STUDY FOR DEPENDENCE OF 'TRANSITION STATE' WITH APPLIED POTENTIAL IN ELECTROKINETIC REACTION OF [ZN(II)-ANTIBIOTICS-VITAMIN-B_2] SYSTEM VIS A VIS KINETICS OF ELECTRODE REACTION

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Abstract. Polarographic technique was used to study the ternary complex formation of Zn(II) with neomycin, chlortetracycline, oxytetracycline, penicillin-V and penicillin-G as primary ligands and vitamin-B_2 as a secondary ligand at pH = 7.30 ± 0.01 and μ = 1.0 M $NaClO_4$ at 298 K. The nature of current voltage curves was quasireversible. Zn(II) formed 1:1:1, 1:1:2 and 1:2:1 complexes with these drugs as confirmed by Schaap and McMaster method. The sequence of stability constant of complexes was neomycin < chlortetracycline < oxytetracycline < tetracycline < penicillin-V < penicillin-G that can be explained on the basis of nature of ligands and steric hindrance between metals ligands. Kinetic parameters were also determined using Tamamushi and Tanaka method. The value of transfer coefficient (α) confirmed that the 'transition state' behaves between dropping mercury electrode and solution interface. A slight variation of potential affects not only the rate but rate constant greatly.

Keywords: stability constant, kinetic parameter, [Zn(II)-antibiotics-vitamin-B_2] complexes

Introduction

Vitamin-B_2 (riboflavin) is a water-soluble vitamin. Its metabolism is controlled by different hormones which regulate its conversion in FAD (flavinadeninedinucleotide) and FMN (flavinmononucleotide) [1,2]. These two coenzymes catalyze many oxidation-reduction reactions and are essential for our production of energy.

On the other hand, antibiotics are natural compound produced mostly by plant microorganisms [3] these antibiotics are used against several fungal and bacterial diseases in plants, animals and human beings [4,5]. Therefore, the study of complexes of antibiotics with riboflavin has great importance. In this paper, we report stability constant(log β) and kinetics parameters of complexes viz. transfer coefficient (α), degree of irreversibility (λ), diffusion coefficient (D) and rate constant (k) of complexes using neomycin, chlortetracycline, oxytetracycline, tetracycline, penicillin-V, and penicillin-G as primary ligands and riboflavin as secondary ligands by polarographic technique for which no reference is available in the literature.

Experimental

All the chemicals used were of A.R. grade and their solutions were prepared in conductivity water. Zn(II), the antibiotics and vitamin-B_2 were taken in the ratios of 1:40:40 and current voltage curves were obtained in different pH values. It has been observed that the maximum shift of $E_{1/2}$ was obtained within the pH range 7.10-8.50, but pH 7.30 was selected for studying the complexes in human blood pH. A Systronic μ pH meter 361 was used to measure the pH of the analyte at 7.30 ± 0.01 adjusted by using dilute solutions of $HClO_4$ or NaOH as required. Potassium dihydrogen phosphate-sodium hydroxide buffer was added to stabilize the pH of the analyte. The current voltage curves were obtained on a manual polarograph using polyflex galvanometer (PL-50). The polarographic cell was of Latinin and Lingane type in which polarographic capillary of 5.0 cm in length with 0.04 mm in diameter was used. The $m^{2/3}\ t^{1/6}$ value was 2.40 $mg^{2/3}\ s^{-1/2}$ at 60.00 cm effective height of mercury. As the resistance of the cell was less than 300 Ω, IR correction was not made.

Results and discussion

Zn(II) gave two electron quasi-reversible reduction wave at pH = 7.30 ± 0.01 and μ = 1.0 M $NaClO_4$ at 298 K [6]. The nature of current-voltage curves for complexes is also quasi-reversible. The concentration of Zn(II) $NaClO_4$, and triton X-100 (as suppressor) in the test solution were 0.5 mM, 1.0 M and 0.001% respectively. Pure nitrogen gas was passed through the test solution before recording the current-voltage curves.

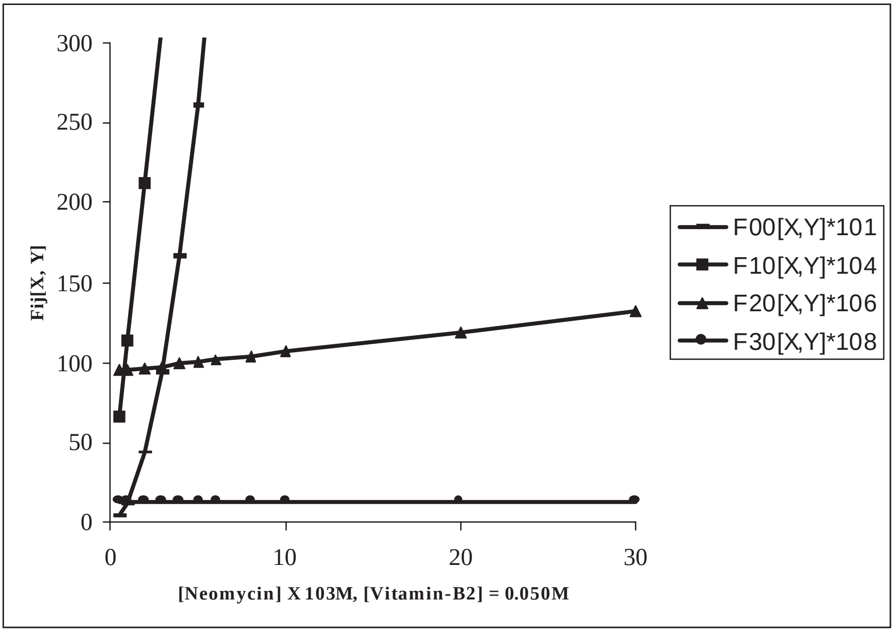

Fig. 1. [Zn-Neomycin-Vitamin-B_2] System

The concentration of antibiotics varied from 0.5 mM to 30.0 mM at two fixed concentration of vitamin-B_2 i.e. 0.025 M and 0.050 M. The $E_{1/2}$ values became more negative with the addition of vitamin-B_2 to the [Zn(II)-antibiotics] system which showed ternary complex formation of 1:1:1, 1:1:2, and 1:2:1 complexes. Gellings [7] method was used to determine the values of $E_{1/2}^{reversible}$ form $E_{1/2}^{quasireversible}$ by plotting (E- RT/nF log i_d-i/i) vs. i for all the complexes. The data and plots of F_{ij} [X,Y] against [X] (where F_{ij} is a Schaap and McMasters [8] function to evaluate the stability constant β_{ij}, X = neomycin, Y = vitamin-B_2 and i and j are their stoichiometric numbers respectively) for [Zn(II)-neomycin-vitamin-B_2] system were given in Table 1 and Fig.1, respectively. The Fig.1 is used to determine the values of functions F_{00}, F_{10}, F_{20} and F_{30} and also to calculate the stability constant.

Table 1. Polarographic Characteristics and F_{ij} [X, Y] Values of [Zn- Neomycin – Vitamin-B_2] System
Zn(II) = 0.5 mM, μ = 1.0 M $NaClO_4$, pH = 7.30 ± 0.01, Temp. = 25ºC

[Vitamin – B_2]= 0.025 M (Fixed)							
[Neo.] X10^3 M	**$(E_{1/2})^r$ -V vs SCE**	**$\Delta E_{1/2}$ V**	**$\log I_m/I_c$**	**F_{00}[X,Y] X 10^1**	**F_{10}[X,Y] X 10^4**	**F_{20}[X,Y] X 10^6**	**F_{30}[X,Y] X 10^8**
0.00	0.985	-	-	-	-	-	-
0.50	1.112	0.0385	0.0074	2.00	32.29	49.35	12.58
1.00	1.118	0.0525	0.0149	6.10	57.60	49.98	12.59
2.00	1.124	0.0690	0.0149	22.40	110.11	51.24	12.59
3.00	1.130	0.0790	0.0226	49.90	165.13	52.50	12.59
4.00	1.137	0.0865	0.0226	89.50	222.69	53.76	12.60
5.00	1.141	0.0924	0.0226	141.80	282.76	55.02	12.60
6.00	1.145	0.0971	0.0304	207.60	345.35	56.28	12.60
8.00	1.151	0.1047	0.0384	382.90	478.15	58.81	12.61
10.00	1.157	0.1109	0.0384	621.40	621.00	61.33	12.61
20.00	1.161	0.1310	0.0384	2974.40	1486.99	73.96	12.62
30.00	1.168	0.1448	0.0465	8896.20	2965.27	98.58	12.62
log A = 0.65, log B = 3.90, log C = 7.65, log D = 9.10							

To know the values of β_{11} and β_{12}, the study has been carried out at two constant concentration of secondary ligand [Y] = [Vitamin-B_2] at 0.025M and 0.050M respectively. The values of stability constant of complexes were given in Table 2.

Table 2. Stability Constant of [Zn- Antibiotics- Vitamin- B_2] System
Zn (II) = 0.5 mM, μ = 1.0 M $NaClO_4$, pH = 7.30 ± 0.01, Temp. = 25ºC

Ligand		Stability Constants							
Primary	Secondary	log β_{01}	log β_{02}	log β_{10}	log β_{20}	log β_{30}	log β_{11}	log β_{12}	log β_{21}
Neomycin	Vitamin-B_2	2.00	3.14	3.60	6.51	9.10	3.70	6.75	9.26
Chlortetracycline	Vitamin-B_2	-	-	4.40	7.61	9.50	4.56	-	9.63
Oxytetracycline	Vitamin-B_2	-	-	4.50	7.81	9.86	4.61	7.87	9.93
Tetracycline	Vitamin-B_2	-	-	4.80	8.01	9.91	4.96	8.12	10.00
Penicillin-V	Vitamin-B_2	-	-	4.91	-	10.00	5.01	8.23	10.13
Penicillin-G	Vitamin-B_2	-	-	4.96	8.12	10.10	5.12	-	10.25

Table 3. Kinetic Parameters of [Zn- Neomycin – Vitamin-B_2] System
Zn(II) = 0.5 mM, μ = 1.0 M $NaClO_4$, pH = 7.30 ± 0.01, Temp. = 25ºC

Vitamin – B_2 = 0.025 M (Fixed)						
[Neo.] $X10^3$ M	$(E_{1/2})^{qr}$ -V vs SCE	Slope mV	α	λ $sec^{-1/2}$	$D^{1/2}X10^{-3}$ cm^2sec^{-1}	k x 10^{-3} cm sec^{-1}
0.00	1.000	36.00	0.45	1.18	4.87	5.74
0.50	1.115	45.50	0.48	1.12	4.96	4.69
1.00	1.120	42.00	0.51	1.36	4.93	5.74
2.00	1.128	42.00	0.51	1.57	4.84	6.48
3.00	1.134	42.00	0.50	1.16	4.77	4.45
4.00	1.139	35.50	0.48	1.68	4.70	4.37
5.00	1.145	40.00	0.47	1.68	4.70	5.74
6.00	1.148	35.00	0.47	1.16	3.70	6.18
8.00	1.153	45.50	0.50	1.36	3.84	6.48
10.00	1.159	40.00	0.50	1.28	3.53	6.18
20.00	1.163	35.00	0.52	1.28	3.63	5.78
30.00	1.170	35.50	0.48	1.16	3.84	5.78

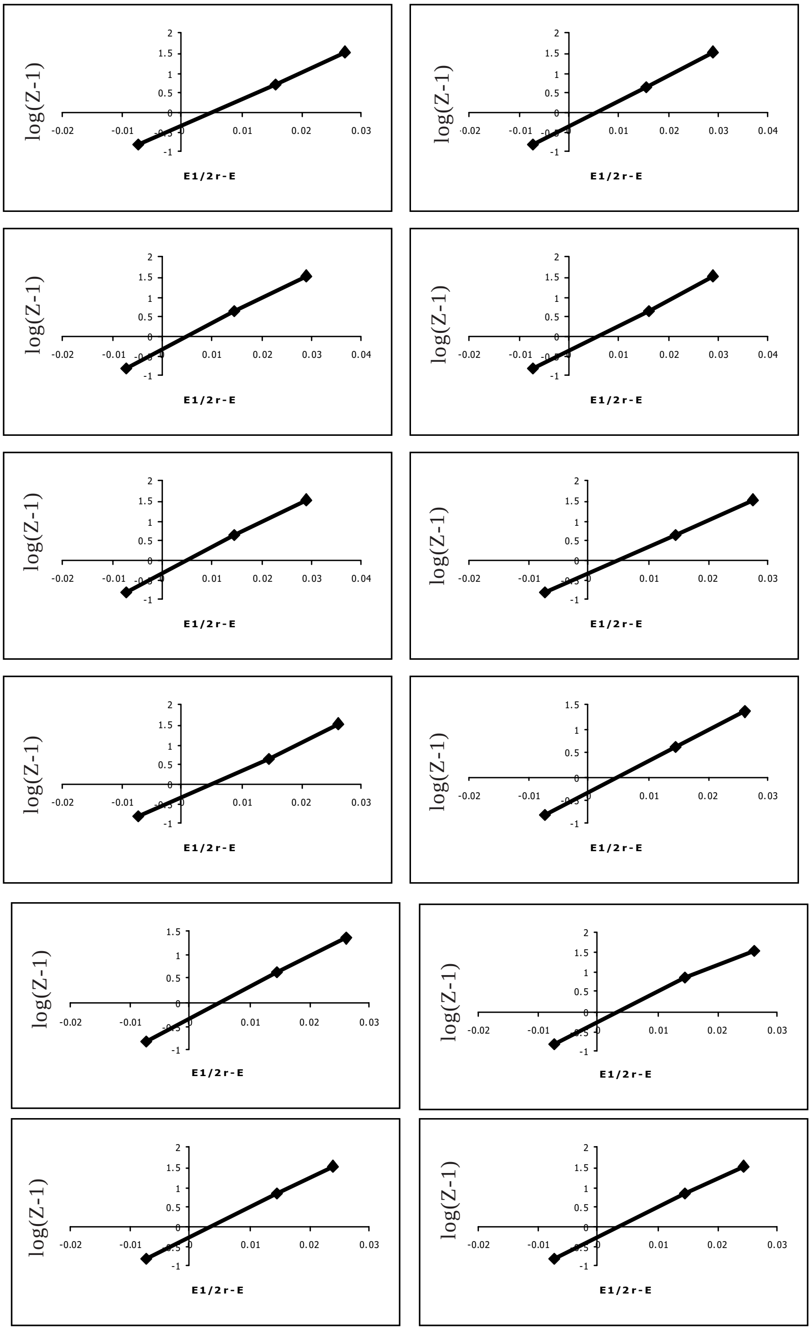

Fig. 2. [Zn-Neomycin-Vitamin-B_2] System, [Vitamin-B_2] = 0.025mM
Plot of ($E_{1/2}^{r}$-E) vs log(Z-1), Y-axis = log(Z-1), X-axis = ($E_{1/2}^{r}$-E)

To compare the stability of binary and ternary complexes, the values of mixing constant log k was calculated by the following equation [8]

$$\log k_m = \log \beta_{11} - ½ [\log \beta_{02} + \log \beta_{20}]$$

The values of log k_m were -1.12, -0.81, -0.86, -0.61 and -0.51 for [Zn(II)-neomycin-vitamin-B_2], [Zn(II)-chlortetracycline-vitamin-B_2], [Zn(II)-oxytetracycline-vitamin-B_2], and [Zn(II)-tetracycline -vitamin-B_2] and [Zn(II)-penicillin-G-vitamin-B_2] respectively. The positive value of log k_m showed that the ternary complex is more stable than their binary complexes while the negative values of log k_m showed that binary complexes are more stable than their ternary complexes. The complexes of compositions 1:2 in case of [Zn(II)-penicillin-V-vitamin-B_2] are not formed therefore; the values of log k_m were not calculated. It is clear from the values of stability constants of complexes that neomycin formed the complexes of lowest stability. In case of tetracycline; all the tetracycline has the same structures except in the difference in R_1 and R_2 position. The lesser stability constant of chlortetracycline complex than that of oxytetracycline complex is due to the presence of more electrons withdrawing Cl at R_1 in the former in place of H in the latter. In case of tetracycline, H is present both at R_1 and R_2 hence; there are least electronic disturbances in tetracycline in comparison to other tetracycline complexes [9]. This order of stability supported the order of their pK values of their ligands [10]. In case of both penicillin-V and penicillin-G, it is the ring nitrogen and O of the carboxylic group which take part in complexation with Zn(II). The greater stability of penicillin-G complexes than that of penicillin-V complexes is also supported by the order of the pK values [11].

In case of vitamin-B_2, it is the N of pyrimidine ring [12, 13], which can take part in bond formation with Zn(II).

It is clear from the values of stability constant of the complexes that vitamin-B_2 and antibiotics used either singly or simultaneously might be effective to reduce the toxicity [14] of Zn(II) in vivo.

The kinetic parameters viz. transfer coefficient (α), degree of irreversibility (λ) and rate constant (k) were determined by Tamamushi and Tanaka method [15,16] by plotting ($E^r_{1/2}$-E) against log (Z-1) (Fig.2 where the terms have the usual significance) [15,16]. The values of kinetic parameters were given in Table 3. It is obvious from the value of α that the values varied from [Zn(II)-neomycin-vitamin-B_2] 0.45 to 0.52 (about 0.50), and value of α for other systems were also about 0.50 which confirmed that 'transition state' lies midway between dropping mercury electrode and solution interface. The value of rate constant (k) showed that the electrode process were quasi-reversible. The values of diffusion coefficient as determined by Ilkovic equation [17] were as expected.

Conclusion

The present study showed that the polarographic reduction of [Zn(II)-antibiotics- vitamin-B_2] was quasar-reversible. The values of transfer coefficient confirmed that the 'transition state' lies in an exact intermediate between DME and mercury solution interface [18].

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REFERENCES

1. **Hardman, J.G., L.E. Limbird, A.G. Gilman (Eds.).** *Goodman & Gilman's The Pharmacological Basis of Therapeutics.* McGraw-Hill, New York, 2001.

2. **Barker, B.M., D.A. Bender (Eds.).** *Vitamins in Medicine.* William Heinemann Medical Books, London, 1995.

3. **Korzybski, T., Z. Kowszyik-Gindifer, W. Kuryloicz.** *Antibiotics - Origin, Nature and Properies.* Polish Scientific Publishers, Warszawa, 1967.

4. **Parihar, M.S., F. Khan.** Stability Constants and Thermodynamic Parameters of Cadmium Complexes with Sulfonamides and Cephapirin. *Eclet. Quim.* **33**, 29-34 (2008).

5. **Chadar, S.N., F. Khan.** Electrode Kinetics and Ternary Complexes of [Mn^{II}-antibiotics-vitamine-B_2] vis-à-vis Kinetics of Electrode Reaction. *J. Indian Chem. Soc.* **83**, 1242-1247 (2006).

6. **Khan, F., L. Tantuvay**. Thermodynamics in [Mn(II)-antibiotics-bacitracin] Mixed System: A Polarographic Approach. *J. Pharm. Biomed. Anal.* **27**, 933-944 (2002).

7. **Gellings, P.J.** *Z. Electrochem. Ber. Bunsenges phys. Chem.* **66**, 481, (1962).

8. **Schaap, W.B., D.L. McMasters.** A Polarographic Study of Mixed-ligand Complex Formation: Complexes of Copper and Cadmium with Oxalate Ion and Ethylendiamine. *J. Amer. Chem. Soc.* **83**, 4699-4706 (1961).

9. **Mulliken, R.S.** Electronic Structures of Polyatom Molecules. VIII. Ionization Potentials. *J. Chem. Phys.* **3**, 514-516 (1935).

10. **De Siqueira, M.J., S. Carvalho, E.B. Paniago, L. Tosi, H. Beraldo.** Metal Complexes of Anhydrotetracycline. 1. A Spectrometric Study of the Cu(II) and Ni(II) Complexes. *J. Pharm. Sci.* **83**, 291-295 (1994).

11. **Parihar, M.S., F. Khan.** Voltammetric study and electrode kinetics of [Mn-sulfonamide-cephazolin] system at dropping mercury electrode *J. Indian Chem. Soc.* **85**, 765-768 (2008).

12. **Zhong, D., A.H. Zewail.** Femtosecond Dynamics of Flavoproteins: Change Separation and Recombination in Riboflavine (Vitamine B_2)-binding Protein and in Glucose Oxidase Enzyme. *Proc. Natl. Acad. Sci. USA* **98**, 11867-11872 (2001).

13. **Khan, F**. Electrochemical Study and Dependence of 'Transition State' in Co(II) and Ni(II) Complexes with Some Antibiotics and Cephalothin. *Eclet. Quim.* **32**, 73-83 (2007).

14. **Walker, M.D., D.R. Williams.** Thermodynamic Considerations in Coordination. Part XVIII. Formation Constants for Cadmium (II)-amino-acid Complexes as Determined By Glass and Solid-State Cadmium-Electrode Potentiometry. *J. Chem. Soc. Dalton Trans.*, 1186-1189 (1974).

15. Tamamushi, R., K. Ishibashi, N. Tanaka. Polarographic Study on the Electrode Reaction of Zinc Ion. *Z. physik. Chem. Neue Folge* **35**, 209-212 (1962).

16. Tamamushi, R., K. Ishibashi, N. Tanaka. A Note on Polarographic Study on the Electrode Reaction of Zinc Ion. *Z. phys. Chem. Neue Folge* **39,** 117-119 (1963).

17. Ilkovic, D. Polarographic Studies with the Dropping-Mercury Electrode. III. The Cause of Maxima in Current-Voltage Curves. *Collections Czech. Chem. Comm.* **8**, 13-34 (1936).

18. Atkins, P.W. *Physical Chemistry.* W.H. Freeman and Co., San Francisco, 1948.

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