration techniques as modified by Irving and Rossotti methods.
- Relative stabilities of mixed ligand complexes were determined in terms of the parameters such as β_{111}, β_{02}, β_{20}, K_D, K_R, Kr and ΔlogK values.
- The concentration of various species formed can be determined with the help of species distribution curve by using special software program in computer SCOGS and Hyperquad (HySS).
- The PH metric study of transition metal complexes with medicinal drugs and amino acids were carried out at different temperature in aqueous or organ aqueous medium.

The Experimental Procedure Involves

➢ The stability constant of binary complexes has been determined by using Irving– Rossotti, pH metric titration technique in this study. The Irving and Rossotti method used for the determination of stability constant is also based on the principle of potentiometric method

➢ Using this method, the formation curve of metal complex can directly be calculated with the help of pH meter.

➢ Another major advantage of this method over the Calvin-Bjerrum's method is that the calculation is simple and does not require hydrogen ion concentration.

➢ Moreover, this method can be used for types of ligands that are conjugate to weak acids.

Result and Discussion

In the present investigation, evidence for the formation of ternary metal complexes of drugs such as Alfuzosin, Lamivudine, Ketamine, Phenibut, Metoprolol and Sitagliptin in the presence of amino acids such as glycine, leucine, valine, arginine, glutamic acid, glutamine, methionine, phenylalanine, tryptophan, and alanine with Cu(II), Cr(III) and Ca(II) have been obtained from a comparison of pH titration curve of ternary and the corresponding binary metal complexes. The following assertions confirm the formation of mixed ligand complexes in solution for all the metal ligand systems studied.

1. The mixed ligand curves lies below metals drug curve indicate the formation of ternary complexes.
2. The negative values of the ΔlogK in majority of the cases indicates the destabilized nature of the ternary complex except in case of the ternary complex formed between Cr(III) metal ion Phenibut with amino acids were found their ΔlogK values positive which is evidence that this types of ternary complexes are relatively more stable than in the case of Cu(II) metal ion complex with other drug molecules and amino acids whose ΔlogK values are negative .
3. As we know that importance of copper in biological systems, it is having good chelating tendency in many inorganic metal complexes and this was observed in case of Phenibut and metoprolol copper

binary complexation system. Though, in the present work, the chelating tendency of Cr3+ ion is greater than that of Cu2+ when complexing with Ketamine and Phenibut.
4. It was also observed that the correlation between copper and chromium ternary complexes was discovered that they are not in agreement; this may be because of a difference in their valances.
5. Species distribution diagram helps understanding the nature of the equilibrium.
6. The study of the ternary complexes of the Cu(II) ion and Alfuzosin with some amino acids like glycine, alanine, methionine, phenylalanine and glutamic acid forms a curve which runs below the corresponding metal ligand curve, which indicates that the entry of secondary ligand faces the steric hindrance and same is the case with Sitagliptin.
7. A decreased pH value when the second ligand (R) is added to 1:1 Metal (M) and first ligand (D) solution indicate the mixed ligand complex formation.
8. In pH metric titration, the mixed ligand titration curve lies below both the binary metal ligand titration curve indicates the formation of mixed ligand complexes.
9. The following findings provide evidence that mixed ligand complexes are present in solution, a) The practically obtained mixed ligand curve and the composite curve are not superposable in the region of mixed ligand complex formation. b) The composite curve for each mixed ligand system is seen in this study that it resides on the left side of the ternary complex titration curve in the area of complex formation. The primary ligands chosen for this study have a wide range of structural properties.
10. The two inflections occurred in the curve while ternary complex formations which are explained based on the step wise formation of the equilibrium, the inflection in the lower pH region corresponds to the completion of the reaction with that of the primary ligands while the second inflection occurring at the higher pH region corresponds to the interaction of the metal to the secondary ligand.

CONCLUSIONS

We came to the conclusion that the complex formation has been extremely important in the biological and medical fields. Since the last decade, there has been a lot of interest in research on metal complex formation using drugs as ligands. It is also found that the stability metal ligand complexes depends upon nature of the bond formed between metal and ligand that can be due to electrostatic or covalent which is related to oxidation state and coordination number of metal ion or characteristic nature of ligand and metal. The mixed ligand curves lies below metals drug curve indicate the formation of ternary complexes and the negative values of the ΔlogK in most of the cases indicate the disrupted nature of ternary complex. The overall outcome of this research be stated that the drug molecules like Phenibut and ketamine has good coordination behavior with metal ions and has very good capacity to form stable complexes with metal chromium therefore they can be used for the detoxification of chromium metal ions in the biological systems.

The studies of complex equilibria of metal ions with drugs are useful in elucidating the mechanism of action of drugs. The function of transition Metal ions and their complexes play a key role in metabolism, transport, and catalytic processes in systems, while amino acids serve as the fundamental building block of proteins and are crucial for cellular structure and function therefore there was much more scope to study the metal complexes of drugs is very important in future also, reason that different drugs forms complexes differently with various metal ions as we studied. Many times, it has noticed that certain biological processes taking inside the human body are interrupted due to excess presence of the metals, contamination of some metals leads to diseases. The observed values of the stability constants among the ternary metal complexes of the Chromium, Copper and Calcium with drugs molecules studied like Alfuzosin, Lamivudine, Ketamine, Phenibut, Metoprolol and Sitagliptin it is found that the chromium can be better complexed with the help of their ΔlogK values. Therefore, those drug molecules is having positive ΔlogK values that drug molecules be used as purifying agent to remove the poisoning metal ions from our body. The observation of stability order is in accordance with the Irving- Williams order. But in some cases, Stability order contradicting to Irving Williams series explained for the reason of the possible linkages of the due to metal in the solution. The negative value of ΔlogK does not mean that the complex is not formed; it

implies that the complexes are less stable. Furthermore, negative values of ΔlogK for ternary complexes are due to electrostatic repulsion due to negative charges on both the ligands as suggested by Thompson and Lorass. It was also observed that the correlation between copper and chromium ternary complexes is not in good agreement; this is being because of a difference in their valances. By using the species distribution diagram, the nature of the equilibrium understanding was easier

For ternary complexation, drug molecules were used as primary Ligands and amino acids as secondary ligands. The species distribution of all the species involved in complex equilibria for ternary complexes were determined by using "SCOGS" programme from species distribution it is observed that the formation of all ternary complexes is maximum at initial pH of titrations.

The relative stabilities of binary and ternary complexes are quantitatively explained on the basis of parameters such as **β_{111}, β_{02}, β_{20}, K_D, K_R, Kr** and **ΔlogK** values. The values of β_{111}, β_{02} and β_{20} reveal the preferential formation of ternary complexes over both binary complexes of primary and secondary ligands. The corresponding high positive values of K_D and K_R indicates that, the ternary complexes are highly stable as compared to the 1:1 binary complexes of primary and secondary ligands. The positive values of Kr support the higher stability of ternary complexes whereas the negative value of Kr supports the less stability of ternary complexes than the 1:2 binary complexes. In general, it is possible that mixed ligand complex of drugs used in the present study can be helpful to continue such type of equilibrium studies using drug molecules. Lastly, it concludes that it's possible to study the drug molecules and its mixed ligand complex used in this study will be useful for future equilibrium studies involving drug molecules. Thus, topic ends with the conclusion drawn from the present study.

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