Study of bioinorganic ternary complexes of manganese with antibiotics and paracetamol by polarographic technique at kinetic parameters

Amul Kumar Kesharwani

Department of Chemistry,
Dr. H.S. Gour Central University,
Sagar-470003, M.P.(India)

***Abstract*: Bioinorganic ternary complexes of manganese with some selected antibiotics viz. neomycin, chlortetracycline, oxytetracycline, tetracycline penicillin-V and penicillin-G as primary ligands and paracetamol as secondary ligand have been studied by polarographic technique to determinate the stability constant (log β) and kinetic parameters at pH = 7.30 ± 0.01 and ionic strength μ = 1.0 M $NaClO_4$ at 298 K. The stability of formed complexes is elucidated on the basis of basic nature and sizes of the selected primary and secondary ligands. The polarographic waves of Mn and its complexes were found to be quasi-reversible and also, Mn (II) formed 1:1:1, 1:2:1 and 1:1:2 complexes with selected legends.**

***Index Terms*—Stability constants, Polar graphic characteristics, Kinetic parameters,[Mn (II)-antibiotics-paracetamol] complexes**

I. INTRODUCTION:

ANTIBIOTICS ARE WELL KNOWN NATURALLY OCCURRING COMPOUNDS PRODUCED MOSTLY BY PLANTS ORGANISMS [1], USED IN SEVERAL DISEASES IN PLANTS, ANIMALS AND HUMAN [2, 3] HAVE GREAT IMPORTANCE IN BIOLOGICAL SYSTEM. ON THE OTHER HAND, PARACETAMOL IS ALSO A BIOLOGICAL DRUG USED AS ANTIPYRETIC AS WELL AS ANALGESIC. THE BIOCHEMICAL, PHARMACOLOGICAL AND MEDICINAL IMPORTANCE OF METAL DRUG COMPLEXES IN VERY WELL ESTABLISHED. SOME WORK ON MN (II) COMPLEXES WITH DIFFERENT TECHNIQUES ARE AVAILABLE IN THE LITERATURE. A SURVEY OF LITERATURE REVEALS THAT NO REFERENCE IS AVAILABLE ON MN (II) TERNARY COMPLEXES WITH THE PRESENTLY SELECTED ANTIBIOTICS AND PARACETAMOL BY POLAROGRAPHIC TECHNIQUE, HENCE, AUTHORS HAVE STUDIES THE MIXED LIGAND COMPLEXATION OF MN (II) WITH NEOMYCIN, CHLORTETRACYCLINE, OXYTETRACYCLINE, TETRACYCLINE, PENICILLIN-V AND PENICILLIN-G AS PRIMARY LIGAND AND PARACETAMOL AS SECONDARY LIGAND, USING POLAROGRAPHIC TECHNIQUE WITH THE VIEW TO DETERMINE THE VALUES OF STABILITY CONSTANTS AND KINETIC PARAMETERS. THE POSITION OF TRANSITION STATE AND EFFECT OF SIZE, BASICITY, AND STERIC HINDERANCE DUE TO LIGANDS ON STABILITY COMPLEXES ALSO DISCUSSED.

II. EXPERIMENTAL:

MANGANESE CHLORIDE (ALDRICH USA), NACLO4 (FLUKA, SWITZERLAND), ANTIBIOTICS (FLUKA) WERE USED AND THEIR SOLUTION WERE PREPARED IN DOUBLE DISTILLED WATER. PARACETAMOL IS USED AS ITS SODIUM SALT. THE CONCENTRATION OF METAL IONS AND $NaClO_4$IN THE TEST SOLUTION WERE 0.5 MM AND 1.0 MM RESPECTIVELY WHILE 1.0 M $NaClO_4$ WAS USED TO MAINTAIN THE IONIC STRENGTH AS WELL AS USED AS SUPPORTING ELECTROLYTE. NACL-AGAR-AGAR PLUG TOGETHER WITH SINTERED DISC WAS USED IN LATININE-LINGANE CELL [4] WHICH CONNECT THE POLAROGRAPHIC CELL WITH SCE [5, 6]. THE RESISTANCE OF CELL WAS LOWER THAN 200 OHMS AS TO MAKE NO CORRECTION FOR IR.THE PH OF THE SOLUTIONS WAS ADJUSTED TO 7.30 ± 0.01 BY ADDING REQUISITE AMOUNT OF SODIUM HYDROXIDE AND PERCHLORIC ACIDSOLUTION. THE C-V DATA FOR THE COMPLEX SYSTEM WERE RECORDED AFTER PASSING THE PURE HYDROGEN GAS IN THE TEST SOLUTION. AN ELICO (LI-120) PH METER FITTED WITH GLASS AND SATURATED CALOMEL ELECTRODE WERE USED TO RECORD THE PH OF THE TEST SOLUTION. THE TEMPERATURE WAS MAINTAINED CONSTANTS AT 298 K.

A manual polar graph with PL-50 Polyflex Galvinometer was use to record the current voltage data. The capillary characteristics were $m^{2/3}t^{1/6}$ =2.40 $mg^{2/3}$ $s^{-1/2}$ at 60.0 cms (calculated) effective height of mercury. The depolariser and ligands (antibiotics and paracetamol) were taken in the ratio 1:40:40 and current voltage curves were obtained at different pH values but pH=7.30 ± 0.01 was selected on account of studying the complex formation in human blood pH.In ternary complexes the concentration of antibiotics was varied from 0.50 mM to 30 mM at two fixed concentrations of paracetamol i.e., 0.025 and 0.050 M. For the calculation of stability constants log β_{11} (1:1:1), log β_{12} (1:2:1) and log β_{21} (1:1:2), Schaap and Mc Master Method [7] was used.

III. RESULT AND DISCUSSION

Mn (II) gave a well-defined two electron quasirevesible reduction wave in 1.0 mM $NaClO_4$ at pH= 7.30 ± 0.01. The values of $E_{1/2}^{(qr)}$ of Mn (II) were found -1.420 V vs SCE which by Gellings method [9] gave $E_{1/2}$ = -1.410 V. Similarly, $E_{1/2}^{(r)}$ from $E_{1/2}^{(qr)}$ of complexes for corresponding ligand concentration was also calculated. In all these cases it has been observed that irreversibility increased with increase of living concentration. Mn formed 1:1 and 1:2 complexes with paracetamol and stability constants [10-13] are given in Table no. 1

3.1. Polarography of [Mn(II)-penicillin-G-paracetamol] complexes

The half wave potential increased with increase of concentrations of secondary ligand i.e., phenacetin to the [Mn-antibiotics] system showed ternary complex formation. The values of stability constants are given in Table No.1. The polar graphic characteristics &F_{ij}[X Y] values for the [Mn(II)-penicillin-G-paracetamol] system are given in Table No 2. The quasireversible waves for Mn(II) and its complexes were confirmed by the slope of current voltage curves and kinetic parameters which are given in Table No. 3.

3.2. Kinetic parameters of [Mn(II)-penicillin-G-paracetamol] complexes

The kinetic parameters such as standard rate constant (k), degree of irreversibility (λ) and charge transfer coefficient (α) for the [Mn(II)-penicillin-G- paracetamol] complexes were given in Table No. 3.

The parameter Z, which is measure of degree of irreversibility, is given by the following equation-

$$Z = \text{antilog}\,[(nF/2.303)RT(E_{1/2}-E)]+\log(i_d - i)/i$$

The values of standard rate constant (k) of Zn and its complexes are found to be order of 10^{-3} cm. sec^{-1}, confirmed that the electrode processes are quasi reversible and the reduction of the electroactive species at the surface of the electrode is not fast. The charge transfer coefficient (α), which can be regarded as the fraction of the applied potential, either assists or hinders the process under consideration, also have the expected values[14-16]. The values of a comes about 0.500 confirming the transition state lies in the mid-point of dropping mercury electrode and mercury solution interface [17].

3.3. Stability constants of the [Mn(II)-antibiotics-paracetamol] complexes

Stability constants for [Mn(II)-antibiotics- paracetamol] complexes are given in Table no 1. Stability of the complexes can be compared by the value of mixing constant (log Km) which is given by the following equation[18]:

$$\log Km = \log \beta_{11} - 1/2\,[\log \beta_{20} + \log \beta_{02}]$$

The values of log Km for the complexes [Mn(II)-neomycin-paracetamol], [Mn(II)-chlortetracycline-paracetamol], [Mn(II)-oxytetracycline-paracetamol], [Mn(II)-penicillin-V-paracetamol] and [Mn(II)-penicillin-G-paracetamol] are +0.145, +3.55, 0,00, +0.010, +0.070 and + 0.130 respectively. Ternary complexes with negative values of log Km are less stable than their parent binary complexes and those with positive log Km are more stable than their parent binary complexes. In our case the values of Km are found to be positive, thus it is clear that the ternary complexes are mor stable than their parent binary complexes. The value of stability constants (from Table No. 1) of neomycin complexes showed that this antibiotic formed the complexes of lowest stability amongst all the selected primary ligands because there is steric hindrance between metal and various groups present in the neomycin. In the complexes of chlortetracycline, oxytetracycline and tetracycline, bonding takes place with metal ion through the oxygen of amide group and the oxygen of carbon atom[19]. All tetracyclines have the same structures but they differ only in the group R_1 and R_2. The chlortetracycline complexes are less stable than oxytetracycline complexes which can be explained on the basis of the presence of electronegative chlorine atom at R_1 in chlortetracycline while oxygen atom in OH group of R_2 in oxytetracycline. Due to higher electronegativity of chlorine, it attracts electrons very rapidly from groups present in the chlortetracycline while oxygen does not attract electron as rapidly as chlorine[20], and so in case of chlortetracycline there is higher electronic disturbance than in oxytetracycline causes the less stability of chlortetracycline complexes than oxytetracycline complexes. The pK values of these drugs are also support this order of stability [21-23].

Since there is no such electronegative atoms are present in case of tetracycline, results no electronic disturbance in tetracycline and so it forms highly stable complexes amongst all the selected tetracyclines.In case of penicillin-V and penicillin-G, oxygen atom of carboxylic group and ring nitrogen may take part in formation of complex with Zn[24]. High stability of penicillin-G complexes than penicillin-V is supported by basic strength of these drugs. In case of penicillin-G the value of log K is 4.77 while in case of penicillin-V it is found[24] 3.98.As a result of lesser steric hindrance in penicillin complexes than other antibiotics, penicillin complexes are highly stable than other. Therefore, the trend of stability of the complexes is neomycin < chlortetracycline < oxytetracycline < tetracycline< penicillin-V < penicillin-G. The stability constants of the complexes of Mn with antibiotics are of great importance in pharmaceutical sciences. The values of stability constants obtained are not high, so Mn toxicity in-vivo can be reduced by using these drugs[25].

Table No. 01: Stability constants of [Mn-antibiotic-paracetamol]complexes (Ref. 15)

Ligands	$Log\beta_{01}$	$Log\beta_{02}$	$Log\beta_{10}$	$Log\beta_{20}$	$Log\beta_{30}$	$Log\beta_{11}$	$Log\beta_{12}$	$Log\beta_{21}$
Paracetamol	1.87	2.90	-	-	-	-	-	-
Neomycin	-	-	3.40	6.31	8.90	4.35	7.65	9.98
Chlortetracycline	-	-	4.00	-	9.13	5.00	7.80	10.02
Oxytetracycline	-	-	4.31	7.50	9.32	5.20	-	10.25
Tetracycline	-	-	4.50	7.80	9.60	5.36	8.00	10.38
Penicillin-V	-	-	4.60	7.96	9.97	5.50	8.32	10.45
Penicillin-G	-	-	4.70	8.00	10.00	5.58	-	10.62

Table No. 02: The polarographic characteristics & $F_{ij}[X\ Y]$ values for the [Mn(II)-tetracycline-paracetamol] system

	Paracetamol = 0.025 M (Fixed)							Paracetamol = 0.050 M (Fixed)					
Tetracycline x 10^3M	$(E1/2)^r$ -V Vs SCE	$\Delta E_{1/2}$ V	$logI_m/I_c$	$F_{00}[x,y]$ X 10^2	$F_{10}[x,y]$ X 10^5	$F_{20}[x,y]$ X 10^9	$F_{30}[x,y]$ X 10^{10}	$(E1/2)^r$ -V vs SCE	$\Delta E_{1/2}$ V	$logI_m/I_c$	$F_{00}[x,y]$ X 10^2	$F_{10}[x,y]$ X 10^5	$F_{20}[x,y]$ X 10^9	$F_{30}[x,y]$ X 10^{10}
0.00	1.4000	-	-	-	-	-	-	1.4000	-	-	-	-	-	-
0.50	1.4691	0.0691	0.0074	2.1915	4.3162	6.6479	3.9810	1.4789	0.0789	0.0074	4.6872	9.2407	12.644	3.9810
1.00	1.4852	0.0852	0.0149	7.6935	7.6601	6.6679	3.9007	1.4944	0.0944	0.0944	15.6499	15.5830	12.664	3.9750
2.00	1.5022	0.1022	0.0226	28.8474	14.4070	6.7074	3.9700	1.5109	0.1109	0.0226	56.7227	28.3279	12.704	3.9905
3.00	1.5124	0.1124	0.0304	63.7366	21.2344	6.7474	3.9810	1.5209	0.1209	0.0304	123.5214	41.1515	12.744	3.9810
4.00	1.5197	0,1197	0.0384	112.5974	28.1410	6.7872	3.9200	1.5281	0.1281	0.0465	216.2969	54.0575	12.784	3.9650
5.00	1.5254	0.1254	0.0465	175.6819	35.1297	6.8275	3.9900	1.5337	0.1337	0.0465	335.2584	67.0383	12.824	3.9800
6.00	1.5301	0.1301	0.0548	253.1698	42.1894	6.8662	3.9700	1.5383	0.1383	0.0548	480.6735	80.1011	12.863	3.9410
8.00	1.5374	0,1375	0.0632	452.5406	56.5634	6.9464	3.9500	1.5456	0.1456	0.0632	851.5445	106.464	12.943	3.9710
10.00	1.5434	0.1434	0.0718	712.5654	71.2532	7.0261	3.9810	1.5524	0.1514	0.0806	1331.549	133.148	13.023	3.9800
20.00	1.5628	0.1618	0.0806	2988.677	149.432	7.4220	3.9400	1.5694	0.1694	0.0896	5426.432	271.318	13.420	3.9650
30.00	1.5728	0.1728	0.0896	7072.299	235.742	7.4250	3.9900	1.5801	0.1801	0.0987	12527.68	417.587	13.822	3.9910

Table No. 03: Kinetic parameters such as standard rate constant (k), degree of irreversibility (λ) and charge transfer coefficient (α) for the [Mn(II)-tetracycline -paracetamol] complexes
Mn(II) = 0.5 mM; μ = 1.0 m $NaClO_4$ pH = 7.30 ± 0.01; Temp. = 25°C

	Paracetamol = 0.025 M (Fixed)						Paracetamol = 0.050 M (Fixed)					
Tetracycline x 10^3M	$(E1/2)^{qr}$ -V Vs SCE	Slope mV	α	λ $sec^{-1/2}$	$D^{1/2}x10^{-2}$ cm^2sec^{-1}	kx10^{-3} cm sec^{-1}	$(E1/2)^{qr}$ -V Vs SCE	Slope mV	α	λ $sec^{-1/2}$	$D^{1/2x10-2}$ cm^2sec^{-1}	kx10^{-3} cm sec^{-1}

0.00	-1.420	40.00	0.487	1.86	4.05	7.53	-1.420	40.00	0.487	1.86	4.05	7.53
0.50	-1.493	40.00	0.460	1.76	3.98	7.00	-1.501	42.50	0.460	1.76	3.98	7.00
1.00	-1.509	42.50	0.460	1.76	3,91	6.88	-1.517	45.00	0.400	2.22	3.91	8.68
2.00	-1.521	42.50	0.460	1.76	3.84	6.75	-1.530	40.00	0.460	1.86	3.84	7.14
3.00	-1.540	45.00	0.485	1.76	3.77	6.63	-1.546	42.50	0.460	1.76	3.77	6.63
4.00	-1.541	40.00	0.460	1.86	3.70	6.88	-1.555	45.00	0.485	1.66	3.63	6.02
5.00	-1.553	45.00	0.460	1.86	3.63	6.75	-1.561	42.50	0.509	1.48	3.63	5.37
6.00	-1.556	42.50	0.460	1.86	3.56	6.62	-1.563	45.00	0.509	1.40	3.56	4.98
8.00	-1.566	45.00	0.460	1.66	3.50	5.81	-1.573	45.00	0.509	1.66	3.50	5.81
10.00	-1.567	37.50	0.509	1.57	3.43	5.38	-1.575	40.00	0.485	1.57	3.36	5.27
20.00	-1.585	40.00	0.509	1.48	3.36	4.97	-1.593	40.00	0.485	1.48	3.29	4.86
30.00	-1.595	40.00	0.509	1.48	3.29	4.86	-1.604	37.50	0.485	1.57	3.22	5.05

IV. ACKNOWLEDGEMENT

The authors are thankful to Head, Department of Chemistry, Dr. HarisinghGour Central University, Sagar, Madhya Pradesh (India).

REFERENCES

[1]. A.M. Geddes and J.D. Williams, "Current Antibiotic Therapy", Edin burgth,London, 1973.
[2]. O.F. William, L.L. Thomas and A.D. Williams, "Principles of MedicinalChemistry", B.I. Waverly Pvt. Ltd., Fourth Edition, New Delhi 1995, 759.
[3]. F.D. Robert, "Wilson and Gisvold`s Text Book of Organic Medicinal andPharmaceutical Chemistry", J.B. Lippincott Co., Eight Edition, 1998, 225.
[4].J.C. Khatri, A.Varshney and N.Singh, J. Ind. Chem. Soc., LX (1983) 30.
[5].L.Meatis, "Polarographic Techniques", Interscience Pub., New York, Second Edition, 1985.
[6].R. Tamanushi, M. Tanaka, Z. Phys. Chem. Neue Foldge 39 (1963) 117.
[7].W.B. Schaap, D.L. McMaster, J. Am. Chem. Soc. 83 (1961) 4999.
[8].T. Devries, J.L. Kroon, J. Am. Chem. Soc. 75 (1953) 2484.
[9].P.J. Gellings, Z. Electrochem. Ber. Bun. Phys. Chem. 66 (1962) 477, 481,799; 67 (1963) 167.
[10]. A.K. Kesharwani, F. Khan, Bull. Elec. Chem. 18 (9) (2002) 413.
[11]. F, Khan, A.K. Kesharwani, J. Ind. Chem. Soc. 80 (2003) 47.
[12]. J.J. Lingane, Chem.Rev. 1 (1941) 29.
[13]. A. K. Kesharwani, F. Khan, Oxid. Commu. (Bulgaria) 33 (3) (2010) 709.
[14]. F. Khan, L. Tantuvay, J. Pharma & Biomedical Analysis, Elsevier 27, 933 (2002)
[15].R. Tamamushi, K.Ishibushi and N. Tanaka, Z. Phys. Chem., (Neue Foldge), 25 (1962) 209-221.
[16].F. Khan and L. Tantuvay, Oxid. Commu. (Bulgaria) 23 (4) (2000) 629.
[17].R.C. Kapoor and B.S. Agrawala, "Principles of Polarography", Wiley EasternLtd., New Delhi (1991) 71.
[18].S. Vajhallya, F. Khan, Bull. Chem. Soc. Jpn. 72 (1999) 397.
[19].K. Katawar, M.S. Kacchawaha, Hindustan Antibiot. Bull. 26 (1984) 9.
[20].(a). R.S. Mulliken, J. Chem. Phys. 2 (1934) 782; (b). R.S. Mulliken, J. Chem. Phys. 3 (1935) 513.
[21].C.R. Stephens, L.H. Conover, R. Posternack, F.A. Hochslein, W.T. Moreland, P.P. Regma, F.J. Pilgrim, K.J. Brunings and R.B. Woodward, J. Am. Chem.Soc. 76 (1954) 3568.
[22].F.A. Hochslein, C.R. Stephens, J. Am. Chem. Soc. 75 (1953) 5455.
[23].J.M. Desiqueria, S. Carvalho, E.B. Paniago, L.Tosi and H. Beraldo, J. Pharma.Sci. 83 (1994) 291.
[24].P.B. Chakrawarti, A. Tiwari and H.N. Sharma, Ind. J. Chem. 21 A, 1982, 200.
[25].J.T. Doluiso and A.N. Martin, J. Med. Chem. 6, 1963, 16.