CHEMIJA. 2008. Vol. 19. Nos. 3–4. P. 1–6

Electrochemical study and thermodynamic parameters of Cd^{2+} complexes with some antibiotics and vitamin B_X system

Santosh Narayan Chadar[1]*,

Farid Khan[1],

Simant Sharma[2]

[1] Electrochemical Laboratory,
Department of Chemistry,
Dr. H. S. Gour University,
Sagar-470 003, Madhya Pradesh, India

2 Pharmaceutical Chemistry
Research Laboratory,
Department of Pharmacy,
Dr. H. S. Gour University,
Sagar-470 003, Madhya Pradesh, India

The polarographic technique was used to determine the stability constants and thermodynamic parameters such as enthalpy change (ΔH), free energy change (ΔG) and entropy change (ΔS) of Cd^{2+} complexes with neomycin, chlortetracycline, oxytetracycline, tetracycline, penicillin-V, and penicillin-G as primary ligands and vitamin B_X as a secondary ligand at pH 7.30 ± 0.01 and ionic strength I = 1.0 M KNO_3. The study was carried out at two different temperatures – 25 °C and 35 °C. Cd^{2+} complexes were formed in 1 : 1 : 1, 1: 1 : 2 and 1 : 2 : 1 ratios. The stability constant sequence of the complexes was neomycin < chlortetracycline < oxytetracycline < tetracycline < penicillin-V < penicillin-G, which can be explained by the nature of ligands and steric hindrance among metal ligands. The electrode processes were reversible and diffusion-controlled. The values of stability constants have shown that these drugs can be used to reduce Cd^{2+} toxicity.

Key words: electrode kinetics, stability constant, thermodynamic parameters, Cd^{2+}–neomycin–vitamin B_X system

INTRODUCTION

PABA is a naturally occurring, water-soluble compound found in many foods as a cofactor of the vitamin B complex (associated with folate) [1]. Para-aminobenzoic acid or PABA is a non-protein amino acid which is widely distributed in nature. PABA is an intermediate in the synthesis of folic acid in bacteria. Sulfonamide antibiotics are structurally similar to PABA and interfere with the synthesis of nucleic acids in sensitive microorganisms by blocking the conversion of PABA to the coenzyme dihydrofolic acid, a reduced form of folic acid. In humans, dihydrofolic acid is obtained from dietary folic acid. Para-aminobenzoic acid (PABA), a component of pteroylglutamate, was once considered a vitamin and named vitamin Bx because it serves as a provitamin for some bacteria. Later studies in humans have demonstrated that it shows no vitamin activity because humans lack the ability to synthesize folate from PABA [2, 3]. On the other hand, antibiotics are natural compounds produced mostly by plant microorganisms [4]. These antibiotics are used against several fungal and bacterial diseases in plants, animal and human beings [5]. Therefore, studies of antibiotics with vitamin Bx are of great importance. Cd^{2+} is the most toxic element in the environment to which industrial civilization has exposed itself. In human beings, the concentration of Cd^{2+} increases, and they suffer from several diseases [6]. The concentration of Cd^{2+} in blood and serum can be reduced by ligand therapy [7]; therefore, the study of Cd^{2+} complexes with these antibiotics and vitamin B_X has great importance.

EXPERIMENTAL

All A. R. grade chemicals and double-distilled water were used for solution preparation. Cd^{2+}, the antibiotics and vitamin B_X were taken in the ratio of 1: 40 : 40, and current voltage curves were obtained at different pH values. 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 a polyflex galvanometer (PL-50). The polarographic cell was of Latinin and Lingane type in which a polarographic capillary 5.0 cm long and 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 60.02 cm effective height of mercury. As the resistance of the cell was less than 300 Ω, no IR correction was made.

* Corresponding author. E-mail: narayan_santosh@rediffmail.com

RESULTS AND DISCUSSION

A well-defined two-electron [8] reversible reduction and diffusion-controlled wave Cd^{2+} was observed in 1.0 M KNO_3 at pH 7.30 to 8.50, but pH 7.30 was selected to study the complex formation in human blood pH. The value of $E_{1/2}^{reversible}$ for Cd^{2+} was –0.586 mV vs SCE. The nature of the C–V curve of Cd^{2+} complexes with antibiotics and vitamin B_X was also reversible and diffusion-controlled.

In this system, the concentrations of antibiotics varied from 0.5 mM to 30.0 mM. The $E_{1/2}$ values became more negative with the addition of antibiotics to Cd^{2+} showing a complex formation. The Deford and Hume method confirmed the formation of 1 : 1, 1 : 2 and 1 : 3 complexes of Cd^{2+} with neomycin, chlortetracycline, oxytetracycline, tetracycline, penicillin-V and penicillin-G, respectively. The $Fi(x)$ vs (x) data and plots where $Fi(x)$, (x) and i are the Deford [9] and Hume function, primary ligand, i. e. antibiotics and stoichiometric number of primary ligand, respectively, for the Cd^{2+}–neomycin system are given in Table 1 and Fig. 1, respectively. The stability constant of ternary complexes was determined by the Schaap and McMaster [10] method which confirmed the formation of 1 : 1 : 1, 1 : 2 : 1 and 1 : 1 : 2 metal ligand complexes. The values of the stability constant of the complexes are given in Table 3. The data and plots of $F_{ij}(x, y)$ against (x), where F_{ij} is the Schaap and McMaster function to evaluate the stability constant β_{ij}, x = neomycin, y = vitamin B_X, and i and j are their stoichiometric numbers respectively, for the Cd^{2+}–neomycin–vitamin B_X system are given in Table 2 and Fig. 2, respectively.

The thermodynamic parameters [11] such as enthalpy change (ΔH), free energy change (ΔG) and entropy change (ΔS) of Cd^{2+} complexes with neomycin, chlortetracyclin, oxytetracyclin, tetracyclin, penicillin-V and penicillin-G served as primary ligands and vitamin B_X as a secondary ligand at pH 7.30 ± 0.01

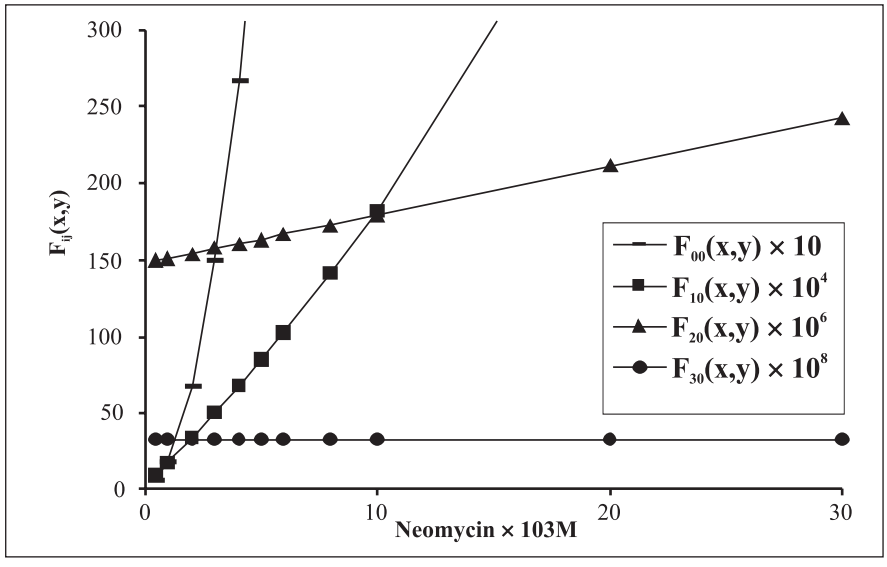

Fig. 1. Cd^{2+}–neomycin system

Table 1. **Polarographic data and $F_i(x)$ values of Cd^{2+}–neomycin system.**
Cd^{2+} = 0.5 mM, I = 1.0 M KNO_3, pH 7.30 ± 0.01, T = 25 °C

Vitamin B_X = 0.025 M (fixed)							
[Neo.] × 10^3 M	$(E_{1/2})^r$–V vs SCE	$\Delta E_{1/2}$ V	$\log I_m / I_c$	$F_{00}(x, y) \times 10$	$F_{10}(x, y) \times 10^4$	$F_{20}(x, y) \times 10^6$	$F_{30}(x, y) \times 10^8$
0.00	0.586	–	–	–	–	–	–
0.50	0.610	0.0167	0.0074	6.30	11.85	82.74	39.81
1.00	0.614	0.0529	0.0074	16.38	16.01	82.94	39.81
2.00	0.617	0.0649	0.0149	49.14	24.38	83.94	39.82
3.00	0.622	0.0790	0.0149	98.89	32.84	83.73	39.82
4.00	0.627	0.0880	0.0149	165.86	41.37	84.13	39.83
5.00	0.631	0.0944	0.0226	250.30	49.98	84.53	39.83
6.00	0.636	0.0997	0.0226	352.42	58.67	84.93	39.84
8.00	0.641	0.1039	0.0304	610.80	76.30	85.73	39.84
10.00	0.646	0.1107	0.0384	942.80	94.24	86.52	39.84
20.00	0.648	0.1163	0.0384	3775.30	188.74	90.51	39.85
30.00	0.652	0.1341	0.0384	8736.8	291.21	94.49	39.85
log A = 0.75, log B = 3.90, log C = 6.50, log D = 9.10							

Table 2. Polarographic characteristics and $F_{ij}(x, y)$ values of Cd^{2+}–Neomycin–Vitamin B_X system
Cd^{2+} = 0.5 mM, I = 1.0 M KNO_3, pH 7.30 ± 0.01, T = 25 °C

	Vitamin B_X = 0.025 M (fixed)							Vitamin B_X = 0.050 M (fixed)						
[Neo.] × 10^3 M	$(E_{1/2})^r$ –V vs SCE	$\Delta E_{1/2}$ V	$\log I_m / I_c$	$F_{00}(x, y)$	$F_{10}(x, y)$ × 10^5	$F_{20}(x, y)$ × 10^5	$F_{30}(x, y)$ × 10^6	$(E_{1/2})^r$ –V vs SCE	$\Delta E_{1/2}$ V	$\log I_m / I_c$	$F_{00}(x, y)$	$F_{10}(x, y)$ × 10^5	$F_{20}(x, y)$ × 10^5	$F_{30}(x, y)$ × 10^6
0.00	0.586	–	–	–	–	–	–	0.586	–	–	–	–	–	–
0.50	0.604	0.0167	0.0074	3.75	23.49	40.66	60.25	0.610	0.0167	0.0074	7.75	30.08	80.29	60.26
1.00	0.608	0.0226	0.0074	5.95	43.97	40.97	60.26	0.615	0.0188	0.0074	11.27	70.38	80.59	60.27
2.00	0.614	0.0293	0.0149	10.22	64.76	41.27	60.26	0.621	0.0220	0.0149	18.85	110.98	80.89	60.27
3.00	0.618	0.0409	0.0149	25.20	107.24	41.87	60.27	0.626	0.0296	0.0149	46.37	193.08	81.49	60.28
4.00	0.624	0.0492	0.0226	49.02	150.92	42.47	60.27	0.632	0.0366	0.0226	90.67	276.38	82.10	60.28
5.00	0.628	0.0558	0.0226	82.07	195.81	43.08	60.28	0.638	0.0425	0.0226	152.11	360.90	82.70	60.29
6.00	0.632	0.0612	0.0226	124.70	241.90	43.68	60.28	0.642	0.0472	0.0226	231.06	446.61	83.30	60.29
8.00	0.637	0.0655	0.0304	177.27	289.21	44.28	60.29	0.648	0.0515	0.0304	327.06	533.54	83.90	60.29
10.00	0.641	0.0726	0.0304	313.69	387.43	45.49	60.29	0.652	0.0582	0.0384	576.56	711.01	85.11	60.30
20.00	0.645	0.0784	0.0384	494.23	490.48	46.69	60.30	0.657	0.0638	0.0384	901.07	893.31	86.32	60.31
30.00	0.648	0.0973	0.0384	2159.91	1078.07	52.27	60.30	0.661	0.0819	0.0384	3762.08	1877.16	92.35	60.31

log A = 0.60, log B = 3.40, log C = 6.60, log D = 7.80 log A = 0.90, log B = 3.50, log C = 6.90, log D = 7.80

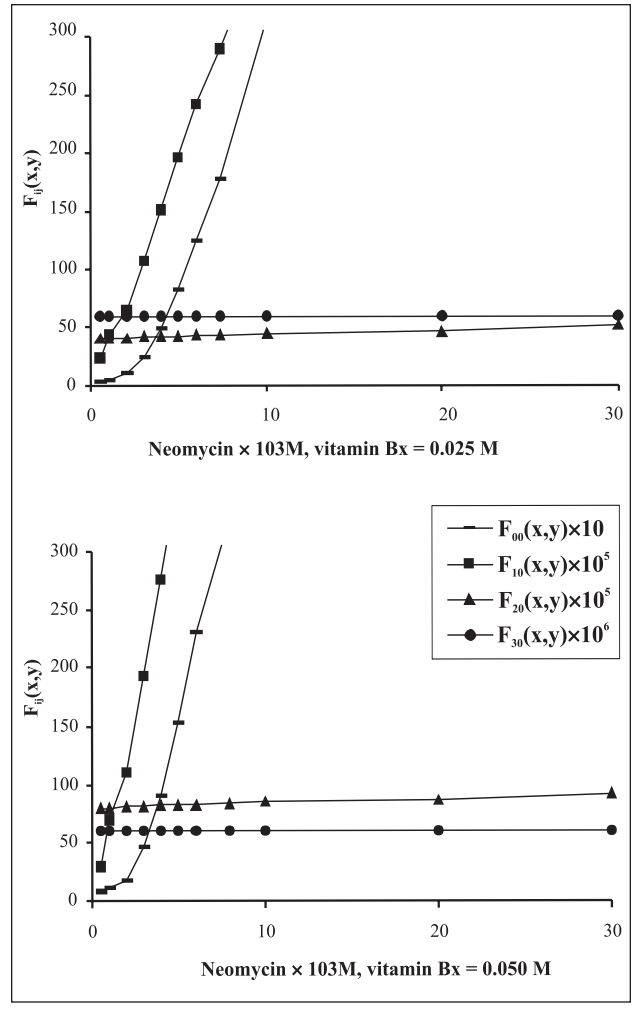

Fig. 2. Cd^{2+}–neomycin–vitamin B_X system

and an ionic strength μ = 1.0 M KNO_3. The study was carried out at two different temperatures, *i. e.* 25 °C and 35 °C to determine the thermodynamic parameters. The values of thermodynamic parameters of the complexes are given in Table 4.

The stability constant log β, which is directly related to free energy change ΔG, is given by the following equation:

$$\Delta G = -2.303\ RT\ \log \beta, \tag{1}$$

where β is the stability constant, T is absolute temperature, and R is a gas constant (1.98 cal K^{-1} mol^{-1}), respectively.

The free energy (ΔG), entropy (ΔS) and enthalpy (ΔH) also contribute to the stability of the complexes.

To calculate the entropy change of complex formation, the change in the stability of the complex with changing the temperature and the bond energy is necessary to know the entropy change. The values of ΔH have been determined with the help of the following equations:

$$\Delta H = \frac{2.303\ RT_1T_2(\log \beta_2 - \log \beta_1)}{(T_2 - T_1)}, \tag{2}$$

were $\log \beta_2$ and $\log \beta_1$ are the values of the stability constant at the kelvin temperature T_2 and T_1 ($T_2 > T_1$), respectively.

Table 3. **Stability constant of Cd^{2+}–antibiotics–vitamin B_x system**
Cd^{2+} = 0.5 mM, I = 1.0 M KNO_3, pH 7.30 ± 0.01, Temp. = 25 °C

Ligand		Stability constants							
Primary	Secondary	$\log \beta_{01}$	$\log \beta_{02}$	$\log \beta_{10}$	$\log \beta_{20}$	$\log \beta_{30}$	$\log \beta_{11}$	$\log \beta_{12}$	$\log \beta_{21}$
Neomycin	Vitamin B_x	1.80	2.40	3.40	5.10	6.85	3.28	5.22	7.02
Chlortetracycline	Vitamin B_x			3.85	5.24	7.20	3.38	5.45	7.45
Oxytetracycline	Vitamin B_x			4.15	5.36	7.34	3.53	5.80	8.08
Tetracycline	Vitamin B_x			4.34	5.48	7.54	–	6.10	8.20
Penicillin-V	Vitamin B_x			4.54	–	7.87	3.88	6.48	8.80
Penicillin-G	Vitamin B_x			4.68	5.60	8.04	4.25	6.87	9.20

Table 4. **Thermodynamic parameters for Cd^{2+}–antibiotics–vitamin B_x complexes**

System	Stability constants			–ΔH Kcal / mol			–ΔG Kcal / mol			–ΔS Cal / deg / mol		
	$\log \beta_{11}$	$\log \beta_{12}$	$\log \beta_{21}$	$\log \beta_{11}$	$\log \beta_{12}$	$\log \beta_{21}$	$\log \beta_{11}$	$\log \beta_{12}$	$\log \beta_{21}$	$\log \beta_{11}$	$\log \beta_{12}$	$\log \beta_{21}$
	25 °C/ 35 °C	25 °C/ 35 °C	25 °C/ 35 °C	25 °C/ 35 °C	25 °C/ 35 °C	25 °C/ 35 °C	25 °C/ 35 °C	25 °C/ 35 °C	25 °C/ 35 °C	25 °C/ 35 °C	25 °C/ 35 °C	25 °C/ 35 °C
Cd^{2+}–neomycin–vitamin B_x	3.28	5.22	7.02	18.24	22.80	20.22	4.76	7.45	10.52	40.37	52.48	34.54
	3.10	4.45	6.85				4.28	6.60	10.10	40.39	52.51	34.56
Cd^{2+}–chlortetracycline–vitamin B_x	3.38	5.45	7.45	17.90	22.48	18.60	5.12	7.43	12.18	36.53	37.35	48.67
	3.03	5.04	7.10				4.80	7.24	11.96	36.54	37.36	48.68
Cd^{2+}–oxytetracycline–vitamin B_x	3.53	5.80	8.08	18.90	24.20	20.14	6.94	8.53	12.34	45.63	48.87	54.23
	3.20	5.40	7.86				5.60	8.10	12.14	45.64	48.88	54.24
Cd^{2+}–tetracycline–vitamin B_x	–	6.10	8.20	–	18.68	23.84	–	10.17	12.17	–	36.87	46.42
	–	6.02	7.81				–	10.02	12.02	–	36.88	46.43
Cd^{2+}–penicillin-V–vitamin B_x	3.88	6.48	8.80	18.70	17.34	23.45	8.31	11.84	12.28	32.14	26.40	42.15
	3.48	6.24	8.43				7.30	11.62	11.88	32.15	26.42	42.16
Cd^{2+}–penicillin-G–vitamin B_x	4.25	6.87	9.20	23.46	21.58	24.62	8.46	11.88	11.58	34.47	31.03	43.73
	4.10	6.52	8.62				8.20	11.34	11.24	34.48	31.01	43.71

On combining the usual equation $\Delta G = -2.303\ RT \log \beta$ and $\Delta G = \Delta H - T\Delta S$, one may obtain the expression

$$\log \beta = (\Delta H - \Delta ST) / -2.303\ RT, \quad (3)$$

where ΔS stand for the entropy change, after determining the values of ΔG and ΔH. The value of ΔS was obtained from the equation

$$\Delta S = (\Delta H - \Delta G) / T. \quad (4)$$

It is clear from the values of ΔS, ΔG and ΔH in Table 4 that the values of ΔG are less negative at a higher temperature and of ΔS more negative at a higher temperature, confirming that the complexes are not stable at a higher temperature [12, 13].

The negative values of ΔH show that the reactions are exothermic in nature [14, 15]. The order of the stability of the Cd^{2+} ternary complexes with respect to the primary ligand was chlortetracycline < oxytetracycline < tetracycline < penicillin-V < penicillin-G.

The value of the mixing constant log k was calculated by the following equation [10]:

$$\log k_m = \log \beta_{11} - \tfrac{1}{2} (\log \beta_{02} + \log \beta_{20}).$$

The values of $\log k_m$ were –0.47, –0.44, –0.35 and –0.25 for Cd^{2+}–neomycin–vitamin B_x, Cd^{2+}–chlortetracycline–vitamin B_x, Cd^{2+}–oxytetracycline–vitamin B_x and Cd^{2+}–penicillin–G–vitamin B_x respectively. The positive value of $\log k_m$ show that the ternary complex is more stable than its binary complexes, while the negative values of $\log k_m$ show that the binary complexes are more stable than their ternary complexes. The complexes of compositions 1 : 2 in case of Cd^{2+}–tetracycline–vitamin B_x and Cd^{2+}–penicillin-V–vitamin B_x are not formed therefore; the values of $\log k_m$ were not calculated. It is clear from the values of the stability constants of the complexes that neomycin formed complexes of a lowest stability. In case of tetracycline, all the tetracycline has the same structures except the difference in R_1 and R_2 positions. The lower stability constant of the chlortetracycline complex than that of the 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 [16]. This order of stability supported the order of the pK values of the ligands [17]. In case of both penicillin-V and penicillin-G, it is the ring nitrogen and O of the carboxylic group that take part in the complexation with Cd^{2+}. The greater stability of penicillin-G complexes than that

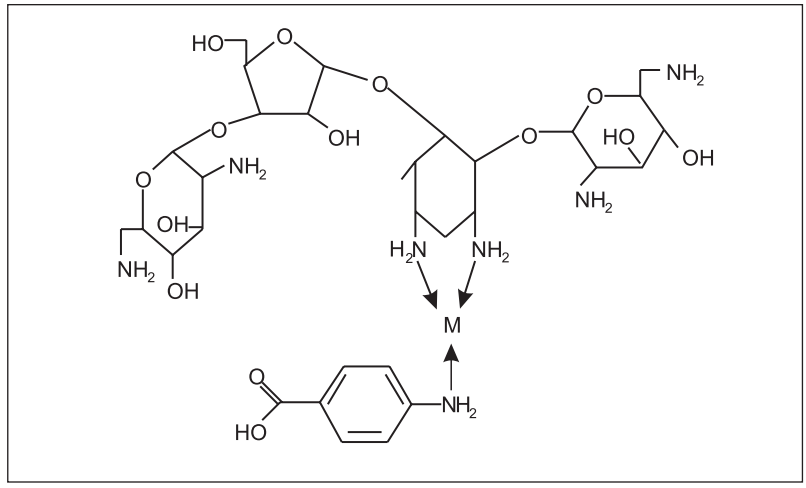

Fig. 3. Cd^{2+}–neomycin–vitamin B_X

of penicillin-V complexes is also supported by the order of the pK values [18, 19].

In case of vitamin B_X, it is the N of the $–NH_2$ group [20, 21] that can take part in bond formation with Cd^{2+}. The complex structure of Cd^{2+} with vitamin B_X is shown above (Fig. 3) where M represents Cd^{2+}.

It is clear from the values of the stability constant of the complexes that vitamin B_X and antibiotics, used both singly and simultaneously, might be effective for reducing the toxicity [22, 23] of Cd^{2+} *in vivo*.

CONCLUSION

It is clear from the study that the shift of $E_{1/2}$ becomes more negative on increasing the concentration of antibiotics and vitamin B_X to Cd^{2+}, which confirms complex formation. Cd^{2+} formed 1 : 1 : 1, 1 : 2 : 1 and 1 : 2 : 1 complexes. The values of their stability constants varied from 1.80 to 9.20 and confirmed that antibiotics alone or in combination could be effective against Cd^{2+} toxicity.

The stability constants (log β) and thermodynamic parameters such as enthalpy change (ΔH) and entropy change (ΔS) of Cd^{2+} complexes with neomycin, chlortetracycline, oxytetracycline, tetracycline, penicillin-V, and penicillin-G as primary ligands and vitamin B_X as a secondary ligand were determined by employing the polarographic technique at pH 7.30 ± 0.01 and the ionic strength I = 1.0 M KNO_3 at 25 °C and 35 °C.

ACKNOWLEDGEMENT

The authors are thankful to the Head of Department of Chemistry, Dr. H. S. Gour University, Sagar, for providing the laboratory facilities.

Received 2 June 2008
Accepted 18 August 2008

References

1. L. O. Derewlany, B. Knie, G. Koren, *J. Pharmacol. Exp. Ther.*, **269**, 756 (1994).
2. A. Szewczuk, M. Wellman-Bednawska, *Clin. Chim. Acta*, **84**, 27 (1978).
3. N. Sato, K. Yamaguchi, K. Yokohata, S. Shimizu, H. Noshiro, K. Mizumoto, K. Chijiiwa, M. Tanaka, *Am. J. Surg.*, **176**, 59 (1998).
4. T. Korzybski, Z. Kowszyk-Gindifer, W. Kurylowicz, *Antibiotics*: *Origin, Nature and Properties*, Vol. 1, Polish Scientific Publishers, Warszawa (1967).
5. F. Khan, *Oxi. Comm.*, **31**, 1 (2007).
6. J. Harte, C. Holdren, R. Schneider, C. Shirtley, *Toxics A to Z: A Guide to Everyday Pollution Hazards*, University of California Press (1991).
7. U. Gubrelay, R. Mathur, S. J. Flora, *Ind. J. Pharmacol.*, **30**, 21 (1998).
8. L. Meites, *Polarographic Technique*, 2nd edn. Interscience Publ., New York (1965).
9. D. Deford, D. N. Hume, *J. Am. Chem. Soc.*, **73**, 5321 (1951).
10. W. B. Schaap, D. L. McMaster, *J. Am. Chem. Soc.*, **83**, 4999 (1961).
11. F. Khan, L. Tantuvay, *J. Pharm. Biomed. Anal.*, **27**, 933 (2002).
12. M. S. Parihar, F. Khan, *J. Indian Chem. Soc.*, **85**, 1 (2008).
13. F. Khan, *J. Indian Chem. Soc.*, **84**, 96 (2007).
14. T. Atalay, E. G. Akgemei, *Turk. J. Chem.*, **24**, 89 (2000).
15. E. G. Akgemei, T. Atalay, *Turk. J. Chem.*, **22**, 123 (1998).
16. R. S. Mulliken, *J. Chem. Phys.*, 513 (1935).
17. J. M. Desiqureria, S. Carvalho, E. B. Paniago, L. Tosi, H. Beraldo, *J. Pharm. Sci.*, 291 (1994).
18. S. N. Chadar, F. Khan, *J. Indian. Chem. Soc.*, **83**, 1242 (2006).
19. F. Khan, *Eclet. Quim.*, **32**, 73 (2007).
20. D. Zhong, A. H. Zewail, *Proceedings of the National Academy of Sciences of the United States of America* (2001).
21. A. Khanm, F. Khan, *J. Indian Chem.*, **85**, 89 (2008).
22. M. D. Walker, D. R. Williams, *J. Chem. Soc.*, 1186 (1974).
23. F. Khan, *J. Chin. Chem. Soc.*, **54**, 673 (2007).

Santosh Narayan Chadar, Farid Khan, Simant Sharma

CD^{2+} KOMPLEKSŲ SU KAI KURIAIS ANTIBIOTIKAIS IR VITAMINO B_X SISTEMA ELEKTROCHEMINIS TYRIMAS IR TERMODINAMINIAI PARAMETRAI

S a n t r a u k a

Cd^{2+} kompleksų su neomicinu, chlortetraciklinu, oksitetraciklinu, tetraciklinu, penicilinu-V ir penicilinu-G, kaip pirminiais ligandais, ir vitaminu-B_x, kaip antriniu ligandu, stabilumo konstantos ir termodinaminiai parametrai, entalpijos pokytis (ΔH), laisvosios energijos pokytis (ΔG) bei entropijos pokytis (ΔS) buvo tiriami poliarografijos būdu pH 7,30 ± 0,01 tirpale esant tirpalo joninei jėgai I = 1,0 M KNO_3. Tyrimai buvo atlikti 25 ir 35°C temperatūrose. Cd^{2+} kompleksai susidaro 1 : 1 : 1, 1 : 1 : 2 ir 1 : 2 : 1 moliniais santykiais. Nustatytoji kompleksų stabilumo konstantų seka neomicinas < chlortetraciklinas < oksitetraciklinas < tetraciklinas < penicilinas-V < penicilinas-G gali būti paaiškinta ligando prigimtimi ir steriniais trukdžiais tarp metalo ligandų. Elektrodiniai procesai yra grįžtami ir kontroliuojami difuzijos. Nustatytosios stabilumo konstantų vertės rodo, kad šios medžiagos gali būti panaudotos Cd^{2+} toksiškumui sumažinti.