

|| Index ||

- 01) Study of Influence of Micro Strain, Porosity and Hopping Length of
R. B. Bhise, Pune || 09
- 02) Study of antifungal activity of 2-[(1-Naphthalen-1-yl-ethylimino)-
Sheetal V. Palande, Dr. Deelip K. Swamy, Nanded || 15
- 03) Some interesting aspects of interaction of 1-tetra-O-acetyl β
Dr. Mrs. Aruna R. Hardas, Nagpur || 19
- 04) SYNTHESIS AND STUDY OF ANTIMICROBIAL ACIVITY OF.....
SURYAKANT B. BORUL, Lonar, S.V. AGARKAR, Digras. || 22
- 05) FACILE AND SIMPLE MICROWAVE ASSISTED SYNTHESIS OF CURCUMIN
Mahesh Shioorkar, Milind Ubale, Aurangabad. || 25
- 06) SYNTHESIS OF PHARMACOLOGICALLY ACTIVITIVE 1-(7-NITRO
Meghasham N. Narule, Vibha Nikase, Wardha.. || 28
- 07) Choline-glycolate green and reusable ionic liquid; a novel efficient
Beg Nawaj Ali, Maqdoom Farooqui, Aurangabad. || 33
- 08) Synthesis of Schiff base from 3-Formylchromone and 4-Nitrosulphonamide
S.K. Ghumbre, S.M. Bhagat, S.S.Sagar, Khed, Dist. Ratnagiri || 37
- 09) Microwave assisted synthesis and characterization of some novel
Dr. Y.K. Meshram, Ku. Rupali M. Mahalle, Ku, Jyoti M. Laghe, Chandrapur || 40
- 10) Alum Catalyzed Microwave Irradiated Solvent Free Synthesis of
Omprakash S. Chavan, Jalna Mohammad A. Baseer, Nanded. || 42
- 11) Mixed ligand complexes of zinc metal ion with antibacterial drug
Shailendrasingh Thakur, S.A. Peerzade, A.J. Khan, R.L.Ware, Beed || 47
- 12) Capital Formation in Agriculture: Problems and Bankers Obligations
Ms. Snehal Bhosale, Vijaypur || 42
- 13) Triethylammonium Hydrogen Sulfate as an Efficient Ionic Liquid
Atul S. Renge, Karjat, Sushil K.Gumbre, Khed, || 54

14) Synthesis and Antimicrobial Activity of Various Pyrazoline From	58
Shrikant A. Patil, Mangesh V. Kadu, Malkapur- Dist. Buldana.	
15) MICROWAVE SYNTHESIS AND ANTIMICROBIAL STUDIES OF TRANSISION	60
K.K. Wavhal and S. B. Borul, Lonar, Dist Buldana.	
16) Estimation of Total flavonoid and antioxidant activity of Tradescantia	64
Pavan M. Kadam, Deulgaon Raja, Dr. D. R. Munde, Nanded.	
17) A Novel approach towards the Synthesis of Furoquinolines Strong	68
Ganesh B. Akat, Khultabad.	
18) Synthesis of some substituted Schiff bases and to study their addesive	73
Dr. Y. K. Meshram, Dr. Kirtiwardhan R. Dixit, J . M . Laghe, R. M . Mahalle	
19) Microbiological and Physicochemical Assessment of Drinking water	76
Mr. S.S. Anjanikar, Naigaon, Dr. S.S. Chandole, Purna	
20) Synthesis of pyran derivatives by using ferrite Nanoparticles	80
Sudarshan D. Tapsale, K. M. Jadhav, D. V. Mane, S. G. Patil	
21) An efficient synthesis of benzodiazepine derivatives under	82
Asghar Jafar khan, Mohammad Abdul Baseer, Mohammed Zamir Ahmed, S. V. Thakur	
22) Thermodynamic properties of binary liquid mixtures of 2- Butanone	85
S. B. Lomate, M. J. Bawa, M. K. Lande, B. R. Arbad, Shirur (Ka.).	
23) Phytochemical extraction and antimicrobial activity of Azadirachta	89
B. U. Kale, P. B. Pawar, R. T. Parihar, Deulgaon Raja	
24) Removal of Lead and Copper from aqueous solution using different	94
Rashmi R. Sharma, Dr. S. R. Warhate, Kelapur	
25) A Study of Electrical and Dielectric Properties of Binary Mixtures of	97
S B Shinde, R N Mathpati, M A Joshi, D N Rander, Y S Joshi, K S Kanse.	
26) PHYTOCHEMICAL ANALYSIS OF FENUGREEK SEED	101
Dr. Prerana P. Bhatkar, Anjangaon Surji	
27) Alum catalyzed one pot three component synthesis of Pyrano.....	103
Khandu D Warad, Chandrashekhar G Devkate, Ramkrushna P Pawar, Rajiv Khobre, AmitTayade	

- 28) Study of Physico chemical Analysis of Terna River Water at the Polluted
Shoeb Peerzade, S. V. Thakur, Mazhar Farooqui, Sayed Abed, Beed. || 106
- 29) The Physico-Chemical Properties of binary liquids mixtures of
M.Bawa, S. Lomte, M. Lande, B. Arbad, Deulgaon Raja. || 109
- 30) Study of antimicrobial activity of 2-Methoxy-6-[(1-naphthalen-1-yl-ethylimino).....
Sheetal V. Palande, Dr. Deelip K. Swamy, Nanded. || 112
- 31) Assessment of Heavy metals in Drinking water and ground water sources.....
Moharir S. P., Sinkar S. N., Jalna || 116
- 32) Nanotoxicity : A Hazardous Approach Towards A Nanoworld
Sunil M. Chore, Kelapur || 119
- 33) Synthetic Study and Interaction of Cobalt (II) Complexes with Different types
Ganesh Babasaheb Akat, Khultabad. || 122
- 34) A THERMODYNAMIC STUDY OF ACRYLATES AND 2-HEXANOL
SUJATA S. PATIL, JALNA || 128
- 35) A Mathematical Insight into Chemical Sciences: With Special
Vishakha Walia || 131
- 36) Ethanol sensing properties of Ga doped ZnO Thin Films
E. U. Masumdar, Latur, M. A. Barote, Ausa || 134
- 37) EFFECT OF CHELATING AGENT AND ITS METAL COMPLEXs ON SEED
Bhagat. T. M., Umarched. || 137
- 38) Molecular Interaction Study of Binary mixtures of DMSO with Water
M A Joshi, S B Shinde, R N Mathpati, D N Rander, K S Kanse, Y S Joshi || 142
- 39) "NONCONVENTIONAL METHODOLOGIES ARE EXCELLENT TOOLS FOR
C.S. Patil, Aurangabad, Sonali S. Chine, Kopargaon. || 146
- 40) Review on Recent Developments and Applications in Green Nanocomposites
Dr. Prashant R. Mahalle, Sakharkherda || 152
- 41) Thiamine Hydrochloride Catalyzed Green Synthesis of Benzoin
PAWAN P. KALBENDE, NILESH B. JADHAV, ACHALPUR || 155

- 42) Synthesis and study of Biological active ligands and Zinc (II) metal complexes
Mr. S.S. Anjanikar, Naigaon. || 159
- 43) Thiadiazoles and its biological activities: A review
Bharat K. Dhotre, Mantha. || 160
- 44) ANTI-MICROBIAL STUDY OF SUBSTITUTED FLAVONES
S. L. Sayre, P. B. Raghuvanshi, Amravati. || 160
- 45) Antimicrobial Study of Ligands and their metal complexes of Mn(II) and Co(II)
S. S. Chandole, Purna Jn.. || 161
- 46) Synthesis of Chalcone from Schiff Base derived from 3-Amino Acetophenone
A. R. Mehetre, S. R. Deshmukh, V. N. Bhosale, Kannad. || 161
- 47) Highly regio-selective hydroformylation of biomass derived eugenol using aqueous
Samadhan A. Jagtap, Eric Monflier, Anne Ponchel, Bhalchandra M. Bhanage. || 162
- 48) "An Efficient One-pot Synthesis of Naphthooxazine Derivatives"
Suresh C. Jadhavar, Ambajogai || 163
- 49) Kinetics of Permagnetic oxidation of 4-amino Acetophenone and 4-hydroxy
Bhagwansing Dobhal, Ravindra Shimpi, Rajesh Fadat, Jalna. || 163
- 50) Comparative kinetic and mechanistic study of oxidation of Antibiotics by
Ravindra Shimpi, Rajesh Fadat, Bhagwansing Dobhal, D M Janrao,
Mazahar Farooqui, Jalna. || 165
- 51) Bioinformatics study of Operational Taxonomic Units of fish Anabas
Kendre T. U., Pagare S. D., Rankhamb S. V., Kalyankar V. B. || 166
- 52) Mixed ligand complexes of zinc metal ion with antibacterial drug
S. V. Thakur, M. A. Sakhare, S. N. Sampal, H.U. Joshi, Beed || 169
- 53) "An Efficient Synthesis of Naphtho-oxazine derivatives using Zinc
Virbhadra G. Kalalawe, Dashrath R. Munde, Raoji D. Gutte || 173

Mixed ligand complexes of zinc metal ion with antibacterial drug Oxytetracycline hydrochloride and amino acids in aqueous media

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Abstract:

The stability constant of the mixed ligand complexes of zinc(II) ion with antibacterial drug Oxytetracycline hydrochloride as primary ligand and eight amino acids glycine, DL-alanine, L-glutamic acid, DL-isoleucine, DL-methionine, DL- α -phenyl alanine, DL-serine and DL-valine as secondary ligands were determined pH metrically in 20%(v/v) ethanol-water medium at 25°C and at an ionic strength of 0.1 M NaClO₄. The formation of complex species has been evaluated by SCOGS computer program and discussed in terms of various relative stability parameters.

Keywords : Stability constant, antibacterial drug, amino acids, mixed ligand complexes.

Introduction :

Metal complexes of drugs are found to

be more potent than parent drugs. Chemistry of drugs attracts many researchers because of its application in medicinal study. The stability of metal complexes with medicinal drugs plays a major role in the biological and chemical activity. Amino acids are the structural unit of proteins. These are essential constituents of all living cells and contain one or more amino and carboxylic groups and have good coordination sites for the metal complexation. In continuation of earlier work with complexation of antibacterial drug¹⁻⁷, we study ternary complexes of zinc metal ion with antibacterial drug Oxytetracycline hydrochloride (OCT) as primary ligand and eight amino acids as secondary ligands in 20% (v/v) ethanol-water medium at 25 °C and at an ionic strength of 0.1 M NaClO₄.

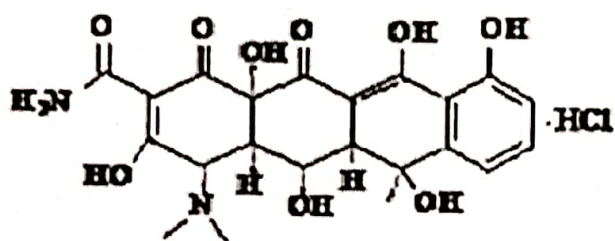


Figure 1: Oxytetracycline hydrochloride
(molecular formula C₂₂H₂₅N₂O₉Cl)

Experimental: Materials and Solution:

The ligand OCT is soluble in ethanol. NaOH, NaClO₄, HClO₄ & metal salts were of AR grade. The solutions used in the potentiometric titration were prepared in double distilled water. The NaOH solution was standardized against oxalic acid solution (0.1M) and standard alkali solution was again used for standardization of HClO₄. The metal salt solutions were also standardized using EDTA titration. All the measurements were made at 25°C in 20% ethanol-water mixture at 0.1M NaClO₄ strength. The thermostat was used to maintain the temperature constant. The pH measurement were made using a digital pH meter model Elico L1-120 in conjunction with a glass and reference Calomel electrode. The pH-meter was adjusted with buffer of pH 4.00, 7.00 and 9.18.

pHmetric procedure:

For evaluating the protonation constant of the ligand & the formation constant of the complexes in 20% ethanol-water mixture with different metal ions we prepared the following six sets of solutions.

- (i) HClO₄ (A)
- (ii) HClO₄ + Drug (A + L)
- (iii) HClO₄ + Drug + Metal (A + L + M)
- (iv) HClO₄ + Amino acid (A + R)
- (v) HClO₄ + Amino acid + Metal (A + R + M)
- (vi) HClO₄ + Drug + Amino acid + Metal (A + L + R + M)

The above mentioned sets prepared by keeping M:L:R ratio, the concentration of perchloric acid & sodium perchlorate (0.1M) were kept constant for all sets. The volume of every mixture was made up to 50ml with double distilled water. The test solutions were magnetically stirred, NaOH was added stepwise and pH reading was recorded. Graphs were obtained by plotting pH vs volume of NaOH added. These data were used to determine the pK_a of ligands and logK values of metal complexes of primary and secondary ligands. The equilibrium constants of ternary complexes were calculated by using SCOGS program. The total concentrations of metal ions, free metals, free ligands and various possible species that are formed during complexation were obtained as computer output of program.

Table 1: Proton-ligand stability constant and metal-ligand stability constant of antibacterial drug OCT and amino acids with zinc(II) at 0.1M ionic strength in 20% (v/v) ethanol-water medium

Ligands	Proton-ligand stability constant PK ₁ /PK ₂	metal-ligand stability constant logK ₁ logK ₂
Oxytetracycline hydrochloride	--- 4.316	3.989 3.107
Glycine	2.4729 582	5.5254 2.59
DL -Alanine	2.3649 658	4.4923 561
Glutamic acid	2.5014 416	2.9212 744
DL -Isoleucine	2.6549 624	6.9605 071
DL -Methionine	2.3039 079	4.8833 655
DL -β-Phenyl alanine	2.2559 174	4.8634 056
DL -Serine	2.3448 983	4.6443 476
DL -Valine	2.4889 501	5.1494 175

Table 2: Parameters based on some relationship between formations of mixed ligand complexes of Zn (II) with OCTdrug and amino acids

Amino Acids	β_{111}	β_{20}	β_{02}	K_L	K_R	K_r	? logk
Glycine	8.0239	7.1058	9.7634	4.0246	2.4992	0.9513	-1.5001
DL -Alanine	6.9912	7.1058	8.0529	2.9919	2.4992	0.9224	-1.5001
Glutamic acid	5.6699	7.1058	5.6647	1.6706	2.7489	0.888	-1.2504
DL -Isoleucine	9.7089	7.1058	12.029	5.7096	2.7492	1.0148	-1.2501
DL -Methionine	8.6319	7.1058	8.538	4.6326	3.7488	1.1036	-0.2505
DL- β -Phenyl alanine	8.8605	7.1058	8.918	4.8612	3.998	1.1059	-0.0013
DL -Serine	7.1424	7.1058	8.1205	3.1431	2.4981	0.9382	-1.5012
DL -Valine	8.6485	7.1058	9.3243	4.6492	3.4991	1.0528	-0.5002

Result and Discussion: Binary complex:

The proton ligand stability constants (pKa) of drug and amino acids were calculated by point wise and half integral method. The metal ligand stability constant logK of Zn(II) transition metal complexes with antibacterial drugs were calculated by using Calvin Bjerrum titration techniques as adopted by Irving and Rossotti.

Titration curves were obtained for different sets. During titration no precipitate was formed indicating that there is no tendency to form hydroxo complexes. The stability constants of the formed complexes were investigated in the pH range of 4-6. The mean value the average number of protons associated with the ligand \bar{n}_A different pH values were calculated. The pKa values were determined from \bar{n}_A . Similarly \bar{n} the metal ligand formation number, which can be defined as average number of ligand molecules co-ordinated to the metal \bar{n}_A ions, were also obtained using Irving & Rossotti method. The values obtained between 0.2 to 0.8 indicates 1:1 complexation and when \bar{n} lies in between 1.2 to 1.8 indicate 1:2 complexation. The values of proton ligand stability constants pKa and metal ligand stability constant logK are represented in Table 1. Since we got \bar{n}_A between 0.2 to 0.8 and 1.2 to 1.8 indicating 1:1 and 1:2 complex formation. The order of $\log K_1 > \log K_2$ is commonly observed. The reason is statistical effect, statistically coordination of a second molecule is difficult when compare to the first due to availability of less number of coordinating sites on the metal ion for the second ligand. The standard deviation for various metal ligand system is 0.036. Irving and Rossotti have proposed a relation between the stability of the complexes and basicity of the ligand by equation

$$\log K = apk + b$$

The relation graph shows a straight line and the value of slope should be unity for a series of closely related ligand.

Mixed ligand complexes:

The formation of 1:1:1 mixed ligand complex were identified by the pH of precipitation of ML, MR and MLR titration curves. These curves indicate the higher value of pH of precipitation of ternary system than corresponding binary systems. The relative stabilities of mixed ligand complexes were quantitatively expressed in terms of $\Delta \log K$, Kr,

K_L and K_R values which are defined by equations:

$$\Delta \log K = \log \beta_{111} - (\log K_{10} + \log K_{01}) \quad (1)$$

$$K_r = \frac{\beta_{111}^2}{(\beta_{20}\beta_{02})} \quad (2)$$

$$K_L = \frac{\beta_{111}}{\log K_{10}} \quad (3)$$

$$K_R = \frac{\beta_{111}}{\log K_{01}} \quad (4)$$

Where β_{111} is the equilibrium constant of ternary system.

β_{20} is the overall stability constant of primary complexes.

β_{02} is the overall stability constant of secondary complexes.

The equilibrium constants β_{111} of ternary systems of Zn(II) transition metal ion and relative stability parameters are shown in Table 2. The ternary complexes of zinc metal ions with DL-isoleucine shows higher values of stability whereas glutamic acid ternary complexes show low values of stability. This may be attributed to the aliphatic nature of secondary ligand, steric effect and chelation formation.

The order of stability of equilibrium constants β_{111} of ternary systems of Zn(II) transition metal ion with respect to secondary ligand is

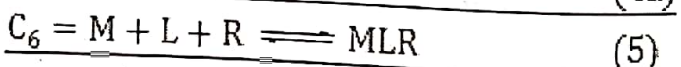
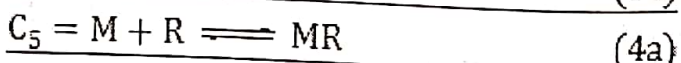
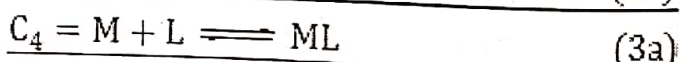
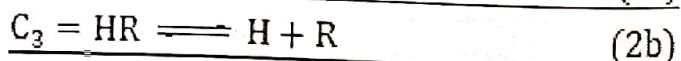
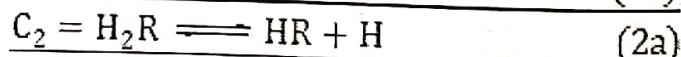
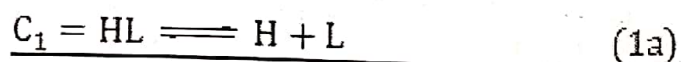
OCT: isoleucine > β -phenyl alanine > valine > methionine > glycine > serine > alanine > glut.acid

The comparison of β_{111} with β_{20} and β_{02} of these systems reveals the preferential formation of ternary complexes over binary complexes. The low positive values of K_L and K_R indicate less stability of ternary complexes with respect to binary complexes of primary as well as secondary ligands. The K_r value is positive but less, which indicates lower stability of ternary complexes. This may be attributed to the interactions outside the coordinated sphere such as formation of hydrogen bonding between coordinated ligands, charge neutralization,

chelate effect and electrostatic interactions between noncoordinated charge groups of ligands. The negative values of $\Delta \log K$ have been found in all systems, which show the formation of ternary complex but less stable and destabilized nature of complexes which has been reported in N and O coordination of amino acids. The negative value of $\Delta \log K$ does not mean that the complex is not formed. The negative value may be due to the higher stability of its binary complexes, reduced number of coordination sites, steric hindrance, electronic consideration, difference in bond type, geometrical structure etc.

Thompson and Lorass pointed out that more negative $\Delta \log K$ value of ternary complexes is due to the electrostatic repulsion between the negative charge on the ligand and amino acids. Steric hindrance consideration is the most important factor because in the present studies of ternary complex, primary ligand coordinates with the metal ion in the lower pH range and form 1:1 and 1:2 complex. In solution, ternary complex forms as the titration curve runs below the Zn(II)-drug titration curve. So, it is evident that the entry of the secondary ligand amino acids faces steric hindrance due to bigger size of the Zn(II)-drug complex as compared to aquo ion, which tries to restrict the entry of the secondary ligand in the coordination sphere of the Zn(II) metal ion and thus reduces the stability of ternary complexes.

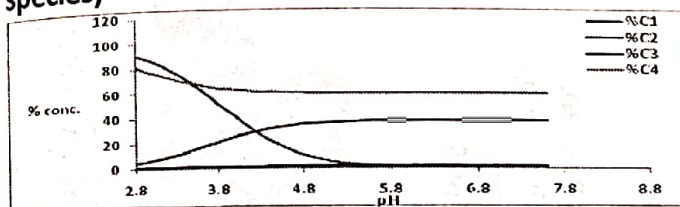
Species distribution curves: According to the result given by SCOGS computer programme, the concentration of different species distributed are as follows:



The species distribution curves of Zn(II)LR systems were obtained by plotting percentage concentration of various possible species formed during complexation versus pH

of solution as shown in figure 2. In Zn(II)LR ternary systems, primary as well as secondary ligands forms 1:1 and 1:2 binary complexes. The species distribution curves of free metal (M), free ligands L and R indicates that there is a slowly decrease in concentration of free metal ions with increase in pH whereas increase in concentration of ligands with pH and indicates higher percentage concentration of FL than FR. The species distribution diagram of Zn(II)LR system shows the formation of mixed ligand complexes. The concentration for the formation of drug (L) and HR represented by C_1 and C_2 show continuous decrease with increasing pH. The concentration of C_6 species continuously increases, confirm the formation of ternary complexes Zn (II)LR.

Figure 2: Species distribution curve of Zn (II) LR system (pH versus % conc. of various possible species)



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