Journal of Medicinal Chemistry and Drug Discovery
ISSN: 2347-9027
Special Issue
Analytical Chemistry Teachers And Researchers Association
National Convention/Seminar
18 January 2015

Study of Stability Constant of Metal-Drug Complexes Using Potentiometric Titration Technique

AmmarQasem[1,2], Mohammad Mohsin[1], Adel Al-Saeedi[2]and Sayyed Hussain[1*]

1. Sir Sayyed College of Arts, Commerce & Science, Aurangabad. (M.S.)
2. P.G. & Research Centre, Maulana Azad College, Aurangabad. (M.S.)

Abstract

In this review article, we described the study of stability constants of some biological activemolecules (drugs) with various metalions by potentiometric titration technique. The literature survey reveals that the compounds containsd on or group are extensively used in biology and medicinal chemistry. The metal chelates of donor groups are also used, in view of the great analytical, biological, industrial and manifold uses of donor groups complexes with metal ions.

Keywords: Stability constants, Metals, ligands, complexes.

1. Introduction:

Metal ligand complexes are made up of a central metal ion and ligands in addition to the solvent molecules required to make up the coordination sphere of the metal ion. Such metal ion ligand complexes are quite common in biological and analytical systems. Thus an understanding of the significance of metal ions in biological systems may unravel the mysteries surrounding the protein-substrate interactions and the control mechanisms that determine the coordination and coordination tendency of the metal ions bound at the active sites of many enzymes in enzyme-metal ion-substrate reactions. Apart from this, the formation of mixed-ligand complexes is also important in understanding the behavior of pollutants in natural waters. Considering the high affinity of ion for donor atoms like oxygen and nitrogen.[1]

Divalent metal ions such as copper, nickel and cobalt metal ions are known essential metals in the human body for maintaining health. Although they have beneficial effects in humans, these ions can be toxic if over-accumulated in the human body. To prevent certain diseases caused by metal poisoning and to reduce the concentration of metal ions in blood and urine in the body, the coordination chemistry of some chelating agents of such metals or recently known ligand therapy has been studied extensively.[2] An understanding of metal ion recognition is of fundamental importance to many areas of both chemistry and biochemistry, with the factors underlying such behavior often being less than straightforward. This occurs because recognition may depend on a range of factors that include the nature of the donor atoms and their spatial arrangement, the backbone structure of the ligand and its ability to accommodate the preferred coordination geometry of the metal ion, the number and size of chelate rings formed on complexation, and the nature of the metal ion to donor atom interactions present. Crystal field effects and electronic interactions of the type underlying the Irving-Williams stability order will also influence the relative metal ion stabilities of transition metal complexes. [3]

1. Importance of stability constants

The stability constant of complexes has been found to be greater than zero, is perhaps one of the most convincing pieces of evidence for the existence of the complex species ML_n in solution. Moreover, if all the possible stability constants for a given system have been determined, it is possible, in principle, to calculate the equilibrium concentration or activity of each of the species present under a known set of experimental conditions.[4-7] Such exact knowledge of the composition of a solution is essential for a correctinterpretation of its optical and kinetic properties of partition equilibrium and of its biological behavior. The importance of mixed ligand complexes in nature is evidence since a great deal of biological reactions occurs within the coordination sphere of metal ion complexes. [8]These species has an important biological implication because of enhanced probability of bringing stability constants of the mixed ligand complex, speciestherefore be well known tools for solution chemists, biochemists and chemist in general to help to determine the properties of metal ligand reactions in aqueous medium of biological relevance.The equilibrium constant K can also be utilized to evaluate the different thermodynamic parameters like free energy ΔG, enthalpy ΔH, entropy ΔS. [9-12] Complex formation is most favored by the negative enthalpy and positive entropy changes as may be expressed by the equation:

$$\log K = \frac{\Delta S - \Delta H/T}{2.303R} \qquad (1)$$

Though significant advances have been made in the field of coordination chemistry, there are still large numbers of mixed ligand complexes whose structures, reactivates, and applications are not known. One of the successful methods to investigate such problems is the study of equilibrium involving the formation of mixed metal chelates in solution. [13-14]

It is, therefore, considered appropriate to deal with some important aspects like the simultaneous and/or stepwise formation of mixed ligand complexes in aqueous and aqua-organic media.

2. Importance of metal ion in biological system

Metal ions play a vital role in biological processes; metal ion concentration must be maintained within proper ranges in the biological fluids. If the concentration of a given essential metal ion is too low, processes, which need to use the same ion, will be adversely affected and the organism can suffer from metal ions deficiency. [15] Once the concentration of a given metal ions is above a lower threshold, there will be enough of that ion to complete biological functions. Show ever, due to industrial uses of some of these metals,some people can be exposed to too much higher concentrations as a result of which they suffer from many serious diseases. [16] Furthermore, diseases release metals into the blood stream. The concentration of these metals in blood and urine of human beings can be reduced by ligand therapy. A lot of ligands have been used as antidote to combat metal poisoning. Transition metals are non-essential heavy metals that are normally present in very low concentration in our environment.

2.1 Cobalt

Cobalt is the essential metal for many organismsincluding mammals. [17] The activity of cobalt is confined to functions of vitamin B_{12} and enzyme. The use of vitamin B_{12} in biology required inarchaebacteria and this association of cobalt with early anaerobic organisms. Cobalt used as catalysts to handle compounds such as CH_4, H_2, H_2S in atmosphere; Cobalt is toxic moderately when injected intravenously to mammals.

2.2 Nickel

Nickelis a rare metal in biology.The activity of nickel is confined to one enzyme, urease, which acts in redox processes, although the symbiotic anaerobic bacteria still use nickel in some dihydrogan reaction. Free anaerobic bacteria, especially methanogens, have also kept the nickel hydrogenase and other nickel enzymes, but the methanogens belong to the special class of bacteria. Nickel is toxic and a dangerous to the health of humans from nickel poisoning is essential. In many microorganisms its transport is highly regulated by the cell. [18]

2.3 Copper

Copperis present in a large number of enzymes, many involved in electron transfer, activation of oxygen and other small molecules such as oxides of nitrogen, methane and carbon monoxide, superoxidedismutation and even invertebrates, oxygen transport, the copperbinding protein in serum that plays an important role in iron metabolism, and by the terminal oxidase of the mitochondrial respiratory chain. Cytochrome oxidase which requires both haem iron and copper for its activity.Copper levels are maintained at extremely low levels by a series of copper chaperone proteins in mammals.[19]

2.4 Zinc

Zinc is an essential element for the normal functioning of most of living organisms and its deficiency can lead to reduction of normal growth. It is a major regulatory ion in the metabolism of cells, the feel for this role comes from gross biological considerations though their molecular nature begins to appear in zinc fingers and in the link to amino acid, nucleotide and haem syntheses. Today it is difficult to know where all the zinc inside cellular systems is located. Zinc is found to be associated with DNA and RNA. It is very important in the activity of many enzymes, bacteria and is toxic in excess. [20]

3. Literature review

The work of coordination chemistry was first begins in the twentieth century. It was mostly related to stepwise formation of complexes. [21] The equilibrium constant involving the formation of a metal complex from the aquo metal ion and the most basic form of the ligand is a standard measure of the effectiveness of the ligand in coordinating metal ions.[22] Most complex formation reactions are measured in aqueous medium under controlled conditions of the ligands which are not soluble in water but are soluble in organic solvents and the stability constant with metal ions are often determined in mixed solvents. Potentiometric measurement was first used for the measurement of stability constants by Arrhenius, Ostwald and Nernst,[23] who provided the basis for the introduction of electrodes resonance reversibly and selectively to only one species present in solution. The potential of electrodes provide sufficient information for the determination of stability constants of complex formation reactions. The investigation of Bjerrum, Bronzed and McGuiness on activity coefficients and the development of theory of strong electrolytes in solution by Debye and Huckel in 1923, formed the basis for exact studies of metal ions and anions in solution. The determination of empirical formulas and overall formation constants were pioneered by workers such as Von Euler and Bodlander. Stepwise formation of complexes was first demonstrated for the system Hg^{2+}, Cl^{-} by Abegg and coworkers. [24] also Bodlander and Grossman[25] were the first to apply the idea of an ionic medium to control the ionic strength of solution. The stepwise hydrolysis constants of Cr^{3+}were described by Bjerrum[26]that described the thiocyanate complexes of Cr^{3+} and calculated the six-step stability constants. The introduction of general methods for computing stepwise stability constants was developed by J.Bjerrum, he used a large excess of the ligand (ammonia) to prevent hydrolysis and developed approximation methods for the calculation of the metal ammonia stability constant of a number of complexes. In 1945 a classic method by Calvin and Wilson appeared in which the stability constant of a number of complexes were calculated without Bjerrum simplifications by the use of exact algebraic treatment of equilibrium constants and mass balance equations. A large part of the work was carried out by three research groups, those of Sillen,[27-28] Bjerrum's group andSchwarzenbachand coworkers Subsequently a group involving Martelland coworkers, [29] the extensive treatment of the determination of stability constants by Rossetti and Rossetti. Other major works that should be mentioned by Bailer and his students in which many reaction mechanisms is described and more modern text by Lewis and Wilkins[30] in which the use of ligand field theory.

4. Importance of complexes between metal ion with medicinal drugs:

The interaction of metal ions with ligand plays vital role in biological systems. The knowledge of metal complexes with drugs is essential to understand the complex physiological process and mode of action drugs and their effect on various body systems. The formation of metal complexes depends on metal ligand selectivity in complex media. The stability constant of metal complexes with drugs are important to measure the metal ligand selectivity in terms of relative strength of metal ligand bonds. The metal complexes of drugs are found to more potent than drugs. It plays a vital role in transportation.[31] To understand the complex formation ability of the ligands and the activities of the complexes, it is necessary to have detailed knowledge about the thermodynamic andsolutionequilibria involved in the reactions. The extent to which a ligand binds to a metal ion is normally expressed in terms of the stability constant, and information about the concentration of a metal complex in an equilibrium mixture can be predicted on the basis of the formation constants in solution.[32]

There is lot ofpublishedwork related to the complexation of metal with drugs in this sectionwedescribe some examples, One of the most studies the proton-ligand dissociation constants of 4-(1*H*-indol-3-yl)butanoicacid and the stability constants of its metal-ligand complexes with divalent metals like Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+}, and UO_2^{2+}have been determined potentiometrically.[33]

Another example, apotentiometric study has been carried out to reveal the coordination properties of 1,2-bis(4-benzylpiperidine) glyoxime (BPG), by its reaction with certain transition metal ions is Ni^{2+}, Cu^{2+}, and Zn^{2+}, and to determine the stability constants of the complexes formed,[34]. The acidbaseequilibrium of the Schiff-base and the complex formation equilibrium with the metal ions as Cu^{2+}, Ni^{2+}, Co^{2+}, Cd^{2+}, Mn^{2+} and Zn^{2+} are investigated potentiometrically.[35]

Mixed Ligand Complexes of Cobalt (II) Metal Ion with Medicinal Drugs Metformin, Imipramine, Adenosine, In Mixed Solvent System.[36]

Mixed ligand complexes of Copper (II) metal ion with some antihypertension drugs and amino acids.[37]

Mixed-ligand complex formation of cadmium (II) with some amino acids and drug efavirenz etc.[38]

All these complexes are formed between metals ions and ligands drugs confining N or O as donating atoms. In most of cases either NH_2 or COOH groups are involved. In some cases N- of five or six-membered rings is also involved. There are few cases in which phenolic-O also participated in the complexation.

5. Conclusion:

Literature survey shows that the compounds contains donor group are extensively used in biology and medicinal chemistry. The metal chelates of donor groups are also used nowadays. In view of the great analytical, biological, industrial and manifold uses of donor groups complexes with metals. The stability of these chelates is therefore, an important factor in determining the effectiveness of these chelates in above mentioned fields.

References:

1. M. S. Balakrishnan, M. Santappa, Ternary Complexes: Equilibrium Studies of Mixed Ligand Complexes of Uranyl Ion with Dicarboxylic Acids in Aqueous Solution, Journal of Inorganic and Nuclear Chemistry, 36, 1974, 3813-3818.
2. E. Hernowo, A. E. Angkawijaya, A. E. Fazary, S. Ismadji, Yi-Hsu Ju, Complex Stability and Molecular Structure Studies of Divalent Metal Ion with l-Norleucine and Vitamin B3, J. Chem. Eng. Data., 56, 2011, 4549-4555.
3. K. R. Adam, D. S. Baldwin, L. F. Lindoy, G. V. Meehan, I. M. Vasilescu, G. Wei, Metal Ion Recognition. Modeling the Stability Constants of Some Mixed-Donor Macrocyclic Metal Ion Complexes Simple Model, Inorg. Chem. Acta., 352, 2003, 46-50.
4. R. B. Hernandez, O. R. Yolac, A. L. RamalhoMerce, Chemical Equilibrium in the Complexation of First Transition Series Divalent Cations Cu2+, Mn2+ and Zn2+ with Chitosan, J. Braz. Chem. Soc., 18, 2007, 1388-1396.
5. W. M. Hosny, S. M. El-Medani, M. M. Shoukry, Equilibrium studies of the binary and ternary complexes involving tetracycline and amino acid or DNA constituents, Talanta, 48,1999, 913-921.
6. P. Gans, A. Sabatini, A. Vacca, Simultaneous Calculation of Equilibrium Constants and Standard Formation Enthalpies from Calorimetric Data for Systems with Multiple Equilibrium in Solution, Journal of Solution Chemistry, 37, 2008, 467-476.

7. S. Bandyopadhyay, G. N. Mukherjee, M. G. B. Drew, Structural and Equilibrium Studies on Mixed Ligand Complexes of Co (Ii), Ni (Ii), Cu (Ii) And Zn (Ii) with N-(2 Benzimidazolyl) Methyliminodiacetic Acid and Typical N, N Donor Ligands, Inorg. Chim. Acta. 358, 2005, 3786-3798.

8. G. B. Kauffman, Theories of Coordination Compounds, J. Am. Chem. Soc., 1, 1994, 2-32.

9. S. Yumnam, L. Rajkumari, Thermodynamics of The Complexation of N - (Pyridin-2 Ylmethylene) Isonicotinohydrazide with Lighter Lanthanides, J. Chem. Eng. Data., 54, 2009, 28-34.

10. N. Sanaie, C. A. Haynes, Formation Constants and Coordination Thermodynamics for Binary and Ternary Complexes of Copper (Ii), L-Hydroxyproline, and an Amino Acid Enantiomer, J. Chem. Eng. Data., 50, 2005, 1848-1856.

11. J. Al-Mustafa, Z. A. Taha, Thermodynamics of the Complexation of Ciprofloxacin with Calcium and Magnesium Perchlorate, Thermochim. Acta., 521, 2011, 9-13.

12. P. R. Reddy, K.V. Reddy, Stabilities and Thermodynamic Parameters of 1:2 Metal Xanthosine Complexes in Solution, Inorg. Chim. Acta., 80, 1983, 95-98.

13. D. A. Brown, A. L. Roche, Design of Metal Chelates with Biological Activity and Amino Hydroxamic Acids. Nickel (II) Complexes of Alkyl, Inorg. Chem., 22, 1983, 2199-2202.

14. R. Thanavelan, G. Manikandan, G. Ramalingam, V. Thanikachalam, Mixed Ligand Chelates of Cd2+ with 2-(1-(Aminomethyl) Cyclohexyl) Acetic Acid and Dicarboxylic Acids, Der ChemicaSinica, 2, 2011, 90-98.

15. J. Lewis, R. G. Wilkins, Modern Coordination Chemistry: Principles and Methods, Published By Interscience, New York, 6, 1960.

16. J. E. Huheey, E. A. Keiter, R. L. Keiter, Inorganic Chemistry Principles of Structure and Reactivity, 4ndedition, 1993.

17. M. M. Khalil, S. A. Mohamed, A. M. Radall, Potentiometric and Conductometric Studies on The Binary and Mixed Ligand Complexes In Solution: M (Ii)-Dipicolinic Acid Glycine Systems, Talanta 44, 1997, 1365-1369.

18. J. N. Butler, Ionic Equilibrium A Mathematical Approach, Printed In The United States of America, 1964.

19. A. E. Martell, R. D. Hancock, Metal Complexes in Aqueous Solutions, Springer, Edition, 1996.

20. Lan-Chi Tran-Ho, P. M. May, G. T. Hefter, Complexation of Copper (I) by Thioamino Acids. Implications for Copper Speciation in Blood Plasma, J. Inorg. Biochem, 68, 1997, 225-231.

21. R. Janes, E. Moore, Metal Ligand Bonding, Royal Society of Chemistry, 2004.

22. W. U. Malik, G. D. Tuli, R. D. Madan, Selected Topic In Inorganic Chemistry, S. Chand, 2009, 485-509.

23. V. Uwamariya, Electrochemical Studies of Metal-Ligand Equilibria Involving Chelatig Ligands. M.Sc. Dissertation, University of the Witwatersrand, 2005.

24. R. S. Tobias, The Determination of Stability Constants of Complex Inorganic Species in Aqueous Solutions, J. Chem. Educ., 35,1958, 592.

25. A. E. Martell, R. D. Hancock, Metal Complexes in Aqueous Solutions, a Division of Plenum Press, New York, 1996.

26. J. Bjerrum, On the Tendency of the Metal Ions toward Complex Formation, Chem. Rev., 46, 2, 1950, 381-401.

27. J. Bjerrum. Metal Amine Formation in Aqueous Solutions, Theory of the Reversible Step Reactions. Copenhagen, Denmark: P. Haase and Son, 1941.

28. L. G. Sillen, Stability Constants, Introductory Lecture, J. Inorg. Nucl. Chem, 8, 1958, 176-195.

29. F. J. C. Rossotti, H. Rossotti , L. G. Sillen, Some Graphical Methods of Determining Equilibrium Constants Iii.A Projection Strip Method for Two Parameter Systems, Acta Chem. Scand.,10, 1956, 203-214.

30. M. M. Khalil, F. E. Hassabelnaby, Potentiometric Investigation of Mixed- Ligand Complexes of Some Lanthanide and Actinide Cations with Hydroxamic Acids and Diamines, Jordan J. Chem., 2, 2007, 275-285.

31. B. K. Magare, M. B. Ubalea, Interaction of Co (Ii), Ni (Ii), Cu (Ii) and Zn (Ii) Transition Metal Ions with Sulfamethoxazole Drug and Phenyl Alanine in 40% Alcohol Water Medium, ActaChim. Pharm Indica, 3, 2013, 227-230.

32. P, D, Thangjam and L, Rajkumari, Potentiometric Studies on the Complexation Reactions of N-(2,2-[1-(3-Aminophenyl)ethylidene]hydrazino-2-oxoethyl)benzamide with Ni^{+2}, Cu^{+2}, and Cd^{+2} Ions in Aqueous Dioxane and Micellar Media, J. Chem. Eng. Data, 55, 2010, 1166-1172.

33. A. T. Mubarak† and A. A. El-Bindary, Potentiometric and Thermodynamic Studies of 4-(1H-Indol-3-yl)butanoic Acid and Its Metal Complexes, J. Chem. Eng. Data, 55, 2010, 5543-5546.

34. F. N. Al-Obaidi, H. Sari, M.Macit, Potentiometric Study of the Coordination Tendency of 1,2-Bis(4-benzylpiperidine)glyoxime Toward Some Transition Metal Ions, J. Chem. Eng. Data,55, 2010, 5576-5580.

35. A. A. Shoukry, M. M. Shoukry, Coordination properties of hydralazine Schiff base Synthesis and equilibrium studies of some metal ion complexes, SpectrochimActa A MolBiomolSpectrose, 3, 2008, 686-691.

36. S. Thakur, M. Farooqui, S. D. Naikwade, Mixed Ligand Complexes of Cobalt (II) Metal Ion With Medicinal Drugs Metformin, Imipramine and Adenosine in Mixed Solvent System, International Journal of Pharm Tech Research CODEN (USA):IJPRIF, 5, 4, 2013, 1508-1515

37. R. Ware, M.Farooqui, S.D. Naikwade, Equilibrium studies on mixed ligand complexes of Copper (II) metal ion with some antihypertension drugs and amino acids, International Journal of Emerging Technologies in Computational and Applied Sciences; 2013, 123-127.

38. R. L. Ware, S.Peerzade, S. D. Naikwade, M.Farooqui, Mixed-Ligand Complex Formation of Cadmium (Ii) with Some Amino Acids and Drug Efavirenz, Journal ofChemical and Pharmaceutical Research, 5, 8, 2013, 59-63.